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Liquisolid Compacts of Active Pharmaceutical Ingredients: A Review

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Abstract:

The poor dissolution rate of water-insoluble drugs is still a substantial problem confronting the pharmaceutical industry. There are several methods used to increase the solubility of drugs, of those liquid-solid compact technique is a new and promising addition towards such a novel aim, that the solubility of the insoluble drug moiety is increased by the aid of non-volatile solvents and hence increasing the dissolution and bioavailability. The Liquisolid process is a novel and effective approach to improving solubility. Bioavailability relies on drug solubility. With the evolution of modern pharmaceutical products, solubility is a big problem for the pharmaceutical industry. One of the most daunting aspects of drug production remains the enhancement of oral bioavailability of poorly water-soluble drugs. A newer methodology "powdered solution technology" or "Liquisolid technology", has been applied to prepare water-insoluble drugs into rapid-release solid dosage forms. This method is efficient, economic, viable for industrial production, also useful in control drug delivery system. Hence due to above reasons Liquisolid technique is most efficient and novel approach for solubility enhancement. To prepare water insoluble drugs into rapid-release solid dosage forms, 'powdered solution technology' or 'Liquisolid technology' has been applied. This approach is reliable, cost-effective, viable for industrial production, and also useful in the drug delivery control system. Therefore, Liquisolid technique is the most effective and novel method for enhancing solubility due to the above factors.

Keywords: Liquid solid compacts, solubility, dissolution, bio availability Coating agents, Carriers, Liquisolid

NTRODUCTION

Bioavailability is the key determinant of a drug for its therapeutic effectiveness, which in turn depends upon the solubility of that drug in gastrointestinal fluid. Solubility is one of the important parameters to achieve the 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. Bioavailability of poorly water-soluble drugs is limited by their solubility and dissolution rate. Several studies have been carried out to increase the dissolution rate of drugs by decreasing the particle size, by creating nano and microparticles. However, the fine drug particles have a 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 the 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 the drug to the carrier. However, due to the presence of the residual solvent in the drug formulation, it is disadvantageous to use toxic solvents [2].

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. Nowadays, the synthesis of poorly soluble drugs increasing steadily. Therapeutic effectiveness of a drug depends upon the bioavailability which is dependent on the solubility and dissolution rate of drug molecules. Solubility is one of the important parameters to achieve the desired concentration of drug in systemic circulation for pharmacological response to be shown. The drugs which are poorly water soluble 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 these drugs is to enhance the rate of dissolution or solubility. This in turn subsequently improves absorption and bioavailability. Formulation methods targeted at dissolution enhancement of poorly soluble substances are continuously introduced [3]. Liquisolid system refers to formulations formed by conversion of liquid drugs, a drug suspension or drug solution in non-volatile solvents into non-adherent, free-flowing and compressible powder mixtures by blending the solution or suspension with selected carriers and coating materials. As large proportions of new drug candidates have a poor aqueous solubility, various formulation strategies were reported to overcome such a problem. Among these techniques is complexation with cyclodextrins, micronization, solid dispersion, co-precipitation and recently, the technique of 'liquisolid compacts'. Several studies have shown that the liquisolid technique is a promising method for promoting the dissolution rate of poorly water-soluble drugs [4]. The concept of ''liquisolid tablets'' was evolved from ''powdered solution technology'' that can be used to formulate ''liquid medication''. The term ''liquid medication'' refers to solid drugs dispersed in suitable non-volatile liquid vehicles. By simple mixing of such ''liquid medication'' with selected carriers and coating materials, dry-looking, non-adherent, free-flowing and readily compatible powder admixtures can be produced. Spireas and Bolton suggested that particles possess porous surface with high absorption properties may be used as the carrier material such as cellulose, starch and lactose. Increasing moisture content of carrier's results in decreased powder flowability. Coating material is required to cover the surface and so maintain the powder flowability. Accordingly, the coating material should be a very fine and highly adsorptive silica powders [5]. Liquisolid compacts are acceptably flowing and compressible powdered forms of liquid medications. The term liquid medication implies oily, liquid drugs and solutions or suspensions of water-insoluble solid drugs carried in suitable non-volatile solvent systems termed the liquid vehicles. Using this new formulation technique, a liquid medication may be converted into a dry-looking, non-adherent, free-flowing, and readily compressible powder by a simple blending with selected powder excipients referred to as the carrier and coating materials Various grades of cellulose, starch, lactose, and so on, may be used as the carriers, whereas very fine-particle-size silica powders may be used as the coating [or covering] materials. In liquisolid compacts, even though the drug is in a tabletted or encapsulated dosage form, it is held in a solubilized liquid state, which consequently contributes to increased drug wetting properties, thereby enhancing drug dissolution. Another advantage of liquisolid systems is that their production cost is lower than that of soft gelatin capsules because the production of liquisolid systems is similar to that of conventional tablets [6].

Historical development of Liquisolid Technique:

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, non adherent powder by mainly adsorbing the liquid onto silica 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 silica 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. Liquisolid compacts, on the other hand, are acceptably flowing and compressible powdered forms of liquid medications, and have industrial application. [7]In addition, the term 'liquid medication' does not only imply drug solutions, as in powdered solutions, but also drug suspensions, emulsions, or liquid oily drugs. Therefore, in contrast to 'powdered solutions', the term 'liquisolid compacts' is more general and it may encompass four different formulation systems namely,

Classification of Liquisolid systems:

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

The first two may be produced from the conversion of drug solutions or [e. g. prednisolone solution in propylene glycol] or drug suspensions [e. g. gemfibrozil suspension in Polysorbate 80], and the latter from the formulation of liquid drugs [e. g. clofibrate, liquid vitamins, etc.], into Liquisolid systems. Since non-volatile solvents are used to prepare the drug solution or suspension, the liquid vehicle does not evaporate and thus, the drug is carried within the liquid system which in turn is dispersed throughout the final product.

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

1. Liquisolid compacts
2. Liquisolid microsystems.

Liquisolid compacts are prepared for the development of tablets or capsules using the previously described process, while Liquisolid microsystems are based on a modern idea that uses similar technique combined with the addition of an additive, e.g., G., Polyvinylpyrrolidone [PVP], in the liquid drug incorporated in the carrier and coating materials to create an acceptably flowing admixture. The advantage stemming from this new technique is that the resulting unit size of Liquisolid microsystems may be as much as five times less than that of Liquisolid compacts[8].

Main components of Liquisolid system

Coating Material and Carrier Material: Coating material forms a uniform film around carrier particles. This prevents particle aggregation and reduces inter-particulate friction. This phenomenon improves flowability and gives a drylooking appearance to the Liquisolid by covering the wet carrier particles and absorbing any excess liquid. Usually, the coating materials are very fine. Example of coating material is colloidal silica of different grades similar to Aerosil 200. And the carrier material should have porous surface and closely matted fibres in its inertial. Carriers are involved in the liquid medication sorption process that improves the effective dissolution surface area. Example of coating material is colloidal silica of different grades similar to Aerosil 200. And the carrier material should have porous surface and closely matted fibres in its inertial. Carriers are involved in the liquid medication sorption process that improves the effective dissolution surface area. These help the compression as well. Carriers have a sufficient adsorption property due to relatively large, preferably porous particles and matted fibres contribute to the interior. E.g., Lactose and cellulose.

Components

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 [9], lactose [9], sorbitol [10] etc.

Coating material

These are flow-enhancing, very fine [10 nm to 5,000 nm in diameter], highly adsorptive coating particles [e. g., silica of various grades like Cab-O-Sil M5, Aerosil 200, Syloid 244FP etc.] contributes in covering the wet carrier particles and displaying a dry-looking powder by adsorbing any excess liquid [9-13].

Non-volatile solvents

Inert, high boiling point, preferably water-miscible and not highly viscous organic solvent systems e. g., propylene glycol, liquid polyethene glycols, polysorbates, glycerin, N, N-dimethylacetamide, fixed oils, etc. are most suitable as vehicles.

Disintegrants

Most commonly used disintegrant is sodium starch glycolate [Explotab13, Pumogel, etc.]

Lubricant

Most commonly used lubricant is magnesium state.

