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LIQUISOLID COMPACT: A NOVEL APPROACH TO ENHANCE SOLUBILITY AND DISSOLUTION RATE

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ABSTRACT

Therapeutic effect depends upon the bioavailability of the drug which in turn depends upon the solubility and dissolution rate. A solubility problem is a major challenge for the pharmaceutical industry with developments of new pharmaceutical products. There are various techniques but liquisolid compact is a new and promising method that can change the dissolution rate of water insoluble drugs. According to the concept of liquisolid systems water-insoluble drugs dissolved in suitable non-volatile solvents, may be transformed into free-flowing and readily compressible powders by a simple admixture with excipients referred to as the carrier and coating materials. Compared to conventional tablets, rapid disintegration rates are observed and therefore, they confirm improved release rates in addition to 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. Hence Liquisolid compacts containing water-insoluble drugs expected to display enhanced dissolution characteristics and consequently improved oral bioavailability.

Keywords *– Liquisolid compact, Insoluble / poorly soluble drugs, bioavailability, etc.*

1. INTRODUCTION

The oral Route is the most chosen route of drug administration because of high patient compliance and drug development. Oral bioavailability and ultimately the therapeutic efficacy of drug are determined by the extent of drug solubility and permeability. Therefore solubility is the important factor to attain desired concentration of drug in systemic circulation for pharmacological response to be shown[1-3]. Solubility problems is a major challenge for the pharmaceutical industry with developments of new pharmaceutical products. The rate of dissolution of a drug is a function of its intrinsic solubility and its particle size and therefore solubility of a drug substance is a major factor that determines its dissolution rate and hence its absorption and bioavailability. If the solubility of the drug is less than desirable, then measures must be taken to improve its solubility or else use another more soluble drug form. The different

properties of drug like salt form, particle size, polymorphism, complexation, wettability etc. that affect drug dissolution and its rate and can be targeted to enhance solubility of poorly water soluble drugs[4-7].

2. NEED OF SOLUBILITY ENHANCEMENT

Most of the drugs like weakly acidic or weakly basic having poor aqueous solubility leads to insufficient and gastrointestinal mucosal toxicity and variable bioavailability. For orally administered drugs solubility is the one of the important rate limiting parameter to reach desired concentration in complete circulation for pharmacological response. Therefore poorly water soluble drugs frequently require high doses and need high dosage regimens in order to influence therapeutic plasma concentrations after administration[8].

The BCS is a scientific framework to classify a drug substance based on its aqueous solubility and membrane permeability. rate limiting step for BCS class II & IV drugs, is the drug release from the dosage form and solubility in gastric fluid, so that it is important to increase solubility of these drugs to provide maximum therapeutic effect for BCS class II & IV drugs[9].

Fig 1: BCS classification

Class I	**Class II**
High permeability High solubility	High permeability Low solubility
Class III	**Class IV**
Low permeability High solubility	Low permeability Low solubility

There are different types of techniques are available to formulate oral drug delivery system to enhance the solubility of poorly water soluble drugs i.e., Micronization[10,11], salt formation[12], solubilisation by surfactants[13,14], Solid dispersions[15], use of complexing agents[16], co solvency[17], chemical modification[18], pH adjustment[19], etc. These techniques have been introduced to increase the dissolution rate in addition to absorption and bioavailability. Micronization is the process of size reduction owing to the reduction in particle size the predictable dissolution & absorption rates may not be attained because the fine particles tend to form aggregates due to increased surface energy & Vander Waals attraction. Effect of micronization is also often unsatisfactory, particularly when the drugs are encapsulated or tableted[20,21]. Solid dispersions are significant for improving solubility, dissolution rate, wettability and further bioavailability of drugs. However, only few products are available commercially, for the reason of their poor physical characteristics for dosage form formulation. Solid dispersions prepared by melting technique may leads to stability problems moreover is difficult to handle for capsule filling and tablet masking process especially when prepared using water soluble carrier such as PEG and PVP which are soft and tacky mass[22-25]. Salt formation may causes hygroscopicity and stability problem. By the making the use of co-solvents, precipitation may possibly take place upon dilution. Solubilization of drugs in organic solvents or in aqueous media by the use of surfactant and co-solvents leads to liquid formulation that are usually undesirable from patient acceptability and compatibility In case of complexation, the size of dosage form may increase, if the complexing agent is of high molecular size. If the ratio of drug and complexing agent increase there is chance of toxicity[2, 26, 27].

