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# A Review on Pioneering Technique - Liquisolid Compact and Applications.

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**ABSTRACT**

Slow dissolution rate of poorly water soluble drugs faces major challenge in the drug development and delivery processes. Improving aqueous solubility and slow dissolution of BCS Class II drugs have been explored extensively. Of the available approaches, liquisolid compact technology is the most latest and novel approach for overcoming the trouble of inadequate solubility of the poorly soluble drugs. This technique is applied to prepare immediate release as well as sustained release formulations and based on the mathematical model proposed by Spireas et al. Concept of liquisolid compact based on altering the solutions or suspensions of water insoluble drugs into free flowing and compressible powders by using appropriate powder excipients to exhibit enhanced release profiles. Generally water miscible solvents, nonvolatile solvents were selected to improve the solubility of drugs, by enhancing the wetting and ensuring the molecular dispersion of drug in the formulations. Selecting hydrophobic carriers along with proper solvent modified the release of the drug (sustained release). This technique has commercial importance.

**Key words:** Dissolution, Solubility enhancement, Liquisolid technology, Solvents, Carrier, Coating materials.

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## INTRODUCTION

Therapeutic effectiveness of the drug depends on the bioavailability which in turn dependent on the solubility and dissolution rate of drug molecules. Dissolution is the key parameter of pharmaceutical dosage forms for the absorption of drugs, especially in the case of water insoluble drugs. Drug substance is said to be highly soluble when the largest dose of drug is soluble in less than 250 ml of water over the pH range from 1-7.5. Solving solubility problems is a major challenge for the pharmaceutical industry with the developments of new pharmaceutical products, and since at present 40 % of the drugs in the development process and 60 % of the drugs coming directly from the synthesis are poorly soluble [1-3].

Diverse techniques has been employed to formulate drug delivery systems, which would augment the drug dissolution like solid dispersion, lyophilization, microencapsulation, micronization, pH adjustment, microemulsion, solid state manipulation, liquid drug into soft gelatin capsule, inclusion complexes, cosolvency, micellization, SEEDS, SMEEDS etc [4]. Liquisolid technique is a novel concept which promotes dissolution rate of water insoluble drugs, since the drugs are utterly solubilized in the suitable solvents before converting it into free flowing mass [5].

The term liquisolid technique refers to immediate release or sustained release tablets or capsules, combined with the inclusion of appropriate adjuvant required for tabletting or encapsulating [6-8]. Liquisolid compacts are acceptably free flowing and compressible powder forms of liquid medications [5]. 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 porous 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. Thus, an apparently dry, free flowing, and compressible powder is obtained. The concentrations of the carriers, coating materials, disintegrants, lubricants and glidants are optimized to get a non-sticky easily compressible blend [9-11].

## SPIREAS MATHEMATICAL APPROACH FOR LIQUISOLID SYSTEMS

This approach for the formulation of liquisolid systems developed by Spireas [5], aims to calculate the minimum amount of powder excipients (carrier and coating materials) required to retain the liquid medication while maintaining acceptable flow and compression properties. For each powder/liquid combination two constants were introduced i.e. flowable (Φ-value) and compressible (Ψ-number) liquid retention [12, 13].

The ***Φ-value and Ψ-number of a powder*** symbolizes the utmost amount of non-volatile liquid taken by the bulk of powder [w/w] while retaining an adequate flowability and compactability (must have sufficient hardness without oozing out liquid) respectively. Acceptable flowability and compressibility is accomplished by retaining the liquid inside powder below or equal to liquid load factor ($L_f$). $L_f$ is the weight ratio of the liquid formulation (*W*) and the carrier material (*Q*) in the system [10, 11]:

$$L_f = W/Q \qquad (1)$$

The weight of the carrier material (*Q*) in the system can be calculated from the equation (2), where *'R'* represents the ratio between the weights of the carrier (*Q*) and the coating (*q*) material present in the formulation:

$$R = Q/q \qquad (2)$$

The liquid load factor that ensures acceptable flowability (Lf ) can be established by:

$$L_f = \Phi + \phi . (1/R)$$

Where Φ and ϕ are the Φ-values of the carrier and coating material, respectively. Similarly, the liquid load factor for production of liquisolid systems with acceptable compactability (Ψ*Lf)* can be calculated by:

$$\Psi L_f = \Psi + \psi (1/R) \qquad (3)$$

Where Ψ and ψ are the Ψ-numbers of the carrier and coating material, respectively [9,10,14,15].

