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DISSOLUTION ENHANCEMENT TECHNIQUES OF POORLY SOLUBLE DRUGS BY LIQUISOLID COMPACTS

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ABSTRACT

Liquisolid compact were used to formulate water insoluble drugs in non-volatile solvent and convert into acceptably flowing and compressible powders. The main aim of this method is enhance the dissolution rate and bioavailability of BCS II drugs. About 40-50% of drugs available in market are water insoluble in nature. The bioavailability of poorly water soluble drugs is the dissolution rate limited. Limited solubility is the major challenge for the development of ideal solid unit dosage form. “Liquisolid compact technique” or “the powder solution technology” is a novel and most promising technology for overcoming this consequence. This is the novel technique of oral drug delivery. This approach is suitable to formulate both immediate release and also sustained release formulations.

KEYWORDS

Liquisolid compact, carrier, coating material, bioavailability, non-volatile and water- insoluble/soluble.

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INTRODUCTION[1]

Most of the 40% of all newly developed drugs suffers from low bioavailability problem. Bioavailability of these hydrophobic drugs (Class II in Biopharmaceutical classification system) is limited due to their poor solubility. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response. 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 dissolution rate of a drug is directly proportional to its solubility as per Noyes-Whitney equation and therefore solubility of a drug substance is a major factor that determines its dissolution rate and hence its absorption and bioavailability eventually. One of the major challenges of present pharmaceutical research is to enhance the dissolution profile, absorption efficiency and bioavailability of water insoluble drugs.

Many methods are available to improve these characteristics, including (i) reducing the particle size to increase surface area, thus increasing the drug dissolution rate; (ii) solubilization in surfactant systems; (iii) formation of water- soluble complexes; (iv) use of pro-drug and drug derivatization such as strong electrolyte salt forms that usually have higher dissolution rates; and (v) manipulation of the solid state of a drug substance to improve drug dissolution, i.e., by decreasing crystallinity of the drug substance through formation of solid solutions[2]. Among them, Liquisolid compacts is one of the most promising and new technique which promotes dissolution rate of water insoluble drugs.

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 nonvolatile 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 materials. In liquisolid compacts, even though the drug is in a tablet 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.

Components of Liquisolid CompactFormulation[3-4]

1. Non volatile solvent
2. Disintegrant
3. Carrier material
4. Coating material

1. Non volatile Solvent

Nonvolatile Solvent should be Inert, high boiling point, preferably water-miscible and not highly viscous organic solvent systems and compatible with having ability to solubilize the drug. The nonvolatile solvent acts as a binding agent in the Liquisolid formulation various non-volatile solvents used for the formulation of Liquisolid systems include Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and propylene glycol.

2. Disintegrant

Super disintegrate increases the rate of drug release, water solubility and wettability of liquisolid granules. Mostly super disintegrates like sodium starch glycolate and crosspovidone.

3. Carrier Materials

Carrier material should be porous material possessing sufficient absorption properties which contributes in liquid absorption. The carrier and coating materials can retain only certain amounts of liquid and at the same time maintain acceptable flow and compression properties hence, increasing moisture content of carrier's results in decreased powder flow ability These include grades of microcrystalline cellulose such as avicel PH 102 and avicel PH 200, 20.

4. Coating Materials

Coating material should be a material possessing fine and highly adsorptive particles which contributes in covering the wet carrier particles and displaying a dry looking powder by adsorbing any excess liquid. Coating material is required to cover the surface and maintain the powder flowability.Coating material includes silica (Cab-O-Sil) M520, 35, Aerosil 2003, syloid.

Mechanisms of Enhanced Drug Release from Liquisolid Formulation[5]

A. 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.

B. Increased drug surface area

When the drug within the Liquisolid system is absolutely dissolved in the liquid vehicle it is positioned in the powder substrate 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. Consequently, with increasing drug content beyond the solubility limit and thus, increasing fraction of undissolved drug in the liquid vehicle the release rate decreases. It has been pragmatic with various drugs that the release rates are directly proportional to the fraction of the molecularly dispersed drug (*FM*) in the liquid formulation. *FM* is defined by Spireas as the ratio between the drug's solubility (*Sd*) in the liquid vehicle and the actual drug concentration (*Cd*) in this vehicle carried by each system.

$FM = Sd/Cd$

Where $FM = 1$ if $Sd \geq Cd$

C. 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. Wettability of these systems has been confirmed by measurement of contact angles and water rising times.

General Method of Preparation[6-7]

A drug substance was initially dispersed in the nonvolatile solvent systems (Polysorbate 80, Polyethylene glycol-200) termed as liquid vehicles with different drug: vehicle ratio. Then a mixture of carrier or different polymers and excipients were added to the above liquid medication under continuous mixing in a mortar. These amounts of the carrier and excipients are enough to maintain acceptable flow and compression properties. To the above binary mixture disintegrant like sodium starch glycolate and other reaming additives were added according to their application and mixed for a period of 10 to 20 minutes in a mortar. The final mixture was compressed using the manual tableting machine to achieve tablet hardness. Characterize the final Liquisolid granules for solubility, dissolution, Flowability, compressibility and other physicochemical properties.

Classification of Liquisolid Systems[11]

Based on the type of liquid medication contained therein, Liquisolid systems may be classified into three sub-groups.

- Powdered drug solutions
- Powdered drug suspensions
- Powdered liquid drugs

Powdered drug solutions and suspensions may be produced from the conversion of drug solutions or drug suspensions into Liquisolid system. Powdered liquid drugs are produced from the formulation of liquid drugs into Liquisolid systems.

Simultaneously, based on the formulation technique used, Liquisolid systems may be classified into two categories namely,

- Liquisolid compacts
- Liquisolid Microsystems

The term “Liquisolid compacts” refers to immediate or sustained release tablets or capsules Prepared, combined with the inclusion of appropriate adjuvant required for tableting encapsulation, such as lubricants, disintegrates or binders.

The term “Liquisolid Microsystems” refers to capsules prepared by combining the drug with Carrier and coating materials, combined with inclusion of an additive e.g., PVP in the liquid.

Advantages[12]

- Number of water insoluble solid drugs can be formulated into liquisolid system.
- Can be applied to formulate liquid medication such as oily liquid drugs.
- Simplicity.
- Better availability of an orally administered water insoluble drugs.
- Lower production cost than that of soft gelatin capsule.
- Production of Liquisolid system is similar to that of conventional tablets.
- Viability of industrial production.
- Can be used for formulation of liquid oily drug
- Exhibit enhanced *in-vitro* and *in-vivo* drug release as compared to commercial counterparts, including soft gelatin capsule preparation.
- Can be used in controlled drug delivery.

Disadvantages[13]

- Only applicable to low dose drugs and only water insoluble or poorly soluble drugs.
- High solubility of drug in the non-volatile liquid drugs for the improvement of dissolution rate and bioavailability.
- It only requires excipients of high adsorption properties and high specific surface area.
- It requires more number of excipients.
- In order to maintain good flow ability and compact ability sometimes requires high amounts of Carrier and coating materials that in turn will increase the weight of the tablet above 1gramwhich is very difficult to swallow.
- It is not applicable to high dose insoluble drugs (>100 mg).
- Sometimes it is very difficult to achieve good flow and compact ability.
- During compression sometimes liquid drug may be squeezed out of the tablet result in improper hardness.

Applications[14]

- 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.
- Flowability and compressibility.
- Designing of Controlled Release Tablet.

Pre-formulation Studies[15]

Pre-formulation Studies includes

- Determination solubility of drug in different non-volatile solvents
- Determination of angle of slide
- Determination of flow able liquid retention potential (Φ value)
- Calculation of liquid load factor (Lf)
- Liquisolid compressibility test (LSC).

Pre Compression Evaluations[15]

The flow ability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to get a uniform feed as well as reproducible filling of tablet dies, otherwise, high dose variations will occur. In order to ensure the flow properties of the Liquisolid systems that will be selected to be compressed into tablets and further evaluated, angle of repose, Carr's index and Hausner's ratios were adopted.

Post compression Evaluations[15]

- Content of uniformity
- Hardness
- Weight variation
- Friability
- Disintegration
- In - vitro dissolution studies
- These are should be in the official limits prescribed by official pharmacopoeia.

Evaluation of Liquisolid Systems[16-17]

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 $\geq 40^{o}$indicate powders with poor flowability.

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. 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.

X-ray diffraction (XRD)

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

Scanning Electron Microscopy (SEM)

After SEM study, complete disappearance of crystals of drug which confirms that drug is totally solubilized in Liquisolid system and this ensures the complete solubility.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR studies are performed to determine the chemical interaction between the drug and excipients used in the formulation. The presence of drug peaks in the formulation and absence of extra peaks indicates there is no chemical interaction.

Estimation of drug content

The Liquisolid compacts are powdered well and powder equivalent to 10 mg of the drug is accurately weighed and suitably diluted using methanolic sulphuric acid. The drug content is calculated by at wavelength using UV-Visible spectrophotometer.

Contact angle measurement

For assessment of Wettability, contact angle of liquisolid tablets is measured according to the imaging method. The commonly used method is to measure contact angle directly for a drop of liquid resting on a plane surface of the solid, the so-called imaging method. A saturated solution of the drug in dissolution media is prepared and a drop of this solution is put on the surface of tablets. The contact angles are calculated by measuring the height and diameter of sphere drop on the tablet.

***In-vitro* drug release study**

The *in-vitro* dissolution study is carried out for a period of 1 hour using USP XXIV type-II (paddle) method with 900 ml of 0.1 N HCl and distilled water as the dissolution media at required rpm and $37^{o}C+0.5^{o}C$. 10 ml of the sample is withdrawn and filtered at periodic time intervals in minutes. 10ml of fresh dissolution fluid is replaced to the baskets to maintain the constant volume (sink condition). The filtered samples are analyzed at wavelength by UV/Visible spectrophotometer.

Table No.1: List of several investigated liquisolid systems for enhanced drug release[8]

1	Aceclofenac	15	Hydrocortisone
2	Bromhexine HCl	16	Ibuprofen
3	Carbamazepine	17	Indomethacin
4	Clofibrate	18	Lamotrigin
5	Ezetimibe	19	Loratadine
6	Famotidine	20	Methyclothiazide
7	Fenofibrate	21	Naproxen
8	Felodipin	22	Nifedipin

9	Flutamide	23	Piroxicam
10	Furosemide	24	Polythiazide
11	Glibenclamide	25	Prednisone
12	Glyburide	26	Repaglinide
13	Griseofulvin	27	Spironolactone

Table No.2: Marketed preparations of liquisolid technique[9, 10]

S.No	Brand name	Generic name
1	Mepron	Atovaquone
2	Infasurf	Calfactant
3	Dermotic oil	Fluocinolone Acetonide Oil Ear Drops
4	Proair HFA	Albuterol Sulfate Inhalation Aerosol
5	Maxalt	Rizatriptan Benzoate
6	Noritate	Metronidazole
7	Angeliq	Drospirenone and Estradiol
8	Renova	Tretinoin Cream
9	Sporanox oral solution	Itraconazole Oral Solution

CONCLUSION

Liquisolid compact refers to formulations formed by conversion of solid state to liquid state, drug suspensions or drug solution in non-volatile solvents into dry, nonadherent, free-flowing and compressible powder mixtures by blending the suspension or solution with selected carriers and coating agents. The formed liquisolid tablets dosage form showed significantly greater extent of absorption due to their solubility and dissolution improvement. The technique is also used to design sustained release systems by using hydrophobic carriers instead of hydrophilic carries in liquisolid systems. Therefore, this formulation of the drug has the potential to be considered for human study in order to be manufactured on large scale.

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