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Formulation development and characterization of liquisolid tablets containing clozapine

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Résumé

L'objectif de ce projet était de développer une formulation liquisolide (LS) de clozapine ayant des propriétés de dissolution améliorées et évaluer sa stabilité et ainsi que sa robustesse à la modification d'excipients. Le propylène glycol (PG), la cellulose microcrystalline (MCC) et le glycolate d'amidon sodique (SSG) ont été utilisés respectivement en tant que véhicule liquide non volatile, agent de masse et agent désintégrant pour la préparation de comprimés LS. Le dioxyde de silicium colloïdal (CSD), le silicate de calcium (CS) et l'aluminométasilicate de magnésium (MAMS) ont été choisis comme agents d'enrobage sec. La caractérisation complète des mélanges et des comprimés a été effectuée. Le taux de libération des comprimés LS était statistiquement supérieur à celui des comprimés réguliers. La surface spécifique des matériaux d'enrobage avait un effet sur les propriétés d'écoulement des mélanges et la taille des particules des matériaux d'enrobage a eu un effet sur la vitesse de dissolution. Le ratio support/enrobage du mélange de poudres (valeur de R) était un paramètre important pour les systèmes LS et devait être plus grand que 20 afin d'obtenir une meilleure libération du médicament. La formulation choisie a démontré une stabilité pour une période d'au moins 12 mois. La technique LS s'est avéré une approche efficace pour le développement de comprimés de clozapine ayant des propriétés de dissolution améliorées.

Les comprimés oro-dispersibles (ODT) sont une formulation innovante qui permettent de surmonter les problèmes de déglutition et de fournir un début d'action plus rapide. Dans l'optique d'améliorer les propriétés de dissolution, un essai a été effectué pour étudier la technique LS dans la formulation des ODT de clozapine. Le PG, la MCC, le CSD et la crospovidone (CP) ont été utilisés respectivement en tant que véhicule liquide non volatile, agent de masse, agent d'enrobage sec et agent superdésintégrant pour la préparation de comprimés oro-dispersibles liquisolides (OD-LST). Le mannitol a été choisi comme agent de masse et agent édulcorant. La saccharine de sodium a été utilisée comme agent édulcorant. La caractérisation complète des comprimés a été effectuée. Le taux de libération des OD-LSTs était statisquement supérieur comparativement aux comprimés ODTs. La formulation choisie a démontré une stabilité pour une période d'au moins 6 mois. Il a été conclu que des ODT de

clozapine peuvent être préparés avec succès en utilisant la technologie LS dans le but d'améliorer la désintégration et le taux de dissolution de la clozapine dans la cavité orale.

Mots-clés : Liquisolide, clozapine, formulation, comprimé, oro-dispersible, excipients, superdésintegrant, dissolution, stabilité.

Abstract

The objective of this research was to develop a liquisolid (LS) formulation of clozapine with improved dissolution properties and evaluate its robustness to excipient modifications as well as its stability. Propylene glycol (PG), microcrystalline cellulose (MCC) and sodium starch glycolate (SSG) were employed as non-volatile liquid vehicle, carrier material and disintegrant respectively for preparing LS compacts. Colloidal silicon dioxide (CSD), calcium silicate (CS) and magnesium aluminometasilicate (MAMS) were selected as coating materials. Complete characterisation of the blends and tablets was performed. The drug release rates of LS compacts were distinctly higher as compared to regular tablets. The specific surface areas of coating materials had an effect on the flow properties of the blends and the particle sizes of coating materials affected the dissolution rate. The carrier : coating ratio of the powder system (R value) was an important parameter for LS systems and had to be larger than 20 to obtain enhanced drug release. The selected formulation demonstrated stability for a period of at least 12 months. The LS technique was an effective approach to prepare clozapine tablets with enhanced dissolution properties.

Orally disintegrating tablets (ODT) constitute an innovative dosage form that overcomes the problems of swallowing and provides a quick onset of action. In view of enhancing dissolution properties an attempt has been made to study LS technique in formulation of ODT of clozapine. PG, MCC, CSD and crospovidone (CP) were employed as non-volatile liquid vehicle, carrier material, coating material and superdisintegrant respectively for preparing orally disintegrating liquisolid tablets (OD-LST). Mannitol was selected as a carrier material and sweetening agent. Sodium saccharin (SS) was employed as a sweetening agent. Complete characterisation of the tablets was performed. The drug release rates of OD-LSTs were distinctly higher as compared to regular ODTs. The selected formulation demonstrated stability for a period of at least 6 months. It was concluded that the ODT of clozapine can be successfully prepared using LS technology in order to improve disintegration and dissolution rate of clozapine in oral cavity.

Keywords : Liquisolid, clozapine, formulation, tablet, orally disintegrating, excipients, superdisintegrant, dissolution, stability.

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List of abbreviations

BCS	Biopharmaceutical classification system
Caprol® PGE-860	1,2,3-propanetriol homopolymer (9Z)-9-octadecenoate
Cremophor® EL	Polyoxyl 35 castor oil
CCD	Charge coupled device
CCS	Croscarmellose sodium
CDER	Center for Drug Evaluation and Research
CMC	Carboxymethyl cellulose
CP	Crospovidone
CS	Calcium silicate
CSD	Colloidal silicon dioxide
DCP	Dibasic calcium phosphate
DCT	Directly compressed tablet
DSC	Differential scanning calorimetry
DTA	Disintegration test apparatus
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
FDA	Food and Drug Administration
FLODT	Felodipine liquisolid orodispersible tablet
FTIR	Fourier transformed infrared spectroscopy
Fujicalin®	Spherically granulated dicalcium phosphate anhydrous
GIT	Gastrointestinal tract
HCl	Hydrochloric acid
HLB	Hydrophilic-lipophilic balance

HPMC	Hydroxypropylmethyl cellulose
Labrasol®	Capryl capryol polyoxy glycerides
Lauroglycol® FCC	Propylene glycol monolaurate (type 1)
LS	Liquisolid
Maisine® 35-1	Glyceryl monolinoleate
MAMS	Magnesium aluminometasilicate
MCC	Microcrystalline cellulose
NF	National Formulary
NSAID	Nonsteroidal antiinflammatory drug
OD	Orally disintegrating
ODT	Orally disintegrating tablet
OD-LST	Orally disintegrating liquisolid tablet
PEG	Polyethylene glycol
PG	Propylene glycol
PK	Pharmacokinetic
RH	Relative humidity
SEM	Scanning electron microscopy
SLS	Sodium lauryl sulphate
SS	Sodium saccharin
SSG	Sodium starch glycolate
Synperonic® PE/L61	Poloxamer 181
Synperonic® PE/L81	Polyoxyethylene-polyoxypropylene block copolymer
Transcutol® HP	Diethylene glycol monoethyl ether
US	United States
USP	United States Pharmacopoeia
XRD	X-ray diffraction

Chapter one

1 Introduction

1.1 Liquisolid (LS) technology

1.1.1 Overview

Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown (Charman and Charman 2003). Poorly water soluble drugs will be inherently released at a slow rate owing to their limited dissolution rate within the gastrointestinal tract (GIT) contents. One challenge for poorly water soluble drugs is to enhance the rate of dissolution (Darwish and El-Kamel 2001).

Various techniques have been employed to formulate oral drug delivery system that would enhance the dissolution profile and in turn, the absorption efficiency of poorly water soluble drugs (Shinde 2007; Patel and Patel 2008): Solid dispersions (Kapsi and Ayres 2001; Shah, Amin et al. 2007; Rane, Mashru et al. 2007; Vanshiv, Rao et al. 2009), micronization (Li, Wang et al. 2007; Nighute and Bhise 2009), use of mesoporous silica carriers (Ahuja and Pathak 2009), ball milling technique (Sonoda, Horibe et al. 2008), use of complexing agents (El-Zein, Riad et al. 1998; Pravin and Nagarsenker 2004; Ghorab, Abdel-Salam et al. 2004; Gowrishankar, Ali et al. 2007), crystal engineering (Blagden, de Matas et al. 2007), solubilization by surfactants (Nazzal, Nutan et al. 2002; Patil and Paradkar 2006) and liquisolid (LS) technique developed by Spireas et al. (Spireas and Bolton 1999; Spireas 2002). These techniques take advantage of the increased dissolution rate resulting from the addition of a solubilizing agent, particle size reduction or the drug being in an already dissolved or amorphous state.

LS technique has been identified as a promising technique to improve the dissolution rate of poorly water soluble drugs (Fahmy and Kassem 2008). When properly formulated, LS

powder blends possess acceptable flowability and compressibility properties. They are prepared by simple blending with selected powder excipients referred to as the carriers and the coating materials.

This technique was successfully applied for low dose poorly water soluble drugs. Drug can be present in a completely or partially dissolved state in the LS formulation. The LS formulation can then facilitate the release of this drug by two mechanisms: (1) Already dissolved drug only need to diffuse out of the formulation and (2) the liquid component of the formulation act as a solubilizing aid to facilitate the wetting and dissolution of undissolved particles. Since dissolution of a non-polar drug is often the rate limiting step in gastrointestinal absorption, better bioavailability of an orally administered poorly water soluble drug is achieved when the drug is formulated using a LS system**.**

1.1.2 Classification of LS systems

The term LS systems refers to the powdered forms of liquid medications formulated by converting liquid lipophilic drugs or drug suspensions or solutions of water insoluble solid drugs in suitable non-volatile solvent systems, into dry, non-adherent, free flowing and readily compressible powder admixtures by blending with the selected carrier and coating materials (Figure 1.1).

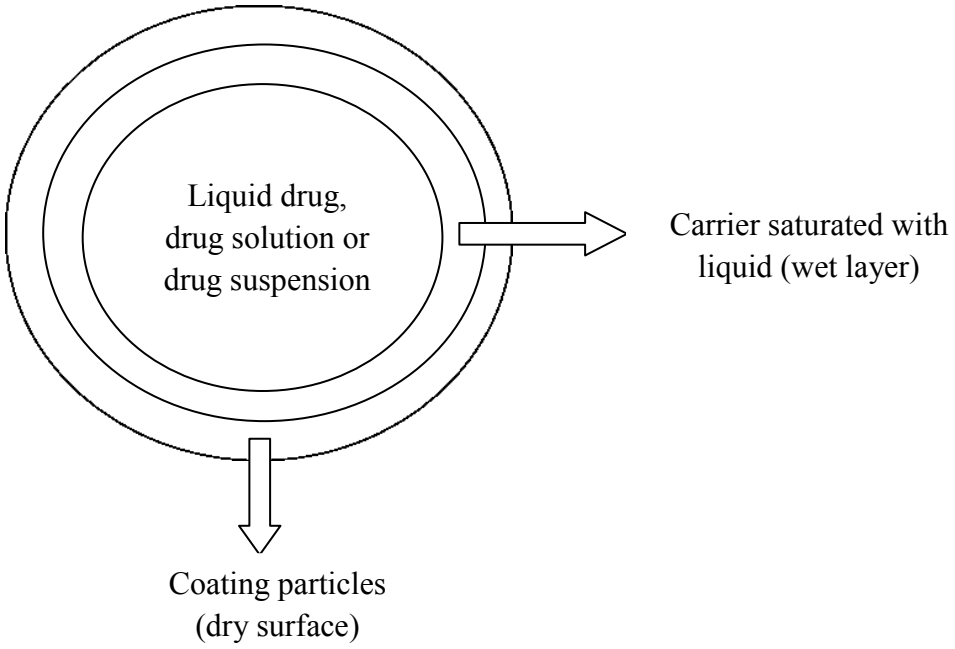

Figure 1.1 Schematic representation of the structure of the liquisolid systems

Based on the type of liquid medication encapsulated, LS systems may be classified into three subgroups: (1) Powdered drug solutions, (2) powdered drug suspensions and (3) powdered liquid drugs.

Simultaneously, based on the formulation technique used, LS systems may be classified into two categories namely: (1) LS compacts and (2) LS microsystems.

The term LS compacts refers to immediate or sustained release tablets or capsules prepared, combined with the inclusion of appropriate excipients required for tableting or encapsulation, such as lubricants and for rapid or sustained release action, such as disintegrants or binders, respectively.

The term LS microsystems refers to capsules prepared by combining the drug with the carrier and the coating materials with inclusion of an additive in the liquid medication wherein the resulting unit size may be as much as five times that of LS compacts (Spireas and Bolton 1999; Spireas 2002).

1.1.3 Excipients used for the preparation of LS systems

1.1.3.1 Non-volatile solvents

With the LS technology as described by Spireas, a liquid may be transformed into free flowing, readily compressible and apparently dry powder by simple blending with selected excipients such as the carriers and coating materials. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile solvents is incorporated into the porous carrier material. Inert, preferably water-miscible, not highly viscous, non-toxic organic solvents with high boiling point such as propylene glycol (PG), liquid polyethylene glycols (PEG), glycerine and polysorbates are best suitable as liquid vehicles (Kulkarni, Aloorkar et al. 2010). Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing and compressible powder is obtained (Spireas 2002).

Non-volatile solvents enhance the solubility of poorly water soluble drugs by formation of micelles and act as dispersants. For immediate release LS compacts, the selection of solvent is based on high drug solubility and for sustained release, solvents with least solubilizing capacity is selected. Since there are no specific non-volatile liquid vehicles used in the preparation of LS compacts, different non-aqueous solvents have been used as non-volatile liquid vehicles in the preparation of immediate release and sustained release LS formulations with different drugs. So, selection of non-volatile solvent in LS technique is important to obtain immediate or sustained release formulation (Baby, Saroj et al. 2012).

In various studies, the effect of different types of non-volatile liquid vehicles has been investigated. The results suggest that the selection of a liquid vehicle with a high solubilizing capacity for the drug and thus, an increased the fraction of molecularly dispersed drug (F_M), leads to enhanced release profiles (Spireas and Sadu 1998; Nokhodchi, Javadzadeh et al. 2005; Javadzadeh, Siahi et al. 2007; Gubbi and Jarag 2009; Akinlade, Elkordy et al. 2010). That means that by the selection of a liquid vehicle with optimum solubilizing properties the amount of liquid and thus, the weight and size of the LS compacts can be reduced. However, in addition to the drug solubility in the liquid vehicle other physicochemical characteristics of

the liquid vehicles such as polarity, viscosity, molecular weight, chemical structure and lipophilicity may also have an effect on drug release (Spireas and Sadu 1998).

Propylene glycol (PG), an inert solvent miscible with water is a suitable liquid vehicle for LS systems. It is not highly viscous (dynamic viscosity: 58.1 cP at 20 °C) and has a high boiling point (188 °C). PG is used in a wide variety of pharmaceutical formulations and is generally regarded as a relatively non-toxic material (Handbook of Pharmaceutical Excipients 2009; Baby, Saroj et al. 2012).

PG was successfully used as non-volatile solvent in LS preparation of drugs such as bromhexine hydrochloride (Gubbi and Jarag 2009), famotidine (Fahmy and Kassem 2008), pioglitazone hydrochloride (Gandhi, Sawant et al. 2013), simvastatin (Burra, Kudikula et al. 2011), to name a few.

1.1.3.2 Carrier materials

In LS approach, the carrier material plays as a major role in obtaining the dry form of the powder from the liquid medication. Each carrier has its unique property. Selection of the carrier will depend upon its liquid holding capacity, the flowability of the powder and which carrier requires less compression force (Kavita, Raju et al. 2011).

When the drug dissolved in liquid is incorporated into a carrier material, the liquid is initially absorbed in the interior of the particles. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating material particles. The coating material provides the conversion from a wet to a dry surface and gives the LS system desirable flow properties (Gavali, Pacharane et al. 2011).

The particles of the carrier materials are compression enhancing, relatively large, preferably porous particles possessing sufficient absorption property which contributes in liquid absorption, *e.g.* various grades of microcrystalline cellulose (MCC) (Spireas 2002),

starch (Spireas 2002), lactose (Javadzadeh, Siahi et al. 2007), sorbitol (Javadzadeh, Siahi et al. 2007), dibasic calcium phosphate (DCP) (Yadav and Yadav 2009) etc.

Microcrystalline cellulose (MCC) is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications. The specific surface areas and particle sizes of carrier materials are important parameters for the optimization of LS systems.

MCC is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes. In addition to its use as a binder/diluent, MCC has some lubricant and disintegrant properties that make it useful in tableting (Handbook of Pharmaceutical Excipients 2009).

MCC was successfully used as carrier material in LS preparation of drugs such as furosemide (Akinlade, Elkordy et al. 2010), griseofulvin (Hentzschel, Alnaief et al. 2011), hydrocortisone (Spireas, Sadu et al. 1998), irbesartan (Boghra, Patel et al. 2011), pioglitazone hydrochloride (Gandhi, Sawant et al. 2013), piroxicam (Javadzadeh, Siahi et al. 2005), rofecoxib (El-Say, Samy et al. 2010), tamoxifen citrate (Walunj, Sharma et al. 2012) to name a few.

1.1.3.3 Coating materials

The particles of the coating materials are flow enhancing, highly adsorptive particles, *e.g.* silica of various grades like medium surface fumed silica, colloidal silicon dioxide (CSD), synthetic amorphous silica, calcium silicate (CS), magnesium aluminometasilicate (MAMS). These particles contribute in covering the wet carrier particles and displaying a dry looking powder by adsorbing any excess liquid (Spireas and Bolton 1999; Spireas and Bolton 2000; Spireas 2002). The coating material is required to cover the surface and so maintain the powder flowability (Yadav and Yadav 2010).

Colloidal silicon dioxide (CSD), a submicroscopic fumed silica is a suitable coating material for LS systems. Its specific surface area is 100–400 m^2/g depending on grade. The specific surface area of Aerosil® 200 is 200 ± 25 m^2/g. Primary particle size is 7–16 nm. Aerosil® forms loose agglomerates of 10–200 μm (Handbook of Pharmaceutical Excipients 2009).

CSD is widely used in pharmaceuticals, cosmetics and food products. Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting and capsule filling.

CSD was successfully used as coating material in LS preparation of drugs such as carvedilol (Pardhi, Shivhare et al. 2010), hydrocortisone (Spireas, Sadu et al. 1998), irbesartan (Boghra, Patel et al. 2011), pioglitazone hydrochloride (Gandhi, Sawant et al. 2013), piroxicam (Javadzadeh, Siahi et al. 2005), rofecoxib (El-Say, Samy et al. 2010), tamoxifen citrate (Walunj, Sharma et al. 2012), valsartan (Lakshmi, Srinivas et al. 2011), to name a few.

Calcium silicate (CS) has large micropores and excellent tabletability, also leads to a physical stabilization of amorphous drugs with enhanced drug release. CS possesses many intraparticle pores on its surface. Moreover, it has been shown that this silicate is also suitable for adsorption of liquid (Sharma, Sher et al. 2005). It can absorb up to 2.5 times its weight of liquids and still remain a free flowing powder (Handbook of Pharmaceutical Excipients 2009). CS is used as a filler aid for oral pharmaceuticals. It has also been used in pharmaceutical preparations as an antacid.

CS is used as coating material in LS preparation of some drugs. Repaglinide is widely used for the treatment of diabetes. It is a poorly water soluble drug which has poor absorption in the upper intestinal tract and has a very low bioavailability (Shams, Sayeed et al. 2011). The LS compacts of repaglinide were prepared using CS as a coating material (El-Houssieny, Wahman et al. 2010).