**Mechanism of Enhanced Drug Release From Liquisolid Systems**

**Improved Drug Surface Area**

In the liquisolid technology, even though the final formulation may be in solid dosage form, the drug is present either in solution or suspension. As the drug is present in solubilized or molecularly dispersed state, more surface area of drug available for release than the drug particles within directly compressed tablets [11].

**Increased Solubility of the Drug**

The relatively small amount of liquid vehicle in a liquisolid compact might not be enough to boost the overall aqueous solubility of the drug. But for release, the microenvironment of individual particle's solid/liquid interface might be adequate to augment the water solubility of the drug if the liquid vehicle plays the role of cosolvent [13,18].

**Enhanced Wetting Properties**

With the help of cosolvents used in this system, the poor water solubility of nonpolar molecules can be improved by altering polarity of the solvent or by reducing the interfacial tension between the aqueous solution and hydrophobic solute. Many poorly soluble drugs have been formulated as liquisolid systems showing enhanced drug release [19,20].

**Classification of Liquisolid Systems**

Based on the state of drug and its solubility in solvent:

- Powdered drug solutions
- Powdered drug suspensions
- Powdered liquid drugs

In powdered drug solution and suspensions, liquid medication is a solution or suspension of poorly soluble drugs in high boiling point water miscible organic solvents like propylene glycol, polyethylene glycol. In powdered liquid drugs, oily liquid is used along with solvent.

Based on the formulation technique used:

- Liquisolid compacts
- Liquisolid Microsystems

**Liquisolid compacts**

This system is immediate sustained-release tablets or capsules that are described under "liquisolid systems".

**Liquisolid Microsystems**

This system is prepared by "liquisolid systems" plus the inclusion of an additive resulting in a unit size that may be as much as five times less than that of a liquisolid compact [10-12, 21, 22].

**Advantages**

- Very slightly or practically water insoluble solid and liquid drugs can be formulated using this technique
- Successfully applied to low or high dose water insoluble drug.

- Liquisolid systems are low cost formulations than soft gelatin capsules.
- Improved drug dissolution due to presence drug in solubilized liquid state (molecularly dispersed) enhanced wetting properties of drugs.
- Production is simple similar to that of conventional tablets, easy, cost effective having capability of industrial production.
- Superior bioavailability can be obtained as compared to conventional tablets.
- Omit the complicated process approaches as in other methods like nano and microtechniques.
- Drug release can be modified using suitable formulation ingredients as immediate or sustained release.

**Shortcoming**

- Applicable to mainly insoluble drug having dose <100 mg.
- High solubility of drug is required in the nonvolatile liquid for preparing solution and suspensions.
- It requires excipient (carrier and coating) of high adsorption properties and high specific surface area.
- In order to maintain good flow and compaction ability, sometimes requires high amounts of carrier and coating materials that in turn will increase the weight of the tablet above 1gram which is very difficult to swallow.
- During compression, sometimes liquid drug may be squeezed out of the tablet result in improper hardness [1-5, 23, 24].

**Components of Liquisolid Compact Formulation**

**Drug candidates**

Mainly poorly water soluble (BCS class II or IV), low dose drugs can be the good candidate for this technique include Carmabazepine, naproxen, furosamide, Ketoprofen etc [8, 25-27].

**Non-volatile solvents**

These solvents should be inert, high boiling point, preferably water-miscible less viscous organic solvent systems, compatible with the drugs and must have high drug solubiliy. These solvents act as binding agents in the liquisolid formulations. Various solvents which are used include polyethylene glycols, glycerine, propylene glycol, polysorbates, tweens, spans, cremophor EL, castor oil, polaxomers, N, N-dimethylacetamide [15,28].

**Carrier materials**

The carrier should be fine and highly porous solid which must hold certain amounts of liquid by maintaining acceptable flow and compression properties. Various carriers used were different grades of microcrystalline cellulose such as avicel PH 102 and avicel PH 200, lactose, methyl cellulose, ethyl cellulose, starch, dibasic calcium phosphate for immegiate release. For sustained release material like Eudragit RL&RS, HPMC K4M etc can be used.

**Coating materials**

These materials should be fine (10 nm to 5000 nm in diameter), porous, flow enhancing and have high absorption which contributes in covering the wet carrier particles and displaying a dry looking powder by absorbing any excess liquid. Coating material is required to cover the surface and maintain the powder flowability. These materials include silica (Cab-o-sil), aerosil, syloid etc [5,7,9].

**Disintegrants**

These materials increase the rate of drug release, water solubility and wettability of liquisolid granules. Mostly superdisintegrants like sodium starch glycolate, crosspovidone, croscarmellose sodium are used [16].

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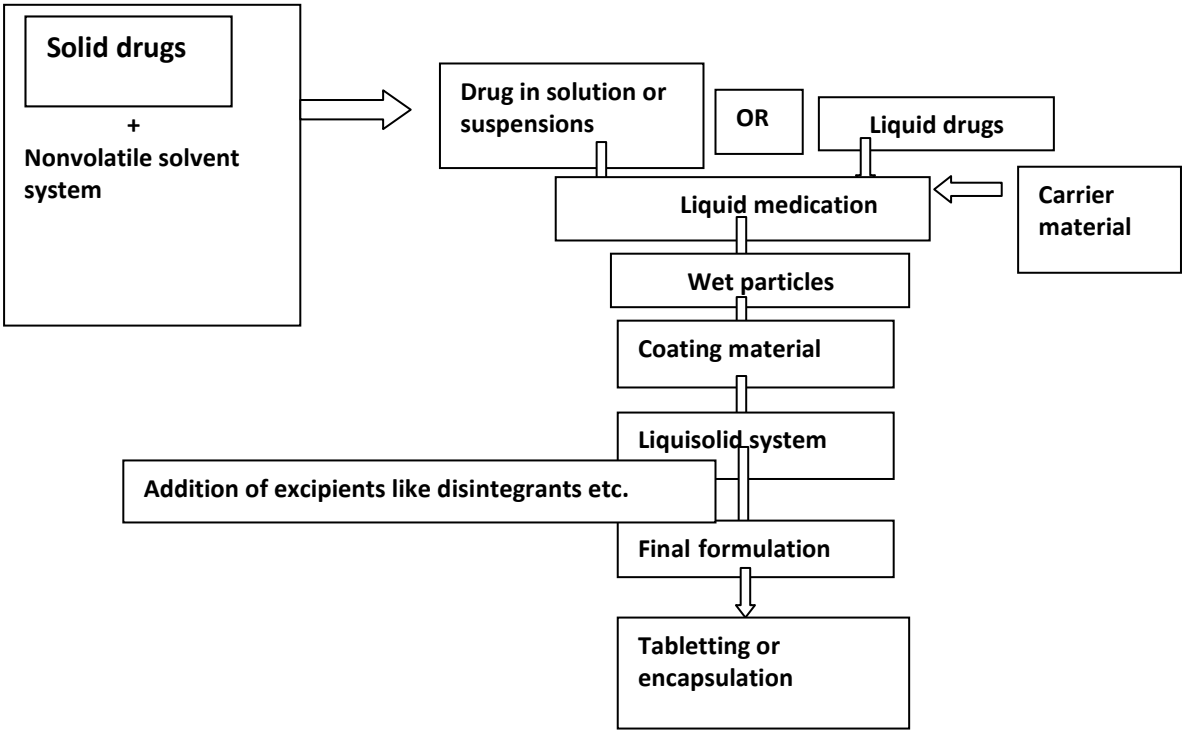
**Preparation of Liquisolid Tablet**

Calculated quantities of drug and non-volatile solvent are accurately weighed in glass beaker and then the drug was dissolved or dispersed. The resulting medication is incorporated into calculated quantities of carrier and coating materials. Mixing process is carried out in three steps:

1. Mathematically calculated amount of pure drug weighed and dissolved in suitable amount of solvent to form solution or suspension.
2. Enough quantity of coating material and carrier material was added to above liquid medication under continuous mixing in mortar to achieve good flow and compression properties.
3. Then the rest of ingredients like disintegrant, lubricant were added as per requirement and final mixture was compressed using tabletting machine or encapsulated [5,9,29,30].

**FLOW CHART FOR PREPARATION OF LIQUISOLID COMPACT:**




**Pre-Formulation Studies**

- Determination of solubility of drug inselected non-volatile solvents
- Determination of angle of slide
- Evaluation of flowability and compressibility of liquisolid powders

**Solubility studies**

In this study excess amount of pure drug was added to the non volatile liquid vehicle shaken it for 72 hrs at 25°C on a rotary shaker. After 72 hours stirring the saturated solution was filtered through milli pore filter paper and analyzed for the drug content by UV spectrophotometer [6,7,31].

**Determination of angle of slide:**

Required amount of the carrier material was weighed and placed on one end of the glass slide and the slide raised slowly till the slide is angular to the horizontal surface. This angle is called as angle of slide. This is useful for the measuring the flow behavior of the material. **33°C** is the ideal angle for the good flow [6,7].

**Evaluation of flowability and compressibility of liquisolid powders**

The flowability of the obtained mixtures was calculated by measuring the angle of repose (direct method). Determination of bulk and tap densities of the obtained mixtures was used to calculate both the Hausner ratio and the Carr's index (indirect method).The obtained mixtures were compressed into tablets and the compressibility of these tablets was determined by measuring the hardness of each tablet.

**Determination of Liquid load factor (Lf)**

Liquid load factor (Lf) is defined as the weight ratio of the liquid medication (w) and carrier powder (Q) in the system (i.e., Lf = W/Q), which must be possessed by an acceptably flowing and compressible preparation. Constant weights of the selected carrier (10g) was placed in different mortars containing different weights of a solvent and triturate well. The final mass was checked for their consistency, flowability, and compressibility properties and then compressed into tablets and their texture, hardness were detected [33].

**Evaluation Studies**

- Flow behaviour
- Differential scanning calorimetry (DSC)
- Fourier transforms infra red spectroscopy (FTIR)
- X-Ray diffraction (XRD)
- Scanning electron microscopy (SEM)
- Dissolution studies of liquisolid tablet

**Flow behaviour:** Estimation of flow properties is important for formulations and industrial production of solid dosage form. Angle of repose is method that can be used to determine the flow rate of powder.

**Differential scanning calorimetry:** Thermotropic properties and thermal behavior of the samples were recorded on the DSC. Samples (3-5mg) are placed in the alluminium pans at constant heating of 15°C/min spanning a temperature range upto 30-300°C. Nitrogen was used as a purge gas through the DSC cell. If the characteristic peak of the drug is absent in the thermogram it indicates that the drug is dispersed molecularly in the liquid solid system (i. e the drug is in the form of solution in the formulation). Thermal properties of the drug and the prepared samples were subjected to DSC.

**Fourier transforms infra red spectroscopy:** FTIR spectrum of the drug and the prepared samples were subjected to IR spectrophotometer under identical conditions by Potassium bromide pellet technique. Spectrum is collected over a region of 4000-400 cm.

**X ray diffraction:** The X-ray diffraction (XRD) patterns are determined for drug, excipients used in formulation, physical mixture of drug and excipients, finally for the prepared liquisolid system. Absence of constructive specific peaks of the drugs in the liquisolid X-ray diffractogram indicate that drug has almost entirely converted from crystalline to amorphous or solubilized form.

**Scanning electron microscopy:** SEM is utilized to assess the morphological characteristics of the raw materials and the drug excipient systems. SEM study shows that the complete disappearance of the crystals of drug confirms that the drug is in molecularly dispersed state or solubilized state in the liquid solid system.

***In vitro*** **dissolution test:** Carried out in USP II at 37+/-0.50C. The aliquots of dissolution media were withdrawn each time at suitable time intervals and replaced with fresh medium. After withdrawing, samples were filtered and analyzed by appropriate analytical method.

***Stability studies:*** Conducted based on ICH guidelines and the samples were taken and analyzed at particular time intervals.

***In-vivo studies:*** Many researchers discovered by estimating the pharmacokinetic parameters in various animals like beagle dogs and rabbits that the absolute bioavailability of drug from liquidsolid tablet was much higher than that of the marketed conventional uncoated formulation [16,17,30,32].

**Liquisolid Technique for Sustained Drug Release**

Liquisolid technique can be an emerging technique used for sustained release formulation with zero order kinetics. In sustained release liquisolid formulation hydrophobic carriers such as Eudragit R L and RS etc are used leading to poor wetting of formulation with slow disintegration and prolonged release. Use of liquid vehicles which acts as plasticizer e.g. polysorbate 80 lowers the glass transition temperature of polymer, resulting matrix of low porosity and high tortuesity formation due to coalescence of polymer particle with liquisolid compact. Addition of polymer like HPMC increases the retardation effect due to swelling of polymer in contact with water with zero order release kinetics [6, 34, 35].

## CONCLUSION

It is well established that the inadequate dissolution of water-insoluble drugs is the major reason for their poor and erratic bioavailability, since it is the rate determining step in the absorption. Liquisolid compacts are improved beneficial technology to overcome the low bioavailability of the drug. This technology refers to the conversion of liquid form of drug or liquid drug into the solid state of non-adhering, dry free flowing and easily compressible powder by using suitable carrier and coating materials in specific ratios. The use of non-volatile solvent in the formulation causes increased wettability of water insoluble drugs and ensures molecular dispersion of drug in the formulation. The enhanced rate of drug dissolution from liquisolid tablets is probably due to an increase in wetting properties and surface area of drug particles available for dissolution. By using suitable combination of excipients the release of the drug also can be controlled.

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