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Review Article

Liquisolid Tablets: A Novel Approach for Drug Delivery

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Abstract

Liquisolid system is a novel concept of drug delivery via oral route. This technique is applied to water insoluble drugs and lipophilic drugs to sustain their release. Formulation and manufacture of the liquisolid tablets is quite simple method according to new mathematical model described by Spireas et al. It involves dissolving the drug in suitable non-volatile solvent and then adding this liquid medication to the mixture of carrier and coating materials. Mixing of this will lead to liquisolid system which is subjected to tabletting by direct compression. Increase in dissolution rate and in turn improvement in bioavailability is observed in case of poorly water soluble drugs. However, sustained effect is achieved in case of water soluble drugs. By use of this technique, liquid medications such as solutions or suspensions of water insoluble drugs in suitable non-volatile liquid vehicles can be easily converted into powder with acceptable flow properties and compression behavior using suitable powder excipients.

Keywords: Dissolution enhancement, Drugs formulation, Drug release, Liquisolid tablets.

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Introduction

Dissolution is the critical parameter of pharmaceutical dosage forms. It is recognized that *in vitro* dissolution testing is often relied upon in screening drug formulations during development and to ensure batch to batch quality control. Under certain conditions, it can be used for the assessment of bioequivalence[1] and sometimes as a means to correlate *in-vitro* with *in-vivo* drug release characteristics. Dissolution remains an important factor for absorption of drugs especially in case of water insoluble drugs[2]. For such type of drugs whose absorption is dissolution rate limited, suitable modifications should be done in the formulation design. To increase dissolution rates of such drugs, various methods have been described. These include the use of solid dispersions[3], inclusion complexes using β-cyclodextrin[4], micronization[5], microwave induced dissolution rate improvement[6] and adsorption onto silica aerogels[7]. A newly developed technique by Spireas et al.[8, 9], liquisilid system, has proved to be important technique for the dissolution rate improvement of water insoluble drugs.

The liquisolid systems show acceptable flow properties and compressibility. Liquid lipophilic drugs or water insoluble solid drugs dissolved in non-volatile solvent and this liquid medication can be converted into free-flowing, non adherent, dry looking, and readily compressible powders with use of carrier and coating materials. As the drug is in the form of liquid medication, it is in either solubilized or molecularly dispersed state. Due to increased wetting and surface area for dissolution, liquisolid tablets of water insoluble drugs show improved dissolution properties and in turn increase in bioavailability.[10] Also the low cost incurred during the manufacture of liquisolid systems prove them useful with respect to industrial production using this technique.

Formulation Design of Liquisolid Systems

To achieve good flow behavior and compressibility of liquisolid systems a mathematical model designed by Spireas et al.[8, 9] 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 Spireas et al's model is based on new fundamental properties of powder called "flowable liquid retention potential" (Φ value) and "compressible liquid retention potential" (ψ value) of powdered excipients used in the formulation. The Φ value is defined as the maximum weight of liquid that can be retained per unit weight of powder material in order to produce an acceptably flowing liquid/powder admixture while the ψ 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 compressible liquid or powder admixture i.e. being able to yield tablets of satisfactory mechanical strength without presenting any liquid squeezing out of liquisolid mass during compression.

The excipients ratio (R) or the carrier: coating material ratio is represented as follows:

$$R = Q / q \quad (1)$$

where, R is ratio of carrier (Q) and coating materials (q). For, a successful formulation design, this ratio R should be suitably selected.

Another term called Liquid load factor (L_f) is defined as ratio of weight of liquid medication (W) to weight of carrier material (Q) in system.

$$L_f = W / Q \quad (2)$$

The Φ value was used to calculate excipient quantities. Equation derived for this is as follows:

$$L_f = \Phi + \Phi (1 / R) \quad (3)$$

where, **Φ** and *Φ* are the constant Φ values of carrier and coating materials, respectively. By calculating L_f and W, we can calculate the amount of Q and q required for the liquisolid system.

Requirements for Preparation of Liquisolid Systems

Drug candidates

Examples of drug candidates include digoxin, digitoxin, prednisolone, hydrocortisone, spironolactone, hydrochlorothiazide, polythiazide, and other liquid medications such as chlorpheniramine, water insoluble vitamins, fish oil, etc.[8, 9]

Non-volatile Solvents

Various non-volatile solvents used for the formulation of liquisolid systems include Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and propylene glycol.[11]

Carrier Materials

These include grades of microcrystalline cellulose such as Avicel PH 102 and 200 [8, 9], Lactose[11], Eudragit RL and RS[12] (to sustain drug delivery), etc.

Coating Materials

Coating material include silica (Cab-O-Sil M5 [8, 9], Aerosil 200[13], Syloid, 244FP[8, 9], etc.)

Disintegrants

Most commonly used disintegrant is sodium starch glycolate (Explotab[13], Pumogel, etc.)

Pre-formulation Studies

These include solubility determination of drug in different non-volatile solvents, determination of angle of slide, determination of Φ values, calculation of liquid load factor (L_f), liquisolid compressibility test (LSC), etc.

Solubility studies

These are carried by preparing saturated solutions of drug in non-volatile solvents and analyzing them spectophotometrically.[14] Saturated solutions are prepared by adding excess of drug to vehicles and shaking them on shaker for specific time period under constant vibration.. After this, the solutions are filtered and analyzed spectrophotometrically[11].

