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A REVIEW ON LIQUISOLID COMPACT

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Abstract:
In the drug development enhancement of oral bioavailability of poorly water soluble drugs is one of the most challenging aspects of drug. The pharmaceutical industry faces the problem of poor dissolution characteristics of insoluble drug. This problem can be solved by applying recent techniques "powdered solution technology" or "liquisolid technology", for formulating water insoluble drugs into rapid-release solid dosage forms. This article gives a brief idea about to enhanced solubility of poor water soluble drugs. The drug is dissolved or dispersed in suitable non-volatile solvent and this liquid medication is converted to free flowing powder by using carrier and coating material. To this powder, suitable excipients are added and tabletting by direct compression. In this case, even though the drug is in a solid dosage form, it is held within the powder substrate in solution or, in a solubilized, almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties. Large scale production of fabricated drug on commercial level. Succesful liquisolid tablet is a determination of optimal flowable liquid retention. The use of non-volatile solvent causes improved wettability and ensures molecular dispersion of drug in the formulation and leads to enhance solubility. By using hydrophobic carriers (nonvolatile solvents) one can modify release (sustained release) of drugs by this technique. Both immediate and sustained release of drug can also be achieved with the help of liquisolid technique. The aim of this study was to review the mechanisms and techniques to improved solubility and dissolution involved in liquisolid compacts.

Key Words: *liquisolid, medication, coating, sustained release, wettability.*

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INTRODUCTION:

The liquisolid technique is governed by Spireas is a novel and newly developed concept, where a liquid may be converted into a free flowing, readily compressible and dry powder by simple physical blending with selected carrier and coating material [6].The more than 40% of new drug developed in pharmaceutical industry are practically insoluble in water. When combined with the in vitro dissolution characteristics of the drug product, the biopharmaceutical classification system (BCS) takes into account three major factors: solubility, intestinal permeability and dissolution rate, all of which govern the rate and extent of oral drug absorption from immediate release solid dosage forms. For BCS class II drugs, the dissolution process is a rate- controlling step, which governs the rate and degree of its absorption. The different techniques have been developed to enhance the solubility of those drugs includes micronization, sublimation, solid dispersion, salt formation complexation, pH adjustment, used of surfactant etc. Among them Liquisolid techniques or powder solution technology is one of the most new technique which promotes the dissolution of water insoluble drugs [3]. The term liquisolid technique its refers to immediate release tablets or sustained release tablets or capsules, combined with the inclusion of appropriate adjuvant required for tabletting or encapsulating. Liquisolid compacts are acceptably free flowing powder and compressible powder forms of liquid medications. The liquid portion, which can be an oily liquid drug, suspension or solution of water insoluble solid drugs in suitable non-volatile liquid vehicles, is incorporated into the carrier material. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Finally the dry, free flowing and compressible powder is obtained. The concentrations of the carrier material, coating materials, disintegrants, lubricants and glidants are optimized to form a non-sticky easily compressible blend [7,8]. The low water soluble compounds show decreased release rate & poor bioavailability. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches. There are three major approaches in overcoming the bioavailability problems due to such causes are [20].

a. The pharmaceutical approach

Modification of the formulation, manufacturing process or the physicochemical properties of the drug without changing the chemical structure.

b. The pharmacokinetic approach

Pharmacokinetics of the drug is altered by modifying the chemical structure.

c. The biological approach

The route of drug administration may be changed such as changing from oral to parenteral route.

TECHNIQUES USED FOR ENHANCED SOLUBILITY:

1 .Micronization
2. Nanonisation
3. Use of surfactants
4. Use of salt forms
6. Solid dispersion
7. Complex with cyclodextrines
8 .pH adjustment
9. High Pressure Homogenization
10. Sonocrystallisation
11. Complexation:
12. Spray drying
13. Liquisolid compact

Micronization:

In this process involves reducing the size of the drug particles to 1 to 10 microns commonly by spray drying or by use of air attrition methods (fluid energy or jet mill).The micronisation is also called as micro milling. e.g. micronization of griseofulvin.

