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THE LIQUISOLID TECHNIQUE, A NOVEL APPROACH FOR DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

The limited solubility of drugs is a challenging issue for industry, during the development of the solid dosage form .Liquisolid technique is a novel and promising approach to overcome this problem. This technique is an efficient method for formulating water insoluble and poorly water soluble drugs. The technique is based upon the dissolving the insoluble drug in the nonvolatile solvent and admixture of drug loaded solutions with appropriate carrier and coating materials to convert into acceptably flowing and compressible powder. The use of non-volatile solvent causes improved wettability and ensures molecular dispersion of drug in the formulation and leads to enhance solubility. By using hydrophobic carriers one can modify release (sustained release) of drugs by this technique. Liquisolid system is characterized by flow behavior, saturation solubility, drug content, differential scanning calorimetry, Fourier transform infra red spectroscopy, powder X-ray diffraction, scanning electron microscopy, in-vitro release and in-vivo evaluation. By using this technique, solubility and dissolution rate can be improved, as well as improved bioavailability.

INTRODUCTION

Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. The drugs which are poorly water soluble will be inherently released at a slow rate owing to their limited solubility within the GI contents. The dissolution rate is the rate determining step in the drug absorption. The challenge for these drugs is to enhance the rate of dissolution or solubility. This technique improves the solubility, dissolution so that improves absorption and bioavailability. Formulation methods targeted at dissolution enhancement of poorly soluble substances[1].

The Biopharmaceutical Classification System (BCS) is an experimental model that measures solubility and permeability. The Biopharmaceutical Classification System (BCS) groups poorly soluble compounds as Class II, compounds which feature poor solubility, high permeability and Class IV, compounds which feature poor solubility and poor permeability respectively[1].

The most promising and new technique for promoting dissolution is the formation of liquisolid tablets among the various novel techniques. Liquisolid compacts promotes dissolution rate of water insoluble drugs to a greater extent and also enhances the drug flow property[35].

In liquisolid technique the drugs are insoluble or poorly soluble drugs are dissolved or dispersed in non-volatile solvent then converted into free flow powder by using carrier material. The liquisolid compacts are acceptably compressible powdered forms of liquid medications. The major challenges of present pharmaceutical research are to enhance dissolution, absorption and bioavailability of water insoluble drugs[7].

Liquisolid compacts are acceptably flowing and compressible powdered forms of liquid medications. The term liquid medication implies oily, liquid drugs and solutions or suspensions of water-insoluble solid drugs carried in suitable nonvolatile solvent systems termed the liquid vehicles[29].

Therapeutic effectiveness of a drug depends upon the bioavailability therefore it ultimately depends upon the solubility and dissolution rate of drug molecules. These solubility and dissolution rate are important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response[7].

In liquisolid compact the use of non-volatile solvent such as water-miscible organic solvent systems with high boiling point like propylene glycol, liquid polyethylene glycols, or glycerinecauses increased wettability and ensures molecular dispersionof drug in the

formulation and by using hydrophobicpolymers and excipients Coating Material scarriers such as microcrystalline cellulose ,Eudragit RL andEudragit RS, andCoating Material such as Aerosil 200 controlled release of drugs from the liquisolidtablets as the dosage forms can be formulated[35].

This paperfocuses on the novel technique and shows potentialtechnology ofliquisolid compact effects on dissolution andbioavailability.

ADVANTAGES:

1) Huge number of Bio-Pharmaceutical classification class II drugs with high permeability, slightly or very slightly water soluble and practically insoluble liquids and solid drugs can be formulated into liquisolid systems.

2) Improvement of bioavailability of an orally administered water insoluble drugs is achieved.

3) This principle governs or administers the mechanism of drug delivery from liquisolid systems of powdered drug solutions and it is mainly responsible for the improved dissolution profiles exhibited by this preparations.

4) In this technique, production cost is low compared to soft gelatin capsules.

5) Drug is formulated in a tablet form or encapsulated dosage form and is held in solubilized liquid state, which confers developed or improved drug wetting properties thereby improving drug dissolution profiles.

6) Greater drug surface area is exposed to the dissolution medium.

7) This liquisolid system is specifically for powdered liquid medications.

8) These liquisolid systems formulate into immediate release or sustained release dosage forms.

9) Optimized sustained release, liquisolid tablets or capsules of water insoluble drugs demonstrate constant dissolution rates (zero order release).

