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Applications of Liquisolid Technique for Different Water Insoluble Drugs: A Review

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ABSTRACT

In the last decade, poorly soluble drugs have been an area of concern for all the researchers in the field of pharmacy. A number of researches have been carried out to enhance the solubility and dissolution properties of such drugs. This study deals with a comprehensive review of liquisolid technique carried out mainly for biopharmaceutical classification system (BCS) class II & IV drugs. These drugs are having problems of poor solubility, dissolution and thus poor bioavailability. Various studies conducted on a number of drugs so far, have been reviewed. A variety of techniques such as micronization, salt formation, complexation, solid solutions, and liquisolid technique etc. have been used to overcome such problems. It has been observed that liquisolid technique is the most promising way for solubility and dissolution enhancement of such drugs. It can be concluded that liquisolid technique results in increased solubility, dissolution and thus bioavailability.

Keywords: Liquisolid, dissolution, solubility, bioavailability.

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INTRODUCTION

The oral route is the most preferred means of drug administration due to the ease, high patient compliance, and low cost of production. The drug must be presented in solution form for absorption through gastrointestinal tract (GIT) when given orally[1]. It has been established that the active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. The rate of absorption of a poorly water-soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid present at the absorption site, i.e. the dissolution rate is often the rate-determining step in drug absorption. Therefore, the solubility and dissolution behavior of a drug are the key determinants of its oral Bioavailability[2] Advancements in the fields of biotechnology and drug discovery have led to the discovery of increasingly large number of active molecules. However, 40% of all newly developed drugs are poorly soluble or insoluble in water, leading to ineffective absorption and therapeutic failure.[3]

This technique is generally used to formulate the drugs of BCS class II and IV[4]. Poorly water soluble drugs are difficult to formulate using conventional techniques. Different techniques have been reported in the literature to achieve better drug dissolution rates, namely: (a) reduction of particle size via micronization or nanonization to increase the surface area; (b) use of surfactants[5]; (c) inclusion with cyclodextrins[6]; (d) use of pro-drug and drug derivatisation; (e) formation of solid solutions or amorphous solids; (f) microencapsulation and inclusion of drug solutions or liquid drugs into soft gelatin capsules or specially sealed hard shell capsules[7,8]

Amongst various techniques to overcome the solubility issue, several researchers reported that the formulation of liquisolid tablets is one of the most promising techniques for promoting drug dissolution[9].

Historical Development

Historically, liquisolid systems are descendants of “powdered solutions”, an older technique which was based on the conversion of a solution of a drug in a non-volatile solvent into a dry-looking, non-adherent powder by mainly adsorbing the liquid onto silica of large specific surfaces. In later studies on powder solution, compression enhancers such as microcrystalline cellulose were added in such dispersions in order to increase the compressibility of the systems. Specifically when such modified powdered solutions were compressed into tablets, they presented significant “liquid squeezing out” phenomenon and unacceptably soft tablets, thereby hampering the industrial application of such systems[10].

The liquisolid compacts are acceptably flowing and compressible powdered forms of liquid medications. The term 'liquid medication' refers to liquid lipophilic (oily) drugs or water-insoluble solid drugs dissolved in suitable water-miscible non-volatile solvent systems termed as the liquid vehicle. The liquid medication is included into the porous carrier material. As the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Such liquid medication may be converted into a dry-looking, nonadherent, free flowing and readily compressible powders by a simple admixture with selected powder excipients referred to as the carrier and coating materials[11-13].

In the liquisolid systems, even though the drug might be in a solid dosage form, it is held within the powder substrate in solution or in a solubilized, almost molecularly dispersed state. Therefore, due to their significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release characteristics and consequently improved oral bioavailability[14-16].

By using hydrophobic polymers and excipients carriers such as Eudragit RL and Eudragit RS controlled release of drugs from liquisolid tablets as the dosage forms can be formulated[17-19].