Nanonisation:

It is the process in which drug powder is converted in to nanocrystals of sizes 200-600nm. eg. Amphotericin B There are three basic technologies currently in use to prepare nanoparticles.

- ❖ Pearl milling
- ❖ Homogenisation in water (wet milling as in a colloid mill)
- ❖ Homogenisation in non aqueous media

Use of surfactants:

The used of surfactant as absorption enhancers and enhance both dissolution rate as well as permeability of drug. They enhance dissolution rate primarily by promoting wetting and penetration of dissolution fluid into the solid drug particles.

Use of salt forms:

The salts have improved solubility and dissolution as compared to the original drug. Alkali metal salts of acidic drugs like penicillin and strong acid salts of basic drugs like atropine are more water soluble than parent drugs.

Solid dispersion:

It is a useful pharmaceutical technique for increasing the dissolution, absorption, and therapeutic efficacy of drugs in dosage forms. It refers to a group of solid products consisting of at least two different components, like a hydrophilic matrix and a hydrophobic drug.

Complex with cyclodextrins:
The β and γ- cyclodextrins and their different derivatives have unique ability to form molecular inclusion complexes with the hydrophobic drugs having a poor aqueous solubility. e.g. thiazide diuretics, benzodiazepines.

Use of Amorphous, Anhydrates, Solvates and Metastable Polymorphs:
The internal structure depending upon the solid drugs, selection of proper form of drug is with greater solubility is important. In general amorphous are more soluble than metastable polymorphs, anhydrates are more soluble than hydrates and solvates are more soluble than non-solvates.

pH adjustment:
The Poor water soluble drugs may potentially dissolve in the water by applying a pH change. To access the solubility of this approach, the buffer capacity and tolerability of the selected pH are important to consider. Solubilized excipients that can increase environmental pH within the dosage form to a range higher than pKa value of weekly acidic drugs and increase the solubility of that drug, those excipients that act as alkalizing agents may increase the solubility of weekly basic drugs.

High Pressure Homogenization:
It is used to prepare nanosuspension of many poorly water soluble or water insoluble drugs. In this method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high pressure homogenizer. The principle of this method is based upon the cavitation in the aqueous phase. The cavitation forces within the particles are sufficiently high to convert in the drug microparticles into nanoparticles. The concern with this method is the need for small sample particles before loading and the fact that many cycles of homogenization are required.

Sonocrystallisation:
The recrystallization of poorly water soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size. The novel approach for particle size reduction on the basis of the crystallization by using ultrasound is sonocrystallisation. The sonocrystallisation utilizes ultrasound power characterised by the frequency range of 20–100 kHz for inducing crystallization.

Complexation:
Complexation of drugs with cyclodextrins has been used to enhance aqueous solubility and drug stability. The cyclodextrine used to improve the solubility of poorly water soluble drug. Cyclodextrins of pharmaceutical relevance contain 6, 7 or 8dextrose molecules (α, β, γ-cyclodextrin) bound in a 1, 4-configuration to form rings of various diameters.

Spray Drying:
The solvent evaporation of drug and polymer solution in different ratio is carried out by using a spray dryer. These solutions are prepared by the dissolving drug in methanol and polymer in distilled water and then mix both solutions, which form a clear solution. The solvent evaporated by using a evaporator. The spray dried mixture of drug with polymer is obtained in 20–30 min [22,23].

LIQUISOLID TECHNIQUE:
When the water insoluble drug and dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior as cellulose, and its having a both properties absorption and adsorption take place; i.e. the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. After, the coating material having high adsorptive properties and also having a large specific surface area gives system the desirable flow properties. In the concept of liquisolid system, liquid drugs having low aqueous solubility dissolved in suitable non-volatile solvents, converted in to free flowing and radially compressible powder by simple admixture with selected powdered excipients referred as carrier and coating materials. Microcrystalline cellulose and silica powders used as coating materials [10,13,14].