Tocopherol acetate (vitamin E acetate) is an oil soluble liquid drug. Hentzschel et al. investigated the suitability of various novel coating materials such as CS (Florite®), MAMS (Neusilin® US2) for LS compacts of tocopherol acetate (Hentzschel, Sakmann et al. 2011).

Neusilin® US2, a synthetic amorphous form of MAMS which is prepared by spray drying and provides an extremely large specific surface area (300 m^2/g) and good flow and tableting properties. The high porosity and large specific surface area of Neusilin® allow a high liquid adsorption capacity (Hentzschel, Sakmann et al. 2011). This may be of interest especially for the preparation of LS compacts. Neusilin® makes hard tablets at low compression forces compared to similar binders. Primary particle size of neutral grade of Neusilin® US2 is 44-177 µm. It is a multifunctional excipient that can be used in both direct compression and wet granulation of solid dosage forms. Neusilin® is widely used for improvement of the quality of tablets, powders, granules and capsules.

Neusilin® was used as coating material in LS preparation of some drugs. Cyclosporine-A is a fat soluble, hydrophobic polypeptide metabolite of fungus beauveria nivea (formerly tolypocladium inflatum gams). It is a hydrophobic cyclic peptide built from non-mammalian aminoacids with low oral bioavailability; which is one of first line immunosuppressive drugs used to prevent transplant rejection and to treat autoimmune diseases. The self-emulsifying cyclosporine-A tablets were prepared by the LS compaction technique using MAMS (Neusilin® S1) as a coating material (Zhao, Zhou et al. 2011).

Griseofulvin is an antifungal drug which has very low solubility in water. The LS compacts of griseofulvin were prepared using colloidal silica and MAMS (Neusilin® US2) as coating materials (Hentzschel, Alnaief et al. 2011).

1.1.3.4 Disintegrants

Disintegrants indirectly affect the dissolution parameter since the immediate next step is dissolution (Kavitha, Raju et al. 2011). To aid dissolution, tablet formulations generally require rapid disintegration, which can be facilitated by the addition of superdisintegrants.

Once a tablet disintegrates, the solubility properties of the drug, either alone or assisted by other formulation ingredients, determine the drug's subsequent dissolution rate and extent of release. The solubility properties of water-soluble drugs result in rapid and high-level drug release, but with poorly water soluble drugs, other ingredients in the formulation, including the disintegrant, play a key role in determining the drug dissolution characteristics exhibited by the finished formulation (Balasubramaniam and Bee 2009). Sodium starch glycolate (SSG), croscarmellose sodium (CCS), pregelatinized starch, crospovidone (CP) etc. are most commonly used disintegrants (Rajesh, Rajalakshmi et al. 2011).

Sodium starch glycolate (SSG) is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct compression or wet granulation processes. The mechanism by which disintegration action takes place is rapid absorption of water and swell leading to an enormous increase in volume of granules which result in rapid and uniform disintegration. The higher dissolution rates observed with superdisintegrants may be due to rapid disintegration and fine dispersion of particles formed after disintegration (Kumar and Nirmala 2012).

SSG is successfully used as disintegrant in LS preparation of drugs such as atorvastatin calcium (Gubbi and Jarag 2010), bromhexine hydrochloride (Gubbi and Jarag 2009), diazepam (Manogar, Hari et al. 2011), irbesartan (Boghra, Patel et al. 2011), pioglitazone hydrochloride (Gandhi, Sawant et al. 2013) etc.

1.1.3.5 Drug candidates

LS technique has been successfully employed to improve the dissolution rate of poorly water soluble or water insoluble drugs which belong to Biopharmaceutical Classification System (BCS) Class II or IV. Some of developed LS systems are listed in Table 1.1. These LS systems are the compacts based on the formulation technique used.

Table1.1 List of some of developed liquisolid systems to enhance dissolution rate

Drug	**Therapeutic class/ BCS class**	**Liquid vehicle**	**Carrier / Coating materials**	**Reference**
Aceclofenac	Nonsteroidal antiinflammatory drug (NSAID)/Class II	PEG 400	MCC, DCP / Hydroxypropylmethyl cellulose (HPMC)	Yadav, Nighute et al. 2009
Amlodipine besylate	Antihypertensive/ Class II	PG	MCC / Silica	Kaur, Bala et al. 2013
Atorvastatin calcium	Lipid lowering agent/ Class II	PEG 400, PG	MCC / Silica	Gubbi and Jarag 2010
Bromhexine HCl	Mucolytic agent/ Class II	PEG 400, PG	MCC / Silica	Gubbi and Jarag 2009
Candesartan cilexetil	Antihypertensive/ Class II	Polysorbate 80	MCC / Silica	Sayyad, Tulsankar et al. 2013
Carbamazepine	Antiepileptic/Class II	PEG 200	MCC, Lactose / Silica	Javadzadeh, Navimipour et al. 2007
Carbamazepine	Antiepileptic/Class II	PG	MCC / Silica	Tayel, Soliman et al. 2008
Carvedilol	Nonselective beta blocker/alpha 1 blocker/ Class II	PEG 400	MCC / Silica	Pardhi, Shivhare et al. 2010; Burra and Reddy 2012

Drug	Therapeutic class/ BCS class	Liquid vehicle	Carrier / Coating materials	Reference
Clofibrate (liquid drug)	Lipid lowering agent	-	MCC / Silica	Spireas 2002
Cyclosporine-A	Immunosuppressive/ Class II	Lauroglycol® FCC, Maisine® 35-1, PEG-35 castor oil, PEG 400	MCC / MAMS	Zhao, Zhou et al. 2011
Diazepam	Antiepileptic, antianxiety agent/ Class II	PEG 600	MCC / Silica	Manogar, Hari et al. 2011
Domperidone	Antidopaminergic/ Class II	Polysorbate 20, Polysorbate 40, Polysorbate 60, Polysorbate 80, PG, PEG 200, PEG 400	MCC / Silica	Ibrahim, El-Faham et al. 2011
Escitalopram oxalate	Antidepressant/Class II	PG	MCC / Silica	Kumbhar, Mujgond et al. 2013
Etoricoxibe	NSAID/Class II	PEG 400	MCC / Silica	Yala, Srinivasan et al. 2012
Ezetimibe	Lipid lowering agent/ Class II	PEG 400, Polysorbate 80, Transcutol® HP, Labrasol®	MCC / Silica	Khanfar, Salem et al. 2013

Drug	Therapeutic class/ BCS class	Liquid vehicle	Carrier / Coating materials	Reference
Famotidine	Antiulcer/Class IV	PG	MCC / Silica	Fahmy and Kassem 2008
Fenofibrate	Antihyperlipidemic/ Class II	PG	MCC / Silica	Karmarkar, Gonjari et al. 2009
Fenofibrate	Antihyperlipidemic/ Class II	PG, PEG 600	MCC / Silica	Sabale, Grampurohit et al. 2012
Furosemide	High-ceiling loop diuretic/Class IV	PEG 400, Synperonic® PE/L81, Caprol® PGE-860	MCC / Silica	Akinlade, Elkordy et al. 2010
Furosemide	High-ceiling loop diuretic/Class IV	Polysorbate 80	MCC / Silica	Burra and Galipelly 2010
Gemfibrozil	Antilipidemic/Class II	Polysorbate 80	MCC / Silica	Spireas 2002
Glibenclamide	Antidiabetic/Class II	PEG 400	MCC / Silica	Darwish and El-Kamel 2001
Glimepiride	Antidiabetic/Class II	PG	MCC / Silica	Singh, Prakash et al. 2011
Glipizide	Antidiabetic/Class II	PG, PEG 200, PEG 400	MCC / Silica	Mahajan, Dhamne et al. 2011
Griseofulvin	Antifungal/Class II	PEG 300	MCC, MAMS / Colloidal silica, MAMS	Hentzschel, Alnaief et al. 2011
Griseofulvin	Antifungal/Class II	PEG 400	MCC / Silica	Yadav and Yadav 2010

Drug	Therapeutic class/ BCS class	Liquid vehicle	Carrier / Coating materials	Reference
Hydrochlorothiazide	Diuretic, antihypertensive/ Class IV	PEG 200	MCC / Silica	Khaled, Asiri et al. 2001
Hydrochlorothiazide	Diuretic, antihypertensive/ Class IV	PEG 400	MCC / Silica	Spireas 2002
Hydrocortisone	Corticosteroid/Class II	PG	MCC / Silica	Spireas, Sadu et al. 1998; Spireas 2002
Ibuprofen	NSAID/Class II	PEG 300	MCC / Silica	Hentzschel, Alnaief et al. 2010
Ibuprofen	NSAID/Class II	PEG 400	MCC / Silica	Chuahan, Patel et al. 2012
Indomethacin	NSAID/Class II	PG	MCC / Silica	Nokhodchi, Javadzadeh et al. 2005
Indomethacin	NSAID/Class II	PEG 400	MCC, DCP / HPMC	Yadav and Yadav 2009
Indomethacin	NSAID/Class II	PEG 200, Glycerin	MCC / Silica	Saeedi, Akbari et al. 2011
Irbesartan	Antihypertensive/ Class II	PEG 400	MCC / Silica	Boghra, Patel et al. 2011
Ketoprofen	NSAID/Class II	PG, Polysorbate 80	MCC, DCP / Silica	Nagabandi, Tadikonda et al. 2011
Ketoprofen	NSAID/Class II	PEG	MCC, DCP, Starch, Lactose / Silica	Nagabandi, Tadikonda et al. 2011

Drug	Therapeutic class/ BCS class	Liquid vehicle	Carrier / Coating materials	Reference
Lamotrigine	Antiepileptic/Class II	PEG 400	MCC / Silica	Yadav and Yadav 2010
Lansoprazole	Proton-pump inhibitor/Class II	Polysorbate 80	MCC / Silica	Kasture, Gondkar et al. 2011
Levothyroxine sodium	Thyroid hormone/ Class II	Olive oil, Soybean oil	MCC / Silica	Spireas 2005
Loratadine	Antihistaminic/Class II	PG	MCC / Silica	El-Hammadi and Awad 2011
Meloxicam	NSAID/Class II	PG, PEG 400, Polysorbate 80	MCC / Silica	El-Gizawy 2007
Meloxicam	NSAID/Class II	PEG 400	MCC / Silica	Emmadi, Sanka et al. 2010
Metaxalone	Muscle relaxant/ Class II	PEG 400, Polysorbate 80,	MCC	Spireas 2011
Methyclothiazide	Diuretic, antihypertensive/ Class II	PEG 400	MCC / Silica	Spireas, Wang et al. 1999; Spireas 2002
Naproxen	NSAID/Class II	PEG 400, Cremophor® EL, Synperonic® PE/L61	MCC / Silica	Tiong and Elkordy 2009
Nifedipine	Vasodilator/Class II	PEG 400	MCC / Silica	Spireas 2002

Drug	Therapeutic class/ BCS class	Liquid vehicle	Carrier / Coating materials	Reference
Nifedipine	Vasodilator/Class II	PG, PEG 400, Polysorbate 80	MCC / Silica	Annapureddy, Preetha et al. 2013
Nimesulide	NSAID/Class II	PG, PEG 400, Polysorbate 80	MCC / Silica	Hassan and El-Saghir 2011
Pioglitazone HCl	Antidiabetic/Class II	PG	MCC / Silica	Gandhi, Sawant et al. 2013
Piroxicam	NSAID/Class II	Polysorbate 80	MCC / Silica	Javadzadeh, Siahi et al. 2005; Javadzadeh, Siahi et al. 2007
Piroxicam	NSAID/Class II	PG	MCC / Silica	Javadzadeh, Shariati et al. 2009
Prednisolone	Glucocorticoid/Class II	PG, PEG 400, Glycerin, Polysorbate 80	MCC / Silica	Spireas and Sadu 1998
Prednisone	Glucocorticoid/ Class II	PG	MCC / Silica	Spireas 2002
Repaglinide	Antidiabetic/Class II	Polysorbate 80	MCC / Calcium silicate	El-Houssieny 2008; El-Houssieny, Wahman et al. 2010
Rifampicin	NSAID/Class II	Polysorbate 80	MCC / Silica	Rajesh, Pinkesh et al. 2013
Rofecoxib	NSAID/Class II	PEG 600	MCC / Silica	El-Say, Samy et al. 2010
Rosuvastatin calcium	Cholesterol lowering agent/Class II	PG, PEG 400, Polysorbate 80	MCC / Silica	Kapure, Pande et al. 2013

Drug	Therapeutic class/ BCS class	Liquid vehicle	Carrier / Coating materials	Reference
Simvastatin	Hypolipidemic/Class II	PG	MCC / Silica	Burra, Kudikula et al. 2011
Spironolactone	Steroid/Class II	PEG 400	MCC / Silica	Spireas 2002
Tamoxifen citrate	Antiestrogenic/Class II	PG	MCC / Silica	Walunj, Sharma et al. 2012
Telmisartan	Antihypertensive/ Class II	PEG 400	MCC / Silica	Swamy and Shiny 2013
Tocopherol acetate (liquid drug)	Vitamin supplement	-	MCC, MAMS, Fujicalin® / Colloidal silica, Calcium silicate, MAMS	Hentzschel, Sakmann et al. 2011
Valsartan	Antihypertensive/ Class II	PG, PEG, Glycerine	MCC / Silica	Lakshmi, Srinivas et al. 2011
Valsartan	Antihypertensive/ Class II	PG	MCC, Lactose, DCP / Silica	Chella, Shastri et al. 2012

Caprol® PGE-860: 1,2,3-propanetriol homopolymer (9Z)-9-octadecenoate.

Cremophor® EL: Polyoxyl 35 castor oil.

Fujicalin®: Spherically granulated dicalcium phosphate anhydrous.

Labrasol®: Capryl capryol polyoxy glycerides.

Lauroglycol® FCC: Propylene glycol monolaurate (type 1).

Maisine® 35-1: Glyceryl monolinoleate.

Synperonic® PE/L61: Poloxamer 181.

Synperonic® PE/L81: Polyoxyethylene-polyoxypropylene block copolymer.

Transcutol® HP: Diethylene glycol monoethyl ether.

1.1.4 Liquid loading capacity of powders

A powder can retain only limited amounts of liquid while maintaining acceptable flow and compression properties. To calculate the required amounts of powder excipients (carrier and coating materials) a mathematical approach for the formulation of LS systems has been developed by Spireas (Spireas and Sadu 1998; Spireas 2002). This approach is based on the flowable (Φ-value) and compressible (Ψ-number) liquid retention potential introducing constants for each powder/liquid combination. The Φ-value of a powder represents the maximum amount of a given non-volatile liquid that can be retained inside its bulk [w/w] while maintaining an acceptable flowability. The flowability may be determined from the powder flow or by measurement of the angle of repose.

The Ψ-number of a powder is defined as the maximum amount of liquid the powder can retain inside its bulk [w/w] while maintaining acceptable compactability resulting in compacts of sufficient hardness with no liquid leaking out during compression. The compactability may be determined by the so-called “pactisity” which describes the maximum (plateau) crushing strength of a one gram tablet compacted at sufficiently high compression forces. The terms “acceptable flow and compression properties” imply the desired and thus preselected flow and compaction properties which must be met by the final LS formulation.

Depending on the excipient ratio (R) of the powder substrate an acceptably flowing and compressible LS system can be obtained only if a maximum liquid load on the carrier material is not exceeded. This liquid/carrier ratio is termed “liquid load factor (L_f)” and is defined as the ratio between the weights of liquid formulation (W) and the carrier material (Q) in the system:

$$L_f = W / Q$$

R represents the ratio between the weights of the carrier (Q) and the coating (q) material present in the formulation:

$$R = Q / q$$

The L_f that ensures acceptable flowability ($^{\Phi}L_f$) can be determined by:

$$^{\Phi}L_f = \Phi + \varphi \cdot (1/R)$$

Where Φ and φ are the Φ-values of the carrier and coating materials, respectively (Spireas and Sadu 1998; Spireas 2002).

Similarly, the L_f for production of LS systems with acceptable compactability ($^{\Psi}L_f$) can be determined by:

$$^{\Psi}L_f = \Psi + \psi \cdot (1/R)$$

Where Ψ and ψ are the Ψ-numbers of the carrier and coating materials, respectively.

The optimum liquid load factor (L_0) required to obtain acceptably flowing and compressible LS systems are equal to either $^{\Phi}L_f$ or $^{\Psi}L_f$ whichever represents the lower value.

As soon as the L_0 is determined, the appropriate quantities of carrier (Q_0) and coating (q_0) material required to convert a given amount of liquid formulation (W) into an acceptably flowing and compressible LS system may be calculated as follows:

$$Q_0 = W / L_0$$

and

$$q_0 = Q_0 / R$$

The validity and applicability of the above mentioned principles have been tested and verified by producing LS compacts possessing acceptable flow and compaction properties (Spireas 2002).

1.1.5 Preparation and optimization of LS systems

The new LS technique may be applied to formulate liquid medications (*i.e.*, oily liquid drugs and solutions, suspensions or emulsions of poorly water soluble solid drugs carried in non-volatile liquid vehicles) into powders suitable for tableting or encapsulation. Simple blending of such liquid medications with calculated quantities of a powder substrate consisting of certain excipients referred to as the carrier and coating powder materials, can yield dry looking, non adherent, free flowing and readily compressible powders (Spireas and Bolton 1999). The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating material particles. The coating material provides the conversion from a wet to a dry surface and gives the LS system desirable flow properties (Figure 1.2).

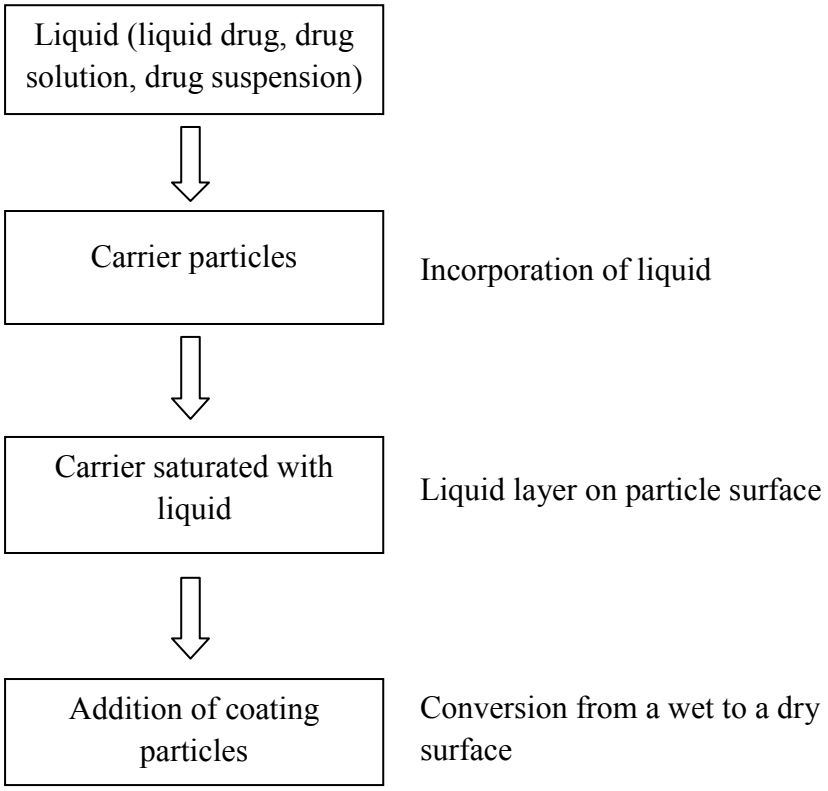

Figure 1.2 Schematic representation of liquisolid systems

To prepare a LS system, first the drug is dispersed or dissolved in the non-volatile solvent, the carrier and coating material mixture in a ratio is then added to the liquid medication. The liquid medication is now converted to powder form. Various excipients such as disintegrants and lubricants may be added to the LS compacts (Figure 1.3). Before preparing into compacts pre-compression studies have to be performed.