Classification of liquisolid systems:

Based on the type of liquid medication contained therein, liquisolid systems may be classified into three subgroups

- Powdered drug solutions
- Powdered drug suspensions
- Powdered liquid drugs

Powdered drug solutions and suspensions may be produced from the conversion of drug solutions or drug suspensions into liquisolid systems.

Powdered liquid drugs are produced from the formulation of liquid drugs into liquisolid systems.

Based on the formulation technique used, liquisolid systems may be classified into two categories namely,

- Liquisolid compacts
- Liquisolid Microsystems

The term "liquisolid compacts" refers to immediate or sustained release tablets or capsules prepared, with the inclusion of appropriate adjuvants required for tabletting or encapsulation, such as lubricants, disintegrants or binders.

The term "liquisolid microsystems" refers to capsules prepared by combining the drug with

carrier and coating materials, combined with inclusion of an additive e.g., PVP in the liquid medication wherein the resulting unit size may be as much as five times less than that of liquisolid compacts[20-25]

Formulation and Designing of Liquisolid Systems

There are mainly five components of liquisolid compact, as follows:

Drug candidates –

This technique have been successfully applied for low dose BCS class II and class IV drugs which are poorly water soluble and have slow dissolution rate. Examples of drug candidates include carbamazepine, famotidine, piroxicam, indomethacin, hydrocortisone, naproxen and prednisolone, digoxin, digitoxin, spironolactone, hydrochlorothiazide, and other liquid medications such as chlorpheniramine, water insoluble vitamins, fish oil etc.

Non volatile Solvent –

Non volatile solvent should be inert, high boiling point, preferably water-miscible and not highly viscous organic solvent systems and compatible with having ability to solubilize the drug. It acts as a binding agent in the liquisolid formulation. Various non-volatile solvents used for the formulation of liquisolid systems include polyethylene glycol 200 and 400, glycerin, polysorbate 80 and propylene glycol[26-29]

Carrier Materials –

Carrier material should be porous material possessing sufficient absorption properties which contributes in liquid absorption. The carrier and coating materials can retain only certain amounts of liquid and at the same time maintain acceptable flow and compression properties hence, increasing moisture content of carrier's results in decreased powder flowability. These include grades of microcrystalline cellulose such as avicel PH 102 and avicel PH 200, lactose, eudragit RL and eudragit RS12 (to sustain drug delivery) etc.

Coating Materials –

It is a material of size range of about 10 to 5,000 nm in diameter, possessing fine and highly adsorptive properties which contribute in covering the wet carrier particles and displaying a dry-looking powder by adsorbing any excess liquid thus maintaining its flowability e.g. silica (Cab-O-Sil), Aerosil 200, Syloid[30].

Disintegrant –

Superdisintigrants increases the rate of drug release, water solubility and wettability of liquisolid granules e.g. sodium starch glycolate and crosspovidone[31,32].

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 liquisolid systems has been developed by Spireas[33].

Designing of liquisolid system includes determination of solubility of drug in different non-volatile solvents, angle of slide, flowable liquid retention potential (Φ value), calculation of liquid load factor (L_f) and liquisolid compressibility test (LSC).

Solubility Studies

Spectroscopic method

It includes determination of solubility of drug in different non-volatile solvents by preparing saturated solutions. Saturated solutions are prepared by adding excess amount of drug to the solvent and placed in orbital shaker for 48 hr at 25^0C. Then the solutions were filtered, diluted and analyzed by U.V. spectrophotometer.

Synthetic method for determination of solubility

In this method 1-40 mg of sample (drug) was taken in screw cap vials to which incremental amounts of solvent is added and was shaken for two minutes after each addition of solvent in vial shaker until clear solution is formed. Determine the solubility of the sample by using the following formula[34,35]

$$\text{Solubility} = \frac{\text{Amount of drug taken (mg)}}{\text{Volume of solvent added (ml)}}$$

Angle of Slide

The required amount of carrier material is weighed and placed on side of a metallic plate. The plate is gradually raised till it is angular to the horizontal. The angle at which carrier slides from the plate is measured as angle of slide. It is used to measure the flow properties of powders. Angle of 33^0 is optimum for flow of powders.

