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A Review on Liquisolid Compact Technique

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ABSTRACT:
The most promising and new technique for promoting dissolution is the formation of liquisolid tablets (liquisolid compacts) among the various novel techniques. Liquisolid compacts promotes dissolution rate of water insoluble drugs to a greater extent and also enhances the drug flow property. 'liquisolid'' technique may be applied to formulate liquid medications (i.e., oily liquid drugs and solutions, suspensions or emulsions of water-insoluble solid drugs carried in nonvolatile liquid vehicles) into powders suitable for tableting or encapsulation. Various excipients such as lubricants and disintegrants (immediate release) or matrix forming materials (sustained release) may be added to the liquisolid system to produce liquisolid tablets.
Release enhancement of poorly soluble drugs may be achieved by an increase of the drug surface area, the drug solubility, or by formulating the drug in its dissolved state.
Nonvolatile solvent present in the liquisolid compacts facilitates wetting of drug particles by decreasing interfacial tension between tablet surface and dissolution medium.
Keywords: Poorly soluble drug, liquisolid, wettability,BCS, preparative methods.

INTRODUCTION:

The most promising and new technique for promoting dissolution is the formation of liquisolid tablets (liquisolid compacts) among the various novel techniques. Liquisolid compacts promotes dissolution rate of water insoluble drugs to a greater extent and also enhances the drug flow property. For poorly soluble (Class II) drugs and (Class IV) the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract.

The new 'liquisolid'' technique may be applied to formulate liquid medications (i.e., oily liquid drugs and solutions, suspensions or emulsions of water-insoluble solid drugs carried in nonvolatile liquid vehicles) into powders suitable for tableting or encapsulation. Since, the liquisolid tablets contain a solution of the drug in suitable solvent; the drug surface available for dissolution is tremendously increased. Due to significantly increased wetting properties and surface area of drug available for dissolution, liquisolid tablets of water-insoluble substances may be expected to display enhanced drug release characteristics and consequently, improved oral bioavailability[1] .

The liquisolid technique is a novel concept where 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 [2].

Inert, preferably water-miscible organic solvent systems with high boiling point such as propylene glycol, liquid polyethylene glycols, or glycerine, tween 80 and Cremophor EL are best suitable as liquid vehicles. 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. Thus, an apparently dry, free flowing, and compressible powder is obtained. Usually, microcrystalline cellulose is used as carrier material and amorphous silicon dioxide (colloidal silica) as coating material[3].

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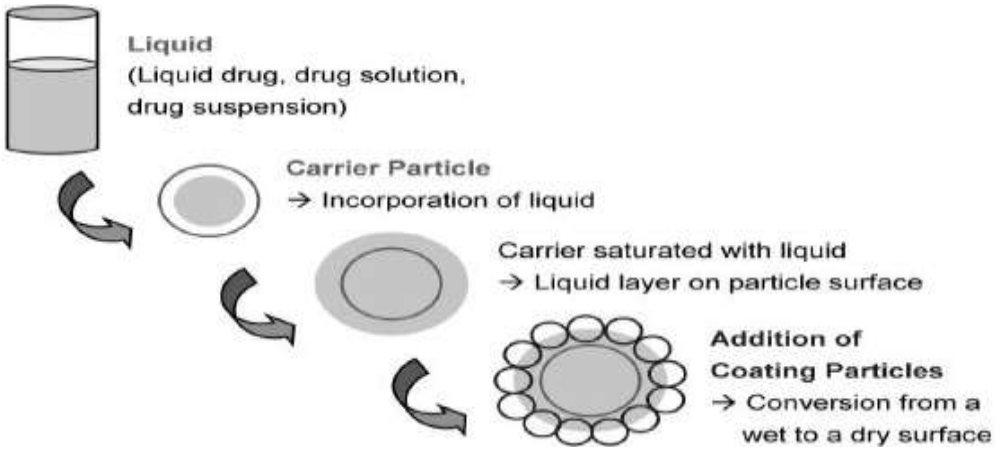

Figure: 2 Schematic representation of liquisolid systems

Various excipients such as lubricants and disintegrants (immediate release) or matrix forming materials (sustained release) may be added to the liquisolid system to produce liquisolid tablets.

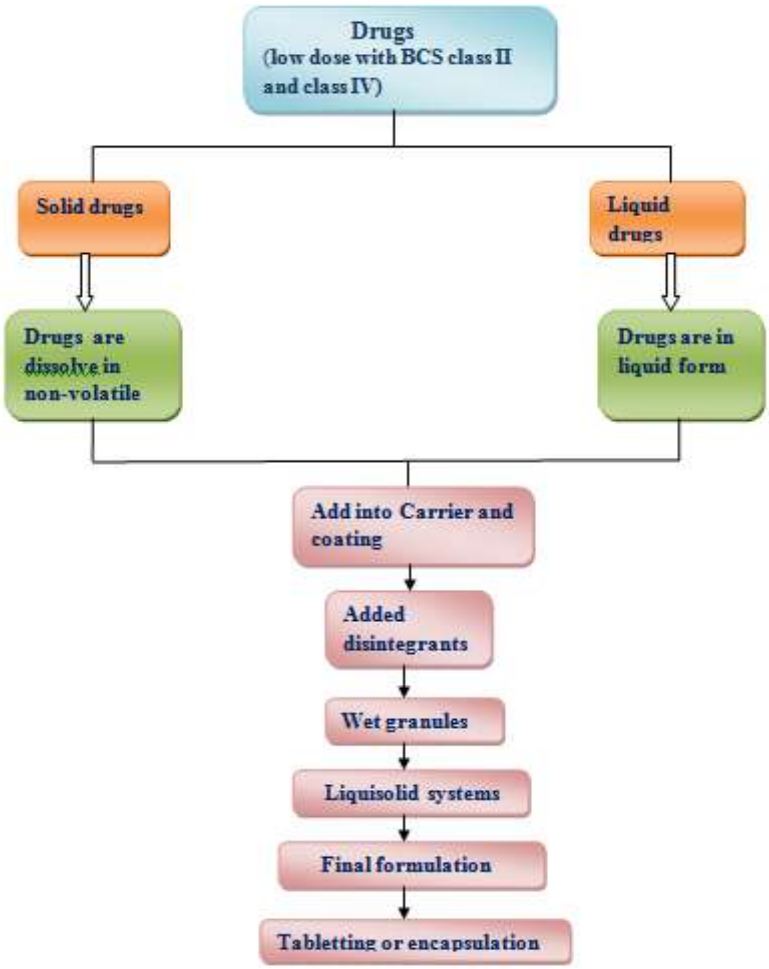

Figure: 3 Schematic outline of the steps involved in the preparation of liquisolid compacts[4]

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Liquisolid tablets of poorly soluble drugs containing a drug solution or drug suspension in a solubilising vehicle show enhanced drug release due to an increased aqueous solubility of the drug, an increased surface area of drug available for release and an improved wettability of the drug particles. Accordingly, this improved drug release may result in a higher drug absorption in the gastrointestinal tract and thus, an improved oral bioavailability. Release enhancement of poorly soluble drugs may be achieved by an increase of the drug surface area, the drug solubility, or by formulating the drug in its dissolved state.

Comparison of wettability between conventional tablet and liquisolid tablets

The wettability of the tablets by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid tablets. Nonvolatile solvent present in the liquisolid compacts facilitates wetting of drug particles by decreasing interfacial tension between tablet surface and dissolution medium.

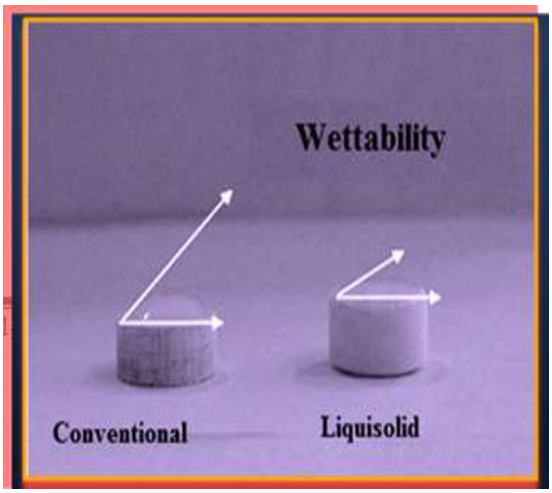

Figure : 4 This figure shows lower contact angle of liquisolid tablets than the conventional tablets and thus improved wettability.

Mechanisms of enhanced drug release from liquisolid systems

Several mechanisms of enhanced drug release have been postulated for liquisolid systems. The three main suggested mechanisms include an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles. Formation of a complex between the drug and excipients or any changes in crystallinity of the drug could be ruled out using DSC and XRPD measurements[5].

a. Increased drug surface area

If the drug within the liquisolid system is completely dissolved in the liquid vehicle it is located in the powder substrate still in a solubilized, molecularly dispersed state. Therefore, the surface area of drug available for release is much greater than that of drug particles within directly compressed tablets.

Accordingly, with increasing drug content exceeding the solubility limit and thus, increasing fraction of undissolved drug in the liquid vehicle the release rate decreases. With various drugs it could be shown that the release rates are directly proportional to the fraction of the molecularly dispersed drug (FM) in the liquid formulation. FM is defined by the ratio between the drug's solubility (Sd) in the liquid vehicle and the actual drug concentration (Cd) in this vehicle carried by each system.

Therefore:
F M= Sd /Cd
where FM= 1 if Sd ≥ Cd

Accordingly, lower FM-values and higher fraction of undissolved drug in the liquid vehicle, respectively, are not sufficient to increase percentage of drug released at 30 min. However, this may not be transferred to other time points of drug release.

b. Increased aqueous solubility of the drug

In addition to the first mechanism of drug release enhancement it is expected that Cs, the solubility of the drug, might be increased with liquisolid systems. In fact, the relatively small amount of liquid vehicle in a liquisolid tablets is not sufficient to increase the overall solubility of the drug in the aqueous dissolution medium. 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. The overall

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increase in the solubility of drugs caused by liquisolid systems was confirmed.

c. Improved wetting properties

Due to the fact that the liquid vehicle can either act as surface active agent or has a low surface tension, wetting of the liquisolid primary particles is improved. Wettability of these systems has been demonstrated by measurement of contact angles and water rising times.

Application of the mathematical model for designing the liquisolid systems

In the following study, polyethylene glycol (PEG 400), propylene glycol, tween 80, cremophor EL and capryol 90 were used as liquid vehicles. Avicel PH 102 and Aerosil 200 were used as the carrier and coating materials, respectively.

In order to address the flowability and compressibility of liquisolid tablets, simultaneously, the ‘‘new formulation mathematical model of liquisolid systems” was employed as follows to calculate the appropriate quantities of excipients required to produce liquisolid systems of acceptable flowability and compressibility.[6]

This mathematical model was based on new fundamental powders properties (constants for each powder material with the liquid vehicle) called the flowable liquid retention potential (Φ-value) and compressible liquid retention potential (ψ-number) of the constituent powders (carrier and coating materials). According to the new theories, the carrier and coating powder materials can retain only certain amounts of liquid while 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 ... (1)

R = Ratio between the weights of carrier (Q) and coating (q) materials present in the formulation.

An acceptably flowing and compressible liquisolid system can be prepared only if a maximum liquid on the carrier material is not exceeded; such a characteristic amount of liquid is termed the liquid load factor (Lf) and defined as the ratio of the weight of liquid medication (W) over the weight of the carrier powder (Q) in the system, which should be possessed by an acceptably flowing and compressible liquisolid system. i.e.:

Lf=W/Q … (2)

Where

Lf = Liquid load factor
W =Weight of liquid medication
Q = Weight of the carrier powder

Flowable liquid retention potentials (Φ - values) of powder excipients used to calculate the required quantities of ingredients, hence, the powder excipients ratios R and liquid load factors Lf of the formulations are related as follows

Lf = Φ + Φ (1/R) … (3)

Where, Φ and Φ are flowable liquid retention potential of carrier and coating material respectively. So in order to calculate the required weights of the excipients used, first, from Eq. (3), Φ and Φ are constants, therefore, according to the ratio of the carrier/ coat materials (R), Lf was calculated from the linear relationship of Lf versus 1/R. next, according to the used liquid vehicle concentration, different weights of the liquid drug solution (W) will be used. So, by knowing both Lf and W, the appropriate quantities of carrier (Q_o) and coating (q_o) powder materials required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible liquisolid tablets could be calculated from equation (1) and (2) (Srinivas Vaskula et al.,2012 and Fahmy R.H).

Classification of liquisolid system

A. Based on the type of liquid medication contained therein, liquisolid systems may be classified into three sub-groups

1. Powdered drug solutions
2. Powdered drug suspensions
3. Powdered liquid drugs

Powdered drug solutions and suspensions may be produced from the conversion of drug solutions or drug suspensions into liquisolid systems and powdered liquid drugs are produced from the formulation of liquid drugs into liquisolid systems.

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

1. Liquisolid compacts
2. Liquisolid Microsystems

The term “**liquisolid compacts”** refers to immediate or sustained release tablets or capsules prepared, combined with the inclusion of

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appropriate adjuvants required for tabletting or encapsulation, such as lubricants, and for rapid or sustained release action, such as disintegrants or binders, respectively.

The term **"liquisolid Microsystems"** refers to capsules prepared by combining the drug with carrier and coating materials, combined with inclusion of an additive resulting in a unit size may be as much as five times that of liquisolid compacts[7].

Components of liquisolid tablet formulations

Liquisolid system mainly includes

1. Non volatile solvent
2. Disintegrant
3. Carrier material
4. Coating material

1**. Non volatile Solvent**

Non volatile Solvent should be inert, high boiling point, preferably water-miscible 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. Various non-volatile solvents used for the formulation of liquisolid tablets includes

1. Polyethylene glycol400
2. Propylene glycol
3. Polysorbate80
4. Cremophor EL
5. Capryol 90

Selection of Solvent

To select the best non-volatile solvent for dissolving or suspending the drug in liquid medication, solubility studies of drug were carried out in different non-volatile liquid vehicles. Saturated solutions were prepared by adding excess drug to the liquid vehicles and it was shaked on the shaker for 48 hours at 25◦C under constant stirring. After this period the solutions were filtered through a 0.45 µm millipore filter, diluted with distilled water and analysed by UV-spectrophotometer at respected wavelength against blank sample (blank sample containing the same concentration of the specific solvent used without drug). Three determinations were carried out for each sample to calculate the solubility of drug. Some of the solvents mentioned can be incorporated to formulate Liquisolid tablets viz. Poly ethylene glycol (PEG 200, 400, 600), Propylene Glycol, Polysorbate 80, Glycerol, Spans, Polyoxyl 35 castor oil, caproyl 90 and poloxamer 181. The solvent should have the characteristic of a non-toxic and non volatile solvent. The formulation liquisolid compacts should neither enhance the dissolution rates nor retard the dissolution rates of the drug it depends upon the selection of solvent and properties of the chemical entities. Prior to selection of solvent selection in the formulation there is need to check the saturation solubility with selected non-volatile solvents. From saturation solubility of solvent the one which has enhance rate of dissolution, the solvent with minimum solubility retards the rate of drug release[8].

2. Disintegrant

Superdisintigrants increases the rate of drug release, water solubility and wettability of liquisolid granules. Mostly superdisintigrants like sodium starch glycolate and crosspovidone.

3. Carrier Materials

Carrier material should be porous material possessing sufficient absorption properties which contributes in liquid absorption. The carrier and coating materials can retain only certain amounts of liquid and at the same time maintain acceptable flow and compression properties hence, increasing moisture content of carrier's results in decreased powder flowability These include grades of microcrystalline cellulose such as avicel PH 102, avicel PH 200.

4. Coating Materials:

Coating material should be a material 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. Coating material is required to cover the surface and maintain the powder flowability. Coating material includes silica (Cab-O-Sil) M5, Aerosil 200**.**

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Characterization of liquisolid tablets

Table: 2. Characterization of liquisolid tablets

Characterization	Purpose
1. UV-spectrophotometer	Assay & uniformity content
2. Infrared Spectroscopy	Interaction studies
3. Powder X-Ray Diffraction Analysis (XRD)	Crystalline Properties
4. Differential Scanning colorimetry (DSC)	Interaction studies, polymorphism
5. In vitro Dissolution studies	Release Properties of drug
6. SEM analysis	Surface morphology

Importance of carrier and coating material ratio (R)

Liquisolid systems precompression and drug release properties increase with powder excipient ratios (R) from 5:1 to 50:1. A linear relationship exists between the liquid load factors Lf and the reciprocal powder excipient ratios (1/R) required to produce acceptable flowing and readily compressible liquid and powder admixtures. The linear relationship between Lf and the 1/ R plot of liquisolid systems possesses Y intercept and slope equal to the Φ values of the cellulose carrier powder and silica coating material.

Liquisolid tablets dissolution rate profiles are affected by powder excipients ratio R in which results exhibited within the 5 minutes of the dissolution process against the r values 5 to 20 range R values. The dissolution rates increased almost proportionally to R until reaching an apparent maximum plateau at powder excipient ratios greater than 20.

Lower R values of liquisolid tablets contain relatively smaller amounts of carrier powder (cellulose), a large amount of fine coating particles (silica), and the ratios of their liquid medication per powder substrate are relatively higher.

From the low liquid and powder ratios, a high presence of cellulose and low presence of silica may be directly associated with enhanced wicking, disintegration, and degradation properties. Low R values should justifiably display relatively poor dissolution profiles. After disintegration, low R values of liquisolid tablets are overloaded with liquid medication producing the primary particles.

On other hand, in some cases, the drug diffusion through the primary particles may be rapid and might lead to overwhelming (solubility-wise) of the stagnant dissolution layers with drug. After maximum levels of dissolution are reached at 35 to 45 R values, a slight gradual decrease of dissolution rate occurs with increasing powder excipient ratios.

For R values higher than 50, they may be attributed to the slower diffusion of the liquid medication through the numerous porous carrier powder particles into which the drug solution has been embedded during the formulation process. To determine the effect of different type of carriers such as Avicel pH 102, lactose, starch or sorbitol, dissolve in solution containing 10% w/w of drug in liquid medication. Carriers show the potential to absorb the liquid medication. Large amounts of these carriers are necessary for regenerating liquid medication to dry looking and non adherent powder.

Avicel PH 102 showed better results, due to its large specific area in comparison with other carriers such as lactose and starch.

Type of carrier might affect the unit size of liquisolid tablets. Higher Avicel PH 102 concentrations show uniform distribution of the drug by either adsorption onto or absorption into the carrier. Between the hydrogen groups, hydrogen bonds on adjacent cellulose molecules in Avicel PH 102 may account exclusively for the strength and cohesiveness of compacts. Avicel PH 102 compressibility and compactness characteristics can be explained by the nature if crystalline cellulosic particles themselves which are held together by hydrogen bonds which when compressed, are deformed plastically and a strong compact is formed due to the extremely excessive number of surfaces brought into contact during the plastic deformation, and the strength of the hydrogen bonds are formed.

Non-volatile liquid vehicles such as propylene glycol, polyethylene glycol 400, tween 80, Cremophor EL and capryol 90 were shown to facilitate wetting of drug particles by decreasing interfacial tension between dissolution medium and the tablet surface. Increase in the wetting properties of liquisolid tablets by the dissolution media is one of the main reasons for the dissolution rate enhancement. High R values 30 to 60 evidence

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better uniform distribution of the drug in the carrier material.[9]

Dissolution studies on liquisolid tablets

Tablets should be sufficiently hard to resist breaking during normal handling and yet quickly disintegrate properly after swallowing.

Dissolution rate (DR) is explained according to the "Noyes – Whitney" equation and "diffusion layer model" dissolution theories.

DR = (D/h) S (Cs- C)

According to this equation, stagnant diffusion layer thickness is h, and formed by the dissolving liquid around the drug particles. D is the diffusion coefficient of the drug molecules transported through it, S is the surface area of the drug available for dissolution, C is the drug concentration in the bulk of the dissolving medium, Cs is the saturation solution of the drug in the dissolution medium. Dissolution tests for liquisolid tablets were done at constant rotational speed and in identical dissolution media, thus allowing estimation of the thickness of the stagnant diffusion layer (h). From this equation, dissolution rate is directly proportional not only to the concentration gradient of the drug in the stagnant diffusion layer (Cs- C), but also to its surface area (S) available for dissolution.

For estimation and comparison, drug dissolution rates (DR) of drug were used, with amount of drug dissolved per min presented by each tablet formulation during the first 10 minutes.

$$DR = \frac{(M \times D)}{1000}$$

Where,

M = Total amount of pure drug in each tablet

D = Percentage of drug dissolved in the first 10 minutes

Liquisolid tablets advantages over the conventional tablets:

1. Liquisolid systems are low cost formulations than soft gelatin capsules.
2. Production of them is similar to that of conventional tablets.
3. Drug release can be modified using suitable formulation ingredients.
4. Drug can be molecularly dispersed in the formulation.
5. Capability of industrial production is also possible.
6. Enhanced dissolution rate and bioavailability can be obtained as compared to conventional tablets.
7. Differentiate the dosage form by admixture of colour into liquid vehicle.
8. To minimize excipients in formulation compare with other formulations.

Advantages

1. Large number of BCS class II drugs with very slightly water soluble & practically water insoluble and high permeability liquids and solid drugs can be formulated into liquisolid systems.
2. Improvement of bioavailability of an orally administered water insoluble drugs is achieved.
3. The mechanism of drug delivery from liquisolid systems of powdered drug solutions is mainly responsible for the improved dissolution profiles exhibited by this preparations.
4. Absolute bioavailability of drug from liquisolid tablet is 15% higher than commercial one.
5. Drug is formulated in a tablet form or encapsulated dosage form and is held in solubilized liquid state, which confers improved drug wetting properties thereby improving drug dissolution profiles.
6. Greater drug surface area is exposed to the dissolution medium.
7. This liquisolid system is specifically for powdered liquid medications.
8. These liquisolid systems formulate into immediate release or sustained release dosage forms depend upon the choice of non volatile liquid vehicles.
9. It is used in controlled drug delivery systems.
10. Omit the process approaches like nanonisation, micronization techniques.
11. This technique is successfully applied for low dose water insoluble drug.

Disadvantages

1. Formulation of high dose water soluble drugs the liquisolid tablet is one of the limitations of this technique[10].
2. It requires more efficient excipients which have higher adsorption capacities which

provide faster drug release with a smaller tablet size to improve liquisolid formulations.

3. In order to achieve acceptable flowability and compactability for liquisolid powder formulation, high levels of carrier material and coating materials should be added. This will increase the tablets weight to above one gram which makes them difficult to swallow. Consequently, it is impossible with conventional tablet methods to convert high dose to liquisolid tablets with a tablet weight of less than 50mg. Dissolution profile enhancement occurs in the presence of low levels of hydrophilic carrier, where coating material is not significant.

Limitations

1. Acceptable compression properties may not be achieved since during compression liquid drug may be squeezed out of the liquisolid tablet resulting in tablets of unsatisfactory hardness.
2. Introduction of this method on industrial scale and to overcome the problems of mixing small quantities of viscous liquid solutions onto large amounts of carrier material may not be feasible.
3. New mathematical calculation require.

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