SOLUBILITY ENHANCEMENT AND DISSOLUTION IMPROVEMENT- LIQISOLID TECHNIQUE

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ABSTRACT:
This technique is based upon the admixture of drug loaded solutions with appropriate carrier and coating materials. 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 (non-volatile solvents) one can modify release (sustained release) of drugs by this technique. Liquisolid system is characterized by flow behavior, wettability, powder bed hydrophilicity, 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. The increased bioavailability is due to either increased surface area of drug available for release, an increased aqueous solubility of the drug, or improved wettability of the drug or particles. According to the new formulation method of liqui-solid compacts, liquid medications such as solutions or suspensions of water insoluble drugs in suitable nonvolatile liquid vehicles can be converted into acceptably flowing and compressible powders by blending with selected powder excipients. It has been speculated that such systems exhibit enhanced release profiles. In this case, even though the drug is in a solid dosage form, it is held within the powder substrate solution or in a solubilized, almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties. According to the new formulation method of liquisolid compacts, 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 by blending with selected powder excipients. Large scale production of fabricated drug on commercial level successfully liquisolid tablet is a determination of optimal flowable liquid retention.

Keywords: Poorly soluble drugs, coating material, carrier, hydrophilic solvent, liquisolid compacts

INTRODUCTION:
The poorly soluble drug having dissolution rate too slow therefore uptake cannot be completed within the time at absorption site. If it remains in GIT for longer period may lead to decomposition of drug. There are two parameters useful for identifying poorly soluble drugs. One is its aqueous solubility should be less than 100ug/ml and another is dose: solubility ratio. Dose: solubility ratio can be defined as volume of gastrointestinal fluids necessary to dissolve the administered dose. 

The liquisolid technique as described by Spireas is a novel concept, where a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material. 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. As the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantaneously adsorbed by the fine coating particles.

Solid dispersions consist of one or more active ingredients dispersed in a readily soluble solid hydrophilic matrix prepared by a melting (fusio) or solvent method. With the melting method the drug is added to the molten carrier and the mixture is stirred until a homogenous melt is obtained. With the solvent method drug and carrier are dissolved in small amounts of solvent with final solvent evaporation. The higher release rates of solid dispersions may be ascribed to a number of factors which include formation of the amorphous form of the drug, reduction of particle size to nearly the molecular level, improved wettability and solubilisation of the drug by the carrier. The advantages of this methodology are the molecular dispersion of the drug within the hydrophilic carrier and the comparably high drug stability. However, for the preparation of solid dispersions usually special equipment is needed such as a spray dryer or a fluid bed apparatus

Liqisolid compact:
Liquisolid technique is a new and promising method that can change the dissolution rate of drugs. It has been used to enhance dissolution rate of poorly water-soluble drugs. For poorly soluble (Class II) drugs and class (Class IV) the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract. The new ‘liquisolid’ technique may be applied to formulate liquid medications (i.e., oily liquid drugs and solutions, suspensions or emulsions of water-insoluble solid drugs carried in nonvolatile liquid vehicles) into powders suitable for tableting or encapsulation. Since, the liquisolid tablets contain a solution of the drug in suitable solvent; the drug surface available for dissolution is tremendously increased. Due to significantly increased wettability properties and surface area of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release characteristics and, consequently, improved oral bioavailability.
Drugs that can be incorporated into liquisolid systems:
- Antiasthmatic: chlorpheniramine
- Antiarrhythmic: digoxin, digitoxin
- Antihypertensive: nifedipine
- Antilipidemics: clofibrate, gemfibrozil
- Antiepileptic: Carbamazepine, valproic acid.
- Chemotherapeutic agent: etoposide.
- Diuretics: Hydrochlorothiazide, methylchloorthiazide, polythiazide, spironolactone.
- Glucocorticoids: prednisolone, hydrocortisone, prednisone.
- NSAIDS: piroxicam, indomethacin, ibuprofen.
- Antihistaminic: chlorpheniramine
- Chemotherapeutic agent: etoposide.
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Advantages of liquisolid tablets over conventional tablets:
- Limitations
  - Formulation of high dose lipophilic drugs the liquisolid tablet is one of the limitations of this technique.
  - This technique is not applicable for high dose insoluble drug.
  - Mathematical calculations require.

Advantages of liquisolid tablets over conventional tablets:
- 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.
- Omit the process approaches like nanonisation, micronization techniques.
- Differentiate the dosage form by admixture of colour into liquid vehicle.
- To minimize excipients in formulation compare with other formulations like solid dispersions.