ADVANTAGES:
1. The water-insoluble solid drug can be formulated into liquisolid systems.
2. The liquisolid compact can be applied to formulate liquid medication such as oily liquid drugs.
3. Simplicity.
4. Better availability of an orally administered water insoluble drug.
5. Lower production cost.
6. The production of liquisolid system is similar to the conventional tablets.
7. Can be used in controlled drug delivery [11,12,21].

DISADVANTAGES:
1. Liquisolid system having a low drug loading capacities.
2. The carrier and coating materials are required.
3. The liquisolid technique is not applicable to high dose insoluble drug.
4. It is only applicable to low dose drug and only water insoluble drugs.
5. It does not require chemical modification of drugs.

APPLICATIONS:
1. It is used to improve bioavailability of water.

2. Several water insoluble drugs on dissolving in different non-volatile solvents have been formulated into liquisolid compacts.
3. The rapid release rates are obtained in liquisolid formulations.
4. These can be efficiently used for water insoluble solid drugs or liquid lipophilic drugs.
5. Solubility and dissolution improvement [15-18].

CLASSIFICATION:

Liquisolid systems may be classified into three subgroups:

1. Powdered drug solution:

The nonvolatile solvents are used to prepared the drug solution , the liquid vehicle does not evaporate and thus, the drug is carried within the liquid system which in turn, is dispersed throughout the final product depending on the consistency of the powder substrate. The quantity of the solid drug dispersed in the liquid medication and the physiochemical properties of the liquid vehicle used the acceptable liquid-to-powder percent ratio will range from 2% to 52%, the most preferable range being 10% to 35%.

2. Powdered drug suspensions

3. Powdered liquid drugs:

The first two may be produced from a conversion of drug solutions or drug suspensions and then from the formulation of liquid drugs into liquisolid system [19].

NEED OF LIQUISOLID SYSTEM:

The oral route is a preferred route of drug administration due to its convenience, good patient compliance and low production costs. In order for a drug to absorb into the systemic circulation following oral administration, the drug must be dissolved in the gastric fluids. Thus, the major challenges to drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water. In addition, up to 50% of orally administered drug compounds suffering from formulation problems related to its low solubility and high lipophilicity. Bioavailability of poorly water soluble hydrophobic drugs (class II in biopharmaceutics classification system) is limited by its solubility and dissolution rate. The dissolution rate of poorly water soluble drugs can be improved by decreasing particle size surface area. The increase the dissolution rate of drugs by decreasing the particle size, to form a nanoparticles and microparticles, to overcome the dissolution problem. The technique of 'liquisolid compacts' is a new and promising approach towards dissolution enhancement. Liquisolid compacts havind a acceptable flowability & compressibility properties [20].

MECHANISMS OF ENHANCED DRUG RELEASE FROM LIQUISOLID FORMULATION:

A.Increased aqueous solubility of the drug:

The mechanism of drug release enhancement it is expected that Cs, the solubility of the drug, might be increased with liquisolid systems. In fact, the 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. At the solid/liquid interface between an individual 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 is a solubilized and molecularly dispersed state. Therefore, the surface area of drug available for release is much greater than that of drug particles within directly compressed tablets. The increasing drug content around the solubility limit and increasing fraction of undissolved drug in the liquid vehicle the release rate can be decreases.

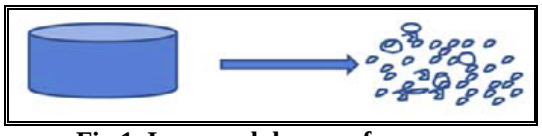

Fig.1. Increased drug surface area

C. Improved wetting properties:

The liquid vehicle can either act as surface active agent (SAA) and has a low surface tension; wetting of the liquisolid primary particles is improved. Wettability of these systems has been demonstrated by the measurement of contact angles and water rising times. The nonvolatile solvent present in the liquisolid system facilitates to wetting of drug particle by decreasing the interfacial tension between the dissolution medium and tablet surface. It shows the lower contact angle of liquisolid compacts than the conventional tablets and thus improved its wettability [19].

