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A Review-Recent Research on Liquisolid Compact for Solubility & Dissolution Enhancement

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ABSTRACT:

Solubility is one of the important parameter to obtain desired concentration of drug in systemic circulation. Liquisolid technique is one of the most promising techniques to achieve enhanced solubility of poorly soluble drugs. This approach is suitable for immediate or sustained release formulations and this depends upon the solubility of the drug in the non-volatile solvents. Non-volatile solvents enhance the solubility of water insoluble drugs by formation of micelles and act as dispersants. For immediate release liquisolid compacts, the selection of solvent is based on high drug solubility and for sustained release, solvents with least solubilising capacity is selected. The solubility of drug in non-volatile solvents can be revealed by differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD). Since there are no specific non-volatile liquid vehicles used in the preparation of liquisolid compacts, different non aqueous solvents have been used as non-volatile liquid vehicles in the preparation of immediate release and sustained release liquisolid tablets with different drugs. So selection of non-volatile solvent in liquisolid technique is important to obtain immediate or sustained release formulation.

KEY WORDS: Poorly soluble drugs, Liquisolid system, Carrier & coating material, solubility enhancement.

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INTRODUCTION:

Liquisolid compacts are new technique to enhance 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].

The liquisolid systems are generally considered as compressible powdered forms of liquid medications. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is included into the porous carrier material. Inert, preferably water-miscible organic solvent systems with high boiling point such as liquid polyethylene glycols, propylene glycol, or glycerine are most excellent fitting as liquid vehicles^[1-2].

Theory of Liquisolid Technology^[3]

When the Drug dissolved in the liquid vehicle or non volatile solvent is mixed with a carrier material which has a porous surface so absorption and adsorption take place. The liquid absorbed in the particles is captured by internal structure, and after this process adsorption of the liquid on to the internal and external surfaces of the porous carrier particles occur. Then, the

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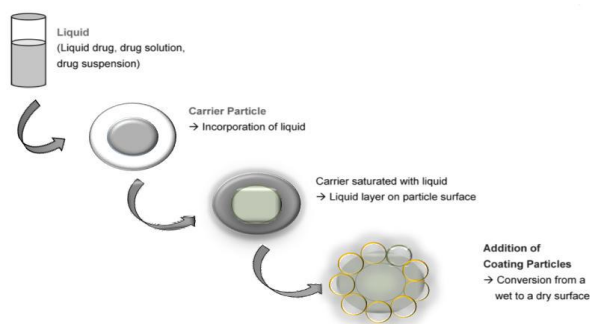


Fig. 1: Schematic representation of liquisolid system

coating material have high adsorptive properties and more specific surface area which gives high flow properties.

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Mechanisms of enhanced drug release from liquisolid compact[3-4]

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.

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:

$$FM = S_d / C_d \dots\dots\dots (1)$$

Where, FM = 1 if $S_d \geq C_d$.

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 reacts as a surfactant, it can enhance the wettability of the liquisolid system by decreasing the surface tension. Wettability of liquisolid system has been demonstrated by measurement of contact of angles and water rising times.

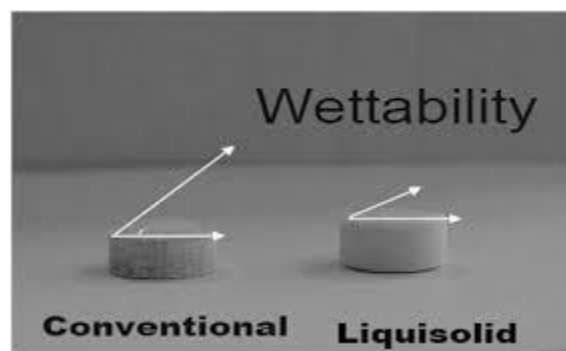


Fig. 2: Comparison of wettability between conventional tablet and liquisolid compacts

Advantages of liquisolid compact [1-4]

- Improvement of bioavailability.
- Improved dissolution profiles exhibited by the preparations.
- In this technique, production cost is low compared to soft gelatin capsules.
- 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.
- Greater drug surface area is exposed to the dissolution medium.
- This liquisolid system is specifically for powdered liquid medications.

- Better availability of an orally administered water insoluble drugs.
- Lower production cost than that of soft gelatine capsule.