Theory of liquid solid systems:
A powder can retain only limited amounts of liquid while maintaining acceptable flow and compression properties. To calculate the required amounts of powder excipients (carrier and coating material) a mathematical approach for the formulation of liquid solid systems has been developed by Spirina. This approach is based on the flowable (Φ-value) and compressible (Ψ-value) liquid retention potential introducing constants for each powder/liquid combination.

The Φ-value of a powder represents the maximum amount of a given non-volatile liquid that can be retained inside its bulk [w/w] while maintaining an acceptable flowability. The flowability may be determined from the powder flow or by measurement of the angle of repose. The Ψ-value of apowder is defined as the maximum amount of liquid the powder can retain inside its bulk [w/w] while maintaining acceptable compactability resulting in compacts of sufficient hardnessness with no liquid leaking out during compression.\(^\text{11, 12}\)

Depending on the excipient ratio (R) of the powder substrate an acceptably flowing and compressible liquid solid system can be obtained only if a maximum liquid load on the carrier material is not exceeded. This liquid/carryer ratio is termed "liquid load factor (Lf) [w/w]" and is defined as the weight ratio of the liquid formulation (W) and the carrier material (Q) in the system:

\[
Lf = W/Q \tag{1}
\]

\(R\) represents the ratio between the weights of the carrier (Q) and the coating (q) material present in the formulation:

\[
R = Q/q \tag{2}
\]

The liquid load factor that ensures acceptable flowability (Lf\(_f\)) can be determined by:

\[
Lf_f = \Phi + \phi \cdot (1/R) \tag{3}
\]

Where \(\Phi\) and \(\phi\) are the Φ-values of the carrier and coating material, respectively. Similarly, the liquid load factor for production of liquid-solid systems with acceptable compactability (ΨLf\(_f\)) can be determined by:

\[
\Psi Lf_f = \Psi + \psi \cdot (1/R) \tag{4}
\]

Where \(\Psi\) and \(\psi\) are the Ψ-numbers of the carrier and coating material, respectively.

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

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

The first two may be produced from the conversion of drug solutions or (e.g., prednisolone solution in propylene glycol) or drug suspensions (e.g., gemfibrozil suspension in Polysorbate 80), and the latter from the formulation of liquid drugs (e.g., clofibrate, valproic acid, liquid vitamins, etc.), into liquisolid systems.

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

- Liquisolid compacts
- Liquisolid microsystems

Liquisolid compacts are prepared using the previously outlined method to produce tablets or capsules, whereas the liquisolid microsystems are based on a new concept which have improved flowability for encapsulations.

Mechanism of enhanced drug release:

From liquid solid systems:

Several mechanisms of enhanced drug release have been postulated for liquisolid systems. The three main suggested mechanisms include an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles.

Formation of a complex between the drug and excipients or changes in crystallinity of the drug could be ruled out using DSC and XRPD measurements.

a. Increased Drug Surface Area

If the drug within the liquisolid system is completely dissolved in the liquid vehicle it is located in the powdersubstrate 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.

b. Increased Aqueous Solubility of the Drug

In addition to the first mechanism of drug release enhancement it is expected that Cs, 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. However, at the solid/liquid interface between an individual liquisolid primary particle and the release medium it is possible that in this microenvironment the amount of liquid vehicle diffusing out of a single liquisolid particle together with the drug molecules might be sufficient to increase the aqueous solubility of the drug if the liquid vehicle acts as a cosolvent.

c. Improved Wetting Properties

Due to the fact that the liquid vehicle can either act as a surfactant 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. Many poorly soluble drugs have been formulated as liquisolid systems showing enhanced drug release. Different liquid vehicles, carrier and coating materials were used to formulate these drug delivery systems.

Principle of Liquisolid Compacts:

Important terminologies in Principle:

Liquid medication includes liquid lipophilic drugs and drug suspensions or solutions of solid water insoluble drugs in suitable non-volatile solvent systems.

Liquisolid system refers to powdered forms of liquid medications formulated by converting liquid lipophilic drugs, or drug suspensions or solutions of water insoluble solid drugs in suitable non-volatile solvent systems, into dry, nonadherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials.

Carrier material refers to a preferably porous material possessing sufficient absorption properties, such as microcrystalline and amorphous cellulose, which contributes in liquid absorption.

Coating material refers to a material possessing fine and highly absorptive 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 non-volatile liquid vehicles, is incorporated into the porous carrier material (Fig. 1).

Inert, preferably water-miscible organic solvent systems with high boiling point such as propylene glycol, liquid polyethylene glycols, or glycerine are best suitable as liquid vehicles. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing, and compressible powder is obtained. Usually, microcrystalline cellulose is used as
carrier material and amorphous silicon dioxide (colloidal silica) as coating material.

