LIQUISOLID TECHNIQUE A NOVEL APPROACH TO ENHANCE SOLUBILITY AND BIOAVAILABILITY

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ABSTRACT
Liquisolid technique is a new approach for delivery of drugs through oral route. This technique is suitable for poorly or water insoluble drugs and also for immediate or sustained release formulations. Design of this technique was according to new mathematical model proposed by Spireas et al. The drug is dissolved or dispersed in suitable non-volatile solvent and this liquid medication is converted to free flow powder by using carrier and coating material. To this suitable excipients were added and tableting by direct compression.

Key words: Liquisolid technique, insoluble drugs, non-volatile solvent, direct compression.

INTRODUCTION
Solubility of drugs is a major factor in the design of pharmaceutical formulations lead to variable oral bioavailability. Dissolution is an important factor for absorption of drugs especially in case of water insoluble or poorly soluble drugs (Brahmankar et al., 2002). The rate limiting step for most of the pharmaceutical formulations is dissolution. Various methods used to increase the solubility of poorly water soluble drugs are solid dispersions (Shinde et al., 2010) inclusion complexes with β-cyclodextrins (Hiremath et al., 2008), micronization (Kornblum et al., 1970), eutectic mixtures (Sekiguchi et al., 1961) and spray-drying technique (Rajarajan et al., 2009). The new developed technique by Spireas (Spireas et al., 2002) liquisolid system improves the dissolution properties of water insoluble or poorly soluble drugs.

In liquisolid technique the drugs which are insoluble or poorly soluble drugs are dissolved or dispersed in suitable non-volatile solvent and converted into free flow powder by using carrier material proposed by Spireas (Bolton et al., 1999). The drug is present in the liquid medicament as solubilized or molecularly dispersed state, so the dissolution is enhanced due to increased surface area, wetting area and also increases bioavailability (Khaled et al., 2001).

Before formulating the liquisolids first perform the preformulation studies these include

1. Solubility studies
2. Angle of slide
3. Liquid load factor
4. Pre-compression studies

Solubility studies
Spectroscopic method
It includes determination of solubility of drug in different non-volatile solvents by preparing saturated solutions. Saturated solutions are prepared by adding excess amount of drug to the solvent and placed in orbital shaker for 48hr at 25°C. Then the solutions were filtered, diluted and analyzed by U.V spectrophotometer.

Synthetic method for determination of solubility
In this method 1-40mg of sample (drug) was taken in screw cap vials to which incremental amounts of solvent is added and was shaken for two minutes after each addition of solvent in vial shaker until clear solution is formed (Furer et al., 1976). Determined the solubility of the sample by using the following formula

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Solubility = \frac{\text{Amount of drug taken (mg)}}{\text{Volume of solvent added (ml)}}

**Angle of slide**

The required amount of carrier material is weighed and placed on a slide and gradually raise the slide till the slide is angular to the horizontal. The angle at which carrier slides from the slide is measured as angle of slide. It is used to measure the flow properties of powders. The 33° is optimum for flow of powders (Tayel et al., 2008).

**Liquid load factor (L)** (Spireas et al., 1993)

It is defined as the ratio of weight of liquid medication (w) to weight of carrier material (Q). It is determined by dissolving or dispersing the drug in non-volatile solvent and to this carrier-coating material admixture is added and blended. The amount of carrier-coating admixture is used to convert into free flow powder and it is determined by using the following formula.

\[ Lf = \frac{W}{Q} \]

W = weight of liquid medication
Q = weight of carrier material

It is used to calculate the amount of carrier and coating material in each formulation.

The excipients ratio R of powders is defined as ratio of weight of carrier and coating material present in the formulation. R is suitably selected for successful formulation.

\[ R = \frac{Q}{q} \]

Q = weight of carrier
q = coating material

**Method of preparation of liquisolid tablets**

1. **DRUG + NON-VOLATILE SOLVENT**
2. Dissolved or dispersed
3. **DISINTEGRANTS**
4. **CARRIER + COATING MATERIAL**
5. Mix and add
6. **POWDER FORM**
7. **COMPRSSED TO TABLETS**
8. **DIRECT COMPRESSION**

First the drug is dispersed or dissolved in the non-volatile solvent, to this carrier and coating material mixture in a ratio, usually 20:1 is added to the liquid medication. The liquid medication is now converted to powder form. Before preparing into compacts pre-compression studies have to be performed.