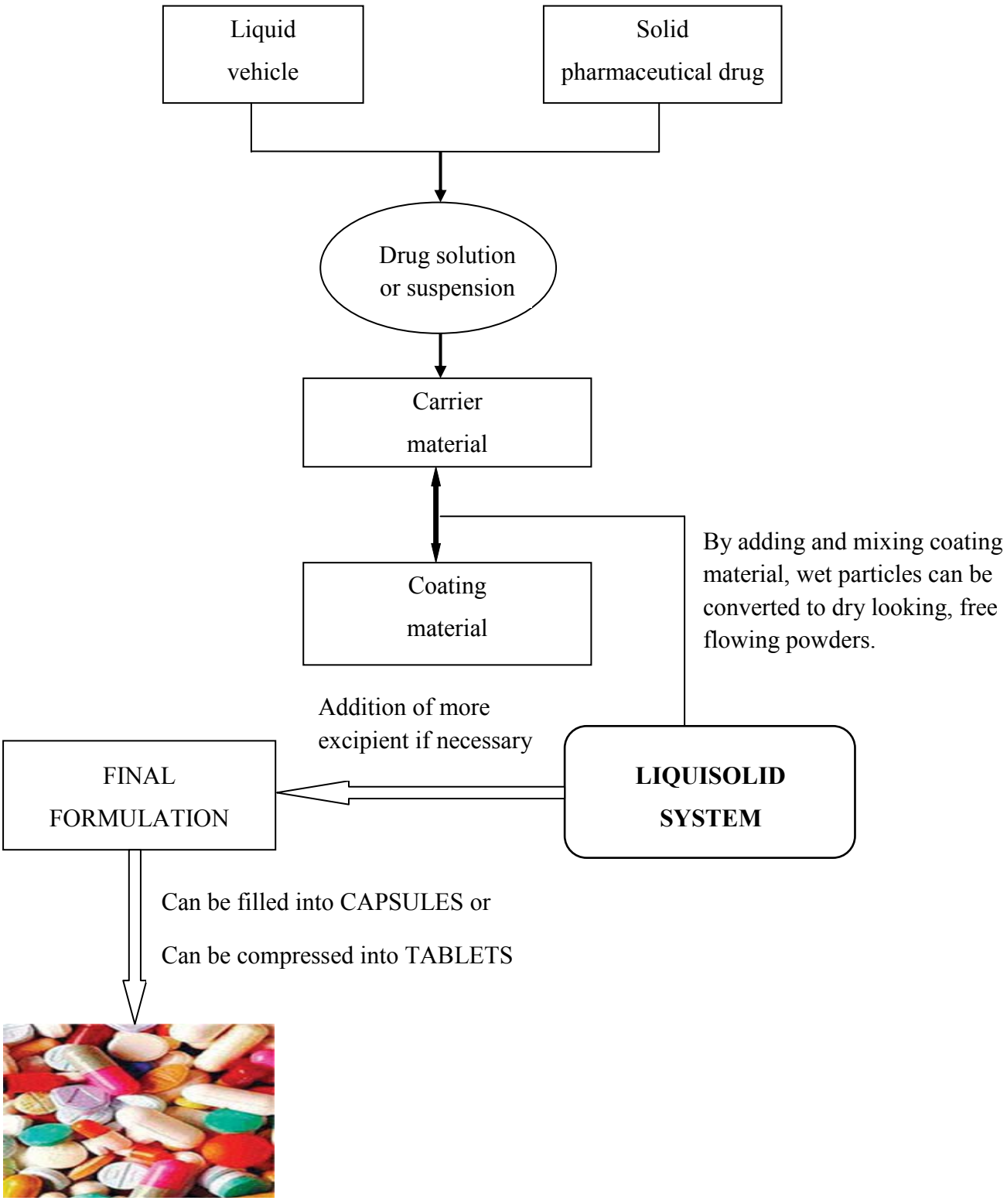

Figure 1.3 Schematic outline of the steps involved in the preparation of liquisolid systems

The LS technology has been successfully applied to low dose, poorly water soluble drugs. The formulation of a high dose, poorly soluble drug is one of the limitations of the LS technology. As the release rates are directly proportional to the fraction of molecularly dispersed drug in the liquid formulation a higher drug dose requires higher liquid amounts for a desired release profile.

Moreover, to obtain LS systems with acceptable flowability and compressibility, high levels of carrier and coating materials are needed. However, this results in an increase in tablet weight ultimately leading to tablet sizes which are difficult to swallow. Therefore, to overcome this and various other problems of the LS technology several formulation parameters may be optimized (Table 1.2).

Table 1.2 Optimization of some formulation parameters for liquisolid systems with immediate drug release

Formulation parameter	**Optimization**	**Effect**
Liquid vehicle	High drug solubility in the vehicle	Increased fraction of the molecularly dispersed drug (F_M)
Carrier and coating materials	High specific surface area	Increased liquid load factor (L_f)
Excipient ratio (R)	High R value	Fast disintegration, inhibition of precipitation

1.1.6 Characterization of LS systems

1.1.6.1 Preformulation studies

Before formulating the LS systems preformulation studies should be performed first, these include; solubility studies, determination of angle of slide, calculation of liquid load factor, determination of flowable liquid retention potential and LS compressibility test.

Solubility studies

To select the best non-volatile solvent for dissolving or suspending the drug in liquid medication, solubility studies are carried out by preparing saturated solutions of drug by adding excess of drug into non-volatile solvents and shaking them on shaker for specific time period under constant vibration. After this, the solutions are filtered and analyzed (Kulkarni, Aloorkar et al. 2010).

Determination of angle of slide

Powder excipient or its mixture is accurately weighed and placed at one end of a metal plate (with a polished surface). This end is raised gradually until the plate makes an angle with the horizontal at which the powder is about to slide. This is called the angle of slide (Ɵ). It is taken as a measure for the flow properties of powders. An angle of slide corresponding to 33^0 is regarded as optimal flow behaviour (Spireas, Jarowski et al. 1992).

Calculation of liquid load factor

Liquid load factor (L_f) is defined as the ratio of weight of the liquid medication (W) to weight of the carrier material (Q) and it can be determined by using the following formula (Spireas and Bolton 2000; Spireas 2002).

$$L_f = W / Q$$

W= Weight of liquid medication
Q= Weight of carrier material

Determination of flowable liquid retention potential

The term "flowable liquid retential potential" (Φ value) of a powder material describes its ability to retain a specific amount of liquid while maintaining good flow properties. The Φ value is defined as the maximum weight of liquid that can be retained per unit weight of the powder material in order to produce an acceptably flowing liquid/powder admixture (Tayel, Soliman et al. 2008).

LS compressibility test

LS compressibility test is used to determine Φ values and involves steps such as preparing carrier-coating material admixture systems, preparing several uniform liquid or powder admixtures, compressing each liquid or powder admixtures to tablets, assessing average hardness, determination of average liquid content of crushed tablets, as well as determining plasticity, sponge index and Φ value and L_f value (Spireas and Bolton 1999; Spireas 2002).

1.1.6.2 Evaluation of LS systems

1.1.6.2.1 Pre-compression evaluations

In order to ensure the suitability of the selected excipients, Differential Scanning Calorimetry (DSC), X-Ray Diffraction (XRD), Fourier Transformed Infrared Spectroscopy (FTIR) and Scanning Electron Microscopy (SEM) studies are performed. In addition, flowability studies are also carried out to select the optimal formula for compression.

Differential Scanning Calorimetry (DSC)

It is used to determine the interactions between drug and excipients, which indicates the success of stability studies. The drug has a characteristic peak, absence of this peak in DSC thermogram indicates that the drug is in the form of solution in liquid formulation and it is molecularly dispersed within the system (Fahmy and Kassem 2008). DSC studies showed that clozapine exhibits a sharp endothermic peak at 182.67^0 (Govda, Ram et al. 2012).

X-Ray Diffraction (XRD)

For characterization of the crystalline state, the XRD patterns are determined for drug, excipients used in formulation, physical mixture of drug and excipients, finally for the prepared LS system (Javadzadeh, Navimipour et al. 2007). Absence of constructive specific peaks of the drug in the LS X-ray diffractogram indicate that drug has almost entirely converted from crystalline to amorphous or solubilized form. Such lack of crystallinity in the LS system is understood to be as a result of drug solubilization in the liquid vehicle *i.e.*, the

drug has formed a solid solution within the carrier matrix. This amorphization or solubilization of drug in the LS system may contribute to the consequent improvement in the apparent solubility and therefore the dissolution rate of the drug (Fahmy and Kassem 2008). XRD pattern of pure clozapine showed a characteristic peaks at $2\theta^0$ = 10.52, 17.39, 19.36, 19.73, 21.05, 21.44, 23.09 and 23.72 (Govda, Ram et al. 2012).

Scanning Electron Microscopy (SEM)

SEM is utilized to assess the morphological characteristics of the raw materials and drug-carrier systems (Fahmy and Kassem 2008).

Fourier Transformed Infrared Spectroscopy (FTIR)

FTIR studies are performed to determine the chemical interaction between the drug and excipients used in the formulation. The presence of drug peaks in the formulation and absence of extra peaks suggest that there are no chemical interactions between the drug and the carrier when formed as LS system (Yadav, Nighute et al. 2009).

Contact angle measurement

For assessment of wettability, contact angle of LS tablets is measured according to the imaging method. The commonly used method is to measure contact angle directly for a drop of liquid resting on a plane surface of the solid, the so-called imaging method. A saturated solution of the drug in dissolution media is prepared and a drop of this solution is put on the surface of tablets. The contact angles are calculated by measuring the height and diameter of sphere drop on the tablet (Javadzadeh, Navimipour et al. 2007).

Flow behaviour

Flow property of a powder is of major importance in the production of tablet dosage forms in order to attain a uniform feed and reproducible filling of tablet dies. Angle of repose, Carr's index, Hausner's ratio and compressibility index are used in order to ensure the flow properties of the powders (Banker and Anderson 1987).

1.1.6.2.2 Post-compression evaluations

The formulated LS systems are evaluated for post-compression parameters such as;

- Weight variation
- Drug content / content uniformity
- Hardness
- Thickness and diameter
- Friability
- Disintegration
- In vitro dissolution studies
- In vivo evaluation
- Stability studies

(Kavitha, Raju et al. 2011; Lakshmi, Kumari et al. 2012)

Evaluation parameters of the tablets mentioned in the Pharmacopoeias need to be assessed, along with some special tests are discussed here:

Stability studies

To obtain information on the stability of LS systems, the effects of storage on the release profile and the crushing strength of LS compacts were investigated. Stability studies of LS systems containing atorvastatin calcium (40 °C / 75% RH, 6 months) (Gubbi and Jarag 2010), carbamazepine (25 °C / 75% RH, 6 months) (Javadzadeh, Navimipour et al. 2007), ezetimibe (30 ^{0}C / 60% RH, 1 month) (Khanfar, Salem et al. 2013), glimepiride (25 °C / 75% RH, 6 months) (Singh, Prakash et al. 2011), hydrocortisone (ambient conditions, 10 months) (Spireas 2002), indomethacin (25 °C / 75% RH, 12 months) (Javadzadeh, Siahi et al. 2007), naproxen (20 °C / 76% RH, 4 weeks) (Tiong and Elkordy 2009) and piroxicam (25 °C / 75% RH, 6 and 9 months, respectively) (Javadzadeh, Siahi et al. 2007; Javadzadeh, Shariati et al. 2009) showed that storage at different conditions neither had an effect on the hardness nor on the release profiles of LS compacts. This indicates that the LS technology is a promising technique to enhance the release rate without having any physical stability issues.

In vivo evaluation

The LS technology is a promising approach for the enhancement of drug release of poorly water soluble or practically water insoluble drugs. Bioavailability assessment is required for LS technique, because it was proved that enhancing the drug releases from the dosage form by determination of in vitro release studies. So, this parameter should establish for determination of the efficacy of the formulation. Some researchers have been evaluated in vivo absorption and bioavailability characteristics of LS compacts as described in Table 1.3.

Table 1.3 List of some in vivo studies

Drug	Therapeutic class	Results	Reference
Carbamazepine	Antiepileptic (sodium channel blocker)	In vivo testing demonstrated that the bioavailability of carbamazepine from the LS capsules was enhanced by 182.7%. The study also showed that a lower drug dose can be administrated using LS capsules to achieve similar clinical effects but minimize the associated adverse effects.	Chen, Wang et al. 2012
Pioglitazone HCl	Antidiabetic	It was found that the relative bioavailability of pioglitazone HCl from the LS tablets was significantly higher than that from the commercial tablets. In addition, the in vivo reduction of blood glucose level through the optimized LS formula was greater than that of marketed product.	Gandhi, Sawant et al. 2013
Repaglinide	Antidiabetic	The study showed that the relative bioavailability of repaglinide from the LS compacts was significantly higher than that from the commercial tablets. The results of the glucose tolerance test showed that the blood glucose level was decreased significantly after the commercial drug (percent change, 18.1%) while in groups treated with the LS formulation the decrease was highly significant with a percent change of 29.98%.	El-Houssieny, Wahman et al. 2010

1.1.7 Sustained release with LS formulations

Development of sustained release oral dosage forms is beneficial for optimal therapy in terms of efficacy, safety and patient compliance. Ideally, a controlled release dosage form will provide therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval. To achieve this aim, several methods have been developed such as preparation of salt form of drug, coating with special materials and incorporation of drugs into hydrophobic carriers. LS technique is a novel method that can change the dissolution rate of drugs (Javadzadeh, Musaalrezaei et al. 2008). If hydrophobic carriers such as acrylic resin polymers (Eudragit® RL and RS) are used instead of hydrophilic carriers in LS systems, sustained release formulations can be obtained. Some drugs have been formulated as LS sustained release systems. Different liquid vehicles, carriers and coating materials were used to formulate these drug delivery systems (Table 1.4).

Table1.4 (a) List of some of developed sustained release liquisolid systems

Drug	**Therapeutic class**	**Liquid vehicle**	**Carrier material**	**Coating material**	**Additional retardant agent**	**Reference**
Lornoxicam	NSAID	Polysorbate 80	MCC, Eudragit® RL PO, Eudragit® S-100, Chitosan, Sodium CMC	Silica	-	Ganesh, Deecaraman et al. 2011
Metoprolol succinate	Antihypertensive, antiarrhythmic	Polysorbate 80	MCC	Silica	HPMC	Jagannath, Maroti et al. 2013
Propranolol HCl	β-adrenergic blocking agent	Polysorbate 80	Eudragit® RL and RS	Silica	HPMC (4000 mPa.s)	Javadzadeh, Musaalrezaei et al. 2008
Theophylline	Antiasthmatic	Polysorbate 80	Eudragit® RL and RS	Silica	HPMC E4M	Nokhodchi, Aliakbar et al. 2010
Tramadol HCl	Opioid analgesic	PG	MCC	Silica	HPMC K4M	Karmarkar, Gonjari et al. 2010
Venlafaxine HCl	Antidepressant	PG, PEG 400, polysorbate 80	Eudragit® RS PO	Silica	HPMC	Khanfar, Salem et al. 2013

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, HPMC: Hydroxypropylmethyl cellulose, Sodium CMC: Sodium carboxymethyl cellulose.

Table1.4 (b) List of some of developed sustained release liquisolid systems

Drug	Results	Reference
Lornoxicam	The results showed retardation in the release rate of the drug from the LS compacts and the kinetic studies showed that the sustained release LS formulations followed zero-order.	Ganesh, Deecaraman et al. 2011
Metoprolol succinate	The study showed the LS technique can be optimized for the production of sustained release matrices of water-soluble drugs. LS formulations containing Polysorbate 80 followed zero-order release kinetics. In this study, wet granulation technique showed more retardation properties compared to direct compression technique.	Jagannath, Maroti et al. 2013
Propranolol HCl	Sustained release LS tablets prepared by wet granulation technique showed greater retardation properties in comparison with conventional matrix tablets and most of LS formulations followed zero-order release pattern.	Javadzadeh, Musaalrezaei et al. 2008
Theophylline	The prepared LS compacts showed more sustained release behaviour as compared to simple sustained release matrix tablets and the results suggested that zero-order release can be achieved with LS formulations.	Nokhodchi, Aliakbar et al. 2010
Tramadol HCl	The prepared LS compacts of water-soluble drug, tramadol HCl showed more sustained release behaviour as compared to marketed sustained release formulations. The release profiles of drug followed the Peppas model.	Karmarkar, Gonjari et al. 2010
Venlafaxine HCl	The prepared LS formulations have shown a better sustained release effect in comparison with directly compressed tablets. The type of liquid vehicle was to found to affect the drug release significantly.	Khanfar, Salem et al. 2013

1.1.8 Advantages and limitations of LS systems

Some advantages and limitations of LS systems are listed in Table 1.5.

Table 1.5 Advantages and limitations of liquisolid systems

Advantages	**Limitations**
Poorly water soluble or water insoluble drugs can be formulated into LS systems.	This technique is only for slightly*/very slightly water soluble** and practically water insoluble*** drugs.
Better availability of an orally administered poorly water soluble drug is achieved when the drug is in solution form.	In order to achieve acceptable flowability and compactability for LS powder formulation, high levels of carrier and coating materials should be added. This will increase the weight of tablets to above one gram which makes them difficult to swallow.
Optimized rapid release LS tablets or capsules of poorly water soluble drugs exhibit enhanced in vitro and in vivo drug release as compared to their commercial counterparts.	The LS systems have drug loading capacities and they require high solubility of drug in non-volatile liquid vehicles.
Can be applied to formulate liquid medications such as oily liquid drugs.	
Enhanced bioavailability can be obtained as compared to conventional tablets.	
Drug release can be modified using suitable formulation ingredients.	
Can be used in controlled drug delivery and zero-order release can be obtained.	
Drug can be molecularly dispersed in the formulation.	
Capability of industrial production is also possible.	

Advantages	Limitations
Their production cost is lower than that of soft gelatine capsules, because the production of LS systems is similar to that of conventional tablets.	

(Saharan, Kukkar et al. 2009; Saharan, Kukkar et al. 2009; Kulkarni, Aloorkar et al. 2010; Bindu, Kusum et al. 2010; Sharma and Jain 2010; Gavali, Pacharane et al. 2011; Rajesh, Rajalakshmi et al. 2011; Burra, Yamsani et al. 2011)

* Slightly soluble: From 100 to 1000 parts solvent needed to dissolve 1 part solute
** Very slightly soluble: From 1000 to 10 000 parts solvent needed to dissolve 1 part solute
*** Practically insoluble or insoluble: More than 10 000 parts solvent needed to dissolve 1 part solute (USP36-NF31, 2013).