Determination of Flowable Liquid Retention Potential (Φ value)

Absorption of a liquid by a powder material occurs when the absorbate molecules diffuse inside the absorbent and are eventually captured and held by the powder particles within their bulk. In some cases, the liquid is not truly absorbed, and instead of being dispersed throughout the interior of the solid, the liquid molecules only cling to its available surface i.e., internal and external. This process is known as adsorption. Sometimes, however, depending on the sorbent properties, both of these processes may occur simultaneously. The combined process is termed

as sorption. The flowable liquid-retention 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, (W_{liquid}) that can be retained per unit weight of the sorbent, (W_{solid}), yielding a mixture with acceptable flowability;

$$\Phi \text{ value} = \text{weight of liquid} / \text{weight of solid}$$

As the flowable liquid-retention potential of the carrier material is approached, the liquid is held entirely in the interior of the particles. This maintains the surface of carrier material relatively dry, thus yielding powders with acceptable flow properties. When the Φ value is exceeded, the interior of particles become saturated, resulting in the formation of a liquid layer on the available surface of carrier particles[36]. Ψ is known as compressible liquid retention potential. Φ-values and Ψ-numbers for various powder-solvent systems are presented in table 1.

Table 1- Liquisolid Formulation Parameters of Various Powder Excipient or System

Powder excipient or system	Flowable Liquid Retention Potential(Φ-values)		Compressible Liquid Retention PotentialΨ-numbers	
	Propylene glycol	PEG 400	Propylene glycol	PEG 400
Avicel PH 102[4]	0.16	0.005	0.224	0.242
Avicel PH 200[4]	0.26	0.02	0.209	0.232
Cab-O-Sil M5 (silica)* with Avicel PH 102[6]	3.31	3.26	0.560	0.653
Cab-O-Sil M5 (silica)* with Avicel PH 200[6]	2.57	2.44	0.712	0.717

*included as coating material in carrier/coating powder system

Liquid Load Factor (L_f)

It is defined as the ratio of weight of liquid medication (W) to weight of carrier material (Q). It is determined by dissolving or dispersing the drug in nonvolatile solvent and to this, carrier-coating material admixture is added and blended. The amount of carrier coating admixture used to convert it into free flowing powder is determined by using the following formula.

$$L_f = W/Q$$

W = weight of liquid medication

Q = weight of carrier material

It is used to calculate the amount of carrier and coating material in each formulation. The excipients ratio R of powders is defined as ratio of weight of carrier and coating material present in the formulation. R is suitably selected for successful formulation[37].

$$R = Q/ q$$

Where q = coating material

Liquisolid Compressibility Test (LSC)

It was developed to determine Ψ values and involves steps such as preparing carrier coating material admixture systems, preparing several uniform liquid/powder admixtures to tablets, determining average hardness, measuring of average liquid content of crushed tablets, as well as determining plasticity, sponge index and Ψ value and L_f[10]. All the research conducted so far, exhibits an increase in solubility and dissolution rate of water insoluble drugs. Various studies conducted on a number of drugs are presented in table 2.

