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LIQUISOLID TECHNIQUE FOR DISSOLUTION AND BIOAVAILABILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUGS

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ABSTRACT

The solubility and bioavailability were major challenge for the pharmaceutical industry with development of new formulations. About 40-50% available marketed drugs are water insoluble. Various techniques are used to increase the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs include micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, hydrotropy etc. The liquid-solid technique is a novel and promising method for altering the dissolution rate of drugs that are insoluble in water by blending with selected powder excipient, liquid medications such as solutions or suspensions of water insoluble drugs in suitable non-volatile liquid vehicles can be converted into acceptably flowing and compressible powders according to the new liquisolid compacts formulation method. Liqui-solid technology or powdered solution technology change the liquid drug into non-sticky, dry free-flowing, rapid release powder. This liquisolid technique enhances the solubility and dissolution of water insoluble drugs by increased wetting properties and surface area of drug available for dissolution. Liquisolid system is characterized by flow behavior, wettability, powder bed hydrophilicity, solubility, drug content, DSC, FTIR, powder x-ray diffraction, SEM, in-vitro drug release.

KEYWORDS: Liquisolid technology, Free flowing, Wettability, bioavailability, dissolution, Lipophilic.

INTRODUCTION

The oral route is the most preferred route of drug administration due to the ease, high patient acceptance, and low cost production. The drug must be presented in solution form for absorption through gastrointestinal tract when given orally.[1] One crucial factor in achieving the optimal medication concentration in systemic circulation is solubility. The slow release rate of poorly water soluble drugs is attributed to its limited solubility within the GI contents. The dissolution rate is often the rate determining step in the drug absorption.[2] The newly developed drugs which are given for oral administration half of them are poorly soluble in water which affects the formulation development process. Many hydrophobic drugs have less dissolution in the gastrointestinal tract hence show incomplete or erratic absorption of the drug. Drugs falling under the BCS class II have low solubility and dissolution rate compared to other class of drugs hence have poor bioavailability. This low solubility and dissolution rate is enhanced using a few common methods like micro ionization, lyophilisation, solid dispersion, co-solvency and complexing agents. Out of these the liquisolid compact technique found to be the best to enhance the bioavailability of BCS class II drugs.[3] The new developed technique by Spireas as liquisolid system improves the dissolution properties of water insoluble or poorly soluble drugs. The term "Liqui-solid" systems (LS) refers to a powdered form of liquid drug created by converting liquid lipophilic drug or drug suspension or solution of waterinsoluble solid drug in suitable non-volatile solvent systems into dry looking, non-adherent, freeflowing, and readily compressible powdered mixtures through the use of selected carrier and coating materials. Liquisolid technology, a liquid is also reworked into a free flowing, without delay compressible and apparently dry powder by easy physical mixing with selected excipient named the carrier and coating material.[4,1]

Ideal Characteristics of Components in Liquisolid Compacts

- **Drug:** BCS class II and IV drugs that are poorly water soluble and have a slow dissolution rate could be designed as liquisolid compacts to improve dissolution rate. Chlorpheniramine, digoxin, nifedipine, clofibrate, gemfibrozil, etoposide, carbamazepine, and other medications are examples.[5]
- **Liquid medication:** Liquid medication includes liquid lipophilic drugs and drug suspensions or

solutions of solid water insoluble drugs in suitable non-volatile solvent systems.[6]

- **Non volatile Solvent:** The solvent should be inert, have a high boiling point, preferably be water-miscible, and not be highly viscous organic solvent systems and be compatible with the ability to solublize the drug. The non volatile solvent acts as a binding agent in the liquisolid formulation various non-volatile solvents includes Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and PG.[7]
- **Carrier Materials:** Carrier material should be porous material possessing adequate absorption properties which contributes in liquid absorption. The carrier and coating materials will retain only bound amounts of liquid and at the constant time maintain acceptable flow and compression properties therefore, increasing moisture content of carrier leads to decreased powder flow ability. These contain grades of microcrystalline cellulose such as avicel PH 102 and avicel PH 200.[8]
- **Coating Materials:** Coating material should be contributes in covering the wet carrier particles and displaying a dry looking powder and maintain the powder flowability by adsorbing any excess liquid. Coating material includes silica (Cab-O-Sil) M520, 35, Aerosil 200.
- **Disintegrants**: sodium starch glycolate is mostly used disintegrants in liquisolid system.[9]

