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Liquisolid Compacts: A Review

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ABSTRACT

Bioavailability is mostly effected by drug dissolution and its release from the dosage form, and it mainly depends on solubility of drug. For the development of new pharmaceutical products the major issue any pharmaceutical industry faces is solubility that ultimately results in low bioavailability. To enhance the solubility of poorly soluble drugs liquisolid compacts is one of the impending techniques. This technique involves a preparation where the liquid drug present in the form of a solution or suspension is transformed into a non sticky, dry, compactable, free-flowing powders, this is accomplished by adding certain coating agents and carriers that are appropriate. This technique with comparison to conventional tablets has the capability of enhancing the absorption of less soluble drugs in its molecularly dispersed form, rate of dissolution, aqueous solubility thereby increasing its bio availability by using less production costs and simpler manufacturing processes.

Keywords: Bioavailabity enhancement, Coating agents, Carriers, Solubility enhancement, Liquisolid compacts, Dissolution

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Introduction

The main criteria taken into consideration before deciding the dosage form is solubility of an active compound. The number of drugs with poor solubility has increased due to the recent developments in high-throughput screening and combinatorial chemistry[1].The newly developed drugs which are given for oral administration half of them are poorly soluble in water which affects the formulation development process. Many hydrophobic drugs have less dissolution in the gastrointestinal tract hence show incomplete or erratic absorption of the drug. Drugs falling under the biopharmaceutical classification system (BCS) class II have low solubility and dissolution rate compared to other class of drugs hence have less bioavailability. This low solubility and dissolution rate cane overcome as well as enhanced using a few common methods like micro ionization, lyophilisation, solid dispersion, co-solvency and complexing agents. Out of these the liquisolid compact technique found to be the best to enhance the bioavailability of the class II drugs of BCS. This technique is also called as powder solution technology. The process involves a preparation prepared by converting a suspension or a solution form of drug into a non-sticky, dry, compressible free flowing powder which is prepared by adding a few designated carriers and coating agents to the liquid form of drug. Using liquisolid technique, delivered an increment in the drug dissolution profile as a result of increased wetting properties and surface area. Unfortunately this method is confined to drugs with low dose and less solubility. The carriers used in the compacts should have a great adsorption property and should show absorption when added to the liquid medication[2]. The most commonly used carrier is microcrystalline cellulose. The uses of the coating material include covering the surface, imparting flowability to powder, providing content uniformity to the manufactured tablet dosage form. Other factors like water solubility, wet ability and rate of release of drug can be incremented by using disintegrants. This technique uses non-volatile solvents that are water miscible and can impart binding action.

Advantages

- The liquisolid compacts are very flexible as they are used for poorly soluble drugs.
- The bioavailability of oral drugs which are insoluble in water is increased.
- The cost of manufacturing is cheap compared to soft gelatin.
- The drug can be formulated in many ways where it is present in a solubilised form that can increase the wetting property and improves drug release profile.
- Depending upon the character of the carriers used instant release or continual release dosage forms can be prepared into liquisolid compacts.

- Using certain hydrophobic carriers and surface active agents can increase the drug release and wetting respectively thereby increases the dissolution profile.
- The manufacturing efficiency and the techniques can be improved.
- The extent of absorption is increased up to 15% more that the conventional tablets.

Limitations

- As it is used only for low dose water insoluble drugs it cannot be used in the preparation of high dose water insoluble drugs.
- The weight of the tablet is increased due to the addition of carrier and coating material.
- Mathematical calculations must be applied[3-5].
- Drug release can be enhanced by adding substances with greater absorption rate but this results in a decreased tablet size.
- If the acceptable compression is not achieved it results in inadequate hardness of the product.
- The bioavailability and rate of dissolution are dependent on solubility of the drug in a non-volatile liquids.

Theoretical Facts in the Liquisolid System

A sufficient quantity of the liquid only should be added as the powder looses its flowability and compression properties if it exceeds. The maximum retention potential of powder with acceptable flow can be estimated by two mathematical approaches given by Spireas, they are ϕ value and excipients ratio. Flowability can be calculated by rate of flow or angle of repose. The compressible nature of the powder along with the maximum liquid retention potential can be calculated by ψ number. Excipient ratio is known as the ratio of weight of carrier to the coating agent[6].

$$ER = C/CA$$

This excipient ratio is mainly dependent on the liquid carrier. A liquid system with sufficient compressibility and flowability is possible only when the load of liquid on carrier material is not over the required limit. This is given by liquid load factor(LLf) which is a ratio of weight of liquid formulation (W) to carrier material(C).