**Materials for preparation of liquisolid systems**

**Solvents:** Non-volatile solvents like PEG 600 and 400, Tween80 and 20, Span80 and 20, Glycerin, propylene glycol (Javadzadeh et al., 2007) etc.

**Carrier materials:** Various grades of microcrystalline cellulose such as pH101and 200(Spireas et al., 2002), Starch 1500, Fujicalin (Fuji Chemicals 2009) etc.

**Hydrophobic carrier:** Eudragit RL and RS (Javadzadeh et al., 2008), HPMC K, M, (Indrajeet et al., 2009) (sustained release) etc.

**Coating material:** Aerosil 200 (Fahmy et al., 2008), silica (Cab-O-Sil M,), Syloid etc.,

**Disintegrants** (Ferrari et al., 1996): Sodium starch glycolate, cross carmelose sodium (Yadav et al., 2009), cross povidone, explotab (Sanjeev Raghavendra et al., 2010), Pregelatinized Starch (Alebiowu et al., 2001) etc.
Pre-compression studies
Flow property (Banker et al., 1987)
Flow property is important in formulation and industrial production of tablet dosage form. Angle of repose, Carr’s index, compressibility index, tapped density etc., have to be performed.

Differential scanning calorimetry (DSC)
It is used to determine the interactions between drug and excipients, which indicates the success of stability studies (Craig et al., 2007). The drug has a characteristic peak, absence of this peak in DSC thermogram indicates that the drug is in the form of solution in liquid formulation and it is molecularly dispersed within the system (Fahmy et al., 2008).

Fourier Transform Infrared spectroscopy (FTIR)
( Bhise et al., 2009)
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.

X-ray diffraction (XRD)
XRD studies are used to determine the whether the drug is solubilised or in amorphous form. The disappearance of characteristic peaks of drug and their by appearance of peaks which belongs to carrier is observed (Spireas et al., 1992).

In vitro release studies (USP 2005)
The in vitro release studies were performed by using the dissolution apparatus and compared the formulated liquisolid tablets with direct compression tablets. The percentage drug release was estimated.

Scanning electron microscopy (SEM)
SEM analysis was performed to determine the crystallinity of drug in liquisolid system. The disappearance of crystalline nature of drug indicate that the drug is solubilised in the system (Fahmy et al., 2008).

Criteria for selection of liquisolid technique
Liquisolid technique was simple method of preparation and applied for low dose water insoluble drugs. The formulation of the high dose insoluble drugs as liquisolid tablets is one of the limitation i.e., more than 50 mg. But this limitation can be overcome by adding some materials such as polyvinyl pyrrolidone (PVP) to liquid medication to produce dry powder containing liquid with high concentration of drug. By using hydrophobic carrier can alter the drug release (sustained release).

Advantages of liquisolid tablets
- Solubility of poorly soluble or insoluble drugs can be increased
- Drug release can be modified
- Bioavailability of drug can be enhanced
- Alter the dissolution rate (sustained release)
- Low cost
- Simple method of preparation
- Industrial applicable

Application of liquisolid technique
1. Enhanced solubility and dissolution rate

Famotidine
Famotidine is a histamine H₂-receptor antagonist that inhibits stomach acid production, and it is commonly used in the treatment of peptic ulcer disease. The liquisolid tablet formulations Famotidine showed higher drug dissolution rates than the conventional directly compressed tablets. The drug release was 78.36% during the first 10 min which is 39% higher than that of the directly compressed tablets (Rania et al., 2008).

Naproxen
Naproxen is a non-steroidal anti-inflammatory drug (NSAID) commonly used for the reduction of pain, fever, and inflammation. Liquisolid technique changes the properties of naproxen particles by simply dispersing the drug particles in a non-volatile hydrophilic liquid vehicle, which increase the wetting properties of drug particles, and hence improve the dissolution profiles and might improve bioavailability of the drug. At present, naproxen is available commercially in high dose tablets between 250 and 500 mg; the liquisolid formulations may help in reduction of the dose (Ngik et al., 2009).

Bromhexine hydrochloride (BXH)
Bromhexine hydrochloride is a mucolytic agent used in the treatment of respiratory disorders associated with viscid or excessive mucus. BXH has a poor solubility which is a major factor in the design of pharmaceutical formulations. Liquisolid compacts of BXH were distinctly higher as compared to directly compressed tablets, which show significant benefit of liquisolid in increasing wetting properties and surface area of drug available for dissolution (Sanjeev Gubbi et al., 2009).