Table 2 - Formulations of Liquisolid Systems with Enhanced Drug Release

Drug	Non-volatile vehicle	Carrier and coating material
Aceclofenac	Propylene glycol, PEG 400 and Tween 80	MCC[10]
Aceclofenac	PEG 400	MCC and colloidal silica[11]
Atorvastatin calcium	Propylene glycol, Polyethylene glycol 400	MCC and colloidal silica[12]
Bromhexine HCL	Propylene glycol	MCC and colloidal silica[13]
Carvedilol	PEG 400	MCC and colloidal silica[14]
Carbamazepine	PEG 200	MCC and colloidal silica[15]
Clofibrate (liquid)	---------	MCC and colloidal silica[16]
Diclofenac sodium	Propylene glycol	MCC and colloidal silica[17]
Etoricoxib	PEG 400	MCC and colloidal silica[18]
Famotidine	Propylene glycol	MCC and colloidal silica[19]
Fenofibrate	Propylene glycol	MCC and colloidal silica[20]
Fenofibrate	PEG 400	MCC and colloidal silica[32]
Furosemide	Synperonic® PE/L 81, Caprol® PGE-860 and PEG 400	MCC and colloidal silica[21]
Glibenclamide	PEG 400	MCC and colloidal silica[22]
Griseofulvin	PEG 400	MCC and colloidal silica[23]
Glipizide	PEG 400	MCC and colloidal silica[24]
Hydrochlorothiazide	PEG 200	MCC and colloidal silica[25]
Hydrocortisone	PEG 400	MCC and colloidal silica[26]
Ibuprofen	PEG 400	MCC and silica gel[27]
Indomethacin	PEG 200, Glycerine	MCC and colloidal silica[28]
Indomethacin	Propylene glycol	MCC and colloidal silica[29]
Indomethacin	PEG 400	MCC and HPMC[30]
Ketoprofen	Propylene glycol and Tween80	Dicalcium phosphate and silica gel[31]
Ketoprofen	PEG 400	MCC, starch, dicalcium phosphate, lactose and silica gel[32]
Lamotrigine	PEG 400	MCC and colloidal silica[32]
Methyclothiazide	PEG 400	MCC and colloidal silica[33]
Naproxen	Cremophor EL, Synperonic PE/L61 and PEG400	MCC and colloidal silica[34]
Nifedipne	PEG 400	MCC and colloidal silica with HPMC[35]

Piroxicam	Tween 80	MCC and colloidal silica[36]
Polythiazide	PEG 400	MCC and colloidal silica[36]
Prednisolone	Tween 80, PEG 400, propylene glycol, Glycerine	MCC and colloidal silica[37]
Prednisolone	N,N dimethylacetamide /PEG400 (7:3v/v)	Various silicas[32]
Prednisone	Propylene glycol	MCC and colloidal silica[32]
Propanolol HCL	Tween 80	Eudragit RS or RL and colloidal silica with HPMC[38]
Repaglinide	Tween 80	MCC and calcium silicate[39]
Rofecoxib	PEG 600	MCC and colloidal silica[40]
Simvastatin	PEG 400	MCC and colloidal silica[41]
Theophylline	Tween 80	Eudragit RS or RL and colloidal silica with HPMC[42]
Tramadol HCL	Propylene glycol	MCC and colloidal silica with HPMC[43]
Valsartan	Propylene glycol	MCC and colloidal silica[44]

OPTIMIZATION OF LIQUISOLID FORMULATIONS WITH ENHANCED DRUG RELEASE

The liquisolid 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 liquisolid technology. As the release rates are directly proportional to the fraction of molecularly dispersed drug (FM) in the liquid formulation a higher drug dose requires higher liquid amounts for a desired release profile. Moreover, to obtain liquisolid systems with acceptable flowability and compactability 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[26-29]. Therefore, to overcome this and various other problems of the liquisolid technology several formulation parameters may be optimized which are available in the literature[45].

CONCLUSIONS

From the reviewed literature, it can be said that the inadequate dissolution of water-insoluble drugs is the major reason for their poor and erratic bioavailability since it is the rate determining step in the absorption. Liquisolid technology was reported to be effective for improving dissolution rate as well as bioavailability in practically water insoluble drugs with non-volatile solvents. The technique also sustained the drug release properties of the water soluble drugs by using suitable biodegradable polymers with appropriate excipient ratios. The use of nonvolatile solvent in the formulation causes increased wettability of water insoluble drugs and ensures molecular dispersion of drug in the formulation. It was found that the enhanced rate of drug dissolution from liquisolid tablets is probably due to an increase in wetting properties and surface

area of drug particles available for dissolution. It can be concluded that the modification of formulation by use of certain agents cause rapid disintegration rates as compared to conventional tablets and therefore, they show improved release rates and hence greater bioavailability. The liquisolid technique proved to be a promising alternative to increase the dissolution of water insoluble drugs and thereby enhance their absorption characteristics.

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