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LIQUIDSOLID TECHNOLOGY - SOLUBILITY AND BIOAVAILABILITY ENHANCER FOR POORLY SOLUBLE DRUGS

Aishwarya Sopan Erande*, Sapana P. Ahirrao, Nishigandha N. Dhokale, Paresh S. Hire

Department of Pharmaceutics, MET's Institute of Pharmacy, Bhujbal Knowledge City, Adgaon, Nashik, 422003, India

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For Correspondence:

Aishwarya Sopan Erande

Department of Pharmaceutics, MET's Institute of Pharmacy, Bhujbal Knowledge City, Adgaon, Nashik, 422003, India

E-mail:

aishwarya.erande201@gmail.com

ABSTRACT

Liquisolid technique is also known as powder solution technology. It is the technique which deals with the solubility enhancement of poorly soluble drugs. As these days there are many drugs in the market with poor solubility which leads to poor dissolution and bioavailability, so solubility is becoming rate limiting factor in the development of new drugs. To overcome this problem there are many techniques but liquisolid technique is most promising technique which is discussed in this article. Liquisolid is mainly composed of drug, non volatile solvent, carrier material, coating material, and disintegrant. In liquisolid technique carrier and coating material which should be in the ratio of 20:1 is mixed into the non volatile solvent and then disintegrant is added and final material is compressed into tablets. Both immediate or sustained release formulation through oral route.

INTRODUCTION

The solubility of the drug is major concern. Solubility is the phenomenon of dissolution of solid in liquid phase. Solubility is one of the major factors to achieve desired concentration of drug in systemic circulation. The poorly water soluble drugs may have poor dissolution rate and incomplete bioavailability. The most of the hydrophobic drugs are sparingly soluble, slightly soluble and very slightly soluble drugs, for such drug substances dissolution is the rate limiting step. The challenge for poorly water soluble drugs is to enhance the dissolution. Therapeutic response of a drug depends upon the bioavailability which is dependent on the solubility and dissolution rate of drug molecules. 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. There are different types of techniques are available to increase the solubility of poorly water soluble drugs there are as,

1. Micronization
2. Lyophilisation
3. Solid dispersions
4. Complexation
5. Co solvency
6. Chemical modification
7. pH adjustment
8. Solubilisation by surfactants
9. Solid solutions
10. Inclusion complex
11. Salt formation.
12. Nanosuspensions

These above mentioned techniques have been introduced to increase the dissolution rate, absorption and bioavailability. But to overcome all these types of problems the "Liquisolid Technique" It is the most promising & novel techniques to improve the dissolution rates of the poorly water soluble drugs.[1-7, 9, 11, 12, 14]

LIQUISOLID TECHNOLOGY

It is a novel concept of drug delivery that can change the dissolution rate of water insoluble drugs. It is also called as "powdered solution technology", applied to prepare water-insoluble drugs into rapid-release solid dosage forms. In this, a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material. A liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing, and compressible powder is obtained by this technique. [2, 5-8, 13, 14, 16]