1.1.9 Conclusion

LS technique is a promising alternative method for formulation of poorly water soluble or water insoluble solid drugs and liquid lipophilic drugs. LS compacts refer to formulations formed by conversion of solid state to liquid state, drug suspensions or drug solutions in non-volatile solvents into dry, non-adherent, free flowing and compressible powder mixtures by blending the suspension or solution with selected carrier and coating materials. When the drug within the LS system is completely dissolved in the liquid vehicle, it is located in the powder substrate still in a solubilized state. Already the dissolved drug only needs to diffuse out of the formulation and the liquid component of the formulation act as a solubilizing aid to facilitate the wetting and dissolution of the undissolved particles. Thus, this shows improved release rates and greater bioavailability. This technique is also used to design sustained release systems by using hydrophobic carriers in LS systems.

1.2 Orally disintegrating tablets (ODTs)

1.2.1 Overview

For the past one decade, there has been an enhanced demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually (Hirani, Rathod et al. 2009). Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency and the production of more cost effective dosage forms**.**

For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration, owing to its several advantages and high patient compliance compared to many other routes (Valleri, Mura et al. 2004). Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available. However, many patient groups such as the elderly, children and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid-intake/diets have difficulties swallowing these dosage forms. Those who are traveling or have little access to water are similarly affected (Hanawa, Watanabe et al. 1995; Mallet 1996; Porter 2001).

To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as “Orally Disintegrating Tablets (ODT)” which disintegrate rapidly in saliva, usually in a matter of seconds, without the need of water. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms (Seager 1998; Bradoo, Shahani et al. 2001; Sreenivas, Dandagi et al. 2005).

Although chewable tablets have been on the market for some time, they are not the same as the new ODTs. Patients for whom chewing is difficult or painful can use these new tablets easily. ODTs can be used easily in children who have lost their primary teeth but do not have full use of their permanent teeth (Mizumoto, Masuda et al. 2005).

Recent market studies indicate that more than half of the patient population prefers ODTs to other dosage forms (Deepak 2004) and most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%) or prefer ODTs to regular tablets or liquids (>80%) (Brown 2003).

ODTs have been developed for numerous indications ranging from migraines (for which rapid onset of action is important) to mental illness (for which patient compliance is important for treating chronic indications such as depression and schizophrenia) (Ghosh, Chatterjee et al. 2005).

1.2.2 Description of orally disintegrating (OD) dosage forms

All fast disintegrating tablets approved by United States Food and Drug Administration (US FDA) are classified as "ODTs". European Pharmacopoeia adopted the term "orodispersible tablets" for tablets that dispersed or disintegrate in less than 3 min in the mouth before swallowing. Such a tablet disintegrates into smaller granules or gel like structure, allowing easily swallowing by patients. As per recent US FDA guideline on ODT, disintegration time of ODT should have an in vitro disintegration time of approximate 30 s or less, when based on United States Pharmacopoeia (USP) disintegration test method or alternative.

ODTs are different from conventional sublingual tablets, buccal tablets and lozenges, which require more than a minute to dissolve in oral cavity. Different OD dosage forms are as follows:

Fast dissolving tablets and ODTs: Fast dissolving tablet (also known as fast dissolving multiparticulate, rapid dissolving, mouth dissolving, fast melting or orodispersible tablet) is an oral tablet that does not require water for swallowing (Hirani, Rathod et al. 2009).

Recently, European Pharmacopoeia has used the term orodispersible tablets. This may be defined as uncoated tablets intended to be placed in the mouth where they disperse readily

within 3 min before swallowing (Fu, Yang et al. 2004). USP has also approved these dosage forms as orodispersible tablets. Thus, orodispersible tablets are solid unit dosage forms like conventional tablets, but are composed of superdisintegrants, which help them to dissolve the tablets within a minute in the mouth in the presence of saliva without any difficulty of swallowing. It offers several advantages with respect to its stability, administration without water, accurate dosing, easy manufacturing, small packaging size and handling (Seager 1998; Habib, Khankari et al. 2000; Brown 2003; Bandari, Mittapalli et al. 2008). Its ease of administration in the population especially for pediatric, geriatric or any mentally retarded persons makes it a very popular dosage form. Due to the presence of superdisintegrants, it gets dissolved quickly, resulting in rapid absorption of drug which in turn provides rapid onset of action (Behnke, Sogaard et al. 2003). Since the absorption is taking place directly from the mouth, so, bioavailability of the drug increases (Clarke, Brewer et al. 2003). Drugs present in orodispersible tablets are also not suffering from first pass metabolism. This type of drug delivery is becoming popular day by day due to its numerous advantages.

US FDA Center for Drug Evaluation and Research (CDER) Nomenclature Standards Committee developed the following definition for an ODT as a new dosage form in 1998: "A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue." (US FDA CDER 2008). The drug is released, dissolved or dispersed in the saliva and then swallowed and absorbed across the GIT.

Freeze-dried wafer: It is a quick-dissolving, thin matrix that contains a medicinal agent that does not need water for swallowing. This fragile dosage form requires unit-dose packaging to ensure physical stability. The wafer disintegrates instantaneously in the oral cavity and releases drug, which dissolves or disperses in the saliva. The saliva is swallowed and the drug is absorbed across the GIT (Dobetti 2000).

1.2.3 Selection of drug candidates

Several factors must be considered when selecting drug candidates for delivery as ODT dosage forms. In general, an ODT is formulated as a bioequivalent line extension of an existing oral dosage form. Under this circumstance, it is assumed that the absorption of a drug molecule from the ODT occurs in the postgastric GIT segments, similar to the conventional oral dosage form. But this scenario may not always be the case. An ODT may have varying degrees of pregastric absorption and thus, the pharmacokinetic (PK) profiles will vary (Lies, Atherton et al. 1993). Therefore, the ODT will not be bioequivalent to the conventional oral dosage form. For example, ODT formulations of selegiline, apomorphine and buspirone have significantly different PK profiles compared with the same dose administered in a conventional dosage form (Ostrander 2003; Pfister and Ghosh 2005).

It is possible that these differences may, in part, be attributed to the drug molecule, formulation or a combination of both. If significantly higher plasma levels have been observed, pregastric absorption leading to the avoidance of first pass metabolism may play an important role. This situation may have implications for drug safety and efficacy, which may need to be addressed and assessed in a marketing application for an ODT. For example, safety profiles may be improved for drugs that produce a significant amount of toxic metabolites mediated by first pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and segments of the pregastric GIT. Drugs having ability to diffuse and partition into the epithelium of the upper GIT (log $P > 1$ or preferable > 2); and those able to permeate oral mucosal tissue are considered ideal for ODT formulations. Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs. Similarly, patients with Sjögren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations. Drugs with a short half-life and frequent dosing, drugs which are very bitter or otherwise unacceptable taste because taste masking can't be achieved or those which require controlled or sustained release are unsuitable candidates of rapidly dissolving oral dosage forms (Hirani, Rathod et al. 2009).

Researchers have formulated ODTs for various categories of drugs used for therapy in which rapid peak plasma concentration is required to achieve the desired pharmacological response. These include neuroleptics, cardiovascular agents, analgesics, antiallergics, antiepileptics, anxiolytics, sedatives, hypnotics, diuretics, antiparkinsonism agents, antibacterial agents, lipid regulating agents, etc. (Sharma 2008).

1.2.4 Excipients used for the preparation of ODTs

1.2.4.1 Overview

Mainly seen excipients in orally disintegrating dosage forms are diluents, superdisintegrants, sweeteners, flavoring agents, lubricants etc. To formulate orally disintegrating dosage forms, superdisintegrants and sweetening agents play an important role.

1.2.4.2 Superdisintegrants

Superdisintegrants increase the rate of disintegration and hence the dissolution rate. For the success of fast dissolving tablet, the tablet having quick dissolving property which is achieved by using the superdisintegrants (Nagar, Singh et al. 2011). SSG, CCS, pregelatinized starch, CP etc. are most commonly used disintegrants (Rajesh, Rajalakshmi et al. 2011).

Crospovidone (CP) quickly wicks saliva into the tablet to generate the volume expansion and hydrostatic pressures necessary to provide rapid disintegration in the mouth. Unlike other superdisintegrants, which rely principally on swelling for disintegration, CP uses a combination of swelling and wicking. CP disintegrants are highly compressible materials as a result of their unique particle morphology (Mohanachandran, Sindhumol et al. 2011).

1.2.4.3 Sweetening agents

There are various drugs which do not taste good. Since ODTs dissolve in mouth, so proper taste masking is very much essential, especially in the case of bitter taste drugs. Various approaches have been explored in order to mask the bitter or any other bad taste of the drugs which include addition of sweeteners and flavors or encapsulating the unpleasant drugs

into the microparticles or by the adjustment of pH. The most popular and general approach is the addition of sweeteners and flavors (Day and Maiti 2010). Artificial sweeteners such as aspartame, sodium saccharin and bulking agents such as dextrose, sucrose, mannitol, sorbitol, xylitol etc. are commonly used for taste masking.

Sodium saccharin (SS) is an intense sweetening agent used in pharmaceutical formulations such as tablets, powders, suspensions, liquids etc. SS considerably more soluble in water than saccharin and is more frequently used in pharmaceutical formulations. Its sweetening power is approximately 300–600 times that of sucrose. SS enhances flavor systems and may be used to mask some unpleasant taste characteristics.

SS is successfully used as sweetening-taste masking agent in orodispersible tablet preparation of drugs such as carbamazepine (Swamy, Shahidulla et al. 2008), domperidone (Islam, Haider et al. 2011), metrodinazole (Mohire, Yadav et al. 2009) etc.

Mannitol has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose and imparts a cooling sensation in the mouth. Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture sensitive active ingredients. Mannitol may be used in direct compression tablet applications, for which the granular and spray dried forms are available or in wet granulations. It is also used as a sweetening agent.

Pearlitol® SD 200 is granulated mannitol, slightly sweet tasting, crystalline powder. It has a unique blend of exceptional physical and chemical stability. It has properties like flowable, excellent compressibility, non-hygroscopic, excellent chemical stability. Pearlitol SD dissolves very rapidly because of its porous crystalline particles (Chaudhary, Chaudhary et al. 2010).

Mannitol is successfully used as a sweetening agent in orodispersible tablet preparation of drugs such as levocetirizine (Gandhi, Mundhada et al. 2011), meloxicam (Singh and Singh 2009), metoprolol tartrate (Shailaja, Latha et al. 2012), valsartan (Ibrahim and El-Setouhy 2010) etc.

1.2.5 Methods of preparation of ODTs

There are several methods for the preparation of ODTs, but the prepared products vary in their properties depending on the method of preparation. The properties in which they vary are mechanical strength of the tablets, swallowability, bioavailability, drug dissolution in saliva, stability and to some extent taste (Bandari, Mittapalli et al. 2008). Various process of manufacturing of ODTs are molding, compaction, spray-drying, freeze-drying, cotton candy, mass extrusion and some special methods are melt granulation, phase transition, sublimation and effervescent techniques.

Molding: Tablets formed by molding process are highly porous in structure, resulting in high rate of disintegration and dissolution. This process includes moistening, dissolving or dispersing the drugs with a solvent then molding the moist mixture into tablets by applying lower pressure in compression molding, but always lower than the conventional tablet compression. The powder mixture may be sieved prior to the preparation in order to increase the dissolution (Dobetti 2000). Molded tablets have low mechanical strength, which results in erosion and breakage during handling.

Compaction: Conventional methods for the preparation of tablets such as dry granulation, wet granulation and direct compression are also exist for the preparation of ODTs. Some superdisintegrants which are used during preparation of ODTs are CP, CCS, SSG, sodium alginate and acrylic acid derivatives (Ozeki T., Yasuzawa et al. 2003; Yang, Fu et al. 2004). Baclofen orodispersible tablets were prepared by direct compression method using CP and SSG as superdisintegrants (Radke, Jadhav et al. 2009). Even orodispersible tablets of carbamazepine were prepared by this method having MCC and CP (Swamy, Shahidulla et al. 2008). In all the cases it has been found that preparation by compression method along with

addition of superdisintegrants in correct concentration obey all the properties of ODTs (Swamy, Shahidulla et al. 2008; Radke, Jadhav et al. 2009).

Spray-drying: ODTs are made up of hydrolyzed or unhydrolyzed gelatin as supporting agent for matrix, mannitol as bulk agent and SSG or CCS as disintegrating agent. Sometimes in order to improve the disintegration and dissolution, citric acid and sodium bicarbonate are used. Finally, the formulation is spray-dried in a spray-drier. ODTs prepared through this method are disintegrated in less than 20 s (Allen and Wang 2001).

Freeze-drying: This is a very popular process for the preparation of ODTs. Tablets prepared by this process have low mechanical strength, poor stability at higher temperature and humidity, but glossy amorphous structure resulting in highly porous, light weight product. There are various patents on this particular technology (Habib, Khankari et al. 2000).

Melt granulation: It is a unique method for the preparation of ODTs by incorporating superpolystate (Abdelbary, Prinderre et al. 2004). Superpolystates are hydrophilic waxy binders with a melting point 33-37 °C and hydrophilic-lipophilic balance (HLB) value is 9. They play a dual role as a binder that increases the physical resistance of the tablets and also as a disintegrant, which helps the tablet to melt in the mouth and solubilize rapidly leaving no residue in the mouth.

Cotton candy process: This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to ODT. This process can accommodate high doses of drug and offers improved mechanical strength. However, high-process temperature limits the use of this process (Meyers, Battist et al. 1995).

Mass extrusion: This technology involves softening the active blend using the solvent mixture of water soluble PEG and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of a product into even segments using heated blade to form tablets (Gupta, Mittal et al. 2012).

Phase transition process: Kuno et al. investigated this process by compressing powder containing two sugar alcohols (Kuno, Kojima et al. 2005). One with high and another with low melting point and they are heated at a temperature between their melting points and then compressed finally in order to get the tablets. Example of sugar alcohols are erythriol (melting point: 122 °C), xylitol (melting point: 93-95 °C), trehalose (melting point: 97 °C), and mannitol (melting point: 166 °C). After heating, tablet hardness is increased due to an increase in interparticle bonds or the bonding surface area in tablets induced by phase transition of lower melting point sugar alcohol.

Sublimation: In this process, subliming material "camphor" is used. It is sublimed in vacuum at 80 °C for 30 min after preparation of tablets. Here, also tablets prepared are porous in nature. In conventional types, sometimes rapid disintegration does not occur. Therefore, in order to improve porosity, volatile substance camphor is added in the preparation, which gets sublimed from the formed tablet (Koizumi, Watanabe et al. 1997).

Effervescent method: ODTs are also prepared by effervescent method by mixing sodium bicarbonate and tartaric acid of concentration 12% (w/w) along with superdisintegrants like pregelatinized starch, SSG, CP and CCS. First, sodium bicarbonate and tartaric acid are preheated at a temperature of 80 °C to remove absorbed/residual moisture and thoroughly mixed in the mortar to get a uniform powder and then added to other ingredients. Finally, the blends are compressed to the tablets (Kaushik, Dureja et al. 2004; Swamy, Divate et al. 2009).

1.2.6 Evaluation of ODTs

Evaluation parameters of tablets mentioned in the Pharmacopoeias need to be assessed, along with some special tests are discussed here.

Hardness

A significant strength of ODT is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of hardness for the ODT is usually kept in a lower range to facilitate early disintegration in the mouth. The hardness of the tablet may be measured using conventional hardness testers (Velmurugan and Sundar 2010).

Friability

To achieve % friability within limits for an ODT is a challenge for a formulator since all methods of manufacturing of ODTs are responsible for increasing the % friability values. Thus, it is necessary that this parameter should be evaluated and the results are within bound limits (Velmurugan and Sundar 2010).

Wetting time and water absorption ratio

Wetting time of dosage form is related to with the contact angle. Wetting time of the ODT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablets can be measured by using the simple procedure (Gohel, Patel et al. 2004). Five circular tissue papers of 10 cm diameter are placed in a petridish. 10 mL of water soluble dye solution is added to a petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time.

For measuring water absorption ratio the weight of the tablet before keeping in the petridish is noted (Wb). The wetted tablet from the petridish is taken and reweighed (Wa). The water absorption ratio (R) can be the determined according to the following equation.

$$R = 100 (Wa-Wb) / Wb$$

Moisture uptake studies

Moisture uptake studies for ODT should be conducted to assess the stability of the formulation. Ten tablets from each formulation are kept in a dessicator over calcium chloride at 37 ^{0}C for 24 hrs. The tablets are then weighed and exposed to 75% RH, at room temperature for 2 weeks. Required humidity is achieved by keeping saturated sodium chloride solution at the bottom of the dessicator for 3 days. One tablet as control (without superdisintegrants) is kept to assess the moisture uptake due to other excipients. Tablets are weighed and the percentage increase in weight was recorded (Velmurugan and Sundar 2010).

Disintegration test

The ODT has remarkable disintegration properties; without water, it is rapidly disintegrated in the mouth within only a few seconds. When the ODT is placed in the oral cavity, saliva quickly penetrates into the tablet causing rapid disintegration.

One of the most important characteristics of the ODT is its disintegration time in the oral cavity; however, a suitable method to access the disintegration properties described in the Pharmacopoeias (US, British, Japan and India) has not been developed. At present, the disintegration time of ODTs is measured utilizing the conventional tests (for tablets) that were described in the Pharmacopoeias. However, it is difficult to assess the disintegration rate for the ODT with these tests due to its rapid disintegration rate even in a small amount of water. Further, the conventional tests employ a volume of 900 mL of test solution compared to the volume of saliva in humans, which is less than 6 mL. Thus, the disintegration rate obtained from the conventional disintegration tests appears not to be reflective of the disintegration rate in the human mouth (Bi, Sunada et al. 1996). To overcome this problem, several new methods have been proposed such as; disintegration test with charge coupled device (CCD) camera, pressurized disintegrating test apparatus (DTA), magnetic signaled DTA, texture analyzer, sinker type DTA, shaker type DTA, test tube analysis, wire basket type DTA, etc. (Sharma,

Hardenia et al. 2009). Among them, the wire basket DTA is considered as a suitable method to access the disintegration properties of ODTs.

Briefly, the apparatus (Figure 1.4) consisting of a glass beaker of 1000 mL capacity with the wire basket is positioned in the beaker with the help of a support in a way that when the beaker is contained 900 mL of disintegrating medium (simulated saliva fluid, pH 6.2), the basket has only 6 mL of it. A magnetic bead is placed at the bottom of the beaker maintaining at 37 ± 2 ^{0}C. Disintegration time is determined at 25 and 50 rpm (Khan, Kataria et al. 2007). Described apparatus is very useful for predicting disintegration time similar in the mouth or oral cavity for fast disintegrating tablets.