Liquisolid technology also called as “Powder Solution Technology”. It is most promising technique for promoting dissolution and ultimately the solubility of drug is the formation of liquisolid compact among the various available techniques. Liquisolid compacts enhance dissolution rate of water insoluble drugs to a greater extent and also enhances the drug flow property. A liquisolid compact is formed by conversion of liquid drugs, drug suspensions or drug solution in a suitable non-volatile solvent, into dry, non-adherent, free-flowing and compressible powder mixtures by blending the suspension or solution with suitable excipients like carriers and coating materials, lubricants, disintegrants and glidants etc (Fig 1). Cellulose, lactose and starch are used as the carrier materials whereas silica

powder is used as the coating material. The compression and good flow properties of liquisolid compact may be attributed due to large surface area and fine particle size of these carrier and coating materials. Hence liquisolid compacts containing water-insoluble drugs expected to show enhanced dissolution characteristics and consequently improved oral bioavailability of drugs[28-35].

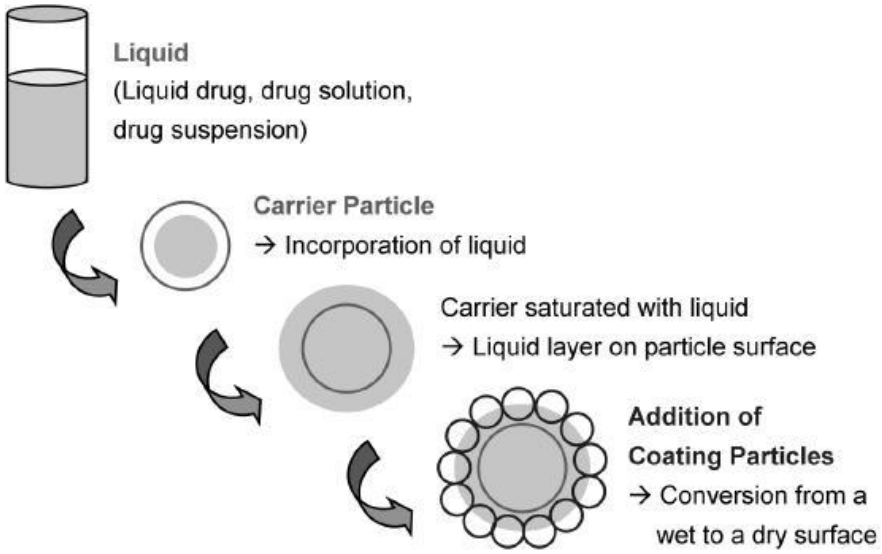

Fig 1. Steps involved in the preparation of liquisolid compacts

3. COMPONENTS OF LIQUISOLID COMPACT

Liquisolid compact mainly includes:

3.1 Non volatile solvent

Non volatile Solvent should be inert, preferably water-miscible, high boiling point and not highly viscous organic solvent systems and compatible with having ability to solubilise the drug. The non volatile solvent acts as a binding agent in the liquisolid formulation. Polyethylene glycol 200 and 400, polysorbate 80, glycerin, and propylene glycol are the non volatile solvents used for the formulation of liquisolid systems include [34,36].

3.2 Disintegrant

Super disintegrate improves the rate of drug release, water solubility also the wettability of liquisolid granules. Mostly super disintegrates like Sodium starch glycolate, Pumogel, Crosspovidone, Sodium crosscarmellose, Pre gelatinized starch[37-40].

3.3 Drug candidate

This technique was successfully applied for water insoluble drugs, lipophilic or highly permeable drugs, drugs having slow dissolution rate, low dose drugs, drugs having slow disintegration rate, drugs having poor oral bioavailability etc [41]. Examples of drug candidates include piroxicam[30] carbamazepine [36], indomethacin [34], hydrocortisone [42], etc. and other liquid medications include water insoluble vitamins and fish oil, etc.

3.4 Carrier material

Carrier material should be porous material possessing sufficient absorption properties which contributes in liquid absorption. This include Microcrystalline cellulose (MCC) PH 101,MCC PH 200,Lactose,Methyl cellulose ,Ethyl cellulose, starch1500,Ethocel are widely

used for the preparation of conventional tablets. The carrier and coating materials capable of retain only certain amounts of liquid so as to maintain acceptable flow and compression properties consequently, increasing moisture content of carrier's results in decreased powder flowability[43-44].

3.5 Hydrophobic carriers

Sustained release formulation be possible using hydrophobic carriers like Eudragit RL, Eudragit RS 12,HPMC K4M,Xanthum gum, Guargum, etc[43-44].

3.6 Coating material

Coating material is required to cover the surface and so maintain the powder flowability. It is a substance 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. These are highly adsorptive, flow-enhancing coating particles ranging from very fine 10 nm to 5,000 nm in diameter. Coating material includes Aerosil 200, Silica (Cab-O-Sil M5),syloid and colloidal silicon dioxide[31,45].

3.7 Carrier

Coating Material Ratio (R): In a formulation, it is the ratio among the quantities of carrier (Q) and coating materials (q) present. It is represented as:

$$R = \frac{Q}{q}$$

3.8 Lubricants

These are proposed to reduce the friction. Eg: Stearic acid and its salts, talc etc[46].

