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LIQUISOLID: A NOVEL SOLUBILITY ENHANCEMENT TECHNIQUE

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ABSTRACT

Liquisolid (LS) technique is a novel concept in which drug is loaded with liquid vehicles like non volatile solvents it improves the wettability and dispersion of drug in the formulation and leads to enhance solubility. 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.

INTRODUCTION

There are various drugs present in the market with poor solubility which leads to poor dissolution & bioavailability so thereby solubility is one of the rate limiting factors in the development of new drugs. 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

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: 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[5]. 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[6].

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) [8], etc.

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)[9]. 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[10].

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[11].

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.

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.

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

$$Q0 = W / L0 \text{ And } q0 = Q0 / R$$

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.

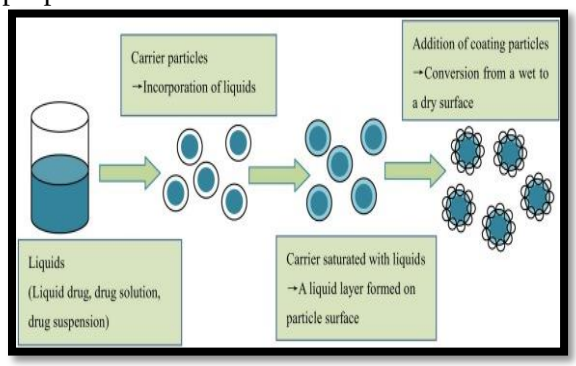

Fig.-1: Schematic representation of liquisolid systems

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.

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].

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].

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 analyze

Table No: 1 Examples of Drugs with different Non solvent, carriers and coating materials:

S. No	Drug	Carrier	Coating material	Non-solvent	Reference
1	Telmistran	Avicel pH 102	Aerosil	PEG 200	Naveen chella *et al.*, 2014.[20]
2	Valstran	Avicel pH 102	Aerosil 200	Propylene glycol	Hitesh jain *et al.*, 2014.[21]
3	Olmesartan Medoxomil.	Neusilin Avicel pH 102	Aerosil	Glyceryl mono caprylate	T.Prajapati *et al.*, 2013.[22]
4	Indomethacin	MCC Avicel	Silica	PEG 200 Glycerine	Majidsaeedi *et al.*, 2009.[23]
5	Glipizide	Avicel PH 102	Aerosil 200 & TGG	PEG 200,PEG 400,pH 7.4	Hitendras *et al.*, 2011.[24]
6	Nifedipine	MCC	Collodial silica Dioxide	PEG 400	Arun Raj.R *et al.*, 2013.[25]
7	Spironolactone	MCC Avicel pH 102	Silica	Glycerine PEG 400	Sadeghi Ghadi *et al.*, 2015[26]
8	Clofibrate	MCC, Starch Lactose	Silica	Propylene glycol	Brahmaiah *et al.*, 2015.[27]
9	Fenofibrate	Avicel pH 102	Aerosil 200	PEG 600	Patel *et al.*, 2014[28]
10	Rosuvastatin calcium	MCC	Silica	Propylene glycol PEG 400 Tween 80	V.j Kapure *et al.*, 2013[29]
11	Gliclazide	Avicel 102	Aerosil 200	PG PEG400 PG+PEG400	Mahajan Hitendras *et al.*, 2014.[30]
12	Ketoprofen	Cellulose Starch Lactose	Silica powder	PEG 400 Tween 40	Vittal *et al.*, 2012[31]

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 behaviour[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 behavior: 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[19]; Weight variation, Drug content / content uniformity, Hardness, Thickness and diameter, Friability, Disintegration, *In vitro* dissolution studies, *In vivo* evaluation and Stability studies.

CONCLUSION

The 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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