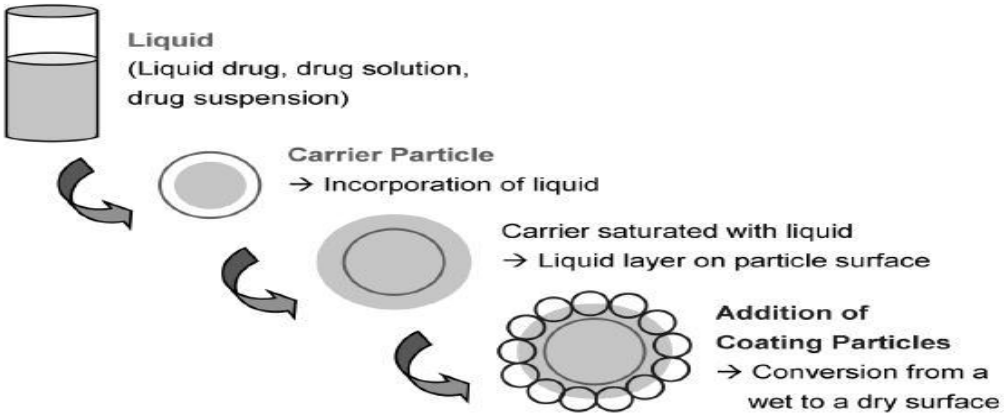

Figure 1: Schematic representation of liquisolid system.

Mechanisms of Improvement of Drug Release

Several mechanisms are being developed to improve drug release. Three important mechanisms include

1. An increase in effective drug surface area.
2. An increase in aqueous solubility.
3. An improved wettability of drugs.[10]

1. Enhancement of surface area: The drug is completely dissolved in the liquid vehicle in the liquisolid system, and it is still solubilized and molecularly dispersed in the powder substrate. As a result, the available surface area for drug release is much greater than that of drug particles within directly compressed tablets.[11]

2. Increased aqueous solubility: Liquisolid systems may improve drug solubility. In fact, the relatively small amount of liquid vehicle in a liquisolid compact is insufficient to increase the drug's overall solubility in the aqueous dissolution medium. However, at the solid/liquid interface between a single liquisolid primary particle and the release medium, the amount of liquid vehicle diffusing out of a single liquisolid particle along with the drug molecules may be sufficient to increase the drug's aqueous solubility if the liquid vehicle acts as a co solvent.[12]

3. Improved wetting properties: Wetting of the liquisolid primary particles is improved because the liquid vehicle can either act as a surface active agent or has a low surface tension. Improved wettability results in improved drug dissolution. Wettability of these systems has been demonstrated by measurement of contact angles and water rising times.[13]

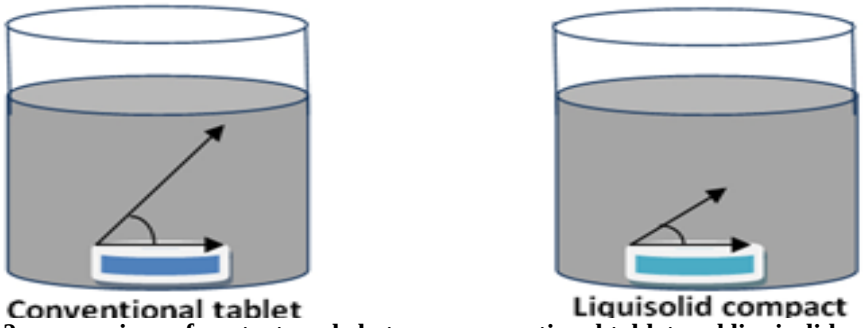

Figure 2: comparison of contact angle between conventional tablet and liquisolid compact.

Pre-Formulation Studies

Solubility Study of Drug in Non-Volatile Solvent

Pure drug liquefies in distinct non-volatile solvents and extreme, pure drug was joined shift to a rotatory shaker at 25 °C under constant vibration for 48 h, 0.45 m Millipore filter used for refining the saturated solution then analyzed.

Determination of angle of slide: In polished metal plates, liquid/powder admixtures were settled and plate tilted. The inclination set up in middle of the plate and horizontal surface (h).

Determination of flowable Liquid Retention Potential (Φ value)

Φ–value= weight of liquid/weight of solid ….

Liquid Load Factor (Lf)

Lf = W/Q ……

W = weight of liquid medication,

Q = weight of carrier material

R = Q/q R (ratio of the weight of carrier and coating material present in the formulation).[14]

Preparation of Liquisolid Tablets

Calculated amounts of drug and non-volatile solvent are accurately weighed in a 20 ml glass beaker and then heated to dissolve the drug in that solvent if necessary. The resulting hot medication is mixed with calculated amounts of carrier and coating materials. Spireas et al. describe the mixing process in three steps. The system is blended at an approximate mixing rate of one rotation per second for approximately one minute during the first stage to evenly distribute liquid medication in the powder. In the second stage, the liquid/powder admixture is evenly spread as a uniform layer on the surfaces of a mortar and allows standing for 5 minutes to allow the drug solution to absorb into the mortar's interior.[15]