**Preparation of liquid solid compacts:**

As shown in figure, a liquid lipophilic drug (e.g., Chlorpheniramine, Clofibrate, etc.) can be converted into a liquid-solid system without being further modified. On the other hand, if a solid water-insoluble drug (e.g., Hydrochlorothiazide, Prednisone, etc.) is formulated, it should be initially dissolved or suspended in a suitable nonvolatile 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 an adequate 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 liquid-solid systems to produce liquid-solid compacts, i.e., tablets or capsules.\(^\text{16, 17, 18}\)

![Figure 2: Schematic outline of the steps involved in the preparation of liquid-solid compacts](image)

**Pre-compression evaluation parameters of liquid solid systems:**

**Flow Properties of the Liqui-Solid System:**\(^\text{19, 20}\)

The flow properties of the liquid-solid system were estimated by determining the angle of repose, Carr’s index, and Hausner’s ratio. The angle of repose was measured by the fixed funnel and freestanding cone method. The Bulk density and Tap densities were determined for the calculation of Hausner’s ratio and Carr’s Index.

**Angle of repose:**

The angle of repose physical mixtures of liquid-solid compacts were determined by fixed funnel method. The accurately weighed physical mixtures of liquid-solid compacts were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through the funnel freely into the surface. The height and diameter of the powder cone was measured, and angle of repose was calculated.

\[
\tan \theta = \frac{h}{r}
\]

Where, \(\theta\) is the angle of repose, \(h\) is the height in cm, \(r\) is the radius in cm.

Values for angle of repose ≤ 30° usually indicate a free-flowing material and angles ≥ 40° suggest a poorly flowing material. 25–30 showing excellent flow properties, 31–35 showing good flow properties, 36–40 showing fair flow properties, 41–45 showing passable flow properties.

**Bulk Density:**

The loose bulk density and tapped density were determined by using bulk density apparatus. Apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (\(V_b\)) and weight of the powder (\(M\)) was determined. The bulk density was calculated using the formula:

\[
Db = \frac{M}{V_b}
\]

where, \(M\) is the mass of powder, \(V_b\) is bulk volume of powder.

**Tapped Density:**

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (\(V_t\)) occupied in the cylinder and the weight (\(M\)) of the blend was measured. The tapped density was calculated using the formula:

\[
Dt = \frac{M}{V_t}
\]

where, \(M\) is the mass of powder, \(V_t\) is tapped volume of powder.

**Carr’s Index (%):**

The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of material because all of these can influence the observed compressibility index. The simplest way for measurement of free flow of powder is Carr’s Index, an indication of the ease with which a material can be induced to flow is given by Carr’s index (CI) which is calculated as follows:

\[
CI(\%) = \left(\frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}\right) \times 100
\]

The value below 15% indicates a powder with usually good flow characteristics, whereas above 25% indicates poor flowability. 1-10 showing excellent flow properties, 11-25 showing good flow properties 16-20 showing fair to passable, 21-25 showing passable.

**Hausner’s Ratio:**

Hausner’s ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

\[
\text{Hausner's Ratio} = \frac{\text{Tapped density (}\rho_t\text{)} \text{ / Bulk density (}\rho_b\text{)}}
\]

Where \(\rho_t\) is tapped density and \(\rho_b\) is bulk density. Lower Hausner’s ratio (<1.25) indicates better flow.
properties than higher ones, between 1.25 to 1.5 showing moderate flow properties and more than 1.5 poor flow.

**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 - 4000 cm\(^{-1}\) at spectral resolution of 2 cm\(^{-1}\) and ratio against background interfereogram. Spectra are analyzed by software.\(^{21}\)

**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.\(^{21, 22, 23}\)

**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.\(^{24}\) 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.\(^{25}\)

**Post compression evaluation parameter of liquid solid compacts:**

**Weight Variation:**

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation three batches were calculated. It passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

**Thickness:**

The thickness of liqui-solid tablets was determined by using digital micrometer. Ten individual tablets from each batch were used and the results averaged.

**Hardness:**

The hardness of the tablets was determined by using Monsanto hardness tester. Five individual tablets from each batch were and results averaged.

**Friability:**

The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min. Percentage friability was calculated using the following equation:

\[
\text{Friability} = \frac{(W_0 - W)}{W_0} \times 100
\]

Where,

\(W_0 = \) Weight of the tablet at time zero before revolution,
\(W = \) Weight of the tablet after 100 revolutions.

**Disintegration Test:**

Six tablets were taken randomly from each batch and placed in USP disintigration apparatus baskets Apparatus was run for 10 minutes and the basket was lifted from the fluid, observe whether all of the tablets have disintegrated.

