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REVIEW ON NOVEL APPROACH TO ENHANCE THE SOLUBILITY: A LIQUISOLID TECHNIQUE

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Abstract:

Liquisolid technology is the new method for enhance the drug solubility bioavailability and dissolution rate of poorly water soluble drugs. Liquisolid system used for formulation of oral solid dosage form and liquid dosage form. Liquisolid system developed by using suitable nonvolatile liquid solvent carrier and coating material with the excipients and this convert the liquid into free flowing powder for direct compression.

Key words: *liquisolid compact, solubility enhancement, carrier, water insoluble drug.*

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INTRODUCTION:

Therapeutic effectiveness of drug depends on bioavailability of drug, which in turn depends upon the solubility of that drug in gastro intestinal fluid. The solubility of drug is important for betterment of pharmacological response. [1]The solubilityof many active pharmaceutical ingredients is one of the challenges in formulating as suitable dosage form for its best use. Currently more than 40%of new chemical entities are practically insoluble in water which is developed by pharmaceutical industry. [2] The number Poorly water soluble drugs will release intrinsically at slow rate owing to their limited solubility within the GI fluid. Dissolution is the rate determining step in the drug absorption. The dissolution rate is enhanced by increasing the solubility of poorly water soluble drug. The increased bioavailability of poorly water soluble drug in systemic circulation is limited by their solubility and dissolution rate. [1] To achieve desired concentration of drug in systemic circulation, solubility is one of the major factors. The highest dose of drug compound is soluble in < 250ml of water over a range of pH from 1.0 to 7.5. Drug substances are considered highly soluble.The compounds with solubilities below 10mg/mL present difficulties related to solubilization during formulation, and compounds with solubilities below 0.1mg/mL that consider to be of low solubility**.** [3]

Table1: USP and BP solubility criteria. [4]

Descriptive term	**Part of solvent required per part of solute**
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

Solubility enhancement techniques:

The various approaches used to enhance the dissolution rate of drugs which as follows.

Micronization:

In this particles size of drug which is reduced up to 1 to 10 microns commonly by spray drying or by use of air attrition methods.

Nanonisation:

This process is similar to Micronization. In case of nanoniztion, the particle size of drug reduced upto 200-600nm.While in case of micronization, particle size reduced up to in micron.

Use of surfactants:

Surfactants are generally used to enhance the absorption rate, dissolution rate as well as permeability of drug. They promote the wetting phenomenon and enhance the penetration of dissolution fluid into the solid drug particles.

Use of salt forms:

Use of salt form of parent drug is also enhanced the solubility and dissolution rate. Pencillins have a poor dissolution rate which is enhanced by using alkali metal salt form of penicillins. [5]

Solid dispersions:

Solid dispersion first introduced by sekiguchi to increase the dissolution and oral absorption of poorly water soluble drug. Poorly water soluble drug and carrier are dissolved in organic solvent and then it is subjected to evaporation to get solid powder.

Solid dispersion classified in 3 groups;

- First generation solid dispersions
- Second generation solid dispersion
- Third generation solid dispersion[6]

Molecular encapsulation with cyclodextrin:

The beta and gamma cyclodextrins are having the ability to form molecular complexes with poorly water soluble drugs.eg Thiazide diuretics, barbiturates, enzodiazepines and number of NSAIDs.

Amorphs, Anhydrates, Solvates and Metastable Polymorphs:

Based on internal structure of solid drug compound, selection of proper form of drug is with greater solubility is important. As compare to metastable polymorphs amorphs are more soluble, hydrates are more soluble than anhydrates and non-solvates are less soluble than solvates[5] The liquisolid compact technique is successful tool to improve the solubility and dissolution of hydrophobic drug. [7]

Liquisolid compact technology:

The liquisolid compact technique refers to immediate release or sustained release tablets or capsules, combined with the inclusion of appropriate adjuvant required for tableting or encapsulating. [8] The liquisolid technique is a new concept, first described by Spires. In this liquid may be transferred into a free

flowing readily compressible dry powder by simple physical blending with selected carrier and coating material. [7]

Research studies on liquisolid technique

Spireas et al. 1998,In this research they prepared directly compressible liquisolid formulations of prednisolone and hydrocortisone. The liquisolid formulation showed increased dissolution rates of these drugs showing the usefulness of the system. [9]***Lloyd et al (2004),***had studied the effect of plasma irradiation on wettability and dissolution profile of Griseofulvin compacts. Dissolution rate of the poorly soluble drug could be increased by using plasma irradiation. [10]***Nokhodchi et al (2005),***he studied the effect of concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from Liquisolid compacts. [11]***Fahmy et al (2008),*** had studied and formulate the liquisolid system of famotidine to improve dissolution rate and studied in vitro and in vivo performance of the drug from the prepared Liquisolid tablets. [12]***Srinivas et al (2014),***had improved the solubility and dissolution rate of drug Piroxicam by using Liquisolid technique. He observed that dissolution rate and bioavailability of poorly water soluble drugs like Piroxicam can increased by Liquisolid technology. [13]***Manish et al (2014),***had developed a new liquid solid technique which enhances the solubility and dissolution rate of water insoluble or poorly water soluble BCS class II drug Nilvadipine. [14]***Jyothi et al (2014),***had enhanced the dissolution rate of Glyburide which is poorly water soluble drug. Different formulations were prepared by using different vehicles and carriers and Aerosil is used as the coating material. [15]***Zafar el al (2015),*** In this research they studied comparison between Liquid-solid technique and solid dispersion formation which are two new approaches for enhancement of dissolution rate of BCS class II drug Hydrochlorothiazide. The results obtained that liquid solid compact formulations were more effective than solid dispersion technique to enhancing the dissolution rate.[16] ***Ayesha et al (2015),*** had prepared Liquisolid compacts of Olmesartanmedoxomil using polyethylene glycol 400, propylene glycol and Tween-80 as non-volatile solvents, and Neusilin as carrier and Aerosil-200 as coating material for enhancement of dissolution rate.[17]

Principle of Liquisolid Compacts:

Liquisolid technique is new approach to increase solubility of poorly water soluble drug in which drug substance dissolved in the liquid vehicle the liquid portion is incorporated into a carrier material which has a porous surface which shows both absorption and adsorption. The liquid firstly absorbed into the interior of the particle is captured by its internal surface. After saturation, liquid portion adsorb onto the internal and external surface of the porous carrier particle occurs. The coating material has high adsorptive properties and large surface area due to this it provide desirable flow property to the liquisolid system. [18] Exclusion of high dose drugs is the major disadvantage of liquisolid technique, because high amount of liquid vehicle is needed. A powder may be able to absorb only limited amounts of liquid vehicle while maintaining acceptable flow and compression properties**.** [19]

Liquisolid system has three main Mechanism for enhancement of solubility such as

1) **Increased surface area of particles**

In liquisolid system, if the drug is completely dissolved in the liquid vehicle, it is located in the powder substrate still in a solubilized, molecularly dispersed state. As a result of, the surface area of drug available for release is much greater than that of drug particles within directly compressed tablets**.** [8]

2) **Increased aqueous solubility of the drug**

In addition to the first mechanism of drug release enhancement it is expected that particle surface (saturation) concentration,the solubility of the drug might be improved with liquisolid systems. Large amount of solvent is required in liqusolid system to increase the solubility of drug in aqueous dissolution medium. It is able to that a small amount of liquid vehicle diffuses from the total amount along with drug and if the liquid vehicle acts as a co-solvent, then less amount of vehicle is sufficient to increase the aqueous solubility of drug**.** [8]

3) **Improved wetting properties**

In this mechanism liquid vehicle can be act as surface active agent or has a low surface tension, it helps to increase the wettability of liquisolid primary particles. [20]

