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LIQUISOLID COMPACTION: A NOVEL TECHNIQUE FOR DISSOLUTION ENHANCEMENT – A REVIEW

Tamma Anil Reddy[1]*,
Srinivasan.S, Kavitha[1]. K, M. Rupesh Kumar[1], Jagadeesh Singh S.D[1], Ch.Nagender Reddy[1].

ABSTRACT
Dissolution rate of poorly water-soluble drugs is rate limiting step for its bioavailability so increase in bioavailability is the major challenge for the pharmaceutical industry with developments of new pharmaceutical products. There are various methods but liquisolid technique is a new and promising method that can change the dissolution rate of water insoluble drugs. In liquisolid technique, suspension and solution of solid drugs in non-volatile solvent systems and liquid drug convert into solid dosage form by using carriers and coating materials. By using hydrophobic carriers (non-volatile solvents) one can modify release (sustained release) of drugs by this technique. Liquisolid system is characterized by flow behavior, wettability, powder bed hydrophilicity, saturation solubility, drug content, differential scanning calorimetry, Fourier transform infra red spectroscopy, powder X-ray diffraction, scanning electron microscopy, in-vitro release and in-vivo evaluation. By using this technique, solubility and dissolution rate can be improved, sustained drug delivery systems be developed for the water soluble drugs.

Keywords:- *Dissolution rate, liquisolid technique**,** bioavailability, hydrophobic carriers etc.*

Correspondence Author

Tamma Anil Reddy

Email: biovenki76@gmail.com

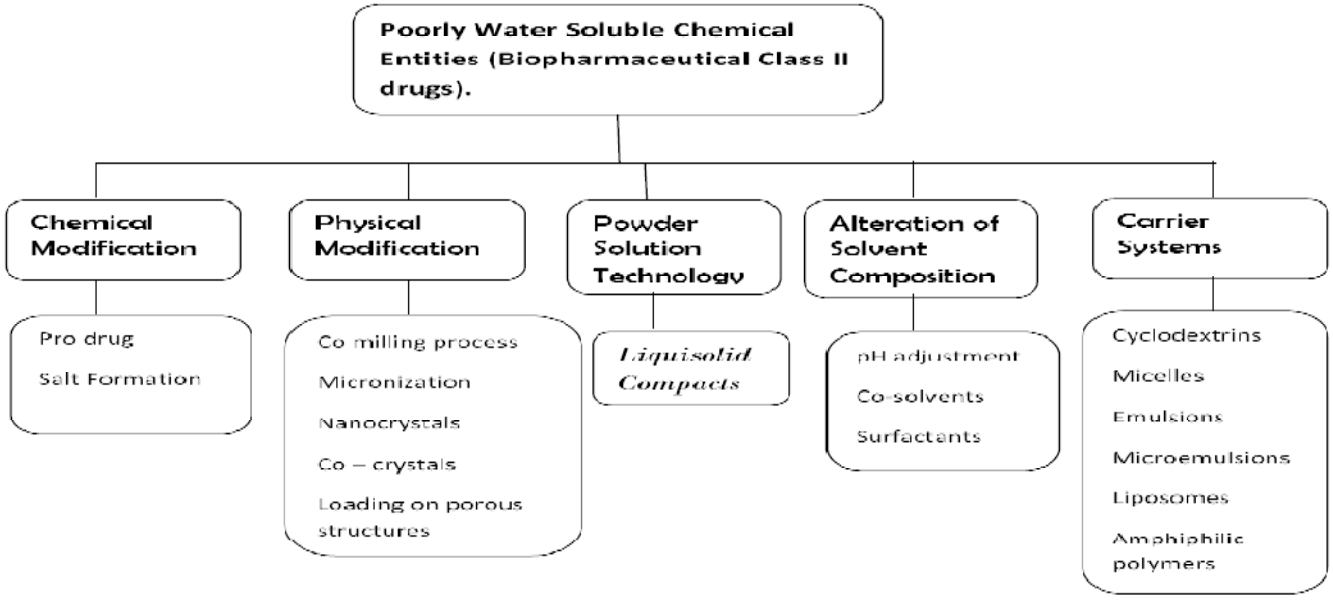
INTRODUCTION

The dissolution properties of a drug and its release from a dosage form have a basic impact on its bioavailability. Solving solubility problems is a major challenge for the pharmaceutical industry with developments of new pharmaceutical products, since nearly half of the active substances being identified through the new paradigm in high throughput screening are either insoluble or poorly soluble in water.[1]

A most important parameter that is useful for poorly soluble drugs is the dose: solubility ratio of the drug. The dose: solubility ratio can be defined as the volume of gastrointestinal fluids necessary to dissolve the administered dose. When this volume exceeds the volume of fluids available, one

may anticipate incomplete bioavailability from solid oral dosage forms.[2]Increasing the dissolution and bioavailability of poorly soluble drugs is a major challenge facing the pharmaceutical industry today as about 40% of potential drugs produced are almost insoluble. There are many methods for increasing the dissolution of drugs such as reducing particle size, conversion of the drug to the salt form or polymorph, the use of complexing agents such as cyclodextrins, the use of surfactants or co-solvents and the synthesis of pro-drugs.[3]

Fig. 1: Different methods to enhance the solubility of drugs



Different methods to enhance the solubility of drugs

Micronization:- The particle size reduction technique enhance the solubility and dissolution rate
of poorly water soluble drugs due to the enormous surface that is generated.