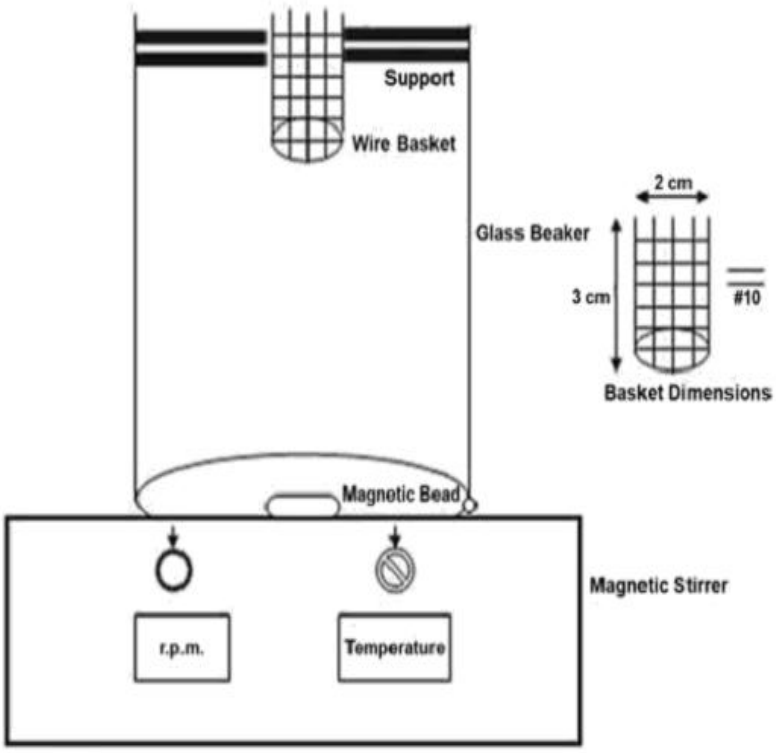

Figure 1.4 Wire basket type disintegrating test apparatus

Dissolution test

The development of dissolution methods for ODT is comparable to approach taken for conventional tablets and is practically identical when ODT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. Other media such as 0.1 N HCl (pH 1.2), pH 4.5 and pH 6.8 buffers should be used for evaluation of ODT in the same way as their ordinary tablet counterparts. Experience has indicated that USP II paddle apparatus is most suitable and common choice for dissolution test of ODTs, where a paddle speed of 50 rpm is commonly used. Typically the dissolution of ODTs is very fast when using USP monograph conditions. Hence slower paddle speeds may be utilized to obtain a comparative profile. Large tablets approaching or exceeding one gram and containing relatively dense particles may produce a mound in the dissolution vessel, which can be prevented by using higher paddle speeds. These two situations expand the suitable range of stirring to 25-75 rpm (Velmurugan and Sundar 2010).

Other tests may be performed for evaluation of ODTs such as; tablet tensile strength, tablet porosity, evaluation of effectiveness of taste masking (in vitro and in vivo) etc. (Shukla, Chakraborty et al. 2009).

1.2.7 Advantages and limitations of ODTs

Some advantages and limitations of ODTs are listed in Table 1.6.

Table 1.6 Advantages and limitations of orally disintegrating tablets

Advantages	**Limitations**
ODTs can be administered to the patients who can't swallow tablets/capsules, such as elderly, stroke victims, bedridden patients, patients with esophageal problems and patients who refuse to swallow such as pediatric, geriatric and psychiatric patients and thus improve patient compliance.	
Increased bioavailability and proved rapid absorption of drugs through pregastric absorption of drugs from mouth, pharynx and esophagus as saliva passes down.	
ODTs are most convenient for disabled, bedridden patients, travelers and busy people, who do not always have access to water.	
Good mouth feel property of ODT helps to change the perception of medication.	Some time it possesses mouth feeling.
The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.	
Conventional manufacturing equipment.	ODT requires special packaging for properly stabilization and safety of stable product.
Good chemical stability as conventional oral solid dosage forms.	ODTs show the fragile, effervescence granules property. ODTs are also hygroscopic in nature so must be keep in dry place.
ODTs provide rapid drug delivery from dosage forms.	
Cost effective.	

Advantages	Limitations
ODTs provide advantage of liquid medication in form of solid preparation.	
Rapid onset of action.	
Rapid drug therapy intervention.	
No chewing needed.	
No water needed.	

(Allen and Wang 1997; Fix 1998; Chang, Guo et al. 2000; Bradoo, Shahani et al. 2001; Nagar, Singh et al. 2011; Indurwade, Rajyaguru et al. 2002; Bhaskaran and Narmada 2002)

1.3 Schizophrenia and Clozapine

1.3.1 Schizophrenia

Schizophrenia is a chronic, severe, and disabling brain disorder that has affected people throughout history. About 1% of Americans have this illness (Regier, Narrow et al. 1993). Risk factors include birth in cities, birth in winter and early spring and viral infections in the mother during the second and third trimesters of gestation. A strong association between hypofrontality and negative symptoms of schizophrenia, as well as with antipsychotic treatment has been reported. Some studies have reported that about half of the chronic cases of schizophrenia show hypofrontality at rest. Studies have shown that individuals with schizophrenia, including those who have never been treated, have a reduced volume of gray matter in their brains, especially in the frontal and temporal lobes. Patients with the worst brain tissue loss also have the worst symptoms, including hallucinations, delusions, psychosis and bizarre behaviour (Sharafi 2005).

There are two types of schizophrenia symptoms: positive symptoms and negative symptoms. Positive symptoms are psychotic behaviors not seen in healthy people. People with positive symptoms often “lose touch” with reality. These symptoms can come and go. Sometimes they are severe and at other times hardly noticeable, depending on whether the individual is receiving treatment. They include hallucinations, delusions, thought disorders

and movement disorders. Negative symptoms are associated with disruptions to normal emotions and behaviors. These symptoms are harder to recognize as part of the disorder and can be mistaken for depression or other conditions. Negative symptoms include flat affect, lack of pleasure in everyday life, lack of ability to begin and sustain planned activities and speaking little, even when forced to interact. People with negative symptoms need help with everyday tasks.

Schizophrenia affects men and women equally. It occurs at similar rates in all ethnic groups around the world. Symptoms such as hallucinations and delusions usually start between ages 16 and 30. Men tend to experience symptoms a little earlier than women. Most of the time, people do not get schizophrenia after age 45 (Mueser and McGurk 2004).

The risk of suicide in the general population is only about 1%. But people with schizophrenia are at a much greater risk of suicide. Approximately 30% to 40% of people with schizophrenia attempt suicide at some point in their lifetime. About 10% will actually die by suicide. In fact, suicide is the most common cause of premature death among people with schizophrenia. And the suicide rate may be even higher for people with schizoaffective disorder. Although suicidal behavior is difficult to predict, research scientists have found several factors that can increase the risk of suicide in people with schizophrenia.

1.3.2 Clozapine

Clozapine, an atypical antipsychotic agent, is commonly prescribed for the management and symptomatic relief from the symptoms of severe schizophrenia. Clozapine is a selective monoaminergic antagonist with high affinity for the serotonin Type 2 (5HT2), dopamine Type 2 (D2), 1 and 2 adrenergic and H1 histaminergic receptors and can also be used for treating various dopamine-mediated behaviours (Ahmed, Li et al. 2010).

Properties of Clozapine:

Formula: $C_{18}H_{19}ClN_4$

Molecular weight: 326.82 g/mol

Melting point: 183-184^0

Solubility in water: 0.189 mg/mL (20 ^{0}C) (slightly soluble in water)

(http://en.wikipedia.org/wiki/Clozapine)

pKa: pKa1 3.70 pKa2 7.60

Log P: Partition coefficient (octanol/water): 0.4 (pH 2), 600 (pH 7), 1000 (pH 7.4), 1500 (pH 8) (http://www/drugfuture.com/chemdata/clozapine.html)

Clozapine is the prototype of atypical antipsychotic drugs that are used to treat patients with schizophrenia who are unresponsive or intolerant to typical antipsychotics. It is effective in treating the positive and negative symptoms of schizophrenia. Clozapine is more effective in schizophrenia than older antipsychotics. It may also help to reduce relapses, suicide and the need for hospitalization (Sharafi 2005). Clozapine reduces suicidal behaviour in patients with schizophrenia. Clozapine has been shown to have a substantial effect on attempted suicide and completed suicide (Novakovic and Sher 2012). Clozapine has a number of characteristics that make it unique. It appears to be more effective than conventional antipsychotics for schizophrenia patients who are severely psychotic and poorly responsive to the mechanism of action of conventional antipsychotic drugs. Another important characteristic of clozapine is its spectrum of antipsychotic activity (Kane, Honifeld et al. 1988). Clozapine has been found superior for both positive and negative symptoms than any other atypical antipsychotics (Preskorn, Burke et al. 1993; Breier, Buchanan et al. 1994).

After oral administration, clozapine is rapidly absorbed, but there is extensive first-pass metabolism and only 27-50% of the dose reaches the systemic circulation unchanged. So the relative bioavailability of clozapine is very low. Clozapine is approximately 95% bound to plasma proteins. Its plasma concentration declines in the biphasic manner and its elimination half-life ranges from 6 to 33 hrs. About 50% of a dose is excreted in urine and 30% in the faeces (Naheed and Green 2001).

1.4 Hypothesis of the thesis

The hypothesis that the drug (clozapine) is dissolved in the liquid vehicle (PG) may be chiefly responsible for its enhanced dissolution rate. According to the LS hypothesis, the phenomena of absorption and adsorption occur when clozapine (dissolved in PG) is incorporated into a carrier and coating system.

1.5 Objectives of the thesis

The principle focus of this project is to formulate LS compacts of poorly water soluble drug, clozapine to enhance its dissolution rate. For this purpose, the LS powder blends and tablets of clozapine were prepared. The specific aims of the project are to:

- Investigate the influence of the type of coating material,
- Investigate the influence of the excipient ratio (R),
- Investigate the influence of the liquid load factor (L_f)

on the flow properties of LS powder blends and on the in vitro release of clozapine from LS tablets.

- Formulate OD-LSTs of clozapine to enhance its dissolution rate.

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Chapter two

2 Research paper: Formulation development and characterization of liquisolid tablets containing clozapine

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2.1 Abstract

The objective of this research was to develop a liquisolid (LS) formulation of clozapine with improved dissolution properties and evaluate its robustness to excipient modifications as well as its stability. Propylene glycol (PG), microcrystalline cellulose (MCC) and sodium starch glycolate (SSG) were employed as non-volatile liquid vehicle, carrier material and disintegrant respectively for preparing LS compacts. Colloidal silicon dioxide (CSD), calcium silicate (CS) and magnesium aluminometasilicate (MAMS) were selected as coating materials. Complete characterisation of the blends and tablets was performed. The drug release rates of LS compacts were distinctly higher as compared to regular tablets. The specific surface areas of coating materials had an effect on the flow properties of the blends and the particle sizes of coating materials affected the dissolution rate. The powder to excipient ratio was an important parameter for LS systems and had to be larger than 20 to obtain enhanced drug release. The selected formulation demonstrated stability for a period of at least 12 months. The LS technique was an effective approach to prepare clozapine tablets with enhanced dissolution properties.

Keywords: Liquisolid, clozapine, formulation, tablet, excipients, dissolution, stability

2.2 Introduction

Dissolved state is a requirement for absorption drugs through gastrointestinal tract. In the case of poorly soluble drugs, dissolution is the rate-limiting step in absorption process (Wong et al., 2006). Generally, compounds with aqueous solubility lower than 100 μg/mL show dissolution-limited absorption (Hörter and Dressman, 2001) and erratic and incomplete absorption after oral administration (Wong et al., 2006). Advancements in the fields of biotechnology and drug discovery have led to the discovery of increasingly large number of active molecules. However, the intestinal absorption of 40% of all newly developed drugs is limited by their aqueous solubility, leading to ineffective absorption and therapeutic failure (Rong, 2008).

Various techniques have been employed to formulate oral drug delivery systems that would enhance the dissolution profile and in turn, the absorption efficiency of poorly water soluble drugs (Shinde, 2007). These techniques take advantage of the increased dissolution rate resulting from the addition of a solubilizing agent, particle size reduction or the drug being in already dissolved or amorphous state: Solid dispersions (Kapsi and Ayres, 2001; Shah et al., 2007; Rane et al., 2007; Vanshiv et al., 2009), micronization (Li et al., 2007; Nighute and Bhise, 2009), use of mesoporous silica carriers (Ahuja and Pathak, 2009), ball milling technique (Sonoda et al., 2008), use of complexing agents (El-Zein et al., 1998; Pravin and Nagarsenker, 2004; Ghorab et al., 2004; Gowrishankar et al., 2007), crystal engineering (Blagden et al., 2007), solubilization by surfactants (Nazzal et al., 2002; Patil and Paradkar, 2006) and LS technique developed by Spireas (Spireas and Bolton, 1999; Spireas, 2002).

LS technique was previously reported to improve the dissolution rate of poorly water soluble drugs (Fahmy and Kassem, 2008). When properly formulated, LS powder blends possess acceptable flowability and compressibility properties. They are prepared by simple blending with selected powder excipients referred to as the carriers and the coating materials.

This technique was successfully applied for low dose poorly water soluble drugs. Drug can be present in a completely or partially dissolved state in the LS formulation. The LS

formulation can then facilitate the release of this drug by two mechanisms: (1) Already dissolved drug only need to diffuse out of the formulation and (2) the liquid component of the formulation act as a solubilizing aid to facilitate the wetting and dissolution of undissolved particles. Since dissolution of poorly water soluble drugs is often the rate limiting step in gastrointestinal absorption, better bioavailability can be achieved when they are formulated using a LS system**.**

LS technique is a powdered solution technology that can be used to formulate liquid medication (Tiong and Elkordy, 2009). LS system is defined as dry, non-adherent, free flowing and compressible powder mixtures converted from liquid drugs, drug suspensions or drug solutions in non-volatile solvents with selected carriers and coating materials (Javadzadeh et al., 2007). The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is rapidly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing and compressible powder is obtained. Since non-volatile solvents are used to prepare the drug solution or suspension, the liquid is not evaporated and the drug is carried in a liquid system and is dispersed throughout the final product. The drug in the solid dosage form is held within the powder substrate in a solubilized or finely dispersed form which is the main reason for the enhanced dissolution rate. The quantity of drug available for dissolution is increased and hence show enhanced drug release characteristics and improved oral bioavailability (Manogar et al., 2011). Besides drug release enhancement, the LS approach is a promising technique because of the simple manufacturing process, low production costs and the possibility of industrial manufacture due to the good flow and compaction properties of the LS formulations.

Clozapine is a poorly water soluble antipsychotic drug used for treatment-resistance schizophrenia. Extent and rate of absorption of clozapine are critical and therefore it could benefit from the LS technology. The objective of this research was to develop a LS

formulation of clozapine with improved dissolution properties and evaluate its robustness to excipient modifications as well as its stability.

Specifically, this project investigated the influence of the type of coating material, powder excipient ratio (R value) and liquid load factor (L_f) on the flow properties of LS powder blends and on the in vitro release of clozapine from LS tablets; a stability study was also performed.

2.3 Materials and methods

2.3.1 Materials

Clozapine was provided by AK Scientific Inc. (USA). Propylene glycol (PG, Medisca, USA), microcrystalline cellulose (MCC, Avicel PH102, FMC, USA), colloidal silicon dioxide (CSD, Aerosil 200, Degussa AG, Germany), calcium silicate (CS, 200 mesh, Sigma-Aldrich, USA), magnesium aluminometasilicate (MAMS, Neusilin US2, Fuji, Japan) and sodium starch glycolate (SSG, Explotab, Mendell, USA) were purchased from major suppliers. All other reagents were of analytical grade and used without further purification.

2.3.2 Methods

2.3.2.1 Use of a mathematical model to design LS compacts

The formulation design of LS systems was done in accordance with a mathematical model proposed by Javadzadeh (2007). In this study, PG was used as a liquid vehicle, MCC was used as carrier material and three different coating materials were used.

The concentration of the drug in solvent was kept constant in all formulations. According to this model, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flowability and compressibility.

Firstly, the excipient ratio R of the powder is defined as,

$$R = Q / q$$

Where R is the ratio of the weight of carrier (Q) and coating (q) materials present in the formulation.

Secondly, the liquid load factor (L_f) is defined as the ratio of the weight of liquid medication (W) to the weight of the carrier material (Q) in the system. This ratio can be correlated with the flow and the compression properties of a given LS system. L_f is defined as,

$$L_f = W / Q$$

2.3.2.2 Preparation of LS powder blends and tablets of clozapine

Calculated quantities of clozapine and PG were accurately weighed and mixed together until a homogeneous drug solution was obtained. The resulting liquid medication was incorporated into calculated quantities of carrier and coating materials. The mixing process was carried out in three steps. In the first, the system was blended in a mortar using pestle at a mixing rate of one rotation per second for one minute in order to evenly distribute the liquid medication in the powder. In the second, the liquid/powder admixture was evenly spread as a uniform layer on the surface of a mortar and left standing for 5 min to allow the drug solution to be absorbed inside powder particles. In the third, the powder was scraped off the mortar surface using a spatula. The final mixture was compressed into tablets by using a manual hydraulic press (15 ton press, Specac, England) equipped with round flat-faced tooling (diameter 12.6 mm) using a compression force of 25 kN.

Preliminary experiments were conducted to identify adequate LS composition (LS-1, Table 2.1) using common excipients. This system was composed of PG as a non-volatile liquid vehicle, MCC as a carrier, CSD as a coating material and SSG as a disintegrant. The robustness of this formulation to excipients modifications was evaluated.

Firstly, LS formulations of clozapine (LS-1, LS-2 and LS-3, Table 2.1) with different R values (10.0, 20.9 and 30.2) were prepared to investigate the influence of the excipient ratio on the flow properties of LS powder blends and on the in vitro release of clozapine from LS tablets.

Secondly, LS formulations of clozapine (LS-1, LS-4 and LS-5, Table 2.1) were prepared to investigate the influence of the type of coating material on the flow properties of LS powder blends and on the in vitro release of clozapine from LS tablets. The particle size and specific surface area of the coating materials may affect the flow properties and the drug release. For this purpose, CSD, CS and MAMS were selected as coating materials. The particle size (d_{50}) of CSD, CS and MAMS were 12 μm, 74 μm and 100 μm and the specific surface area of these materials were 200 m^2/g (Hentzschel 2011), 142 m^2/g (Hentzschel et al., 2011) and 339 m^2/g (Shah et al., 2012), respectively.

Thirdly, LS formulations of clozapine (LS-1, LS-6, LS-7 and LS-8, Table 2.1) with different L_f values (0.427, 0.382, 0.345 and 0.315) were prepared using PG as a non-volatile liquid vehicle to investigate the influence of the liquid load factor on the flow properties of LS powder blends and on the in vitro release of clozapine from LS tablets.

Each system (LS-1 to LS-8, Table 2.1) was containing 100 mg of clozapine and 65 mg of PG. The detailed formulation characteristics of these systems are shown in Table 2.1.

2.3.2.3 Preparation of conventional tablets of clozapine

Conventional tablets of clozapine were prepared for comparison purposes. These tablets were produced by direct compression using a manual hydraulic press (15 ton press, Specac, England) equipped with round flat-faced tooling (diameter 12.6 mm) using a compression force of 25 kN. Each tablet contained clozapine (100 mg), MCC (405 mg), CSD (17 mg) and SSG (28 mg).

