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LIQUISOLID TECHNOLOGY: A REVIEW

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ABSTRACT
The liquisolid (LS) technique is a novel approach for delivery of drugs through the oral route. This technique is suitable for poorly soluble or water insoluble drugs, highly permeable drugs (BCS Class II drugs) and also for immediate or sustained release formulations. The design of liquisolid systems are mainly intended for enhancement of solubility, dissolution rate and bioavailability of poorly water-soluble and highly lipophilic drugs. Improvement in bioavailability may be due to increased surface area, increased aqueous solubility and increased the wettability of the drug. Liquisolid technique also has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems. Overall, liquisolid technique is a most promising and novel technique for enhancing the dissolution and bioavailability of poorly water soluble drugs and sustaining drug release from tablet matrices. The current review mainly focuses on different carriers, solvents and coating materials employed in liquisolid technique. Literature reports on the applicability of liquisolid compact techniques over a wide range of pharmaceutical formulations are also explicated.

KEYWORDS: Bioavailability, Wettability, Carrier and Sustained Release.

INTRODUCTION
Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Poorly water soluble drugs will be inherently released at a slow rate owing to their limited dissolution rate within the gastrointestinal tract (GIT) contents. One challenge for poorly water soluble drugs is to enhance the rate of dissolution. Various techniques have been employed to formulate oral drug delivery system that would enhance the dissolution profile.[1] Solid dispersions, micronization, use of mesoporous silica carriers, ball milling technique, use of complexing agents, crystal engineering, solubilization by surfactants and liquisolid (LS) technique developed. These techniques take advantage of the increased dissolution rate resulting from the addition of a solubilizing agent, particle size reduction or the drug being in an already dissolved or amorphous state.

LS technique has been identified as a promising technique to improve the dissolution rate of poorly water soluble drugs.[2] When properly formulated, LS powder blends possess acceptable flowability and compressibility properties. They are prepared by simple blending with selected powder excipients referred to as the carriers and the coating materials. This technique was successfully applied for low dose poorly water soluble drugs. Drug can be present in a completely or partially dissolved state in the LS formulation. The LS formulation can then facilitate the release of this drug by two mechanisms: (1) Already dissolved drug only need to diffuse out of the formulation and (2) the liquid component of the formulation act as a solubilizing aid to facilitate the wetting and dissolution of undissolved particles. Since dissolution of a non polar drug is often the rate limiting step in gastrointestinal absorption, better bioavailability of an orally administered poorly water soluble drug is achieved when the drug is formulated using a LS system**.**

Advantages
1. Poor water soluble or water insoluble drugs can be formulated into LS systems.
2. Better availability of an orally administered poorly water soluble drugs.
3. LS tablets or capsules of poorly water soluble drugs exhibit enhanced *in vitro* and *in vivo* drug release.
4. Can be applied to formulate liquid medications such as oily liquid drugs.
5. Enhanced bioavailability can be obtained as compared to conventional tablets.

6. Drug release can be modified using suitable formulation ingredients.
7. Can be used in controlled drug delivery and zero-order release can be obtained.
8. Capability of industrial production is also possible.
9. Production cost is lower than that of soft gelatine capsules.

Limitations

1. This technique is only for slightly / very slightly water soluble and practically water insoluble drugs.
2. In LS formulation, high levels of carrier and coating materials should be added. This will increase the weight of tablets to above one gram which makes them difficult to swallow.
3. The LS systems have drug loading capacities and they require high solubility of drug in non-volatile liquid vehicles.

Classification of Ls Systems

The term LS systems refers to the 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, non-adherent, free flowing and readily compressible powder admixtures by blending with the selected carrier and coating materials. Based on the type of liquid medication encapsulated, LS systems may be classified into three subgroups: (1) Powdered drug solutions, (2) powdered drug suspensions and (3) powdered liquid drugs. Simultaneously, based on the formulation technique used, LS systems may be classified into two categories namely: (1) LS compacts and (2) LS microsystems.

