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Review Article

Recent research on liquisolid technology for solubility enhancement- A review

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Carrier & coating material.

Abstract

Liquisolid system is a novel and promising approach to enhance aqueous solubility, dissolution rate as well as bioavailability of water insoluble solid drugs or liquid lipophilic drugs by conversion of liquid drugs, drug suspensions or drug solution in non-volatile solvents, into dry, non-adherent, free flowing and compressible powder mixtures by simple blending with selected carriers and coating materials. This technology is based on a new mathematical model proposed by Spireas *et al*. The three main proposed mechanisms by which bioavailability of drug is increased that are increased surface area of drug, increase aqueous solubility of drug and improved wettability of the drug.

1. Introduction

Liquisolid compacts are one of the most promising and new technique which promotes the dissolution rate of water insoluble drugs. The term liquisolid compact refers to immediate release or sustained release tablets or capsules, combined with the inclusion of appropriate adjuvant required for tableting or encapsulating [1, 2, 6].

The liquisolid systems are generally considered as acceptably flowing and compressible powdered forms of liquid medications (that implies liquid lipophilic (oily) drugs, or water-insoluble solid drugs dissolved in suitable water-miscible nonvolatile solvent systems). Such liquid medication may be switched into a dry looking, non-adherent, free-flowing, and readily compressible powders by a simple admixture with selected powder excipients referred to as the carrier and coating materials. Three major components are involved in the formulation of liquisolid compacts that are liquid medication, carrier and coating material. Other excipients are also used as per the need and objective of the formulation such as disintegrants, release retard polymers, etc.

2. Mechanism of Enhanced Drug Release from Liquisolid Systems: [1, 2]

The three main mechanisms involved that are an increased surface area of drug available for release, an increased aqueous solubility of the drug and an improved wettability o the drug particles. Here, DSC and XRPD Measurements are used to determine any change in crystallinity of the drug or formation of the complex between the drug and excipients.

A. Increased drug surface area:

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

Consequently, with increasing drug content, the solubility limit also increases and thus, increasing the fraction of

undissolved drug in the liquid vehicle and thus, the release rate decrease. The release rate is directly proportional to the fraction of the molecularly dispersed drug (FM) in the liquid formulation. FM is defined by spireas as the ratio between the drug solubility (Sd) in the liquid vehicle and the actual drug concentration (Cd) in this vehicle carried by each system. Therefore:

$$FM = Sd / Cd \qquad \text{Eq. (7)}$$

Where, $FM = 1$ if $Sd \geq Cd$.

B. Increased aqueous solubility of the drug:

In addition, of the first mechanism of drug release enhancement it is anticipated that Cs, the solubility of the drug, might be increased with liquisolid system. In fact, the relatively small amount of the liquid vehicle in a liquisolid compact is not sufficient to increase the overall solubility of the drug in the aqueous dissolution medium. It is possible that a small amount of liquid vehicle diffuses from the total amount along with drug and if the liquid vehicle acts as a co-solvent, this less amount of vehicle is adequate to increase the aqueous solubility of drug.

C. Improved wetting properties:

If the liquid vehicle acts as a surfactant, it can improve the wettability of the liquisolid system by reducing the surface tension. Wettability of liquisolid system has been demonstrated by measurement of contact of angles 8 and water rising times.

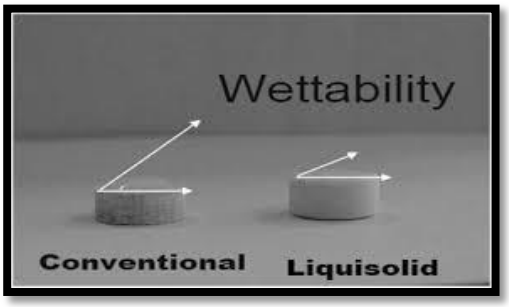

Fig. 1: Comparison of wettability between conventional tablet and liquisolid compacts

3. Concept of Liquisolid Technology:

When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fiber in its interior such as cellulose, both absorption and adsorption take place. The liquid initially absorbed into the interior of the particle is captured by its internal surface. After saturation, adsorption of the liquid onto the internal and external surface of the porous carrier particle occurs. Then, coating material provides the desirable flow property to the liquisolid system due to its high adsorptive properties and large surface area (Fig. 2) [1, 2].