10) It is used in controlled drug delivery systems.

11) Drug can be molecularly dispersed in the formulation.

12) Drug release can be modified using suitable formulation ingredients.

13) Capability of industrial production is also possible.

14) Enhanced bioavailability can be obtained as compared to conventional tablets[9].

DISADVANTAGES

1) Formulation of high dose lipophilic drugs the liquisolid tablet is one of the limitations of this technique.

2) In order to achieve acceptable flowability and compactability for liquisolid powder formulation, high levels of carrier material and coating materials should be added. This will increase the weight of tablets to above one gram which makes them difficult to swallow. Consequently, it is impossible with conventional tablet methods to convert high dose to liquisolid tablets with a tablet weight of less than 50mg. Dissolution profile enhancement occurs in the presence of low levels of hydrophilic carrier, where coating material is not significant[9].

List of Drugs that can be incorporated into liquisolid systems

- Antihistaminic: chlorpheniramine
- Antiarrthymic: digoxin, digitoxin

- Antihypertensive: nifedipine
- Antilipidemics: clofibrate, gemfibrozil
- Antiepileptic: Carbamazepine, valproic acid.
- Chemotherapeutic agent: etoposide.
- Diuretics: Hydrochlorothiazide, methylchlorthiazide, polythiazide, spironolactone.
- Glucocorticoids: prednisolone, hydrocortisone, prednisone.
- NSAIDS: piroxicam, indomethacin, ibuprofen.
- Water-insoluble vitamins: vitamin A, D, E, and K[12].

REQUIREMENTS FOR LIQUISOLID SYSTEMS :

Drug candidates

Examples of drug candidates include digoxin, digitoxin, prednisolone, hydrocortisone, spironolactone, hydrochlorothiazide, polythiazide, and other liquid medications such as chlorpheniramine, water insoluble vitamins, fish oil, etc[3].

Non-volatile solvents

Various non-volatile solvents used for the formulation of liquisolid systems include Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and propylene glycol[3].

Carrier materials

It Refers to a preferably porous material possessing sufficient absorption properties, such as microcrystalline and amorphous cellulose, which contributes in liquid absorption. such as Avicel PH 102 and 200, Lactose, Eudragit RL and RS (to sustain drug delivery), etc[3].

Coating materials

It Refers to a material possessing fine and highly adsorptive particles, such as various types of silica, which contributes in covering the wet carrier particles and displaying a dry looking powder by adsorbing any excess liquid. With the liquisolid technology, a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients named the carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable nonvolatile liquid vehicles, is incorporated into the porous carrier material[3].

Disintegrants

Most commonly used disintegrant is sodium starch glycolate[3].

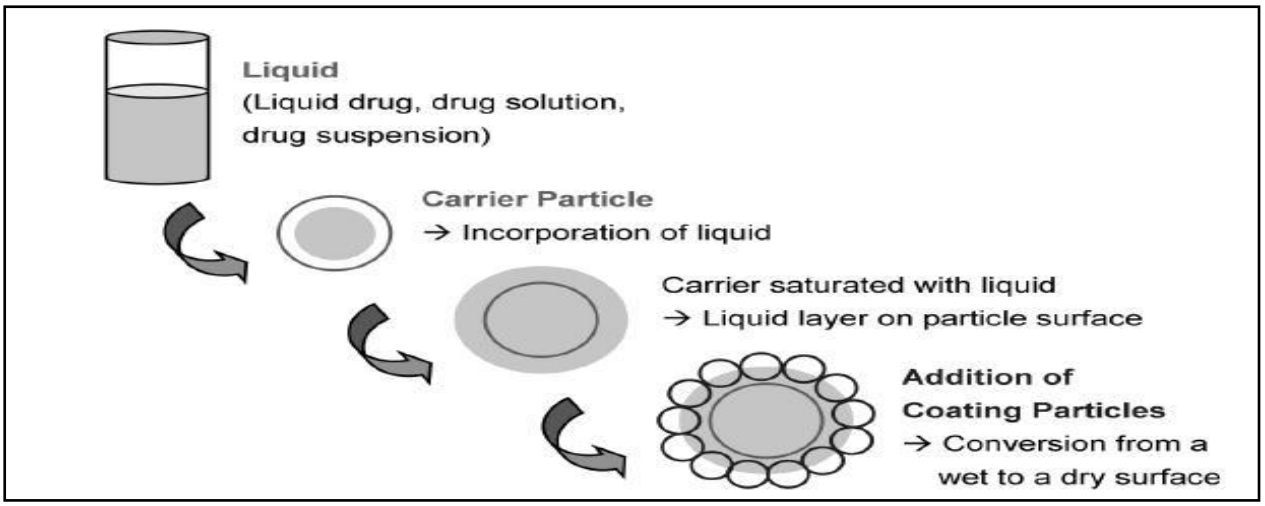

Fig 1. Schematic representation of liquisolid system[35].