Rational of liquisolid technology

Liquisolid drug delivery system is a novel and most important to increase aqueous solubility of water insoluble solid drug [BSC Class II & IV]. It can enhance dissolution rate as well as bioavailability of Drug. 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.

Research studies on liquisolid technology

Vijayaranga G. et al (2016), Liquisolid technique is used in delivery of lipophilic and poorly water soluble drugs through oral route. It involves dissolving water insoluble drugs in nonvolatile solvents and converting into acceptably flowing and compressible powders. The objective of the present work was to enhance the dissolution rate of ketoprofen using microcrystalline cellulose as carrier, aerosil 200 as coating material, and polyethylene glycol as nonvolatile water miscible liquid vehicle. The drug concentration was kept constant in all formulations. Optimization was carried out using Box–Behnken design by selecting liquid load factor, amount of coating material, and amount of magnesium oxide as independent variables; cumulative percentage drug release and angle of repose were considered as dependent variables. The Fourier transform infrared (FTIR) and differential scanning calorimetry (DSC) studies revealed that there was no possible interaction between drug and tablet excipients. Prepared ketoprofen liquisolid tablets were evaluated for hardness, weight variation, friability, in-vitro disintegration time, drug content uniformity, and invitro dissolution studies. The optimized formulation yielded the response values, which were very close to the predicted values. The accelerated stability studies conducted showed that liquisolid tablets were not affected by ageing and there were no appreciable changes in the drug content. In the present study, the potential of liquisolid systems to improve the dissolution properties of water-insoluble drug was investigated using ketoprofen as the model drug. Optimization of ketoprofen liquisolid compacts was carried out using Box–Behnken design by selecting liquid

load factor, amount of coating material and amount of magnesium oxide as independent variables and cumulative percentage drug release and angle of repose as dependent variables. The results showed that solubility of water insoluble drug ketoprofen was increased to greater extent thereby improving its dissolution rate. Thus liquisolid technology shall be used to improve the release rate of poorly water soluble drugs that will make the dosage form will be cost effective.[5]

Amjad K. et al (2015), had described Liqui-solid technique and solid dispersion formation are two novel approaches for enhancement of dissolution rate of BCS class II drugs. Liqui-solid 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, Liqui-solid and solid dispersion techniques were applied to enhance the dissolution of the Hydrochlorothiazide. Three formulations of Hydro-chlorothiazide were prepared by liqui-solid 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 liqui-solid compact formulations were more effective in enhancing the dissolution rate compared with solid dispersion technique. The study showed that both the novel techniques enhanced dissolution rate of HCTZ to a larger extent when compared with conventional tablet in terms of dissolution efficiency, similarity factor and dissimilarity factor. Dissolution efficiency of the novel techniques has increased in comparison with conventional tablets. Liqui-solid technique was observed to be more effective in enhancing rate and extent of drug release. Due to a large variety of hydrophilic polymers smaller tablets with improved dissolution rate and better physical characteristics can be obtained by solid dispersion technique. Excipients used in formulation of liqui-solid compact and solid dispersions were commonly used in pharmaceutical industries. All of the excipients

are economical and will not affect cost of the final product to a larger extent.[6]

Sateesh K. et al (2015), had concluded Development of liquisolid compacts is one of the new pharmaceutical formulation technologies to improve the dissolution rate of poorly soluble drugs. The intent of present investigation was to enhance the dissolution rate of poorly soluble drug flurbiprofen by delivering the drug as a liquisolid compact. Liquisolid compacts were developed using polyethylene glycol 400 (PEG 400) as solvent, Avicel PH102 or starch or HPMC or PEG 4000 or PEG 6000 as the carrier powder and Aerosil 200 as the coating material. The crystallinity of the newly formulated drug and the interaction between excipients was examined by differential scanning calorimetry. The dissolution studies for the liquisolid formulation and the marketed product were carried out to determine the improvement in dissolution rate and finally the best formulation was subjected to stability studies to assess the drug stability in the formulation. The results of interaction studies showed no change in the crystallinity of the drug and no interaction between excipients. In conclusion, the liquisolid technique was considered as a promising approach to improve the dissolution of poorly soluble drugs like flurbiprofen. The Liquisolid technique was found to be a promising approach for improving the dissolution rate of poorly soluble drug like flurbiprofen. The dissolution of flurbiprofen was significantly increased in liquisolid formulation compared to conventional tablets. The DE of flurbiprofen was increased by four times in optimized liquisolid formulation F5 when compared with conventional tablet. DSC studies indicate there were no interactions between drug and excipients. From the stability studies, the similarity index was found as above 50 indicated the stability of drug in the formulation. The increased dissolution rate may be due to increased wetting and increased surface area of the particles. Thus the liquisolid technique can be a promising approach to improve the dissolution rate of poorly soluble drugs.[7]

