

**Physiochemical and drug release properties
of liquisolid formulations in comparison
to their physical mixture counterparts**

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Physiochemical and drug release properties of Liquisolid formulations in comparison to their physical mixture counterparts

By

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**A thesis submitted in partial fulfilment of the requirements of the University of
Wolverhampton for the degree of Doctor of Philosophy (PhD)**



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ABSTRACT

Various techniques have been used for modifying the release properties of drugs over the past years. Techniques such as liquisolid technology have raised a lot of interest in many researchers which can be employed to enhance or sustain dissolution. Various liquisolid (LS) tablets of diltiazem containing Polysorbate 80 as a non-volatile solvent for sustained release were prepared. PolyoxTM is an attractive pharmaceutical polymer used in controlled release dosage forms mainly because of its insensitivity to the pH of the biological medium and ease of production. The aim of this study was to investigate the influence of several formulation factors i.e., the PolyoxTM grade at different molecular weight (MW), PolyoxTM particle size and ratio, the AEROSIL[®] grade, the use of diluent, polymer type and the drug type as well as their interactions on drug release from LS formulation in comparison to their physical mixture (PM). The result showed that PolyoxTM MW was a key determining step in achieving sustained release, with the higher MW of PolyoxTM resulting in a more delayed release profile. The delayed DTZ release could be related to the rate and extend of hydrogel formation on the tablet surface. The P-CMRs and net-CMRs of both LS and PM formulation powders also showed increasing trends with increasing the MW of PolyoxTM. The release of DTZ from both LS and conventional tablets showed mostly decreasing trends with increasing PolyoxTM concentration and decreasing PolyoxTM particle size distribution. This could be attributed to the formation of stronger and thicker gel layers on the tablet surfaces in the case of higher concentrations of PolyoxTM. The results also showed LS tablets to produce slower release of drug than their PM counterparts, regardless of PolyoxTM particle size. The release profile of the DTZ from both LS tablets and their counterpart PM tablets showed decreasing trends with increasing the surface area of hydrophilic AEROSIL[®] (from 65 m²/g to 225 m²/g). This could be due to the higher tensile strength (TS) of the tablets containing AEROSIL[®] particles with higher surface area compared to those prepared using AEROSIL[®] particles having lower surface areas. Also, the result showed that comparing the different diluents showed that hydrogenated vegetable oil (HVO) provided the slowest release pattern of DTZ across diluents used in both the LS compacts and PM tablets. This could be attributed to hydrophobicity imparted by HVO to matrix system when in contact with aqueous medium it takes a longer time to penetrate into the tablet. Drug release from LS tablets was affected by the polymer type. The release was in the order: Eudragit[®] RL < Eudragit[®] RS < Hypromellose < PolyoxTM < Psyllium. Hydrophilic Psyllium provided a slowest DTZ release across the different polymers used in the preparation of both the LS and PM compacts. The incorporation of Psyllium into PolyoxTM further elicited a decrease in drug release rate from individual polymer matrices. This was ascribed to the reduced entrance of aqueous media into the matrix due to the presence of the stronger viscose gel within the two hydrophilic matrices compared to individual Psyllium and PolyoxTM. The ratio between PolyoxTM and Psyllium has critically influenced diltiazem release profile. The results showed that matrices containing (Psyllium:PolyoxTM) at 1:1 ratio can slow down the drug release more than the matrices compacts containing 1:3 and 3:1 (Psyllium:PolyoxTM) ratio. The results also suggest that the

combination of PolyoxTM and Psyllium at 1:1 ratio showed robust dissolution against pH and rotational speed and therefore indicates an appropriate sustained-release profile. The dissolution rate of PolyoxTM:Psyllium from different pure drugs showed a decreasing trend with an increase in their solubility. The solid state analysis studied in this work confirms the presence of a fraction of the drug mass in a solubilised state within polysorbate 80 in LS powders. Regardless of all variables used in this study, LS formulations showed slower drug release than their PM counterparts. In conclusion, the mechanical properties of LS formulation are poor in comparison to their counterpart PM. Therefore, further work is required to improve the hardness of LS tablet comprehensively.

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Abbreviations

ATR, Attenuated total reflectance; D_b , Bulk density; BCS, Biopharmaceutics classification system; CD, Cyclodextrins; CI, Carr's index; DCP, dibasic calcium phosphate; DTZ, Diltiazem; DE, Dissolution efficiency; EC, Ethylcellulose; E-HEC, Ethylhydroxyethylcellulose; ER, Extended release; f_2 , Similarity factor; FT-IR, Fourier Transform Infrared; GI, gastrointestinal; HCL, Hydrochloric acid; HVO, Hydrogenated vegetable oils; HEC, Hydroxyethylcellulose; HLB, hydrophilic-lipophilic balance; HPC, Hydroxypropylmethylcellulose (hypromellose); LS, Liquefied; MC, Methylcellulose; MDR, Mean dissolution rate; MDT, Mean dissolution time; MEC, Minimum effective concentration; MPE, mean percentage error; MTC, Minimum toxic concentration; Na, Sodium; NaCMC, Sodium carboxy methylcellulose; N-CMR, Negative-charge-to-mass ratio; MW, Molecular weight; $D_{10\%}$, Particle diameter at 10% volume distribution; $D_{50\%}$, Particle diameter at 50% volume distribution (median diameter); $D_{90\%}$, Particle diameter at 90% volume distribution; P-CMR, Positive-charge-to-mass ratio; PEG, Polyethylene glycols; PS 80, Polysorbate 80; PG, Propylene glycol; pH, potential of hydrogen; PM, Physical mixture; PSD, Particle size distribution; PVP, Polyvinylpyrrolidone; PXRD, Powder X-ray powder diffraction; R_g , Radius of gyration; SEM, Scanning electron microscope; SSA, surface area; SE, Sucrose esters; SLS, Sodium lauryl sulphate; SR, Sustained release; SRMS, Sustained release matrix systems; SD, Standard deviation; T_g , glass temperature; THP, Theophylline; VMD, Volume mean diameter; WSR, Water soluble resin. ZNM, Zonisamide; ΔDE , Differences in Dissolution efficiency

1 CHAPTER 1: INTRODUCTION

1.1 Drug delivery

Humankind's attempts to confront illness date back to early civilization. Substances obtained from nature were used and tested to treat dysfunctions of physiological life processes, discomfort and pain (Clark, 1996). With the advancement of science, the active ingredients of these substances along with their mechanism of action have been illustrated (Sindrup and Jensen, 1999). Today, new drug candidates are tested to add more effective tools to illness (Zhang *et al.*, 2006). Drugs, even those drugs proposed to treat the same symptoms, usually exhibit dramatically different physicochemical properties such as hydrophobicity, chemical composition, size and potency (Fini *et al.*, 1995). At the molecular level, there is an increased knowledge of cellular biology that is combined with the (decoding) of the human genome (Venter *et al.*, 2001), with a technological discovery in the field of proteomics plus DNA micro-arrays (Cahill and Nordhoff, 2003) that has introduced even more applications such as nucleic acids (gene delivery) (Naldini *et al.*, 1999) and peptide drug delivery (Morishita and Peppas, 2006). Drug activity is a result of molecular interaction(s) in specific cells. It is therefore easily assumed that it is required for the drug to reach somehow the site of action following treatment (oral, local, transdermal, intravenous, etc.) at adequate concentrations (Sindrup and Jensen, 1999). The process of administering a medicinal compound for the purpose to produce a therapeutic outcome for animals and humans is called *drug delivery*. Drug delivery therefore, is a form of technology, which alters the absorption, release profile, elimination and distribution of drug for the sake of increasing the safety and effectiveness of the dosage form to offer compliance and suitability to the patients (Srikanth *et al.*, 2013). Drug delivery aims to deliver the drug at the right concentration for the right period and the right place (Langer, 1998). Although this is difficult by simply choosing an appropriate administration route, strategies based on the relationship of the drug with a carrier (a drug delivery system) are an option (Allen and Cullis, 2004). Additional

motives for developing drug delivery systems include the reduction of needed resources for therapy, the drug's therapeutic index and expensive treatments or unpleasant drug achieved by the prevention of frequent dosing (Ranade and Cannon, 2011).

1.1.1 Oral drug delivery

There are numerous techniques by which a drug can be delivered to the body, such as oral (through swallowing), parenteral (through injection), sub-mucosal (through buccal and sublingual mucosa), transdermal (through the skin) and pulmonary (through inhalation) drug delivery. The centre for the delivery of a large number of essential drugs in various therapeutic areas is the oral route of administration (Perrie and Rades, 2012). The oral drug delivery market is growing at a compounded 10.3% increase of yearly growth rate from 2010 to 2017. This favourite stems from different factors such as the ease-of-use, non-invasiveness and reliability of oral dosage forms (Perrie and Rades, 2012). Indeed, oral administration is the most popular route due to simplicity of ingestion, pain evasion, flexibility (to accommodate several types of drug candidates), and most significantly patient compliance. In addition, solid oral delivery systems do not need sterile conditions, and therefore, these systems are less costly to manufacture (Spireas, 2002).

Table 1.1: Advantage and disadvantages of different type of drug release

Type of drug release	Advantages	Disadvantages
Sustained	<ul style="list-style-type: none"> • Improved control over plasma levels of drug <ul style="list-style-type: none"> ○ maintaining therapeutic plasma concentrations of a drug for (8 to 24) h ○ reduction in drug plasma level fluctuations and thus better control of the disease ○ useful for once daily dosing • Economic savings <ul style="list-style-type: none"> ○ For pharmaceutical companies: cheaper to reformulate an established drug into a SR drug delivery system than to develop new drugs. <p>For health care services: fewer doses leads to lower volume purchasing of drugs</p>	<ul style="list-style-type: none"> • Variable physiological factors (e.g. pH, food, etc.) may all affect drug the release, leading to <ul style="list-style-type: none"> ○ poor <i>in vitro-in vivo</i> correlation ○ increased instability ○ potential dose dumping* • GI transit time is usually less than 12 hours. This potentially limits time for therapeutic levels to be reached and maintained, leading to poor systemic drug bioavailability due to incomplete release
Controlled	<ul style="list-style-type: none"> • Therapeutic plasma concentration is maintained for a prolonged period of time • Higher blood concentration is avoided. • Economical: the overall treatment cost will be less due to less dosing frequency, although the initial cost of treatment is high. 	<ul style="list-style-type: none"> • Release rate continuously decreases due to decrease in effective area at the diffusion front and enhanced diffusional resistance. • Food and the rate penetration influence release rates through the gut.
Immediate	<ul style="list-style-type: none"> ▪ Proper for controlled/sustained release actives. 	<ul style="list-style-type: none"> ▪ Rapid drug treatment intrusion is not possible.

	<ul style="list-style-type: none"> ▪ Enhanced solubility of the pharmaceutical composition. 	<ul style="list-style-type: none"> ▪ Sometimes may need more frequency of administration.
Extended	<ul style="list-style-type: none"> ▪ Extended-release (ER) formulations have the potential to develop the patient compliance and convenience. ▪ Improve the stability by defending the drug from degradative changes or hydrolysis in GI tract 	<ul style="list-style-type: none"> ▪ For oral controlled release formulation, effective drug release period is limited and determined by G.I residence time. ▪ Poor systematic availability and Increase potential for first pass clearance.
Enteric	<ul style="list-style-type: none"> ▪ Coatings are needed for tablets providing a smoother finish, mask the unpleasant taste and also to produces large tablets easier to swallow. 	<ul style="list-style-type: none"> ▪ Controls of sugar coating such as approximately high cost, high bulk and long coating time have led to the use of other coating materials. ▪ It needs the expertise of extremely skilled technician.
Time–Release	<ul style="list-style-type: none"> ▪ Once-daily dosing is possible with most time-release formulations. This improves the ease of dosing and can increase drug compliance. ▪ Some of these advantages involve reduction in adverse effects connected with peak blood levels, reduction in GI adverse effects, and extension of the active half-life of the drug 	<ul style="list-style-type: none"> ▪ Time-release formulations are connected with some limitations. As a result of the continuous release, in most cases, the tablet enters the colon before absolute dissolution. Absorption from the colon is not as great as that of the small intestine

In general oral drugs are designed for either *immediate release* or *modified release*. Immediate release tablets are those that disintegrate quickly and get dissolved to release the drug rapidly. Immediate release may be provided for by the use of a suitable pharmaceutically acceptable carrier or diluent, in which carrier or diluent does not prolong, to a significant extent, the rate of drug release or absorption (Nyol and Gupta, 2013). The term modified release product is used to specify products that change the rate and the timing of the release of the drug substance. *ER* dosage forms offer at least a double reduction in dosage rate as compared to that drug given an immediate release form (Leon, 2005). *Timed release* drug delivery is used to achieve the drug release following a delayed time. *Enteric release* dosage forms are those systems that release the drug slower than usual behaviour at proposed rate & significantly reduce the dosage frequency by two folds (Ankit et al., 2013).

1.2 Controlled release

Controlled release controlled release drug is a drug delivery system that produces the constant oral delivery of drugs at reproducible and predictable kinetics for a proposed period during the course of GI transit and also the method that target the delivery of a drug to a particular region in the GI tract for either a systemic or local action (Rathore et al. 2013). In the last three decades, controlled release oral products have brought the attention of formulation scientists due to an array of advantages (Abdelkader et al., 2007). Essentially the term controlled release can be applied to the systems showing some type of 'control' over the drug release, viz. control over the place of drug release (as in enteric coated dosage forms), control over slow and constant release of the drug from the dosage form (as sustained release systems) or in targeted drug release to a distinct organ (Lachman et al., 1990). However, controlled release dosage forms do have some limitations. Cure cannot be stopped immediately should it be required in case of severe adverse effects. Additionally, there is less room for dosage alteration. Different factors like pH, motility and contents of the gastrointestinal tract (GIT) might change the drug release from the transit time of control release dosage form, and therefore, these

factors should be taken into account in order to regulate the drug release and the transition time of the dosage form into GIT (Zalte and Saudagar, 2013). Ideally, a controlled release drug delivery system strives to deliver drug at a rate administered by the dosage form design. Practically, the controlled drug delivery systems attempt to keep the required concentration at the target tissues across the therapeutic window (Chen *et al.*, 2013). The controlled release systems try to keep drug plasma concentration at a constant state level where ideally the rate of drug display in the blood matches the rate of drug clearance from the blood. It is understood in the system that the absorption of the drug is not the rate defining step such that the rate of occurrence in the blood meets the rate of release from the dosage form.

1.3 Sustained release

The new and novel drug delivery systems are replacing conventional drug dosage forms. A sustained release (SR) dosage form is a drug delivery system that allows a reduction in dosing frequency to that presented by a conventional or immediate release dosage form (Figure 1.1). A SR drug delivery system therefore, produces prolonged therapeutic effect by constantly releasing the drug over an extended period of time subsequent of single dose administration. SR formulations are designed to provide an initial release of drug sufficient enough to achieve the desired therapeutic response promptly after administration, and then the remaining (maintenance) dose is released gradually over an extended period of time to achieve a therapeutic level that is prolonged but not maintained constant. The system is not capable of maintaining constant drug levels.

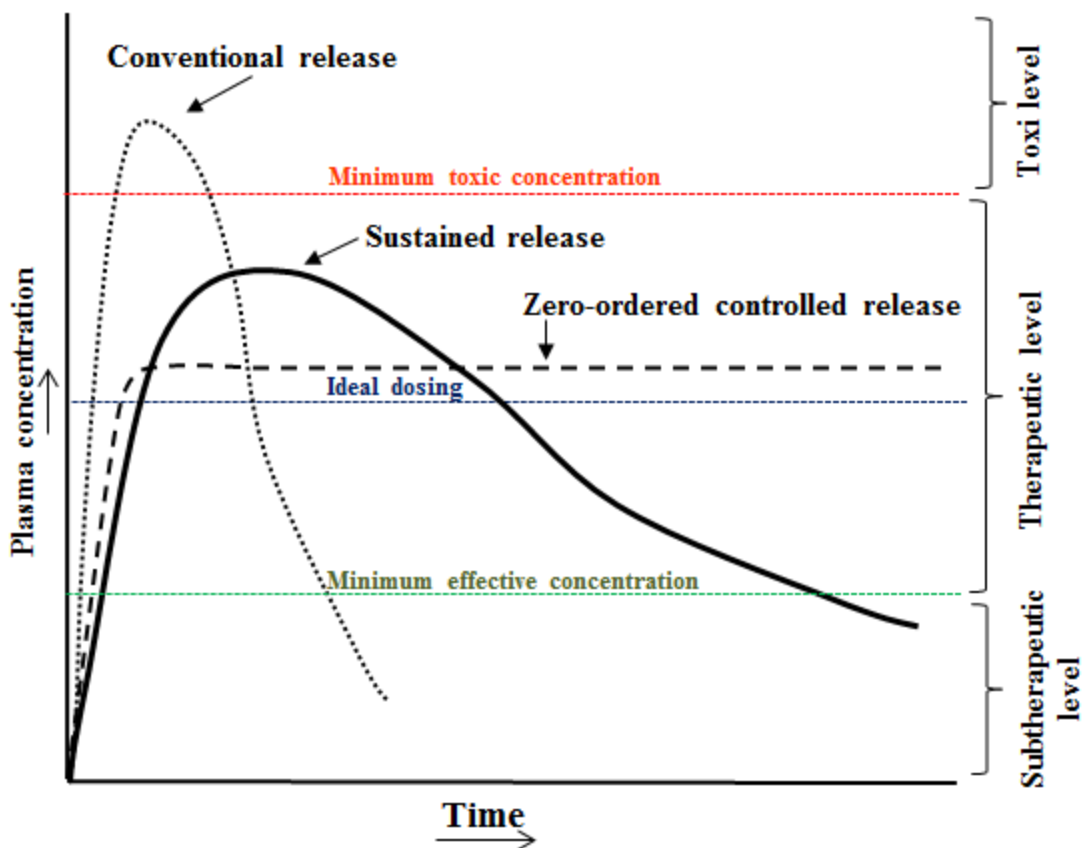


Figure 1. 1: A hypothetical plasma concentration-time profiles from conventional, sustained and zero-order controlled release delivery systems following single doses.

The plasma concentration-time profiles of conventional release systems are associated with peaks (above the minimum toxic concentration (MTC), potentially resulting in toxic side effects) and valleys (below the minimum effective concentration (MEC), potentially resulting in no therapeutic outcome) that reduce optimum drug therapy. The main goals of designing a SR form is to achieve a steady state blood level that is non-toxic and therapeutically effective for an extended period of time (i.e. to reduce fluctuations in drug levels in the blood) and thereby reduce dosing frequency (Figure 1.1). The design of SR system therefore, requires an understanding of the pharmacokinetic and pharmacodynamic properties of the drug (Robinson and Lee, 1997). The ideal SR drug delivery system is expected to achieve a release of a highly soluble drug to the target organ or cell at a rate that matches an intended purpose. The advantages and limitations of SR dosage forms are summarised in Table 1.1.

1.4 Common candidate Drugs for Sustained Release

Certain properties of the drug candidate should be viewed into before developing it into sustained release dosage form. Normally, a drug can be formed into a sustained release dosage form if it has a comparatively shorter biological half-life, is absorbed and excreted quickly, is completely absorbed in the lower intestine, and has a broad therapeutic index. The time taken to eliminate 50% of the drug from a systemic circulation is referred to as the drug's half-life. To achieve a consistent therapeutic blood level of the drug the rate of absorption and elimination should be retarded. Biological half-life of a drug plays a vital role in this case. In general, a drug with approximately shorter half-life is a better candidate for a sustained release dosage form ([Lachman and Lieberman, 1990](#)).

Table 1. 2: List of some developed drugs for sustained release

Drug	Category	Water solubility at 22 °C	Pka	Log P	Dose (mg)	Half-life (h)	t _{max} (h)	Commercial product(s)	References
Alfuzocin HCl	Selective antagonist of post-synaptic alpha	25	14.64 and 7.3	1.4	10	10	8	Extended Release	Nicholas <i>et al.</i> , 2011
Diltiazem HCl	Calcium channel blocker	465	12.86 and 8.18	2.8	120 to 180	3 to 5	1 to 1.5	Extended-Release Tablets	Elkhodairy <i>et al.</i> , 2012
Gliclazide	Anti-diabetic	0.19 mg/mL	4.07 and 1.38	2.6	40 to 120	10-24	2 to 8	Extended-Release Tablets	Panchal <i>et al.</i> , 2011
Losartan potassium	Antihypertensive	0.82 mg/L	5.5	6.1	50 to 100	1.5 to 2.5	2 to 4	Extended-Release Tablets	Vohra <i>et al.</i> , 2012
Metformin HCl	Antihyperglycemic	1.38 mg/mL	12.4	-0.5	500 to 2500	1.5-4.5	24 to 48	Extended-Release Tablets	Riedmaier, 2013
Propranolol HCl	Beta blocker	61.7 mg/L	9.5	3.48	60 to 160	4	11.5 to 15.4	Extended-Release Tablets	Reiter, 2004
Pregabalin	Anti-epileptic, Anti convulsant	11.3 mg/mL	4.2 and 10.6	-1.35	25 to 300	6.3	1.5 to 3	Extended-Release Tablets	Pawar <i>et al.</i> , 2011
Theophylline	Anti-asthmatic	8.0 mg/L	8.81	-0.02	400 to 800	6 to 8	1 to 2	Extended-Release Tablets	Shojaee <i>et al.</i> , 2014
Venlafaxine HCl	Anti-depressant	572 mg/mL	14.42 to 8.91	2.69	75 to 225	5-11	5.5 to 9	Extended-Release Tablets	Radhika <i>et al.</i> , 2011
Zonisamide	Antiepileptic drug	0.8 mg/mL	10.2	0.5	100 to 400	60	2 to 5	Extended-Release Tablets	Biton, 2007
Naproxen Na	Nonsteroidal anti-inflammatory drugs (NSAIDs)	15.9	3.18	4.14	200 to 220	12 to 15	0.5 to 3	Extended-Release Tablets	Rashid <i>et al.</i> , 2009

- *Diltiazem hydrochloride* (HCl)

Diltiazem HCl (DTZ) is a calcium channel blocker that is generally employed in the treatment of angina pectoris and hypertension (Elkhodairy *et al.*, 2012). DTZ is largely metabolized by the liver, excreted by the kidney, and absorbed up to about 80%; however, due to an extended first-effect, DTZ is subjected to an entire bioavailability of about 40%. The plasma elimination half-life after single or multiple administrations is almost (3–5) h. A sustained and slow release of DTZ is useful to patients to maintain sustainable levels of DTZ in the blood plasma (Piepho *et al.*, 1982).

- *Theophylline*

Theophylline (THP) is used in therapy of chronic obstructive pulmonary disease essentially in bronchial asthma (Yoon *et al.*, 2007). It is given as conventional tablets in a dose of 400 mg to 800 mg daily in divided doses. It is quickly absorbed and eliminated by a plasma half-life of 6 to 8 h and a t_{max} (the amount of time that a drug is present at the maximum concentration in serum) of 1 to 2 h. Due to fast absorption and elimination of drug the plasma concentration-time profile of its proper system results in a regular peak-valley curve, a phenomenon making it hard to keep a steady plasma level. Therefore, frequent dosing is needed to maintain a uniform concentration of drug in blood to give its therapeutic effect (Yasir *et al.*, 2010).

- *Zonisamide*

Zonisamide (ZNM) is quickly absorbed, with reaching the t_{max} in (2–5) hrs with 100% bioavailability (Sills and Brodie, 2007). Food decreases the rate but not the limit of absorption, improving the t_{max} to (4–6) h (Brodie *et al.*, 2012). ZNM exhibits dose-dependent pharmacokinetics, with highest plasma concentrations and the area under the time-plasma concentration curve leading linearity following single doses of (100–800) mg and various

subsequent doses of (100–400) mg every day (Kochak *et al.*, 1998). It has a long half-life of 60 hours, leaving for once-daily dosing. The sustaining dosage is (100–600) mg/d in adults and 8 mg/kg/d in children. It is approximately 40% to 50% protein bound and the therapeutic limit is (10–40) µg/mL. There is no clear correlation between clinical efficacy and ZNM serum levels (Sills and Brodie, 2007).

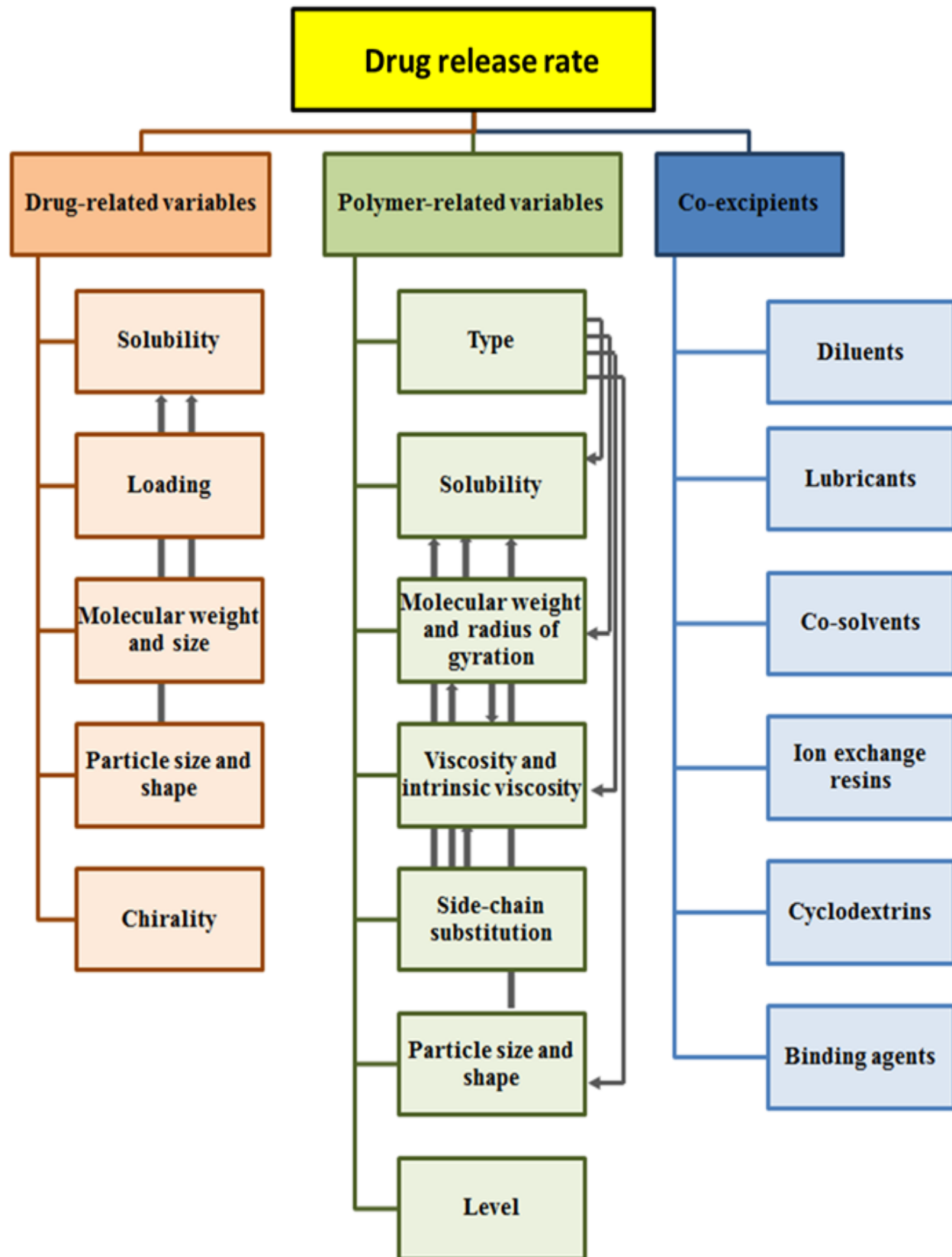


Figure 1. 2: Schematic, simplified summary of drug-related, polymer-related, and co-excipient variables affecting drug release from sustained release matrix systems.

1.5 Matrix systems

Matrix (monolithic) systems are one of the most frequently used dosage forms for oral controlled drug delivery systems. Matrix SR systems are often administered via the oral administration, owing to its advantages including the ease of administration and the high acceptance by patients. Historically, hydrophilic matrix systems were first introduced to the academic community in the early 1960s, with a patent from (Christensen and Dale, 1969), after which the inventors published a research describing the technology and its applications (Huber *et al.*, 1996).

Matrix systems are polymer-based delivery systems that enable a slow controlled drug release into the body. Matrix formulations usually consist of (i) drug, (ii) polymer, and (iii) co-excipient(s). In a matrix system, the drug is dispersed/embedded as solid particles within a porous hydrophilic or eroding matrix formed of a soluble or an insoluble polymer, which enables the drug release to be controlled. The drug is combined and made into granules with slowly dissolving/eroding excipients, progressively releasing the drug for absorption. The direct compression of the drug, materials and additives to form a tablet in which the drug is embedded in a matrix core of the polymer retardant forms a matrix tablet. The main advantages and limitation of matrix systems are summarised in Table 1.3.

When a matrix that contains swellable glassy polymer is in contact with an aqueous solution (or gastric fluid), the hydrophilic matrix takes up water, leading to a decrease in the glass transition temperature of the polymer (i.e. water plasticising the polymer) causing a change from a glassy state to a rubbery state. Such initial wetting stage of the tablet surface followed by polymer swelling/hydration leads to forming a gel layer at the system surface (Figure 1.3). The quick formation of such gel layer is important because it helps to hold the structural integrity of the

matrix, halts water entering the core of the matrix, and constraints tablet disintegration (Colombo *et al.*, 2000). As more water penetrates into the free spaces between the macromolecular chains, the thickness of the gel layer increases, the polymer chains become more flexible and the matrix swells, this then causes the diffusion of the encapsulated drug out of the matrix (Figure 1.3). A water gradient is present within the hydrated gel layer, the outer surface of this layer is the most dilute with polymer here approaching complete disentanglement is prone to erosion. Eventually, the outer tablet layer reaches a dilution point as it is highly hydrated, causing disentanglement of the polymer from the surface of the matrix (Khan *et al.*, 1995). Drug release rate therefore depends on polymer swelling rate, length of diffusion pathway, and strength/tortuosity of the gel layer. The mechanisms and kinetics of release from hydrophilic matrices are comprehensively reviewed elsewhere (8).

According to the Higuchi equation (Higuchi, 1963), (Eq. 1.1), the release of drug from a matrix system is controlled by the initial drug concentration, drug solubility, polymer system, as well as matrix porosity, tortuosity, size and shape.

$$A = [D(2C - C_c)C_c \times t]^{1/2} \quad (1.1),$$

where, A is the amount of drug released in time t per unit area, D is the diffusivity of drug molecules in the matrix substance, C is the initial drug concentration, and C_s is the drug solubility in the matrix media. It is therefore possible to manipulate drug release from sustained release matrix systems (SRMS) by manipulating drug-, polymer and formulation related variables. This research reviews the influence of drug-, polymer-, and co-excipient-related variables and their interactions on the rate and mechanism drug release from SRMS (Figure 1.2).

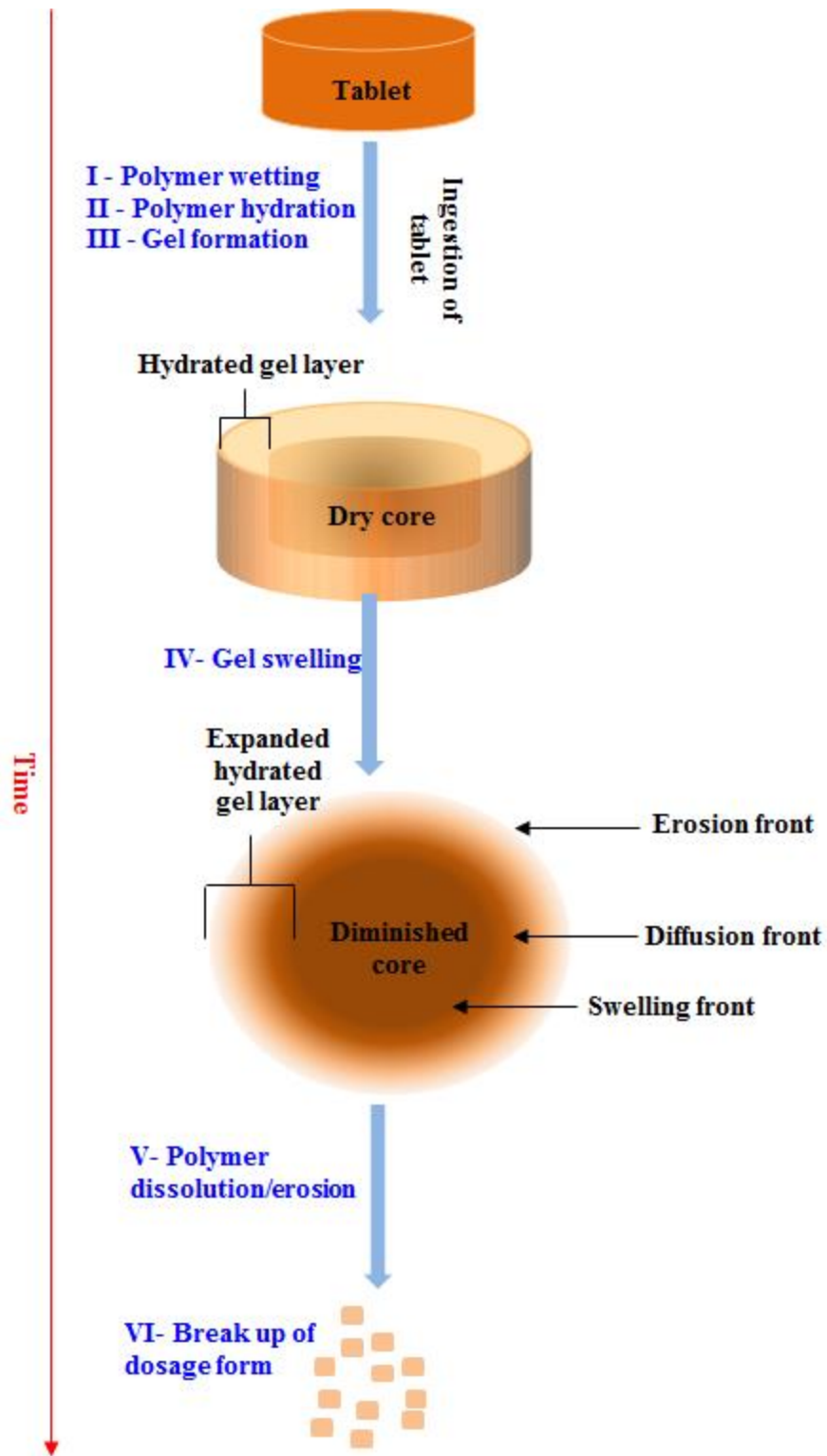


Figure 1. 3: Mechanism of drug release from a hydrophilic matrix tablet.

1.6 Drug-related variables

In a successful SR system, the drug is released from the dosage form at a predetermined rate, dissolve in the GI fluids, maintain sufficient GI residence, and absorbed at a rate that will replace the amount of drug being metabolized and excreted (Ansel *et al.*, 2000). The characteristics for candidate drugs for SR drug delivery systems and examples of drugs unsuitable for oral SR dosage forms are summarised in [Tables 1.3](#) and [1.4](#) respectively.

The release of drug from its matrix system is reliant on its physicochemical properties such as solubility, molecular weight (MW), size and shape, particle size and shape, and chirality (Abdou, 1989). Such properties of a drug may determine the type and grade of the retardant polymer ([Section 1.7](#)) as well as the co-excipient(s) ([Section 1.8](#)) that need to be incorporated to achieve a desirable drug release.

Table1.3: A summary of characteristics for candidate drugs for SRDDSs

Characteristic	Rational
Exhibit neither very slow nor very fast rates of absorption and excretion, i.e. half-life should be between 2 h and 8 h (ideally 4 h to 6 h).	Drugs with long biological half-life are inherently long acting, whereas drugs with very fast biological half-live require too large dose to be pharmacologically active
Absorbed reasonably quickly	The concentration of drug in the plasma should be limited by the release rate rather than the rate of absorption
Maintain adequate residence time in the GIT	Drugs that are absorbed poorly and at unpredictable rates are poor candidates because their release rate and absorption depend on drug positioning in the GIT.
Highly potent (dose usually 2–3× that of immediate release system)	High does reduce the polymer and co-excipient level to the extent that it would be difficult to attain a strong gel layer, whereas including a sufficiently high level of polymer would increase the unit dose to an extent where it becomes difficult to swallow by the patient.
Good margin of safety	The level of drugs having narrow therapeutic range may be out with the safe or effective plasma concentrations. If dose dumping occurred, then narrow therapeutic index drugs lead to overdose
Intended to treat chronic rather than acute diseases	SR systems are not suitable for acute conditions
Absorbed uniformly from the GIT	Drugs absorbed by active transport in selected regions of the GIT are not good candidates for SR dosage forms
Intermediate water solubility	The dissolution of very poorly soluble drugs is inherently sustained. SR formulations of such drugs should aim at making their dissolution more uniform rather than reducing it. Extremely lipid soluble drugs might also demonstrate low flux into the tissues or rapid flux followed by accumulation in tissues
Stable at biological pH range	Very highly soluble drugs are difficult to formulate should not undergo degradation due to pH or enzymatic activity (at any given time point the concentration in the GI fluid is lower than that of an immediate release dosage form)
MW below 500 D	Drugs with MWs above 500 Da show very small diffusion coefficients

Table 1.4: Examples of some drugs unsuitable for oral SRMS dosage forms.

Drug	Characteristic(s)
Diazepam and phenytoin	Long biological half-lives (>12 h)
Riboflavin and ferrous salts	Poorly absorbed in the lower intestine at unpredictable rates
Penicillin G and furosemide	Short biological half-lives (<1 h)
Sulphonamides	Large doses (>1 g) required for therapeutic activity
Phenobarbital and digitoxin	Low therapeutic indices
Anticoagulants, cardiac glycosides	Personalized dosage is required
Griseofulvin	Poorly soluble and thus inherently sustained

1.6.1 Solubility

Solubility is one of the most important physiochemical properties of a drug. This is because following oral administration, the bioavailability of a drug depends primarily on its solubility in the GIT and its permeability across the cell membranes. This is the basis on which the Biopharmaceutics Classification System (BCS) runs (Amidon *et al.*, 1995) (Figure 1.4). Solubility according to the BCS framework is determined by obtaining the pH–solubility profile of the drug substance in question in an aqueous media of pH range 1 to 7.5 at an established temperature of $37\text{ }^{\circ}\text{C} \pm 1\text{ }^{\circ}\text{C}$. A drug substance is thus considered to be highly soluble when its highest dose strength proves to be soluble in 250 mL or less of an aqueous media over the pH range of 1.0 to 7.5 (Blume and Schug, 1999); FDA, 2017). BCS *Class I* compounds are thus those that have high solubility and high permeability. *Class II* compounds are those that exhibit high permeability but because of their low solubility they fail to meet the criterion for solubility across the physiological pH range 1 to 7.5. Most of the compounds or drug substances that fall in this category tend to have high solubilities in part of the pH ranges of 1 to 7.5 because they are either weak acids or weak bases. The *Class III* compounds are the compounds with high solubility but low permeability. In this case, the pH of the medium selected for the compound or product is not influenced by the compound’s solubility due to its high solubility (Grundy *et al.*,

1997). *Class IV* drugs or compounds have low solubility and low permeability – the rate of *in vivo* absorption of those drugs therefore depends on the relative rate of the two plus whether the drug’s low permeability is a borderline or is because of metabolism (Amidon *et al.*, 1995). Knowledge of the solubility of a drug is therefore important when direct administration into the bloodstream is desired because low aqueous solubility could either delay or limit drug absorption (Amidon *et al.*, 1995). Drug solubility is thus one of the important parameters that should be taken into account in drug release studies on a case–bycase basis (Tahara *et al.*, 1995).

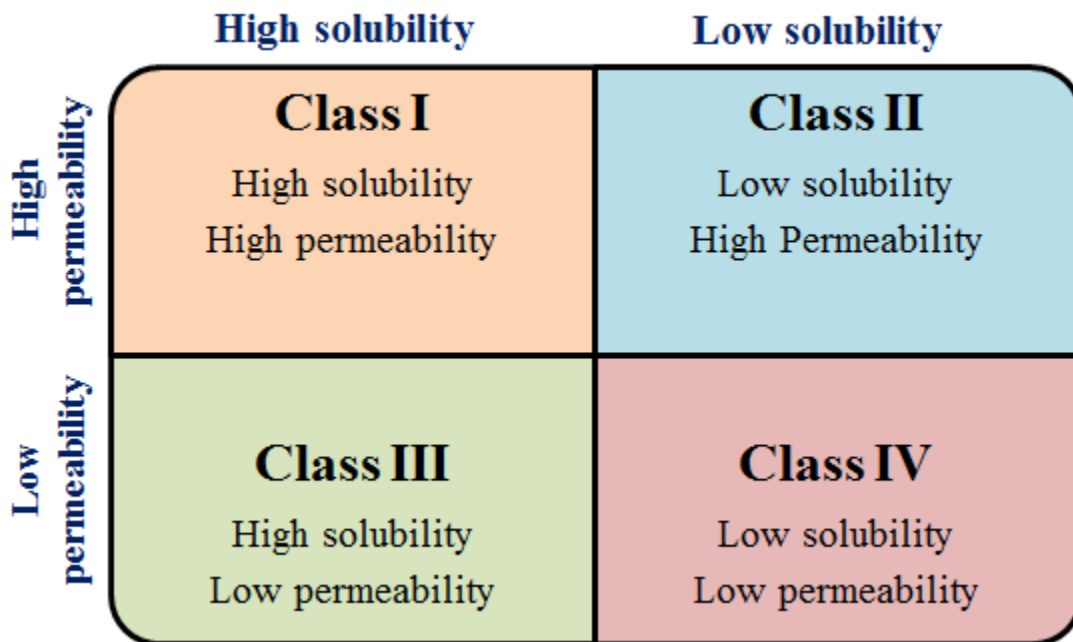


Figure 1.4: The Biopharmaceutics Classification System (BCS).

Matrix technology allows successful formulation of insoluble and soluble drugs. In general, the more soluble a drug is the faster its release. For example, (Kim, 1998) (Figure 1.5) and (Li *et al.*, 2008) showed the rate of various drugs from PolyoxTM matrix systems to reduce with the decrease in aqueous drug solubility.

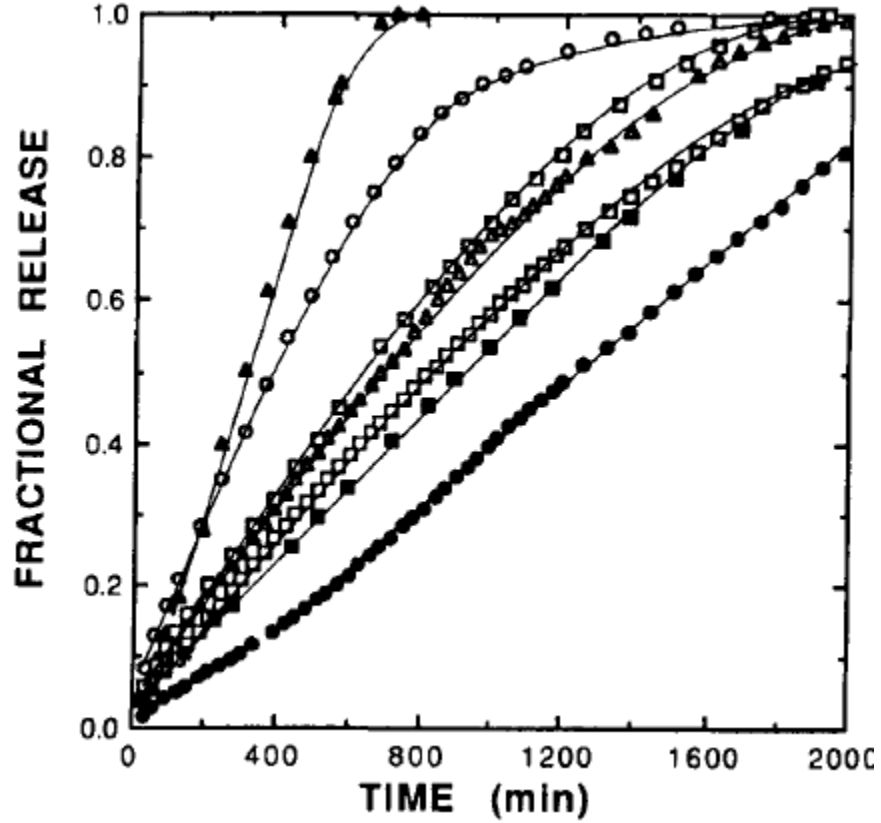


Figure 1. 5: Effect of drug solubility on the release of drugs from PE04 tablets (39% loading): (○) diclofenac Na, (□, Δ) theophylline, (□, ■) salicylic acid, (●) sulfathiazole, and (▲) sulfapyridine. Reprinted with permission from (Kim 1998).

For a soluble drug to be released from a matrix, the water (or biological fluids) should wet/infiltrate the matrix, after which the drug is dissolved and then diffused out of the matrix. Solubility often decides the mechanism of drug release because the drug usually occupies a substantial portion of the formulation. When matrix swelling and erosion reach equilibrium, the local volume fraction of a drug (γ_{ds} , $\text{cm}^3\text{drug}/\text{cm}^3\text{gel}$) in the gel layer is a function of drug solubility and loading, as described by the following equation (Colombo *et al.*, 1999a).

$$\gamma_{ds} = C_s \frac{\gamma_w}{\varepsilon_d} \quad (1.2),$$

where C_s is the solubility of drug in water, γ_w is the volume fraction of water at that point, and ε_d is the density of drug.

Drug solubility also affects the mechanism of drug release by affecting gel characteristics (Kim, 1999). In particular, drug solubility (and drug loading (Section 1.6.2)) governs the place occupied by the diffusion front in the gel layer (Colombo *et al.*, 1999b). This is because the amount of drug dissolved in the gel layer (along with polymer relaxation) affects the distance between the diffusion and erosion fronts, which is fundamental in the drug release mechanism (Colombo *et al.*, 1999a; Colombo *et al.*, 1999) (Figure 1.5). The polymer volume fraction will be high towards the swelling front whereas the volume fraction of water will be high towards the erosion front.

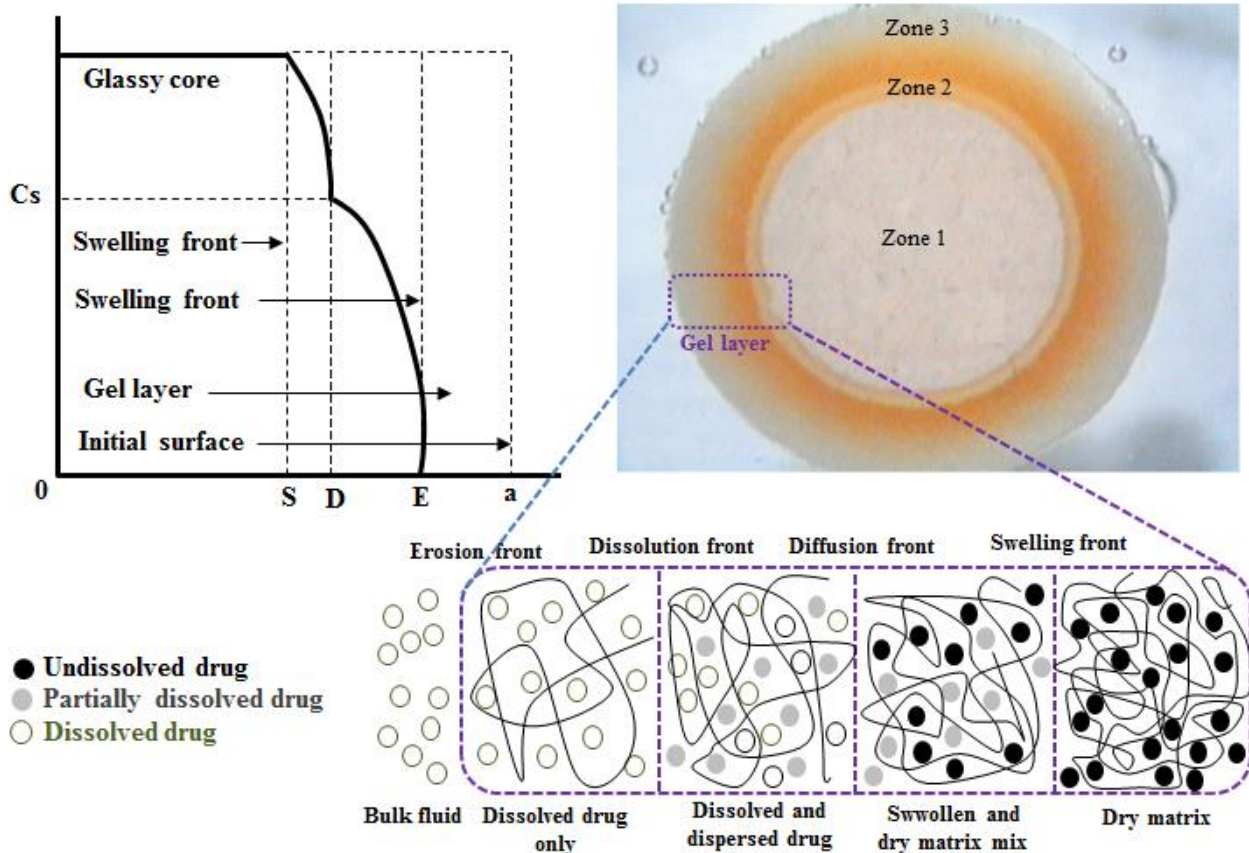


Figure 1.6: Physical situation and schematic illustration of different fronts position in a swellable-soluble matrix tablet during drug release. The three distinct moving fronts are indicated. At all times, the dissolved drug profile extends from the diffusion to the erosion front and the water profile from the swelling to the erosion front (i.e. the entire gel layer). Modified from (Kiil and Dam-Johansen, 2003).

In theory, the effect of solubility on drug dissolution can be described using Fick's first law (Martin *et al.*, 1993).

$$J = -D \frac{dC}{dX} \quad (1.3),$$

where J is the mass flux (the amount of material flowing through a unit cross-section of a barrier in unit time), D is the diffusion coefficient (which is controlled by structural characteristics of the

drug), and dC/dx is the concentration gradient (which is dependent on water solubility). From Eq. 2, the diffusion coefficient (D) is controlled by structural characteristics of the drug. In the case of a poorly soluble drug, both dissolved and undissolved particles are present within the matrix, from which only the dissolved drug can diffuse into the dissolution media.

In general, highly soluble drugs (e.g. Propranolol HCl and DTZ HCl) are primarily released from hydrophilic polymer matrices by diffusion of dissolved drug molecules through the gel layer, and to a lesser extent via erosion of the gel matrix. This is because highly soluble drugs promote swelling/hydration of the hydrophilic matrix (Zuleger and Lippold, 2001). In contrast to poorly soluble drugs, osmotic stress and acceleration of water permeation into the matrix occur with substances having high solubility. This causes a high degree of polymer swelling/hydration and the formation of more microcavities, and as such diffusion becomes the mechanism of drug release for highly soluble drugs (Caraballo, 2010). Additionally, the diffusivity of a solute depends on the chemical gradient across the dissolution medium, which is a function of solute solubility. Therefore, the mass transfer coefficient of various drugs (Cimetidine HCl, Diclofenac Na, and Diprophylline) has been shown to be a function of drug solubility (Harland *et al.*, 1988), (Table 1.5). In some cases, highly soluble drugs could dissolve instantly after being exposed to a dissolution medium, causing a very rapid initial drug release even *before* the formation of a gel layer on the tablet surface, leading to the ‘burst effect’ Li *et al.*, 2008; Huang and Brazel, 2001). This is because highly soluble drugs act as pore-formers, thus the gel structure becomes more porous resulting in faster drug release (Li *et al.*, 2005). Such burst effect is not wanted in SR formulations because it may lead to producing concentrations of drug above the MTC (due to rapid absorption) or below the MEC (due to rapid metabolism) (Huang and Brazel, 2001).

Table1. 5: Effect of drug solubility of the release mechanism (determined using the diffusion coefficient (Peppas, 1985) from Carbopol[®] matrices. Solubility data were taken from (Yalkowsky and Dannenfelser, 1992) whereas diffusion coefficient data were taken from (Lubrizol, 2011).

Drug	BCS	Solubility (mg/mL)	Diffusion coefficient (<i>n</i>)	Mechanism of drug release
Theophylline	Class IV	7.3	0.59	Anomalous diffusion
Hydrochlorothiazide	Class IV	0.722	1.11	Relaxation
Ketoprofen	Class II	0.051	1.48	Relaxation

In contrast to highly soluble drugs, poorly soluble drugs have low dissolution rates because of their low diffusion rates and hence the drug release rate that tends to follow diffusion mechanism would be low. The release of poorly soluble drugs (e.g. indomethacin, diazepam and isosorbide dinitrate) from hydrophilic polymer matrices is dominantly by osmosis and polymer relaxation (Kim 1998; Bettini *et al.*, 2001). For example, the in the case of Carbopol[®] matrices, a highly soluble drug (THP, BCS Class IV) was released by diffusion, whereas poorly soluble drugs (e.g. carbamazepine, hydrochlorothiazide, and ketoprofen) tend to partition into the more hydrophobic domains of the system (such as the acrylic backbone of the Carbopol[®] polymer), from where they showed an almost linear release profiles (Lubrizol, 2011) (Table 5). (Pérez-Marcos *et al.*, 1991), showed atenolol (a highly soluble drug, 26.5 mg/mL, BCS Class III) to be released from carbomer matrix systems via diffusion kinetics, whereas the release of furosemide (a poorly soluble drug, 0.073 mg/mL) followed zero-order profile. In another study, (Efentakis *et al.*, 2000) showed the release of furosemide from Carbopol[®] 974P NF matrices to occur through polymer relaxation mechanism due to the hindered movement of drug molecules from the interior of the polymer mass towards the surface caused by strong entanglement of polymer molecules. Only after complete matrix hydration (i.e. complete matrix transformation into the rubbery state), the contribution of erosion to drug release increases as the solubility of the drug

decreases (Tahara *et al.*, 1996; Ford *et al.*, 1991). This explains the conflicting results obtained from few studies which showed faster drug release in the case of less soluble drugs due to the hindered gel formation (Mitchell *et al.*, 1993a). This is because poorly soluble drugs are usually hydrophobic, thus a region of hydrophobicity is created upon their inclusion in a hydrophilic matrix. These hydrophobic substances also remain as solid particles for a longer period of time in the gel. The regions of hydrophobicity created to reduce the entanglement of the polymer chains and gel strength (i.e. hinders the expansion of the polymer), meaning that erosion becomes favourable as the mechanism by which drug release occurs after complete matrix hydration. Therefore, poorly soluble drugs tend to show a pulse release at the end of their release profile, attributable to the displacement of insoluble particles through the gel layer, pushing the particles through the gel layer and thereby increasing the exposure of the particles to water (Bettini *et al.*, 2001) (Figure 1.7). Due to their poor solubility (<0.01 mg/mL) and dissolution rate, poorly soluble drugs could also show incomplete release. The solubility of such poorly soluble drugs in hydrophilic matrices has been improved using various strategies such as the use of hydrophilic carrier systems (Giunchedi *et al.*, 1994), surfactants (Efentakis *et al.*, 1991), drug-cyclodextrin inclusion complexes (Rao *et al.*, 2011), and nanosized formulations (Kaialy and Al Shafiee, 2015).