3.9 Glidants

These are intended to improve the flow performance between the particles by reducing the friction. eg: Talc, corn starch and Silica derivatives, etc[46].

4. MECHANISMS OF ENHANCEMENT OF DRUG RELEASE

Several mechanisms are developed to enhance the drug release rate of a drug and hence dissolution from a liquisolid system. Three important mechanisms include an increase in effective drug surface area, an increase in aqueous solubility and an improved wettability of drugs.

4.1 Enhancement of surface area

By increasing the effective surface area of drug leads to the dissolution of drug with the liquid vehicle is increased. If the drug within the liquisolid system is completely dissolved in the liquid vehicle it is positioned in the powder substrate still in a solubilised, molecularly dispersed state. The surface area available for drug release is therefore much greater than that of drug particles within directly compressed tablets. Consequently the release rate decreases, with increasing the fraction of undissolved drug exceeding the solubility limit in the liquid vehicle. It has been realistic with various drugs that the release rates are directly proportional to the fraction of the molecularly dispersed drug (*FM*) in the liquid formulation. Spireas defined the *FM* as the ratio among the drug's solubility (*Sd*) and the actual drug concentration (*Cd*) in a vehicle.

***FM* =Sd/Cd**

Where, FM =1 if Sd ≥ Cd(41,47)

4.2 Enhancement of aqueous solubility

A relatively small quantity of liquid vehicle is not sufficient to solubilize the total quantity of drug. 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[47,48].

4.3 Enhancement of wetting properties

The liquid vehicle can promotes the wettability of liquisolid particle by acting as a surface active agent by lowering the surface tension between dissolution medium and tablet surface. Wettability of liquisolid systems has been demonstrated by measurement of contact angles and water rising times. Figure 3 represents the comparison of wettability between a conventional tablet and a liquisolid tablet[39,49].

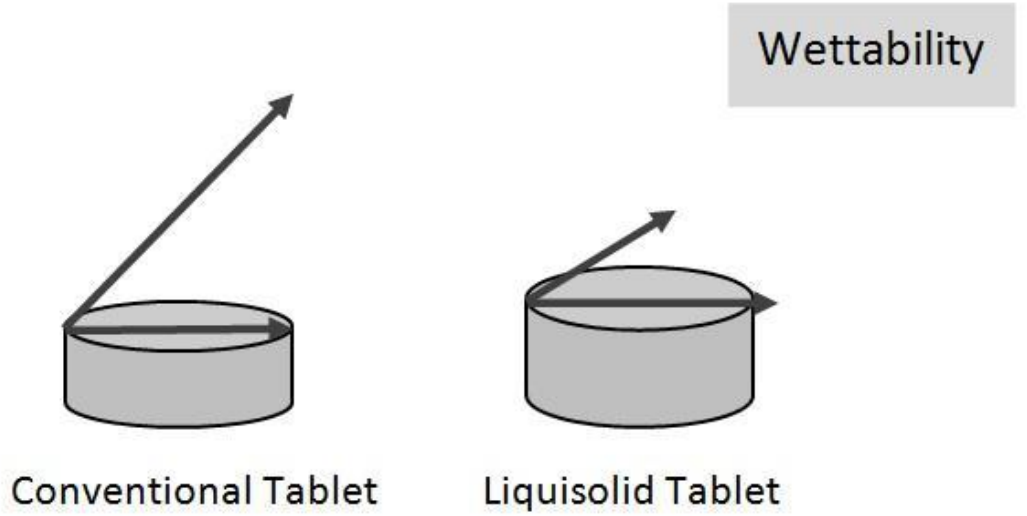

Fig.3. Assessment of Wettability between a Conventional tablet and a Liquisolid tablet

5. **CLASSIFICATION OF LIQUISOLID SYSTEMS**

Based on the formulation technique used, systems may be classified into two categories namely,

a.Liquisolid compacts

b.Liquisolid Microsystems

The term “Liquisolid compacts” refers to immediate or sustained release tablets or capsules Prepared, combined with the inclusion of suitable adjuvant required for tableting encapsulation, such as lubricants, disintegrates or binders. The term “Liquisolid Microsystems” refers to capsules prepared by addition of drug with carrier and coating materials with incorporation of an additive e.g., PVP in the liquid medication. The advantage of this new technique is that the resulting unit size of liquisolid Microsystems may as much as five times less than that of liquisolid compacts.[50-52]

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

a.Powdered drug solutions

b.Powdered drug suspensions

c.Powdered liquid drugs

Powdered drug solutions(e.g. prednisolone solution in propylene glycol) and suspensions(e.g. gemfibrozil suspension in polysorbate 80) may be produced from the conversion of drug solutions or drug suspensions into Liquisolid system. Powdered liquid drugs(e.g. clofibrate, liquid vitamins, etc.) are produced from the formulation of liquid drugs into Liquisolid systems. [29,41,42]

6. **ADVANTAGES** [28,29,31,34,53-56]

✓Rapid release liquisolid tablets (or) capsules exhibit enhanced *in vitro & in vivo* drug release compared to their commercial products.