Conventional Tablet **Liquisolid Tablet**

Fig.2 Comparison of wettability between a conventional tablet and a liquisolid Tablet

COMPONENT OF LIQUISOLID COMPACT:

1. Drug candidates:

Ex. digoxin, digitoxin, prednisolone, hydrocortisone, polythiazide etc.

2. Non-volatile solvents:

Different non-volatile solvents used to formulate liquisolid compact.

Ex. PEG 200 and 400, glycerin, polysorbate 80 and propylene glycol, Tween 20, 80 etc.

3. Carrier materials:

Carrier material having sufficient ingestion properties.carrier material having a adsorbing properties.

Ex. Avicel PH 102 and 200, LactoseEudragit RL and RS (to manage drug conveyance), etc

4. Coating materials:

The coating material having a fine and profoundly adsorptive particles, for example, different forms of silica, which helps in covering the wet transporter particles and showing a dry looking powder by adsorbing any overabundance fluid. The fluid parcel, which can be a fluid medication, a medication suspension or a medication arrangement in a suitable nonvolatile fluid vehicle, is consolidated into the permeable bearer material. (Fig.3)

5. Disintegrants:

Disintegrants like sodium starch glycolate & crosspovidone etc.[1,2].

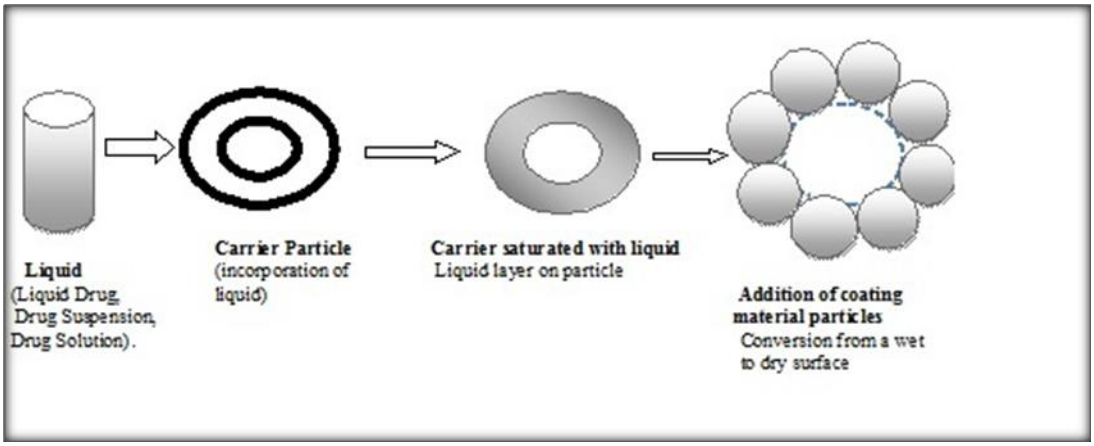

Fig.3. Schematic Representation of Liquisolid System

PREFORMULATION STUDY OF LIQUISOLID COMPACT:

Preformulation Studies incorporates:

1. Determination solvency of medication in diverse non-volatile solvents
2. Determination of angle of slide
3. Determination of flowable liquid retention potential (Φ value)
4. Calculation of liquid load factor (Lf)
5. Liquisolid compressibility test (LSC)

1. Solvency (solubility) studies:

The solubility studies are completed by get ready immersed arrangements of medication in non-volatile dissolvable and examining then spectrophotometrically. Immersed arrangements are arranged by adding over the medication to non volatile solvents and shaking them on shaker for particular time period under the vibration. Then analysed by using a UV spectrophotometer.