CLASSIFICATION OF LIQUISOLID SYSTEMS :

Based on the type of liquid medication contained therein, liquisolid systems may be classified into three sub-groups.

- 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 and powdered liquid drugs are produced from the formulation of liquid drugs into liquisolid systems. Simultaneously, 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, combined with the inclusion of appropriate adjuvants required for tabletting or encapsulation, such as lubricants, and for rapid or sustained release action, such as disintegrants or binders, respectively.

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 that of liquisolid compacts[26,28].

GENERAL METHOD OF PREPARATION:

PREFORMULATION:

The Preformulation studies include,

1. Determination of drug in different non-volatile solvents
2. Determination of angle of slide
3. Determination of flowable liquid retention potential (Ø value)
4. Calculation of liquid load factor (Lf)
5. Liquid solid compressability test (LSC).

Determination of drug in different non-volatile solvents: These are carried by preparing saturated solutions of drug in non-volatile solvents, and analyzing them spectophotometrically. Saturated solutions are prepared by adding excess of drug to vehicles and shaking them on shaker for specific time period under steady vibration. After this, the solutions are filtered and analyzed spectrophotometrically[12].

Determination of angle of slide: The required amount of carrier is weighed and placed at one of a metal plate with a polished surface and it is gradually raised till the plate becomes angular to the horizontal at which powder is about to slide. It was used to measure the flow properties of powders. The angle of 33° is optimum for flow of powders[13].

Determination of liquid flowable liquid retention potential (Φ): –It is defined as the maximum weight of liquid that can be retained per unit powder material in order to produce and acceptably flowing liquid/powder admixture. This Φ –value of powders may be determined using a new procedure, the liquisolid flowability (LSF) test. The Ø value was used to calculate excipients quantities. Equation for this is as follows:

Lf= Ø + Ø (1 / *R*)

Where **Ø** and Ø are the constant Ø values of carrier and coating materials, respectively. By calculating Lf and W, we can calculate the amount of Q and q required for liquisolid systems[12,14].

Calculation of liquid load factor (Lf)) It is defined as the ratio of weight of liquid medication (w) to weight of carrier material (Q). Different concentrations of nonvolatile solvents are taken and the drug is dissolved and the carrier coating material is added and blended.

Lf=W/Q

W=ratio of weight of liquid medication

Q= weight of carrier material

The liquid load factor that ensures acceptable flowability (Lf), and canbe measured by: Lf= (1/R)

Liquisolid compressability 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 Lf[12,13,14].

PREPARATION OF LIQUISOLID TABLETS:

As shown in figure 2, a liquid lipophilic drug is formulated, it should be initially dissolved or suspended in a suitable non-volatile solvent system to produce a drug solution or drug suspension of desired concentration. Next, a certain amount of the prepared drug solution or suspension, or the liquid drug itself, is incorporated into a specific quantity of carrier material which should be preferably of a porous nature and possessing sufficient absorption properties, such as powder and granular grades of microcrystalline and amorphous cellulose are most preferred as carriers. The resulting wet mixture is then converted into a dry-looking, non adherent ,free-flowing and readily compressible powder by the simple addition and mixing of a calculated amount of coating material. Excipients possessing fine and highly adsorptive particles, such as various types of amorphous silicon dioxide (silica), are most suitable for this step. Before compression or encapsulation, various adjuvants such as lubricants and disintegrants (immediate) or binders (sustained-release) may be mixed with the finished[30,32,35].