The term **LS compacts** refers to immediate or sustained release tablets or capsules prepared, combined with the inclusion of appropriate excipients required for tableting or encapsulation, such as lubricants and for rapid or sustained release action, such as disintegrants or binders, respectively.

The term **LS microsystems** refers to capsules prepared by combining the drug with the carrier and the coating materials with inclusion of an additive in the liquid medication wherein the resulting unit size may be as much as five times that of LS compacts.[3]

EXCIPIENTS USED IN PREPARATION OF LS SYSTEMS

Non-volatile Solvents

With the LS technology as described by Spireas, a liquid may be transformed into free flowing, readily compressible and apparently dry powder by simple blending with selected excipients such as the carriers and coating materials. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile solvents is incorporated into the porous carrier material. Inert, preferably water-miscible, not highly viscous, non-toxic organic solvents with high boiling point such as propylene glycol (PG), liquid polyethylene glycols (PEG), glycerine and polysorbates are best suitable as liquid vehicles.[4] 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.

Non-volatile solvents enhance the solubility of poorly water soluble drugs by formation of micelles and act as dispersants. For immediate release LS compacts, the selection of solvent is based on high drug solubility and for sustained release, solvents with least solubilizing capacity is selected. Since there are no specific non-volatile liquid vehicles used in the preparation of LS compacts, different non-aqueous solvents have been used as non-volatile liquid vehicles in the preparation of immediate release and sustained release LS formulations with different drugs. So, selection of non-volatile solvent in LS technique is important to obtain immediate or sustained release formulation.[5]

Propylene glycol (PG), an inert solvent miscible with water is a suitable liquid vehicle for LS systems. It is not highly viscous (dynamic viscosity: 58.1 cp at 20 °C) and has a high boiling point (188 °C). PG is used in a wide variety of pharmaceutical formulations and is generally regarded as a relatively non-toxic material.[5] PG was successfully used as non-volatile solvent in LS preparation of drugs such as bromhexine hydrochloride, pioglitazone hydrochloride[6], to name a few.

Carrier materials

In LS approach, the carrier material plays as a major role in obtaining the dry form of the powder from the liquid medication. Each carrier has its unique property. Selection of the carrier will depend upon its liquid holding capacity, the flowability of the powder and which carrier requires less compression force.[7] The particles of the carrier materials are compression enhancing, relatively large, preferably porous particles possessing sufficient absorption property which contributes in liquid absorption, *e.g.* various grades of microcrystalline cellulose (MCC), starch, lactose, sorbitol, dibasic calcium phosphate (DCP), etc.

Microcrystalline cellulose (MCC) is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications. The specific surface areas and particle sizes of carrier materials are important parameters for the optimization of LS systems.

MCC is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes. In addition to its use as a carrier

material in LS preparation of drugs such as furosemide, pioglitazone hydrochloride[8] to name a few.

Coating materials

The particles of the coating materials are flow enhancing, highly adsorptive particles, *e.g.* silica of various grades like medium surface fumed silica, colloidal silicon dioxide (CSD), synthetic amorphous silica, calcium silicate (CS), magnesium aluminometasilicate (MAMS). These particles contribute in covering the wet carrier particles and displaying a dry looking powder by adsorbing any excess liquid. The coating material is required to cover the surface and so maintain the powder flowability.[9]

Colloidal silicon dioxide (CSD), a submicroscopic fumed silica is a suitable coating material for LS systems. Its specific surface area is 100–400 m2/g depending on grade. The specific surface area of Aerosil® 200 is 200 ± 25 m2/g. Primary particle size is 7–16 nm. Aerosil® forms loose agglomerates of 10–200 µm. Griseofulvin is an antifungal drug which has very low solubility in water. The LS compacts of griseofulvin were prepared using colloidal silica as coating materials.[10]