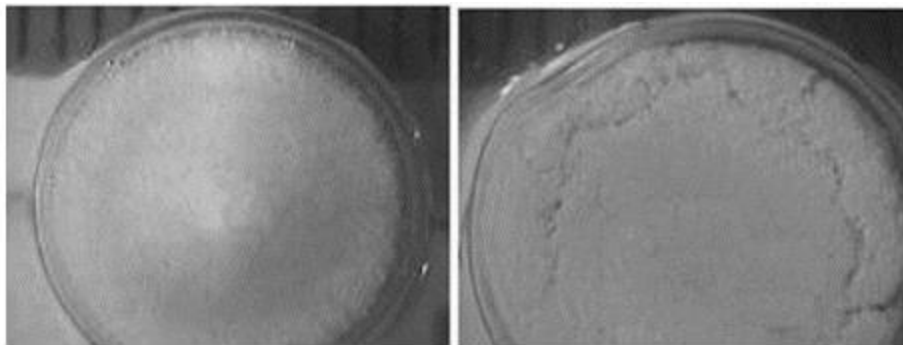


Figure 1.7: Pictures of the base of HPMC matrices containing nitrofurantoin (BCS Class II) taken after 1 h (left) and 24 h (right). Reprinted with permission from (Bettini *et al.*, 2001).

Finally, it should be kept in mind that aqueous solubility of a drug depends on its chemical structure, stereochemical configuration, and polymorphic form, all of the latter properties could affect drug release properties by altering drug solubility. The pH of the dissolution medium and polymer-related variables (Section 1.7) could also interact with the effect of drug solubility on drug release from SRMS. Some examples are given below.

1.6.2 Loading

In general, providing that drug solubility is not high enough, drug release rate increases with increasing drug loading, attributable to higher chemical gradient at the diffusion front as well as greater channel formation in the swollen matrix. For example, (Lapidus and Lordi, 1966) showed the increase in chlorpheniramine maleate loading to cause an increase in drug release rate from methylcellulose matrix systems (Figure 1.8). In the same line, increasing the loading of U-78875 (Tahara *et al.*, 1995) and prednisolone (Rao *et al.*, 2011) have been reported to lead to an increase in the percentage of drug release from hypromellose matrix systems.

A rationally SR profile is usually obtained if the gel structure is formed within the first 5 minutes of contact of the matrix tablet with dissolution medium. If such formation of a gel

structure failed, a premature drug release could be observed due to quick matrix erosion (Velasco *et al.*, 1999; Nellore, 1998). Some authors reported a burst effect in the case of SR formulations containing a high loading of highly soluble drugs (Velasco *et al.*, 1999) because of the presence of few areas on the matrix surface not covered by polymer. Producing burst effect from SR formulations also depends on other variables such as polymer particle size (Section 1.7.6) as discussed later.

The loading level of a drug is fundamental to explaining its drug release behaviour from inert matrices, drug loading showed relatively less influence on the drug release behaviour from hydrophilic matrices. This is because water enters the system through the hydrophilic polymer and through the pores that arise through the swelling process, thus the need of a cluster of soluble substances at the onset of the drug release process is not a necessity (Miranda *et al.*, 2007; Fuertes *et al.*, 2010).

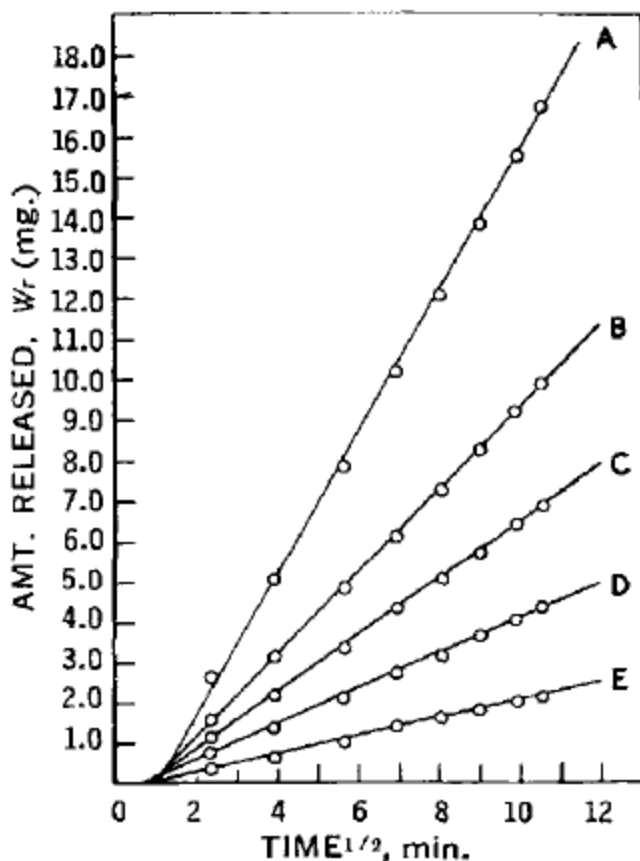


Figure 1.8: Drug release profiles for tablets containing 150 mg (A), 100 mg (B), 75 mg (C), 50 mg (D), and 25 mg (E) of chlorpheniramine maleate. Reprinted with permission from (Lapidus and Lordi, 1966).

1.6.3 Molecular weight, size and shape

According to Higuchi's model (Higuchi, 1963), (Eq. 1), solute MW is one of the variables (along with the diameter of the solute molecule and the viscosity of the diffusion medium) that determines the diffusion coefficient, of which the release rate from matrix-based SR dosage form systems is proportional to the square root. The release of drugs having MWs above 500 Da is likely to be constrained by interaction with the aqueous gel network leading to poor diffusivity in hydrophilic matrices (Flynn *et al.*, 1974). (Baveja *et al.*, 1987) reported that molecular size and shape are important variables that affect the release rate of structurally related

water-soluble bronchodilators (namely ephedrine HCl, salbutamol sulphate, terbutaline sulphate, aminophylline, and reproterol HCl) from hypromellose matrix systems. This conclusion was supported by another research group, who showed the mean dissolution time of drugs having various MWs to decrease for drugs having lower MW (Talukdar *et al.*, 1996). In another study, (Fyfe *et al.*, 2000) showed that the release rate of triflupromazine HCl was slower than that of 5-fluorouracil due to its smaller molecular size and higher MW. Such results can be explained as drug diffusion through the gel layer tends to be easier as the drug MW and size decrease (Figure 1.9).

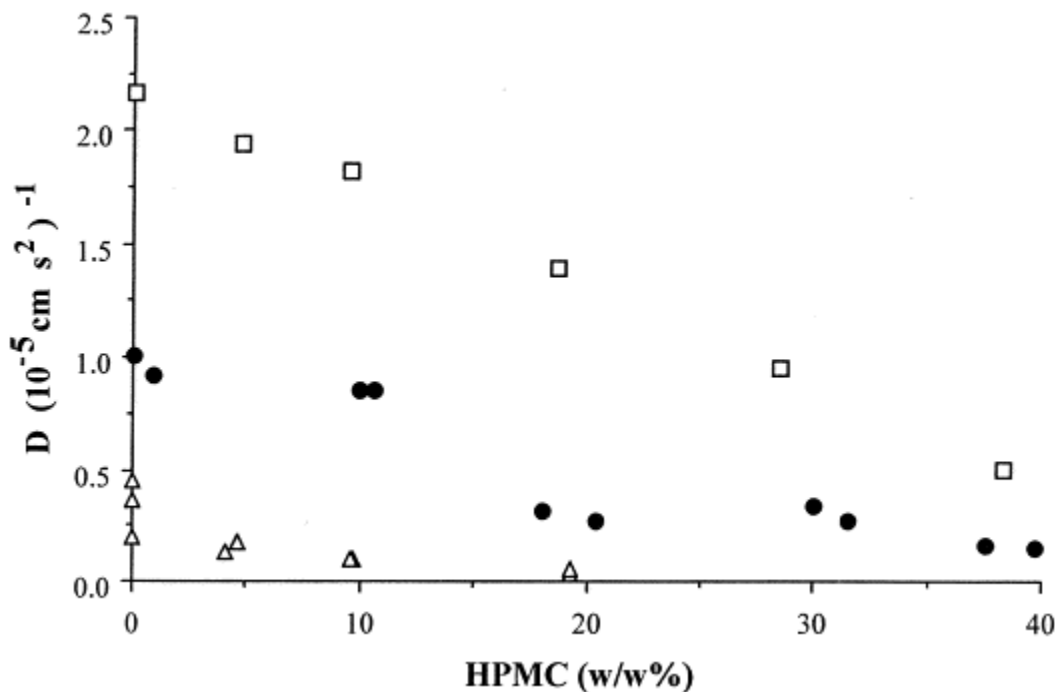


Figure 1.9: Self-diffusion coefficients of water (open squares), triflupromazine-HCl (open triangles) and 5-fluorouracil (filled circles) in selected hypromellose mixtures. Reprinted with permission from (Fyfe *et al.*, 2000).

1.6.4 Particle size and shape

Particles having varied sizes and shapes usually show different intrinsic *in vitro* dissolution profiles, attributable to differences in particle surface area (Blagden *et al.*, 2007), or increased abundance of polar groups (Kaialy *et al.*, 2014), potentially leading to different release rates from SRMS. For example, rod-shaped dipyridamole particles demonstrated considerable enhanced *in vitro* dissolution rate with potential improved bioavailability in comparison to rectangular needle-shaped particles (Adhiyaman and Basu, 2006).

In theory, drug particle size alters the tortuosity of the hydrated gel layer and thus can affect drug diffusion through the gel layer, leading to altered drug release rate, as described by Lapidus and Lordi equation (Lapidus and Lordi, 1966).

$$D^* = \frac{D}{t} \quad (1.4),$$

where D^* is the apparent diffusion coefficient of the drug in the gel layer, D is the real diffusion coefficient of the drug in the dissolution medium, and t represents the tortuosity of the gel. It is known that drug diffusion through the gel layer decreases with increasing tortuosity leading to a decrease in drug release rate.

Apparently conflicting results were however reported on the effect of drug particle size on drug release rate from matrix systems. Some studies showed larger drug particle sizes to lead to faster drug release rates for both highly soluble (e.g. DTZ) (Li *et al.*, 2008), and poorly soluble drugs (e.g. rifampicin) (Hiremath and Saha, 2008). In the case of highly soluble drugs, the larger the particle size of the drug the larger the size of the channels (pores) that cross the gel layer. Such increased porosity of the swollen matrix system leads to facilitated complete release (Kim 1999). Additionally, the greater surface area of highly soluble drug particles present on the

surface of the matrix (in the case of drug particles having smaller size distributions) lead to a quicker formation of gel layer. In the case of poorly soluble drugs, the faster drug release from the matrix systems in the case of drug particles having larger particle size is due to a greater degree of erosion of the matrix (Ford *et al.*, 1987). Such release behaviour could also provide a probable mechanism for dose dumping from this type of matrix tablets. In contrast, (Velasco *et al.*, 1999), showed the decrease in particle size of diclofenac Na (a moderately soluble drug) to increase in the dissolution rate of that drug in the external media via a diffusion-controlled release mechanism. These findings were in accordance with other studies who showed the decrease in the particle size of oxazepam (de Llarduya *et al.*, 1997), and propranolol HCl (Ford *et al.*, 1985), to cause an increase in drug dissolution rate from hypromellose K100M (de Llarduya *et al.*, 1997), and hypromellose K15M (Ford *et al.*, 1985), matrices. In another study, (Salomon *et al.*, 1979), reported the use of two particle sizes of potassium chloride particles (63 μm to 100 μm and 315 μm to 400 μm) to lack significant effect on the release rate of potassium chloride from hypromellose matrices. Such seemingly conflicting results is because the effect of drug particle size on drug release rate from matrix systems depends on other variables such as drug solubility (Section 1.6.1), polymer level (Section 1.6.7), and pH of the dissolution medium, particularly in the case of moderately soluble drugs (Vazquez *et al.*, 1992).

- *Drug solubility and polymer level*

Some studies showed the effect of drug particle size on drug release rate is only important (or more important) in the case of matrices containing low polymer level (since such matrices have inherently high porosity/low tortuosity characteristics (Velasco *et al.*, 1999; Campos-Aldrete and Villafuerte-Robles, 1997; Ford *et al.*, 1985; Mitchell *et al.*, 1993b), and

poorly soluble drugs (since those drugs are predominantly released via an erosion mechanism) (Ford *et al.*, 1985a; Ford *et al.*, 1985c; Ford *et al.*, 1985d).

1.7 Polymer-related variables

Polymers are high MW long chain molecules formed from smaller molecules called monomers with unique size and 3D arrangement bound covalently to one another. Polymeric materials are widely used for controlling drug release. Hydrophilic soluble polymers have been used in controlled release systems via the oral route, whereas biodegradable polymers based on polylactic acid or polyanhydrides have been used to control drug release from implants and other drug delivery systems. The release rate from matrix systems is governed by polymer internal structure, which depends on its chemical structure, solubility/hydrophilicity, MW, substitution degree and cross-linking. The effect of some polymer-related variables on drug release from SRMS is discussed below.

1.7.1 Type

Since polymers have different structural, physicochemical and mechanical characteristics, the type of polymer is a key factor that can affect the mechanism of drug release from matrix systems (Alderman, 1984; Mitchell *et al.*, 1993c). A range of natural hydrophilic polymers, cellulosic or non-cellulosic, hydrophilic (soluble and swell in water) or hydrogels (insoluble but swell in water), alone or in mixtures have been used to modulate drug release from SRMS, including starch derivatives, alginates, xanthan gum, polyethylene oxides, carrageenan, and remarkably derivatives of cellulose, which are the most commonly used groups of polymers in SRMS (Ravi *et al.*, 2008), (Table 1.6).

Table1.6: Some polymers commonly used in SRMS.

Cellulosic	Hydrophilic	Methylcellulose
		Hydroxypropylmethylcellulose (hypromellose)
		Hydroxyethylcellulose
		Ethylhydroxyethylcellulose (E-HEC)
		Sodium carboxymethyl cellulose
		Hydroxypropylcellulose
	Hydrogel	Ethylcellulose
		Hypromellose acetate succinate
		Cellulose acetate
		Cellulose acetate propionate
Non-Cellulosic	Hydrophilic	Carrageenan
		Carbomer
		Xanthan gum
		Sodium alginate
		Chitosan
		Guar gum
		Pectin
	Hydrogels	Crosslinked high amylose starch
		Poly-(ethyleneoxides)
		Polymethacrylates
		Polyvinyl acetate

Except for cellulose esters and ethylcellulose (EC), cellulose have a derivatives of certain degree of hydrophilia of all the hydrophilic polysaccharides, hypromellose is the most commonly used polymer used to retard drug release from hydrophilic matrix systems, due to its water solubility, non-ionic nature, and stability at biological pH range from 3.0 to 11.0 (Kaialy *et al.*, 2014; Asare-Addo *et al.*, 2013a; Asare-Addo *et al.*, 2013b). In contrast to hypromellose which usually lead to type-I or diffusion drug release kinetics, xanthan gum has been shown to elicit zero-order (or at least time-independent) kinetics from matrix systems (Talukdar and Kinget, 1995), attributable to its faster hydration rate compared to hypromellose (Talukdar *et al.*, 1996). Sucrose esters (SE) have been shown to sustain the release of highly soluble drugs via gelation as well as enhancing the mechanical properties of matrix systems, making them promising excipients for the preparation of directly compressed tablets (Chansanroj and Betz, 2010). (Sinha

Roy and Rohera, 2002), showed hydroxyethylcellulose (HEC) and hydroxypropylcellulose (HPC) matrices to elicit different release mechanisms. The release of chlorpheniramine maleate from HEC matrices followed non-Fickian mechanism (in which drug diffusion as well as polymer swelling and erosion is involved), whereas the release of drug from HPC matrices followed Fickian mechanism (in which only drug diffusion as is involved). Polymer crosslinker levels also affect the rate of hydration/swelling of the polymer hydrogel and thereby affect drug release from matrix systems. In general, highly crosslinked polymers tend to be less efficient in controlling drug release than lightly crosslinked polymers. For example, at 10% polymer level, Carbopol® 971P NF polymer (lightly crosslinked) produced slower release rates of THP than Carbopol® 974P NF polymer (highly crosslinked) (Lubrizol, 2011) (Figure 1.10).

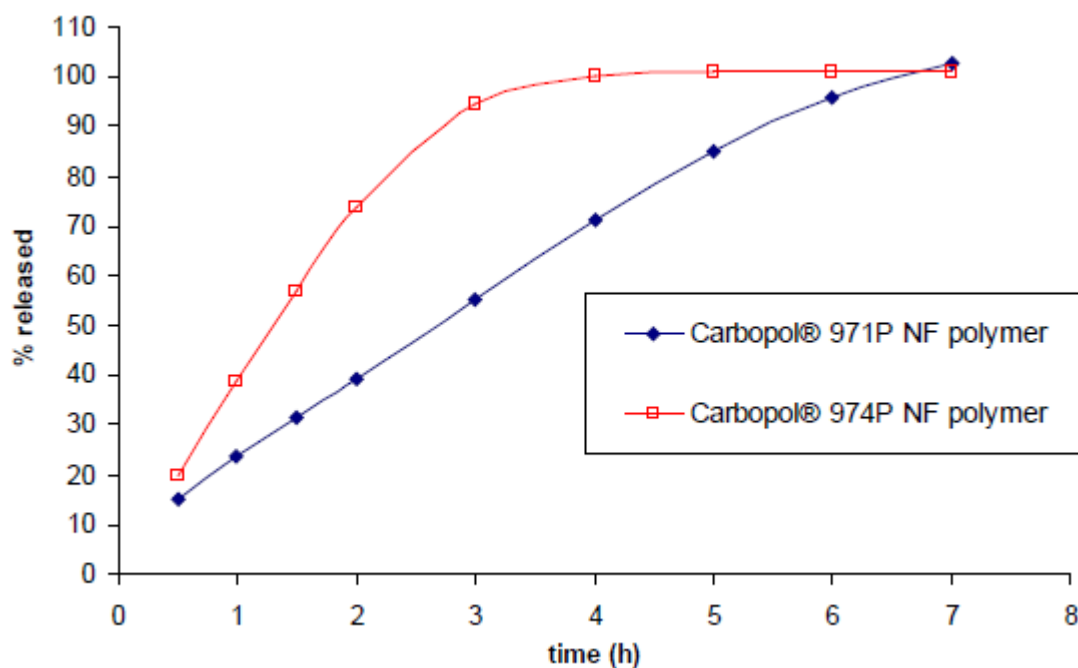


Figure 1.10: Effect of Carbopol® polymer type on the release rate of theophylline release (USP apparatus 2, pH 6.8 buffer) from wet granulated tablets (Lubrizol, 2011).

1.7.2 Solubility

Swellable polymers can be broadly classified into hydrophilic polymers and hydrogels (Ebube *et al.*, 1997), (Table 1.6).

In general, hydrophilic polymers elicit faster drug release rates than hydrogels (Reza *et al.*, 2003). Dissolution of a polymer includes absorption/adsorption of water in more accessible place, rupture of polymer-polymer linking with the simultaneous forming of water-polymer linkage, separation of polymeric chain, swelling, and finally dispersion of polymeric chain in the dissolution medium (Figure 1.6). Polymer hydrophilicity is known to influence the kinetics of drug release from matrix systems. Hydrophilic matrix systems typically release drug through diffusion across the hydrated gel layer, whereas hydrophobic matrix systems release drug through aqueous pores formed in the drug depletion zone. This is because polar polymers can produce adequate energy to disperse polymer chains from the glassy state via interaction with an aqueous dissolution medium. Hydrophilic polymers, particularly cellulose ethers (Salsa *et al.*, 1997), are therefore usually preferred in the formulation of SRMS because they have good swelling properties that lead to a rapid formation of the external gel layer through which the drug is released via diffusion, and additionally they often give good compression characteristics even when compressed directly.

Freely soluble drugs (e.g. metoprolol succinate) may require a large quantity of polymer to attain a desirable retarded release of drug, which ultimately results in large tablets that are difficult to swallow. The use of water-insoluble polymers can often resolve this problem. Therefore, water-insoluble (e.g. EC and acrylic resins) and pH-dependent soluble polymers (e.g. hypromellose acetate succinate) have also been used to sustain drug release from matrix systems. For example, Eudragit[®] RS and RL have been used in LS formulations to allow for better

prolongation of the release of a highly soluble drug (propranolol HCl) compared to conventional formulations due to better encapsulation of drug particles within the hydrophobic polymers (Javadzadeh *et al.*, 2008). The combination of hydrophilic and hydrophobic polymers has also been shown to effectively control the release of freely water-soluble drugs from SR formulations (Gade and Murthy, 2014).

1.7.3 Molecular weight and radius of gyration

Polymer MW determines gel strength and thus water penetration through the gel layer during swelling (Brady *et al.*, 2009). Radius of gyration (Rg) is a parameter directly related to polymer MW. It refers to the statistical average of the molecular length and is used to describe the dimensions of the polymer side-chain (Beignon *et al.*, 1998). With increasing polymer MW, the degree of polymer swelling increases whereas the polymer's ability to erode decreases. Some studies showed that at low PolyoxTM MW (WSRN 1105 and WSR 303), DTZ (Maggi *et al.*, 2002) and metronidazole (Kiss *et al.*, 2008), were released primarily by erosion and diffusion of the PolyoxTM, whereas at high MW of PolyoxTM the drugs were released through the swelling of the polymer and the diffusion of the drug across the hydrogel layer. In an attempt to provide better understanding of the effect of polymer MW and Rg on the mechanism of drug release from SRMS, (Viridén *et al.*, 2009), evaluated the drug release rates from matrices containing polymers having similar MWs. Different drug release rates were obtained from polymers having similar MW and Rg, namely hypromellose 60SH50, 65SH50, 90SH100 and 90SH100SR, indicating that predicting drug release rates from polymer MW or Rg alone is not possible.

1.7.4 Particle size and shape

Numerous studies showed polymer particle size to play an important role in moderating drug release from SRMS due to its effect on polymer disintegration/hydration/erosion rate (Heng *et al.*, 2001; Miranda *et al.*, 2007; Caraballo, 2010; Velasco *et al.*, 1999; Mitchell *et al.*, 1993d). Different commercial grades of a polymer may also have different particle shape distributions. For example, in one study, fibrous-shaped interlocking particles have been shown to produce stronger matrices that could potentially modify the swelling characteristics of the matrix, leading to reduced burst effect along with decreased drug release rates (Bonferoni *et al.*, 1996).

In general, polymer particle size affects the availability of contact points as well as the porosity/tortuosity of the matrix. The change in matrix porosity in turn changes the resistance for water penetration and the diffusibility of the drug through the hydrated gel layer of the polymer, potentially leading to a meaningful change in the drug release rate (Mulye and Turco, 1996). The decrease in particle size of both water-soluble (e.g. hypromellose (Heng *et al.*, 2001) and PolyoxTM (Shojaee *et al.*, 2015) and water-insoluble (e.g. Eudragit[®] RS-PM and Ethocel[®] 100) (Sánchez-Lafuente *et al.*, 2002) polymers have been shown to elicit slower drug release rates from matrix systems. For example, (Alderman, 1984) showed a premature drug release from matrices containing coarse particles of K chemistry-hypromellose. Other studies showed that the release rate of propranolol HCl (Mitchell *et al.*, 1993b) and metronidazole (Campos-Aldrete and Villafuerte-Robles, 1997) from hypromellose matrices to decrease as the particle size of hypromellose decreased. In another study, (Parojčić *et al.*, 2004) attributed the differences in the release rates of paracetamol (BCS Class IV) between matrices containing Carbopol[®] 71G NF polymer (granular polymer) and Carbopol[®] 971P NF polymer to their varied sizes. The

Carbopol[®] 71G NF polymer allowed a quicker penetration of the dissolution medium into the matrix, leading to faster drug release compared to Carbopol[®] 971P NF.

Polymer particle size can affect drug release rate because coarse polymer particles (typically > 200 μm) need more time to capture water and to swell to form a stable gel barrier (i.e. hydrate too slowly), resulting in a faster drug release by disintegration rather than by diffusion (Colombo *et al.*, 2000; Mitchell *et al.*, 1993a; Campos-Aldrete and Villafuerte-Robles, 1997; Alderman, 1984). For example, coarse (> 355 μm) hypromellose K15M particles produced larger pore sizes when a gel layer is obtained, resulting in a decrease in the stability of the gel structure and thus rapid drug release. In contrast, the polymer grade having smaller particle size (< 150 μm) prompted the development of gel layer, sealed the pores on the surface of matrix systems, and thereby prevented disintegration of the system (Dow, 2006). (Velasco *et al.*, 1999), showed the particle size of hypromellose to affect lag time and release mechanism. Larger particle size fractions of hypromellose showed less lag period, indicating a degree of burst effect occurred during the initial stages before the formation of the gel layer. In another study, (Heng *et al.*, 2001) showed large (> 180 μm), medium (113 μm to 180 μm) and fine (<113 μm) size fractions of hypromellose to release aspirin (BCS Class IV) from matrix systems via disintegration, diffusion, and a combination of diffusion and erosion respectively. Similar observations were obtained in the case of hydrogels. For example, small-size fractions (< 125 μm) of EC produced a slower release rate of propranolol HCl compared to larger size fractions (385 μm to 420 μm), which facilitated water penetration into matrices (Dabbagh *et al.*, 1996). Additionally, from a physical viewpoint, polymers having small particle sizes can produce stronger tablets compared to those having larger particle sizes, attributable to their higher bulk (packing) density and thereby increased interparticle average contact points leading to better

interparticle bonding (Velasco *et al.*, 1999). Therefore, micronized hydrophilic polymers are today available in small particle sizes to ensure quick and consistent polymer hydration and thereby prevent prompt tablet disintegration, and to allow for the preparation of controlled release tablets via direct compression (Colombo *et al.*, 2000).

Finally, it should be kept in mind that the effect of polymer particle size on drug release from matrix systems depends on other variables such as drug solubility (Section 1.6.1) and polymer level (Section 1.7.7).

- *polymer level*

Several authors reported that polymer particle size is only important in the case of formulation matrices containing relatively low levels of polymer (Zuleger and Lippold, 2001; Campos-Aldrete and Villafuerte-Robles, 1997; Heng *et al.*, 2001; Velasco *et al.*, 1999). For example, (Mitchell *et al.*, 1993d) showed that the effect of hypromellose particle size on the release rate of propranolol HCl decreased with decreasing polymer level. This was because at low polymer levels, there will be a lack of polymer particles in particular areas of matrices leading to a burst effect. (Campos-Aldrete and Villafuerte-Robles, 1997) showed that the effect of reducing hypromellose particle size on retarding metronidazole release from a matrix system could only be observed when hypromellose (Demacol[®]) levels were below 20% (*w/w*). Likewise, (Heng *et al.*, 2001) showed that changes in particle size of hypromellose K15M did not affect the mechanism of aspirin release when the hypromellose levels were higher than 20% (*w/w*). The behaviours reported by the latter studies (Campos-Aldrete and Villafuerte-Robles, 1997; Heng *et al.*, 2001; Mitchell *et al.*, 1993d) could be explained by the so-called *percolation threshold* of polymer. Historically, percolation theory was first introduced into the pharmaceutical field by (Leuenberger *et al.*, 1987). According to this theory, a cluster is defined as a group of

neighbouring particles of the same component. A cluster could be considered finite or infinite. In general, the percolation threshold corresponds to the concentration of one component for which there is a maximum probability of appearance of an infinite or percolating cluster of this component (Caraballo, 2010). The percolation threshold of a polymer corresponds to the volume fractions of the polymer that is needed to produce a robust matrix system (Miranda *et al.*, 2006). In general, polymer particle size does not affect drug release when polymer level is above the threshold due to a consistent formation of gel layer, whereas polymer particle size does affect drug release when polymer level is below the threshold due to a heterogeneous formation of gel layer (Miranda *et al.*, 2007).

1.7.5 Level

Since hydration plays a key role in the choice of polymer selected for SR systems, the presence of a sufficient amount of polymer is important to form a uniform barrier that protects the incorporated drug from inconstant release and initial burst effect upon contact with water (Mandal *et al.*, 2007). Polymer level is therefore one of the most important drug release controlling factors in hydrophilic matrices (Velasco *et al.*, 1999; Nellore, 1998; Ford *et al.*, 1985; Ford *et al.*, 1985b; Mitchell *et al.*, 1993e).

In theory, a linear relationship can be obtained when plotting the release rates (R_H , $\log \% \text{ min}^{-1/2}$) against the reciprocal of the mucilage concentration at which they were obtained, as described by equation 1.7 (Ford *et al.*, 1985a).

$$\log R_H = M (1/W) + C \quad (1.5),$$

where M ($\% \text{ min}^{-1/2} \text{ mg}^{-1}$) is the slope of derived straight line, W (mg) is polymer weight, and C ($\% \text{ min}^{-1/2}$) is a constant. This confirms that formulators could obtain desirable release profiles by changing polymer level in the matrix formulation. Although the above relationship (Eq. 1.6) could be used to estimate the release rate at a range of polymer content, it cannot be used in the case of very low polymer content (particularly low-viscosity grades of polymers such as hypromellose K100LV) which could promote burst release of drug and thereby deviation from Higuchi's equation.

In general, the level of polymer in SR matrix formulations typically ranges between 20% and 50% (w/w), depending on drug-related variables (Section 1.6), co-excipients (Section 1.8), processing parameters, and the anticipated release pattern. In the case of matrix systems containing highly soluble drugs, polymer levels $\geq 30\%$ (w/w) in the matrix system are recommended to obtain a robust formulation that eliminates the effect of minor variations in manufacturing method or raw materials (Tiwari *et al.*, 2003; Ford *et al.*, 1985).

Previous studies showed drug release rate from hydrophilic matrix systems to decrease with increasing polymer level regardless of polymer physicochemical characteristics (Reza *et al.*, 2003). For example, (Ebube *et al.*, 1997) showed increasing the levels of cellulose ether polymers (from 3.5% to 19.2%) to decrease the release rates of paracetamol from hypromellose/polyvinylpyrrolidone mixture matrices. Other studies showed the increase in hypromellose level to result in slower release rate of THP (Figure 1.11), tetracycline HCl (Ford *et al.*, 1987b), Metoprolol tartrate (Nellore, 1998) and Atenolol (Vázquez *et al.*, 1996) from matrix tablets. Similar conclusions were attained in the case of insoluble polymers. For example, increasing the level of carbomer 934 has been shown to lead to a decrease in the release rate of atenolol (Perez-Marcos *et al.*, 1996). In another study, increasing the level of Carbopol[®] 974P

NF has been shown to decrease and linearize the release rate of ibuprofen (BCS Class II) along with shifting the release mechanism from anomalous type towards a swelling-controlled, a phenomenon caused by the closing of micropores and a reduction in regions of low microviscosity in the swollen tablets (Khan and Jiabi, 1998). Increasing the level of both Carbopol[®] 71G NF (from 15% to 30%) and Carbopol[®] 971P (from 2.5% to 20%) polymers led to a slower and more linear release profiles for a soluble (THP) and a poorly soluble (ketoprofen) drug respectively (Lubrizol, 2011) (Figure 1.12).

In general, increasing the content of hydrophilic polymers (e.g. hypromellose) in a matrix formulation increases the strength/viscosity of the gelatinous diffusion gel layer around the tablets, thus retarding the penetration of water into the dry glassy core and increasing the length/tortuosity of the diffusional path (due to fewer interstitial spaces between the microgels) (Mitchell *et al.*, 1993a; Alderman, 1984; Dabbagh *et al.*, 1996; Klančar *et al.*, 2015). This results in a decrease in the effective diffusional coefficient of both soluble and insoluble solutes, leading to a reduction in drug release rate (Campos-Aldrete and Villafuerte-Robles, 1997; Ford *et al.*, 1985a; Ford *et al.*, 1985d; Alderman, 1984; Dabbagh *et al.*, 1996; Mitchell *et al.*, 1993d; Lotfipour *et al.*, 2004), although the slow hydration of the polymer is preferred for insoluble or poorly soluble drugs to minimise or limit the thickness of the gel layer.

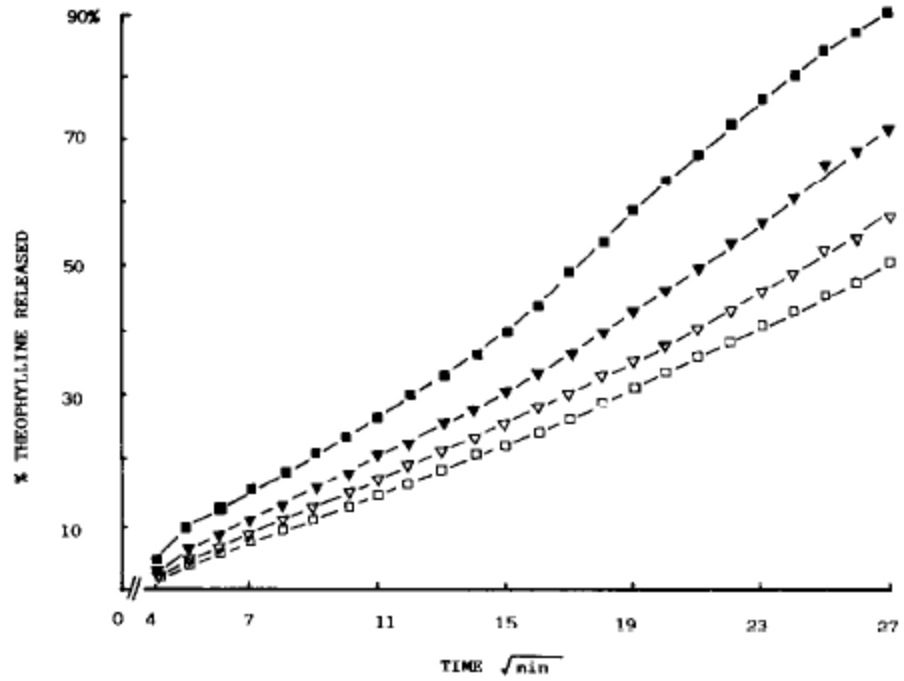


Figure 1.11: The effect of hypromellose K15M content (■ 45 mg, ● 60 mg, ▼ 90 mg, ▽ 180 mg, and □ 270 mg) on the release profiles of theophylline from matrix tablets. Reprinted with permission from (Ford *et al.*, 1987b).

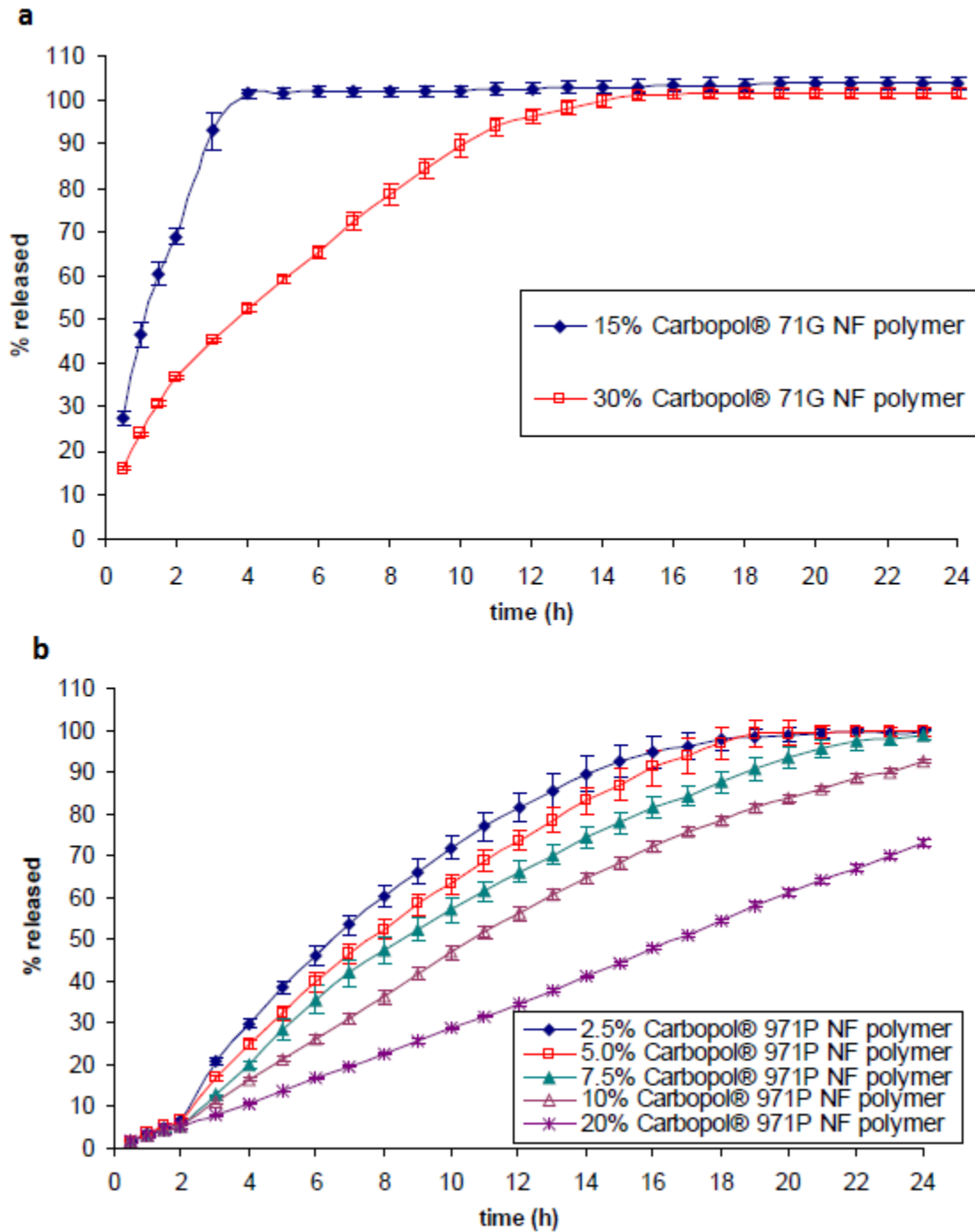


Figure 1.12: Effect of Carbopol® 71G NF polymer level on theophylline release (a) and effect of Carbopol® 971P NF polymer level on ketoprofen release (b) from roller compacted tablets (Lubrizol, 2011).

In contrast to the foregoing studies, few authors reported that the increased levels of polymer did not significantly affect (Tiwari *et al.*, 2003) or promoted (Gade and Murthy, 2014) drug release from matrix systems. (Tiwari *et al.*, 2003), reported that changes in the hypromellose level failed to significantly affect the release rate of a highly soluble drug (tramadol). (Gade and Murthy, 2014), showed the increased concentrations of an insoluble polymer (ethyl cellulose) in matrix formulation to lead to faster release rate of metoprolol succinate the drug due to erosion of the matrix. This could be because there is an optimum concentration (i.e. a threshold level, e.g. 20% for Demacol[®] (Campos-Aldrete and Villafuerte-Robles, 1997) and between 20.76% and 26.41% for hypromellose K4M (Fuertes *et al.*, 2006), of hydrophilic polymer that is needed to be incorporated into matrix formulation to make a gel structure around the matrix to control the release of highly soluble drugs, after which further increase in polymer level might not lead to slower drug release rate. Additionally, above a particular polymer level, the effect of polymer content dominates over the effect of polymer viscosity and particle size on the effect on drug release from matrix systems. Therefore, at hypromellose level of 30% to 40%, different grades of hypromellose (hypromellose 2208, 2906, and 2910) showed similar drug release profiles (Nellore, 1998; Ford *et al.*, 1985b). In another study, formulations containing hypromellose level of 30% to 40% showed similar release profiles of THP regardless of the diluent used (Vargas *et al.*, 1999).

Finally, it should be kept in mind that polymer level in a formulation may not always affect drug release in the same way as expected due to possible interactions between drug/polymer/co-excipient (Sections 1.8.4 and 1.8.5). For example, ionic polymers such as sodium carboxymethylcellulose (NaCMC) and chitosan have been reported to show pH-dependent drug release. The release rate from chitosan matrix systems has also been shown to be

influenced by the interaction between chitosan and anionic drugs (Kristmundsdottir *et al.*, 1995). Such chemical interactions of some polymers with different classes of drugs complicate the mechanism and kinetics of drug release from matrix tablets.

1.7.6 Mixture of polymer

For decades polymers have been one of the most broadly applied alternatives for the formulation of sustained release mixtures to modulating the release profiles of drugs competently, and in this situation, it is obvious to find mixtures of various kinds of polymer (Tiwari *et al.*, 2003). One combination that has been broadly examined is that of ethylcellulose (a cellulose derivative related Hypromellose but water insoluble) and Hypromellose (Sankalia *et al.*, 2008). In investigations made with Tramadol in Hypromellose matrices, without and with ethylcellulose, it was noted that this latter acted as a retardant of Tramadol release; this was attached to the decreased approach of solvent into the matrix due to the appearance of the hydrophobic matrix (Quinten *et al.*, 2009). Traconis *et al.*, 1997 noted that the addition of ethylcellulose (EC) to Hypromellose matrices of Metronidazole decreased the dissolution rate of the drug although did not alter its release pattern. Release rate of the drug reduced linearly by the percentage increase of ethylcellulose when EC rate was below a threshold. Over this threshold, the dissolution rate improved with increasing concentration of EC. Other writers have studied the chance of formulating with mixtures of Carbopol and Hypromellose both polymers being generally employed in the field of modified release (Samani *et al.*, 2003). In this case, the synergies established among the two polymers afford excellent results as regards to the release properties of drug because the enable the fluctuations characteristic of Carbopol to be reduced, this compound first gives slow release rates in the initial phases, after which they improve to a large extent (Perez-Marcos *et al.*, 1996). Perez-Marcos *et al.*, 1996), examined the same mixture

of polymers, but in this situation with Propranolol HCl, to investigate the impact of pH on drug release. While the pH enhanced, Carbopol was more ionized leading to the formation of an insoluble drug-polymer complex holding its release to the dissolution. Likewise, the authors concluded that the influence of the Hypromellose /Carbopol ratio in the drug release rate improved with pH.

Table 1.7: Polymers mixture investigated to retard the dissolution profiles of drugs.

Mixture of polymers	Drug used	Results	Reference
Ethylcellulose (EC) + Hypromellose	Tramadol	A retardant of Tramadol release was observed	Sankalia <i>et al.</i>, 2008
Carbopol+ Hypromellose	Propranolol Hcl	The influence of the Hypromellose /Carbopol ratio in the drug release rate improved with Ph.	Perez-Marcos <i>et al.</i>, 1996
Hypromellose +Na–CMC	Metronidazole	The dissolution rate decreased when Na CMC increased in the polymer blend and resulting in zero-order kinetics	Traconis <i>et al.</i>, 1997
	Atenolol	The results showed that both diffusion and erosion controlled drug release,	Lotfipour <i>et al.</i>, 2004
	Captopril	The dissolution retard drug release from tablet matrices	Nokhodchi <i>et al.</i>, 2008
	Ketoprofen	Sustained release was achieved	Chopra <i>et al.</i>, 2007
	Naproxen Na	The dissolution retard drug release from tablet matrices	Rao <i>et al.</i>, 1990
	Zidovudine	It shows slower drug release	
Hypromellose C+HPC	Acetaminophen	Sustained release was achieved	Ebube and jones, 2004
Hypromellose +Polyethyloxazoline (PEOX)	Dyphylline	Controlled release was observed in the combination of the mixed polymer	Shenouda <i>et al.</i>, 1990
EC+Xanthan gum	Ibuprofen	The results showed that drug release was controlled by both diffusion and erosion,	Verhoeven <i>et al.</i>, 2006
	Metoprolol tartrate	Sustained release was seen in Metoprolol tartrate with two polymer mixture	Verhoeven <i>et al.</i>, 2008
Hypromellose /hydroxypropyl cellulose	Caffeine	Drug release rate with higher polymer levels leading to slower drug release	Hardy <i>et al.</i>, 2007

1.8 Co-excipients

It is necessary to add co-excipients to drug-polymer SR powder formulations to improve their mechanical properties (i.e. flowability and compressibility). Similar to drug (Section 1.6) and polymer (Section 1.7), the physicochemical properties of the co-excipient(s) present can affect the rate and mechanism of drug release from SRMS (Williams *et al.*, 2002).

1.8.1 Diluents

Diluents are fillers that can be used to make up the required bulk of a tablet formulation. They can also be used to improve the mechanical (i.e. flow and tableting) and/or modify the rate of drug release. Diluents added to matrix formulations can be soluble (e.g. lactose), insoluble (e.g. DCP), or partially soluble (e.g. partially pregelatinized starch). In general, the incorporation of fillers in matrix formulations usually increases drug release rate regardless of diluent and/or drug solubility (Ford *et al.*, 1987a; Khan and Jiabi, 1998; Lotfipour *et al.*, 2004).

Increasing the amount of diluent agents has also been shown to increase drug release rate (Lotfipour *et al.*, 2004). In general, more soluble excipients (e.g. lactose) cause the drug to be released at a relatively faster rate and to a greater extent than insoluble (e.g. dibasic calcium phosphate (DCP) and microcrystalline cellulose), or less soluble, excipients (Williams *et al.*, 2002). For example, (Rekhi *et al.*, 1999) showed lactose to afford faster release rates of metoprolol tartrate than that of dicalcium phosphate from hypromellose matrices. Soluble fillers increase drug dissolution rate by enhancing the wettability, and increasing the porosity of the path of the drug by encouraging water penetration and thereby the formation of channels within the matrix (Levina and Rajabi-Siahboomi, 2004). This leads to the creation of more permeable (i.e. weaker) hydrated gel layer than that for insoluble excipients, leading to faster drug diffusion and increased erosion rate (Ford *et al.*, 1987b).

Finally, it should be acknowledged that the magnitude at which diluents manipulate the drug release from matrix formulations depends on the concentration at which they were incorporated as well as drug solubility

- *Diluent concentration*

Insoluble (but weakly swellable) diluents at a high level (above 20%, w/w) can remain within the gel structure, thus decreasing matrix wettability and retard the penetration of dissolution medium leading to reduced drug release via diffusion (Vidyadhara *et al.*, 2013). However, some studies found evidence that the incorporation of a small amount of insoluble filler may increase drug release rate by preventing the quick formation of a homogeneous gel layer and disturbing uniform swelling due to erosion of its particles (Zuleger and Lippold, 2001; Ford *et al.*, 1987a; Williams *et al.*, 2002; Rekhi *et al.*, 1999). For example, in one study, (Alderman, 1984), showed that only 10% of Methocel™ K4M (a non-swelling insoluble filler) may disturb the integrity of the gel layer leading to premature disintegration of a matrix tablet. In another study (Levina and Rajabi-Siahboomi, 2004), lactose has been shown to afford slower release rates of two drugs having different solubilities (chlorpheniramine maleate and THP, at 30% loading) compared to pre-gelatinized maize starch (Starch 1500™) from hypromellose matrices. This is because starch has a swelling nature when it is exposed to the dissolution medium, thus it can become integrated into the structure of the gel layer, making it denser.

1.8.2 Surfactants

Surfactants are usually classified based on the nature of hydrophilic groups as follows: anionic surfactants (e.g. carboxylates, sulphates and phosphates), cationic surfactants (e.g. quaternary ammonium compounds), amphoteric surfactants (e.g. lecithin and betains) and non-ionic surfactants (e.g. spans and tweens).

Numerous studies showed the incorporation of surfactants, particularly those of high hydrophilic-lipophilic balance (HLB), in controlled release dosage forms to promote faster drug release by acting as wetting agents (leading to facilitated fluid entrance into the dosage form), reducing interparticle adhesion in the wetted tablet, and reducing the interracial tension between the gel layer and the dissolution fluid leading to enhanced drug diffusion rate (Efentakis *et al.*, 1991; Baveja *et al.*, 1987).

In contrast, other studies showed the incorporation of some surfactants to result in slow drug release from matrix formulations via forming insoluble drug-surfactant complexes with subsequent precipitation, providing less porous matrix through which the dissolved drug could diffuse (Wells and Parrott, 1992). For example, the release rate of propranolol HCl (cationic drug) was shown to reduce with increasing the concentration of sodium lauryl sulphate (SLS, anionic surfactant) due to the formation of propranolol–SLS complex which is less soluble in water than propranolol HCl (Nokhodchi *et al.*, 2002). A slower release pattern of quinine sulphate was also observed from the matrix containing SLS compared to that containing polyoxyl 40 stearate (Choulis and Papadopoulos, 1975). Surfactants have also been shown to modify drug release rate from matrix systems by forming interactions with polymeric materials and thereby altering their swelling properties (Vlachou *et al.*, 2000). For example, anionic surfactants can bind to non-ionic polymers and thereby increase their viscosity, leading to slower drug release rates. Therefore, the incorporation of sodium dodecyl sulphate (an anionic surfactant) in hypromellose matrices has been shown to decrease the release rate of propranolol HCl, whereas the incorporation of cetrimide (quaternary ammonium) has been shown to afford an opposite effect (Ford *et al.*, 1991). Likewise, the incorporation of SLS (an anionic surfactant) has been shown to reduce the release rate of chlorpheniramine maleate from hypromellose

matrices (Feely and Davis, 1988). In another study, the incorporation of dioctyl sodium sulphosuccinate (an anionic surfactant) has been shown to retard the release of ascorbic acid from cellulose-based controlled system during the first hour (Gaylord and Schor, 1989).

In conclusion, depending on their structure, the incorporation of surfactants could lead to either faster or slower release from matrix formulations (Baveja *et al.*, 1987; Wells and Parrott, 1992; Vlachou *et al.*, 2000; Feely and Davis, 1988; Gaylord and Schor, 1989). For example, in contrast to anionic surfactants which could bind to the non-ionic cellulose ethers to form a strong gel network leading to slow drug release, cetyl trimethylammonium bromide (CTAB, cationic surfactant) could hardly bind to cellulose ethers leading to scarcely modified drug release process (Walderhaug *et al.*, 1995). Finally, it has to be kept in mind that although the incorporation of anionic surfactants with cationic drug form insoluble drug-surfactant complexes, the dissolution rate of such drug-surfactant complexes could increase significantly by the formation of micelles if the surfactant was present at concentrations above its critical micelle concentration (Wells and Parrott, 1992).

1.8.3 Binding agents

Binding agents can coat drug particles, thus change the rheology of the gel layer resulting in slow drug release rates. For example, when incorporated in hypromellose matrices, polyvinylpyrrolidone has been shown to afford zero-order release profiles of anhydrous caffeine instead of bimodal profiles (Hardy *et al.*, 2007).

More investigations are needed in the future to deliver better understanding of the mechanism of drug release from sustained release matrix systems *in vivo*. To this end, more techniques are required in the future to characterise drugs and polymers used in matrix systems in a non-invasive manner. More systematic studies based on Design of Experiment approach are

also needed in the future to evaluate the influence of drug-, polymer-, and co-excipient related variables on drug release and thus evolve predictive approach(es) to develop such systems. This will allow the creation of desired sustained release formulations based on a robust Quality by design approach.

1.8.4 Co-solvents in liquisolid systems

The liquisolid (LS) technique refer to the conversion liquid medications prepared using non-volatile organic solvents into powder mixtures by mixing a liquid medication with a solid phase containing carriers and coating materials (Spireas, 1998). Although LS systems were initially designed to improve the solubility and dissolution rate of poorly soluble drugs, they have recently been employed to sustain the release of highly soluble drugs using polymeric carriers such as hypromellose, Eudragit[®] (Spireas and Bolton, 1998) and Polyox[™] (Kaialy *et al.*, 2016).

The type of LS vehicle (i.e. non-volatile solvent) incorporated in LS formulations has recently been shown to have a major influence on the drug release from LS tablets. In a recent study, (Kaialy *et al.*, 2016), showed polysorbate 80 to cause greater retardation of the release of a highly soluble drug (DTZ) as compared to Propylene glycol (PG) and polyethylene glycol (Figure 1.13). The retardation effect was shown to increase with increasing polysorbate content within LS formulations. It was suggested that the solvent capability for retaining the release of drug molecules from LS matrix increases with increasing the solubility of the drug in the solvent used.

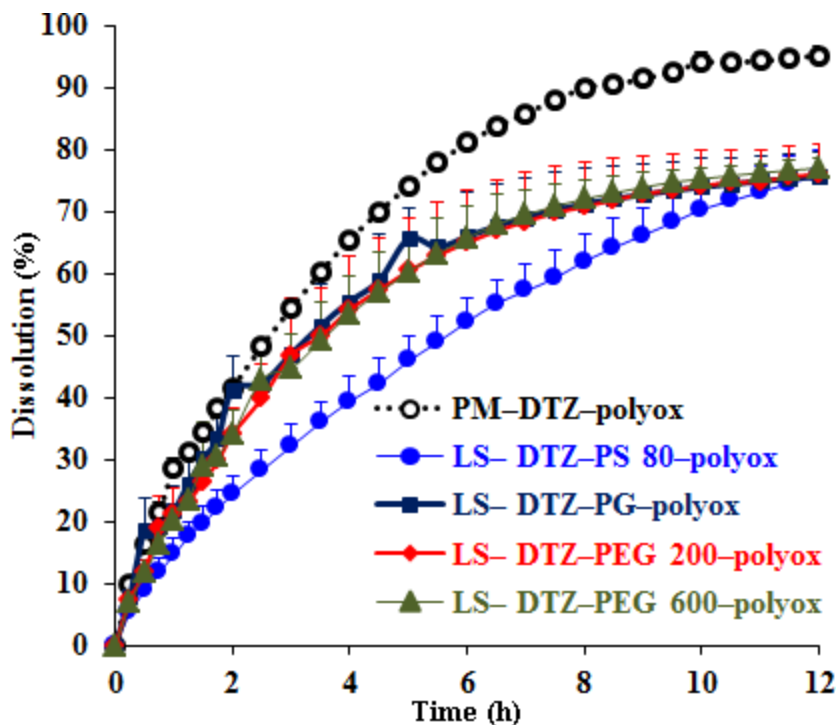


Figure 1.13: Release profiles (mean \pm SD, $n = 4$) of diltiazem HCl from physical mixture (PM) and liquid solid (LS) formulations prepared using polysorbate 80 (PS 80), propylene glycol (PG) and polyethylene glycol (PEG–200 and PEG–600). Reprinted with permission from (Kaiyal *et al.*, 2016).