Table 2.1 Formulation design of clozapine liquisolid tablets

System	L_f	R	Clozapine (mg)	PG (mg)	MCC (mg)	CSD (mg)	MAMS (mg)	CS (mg)	SSG (mg)	Total (mg)
LS-1	0.427	20.9	100.0	65.0	386.5	18.5	-	-	30.0	600
LS-2	0.448	10.0	100.0	65.0	368.0	37.0	-	-	30.0	600
LS-3	0.421	30.2	100.0	65.0	392.0	13.0	-	-	30.0	600
LS-4	0.427	20.9	100.0	65.0	386.5	-	18.5	-	30.0	600
LS-5	0.427	20.9	100.0	65.0	386.5	-	-	18.5	30.0	600
LS-6	0.382	21.6	100.0	65.0	432.0	20.0	-	-	33.0	650
LS-7	0.345	22.3	100.0	65.0	478.5	21.5	-	-	35.0	700
LS-8	0.315	22.8	100.0	65.0	524.0	23.0	-	-	38.0	750

2.3.2.4 Flow properties of LS systems

The tapping method was used to investigate the flow properties of prepared LS powder blends. Bulk density measurements were carried by placing fixed weight of powder in graduated cylinder and volume occupied was measured and initial bulk density was calculated. 20 grams of the prepared powder blends were placed in a 50 mL cylinder. The cylinder was then tapped 1000 times at a constant velocity. The tapped density was determined on a tapped volume determination apparatus (Vanderkamp, Vankel Ind., New Jersey, USA). Each analysis was carried out in triplicate.

2.3.2.5 Weight variation, hardness, friability and content uniformity tests

The prepared tablets were evaluated by carrying out tests for weight variation, hardness, friability and drug content uniformity. For estimating weight variation, 20 tablets were taken randomly from each tablet formulation and weighed individually. The average weight of all tablets and percentage deviation from the mean for each tablet were determined.

The hardness of formulated tablets was assessed using a hardness tester (PTB 301, Pharma Test AG, Hainburg, Germany) and the mean hardness of three tablets was determined. The friability was determined on ten tablets using a friability tester (PTF II, Pharma Test AG, Hainburg, Germany) and the percentage loss in weight was calculated.

For drug content uniformity test, ten tablets were crushed individually and powder equivalent to 100 mg of clozapine was dissolved in 100 mL of methanol. The solution was then passed through a 0.45 µm nylon filter and analyzed using UV spectrophotometer (WPA, Biochrom Ltd., Cambridge, England) at 290 nm after sufficient dilution with pH 4.5 acetate buffer.

2.3.2.6 In vitro dissolution studies

The USP apparatus II (paddle method) (DTB 678 equipment with thermostatic bath and circulation pump VTC-100, Logan Instruments Corporation, New Jersey, USA) was used for all the in vitro dissolution studies. In this method, acetate buffer having the pH of 4.5 was

used as dissolution media. The rate of stirring was 50 rpm. The dosage forms were placed in 900 mL of pH 4.5 acetate buffer maintained at 37 ± 0.5 °C. At appropriate intervals (5, 10, 15, 20, 30 and 45 min), 5 mL of the samples were taken. The dissolution media was then replaced by 5 mL of fresh dissolution fluid to maintain a constant volume. After proper dilution, the samples were analyzed at 290 nm spectrophotometrically (WPA, Biochrom Ltd., Cambridge, England). The mean of three determinations was used to calculate the drug release from each of the formulations.

2.3.2.7 Stability study

The effect of aging on the hardness and dissolution of LS tablets (LS-1) was determined by storing the tablets at 22 ^{0}C for up to 12 months. After that, the samples were tested for their dissolution profiles and hardnesses at the conditions that have been used with freshly prepared tablets. The results were compared with the freshly tested tablets.

2.4 Results and discussion

2.4.1 Flow properties

Good flow properties are critical for larger scale production of tablet dosage forms. To evaluate the flow properties of the prepared LS powder blends, Carr's index was calculated from the bulk and tapped densities of the blends. According to the USP, powders are considered to have passable flow properties if they have a Carr's index value of less than 25% (USP36-NF31, 2013).

R value is an important formulation parameter for LS systems that may be optimized. The R values of LS-1, LS-2 and LS-3 were 20.9, 10.0 and 30.2 respectively. As shown in Table 2.2, LS-1 and LS-3 had fair flow properties because the formulations were containing high quantities of MCC and low quantities of colloidal silica. LS-2 exhibited passable flow properties because the formulation was containing high amounts of colloidal silica.

As shown in Table 2.2 the LS-1 had fair and LS-4 had good flow properties according to the Carr's index, but LS-5 exhibited poor flow properties. CS with its petaloid crystal

structure and large micropores exhibited the smallest specific surface area which is lower than that of CSD with its loose particle aggregates. MAMS which is prepared by spray drying resulting in spherically shaped, porous, ultralight granules showed an almost 1.5 fold larger specific surface area than CSD (Hentzschel, 2011). LS-5 powder system prepared using CS showed poor flow properties, because CS has the lowest specific surface area in comparison to CSD and MAMS. This study showed that the nature of the coating agent and most likely its specific surface area has an effect on the flow properties of LS powders.

As shown in Table 2.2, the LS-1 and LS-6 had fair and LS-7 and LS-8 had good flow properties according to the Carr's index. It was found that there is a relationship between L_f and the flow properties of LS powder blends. The LS systems with low L_f values have better flow properties. This can be explained by the fact that, the LS systems with high L_f values contain high amounts of liquid and low quantities of powder excipient. In contrast, the LS systems with low L_f values contain high amounts of carrier material (MCC) and low quantities of liquid.

Table 2.2 Flow properties of liquisolid powder blends

System	Carr's index (%)	Type of flow
LS-1	19.8 ± 0.3	Fair
LS-2	24.6 ± 0.3	Passable
LS-3	16.5 ± 0.7	Fair
LS-4	11.5 ± 0.4	Good
LS-5	30.0 ± 0.4	Poor
LS-6	17.6 ± 0.7	Fair
LS-7	15.2 ± 0.8	Good
LS-8	15.5 ± 0.5	Good

2.4.2 Weight variation, friability, hardness and content uniformity tests

The results of weight variation, friability, hardness and drug content are represented in Table 2.3. Average weight of LS tablets ranged from 598 ± 2 mg to 748 ± 2 mg.

All the clozapine LS tablets had acceptable friability as none of the tested formulae had percentage loss in tablet's weights that exceed 1%, also no tablet was cracked, split or broken in either formula. Since all prepared tablets met the standard friability criteria, they are expected to show acceptable durability and withstand abrasion in handling, packing and shipment.

In general, formulation should be directed at optimizing tablet hardness without applying excessive compression force, while at the same time assuring rapid tablet disintegration and drug dissolution. In other words, tablets should be sufficiently hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing. The mean hardness of each LS tablet was determined and is presented in Table 2.3 providing that all the LS tablets had acceptable hardness. All LS formulations have shown lower hardness compared with that of conventional formula (DCT). This was due to the presence of the liquid in the LS formulations that hinder the formation of the interparticle bonds (H-bonds in case of MCC) which are the main reason for the higher specific hardness obtained in DCT.

It was found that there is a relationship between R value and the hardness of the tablets. The R value was inversely proportional to the hardness of the tablets i.e., when the R value increases, the hardness of the tablet will decrease. This was obvious from the following results. LS-2 had R value equal to 10.0 and the mean hardness was 171 N. LS-3 had R value equal to 30.2 and the mean hardness was 104 N. This can be explained by that, increasing R value increases the amount of carrier powder (MCC) used which is a highly porous material and the amount of coating material (colloidal silica) will decrease and this subsequently leads to decreased hardness of the tablets.

It was found that there is a relationship between L_f and the hardness of the tablets in the LS formulation having approximately the same R value. The L_f was inversely proportional to the hardness of the tablets i.e., when the L_f increases, the hardness of the tablets will decrease. This was obvious from the following results. LS-1, LS-6, LS-7 and LS-8 were having L_f 0.427, 0.382, 0.345 and 0.315 and the mean hardness of them was 120, 123, 167 and 194 N, respectively. This can be explained by that, increasing L_f of the formulation increases the amount of solvent used and decreases the amount of the powder excipient and this subsequently decreases the hardness of the tablets.

It was clear from Table 2.3 that all the investigated clozapine LS tablets complied with the pharmacopoeial requirements as regard their content uniformity which was found to lie within the range 90-110%.

Table 2.3 Evaluation of clozapine liquisolid tablets

LS system	Hardness (N)	Friability		Weight variation (mg)	Drug content (%)
		Fines (%)	No. of broken tablets		
LS-1	120 ± 2	0.25	None	599 ± 2	100 ± 2
LS-2	171 ± 5	0.12	None	598 ± 2	98 ± 3
LS-3	104 ± 8	0.34	None	600 ± 2	98 ± 5
LS-4	124 ± 4	0.23	None	599 ± 1	100 ± 4
LS-5	95 ± 7	0.14	None	599 ± 2	97 ± 5
LS-6	123 ± 7	0.28	None	649 ± 4	99 ± 3
LS-7	167 ± 8	0.18	None	699 ± 3	96 ± 5
LS-8	194 ± 10	0.45	None	748 ± 2	99 ± 3
DCT	216 ± 6	0.45	None	549 ± 2	101 ± 3

2.4.3 In vitro dissolution studies

The dissolution profiles of clozapine LS tablets (LS-1) and directly compressed tablets (DCT) in pH 4.5 acetate buffer are shown in Figure 2.1. Dissolution rates of LS tablets were compared with DCT. LS formulation showed greater release than DCT formulation. The percentages of drug released from LS-1 and DCT after 5 min were 99.6% and 32.5% respectively at pH 4.5 acetate buffer. This showed that the LS compacts produced faster dissolution rate in comparison with DCT.

The enhanced dissolution rates of LS tablets compared to DCT may be attributed to the fact that, the drug is already in solution in PG, while at the same time, it is carried by the powder particles (MCC and CSD). When the drug within the LS system is completely dissolved in the liquid vehicle, it is located in the powder substrate still in a solubilized state. Therefore they show improved release rates.

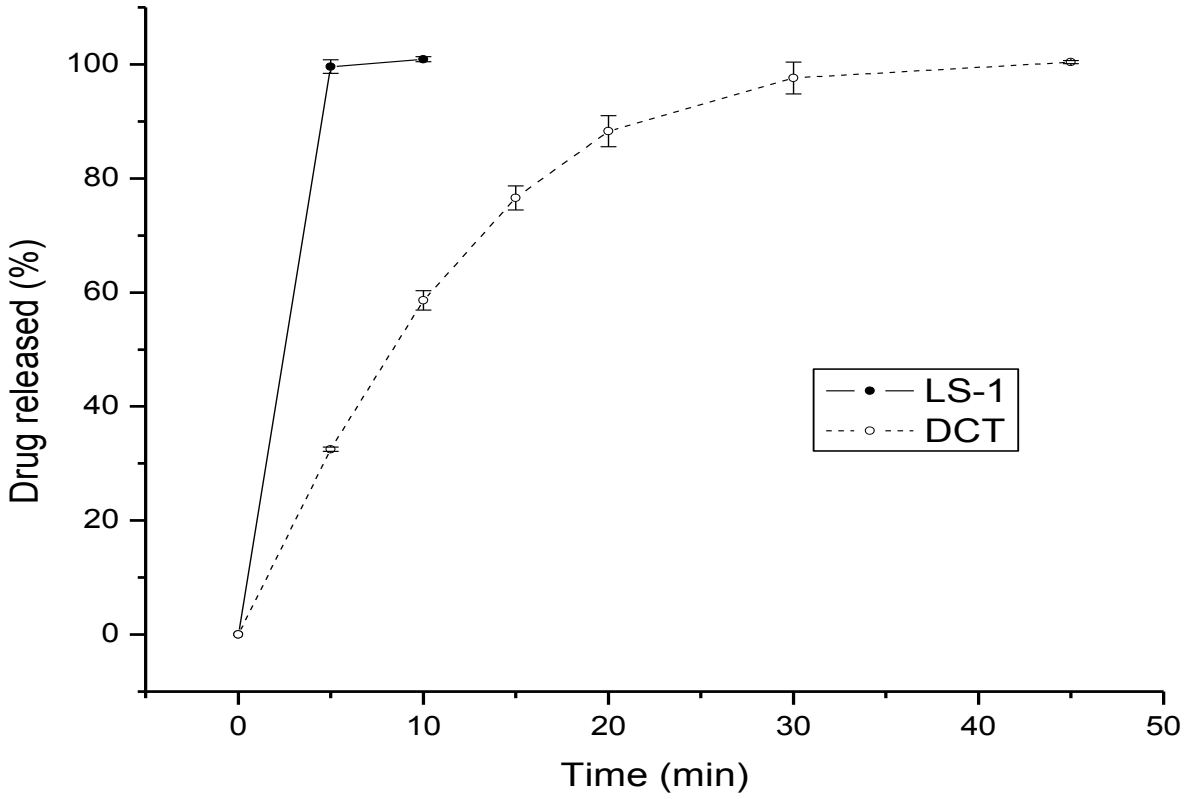

Figure 2.1 Dissolution profiles of clozapine from liquisolid tablets and directly compressed tablets (means ± SD; n=3)

The R value is an important parameter which is the ratio between the weights of the carrier and the coating material that may be optimized. An increase in the R value results in an enhanced release rate, if MCC and colloidal silica are used as carrier and coating materials, respectively. LS compacts with high R values contain high amounts of MCC, low quantities of CSD and low liquid to powder ratios. This is associated with enhanced wicking, disintegration and thus, enhanced drug release. In contrast, if high amounts of colloidal silica are used, which means that the R value is low, the LS compact is overloaded with liquid formulation due to a high L_f. In such cases, even though drug diffusion out of the primary particles may be rapid, oversaturation might occur resulting in local precipitation or recrystallization of the drug and thus decreased release rates (Javadzadeh et al., 2007).

As shown in Figure 2.2, the LS formulations that had R values of 20.9 (LS-1) and 30.2 (LS-3) exhibited similar drug release profiles with small variations while the LS formulation that had low R value of 10.0 (LS-2) showed lower drug release. This study confirmed that the R value is an important parameter for LS systems and must be minimum 20 to obtain enhanced drug release (Spireas et al., 1999).

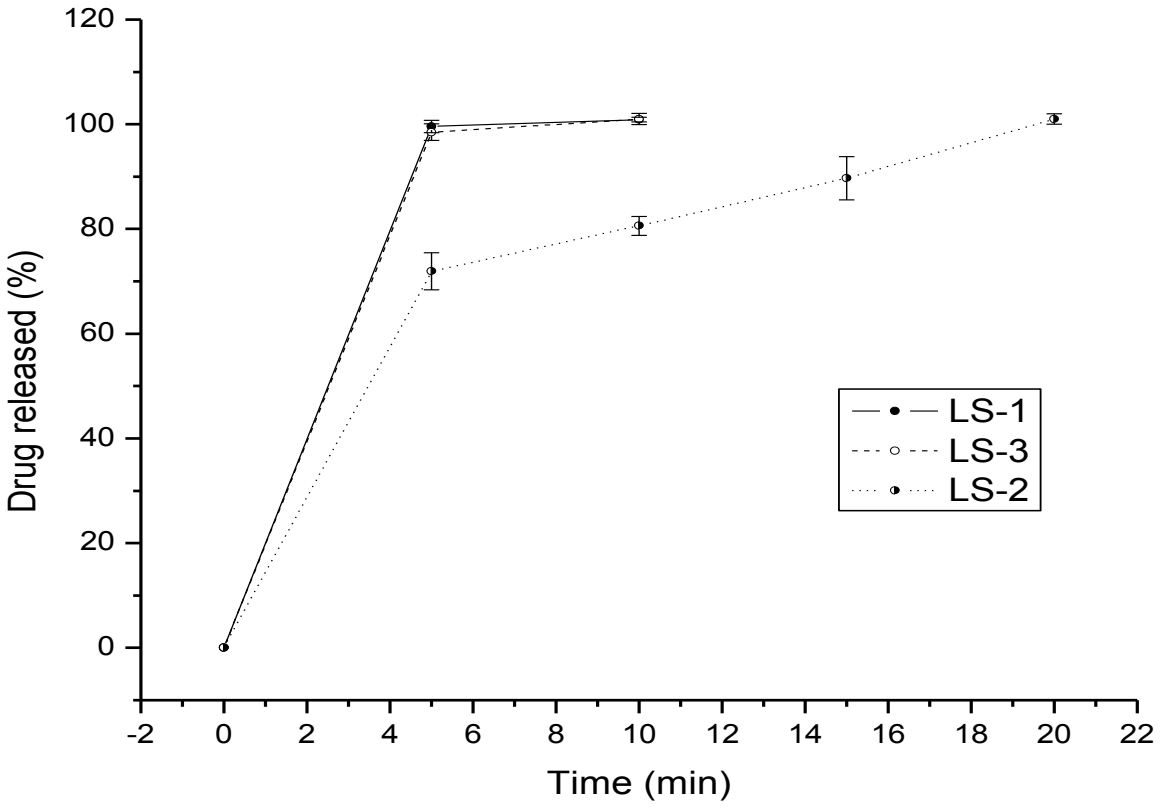

Figure 2.2 Dissolution profiles of clozapine from liquisolid tablets that had different R values (means ± SD; n=3)

The dissolution profiles of clozapine from LS tablets containing different coating materials in pH 4.5 acetate buffer are shown in Figure 2.3. The dissolution test results showed that LS-1 containing CSD had the highest drug release compared with LS-4 containing MAMS and LS-5 containing CS. The particle size of CS (74 μm) is smaller than that of MAMS (100 μm), but is much higher than that of CSD (12 μm). Therefore the drug release from LS-5 was higher than that of LS-4, but was lower than that of LS-1 as expected. This study confirmed that the particle size of the coating materials has an effect on the release of clozapine from LS tablets and CSD is the best suitable coating material for preparing LS compacts of clozapine.