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 the drug is more than 50 mg, dissolution enhancement in the presence of low levels of hydrophilic carrier and coating material is not significant. But by adding some materials such as polyvinylpyrrolidone (PVP) to liquid medication (microsystems), it would be possible to produce dry powder formulations containing a liquid with a high concentration of the drug. By adding such materials to the liquid medication, low amount of carrier is required to obtain a dry powder with free flowability and good compatibility[14]

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, whereas silicas of very fine particle size can be used as coating materials. In order to have acceptable flowability and compactibility 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 difficult to swallow. Therefore, in practice, it is impossible with the conventional method to convert high dose drugs to a 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, on-adherent, dry looking powders. In further studies, compression enhancers were added to these resulted in a significant "Liquid Squeezing Out" phenomenon. [15]

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 the 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[16]

Limitations

1) Not applicable for the formulation of high dose insoluble drugs.
2) 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.
3) 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.
4) Introduction of this method on an 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 [17]

Evaluation of liquisolid granules[18]

Flow behaviour

The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to reduce high dose variations · Angle of repose, Carr's index and Hausner's ratio were used in order to ensure the flow properties of the liquisolid systems.

Angle of repose

This is the maximum angle possible between the surface of a pile of powder and the horizontal plane.10 gm of powder was allowed to flow by funnel from 4 cm of height from the base. The height of pile and diameter of the base was measured and calculate the angle of repose by the following the formula.

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

$$\theta = \tan^{-1} h/r$$

Where = angle of repose,

h = Height of the heap,

r = Radius of the heap.

Bulk density

An accurately weighed quantity of powder, which was previously passed through sieve # 40 [USP] and carefully poured into a graduated cylinder. Then after pouring the powder into the graduated cylinder, the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume measured was called as the bulk volume and the bulk density is calculated by following formula;

Bulk density = Weight of powder/Bulk volume.

Tapped density

After measuring the bulk volume the same measuring cylinder was set into tap density apparatus. The tap density apparatus was set to 300 taps drop per minute and operated for 500 taps. Volume was noted as [Va] and again tapped for 750 times and volume was noted as [Vb].

If the difference between Va and Vb not greater than 2% then Vb is to consider as final tapped volume. The tapped density is calculated by the following formula

Tapped density = Weight of powder/Tapped Volume.

Carr's index [compressibility index]

It is one of the most important parameters to characteristic the nature of powders and granules. It can be calculated from the following equation-

Carr's index = Tapped density-Bulk density/Tapped density X 100.

Hausner's ratio [26]

Hausner's ratio is an important character to determine the flow property of powder and granules. This can be calculated by the following formula-

Hausner's ratio = Tapped density/Bulk density.

Evaluation of liquisolid tablets [19-21]

Weight variation

Weight variation was measured by weighing 20 Tablets and average weight was found and percentage weight variation of the individual tablet should fall within specified limits in terms of percentage deviation from the mean.

Thickness

The thickness of the tablet was measured by vernier caliper.

Hardness

It is a measure of the mechanical strength of a tablet using a hardness tester [Monsanto hardness tester]. The mechanical strength of a tablet is associated with the resistance of a tablet to fracture or attrition.

Friability

It was determined using Roche friabilator, the percentage loss in tablet weight before and after 100 revolutions of tablets was calculated and taken as a measure for friability.

Disintegration time

The time necessary to disintegrate 3 tablets of each tablet formulation was determined using a disintegration tester.

***In vitro* dissolution studies**

It is carried out as given in particular monograph of the drugs tablet formulation.

Advantages of Liquisolid Technique:[22-23]

- Several slightly and very slightly water-soluble and practically water-insoluble liquid and soliddrugs, 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.
- Production cost is lower than soft gelatin capsules.
- 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.
- Lower production cost than that of soft gelatin capsules.
- Production of liquisolid systems is similar to that of conventional tablets.
- Viability of industrial production.

Applications of liquisolid technique:[24-25]

- Liquisolid compact technology is an innovative method to improve bioavailability of water insoluble drug by their solubility enhancement. Various water insoluble drugs on dissolving in different non- volatile solvents have been formulated into liquisolid compacts.
- Formulations prepared by liquisolid technique possess acceptable flowability and compressibility properties.
- Release rates of many poorly water soluble drugs or water insoluble drugs are enhanced by using liquisolid system.
- Designing of Sustained Release Tablets by the use of hydrophobic polymers such as Eudragit RL andRS is done practically in many industries.
- Bioavailability of many class II and class IV drugs get enhanced by using liquisolid technique.
- This technique is used as a tool to minimize the influence of pH variation on drug release.
- It acts as a promising tool to improve drug photostability in solid dosage form.

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