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Review Article

A REVIEW ON LIQUISOLID TECHNOLOGY

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ABSTRACT

This review discusses, out of several techniques available, liquisolid system to improve dissolution rate of water insoluble drugs and to enhance dissolution rate of water soluble drugs. The limited solubility of drugs is the challenging issue for industry during development of the ideal solid dosage unit. Liquisolid technique is a new and promising method that can change the dissolution rate of water insoluble drugs. The technique is based upon the admixture of drug loaded solutions (or) liquid drug with appropriate carrier (microcrystalline cellulose, starch, lactose) and coating material (silica gel). The selection of non-toxic hydrophilic solvent, carrier, coating excipients and its ratios are independent of the individual chemical entities. Liquid drugs can be mixed directly with carriers to produce liquisolid systems. Liquisolid systems can be used to either enhance or retard drug release.

Keywords: Liquisolid compacts, Dissolution rate, Liquid loading factors and poorly water-soluble drugs.

INTRODUCTION

Bioavailability is the key determinant of a drug for its therapeutic effectiveness, which in turn depends upon the solubility of that drug in gastro intestinal fluid. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response [1]. Poorly water soluble drugs will be inherently released at a slow rate owing to their limited solubility within the GI contents. The dissolution rate is often the rate determining step in the drug absorption. The challenge for poorly water soluble drugs is to enhance the rate of dissolution. This in turn subsequently improves absorption and bioavailability .Formulation methods targeted at dissolution enhancement of poorly soluble substances are continuously introduced.

The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and low medicine production costs. In order for a drug to be absorbed into the systemic circulation following oral administration, the drug must be dissolved in the gastric fluids. The active pharmaceutical ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. For hydrophobic drugs, the dissolution process acts as the rate-controlling step and, which determines the rate and degree of absorption. Consequently, many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract ,Thus, one of the major challenges in drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water. In addition, up to 50% of orally administered drug compounds suffer from formulation problems related to their low solubility and high lipophilicity [6,7].

Bioavailability of poorly water-soluble drugs is limited by their solubility and dissolution rate [2,3]. Several studies have been carried out to increase the dissolution rate of drugs by decreasing the particle size, by creating Nano-and micro particles. However, the fine drug particles have high tendency to agglomerate due to van-der Waals attraction or hydrophobicity, which result in a decrease in surface area over time. Another way of increasing the dissolution rate is adsorption of the drug onto a high-surface-area carrier. In this technique, the drug is dissolved in an organic solvent followed by soaking of the solution by a high-surface-area carrier such as silica. Here, agglomeration of the drug particles is prevented due to the binding of drug to the carrier. However, due to the presence of the residual solvent in the drug formulation, it is disadvantageous to use toxic solvents.

Over the years, various techniques have been employed to enhance the dissolution profile and, in turn, the absorption efficiency and bioavailability of water insoluble drugs and/or liquid lipophilic medications. There are certain method available such as. [4]

1) Pharmaceutical approach

Involves modification of formulation. E.g modification of formulation manufacturing process.

2) Pharmacokinetic approach

Pharmacokinetic of drug is altered e.g. pharmacokinetic is altered by modifying its chemical structure.

3) Biologic approach

Route of administration changed e.g oral to parenteral.

Pharmaceutical approaches to enhance dissolution of drugs.

Micronization: In which particle size of solid drug is reduced to 1to 10µ by spray drying or fluid energy mill example: sulpha drugs.

Use of surfactants: surface active agents enhance dissolution rate by promoting Wetting and penetration of dissolution fluid into solid drug particles example steroids like spironolactone.

Use of salt forms: salts have improved solubility and dissolution characteristics in comparison to the original drug. Example salt of basic drug like Atropine is more soluble than parent drug.

Alteration of pH of the Drug Microenvironment: achieved in two ways in situ salt formation and addition of buffers to the formulation e.g buffered aspirin tablets.

Use of metastable polymorphs: Metastable polymorphs are more soluble than the stable polymorphs of drug that exhibits polymorphism, e.g chloramphenicolpalmitate.

Solute – solvent complexation: solvates of drugs with organic solvents generally have higher aqueous solubility than the original drug, e.g. 1:2 grieofulvinbenzene solvate.

Solvent deposition: In this method poorly aqueous soluble drug is dissolved in organic solvent and deposited on an inert hydrophilic, solid matrix, e.g. nifedipine is dissolved in alcohol and deposited in starch by evaporation of solvent.

Selective adsorption on insoluble carriers: A highly active adsorbent can enhance the dissolution rate, e.g. bentonite.