Determination of angle of slide

Required amount of carrier is weighed and placed at one end of a metal plate with a polished surface. The end is gradually raised till the plate becomes angular to the horizontal at which powder is about to slide. This angle is known as angle of slide. It was used as a measure of the flow properties of powders. Angle of 33^o is regarded as optimum.[15]

Determination of flowable liquid retention potential (Φ value) [15]

Increasing amounts of liquid paraffin is added to a powdered material and mixed well. The powder absorbs or adsorbs only the liquid paraffin giving a change in flow properties. At each concentration of the liquid paraffin added, the angle of slide is re-determined according to previously described procedure. The Φ values are calculated according to equation:

$$\Phi \text{ value} = \text{weight of liquid} / \text{weight of solid} \quad (4)$$

Calculation of liquid load factor (L_f) [11]

Different concentrations of non-volatile solvents are taken and the drug is dissolved. Such liquid medication is added to the carrier-coating material admixture and blended. Using equation (2), drug loading factors are determined and used for calculating the amounts of carrier and coating materials in each formulation.

Liquisolid compressibility test (LSC) [8, 9]

It was developed to determine ψ values and involves steps such as preparing carrier coating material admixture systems, preparing several uniform liquid/powder admixtures, compressing each liquid/powder admixtures to tablets, assessing average hardness, determination of average liquid content of crushed tablets, as well as determining plactisity, sponge index and ψ value and L_f.

Pre-compression Studies of Liquisolid Systems

Before compression of liquisolid tablets, it is essential to perform pre-compression studies such as the determination of angle of repose, Carr's index, Hausner's ratio, Differential Scanning Calorimetry (DSC), X-ray diffraction (XRD) and Scanning Electron Microscopy (SEM).

Preparation of Liquisolid Tablets

Calculated quantities of drug and non-volatile solvent is accurately weighed in 20 ml glass beaker and then heated to dissolve the drug in that solvent. The resulting hot medication is incorporated into calculated quantities of carrier and coating materials. Mixing process is carried out in three steps as described by Spireas et al.[8,9] During the first stage, the system is blended at an approximate mixing rate of one rotation per second for approximately one minute in order to evenly distribute liquid medication in the powder. In the second stage, the liquid/powder admixture is evenly spread as a uniform layer on the surfaces of a mortar and left standing for approximately 5 min to allow drug solution to be absorbed in the interior of powder particles. In the third stage, the powder is scraped off the mortar surfaces by means of aluminum spatula and then blended with sodium starch glycolate for another 30 seconds in a similar way to the first stage. This gives final formulation of liquisolid tablets. Prepared liquisolid formulation is compressed by single punch tablet press machine.

Evaluation of Liquisolid Systems

Precompression studies

Flow behavior

Flow properties are the important concern in the formulation and industrial production of tablet dosage form. Angle of repose is characteristic to the flow rate of powder. In general, values of angle of repose ≥ 40^o indicate powders with poor flowability[16]

Differential Scanning Calorimetry (DSC)

It is necessary to determine any possible interaction between excipients used in the formulation. This will also indicate success of stability studies[17]. If the characteristic peak for the drug is absent in the DSC thermogram, there is an indication that the drug is in the form of solution in liquisolid formulation and hence it is molecularly dispersed within the system.[13]

X-ray diffraction (XRD)

Generally, disappearance of characteristic peaks of drug in the liquisolid formulation and retaining peaks of carrier material is observed[13]. This indicates that drug gets converted to amorphous form or in solubilized form in the liquisolid formulation.

Scanning Electron Microscopy (SEM)

According to Kassem et al.[13] SEM study show complete disappearance of crystals of drug and confirms that drug is totally solubilized in liquisolid system.

Dissolution testing of Liquisolid formulations

Works of many researchers[11,13,14,15] revealed that dissolution rate improvement is observed in case of liquisolid formulation. It was also proved that at low drug concentrations in liquid medication, more

rapid release rates are observed. This may be due to the precipitation of drug within silica pores at high drug concentration.[18]

In vivo evaluation of Liquisolid tablets[10]

Khaled et al.[10] evaluated liquisolid tablets in beagle dogs. They found that absolute bioavailability of drug from liquisolid tablets was 15% higher than marketed tablets.

Applications of Liquisolid Tablets

Rapid release rates are obtained in liquisolid formulations[11, 13, 14, 15]. These can be efficiently used for water insoluble solid drugs or liquid lipophilic drugs[8, 9]. Sustained Release of drugs which are water soluble drugs such as propranolol hydrochloride has been obtained by the use of this technique[7].

Advantages of Liquisolid Tablets

Liquisolid tables have many advantages. These include:

- Liquisolid systems are low cost formulations than soft gelatin capsules.
- Production of them is similar to that of conventional tablets.
- 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.

Conclusion

Liquisolid formulations are designed to contain liquid medications in powdered form, and hence possess drug delivery mechanisms similar to that of soft gelatin capsule preparations containing liquids. This novel technique is found to be efficient method for formulation of water insoluble solid drugs and liquid lipophilic drugs. Rapid disintegration rates are observed compared to conventional tablets and therefore, they show improved release rates and hence greater bioavailability. The use of non-volatile solvent in the formulation causes increased wettability of water insoluble drugs and ensures molecular dispersion of drug in the formulation. Modification of formulation by use of certain agents cause sustained release of drugs from the liquisolid tablets.

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