$$LLf = W/C$$

Adequate flow behaviour (ϕLLf) is attained by this liquid load factor(LLf)

$$\phi LLf = \phi + \psi.(1/ER)$$

the satisfactory compatibility (ψLLf) for a liquisolid system can also be determined as

$$\psi LLf = \psi + \psi.(1/ER).$$

Either ϕLLf or ψLLf (whichever has lesser magnitude) is the optimum liquid load factor (LLo) required to get an acceptable compressibility and flow behaviour of the system. As soon as the Llo is measured, the sufficient amounts of coating agent and carrier required for the liquid formulation to convert into a compactable, free flowing system can be calculated as

$$AC = W/Llo \qquad AC = AC/ER$$

Mechanism Involved In Improved Drug Release Profile from Liquisolid Systems

Different research reports accentuated that the release rate of poorly soluble and less dose drugs is increased by the liquisolid technique. Additives like polyvinyl pyrrolidine (PVP), hydroxyl propyl methyl cellulose (HPMC), polyethene glycol 35000 (PEG) can be added in order to incorporate a high dose water insoluble drugs, and also to enhance coating and carrier material absorption capacity. The mechanisms utilized to increase the drug release are

Augmented Surface Area

When there is a complete dissolution of the drug in the liquid vehicle in liquisolid system results in an increased surface are of drug and also indicate that the drug is in a molecularly dispersed state and in solubilised form.

The drug release from the tablets prepared by liquisolid technique is at high rate this was confirmed by a comparison between directly compressed tablets and tablets from this technique. Dividing the solubility of drug by concentration of drug gives the fraction molecularly dispersed drug.

$$Fm = S/C$$

Where,

$$Fm = 1\ S \geq C$$

Improved Aqueous Solubility Of Drug

A solid liquid boundary present in between the liquisolid primary particles and the media around it increases the drugs water solubility[8]. The amount of vehicle that gets diffused along with the drug particles also plays a role in the enhancement of aqueous solubility which can be mainly due to co-solvent effect.

Improved Wetting Properties

Wetting of primary particles is due to reduced surface tension which is a result of surface active properties present in the liquid vehicle, water rising time and contact angle measurement are the methods used for determining wet ability.

Porosity

As stated by Pezzini et al liqusolid technology lead to the production of soft substances with increased porosity that augmented both disintegration and dissolution processes.

Mechanism of Sustained Drug Release from Liquisolid Systems

A simple substitution of hydrophobic carrier in the place of a hydrophilic carrier reduces the wetting thereby reducing disintegration and thus prolongs the drug release. Processing of liquisolid compacts does not show any change in crystalline nature or complex formation of the drug. These studies are confirmed by X-ray crystallography and DSC measurements[9]. The drug release can also be reduced by the effect of liquid vehicle which can be confirmed from the comparative study between directly compressed and liquisolid prepared tablets. Liquisolid compacts have less or reduced coalescence with polymer particles compared to traditional matrix tablets this may also be a reason for decreased drug release leading to reduced porosity an increase in tortuosity. For the sustained release of drug hydrophobicity plays a major role .

Formulation of Liquisolid Compacts

Carriers, binding agents, non-volatile solvents, disintegrants, coating materials, lubricants are used in the formulation of liquisolid compacts.

Carrier materials

The carrier materials should maintain flowability and compressibility, should be spongy in nature and must have required absorption properties both carrier and coating material should posses only a limited water quantity. Eg: microcrystalline cellulose(MCC).

Coating Materials

They are generally coarse powdered materials that help in covering the particles which have been wet by adsorbing of the liquid in excess amounts thereby producing a dry free flowing powder.

Non-Volatile Solvents

Non volatile, inert and not extremely viscous solvents are used in the formulation, they must also posses high boiling point and good solubilisation power. These liquids also provide binding action. Eg: glycine, polysorbate 80, propylene glycol, polyethylene glycol200 and 400.

Disintegrating Agents

Use of these agents increases wet ability, drug release rate and water solubility as they take in water. They play a role in breaking the compacts into smaller particles. Eg: sodium starch glycolate and cross povidene, explotab and pregelatinized starch.

Drug Candidate

Less soluble drugs like BSC class II drugs and class-IV drugs used as drug candidates for this technique this provides increased water solubility of these drugs. Eg: g-naproxen, digitoxin, bednisolone, hydrocortisone, ketoprofen[10].

Methodology

The needed amounts of the drug candidate and given amount of non-volatile solvent is weighed and then added, the mixture is agitated, subjected to heat if necessary. This produces a drug solution and to this solution carrier particle and coating materials are added. The process of mixing should be done in three stages format as stated by Spireas et al

First Stage

The elements which are weighed were mixed at a measured mixing rate of one rotation / second or minute, that can help the aqueous medicament to devote its part in the powder.

Second Stage

The thorough absorption of the drug solution into the powder particle voids takes place when the mixture from the first stage id spread uniformly on a mortar surface for about 5min.

Third Stage

The final blend accessible for compression is produced when the blend formed from the above stage is agitated with a super disintegrate for 30 sec at a blending speed.

Preformulation Studies

The physiochemical characteristics can be confirmed by the preformulations studies like:

- Solubility studies of drug in solvents
- Angle of slide
- Flowable liquid retention potential
- Liquid load factor(LLf)
- Liquid solid compressibility test

Solubility Studies of Drug In Non Volatile Solvents

To study the solubility a saturated solution must be prepared, this solution is prepared by adding excess amount of drug to the liquid and mixed with the help of a shaker at a given period of time under steady vibration. The filtrate so produced is used for analysis by spectrophotometry**.**

Angle of Slide

To determine the flow behaviour of the powder sliding angle is measured by using a metallic plate with a smooth surface as a test where the powder is kept at one end and is increased in height till the plate is angular to horizontal plane where the powder can slide, an angle of 33° generally gives optimum flow properties.