1.9 Preparation and optimization of LS systems

The LS technique can be employed to form liquid medications (i.e., liquid drugs and drug solutions, drug suspensions or emulsions of poorly soluble solid drugs provided in non-volatile liquid vehicles) into powders proper for tableting or encapsulation. A simple blending of such liquid medications with calculated amounts of a powder substrate consisting of specific excipients such as the carrier and coating powder materials can produce dry looking, non-adherent, free-flowing and easily compressible powders (Spireas and Bolton 1999). The liquid part, which can be a liquid drug, a drug suspension or a drug solution in proper non-volatile liquid vehicles, is dispersed into the acceptable carrier material. Once the carrier is soaked with liquid, a liquid layer is developed on the particle surface which is immediately absorbed by the

fine coating material particles. The coating material renders the conversion from a wet to a dry surface and provides the LS system with excellent flow properties (Figure 1.14).

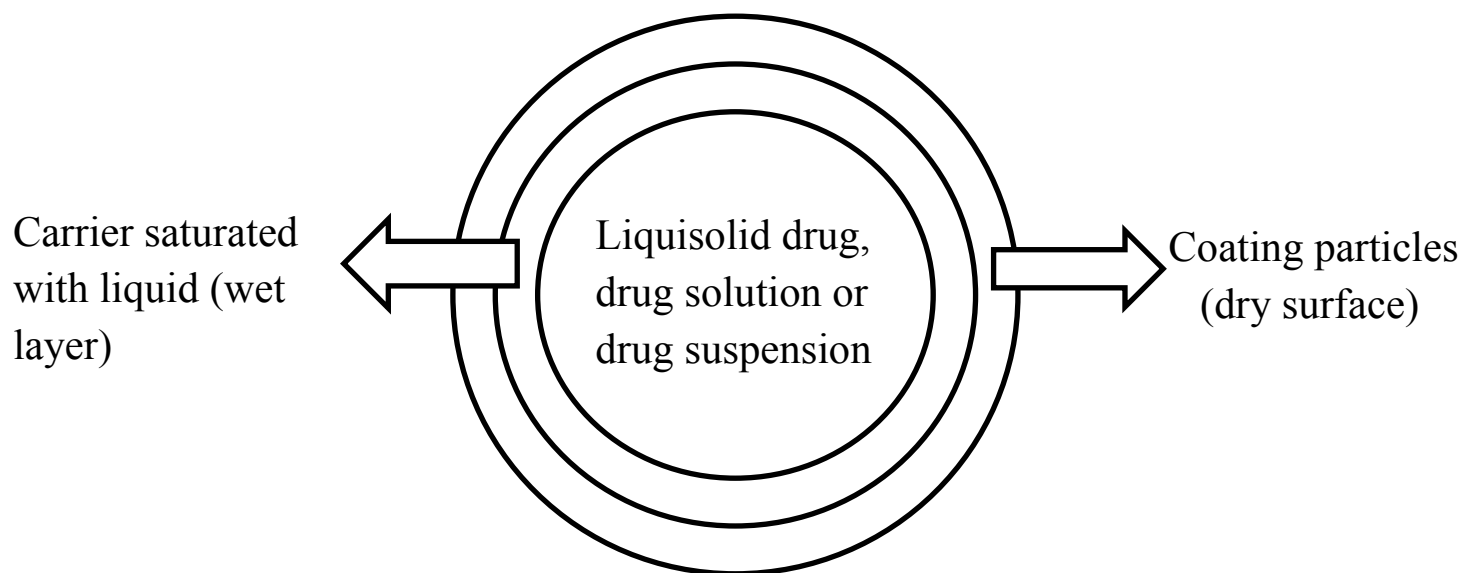


Figure 1.14: Schematic representations of the LS systems

Spireas *et al.*, (1998) were pioneers in formulating LS tablets, where the dissolutions of pridinsolone and hydrocortisone were improved by using the LS technique. Since then, many research articles were performed using the same approach to improve dissolution of many drugs (Hentzschel *et al.*, 2012). The improved drug dissolution by LS method could be attributed to increased surface area, increased aqueous solubility, and improved wettability of drug particles (Javadzadeh *et al.*, 2007). By the proper design of the LS formulation, a powder mixture of good flow and compaction properties could be obtained. Therefore, this technique is industrially applicable due to simplicity and comparatively low cost (Hentzschel *et al.*, 2012). Moreover, stability issues are of no major concern as it was reported that these compacts are not greatly affected by different storage conditions (Sheth and Jarowski, 1990). Several excipients such as

disintegrants, (immediate release) and lubricants or matrix forming materials (sustained release) may be added to the LS system to produce LS compacts.

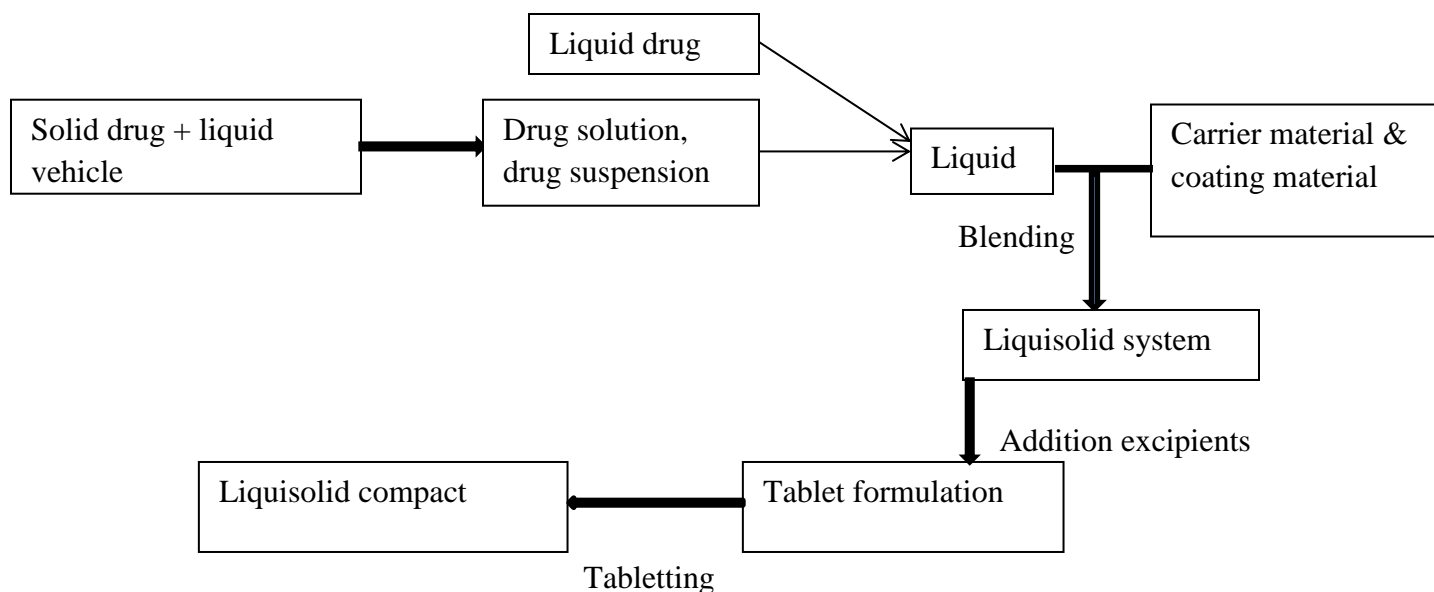


Figure 1.15: Schematic outline of the steps in the preparation of LS compacts

LS compact of Poorly water-soluble drugs carrying a drug suspension or drug solution in a solubilising vehicle that show enhanced drug release due to an improved surface area of drug available for release, an improved wettability of the drug particles and an increased aqueous solubility of the drug, (Nokhodchi *et al.*, 2011). Accordingly, such improved drug release may occur in higher drug digestion in the GIT and, therefore, enhanced oral bioavailability may occur (El-Houssieny, *et al.*, 2010). The mechanism of release prolongation is possible to be a more effective encapsulation of drug particles by the hydrophobic polymers. The appearance of nonvolatile solvent lessens the glass change temperature (T_g) of allows flexibility and polymers. As a result, reducing of T_g of the polymer might be the cause for the release prolongation of LS tablets. In the above temperature the T_g , a better coalescence of the polymer particles, transpires that forms a fine matrix and a network with a higher tortuosity and lower porosity. In this way, the drug is entangled and surrounded by the polymer network, resulting in the limited leaching of

the drug, therefore, sustaining the release of drug from LS matrices. LS technique has been suggested to have the potential to be optimized for the reduction of drug dissolution rate and thereby product of sustained release systems. According to [Javadzadeh *et al.*, 2008](#), propranolol HCl was separated in polysorbate 80 as the liquid vehicle. The liquid vehicle chose by least solubility of liquid vehicle, and then a binary mixture of carrier–coating materials (Silica as the coating material and Eudragit[®] RL or RS as the carrier) was added to the liquid medication under constant mixing in a mortar. The effect of drug concentration, thermal treating, loading factor and growing on the release profile of propranolol HCl from LS compacts was examined at two pH values (1.2 and 6.8). LS technique prepared tablets showed greater retardation properties in comparison with conventional matrix tablets. This result also showed that wet granulation had an exceptional impact on release rate of propranolol HCl from LS compacts, reducing the release rate of drug from LS compacts. The kinetics studies showed that most of the LS formulations resulted to the zero-order release pattern ([Javadzadeh *et al.*, 2008](#)).

1.9.1 Advantages of liquisolid system

A great number of slightly water–soluble and efficiently water-insoluble liquid and solid drugs such as Prednisolone, Digitoxin and Hydrocortisone can be formed into LS systems the new formulation–mathematical model. Excellent availability of an orally administered water-insoluble drug is obtained when the drug is in solution form. Despite the drug is in an encapsulated or tabletted dosage form, it is held in a solubilized liquid state, which consequently provides to improved drug wetting properties, thereby enhancing drug dissolution. Optimized rapid-release LS tablets or capsules of water-insoluble drugs show improved in-vitro and in-vivo drug release as compared to their commercial counterparts. Optimized sustained–release LS tablets or capsules of water-insoluble drugs show surprisingly steady dissolution rates (zero–

order release) comparable only to valuable commercial preparations that combine laser–drilled tablets and osmotic pump technology.

1.9.2 Disadvantages of Liquisolid system

Limitations of LS include the demand of high solubility of the drug in non-volatile liquid vehicles if drug solutions are employed (Singh *et al.*, (2012)). The main disadvantage of LS is the uncertain formulation of a high dose of poorly water-soluble drugs (e.g. flutamide, carbamazepine). These drugs need a large number of liquid vehicles and also carrier and coating material to provide a dry powder with proper flowability and compressibility. This could improve the mass of each tablet above the limit for easy use (Gavali *et al.*, 2011).

Although, its has been confirmed that it is likely to load a large amount of drug into a LS system applying additives (such as hypromellose, Polyvinylpyrrolidone, and polyethylene glycol 35000), which can be combined with the drug in liquid state to decrease the amount of carrier and coating material (Javadzadeh *et al.*, 2007). Singh *et al.*, (2012), have revealed that higher viscosity of the additives leads to smaller quantities of carrier and coating material required to provide a flowable powder. The use of advanced carriers and coating materials with a large particular surface area and high absorption volume (e.g., Neusilin®) is another way of inclusion of higher doses of water-insoluble drugs into LS systems.

1.9.3 Application of liquisolid systems

Dosage forms with improved bioavailability and enhanced release rates. Sustained release of water-soluble drugs (propranolol HCl) can be achieved. LS technique can be strongly applied in formulation of orodispersible tablets (Nagabandi *et al.*, 2011).

Various LS formulations, which were investigated in vivo, have previously been reported in findings. For example, El-Houssieny *et al.*, (2010) studied the influence of LS compacts

comprising repaglinide on glucose tolerance in rabbits. They confirmed that the bioavailability of repaglinide was increased significantly if it was applied orally in the form of LS compacts in comparison to commercially prepared tablets. In vivo the behaviour of LS tablets with hydrochlorothiazide in beagle dogs was evaluated (Khaled *et al.*, 2001). LS tablets exhibited higher values of AUC_μ, AUC_t, C_{max} and F parameters than commercial hydrochlorothiazide tablets. The mean values of total bioavailability of hydrochlorothiazide from LS tablets were raised by ~15 % in compared with commercially available tablets. When in vivo evaluation of carbamazepine LS tablets, it was seen by Chen *et al.*, (2013) that complete bioavailability of carbamazepine was raised by 82 % when compared with commercially available tablets. Evaluation of LS tablets carrying famotidine exhibited a higher dissolution rate compared the conventional, directly compressed tablets. LS formulation released 78 % of famotidine in the first 10 min, which is 39 % more than the release from directly compressed tablets (Fahmy and Kassem, 2008).

1.9.4 Rationale of liquisolid system

The oral route remains the most favoured route of drug administration due to its good patient compliance, convenience and low drug production costs. The poorly soluble hydrophobic drugs bioavailability (class II in BCS) is restrained by their dissolution pattern, solubility and for a drug to be absorbed into the systemic circulation resulting oral administration; the drug must be dispersed in the gastric fluids. The dissolution pattern of these drugs can be increased by or improving the surface area, decreasing crystallinity and decreasing particle size. Various studies have been investigated to increase the dissolution behaviour of drugs by decreasing the particle size, by creating nanoparticles and microparticles (Spireas, 2002).

1.9.5 Excipients for liquid systems

- *Non-volatile solvents.*

Different high-boiling point, non-volatile, preferably water-miscible and not highly viscous solvents are employed for the formulation of LS systems. The solvent had a significant effect on drug release from LS systems as shown in various studies ([Nokhodchi *et al.*, 2010](#)). For improved drug release from LS preparations, a liquid vehicle in which the active component is most soluble is usually chosen. In the case of formulating LS systems with limited release, solvents with a low capability to solubilize the drug are employed.

PG is usually applied in the pharmaceutical industry as a stabilizer for vitamins and co-solvent in ointments for medicinal purposes. The main role of PG is to solubilize and give homogeneous dispersion of the active component in the formulation ([Hassan *et al.*, 2007](#)). According to [Gubbi and Jarag, \(2009\)](#) discovered that LS compacts with bromhexine HCl provided using PG exhibited a higher dissolution rate compared to bromhexine HCl with PEG 400. The slower release of bromhexine HCl from PEG 400 LS compacts can be attached to lower solubility of bromhexine HCl in PEG 400. Liquid PEG 200-600 are applied as solvents and solubilizing agents for active substances and excipients in liquid and semi-solid preparations ([Daher *et al.*, 2003](#)).

[Mahajan *et al.*, \(2011\)](#) studied the influence of the type of non-volatile solvent on the dissolution profile of glipizide of LS tablets. PG, PEG 200 and PEG 400 were employed to prepare LS formulations in that research. It was seen that all three liquid vehicles were able to improve the dissolution rate of glipizide from LS tablets when compared to their commercial counterparts. LS tablets carrying PEG 400 as liquid vehicle revealed higher dissolution rates in comparison to LS tablets containing PG and PEG 200 as liquid vehicles. Polyoxyethylene sorbitan fatty acid esters (Tween, Polysorbate) are broadly used in pharmaceutical and cosmetic industry as dispersants,

emulsifiers or stabilizers because of their effectiveness at low toxicity and relatively low concentrations and (Tatsuishi *et al.*, 2005). Also, Polysorbate is fit with the majority of active ingredients (Wang *et al.*, 2008). The most commonly employed polysorbate in LS systems is Polysorbate 80. Polysorbate 80 was successfully employed to dissolve the drug in different LS systems containing carbamazepine (Tayel *et al.*, 2008), indomethacin (Saeedi *et al.*, 2010a), propranolol HCL (Javadzadeh *et al.*, 2008), piroxicam (Javadzadeh *et al.*, 2005), etc.

- *Carrier materials*

Carrier material refers to a preferably porous material possessing sufficient absorption properties, such as microcrystalline and amorphous cellulose, which contributes in liquid absorption. In the LS preparation technique, carrier materials play the main function in getting the dry form of powder from the drug in liquid state. Each carrier has its unique features, but each should be a porous material maintaining adequate absorption capacity for liquids (Gavali *et al.*, 2011). It was seen that the particular surface area (SSA) (Table 1.8) of the carrier is a major factor in the formulation of LS systems (Karmarkar *et al.*, 2010). Carrier choice depends on its liquid binding size, flowability of powders and compressibility (Kavitha *et al.*, 2011). Carriers can be classified into four classes based on their chemical structure, (Table 1.8). MCC, Avicel[®], Ceolus[®], Vivapur[®], Emcocel[®]) is the most regularly used carrier in LS formulations based on its long-term use in the pharmaceutical industry, its availability and stability. It was used to formulate LS system comprising Nifedipine (Gubbi and Jarag, 2009), Tramadol HCl (Gonjari *et al.*, 2009), furosemide (Akinlade *et al.*, 2010), etc.

It was seen in previous investigations that carriers other than MCC (such as lactose, starch or sorbitol) were needed in larger amounts for conversion of liquid preparations to the dry, non-

adherent, free-flowing powder form. This was attached to the larger particular SSA of MCC (Table 1.8) (Karmarkar *et al.*, 2010).

Table 1.8: Classification of carrier material into four categories and their SSA

Carrier category	Carrier	SSA[m ² /g]
Cellulose and cellulose	Microcrystalline cellulose	~1.18
Derivatives	Hypromellose	-----
Saccharides	Lactose	~0.35
	Sorbitol	~0.37
Silicates	Magnesium aluminometasilicate	110–300
	Kaolin	~24
	Diosmectite	-----
	Ordered mesoporous silicates	up to 1500
Others	Anhydrous dibasic calcium phosphate	30
	Polymethacrylates	----
	Starch	~0.60
	Magnesium carbonates	~10

^a Carrier material for LSS with controlled drug delivery

- *Coating materials*

Coating material refers to a material maintaining fine and highly adsorptive particles, such as several types of silica, which provides in covering the wet carrier particles and displaying a dry looking powder by adsorbing any excess liquid (Spireas, 2002). Coating material should be a material maintaining fine (0.01–5 µm in diameter) and highly absorptive particles, which provide to coating the wet carrier particles and illustrating a dry powder by adsorbing surplus liquid to assure good flowability of the produced blend (Kulkarni *et al.*, 2010). In LS system

formulations, this function is performed by materials with a large particular surface area and absorption capacity, which cannot be utilized as carriers due to their poor flowing or compressing properties. Nowadays, the most commonly employed coating material in LS formulations is colloidal silicon dioxide (Aerosil[®], Cab-O-Sil[®] M5). It was strongly used with Tramadol HCl (Gonjari *et al.*, 2009), Trimetazidine Dihydrochloride (Pavani *et al.*, 2013), propranolol HCl (Javadzadeh *et al.*, 2008), etc.

Pre-formulation studies are required to attain a powder mixture with adequate powder flow and LS formulations that provide all conditions generally required on capsules, granules and tablets. These investigations are closely relevant to selection of the best non-volatile solvent to calculate the appropriate amount of powder excipients-carrier and coating material and to solubilize drugs (El-Say *et al.*, 2010).

Solubility studies are carried out by preparing a saturated solution of the drug by combining an excess of drug into non-volatile solvents and allowing it stay to gain the equilibrium state (e.g. by stirring, shaking). At the end of this step, the amount of drug diffused in a specific solvent is estimated analytically (Gavali *et al.*, 2011). Solvents with higher ability to solubilize the drug are chosen for the formulation of LS systems for enhanced release (Karmarkar *et al.*, 2010). Measurement of the angle of slide (θ) is used to estimate the flow property of powder excipients (Tiong and Elkordy, 2009). Spireas *et al.*, (1992), required that the angle of slide is the preferred approach to ascertain the flowability of powders by particles smaller than 150 μm . The needed amount of carrier is placed and weighed on one end of a metal plate with a polished surface. This end is constantly increased until the plate produces an angle with the plane surface at which powder is about to slide. This angle is called the angle of slide. The angle of slide of 33° is considered as optimal flow behaviour for the following processing

from LS system admixtures (compressing into tablets and filling into capsules) (Karmarkar *et al.*, 2009).

- *Additives*

The disintegration of solid dosage forms certainly affects drug release. Hence, disintegrants are normally introduced in LS compacts to enable a fast disintegration. Some generally employed disintegrants in LS system comprise croscarmellose sodium, low substituted hydroxypropyl cellulose and sodium starch glycolate (Yadav and Yadav, 2009). Polyvinylpyrrolidone (PVP) is another encouraging additive, which has the potential to combine high amount of drug into LS systems and therefore decrease the compact weight (Javadzadeh *et al.*, 2007). Also, due to the crystal growth inhibition influence of PVP, LS compacts carrying PVP show an enhancement of dissolution rate (Singh *et al.*, 2012). LS system has another additive - Hypromellose, which normally performs as a release retarding agent to prolong drug release (Karmarkar *et al.*, 2010).

1.9.6 Liquisolid technique as a tool to minimize the influence of pH variation on drug release

The weak acids and bases solubility depend on the pH of the local environment and ionization constant (pKa) of the compound. Hence, the bioavailability and dissolution of these drugs are considerably affected by the pH of GI fluids. This further leads to a high degree of intravariability and intervariability in therapeutic effects and drug bioavailability (Badawy *et al.*, 2016). El-Hammadi *et al.*, (2012) first investigated the feasibility of using LS technique to reduce the impact of pH variation on the release of loratadine. Various LS formulations were prepared using MCC as a carrier, silica as a coating material and PG as a liquid vehicle. The dissolution rate of the prepared LS compacts was studied in three different buffered media with

pH values of 1.2, 2.5, and 5, respectively. In comparison between the directly compressed tablets and marketed tablets (Clarityn[®]), the results indicate that the dissolution profiles of LS compacts were significantly higher and less influenced by pH variation. These results also suggested that LS technique is a promising and encouraging method to minimize the influence of pH variation on the dissolution profile of poorly water-soluble drugs. Similar result were also published by [Chella *et al.*, 2014](#), whereas an optimized LS formulation was achieved with a significant enhancement in dissolution rate and a less pH-dependent release profile compared to its commercial formulation or drug alone. [Badawy *et al.*, \(2016\)](#) described the robustness of mosapride citrate (a poorly soluble weak base) LS compacts that minimize the influence of pH variation on drug release along the GIT with bio-relevant media.

1.9.7 Sustained release with liquisolid formulations

Accordingly, with LS compacts the coalescence of the polymer particles occurs at lower temperatures than with conventional matrix tablets. This more pronounced coalescence of polymer particles of LS compact leads to a matrix with lower porosity and higher tortuosity. Consequently, the drug is surrounded by a fine network of the hydrophobic polymer resulting in a sustained release of the drug ([Azarmi *et al.*, 2005](#)). Moreover, it has been shown that the addition of Hypromellose increases the retardation effect of LS compacts ([Spireas, 2002](#)). Hypromellose is commonly used for the preparation of hydrophilic matrix systems. Depending on its MW the polymer either swells in contact with water or forms a hydrated matrix layer through which the drug has to diffuse or erodes resulting in a zero order drug release kinetic ([Shoaib *et al.*, 2010](#)). In the case of Hypromellose it was also found that a stronger retardation effect was observed with LS compacts as compared to directly compressed tablets (conventional formulation) ([Gonjari *et al.*, 2009](#))

LS tablets were prepared by mixing liquid medication with silica–Eudragit® RL or RS followed by the compaction. The effect of Hypromellose and co–solvent on THP release was determined. The sustained release was improved in LS compacts by Hypromellose (Nokhodchi *et al.*, 2010) (Table 1.9). Similar conclusions obtained from Khanfar *et al.*, (2014), where LS formulation containing venlafaxine HCl tablets showed greater retardation properties in comparison to the directly compressed tablets. The type of liquid vehicle was seen to influence drug release significantly (Table 1.9). Other major factors involved drug concentration in the excipients ratio (R) and liquid medication. Specifically, dissolution rate from LS tablets could be decreased with the increase of drug concentration. A reduction of dissolution rate was seen in LS tablets with higher R value. This was because the volume of carrier and swelling agents (Hypromellose) was improved in these formulations, which lead to slow diffusion of drug within the porous carrier and the gel layer made by Hypromellose. The studies further concluded that prolonged venlafaxine HCl release behaviour was taken from LS tablets containing Tween 80 as a non-volatile solvent with suitable carrier and coating material.

According to Javadzadeh *et al.*, 2007, liquid medications containing the drug were adsorbed on the surface of carrier materials during the preparation of LS compacts. When this method is shown to dissolution medium, the drug on the surface of the compact dissolves quickly and spread into the dissolution medium. These can be considered to be the cause of the burst release effect perceived. The concentration of drug in liquid medication is an essential aspect as it affects drug release. As these were also shown in previous studies, an increase in drug concentration in liquid medication leads to a lower drug release rate. These happen, when drug tends to precipitate within silica (Aerosil 200) pores at a higher drug concentration. Propranolol tablets prepared by LS technique showed excellent retardation properties in comparison with

conventional matrix tablets. For example, LS compact carrying 30% liquid medication with a loading factor of 0.225 delivered only 80% of drug in 8 h but this amount of release in its counterpart, the conventional matrix tablet, was achieved within 3 h. This suggested that LS systems showed much retardation in comparison with conventional matrix system. The outcomes also showed that wet granulation had a remarkable influence on the release rate of propranolol from LS compacts, lessening the release rate of drug from LS compacts. The kinetics studies reported that most of the LS formulations followed the zero-order release pattern. X-ray crystallography and DSC ruled out any variations in crystallinity or complex formation during the production process of LS formulations (Nokhodchi *et al.*, 2007). It was also shown that by replacing the type of liquid medication a good release profile is obtainable and sustained release action of Hypromellose in LS formulations is increased. These results suggested that zero-order release can be realized with LS formulations (Nokhodchi *et al.*, 2010).

Table1.9: Liquisolid formulation with sustained drug release.

Drug	Non-volatile solvent	Carrier and coating material	Polymer	Result	Reference
Propranolol HCl	Polysorbate 80	Eudragit [®] RL or RS and Colloidal silica	Hypromellose (K4M)	The results showed that wet granulation had a remarkable impact on release rate of propranolol HCl from LS compacts, reducing the release rate of drug from LS	Javadzadeh et al., 2008
Tramadol HCl	PG	Avicel PH 102 and AEROSIL [®] 200	Hypromellose (K4M)	The prepared LS compacts are new dosage forms showing more sustained release behaviour as compared to marketed sustained formulations	Gonjari et al., 2009
Theophylline	Polysorbate 80	Silica–Eudragit RL or RS	Hypromellose	LS compacts have a potential to produce zero–order release kinetics for less water-soluble drugs	Nokhodchi et al., 2010
Nifedipine	PEG 400	MCC and Colloidal Silica	Hypromellose	Sustained release was achieved	Gubbi and Jarag, 2009
Tramadol HCl		MCC and Colloidal Silica	Hypromellose	Sustained release was achieved	Gonjari et al., 2009
Trimetazidine Dihydrochloride	polysorbate 80	Eudragit [®] L–100 and RS–100and AEROSIL [®]	Ethyl cellulose (EC)	Drug release profiles on model fitting follow Peppas model as the best fit model, which indicates TZH released from this tablet follows sustained release profile.	Pavani et al., 2013
Diltiazem HCl	(PEG 200 and 400)	Eudragit [®] RS and RL	Hypromellose (K4M)	The optimized new technique can be used in the preparation of sustained release formulations of water-soluble drugs.	Adibkia et al., 2014

Diltiazem HCl	Polysorbate 80	AEROSIL® X50 and Lactose	Polyox™	The dissolution behaviours of DTZ release from both LS and conventional tablets showed retardation properties at high MW of Polyox™.	Kaialy et al., 2016
Venlafaxine HCl	PG, PEG 400, polysorbate 80	Eudragit® RS PO and Colloidal Silica	Hypromellose	LS formulations have shown better retardation properties in comparison to conventional tablets. The type of liquid vehicle was to found to influence the drug release significantly	Khanfar et al., 2014

Eudragit® RL: Acrylic resin RL polymer, Eudragit® RL PO: A copolymer of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups, Eudragit® RS: Acrylic resin RS polymer, Eudragit® S-100: Anionic copolymer based on methacrylic acid and methyl methacrylate, Hypromellose: Hydroxypropylmethyl cellulose, Sodium CMC: Sodium carboxymethyl cellulose

This study aims to retard the release of highly water-soluble drugs, such as DTZ, from LS matrix tablets. The influence of several formulation factors, i.e., the PolyoxTM grade (WSRN10, WSRN80, WSRN750, WSRN1105, WSR301 and WSR303) at different MWs, polyoxTM particle size and ratio, the coating material (e.g. AEROSIL[®] X50, 130, R812 and 200 at different surface area), the use of diluents (including lactose, mannitol, sorbitol, compressolSM and hydrogenated vegetable oil), polymer type (e.g. PolyoxTM, hypromellose, psyllium Eudragit RL and Eudragit RS), and the drug type (e.g. DTZ, THP and ZNM) on the retardation properties of drug LS tablets will be investigated. LS formulation powders will be prepared and characterized in terms of solid-state (powder X-ray diffractometry and thermogravimetric analysis), size (laser diffraction), shape (scanning electron microscopy), density and flowability. LS compacts will be prepared and evaluated in terms of physical properties e.g., hardness and in vitro drug release profiles. Independent models including dissolution efficiency, mean dissolution time and mean dissolution rate will be calculated to quantify the drug release profiles from different LS tablets in comparison to conventional tablets.

2 CHAPTER 2: MATERIALS AND METHOD

2.1 Materials

Diltiazem, Theophylline and Zonisamide were obtained from TCI, USA. Poly (ethylene) Oxide with several grades, i.e., WSRN10 (MW =100,000), WSRN80 (MW = 200,000), WSRN750 (MW = 300,000), WSRN1105 (MW = 900,000), WSR301 (MW = 3,000,000) and WSR303 (MW = 7,000,000) were obtained from Colorcon Dartford, Kent, Polysorbate 80 (PS 80, Sigma Aldrich, Kosher, USA) are used. Hypromellose was obtained from Sigma Aldrich, USA. Psyllium Husk, Oxford Vitality, UK. Eudragit RLPO, RSPO were obtained from Evonik, Germany. Colloidal silicon dioxide (AEROSIL[®] X50, AEROSIL[®] 130, AEROSIL[®] 200 and AEROSIL[®] R812) was obtained from Evonik, Germany. Lactose was obtained DFE Pharma, UK. Mannitol mannogem granular was obtained from SPI Pharma, UK. CompressolSM from SPI Pharma, UK. Hydrogenated Vegetable oil was obtained from JRS Pharma, Germany. Sorbitol was obtained from TCI, USA.

2.2 UV calibration curve of DTZ in aqueous media

A stock solution of DTZ, THP and ZNM reference standard was prepared by transferring 4.9 mg of each drug into a 100 ml of volumetric flask and diluting with water. From this stock solution, seven various concentrations (0.049, 0.25, 0.49, 0.75, 0.98, 1.47 and 4.9 mg/ml) of each solution were transferred to 100 ml volumetric flasks and diluted with distilled water. The UV absorbance readings of these solutions were measured at 240 nm (DTZ) 271 nm (THP) and 251 (ZNM) using UV/Visible spectrophotometer (UV-160, Shimadzu, Japan). Distilled water was used as a reference. Then, the absorbance versus concentration of solutions was plotted to obtain the calibration curve which resulted in a very good R-square value (Figure 2.1, 2.2 and 2.3).

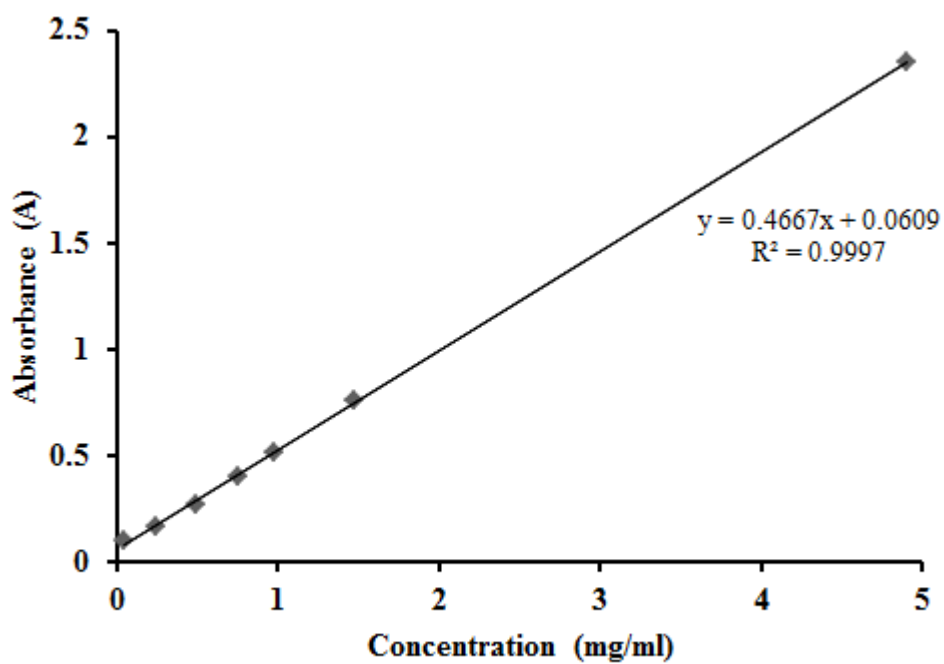


Figure 2. 1: UV absorption calibration curve of DTZ reference standard in aqueous media at 240 nm

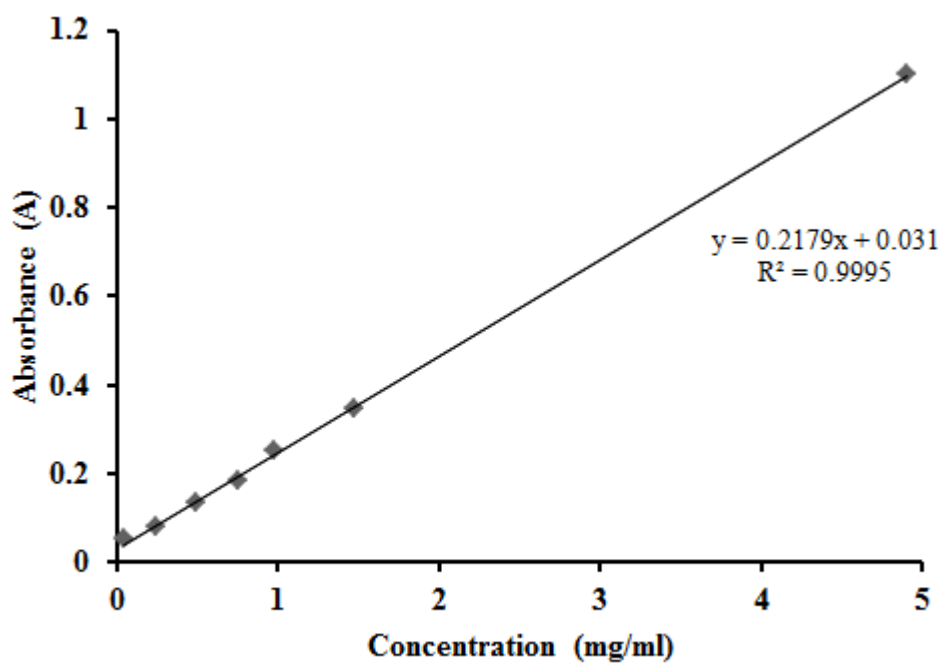


Figure 2. 2: UV absorption calibration curve of THP reference standard in aqueous media at 271 nm.

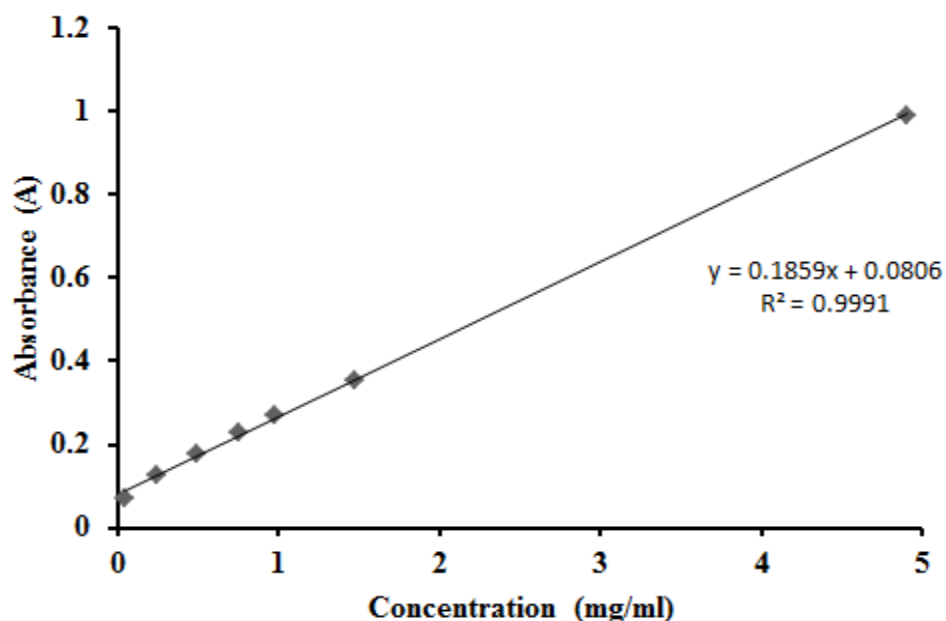


Figure 2. 3: UV absorption calibration curve of ZNM reference standard in aqueous media at 251 nm.

2.3 Particle Size Fractions of Polyethylene Oxides

To study the effect of particle size on drug release, PolyoxTM WSR303 particles with various size fractions were obtained using mechanical sieving via mechanical shaker (an Endecott sieve shaker) with different sieve meshes (<63, 63–150, 150–180 and >180 μm). A stack of sieves with cover and collection pan were prepared in the following order from top to bottom: >180 μm , 150–180 μm , 63–150 μm and <63 μm . The bulk PolyoxTM powder was poured onto the top sieve (>180), and the mechanical shaker was tightened closely and operated for 30 min, in which the respected size fractions of PolyoxTM were collected and kept in sealed glass vials until used.

2.4 General Preparation of LS and physical PM formulations

A calculated quantity of DTZ, THP and ZNM was separately dispersed in a non-volatile water-miscible solvent, i.e., PS 80 used as liquid vehicles to form liquid medication phase. A fixed drug:solvent ratio of 1:1 (w:w) was used. An accurately weighed Polymer in (g) was

separately mixed with coating material at a constant carrier: AEROSIL[®] ratio of 10:1. This blending was performed in a plastic container in a Turbula[™] blender (Basel, Maschinenfabrik, Switzerland) at a fixed speed of 100 rpm for 10 min. The resulting mixture of carrier:coating material (g) was introduced in a mortar, then the liquid medication phase (drug:solvent) from the beaker was slowly incorporated to the solid phase under continuous and thorough mixing using the pestle repeatedly until the liquid medication phase was absorbed onto the solid phase. Finally, a dry-looking mixture with apparent uniformity was achieved. For comparison purpose, conventional PM formulations (without a solvent) were also produced. Each PM formulation contained a solid phase as mention above. The mixing was performed using a V-shape powder mixer (GHP72, Zhejiang wisely machinery, Jiangsu, China) at a rotation speed of 100 rpm (ten rotations clockwise followed by ten rotation anticlockwise repetitively) for 5 minutes in laboratory conditions (22°C, RH = 50%). All formulations prepared in this thesis were stored in sealed glass vials for at least 7 days in laboratory conditions (22°C, RH = 50%) before further investigation. Different PM and LS formulations were prepared accordingly.

2.5 Laser diffraction

Volume-weighted particle size analysis of LS and PM formulation powders were conducted using a Malvern Mastersizer 2000 (Malvern Instruments Ltd, Germany) laser diffraction particle size analyser equipped with a dry sampling system (Aero S, Malvern Instruments, UK) as the particle size range covered by this laser diffractometer is from 0.1 μm to 3500 μm . Before measurement, a background reading was taken. The dispersion of air pressure was adjusted to 2.0-bar and a feed rate of 30% was applied. The measurement time was 5 s. The particle sizes at 10% ($d_{10\%}$), 50% ($d_{50\%}$, median diameter) and 90% ($d_{90\%}$) of the volume distribution, and the volume mean diameter (VMD, the average diameter based on the unit volume of a particle) was calculated automatically using the Malvern Software (Version

2.20). The span (calculated using Eq. 2.1) of the volume distribution was used as a measure of the width of the distribution of size relative to the median diameter.

$$\text{Span} = \frac{d_{90\%} - d_{10\%}}{d_{50\%}} \quad (2.1)$$

Three samples were measured for each formulation and results were averaged.

2.6 Characterization of powder density and flowability

All the formulation samples in this study were gently poured into a 100 mL measuring cylinder using a glass funnel and weighed accurately. The bulk volume of each powder was recorded, and then the cylinder was tapped 200 times using a tapping machine (JV 1000, Copley Scientific, UK) under laboratory conditions (20 °C, 50% RH) and the tapped volume after each tapping of each powder was recorded. The experiments showed that the 200 taps were adequate to reach the maximum reduction in the volume of the powder beds. Tap density was calculated as powder weight over powder tap volume.

Compressibility is one factor contributing to flow. The Carr's compressibility index (CI, Eq. 2.2) was calculated as the percentage change in the volume of constant mass of powder as a result of tapping.

$$\text{CI} = \left(\frac{\text{Tap density} - \text{Bulk density}}{\text{Tap density}} \right) \times 100 \quad (\text{Eq. 2.2}).$$

2.7 Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) makes use of electrons to form an image. A focused beam of energy high energy electron produced at the top of the microscope is used to generate a variety of signals at the surface of solid specimens. The accelerated electrons then discharge their energy as a variety of signals produced by the electron-sample interactions when the incident electrons are decelerated in the solid sample. These signals together with the secondary electrons produce SEM image. All samples during this research were analysed

using a Zeiss EV050–EP scanning electron microscope with EM scope of (Sc 500) (Polaron equipment, Watford, UK), operated using beam current of 10 μ A at an accelerated voltage of 10 KV; the samples preparation was done by sticking few milligrams of each formulation on a separate aluminium stub using an adhesive carbon tab then sputter coating them with gold, The SEM images were obtained at different magnitudes with the aim to ascertain their representativeness (Mcconville *et al.*, 2015)

2.8 Electrostatic charging analysis

The charge properties of commercial DTZ, PM and LS formulation powders were analysed using a recent novel instrument developed in our laboratory, as described in detail elsewhere (Hassan *et al.*, 2016). The experimental apparatus consists of a single non-contact electrostatic inductive sensor (probe), a charge amplifier unit, national instrument data acquisition equipment and a personal computer for data recording and processing. An example of processed charge signal obtained from pure DTZ particles moving through the sensor using a vibratory orifice feeder under gravity. This novel method allows the detection and measurement of charge distribution on the charge sign basis in a population of particles. The positive charge is the sum of all positive charges whereas the negative charge is the sum of all negative charges. The netcharge is the sum of positive and negative charges. The charge-to-mass ratio (CMR or charge density) is the charge (negative charge for N–CMR, positive charge for P–CMR, netcharge for net–CMR) per unit mass, in nC/g.

2.9 Fourier Transform Infrared (FT-IR)

Infrared spectra of DTZ HCl were obtained using (Bruka Alpha UK) FT-IR equipped with a single bounce attenuated total reflectance (ATR) accessory; using micro spatula, a few milligrams of each drug/polymer samples were placed on the middle of the sample stage after cleaning with acetone, the knob was then slowly rotated clockwise, so that is above the sample and was then compressed by rotating the screw on the top of the arm to fixate the

sample and then start button was pressed on the monitor until green bar appears; a scanning range between 400 to 4000 cm^{-1} with resolution of 4cm^{-1} was employed and the spectra obtained were the results of averaging 16 scans.

2.10 Powder X-ray diffractometry

This is an analytical technique used in the identification of crystalline phase by the diffraction patterns for the characterisation of crystallinity index. This was carried out at the University of Wolverhampton. Powder PXRD patterns of LS and PM formulations were collected on a Empyrean PANalytical powder diffractometer (Philips: PW1770 UK). The tube voltage and amperage were set at 40 kV and 40 mA, respectively. The monochromator slit was set at 20 mm sample size. Each sample was scanned between 5° and 45° in 2Θ with a step size of 0.01° at 1 step/s. The sample stage was spun at 30 rpm. The instrument was calibrated before use using a silicon standard.

2.11 Preparation of compacts

Accurately weighed samples of each LS–formulation and PM–formulation were separately weighed and then compressed on 8 mm punch and die using a manual tableting machine (Globpharma, USA) at a fixed pressure of 2000 psi. Each tablet contained 60 mg of DTZ. Before direct compression of compacts, 1% *w:w* magnesium stearate (Acrōs Organics, New Jersey, USA) in acetone (Fisher Scientific, UK) was applied to the die and punch as a lubricant to aid ejection.

2.12 In vitro dissolution studies

Dissolution testing was performed to give a reasonable prediction of the product's *in-vitro* dissolution and the rate at which the drug is released from its tablet dosage form. A USP dissolution apparatus 2 (paddle method) was used with a rotational speed of 75 rpm. The dissolution testing system comprised of a VK7010 dissolution apparatus (Varian, USA) and an automated sampling manifold (Varian, UK). The dissolution test was performed according

to the [British Pharmacopoeia \(2011\)](#), conditions for DTZ dissolution. The dissolution media consisted of 900 mL of distilled water equilibrated to $37\text{ }^{\circ}\text{C} \pm 0.5\text{ }^{\circ}\text{C}$. Samples were withdrawn from the dissolution flask using a peristaltic pump at different time intervals for up to 8 h (every 15 min for the first 2 h and then every 30 min up to 8 h). The absorbances were recorded using a UV spectrophotometer (UV-160, Shimadzu, Japan) at 240 nm. Three compacts were tested for each formulation.

- For effect of various drugs, drug release study (n=3) was performed in a paddle apparatus 2 (paddle method) at a rotational speed of 75 rpm. The dissolution media consisted of 900 mL of distilled water equilibrated to $37\text{ }^{\circ}\text{C} \pm 0.5\text{ }^{\circ}\text{C}$. Each tablet was inserted in a stainless steel basket and samples were withdrawn from the dissolution flask using a peristaltic pump at different time intervals for up to 8 h (every 15 min for the first 2 h and then every 30 min up to 8 h). Drug release was measured using a UV-spectrophotometer at 240, 271 and 250 nm for DTZ, THP and ZNM respectively.
- For effect of rotational speed, drug release study (n=3) was performed in a paddle apparatus 2 (paddle method) at a rotational speed of 25, 50 75 and 100 rpm using 900 ml of distilled water. A UV spectrophotometer determined the amount of drug released at a wavelength of 240 nm for DTZ. The samples were withdrawn from the dissolution flask using a peristaltic pump for 8hrs as seen in the previous method.
- For effect of pH, Drug release behaviour of the PolyoxTM and PolyoxTM:Psyllium was investigated in a series of buffer solutions that simulated the stomach and intestinal conditions with the pH values of 1.2, 2.2, 5.8, 6.8, 7.2 and 7.5 using 900 ml. The dissolution was conducted for 8hrs for all formulations using a UV-spectrophotometer at a wavelength of 240 nm for DTZ. The same withdrawal procedure was used as seen in the previous method.

2.13 Dissolution parameters

Independent models including dissolution efficiency (DE, Eq. 2.3) (Khan, 1975), mean dissolution time (MDT, Eq. 2.4) and mean dissolution rate (MDR, Eq. 2.5) were employed to quantify the drug release profiles from different LS tablets in comparison to conventional tablets. Such mathematical analyses enable the statistical comparison between different formulations and evaluate how each formulation factor affects the dissolution rate of DTZ.

The DE is the area under the dissolution curve produced up to a certain time, t , expressed as the percentage of the area of the rectangle.

$$DE_t = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100 \quad (\text{Eq. 2.3}),$$

where t is the total time of drug release, y is the percentage of drug release at time t and Y_{100} is a 100% drug release.

MDT is a model-independent method that is suitable for dosage forms having different mechanisms of drug release. MDT the time at which 50% of the drug is dissolved from its solid state under dissolution conditions, whereas MDR is the percent release of the drug every min.

$$MDT = \frac{\sum_{j=1}^n t_j \Delta M_j}{\sum_{j=1}^n \Delta M_j} \quad (\text{Eq. 2.4})$$

$$MDR = \frac{\sum_{j=1}^n \Delta M_j / \Delta t}{n} \quad (\text{Eq. 2.5}),$$

where j is the sample number, n is the number of dissolution samples, Δt or t_j is the time at the midpoint between t and t^{-1} (which can be calculated using $(t + (t^{-1}) / 2)$), and ΔM_j is the additional amount of drug dissolved between t and t^{-1} .

2.14 Similarity factor

A similarity factor (f_2 , Eq. 2.6) (Moore and Flanner, 1996) was used to compare the in vitro release profiles of LS tablets and conventional tablets.

$$f_2 = 50 \times \text{Log} \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right] \right\}^{-0.5} \times 100 \quad (\text{Eq. 2.6}),$$

Where: n is the number of test points for the samples; R_t is the reference assay at time point t , and T_t is the test assay at time point t . An f_2 value between 50 and 100 suggests a similarity between the two release profiles and the closer the value is to 100 the more similar or identical the profiles are. Also dissimilarity occurs with decreasing values less than 50 (Moore and Flanner, 1996).

2.15 Release Kinetics

In addition to dissolution parameters, the kinetics of drug release from all formulations under investigation was determined to obtain information on the mechanism of drug release from the LS matrix tablets.

The release data obtained were analysed using the Power law proposed by Peppas and Korsmeyer and known as the Peppas model (Korsmeyer and Peppas, 1983). In this method, the log cumulative percentage of the drug release is plotted against the log of time. As this model assumes a uniform distribution of drug through a polymeric matrix (diffusion model), the release kinetics are evaluated by using drug release from 5 % to 60 % and fitting it into equation 2.7 as proposed by Ritger and Peppas (Ritger and Peppas, 1987).

$$Q = k t^n \quad (\text{Eq. 2.7}),$$

where Q is the percentage of drug released at time t , k is the release constant and n is the diffusional release exponent indicative of the operating release mechanism.

The value of n characterises the release mechanism of drug in this model. Since the tablet matrices prepared in this investigation had a cylindrical shape, Fickian diffusion is suggested

for n values up to 0.45, whereas Case-II transport is suggested when values are above 0.89. Values of n between these two suggest anomalous transport occurring ([Siepmann and Peppas, 2001](#)).

2.16 Swelling behaviour

To evaluate the effect of PolyoxTM dissolution on DTZ release kinetics, PolyoxTM tablets were separately weighed (W_0) and then placed in small containers with a metal mesh underneath them. Another mesh was placed on the top of each container to make sure the tablets are held inside the chamber. To simulate the in vitro dissolution conditions, the small containers carrying the tablets were placed in the bottom of dissolution vessels containing distilled water equilibrated to $37\text{ }^\circ\text{C} \pm 0.5\text{ }^\circ\text{C}$. Paddles were used to stir the dissolution medium at a rate of 75 rpm at $37\text{ }^\circ\text{C} \pm 0.5\text{ }^\circ\text{C}$. At various time intervals (0, 2, 5, 15 and 30 min), the tablets were withdrawn using a small basket, soaked on a tissue paper (to remove excess water). The percentage increase in weight of each tablet due to water uptake was calculated using the following equation.

$$\% \text{ swelling} = \frac{M_t - M_0}{M_0} \times 100 \quad (\text{Eq. 1.8}),$$

where M_t is the weight of tablet at time ' t ' and M_0 is the weight of tablet at time 0. The experiments were performed in triplicate for each time point. Fresh samples were used for each time point.

3 CHAPTER 3: EFFECT OF POLYOX™ MOLECULAR WEIGHT

3.1 Introduction

Diltiazem HCL (DTZ) is a calcium channel blocker employed in the treatment of angina pectoris and hypertension. DTZ is largely metabolized by the liver and excreted by the kidney. Although DTZ is absorbed up to about 80%, it is subjected to an entire bioavailability of ~ 40% due to an extended first-effect (Chaffman and Brogden, 1985). Additionally, the plasma elimination half-life resulting from single or multiple administrations is relatively short (~ 3 to 5 hrs). Therefore, DTZ is a good candidate for a sustained release dosage form (Lachman *et al.*, 1990), which is useful to patients to maintain sustainable levels in the blood plasma (Piepho *et al.*, 1982). The main goals of designing a sustained release form is to achieve a steady state blood level of drug that is nontoxic and therapeutically effective for an extended time to reduce dosing frequency and fluctuations of drug levels in the blood (Putney and Burke, 1998). Polymers are long chain molecules formed from smaller molecules called monomers. Numerous studies reported the influence of various factors associated with hypromellose polymers, such as MW (Krögel and Bodmeier, 1999), concentration (Mitchell *et al.*, 1993), particle size distribution (PSD) (Velasco *et al.*, 1999), on drug release. However, there is a shortage of data on the influence of factors associated with polyethene oxide (PolyoxTM). PolyoxTM is an attractive hydrophilic polymer for the use in the preparation of pharmaceutical formulations because of its nontoxicity, ease of production, high water-solubility, high swellability, and insensitivity to the pH of the biological medium (Shojaee *et al.*, 2014). LS systems were initially designed to improve the solubility and dissolution rate of poorly soluble drugs (Nokhodchi *et al.*, 2016). Recently, it has been employed to sustain the release of highly soluble drugs. The influence of PolyoxTM MW on the physicochemical and pharmaceutical properties of LS formulations was not reported previously. To this end, LS formulations containing various grades of PolyoxTM having MWs ranging from 1×10^5 to 70

$\times 10^5$ were prepared and studied for their physicochemical and drug release properties in comparison to their PM counterparts.

3.2 Formulation

DTZ powder (2.4 g) was dissolved in 2.4 g of polysorbate 80 (PS 80) (60 °C, 200 rpm), a non-volatile water-miscible solvent used as a liquid vehicle to form liquid medication phase at a fixed drug:solvent ratio of 1:1 (w:w). Each grade of PolyoxTM powder under investigation (3.6 g, solid phase) was introduced to a mortar, and the mixing process was carried out as described earlier (Section 2.5). For comparison purpose, PM formulation contained a mixture of DTZ (2.4 g) and PolyoxTM (3.6 g). The mixing was performed as described in Section 2.5. Accurately weighed samples of each liquisolid (300 mg) and PM (240 mg) formulation were separately weighed and then compressed on 8 mm punch and die using a manual tableting machine at a fixed pressure of 2000 psi.