Calcium silicate (CS) has large micropores and excellent tabletability, also leads to a physical stabilization of amorphous drugs with enhanced drug release. CS possesses many intraparticle pores on its surface. Moreover, it has been shown that this silicate is also suitable for adsorption of liquid. It can absorb up to 2.5 times its weight of liquids and still remain a free flowing powder. CS is used as coating material in LS preparation of some drugs. Repaglinide is widely used for the treatment of diabetes. It is a poorly water soluble drug which has poor absorption in the upper intestinal tract and has a very low bioavailability. The LS compacts of repaglinide were prepared using CS as a coating material.[11]

Disintegrants

Disintegrants indirectly affect the dissolution parameter since the immediate next step is dissolution. To aid dissolution, tablet formulations generally require rapid disintegration, which can be facilitated by the addition of superdisintegrants. Once a tablet disintegrates, the solubility properties of the drug, either alone or assisted by other formulation ingredients, determine the drug's subsequent dissolution rate and extent of release. The solubility properties of water-soluble drugs result in rapid and high-level drug release, but with poorly water soluble drugs, other ingredients in the formulation, including the disintegrant, play a key role in determining the drug dissolution characteristics exhibited by the finished formulation. Sodium starch glycolate (SSG), croscarmellose sodium (CCS), pregelatinized starch, crospovidone (CP) etc. are most commonly used disintegrants.

Sodium starch glycolate (SSG) is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct compression or wet granulation processes. The mechanism by which disintegration action takes place is rapid absorption of water and swell leading to an enormous increase in volume of granules which result in rapid and uniform disintegration. The higher dissolution rates observed with superdisintegrants may be due to rapid disintegration and fine dispersion of particles formed after disintegration. SSG is successfully used as disintegrant in LS preparation of drugs such as pioglitazone hydrochloride[6] etc.

Drug candidates: LS technique has been successfully employed to improve the dissolution rate of poorly water soluble or water insoluble drugs which belong to Biopharmaceutical Classification System (BCS) Class II or IV.

Drug	Therapeutic class / BCS class
Candesartan cilexetil	Antihypertensive/ Class II
Escitalopram oxalate	Antidepressant/ Class II
Zetimibe	Lipid lowering agent/ Class II
Nifedipine	Vasodilator/Class II
Pioglitazone HCl	Antidiabetic/Class II
Rifampicin	NSAID/Class II
Rosuvastatin	Cholesterol lowering

Liquid Loading Capacity of Powders

To calculate the required amounts of powder excipients (carrier and coating materials) a mathematical approach for the formulation of LS systems has been developed by Spireas.[12] This approach is based 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 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-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 leaking out during compression. The compactability may be determined by the so-called “pactisity” 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 desired and thus preselected flow and compaction properties which must be met by the final LS formulation.

Depending on the excipient ratio (R) of the powder substrate an acceptably flowing and compressible LS 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 (Lf)" and is defined as the ratio between the weights of liquid formulation (W) and the carrier material (Q) in the system:

$$Lf = W / Q$$

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

$$R = Q / q$$

The Lf that ensures acceptable flowability (ΦLf) can be determined by:

$$\Phi Lf = \Phi + \varphi \cdot (1/R)$$

Where Φ and φ are the Φ-values of the carrier and coating materials, respectively, Similarly, the Lf for production of LS systems with acceptable compactability (ΨLf) can be determined by:

$$\Psi Lf = \Psi + \psi \cdot (1/R)$$

Where Ψ and ψ are the Ψ-numbers of the carrier and coating materials, respectively.

The optimum liquid load factor (L0) required to obtain acceptably flowing and compressible LS systems are equal to either ΦLf or ΨLf whichever represents the lower value.

As soon as the L0 is determined, the appropriate quantities of carrier (Q0) and coating (q0) material required to convert a given amount of liquid formulation (W) into an acceptably flowing and compressible LS system may be calculated as follows

$$Q0 = W / L0$$

And

$$q0 = Q0 / R$$

The validity and applicability of the above mentioned principles have been tested and verified by producing LS compacts possessing acceptable flow and compaction properties.