Flowable Liquid Retention Potential

It gives the potential of the liquid retention of the powder with an acceptable flow behaviour.

Liquid Load Factor

It can be determined by using adequate quantities of non volatile solvent and the drug is dissolved to produce a free flowing powder after the carrier and coating materials are added. It is given as the ratio of weight of liquid medication(W) to weight of carrier material(C).

Liquisolid Compressibility Test

The test is used to determine the compressible liquid retention value (ψ) by preparing an admixture of carrier and coating materials and converting them to tablets. The average liquid content of crushed tablets gives average rigidity.

Evaluation of Liquisolid System

- Flow behaviour
- Differential scanning calorimetry
- X-ray diffraction
- Scanning electron microscopy
- Dissolution testing
- In-vivo evaluation

Flow Behaviour

Bulk Density

The powder blend is weighed (W) and transferred into a measuring cylinder that is graded and the bulk volume (Vb) is calculated. Bulk density is determined by the formula

$$\text{Bulk density} = W/Vb$$

Tapped Density

The powder is weighed (W) and shifted into a graded measuring cylinder and tapped for a fixed number of times then the tapped volume (Vt) is measured. The tapped density is given as

$$\text{Tapped density} = W/Vt$$

Compressibility Index

Good flow properties are seen if compressibility index value is less than 15% and poor flow properties is seen if the

compressibility index value is more than 25%. Compressibility index is measured as

Compressibility index = (tapped density – bulk density) / tapped density × 100

Hausner's Ratio

It varies depending on the choice of method selected to determine, hence it is not considered as a critical parameter. Good flow property indicates that the value is below 1.25 and if it is above 1.5 it indicates poor flowability, it is estimated as

Hausner's ratio = tapped density/bulk density

Angle of Repose

It is determined by using a funnel where the powder is allowed to flow through the funnel till its tip touches the powder pile. It can be written as

$$Ø = \tan^{-1} h/r$$

Where, h = height of pile
r = radius of powder pile base

Differential Scanning Calorimetry

These DSC studies are used to assess the thermal behaviour of the liquisolid compacts and pure components. To determine the DSC 3 to 5mg of drug is vacuum packed in aluminium pans exposed to a temperature range of 30 to 300°C. Vacant aluminium pans are used as reference and by purging nitrogen, the thermal behaviour is studied.

X-Ray Diffraction Studies

XRD are used to determine the crystalline property of liquisolid compacts. These studies use a 30mA current and a copper target of voltage 40KV. The equipment generally works at an angle 5 to 70° and counting rate of 0.45/step. The peak pattern change tells about the conversion of drug nature from crystalline to amorphous.

Scanning Electron Microscopy

This method is used to know whether the drug is crystallised from the liquisolid system and also helps in measuring the surface behaviour of drug. These molecular forms can be disappeared due to the solubilising nature of the drug.

***In-Vitro* Drug Release Studies**

USP dissolution apparatus type II is the apparatus used for the study of in-vitro drug release. Using this apparatus the studies are done in 900ml 0.1N HCl at constant temperature of 37°C±2 and at a stirring speed of 50 to 200 rmp[11]. The percentage of known amount of drug dissolved is measured by withdrawing samples at regular intervals and maintenance of sink conditions.

***In-Vivo* Evaluation Of Liqisolid Tablets**

Peak plasma concentration, relative bioavailability and area under plasma concentration must show variable differences between the liquisolid compact and a commercial tablet.

Applications

- Drug Dissolution Can Be Improved:

  Drug dissolution rate is increased in low dose drugs like valsartan, famotidine etc. by the use of liquisolid technique.

- Incorporation of High Dose Water Insoluble Drugs

  High dose less soluble drugs can be added to the system by simply incorporating additives like PVP, HPMC etc. As these additives can rise the liquid uptake of coating and carrier materials. Also addition of modern carriers show great capacity of absorption.

- Sustained Drug Release

It is a guaranteed method for producing sustained release drugs and also pH deviation. Control on drug release is decreased by using liquisolid technique, photo stability of drug in solid dosage form is also increased and this technique can be applied probiotics also.

Conclusion

Liquisolid technique is an approaching method for increasing the solubility and rate of dissolution thereby increasing the bioavailability and the extent of absorption of water-insoluble drugs compared to other conventional tablets using less production costs and simple manufacturing process. It is also used to formulate sustained release drugs and immediate release drugs by using hydrophobic and hydrophilic carriers. The drug release from liquisolid compacts is further enhanced by the use of disintegrant along with carriers and coating agents. Thus the selection of the excipients used like carriers, coating materials and detergents play a major role. Furthermore this technology has been truly favourable as the dissolution, bioavailability, solubility of most of the water-insoluble drugs has been enhanced to a noticeable value, especially to BCS class II and class IV drugs.

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