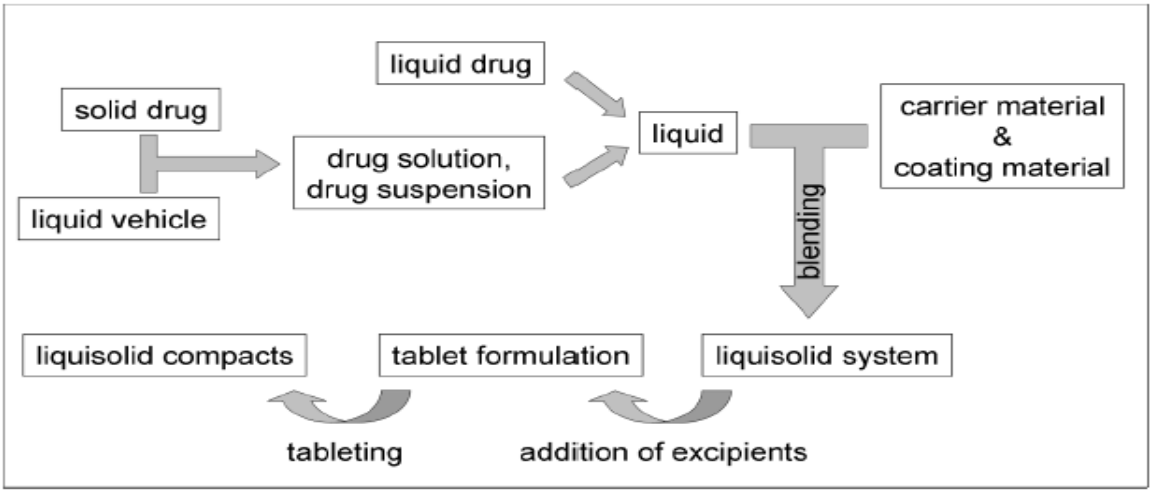

Fig: General method of preparation of liquisolid compacts

CLASSIFICATION OF LIQUISOLID SYSTEMS

The liquisolid systems are classified into two types are as,

1) Based on the formulation technique used, there are two types,
   a) Liquisolid compacts
   b) Liquisolid Microsystems
2) Based on type of liquid medication contained therein, there are 3 different formulation systems are as,
   a) Powdered drug solutions e. g. Prednisolone solution in propylene glycol
   b) Powdered drug suspensions e. g. Gemfibrozil suspension in Polysorbate 80
   c) Powdered liquid drugs e. g. Clofibrate, vitamins etc.

Non-volatile solvents are used to dissolve the drug. The liquid vehicle does not evaporate so the drug carried as it is throughout the product. [9, 17-19, 24]

ADVANTAGES:

1. Formulate slightly and very slightly water-soluble and practically water-insoluble liquid and solid drugs.
2. Increases bioavailability of poorly water soluble drugs.
3. Less production cost compared to soft gelatin capsules.
4. Suitable for industrial production.
5. Suitable for controlled drug delivery
6. Production cost is lower than soft gelatin capsules.
7. useful for formulation of liquid medications
8. Drug release can be modified by changing suitable ingredients
9. Improvement in drug wetting properties and also improving the drug dissolution profiles.
10. Sustained release formulations having water insoluble drugs exhibit zero order release.
11. Exhibits enhanced in-vitro and in-vivo drug release as compared to commercial products, including soft gelatin capsule preparations.
12. Used for formulation of liquid oily drugs. [1, 2, 4-9]

DISADVANTAGES:

1. Liquisolid system requires low drug loading capacities.
2. Requires more efficient excipients and provide faster drug release with smaller tablet size.
3. Higher amounts of carrier and coating materials are required. [3, 4, 7]

LIMITATIONS:

1. Not suitable for formulation of high dose water insoluble drugs.
2. If more amounts of carrier is added it increase the flow properties of powder, it may increases the tablet weight too, hence it is difficult to swallow.
3. It does not require chemical modification of drugs.
4. Acceptable compression may not be achieved because the liquid drug may be squeezed out during compression resulting in unsatisfactory tablet weight. [5, 6, 9]

COMPONENTS: Table: Components & their examples

Drug candidates	Hydrochlorothiazide,Digitoxin Prednisolone, Digoxin , Hydrocortisone, Spironolactone etc.
Non Volatile Liquids	Poly Ethylene Glycol 200, Poly Ethylene Glycol 300, Poly Ethylene Glycol 400, Glycerine, Propylene Glycol, fixed oils.
Carrier Materials	Microcrystalline Cellulose PH 101, Microcrystalline Cellulose PH 200, Lactose, Methyl Cellulose, Ethyl Cellulose, Starch1500, Ethocel, Eudragit RL, Eudragit RS 12, Hydroxy Propyl Methyl Cellulose K4M, Hydroxy Propyl Methyl Cellulose K100M, Xanthum Gum, Guargum.
Coating Materials	Aerosil 200, Silica (Cab-O-Sil M5), Syloid 244FP, and Colloidal Silicon Dioxide.
Disintegrant	Sodium Starch Glycolate (Explotab, Primogel), Croscarmellose Sodium, Cross Polyvinyl Pyrrolidine, Pregelatized Starch.
Lubricant	Magnesium Stearate
Release rate retarder	Eudragit RS, RL, Hydroxy Propyl Methyl Cellulose K100M, K15M, K4M.