Preparation and Optimization of Ls Systems

The new LS technique includes 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. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating material particles. The coating material provides the conversion from a wet to a dry surface and gives the LS system desirable flow properties.

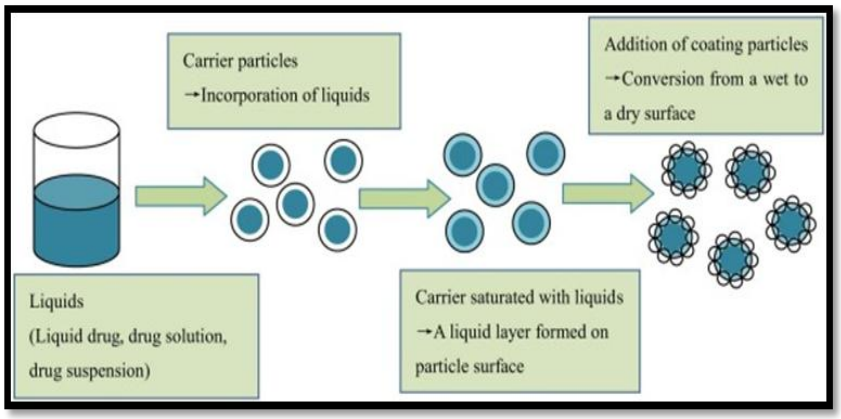

Fig 1: Schematic representation of liquisolid systems.

To prepare a LS system, first the drug is dispersed or dissolved in the non-volatile solvent, the carrier and coating material mixture in a ratio is then added to the liquid medication. The liquid medication is now converted to powder form. Various excipients such as disintegrants and lubricants may be added to the LS compacts (Figure 1). Before preparing into compacts pre compression studies have to be performed.

Drug Release Mechanism From Liquisolid

Three main mechanisms are involved for enhancement of drug release from liquisolid systems are as follows

Increased drug surface area: In liquisolid system the surface area of drug available for drug release is much greater than drug particles within directly compressed tablets because the drug present in the liquisolid system is completely dissolved in the liquid vehicle and present in the powder substrate still in a solubilized, molecularly dispersed state. 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 decreases. In the liquid solid formulation, the release rate of the drug is directly proportional to the fraction of the molecularly dispersed drug (FM).[12] Spireas defined FM as the ratio of the drug solubility (Sd) and the actual drug concentration (Cd) in the liquid vehicle.

Fig. 2: Increased drug surface area.

Increased aqueous solubility of the drug: The solubility of the drug may be increased with liquisolid system. In fact, the 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. If the small amount of liquid vehicle acts as a co-solvent in liquisolid system this less amount of vehicle is sufficient to increase the aqueous solubility of the poorly water soluble drug.[12]

Fig. 3: Increased aqueous solubility of drug.

Increased wettability: The non-volatile solvent present in the liquisolid system provides wetting of drug particles by decreasing interfacial tension between tablet surface and dissolution medium so the contact angle of liquisolid system is lower when compared to the conventional formulation thus improved wettability.[12]

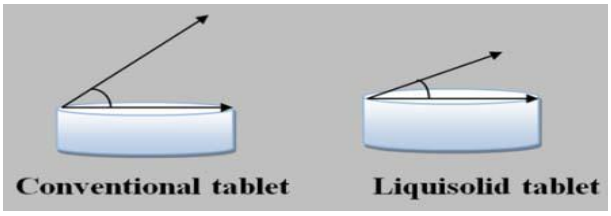

Fig. 4: Contact angle of conventional and liquisolid tablets.

CHARACTERIZATION OF LS SYSTEMS

Preformulation studies

Before formulating the LS systems preformulation studies should be performed first, these include; solubility studies, determination of angle of slide, calculation of liquid load factor, determination of flowable liquid retention potential and LS compressibility test.

