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Review Article

LIQUISOLID COMPACTS: A PROMISING APPROACH FOR SOLUBILITY ENHANCEMENT

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ABSTRACT

At present 40% of the drugs within the development pipelines, and approximately 60 % of the drugs coming directly from synthesis area unit poorly soluble. Solubility is one of the important parameter to obtain desired concentration of drug in systemic circulation. Liquisolid compacts technique is a new and promising approach to overcome this consequence and that can change the dissolution rate of water insoluble drugs and increase the bioavailability of the drugs. This technique is an efficient method for formulating water insoluble and water soluble drugs. This technique relies upon the admixture of drug loaded solutions with applicable carrier and coating materials. Liquisolid system is characterized by flow behaviour, 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. This review article explains the preparation, classification and application of liquisolid system.

Key word: Liquisolid system, water insoluble drug, carrier material, coating material.

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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 (GIT) when given orally. The solubility and dissolution behaviour of a drug is the key determinants of its oral Bioavailability¹. Release improvement of poorly soluble drugs is rise achieved by a rise of the drug surface area, the drug solubility, or by formulating the drug in its dissolved state. Numerous techniques are used to formulate oral drug delivery system that might enhance the dissolution profile and successively, the absorption potency of water insoluble drugs likes micronization, adsorption onto high surface area transporters, lyophilization, co-grinding,

formulation of inclusion complexes, solubilization by surfactants, solid dispersions, solid solutions, hydrotrophy, inclusion of the drug resolution or liquid drug into soft gelatin capsules, and cosolvency and liquisolid compact technology². The Liquisolid compact concept described by Spireas *et. al.* in this system oily liquid drug and solution or suspension of water insoluble drug in to non-volatile solvent³. Liquisolid technology, a liquid is also reworked into a free flowing, without delay compressible and apparently dry powder by easy physical mixing with elect excipients named the carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in to suitable non-volatile liquid vehicles, is combined into the carrier material. The foremost promising and new technique for supporting dissolution is that the formation of liquisolid tablets among the numerous novel

techniques. Liquefied compacts promote dissolution rate of water insoluble drugs to a greater extent and additionally enhance the drug flow property^{4,5}.

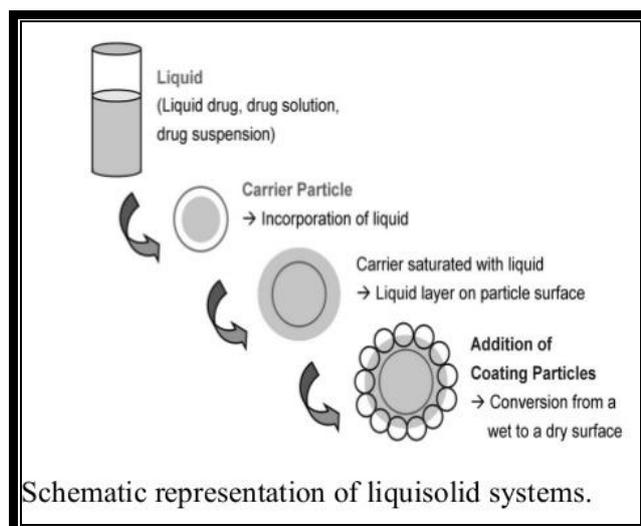


Fig. 1: Schematic representation of liquisolid system.

CLASSIFICATION

A. Based on the liquid medication, it is divided into three sub groups:

1. Powdered drug solutions
2. Powdered drug suspensions
3. Powdered liquid drug

The major two are also made from the conversion of drug solutions or drug suspensions (e.g. gemfibrozil suspension in Polysorbate 80), and therefore the formulation of liquid drugs (e.g. clofibrate, valproic acid, liquid vitamins, etc.), into liquisolid systems.

B. Based on the formulation technique, liquisolid systems are classified into two groups,

1. **Liquisolid compacts:** It refers to immediate sustained release tablets or capsules that are described under liquisolid systems.
2. **Liquisolid microsystems:** It refers to capsules ready by liquisolid systems with the inclusion of an additive resultant in a unit size that may be as much as five times less than that of a liquisolid compact⁶.

Theory of Liquid Solid Systems:

A powder can retain only restricted amounts of liquid whereas maintaining acceptable flow and compression properties. To calculate the essential amounts of powder excipients (carrier and coating materials) a mathematical approach for the formulation of liquisolid systems has been developed by Spireas. This approach is predicated on the flowable (Φ value) and compressible (Ψ -number) liquid retention potential introducing constants for each powder/liquid combination. The Φ -value of a powder represents the determined amount of a given non-volatile liquid which will be maintained within its bulk [w/w] whereas maintaining a suitable flowability. The

flowability may be determined from the powder flow or by measurement of the angle of repose⁷.

The Ψ -number of a powder 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 hardness with no liquid permeable out throughout compression.