**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 measure contact angle directly for a drop of liquid resting on a plane surface of the solid, the so-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.\(^{24}\)

**Scanning electron microscopy (SEM):**

Scanning electron microscopy (SEM) is utilized to assess the morphological characteristics of the raw materials and the drug-carrier systems.\(^{25}\)

**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.\(^{24}\) Also several water insoluble drugs nifedipine, gemfibrozil, and ibuprofen, have shown higher bioavailability in rats as compared to their commercial counterparts.

9. **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 hydrochlorothiazide-lquisolid compact 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 the rate of absorption no significant differences were found. The absolute bioavailability of the drug from liquisolid compacts was 15% higher than that from the commercial formulation.\(^{20}\)

**Stability studies:**

Drug content was determined after the crystals were charged for accelerated stability studies according to ICH.
guidelines. Samples were taken and analysed for specified intervals.

**Bioavailability assessment for different active pharmaceutical ingredients:**

Bioavailability assessment is required for liquisolid technique. Because it was proved that enhancing the drug release from the dosing form by determination of in-vitro release studies. So, this parameter should establish for determination of the efficacy of the formulation.

Atorvastatin calcium (ATR) is a BCS class II drug used as a lipid lowering agent by acting as HMGCoA reductase inhibitor. The prepared liquisolid compacts of ATR showed higher release rates compared to the directly compressed tablets. The pharmacokinetic parameters of liquisolid compacts of ATR, such as the AUC, t\text{max} and C\text{max} showed the better bioavailability compared with the conventional formulation.

Liquisolid Compacts of Aceclofenac orodispersible tablets were formulation and evaluated. The study is based on the effect of combined mixture of super disintegrants disintegrating action on drug release. Propylene glycol, PEG 400, Tween 80, microcrystalline cellulose were used as carrier. The liquisolid compacts with Sodium starch glycololate added intra granularly and Crosspovidone extra granularly showed highest dissolution rate. Orodispersible liquisolid compacts prepared with Tween 80 enhance the dissolution rate of aceclofenac to a larger extent.

**Approaches to augment dissolution of active pharmaceutical ingredient release from its immediate release tablets:**

Liquisolid compacts confirmed significantly higher drug release rates, in different dissolution media, compared to tablets prepared by the direct compression method. It was also observed that the drug dissolution rate from liquisolid tablets were independent of the volume of dissolution medium, in difference to the plain tablets which exposed declining drug release patterns with decreasing dissolution volumes.

Cyclosporine (CS) Self Micro-Emulsifying Tablet (SME), the tablets were prepared by the liquisolid compaction technique. Formulation consists of oil, surfactant and cosurfactant which were selected on the basis of solubility and emulsification ability for the SME formulation. In this study, the mixture of Lauroglycol FCC: Maisine 35-1 (1:1 w/w) was selected as the oil phase, PEG-35 Castor Oil was selected as the surfactant and PEG-400 was selected as the co-surfactant. 1 to 6 was selected as the ratio between the drug and the mixture. An Emulsion could not be formed in several oils, such as Carpyrol 90, Lauroglycol 90 and Lauroglycol FCC even in which the CS has good solubility. Due to the cyclic structure of CS-A, some excipients absorbed the drug and could not be selected as carrier material and coating material, e.g., silica powders. The liquisolid tablets were effective in enhancing dissolution of CS-A, a poorly water-soluble drug. The tablets exhibited good flowability and compactability. The results showed that the liquisolid compaction technique is a promising alternative technique to improve the solubility and the dissolution rate, for poorly water-soluble drugs CS-A.

Naproxen is a non-steroidal anti-inflammatory drug (NSAID) commonly used for the reduction of fever, pain and inflammation. Liquisolid compacts change the properties of naproxen particles by simply dispersing the drug particles in a non-volatile hydrophilic liquid vehicle, which increase the wetting properties of drug particles, and enhances the dissolution rate and shows improved bioavailability of the drug. At present, naproxen is available commercially in high dose tablets between 250 and 500 mg; the liquisolid formulations may help in reduction of the dose also.

**CONCLUSION:**

This technique is a potential substitute for formulation of water-insoluble/soluble drugs. The improved rate of drug dissolution from liquisolid tablets is almost certainly due to an amplify in wetting properties and surface area of drug particles obtainable for dissolution. Rapid disintegration rates are experimentally compared to conventional tablets. Hence they show improved release rates and greater bioavailability. By this technique, sustained drug delivery systems were also be developed for the water soluble drugs in which hydrophobic non-volatile solvents are used as vehicles. Alteration of formulation by use of definite agents’ source it control the release of drugs from the liquisolid tablets.
REFERENCES: