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LIQUISOLID COMPACTS: A REVIEW

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ABSTRACT
It is well established that the active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. About 40% of the newly discovered drugs fall into poorly water soluble or water insoluble categories [1]. The aqueous solubility for poorly water-soluble drugs is usually less than 100ug/ml [2]. Liquisolid compact system is a novel concept of drug delivery that can change the dissolution rate of water insoluble drugs. Formulation and manufacture of the liquisolid compacts is quite simple method according to new mathematical model described by Spireas et al. The technique is based upon dissolving the insoluble drug in the nonvolatile solvent and admixture of drug loaded solutions with appropriate carrier and coating materials to convert into acceptably flowing and compressible powders. 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. 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.

Keywords *Liquisolid compacts; liquid medication; poorly soluble drugs; coating material; carrier.*

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INTRODUCTION

The poor dissolution rates of water insoluble drugs are 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. The rate limiting step for most of the pharmaceutical

formulations is dissolution. For drugs belonging to biopharmaceutics classification system (BCS) class II (poor water solubility and high permeability) dissolution rate is rate determining step in drug absorption [3]. The challenge for poorly water soluble drugs is to enhance the rate of dissolution. This in turn subsequently improves absorption and bioavailability [4]. To increase dissolution rates of such drugs, various methods have been described. These include the use of solid dispersions[5], inclusion complexes using cyclodextrin[6], micronization[7], microwave induced dissolution rate improvement[8] and adsorption onto silica aerogels[9]. Among them, liquisolid compacts is one of the most promising and new technique which promotes dissolution rate of water insoluble drugs [10]. It is believed that better bioavailability of poorly soluble drugs could be achieved when drug is present in solution as in liquisolid formulations [11]. The concept of Liquisolid compacts can be used to formulate liquid medication such as oily liquid drug and solutions or suspensions of water-insoluble solid drugs in non-volatile vehicles, into acceptably flowing and compressible powders[12]. 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 carrier and coating materials. Various grades of cellulose, starch, lactose, etc, may be used as the carrier, whereas a very fine particle size silica powder may be used as the coating material.

Besides drug release enhancement, the liquisolid approach is a promising technique because of the simple manufacturing process, low production costs, and the possibility of industrial manufacture due to the good flow and compaction properties of the liquisolid formulations.

MATERIALS AND METHODS:

Materials:

Drugs:

Drugs which are poorly soluble or else insoluble in water. Examples of drugs that can be incorporated into liquisolid systems include: digoxin, digitoxin, prednisolone, hydrocortisone, spironolactone, hydrochlorothiazide, polythiazide, and other liquid medications such as chlorpheniramine, water insoluble vitamins, fish oil, etc. [13, 14].

Non- volatile solvent :

These may be hydrophilic or lipophilic in nature based on selection of type of formulation like immediate or control release. Inert, high boiling point, preferably water-miscible and not highly viscous organic solvent systems are most suitable as vehicles.

Some of them are: Polyethylene glycol, Propylene glycol, Tween 80, 20, Span 80,20, Liquid Paraffin, Cremophore L etc.

Carrier :

These are preferred to be coarser and granular for acceptable flow. These are compression-enhancing, relatively large, preferably porous particles possessing a sufficient absorption property which contributes in liquid absorption. Eg. various grades of cellulose, lactose, sorbitol, etc. [13, 14].

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[13, 14].

Super disintegrant :

Most commonly used disintegrant is sodium starch glycolate, Explotab[14], pumogel, etc.

Necessary equipments:

Shaking water bath, Electric balance, Ultraviolet spectrophotometer, Single Punch tablet press, Tablet Hardness tester, Friability tester, Thickness tester, Disintegration tester, and Dissolution apparatus [15].

METHOD OF PREPARATION:

Both solid as well as liquid drugs can be used for the preparation of liquisolid compacts. If the drug is solid it must be initially dissolved or suspended in a suitable non volatile solvent to produce drug solution or drug suspension of desired

concentration. It may require heating. The prepared drug solution or drug suspension, or the liquid drug itself, is incorporated into a specific quantity of carrier material which should be preferably of a porous nature and possessing sufficient absorption properties. The resulting wet mixture is then converted into a dry-looking, non adherent, free-flowing and readily compressible powder by the simple addition and mixing of a calculated amount of coating material. Mixing is done with a great care and is an important step in the formulation as it gives even distribution of liquid medication in the powder and also allows the drug solution to be absorbed in the interior of powder particles. This formulation is compressed by single punch tablet press machine [13, 14].

MECHANISM OF SOLUBILITY ENHANCEMENT:

The mechanisms by which the liquisolid compacts show increased solubility and hence bioavailability 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[16]. When the drug is dissolved or dispersed in a 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. The drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface. The liquid initially absorbed in the interior of the particles and 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. Both absorption and adsorption take place[10]. Here 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 increases the aqueous solubility of the drug [12].

The liquid vehicle (Nonvolatile solvent) present in the liquisolid system can either act as surface active agent or has a low surface tension. Thus improves wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface [17].

Formulation Design of Liquisolid Systems:

The mathematical model given by Spireas et Al[13, 14] is used as formulation design model for the liquisolid tablets. 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 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.

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:

$$R = Q / q \text{-------- (1)}$$

where, R is ratio of carrier (Q) and coating materials (q). For, a successful formulation design, this ratio R should be suitably selected. Depending on the excipient ratio (R) of the powder substrate an acceptably flowing and compressible liquisolid 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 [w/w] and is defined as the weight ratio of the liquid formulation (W) and the carrier material (Q) in the system:

$$Lf = W/Q \text{-------- (2)}$$

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

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

$$Lf = \Phi + \phi . (1/R) \text{ -------- (3)}$$

Where Φ and ϕ are the Φ-values of the carrier and coating material, respectively. Similarly, the liquid load factor for production of liquisolid

systems with acceptable compactability (ΨLf) can be determined by:

$$^{\Psi}L_f = \Psi + \psi \cdot (1/R) \quad \text{-------- (4)}$$

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

Pre-formulation Studies:

Before starting with the formulation it is necessary to check particle size of the drug, determine solubility of drug in different non-volatile solvents. Also determination of angle of slide, determination of Ø values, calculation of liquid load factor (Lf), liquisolid compressibility test (LSC) is also essential.

Particle size of the drug:

The mean particle size of pure drug and prepared crystals is determined by laser light scattering technique using particle size analyzer[18]. The particle size distribution of drug is determined by laser diffraction using a dry dispersing system [19].

Solubility studies:

Solubility of the drug is determined by preparing a saturated solution in non-volatile solvents and drug content in the solvent is assessed spectrophotometrically. Excess drug was made soluble in the suitable solvent by using rotary shaker or by sonicator for specific time period under constant vibration [20].

Angle of slide:

Angle of slide is used to determine flowable liquid-retention potentials (which is needed for calculation of the Lf) [12], claimed that angle of slide is the preferred method to determine the flowability of powders with particle size less than 150 µm. Therefore, angle of slide had been preferred over the other methods like angle of repose, to determine the flow properties of powder excipients and liquid/ powder admixtures. The validity of angle of slide has been proven to be effective. 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 Is used as a measure of the flow properties of powders. Angle of 33^{o} is regarded as optimum [21].

Determination of flowable liquid retention potential (Ø value) [21]:

The appropriate amounts of carrier and coating materials to produce acceptable flowing and compactible powders are based on the physical properties of powders termed ‘‘flowable liquid-retention potential” (Ø -value). Here 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 redetermined according to previously described procedure. The Ø values are calculated according to equation:

Ø value = weight of liquid / weight of solid.

Calculation of liquid load factor (Lf):

An acceptably flowing and compressible liquisolid system can be prepared only if a maximum liquid on the carrier material is not exceeded; such a characteristic amount of liquid is termed the liquid load factor (Lf) [22] Liquid load factor (Lf): defined as weight of liquid medicament (W) to weight of carrier (Q).

$$L_f = W/Q$$

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 above equation, drug loading factors are determined and used for calculating the amounts of carrier and coating materials in each formulation.