Carbamazepine
Carbamazepine (CBZ), 5H-dibenzazepine-5-carboxamide, is a sodium channel blocker belongs to BCS class II drug and its bioavailability is limited by its poor dissolution rate in GI. It is used in the treatment of epilepsy and trigeminal neuralgia for over 40 years.
Different liquisolid formulations of carbamazepine were prepared by dissolving the drug in the non-volatile solvents and adsorbing the liquid medication onto the surface of carrier coating material. In order to reduce the amounts of carrier and aerosol in liquisolid formulations, some additives polyvinylpyrrolidone (PVP), hydroxypropyle methylcellulose (HPMC) and polyethylene glycol (PEG 35000) were added. The increase in PVP concentration in liquid medication caused a dramatic increase in dissolution rate (Javadzadeh et al., 2007).

Rofecoxib
Rofecoxib is a practically insoluble non-steroidal anti-inflammatory drug. The liquisolid tablets of Rofecoxib showed significant increased in dissolution profiles compared to the commercial tablets (Khalid et al., 2010).

Piroxicam
Piroxicam belongs to BCS class II, the rate of its oral absorption is often controlled by the dissolution rate in the gastrointestinal. The dissolution behaviour of piroxicam liquisolid compacts was investigated in simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 7.2) showed markedly increase in dissolution rate compared to commercial formulations (Javadzadeh et al., 2005).

2. Enhancement of bioavailability
Atorvastatin calcium
Atorvastatin calcium (ATR) is a BCS class II drug used as a lipid lowering agent by acting as HMGCoA reductase inhibitor. The prepared liquisolid compacts of ATR showed higher release rates compared to the directly compressed tablets. The pharmacokinetic parameters of liquisolid compacts of ATR, such as the AUC, tmax and Cmax, showed the better bioavailability compared with the conventional formulation (Sanjeev Gubbi et al., 2010).

Hydrochlorothiazide
Hydrochlorothiazide is often used in the treatment of hypertension and diuretic. The prepared liquisolid formulations of hydrochlorothiazide tablets showed significantly greater extent of absorption and bioavailability than the commercial tablets which was evaluated in beagle dogs (Khaled et al., 2001).

3. Formulation of Sustained release tablets
Sustained release dosage forms are designed to release the drug at a predetermined rate by maintaining a constant drug release for specific period of time with minimum side effects in terms of efficacy, safety and patient compliance. Ideally, controlled release formulations will provide therapeutic concentration of the drug in the blood which is maintained throughout the dosing interval (Chien et al., 1990, Fukuda et al., 2006).

Liqisolid technique was a new approach to alter the dissolution properties of the drug by using hydrophobic carriers instead of hydrophilic carriers (Bolton et al., 1998).

Propranolol hydrochloride
Propranolol hydrochloride is a β- adrenergic blocking agent having short elimination half-life of 3 hr. Propranolol hydrochloride liquisolid compacts were prepared by dispersing the drug in polysorbate 80 and used hydrophobic carrier, Eudragit RL. This investigation showed that the release of drug from the formulations followed zero-order release kinetics and Tween 80 has important role in sustaining the release of drug from liquisolid compacts (Javadzadeh et al., 2008).

Tramadol hydrochloride
Tramadol hydrochloride is a centrally acting opioid analgesic, used in treatment of moderate to severe pain with half life of 5.5hr. Liquisolid sustained release formulations were prepared by using HPMC K4M as a sustained release agent and compared with the marketed preparations. The release profiles of drug followed the Peppas model which is the best-fit model for sustained release dosage forms (Amrit et al., 2010).

Theophylline
Theophylline, is a methylxanthine drug used in therapy for respiratory diseases such as Chronic obstructive pulmonary disease (COPD) and asthma. Liquisolid tablets were prepared by mixing liquid medication with silica–Eudragit RL or RS followed by the compaction. The effect of co-solvent and HPMC on theophylline release was determined. The sustained release was enhanced in liquisolid compacts by HPMC (Ali Nokhodchi et al., 2010).

Conclusion
Liquisolid system contains liquid medications in powdered form and this novel technique is an efficient method for formulating water insoluble drugs. Rapid disintegration rates are observed compared to conventional tablets showed improved release rates and greater bioavailability. The use of non-volatile solvent causes increased wettability and ensures molecular dispersion of drug in the formulation. By using hydrophobic carriers can modify release (sustained release) of drugs from the liquisolid tablets.
REFERENCES