Solid solution

Use of solid solution: solid solution is binary system comprising of solid solute molecularly dispersed in a solid solvent.

Use of eutectic mixtures: These system are also prepared by fusion method it is slightly differ from solid solution in that fused melt of solute –solvent show complete miscibility but negligible solid –solid solubility. Use of solid dispersion: These are generally prepared by solvent or co -precipitation method where both guest solute and the solid carrier solvent are dissolved in common volatile liquid such as alcohol. The liquid removed by evaporation under reduced pressure or by freeze drying which result in amorphous precipitation of guest in crystalline carrier.

Molecular encapsulation with cyclodextrins

The beta and gamma cyclodextrins and several of their derivatives are unique in having the ability to form molecular inclusion with hydrophobic drugs having poor aqueous solubility. These cyclodextrin molecule are versatile in having a hydrophobic cavity of size suitable enough to accommodate hydrophilic drug as a guests; the outside of the host molecule is relatively hydrophilic. Thus the molecularly encapsulated drug has greatly improved aqueous solubility and dissolution rate. However, among them, the technique of ‘‘liquisolid compacts” is one of the most promising technique. Low cost, simple formulation technique and capability of industrial production serve to be advantages of this technique

INTRODUCTION TO LIQUISOLID SYSTEM [1,2,14,17]

The poor dissolution rate of water insoluble drugs is still a substantial problem confronting the pharmaceutical industry. A great number of new and possibly, beneficial chemical entities do not reach the public merely because of their poor oral bioavailability due to inadequate dissolution. Over the years, various solid dosage formulation techniques, to enhance the dissolution of poorly soluble substances, have been introduced with different degrees of success.

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 especially those belonging to the biopharmaceutical classification system (BCS) class II and IV, dissolve slowly, poorly and irregularly, and hence pose serious delivery challenges, like incomplete release from the dosage form, poor bioavailability, increased food effect, and high inter-patient variability.

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 wetting 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.

In this case, even though the drug is in a solid dosage form, it is held within the powder substrate in solution or, in a solubilized, almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties.

Definition [9]

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) and (Class IV) drugs 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 wetting 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. In this case, even though the drug is in a solid dosage form, it is held within the powder substrate in solution or, in a solubilized, almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties.

Historical development

Historically, liquisolid compacts are descendants of ‘powdered solutions, an older technique which was based on the conversion of a solution of a drug in a nonvolatile solvent into a dry-looking, no adherent powder by mainly adsorbing the liquid onto silica’s of large specific surfaces. Such preparations, however, have been investigated for their dissolution profiles while being in a powder dispersion form and not as compressed entities, simply because they could not be compressed into tablets. In later studies on powdered solutions, compression enhancers such as microcrystalline cellulose were added in such dispersions in order to increase the compressibility of the systems.

In these studies, however, large quantities of silicas were still being used, and the flow and compression properties of the products were never validated and standardized to industrial specifications and requirements. Specifically, when such modified powdered solutions were compressed into tablets, they presented significant ‘liquid squeezing out’ phenomena and unacceptably soft tablets, thereby hampering the industrial application of such systems

COMPONENTS OF LIQUISOLID SYSTEM [1,3,24,26]

The major formulation components of liquisolid compacts are

Carrier material

These are compression-enhancing, relatively large, preferably porous particles possessing a sufficient absorption property which contributes in liquid absorption.

E.g. various grades of cellulose, starch.

Coating material

These are flow-enhancing, very fine (10 nm to 5,000 nm in diameter), highly adsorptive coating particles (e.g., silicaof various grades like Cab-O-Sil M5, Aerosil 200, Syloid244FP etc.) contributes in covering the wet carrier particles and displaying a dry-looking powder by adsorbing any excess liquid.

Non-volatile solvents

Inert, high boiling point, preferably water-miscible and nothighly viscous organic solvent systems e.g., propyleneglycol, liquid polyethylene glycols, poly sorbates, glycerin N, N-dimethylacetamide, fixed oils, etc. are most suitable as vehicles.

Disintegrants

Most commonly used disintegrant is sodium starch glycolate.

CLASSIFICATION OF LIQUISOLID SYSTEM [3],

A. Based on the type of liquid medication contained therein, liquisolid systems may be

Classified into three subgroups:

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

B. Based on the formulation technique used, liquisolid systems may be classified into two Categories:

1. Liquisolid compacts

2. Liquisolid Microsystems

Liquisolid compacts: refers to immediate sustained-release tablets or capsules that are

Described under “liquisolid systems”.