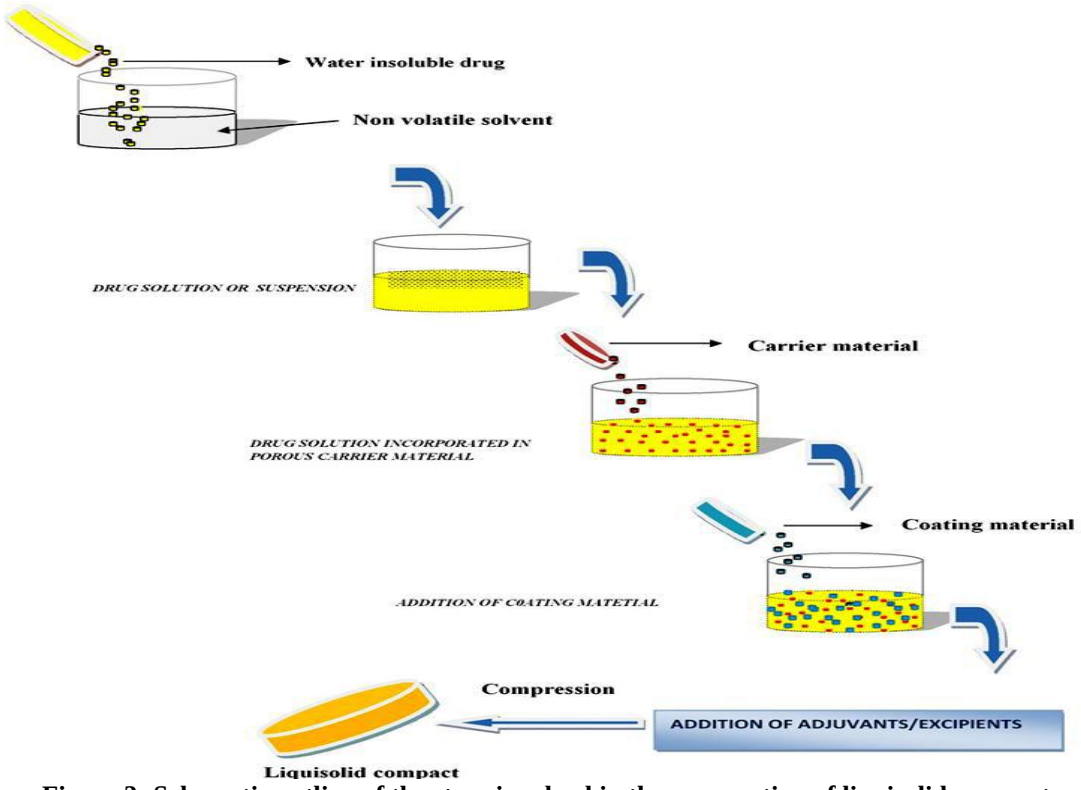

Figure 3: Schematic outline of the steps involved in the preparation of liquisolid compacts.

In Designing Controlled Release Tablets and Sustained Release Tablet

There are several techniques for preparing sustained release formulations, with drug dissolution control being one of the best and most successful due to its simplicity and low cost. Several methods have been developed to achieve this goal, including drug salt preparation, coating with special materials, and drug incorporation into hydrophobic carriers. The Liqui-solid technique is a novel and promising method for altering drug dissolution rates. It is claimed that in liquisolid systems, sustained release systems can be obtained by using hydrophobic carriers such as Eudragit RL and RS instead of hydrophilic carriers. Therefore, it is suggested that the method have the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems.[16]

Pre-Compression Studies Of The Liquisolid System

Solubility Studies

Solvency studies are completed by preparing immersed arrangements of medication in non-volatile dissolvable and spectrophotometrically examining them. Immersed arrangements are arranged by adding over abundance of medication to non unpredictable dissolvable and shaking them on shaker for particular time period under

consistent vibration. After this, the arrangements are sifted and dissected spectrophotometrically.[17]

Differential Scanning Calorimetry (DSC)
Any potential interaction between excipient used in the formulation must be determined. This will also indicate that the stability studies were successful. If the drug's characteristic peak is missing from the DSC thermogram, it means the drug is in the form of a solution in a liquisolid formulation and is thus molecularly dispersed within the system.[18]

Flow Properties of the Liquisolid System
The flow properties of the liquisolid systems were estimated by calculating the angle of repose, Carr's index, and Hausner's ratio. The Bulk and Tap densities were calculated in order to calculate Hausner's ratio and Carr's Index.[19]