The compactability determined by the plasticity, which describes the maximum (plateau) crushing strength of a one-gram tablet compacted at sufficiently high compression forces.

The terms "acceptable flow and compression properties" imply the specified so preselected flow and compaction properties that has to be met by the ultimate word liquisolid formulation.

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

$$L_f = W/Q \quad \text{Eq. (1)}$$

R represents the quantitative relation between the weights of the carrier (Q) and also the coating (q) material given within the formulation:

$$R = Q/q \quad \text{Eq. (2)}$$

The liquid load factor that ensures acceptable flowability (ΦL_f) can be determined by:

$$\Phi L_f = \Phi + \phi \cdot (1/R) \quad \text{Eq. (3)}$$

where Φ and ϕ are the Φ -values of the carrier and coating material, respectively. Similarly, the liquid ratio for production of liquisolid systems with acceptable compactability (ΨL_f) is decided by:

$$\Psi L_f = \Psi + \psi \cdot (1/R) \quad \text{Eq. (4)}$$

where Ψ and ψ are the Ψ -numbers of the carrier and coating material, respectively. In **Table-1** sample of liquisolid formulation parameters of different powder excipients with usually used liquid vehicles are listed.

Therefore, the optimum liquid load factor (L_o) needed to get tolerably flowing and compressible liquisolid systems are adequate to either ΦL_f or ΨL_f , whichever represents the lower value.

As soon as the optimum liquid load factor is determined, the appropriate quantities of carrier (Q_o) and coating (q_o) material required to convert a given amount of liquid formulation (W) into an acceptably flowing and compressible liquisolid system is additionally calculated as follows:

$$Q_o = W/L_o \quad \text{--- (5)}$$

$$\text{And } q_o = Q_o/R \quad \text{--- (6)}$$

Table 1: Lquisolid formulation parameters of various powder excipients with commonly used liquid vehicles

Powder Excipient or System	Φ -values		Ψ -numbers	
	Propylene glycol	PEG 400	Propylene glycol	PEG 400
Avicel pH 102	0.16	0.005	0.224	0.242
Avicel pH 200	0.26	0.02	0.209	0.232
Cab-O-Sil M5 M5(silica)* With Avicel pH 102	3.31	3.26	0.560	0.653
Cab OSilM5(silica)* With Avicel pH 200	2.57	2.44	0.712	0.717

The validity and applicability of the above mentioned principles have been tested and verified by producing lquisolid compacts possessing acceptable flow and compaction properties ^{8,9}.

MECHANISMS OF ENHANCED DRUG RELEASE FROM LIQUISOLID SYSTEMS

Several mechanisms of increased drug release have been proposed for lquisolid systems. The three main mechanisms include increased surface area of drug, increased aqueous solubility of the drug, and improved wettability of the drug particles. Formation of a complex between the drug and excipients or any changes in crystalline of the drug could be ruled out using DSC and XRPD measurements.

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

a) Increased Drug Surface Area

If the drug within the lquisolid system is totally dissolved within the liquid vehicle it is situated in the powder substrate still in a solubilized, molecularly spread state. Therefore, the surface area of drug available for release is way larger than that of drug particles inside directly compressed tablets. Accordingly, with increasing drug content surpassing the solubility limit and so, increasing fraction of undissolved drug within the liquid vehicle the discharge rate decreases ¹⁰.

b) Increased Aqueous Solubility of the Drug

In addition to the primary mechanism of drug release improvement it is expected that cs , the solubility of the drug might be increase with lquisolid system. In fact the relatively small amount of liquid vehicle in a lquisolid compact is not adequate to extend the general solubility of the drug within the binary compound dissolution medium. However at the solid liquid interface between an distinct lquisolid primary particles and the release medium it is promising that in this micro environment the quantity of liquid vehicle spreading out of a single lquisolid particle together with the drug molecules might be adequate to extend the aqueous solubility of the drug if the liquid vehicle acts as co solvent ¹¹.

c) Increased Wettability

Due to the very fact that the liquid vehicle will either act as surface chemical agent or contains a low surface tension, wetting of the lquisolid primary particles is

improved. Wettability of these systems has been confirmed by measurement of contact angles and water rising times ¹².

GENERAL PROCEDURE FOR PREPARATION OF LIQUISOLID COMPACT TABLETS

- A drug substance should be initially dissolved or suspended in a suitable non-volatile solvent system to produce a drug solution or drug suspension of desired concentration.
- Then a mixture of carrier or different polymers and excipients were added to the above liquid medication under continuous mixing in a mortar. These amounts of the carrier and excipients are enough to maintain acceptable flow and compression properties.
- To the above binary mixture disintegrant like sodium starch glycolate and other remaining additives were added according to their application and mixed for a period of 10 to 20 min. in a mortar.
- The final mixture was compressed using the manual tableting machine to achieve tablet hardness.
- Characterize the final lquisolid granules for solubility, dissolution, flowability, compressibility and other physicochemical properties ¹³.

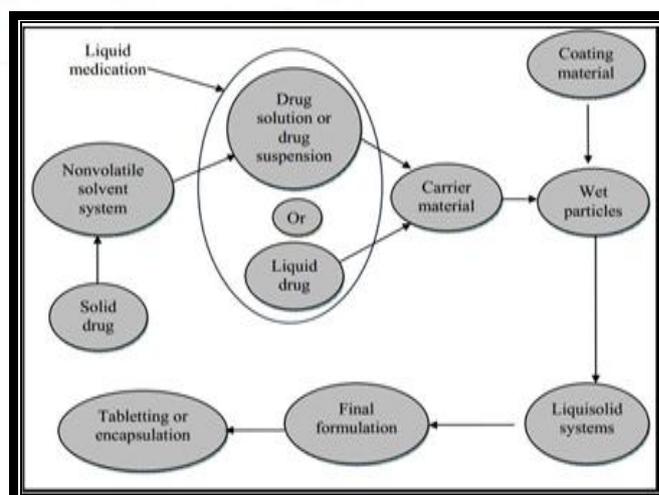


Figure 2: Schematic Diagram Representing Preparation of Lquisolid Compacts

COMPONENTS OF LIQUISOLID COMPACT FORMULATIONS

1. Non-volatile Solvent

Non-volatile Solvent should be Inert, high boiling point, ideally water-miscible and not extremely viscous organic solvent systems and compatible with having ability to solubilise the drug. The non-volatile solvent acts as a binding agent within the liquisolid formulation. Various non-volatile solvents used in the formulation of liquisolid compact. Eg. Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and propylene glycol.

2. Disintegrant

Super disintegrants rises the rate of drug release, water solubility and wettability of liquisolid granules. Mostly super disintegrants like sodium starch glycolate and cross povidone.

3. 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 solely 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.

4. Coating Materials

Coating material should be a material possessing fine and extremely surface-assimilative particles that contributes in covering the wet carrier particles and displaying a dry looking powder by adsorbing any excess liquid. Coating material is required to cover the surface and maintain the powder flowability³⁴. Coating material includes silica (Cab-O-Sil) M520, 35, Aerosil 20030, Syloid, 244FP 20,35 etc^{14,15}.

Examples of some drugs that can be incorporated into liquisolid systems:

- ❖ Chlorpheniramine
- ❖ Digoxin
- ❖ Nifedipine
- ❖ Clofibrate
- ❖ Gemfibrozil
- ❖ Etoposide
- ❖ Carbamazepine
- ❖ Hydrochlorothiazide
- ❖ Methyclothiazide
- ❖ Spironolactone
- ❖ Hydrocortisone
- ❖ Piroxicam
- ❖ Indomethacin
- ❖ Ibuprofen

PRE-COMPRESSION STUDIES OF THE LIQUISOLID SYSTEM

Flow Properties of the Liquisolid System:

The flow properties of the liquisolid systems were calculable by determining the angle of repose, Carr's index, and Hausner's ratio.

Angle of repose:

The angle of repose physical mixtures of liquisolid compacts were determined by fixed funnel method. The accurately weighed physical mixtures of liquisolid compacts were taken in a funnel. The height of the funnel was adjusted in such how that the tip of the funnel simply 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.

$$\tan \theta = h/r$$

Where, θ is the angle of repose, h is the height, r is the radius.

Values for angle of repose ≤ 300 usually indicate a free flowing material and angles ≥ 400 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 firm. The bulk density was calculated using the formula:

$$D_b = M/V_b$$

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 within the cylinder and therefore the weight (M) of the mix was measured. The tapped density was calculated using the Formula:

$$D_t = M/V_t$$

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 method for measurement of free flow of powder is Carr's Index, a indication of the benefit with which a material can be induced to flow is given by Carr's index (CI) which is calculated as follows:

$$CI (\%) = [(Tapped \text{ density} - Bulk \text{ density}) / Tapped \text{ density}] \times 100$$

The value below 15% indicates a powder with sometimes offers rise to good flow characteristics, where as above 25% indicates poor flow ability.

Hausner's Ratio:

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

Hausner's Ratio = Tapped density (ρ_t) / Bulk density (ρ_b)

Where ρ_t is tapped density and ρ_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^{16,17}.

POST COMPRESSION STUDIES OF LIQUID-SOLID COMPACTS**Hardness:**

Monsanto hardness tester can be used for the determination of the hardness. The tablet to be tested was held between a fixed and moving jaw and reading of the indicator adjusted to zero. The force applied to the edge of the tablet is gradually increased by moving the screw knob forward until the tablet breaks. Reading is noted down and is expressed in kg/cm.