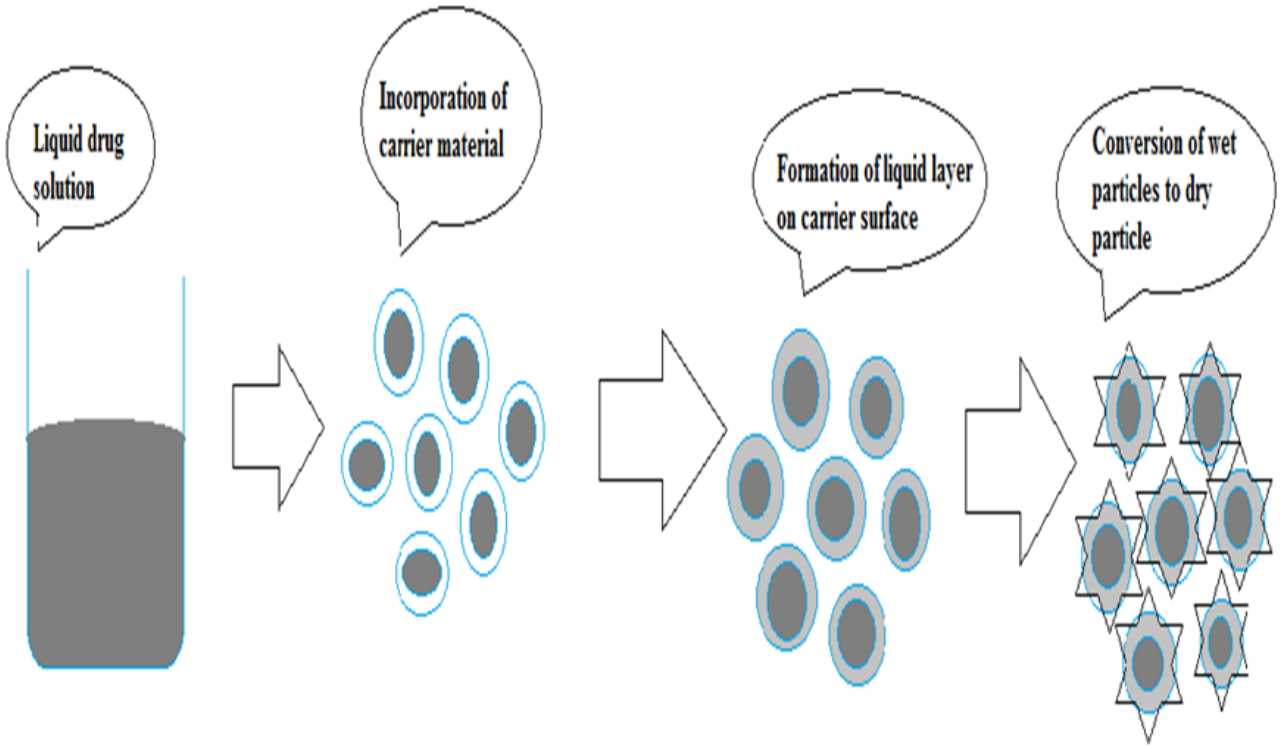

Fig.1 shows Mechanism of liquisolid compact formation.fig adapted from reference [21]

Advantages: [22]

- BCS class II drugs with high permeability, and low aqueous soluble or insoluble in liquid that can be formulate in the liquisolid system.
- We canformulate modified drug delivery by using suitable formulation ingredients.
- Industrial production is also possible.
- Enhanced bioavailability can be determined as compared to conventional tablets.
- By using color in liquid vehicle we differentiate the dosage form.
- It required less excipients in formulation compare with other formulations like solid dispersions.
- minimizesthe processes like nanonisation, micronization techniques

Disadvantages: [23]

- This technique is generally used for water insoluble drugs.
- In this technique for the formulation of high dose insoluble drugs, liquisolid tablet is one of the limitations.
- For achieving acceptable flow ability and compactability for liquisolid powder formulation, it required high levels of carrier material and coating materials. This will increase the weight of tablets to above one gram which makes them difficult to swallow.

Theory of liquisolid compact:

For maintaining flowability and compressibility of powder, the powder can only retain limited amount of liquid vehicle in liquisolid system [7]. The spires introduces a mathematical model for liquisolid system to attain a acceptable flowability and compressibility properties, required to calculate appropriate quqntities of carrier and coating material.[21] The carrier (Q) and coating (q) powder materials can retain only small amount of liquid, by the new theories. when maintaining acceptable flow and compression properties. Depending on the excipients ratio (R) or the carrier: coating ratio of the powder system used,

Where

$$R=Q/q \quad \ldots\ldots (1)$$

In case of the formulation the ratio between the weights of carrier (Q) and coating (q) materials presented by (R) [24]. Liquid load factor (Lf) is defined as the ratio of the weight ofliquid medication

(W) over the weight of the carrier powder (Q)in the system, which should be possessed by an acceptablyflowing and compressible liquisolid system, i.e.,[7]

Lf=W/Q ……. (2)

The flowable liquid retention potentials (ϕ-value) of powder excipients are considered to calculate the required ingredient quantities [25]. Hence, the powder excipients ratios *R*andliquid load factors $Lf$of the formulations are related as follows:

$Lf=\phi+(1/R)$ …..... (3)

By using equation (3) calculate the required weights of the excipients used, in which$\phi$and $\phi$are constants; therefore, according to the ratio of the carrier/coat materials (*R*), $Lf$was calculated from the linear relationship of Lfversus 1/ R.[24]

Formulation of liquisolid compact:

Liquid vehicle: Liquid vehicle used in liquisolid systems should be orally safe, inert, not highly viscous, and preferably water-miscible nonvolatile high boiling point organic solvents, such as propylene glycol, glycerin, PEG 200 and 400, polysorbate 20 and 80, etc.[21]

Carrier material: These are as porous substance possessing adequate absorption properties.[2] As carriers allow an incorporation of large amount of liquid medication into the liquisolid structure, the properties of carriers, such as (SSA) and liquid absorption capacity, are of great importance in designing the formulation of liquisolid system. [21] The carrier materials are used for liquisolid compact preparation are Avicel PH102,microcrystalline cellulose, Eudragit L-100, Eudragit RS-100, [2,21]

Coating material: Coating materials refer to very fine and highly adsorptive materials,
such as Aerosil® 200, Neusilin®, and calcium silicate or magnesium aluminometasilicates in a powder form.[21]

Additives:

Disintegrants: are the agent added into formulation to break the compacts to smaller particles. e.g: Crosscarmellose sodium, Crosspovidone, etc.

Lubricants: These are intended to reduce the friction. e.g: Stearic acid, Stearic acid salts and Talc etc.

Glidants: Intended to promote the flow between particles by reducing the friction. e.g: Silica derivatives, Talc and Corn starch etc. [26]

Classification of liquisolid system

Liquisolid system are divided in two form which are as follows

- **Based on type of medication contained in formulation**
- **Based on formulation technique used**
- **Based on type of medication contained in formulation**

  This was further divided into three groups
  - Powdered drug solution
  - Powdered drug suspension
  - Powdered liquid drug

The first two may produce from the conversion of drug in solution or drug suspension and the letter form the formulation of liquid drug into liquisolid system

- **Based on formulation technique used**

Based on formulation are divided in subgroup
- Liquisolid compacts
- Liquisolid microsystem

Liquisolid compact are prepared using previously mentioned method to produced tablets or capsule. liquisolid microsystem is new concept which have similar methodology combine with inclusion of an addatives. [27]

General method of preparation of liquisolid compact:

First step in which weigh the calculated amount of drug and dissolved in a suitable solvent. The liquid solution incorporate on to the carrier material blend it properly .then add the coating material in physical mixture keep it for 5 min. for proper adsorption of coating an carrier material. And the mixture used for encapsulation and direct compression. [21, 23]

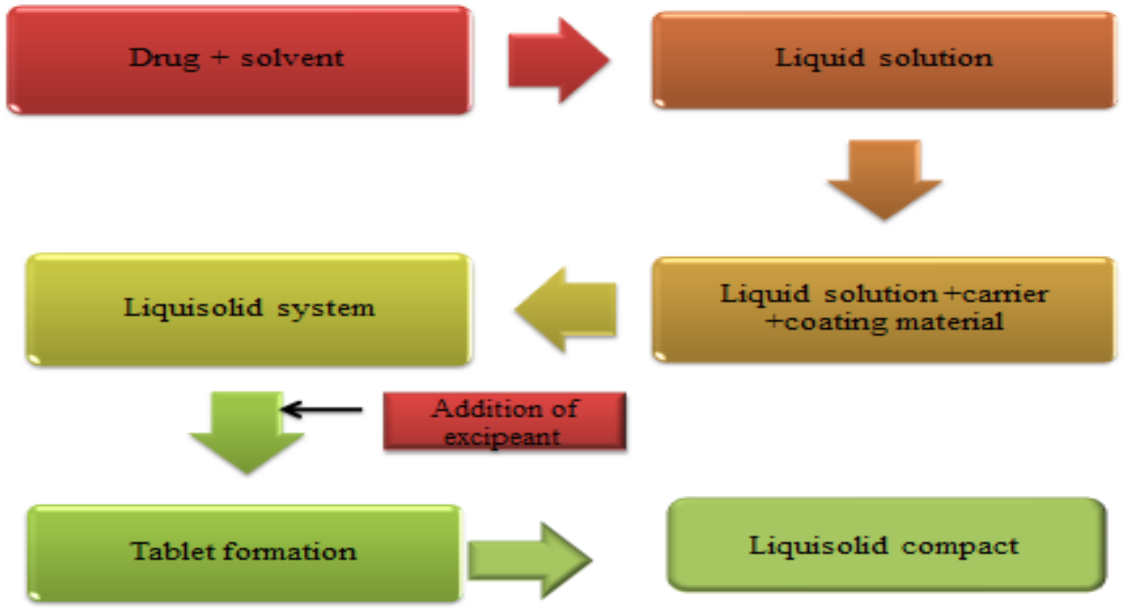

Fig: Process of liquisolid compact formation

Fig.2: Shows General method of liquisolid compact preparation, fig adapted from reference no 26.

Preparation of liquisolid tablets

Required quantities of drug and nonvolatile solvent accurately weighed and transfer to glass beaker. After that glass beaker heated to dissolve the drug in solvent. The resulting hot mixtureis incorporated intorequired quantities of carrier and coating materials. After that Mixing is carried out in three steps as described by Spireas et al. For evenly distribution of liquid medication in the powder in first stage, the system is blended at an approximate mixing rate of one rotation per second for one minute to form liquid/powder admixture. The liquid/powder admixture is evenly spread on the surfaces of a mortar and left standing for approximately 5 min to allow drug solution to be absorbed in the interior of powder particles. After that powder is scraped from mortar surfaces and then blend with super disintigrentsfor 30 seconds in a similar way to the first stage. This gives final liquisolid formulation to be compressed. [28]

Evaluation of liquisolid compact:

Evaluation of flow properties

The formulations were evaluated for the following properties such as angle of repose, bulk density, tapped density, Hausner's ratio, Carr's index. [29]

Angle of repose: Angle of repose was measured by fixed funnel method. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Thus, r being the radius of the base of the conical pile

$$\mathbf{Tan\theta = (h/r)}.$$

Bulk density: Bulk density refers to the measure used to describe a packing of particles. Bulk density is defined as the mass of powder divided by the bulk volume.

$$\mathbf{\rho b = M / Vb}.$$

Tapped density: Tapped density can be defined as mass of blend in the measuring cylinder divided by its tapped volume.

$$\mathbf{\rho t = M / Vt}\ [30]$$

Carr's compressibility index

The compressibility index (Carr's index) is a measures the tendency of a powder to be compressed.

Carr's index (%) = [(tapped density − bulk density) × 100]/ tapped density

Hausner's ratio

Hausner's ratio = tapped density/bulk density. [31]

Evaluation of liquisolid tablet

Different evaluation parameter for liquisolid tablet such as drug content uniformity, weight variation,

tablet hardness, friability, tablet dimensions, disintegration time test, and *in vitro* drug release [32]

Tablet dimensions
Thickness and diameter were measured using vernier caliper. Three tablets from each formulation were used, and average values were calculated. [32]

Hardness Test: 10 tablets were selected and the hardness was tested using Monsanto tester. [33]
Friability Test: Roche friabilator was used to measure the friability of the tablet. [33]

Content uniformity:
10 tablets were crushed and an accurately weighed amount of powder equivalent to unit dose of a single tablet. This was dissolved in 100 ml suitable solvents, subjected to sonication and then filtered through a membrane filter (Millipore, 0.45 µm pore size). The drug content was determined by HPLC analysis. Each study was carried out in triplicate, and mean data were recorded. [34]

Uniformity of weight
20 tablets from each formulation batch were individually weighed and the mean weight was calculated. Percentage weight variation was calculated for each batch. [34]

Disintegration test:
The disintegration time was determined in Disintegration apparatus with a basket rack assembly containing six open-ended tubes and 10-mesh screen on the bottom was used. A tablet was placed in each tube of the basket and the time for complete disintegration ofthe six tablets was recorded. [33]

***In vitro* dissolution studies of liquisolid tablet:**
The USP paddle method used for all the in vitro dissolution studies. Inthis method, simulated gastric fluid (pH 1.2), and intestinal fluid (pH 6.8) without enzyme were used as dissolution media. The rate of stirring was 50+/- 2 rpm. The amount of piroxicam was 10 mg in allformulations. The dosage forms were placed in 900 mL of gastric fluid (HCl solution) or intestinal fluid (phosphate buffer) and maintained at 37 +/- 0.1°C. At appropriate intervals (5, 10, 20, 30, 40, 50, 60, and 70 min), 5 mL of the samples were taken and filtered through a 0.45-mm Millipore filter. [35]

Scanning Electron Microscopy (SEM)
It is used to determine the morphological characteristics of the raw materials and the drug carrier systems. [36]

FTIR (**Fourier Transform Electron Microscopy**)**:**
It is used to check the compatibility of drug and excipients in the liquisolid formulation. [37]

Differential Scanning Calorimetry (DSC)
DSC use for stability study. It determines the drug excipeants interaction 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. [26]

Application

1. Liquisolid technique is powerful tool to improve dissolution and bioavailability of poorly water soluble drugs.
2. Liquisolid technique could be utilized to preparing sustained release formulations**.**
3. Liquisolid technique as a promising tool to prevent drug photostability in solid dosage forms,[21]
4. liquisoild technique show rapid release of drug in formulation.
5. These technique mainly used for water insoluble drugs or liquid lipophilic drug.
6. Improvement of Flowability and compressibility of powder.
7. It also used for Controlled Release Tablets formulation.
8. It also Applicable in probiotics. [38]

CONCLUSION:

A poorly soluble drug has a problem related with the bioavailability and dissolution. Low solubility create problem in formulation development. The liquisolid compact is the successful tool for enhance solubility solubility and dissolution rate. It is promising tool for ligh loading dose of drug by using suitable carrier. We can formulate good flow and good compaction property liquisolid compact formulation.

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