Fourier Transforms Infrared Spectroscopy (FTIR)
To determine drug-excipient compatibility, pure drug and drug with excipient were mixed with dry potassium bromide powder and compressed into transparent discs, which were then scanned with an infrared spectrophotometer over a range of 4000-400 cm-1.[20]

Scanning Electron Microscopy (SEM)
After SEM analysis, the complete disappearance of drug crystals confirms that the drug is completely solubilized in the Liquisolid system, ensuring complete solubility.[21]

Post Compression Evaluations
Weight Variation Test
Twenty tablets from each formulation were chosen at random, and the average weight was calculated. The individual tablets were then weighed and compared to the average weight. Individual weight deviates by no more than a percentage, and none deviates by more than twice that percentage.[22]

Hardness
The hardness of each formulation's tablet was determined in triplicate by measuring the force required to crush the tablet in Kg/cm2 269 using a hardness tester.[23]

Friability Test
By using Roche Friabilator the % friability of the prepared liquisolid tablets was measured previously, weighed tablets (20 tablets) were placed in the Friabilator and it was rotated at 25 rpm for 4 minutes. The tablets were reweighed at the end of the test; loss in tablet weight is a measure of friability and is expressed as a percentage.
% Friability= $[(W1-W2)/W1]\times100$

Where,
W1=Initial weight of 20 tablets,
W2=Weight of the 20 tablets after testing.[24]

Disintegration Time
The time necessary to disintegrate 3 tablets of each tablet formulation was determined using a disintegration tester.[25]

Drug Content
Ten randomly selected tablets from each batch were tested for drug content Samples were filtered and then analyzed spectrophotometrically with respective nanometers. The percentages of individual drug contents were calculated and compared to the theoretical drug contents.[26]

Thickness
A digital micrometer was used to measure the thickness of liquid-solid tablets. Ten tablets from each batch were used, and the results were averaged.[27]

In-Vitro Drug Release Studies
The dissolution rates of all formulations were measured in dissolution test apparatus by tablet dissolution apparatus USP Type II. Dissolution studies were carried out using 900 ml dissolution media, at respective rpm and at temperature of 370 C. Appropriate aliquots were withdrawn at suitable time interval (5, 10, 15, 20, 25, 30 40, 50, 60 min) and filtered through Whatman filter paper. Sink conditions were maintained throughout the study. The samples were then analyzed at respective ʎmax by UV/visible spectrophotometer.[28]

Advantages of Liquisolid Tablets
Liquisolid tables have many advantages. These include

- Liquisolid systems are less expensive formulations than soft gelatin capsules.
- Production of them is similar to that of conventional tablets.[29]
- A variety of water-insoluble solid drugs can be formulated using liquisolid systems. Can be used to create liquid medications such as oily liquid drugs.
- Improved availability of an orally administered water-insoluble drug.
- Can be used in controlled drug delivery.
- Using appropriate formulation ingredients, drug release can be modified.
- The drug can be dispersed molecularly in the formulation.
- Industrial production capability is also possible.
- Enhanced bioavailability can be obtained as compared to conventional tablets.[30]

Disadvantages/Limitations

- High solubility of drug in the non-volatile liquid drugs for the improvement of dissolution rate and bioavailability.
- It requires excipient of high specific surface area and high adsorption properties.
- In case of high dose insoluble drugs (>100 mg) it is not applicable.

- During compression sometimes liquid drug may be squeezed out of the tablet result in improper hardness.[31]

Applications of Liquisolid Technique in Pharmaceutics

1. The Liqui-solid technique as a tool for improving drug dissolution
2. Liqui-solid technology has been widely used to improve the dissolution rate of low dose insoluble drugs, such as prednisolone, famotidine, valsartan, ketoprofen and raloxifene hydrochloride ect.
3. The liquisolid technique is used to design sustained drug release
4. Sustained release formulations are intended to slowly release the drug at a predetermined rate for a set period of time while maintaining high efficacy, patient compliance, and minimal side effects.
5. Liquisolid technique as a tool to decrease the influence of pH variation on drug release.
6. Liquisolid technique is a promising tool to improve drug photo stability in solid dosage forms.[32]

CONCLUSION

Various methods are used to improve water solubility and drug release, among which the liquisolid technology is one of the most promising approaches. Liquisolid system refers the liquid drugs, drug suspensions or drug solution in non-volatile solvents are converted into to dry, non-adherent, freeflowing and compressible powder mixtures by blending with selected excipient named as carrier and the coating material. The liquisolid tablets dosage forms showed significantly greater extent of absorption due to their improved solubility and dissolution rate. The technique is also used to design sustained release or controlled systems by using hydrophobic carriers instead of hydrophilic carries in liquisolid systems. The liquisolid system 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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