3.3 Results and discussion

3.3.1 Solid state

Polymorphic change of drug is one of the main features that may affect the drug dissolution rate and bioavailability (Abdou, 1989). Therefore, it is vital to study the polymorphic changes of DTZ in the prepared LS tablets. No polymorphs have been reported for DTZ to date (Mazzo *et al.*, 1994). The PXRD patterns and FT-IR spectra of commercial DTZ, LS formulations and PM formulations are shown in Figure 3.1 and Figure 3.2. DTZ displayed sharp peaks at 8.10°, 10.12°, 18.30°, 19.53°, 20.10°, 21.66°, 24.77°, 28.10°, 30.01°, 32.10°, 40.23° and 42.10° 2 θ , suggesting a typical crystalline pattern (Mazzo *et al.*, 1994). It can be observed that, LS formulations and PM formulations showed two prominent peaks with the highest intensity at 2 θ of 18.33° and 23.57°. This indicate the presence of PolyoxTM in both the PM and LS formulations (Figure 3.1). No significant changes were also observed in the FT-IR spectra of LS formulations in comparison to their PM counterparts. The characteristic

bands at 2931.90 cm^{-1} (O-CH₃ and C-H stretching), 2387.93 cm^{-1} (amine HCl, N-H stretching), 1741.78 cm^{-1} (acetate C=O stretch), 1678.13 cm^{-1} (lactam C=O stretch), 831.33 cm^{-1} (O-substituted aromatic C-H out of plane deformation), and 673.48 cm^{-1} (P-substituted aromatic C-H out of plane) were present in all samples. Such observations confirmed that there was no significant change in the solid state of the drug during the preparation of LS formulations. The results also ruled out the existence of significant drug-excipient interaction within both LS and PM formulations.

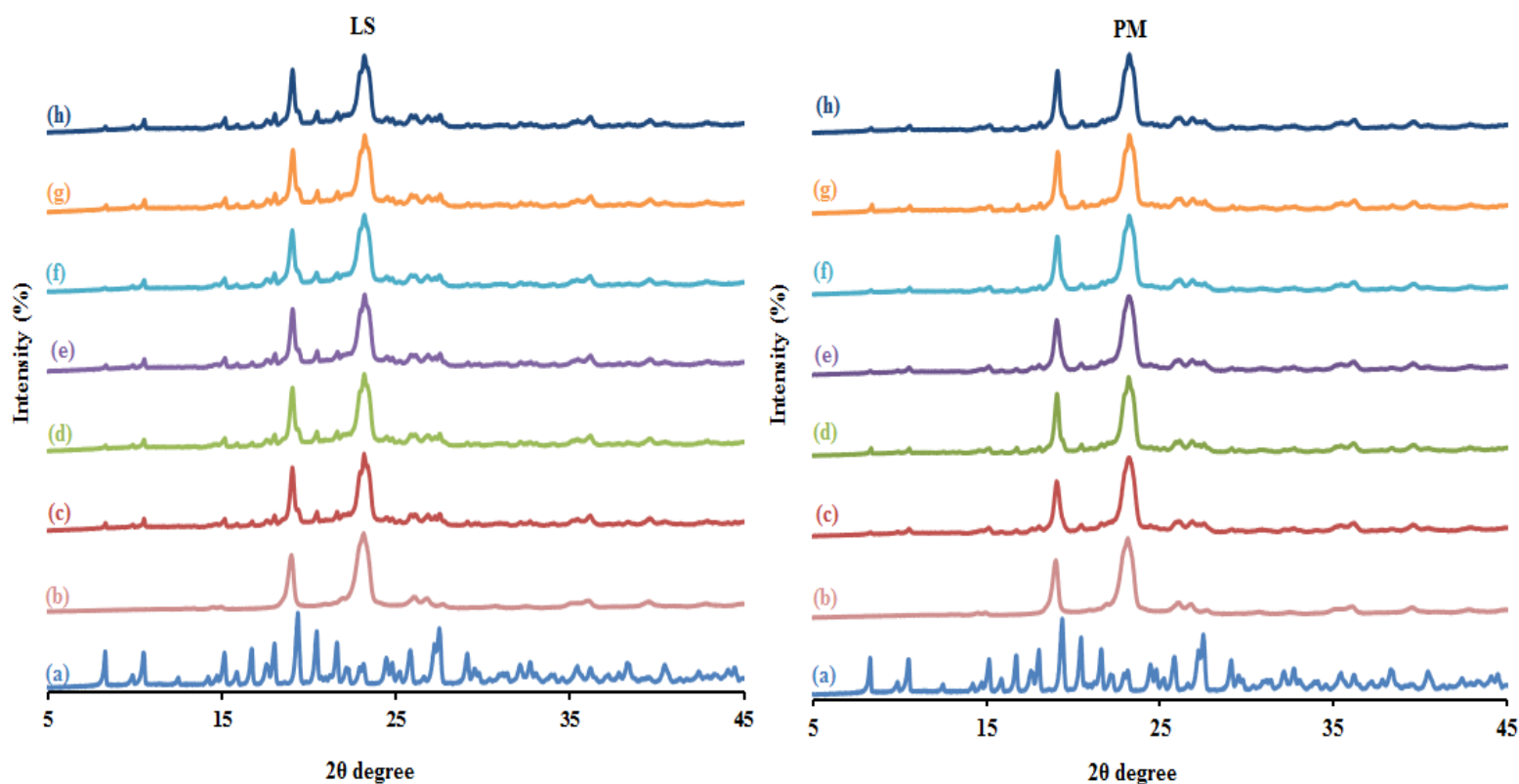


Figure 3.1: PXRD patterns of physical mixture (PM) and LS (LS) formulations containing various grades of PolyoxTM (a) Pure DTZ, (b) Pure PolyoxTM (c) DTZ-WSR 10, (d) DTZ-WSR 80, (e) DTZ-WSR 750, (f) DTZ-WSR 1105, (g) DTZ-WSR 301 and (h) DTZ-WSR 303.

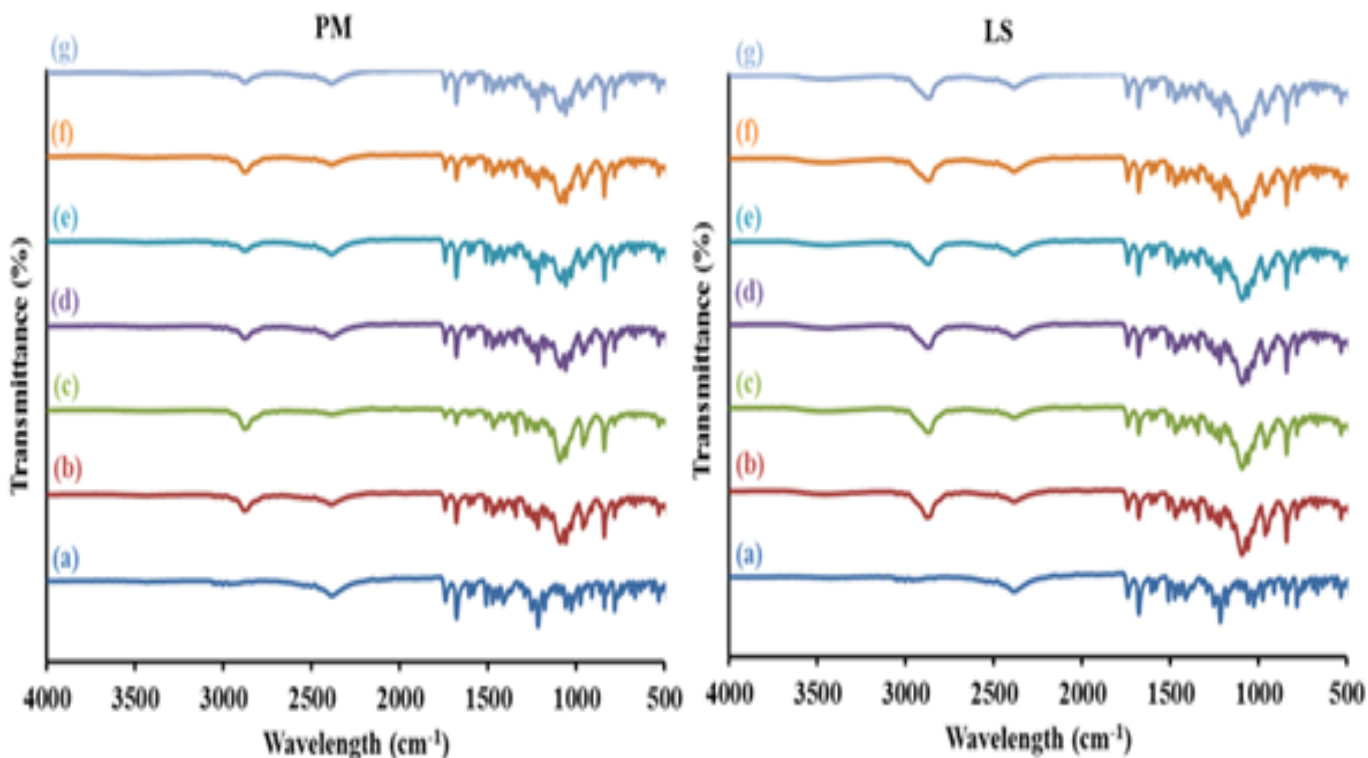


Figure 3.2: FTIR patterns of physical mixture (PM) and liquid solid (LS) formulations containing various grades of PolyoxTM (a) Pure DTZ, (b) DTZ-WSR 10, (c) DTZ-WSR 80, (d) DTZ-WSR 750, (e) DTZ-WSR 1105, (f) DTZ-WSR 301 and (g) DTZ-WSR 303.

3.3.2 Particle size distributions

LS formulations showed larger PSDs compared to their PM counterparts, although such increase in particle size was not statistically different (VMD, $P > 0.05$) in the case of PolyoxTM grades with MW $> 9 \times 10^5$ (Table 3.1). This could be attributed to increased particle aggregation for LS formulations (Figure 3.3). Different degrees of aggregation were observed in LS formulations. Smaller DTZ particles were generally not presented as distinct particles in the case of LS formulations but as aggregates due to strong DTZ–PolyoxTM cohesion (Figure 3.3). All formulations showed a span value higher than unity, denoting broad PSDs (Table 3.1). Nevertheless, LS formulations showed relatively narrower size distributions compared to their PM counterparts as indicated by their lower span values (Table 3.1). The

significant reduction of fine particulates content recorded for LS formulations compared to their PM counterparts, as indicated by the higher $d_{10\%}$ values (Table 3.1), could account for their improved size homogeneity. This could be attributed to the adhesion of such fines on the surfaces of larger particles in the case of LS formulations as confirmed by SEM observations (Figure 3.3). Additionally, the striking morphological differences in the blend structures between LS and PM formulation mixtures support the higher span values obtained for LS formulations compared to PM formulations (Figure 3.3). Two different populations of particles could be observed in the PMs accounting for morphologies of both DTZ (slabby) and PolyoxTM (botryoidal) particles, whereas no distinct DTZ or PolyoxTM particles were observed in LS formulations (Figure 3.3). The improved mass distribution for LS formulations is of great importance because it relates directly to dose uniformity. In contrast to LS formulations, the different sized particles in the case of PM formulations will lead to a different amount of drug per unit mass. When the various sized particles segregate (e.g. by percolation segregation), drug-rich areas may result where the small particles congregate (Kaialy, 2016–a), as confirmed by SEM observations for PM formulations (Figure 3.3).

Table3 1: Particle size distribution (i.e. particle size at 10% ($d_{10\%}$), 50% ($d_{50\%}$), 90% ($d_{90\%}$), volume mean diameter (VMD), and span; mean \pm SD, $n = 3$) of DTZ–Polyox™ liquisolid (LS) formulation powders and their physical mixture (PM) counterparts.

Formulation	Polyox™ MW ($\times 10^5$)	$d_{10\%}$ (μm)		$d_{50\%}$ (μm)		$d_{90\%}$ (μm)		VMD (μm)		Span	
		PM	LS	PM	LS	PM	LS	PM	LS	PM	LS
DTZ (alone)		8.2 \pm 0.		129.2 \pm 0.3		147.3 \pm 8.0		167.0 \pm 4.5		4.0 \pm 1.5	
DTZ–WSRN10	1	23.0 \pm 4.7	59.5 \pm 0.0	119.0 \pm 9.2	163.1 \pm 0.1	337.0 \pm 49.0	486.0 \pm 0.0	167.7 \pm 38.1	273.0 \pm 0.0	2.6 \pm 0.2	2.5 \pm 0.0
DTZ–WSR 80	2	21.2 \pm 0.3	52.8 \pm 0.4	114.7 \pm 9.3	143.2 \pm 1.1	346.3 \pm 44.8	343.7 \pm 5.0	156.3 \pm 19.1	174.3 \pm 1.5	2.8 \pm 0.2	2.0 \pm 0.0
DTZ–WSR 750	3	27.7 \pm 3.5	56.6 \pm 0.6	144.3 \pm 20.8	159.0 \pm 4.6	387.7 \pm 42.8	421.0 \pm 5.1	188.0 \pm 18.1	230.7 \pm 38.0	2.5 \pm 0.1	2.3 \pm 0.2
DTZ–WSR 1105	9	24.9 \pm 2.6	60.0 \pm 0.4	139.7 \pm 20.6	155.0 \pm 0.6	389.3 \pm 47.5	378.7 \pm 9.0	184.7 \pm 26.6	195.3 \pm 8.5	2.6 \pm 0.1	2.1 \pm 0.0
DTZ–WSR 301	40	36.1 \pm 3.5	58.0 \pm 0.3	167.7 \pm 9.3	166.1 \pm 1.7	439.3 \pm 19.6	439.7 \pm 11.5	211.7 \pm 10.0	218.3 \pm 9.2	2.4 \pm 0.1	2.3 \pm 0.0
DTZ–WSR 303	70	35.0 \pm 1.1	51.6 \pm 13.4	152.0 \pm 11.3	163.2 \pm 1.2	390.5 \pm 31.8	395.7 \pm 1.1	190.0 \pm 14.1	199.7 \pm 2.3	2.3 \pm 0.0	2.1 \pm 0.1

3.3.3 Powder density

LS formulations showed significantly ($P < 0.05$) lower bulk densities compared to PM formulations (Table 3.2), indicating that there are fewer average points of physical contact between particles within LS powders compared to PM powders. The wider polydispersity of particle size for PM formulations compared to LS formulations (Table 3.1) could account for their higher bulk and tapped densities because polydispersed particles pack more efficiently (i.e. smaller particles filling in the interstices created by the large particles). LS powders showed poorer flow properties compared to PM powders as indicated by their higher CI values (Table 3.2). Undoubtedly, the nature and extent of interparticle forces provide a major influence in powder flowability. The poorer flow properties of LS powders in comparison to PM powders (Table 3.2), despite their lower content of fine particulates (Table 3.1), is due to the high viscosity of PS 80, which increases the cohesive properties of the LS powders. SEM photographs showed LS powders to be composed of irregular, deformed particles with rough/uneven surfaces and increased particle aggregation due to increased interparticle cohesion (Figure 3.3). Therefore, LS powders will have a higher propensity to geometrical interlocking upon packing (i.e. increased frictional forces) resulting in poorer flow properties as compared to PM powders. The tap density and CI of both LS and PM formulations showed generally decreasing trends with increasing the MW of PolyoxTM (Table 3.2), indicating that powders containing PolyoxTM grades with higher MWs have better flow properties.

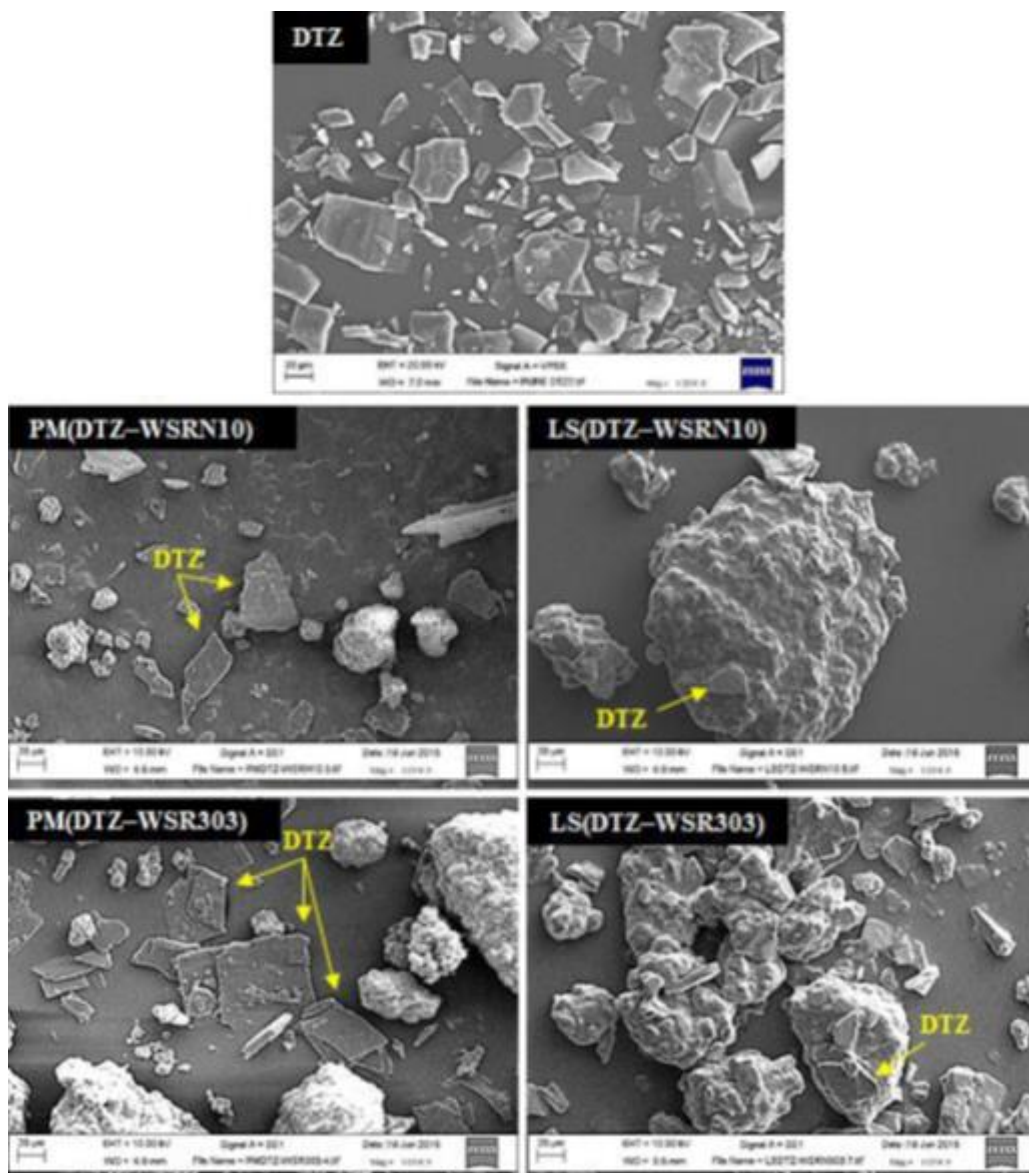


Figure 3. 3: Representative scanning electron microscopy (SEM) photographs of commercial diltiazem HCl (DTZ) and LS formulations containing DTZ drug and formulated with Polyox™ WSRN10 or Polyox™ WSR303 in comparison to their physical mixture (PM) counterparts.

Table 3 2: Bulk density, tap density and Carr’s index (CI) (mean \pm SD, $n = 5$) for DTZ–PolyoxTM liquisolid (LS) formulation powders and their physical mixture (PM) counterparts.

Formulation	Polyox TM MW ($\times 10^5$)	Bulk density (g/cm ³)		Tap density (g/cm ³)		CI (%)	
		PM	LS	PM	LS	PM	LS
DTZ–WSRN10	1	0.42 \pm 0.01	0.35 \pm 0.01	0.57 \pm 0.00	0.55 \pm 0.01	25.7 \pm 0.9	36.5 \pm 1.2
DTZ–WSR 80	2	0.41 \pm 0.01	0.34 \pm 0.01	0.54 \pm 0.01	0.52 \pm 0.02	23.7 \pm 1.1	34.1 \pm 2.8
DTZ–WSR 750	3	0.36 \pm 0.01	0.33 \pm 0.01	0.50 \pm 0.01	0.49 \pm 0.03	23.0 \pm 0.4	33.3 \pm 3.1
DTZ–WSR 1105	9	0.40 \pm 0.01	0.34 \pm 0.01	0.52 \pm 0.02	0.50 \pm 0.02	23.0 \pm 1.2	32.1 \pm 5.4
DTZ–WSR 301	40	0.38 \pm 0.01	0.34 \pm 0.01	0.48 \pm 0.01	0.50 \pm 0.01	20.0 \pm 1.3	31.7 \pm 1.7
DTZ–WSR 303	70	0.40 \pm 0.01	0.36 \pm 0.02	0.51 \pm 0.00	0.51 \pm 0.03	21.4 \pm 1.5	30.0 \pm 1.0

3.3.4 Drug release

The release profiles of DTZ from various PM and LS formulations under investigation are shown in [Figure 3.4](#). No tablet exhibited any initial burst drug release ([Figure 3.4](#)). This is because PolyoxTM forms a viscous gel layer when it is exposed to aqueous media, allowing the retardation of the release of highly water-soluble drugs ([Shojaee et al., 2015](#)). The dissolution rate of DTZ from both LS and PM tablets decreased as the MW of PolyoxTM increased ([Figure 3.4](#)). This was confirmed by dissolution parameters analyses that showed both LS and PM tablets containing PolyoxTM grades with higher MWs to produce lower DEs, higher MDTs and lower MDRs compared to those containing lower MWs ([Table 3.3](#)). The delayed DTZ release could be related to the rate and extent of hydrogel formation on the tablet surface. Soluble drugs such as DTZ are predominately released by diffusion mechanism through the gel layer. Upon immersion in an aqueous medium, the hydrophilic PolyoxTM matrix physically swells to form a hydrogel layer around the tablet. The quick formation of such gel layer is vital as it contributes to retaining structural integrity, slows down water entering the interior of the matrix tablet and prevents tablet disintegration ([Khan et al., 1995](#)). It could be assumed that the solvent penetrates the free spaces between the macromolecular chains of PolyoxTM, and the PolyoxTM chains become flexible, enhancing the thickness of the gel layer and allowing drug release through the gels outer surface ([Colombo et al., 1995](#)). This could also be described as water plasticising the PolyoxTM and transforming it from glassy state to rubbery state. When it is highly hydrated, the outer layer ultimately reaches a dilution point leading to PolyoxTM disentanglement from the surface of the matrix. The gel layer is then constantly replaced with the hydrated PolyoxTM from inside the core. In comparison to matrices containing a PolyoxTM grade with a lower MW, matrices containing a PolyoxTM grade with a higher MW could produce more coherent (thicker or more viscous) hydrogel layers, acting as a barrier against release of drug and thus resulting in

a slower drug release since it takes time for DTZ molecules to travel across the gel layer and reach the dissolution medium. In contrast, PolyoxTM grades with low MWs are more susceptible to erosion due to the formation of thinner (softer) hydrogel layers (Wu *et al.*, 2005). It can also be argued that PolyoxTM grades with higher MWs produce slower drug release due to higher viscosity and thus higher energy required for pulling longer chains of the polymer off the matrix (Hiremath and Saha, 2008).

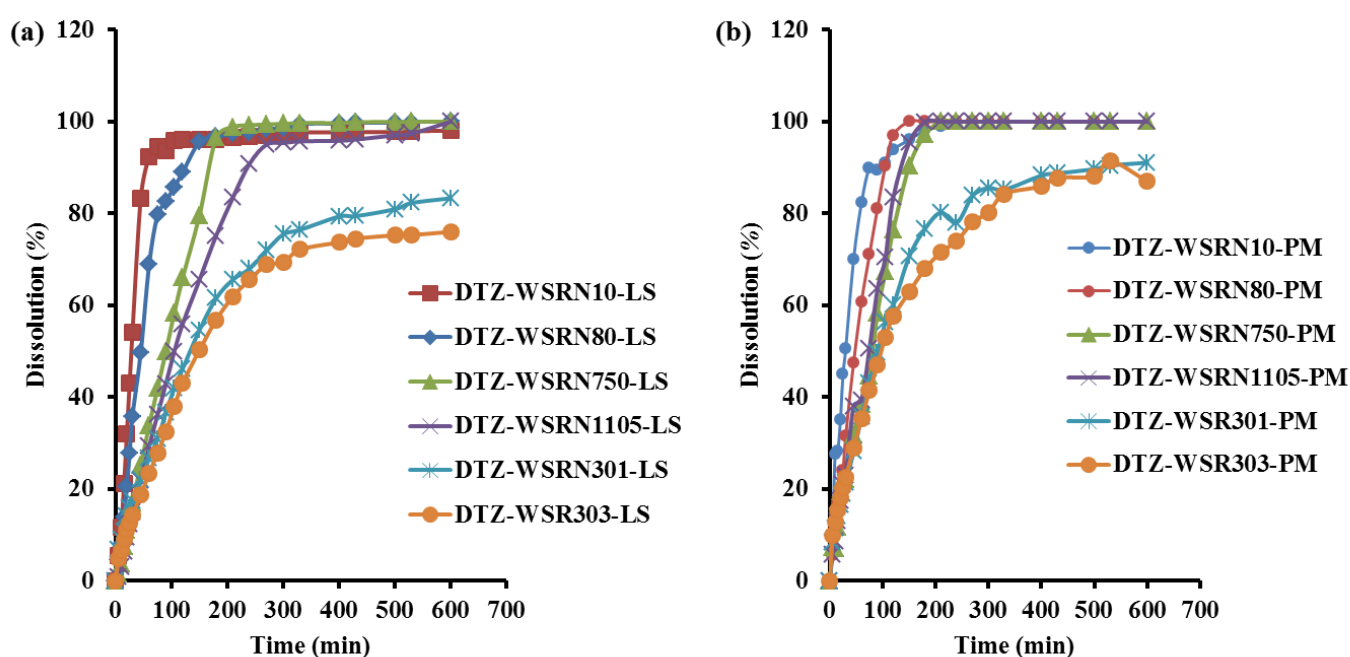


Figure 3.4: Release patterns (mean \pm SD, $n = 3$) of diltiazem HCl (DTZ) from physical mixture (PM) and liquisolid (LS) formulations containing various grades or PolyoxTM (WSRN10, WSRN80, WSRN750, WSRN1105, WSR301 and WSR303).

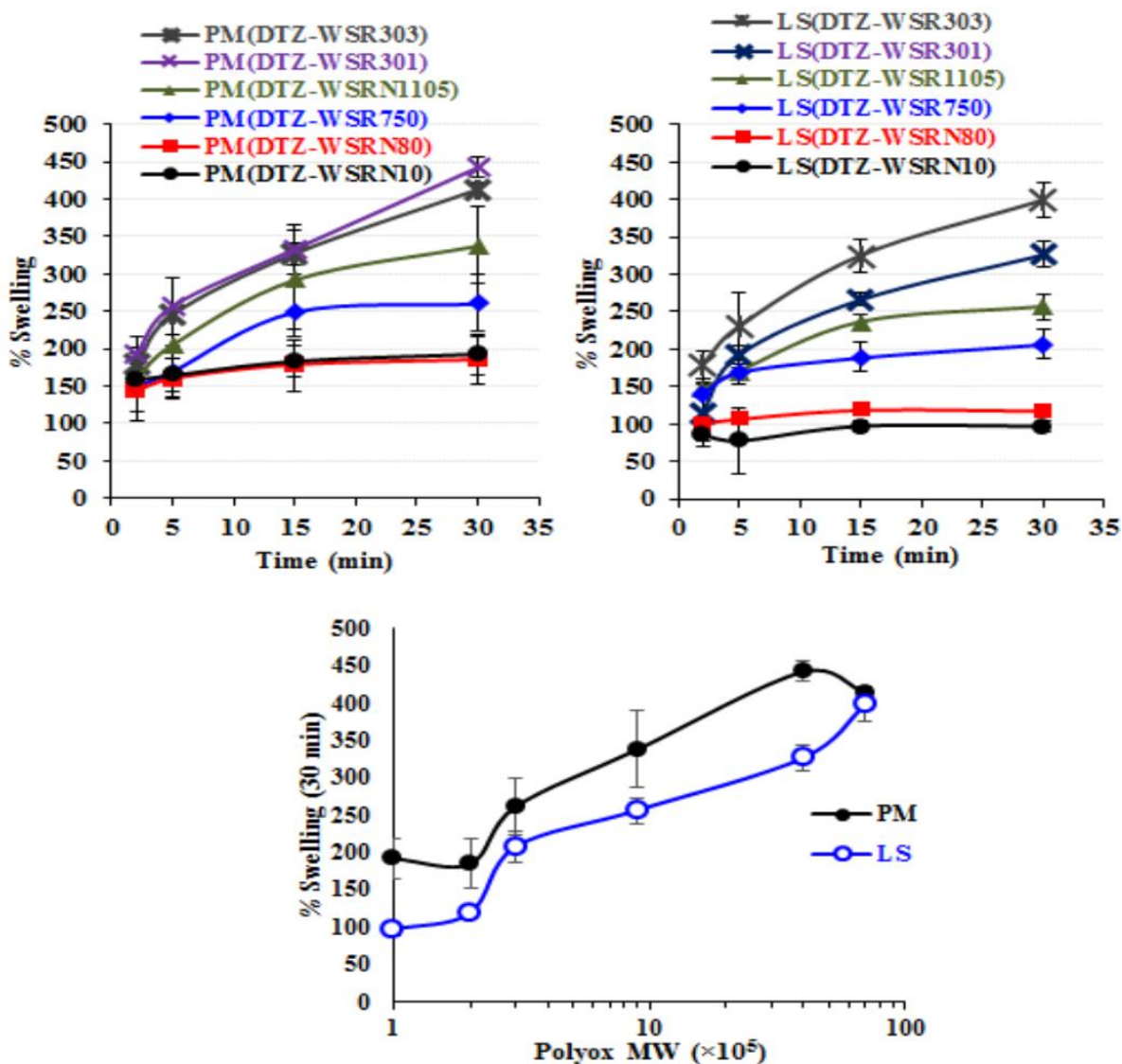


Figure 3.5: Percent swelling of physical mixture (PM) and liquisolid (LS) formulation tablets containing various grades or Polyox™ (WSRN10, WSRN80, WSRN750, WSRN1105, WSR301 and WSR303), and the effect of MW on % swelling (mean \pm SD, $n = 3$).

This was confirmed by swellability studies which showed the water uptake of both LS and PM tablets to increase as the MW of Polyox™ increased (Figure 3.5). Similar findings were reported in the case of hypromellose by (Wan *et al.*, 1993), where an increase in gel layer thickness after 30 min of swelling was reported for matrix tablets containing hypromellose grades with higher MWs. LS tablets showed lower swellabilities than their PM counterparts tablets (Figure 3.5). Such differences could be attributed to the differential expansion of the

glassy core of the matrix. In general, LS tablets showed slower release patterns compared to PM tablets, although whether such decrease in drug release rate is statistically different was dependant on PolyoxTM MW (Table 3.3). Statistical analysis confirmed that DTZ release profiles from LS tablets containing PolyoxTM grades with MWs below 9×10^5 (i.e. WSRN10, WSRN80 and WSRN750) was not significantly different ($f_2 > 50$, Table 3.3) in comparison to their PM counterparts (Figure 3.4). In contrast, better retardation properties were observed for LS tablets containing Polyoxes with MWs $\geq 9 \times 10^5$ (i.e. WSR1105, 351 WSR301 and WRS303) in comparison to the conventional tablets (Figure 3.4), as substantiated by f_2 values below 50 (Table 3.3). Similar conclusions could, in general, be obtained when considering MDT and MDR results.

Table 3 3: Dissolution efficiency (DE), mean dissolution rate (MDT), mean dissolution rate (MDR), similarity factor (f_2) and in vitro release kinetic parameters (r^2 , correlation coefficient squared; n value, and MPE, mean percentage error based on Korsemeyer-Peppas equation, $Q = k_{\text{ttn}}$ (Eq. 8) of diltiazem HCl obtained for liquisolid (LS) formulations containing various grades or PolyoxTM (WSRN10, WSRN80, WSRN750, WSRN1105, WSR301 and WSR303) in comparison to their physical mixture (PM) counterparts. The counterpart physical mixture was chosen as the standard for each liquisolid formulation when calculating f_2 values. The results are expressed as the mean \pm SD, $n = 3$ (*indicates a significant difference, $P < 0.05$).

Formulation	Polyox TM MW ($\times 10^5$)	DE (%)		MDT (min)		MDR (min^{-1})		f_2	r^2		n		MPE (%)	
		PM	LS	PM	LS	PM	LS		LS vs PM	LS	PM	LS	PM	LS
DTZ-WSRN10	1	90.6 \pm 2.4	91.6 \pm 1.2	31.5 \pm 10.0	34.0 \pm 4.5	0.60 \pm 0.01	0.59 \pm 0.01	62.7	0.997	0.931	1.301	0.871	3.51	9.63
DTZ-WSR 80	2	90.3 \pm 1.3	89.0 \pm 0.9	48.4 \pm 6.6	57.8 \pm 5.7*	0.49 \pm 0.02*	0.48 \pm 0.01*	70.2	0.989	0.975	1.150	0.812	6.98	7.72
DTZ-WSR 750	3	86.7 \pm 3.0	82.3 \pm 1.4*	79.9 \pm 12.2*	93.5 \pm 3.5*	0.37 \pm 0.02*	0.34 \pm 0.01*	64.0	0.989	0.952	1.169	0.771	10.11	11.69
DTZ-WSR 1105	9	87.9 \pm 0.4	78.4 \pm 2.1*	72.7 \pm 2.4*	101.4 \pm 16.0*	0.38 \pm 0.01*	0.38 \pm 0.05*	43.7	0.972	0.990	1.239	0.828	16.82	5.51
DTZ-WSR 301	40	74.4 \pm 2.5*	64.4 \pm 0.7*	109.4 \pm 6.2*	136.5 \pm 0.4*	0.32 \pm 0.01*	0.27 \pm 0.01*	49.0	0.989	0.987	0.726	0.650	5.39	5.96
DTZ-WSR 303	70	69.4 \pm 8.7*	58.0 \pm 2.5*	131.3 \pm 24.4*	119.4 \pm 5.9*	0.35 \pm 0.05*	0.25 \pm 0.01*	47.5	0.994	0.998	0.712	0.580	4.84	5.10

For example, The DEs obtained from LS and PM tablets were statistically similar ($P > 0.05$) in the case of Polyoxes with MWs below 9×10^5 , whereas LS tablets produced lower DEs than conventional tablets in the case of Polyoxes with MWs $\geq 9 \times 10^5$ (Table 3.3). An interesting trend was obtained when plotting the difference in the dissolution efficiency of DTZ obtained from PM and LS formulations ($\Delta DE = DE_{PM} - DE_{LS}$) against the MW of PolyoxTM. ΔDE increased with increasing PolyoxTM MW (Figure 3.6). This indicates that only polyoxTM with higher MW to produce more sustained drug release from LS tablets in comparison to their PM compact. The dissolution data were fitted into Eq. 8 and the in vitro release kinetic parameters are listed in Table 3.3.

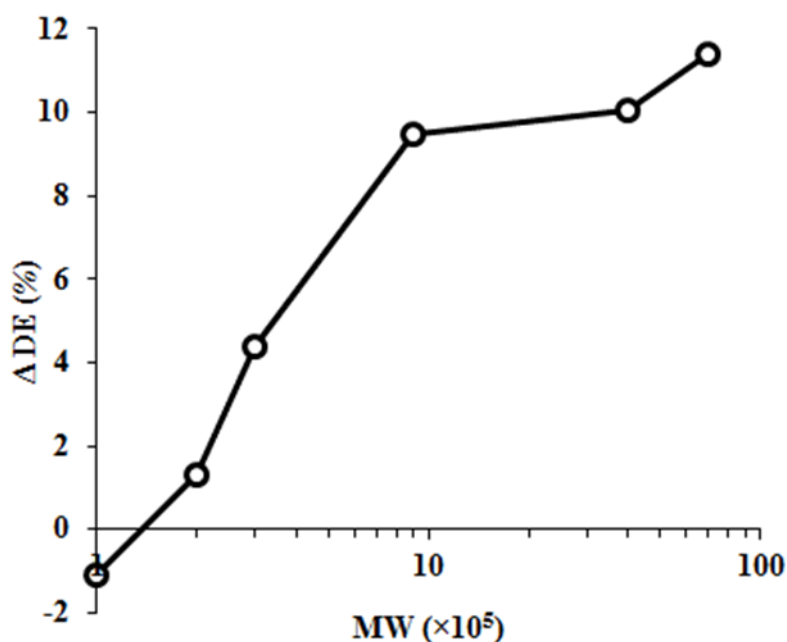


Figure 3.6: Difference in dissolution efficiency (ΔDE , %) of diltiazem HCl (DTZ) between liquid (LS) and (PM) formulations in relation to PolyoxTM molecular weight (MW).

All profiles were well fitted as indicated by the excellent r^2 values obtained. In comparison to PM formulations, all LS formulations showed higher n values regardless of PolyoxTM MW

(Table 3.3), indicating a higher contribution of macromolecular relaxation and erosion mechanisms and near zero-order release. The release of DTZ from all PM formulations followed the anomalous transport mechanism ($0.45 < n < 0.89$) regardless of PolyoxTM MW (Table 3.3). In contrast, the mechanism by which DTZ was released from LS formulations was dependent on polyoxTM MW. LS formulations containing Polyoxes with MWs above 9×10^5 released the drug via anomalous transport (or non-fickian diffusion) mechanism ($0.45 < n < 0.89$) whereas LS formulations containing Polyoxes with $MW \leq 9 \times 10^5$ released the drug via case-II transport mechanism ($n > 0.89$) (Table 3.3). This indicated that only PolyoxTM grades with $MWs \geq 9 \times 10^5$ (WSR301 and WSR 303) are better candidates to produce more sustained drug release from LS tablets in comparison to PM tablets. More efficient encapsulation of the drug particles by the PolyoxTM particles could be a mechanism of drug release prolongation in the case of LS tablets. The solvent incorporated in LS formulations could exert a plasticising effect within the membrane of PolyoxTM after the swelling and diffusion processes (Gruetzmann and Wagner, 2005). Polysorbate was shown to reduce the Tg of polymers such as PolyoxTM (Javadzadeh *et al.*, 2008) and thus it could slow the release rate of DTZ from LS tablets compared to the PM tablets through affecting the intermolecular bonds between PolyoxTM chains.

3.3.5 Electrostatic charge

Triboelectrostatic charging is a multifaceted complex phenomenon that depends on several factors such as contact surface resistivity, particle surface roughness, PSD, particle surface resistivity, and environmental relative humidity. The charge sign of a group of particles depends on their relative electron-donor or -acceptor properties and work functions (Kaialy, 2016–b). Commercial DTZ, LS and PM formulation powders showed strong bipolar charging behaviours (Figure 3.7), a phenomenon that has been particularly recognised in polydispersed powder mixtures having similar or dissimilar chemical compositions (Kaialy, 2016–b). Commercial DTZ showed an electronegative net-CMR (netcharge) (Figure 3.7). In general, the P-CMRs and net-CMRs of both LS and PM formulation powders showed increasing trends with increasing the MW of PolyoxTM (Figure 3.7). Compared to their PM counterparts, LS formulations containing PoyloxTM grades with MWs below 9×10^5 showed higher netcharges, whereas the reverse trend could be observed for LS formulations containing PoyloxTM grades with MWs $\geq 9 \times 10^5$ (Figure 3.7). This suggested that LS formulation containing high MW PolyoxTM provide improved handling compared to their PM counterparts. The differences in electrostatic behaviour between LS and PM powders are because particles can roll, slide, and collide with each other during the preparation of LS formulations, all the foregoing actions can induce electrostatic charge development at the level of the particle surfaces. It should also be noted that although PM formulations containing Polyoxes with MWs below 9×10^5 showed negligible absolute magnitude of netcharge (≤ 0.3 nC/g), these formulations showed considerable levels of both positive charging and negative charging (Figure 3.7). This suggests that measuring only the netcharge (i.e. the sum of electrostatic charges carried by a powder sample) for powders exhibiting bipolar charge behaviour is not a good indicator of charging behaviour as it can produce erroneous conclusions. Thus, it is necessary to characterise particulate materials for their

bipolar electrical characteristics to recognise the underlying phenomenon of tribocharging so that a corrective action can be taken.

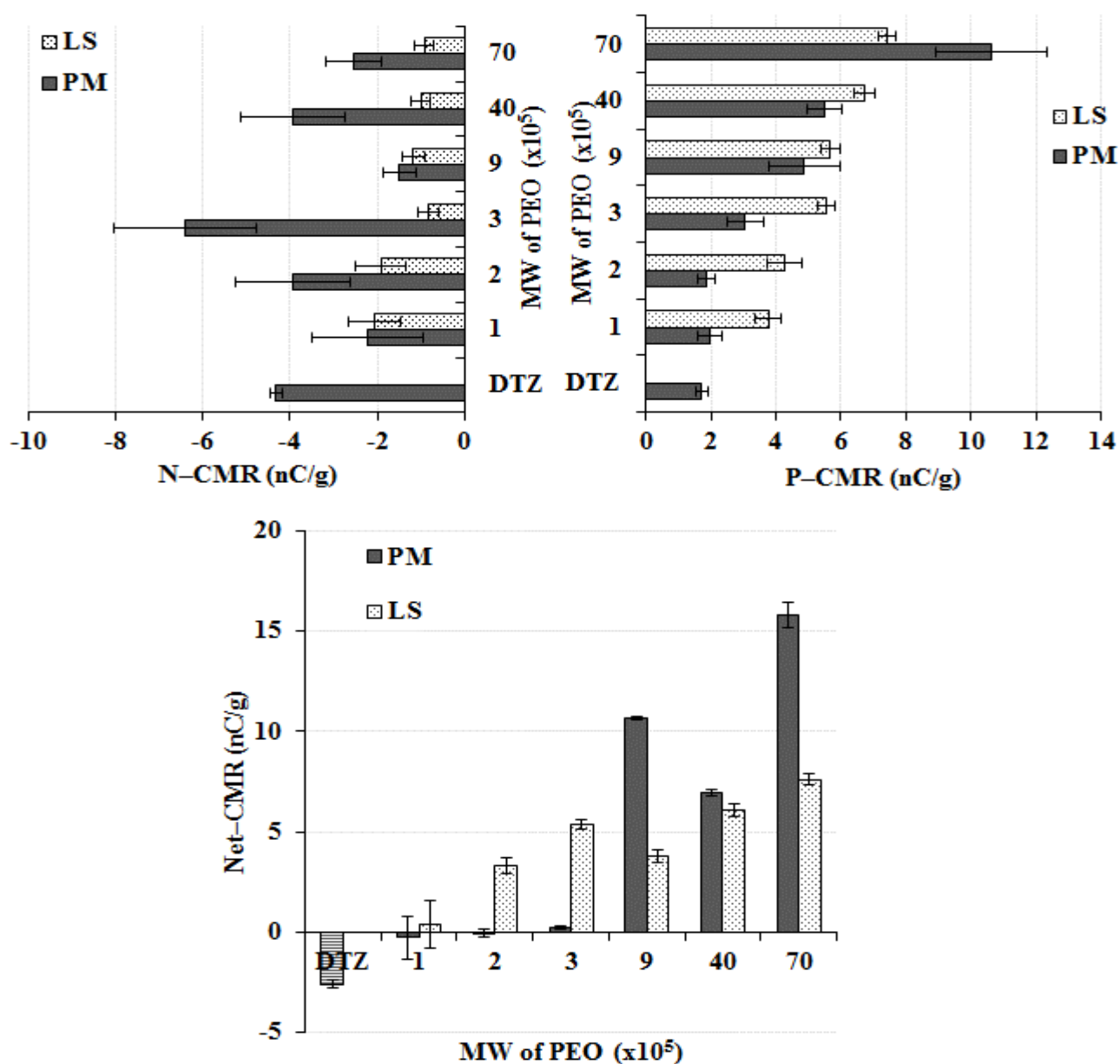


Figure 3.7: Positive-charge-to-mass ratio (P-CMR), negative-charge-to-mass ratio (N-CMR) and net-charge-to-mass ratio (net-CMR) (mean \pm SD, $n = 3$) for commercial diltiazem HCl (DTZ), liquisolid (LS) formulations containing various grades or Polyox™ (WSRN10, WSRN80, WSRN750, WSRN1105, WSR301 and WSR303) in comparison to their physical mixture (PM) counterparts.

3.4 Conclusion

PolyoxTM-based LS tablets have a potential to produce zero-order release kinetics for a highly water-soluble drug, DTZ, although a careful selection of PolyoxTM grade is nevertheless vital to producing slower release pattern of LS tablets in comparison to PM tablets. Only when the MW of PolyoxTM was sufficiently high (i.e. $\geq 9 \times 10^5$) was the rate and extent of drug release lower for LS tablets in comparison to conventional tablets. Being simple and easily scaled up, the LS method should have general applicability to many highly water-soluble drug entities. Further work is therefore required to comprehensively explore LS technique as a robust and reliable method of retarding the release rate of highly soluble drugs. This will aid in the design and development of improved ER delivery systems in the future.

4 CHAPTER 4: EFFECT OF POLYETHYLENE OXIDE PARTICLE SIZE AND LEVEL

4.1 Introduction

LS technique is a relatively new concept in which a liquid lipophilic medication or a water-insoluble solid drug is dissolved in a suitable non-volatile solvent (to form a solution or a suspension), and then this liquid medication is converted to into a free-flowing, non-adhering and dry-looking compactable powder mixtures with a use of carrier and coating material (Gubbi and Jarag, 2009). The advantages of LS techniques include the low cost, suitability for industrial production and simplicity of the process needed to produce the formulation (i.e. less time-consuming than other methods) (Nokhodchi *et al.*, 2011). Sustained release dosage forms are designed to release the drug at a decided rate by controlling a constant drug release for a particular period of time, leading to less side effects, better efficacy, improved patient compliance and higher safety. Many researchers have investigated the influence of polymer particle size on drug release from sustained release dosage forms. Mitchell *et al.*, (1993) investigated the effect of particle size of hypromellose on the release rate of propranolol HCl from tablet matrices. The findings showed that the dissolution rate generally decreased as the particle size distribution decreased from 350 μm to 150 μm . (Campos-Aldrete and Villafuete-Robles, 1997) also observed that hypromellose with smaller particle size distributions produced slower release rates of metronidazole when a higher concentration of drug:Polymer is used. In the same line, Novak *et al.*, (2012), reported that when the smallest particle size distribution ($< 75 \mu\text{m}$) of hypromellose is used, slower dissolution rates were observed for diclofenac Na. In another study, (Crowley *et al.*, 2004) showed that the compacts containing ethylcellulose with a smaller particle size 80 μm to 30 μm released guaifenesin, a model water-soluble drug, more slowly as compared to the ones having larger particles 325 μm to 80 μm . A mean particle size of hypromellose K15M smaller than 113 μm was shown to lead to the release of Aspirin from tablet matrices through a combination of erosion and diffusion mechanisms, whereas matrix tablets containing hypromellose with mean particle size larger

than 113 μm produced fast Aspirin release behaviour through an erosion-based mechanism (Heng *et al.*, 2001). Miranda *et al.*, (2007) showed that the larger hypromellose K4M particle sizes were less effective in the formation of a homogeneous gel layer. To my knowledge, the influence of PolyoxTM particle size and concentration on the physicochemical and pharmaceutical properties of LS formulations was not investigated recently. To this end, LS formulations containing various particle size and concentration of PolyoxTM containing 70×10^5 were prepared and studied for their physicochemical and drug release properties in comparison to their PM counterparts.

4.2 Formulation

DTZ powder (1.2 g) was dissolved in 1.2 g of polysorbate 80 (PS 80) (60 °C, 200 rpm), a non-volatile water-miscible solvent used as a liquid vehicle to form liquid medication phase at a fixed drug:solvent ratio of 1:1 (w:w). An accurately weighed 3.6 g of each PolyoxTM particle size and 3.6 g (1:3), 4.8 g (1:4) and 6 g (1:5) drug: PolyoxTM ratio was separately mixed with 4.24 g (1:3), 5.12 g (1:4) and 6 g (1:5) of lactochem as a carrier and 0.36 g (1:3), 0.48 g (1:4) and 0.6 g (1:5) of the AEROSIL[®] coating material at a constant carrier: coating material ratio of 10:1. Detailed of formulation process was given in (section 2.5). For comparison purpose, conventional PM formulations were also produced. PM formulation contained a mixture of DTZ (1.2 g), 3.6 g PolyoxTM and AEROSIL[®] as seen above with 3.44 g (1:3), 4.32 g (1:4) and 5.2 g (1:5) of lactochem as a carrier. The mixing was performed as described earlier in section 2.5

Accurately weighed samples of each liquisolid 530 mg (1:3), 640 mg (1:4) and 750 mg (1:5) and PM 430 mg (1:3), 540 mg (1:4) and 650 mg (1:5) formulation were separately weighed and then compressed on 8 mm punch and die using a manual tableting machine at a fixed pressure of 2000 psi.

4.3 Results and discussion

4.3.1 Solid state

If the drug interacts with the excipients and the liquid vehicle, the peaks consistent to the functional groups in the drug FT-IR will shift to various wavenumbers compared to spectra of the pure drug and pure excipients (Silverstein *et al.*, 2014). This study was carried out to investigate if there was any chemical interaction between pure DTZ and different size fraction and drug:PolyoxTM ratio within both the LS formulations and their counterpart PM. From Figure 4.1, it can be observed that, LS formulations and PM formulations showed a remarkable change compared to that of commercial drug, DTZ, where a band at 2393 cm⁻¹ was completely disappeared. This confirmed the interaction between dimethylamino group of the DTZ and oxygen of PolyoxTM (Figure 4.1). These results agreed with the findings of (Abd *et al.*, 2012), where DTZ HCl – carbopol formulation showed a complete disappearance of the band at 2393 cm⁻¹ when compared to the commercial DTZ. This confirmed the interaction between dimethylamino group of DTZ and carboxylate group of the polymer. The PXRD patterns of commercial DTZ, LS formulations and PM powders are shown in (Figure 4.2). The diffraction pattern of the commercial DTZ demonstrates that it has a very crystalline solid state in nature, with sharp intensive peaks throughout its pattern. In comparison to the pure drug diltiazem, both the LS formulations and PM powders showed less intensity peaks at 8.10°, 10.12°, 18.30° and 28.10° with the highest intensity at 2θ of 18.33° and 23.57° regardless of their concentration and particle sizes fractions used (Figure 4.2).

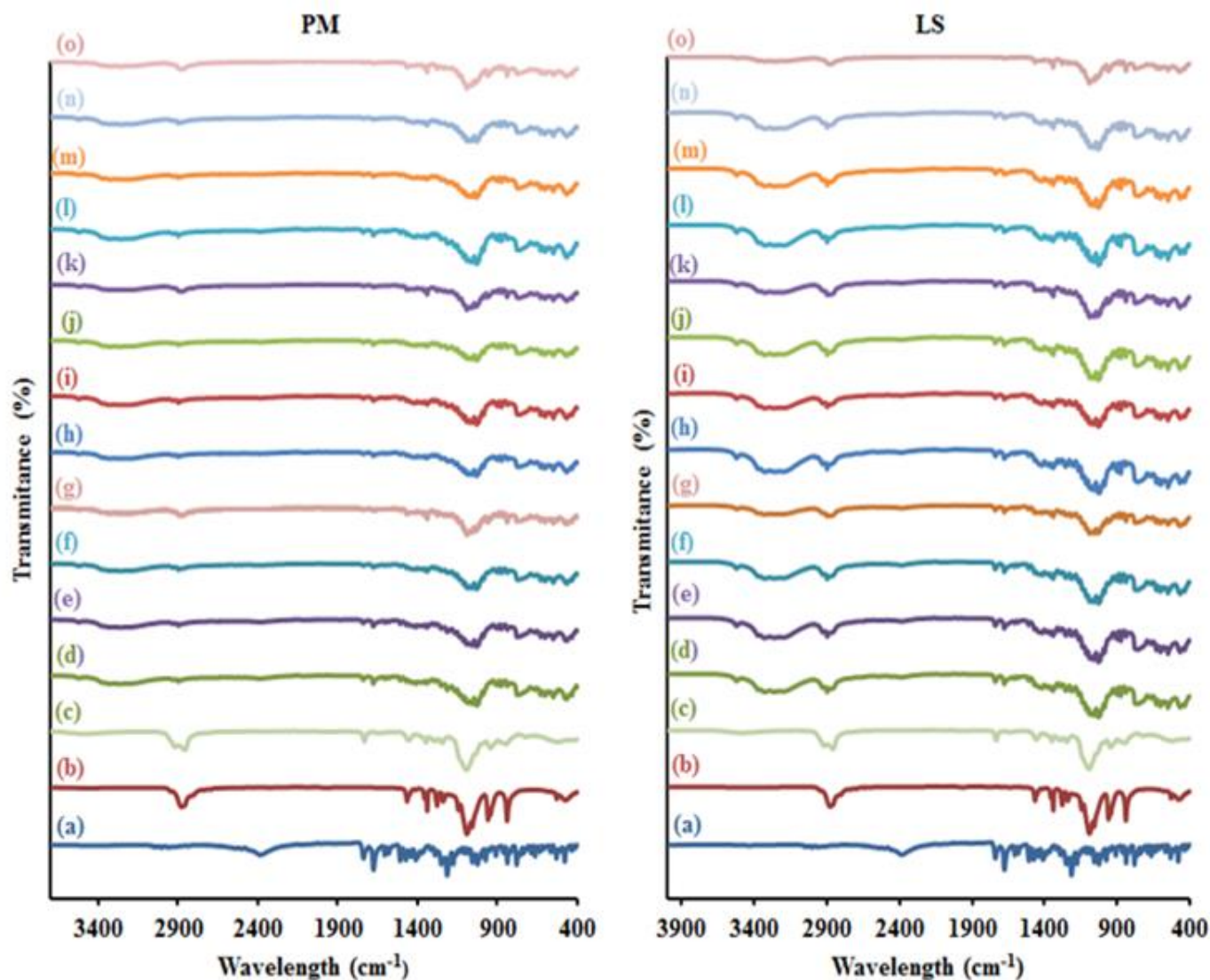


Figure 4.1: FTIR patterns of physical mixture (PM) and liquidolid (LS) formulations containing various grades of PolyoxTM (a) Pure DTZ, (b) PolyoxTM, (c) Polysorbate 80, (d) DTZ-WSR303 >180 (1:3), (e) DTZ-WSR303 150-180 (1:3), (f) DTZ-WSR303 63-150 (1:3), (g) DTZ-WSR303 <63 (1:3), (h) DTZ-WSR303 >180 (1:4), (i) DTZ-WSR303 150-180 (1:4), (j) DTZ-WSR303 63-150 (1:4), (k) DTZ-WSR303 <63 (1:4), (l) DTZ-WSR303 >180 (1:5), (m) DTZ-WSR303 150-180 (1:5), (m) DTZ-WSR303 63-150 (1:5), (o) DTZ-WSR303 <63 (1:5).