Solvent Deposition:- In this method, the poorly aqueous soluble drug such as nifedipine is dissolved in an organic solvent like alcohol and deposited on a inert, hydrophilic, solid matrix such as starch or microcrystalline cellulose evaporation of solvent.

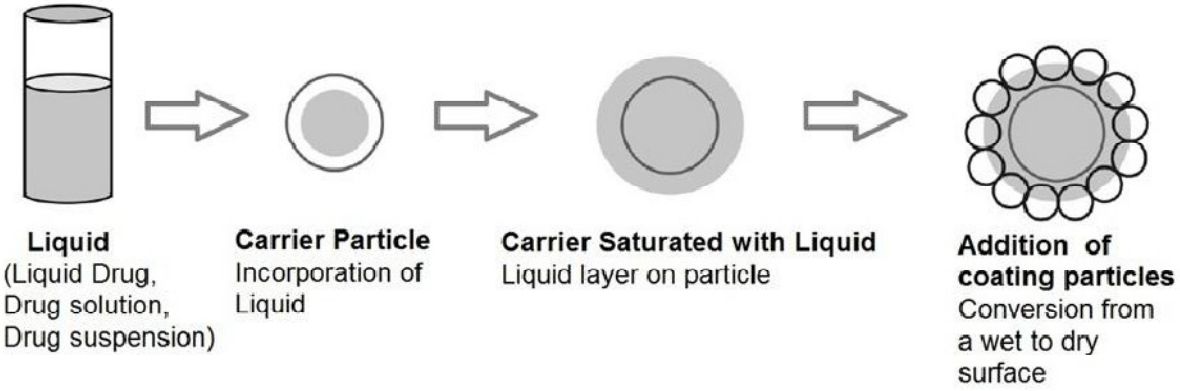
Use of soluble Prodrug:- Wherein the physico-chemical properties of the drug are improved by bio-reversible chemical alteration. The most common prodrug strategy involves the incorporation of polar or ionizable moiety into the parent compound to improve aqueous solubility.[4]

Solid dispersion:- It involves dispersion of one or more active ingredients in an inert carrier or
matrix at solid state. Melting (fusion) method, solvent evaporation method or melting evaporation methods can be employed for the preparation of the solid dispersions. The dissolution rate of the solid dispersion depends on the type of carriers used or the type of the matrix forming polymers used.[5]

Over past few decades, various approaches have been introduced to solve the problem of formulation of poorly soluble drug substances, with the original seek of enhancing drug dissolution characteristics, with different degrees of success. The liquisolid technique is a new and promising addition towards such a novel aim.[6]

Liquisolid technique:- Spireas described the method for promoting dissolution i.e. the formation of liquisolid compacts. A liquid may be

transformed into a free flowing, readily compressible and apparently dry powder with the liquisolid technology by simple physical blending with selected excipients named the 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.[7] Inert, preferably water-miscible organic solvent systems with high boiling point such as propylene glycol, liquid polyethylene glycols, or glycerine 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. Figure 2 represents the schematic representation of a liquisolid system. 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 compacts.[8,9]



Schematic representation of Liquisolid System

ADVANTAGES AND LIMITATIONS

Advantages:

- Several slightly and very slightly water-soluble and practically water-insoluble liquid and solid drugs, can be formulated into liquisolid systems.
- Even though the drug is in a tablet or capsule form, it is held in a solubilised liquid state, which contributes to increased drug wetting properties, thereby enhancing drug dissolution.
- Production cost is lower than soft gelatin capsules.
- Rapid release liquisolid tablets or capsules of water insoluble drugs exhibit enhanced in-vitro and in-vivo drug release when compared to their commercial counter parts, including soft gelatin capsules preparation.
- Sustained release liquisolid tablets or capsules of water insoluble drugs exhibit constant dissolution rates (zero-order release) comparable only to expensive commercial preparations that combine osmotic pump technology and laser-drilled tablets.