Solubility studies

To select the best non-volatile solvent for dissolving or suspending the drug in liquid medication, solubility studies are carried out by preparing saturated solutions of drug by adding excess of drug into non-volatile solvents and shaking them on shaker for specific time period under constant vibration. After this, the solutions are filtered and analyzed.

Determination of angle of slide

Powder excipient or its mixture is accurately weighed and placed at one end of a metal plate (with a polished surface). This end is raised gradually until the plate makes an angle with the horizontal at which the powder is about to slide. This is called the angle of slide (Θ). It is taken as a measure for the flow properties of powders. An angle of slide corresponding to 33^0 is regarded as optimal flow behavior.[13]

Calculation of liquid load factor: Liquid load factor (Lf) is defined as the ratio of weight of the liquid medication (W) to weight of the carrier material (Q) and it can be determined by using the following formula.

$$Lf = W / Q$$

W= Weight of liquid medication
Q= Weight of carrier material

Determination of flowable liquid retention potential

The term "flowable liquid retential potential" (Φ value) of a powder material describes its ability to retain a specific amount of liquid while maintaining good flow properties. The Φ value is defined as the maximum weight of liquid that can be retained per unit weight of the powder material in order to produce an acceptably flowing liquid/powder admixture.[14]

LS compressibility test

LS compressibility test is used to determine Φ values and involves steps such as preparing carrier-coating material admixture systems, preparing several uniform liquid or powder admixtures, compressing each liquid or powder admixtures to tablets, assessing average hardness, determination of average liquid content of crushed tablets, as well as determining plasticity, sponge index and Φ value and Lf value.[15]

Evaluation of LS systems

Pre-compression evaluations

In order to ensure the suitability of the selected excipients, Fourier Transformed Infrared Spectroscopy (FTIR) and Scanning Electron Microscopy (SEM) studies are performed. In addition, flowability studies are also carried out to select the optimal formula for compression.

Fourier Transformed Infrared Spectroscopy (FTIR)

FTIR studies are performed to determine the chemical interaction between the drug and excipients used in the formulation.[16]

Scanning Electron Microscopy (SEM)

SEM is utilized to assess the morphological characteristics of the raw materials and drug-carrier systems.[17]

Flow behaviour

Flow property of a powder is of major importance in the production of tablet dosage forms in order to attain a uniform feed and reproducible filling of tablet dies. Angle of repose, Carr's index, Hausner's ratio and compressibility index are used in order to ensure the flow properties of the powders.[18]

Post-compression evaluations

The formulated LS systems are evaluated for post-compression parameters such as;

1. Weight variation
2. Drug content / content uniformity
3. Hardness
4. Thickness and diameter
5. Friability
6. Disintegration
7. In vitro dissolution studies
8. In vivo evaluation
9. Stability studies

Evaluation parameters of the tablets mentioned in the Pharmacopoeias need to be assessed, along with some special tests are discussed here:

Sustained Release With LS Formulations

LS technique is a novel method that can change the dissolution rate of drugs.[19] If hydrophobic carriers such as acrylic resin polymers (Eudragit® RL and RS) are used instead of hydrophilic carriers in LS systems, sustained release formulations can be obtained. Some drugs have been formulated as LS sustained release systems. Different liquid vehicles, carriers and coating materials were used to formulate these drug delivery systems.

CONCLUSION

Enhancement of the solubility and dissolution rate of poorly water-soluble drugs is still a major challenge for pharmaceutical scientists. At the same time sustaining the drug release from dosage forms helps in a better and proper utilization of the drug. Both of these applications are major requisites for enhancement of drug bioavailability. Finally, from this review, it can be concluded that, among the various techniques involved for the drug solubility enhancement, liquisolid technology is one of the most promising approaches. It is found to be a multipotential and promising technology for dosage form development, because of the process simplicity, low economic inputs during production and possible industrial feasibility due to the good flow and compaction characteristics of liquisolid formulations.

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