THE STEPS INVOLVED IN THE PREPARATION OF LIQUISOLID COMPACTS:

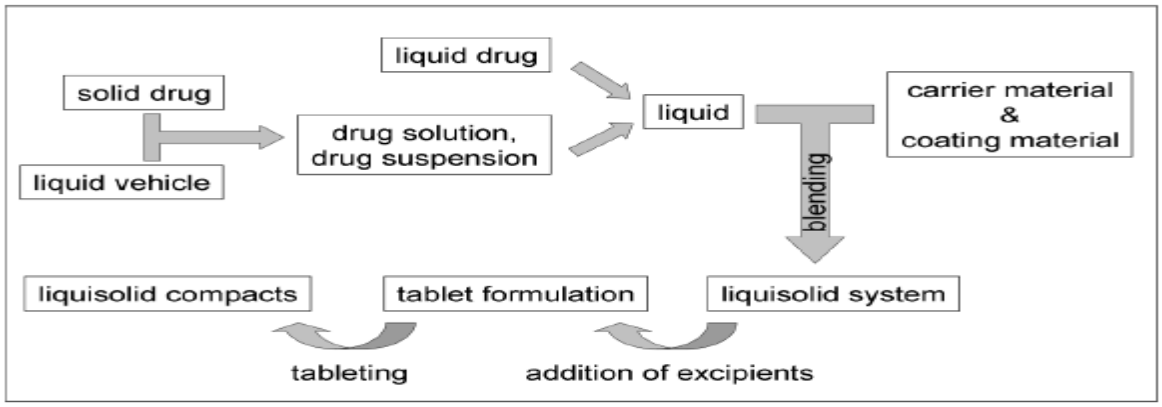

Fig 2. Schematic representation of steps involved in liquisolid system[35].

MECHANISMS OF ENHANCED DRUG RELEASE FROM LIQUISOLID SYSTEM

- Increased Drug Surface Area.
- Increased Aqueous Solubility.
- Increased Wettability.

Increased drug surface area

If the drug within the liquisolid system is completely dissolved in the liquid vehicle it is located in the powder substrate still in a solubilized, molecularly dispersed state. Therefore, the surface area of drug available for release is much greater than that of drug particles within directly compressed tablets[15].

Increased aqueous solubility of the drug

In addition to the first mechanism of drug release enhancement it is expected that the solubility of the drug, might be increased with liquisolid systems. In fact, the relatively small amount of liquid vehicle in a liquisolid compact is not sufficient to increase the overall solubility of the drug in the aqueous dissolution medium[18].

Improved wetting properties

Due to the fact that the liquid vehicle can either act as surface active agent or has a low surface tension, wetting of the liquisolid primary particles is improved Wettability of these systems has been demonstrated by measurement of contact angles and water rising times. Nonvolatile solvent present in the liquisolid system facilitates wetting of drug particles[15,18].

EVALUATION OF LIQUISOLID SYSTEMS:

Flow behavior:

The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to reduce high dose variations. Angle of repose, Carr's index and Hausner's ratio were used in order to ensure the flow properties of the liquisolid systems[22,23,25,38].

Pre compression studies of the prepared liquisolid Powder systems:

In order to ensure the suitability of the selected excipients, Fourier Transform Infra Red Spectroscopy, Differential scanning Calorimetry, X-ray Diffraction and Scanning Electron Microscope studies are to be performed. In addition, flowability studies are also to be carried out to select the optimal formulae for compression, prior to the compression of the powders the dosage forms such as into tablets and capsules[22,38].

Fourier Transform Infra Red Spectroscopy (FT-IR):

FT-IR spectra of prepared melt granules are recorded on FTIR-8400 spectrophotometer. Potassium bromide (KBr) pellet method is employed and background spectrum is collected under identical situation. Each spectrum is derived from single average scans collected in the region 400 - 4000cm-1 at spectral resolution of 2cm-2 and ratio against background interfereogram. Spectra are analyzed by software[22,37,38].

Differential scanning calorimetry (DSC):

Differential scanning calorimetry (DSC) is performed in order to assess the thermotropic properties and the thermal behaviors of the drug, excipients used in the formulation of the liquisolid system. Complete disappearance of characteristic peaks of drug indicates the formation of drug solution in the liquisolid powdered system, i.e., the drug is molecularly dispersed within the liquisolid matrix[23,25,38].

X-ray diffraction (XRD):

For the characterization of crystalline state, X-ray diffraction (XRD) patterns are determined for physical mixture of drug and excipients used in formulation and for the prepared liquisolid compacts. Absence of constructive specific peaks of the drug in the liquisolid compacts in X-ray diffractogram specify that drug has almost entirely converted from crystalline to amorphous or solubilized form. Such lack of crystallinity in the liquisolid system was 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 liquisolid compacts it may contribute to the consequent improvement in the apparent solubility and enhancement of dissolution rate of the drug[25,38].