Liquisolid compressibility test (LSC) [13,14] :

It is 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 plasticity, sponge index and Ψ value and Lf .

Evaluation of liquisolid systems:

Flow behavior:

To select the optimal formulae for compression, flowability studies are carried out. The flowability

of a powder is of critical importance in the production of tablet dosage forms in order to reduce high dose variations[23]. The flow properties of powders are affected by their particle size, shape, porosity, density, moisture content, and surface roughness[24]. Angle of repose, Carr's index and Hausner's ratio are used in order to ensure the flow properties of the liquisolid systems.

Pre-compression studies: Prior to the compression of the formulations into tablets, in order to ensure the suitability of the selected excipients, various studies are performed including, differential scanning calorimetry (DSC), X-ray diffraction (XRD), and scanning electron microscope (SEM).

Differential Scanning Calorimetry (DSC):

The thermal behavior and the thermotropic properties of the drug, excipients used in the formulation, as well as the liquisolid system prepared are determined by DSC. It also gives any possible interaction between excipients used in the formulation. It will also indicate success of the stability studies[24]. If the drug is in the form of solution in liquisolid formulation, i.e., the drug is molecularly dispersed within the liquisolid matrix, then the characteristic peak for the drug is absent in the DSC thermogram[10].

X-ray diffraction (XRD):

For characterization of the crystalline state, the X-ray diffraction (XRD) patterns are determined for drug, excipients, physical mixture of drug and excipients, finally for the prepared liquisolid system[17]. Absence of characteristic peaks of the drug in the liquisolid XRD indicate that drug has almost entirely converted to amorphous or solubilized form. This amorphization or solubilization of drug in the liquisolid system contributes to the consequent improvement in the apparent solubility and therefore the dissolution rate of the drug[15].

Scanning Electron Microscopy (SEM):

Scanning electron microscopy (SEM) is utilized to assess the morphological characteristics of the raw materials and the drug–carrier systems. This study confirms if there are any crystals present, or else drug is present in completely solubilised form by absence of crystals of drug [10].

Dissolution testing:

The drug is in the solution form and at the same time, it is carried by the powder particles hence the liquisolid compacts show better dissolution rates than the pure one[10]. The use of nonvolatile solvent in the formulation causes increased wettability of water insoluble drugs. Thus, release is accelerated due to its markedly increased wettability and surface availability to the dissolution medium. Many researchers[10,12,17,18,21,25-28] revealed that dissolution rate improvement is observed in case of liquisolid formulation. It is also proved that at low drug concentrations in liquid medication, more rapid release rates are observed [10].

Applications of Liquisolid systems:

- ✓ Solubility and dissolution enhancement.
- ✓ Used efficiently for water insoluble solid drugs or liquid lipophilic drugs[13], [14].
- ✓ Rapid release rates.
- ✓ Designed for controlled release tablets.
- ✓ Designed for sustained release of water soluble drugs such as Propranolol hydrochloride.
- ✓ Application in probiotics.

Advantages of Liquisolid systems [1-5]:

- ✓ Number of water-insoluble solid drugs can be formulated into liquisolid systems.
- ✓ 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.
- ✓ Exhibits enhanced in-vitro and in-vivo drug release as compared to commercial counterparts, including soft gelatin capsule preparations.
- ✓ Drug release can be modified using suitable formulation ingredients
- ✓ Capability of industrial production is also possible.

- ✓ Enhanced bioavailability can be obtained as compared to conventional tablets.

Limitations:

- ✓ Requirement of high solubility of drug in non-volatile liquid vehicles.
- ✓ Low drug loading capacities.

CONCLUSION:

The Liquisolid technique is a promising strategy for improvement of dissolution property of water-insoluble 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 nonvolatile 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. The simple manufacturing process, low production costs and the possibility of industrial manufacture due to the good flow and compaction properties of liquisolid formulations, makes the Liquisolid approach a promising technology.

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