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 be 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.[8]

Elkordy et al (2014), had investigated 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 and Synperonic PE/L-61. The Liquisolid formulations of norfloxacin were tested according to the specification of British Pharmacopoeia quality control tests. Moreover, the pre-preparation evaluation tests, such as powder flowability Carr's index, differential scanning calorimetry and Fourier transform infrared, 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 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 is much higher than in Synperonic PE/L-61. 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.[9]

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 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.[10]

Fahim J. et al (2013), had described Candesartan cilexetil is an angiotensin-II receptor antagonist used for the treatment of hypertension. It is hydrophobic drug which belongs to BCS class II and its half life is 5.1 h with 15e40% bioavailability. Attempt had made to investigate the use of liquisolid technique in improving the dissolution of candesartan cilexetil in a solid dosage form. The liquisolid tablets were formulated by using Tween 80, as liquid vehicle, microcrystalline cellulose as a carrier material, silica as a coating material and sodium starch glycolate used as a superdisintegrant. The new mathematical model and 32 full factorial design was utilized to formulate various liquisolid powder systems. All prepared liquisolid batches were subjected to, weight variation, drug content uniformity, hardness, friability test, disintegration test and dissolution tests. Liquisolid system is also tested for DSC, XRD and IR. All the tested liquisolid tablet formulations showed higher drug dissolution than the conventional, directly compressed tablet. DSC and XRD study suggested loss of candesartan

cilexetil crystallinity upon liquisolid formulation which was further confirmed by SEM, it indicates that drug is held within the powder substrate in a solubilized, almost molecularly dispersed state, which lead to the enhanced drug dissolution properties.[11]

Shailesh T. et al (2013), had Olmesartan medoxomil is an angiotensin type II receptor blocker, antihypertensive agent, administered orally. It is highly lipophilic and a poorly water-soluble drug with absolute bioavailability of 26%. The poor dissolution rate of water-insoluble drugs is still a major problem confronting the pharmaceutical industry. The objective of the present investigation was to develop liquisolid compacts for olmesartan medoxomil to improve the dissolution rate. Liquisolid compacts were prepared using Acrysol EL 135 as a solvent, Avicel PH 102, Fujicalin and Neusilin as carrier materials, and Aerosil as coating material in different ratios. The interaction between drug and excipients was characterized by DSC and FT-IR studies, which showed that there is no interaction between drug and excipients. The powder characteristics were evaluated by different flow parameters to comply with pharmacopoeial limits. The dissolution studies for liquisolid compacts and conventional formulations were carried out, and it was found that liquisolid compacts with of Acrysol EL 135 to the drug showed significant higher drug release rates than conventional tablets. Amongst carriers used Fujicalin and Neusilin were found to be more effective carrier materials for liquid adsorption. Acrysol EL 135 proved to be promising liquid vehicle for formulation of liquisolid preparations. Olmesartan liquisolid tablets formulated from 80% w/w Acrysol EL 135 to the drug was found to be superior in terms of dissolution properties in comparison with other liquisolid formulations. Fujicalin and Neusilin are used as carrier materials instead of Avicel, the liquid adsorption capacity increases by many folds. Thus, tablet weights are reduced in case of Fujicalin and Neusilin in comparison to commonly used carrier materials like Avicel.[12]