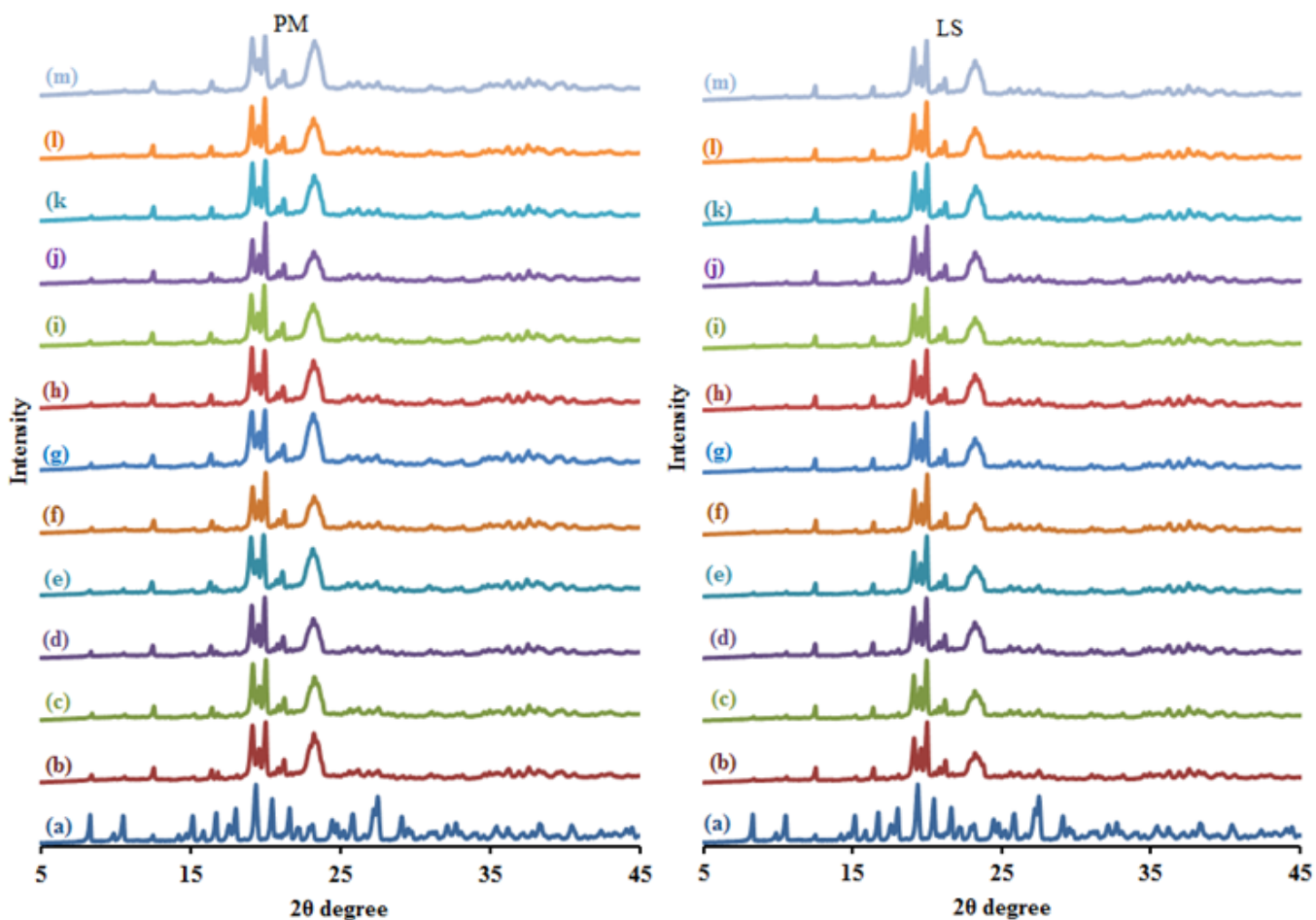


Figure 4.2: PXRD patterns of physical mixture (PM) and liquisolid (LS) formulations containing various grades or Polyox™ (a) Pure DTZ, (b) DTZ–WSR303 >180 (1:3), (c) DTZ–WSR303 150–180 (1:3), (d) DTZ–WSR303 63–150 (1:3), (e) DTZ–WSR303 <63 (1:3), (f) DTZ–WSR303 >180 (1:4), (g) DTZ–WSR303 150–180 (1:4), (h) DTZ–WSR303 63–150 (1:4), (i) DTZ–WSR303 <63 (1:4), (j) DTZ–WSR303 >180 (1:5), (k) DTZ–WSR303 150–180 (1:5), (l) DTZ–WSR303 63–150 (1:5) and (m) DTZ–WSR303 <63 (1:5).

4.3.2 Particle size distribution

The LS formulations and their counterpart PM powders showed the larger particle size fraction (>180 μm) had the widest particle size distribution, whereas smaller particles fractions (<63 μm) had the narrowest distribution i.e., the VMD has increased with increasing the particle size fraction ranging from (<63 μm to >180 μm) irrespective of their drug:Polyox™ ratio used (Table 4.2). This indicates that both the LS formulations and their

counterparts PMs powders fell between the nominal sieve sizes, suggesting that the applied sieving process was satisfactorily efficient. On the other hand, the mean particle size of both the LS formulation was found to be decreasing with an increase in the concentration of drug:PolyoxTM ratio in the case of smaller particle fraction (<63 μm) (Table 4.2).

4.3.3 Powder bulk properties

The bulk densities and tapped densities of both PM and LS formulation powders showed increasing trends with increasing particles size fraction regardless of drug:PolyoxTM ratio (Table 4.1). This indicated that the cohesivity of both PM and LS formulation powders increased with decreasing PolyoxTM particle size fraction. The CI values obtained for both PM powders and LS formulation also showed decreasing trends with decreasing particles size fraction (Table 4.1), indicating better flow properties for the formulations containing smaller particle size distribution than those formulations containing larger particle size distribution in the case of higher concentration. Even though all formulations had CI value higher than 25% confirming to have poor flow properties as indicated in (Table 4.1). Certainly, the major influence in powder flowability is possibly due to the nature and extent of interparticle forces. The high viscosity of non-volatile solvent (PS 80) could be responsible for poorer flow properties of LS formulations when compared to their PMs powders which increases the cohesive properties of the LS powders. The CI value of LS formulations at smaller particles size of PolyoxTM decreased as the PolyoxTM concentration increased (Table 4.1). This indicates that powders containing (1:5) higher concentration have better flow properties than those formulations with lower concentration (1:3 and 1:4). The same trend is demonstrated using PMs Powders.

Table 4.1: Bulk density, tap density and Carr’s index (CI) (mean \pm SD, n = 5) for DTZ–PolyoxTM liquisolid (LS) formulation powders and their physical mixture (PM) counterparts.

Product	Particle size	Bulk density (g/cm ³)		Tapped density (g/cm ³)		CI (%)	
		PM	LS	PM	LS	PM	LS
DTZ-WSR303 (1:3)	<63	0.36 \pm 0.00	0.36 \pm 0.01	0.53 \pm 0.03	0.49 \pm 0.01	32.0 \pm 4.5	31.8 \pm 1.6
DTZ-WSR303 (1:3)	63–150	0.41 \pm 0.00	0.42 \pm 0.00	0.60 \pm 0.01	0.56 \pm 0.01	31.8 \pm 0.4	23.8 \pm 0.7
DTZ-WSR303 (1:3)	150–180	0.44 \pm 0.01	0.44 \pm 0.00	0.61 \pm 0.01	0.64 \pm 0.00	29.0 \pm 1.0	31.4 \pm 0.5
DTZ-WSR303 (1:3)	>180	0.48 \pm 0.01	0.48 \pm 0.00	0.64 \pm 0.00	0.67 \pm 0.00	25.0 \pm 1.0	25.2 \pm 1.1
DTZ-WSR303 (1:4)	<63	0.37 \pm 0.00	0.36 \pm 0.01	0.52 \pm 0.00	0.49 \pm 0.01	30.4 \pm 1.3	29.8 \pm 3.7
DTZ-WSR303 (1:4)	63–150	0.42 \pm 0.01	0.41 \pm 0.00	0.57 \pm 0.01	0.55 \pm 0.01	26.8 \pm 0.8	25.4 \pm 1.3
DTZ-WSR303 (1:4)	150–180	0.44 \pm 0.00	0.45 \pm 0.00	0.62 \pm 0.01	0.62 \pm 0.00	29.8 \pm 1.1	28.4 \pm 0.9
DTZ-WSR303 (1:4)	>180	0.47 \pm 0.01	0.47 \pm 0.01	0.64 \pm 0.01	0.63 \pm 0.01	26.8 \pm 0.8	25.4 \pm 1.6
DTZ-WSR303 (1:5)	<63	0.44 \pm 0.00	0.37 \pm 0.00	0.62 \pm 0.00	0.52 \pm 0.00	29.7 \pm 0.5	28.0 \pm 0.02
DTZ-WSR303 (1:5)	63–150	0.46 \pm 0.01	0.41 \pm 0.00	0.59 \pm 0.01	0.57 \pm 0.01	30.8 \pm 1.1	30.0 \pm 1.8
DTZ-WSR303 (1:5)	150–180	0.47 \pm 0.01	0.45 \pm 0.00	0.66 \pm 0.01	0.63 \pm 0.01	32.2 \pm 1.8	31.8 \pm 1.6
DTZ-WSR303 (1:5)	>180	0.49 \pm 0.00	0.47 \pm 0.02	0.70 \pm 0.00	0.68 \pm 0.03	34.8 \pm 0.8	33.2 \pm 1.1

4.3.4 Hardness

The hardness of both PM and LS tablets showed increasing trends with both decreasing PolyoxTM particle size and increasing drug:PolyoxTM ratio (Figure 4.3a and 4.3b). For example, the hardness of LS tablet containing DTZ:PolyoxTM at a ratio of 1 : 5 (w:w) increased from 14.2 N to 31.6 N when the mean particle size of PolyoxTM decreased from 245 μ m to 84.7 μ m (Table 4.2). The results are in agreement with those published by (Shojaee *et al.*, 2015) for THP matrices. The hardness of THP–PolyoxTM matrices decreased from 52.0 N to 45.0 N as the PolyoxTM particle size fraction increased from (20 to 45) μ m to (180 to 425) μ m. This could be due to a difference in the surface area of particles available for bonding. Smaller particles show a higher ratio of surface/volume compared to larger particles, resulting

in an increase in the number of contact points between particles and thus better bounding. PM tablets recorded higher hardness values in comparison to their LS formulation. This was due to the presence of the polysorbate 80 in the LS tablets which hinder the formation of the interparticle bonds that are the main reason for the higher hardness obtained in PM tablets. [Khanfar *et al.*, 2014](#), also reported similar conclusion, where all LS tablets showed weaker hardness than their counterpart conventional tablets. A trend of reasonably increasing hardness was also observed from 1:3 to 1:5 DTZ:PolyoxTM ratio of the resultant tablets ([Figure 4.3a and 4.3b](#)). For example, in the case of PolyoxTM with the smallest particle size fraction (<63 µm), the hardness of LS tablets increased from 10.1N to 30.6N with increasing DTZ:PolyoxTM ratio from 1:3 to 1:5 ([Figure 4.3b](#)). This could be attributed to a relatively higher concentration of PolyoxTM, and therefore less DTZ particles, in the formulations that give more available bonding place beside physically combined polymer chains. In comparison to their PM formulation tablets, LS tablets also demonstrated lower hardness regardless their drug to polyoxTM ratio used.

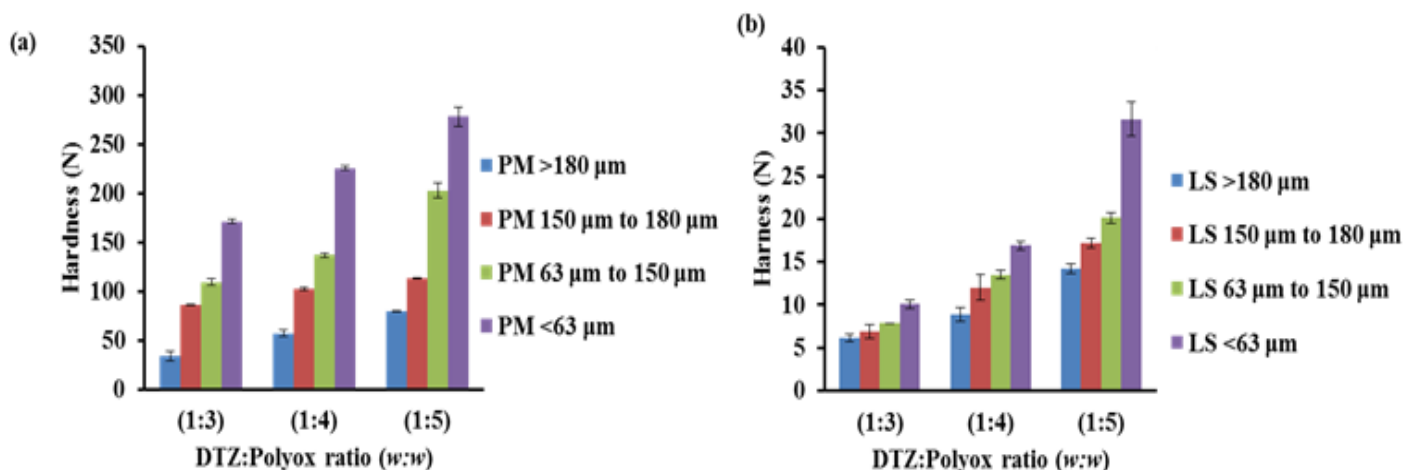


Figure 4. 3: Hardness of DTZ from (a) physical mixture (PM) and (b) liquisolid (LS) matrix tablets containing various particle size distributions and ratio of Polyox™.

4.4 Drug release studies

4.4.1.1 Effect of Polyox™ particle size fraction

The effect of four different particle size fractions of Polyox™ on the release rate of DTZ from both LS and PM tablets matrices were investigated. The results showed that all formulations enabled prolonged drug release irrespective of the Polyox™ particle size fraction used (Figures 4.4a–4.4f). The release of DTZ from LS tablets showed mostly decreasing trends with decreasing Polyox™ particle size distribution. This can be explained as, for the same quantity of polymer, a decrease of polymer particle size statistically increased the number of particles and therefore increased the number of contact points available for binding of the swelling particle. This would support the structure of a continuous gel layer that would delay drug release, as well as hinder more water penetrating into the tablet core. Additionally, a smaller polymer particle size distribution would provide a lower pressure differential expansion on swelling when related to a larger particle. Therefore, the smaller polymer particles were less liable to cause disintegration of the matrix tablets compared to larger particles. The above effects explain the lower release rate with decreasing Polyox™ particle size. This was in complete agreement with the findings obtained by (Velasco *et al.*, 1999;

Campos-Aldrete and Villafuete-Robles, 1997 and Mitchell *et al.*, 1993). They reported that the effect of particle size on the release rate of a drug from tablet matrices showed that the dissolution rate generally decreased as the particle size distribution decreased from larger particle to smaller ones. The tablets containing smaller particle size fractions have greater surface area related to similar weights of fractions with a larger particle size fraction. This larger surface area enables for better polymer–water contact thereby improving the overall rate by which absolute polymer hydration occur (Cahyadi *et al.*, 2011). At 1:3 and 1:4 drug:PolyoxTM (*w:w*) ratios, and regardless of PolyoxTM particle size distribution, LS formulations produced statistically similar release profiles compared to conventional formulation tablets (Figure 4.4a–4.4e). From the above findings, particle size fraction is known as an important variable. Decreasing PolyoxTM ratio to 1:3 and 1:4, exert similarities for all PolyoxTM particle size fraction on DTZ release profile. This was supported by similarity factor results where f_2 values for PolyoxTM particle size are greater than 50 which indicate that the dissolution profiles were similar. The influence of PolyoxTM particle size was significantly reduced when the PolyoxTM ratio increased to 1:5. The release profiles shown in Figure 4.4 can be correlated with the hardness (Figure 4.3). Comparing Figure 4.4 and Figure 4.3 shows that there should be a direct relationship between the hardness and drug release. However, LS formulation tablets produced significantly slower release profiles compared to conventional formulation tablets in the case of higher concentration of drug:PolyoxTM ratio 1:5 (*w:w*) ($f_2 < 50$). This indicated that the performance of PolyoxTM as a retardant agent in LS tablets is better than it is in the PM compacts. The results were also supported by the dissolution parameters that showed LS compacts to have lower DEs. For instance, the DE value of fractions from (<63 μm to >180 μm) was ($19.4\% \pm 3.4$ to $36.2\% \pm 0.2$) compared to the PM compacts (DE = $27.0\% \pm 1.4$ to $39.0\% \pm 0.5$). Similar conclusions could be drawn when considering MDT values (Table 4.2). An interesting trend was obtained when plotting the DE

of DTZ obtained from PM and LS formulations against the PolyoxTM particle size faction. DE increased with increasing PolyoxTM particle size faction regardless of the drug to PolyoxTM ratio used (Figure 4.5). This trend indicated that the ability of PM and LS formulations to produce slower drug release with decreasing PolyoxTM particle size faction.

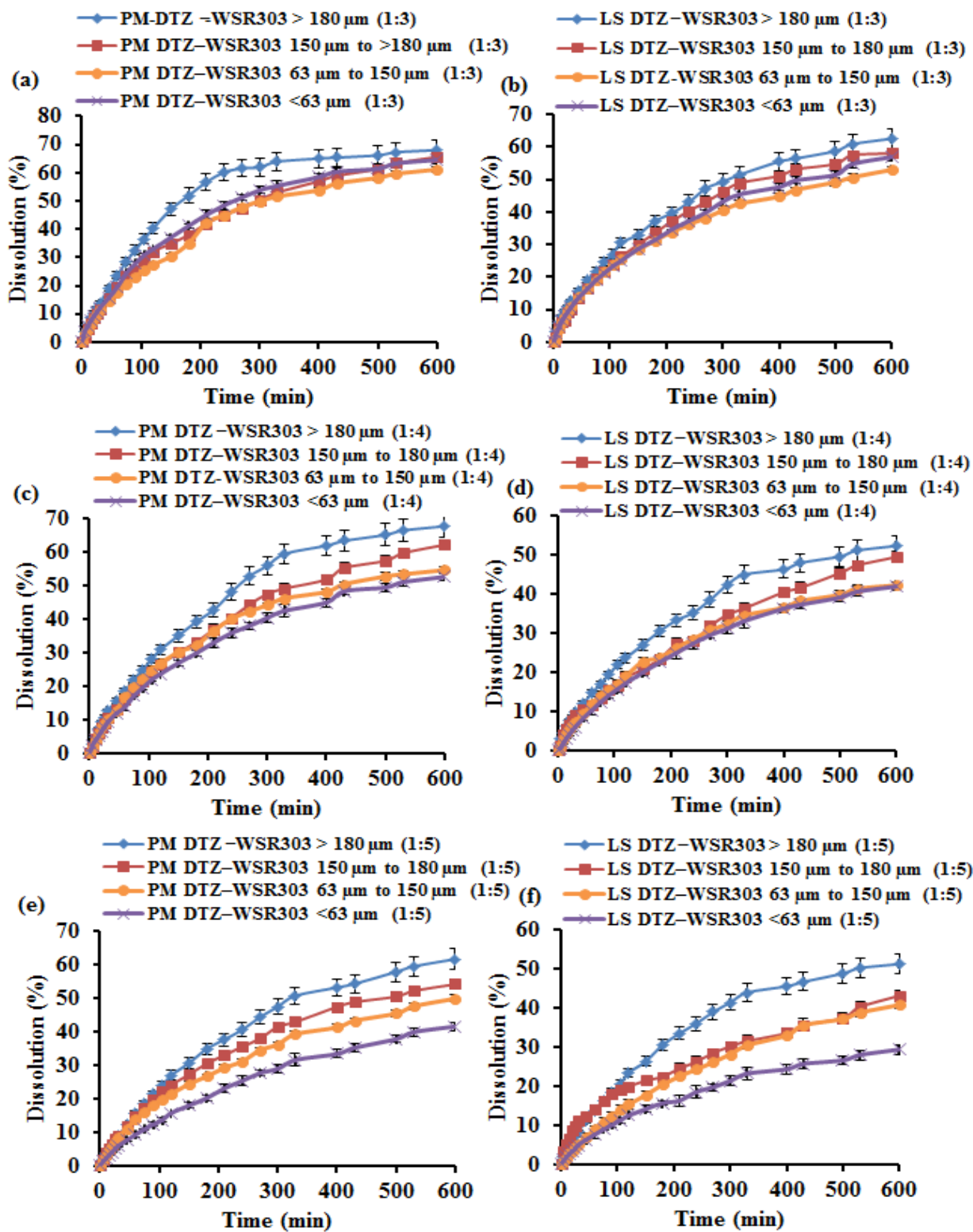


Figure 4.4: Physical mixture (PM) and liquisolid (LS) matrix containing Polyoxes at different DTZ:PolyoxTM concentration, i.e. (a and b) 1:3, (c and d) 1:4, (e and f) 1:5 (w:w).

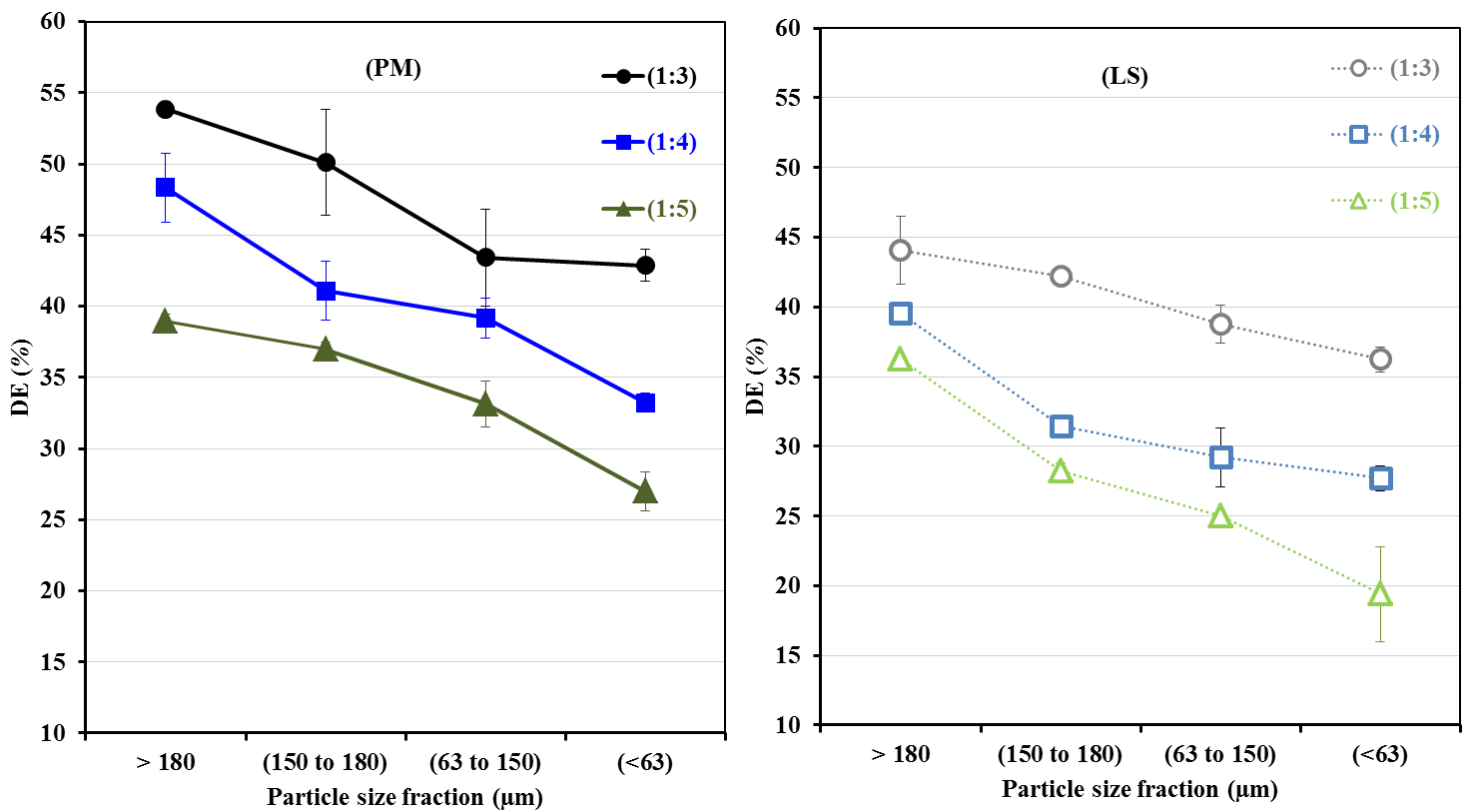


Figure 4.5: Dissolution efficiency (DE, %) of diltiazem HCl (DTZ) of liquisolid (LS) and (PM) formulations in relation to PolyoxTM particle size fraction.

4.4.1.2 Effect of PolyoxTM concentration

Four various particle size fractions of PolyoxTM were chosen to investigate the influence of PolyoxTM concentration (1:3, 1:4 and 1:5 w:w) on DTZ release. The results obtained from both LS formulations and PM tablets showed the release rate of DTZ became slower with increasing the concentration of drug:PolyoxTM ratio (from 1:3 to 1:5 w:w) i.e., the dissolution rate of DTZ to decrease with increasing the concentration of drug:PolyoxTM ratio, regardless of their PolyoxTM particle size fractions used, which can be attributed to the greater binding of the drug with the PolyoxTM in the case of higher concentration (Figure 4.6). This may be explained as the concentration of the polymer increased, tablet matrix resulted in rapid hydration and formation of a stable gel-like structure of high viscosity and low-swelling

degree that acted as a barrier for the penetration medium hence retarding the diffusion of DTZ from the swollen PolyoxTM. This was in complete agreement to the findings obtained by (Ebube *et al.*, 1997; Ford *et al.*, 1987b; Nellore, 1998; Perez-Marcos *et al.*, 1995). Such decrease in drug release rate is not statistically different in the case of (>180 μm and 150 μm – 180 μm) larger PolyoxTM particle size fraction (Figure 4.6a–4.6f). Statistical analysis confirmed that DTZ release profiles obtained from LS and PM tablets containing (1:3 to 1:5 w/w) drug:PolyoxTM ratio was significantly different ($f_2 < 50$), in the case of (<63 μm) smaller particle size fraction. The swelling studies (i.e. water uptake) of both LS and PM tablets decrease as the concentration (from 1:3 to 1:5 w:w) of drug (DTZ) to PolyoxTM ratio increased when smaller particle size was used (Figure 4.7). This may be attributed to the slow erosion of the gelled layer from the tablets containing higher ratio (1:5) PolyoxTM. In general, slower drug releases were obtained in LS tablets in comparison to the PMs tablets (Figure 4.6a–4.6h).

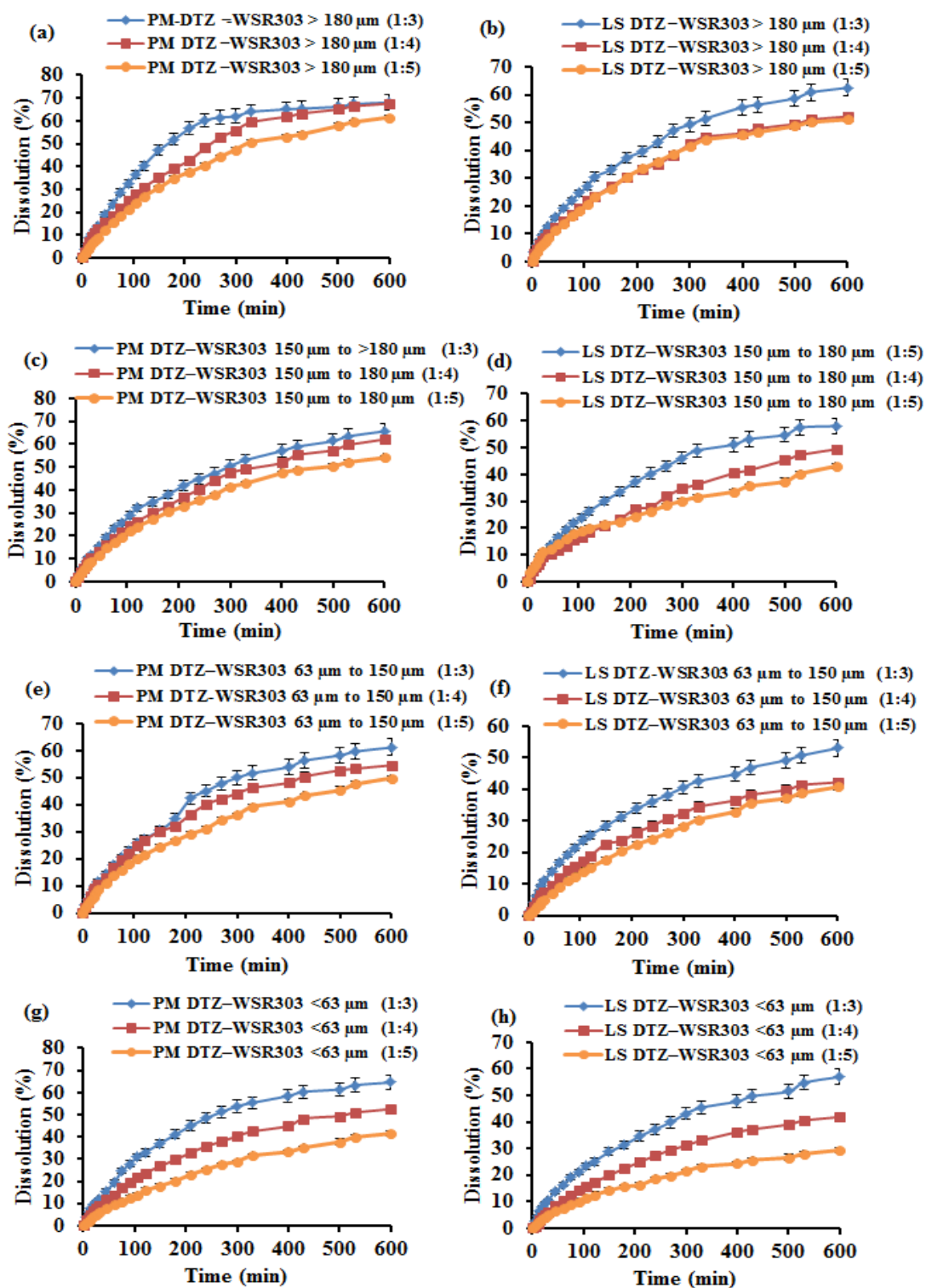


Figure 4.6: Physical mixture (PM) and liquisolid (LS) matrix containing Polyoxes concentration at different PolyoxTM particles size distribution, i.e. (a and b) >180 μm ; (c and d) 150 to 180 μm ; (e and f) 63 to 150 μm and (g and h) < 63 μm respectively.

When plotting the DE of DTZ from both the LS and PM formulation tablets against their PolyoxTM ratio, the DE decreased as the drug to PolyoxTM ratio increased regardless of their PolyoxTM particle size fraction used. These indicate the ability of PolyoxTM with higher ratio to produce slower drug release than those matrices containing PolyoxTM with lower ratio (Figure 4.8). For instance, at smaller particle size (<63), the DE value of 1.3 DTZ:PolyoxTM ratio was (36.2 ± 0.90) whereas this value decreased to (19.4 ± 3.40) for matrices with DTZ:PolyoxTM ratio (1:5 w:w). Similar consideration was obtained as seen with the PM tablets (Table 4.2). DEs value is consistent with dissolution behaviours confirming that the drug release rate from all the particle size used is slower in LS formulation tablets than their counterparts PM tablets (Figure 4.8). PolyoxTM ratio was known to be very useful due to its effect on the influences of PolyoxTM particle size distribution. It was found that retaining PolyoxTM ratio 1:5 was helpful in developing a robust ER matrices system.

Table 4.2: Dissolution efficiency (DE), mean dissolution rate (MDT), mean dissolution rate (MDR), VMD and in vitro release kinetic parameters; *n* value of diltiazem HCl obtained for liquisolid (LS) formulations containing various particle size and ratio in comparison to their physical mixture (PM) counterparts. The results are expressed as the mean \pm SD.

Formulation (s)	Particle size	DE (%)		MDT (min ⁻¹)		MDR (min ⁻¹)		VMD (μm)		n value	
		PM	LS	PM	LS	PM	LS	PM	LS	PM	LS
DTZ–WSR303 (1:3)	<63	42.9 \pm 1.10	36.2 \pm 0.90	170 \pm 12.0	185 \pm 1.63	0.17 \pm 0.01	0.17 \pm 0.00	61.3 \pm 25.0	99.7 \pm 11.3	0.633	0.634
DTZ–WSR303 (1:3)	63–150	43.4 \pm 3.42	38.8 \pm 1.39	174 \pm 8.17	165 \pm 15.2	0.19 \pm 0.01	0.20 \pm 0.04	98.2 \pm 6.52	110 \pm 17.4	0.650	0.704
DTZ–WSR303 (1:3)	150–180	50.1 \pm 3.70	42.2 \pm 0.03	158 \pm 40.6	178 \pm 1.83	0.20 \pm 0.03	0.18 \pm 0.01	113 \pm 2.31	145 \pm 3.46	0.735	0.709
DTZ–WSR303 (1:3)	>180	53.8 \pm 0.57	44.1 \pm 2.45	125 \pm 2.91	166 \pm 10.1	0.25 \pm 0.00	0.24 \pm 0.01	189 \pm 4.62	253 \pm 4.73	0.779	0.581
DTZ–WSR303 (1:4)	<63	33.2 \pm 0.66	27.7 \pm 0.92	188 \pm 4.13	189 \pm 6.14	0.14 \pm 0.01	0.11 \pm 0.00	95.8 \pm 9.99	90.6 \pm 4.37	0.635	0.658
DTZ–WSR303 (1:4)	63–150	39.2 \pm 1.40	29.2 \pm 2.10	190 \pm 17.7	183 \pm 0.23	0.13 \pm 0.06	0.12 \pm 0.01	85.1 \pm 3.34	121 \pm 5.57	0.747	0.646
DTZ–WSR303 (1:4)	150–180	41.1 \pm 2.09	31.5 \pm 0.50	191 \pm 0.60	176 \pm 7.50	0.14 \pm 0.01	0.17 \pm 0.02	169 \pm 85.1	151 \pm 0.58	0.696	0.670
DTZ–WSR303 (1:4)	>180	48.3 \pm 2.39	39.6 \pm 0.23	176 \pm 24.2	170 \pm 0.78	0.18 \pm 0.02	0.15 \pm 0.00	204 \pm 7.21	262 \pm 29.6	0.686	0.648
DTZ–WSR303 (1:5)	<63	27.0 \pm 1.39	19.4 \pm 3.40	206 \pm 1.58	197 \pm 5.05	0.16 \pm 0.01	0.12 \pm 0.01	57.1 \pm 2.04	84.7 \pm 6.2	0.709	0.781
DTZ–WSR303 (1:5)	63–150	33.1 \pm 1.60	25.0 \pm 0.33	195 \pm 5.02	206 \pm 23.6	0.14 \pm 0.00	0.11 \pm 0.02	89.7 \pm 5.04	118 \pm 5.13	0.703	0.780
DTZ–WSR303 (1:5)	150–180	37.0 \pm 0.48	28.2 \pm 0.60	191 \pm 0.45	183 \pm 1.32	0.15 \pm 0.00	0.14 \pm 0.01	125 \pm 0.58	147 \pm 2.65	0.676	0.696
DTZ–WSR303 (1:5)	>180	39.0 \pm 0.50	36.2 \pm 0.22	193 \pm 1.30	178 \pm 2.14	0.16 \pm 0.01	0.12 \pm 0.01	187 \pm 2.08	245 \pm 4.36	0.735	0.635

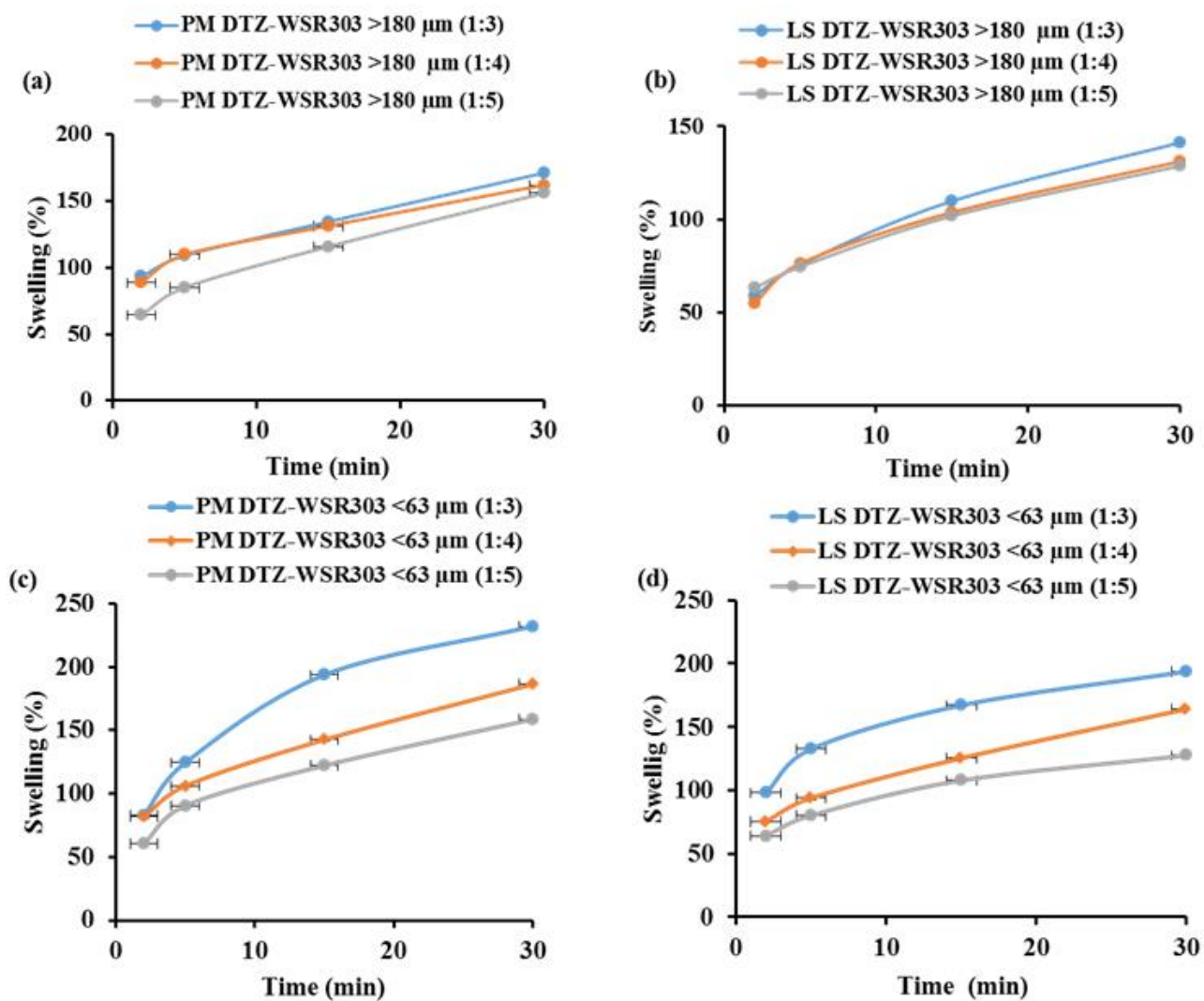


Figure 4.7: Percent swelling of physical mixture (PM) and liquisolid (LS) formulation tablets containing Polyoxes concentration at different PolyoxTM particles size fraction i.e. (a and b) >180 and (c and d) <63.

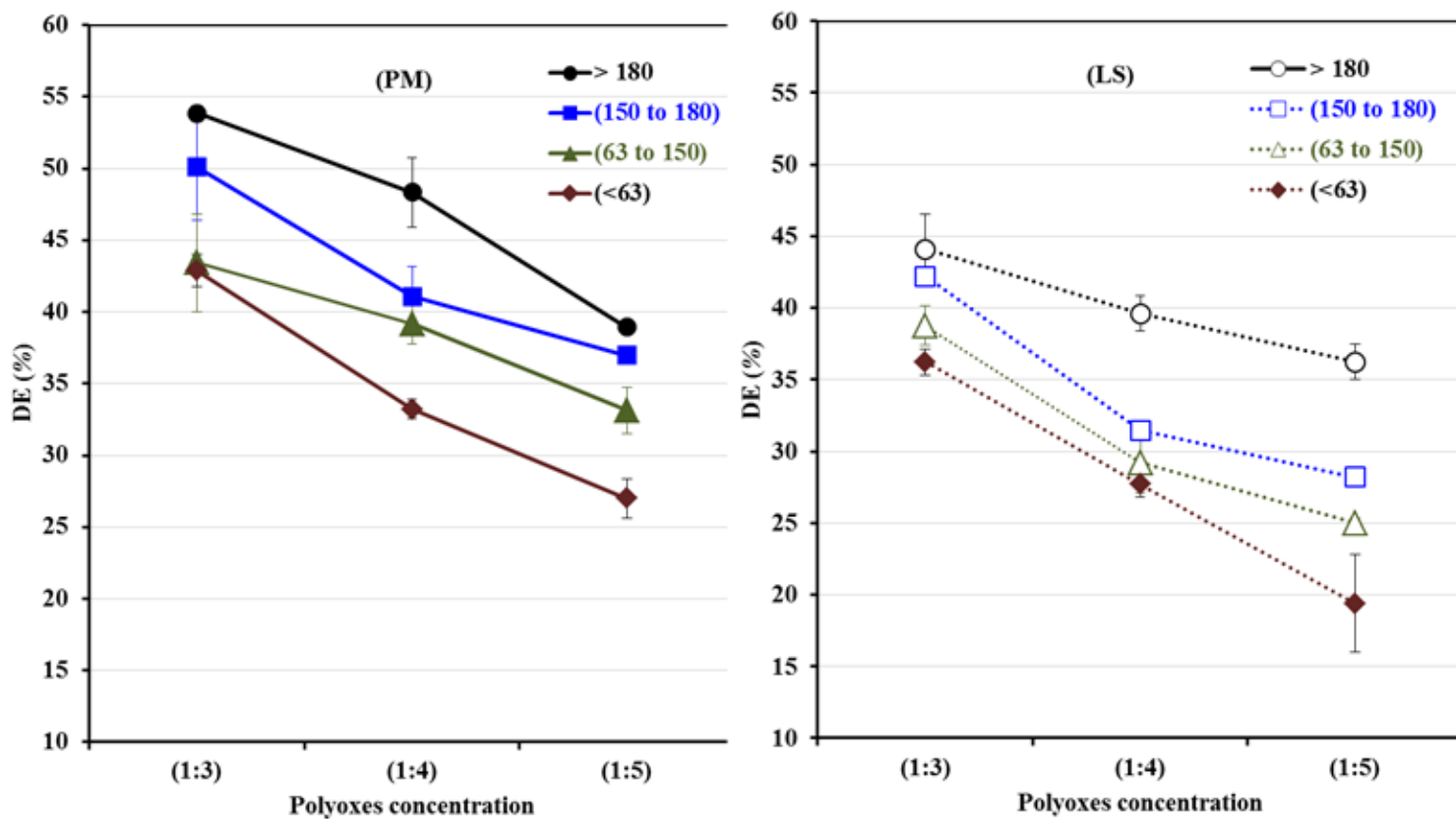


Figure 4.8: Dissolution efficiency (DE, %) of diltiazem HCl (DTZ) of liquisolid (LS) and (PM) formulations in relation to PolyoxTM concentration.

The mechanism of drug release from the matrix tablets was analysed and the dissolution data were fitted to Korsmeyer-Peppas kinetic models (Table 4.2). In this study, the drug release from both the LS and their PMs tablet from various particle sizes were fitted into Korsmeyer-Peppas equation which indicates the combined influence of diffusion and erosion mechanisms for drug release (Korsmeyer, *et al.*, 1983). The n values from LS formulations varied between 0.581 and 0.781, corresponding to an anomalous (non-Fickian) diffusion mechanism, which suggests that diffusion of the drug and erosion (polymer matrix relaxation) both contribute to the overall drug release mechanisms. It was also noticed that the n values obtained from LS

formulations increase from (0.635 to 0.781) as DTZ:PolyoxTM concentration increased from (1:3 to 1:5 w:w), indicating a trend of gradual drug release in the case of smaller PolyoxTM particle size (<63). A similar conclusion was shown in the case of PM tablets.

4.5 Conclusion

The results in this study showed that LS formulation and their counterpart PM with smaller particle size fractions of PolyoxTM (<63 μm) had a slowest DTZ release behaviour than the larger particles fraction (150–180 μm). Decreasing PolyoxTM ratio to 1:3 and 1:4, exert similarities for all PolyoxTM particle size fraction on DTZ release profile. The influence of PolyoxTM particle size was significantly reduced when the PolyoxTM ratio increased to 1:5. The results also showed significant retardation properties of drug release with high concentration of drug:PolyoxTM (1:5) when compared to lower concentration (1:3) in the case of small particles size fraction used. The hardness of DTZ tablets from both the LS formulation and their counterpart PM were also shown an increasing trend with decreasing PolyoxTM particle size and increasing concentration. Therefore, smaller PolyoxTM particle size fraction and higher concentration of DTZ:PolyoxTM is an important formulation factor that should be optimised to improve the desirability of sustained release formulations prepared using the LS technique. LS tablets with better mechanical and slower drug release properties can be produced using smaller size fractions of PolyoxTM. In conclusion, concentration and particle size distribution of PolyoxTM are important variables in determining the release of a highly soluble drug from PolyoxTM-based LS formulations.

5 CHAPTER 5: EFFECT OF AEROSIL® GRADE

5.1 Introduction

Colloidal silicon dioxide (AEROSIL[®]) is broadly used as glidants in the production of capsules, tablets and powders (Müller *et al.*, 2008). As its agglomerates, as well as its primary particles, are very small, they are completely adsorbed at surfaces of larger particles, e.g., corn starch (Meyer and Zimmermann, 2004). Though, due to the very fine particles that possess a strong tendency to produce segregation, agglomerates following simple mixing with different excipients can also transpire because of variations in the density. Therefore, proper dispersion of the glidants is a very relevant concern for achieving flowability and uniform coating improvement (Yang *et al.*, 2005). AEROSIL[®] was introduced in both LS formulations and PM as a coating material to improve the flow of model drugs such as Ketoprofen (Deore *et al.*, 2009) Due to its large surface area, high porosity, and unique adsorption properties, AEROSIL[®] has also been successfully used as a dispersing agent to increase the dissolution rate of sparingly soluble drug, Polythiazide (Sheth and Jarowski, 1990). AEROSIL[®] is one of the commercially accessible coating material in pharmaceutical production which is formed by high-temperature hydrolysis of silicon tetrachloride in an oxygen gas flame. It consists completely of a highly amorphous, dispersed and submicroscopic silica whose features can be controlled by suitable reaction states and surface changes (Morefield and Seyer, 2003). These changes do not affect the silica content or amorphous form. However, surface areas, hydrophilic nature, particle size and densities are influenced. Siloxane and silanol groups are generally situated on the surface of AEROSIL[®] particles and the latter is responsible for the hydrophilic behaviour unless they are bound to proper hydrophobic compounds. In particular, hydrophilic AEROSIL[®] shown by a number which refers to the specific surface area (m²/g), for example, AEROSIL[®] X50, AEROSIL[®] 130, AEROSIL[®] 150, AEROSIL[®] 200, etc. Nevertheless, the influence of SiO₂ commercial grade on the mechanical and drug release properties of LS formulations has not been reported previously. The aim of this research was

therefore to investigate the influence of various AEROSIL[®] grades, namely AEROSIL[®] OX50 (hydrophilic, 35–65 m²/g), AEROSIL[®] 130 (hydrophilic, 105–155 m²/g), AEROSIL[®] 200 (hydrophilic, 175–225 m²/g), and AEROSIL[®]R812 (hydrophobic, 230–290 m²/g), on the mechanical and drug release properties of LS Polyox[™]-based formulations containing a model high soluble drug, DTZ, in comparison to their PM counterparts.

5.2 Formulation

The solid phase consisted of Polyox[™] powder (6 g), each grade of AEROSIL[®] contain (0.6 g), and lactose (5.2 g) in the case of PM formulations and 6.0 g in the case of LS formulations), whereas the liquid phase consisted of commercial DTZ powder dispersed in polysorbate 80 (PS 80) (60 °C, 200 rpm) at a drug:solvent ratio of 1:1 (w:w). Detailed of formulation process was given in [section 2.5](#).

Accurately weighed samples of each liquisolid (750 mg) and PM (650 mg) formulation were separately weighed and then compressed on 8 mm punch and die using a manual tableting machine at a fixed pressure of 2000 psi.

5.3 Results and discussion

5.3.1 Solid state

This study was carried out to investigate if there is any chemical interaction between pure DTZ and different AEROSIL[®] surface area in both the LS formulations and PM powders. No significant changes were also observed in the FT-IR spectra of LS formulations in comparison to their PM counterparts ([Figure 5.1](#)). Such observations indicated that virtually complete recrystallization of DTZ occurred during the preparation of liquisolid formulations. The results also ruled out the existence of significant drug-exciipient interaction within both LS and PM ([Figure 5.1](#)). The PXRD patterns of commercial DTZ, LS formulations and PM powders are shown in ([Figure 5.2](#)). The diffraction pattern of the commercial DTZ

demonstrates that it has a very crystalline solid state in nature, with sharp intensive peaks throughout its pattern. The XRD pattern of AEROSIL[®] alone appears to be amorphous which tend to agree with [Morefield and Seyer, 2003](#) as state in the introduction above. The same peaks were observed from both LS formulations and PM powders, regardless of their surface area ([Figure 5.2](#)).

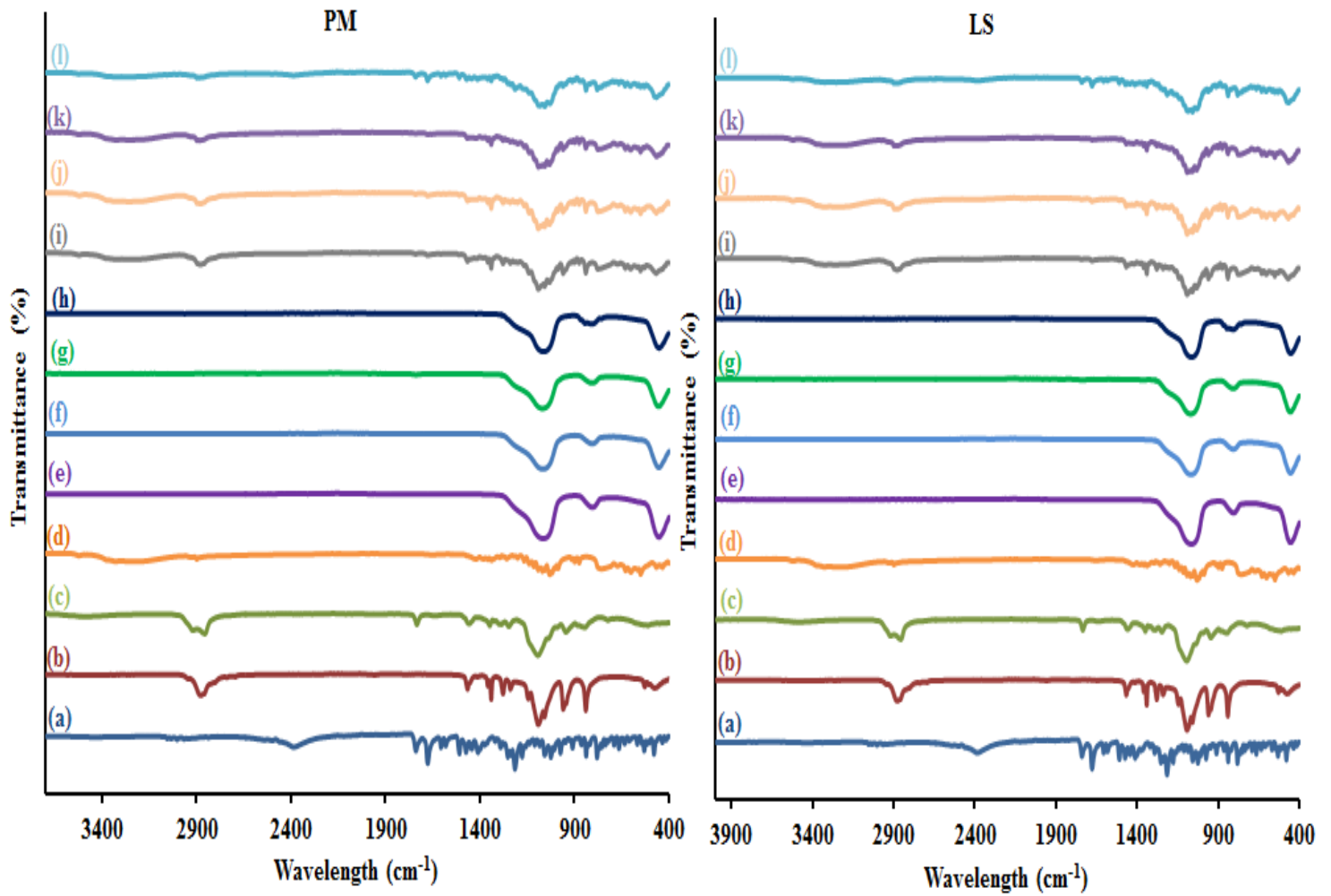


Figure 5.1: FTIR patterns of physical mixture (PM) and liquisolid (LS) formulations containing various grades or surface area (i.e. (a) Pure DTZ, (b) Polysorbate 80, (c) PolyoxTM, (d) Pure lactose, (e) Pure AEROSIL[®] OX50, (f) Pure AEROSIL[®] 130, (g) Pure AEROSIL[®] 200, (h) Pure AEROSIL[®] R812), (i) AEROSIL[®] OX50, (j) AEROSIL[®] 130, (k) AEROSIL[®] 200, (l) AEROSIL[®] R812).