PREPARATION OF LIQUISOLID TABLET

Drug + non-volatile solvent

Hot medication is added into carrier and coating material

This mixture is continuously mixed in a mortar

Mixing process is carried out in three steps

Step 1: Mixture is rotated for 1 rotation per second for one minute for a complete mixing of liquid medication in powder

Step 2: This mixture is spread over the mortar for 5 minute so that drug get absorb in the interior of powder

Step 3: Powder is scraped off

Disintegrant is added and left for 10-20 minutes

Other additive are added and the punched into tablets

Steps of Liquisolid Technique

A calculated quantity of drug should be dispersed in the non volatile solvent system (Polysorbate 80, Poly Ethylene Glycol-200) termed as liquid vehicle with different drug: vehicle ratio. Then resulting hot medication should be incorporated into carrier and coating material under continuous mixing in a mortar. Mixing process is to be carried out in three steps which is shown in fig. above. Step1. System is blended at an appropriate mixing rate of one rotation per second for approximately one minute in order to evenly distribute liquid medication in the powder. Step 2: The liquid / powder admixture is evenly spread as a uniform layer on the surface of a mortar and left standing for approximately 5 minute to allow dug solution to be absorbed in the interior of powder particle. Step 3: Powder is scraped off the motor surface by mean of aluminium spatula and then blended with disintegrant like Sodium Starch Glycolate and other remaining additives are added according to their application and mixed for a period of 10 to 20 minute in a mortar. The final mixture should be compressed using the manual tabletting machine to achieve tablet hardness. [3-8, 13, 14, 22]

CHARACTERISATION:

1) Differential scanning calorimetry (DSC): Is a thermoanalytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the experiment. It is used to know the possible interactions between drug and excipients used in the formulation. 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. Thermal properties of the untreated drug and prepared samples are analyzed by DSC. About 5 mg of sample is heated in a hermetically sealed aluminium pans. Heat runs for each sample were set from 30°C to 350°C at a heating rate of 10°C/ min, using nitrogen atmosphere of flow rate 100ml/ minute.16

2) Fourier transform infra-red spectroscopy (FTIR): It is a technique which is used to obtain an infrared spectrum of absorption, emission and Raman scattering of a solid, liquid or gas. FTIR spectrometer simultaneously collects spectral data in a wide spectral range. FTIR spectrum of the drug and the prepared samples were subjected to IR spectrophotometer under identical conditions by Potassium Bromide pellet technique. Spectrum is collected over a region of 4000-400 cm-1.16

3) X-ray diffraction (XRD): A primary use of the technique is the identification and characterization of compounds based on their diffraction pattern. For the characterization of crystalline state, (XRD) patterns are determined for physical mixture of drug and excipients used in formulation and for the prepared liquisolid compacts. Absence of constructive specific peaks of the drug in the liquisolid compacts in X-ray diffractogram. specify that drug has almost entirely converted from crystalline to amorphous or solubilised form. Such lack of crystallinity in the liquisolid system was understood to be as a result of drug solubilization in the liquid vehicle i.e., the drug has formed a solid solution within the carrier matrix. This solubilization of drug in the liquisolid compacts it may contribute to the consequent improvement in the apparent solubility and enhancement of dissolution rate of the drug. [2, 3, 6, 13, 15, 21]

PRE-COMPRESSION STUDIES OF LIQUISOLID PREPARATION:

1) Angle of repose: Angle of repose can be measured by fixed funnel method. The frictional forces in loose powder or granules can be measurement by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. Thus r being the radius of the base of the conical pile. This is shown in table below,

$$\text{Tan } \theta = h/r$$

Flow property	Angle of repose (degrees)

Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65

2) Bulk density:

Bulk density refers to the measure used to describe a packing of particles or granules. Bulk density is defined as the mass of powder divided by the bulk volume and is expressed in grams per milliliter (g/mL) although the international unit is kilogram per cubic meter (1 g/mL = 1000 kg/m3) because the measure are made using cylinders. It may also be expressed in grams per cubic centimetre (g/cm3). The equation for determining bulk density (ρb) is follows,

$$\rho b = M / Vb$$

where,

ρb = Bulk density

M = Mass of sample in g

Vb = Total volume of packing

3) Tapped density: Tapped density can be defined as mass of blend in the measuring cylinder divided by its tapped volume. The formula is follows,

$$\rho t = M / Vt$$

Where,

ρt = Tapped density

M = Mass of blend in g

Vt = Tapped volume of blend in cm3

4) Carr's index: The compressibility index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities and is calculated using the following formula as,

$$\text{Carr's Index} = \rho t - \rho b / \rho t * 100$$

Where,

ρb = bulk density

ρt = tapped density

5) Hausner's ratio: A flow property of powder mixure can be determined by Hausner's ratio. It is calculated by following formula,

Hausner's ratio = Tapped density/ Bulk density

A Hausner ratio greater than 1.25 is considered of poor flow ability. [5-6, 9, 11, 12, 15-18]

POST COMPRESSION EVALUATIONS

1) Hardness:

Monsanto hardness tester can be used for the determination of the hardness. The tablet to be tested was held between a fixed and moving jaw and reading of the indicator adjusted to zero. The force applied to the edge of the tablet is gradually increased by moving the screw knob forward until the tablet breaks. Reading is noted down and is expressed in kg/cm.

2) Thickness:

The crown to crown thickness of tablets is measured by Vernier Caliper. It is expressed in mm. the thickness variation allowed are ± 5% of the size of the tablet.

3) Weight variation:

20 tablets are selected randomly from the lot and weighed individually to check for weight variation. Pharmacopoeial limits are shown as,

Limits	IP/BP	USP
10%	120 mg or less	130mg or less
7.5%	120mg-250mg	130mg -324 mg
5%	250mg or more	324mg or more

4) Uniformity of Drug content:

The drug content can be determined by triturating sufficient amount of tablets and powder equivalent to average weight was added in 100 ml of suitable buffer solution. Followed by stirring for 30 min. Dilute suitably and the absorbance of resultant solution was measured spectrophotometrically.

5) In-vitro drug release studies:

The release rate of drug from tablets can be determined using USP dissolution testing apparatus 2 (paddle method). The dissolution test performed using 900 ml of suitable buffer solution at 6.

6) Friability:

The friability of the tablet can determined Roche Friabilator. It is expressed percentage (%). 10 tablets were initially weighed (Winitial) and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 minutes. The tablets were weighed again (Wfinal). And the % friability was calculated as,

$$F= (Winitial)-(Wfinal)/(Winitial) \times 100$$

7) Stability Studies:

The stability studies are conducted to know the shelf life of the products. Shelf life is defined as the time required reducing the concentration of the reactant to 90 percent of its initial concentration. To know the information on the stability of liquisolid systems, the effect of storage on drug release profile and thecrushing strength of liquisolid compacts were investigated. Stability studies of liquisolid systems containing hydrocortisone (ambient conditions, 10 months), Piroxicam (24oC/76% R.H., 4 weeks), carbamazepine (24oC/76% R.H., 6 months), Indomethacin (24oC/76% R.H.,12 months) showed that storage at different conditions may not affect the hardness and drug release profile of liquisolid compacts. This indicates that the technology is a promising technique to enhance the release rate without any physical stability problem. [9, 11, 14, 15, 17-24]

CONCLUSION:

Poor bioavailability is solely caused by low water solubility. One of the technique to increase solubility is liquisolid technique which is discussed above. As highest drug release rates are observed with liquisolid technique, liquisolid compacts may be optimized by selection of proper non volatile solvent, carrier and coating materials. The technique also sustained the drug release properties of the water soluble drugs by using suitable biodegradable polymers with appropriate excipient ratios.

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