Enugula P. et al (2013), had described that liquisolid technique has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release tablets matrices of Trimetazidine Di hydrochloride (TZH a water soluble drug). TZH was dispersed in polysorbate-80 a non-volatile liquid vehicle. Then a binary mixture of carrier coating materials (Ethyl cellulose, Eudragit L- and RS-100 as the carrier and aerosil as the coating material) was added to

the liquid medication under continuous stirring. 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 matrix tablets were evaluated by hardness, friability, and in vitro dissolution studies. The dissolution profile of the prepared SR matrix tablets were compared with a marketed formulation (MR). TZH tablets prepared by liquisolid technique showed greater retardation, when compared with marketed matrix tablets. This investigation provided evidence that Polysorbate-80 (Tween 80) has important role in sustaining the release of drug from liquisolid matrices. The dissolution profile followed the Higuchi and Peppas model, shows near zero order release for prolonged period. The FT-IR spectra revealed that there is no interaction between drug-excipients used; there is no significant difference in the mean percentage of drug released from formulation. The present work showed that liquisolid compacts technique can be effectively used for preparation of sustained release (SR) matrix tablets of water soluble drug TZH along with Polysorbate-80 was used as liquid vehicle. Drug release profiles on model fitting follow Peppas model as the best fit model, which indicates TZH released from this tablet follows sustained release profile. From the above study, we may also infer that Eudragit L-100, along with Aerosil as coating material provided better SR of TZH.[13]

Chella N. et al (2012), had described The aim of this study was to improve the dissolution rate of the poorly soluble drug valsartan by delivering the drug as a liquisolid compact. Liquisolid compacts were prepared using propylene glycol as solvent, Avicel PH102 as carrier, and Aerosil 200 as the coating material. The crystallinity of the newly formulated drug and the interaction between excipients was examined by X-ray powder diffraction and Fourier-transform infrared spectroscopy, respectively. The dissolution studies for the liquisolid formulation and the marketed product were carried out at different pH values. The results showed no change in the crystallinity of the drug and no interaction between excipients. The increase in the dissolution rate was also found to be significant compared to the marketed product at lower pH values, simulating the gastric environment where valsartan is largely absorbed. The liquisolid technique appears to be a promising approach for improving the dissolution of poorly soluble drugs like valsartan. The liquisolid technique was found to be a promising approach for improving the dissolution of a

poorly soluble drug like valsartan. The dissolution of valsartan was significantly increased in liquisolid formulation compared to the marketed product. XRD and IR spectra indicate that there was no change in the crystalline state of the drug and no interactions between the drug and excipients. The increased dissolution rate may be due to increased wetting and increased surface area of the particles.[14]

Babatunde A. et al (2010), had A liquisolid system has the ability to improve the dissolution properties of poorly water soluble drugs. Liquisolid compacts are flowing and compactable powdered forms of liquid medications. The aim of this study was to enhance the in vitro dissolution properties of the practically water insoluble loop diuretic furosemide, by utilising liquisolid technique. Several liquisolid tablets were prepared using microcrystalline cellulose and fumed silica as the carrier and coating materials, respectively. Polyoxyethylene-polyoxypropylene-polyoxyethylene block copolymer, 1,2,3-propanetriol, homopolymer, -9-octadecenoate and polyethylene glycol 400 were used as non-volatile water-miscible liquid vehicles. The liquid loading factors for such liquid vehicles were calculated to obtain the optimum amounts of carrier and coating materials necessary to produce acceptable flowing and compactible powder admixtures viable to produce compacts. The ratio of carrier to coating material was kept constant in all formulations at 20 to 1. The formulated liquisolid tablets were evaluated for post compaction parameters such as weight variation, hardness, drug content uniformity, percentage friability and disintegration time. The in-vitro release characteristics of the drug from tablets formulated by direct compression and liquisolid technique, were studied in two different dissolution media. Differential scanning calorimetry and Fourier-Transform infrared spectroscopy (FT-IR) were performed. The results showed that all formulations exhibited higher percentage of drug dissolved in water compared to that at acidic medium. Liquisolid compacts containing Synperonic® PE/L 81 demonstrated higher release rate at the different pH values. Formulations with PEG 400 displayed lower drug release rate, compared to conventional and liquisolid tablets. DSC and FT-IR indicated a possible interaction between furosemide and tablet excipients that could explain the dissolution results. Caprol® PGE-860, as a liquid vehicle, failed to produce furosemide liquisolid compacts.[15]

CONCLUSION

The liquisolid system is the new technique for the formulation of water insoluble drugs to increase 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. 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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