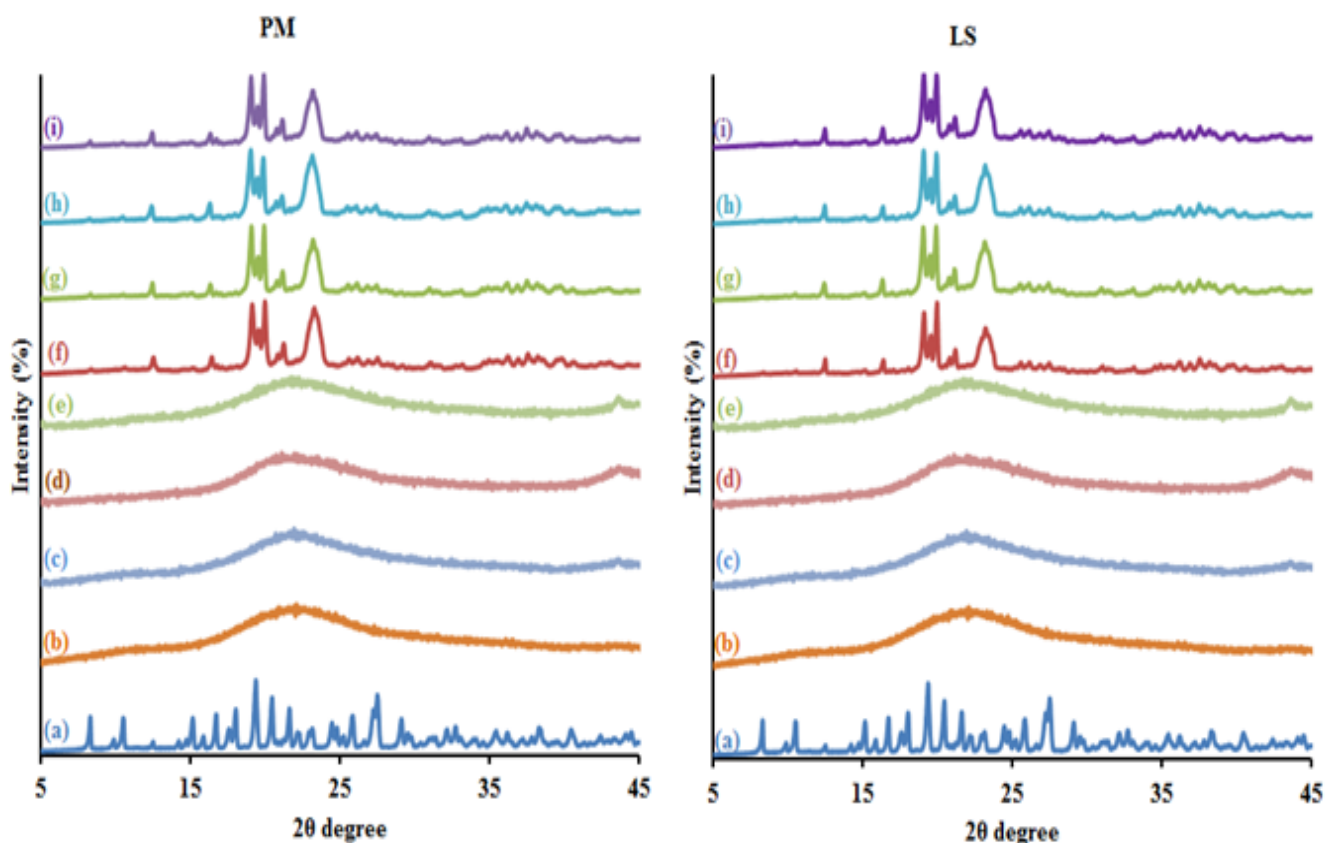


Figure 5.2: PXRD patterns of physical mixture (PM) and liquidolid (LS) formulations containing various grades or PolyoxTM (a) Pure DTZ, (b) Pure AEROSIL[®] OX50, (c) Pure AEROSIL[®] 130, (d) Pure AEROSIL[®] R812, (e) Pure AEROSIL[®] 200), (f) AEROSIL[®] OX50, (g) AEROSIL[®] 130, (h) AEROSIL[®] 200), (i) AEROSIL[®] R812.

5.3.2 Particle size distribution

The effect of four different AEROSIL[®] surface areas on the PSD from both LS formulations and PM powders was investigated. The results showed an increase in the AEROSIL[®] grade containing different surface areas from (65 m²/g to 290 m²/g) generally leads to a reduction in PSD. The widening of the particle size distribution was regarded as an indication of particle breakdown. Formulations containing AEROSIL[®] OX50 within both PM and LS formulations had the lowest VMD value than those formulations containing AEROSIL[®] 130, 200 and R812 (Table 5.1). This may be caused by the smaller particle size which possessed high cohesion force leading to aggregation. LS formulations produced significantly higher PSDs compared

to their PM counterparts. SEM depicted pictures showed less spherical and mostly irregular particles in PM powders which interlock with each other increasing the cohesive strength and hence friction, whereas the LS formulations have mostly spherical powders which generally flow better than PM powders (Figure 5.3). Spherical particles provide fewer contact points between neighbouring particles as compared to irregular particles, therefore, spherical particles cause less friction and hence assist in flow indicating that the flowability improves as the particles become more spherical. In general AEROSIL[®] R812 (hydrophobic, 230–290 m²/g) were found to be spherical in both the LS formulations and PM powders (Figure 5.3).

Table 5.1: Particle size distribution (i.e. particle size at 10% ($d_{10\%}$), 50% ($d_{50\%}$), 90% ($d_{90\%}$), volume mean diameter (VMD), and span; mean \pm SD, n = 3) of DTZ–PolyoxTM containing various AEROSIL[®] surface area from liquisolid (LS) formulation powders in comparison to their physical mixture (PM) counterparts.

Product (s)	Surface area (m ² /g)	$d_{10\%}$		$d_{50\%}$		$d_{90\%}$		VMD (μ m)		Span	
		PM	LS	PM	LS	PM	LS	PM	LS	PM	LS
AEROSIL[®] 50	65	10.9 \pm 0.2	56.1 \pm 1.4	42.2 \pm 0.9	40.0 \pm 0.3	135.0 \pm 8.8	94.5 \pm 1.5	57.1 \pm 2.0	84.7 \pm 6.2	1.6 \pm 0.2	2.2 \pm 0.1
AEROSIL[®] 130	155	53.3 \pm 6.1	393.0 \pm 43.0	650.0 \pm 39.5	725.7 \pm 0.3	1126.7 \pm 25.2	1200.0 \pm 96.4	641.0 \pm 24.2	750.3 \pm 65.2	1.2 \pm 0.0	1.7 \pm 0.1
AEROSIL[®] 200	225	40.8 \pm 13.2	322.0 \pm 21.1	577.3 \pm 29.4	639.3 \pm 26.3	1083.3 \pm 37.9	1083.3 \pm 34.0	560.7 \pm 42.5	664.7 \pm 31.2	1.1 \pm 0.2	1.6 \pm 0.1
AEROSIL[®] R812	290	62.2 \pm 12.7	51.4 \pm 27.5	564.7 \pm 24.9	710.6 \pm 59.5	1069.7 \pm 33.1	1453.3 \pm 43.0	564.7 \pm 46.3	734.7 \pm 90.2	2.0 \pm 0.1	1.8 \pm 0.0

5.3.3 Powder density

The PM formulation tablets produced lower bulk properties and higher Carr's Index (CI) values than LS powders (Table 5.1). These indicate that PM powders have fewer average points of physical interaction among particles compared to LS formulations. The reason for this behaviour could be due to mechanical interlocking between adjacent particles found in PM powders than LS formulations. The CI values from PM and LS formulations showed decreasing trend with an increase in their AEROSIL[®] surface areas which indicate powders containing AEROSIL[®] grade with higher surface area have better and free-flowing behaviour than those containing lower surface area whereas LS formulations produced less than 25 CI value (Table 5.1), indicating acceptable values. In comparison to the LS powders, PM formulations produced higher CI values which indicate they have poorer flow properties compared to LS formulations. Additionally, matrices containing AEROSIL[®] R812 (hydrophobic, 290 m²/g) also shown acceptable CI values in both the LS powder and PM formulations (Table 5.1).

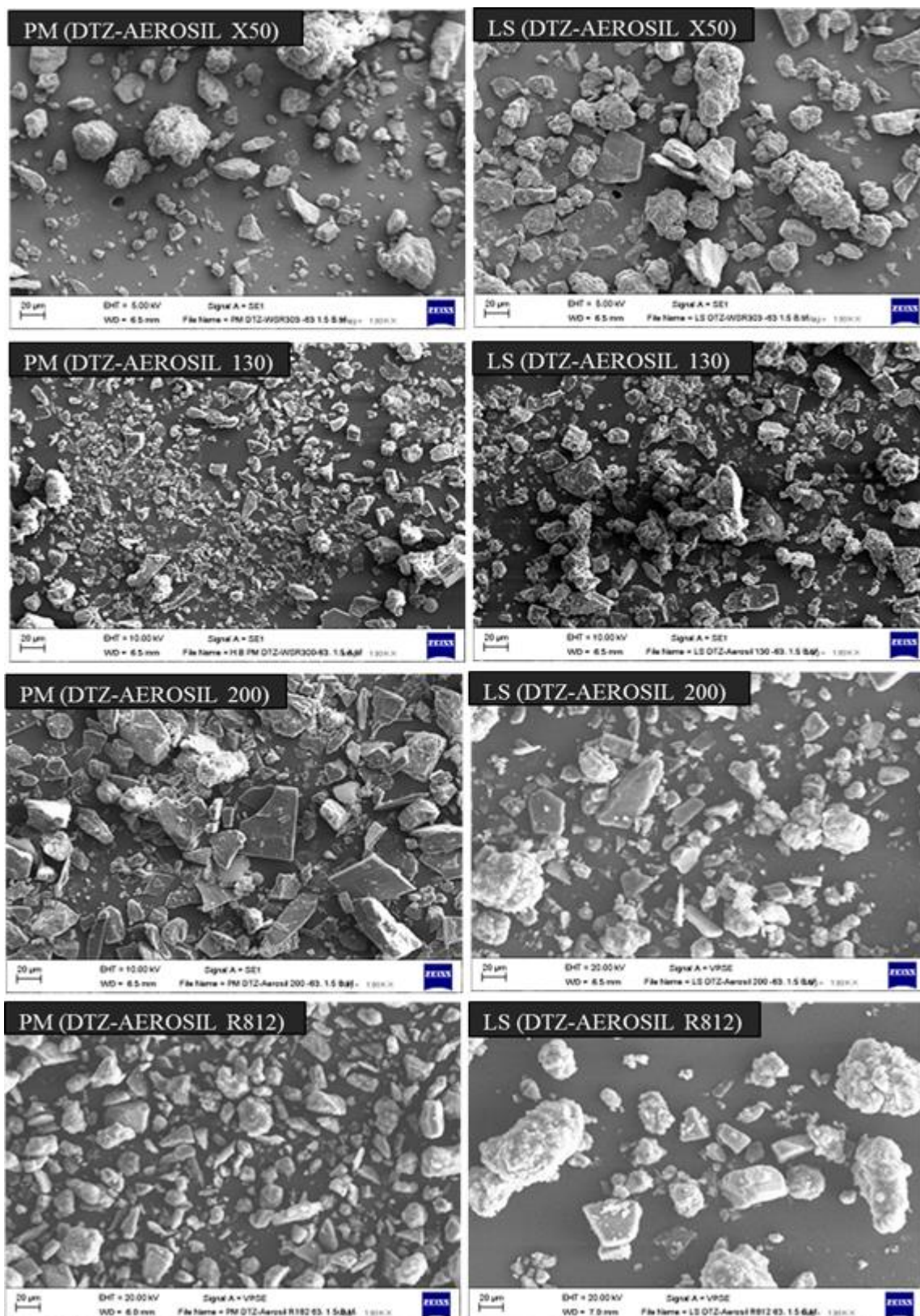


Figure 5.3: SEM of diltiazem HCl (DTZ) from physical mixture (PM) and liquisolid (LS) formulations containing various grades or surface area (i.e. AEROSIL[®] OX50, AEROSIL[®] 130, AEROSIL[®] 200 and AEROSIL[®] R812).

Table 5.2: Bulk density, tap density, Carr’s index (CI) and tensile strength (mean \pm SD, $n = 5$) for DTZ– AEROSIL[®] Surface area liquidolid (LS) formulation powders and their physical mixture (PM) counterparts.

Product (s)	Surface area (m ² /g)	Bulk density (g/cm ³)		Tap density (g/cm ³)		CI (%)		Tensile strength (TS)	
		PM	LS	PM	LS	PM	LS	PM	LS
AEROSIL [®] 50	65	0.44 \pm 0.00	0.37 \pm 0.00	0.62 \pm 0.00	0.52 \pm 0.00	29.7 \pm 0.5	28.0 \pm 0.02	8.95 \pm 0.3	1.02 \pm 0.1
AEROSIL [®] 130	155	0.32 \pm 0.01	0.35 \pm 0.00	0.45 \pm 0.00	0.49 \pm 0.01	28.5 \pm 1.0	24.4 \pm 0.57	10.3 \pm 0.2	1.92 \pm 0.1
AEROSIL [®] 200	225	0.26 \pm 0.00	0.33 \pm 0.00	0.40 \pm 0.00	0.45 \pm 0.01	24.6 \pm 0.3	23.5 \pm 1.00	13.0 \pm 1.6	2.83 \pm 0.1
AEROSIL [®] R812	290	0.35 \pm 0.01	0.36 \pm 0.00	0.50 \pm 0.00	0.47 \pm 0.00	24.5 \pm 0.6	24.0 \pm 0.00	8.98 \pm 0.5	2.34 \pm 0.3

5.3.4 Tensile strength

The TS values of tablets made by various surface area of AEROSIL[®] in LS produced weaker tablets than those prepared by PM formulations (Table 5.2). This could also be because the solvent incorporated in LS formulations exerts a plasticizing effect on Polyox[™], thus decreases the intermolecular bonds between Polyox[™] chains. Interestingly, the TS of LS tablets and their counterparts PM formulations showed increasing trend with an increase in the AEROSIL[®] surface area (ranging from 65 m²/g to 225 m²/g) (Table 5.2). For example, the TS of LS formulations increased from (1.02 MPa to 2.83 MPa), as the surface area of AEROSIL[®] increased from (65 m²/g to 290 m²/g). The results obtained were attributed to an increase in contact points between particles with the increase in the surface area of the coating material resulting in an increased interparticle bounding. A grade of AEROSIL[®] 200 shows a higher ratio of surface/volume compared to a lower surface area of AEROSIL[®] grade (AEROSIL[®] X50, AEROSIL[®] 130). Although AEROSIL[®] R812 has higher surface areas than AEROSIL[®] 200 (Table 5.2), both the LS and PM tablets containing AEROSIL[®]R812 (hydrophobic, 290 m²/g) showed lower TS values 2.34 MPa and 8.98 MPa than the TS values (2.83 MPa and 13.0 MPa) of AEROSIL[®]200 (hydrophilic, 225 m²/g). This could be due to the lubricating effect that AEROSIL[®] R812 could exert due to its hydrophobic properties, thereby interrupting interparticulate bonding with hydrophilic DTZ, PS 80 and Polyox[™] particles. It could also be explained that the affinity of hydrophobic grade of silica–DTZ is weaker compared to that of hydrophilic silica–DTZ.

5.3.5 Drug release studies

To evaluate the effect of different AEROSIL[®] surface area on the retardation of model highly soluble drug, DTZ, four different AEROSIL[®] surface area (that is 65 m²/g), AEROSIL[®]130 (hydrophilic, 155 m²/g), AEROSIL[®]200 (hydrophilic, 225 m²/g) and AEROSIL[®]R812 (hydrophobic, 290 m²/g) were investigated. It can be seen that DTZ containing higher surface area (225 m²/g) showed slower release behaviour among the various grades used in both the LS and PM formulations, i.e. the dissolution pattern has decreased with increase in the surface area of AEROSIL[®] powders from (65 m²/g to 290 m²/g). This could be due to the higher TS of the tablets containing AEROSIL[®] particles with higher surface area compared to those prepared using AEROSIL[®] particles having lower surface areas (Table 5.2). Additionally, AEROSIL[®] particles with higher surface areas can afford higher viscosity and density of its gel-layer, acting as a barrier against drug release via diffusion due to its increased tortuosity from both the LS formulations and their counterpart PM tablets. However, the dissolution profiles of LS tablets containing (AEROSIL[®] R812) showed different release behaviour than their PM tablets (Figure 5.4).

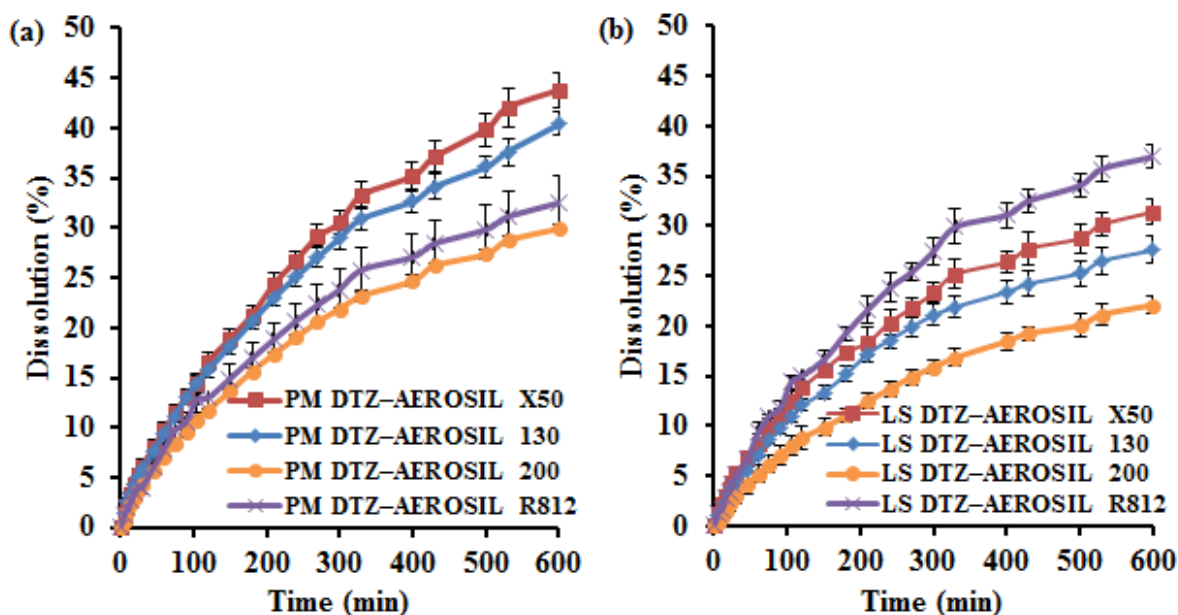


Figure 5.4: Release patterns (mean \pm SD, $n = 3$) of diltiazem HCl (DTZ) from (a) physical mixture (PM) and (b) liquisolid (LS) formulations containing various grades or surface area (i.e. AEROSIL[®] OX50, AEROSIL[®] 130, AEROSIL[®] 200 and AEROSIL[®] R812,)

This may be attributed to the decreased penetration of the dissolution media in the presence of the hydrophobic silica (AEROSIL[®] R812), in the PM compact leading to reduced diffusion of the drug from the matrix. Drug release occurs by dissolution of the active ingredient through capillaries formed of interconnecting drug particle clusters and the pore network, when a matrix is composed of water-soluble drug and a water-insoluble polymer (Shimpi *et al.*, 2004). This is supported by dissolution parameters that pointed out in both LS and PM tablets containing AEROSIL[®] grades with higher surface area to give lower DEs higher MDTs and MDRs in comparison to those with lower surface area (Table 5.3). However, LS tablets showed slower release patterns compared to PM tablets regardless of the hydrophilic AEROSIL[®] surface area used (Table 5.3). It could be assumed that the solvent penetrates the free spaces between the macromolecular chains of Polyox[™], and the Polyox[™] chains become flexible, enhancing the thickness of the gel layer and allowing drug release

through the gels outer surface. This could also be described as water plasticising the PolyoxTM and transforming it from a glassy state to a rubbery state.

Table 5.3: Dissolution efficiency (DE), mean dissolution rate (MDT), mean dissolution rate (MDR) and in vitro release kinetic parameters; *n* value of diltiazem HCl obtained for liquid (LS) formulations containing various grades AEROSIL[®] Surface area in comparison to their physical mixture (PM) counterparts. The results are expressed as the mean ± SD.

Product (s)	Surface area	DE (%)		MDT (min ⁻¹)		MDR (min ⁻¹)		n value	
		PM	LS	PM	LS	PM	LS	PM	LS
AEROSIL[®] 50	65	27.0 ± 1.39	19.4 ± 3.40	206 ± 1.58	197 ± 5.05	0.16 ± 0.01	0.12 ± 0.01	0.709	0.781
AEROSIL[®] 130	155	25.0 ± 0.14	16.3 ± 1.04	202 ± 0.02	189 ± 4.68	0.10 ± 0.05	0.08 ± 0.02	0.696	0.724
AEROSIL[®] 200	225	19.6 ± 0.07	14.4 ± 0.78	205 ± 4.64	210 ± 4.87	0.08 ± 0.01	0.05 ± 0.01	0.740	0.821
AEROSIL[®] R812	290	21.5 ± 4.07	24.5 ± 1.01	203 ± 0.10	201 ± 3.45	0.08 ± 0.02	0.09 ± 0.01	0.705	0.741

This is further supported by the dissolution parameters that confirmed the LS tablets containing all AEROSIL[®] grade to produce lower DEs irrespective of their surface area used (Table 5.3). In order to investigate the mechanism of drug release from LS tablets and their PM tablets, all release data were fitted into Peppas equation (Table 5.3). Regardless of AEROSIL[®] surface area, the n values obtained from LS tablets showed higher values than those from PM compacts (Table 5.3). The release rate of DTZ from all PM formulations and LS powders followed the anomalous transport mechanism ($0.45 > n > 0.89$) regardless of their AEROSIL[®] surface area (Table 5.3).

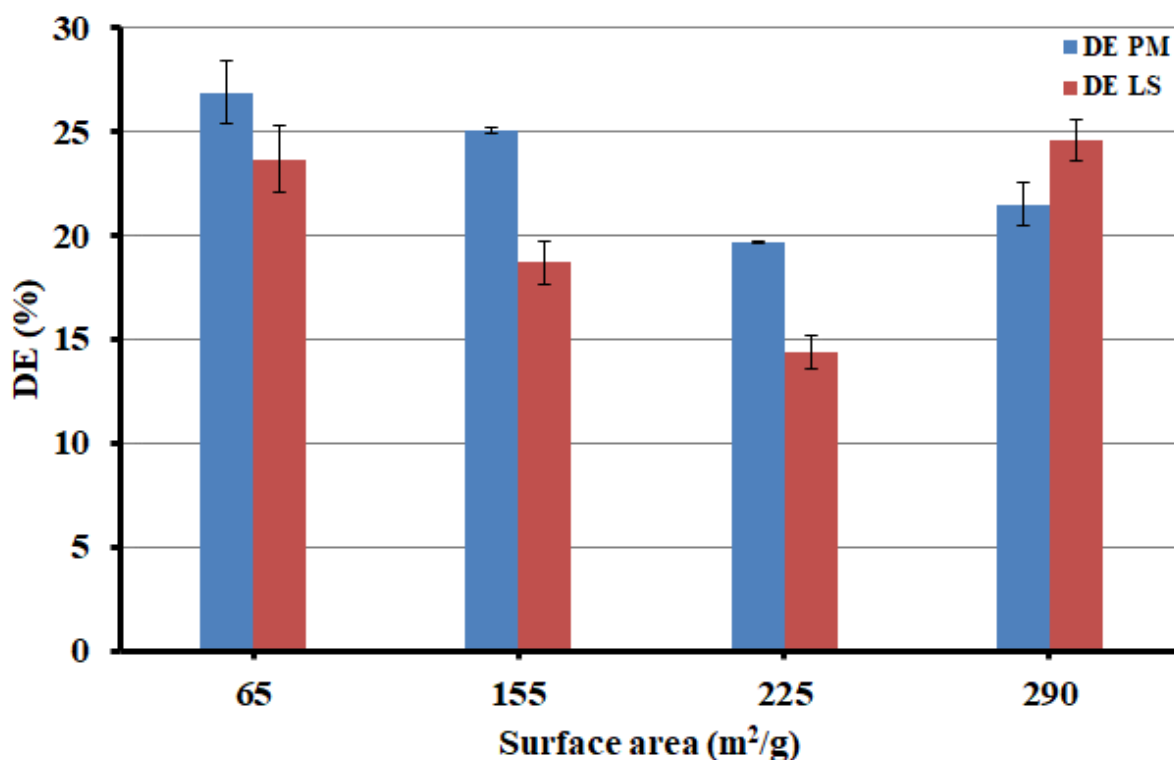


Figure 5.5: Dissolution efficiency (DE, %) of diltiazem HCl (DTZ) of liquisolid (LS) and (PM) formulations in relation to surface area (m²/g).

5.4 Conclusion

Based on this result, it could be concluded that AEROSIL[®] 200 (hydrophilic, 225 m²/g) satisfactorily decreased the drug release profile from both the LS and PM tablets. Among all the AEROSIL[®] grades used in these formulations, AEROSIL[®]200 was found to be the best, at the same ratio compared to different AEROSIL[®] surface area. As indicated by the release kinetics it could be concluded that the release method may transpire by diffusion and the mechanism of diffusion is anomalous. Polyox[™]-based LS tablets have a potential to produce zero-order release kinetics for a highly water-soluble drug, DTZ, although a careful selection of AEROSIL[®] coating material grade is nevertheless vital to producing slower release pattern of LS tablets in comparison to conventional tablets. Being simple, the LS method should have general applicability to many highly water-soluble drug entities. Finally, AEROSIL[®] interacts with the other components of the formulations. Further work is therefore required to comprehensively explore LS technique as a robust and reliable method of retarding the release rate of highly soluble drugs.

6 CHAPTER 6: EFFECT OF DIFFERENT DILUENTS

6.1 Introduction

Diluents can be applied in compact formulations to produce the desired optimum size when the drug produces a small percentage of the formula. The need of a compact to consolidate the drug and fillers is the need to improve the bulk volume and consequently the size of the compact in order to help the handling and administration of the compact formulation (Lotfipour *et al.*, 2004). They can be used to change the rate of drug release and also increase the mechanical strength (i.e. flow and tableting). Diluents should be non-hygroscopic, that have good biopharmaceutical properties (e.g., water-soluble or hydrophilic), cheap and have an acceptable taste (Turkoglu and Sakr, 2002). Soluble diluents (e.g. lactose), insoluble (e.g. DCP), or partially soluble diluents (e.g. partially pregelatinized starch) are usually attached to matrix formulations. In general, the inclusion of diluents in matrix formulations normally improves drug release rate regardless of drug solubility (Ford *et al.*, 1987; Lotfipour *et al.*, 2004). Drug release rate is improved using soluble fillers by increasing the porosity of the path of the drug by stimulating water entrance and enhancing the wettability and through the formation of channels within the matrix (Miranda *et al.*, 2007). This influences the production of more permeable (i.e. weaker) hydrated gel layer than that for insoluble excipients, leading to faster drug diffusion and enhanced erosion rate (Ford *et al.*, 1987). Lactose is a common water-soluble diluent broadly applied in various sustained release formulations due to its versatility. Lactose is usually employed as filler in tablets and capsules and as a component in the dairy source products (Smyth and Hickey, 2005). The inclusion of lactose in most pharmaceutical formulations has been shown to result in faster drug release from PolyoxTM. For example, El-Malah *et al.*, (2006), showed the inclusion of lactose in the formulation to afford faster release rates of THP from PolyoxTM. The incorporation of lactose has also been shown to increase the release rate of a poorly soluble drug, Methylparaben from hypromellose matrices (Tahara *et al.*, 1995). Asaduzzaman *et al.*, (2011), reported that addition of mannitol

in the formulation demonstrate slower dissolution rate of Ranolazine from Methocel K4M. Another investigation discovered evidence that the inclusion of mannitol in the release rate Ciprofloxacin HCl from hypromellose matrices shown to have retardation properties (Mortazavi *et al.*, 2010).

Mannitol is a white crystalline polyol commonly used in a pharmaceutical formulation that incorporated industrially by catalytic hydrogenation of glucose syrup or fructose. Mannitol is a non-hygroscopic ingredient, water-soluble and non-toxic which is widely employed in food and pharmaceutical preparations (Debord *et al.*, 1987). They are generally recognized as safe registered ingredient and are applied in various dosage forms obtainable commercially. Mannitol has been used as an alternative carrier to lactose because due to its non-reducing effect, it has limited hygroscopic tendencies than some of the other fillers, provides a high sweet taste that proves that a dose has been successfully delivered, (Saint-Lorant *et al.*, 2007). It has been reported that mannitol improves dissolution of carteolol HCl matrix from Eudragit[®] RL as it forms pores within the dosage form matrix (Holgado *et al.*, 1995). An investigation was carried by Jaipal *et al.*, (2015), which shows the incorporation of mannitol from (HPMC 15K) retard the dissolution rate of Buspirone HCl. Hydrogenated vegetable oils (HVO) are achieved by catalytic hydrogenation of the unsaturated bonds with nickel. The method produces hydrophobic solids with a 'waxy' appearance, proper for controlled-release applications (Reitz and Kleinebudde, 2007). In this study, the incorporation of HVO has been shown to retard the release of highly soluble drug from calcium sulphate with a 4% drug loading within 24hrs (Martini *et al.*, 2000). Sorbitol is also one of polyols commonly applied in the pharmaceutical formulation. Sorbitol has been used as a diluent in tablets because of its non-toxicity, cheap and has an acceptable taste (Ma *et al.*, 2014). Enhanced release properties of sorbitol have been reported for dispersions of different drugs, including Nitrofurantoin (Ali

and Gorash, 1984), Prednisolone (Jachowicz, 1987) and Ofloxacin (Okonogi *et al.*, 1997). In most of these cases, other carriers provided better effects. Interestingly, Nitrofurantoin gave better release from sorbitol than mannitol dispersions (the two sugars are isomers) (Ali and Gorash, 1984). Certainly, a dispersion of Prednisolone in sorbitol released the drug faster than all other carriers tested, including PEG, PVP, urea and mannitol (Jachowicz, 1987). However, the effects of diluent as a potential carrier in the release rate of a model soluble drug, DTZ, from LS matrices up to date have not been investigated. Although to best of our knowledge, there are no systematic studies to explore the influence of different diluent type used in LS matrix tablets to modulate drug release. Therefore, the influence of those diluents (i.e. sorbitol, mannitol, compressolSM, HVO and lactose) on the physicochemical, mechanical and drug release properties of LS PolyoxTM-based formulations containing a highly soluble model drug, DTZ, in comparison to their PM counterparts were investigated.

6.2 Formulation

The solid phase consisted of PolyoxTM powder (6 g), AEROSIL[®] OX contain (0.6 g), and each diluent type contain (5.2 g) in the case of PM formulations and 6.0 g in the case of LS formulations), whereas the liquid phase consisted of commercial DTZ powder dispersed in polysorbate 80 (PS 80) (60 °C, 200 rpm) at a drug:solvent ratio of 1:1 (*w:w*). Details of the formulation process were given in [section 2.5](#). Accurately weighed samples of each liquisolid (750 mg) and PM (650 mg) formulation were separately weighed and then compressed on 8 mm punch and die using a manual tableting machine at a fixed pressure of 2000 psi.

6.3 Results and discussion

6.3.1 Solid state

The PXRD patterns and FT-IR spectra of LS formulations were investigated and compared to those obtained from the PM powders (Figure 6.1 and figure 6.2). LS formulations and PM powders indicated the absence of the characteristic band of the DTZ at 2387.93 cm^{-1} (amine HCl, N-H stretching) (Figure 6.1). Such investigations proved that there was a notable disappearance in the solid state of the drug during the preparation of both LS and PM formulations. This was also reported by Abd *et al.*, 2012 as seen in section 3.3.1. The XRD study revealed there is a slight reduction in the intensity of LS formulations in comparison to their PM powders as reported from previous Chapters.

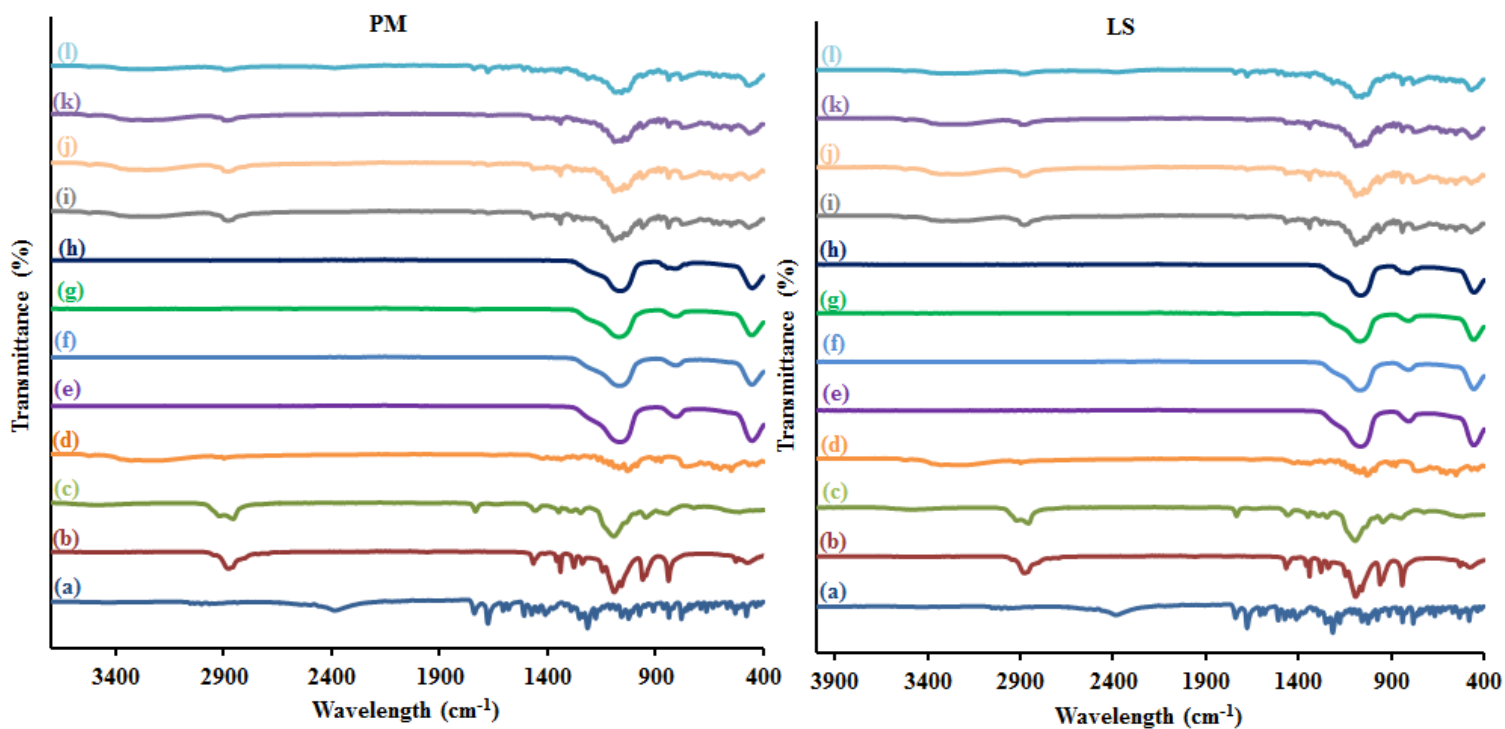


Figure 6.1: FTIR patterns of physical mixture (PM) and liquid solid (LS) formulations containing DTZ and various diluents (i.e. (a) Pure DTZ, (b) Pure PolyoxTM, (c) Pure Polysorbate 80 (d) Pure Sorbitol, (d) Pure Mannitol, (e) Pure Compressol, (f) Pure HVO, (g) Pure Lactose, (h) Sorbitol, (i) Mannitol, (j) Compressol, (k) HVO and (i) Lactose.

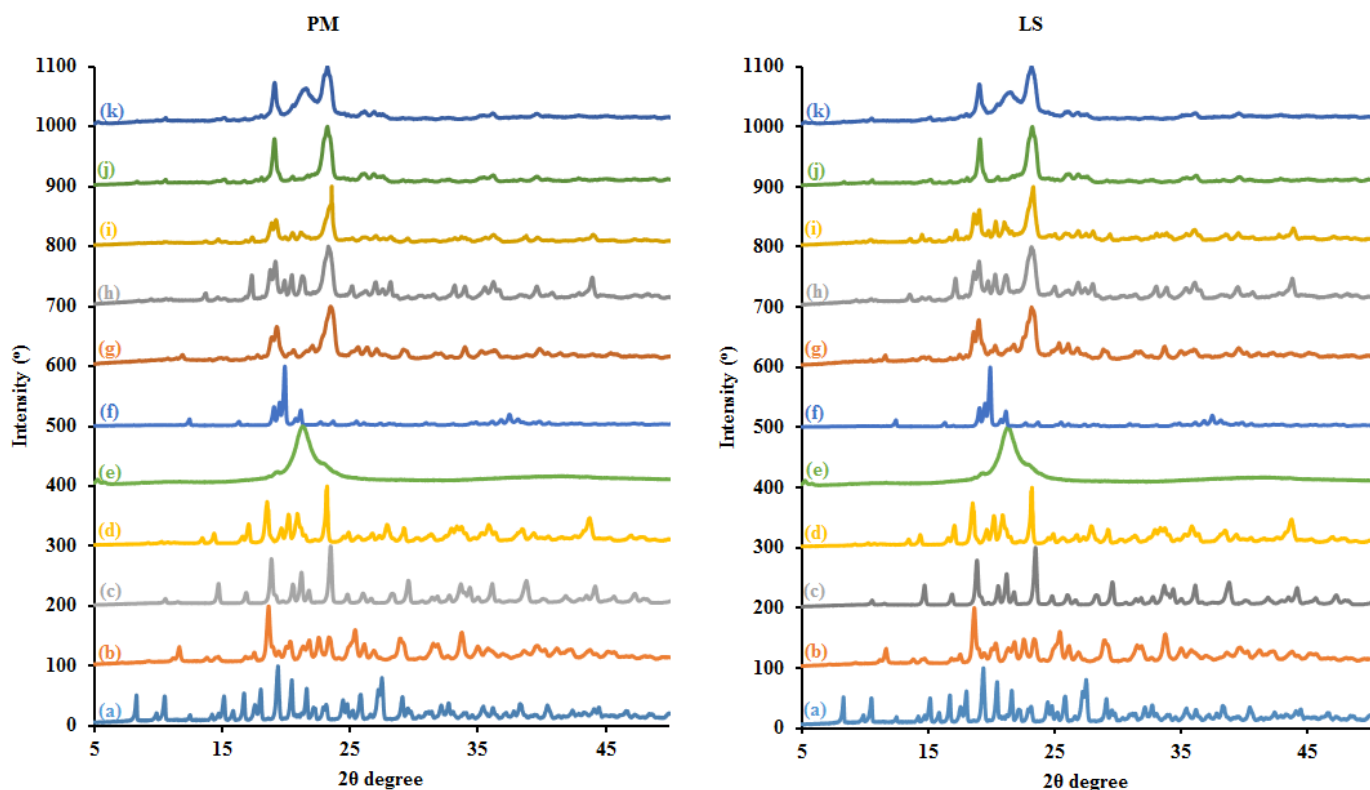


Figure 6.2: PXRD patterns of physical mixture (PM) and liquid-solid (LS) formulations containing various diluents (i.e. (a) Pure DTZ, (b) Pure Sorbitol, (c) Pure Mannitol, (d) Pure Compressol, (e) Pure HVO, (f) Pure Lactose, (g) Sorbitol, (h) Mannitol, (i) Compressol, (j) Lactose and (k) HVO

6.3.2 Particle size distribution

The particle size distribution from various diluent in both LS formulations and PM powders were measured and presented as depicted in [Table 6.1](#). The calculated span values were highest for mannitol in both LS formulation and PM powder and lowest for compressolSM in LS and HVO (1.9 ± 0.1) in PM ([Table 6.1](#)). Hence, mannitol demonstrated higher polydispersity than HVO, whose particle sizes were more closely centred on the median value of $123.7 \mu\text{m}$, which was the highest median value obtained in the case of PM powder. LS formulations containing sorbitol showed higher VMDs than other formulations, whereas HVO demonstrated higher VMDs in the case of PM powders than the LS formulations ([Table 6.1](#)). All the LS formulations were found to have higher VMDs than their counterpart PM powders. For example, the VMD in LS formulations ranged from $84.7 \pm 6.2 \mu\text{m}$ to $259.0 \pm 2.6 \mu\text{m}$

whereas the range for the PM powders was $57.1 \pm 2.0 \mu\text{m}$ to $138.3 \pm 1.2 \mu\text{m}$ due to the occurrence of aggregated particles. SEM images of various diluents particles exhibited crystalline particles in both the LS and PM and its morphological variations were seen between different diluents particles (Figure 6.3). CompressolSM displayed the normal angular–subangular shape. Representative SEM image of HVO demonstrated spherical (rounded–subrounded, orange–like) particles with nearly uniform (regular) shape, well curved–plane surfaces, and well-rounded corners and edges (Figure 6.3). No indication of particle needle-like was seen in case of matrices containing compressolSM and HVO samples in both their LS formulation and PM powder as depicted in (Figure 6.3). SEM image of lactose exposed irregular–deformed particles with sharp edges and mostly elongated morphology (Figure 6.3). It was clear that, in comparison to compressolSM and HVO, lactose particles are less consistent in terms of shape and size, since different morphologies could be identified (Figure 6.3).

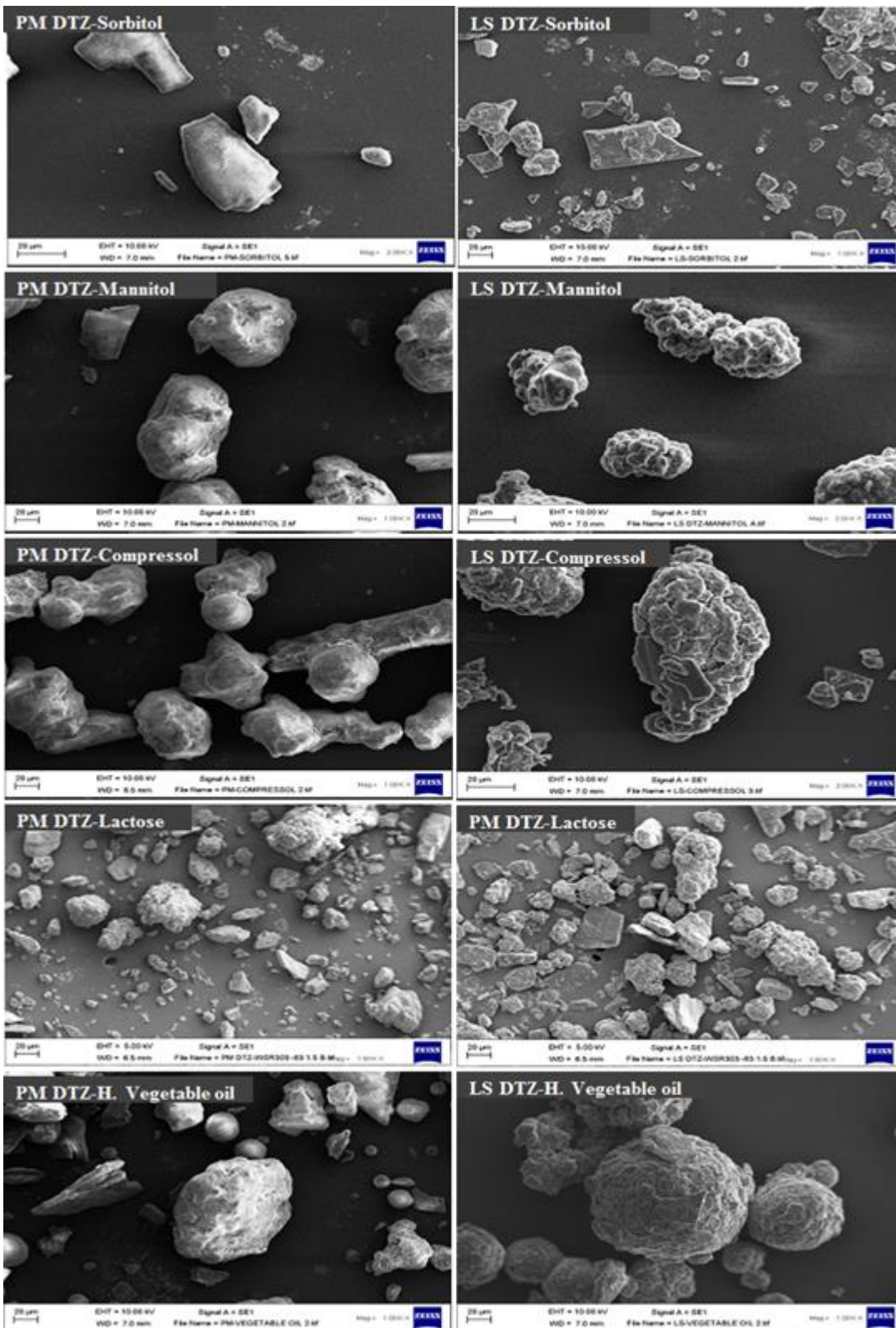


Figure 6.3: SEM of diltiazem HCl (DTZ) from physical mixture (PM) and liquisolid (LS) formulations containing various diluents (i.e. DTZ–sorbitol, DTZ–Mannitol, DTZ–CompressolSM and DTZ–Lactose, DTZ–HVO).

Table 6. 1: Particle size distribution (i.e. particle size at 10% ($d_{10\%}$), 50% ($d_{50\%}$), 90% ($d_{90\%}$), volume mean diameter (VMD), and span; mean \pm SD, $n = 3$) of DTZ with various diluent type from liquisolid (LS) formulation powders and their physical mixture (PM) counterparts.

Product (s)	$d_{10\%}$		$d_{50\%}$		$d_{90\%}$		VMD (μm)		Span	
	PM	LS	PM	LS	PM	LS	PM	LS	PM	LS
DTZ-Sorbitol	11.5 \pm 64.3	82.1 \pm 2.4	50.9 \pm 2.5	237.0 \pm 1.0	282.7 \pm 11.7	469.3 \pm 13.7	97.8 \pm 6.1	259.0 \pm 2.6	5.3 \pm 0.1	1.6 \pm 0.1
DTZ-Mannitol	14.0 \pm 0.3	22.5 \pm 0.2	47.5 \pm 0.7	61.8 \pm 1.1	280.0 \pm 9.8	365.7 \pm 11.9	96.6 \pm 3.8	141.7 \pm 4.0	5.6 \pm 0.6	5.6 \pm 0.1
DTZ-CompressolSM	16.2 \pm 0.8	51.1 \pm 1.5	53.9 \pm 1.1	132.7 \pm 0.6	155.0 \pm 3.0	247.0 \pm 2.6	71.3 \pm 1.3	142.0 \pm 1.0	2.6 \pm 0.0	1.4 \pm 0.0
DTZ-HVO	29.2 \pm 0.3	55.9 \pm 0.3	123.7 \pm 1.5	135.0 \pm 1.0	266.3 \pm 1.5	287.0 \pm 1.0	138.3 \pm 1.2	154.7 \pm 0.8	1.9 \pm 0.1	1.7 \pm 0.0
DTZ-Lactose	10.9 \pm 0.2	56.1 \pm 1.4	42.2 \pm 0.9	40.0 \pm 0.3	135.0 \pm 8.8	94.5 \pm 1.5	57.1 \pm 2.0	84.7 \pm 6.2	2.2 \pm 0.1	1.6 \pm 0.1

6.3.3 Powder density

The bulk and tap densities of LS formulations and PM powders were varied (Table 6.2). In comparison to PM powders, the formulations containing various diluent in LS powders demonstrated lower bulk density, lower tapped density and higher CI (Table 6.2) indicating a lower degree of interparticle cohesive forces (e.g. van der Waals forces). Although good flow properties were observed from both LS formulations and their PM powders as indicated by their CI values (Table 6.2). The formulation containing lactose showed a poorer flow property (CI: $29.7\% \pm 0.9$, (PM) and CI: $28.0\% \pm 0.0$, (LS) very poor flowability) in both LS and PM powders (Table 6.2). This is ascribed to the more irregular, deformed particles with rough/uneven surfaces which can cause interlocking between particles and hence leading to an increased internal friction between particles containing lactose from LS and PM particles and thereby leading to poor flow properties (Table 6.2). In contrast, the formulations containing sorbitol and mannitol particles have less angular edges in comparison to lactose formulations as shown in SEM image (Figure 6.3), resulting in less geometric interlocking among sorbitol or mannitol formulations and thus improved powder flowabilities (Table 6.2). Formulations containing compressolSM and HVO also produced better flow properties indicating lower degree of cohesivity and adhesivity. This could be due to its morphology and the existence of the rounded shape of these particles.

Table 6.2: Bulk density, tap density, Hardness and Carr's index (CI) (mean \pm SD, n = 5) for DTZ–diluent liquisolid (LS) formulation powders and their physical mixture (PM) counterparts

Product	Bulk density (g/cm ³)		Tapped density (g/cm ³)		Hardness (N)		CI (%)	
	PM	LS	PM	LS	PM	LS	PM	LS
DTZ–Sorbitol	0.49 \pm 0.00	0.46 \pm 0.00	0.59 \pm 0.00	0.56 \pm 0.00	134 \pm 3.4	31.1 \pm 1.7	16.8 \pm 0.5	18.0 \pm 0.0
DTZ–Mannitol	0.41 \pm 0.00	0.39 \pm 0.00	0.51 \pm 0.00	0.48 \pm 0.00	169 \pm 2.6	37.0 \pm 0.5	18.8 \pm 0.5	19.2 \pm 0.5
DTZ–Compressol SM	0.43 \pm 0.00	0.40 \pm 0.00	0.53 \pm 0.00	0.49 \pm 0.01	168 \pm 3.3	39.2 \pm 6.6	18.2 \pm 0.5	18.8 \pm 0.3
DTZ–HVO	0.45 \pm 0.00	0.33 \pm 0.00	0.56 \pm 0.01	0.42 \pm 0.00	185 \pm 2.7	57.8 \pm 0.8	19.0 \pm 1.2	21.3 \pm 0.5
DTZ–Lactose	0.44 \pm 0.00	0.37 \pm 0.00	0.62 \pm 0.00	0.52 \pm 0.00	278 \pm 2.4	31.6 \pm 1.4	29.7 \pm 0.5	28.0 \pm 0.0

6.3.4 Hardness

Hardness of tablets made from various diluents was investigated in both the LS formulations and PM formulations. Matrices containing HVO recorded higher hardness tablets values in comparison to those matrices containing other diluents. The hardness was in the following rank order of HVO > compressolSM > mannitol > lactose > sorbitol. In contrast, the tablets containing lactose showed higher hardness (or breaking force) among the various diluent used in the case of PM (Table 6.2). This could be due to the plastically deforming material of formulation containing lactose tablets which render it harder among diluents used in the PM tablets. In comparison to LS tablets, PM compacts produced a considerable higher hardness tablets in all the diluent used in the preparation these formulations. For example, the hardness of LS tablets containing HVO demonstrates lower hardness (57.8N) compared to PM compacts (185.2N) (Table 6.2).

6.3.5 Drug release studies

The dissolution rate of DTZ from LS compacts prepared using various diluents compared to their counterpart conventional PM compacts is shown in (Figure 6.4). It can be seen that LS compact demonstrated slower release rates of the drug compared to the conventional compacts irrespective of the diluent used in the formulations (Figure 6.4). This is supported by the dissolution parameters that showed LS compacts to have lower DEs values than their counterpart PM tablets. For example, the LS formulation containing HVO produced lower DE ($18.1\% \pm 0.4\%$), higher MDT ($185.6\% \pm 2.4\%$) and lower MDR ($0.08 \text{ min}^{-1} \pm 0.01 \text{ min}^{-1}$) compared to the conventional compacts ($\text{DE} = 26.0\% \pm 2.2\%$, $\text{MDT} = 173.2 \text{ min}^{-1} \pm 8.42 \text{ min}^{-1}$ and $\text{MDR} = 0.12 \text{ min}^{-1} \pm 0.01 \text{ min}^{-1}$) (Table 6.3).

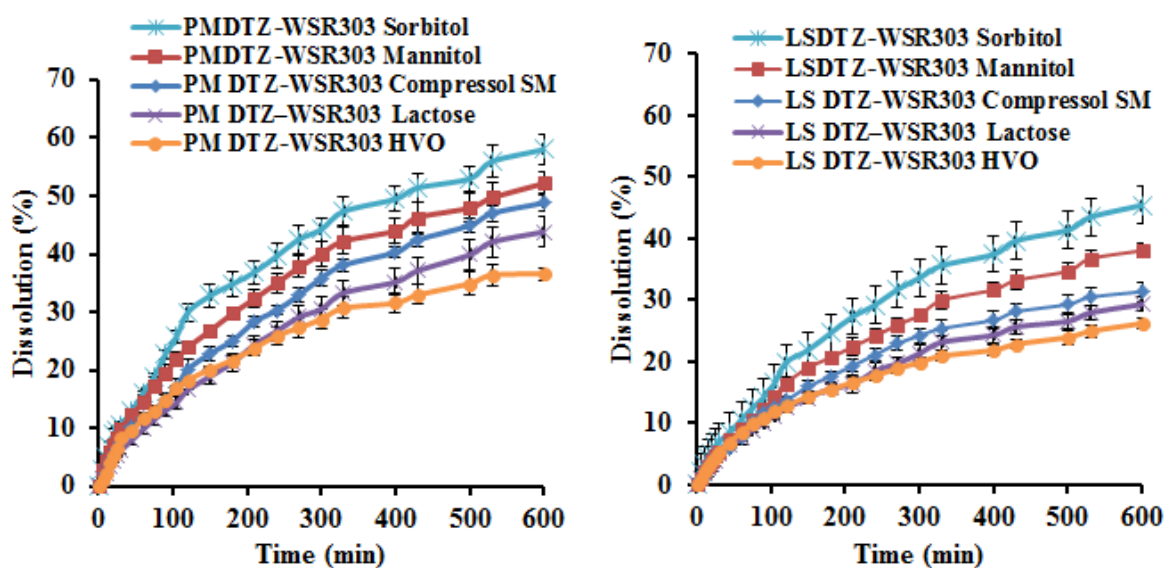


Figure 6.4: Dissolution profiles of DTZ from physical mixture (PM) and liquisolid (LS) matrix tablets containing various diluents.

The presence of the non-volatile solvent could be the reason for as mentioned in previous Chapters. Comparing the different diluents showed that HVO provided the slowest release pattern of DTZ across diluents used in the preparation of both the LS compacts and PM tablets (Figure 6.4).