✓It can be used to formulate liquid medications.

✓Used in controlled drug delivery

✓Simple method of preparation and that is similar to that of conventional tablets preparation.

✓Distinguish the dosage form by incorporation of color into liquid vehicle.

✓Drug release can be modified by changing suitable ingredients.

✓Reduce the excipients in formulation in contrast to other formulations like solid dispersions.

✓Sustained released tablets (or) capsules of water insoluble drugs exhibit zero order release.

✓Low dose drugs can be formulated

✓Suitable for industrial production.

✓Drug can be present in molecularly dispersed form.

✓Less production cost compared to soft gelatin capsules.

✓Exclude the process approaches like micronization, nanonisation techniques

✓Rapid-release optimized liquisolid tablets or capsules of BCS class II & IV drugs exhibit enhanced in-vitro and invivo drug release as compared to their commercial counterparts.

✓Increased bioavailability of poorly water soluble drugs.

7. **DISADVANTAGES** [38,44,46,47, 54-58]

✓Higher amounts of carrier and coating materials are required. This will increase the weight of tablets to above one gram which makes them difficult to swallow.

✓It is not appropriate to high dose insoluble drugs (>100 mg).

✓Requires more efficient excipients and it should provide faster drug release with smaller tablet size.

✓It just depends on excipients of high adsorption property and high specific surface area.

✓Liquisolid system requires low drug loading capacities.

✓At times it is very difficult to achieve good flow and compactability.

✓Sometimes liquid drug may be squeezed out of the tablet during compression result in improper hardness.

8. APPLICATIONS

Liquisolid technique gives a design to enhance the absorption as well as dissolution rate their by it may enhance the bio availability of a poorly soluble/insoluble or lipophilic drug and to formulate them into immediate release or else sustain release by selection of suitable

solvent and carrier. Liquisolid Formulations offers several applications for drugs having poor bioavailability because of limited or no water solubility. These are summarized as follows.

I. This technique is widely employed for enhancement of dissolution rate and solubility of poorly water soluble drugs like Carbamazapine, Rofecoxib, Famotidine, Bromhexine hydrochloride, Furosemide, Naproxen, Piroxicam, Prednisolone, Indomethacin, etc and also for lipophilic drugs like vitamin A, Clofibrate, etc.

II. Enhancement of bioavailability of drugs like Nifedipine, Hydrochlorthiazide, Repaglinide, Famotidine.

III. Sustained and Controlled release formulations tablets are also prepared by the use of hydrophobic carriers that may show the zero order release similar to osmotic pumps. It is also applicable in probiotics.

IV. Liquisolid Formulations shows better flowability and compressibility

Table 2: Examples and Application of Liquisolid Technique

Sr. No.	Applications	Examples
1.	Enhancement of dissolution rate and solubility	Aceclofenac[39], Prednisolone[41], Naproxen[59], Bromhexine hydrochloride [60],
2.	Enhancement of bioavailability of drugs	Nifedipine [15], Carbamazapine [36]
3.	Sustained and Controlled release formulations	Propranolol [44]. Hydrochlorothiazide [58]
4.	Better flowability and compressibility	Atorvastatin [38]

9. MARKETED PREPARATIONS OF LIQUISOLID TECHNIQUE

There are several commercial products available based on the research activity of liquisolid compaction technology as listed in Table 3. Popularity of liquisolid technique on commercial scale is due to increased bioavailability either by an increased aqueous solubility of the drug, increasing the surface area of drug available for release, or improved wettability of the drug particles.

Table 3: Drugs and their marketed preparations of liquisolid technique [41,61,62]

Sr. No.	Drugs	Brand Nmae
1.	Atovaquone	Mepron
2.	Calfactant	Infasurf
3.	Fluocinolone Acetonide Oil Ear Drops	Dermotic oil
4.	Albuterol Sulfate Inhalation Aerosol	Proair HFA
5.	Rizatriptan Benzoate	Maxalt
6.	Metronidazole	Noritate
7.	Drospirenone and Estradiol	Angeliq
8.	Tretinoin Cream	Renova

10. CONCLUSION

According to liquisolid technology, liquid medications such as solutions or suspensions of poorly water soluble drug in suitable nonvolatile liquid vehicles can be converted into acceptably flowing and compressible powders by blending with selected carriers and coating materials. On the basis its simplicity, low cost and capability of industrial production, Liquisolid technique is a promising alternative for improvement of dissolution property of water-insoluble drugs. Therefore, this formulation of the drug has the potential to be considered for further studies in human in order to be manufactured on a large scale.

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