Liquisolid Microsystems: refers to capsules prepared by “liquisolid systems” plus the

Inclusion of an additive resulting in a unit size that may be as much as five times less than that of a liquisolid compact.

CONCEPT OF LIQUISOLID SYSTEM

When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior as cellulose, both absorption and adsorption take place; i.e., the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics .

In liquisolid systems the drug is already in solution in liquid vehicle, while at the same time, it is carried by the powder particles (microcrystalline cellulose and silica).Thus, due to significantly increased wetting 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. Since dissolution of a non-polar drug is often the rate limiting step in gastrointestinal absorption, better bioavailability of an orally administered water-insoluble drug is achieved when the drug is already in solution, thereby displaying enhanced dissolution rates. That is why soft gelatin elastic capsules containing solutions of such medications demonstrate higher bioavailability when compared to conventional oral solid dosage forms. A similar principle underlies the mechanism of drug delivery from liquisolid compacts and is chiefly responsible for the improved dissolution profiles exhibited by these preparations.

THEORETICAL ASPECTS OF LIQUISOLID SYSTEMS [16]

For getting good flow behavior and compressibility of liquisolid systems a mathematical model designed by Spireas et al. was used as formulation design model for the liquisolid tablets. Prerequisites for this include suitable drug candidate, suitable non-volatile solvent, carrier and coating materials. The amounts of excipients (carrier and coating materials) used to prepare liquisolid compacts depend on the flowable liquid retention potential values (Φ-value) and the liquid loading factors (Lf).

Flowable liquid retention potential values (Φ- value)

The Φ-value of a powder is the maximum amount of a given non-volatile liquid that can be retained inside powder bulk (w/w) while maintaining acceptable flowability. Therefore, in order to calculate the required weight of excipients, we need to determine the liquid retention potential value for both carrier (ΦCA-value) and coating (ΦCO-value) materials for each formulation. These values are constant for the given vehicle/powder system.

Liquid loading factors (Lf)

It is defined as the weight ratio of the liquid formulation **(*W*)** and the carrier material (*Q*) in the system:

Lf* = *W/Q------ (1)

(W is the weight of the liquid medication (the drug + non-volatile liquid vehicle) and

Q is the weight of the carrier.)

Rrepresents the **ratio** between the weights of the carrier **(*Q*)** and the coating **(*q*)** material present in the formulation:

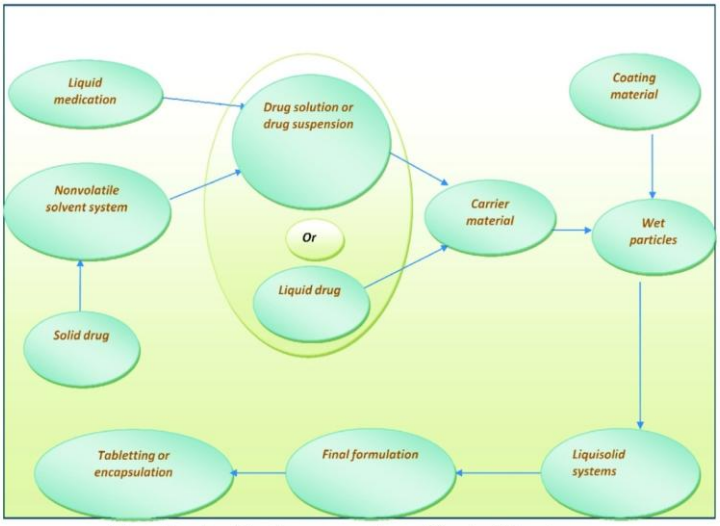
Then optimum weight of the coating material (q) could also be obtained (Equation 2).

R =Q/q------ (2)

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

Lf =Φ+ φ. (1/R) ----- (3)

By calculating Lf and W, we can calculate the amount of Q and q required for the liquisolid system.



Steps involved in the preparation of liquisolid systems

Fig.1: Schematic Diagram Of Liquisolid Preparation.[2]

MECHANISMS OF ENHANCED DRUG RELEASE FROM LIQUISOLID SYSTEMS [3]

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.

1. Increased drug surface area

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

2. 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 co solvent.

3. Improved wetting properties

Due to the fact that the liquid vehicle can either act as surface active agent or has a low surface tension, wetting of the liquisolid primary particles is improved (fig 2) Wettability of these systems has been demonstrated by measurement of contact angles and water rising times.