This could be attributed to hydrophobicity imparted by HVO to matrix system, which upon contact with aqueous medium it takes a longer time to penetrate into the tablet and therefore diffusion and dissolution of the drug were found to be less than hydrophilic diluents. The excipients, which are used in the formation of hydrophobic matrix tablets and have no dissolving or swelling properties, are usually polymers and waxes. Waxes are high MW excipients without liquid components composed of hydrocarbons comprising straight, branched or cyclic alkanes (Walters and Brain, 2001). The lipophilicity of wax matrix system delays entry of aqueous medium in matrix producing retardation properties in release profile of drug (Li *et al.*, 2006). In general, release retardation effect was found to be in order of HVO > lactose > compressolSM > mannitol > sorbitol. It was also observed that the drug release from the various diluent did not correlate the diluent solubility. Lactose retarded the drug release better compared to sorbitol, mannitol and compressolSM, however, HVO was more robust compared to lactose. This was further confirmed by dissolution parameters that showed LS compacts formulated with HVO to have a lower DE (18.1% ± 0.4%) and lower MDRs (from 0.08 min⁻¹ ± 0.01 min⁻¹) than those LS compacts formulated with compressolSM, mannitol, sorbitol and or lactose (DE: from 19.4% ± 3.4% to 30.1% ± 2.2 %). The same consideration was also obtained from PM powders. The 'n' values obtained from both the LS formulation and PM powders in (Table 6.3) followed anomalous transport mechanism with values ranging from 0.612 to 0.791 (Table 6.3).

Table 6.3: Dissolution efficiency (DE), mean dissolution rate (MDT), mean dissolution rate (MDR) and in vitro release kinetic parameters; *n* value of diltiazem HCl obtained for liquisolid (LS) formulations containing various grades diluent in comparison to their physical mixture (PM) counterparts. The results are expressed as the mean \pm SD.

Formulation (s)	DE (%)		MDT (min^{-1})		MDR (min^{-1})		n value	
	PM	LS	PMs	LS	PMs	LS	PMs	LS
DTZ–Sorbitol	40.3 \pm 3.18	30.1 \pm 2.22	183 \pm 0.89	202 \pm 8.62	0.18 \pm 0.01	0.13 \pm 0.02	0.612	0.665
DTZ–Mannitol	35.7 \pm 3.11	25.3 \pm 3.23	189 \pm 8.90	203 \pm 26.4	0.16 \pm 0.02	0.10 \pm 0.01	0.615	0.748
DTZ–Compressol SM	32.0 \pm 1.82	21.5 \pm 1.06	206 \pm 12.5	190 \pm 8.96	0.13 \pm 0.02	0.09 \pm 0.01	0.791	0.729
DTZ–Lactose	27.0 \pm 1.39	19.4 \pm 3.40	206 \pm 1.58	197 \pm 5.05	0.12 \pm 0.01	0.08 \pm 0.01	0.706	0.781
DTZ–HVO	26.0 \pm 2.23	18.1 \pm 0.45	173 \pm 8.42	185 \pm 2.38	0.12 \pm 0.01	0.08 \pm 0.00	0.661	0.644

6.4 Conclusion

From the five diluents (HVO, compressolSM, mannitol, lactose and sorbitol) studied, HVO produced tablets with the highest mechanical strength in the case of LS compact. It can be observed that there was a general increase in tablets mechanical strength and a decrease in DTZ release. The type of diluents has a considerable effect on the DTZ release from LS compacts. HVO caused retardation of DTZ as compared to formulations containing compressolSM, mannitol, lactose and sorbitol respectfully. Therefore, the HVO was shown as the main factor leading the control of drug release from both the LS and PM formulations. Regardless of different diluents used, LS formulations produced slower DTZ release profile than those obtained in PM tablets. DTZ release from both the LS and PM tablets followed anomalous transport mechanism. FT-IR was investigated, and found interaction between drug and various diluent within both the LS and PM formulations and XRD had a crystalline solid state in nature. In conclusion, a careful selection of diluent is vital in slowing more highly soluble model drug release from LS matrices.

7 CHAPTER 7: INFLUENCE OF POLYMER TYPE

7.1 Introduction

Psyllium fiber is gel-forming mucilage which lowers blood lipid concentrations due to its effectiveness, cheap therapy for chronic diarrhoea and promoting healthy bowel function as a bulking agent or laxative (Fischer *et al.*, 2004). Moreover, it appears as a substrate for microbial growth that increases stool mass (Spiller 2001). Psyllium lowers post-prandial glucose concentrations in men with type II diabetes (Ziai *et al.*, 2005). Recently, Psyllium was employed for the controlled delivery of peptides such as insulin²². However, Psyllium can be employed in the therapy of critical bowel syndrome (Washington *et al.*, 1998), which inhibits the carcinogenic and sustaining remission in ulcerative colitis processes (Morita *et al.*, 1998). Psyllium also has shown to reduce the concentration of cholesterol and low-density lipoprotein in the plasma (Fukagawa *et al.*, 1990). Psyllium not only has a pharmacological effect but it can be applied to sustained release matrix compacts and hydrogels. Psyllium has a unique way of producing a viscous gel almost immediately upon contact with dissolution medium, thereby retarding the release rate of a drug quicker (Fischer *et al.*, 2004). The hydrogel matrix developed by psyllium resists hydrolysis; consequently, psyllium can therefore resist colonic bacterial degradation and the double potential of the psyllium hydrogel can be employed to provide novel drug-delivery systems (Singh *et al.*, 2008). Psyllium is also cost-effective, safe with low toxicity (Oliver, 2000) and has a global consumer recognition having been employed for hundreds of years in traditional medicines which have been approved by the FDA (Anderson *et al.*, 2000). Various studies carried out their investigations on the modified psyllium husk powder to improve its importance in drug-delivery systems. The modified psyllium husk powder gave better gelling and swelling properties when tartaric, and succinic acid was used in developing a suitable sustained release compact from DTZ using direct compression (Gohel *et al.*, 2003). Modified psyllium hydrogels in the presence of acrylic acid and radiation showed the psyllium hydrogels formed

can produce drug release in a sustained and controlled manner and to be employed as a possible double drug–delivery device in the colon (Singh *et al.*, 2008). Siahi-Shadbad *et al.*, (2011) investigated the effect of various concentration of hypromellose K4M, sodium alginate, sodium carboxymethylcellulose (NaCMC) on the release rate of propranolol HCl from psyllium matrices. The finding showed that the binary mixtures of psyllium and hypromellose, psyllium and sodium alginate and NaCMC and psyllium in different ratios produced a significant decrease in the release behaviour of propranolol HCl. It was also reported that psyllium was shown to be a promising polymer to sustain the THP release rate from granulated formulations in comparison to their counterpart PM. The results showed more effective controlled drug release with no burst release and the inclusion of Hypromellose within psyllium formulations modified the THP release kinetics from Fickian diffusion to anomalous transport (Kaialy *et al.*, 2014). Hypromellose gains much attention due to its unique features, and they can exhibit good compression properties, including when directly compressed. They are non–toxicity and can produce a high level of drug loading, and also having enough swelling characteristics that enables a rapid form of an external gel layer which plays or retards an important role in controlling drug release. Besides, Hypromellose is fully identified as pH-independent materials; this advantage allows them to resist fluctuations of pH caused by intra and inter–subject differences of both GI transit time and gastric pH. They have been employed alone or in mixture in the formulation of matrix compacts, hence the gel–forming hydrophilic matrix compacts are widely employed for extended oral release dosage forms due to their cost–effectiveness, simplicity and reduction of the risk of systemic toxicity which occurs as a result of dose dumping (Huang *et al.*, 2005). Eudragit[®] polymers are a range of acrylate and methacrylate polymers obtainable in various ionic forms. Eudragit[®] RLPO and Eudragit[®] RSPO are water–insoluble but can yield pH–independent release profiles, and they are permeable. The permeability of Eudragit[®] RLPO and RSPO in

aqueous media could be due to the presence of quaternary ammonium groups in their formation; Eudragit[®] RLPO has a greater relationship of these functionalities groups and as such is more permeable than Eudragit[®] RSPO grade (Haznedar and Dortunç, 2003). However, the effects of polymer type in the release rate of a model soluble drug, DTZ, from LS matrices up to date have not been investigated. Therefore, this Chapter aimed to retard the release of a model highly water-soluble drug, DTZ, from LS matrix compacts in comparison to their PM tablets.

7.2 Formulation

The solid phase consisted of AEROSIL[®] (0.6 g), each polymer type under investigation contain (6 g), and lactose (5.2 g in the case of PM formulations and 6.0 g in the case of LS formulations), whereas the liquid phase consisted of commercial DTZ powder dispersed in polysorbate 80 (PS 80) (60 °C, 200 rpm) at a drug:solvent ratio of 1:1 (w:w). Also a binary mixture of Polyox[™]:Psyllium at ratios of 1:1, 1:3 and 3:1 was prepared for further investigations in this Chapter using the same procedure. The solid phase was introduced to a mortar and the mixing process was carried out as described earlier [section 2.5](#). Accurately weighed samples of each liquisolid (750 mg) and PM (650 mg) formulation were separately weighed and then compressed on 8 mm punch and die using a manual tableting machine at a fixed pressure of 2000 psi.

7.3 Results and discussion

7.3.1 Solid state

This study was carried out to investigate if there is any chemical interaction between pure DTZ and various polymer and binary mixture of psyllium and Polyox[™] in the ratios of 1:1, 3:1 and 1:3 in both the LS formulations and PM powders ([Figure 7.1](#) and [Figure 7.2](#)). The FT-IR observed in both LS formulations and their counterpart PM showed a considerable change when compared to that of pure DTZ, where a complete disappearance of the band at

2393 cm^{-1} was observed as seen in the previous Chapters. This confirmed the interaction between DTZ and various polymers and ratio. Additionally, the PXRD patterns of LS formulations were investigated and compared to that obtained from the PM powder (Figure 7.2). This study revealed a slight reduction in the intensity of LS formulations in comparison to their PM powders as also reported from previous Chapters. This may be attributed to the presence of a solvent in the LS formulation that renders it different.

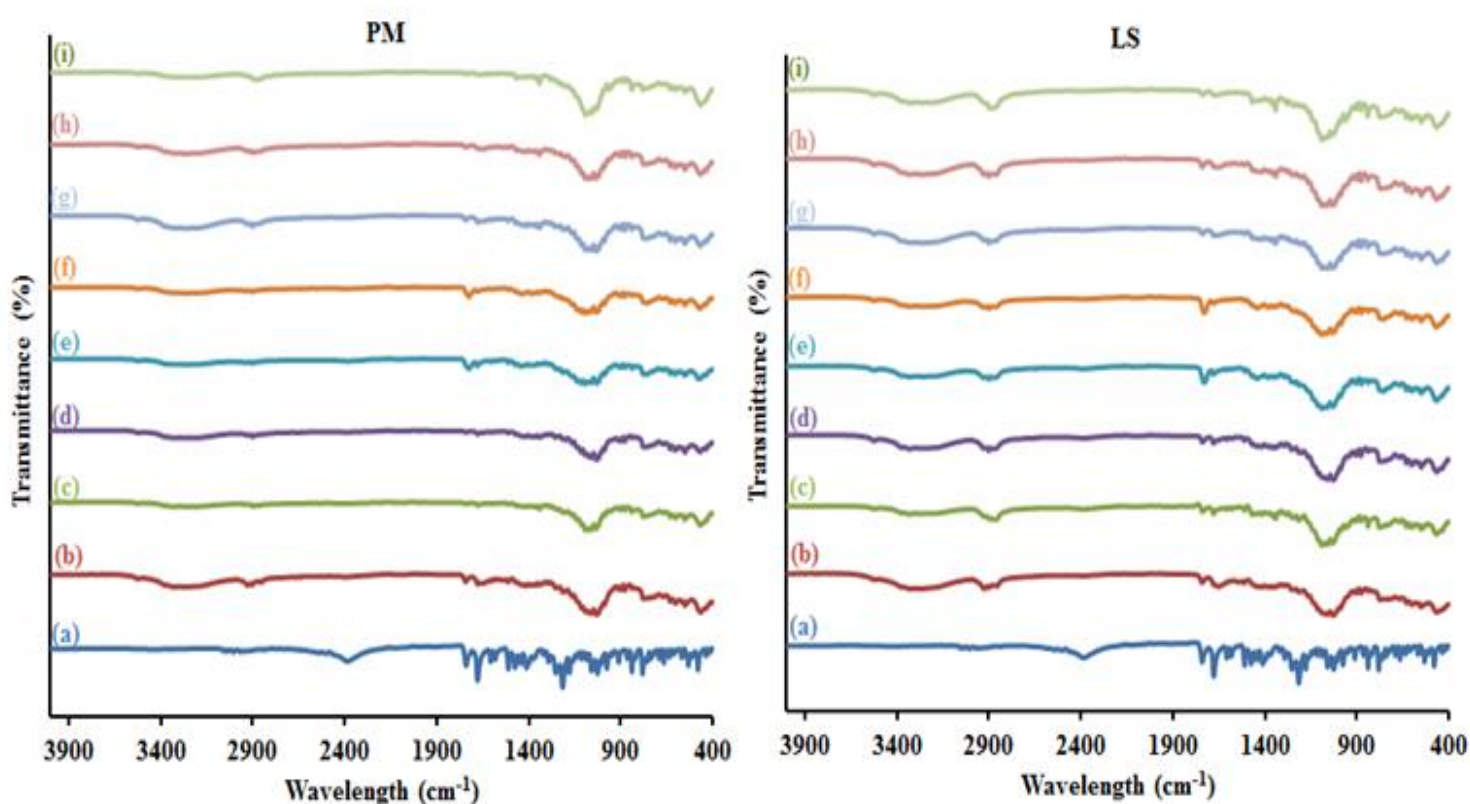


Figure 7. 1: FTIR patterns of physical mixture (PM) and liquid solid (LS) formulations containing various diluents (i.e. (a) Pure DTZ, (b) DTZ–Psyllium, (c) DTZ–PolyoxTM, (d) DTZ–Hypermellose, (e) DTZ–Eudragit[®] RS, (f) DTZ–Eudragit[®] RL, (g) DTZ–(Psyllium:PolyoxTM) 1:1, (h)DTZ–(Psyllium:PolyoxTM) 1:3 and (i) DTZ–(Psyllium:PolyoxTM) 3:1.

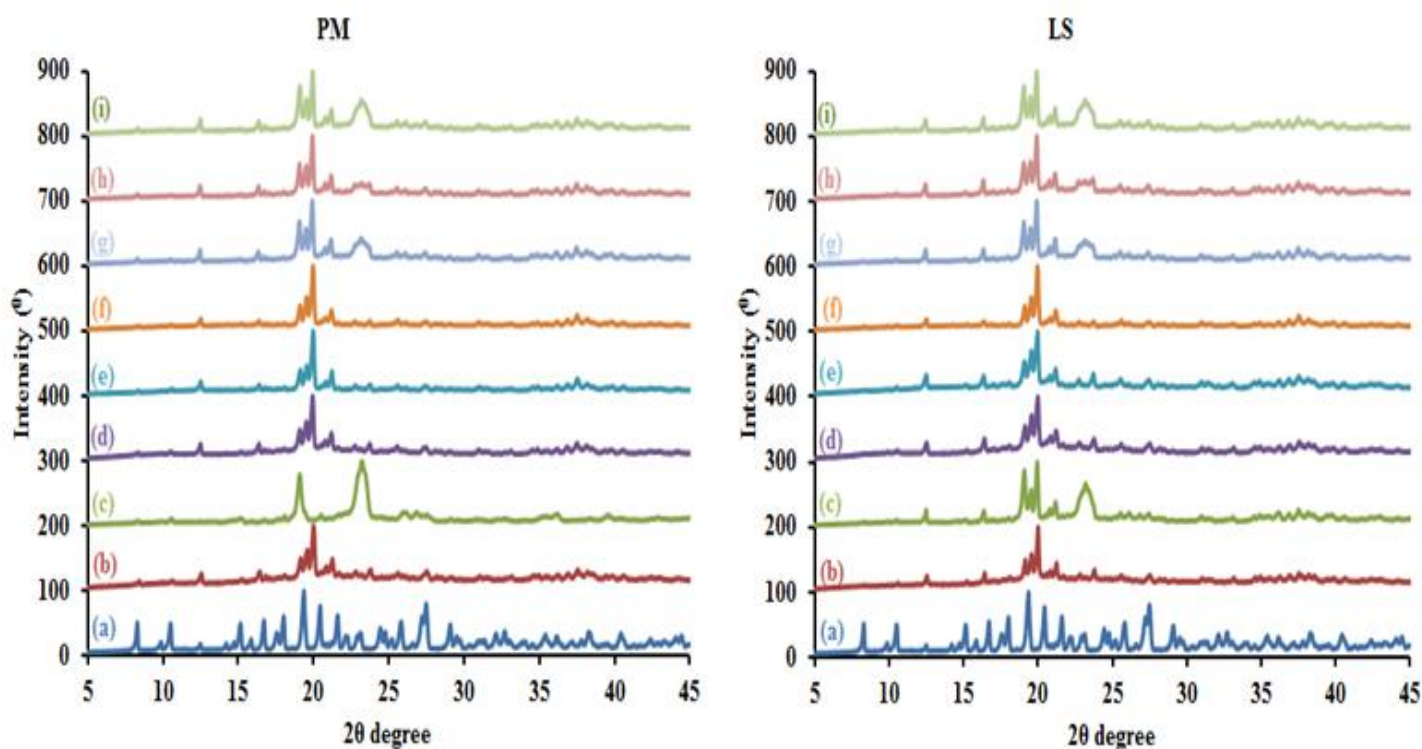


Figure 7.2: PXRD patterns of physical mixture (PM) and liquid solid (LS) formulations containing various Polymers (a) Pure DTZ, (b) DTZ–Psyllium, (c) DTZ–PolyoxTM, (d) DTZ–Hypromellose, (e) DTZ–Eudragit[®] RS, (f) DTZ–Eudragit[®] RL, (g)(DTZ–Psyllium:PolyoxTM) 1:1, (h) (DTZ–Psyllium:PolyoxTM) 1:3 and (i) (DTZ–Psyllium:PolyoxTM) 3:1.

7.3.2 Particle size distribution

The polymer's distinct properties such as VMD and span of the LS formulations and the PM powders comparing each property are shown in this table 7.1. Regardless of their polymer type, all LS formulations showed a significant difference in the VMD than their counterpart PM powders. For example, the VMD in LS formulations ranged from $118.7 \mu\text{m} \pm 2.9 \mu\text{m}$ to $911.3 \mu\text{m} \pm 2.8 \mu\text{m}$ whereas the range for the PM powders was $68.0 \mu\text{m} \pm 0.6 \mu\text{m}$ to $672.3 \mu\text{m} \pm 8.6 \mu\text{m}$ due to the occurrence of aggregated particles. Due to the particles aggregation, formulations that were produced through LS showed smaller span values (narrower size distribution) compared to their PM powders (Table 7.1) as indicated by the higher $d_{10\%}$

values, fine particulates content showed a significant reduction for LS formulations compared to their PM counterparts (Table 7.1), that could account for their improved size homogeneity. This could be ascribed to the adhesion of such fines on the surfaces of larger particles in the case of LS formulations (Table 7.1). The breadth of the particle distribution and span value was higher for the formulation containing psyllium (3.6 ± 0.1) and lower for PolyoxTM (2.2 ± 0.1) in the case of PM powders. Therefore, psyllium demonstrated higher polydispersity than PolyoxTM. Eudragit[®] RS had the highest span value of (8.2 ± 0.7) in the case of LS formulations. The VMD of both the LS formulations and PM powders showed increasing trend with an increase in a PolyoxTM to Psyllium ratio. LS formulations demonstrated significantly higher VMD value ($p < 0.05$) than those of the PM powders (Table 7.1) which indicate broader size distributions. Images analysis from SEM in LS formulations and PMs powders showed that the particles of Eudragit[®] RL and Hypromellose powders were found irregular in shape, the particles of Eudragit[®] RS powders consisting of irregular and needle shape, and the particles of psyllium were nearly spherical and the PolyoxTM was found to be irregular. From this Figure 7.3 and Figure 7.4, it can be observed that the powders exhibited various shapes. The mixture of PolyoxTM: Psyllium at (1:3 and 3:1) ratio was found to be spherical and consisting of small angular shape (Figure 7.4).

Table 7.1: Particle size distribution (i.e. particle size at 10% ($d_{10\%}$), 50% ($d_{50\%}$), 90% ($d_{90\%}$), volume mean diameter (VMD), and span; mean \pm SD, $n = 3$) of DTZ–Polyox™ liquisolid (LS) formulation powders and their physical mixture (PM) counterparts.

Formulation	Polyox™:Psyllium	$d_{10\%}$ (μm)		$d_{50\%}$ (μm)		$d_{90\%}$ (μm)		VMD (μm)		Span	
		PM	LS	PM	LS	PM	LS	PM	LS	PM	LS
PM–DTZ–Psyllium		15.9 \pm 1.0	126.2 \pm 95.1	427.3 \pm 19.7	743.3 \pm 53.0	1560.0 \pm 26.5	1930.0 \pm 45.8	611.3 \pm 17.9	911.3 \pm 2.8	3.6 \pm 0.1	2.4 \pm 0.2
PM–DTZ–Polyox™		18.8 \pm 2.1	56.1 \pm 1.4	100.7 \pm 1.4	143.3 \pm 3.1	247.3 \pm 2.8	289.3 \pm 3.1	121.7 \pm 2.0	156.7 \pm 4.2	2.2 \pm 0.1	1.6 \pm 0.2
PM–DTZ–Hypromellose		10.2 \pm 0.3	33.3 \pm 0.3	49.2 \pm 0.5	82.1 \pm 0.5	156.0 \pm 1.0	254.7 \pm 6.4	68.0 \pm 0.6	118.7 \pm 2.9	2.9 \pm 0.0	2.7 \pm 0.1
PM–DTZ–Eudragit® RS		28.4 \pm 2.3	63.4 \pm 3.5	482.0 \pm 20.1	283.3 \pm 35.3	1710.0 \pm 87.1	2373.2 \pm 119	672.3 \pm 8.6	859.0 \pm 8.7	3.5 \pm 0.5	8.2 \pm 0.7
PM–DTZ–Eudragit® RL		11.2 \pm 0.6	40.1 \pm 0.1	48.9 \pm 0.4	98.2 \pm 1.6	166.7 \pm 2.5	307.0 \pm 15.8	70.1 \pm 0.22	141.0 \pm 7.0	3.1 \pm 0.1	2.7 \pm 0.1
DTZ–Polyox™:Psyllium	1:1:1	8.1 \pm 0.7	14.7 \pm 4.1	33.6 \pm 0.8	48.6 \pm 2.2	261.3 \pm 32.7	249.7 \pm 80.5	81.1 \pm 21.3	91.8 \pm 21.3	7.5 \pm 0.8	4.7 \pm 1.4
DTZ–Polyox™:Psyllium	1:1:3	7.0 \pm 0.1	21.3 \pm 0.5	32.0 \pm 0.4	106.4 \pm 8.7	174.0 \pm 1.0	1396.6 \pm 35.1	92.2 \pm 0.61	446.3 \pm 18.5	5.2 \pm 0.1	13.0 \pm 0.7
DTZ–Polyox™:Psyllium	1:3:1	15.6 \pm 0.7	21.5 \pm 0.7	205.7 \pm 82.8	286.0 \pm 80.7	1806.6 \pm 49.3	1803.3 \pm 23.1	638.7 \pm 28.4	649.7 \pm 24.9	10.1 \pm 5.0	6.5 \pm 1.6

7.3.3 Powder density

LS formulations showed a lower flowability in comparison to their PM powders (Table 7.2). Moreover, the addition of liquid might increase cohesive and adhesive forces among particles due to the wall effect. Hence, a reduction in flow rate is likely for LS formulations which agree with other investigations (Nazzal *et al.*, 2002). The values of CI obtained from PM formulations was higher for Eudragit[®] RS (32.0%), indicating that it is a highly compressible powder, whereas CI is lower for the Psyllium (23.8%) which indicates its free-flowing behaviour. As observed in (Table 7.2), LS formulations showed increasing flow properties based on CI value ranges from Eudragit[®] RS > Eudragit[®] RL > Polyox[™] > Hypromellose > Psyllium. It was observed that for all LS formulations, with the exception of Eudragit[®] RS and Eudragit[®] RL produced CI values less than 25%, which indicates they have better flow properties. Psyllium produced better flow behaviours indicating a lower degree of cohesivity in both formulations, therefore, improved powders flowability. This could be due to the existence of its spherical shape from these particles (Table 7.2). The improvement of flow properties recommends that they can easily handle during processing. The mixture of (Polyox[™] and Psyllium) at 1:1, 1:3 and 3:1 (Polyox[™]:Psyllium) ratio also produced good flow properties that show a nearly spherical shape in LS and PM formulations (Table 7.2).

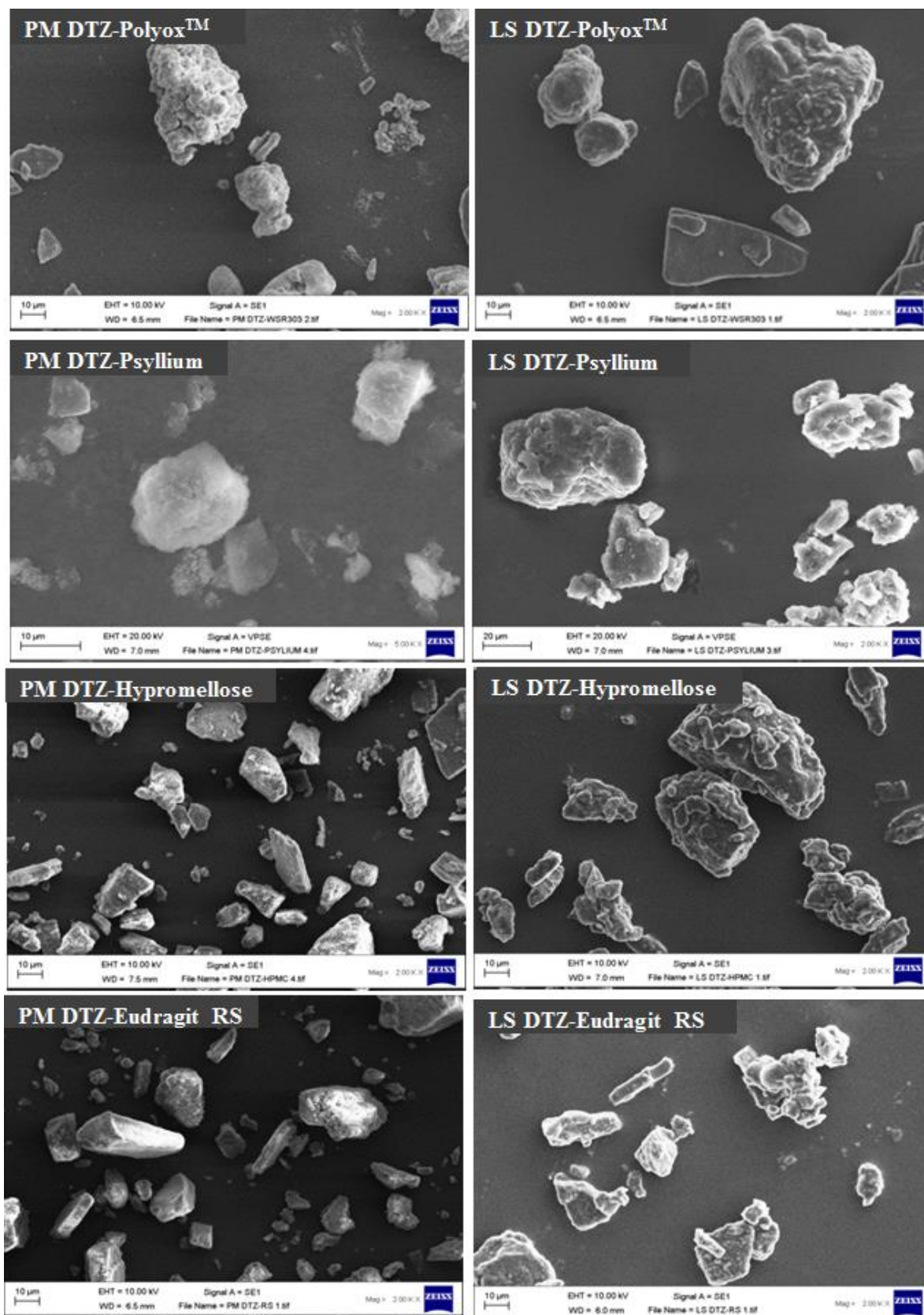


Figure 7.3: SEM of diltiazem HCl (DTZ) from physical mixture (PM) and liquisolid (LS) formulations containing polymer type and ratio.

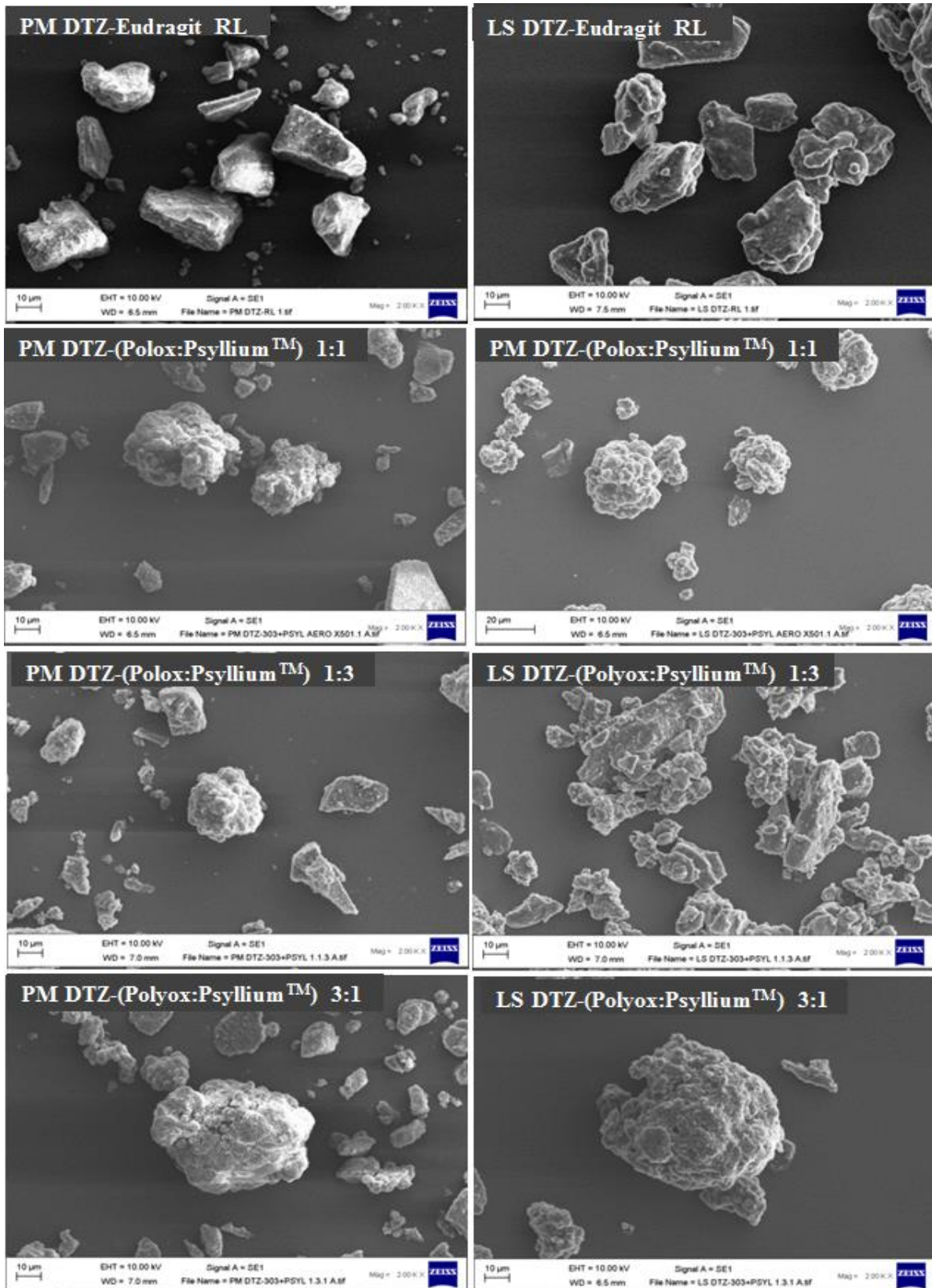


Figure 7.4: SEM of diltiazem HCl (DTZ) from physical mixture (PM) and liquisolid (LS) formulations containing polymer type and ratio.

Table 7.2: Bulk density, tap density and Carr's index (CI) and Hardness (mean \pm SD, $n = 5$) for DTZ– Polymer type and PolyoxTM:Psyllium ratio liquisolid (LS) formulation powders and their physical mixture (PM) counterparts.

Formulation	Ratio	Bulk density (g/cm ³)		Tap density (g/cm ³)		CI (%)		Hardness (N)	
		PM	LS	PM	LS	PM	LS	PM	LS
DTZ–WSR 303		0.36 \pm 0.02	0.32 \pm 0.01	0.46 \pm 0.10	0.42 \pm 0.02	22.3 \pm 1.2	23.7 \pm 0.02	155 \pm 0.2	13.7 \pm 1.4
DTZ–HPMC		0.45 \pm 0.01	0.41 \pm 0.02	0.66 \pm 0.01	0.54 \pm 0.01	30.8 \pm 1.11	23.2 \pm 0.03	78.0 \pm 1.3	21.3 \pm 2.8
DTZ–Psyllium		0.42 \pm 0.01	0.39 \pm 0.00	0.55 \pm 0.01	0.50 \pm 0.01	23.8 \pm 0.50	22.8 \pm 0.50	61.2 \pm 1.4	9.61 \pm 0.5
DTZ– Eudragit[®] RS		0.44 \pm 0.00	0.39 \pm 0.00	0.65 \pm 0.01	0.53 \pm 0.01	32.0 \pm 0.82	28.2 \pm 0.82	112 \pm 5.3	46.6 \pm 0.5
DTZ– Eudragit[®] RL		0.46 \pm 0.01	0.37 \pm 0.01	0.67 \pm 0.01	0.54 \pm 0.01	31.5 \pm 0.57	28.5 \pm 1.00	113 \pm 8.0	56.4 \pm 2.3
DTZ-(PolyoxTM:Psyllium)	1:1	0.42 \pm 0.02	0.46 \pm 0.02	0.53 \pm 0.01	0.58 \pm 0.01	22.3 \pm 0.43	20.0 \pm 0.51	80.9 \pm 3.6	17.7 \pm 0.0
DTZ-(PolyoxTM:Psyllium)	1:3	0.39 \pm 0.00	0.45 \pm 0.00	0.51 \pm 0.00	0.57 \pm 0.01	23.3 \pm 0.52	21.8 \pm 0.54	48.3 \pm 0.9	14.2 \pm 0.6
DTZ-(PolyoxTM:Psyllium)	3:1	0.35 \pm 0.01	0.51 \pm 0.01	0.38 \pm 0.01	0.48 \pm 0.01	27.8 \pm 0.51	22.0 \pm 0.02	116 \pm 2.6	23.8 \pm 1.5

7.3.4 Hardness

The hardness value of tablets made by various polymer in LS formulations produced weaker tablets than those prepared by PM powders (Table 7.2). For example, LS tablets containing Eudragit[®] RL showed lower hardness (56.4N) compared to PM compacts (113.1N). This was due to the presence of the PS 80 as shown in the previous Chapters. However, formulations containing Eudragit[®] RL recorded higher hardness tablets values in comparison to those matrices containing other polymers in LS formulations (Table 7.2). The hardness was in the following rank order Eudragit[®] RL > Eudragit[®] RS > Hypromellose > Polyox[™] > Psyllium. In contrast, the tablets containing Polyox[™] showed higher hardness (or breaking force) among the various polymers used in the case of PM (Table 7.2). This may be due to the formation of stronger hydrogen bridge linkages between the primary particles of Polyox[™]. Formulation containing psyllium recorded lower hardness value from both the LS and PM formulations. This was also reported by (Saeedi *et al.*, 2010b), where psyllium produced lower hardness values from (3.85 ± 0.24 to 5.09 ± 0.31). The matrices tablets containing (3:1) Polyox[™]:Psyllium ratio obtain from both the LS formulations and their counterpart PM powders showed higher hardness as compared to those formulations made by 1:1 and 1:3 Polyox[™]:Psyllium ratio (Table 7.2).

7.3.5 Drug release studies

Drug release from LS tablets was affected by the various polymers. The release was in the order of: Eudragit[®] RL > Eudragit[®] RS > Hypromellose > Polyox[™] > Psyllium. Hydrophilic Psyllium provided a slowest DTZ release across the various polymer used in both the LS and PM compacts (Figure 7.5). The swellable hydrophilic matrix initiates the release of a drug with the penetration of water into the matrix. The drug is homogeneously dispersed in the matrices system throughout a rate controlling medium. Then, the drug is dissolved and the polymer hydrated by penetrated water causes swelling to form a gel-like structure, thereby

producing a polymer chains relaxation and consequently, the polymer size increases. This allows the drug to diffuse into the swollen network of the matrix out of the external environment. Hence, the release of the drug is very firmly related to the swelling property of the psyllium hydrogel. This was confirmed by the dissolution parameters which showed that both the LS and PM compacts formulated with psyllium to have lower DEs and lower MDR. For example, in LS formulations, psyllium tablets to produce lower DE ($18.9\% \pm 1.1\%$) and a lower MDR ($0.08 \text{ min}^{-1} \pm 0.01 \text{ min}^{-1}$) than those obtained from formulations containing PolyoxTM ($29.1\% \pm 0.9\%$) and ($0.13 \text{ min}^{-1} \pm 0.01 \text{ min}^{-1}$), Eudragit[®] RL ($47.5\% \pm 0.2\%$) and ($0.49 \text{ min}^{-1} \pm 0.01 \text{ min}^{-1}$), Hypromellose ($54.7\% \pm 0.3\%$) and ($0.21 \text{ min}^{-1} \pm 0.01 \text{ min}^{-1}$) and Eudragit[®] RS ($56.5\% \pm 1.1\%$) and ($0.42 \text{ min}^{-1} \pm 0.01 \text{ min}^{-1}$) (Table 7.3). The same consideration was also seen in the case of PM compacts. The release rate of DTZ was generally faster in both the PM and LS formulations containing Eudragit[®] RL and RS polymer although they have clear similarity in their properties (Figure 7.5). This might be due to the greater permeability of Eudragit[®] RL and higher number of quaternary ammonium groups. When exposed to the aqueous media, the media penetrates into the free spaces within macromolecular chains of Eudragit[®] RL (Haznedar and Dortunç, 2003). The dimensions of the polymer molecule increase due to polymer relaxation by the stress of the penetrated media after solvation of the polymer chains. This phenomenon may be attributed to initial disaggregation or surface erosion of the matrix tablet prior to gel layer formation within the tablet core. These results are in complete agreement with those published by (Wadher *et al.*, 2011), for metformin. These authors showed that when Eudragit[®] RL was used as the retarding agent, the entire metformin content was released within 2 hrs.

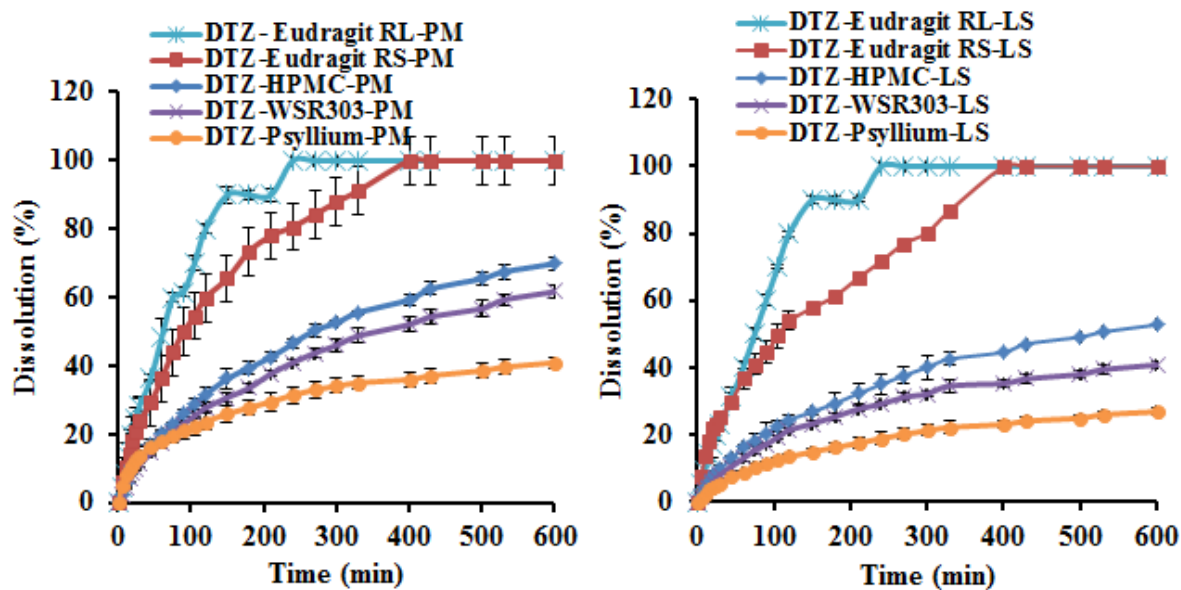


Figure 7.5: Dissolution profiles of DTZ from physical mixture (PM) and liquidolid (LS) matrix tablets containing various Polymer type.

RS and RL do not dissolve in water. Hence, the drug can only diffuse out much faster within the polymer gaps and most of the drug release will depend on the disintegration or higher degree of erosion of the polymeric matrix leading to a faster drug release rate as demonstrated in (Figure 7.5). They are copolymers of partial esters of acrylic and methacrylic acids carrying low volumes of quaternary ammonium groups, roughly 5% and 10% for RS and RL, respectively (Haznedar and Dortunç, 2003). Statistical analysis confirmed that DTZ release profiles from both LS tablets and PM compact containing RS were not significantly different ($f_2 > 50$) in comparison to RL (Table 7.3). In general, the dissolution rate of DTZ from LS compacts prepared using various Polymers compared to the counterpart conventional PM compacts are shown in (Figure 7.5). It can be seen that the dissolution behaviours of LS compacts showed a slower release of DTZ compared to the conventional compacts (Figure 7.5) as seen in the previous Chapters.

Table 7.3: Dissolution efficiency, mean dissolution rate, mean dissolution rate, similarity factor (f_2) and in vitro release kinetic parameters n value of diltiazem HCl obtained for liquisolid formulations containing various Polymers type and ratio in comparison to their physical mixture counterparts. The counterpart physical mixture was chosen as the standard for each liquisolid formulation when calculating f_2 values. The results are expressed as the mean \pm SD, n = 3 (*indicates significant difference, P< 0.05).

Formulation	Ratio	DE (%)		MDT (min^{-1})		MDR (min^{-1})		f_2	n value	
		PM	LS	PM	LS	PM	LS		PM vs LS	PM
PM-DTZ-Psyllium		31.0 \pm 2.2	18.9 \pm 1.1	146.4 \pm 13.7	175.7 \pm 9.4	0.16 \pm 0.02	0.08 \pm 0.01	48.4	0.413	0.654
PM-DTZ-PolyoxTM		41.9 \pm 1.1	29.1 \pm 0.9	192.7 \pm 1.0	172.3 \pm 1.8	0.18 \pm 0.01	0.13 \pm 0.01	48.1	0.615	0.748
PM-DTZ-Hypromellose		68.4 \pm 11.0	54.7 \pm 0.3	167.6 \pm 41.6	139.4 \pm 26.3	0.29 \pm 0.05	0.21 \pm 0.01	46.0	0.663	0.653
PM-DTZ-Eudragit[®] RS		62.5 \pm 3.8	56.5 \pm 1.1	104.0 \pm 11.5	115.3 \pm 6.7	0.43 \pm 0.02	0.42 \pm 0.01	61.1	0.505	0.566
PM-DTZ-Eudragit[®] RL		57.3 \pm 1.2	47.5 \pm 0.2	59.2 \pm 1.1	75.2 \pm 0.5	0.59 \pm 0.01	0.49 \pm 0.01	51.6	0.971	0.725
DTZ-(PolyoxTM:Psyllium)	1:1:1	25.1 \pm 0.4	13.0 \pm 0.4	218.1 \pm 2.4	212.2 \pm 4.9	0.11 \pm 0.01	0.05 \pm 0.01	47.4	0.684	0.915
DTZ-(PolyoxTM:Psyllium)	1:1:3	25.9 \pm 0.5	19.7 \pm 0.9	180.0 \pm 8.7	195.1 \pm 7.0	0.12 \pm 0.01	0.08 \pm 0.01	49.37	0.641	0.748
DTZ-(PolyoxTM:Psyllium)	1:3:1	29.2 \pm 1.3	23.2 \pm 0.3	191.1 \pm 8.9	217.3 \pm 16.2	0.13 \pm 0.01	0.09 \pm 0.01	49.44	0.673	0.822

This is also supported by the dissolution parameters that showed LS compacts to have lower DEs and lower MDR than their PM counterparts regardless of the polymer used. For example, LS formulation containing Psyllium tablets to produce lower DE (from $18.9\% \pm 1.1\%$ and lower MDRs (from $0.08 \text{ min}^{-1} \pm 0.01 \text{ min}^{-1}$) compared to the conventional compacts (DE = $31.0\% \pm 2.2\%$ and MDR = $0.16 \text{ min}^{-1} \pm 0.02 \text{ min}^{-1}$) (Table 7.3). Statistical analysis confirmed that DTZ release profiles from LS tablets were significantly different ($f_2 < 50$) in the case of formulations containing all the hydrophilic polymers such as psyllium, PolyoxTM and hypromellose as compared to their PM tablets (Table 7.3).

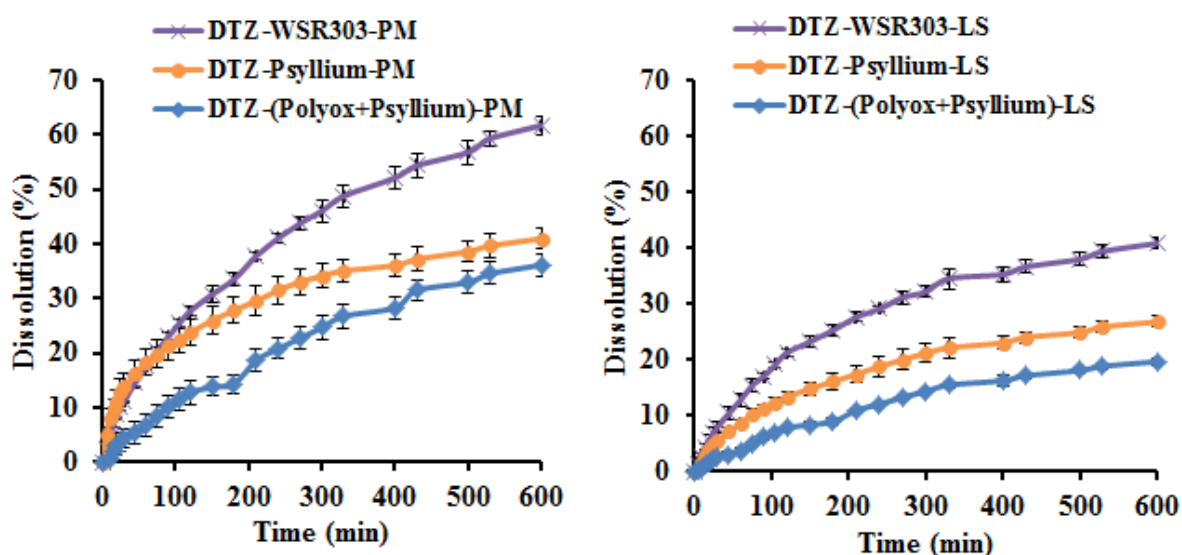


Figure 7.6: Release patterns (mean \pm SD, $n = 3$) of diltiazem HCl (DTZ) from physical mixture (PM) and liquid solid (LS) formulations containing psyllium, PolyoxTM and PolyoxTM:Psyllium.

Two polymers (i.e. PolyoxTM and Psyllium) were selected for further investigation due to its excellent retardation properties from the previous studies. The influence of the inclusion of Psyllium into PolyoxTM at 1:1 ratio on the release profile of DTZ in comparison to the individual of Psyllium and PolyoxTM are shown in (Figure 7.6). Interesting results were

obtained when binary mixtures of Psyllium and PolyoxTM were used as a release retardant. The release profiles of DTZ showed the use of a binary mixture of Psyllium and PolyoxTM matrices produce slower release rate in both LS formulations and PM tablets. This was ascribed to the reduced entrance of aqueous media into the matrix due to the presence of the stronger viscose gel within the two hydrophilic matrices compared to individual psyllium and PolyoxTM. A similar explanation is also studied previously showing the addition of Viscarin to Hypromellose in formulations gave slower release rate of ibuprofen for 10hrs which are possibly due to slower erosion of hypromellose (Nerurkar *et al.*, 2005). PolyoxTM has been reported in many combinations in sustained release formulations as seen in [section 7.1](#). This is also confirmed by the dissolution parameters that showed (PolyoxTM: Psyllium) to produce lower DE and lower MDR than the individual Psyllium and PolyoxTM alone. For example, in LS formulation, (PolyoxTM: Psyllium) tablet produce lower DE ($13.0\% \pm 0.4\%$ and $MDR = 0.05 \text{ min}^{-1} \pm 0.01 \text{ min}^{-1}$) than Psyllium ($18.9\% \pm 1.1\%$ and $MDR = 0.08 \text{ min}^{-1} \pm 0.01 \text{ min}^{-1}$) and PolyoxTM ($29.1\% \pm 0.9\%$ and $MDR = 0.13 \text{ min}^{-1} \pm 0.01 \text{ min}^{-1}$) ([Table 7.3](#)). LS formulations produced better retardation properties in comparison to PM counterpart. Statistical analyses using f_2 value confirmed that the release rate of DTZ from LS tablets was significantly different from PM tablets, i.e. they are not similar in all the formulations ($f_2 < 50$) ([Table 7.3](#)). This is also supported by dissolution parameters which confirmed LS tablets produced lower DE and lower MDR than PM tablets in respective of the polymer used. Based on the release profiles in ([Table 7.3](#)), I came to this conclusion that the inclusion of Psyllium into PolyoxTM at PolyoxTM:Psyllium (1:1) gives more sustained release profile for a period of 8hrs. Therefore, this ratio 1:1 was chosen for further investigation as discussed below.

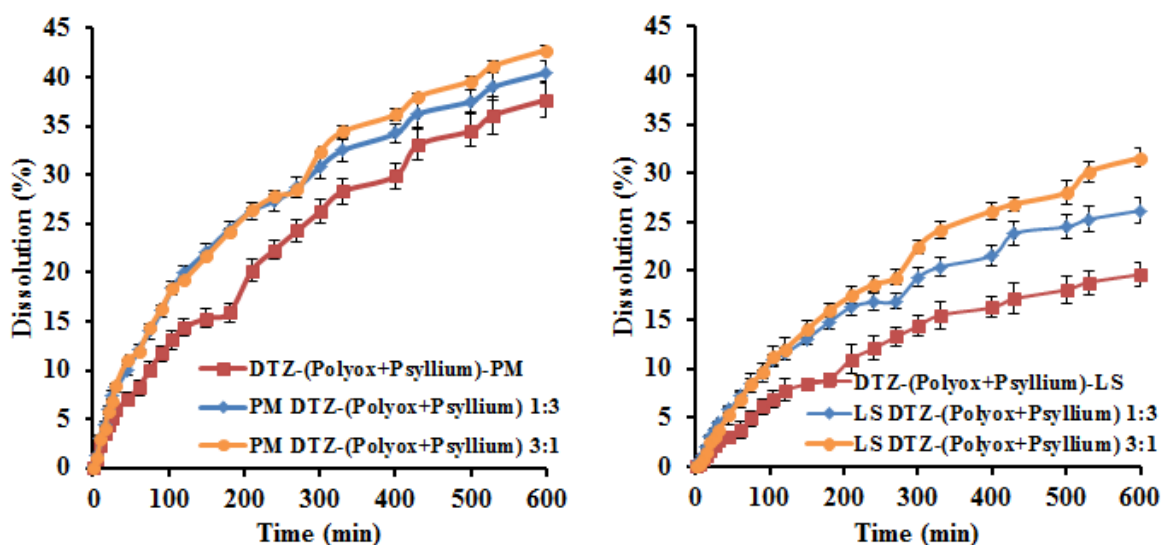


Figure 7.7: Release patterns (mean \pm SD, $n = 3$) of diltiazem HCl (DTZ) from physical mixture (PM) and liquisolid (LS) formulations containing binary mixture of Psyllium and PolyoxTM at different ratio.

Following the previous results, PolyoxTM–Psyllium was selected for further investigation. The influence of Psyllium:PolyoxTM ratio at 1:1, 1:3 and 1:3 on drug release was assessed. The results were depicted in (Figure 7.7). The results showed that matrices containing (Psyllium:PolyoxTM) at 1:1 ratio can slow down the drug release than the matrices compacts containing 1:3 and 3:1 (Psyllium:PolyoxTM) ratio. , i.e., the dissolution rate has decreased with decreasing the percentage of (PolyoxTM:Psyllium) (Figure 7.7). Statistical analyses confirm all formulations showed significant differences in the release rate of DTZ from LS formulation in comparison to their PM tablets ($f_2 < 50$). In general LS tablets produce slower drug release than their PM tablets. Dissolution parameters also supported the above results. For example, in LS containing 1:1 (PolyoxTM: Psyllium) tablet ratio produce lower DE ($13.0\% \pm 0.4\%$ and $MDR = 0.05 \text{ min}^{-1} \pm 0.01 \text{ min}^{-1}$) than their counterpart PM (DE $25.1\% \pm 0.4\%$ and $MDR = 0.11 \text{ min}^{-1} \pm 0.01 \text{ min}^{-1}$).

The kinetics release for the polymer type is shown in (Table 7.3). The results of this investigations demonstrated the release of DTZ from all the hydrophilic polymer matrices was

typically non-fickian (anomalous) fitting well to Korsmeyer-Peppas indicating DTZ release was by the incorporation of diffusion and erosion (Table 7.3). Other values of n obtained from matrices containing Eudragit[®] RS and Eudragit[®] RL indicating a diffusional-controlled release in both the LS tablets and PM formulations. With the exception of Eudragit[®] RLPO, in the case of PM formulations released drug via case-II transport mechanism ($n > 0.89$) which caused from the erosion of the matrix was the main factor controlling the release of a drug (Table 7.3). The binary mixture of psyllium and Polyox[™] in the ratios of 1:1, 3:1 and 1:3 followed anomalous transport mechanism in the case of PM formulations whereas with the exception of binary mixture of psyllium and Polyox[™] in the ratios of 3:1, all LS formulations release drug via case-II transport mechanism (Table 7.3). Regardless of their ratio, the n values from all LS formulations were higher than the values obtained from PM formulations.

7.4 Conclusion

In this study, the possibility of using psyllium polymer-based matrix system for sustained release of highly water-soluble drug and the combination of Polyox[™] and psyllium were demonstrated. Psyllium was able to retard DTZ release from the various matrices tablet used in this formulation. Among them, drug release from Polyox[™]-psyllium based matrix system demonstrated the best-sustained release behaviour and was still slower by the modification of Polyox[™]:psyllium ratio. The combination of the polymers has shown a very useful in being able to produce different drug release profiles.