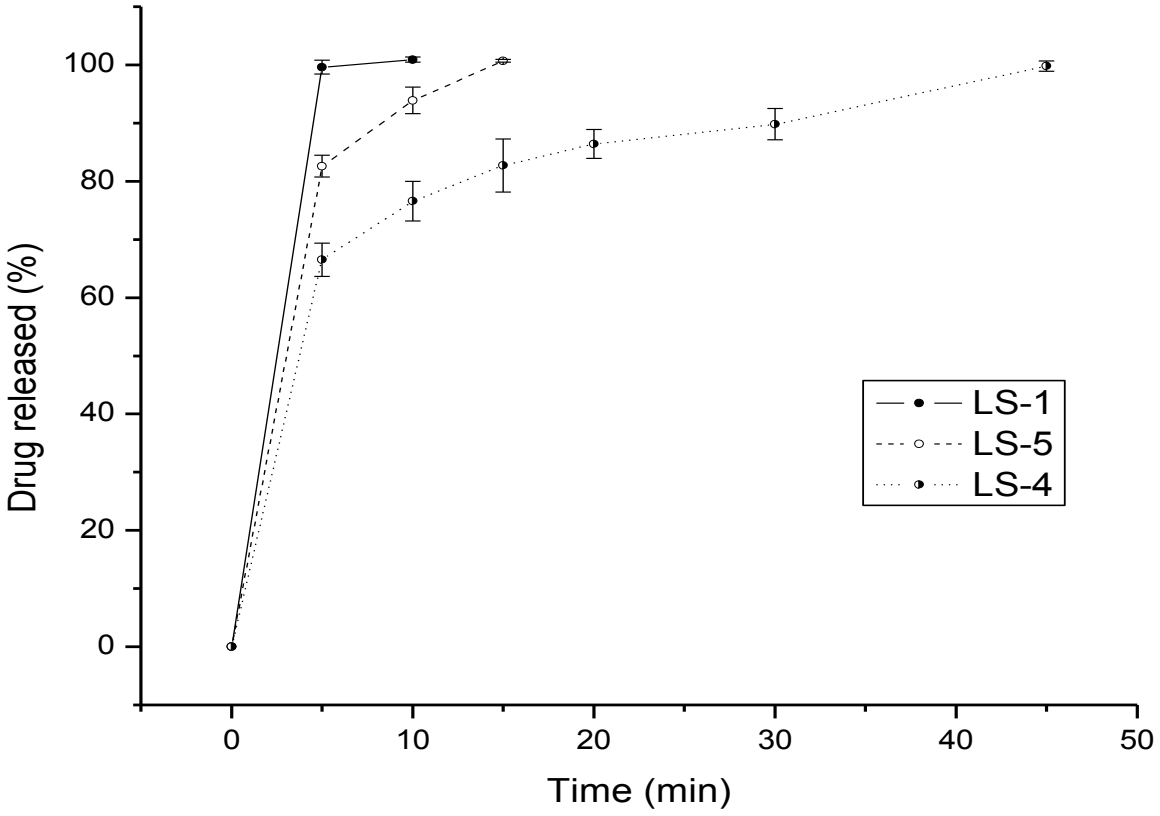

Figure 2.3 Dissolution profiles of clozapine from liquisolid tablets containing different coating materials (means ± SD; n=3)

The dissolution profiles of clozapine from LS tablets with different L_f values in pH 4.5 acetate buffer are shown in Figure 2.4. The LS formulations with different L_f values exhibited similar drug release profiles with small variations. This study showed that the L_f values did not cause important differences on the drug release from LS tablets.

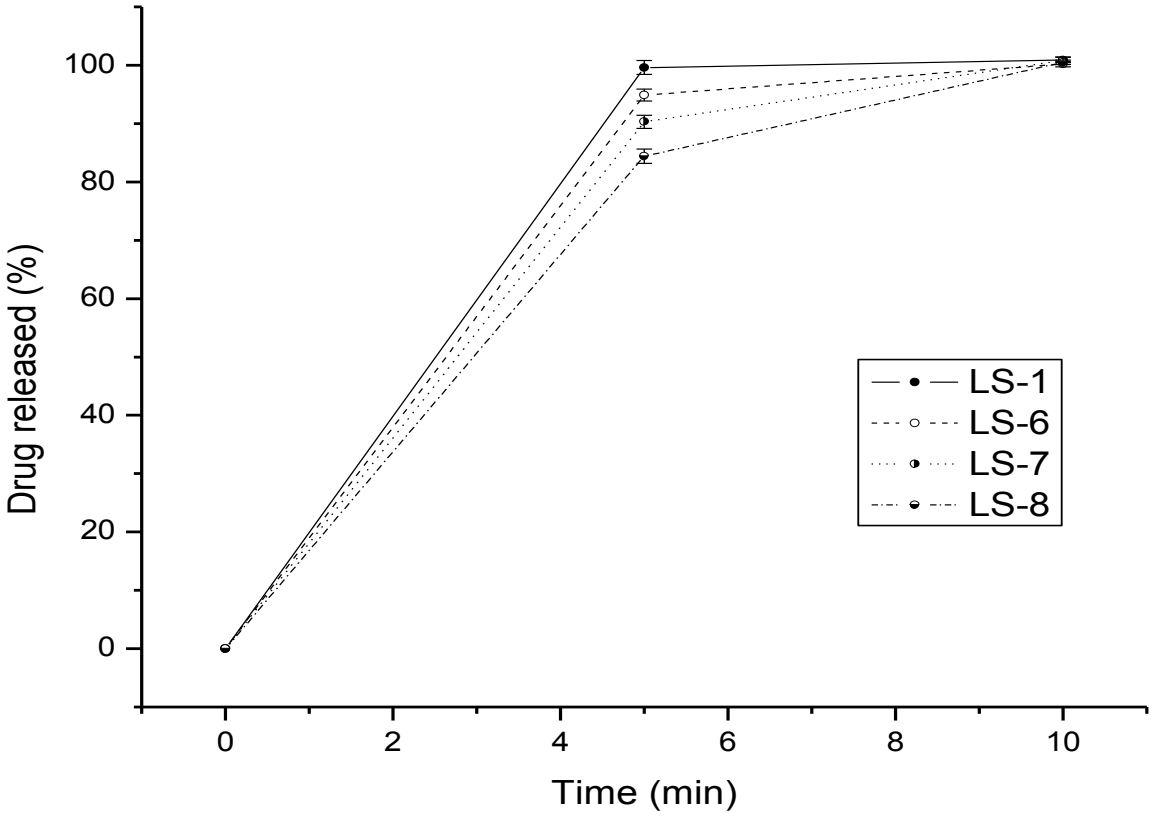

Figure 2.4 Dissolution profiles of clozapine from liquisolid tablets that had different L_f values (means ± SD; n=3)

2.4.4 Stability study

The effect of aging on the hardness and dissolution rate of LS tablets (LS-1) was determined by storing the tablets at 22 ^{0}C for up to 12 months. The dissolution rate and hardness were measured for the LS tablets at the end of 3, 6 and 12 months. The results showed that storage at 22 ^{0}C neither had an effect on the hardness (Table 2.4) nor on the release profiles (Figure 2.5) of LS compacts. These results indicate that in the case of clozapine the LS technology is a promising technique to enhance the release rate without having any stability issues.

Table 2.4 Hardness results of clozapine liquisolid tablets (fresh and aged)

LS system	Hardness (N) (fresh)	Hardness (N) (aged, 3 months)	Hardness (N) (aged, 6 months)	Hardness (N) (aged, 12 months)
LS-1	120 ± 2	110 ± 5	116 ± 6	114 ± 5

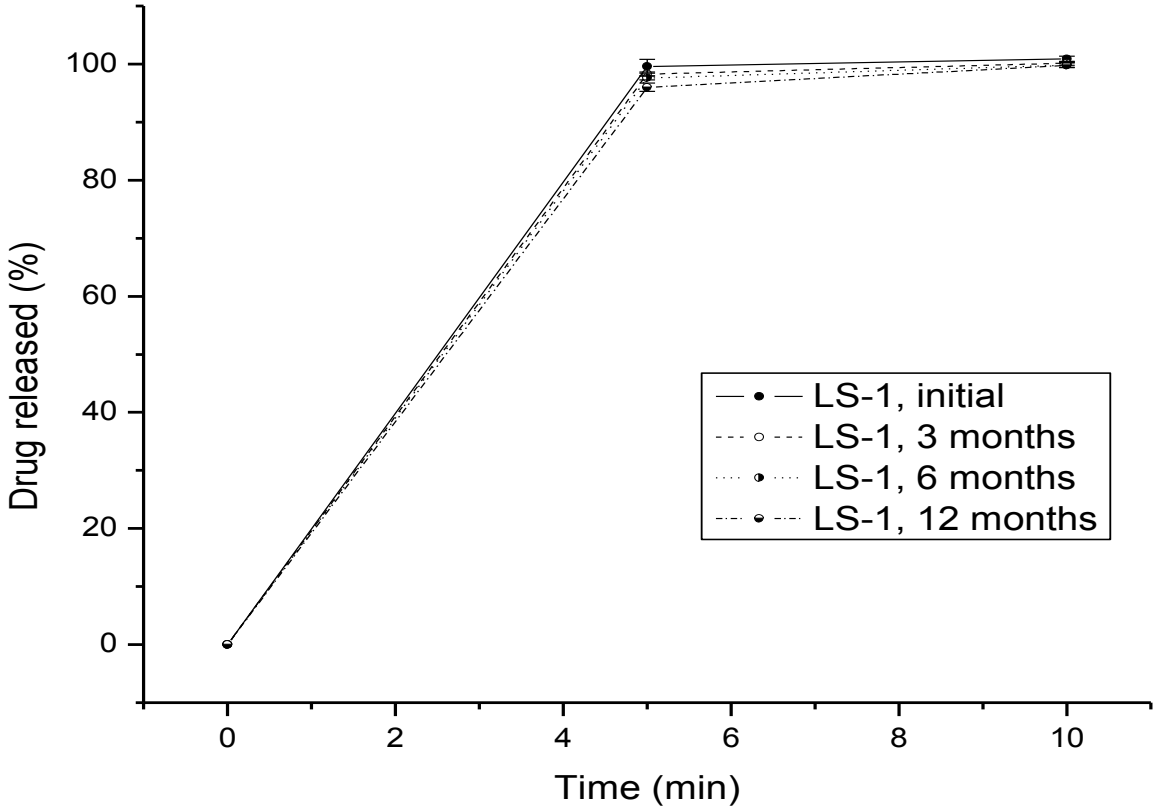

Figure 2.5 Dissolution profiles of clozapine from liquisolid tablets (fresh and aged) (means ± SD; n=3)

2.5 Conclusion

LS technique has been used successfully to produce a tablet dosage form of clozapine with faster dissolution rate than the regular tablet. Various trials were characterized based the blend and tablet parameters which showed the LS formulation containing MCC, CSD and SSG with clozapine dissolved in PG as a robust formula with required parameters. It showed significant increase in dissolution as compared DCT. It was found that there is a relationship between the carrier to coating material ratio (R value) and the in vitro release of clozapine from LS tablets. The R value was directly proportional to the in vitro release of clozapine from LS formulations. This study showed that the specific surface area of coating materials has an effect on the flow properties of LS powder blends and the particle size of coating materials affects the drug release from LS tablets. It was found that the liquid load factor (L_f) has an effect on the flow properties of LS powder blends but had no significant effect on the drug release from LS tablets. It was observed that aging had no significant effect on the hardness and dissolution profile of clozapine LS compacts. Although, better flow properties could be obtained using MAMS when compared to CSD, this former material resulted in slower dissolution rate. The LS-1 formulation was therefore considered optimal as it provided improve dissolution properties while being stable and robust to excipients modifications.

In conclusion, this study showed that LS technique could be a promising strategy in improving dissolution of poorly water soluble drugs such as clozapine and formulating immediate release dosage forms.

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Chapter three

3 Formulation development and dissolution rate enhancement of clozapine by orally disintegrating liquisolid systems

3.1 Overview

Patients, particularly pediatric and geriatric patients have difficulty in swallowing solid dosage forms. These patients are unwilling to take these solid preparations due to fear of choking. In order to assist these patients, several mouth dissolving drug delivery systems have been developed. ODTs dissolve rapidly in the saliva without the need for water and release the drug. Some drugs are absorbed from the oral cavity as the saliva passes down into stomach. In such cases, bioavailability of drug is significantly greater than those observed conventional tablet dosage forms (Reddy, Ahad et al. 2011). ODTs can be preferred for dosage forms for patients suffering from schizophrenia because they can be taken without water intake and disintegrate immediately upon contacting the tongue or buccal cavity, thereby improving patient compliance (Ahmed, Li et al. 2010).

Clozapine is an antipsychotic drug used to alleviate the symptoms and signs of schizophrenia, hallucinations, delusions and unusual behavior. The main criteria for ODTs is to disintegrate/dissolve rapidly in oral cavity with saliva without need of water and should have pleasant mouth feel (Reddy, Ahad et al. 2011). Clozapine is subject to first pass metabolism, resulting in an absolute bioavailability of 50 to 60% which is very low (Quitkin, Adams et al. 1998). It is poorly water soluble drug and rate of absorption of clozapine is often controlled by its solubility and dissolution rate. Some schizophrenic patients hide a conventional tablet under their tongue to avoid its daily dose of atypical antipsychotic. Also

schizophrenic patients with dsyphagia are not able to swallow conventional tablets (Shankarrao, Mahadeo et al. 2010). ODTs are a perfect fit for all these patients.

LS technology promotes the dissolution rate of poorly water soluble drugs to a greater extent. LS compacts of poorly water soluble drugs containing a drug molecularly dispersed in a liquid vehicle show enhanced drug dissolution. Accordingly, the improved drug dissolution may result in higher drug absorption and thus, improved oral bioavailability (Basalious, El-Sebaie et al. 2013). This technique was successfully applied for low dose poorly water soluble drugs. Drug can be present in a completely or partially dissolved state in the LS formulation. The LS formulation can then facilitate the release of this drug by two mechanisms: (1) Already dissolved drug only need to diffuse out of the formulation and (2) the liquid component of the formulation act as a solubilizing aid to facilitate the wetting and dissolution of undissolved particles. Since dissolution of poorly water soluble drugs is often the rate limiting step in gastrointestinal absorption, better bioavailability can be achieved when they are formulated using a LS system.

Literature lacks any data about application of LS technique for development of clozapine orally disintegrating LS tablets (OD-LST) useful for management of schizophrenia crisis. The developed clozapine OD-LSTs with enhanced dissolution rate may hasten the absorption of clozapine and avoid its hepatic first pass metabolism through the partial absorption from buccal mucosa and esophagus. Thus, in this study, it was proposed to formulate an oral delivery system containing clozapine, in the formulation of OD-LST to enhance its dissolution rates.

3.2 Literature review on orally disintegrating liquisolid tablets (OD-LSTs)

Aceclofenac is a NSAID, showing effective anti-inflammatory and analgesic properties mainly used in osteroarthritis, rheumatoid arthritis and anklysoling spondylitis (Legrand 2004). Aceclofenac being poorly soluble in water its rate of oral absorption is often controlled by the dissolution rate in the GIT (Amidon, Lennernäs et al. 1995). In the present study, LS compacts of aceclofenac were prepared by dispersing drug in various non-volatile solvents

(PEG 400, PG, polysorbate 80). MCC was added as a carrier. CCS, SSG and CP were used as superdisintegrants. Magnesium stearate and silica were mixed with granules as a glidant and lubricant respectively. Finally granules were compressed using manual tableting machine. Orodispersible LS compacts prepared with polysorbate 80 enhance the dissolution rate of aceclofenac to a greater extent. Compacts with SSG added intragranularly and CP extragranularly showed highest dissolution rate (Yadav, Shete et al. 2005).

Felodipine is a calcium channel blocker used as antihypertensive and antianginal drug. Felodipine has poor water solubility and hence poor dissolution and bioavailability after oral administration (Acholu, Yajaman et al. 2013). Felodipine was proposed as a candidate drug in emergency and treatment of hypertensive crisis. Literature lacks any data about the application of LS technique for development of felodipine LS orodispersible tablet (FLODT) useful for management of hypertension crisis. Thus, in the present study, orodispersible LS compacts of felodipine were prepared using PEG 400 and PG as non-volatile liquid vehicles, MCC and silicified MCC as carrier materials, silica as a coating material, CP as a superdisintegrant and aspartame as a sweetening agent. The optimized FLODT formulation showed a significant increase in dissolution rate compared to felodipine solution in PEG filled in soft gelatin capsule in 0.5% sodium lauryl sulphate (SLS) solution. The in vivo PK study suggests that the optimized FLODT developed in this work may be useful for management hypertensive crisis due to enhanced dissolution and rapid absorption of felodipine through the buccal mucosa (Basalious, El-Sebaie et al. 2013).

3.3 Materials and methods

3.3.1 Materials

Clozapine was provided by AK Scientific Inc. (USA). Propylene glycol (PG, Medisca, USA), microcrystalline cellulose (MCC, Avicel PH102, FMC, USA), colloidal silicon dioxide (CSD, Aerosil 200, Degussa AG, Germany), mannitol (Pearlitol 200 SD, Roquette, France), crospovidone (CP, Polyplasdone XL-10, ISP, USA), lactose monohydrate (Galenova, Canada) and sodium saccharin (SS, Giroux Lab., Canada) were purchased from major suppliers. All other reagents were of analytical grade and used without further purification.

3.3.2 Methods

3.3.2.1 Preparation of OD-LSTs of clozapine

Calculated quantities of clozapine and PG were accurately weighed and mixed together until a homogeneous, fine dispersion was obtained. The resulting liquid medication was incorporated into calculated quantities of carrier and coating materials. The mixing process was carried out in three steps. In the first, the system was blended at a mixing rate of one rotation per second for one minute in order to evenly distribute liquid medication in the powder. In the second, the liquid/powder admixture was evenly spread as a uniform layer on the surface of a mortar and left standing for 5 min to allow the drug solution to be absorbed inside powder particles. In the third, the powder was scraped off the mortar surface using a spatula. The final mixture was compressed into tablets by using a manual hydraulic press (15 ton press, Specac, England) equipped with round flat-faced tooling (diameter 12.6 mm) using a compression force of 25 kN after addition of sweetening agent and superdisintegrant. The ODTs were prepared using direct compression technique. The simplicity and cost effectiveness of the direct compression technique have positioned direct compression as an alternative to the other techniques such as spray-drying, melt granulation, freeze-drying etc.

Preliminary experiments were conducted to identify adequate OD-LST composition (OD-LST, Table 3.1) using common excipients. This system was composed of PG as a non-volatile liquid vehicle, MCC as a carrier material, mannitol as a carrier material and sweetening agent, CSD as a coating material, CP as a superdisintegrant and SS as a sweetening agent.

Table 3.1 Formulation design of clozapine orally disintegrating liquisolid tablets

System	OD-LST
L_f^*	0.210
R^{**}	20.0
Clozapine (mg)	25.0
PG (mg)	15.0
MCC (mg)	40.0
Mannitol (mg)	150.0
CSD (mg)	9.5
CP (mg)	58.0
SS (mg)	2.5
Total (mg)	300

*L_f : Liquid load factor

**R : The carrier : coating ratio of the powder system

3.3.2.2 Preparation of conventional ODTs of clozapine

Conventional ODTs (DC-ODT) of clozapine were prepared for comparison purposes These tablets were produced by direct compression using a manual hydraulic press (15 ton press, Specac, England) equipped with round flat-faced tooling (diameter 12.6 mm) using a compression force of 25 kN. Each tablet contained clozapine (25 mg), MCC (70 mg), mannitol (90 mg), lactose monohydrate (27 mg), CSD (8 mg) and CP (55 mg).

3.3.2.3 Weight variation, hardness, friability, content uniformity, disintegration time, wetting time and water absorption capacity tests

The prepared OD-LSTs were evaluated by carrying out tests for weight variation, hardness, friability, content uniformity, disintegration time, wetting time and water absorption percent. For estimating weight variation, 20 tablets were taken randomly from each tablet formulation and weighed individually. The average weight of all tablets and percentage deviation from the mean for each tablet were determined.