Scanning electron microscopy (SEM):

Scanning electron microscopy (SEM) is utilized to assess the morphological characteristics of the raw materials and the drug-carrier systems[25,38].

Contact angle measurement:

For assessment of wettability, contact angle of liquisolid tablets is measured according to the imaging method. The commonly used method is to measurecontact angle directly for a drop of liquid resting on a plane surface of the solid, 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[25,38].

***In vitro* dissolution studies:**

Works of many researchers revealed that technique of liquisolid compacts could be a promising alternative for formulation of water-insoluble drugs. This technique of liquisolid compacts has been successfully employed to improve the *in-vitro* release of poorly water soluble drugs as hydrocortisone, Prednisolone Carbamazepine Piroxicam. Also several water insoluble drugs nifedipine, gemfibrozil, and ibuprofen, have shown higher bioavailability in rats as compared to their commercial counterparts[22,23,25].

***In vivo evaluation* of liquisolid systems:**

This liquisolid technology is a promising tool for the enhancement of drug release of poorly soluble drugs. The absorption characteristics of Hydroclorothiazideliquisolid compacts in comparison with commercial tablets were studied in beagle dogs. Significant differences in the area under the plasma concentration-time curve, the peak plasma concentration and the absolute bioavailability of the liquisolid and the commercial tablets were observed. However, for the mean residence time, the mean absorption time, and therate of absorption no significant differences were found. The absolute bioavailability of the drugfrom liquisolid compacts was 15% higher than that from the commercial formulation[22,23,25].

LIST OF SEVERAL INVESTIGATED LIQUISOLID SYSTEMS FOR ENHANCED DRUG RELEASE:

1	Repaglinide	16	Glyburide
2	Furosemide	17	Ezetimibe
3	Nifedipine	18	Aceclofenac
4	Naproxen	19	Piroxicam
5	Felodipine	20	Hydrocortisone
6	Clofibrate	21	Glibenclamide
7	Ibuprofen	22	Polythiazide
8	Lamotrigine	23	Carbamazepine
9	BromhexineHCl	24	Indomethacin
10	Loratadine	25	Clofibrate
11	Methyclothiazide	26	Loratadine
12	Flutamide	27	Griseofulvin
13	Atorvastatin	28	Rofecoxib
14	Prednisolone	29	Propranolol HCL
15	Itraconazole	30	Tramadol HCL

APPLICATIONS:

1. Liquisolid compact technique is a powerful tool to improve bioavailability of water insoluble drugs. Several water insoluble drugs on dissolving in different non-volatile solvents, have been formulated into liquisolid compacts.
2. Rapid release rates are obtained in liquisolid formulations.
3. Sustained Release of drugs which are water soluble drugs such as propranolol hydrochloride has been obtained by the use of this technique.
4. Solubility and dissolution improvement.
5. Flowability and compressibility
6. Designing of Controlled Release Tablets
7. Application in probiotics.
8. Bioavailability Enhancement[7,24,35].

FUTURE POTENTIAL

Poor bioavailability is a major limitation in successful drug delivery by oral route. Lot of research work is focused on oral bioavailability enhancement of the poorly absorbed drugs. It is necessary to understand the reason behind the poor bioavailability before designing a delivery system. The positive results obtained with the use of various delivery systems or different approaches of bioavailability enhancement seem to be promising. However, the commercial development of the product demands much more research for overcoming the challenges such as scale up, cost effectiveness and instability of some of the formulations.

CONCLUSION

New chemical entities often possess a high molecular weight and a high lipophilicity. Especially poorly soluble and highly permeable active pharmaceutical ingredients represent a technological challenge, as their poor bioavailability is solely caused by poor water solubility, which may result in low drug absorption. To improve water solubility and drug release, the liquisolid technology is one of the most promising approaches. As highest drug release rates are observed with liquisolid compact. containing a drug solution as liquid portion, liquisolid compacts may be optimized by selection of the liquid vehicle and the carrier and coating materials. The liquisolid approach is a promising technology because of the simple manufacturing process, low production costs and the possibility of industrial manufacture due to the good flow and compaction properties of liquisolid formulations.

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