Thickness:

The crown to crown thickness of tablets is measured by Vernier Caliper. It is expressed in mm. the thickness variation allowed are $\pm 5\%$ of the size of the tablet.

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 less than two of the individual tablet weights deviate from the everyday weight by quite than the allowed proportion deviation and none deviate by more than twice the proportion shown. It was calculated on an electronic weighing balance.

Friability:

The friability of the tablet can determined using Roche Friabilator. It is expressed percentage (%). 10 tablets were at first weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 minutes. The tablets were weighed again. And the % friability was calculated as.

$$\text{Friability} = \frac{[WO - W]}{WO} \times 100$$

Where, WO = Initial weight of tablet.

W = after test weight of tablet.

Disintegration Test:

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

In-vitro Release:

Drug release from liquid solid tablets was determined by using dissolution test apparatus United States Pharmacopoeia (USP) type II (paddle). 5ml aliquots of sample were withdrawn each time at suitable time

intervals (5, 10, 15, 20, 25, 30, 45 and 60 minutes.) and replaced with fresh medium. After withdrawing, samples were filtered and analyzed after appropriate dilution by appropriate analytical method. The concentration was calculated using standard calibration curve.

Uniformity of Drug content:

The drug content can be determined by triturating sufficient amount of tablets and powder equivalent to average weight was added in 100 ml of suitable buffer solution. Followed by stirring for 30 min. Dilute suitably and the absorbance of resultant solution was measured spectrophotometrically¹⁸.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) is performed in order to assess the thermo tropic properties and the thermal behaviors of the drug, excipients used in the formulation of the liquid solid system. Complete disappearance of characteristic peaks of drug indicates the formulation of the drug solution in the liquid solid powder system, i.e., the drug is molecularly dispersed within the liquid matrix¹⁹.

Fourier Transform Infrared Spectroscopy (FTIR)

These studies are performed to estimate the chemical interactions between excipients and drug. If there's the presence of characteristic peaks and absence of additional peaks in formulation indicates that there are not any chemical interactions.

Powder X-ray Diffraction (PXRD)

The disappearance of characteristic peaks and holding of additional peaks of carriers within the liquid solid formulation is observed. It indicates that drug converted to amorphous form or to stabilized form²⁰.

APPLICATIONS OF LIQUID-SOLID COMPACTS²¹

- ❖ Rapid release rates are obtained in liquid solid formulations.
- ❖ Liquid solid compact technology is a powerful tool to improve bioavailability of water insoluble drugs. Several water insoluble drugs on dissolving in different non-volatile solvents have been formulated into liquid solid compacts.
- ❖ These can be powerfully used for water insoluble solid drugs or liquid lipophilic drugs.
- ❖ Sustained release of drugs which are water soluble drugs such as propranolol hydrochloride has been obtained by the use of this technique.
- ❖ Solubility and dissolution enhancement.
- ❖ Flowability and compressibility.
- ❖ Designing of controlled release tablets.
- ❖ Application in probiotics.

ADVANTAGES OF LIQUISOLID SYSTEMS ²²

- ❖ A countless number of slightly and very slightly water-soluble and practically water-insoluble liquid and solid drug can be formulated into liquisolid systems using the new formulation-mathematical mode
- ❖ Number of water-insoluble solid drug can be formulated into liquisolid systems.
- ❖ This technique is successfully applied for low dose water insoluble drug.
- ❖ Lower production cost than that of soft gelatin capsules.
- ❖ Drug dissolution from liquisolid compact is independent to the volume of dissolution media.
- ❖ Maximum of liquid or solid 'water-insoluble drug' may be formulated into immediate release or sustained release 'Liquisolid compact'
- ❖ 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.
- ❖ Increase bioavailability as compared to conventional tablets.
- ❖ Drug release can be modified using proper formulation ingredients.

LIMITATIONS ²³

- Not applicable for the formulation of high dose insoluble drugs.
- If more amount of carrier is added to produce free flowing powder, the tablet weight increases to more than one gram which is difficult to swallow.
- Suitable compression properties might not be achieved since throughout compression liquid drug may be squeezed out of the liquid-solid tablet resulting in tablets of inadequate hardness.
- Introduction of this method on industrial scale and to overcome the problems of mixing small quantities of viscous liquid solutions onto large amounts of carrier material may not be feasible.

CONCLUSION

In conclusion, the liquisolid system is that the new technique for the formulation of water insoluble drugs to improve their aqueous solubility, absorption still as dissolution rate, which leading to improvement of bioavailability of drugs as compared to conventional directly compressed tablets. Liquisolid formulations were designed to contain liquid medications in powdered form. The technique is also used hydrophilic carries in liquisolid systems. Therefore, increase the wetting properties and surface area of drug particles, and hence improve the dissolution profiles and might be oral bioavailability of the drug.

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