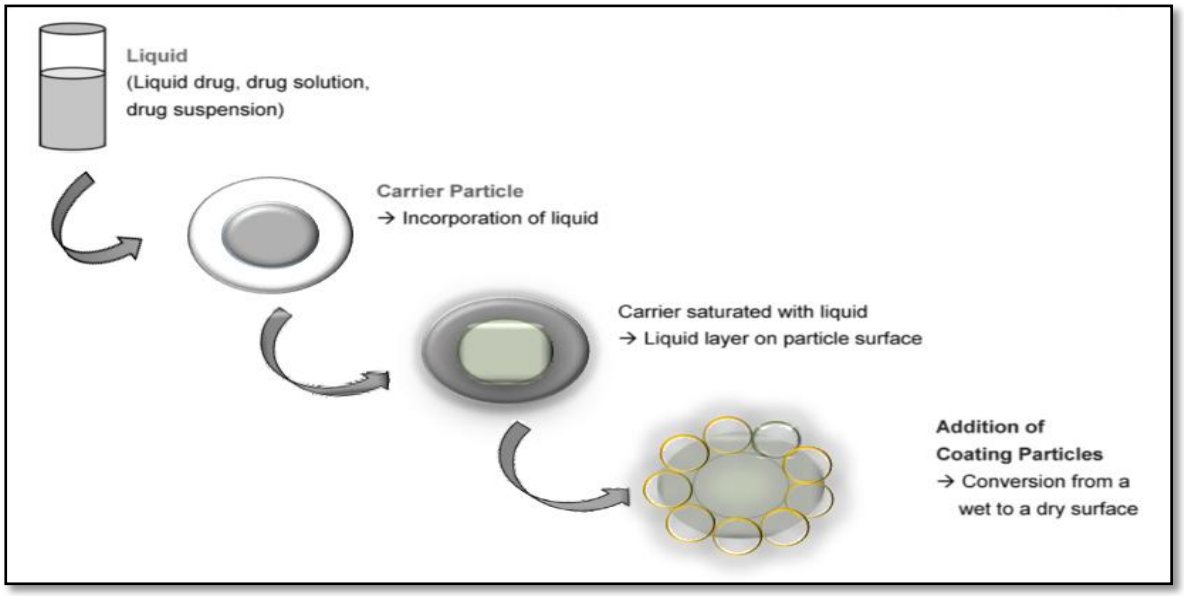

Fig. 2: Schematic representation of liquisolid system

(Concept of Liquisolid System)

3.1 Advantages of liquisolid technology [3-6]:

- In liquisolid systems, a number of water-insoluble solid drugs can be formulated. Can be applied to formulate liquid medications such as oily liquid drugs.
- Better availability of an orally administered water insoluble drug.
- Lower production cost than that of soft gelatin capsules.
- Production of liquisolid systems is similar to that of conventional tablets.
- Exhibits enhanced in-vitro and in-vivo drug release as compared to commercial counterparts, including soft gelatin capsule preparations.
- Can be used in controlled drug delivery.
- Drug release can be modified using suitable formulation ingredients.
- The drug can be molecularly dispersed in the formulation.
- Capability of industrial production is also possible.
- Enhanced bioavailability can be obtained as compared to conventional tablets.

3.2. Limitations [3]:

- Low drug loading capacities
- Requirement of high solubility of drug in non-volatile liquid vehicles

3.3 Rational of liquisolid technology:

Liquisolid drug delivery system is a novel and most promising system to increase aqueous solubility of water insoluble solid drug or liquid lipophilic drug. It can enhance dissolution rate as well as bioavailability of API. Liquisolid system gives acceptable free flow and compression properties. The three main proposed mechanisms responsible for enhancement of solubility, include increased surface area of drug available for release, increased aqueous solubility of drug and improved wettability of the drug particles.

3.4 Research studies on liquisolid technology

Spireas developed and patented a method of producing a free-flowing and compressible liquid/powder admixture of a liquid medication. The method involves conversion of the liquid medication into a liquisolid system using a carrier material and a coating material to be included in the liquisolid system. The patent describes the process of admixture of the liquid medication with optimum quantity of carrier material to make a wet mixture and blending it with the coating material to produce a non-adherent, free-flowing and compressible liquid/powder admixture. The amounts of liquid medication, carrier material and coating material were calculated by a mathematical model to optimize flow and compressibility according to values predetermined by liquisolid flowability and liquisolid compressibility tests. [1]

Spireas et al. in various studies, prepared directly compressible liquisolid formulations of prednisolone and hydrocortisone by applying the principles of patented procedure. The liquisolid formulation showed increased dissolution rates of these drugs showing the usefulness of the system. [6]

Zafar el al (2015), had compared Liquid-solid technique and solid dispersion formation which are two novel approaches for enhancement of dissolution rate of BCS class II drugs. Liquisolid compact converts a liquid drug or drug solution into a free flowing powder with enhanced dissolution rate. In case of solid dispersion drug is molecularly dispersed in a hydrophilic polymer in solid state. In the present study, Liquisolid and solid dispersion techniques were applied to enhance the dissolution of the Hydrochlorothiazide. Three formulations of Hydrochlorothiazide were prepared by Liquisolid technique using micro crystalline cellulose as carrier material and colloidal silicon dioxide as coating material. Water, poly ethylene glycol- 400 and Tween-60 were used as solvent system. Solid dispersions of Hydrochlorothiazide were prepared by solvent fusion method using PEG-4000 as carrier polymer. Tablets were subjected to evaluation of various physical and chemical characteristics. Dissolution profiles of tablets prepared by the novel techniques were compared with marketed conventional tablets. Model independent techniques including similarity factor, dissimilarity factor and dissolution efficiency were applied for comparison of dissolution profiles. The results obtained indicated that liquid solid compact formulations were more effective in enhancing the dissolution rate compared with solid dispersion technique. The Liquisolid compacts improved the dissolution rate up to 95% while the solid dispersion increased it to 88%. [7]

Ayesha et al (2015), had prepared Liquisolid compacts using polyethylene glycol 400, propylene glycol and Tween-80 as non-volatile solvents. Neusilin as carrier material and Aerosil-200 as coating material for enhancement of dissolution rate of Olmesartan medoxomil. From the study, it was concluded that the dissolution studies for Liquisolid compacts and conventional formulations were performed and it was found that Liquisolid compacts with Neusilin and

Tween-80 showed significant higher drug release than conventional. [8]

Prakash et al (2014), had investigated Liquisolid powder compacts (LSPCs) proved to be the potential solubility improvement strategy for efficient oral delivery of BCS class II and IV drugs.

The LSPCs were formulated using propylene glycol as non-volatile solvent. The effect of different formulation variables on LSPCs performance was evaluated using 32 factorial design. The selected independent variables were % of clonazepam in propylene glycol (X1) and % of sodium starch Glycolate (X2) and dependent variables were disintegration time (YDT) and % cumulative drug release at 15th minute (YQ15). LSPCs of CLZ formulated with propylene glycol at optimum drug concentration produced high dissolution profile with acceptable tablet properties. Fourier transform infra-red spectroscopy (FTIR) studies revealed that there was no interaction between drug and polymers, differential scanning calorimetry (DSC) and X Ray Diffraction (XRD) indicated conversion of crystalline to amorphous form of the CLZ. The permeation studies carried out in isolated rat intestine revealed that potential of LSPCs for enhanced permeation of CLZ across rat intestinal barrier. The increase in permeation of clonazepam from LSPCs formulation across rat intestine suggests the potential of LSPC formulation for improved oral delivery of CLZ. In conclusion, the present study showed that LSPC technique could be a promising strategy in improving dissolution of poorly water soluble CLZ and wettability was improved by making a suspension in propylene glycol, the water soluble, nonvolatile solvent. LSPCs could be prepared using MCC PH 102 as a carrier, and AEROSIL® 200 as a coating material. The FTIR studies revealed that excipients were compatible with the drug. DSC and XRD studies showed that there is a decrease in crystallinity of the CLZ in Liquisolid compact formulation. A fall in crystallinity means improved dissolution release profile. The optimized formulation showed higher dissolution rate when compared with that of pure drug. [9]

Elkordy et al (2014), had investigate dissolution behavior of norfloxacin as a model hydrophobic drug through application of Liquisolid technology. Norfloxacin was prepared as Liquisolid formulations using either flowability or compressibility Liquisolid tests. The dissolution profiles were evaluated and compared to counterpart conventional norfloxacin tablets. Two non-volatile liquid vehicles were used in the preparation of norfloxacin Liquisolid formulations; Poly Ethylene Glycol (PEG200) and Synperonic PE/L-61. The Liquisolid formulations of norfloxacin were tested according to the specification of British Pharmacopoeia (BP) quality control tests. Moreover, the pre-preparation evaluation tests, such as powder flowability Carr's index, differential scanning calorimetry (DSC) and Fourier transform infrared (FT-IR), were applied for further investigation of the physicochemical properties of the Liquisolid formulations. The results indicated that the percentage of norfloxacin release in acetate buffer solution (pH = 4.0) is higher than in distilled water. Also, at the first 20 min, the percentage of the drug release is higher only in the decreased amount of liquid vehicle formulations compared with the conventional tablet. Generally, the conventional tablet dissolution profile is either similar or higher than Liquisolid tablets. Moreover, Synperonic PE/L-61 Liquisolid tablets showed higher dissolution profiles than PEG200 Liquisolid tablets, although the solubility of norfloxacin in PEG200 (2.507 mg/ml) is much higher than in Synperonic PE/L-61 (0.167 mg/ml). In conclusion, increasing the percentage of liquid vehicle in the prepared norfloxacin Liquisolid formulations does not necessarily lead to increase in the percentage of the drug release in distilled water dissolution medium. [10]

Yousef et al (2014), had investigated the effect of solvent type on Diltiazem hydrochloride release profile from Liquisolid compacts. To examine aforementioned idea, the drug solubility was studied in several conventional nonvolatile solvents. Liquisolid formulations of diltiazem HCl in the different solvents were prepared and their release profiles were also obtained. Effect of aging on the hardness and drug release profile was studied as well. X-ray crystallography and differential scanning calorimetry (DSC) were used to investigate the formation of any complex between drug and carrier or any crystallinity changes during the manufacturing process. The results showed that diltiazem HCl had lowest solubility in polysorbate 20. Highest amount was devoted to polysorbate 80 and propylene glycol. Type of nonvolatile solvent and its physicochemical properties as well as solubility of the drug in the applied solvent found to have important role on release profile of the drug from Liquisolid compacts. Hardness and dissolution profile of the drug were not affected by aging. Amorphous form was obtained during the process of Liquisolid formulation. It follows that the optimized new technique can be used to prepare sustained release formulations of water-soluble drugs. [11]

Srinivas et al (2014), had improved the solubility and dissolution rate of poorly soluble drug Piroxicam by using Liquisolid technique. This technique of delivering drugs is suitable mostly for lipophilic drugs and poorly water soluble drugs. However, an apparent limitation of this technique is the formulation of a high dose because a large amount of liquid vehicle is needed, which finally results in a low-dose liquid solid formulation. This approach is suitable for both immediate and sustained release formulations. Solubility is increased by using non-volatile solvents such as PEG 400, Labrosol, Span

20 and Tween 80 in single or combination which are suitable for drug and dissolving the drug in those nonvolatile solvents, which is termed as 'liquid medicament'. The liquid medicament is blended with carriers such as microcrystalline cellulose and Aerosil to convert the liquid medicament into a non-adhering, dry looking powder which has acceptable flow properties and compression behavior. These Liquisolid systems are evaluated by micromeritics studies like flow behavior, bulk density, tapped density, compressibility index, drug content, in vitro release, Fourier transform infra-red spectroscopy and powder X-ray diffraction. He concluded that dissolution rate and bioavailability of poorly water soluble drugs like Piroxicam can increased by applying Liquisolid technology. He also observed, In-vivo drug release study of Liquisolid compacts using animal model to claim success in the development of Liquisolid compacts of Piroxicam. [12]

Iizhar S. and Bhavani (2014), had studied the effect of carrier: coating ratio, concentration of disintegrant and non-volatile solvents on disintegration time and dissolution rate in the formulation of Liquisolid compacts of Nateglinide. An apparent limitation of this technique is the formulation of a high dose because a large amount of liquid vehicle is needed, which finally results in a low-dose liquid solid formulation. NTG was dispersed in PEG-400 as a liquid vehicle. Then a binary mixture of carrier–coating materials (MCC- Aerosol) was added to the liquid medication under continuous mixing. Precompression studies, such as flow properties were also carried out. The formed mixture was compressed to get tablets matrices by using the tableting machine. The prepared Liquisolid tablets were evaluated by hardness, friability, disintegration test and in vitro dissolution studies. The dissolution property of a water-insoluble drug Nateglinide (NTG) was investigated. The dissolution profile of the prepared Liquisolid tablets was also compared to that of a marketed formulation (MR). The results indicate that Liquisolid based tablets (F3) showed greater disintegration and dissolution rate. It might be due to the presence of PEG-400 as it showed the enhancement in the solubility of NTG. FT-IR results showed compatibility of Nateglinide with excipients used. He concluded that as the carrier: coating ration increases with the concentration of disintegrant, disintegration and dissolution rate of Liquisolid compacts of Nateglinide was increased. [13]

Poluri et al (2014), had formulated fast disintegrating tablets by using Liquisolid technology. Sodium starch Glycolate, crospovidone are used as superdisintegrant in this invention to reduce disintegration time by which fast absorption can take place which ultimately increase dissolution of the drug. As a result of comparison with marketed formulation using similarity dis-similarity factor, both formulations shows similar in-vitro dissolution profile of Lamotrigine. [14]

Manish et al (2014), had developed a novel liquid solid technique which enhances the dissolution rate of water insoluble or poorly water soluble drugs of Nilvadipine, which belong to class II of BCS. Liquisolid Formulations shows better Flowability, Compressibility, improves solubility, dissolution and better absorption. Rapid disintegration rates are observed compared to conventional tablets and therefore, they show improved release rates and hence greater bioavailability. The use of non-volatile solvent in the formulation causes increased wettability of water insoluble drugs and ensures molecular dispersion of drug in the formulation. [15]

Jyothi et al (2014), had enhanced the dissolution rate of Glyburide which is insoluble in water. Different formulations were prepared by using different vehicles and carriers and Aerosil is used as the coating material. The empirical method as introduced by Spireas and Bolton was applied to calculate the amounts of coating and carrier materials required to prepare glyburide Liquisolid tablets. In vitro dissolution profiles of the Liquisolid formulations were studied and compared with conventional formulation in 0.1N HCl. It was found that Liquisolid tablets formulated with PEG 400 and Avicel pH102 produced high dissolution profile and they showed significant higher drug release rates than conventional tablets due to increase in wetting properties and surface of drug available for dissolution. Drug-excipient interaction studies showed that there is no interaction between the drug and excipients. In conclusion, development of glyburide Liquisolid tablets is a good approach to enhance the dissolution rate which increases bioavailability. [16]

Ujwala R., Venkateswara R. and Navaneetha (2014), had developed a novel liquid-solid technique to enhance the dissolution rate of candesartan which is poorly water soluble drug which is a BCS class II drug. The selection of non-toxic hydrophilic solvent, carrier, coating excipients and its ratios are independent of the individual chemical entities which is indirectly leads to enhancement of bioavailability. Liquisolid tablets were prepared by using PEG -400, PG as non-volatile liquid vehicles and Avicel PH 102, Aerosil 200 as carrier and coating materials, CCS as super disintegrants respectively. Among all formulations F7 was shown best drug release and result shows increased dissolution profile i.e., 98.1% with polypropylene glycol. The invitro dissolution study confirmed enhanced drug release from liquid solid compacts compared with conventional and marketed tablets. [17]

Amrit et al (2009), carried out comparison of in-vitro dissolution study profile of conventional formulation of and Liquisolid compacts of Fenofibrate in part 2 of his invention. Model independent method (Similarity factor, dissimilarity

factor); Model dependent methods (Zero order, First order, Hixson-Crowell, Matrix, Peppas, Higuchi models) and statistical methods based on ANOVA used for comparison of dissolution rate. As the conclusion, statistical method is more effective than the model independent method for comparison of dissolution profile of Liquisolid technology. [18]

Fahmy et al (2008), had attempted to improve famotidine dissolution through its formulation into Liquisolid systems and investigated in vitro and in vivo performance of the drug from the prepared Liquisolid tablets. The bioavailability study indicated that bioavailability from the prepared optimal Liquisolid formula did not differ significantly from bioavailability from the marketed famotidine tablets. [19]

Louis et al (2008), had proved that the wettability of Carbamazepine was improved by making a suspension in propylene glycol, the water soluble, nonvolatile liquid. CBZ Liquisolid tablets could be prepared using Avicel PH 102 as a carrier, and Aerosoil 200 as a coating material. A liquid load factor Lf = 0.25, and an excipient ratio R = 20, produced a powder of optimal flow properties and readily compressible into tablets without any liquid oozing out phenomenon. [20]

Javadzadeh et al (2007), had in another study prepared different Liquisolid formulations of carbamazepine by dissolving the drug in the hydrophilic liquids and adsorbing the solution onto the surface of silica. In order to reduce the amounts of carrier and coat material in Liquisolid formulations, some additives like PVP, HPMC and PEG 35000 were added to liquid medication to increase loading factor. The effects of various ratios of carrier to coating material, PVP concentration, and the effect of aging and the type of the carrier on the dissolution rate of Liquisolid compacts were studied. [21]

Javadzadeh et al (2005), had studied the dissolution behavior of piroxicam from Liquisolid compacts in simulated gastric fluid and simulated intestinal fluid. Several Liquisolid tablet formulations were prepared containing various ratios of drug and Tween 80. [21]

Nokhodchi et al (2005), had studied the effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from Liquisolid compacts. The authors attempted to correlate the dissolution rate and fraction of drug in the molecularly dispersed form (FM). [21]

Javadzadeh et al (2005), had studied the effect of addition of surfactant on the dissolution behavior of piroxicam from Liquisolid compacts in simulated gastric fluid and simulated intestinal fluid. Liquisolid tablet formulations containing various ratios of drug to Tween 80 were prepared keeping the ratio of microcrystalline cellulose (carrier) to colloidal silica (coating material) constant. The liquisolid compacts demonstrated significantly higher drug release rates than those of conventionally made capsules and directly compressed tablets containing micronized piroxicam. The addition of surfactant facilitated the drug release from liquisolid formulations.

In another study, **Javadzadeh et al (2005),** had investigated the effect of the amount of different co-solvents (non-volatile vehicles) in Liquisolid compacts on the dissolution behavior of indomethacin. Liquisolid tablets showed the enhanced rate of indomethacin dissolution. It was interpreted that the fraction of molecularly dispersed drug (FM) in the liquid medication of Liquisolid systems was directly proportional to their indomethacin dissolution rate. [22]

Lloyd et al (2004), had studied the effect of plasma irradiation on wettability and dissolution profile of Griseofulvin compacts. Dissolution rate of the poorly soluble drug could be increased by using plasma irradiation. Oxygen containing functional group on the surface of compact formed by treating Griseofulvin compact with oxygen plasma which is responsible for increasing wettability. Plasma treated and untreated compacts were analyzed, from which it was concluded that plasma treated compacts shows increased wettability in comparison to plasma untreated compacts. It was also found that dissolution rate was increased due to surface fusion material caused by treatment. [23]

4. Conclusion

The liquisolid system is the new technique for the formulation of water insoluble drugs to enhance their aqueous solubility, absorption as well as dissolution rate, which leading to enhancement of bioavailability of drugs as compared to conventional directly compressed tablets. The liquisolid technology can be used for the purpose of formulating modified the drug release system by selecting the right excipient. It is an effective technology in terms of production capability and low cost of formulation. Thus, this technology has the potential for large scale manufacture. The excipients required in the liquisolid system are conventional and commonly available in the market. On the base of the advantages of liquisolid system, it is envisaged that liquisolid system could play an important role in modern solid dosage forms.

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