2. Determination of angle of slide:
The angle of slide is used to determined the flow properties of powders. Determination of angle of slide is carried out by weighing the measure of carrier material and set toward one side of a metal plate with a polish surface. The end is step by step raised till the plate gets to be precise to the flat at which powder is going to slide. This plot is known as a angle of slide. Point of 33^0 is viewed as ideal.

3. Determination of flowable fluid maintenance potential:
The "flowable fluid retention potential" (Φ-quality) of a powder material its capacity to hold a particular measure of fluid while keeping up great stream properties. The Φ-worth is characterized as the greatest weight of fluid that can be held every unit weight of the powder material to create an acceptably streaming liquid/powder admixture. The Φ qualities are ascertained as indicated by mathematical statement,
Φ esteem = weight of fluid/ weight of solid

4. Calculation of liquid load factor (Lf):
Different concentration of non- volatile solvents is taken and the drug is disintegrated to formed a liquid medication. Such liquid medication is added to the carrier coating material admixture and mixed. Utilizing mathematical medication loading factor are determine and used for calculating the amount carrier and coating materials in every detailing.
Lf = weight of liquid medicament / weight of carrier material.

5. Liquisolid compressibility test (LSC):
Liquisolid compressibility test is used to determine Φ values and involves steps such as preparing carrier coating material admixture systems, preparing several uniform liquid or powder admixtures, compressing each liquid or powder admixtures to tablets, assessing average hardness, determination of average liquid content of crushed tablets, as well as determining plasticity, sponge index and Φ value and Lf [24-33].

EVALUATION PARAMETERS:

1. Weight variation:
20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation is given by the formula:
% Weight variation: Individual wt. –average wt. / Average wt.*100

2. Hardness:
Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets.

3. In vitro drug release:
Release of the drug in vitro, was determined by estimating the dissolution profile, USP 2 Paddle apparatus was used and paddle was allowed to rotate at 50 rpm, phosphate buffer (PH 6.8) (900 ml) and HCL(PH 1.2) (900ml) was used as a dissolution medium.

4. In-vitro disintegration test:
The test was carried out on 6 tablets using a tablet disintegration tester. Water at 37 ± 2 °C was used as a disintegration medium and the time taken for the complete disintegration of the tablet was noted with no palpable mass remaining in the apparatus was measured

5. Content uniformity:
It is the pharmaceutical analysis parameter for the quality control of capsules or tablets. Multiple tablets are selected at random and a suitable analytical method is applied to assay the the individual content of the active ingredient in each tablet. The test for uniformity of content is based on the assay of the individual content of drug substance(s) in a number of individual dosage units to determine whether the individual content is within the limit.

6. Wetting time:
A piece of tissue paper was folded and placed twice and placed in a small petri dish containing sufficient water. A tablet was kept on the paper and the time for complete wetting of the tablet was measured.

7. Water absorption ratio (R):
The weight of the tablet prior to placement in the petri dish was noted (Wb). The wetted tablet was removed and weighed (WA). Water absorption ratio, R, was then determined according to the following equation.
$R=100 \times (Wa-Wb)/Wb$
Where, Wb and Wa are tablet weights before and after water absorption, respectively.

CONCLUSION:

The liquisolid system is the new technique for the formulation of water insoluble drugs to enhance their aqueous solubility, absorption as well as dissolution rate, which leading to enhancement of bioavailability of drugs as compared to conventional directly compressed tablets. The liquisolid technology can be used for the purpose of formulating to modified the drug release system by selecting the right excipient. It is an effective technology in terms of production capability and low cost of formulation. Thus, this technology has the potential for large scale manufacture. The excipients required in the liquisolid system are conventional and commonly available in the market. On the base of the advantages of liquisolid system, it is envisaged that liquisolid system could play an important role in modern solid dosage forms.

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