The hardness of formulated tablets was assessed using a hardness tester (PTB 301, Pharma Test AG, Hainburg, Germany) and the mean hardness of three tablets was determined. The friability was determined on ten tablets using a friability tester (PTF II, Pharma Test AG, Hainburg, Germany) and the percentage loss in weight was calculated.

For drug content uniformity test, ten tablets were crushed individually and powder equivalent to 25 mg of clozapine was dissolved in 25 mL of methanol. The solution was then passed through a 0.45 µm nylon filter and analyzed using UV spectrophotometer (WPA, Biochrom Ltd., Cambridge, England) at 290 nm after sufficient dilution with pH 6.4 phosphate buffer.

One of the most important characteristics of the ODT is its disintegration time in the oral cavity; however, a suitable method to access the disintegration properties described in the Pharmacopoeias (US, British, Japan and India) has not been developed. At present, the disintegration time of ODTs is measured utilizing the conventional tests (for tablets) that were described in the Pharmacopoeias. However, it is difficult to assess the disintegration rate for the ODT with these tests due to its rapid disintegration rate even in a small amount of water. Further, the conventional tests employ a volume of 900 mL of test solution compared to the volume of saliva in humans, which is less than 6 mL. Thus, the disintegration rate obtained from the conventional disintegration tests appears not to be reflective of the disintegration rate in the human mouth (Bi, Sunada et al. 1996). To overcome this problem, several new methods

have been proposed such as; disintegration test with charge coupled device (CCD) camera, pressurized disintegrating test apparatus (DTA), magnetic signaled DTA, texture analyzer, sinker type DTA, shaker type DTA, test tube analysis, wire basket type DTA, etc. (Sharma, Hardenia et al. 2009). Among them, the wire basket DTA is considered as a suitable method to access the disintegration properties of ODTs.

Briefly, the apparatus (Figure 3.1) consisting of a glass beaker of 1000 mL capacity with the wire basket is positioned in the beaker with the help of a support in a way that when the beaker is contained 900 mL of disintegrating medium the basket has only 6 mL of it. A magnetic bead is placed at the bottom of the beaker maintaining at 37 ± 2 ^{0}C. Disintegration time is determined at 25 and 50 rpm (Khan, Kataria et al. 2007).

During this study we made an attempt to develop a more suitable apparatus (Figure 3.2) for the disintegration test. A glass beaker of 10 mL capacity contained 6 mL of pH 6.4 phosphate buffer as a disintegration medium was placed on the magnetic stirrer. A very small magnetic bead was placed at the bottom of a beaker and temperature was maintained at 37 ± 2 ^{0}C. Disintegration time was determined at 50 rpm. The disintegration test was carried out on six tablets.

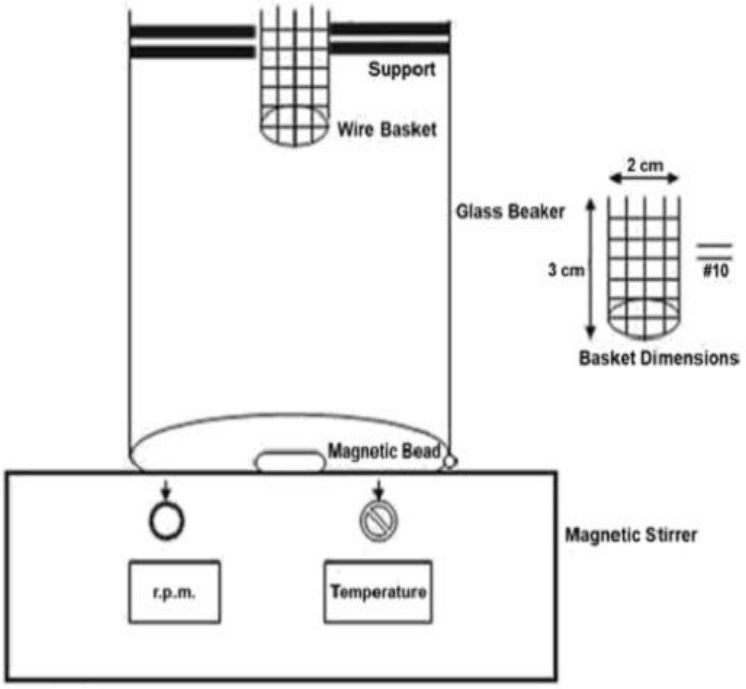

Figure 3.1 Wire basket type disintegration test apparatus

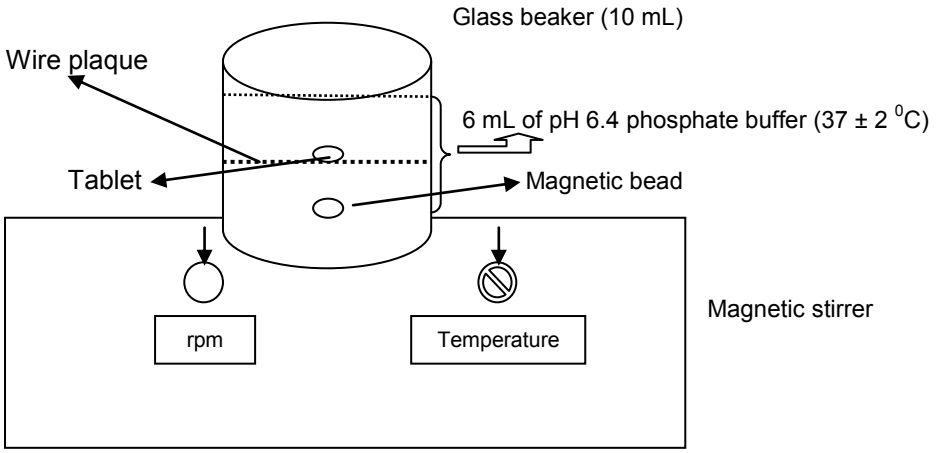

Figure 3.2 Modified disintegration test apparatus

Wetting time was determined by placing five circular tissue papers in a petri dish of 10 cm diameter (Gohel, Patel et al. 2004). 10 mL of water containing water-soluble blue dye (metylene blue) (0.1% w/w) was added to the petri dish. The dye solution was used to identify complete wetting of the tablet surface. A tablet was carefully placed on the surface of tissue paper in the petri dish at room temperature. The time required for water to reach the upper surface of the tablet was noted as the wetting time. These measurements were carried out in replicates of three.

The weight of the tablet prior to placement in the petri dish was noted (Wb). The wetted tablet was removed and reweighed (Wa). Water absorption ratio (R) was then determined according to the following equation.

$$R = 100 \times \frac{W_a - W_b}{W_b}$$

W_a: Weight of tablet after water absorption

W_b: Weight of tablet before water absorption

3.3.2.4 In vitro dissolution study

The USP apparatus II (paddle method) (DTB 678 equipment with thermostatic bath and circulation pump VTC-100, Logan Instruments Corporation, New Jersey, USA) was used for all the in vitro dissolution studies. In this method, phosphate buffer having the pH of 6.4 was used as dissolution medium. Phosphate buffer of pH 6.4 was selected as the dissolution medium to simulate the pH value of the saliva. The rate of stirring was 100 rpm. The dosage forms were placed in 400 mL of the phosphate buffer maintained at 37 ± 0.5 °C. At appropriate intervals (5, 10, 20, 30 and 45 min) 5 mL of the samples were taken. The dissolution media was then replaced by 5 mL of fresh dissolution fluid to maintain a constant volume. After proper dilution, the samples were analyzed at 290 nm spectrophotometrically

(WPA, Biochrom Ltd., Cambridge, England). The mean of three determinations was used to calculate the drug release from each of the formulations.

3.3.2.5 Stability study

The effect of aging on the disintegration time and dissolution rate of OD-LSTs was determined by storing the tablets at 22 ^{0}C for up to 6 months. After that, the samples were tested for their dissolution profiles and disintegration times at the conditions that have been used with freshly prepared tablets. The results were compared with the freshly tested tablets.

3.4 Results and discussion

3.4.1 Weight variation, hardness, friability, content uniformity, disintegration time, wetting time and water absorption capacity tests

The results of weight variation, hardness, friability, drug content, disintegration time, wetting time and water absorption capacity tests are represented in Table 3.2. Average weight of OD-LST was 299 ± 2 mg. Average hardness of OD-LST was 45 ± 3 N and the tablets possessed acceptable hardness. All the clozapine OD-LSTs had acceptable friability as none of the tablets had percentage loss in tablet's weights that exceed 1%, also no tablet was cracked, split or broken. Average percentage drug content was 99 ± 3 % indicating the compliance with the pharmacopoeial limits (90-110%).

The most important parameter that needs to be evaluated in the development of ODTs is the disintegration time. As per recent US FDA guideline on ODT, disintegration time of ODT should have an in vitro disintegration time of approximate 30 s or less (US FDA CDER 2008), when based on USP disintegration test method or alternative. In the present study, all the tablets disintegrated in less than 30 s fulfilling the official requirements for ODTs. The OD-LST of clozapine disintegrated within 20 s. CP quickly wicks saliva into the tablet and provides rapid disintegration in the mouth (Mohanachandran, Sindhumol et al. 2011). The rapid disintegration of OD-LST could be explained by its rapid wetting (wetting time 8 s) and its high water absorption capacity (128%). The wetting time is important step for

disintegration process to take place (Shankarrao, Mahadeo et al. 2010). The OD-LST showed quick wetting, this may be due to ability of swelling and also capacity of absorption of water.

Table 3.2 Physical characterization of clozapine orally disintegrating liquisolid tablets

Test	OD-LST
Weight variation (mg)	299 ± 2
Hardness (N)	45 ± 3
Friability (%)	0.22
Drug content (%)	99 ± 3
Disintegration time (s)	20 ± 1
Wetting time (s)	8
Water absorption (%)	128 ± 2

3.4.2 In vitro dissolution study

The dissolution profiles of clozapine OD-LSTs and DC-ODTs in pH 6.4 phosphate buffer are shown in Figure 3.2. It was obvious that drug release from OD-LSTs was much faster than that from the regular ODTs. Within 45 min only 68.8% of clozapine was released from DC-ODTs as compared to the OD-LSTs with 99.8% drug release.

The enhanced dissolution rates of OD-LST compared to DC-ODT may be attributed to the fact that, the drug is already in solution in PG, while at the same time, it is carried by the powder particles (MCC, mannitol and CSD). When the drug within the LS system is completely dissolved in the liquid vehicle, it is located in the powder substrate still in a solubilized state. Therefore they show improved release rates.

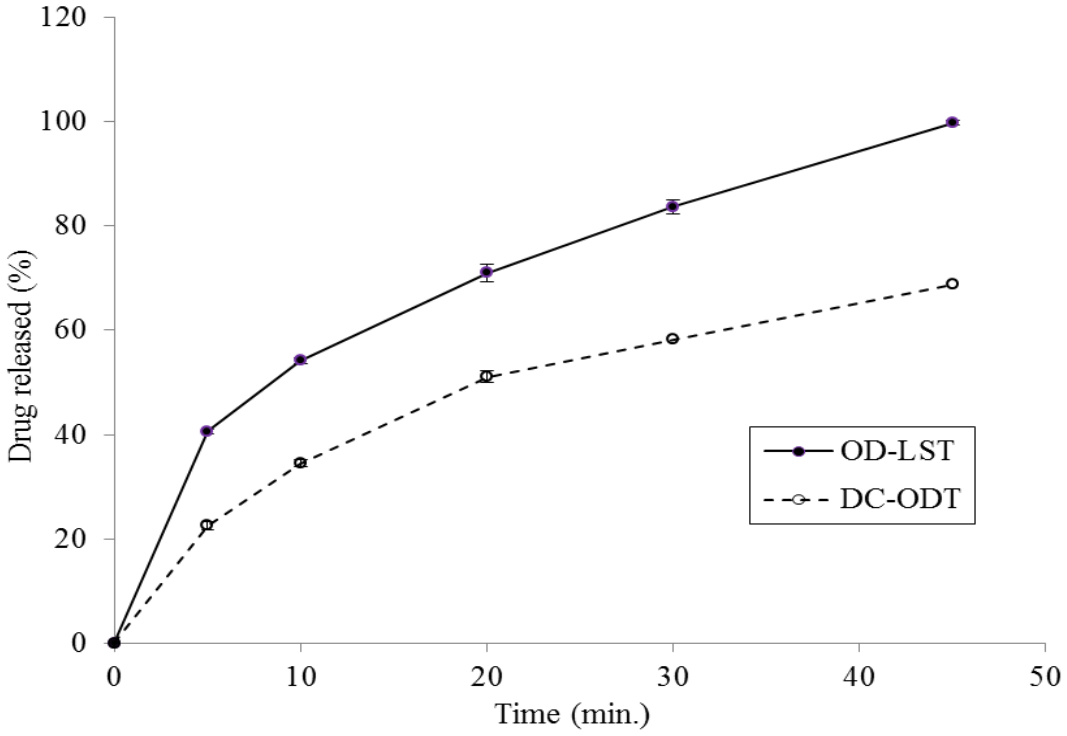

Figure 3.3 Dissolution profiles of clozapine from orally disintegrating liquisolid tablets and directly compressed orally disintegrating tablets (means ± SD; n=3)

3.4.3 Stability study

The effect of aging on the disintegration time and dissolution rate of OD-LSTs was determined by storing the tablets at 22 ^{0}C for up to 6 months. The dissolution rate and disintegration time were measured for the OD-LSTs at the end of 3 and 6 months. The results showed that storage at 22 ^{0}C neither had an effect on the disintegration time (Table 3.3) nor on the release profiles (Figure 3.4) of OD-LSTs. These results indicate that in the case of clozapine the OD-LS technology is a promising technique to enhance the release rate without having any stability issues.

Table 3.3 Disintegration time results of clozapine orally disintegrating liquisolid tablets (fresh and aged)

LS system	Disintegration time (s) (fresh)	Disintegration time (s) (aged, 3 months)	Disintegration time (s) (aged, 6 months)
OD-LST	20 ± 1	19 ± 1	20 ± 2

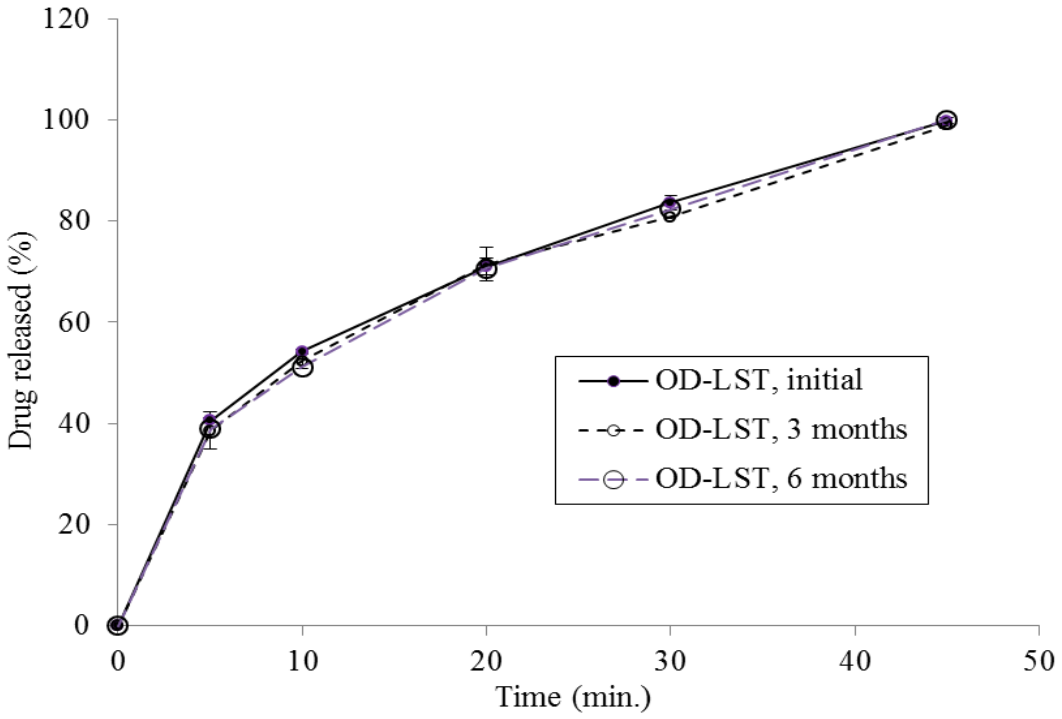

Figure 3.4 Dissolution profiles of clozapine from orally disintegrating liquisolid tablets (fresh and aged) (means ± SD; n=3)

3.5 Conclusion

LS technique has been used successfully to produce an ODT dosage form of clozapine with enhanced dissolution rate. This study demonstrated that formulation of clozapine as OD-LST is feasible for enhancing the in vitro dissolution of the drug so it would be possible to

hasten the absorption of clozapine and avoids its hepatic first pass metabolism through the partial absorption from buccal mucosa and esophagus. The physicochemical properties and stability of the prepared LS tablets were satisfactory.

It was concluded that the ODTs of clozapine can be successfully prepared using LS technology in order to improve disintegration and dissolution rate of clozapine in oral cavity.

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Chapter four

4 Conclusion

LS technique has been used successfully to produce a tablet dosage form of clozapine with faster dissolution rate than the regular tablet. Various trials were characterized based the blend and tablet parameters which showed the LS formulation containing MCC, CSD and SSG with clozapine dissolved in PG as a robust formula with required parameters. It showed significant increase in dissolution as compared DCT. It was found that there is a relationship between the carrier to coating material ratio (R value) and the in vitro release of clozapine from LS tablets. The R value is an important parameter which is the ratio between the weights of the carrier and the coating material that may be optimized. An increase in the R value results in an enhanced release rate, if MCC and colloidal silica are used as carrier and coating materials, respectively. LS compacts with high R values contain high amounts of MCC, low quantities of CSD and low liquid to powder ratios. This is associated with enhanced wicking, disintegration and thus, enhanced drug release. In contrast, if high amounts of colloidal silica are used, which means that the R value is low, the LS compact is overloaded with liquid formulation due to a high L_f. In such cases, even though drug diffusion out of the primary particles may be rapid, oversaturation might occur resulting in local precipitation or recrystallization of the drug and thus decreased release rates (Javadzadeh et al., 2007).

This study showed that the liquid load factor (L_f) has an effect on the flow properties of LS powder blends but had no significant effect on the drug release from LS tablets. It was observed that aging had no significant effect on the hardness and dissolution profile of clozapine LS compacts. In conclusion, this study showed that LS technique could be a promising strategy in improving dissolution of poorly water soluble drugs such as clozapine and formulating immediate release dosage forms.

In this study OD-LSTs of clozapine were prepared and in vitro evaluated. The optimized OD-LST formulation of clozapine showed a significant increase in dissolution rate

compared to the regular ODTs. This study demonstrated that formulation of clozapine as OD-LST is feasible for enhancing the in vitro dissolution of the drug so it would be possible to hasten the absorption of clozapine and avoids its hepatic first pass metabolism through the partial absorption from buccal mucosa and esophagus. It was observed that aging had no significant effect on the disintegration time and dissolution profile of clozapine OD-LSTs. It was concluded that the ODTs can be successfully prepared using LS technology and adding superdisintegrants to the formulation in order to improve disintegration and dissolution rate of poorly water soluble drugs such as clozapine.