8 CHAPTER 8: INFLUENCE OF pH AND ROTATIONAL SPEED

8.1 Introduction

Hydrophilic matrix tablets are broadly employed for oral sustained-release design dosage forms due to its cost-effectiveness, simplicity and less risk in term of its toxicity (Huang *et al.*, 2005). The dissolution is a rate-limiting step for drug bioavailability from a hydrophilic based matrix system. Media penetrated into the matrix system then the drugs dissolve and diffuse it out of the matrices system in a controlled behaviour (Siepe *et al.*, 2006). As mention in Chapter 1, PolyoxTM is linear, hydrophilic and uncrosslinked polymers (Kim, 1995). PolyoxTM hydrate rapidly upon exposure to GI fluid and then swell to form a hydrogel layer on the surface of the tablet. This is accompanied by erosion of the PolyoxTM. The swelling and erosion characteristics of PolyoxTM control and delayed drug release (Petrovic *et al.*, 2009). Therefore, PolyoxTM has been broadly accepted in matrix tablets, including direct compression (Crowley *et al.*, 2002), granulation (Petrovic *et al.*, 2009), hot-melt extrusion (Nanjwade *et al.*, 2011) and LS (Kaialy *et al.*, 2016). Importantly, the PolyoxTM are widely available in a range of MWs between (1×10^5 to 6×10^6), giving them good candidates for control release, due to PolyoxTM containing low MW produce a complete release, while high MW PolyoxTM allows greater control release (Kim, 1995). In addition, the drug release will offer better retardation properties when PolyoxTM have been employed in combination with other hydrophilic excipients, that including stearic acid (Tajiri *et al.*, 2010), PEG (Lyons *et al.*, 2008), poly (ε-caprolactone) (Verhoeven *et al.*, 2009), ethylcellulose (Vechia *et al.*, 2011), hypromellose (Palmer *et al.*, 2013), and sodium carboxymethylcellulose (Ma *et al.*, 2014). Usually, the incorporation of hydrophilic excipients gives better drug release. Drug solubility administers the entire process in the dissolution medium. Many drugs have a pH-dependent solubility, showing different release rates with varying pH in the GI (Streubel *et al.*, 2000). Penetration of GI fluids with changing pH causes reduction of the further ionizable drug (soluble form) to a less soluble form. Therefore, the diffusion rate of the drug is reduced

through the matrix. This conversion into an insoluble drug depends on the pH of the intestinal fluids and pKa value of the drug. It is desirable to obtain drug release with a pH-independent environment for making the necessary dose bioavailable (Streubel *et al.*, 2000). As the pH of GI fluids cannot be modified, an optimised pH in the design dosage form can be employed to modulate the release.

In this Chapter, PolyoxTM and Psyllium were selected as retardant agent for a sustained release matrix tablet. The matrix tablets with a combination of PolyoxTM and Psyllium were prepared at 1:1 PolyoxTM:Psyllium ratio and the characterisation of dissolution properties in some test environments were evaluated, including pH and mechanical stress in the GIT.

8.2 Results and discussion

8.2.1 Drug release studies

The LS and PM formulations containing 1:1 PolyoxTM:Psyllium ratios that gave the slowest drug release were chosen to study the influence of changing the pH medium and rotational speed on drug dissolution profile (Figure 8.1 and 8.2). The drug release profile of DTZ obtained from LS and PM tablets were compared in various pH media, which include pH 1.2, 2.2, 5.8, 6.8, 7.2 and 7.5 respectively, although DTZ release was sustained irrespective of their pH dissolution media. The dissolution behaviour of DTZ obtained from both LS and PM tablets showed a decreasing trend with increasing pH media, range (from pH 1.2 to pH 7.8). This is further supported by dissolution parameters, that indicate LS tablets prepared with pH 7.8 have lower DE ($13.7\% \pm 0.40\%$) than those obtained from matrices containing pH 1.2 ($24.5\% \pm 0.50\%$), pH 2.2 ($20.5\% \pm 0.82\%$), pH 5.8 ($18.7\% \pm 0.40\%$), pH 6.8 ($15.6\% \pm 0.70\%$) and pH 7.2 ($14.8\% \pm 1.00\%$) (Table 8.1). Although using f_2 values, confirmed that such decrease in drug release rate is not significantly different (Table 8.1). The f_2 value was higher than 50, showing that the release was independent of the pH ($f_2 > 50$).

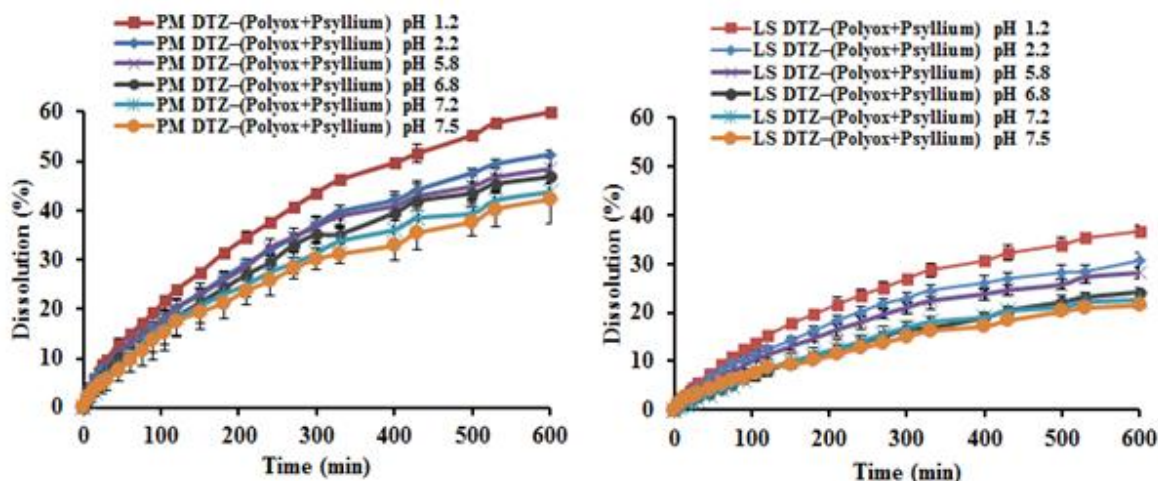


Figure 8.1: Release patterns (mean \pm SD, $n = 3$) of diltiazem HCl (DTZ) from physical mixture (PM) and liquisolid (LS) formulations containing various pH media.

The drug release was not affected by the pH in the mimicked gastric condition. The results suggest that inclusion counter polymer Psyllium into PolyoxTM matrices is an effective way to achieving more sustained drug release with less pH dependency. Sustained release of DTZ has been reported previously to be unaffected by speed rate and pH (Peh and Wong, 2000). In general, the dissolution behaviour of LS tablets exhibited significantly slower release rates of DTZ than the PM tablets regardless of the pH media used (Figure 8.1), as validated by f_2 values below 50 (Table 8.1). This was further confirmed by dissolution parameters which showed the LS tablets to have lower DEs higher MDT than their counterpart PM tablets. For example, LS formulations containing pH 7.5 produced lower DE ($13.7\% \pm 0.40\%$) compared to the conventional tablets DEs ($27.1\% \pm 2.61\%$) (Table 8.1).

Table 8.1: Dissolution efficiency (DE), mean dissolution rate (MDT), mean dissolution rate (MDR), similarity factor (f_2) and in vitro release kinetic parameters n value of diltiazem HCl obtained for liquisolid (LS) formulations containing various pH media in comparison to their physical mixture (PM) counterparts. The counterpart physical mixture was chosen as the standard for each liquisolid formulation when calculating f_2 values. The results are expressed as the mean \pm SD, n = 3 (*indicates significant difference, P < 0.05).

pH Media	DE (%)		MDT (min)		MDR (min^{-1})		f_2	n Value	
	PM	LS	PM	LS	PM	LS		LS vs PM	PM
DTZ–(PolyoxTM:Psyllium) pH 1.2	40.0 \pm 0.73	24.5 \pm 0.50	205.2 \pm 3.10	201.0 \pm 9.60	0.16 \pm 0.01	0.10 \pm 1.70	44.2	0.660	0.700
DTZ–(PolyoxTM:Psyllium) pH 2.2	33.7 \pm 1.71	20.5 \pm 0.82	206.1 \pm 2.70	199.8 \pm 13.5	0.14 \pm 0.01	0.08 \pm 0.00	47.5	0.615	0.698
DTZ–(PolyoxTM:Psyllium) pH 5.8	32.8 \pm 0.90	18.7 \pm 0.40	194.4 \pm 1.10	201.9 \pm 2.02	0.14 \pm 0.00	0.07 \pm 0.01	46.3	0.623	0.690
DTZ–(PolyoxTM:Psyllium) pH 6.8	31.0 \pm 1.64	15.6 \pm 0.70	203.3 \pm 11.4	231.1 \pm 8.20	0.13 \pm 0.01	0.05 \pm 0.01	43.4	0.717	0.642
DTZ–(PolyoxTM:Psyllium) pH 7.2	28.8 \pm 2.42	14.8 \pm 1.00	206.1 \pm 18.4	207.0 \pm 26.7	0.12 \pm 0.01	0.05 \pm 0.01	46.3	0.702	0.859
DTZ–(PolyoxTM:Psyllium) pH 7.5	27.1 \pm 2.61	13.7 \pm 0.40	210.0 \pm 19.1	214.0 \pm 6.40	0.11 \pm 0.01	0.60 \pm 0.00	47.4	0.605	0.963

To investigate the effects of rotational speed on the release rate of DTZ, four different RPM (25, 50, 75 and 100) were studied for choosing the best-optimised formulation. The release rate of DTZ from both the LS formulations and PM tablets were similar despite having different rotational speed (Figure 8.2). Therefore, it could be detailed that the adhesive force between polymers and DTZ particles is great enough, not being affected at higher rotational speeds. To confirm the above finding, the similarity factor (f_2) was calculated and f_2 value (Polyox™:Psyllium) is greater than 50 irrespective of their speeds, which indicate that there is no significant difference between drug release from various rotational speeds ($f_2 > 50$). In general, LS tablets produced slower release rate of DTZ when compared to their conventional PM tablets. To confirm the above finding, the similarity factor (f_2) was also calculated and data are presented in (Table 8.1). This table shows that all f_2 value (Polyox™:Psyllium) is less than 50 irrespective of their speeds, which indicate that there is a significant difference between drug release from LS formulations in comparison to their PM various rotational speeds ($f_2 < 50$) (Table 8.1)

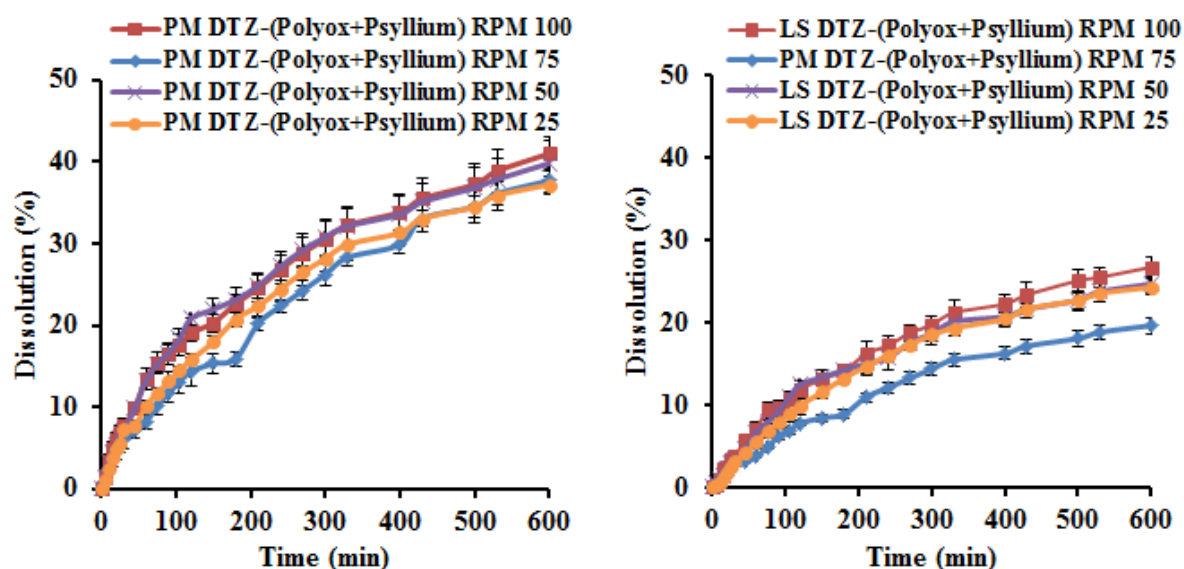


Figure 8.2: Release patterns (mean \pm SD, $n = 3$) of diltiazem HCl (DTZ) from physical mixture (PM) and liquisolid (LS) formulations containing various rotational speeds.

To study the drug release mechanism, the drug release kinetics using different rotational speed were investigated by relating the empirical exponential equation ($M_t/M_\infty = ktn$) (Table 8.1). For matrix tablets, an n value of ~ 0.5 indicates diffusion control and an n value of ~ 1.0 indicates erosion control. The n values of the PolyoxTM:Psyllium matrix tablets were found to be between 0.620 and 0.684 in the case of PM formulations whereas LS formulations containing PolyoxTM:Psyllium matrix tablets were found to be between 0.812 and 0.898 in the aqueous media, suggesting a non-Fickian or anomalous transport, which is a combination of both Fickian transport through the hydrated matrix gel layers and polymer chain relaxation/erosion (Baumgartner *et al.*, 2006). These results showed that the drug release from the PolyoxTM:Psyllium matrix tablet was categorised as a combination of diffusion and erosion control. Regardless of their rotational speed, LS formulations containing PolyoxTM:Psyllium obtained higher n value than PM matrices tablets. This showed that LS matrices tablets are better candidates to produce more sustained drug release than their PM tablets. And for the formulations with various pH media, the drug release from both the LS formulation and PM tablet also followed anomalous transport mechanism (Table 8.1).

Table 8.2: Dissolution efficiency (DE), mean dissolution rate (MDT), mean dissolution rate (MDR), similarity factor (f_2) and in vitro release kinetic parameters n value of diltiazem HCl obtained for liquisolid (LS) formulations containing various pH media in comparison to their physical mixture (PM) counterparts. The counterpart physical mixture was chosen as the standard for each liquisolid formulation when calculating f_2 values. The results are expressed as the mean \pm SD, n = 3 (*indicates significant difference, P< 0.05).

Rotational speed	DE (%)		MDT (min)		MDR (min^{-1})		f_2 LS vs PM	n Value	
	PM	LS	PM	LS	PM	LS		PM	LS
DTZ–(PolyoxTM:Psyllium) 25	25.2 \pm 0.6	16.3 \pm 1.1	193.6 \pm 2.0	197.6 \pm 5.8	0.11 \pm 0.00	0.06 \pm 0.01	56.0	0.678	0.898
DTZ–(PolyoxTM:Psyllium) 50	27.6 \pm 0.1	16.8 \pm 0.7	184.2 \pm 7.6	190.7 \pm 15.9	0.11 \pm 0.01	0.07 \pm 0.00	49.6	0.654	0.809
DTZ–(PolyoxTM:Psyllium) 75	25.1 \pm 0.4	13.0 \pm 0.4	218.1 \pm 2.4	212.1 \pm 5.0	0.11 \pm 0.00	0.05 \pm 0.01	48.7	0.684	0.822
DTZ–(PolyoxTM:Psyllium) 100	27.8 \pm 0.6	18.0 \pm 1.2	194.1 \pm 3.0	197.0 \pm 11.5	0.12 \pm 0.01	0.07 \pm 0.01	47.2	0.620	0.812

8.3 Conclusion

This study revealed that LS technique could be optimised for the preparation of sustained release matrices of water-soluble drug. DTZ release matrix tablet with the inclusion of PolyoxTM and Psyllium was considered with respect to its dissolution properties. The dissolution profile from the PolyoxTM:Psyllium matrix tablet could be controlled and showed a constant release profile in different media. Also, the PolyoxTM:Psyllium matrices tablet was assessed to have adequate strength against mechanical stress. These results suggest that the combination of PolyoxTM and Psyllium showed robust dissolution against pH and rotational speed, and therefore indicates an appropriate sustained-release profile.

9 CHAPTER 9: INFLUENCE OF DRUGS SOLUBILITY

9.1 Introduction

Solubility has been well explained in [section 1.6.1](#) as one of the most important physiochemical properties of a drug. This is because following oral administration, the bioavailability of a drug depends primarily on its solubility in the GIT and its permeability across the cell membranes. The release rate for both water-soluble (promethazine HCl, aminophylline and propranolol HCl) and less soluble (indomethacin) drugs from hypromellose matrix systems was studied previously ([Ford *et al.*, 1985](#)). For less soluble indomethacin, both the particle size of the drug and viscosity grade of hypromellose was reported to retard more drug release than those matrices obtained from water-soluble drugs. This was primarily attributed to the dominant erosion mechanism of drug release in the case of less soluble drugs. Excipients and high concentrations of insoluble drugs may cause non-uniform swelling of the hydrophilic matrix tablet. It has been suggested that highly soluble drugs can be released by diffusing through the gel matrices and this is acknowledged to be the main passage way for their release. However, drug release also transpires through erosion of the gel matrix. With the formation of micro-cavities, highly soluble drugs can also act as pore formers, providing the gel structure more acceptable and weaker, therefore lead to increased drug release profiles. The release of poorly soluble drug is predominantly by erosion of the polymeric excipient, as the drug particles translocate and their behaviour compromises the structural integrity of the gel layer existing on the surface of the matrix tablet, thereby leading to drug release through matrix erosion ([Bettini *et al.*, 2001](#)). [Kim \(1998\)](#), described the release profile of Diclofenac Na (solubility: 25 mg/mL) from the PolyoxTM (MW of 4,000,000) matrices was faster than that of Sulfathiazole (0.59 mg/mL). [Chakraborty *et al.*, \(2009\)](#) also showed the release of Verapamil HCl (a highly water-soluble drug) from hypromellose matrices is faster when compared to matrices containing Aceclofenac (a poorly water-soluble drug). From the above discussion, there are various studies attempting to investigate the effect

of drug solubility for drug delivery purposes, but there is no data reported in the literature about the release profile of PolyoxTM:Psyllium-based matrix tablets comprising various drugs. Therefore, in the present Chapter, the effect of drug solubility on drug release from a binary mixture of PolyoxTM and Psyllium in both LS and PM powder formulations was investigated.

9.2 Formulation

Each drug type, such as DTZ, THP and ZNM (4 g) under investigation was separately dissolved in 4 g of non-volatile water-miscible solvents, i.e., PS 80, used as liquid vehicles to form liquid medication phases. A fixed drug:solvent ratio of 1:1 (*w:w*) was used. An accurately weighed 6 g of each binary mixture PolyoxTM and Psyllium fixed at 1:1 was separately mixed with 1.2 g of the AEROSIL[®] coating material and lactose (11.5 g) in the case of PM formulations and 14.1 g in the case of LS formulations). This blending was performed as described in section 2.5.

Accurately weighed samples of each liquid (750 mg) and PM (650 mg) formulation were separately weighed and then compressed on 8 mm punch and die using a manual tableting machine at a fixed pressure of 2000 psi.

9.3 Results and discussion

9.3.1 Solid state

The FT-IR spectrum of formulations containing THP and ZNM revealed considerable change within both the LS and PM formulations. In contrast PM and LS formulations indicated the presence of the characteristic bands of the DTZ almost at the same wave numbers especially for the bands observed at 1679 cm⁻¹ which corresponding to carbonyl group stretching of the lactam ring and acetate group, respectively, but strong band at 2393 cm⁻¹ which corresponding to N-H stretching of amine HCl were completely disappeared from both LS and PM formulations in the case of Pure DTZ. This disappearance in the band indicates the presence

of hydrophobic interactions between the DTZ and PolyoxTM (Figure 9.1). XRD pattern of pure drugs, PM and LS formulations of various drugs are shown in Figure 9.2. The highest crystalline PolyoxTM peak occurred at a 2θ angle of 23.5° and a smaller distinct peak was also observed at 2θ angle of 19.1° . Psyllium appears in an amorphous form. THP has distinct crystalline peaks at 2θ angles of 12.1° and a series of smaller peaks at 2θ angles of 24° , 25° , 27° and 44° . The diffraction patterns of the LS formulations and PM powders exhibit crystalline peaks corresponding to DTZ with less intense. Whereas PM and LS formulations indicated the presence of distinct crystalline peaks at 2θ angles of 19.1° in the case ZNM. The XRD pattern of prepared LS formulations containing various drugs has the same diffraction pattern with relatively less intensity peaks compared to their the counterpart PM powder. This may be attributed to the presence of a fraction of the drug mass in a molecular state (dissolved) within polysorbate in liquisolid powders. This was in good agreement with the data reported by Javadzadeh *et al*, 2008, where they XRD pattern from both the LS and PM formulations have relatively the same diffraction pattern.

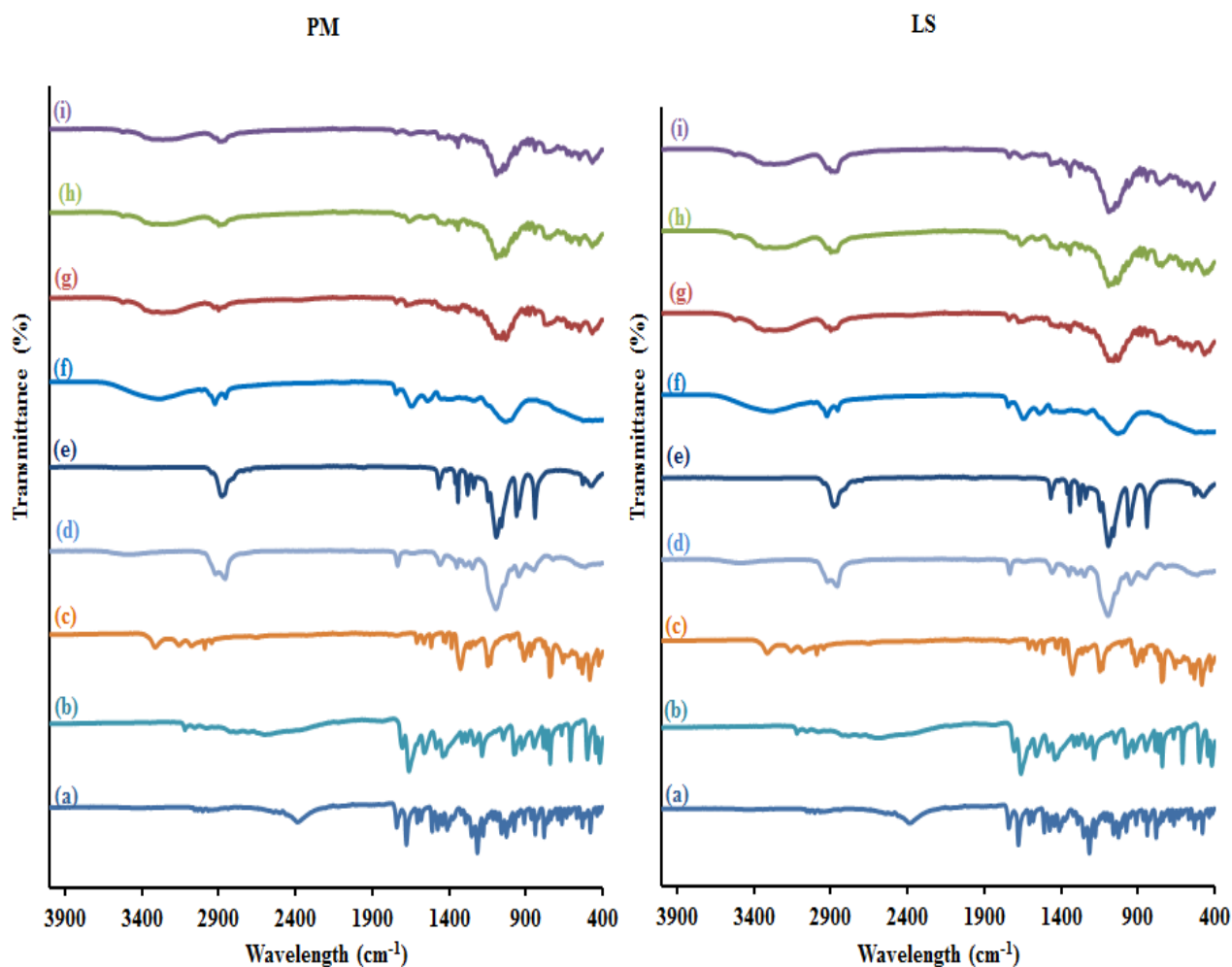


Figure 9.1: FTIR patterns of physical mixture (PM) and liquisolid (LS) formulations containing Polysorbate 80 and various drugs i.e. (a) Pure DTZ, (b) Pure theophylline, (c) Pure zonisamide, (d) Polysorbate 80, (e) Pure PolyoxTM (f) Pure Psyllium (g) DTZ–(PolyoxTM:Psyllium), (h) THP–(PolyoxTM:Psyllium) and (i) ZNM–(PolyoxTM:Psyllium).

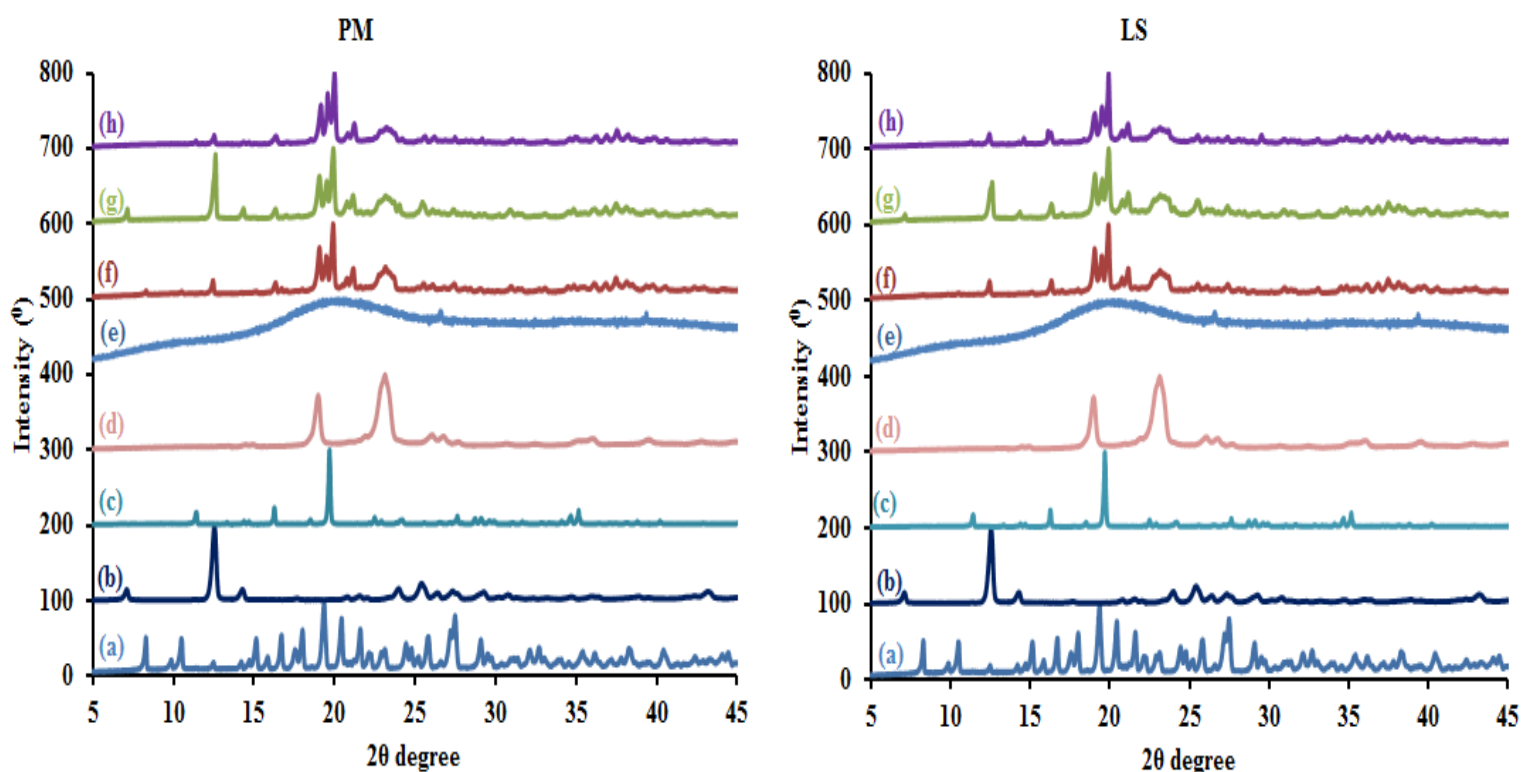


Figure 9.2: PXRD patterns of physical mixture (PM) and liquisolid (LS) formulations containing various drugs (a) Pure DTZ, (b) Pure theophylline, (c) Pure zonisamide, (d) Polysorbate 80, (e) Pure PolyoxTM (f) Pure Psyllium (g) DTZ–(PolyoxTM:Psyllium), (h) THP–(PolyoxTM:Psyllium) and (i) ZNM–(PolyoxTM:Psyllium).

9.3.2 Particle size distribution

Particle size distribution of formulations containing DTZ, THP and ZNM is shown in [Table 9.1](#). LS formulations demonstrated a considerably higher $d_{10\%}$ values compared to their PM counterparts ([Table 9.1](#)) which could account for their improved size homogeneity. For example, $d_{10\%}$ value of LS formulation obtained from ZNM has $46.9 \mu\text{m} \pm 0.2 \mu\text{m}$ whereas the value obtained from ZNM is $16.2 \pm 0.8 \mu\text{m}$ in the case of PM powder. This could be ascribed to the adhesion of such fines on the surfaces of larger particles in the case of LS formulations ([Table 9.1](#)). Regardless of their drug type, all LS formulations showed a significant difference in their median value than their counterpart PM powders ([Table 9.1](#)). The median value also showed increasing trend with a decrease in their drug solubility. For example, the mean

diameter of LS formulations increased from ($48.6 \mu\text{m} \pm 2.2 \mu\text{m}$ to $147.3 \mu\text{m} \pm 8.6 \mu\text{m}$), as the solubility of drugs decreased from (625 mg/mL to 0.8 mg/mL). This was in complete agreement to the findings of (Krejcová *et al.*, 2006), which described THP having the lowest solubility has ($d = 277.5 \mu\text{m}$) largest particles and smaller mean diameter particles were observed from DTZ ($d = 156.0 \mu\text{m}$) with the highest solubility. In general, the span value obtained from LS formulations containing DTZ (4.7 ± 1.4) was smaller than the span values obtained from ZNM (5.4 ± 0.8) and THP (9.4 ± 0.6) (Table 9.1). This indicated that THP showed a wider PSD (high polydispersity) in comparison to DTZ and ZNM (Table 9.1). SEM images of drug type particles exhibited crystalline particles in both the LS and PM and there are no much morphological variations seen between DTZ and ZNM particles (Figure 9.3). DTZ and ZNM demonstrated spherical particles with nearly uniform (regular) shape. This might be the reason for the good powder flow properties in both the formulations. THP displayed the normal angular–subangular shape with less irregular particles (Figure 9.3).

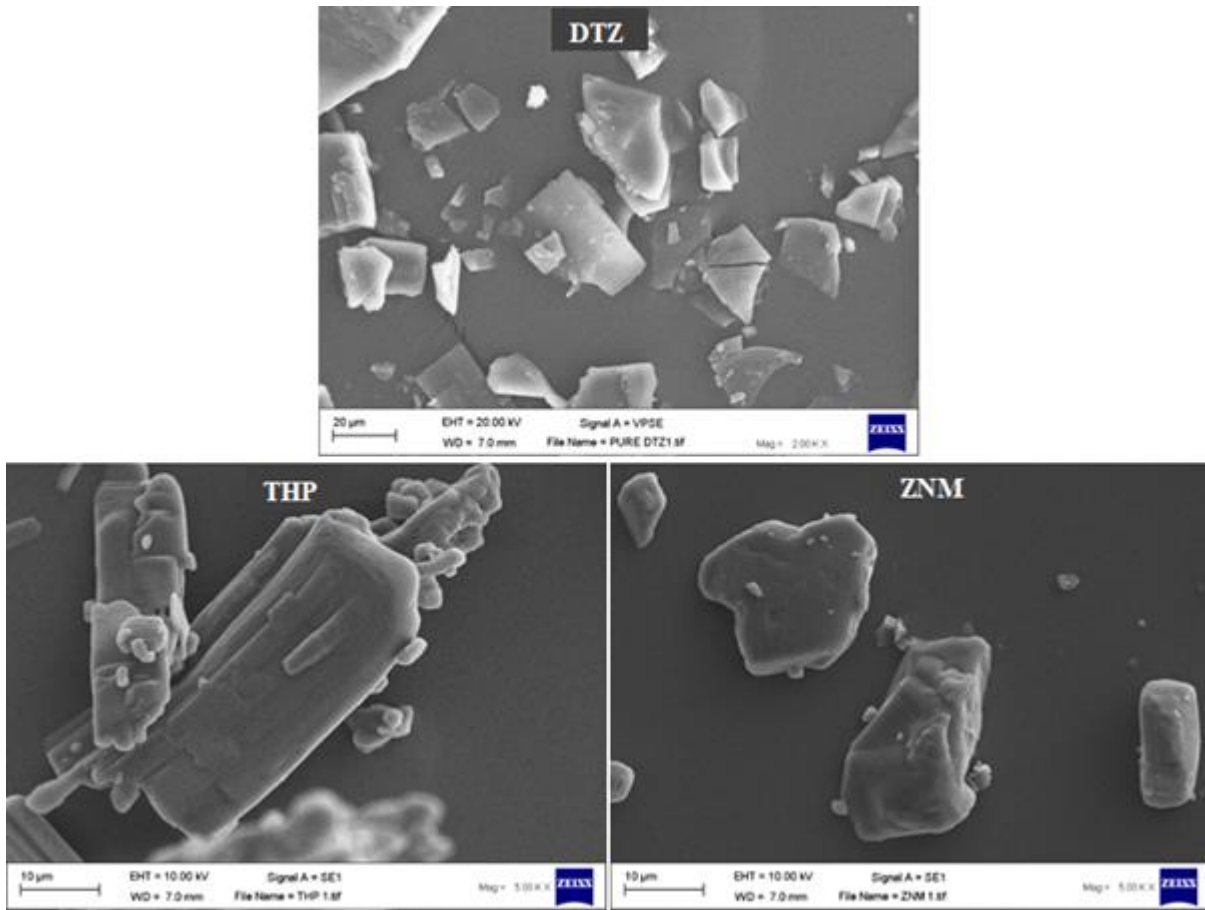


Figure 9.3: SEM of commercial diltiazem HCl (DTZ), theophylline (THP) and Zonisamide (ZNM).

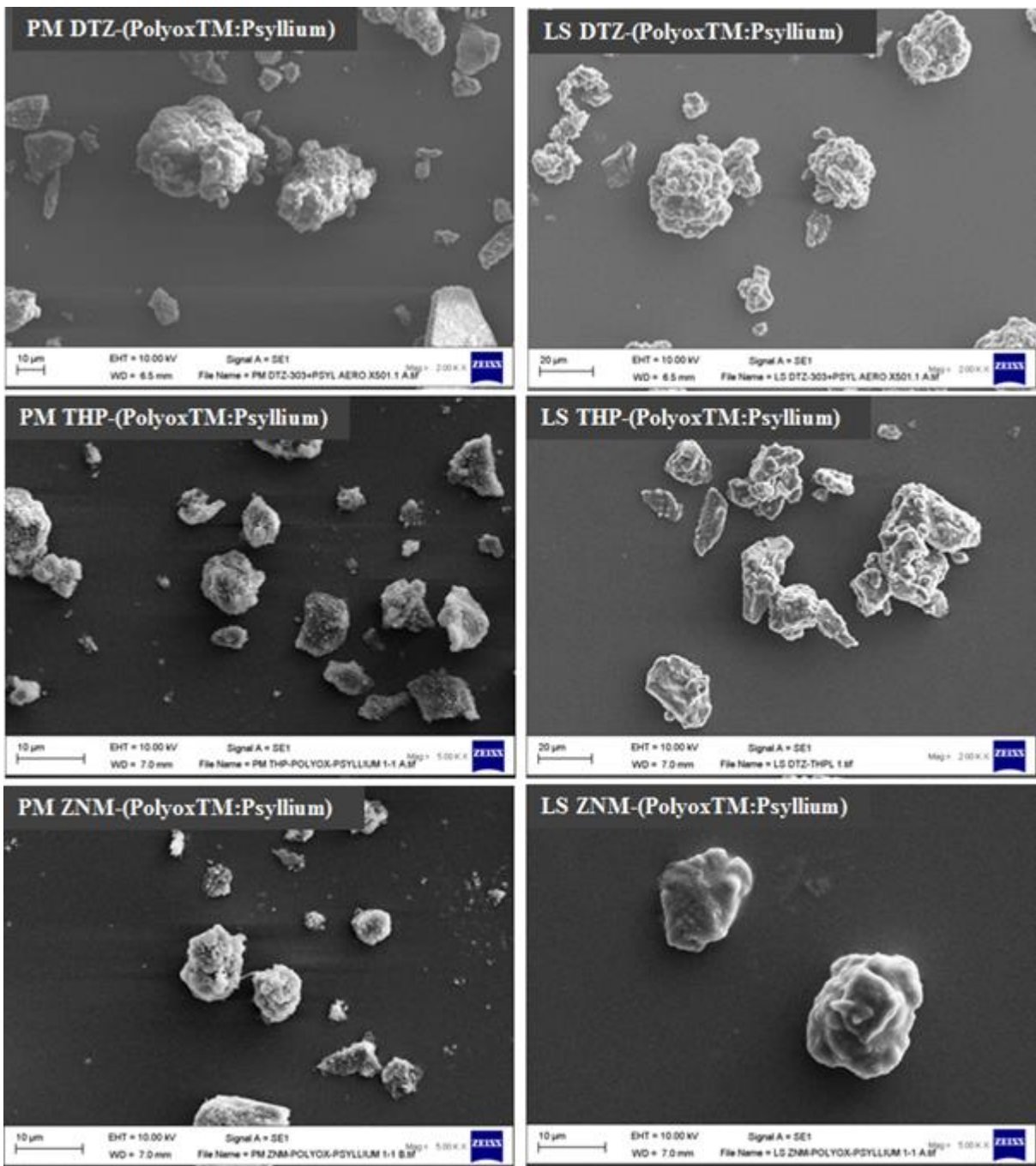


Figure 9. 4: SEM of diltiazem HCl (DTZ) from physical mixture (PM) and liquid solid (LS) formulations containing different drug type

Table 9. 1: Particle size distribution (i.e. particle size at 10% ($d_{10\%}$), 50% ($d_{50\%}$), 90% ($d_{90\%}$), volume mean diameter (VMD), and span; mean \pm SD, $n = 3$) of various drug type liquisolid (LS) formulation powders and their physical mixture (PM) counterparts.

Product (s)	$d_{10\%}$		$d_{50\%}$		$d_{90\%}$		VMD (μm)		Span	
	PM	LS	PM	LS	PM	LS	PM	LS	PM	LS
Pure DTZ										
	8.21 \pm 0.2		129.2 \pm 0.3		147.3 \pm 8.0		167.0 \pm 4.5		4.0 \pm 1.5	
Pure THP										
	11.1 \pm 1.7		63.8 \pm 20.5		237.0 \pm 12.0		98.3 \pm 37.7		4.2 \pm 1.8	
Pure ZNM										
	69.4 \pm 4.7		271 \pm 6.1		532.3 \pm 3.1		290.7 \pm 4.2		1.7 \pm 0.1	
Pure Polyox TM										
	16.3 \pm 0.1		39.5 \pm 0.2		77.7 \pm 1.3		43.7 \pm 0.4		1.6 \pm 0.1	
Pure Psyllium										
	10.1 \pm 0.1		85.1 \pm 2.1		231.3 \pm 8.3		104.3 \pm 3.2		2.6 \pm 0.1	
DTZ-(PolyoxTM:Psyllium)	8.12 \pm 0.8	14.7 \pm 4.1	33.6 \pm 0.8	48.6 \pm 2.2	261.3 \pm 32.7	249.7 \pm 34.7	84.1 \pm 8.8	91.8 \pm 21.3	7.5 \pm 0.8	4.7 \pm 1.4
THP-(PolyoxTM:Psyllium)	7.10 \pm 0.7	27.3 \pm 0.3	35.8 \pm 1.1	86.1 \pm 2.1	136.7 \pm 4.7	586.7 \pm 164.4	54.9 \pm 0.9	463.3 \pm 45.2	4.0 \pm 0.2	9.4 \pm 0.6
ZNM-(PolyoxTM:Psyllium)	16.2 \pm 0.8	46.9 \pm 0.2	46.3 \pm 0.2	89.3 \pm 3.1	175.3 \pm 2.9	346.3 \pm 149.3	69.4 \pm 0.8	319.3 \pm 47.1	3.6 \pm 0.0	5.4 \pm 0.6

9.3.3 Powder density

In comparison to PM formulations, all LS formulations with various drug solubility produced higher bulk density and higher tapped density as depicted in (Table 9.2), indicating larger points of physical contact between particles within LS powders. PM powders and their counterpart LS formulations with different drug solubilities showed acceptable flow properties as indicated by the CI values (Table 9.2). CI value for LS formulations obtained from DTZ, THP and ZNM was $20.0 \pm 0.5\%$, $21.6 \pm 1.1\%$ and $23.6 \pm 0.4\%$. Whereas CI values for PM powders were generally higher and ranged between ($22.3 \pm 0.5\%$ and $24.2 \pm 0.2\%$), i.e. both the LS formulations and PM powders showed increasing trend with decreased in drug solubility (Table 9.2).

9.3.4 Hardness

The hardness of tablets formulated using THP-based drug was found to be higher than tablets formulated using DTZ and ZNM, i.e. the hardness obtained from both the LS and PM tablets recorded lower hardness with formulation containing higher drug solubility to formulation containing THP (Table 9.2). For example, PM formulation containing THP tablets produce higher hardness 87.8 N compared to DTZ with the highest solubility produced lower hardness value 80.9N. The results are in agreement with those published by (Krejcová *et al.*, 2006), for different drugs. The matrices tablet containing THP gives higher hardness compared to DTZ and diclofenac Na tablets. This was linked to the better binding properties between THP and PolyoxTM:Psyllium that gives more available hydrogen bonding place beside physically combined polymer chains. A similar trend was also seen for the pure drugs where the THP produced higher hardness than DTZ and ZNM (Tablet 9.2). PM tablets recorded higher hardness values in comparison to their LS formulations (Table 9.2).

Table 9.2: Bulk density, tap density, Carr's index (CI) and Hardness (mean \pm SD, n = 5) for various drugs to PolyoxTM and Psyllium at 1:1 ratio.

Product	Bulk density (g/cm ³)		Tap density (g/cm ³)		CI (%)		Hardness (N)	
	PM	LS	PM	LS	PM	LS	PM	LS
Pure DTZ	0.33 \pm 0.01		0.53 \pm 0.01		38.0 \pm 0.00		38.0 \pm 0.94	
Pure THP	0.39 \pm 0.00		0.61 \pm 0.02		36.1 \pm 1.84		60.5 \pm 10.5	
Pure ZNM	0.74 \pm 0.07		0.92 \pm 0.09		19.1 \pm 1.50		13.7 \pm 1.39	
DTZ–(PolyoxTM:Psyllium)	0.42 \pm 0.02	0.46 \pm 0.02	0.53 \pm 0.01	0.58 \pm 0.01	22.3 \pm 0.43	20.0 \pm 0.5	80.9	17.7
THP–(PolyoxTM:Psyllium)	0.37 \pm 0.04	0.36 \pm 0.04	0.51 \pm 0.06	0.54 \pm 0.05	22.9 \pm 0.50	21.6 \pm 1.1	87.8	11.5
ZNM–(PolyoxTM:Psyllium)	0.36 \pm 0.01	0.41 \pm 0.01	0.54 \pm 0.14	0.58 \pm 0.02	24.2 \pm 0.17	23.6 \pm 0.4	74.1	7.8

9.3.5 Drug release studies

The release profile of PolyoxTM:Psyllium-based matrix tablets comprising various drugs were assessed. [Figure 9.5](#) shows the release behaviour of three (3) different drugs from PolyoxTM:Psyllium matrices. The solubility of drug type such as DTZ, THP and ZNM in aqueous media was found to be 625 mg/mL ([Li et al., 2016](#)), 8.0 mg/mL ([Shojaee et al., 2014](#)) and 0.8 mg/mL ([Shojaee et al., 2014](#)) respectively. The dissolution rate of PolyoxTM:Psyllium from different pure drugs tablet was extremely faster than their formulations from both LS and PM tablets ([Figure 9.5](#)). All formulations from both the LS and PM formulations showed sustained drug release patterns ([Figure 9.5](#)). The release rate for the drugs from PolyoxTM:Psyllium matrix tablets increased with an increase in their solubility. The release rates from less soluble drug, ZNM demonstrate slower release profile than DTZ and THP ([Figure 9.5](#)). This could be attributed to their increase in aqueous solubility for DTZ and THP in comparison to ZNM. These results also suggested that DTZ could easily diffuse out through PolyoxTM:Psyllium matrices, resulting in faster drug release rates than those of less water-soluble ones such as THP and ZNM. Drug solubility could enable the hydration process by allowing constant penetration of water via diffusion and dissolution. This was in complete agreement to the findings obtained by ([Ford et al. 1985](#); [Kim 1998](#); [Chakraborty et al., 2009](#)). A similar finding was also observed by ([Shojaee et al., 2014](#)), where drug release is faster when highly water soluble drug was used compared to less water-soluble drug combined in PolyoxTM matrices. This was confirmed by the dissolution parameters which indicate that ZNM to have lower DEs, higher MDT and lower MDR in both LS and PM tablets ([Table 9.4](#)). For example, LS formulation containing ZNM to produce lower DE (5.66% ± 0.54%), higher MDT (263% ± 2.31%) and lower MDRs (0.02 min⁻¹ ± 0.01 min⁻¹) compared to those formulations containing THP with DE (10.9% ± 2.13%), MDT (235% ± 2.14%) and MDRs (0.05 min⁻¹ ± 0.01 min⁻¹) and DTZ (DE 13.0% ±

0.40%), MDT ($212\% \pm 4.93\%$) and MDRs ($0.10 \text{ min}^{-1} \pm 0.01 \text{ min}^{-1}$). However, despite the trend in their solubility, statistical analyse confirmed that there is no significant difference in dissolution profiles between the drug type $f_2 > 50$ (Table 9.4).

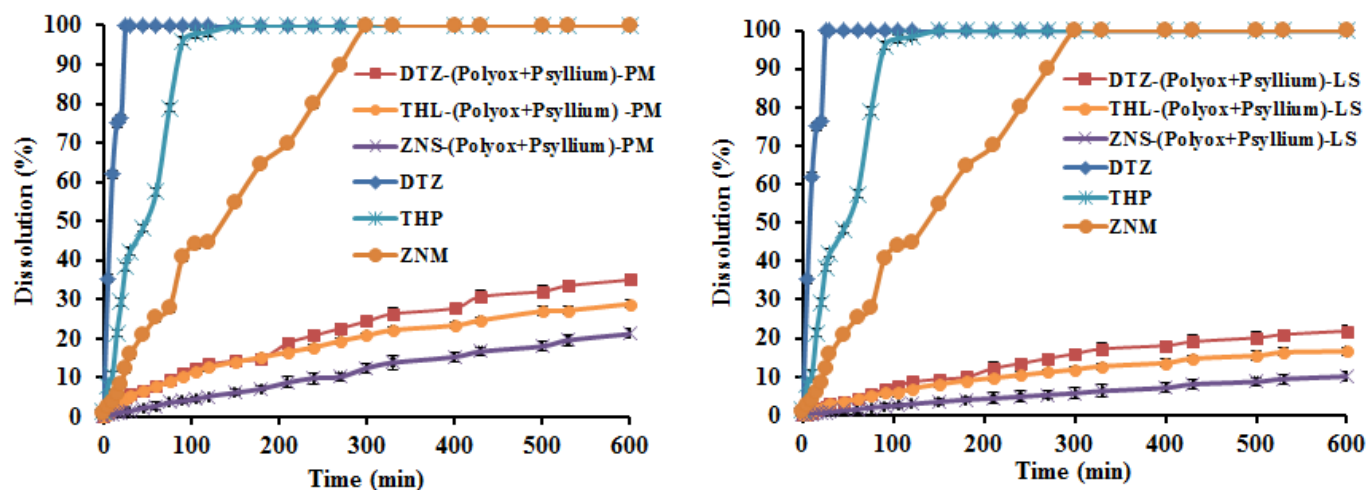


Figure 9.5: Release patterns (mean \pm SD, $n = 3$) of diltiazem HCl (DTZ) from physical mixture (PM) and liquisolid (LS) formulations containing various drug type.

In general, it is evident that the tablets prepared by LS formulations showed retardation properties compared to PM tablets. This could be attributed to the presence of viscous liquid medication (PS 80) as seen in section 3.3.4. This was further confirmed by the dissolution parameter which showed LS formulation gives lower DE and lower MDR than their counterpart PM tablets (Table 9.4). For example, ZNM produce lower DE ($5.66\% \pm 0.54\%$) and lower MDRs ($0.02 \text{ min}^{-1} \pm 0.01 \text{ min}^{-1}$) than their PM tablets DE ($11.6\% \pm 0.25\%$) and MDRs ($0.04 \text{ min}^{-1} \pm 0.00 \text{ min}^{-1}$).

Table 9.3: Dissolution efficiency (DE), mean dissolution rate (MDT), mean dissolution rate (MDR) and in vitro release kinetic parameters; *n* value of diltiazem HCl obtained for liquisolid (LS) formulations containing various drug type in comparison to their physical mixture (PM) counterparts. The results are expressed as the mean \pm SD.

Formulation (s)	DE (%)		MDT (min^{-1})		MDR (min^{-1})		n value	
	PM	LS	PMs	LS	PMs	LS	PMs	LS
Pure DTZ	97.5 \pm 0.02		15.3 \pm 0.11		0.83 \pm 0.01			
Pure THP	92.2 \pm 0.69		47.2 \pm 4.19		0.52 \pm 0.02			
Pure ZNM	74.1 \pm 8.93		157.6 \pm 12.6		0.29 \pm 0.02			
DTZ–(PolyoxTM:Psyllium)	22.3 \pm 0.26	13.0 \pm 0.40	218 \pm 2.36	212 \pm 4.93	0.10 \pm 0.01	0.10 \pm 0.01	0.684	0.915
THP–(PolyoxTM:Psyllium)	19.1 \pm 1.09	10.9 \pm 2.13	203 \pm 2.61	235 \pm 2.14	0.08 \pm 0.01	0.05 \pm 0.01	0.730	0.800
ZNM–(PolyoxTM:Psyllium)	11.6 \pm 0.25	5.66 \pm 0.54	271 \pm 6.68	263 \pm 2.31	0.04 \pm 0.00	0.02 \pm 0.01	0.865	0.889

Mathematical models were also applied to assess the kinetics and mechanisms of drug release from the tablets. It was concluded from these results that regardless of drug solubility, the release from tablets containing a mixture of PolyoxTM and Psyllium followed anomalous transport mechanism (Table 9.4) in the case of PM tablets. All LS formulations showed higher n values regardless of drug solubility. The LS formulations containing highly soluble drug DTZ followed Case II transport, whereas the diffusion component of LS formulations containing THP and ZNM ranging from 0.800 to 0.950 was much nearer to the upper boundary value (0.89/1.00) than the lower boundary value (0.43/0.50). It was therefore concluded that Case II transport resulted from the erosion of the matrix was the predominant factor controlling the drug release.

9.4 Conclusion

The results in this Chapter showed that both the LS formulations and PM powders containing DTZ with higher water solubility were released faster from the PolyoxTM:Psyllium matrices than THP and ZNM. The drugs release increases with increasing drug solubility. However, despite the trend in their solubility's, there is no significant difference in dissolution profiles. The results suggest that inclusion of psyllium into PolyoxTM matrices is an effective way to attaining more sustained release with various drugs.

10 Summary and Conclusion

Liquisolid technique is a relatively new approach to formulating sustained release dosage forms. In the study on polymer particle in hydrophilic matrix system, PolyoxTM MW was identified as the key step in obtaining consistent sustained drug release profile. The dissolution rate of DTZ from both LS and conventional compacts decreased as the MW of PolyoxTM increased. An interesting trend was obtained when plotting the differences in DE from both LS and PM formulations against the MW of PolyoxTM. PolyoxTM-based LS tablets have a potential to produce sustain release for a highly water-soluble drug, DTZ, although a careful selection of PolyoxTM grade is nevertheless vital to producing slower release pattern of LS tablets in comparison to PM tablets. DTZ was also influenced by the PolyoxTM Particle size and ratio. The rate of DTZ released from both LS and conventional tablets generally showed decreasing trends with increasing PolyoxTM concentration and decreasing PolyoxTM particle size distribution. At 1:3 and 1:4 drug:PolyoxTM (w:w) ratios, and regardless of PolyoxTM particle size distribution, LS formulations produced statistically similar release profiles compared to conventional formulations. However, LS formulations produced slower release profiles compared to conventional formulations when the concentration of PolyoxTM increased to 1:5 drug:PolyoxTM (w:w) ratio. PolyoxTM level is often the dominant factor controlling drug release rate from matrix systems. The increase in polymer level can suppress the impact of drug particle size as well as polymer particle size. Maintaining PolyoxTM ratio at 1:5 was helpful in developing a robust matrix system. The release profile of the DTZ from both LS tablets and their counterpart PM tablets showed decreasing trends with increasing hydrophilic AEROSIL[®] surface area (from 65 m²/g to 225 m²/g). LS tablets produced slower release patterns compared to PM tablets regardless of the hydrophilic AEROSIL[®] surface area used. This showed that AEROSIL[®] surface area as coating materials affects the DTZ release profile. Therefore a careful selection should be considered when using AEROSIL in both methods. The polymer type also influenced drug release. Drug release was in the order:

HVO < lactose < compressolSM < mannitol < sorbitol. The incorporation of polymers further elicits a decrease in drug release rate from individual polymer matrices. Increasing drug solubility, irrespective of the preparation methods, increased the drug release. In general, this thesis showed that LS technique could be a promising approach in retarding the dissolution rate of highly soluble drug, DTZ and formulating sustain release dosage forms in comparison to their counterpart PM. Further work is therefore required to explore the hardness of LS tablet comprehensively. This will aid in the design and development of improved ER delivery systems in the future.

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