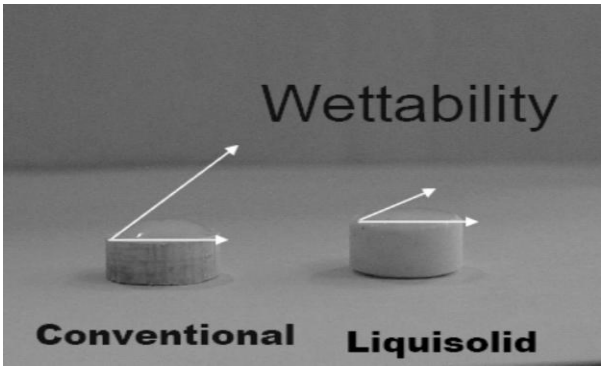


Fig. 2: wetting property of liquisolid system.

ADVANTAGES

Liquisolid tables have many advantages. These include:

- Liquisolid systems are low cost formulations than soft gelatin capsules.
- Drug release can be modified using suitable formulation ingredients
- 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.
- Several slightly and very slightly water-soluble and practically water-insoluble liquid and solid drugs can be formulated into liquisolid systems.
- Even though the drug is in a tablet or capsule form, it is held in a solubilized liquid state, which contributes to increased drug wetting properties, thereby enhancing drug dissolution [5].
- Rapid release liquisolid tablets or capsules of water insoluble drugs exhibit enhanced *In-vitro* and *in-vivo* drug release when compared to their commercial counter parts, including soft gelatin capsules preparation.
- Sustained release liquisolid tablets or capsules of water insoluble drugs exhibit constant dissolution rates (zero-order release) comparable only to expensive Commercial preparations that combine osmotic pump technology and laser-drilled tablets.
- Can be applied to formulate liquid medications such as oily liquid drugs.
- Better availability of an orally administered water insoluble drug.
- Production of liquisolid systems is similar to that of conventional tablets.
- Can be used for formulation of liquid oily drugs.
- Can be used in controlled drug delivery.

LIMITATIONS

- Not applicable for 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.
- Acceptable compression properties may not be achieved since during compression liquid drug may be squeezed out of the liquisolid tablet resulting in tablets of unsatisfactory hardness.

APPLICATIONS [3]

- Liquisolid 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 liquisolid compacts.
- Literature cites different drugs successfully incorporated into liquisolid compacts.
- Rapid release rates are obtained in liquisolid formulations.
- These can be efficiently 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 improvement

This technique was successfully applied for low dose water insoluble drugs. However, formulation of the high dose insoluble drugs as liquisolid tablets is one of the limitations of the liquisolid technique. In fact, when the therapeutic dose of drug is more than 50mg, dissolution enhancement in the presence of low levels of hydrophilic carrier and coating material is not significant But by adding some materials such as polyvinyl pyrrolidone(PVP) to liquid medication (micro systems), it would be possible to produce dry powder formulations containing liquid with high concentration of drug. By adding such materials to the liquid medication, low amount of carrier is required to obtain dry powder with free flowability and good compatibility.

Flowability and compressibility

Liquisolid compacts 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. Many grades of cellulose, starch, lactose, etc. can be used as carriers, where as silica of very fine particle size can be used as coating materials. In order to have acceptable flowability and compatibility for liquisolid powder formulation, high levels of carrier and coating materials should be added and that in turn will increase the weight of each tablet above 1 gm. which is very y difficult to swallow. Therefore, in practice it is impossible with conventional method to convert high dose drugs to liquisolid tablet with the tablet weight of less than 1 gm. In such systems, the drug existed in a molecular state of subdivision and systems were free flowing, non-adherent, dry looking powders. In further studies, compression enhancers were added to these powdered solutions like microcrystalline cellulose. However, the compression of these latter systems resulted in a significant 'Liquid Squeezing Out' phenomenon.

Bioavailability improvement

In the liquisolid and powdered solution systems the drug might be in a solid dosage form, it is held within the powder substrate in solution, or in a solubilized, almost molecularly dispersed state. Therefore, due to their significantly increased wetting properties and surface of drug available for dissolution, liquisolid compacts of water- insoluble substances may be expected to display enhanced drug release properties, and consequently, improved bioavailability.

CONCLUSION

Liquisolid technique is a new and promising method used to enhance dissolution rate of poorly water-soluble drugs (BCS Class II and IV Drugs). Since, the liquisolid tablets contain a solution of the drug in suitable solvent, the drug surface available for dissolution and wetting property of the drug tremendously increases. So the liquisolid tablets shows an enhanced drug release characteristics and, consequently, improved oral bioavailability

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