Limitations:

- Not applicable for formulation of high dose insoluble drugs.
- If more amount of carrier is added to produce free-flowing powder, the tablet weight increases to more than one gram which is difficult to swallow.
- 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.
- 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.[10]

Fig.3: Mechanism represents formulation of liquisolid system

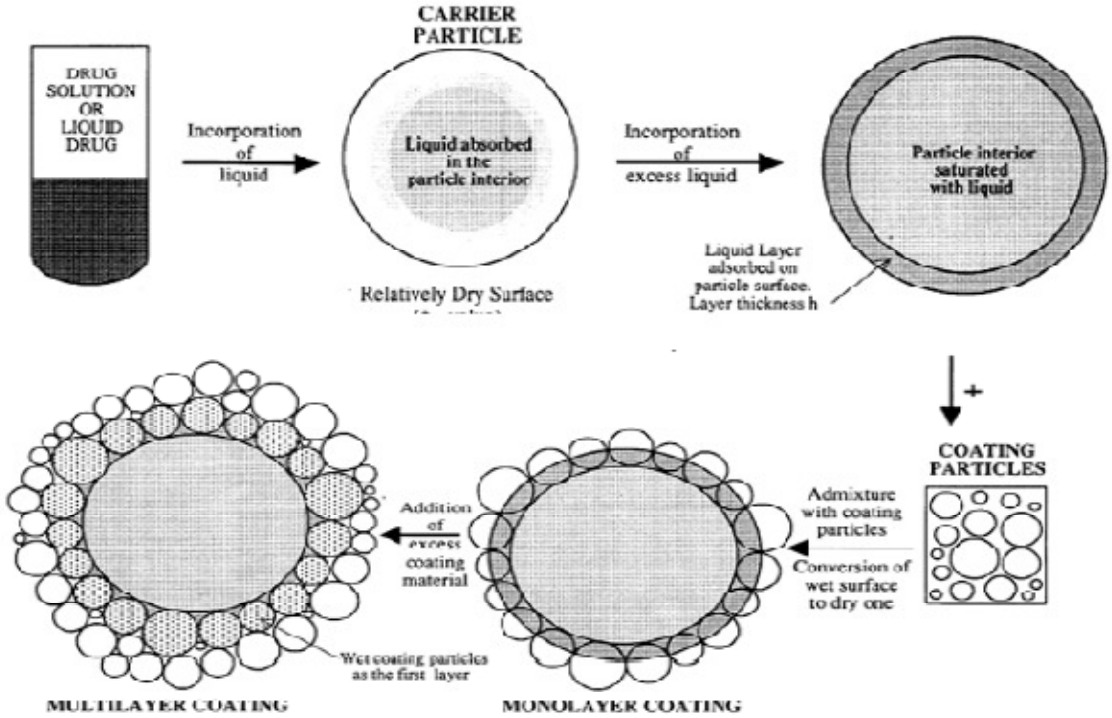
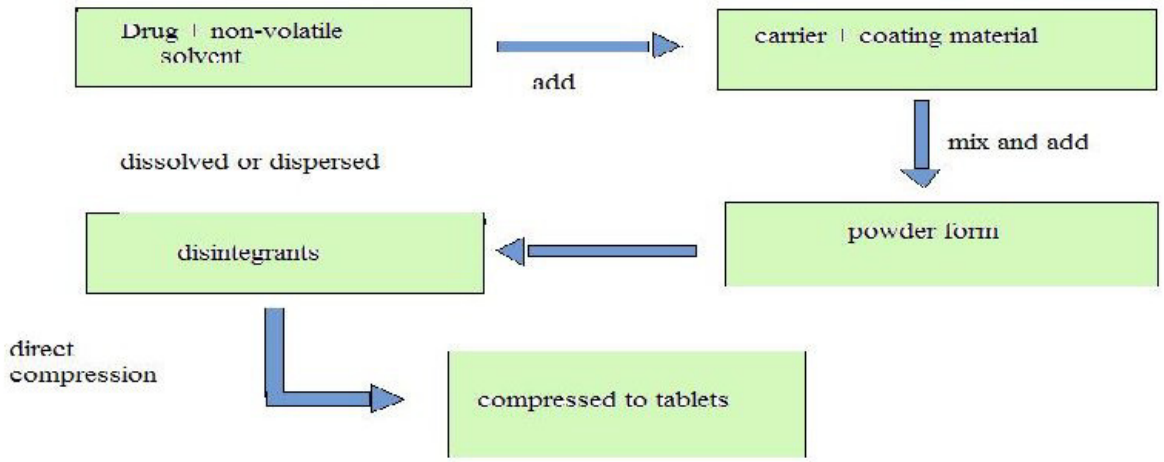


Fig. 4: Method of Preparation of Liquisolid Tablets



Definitions

Liquid medication includes liquid lipophilic drugs and drug suspensions or solutions of solid water insoluble drugs in suitable non-volatile solvent systems.

Liquisolid system refers to powdered forms of liquid medications formulated by converting liquid lipophilic drugs, or drug suspensions or solutions of water insoluble solid drugs in suitable nonvolatile solvent systems, into dry, nonadherent, free-flowing and readily compressible powder

admixtures by blending with selected carrier and coating materials.[11]

Liquisolid compacts: It refers to immediate sustained release tablets or capsules that are described under liquisolid systems.

Liquisolid microsystems: It refers to capsules prepared by liquisolid systems with the inclusion of an additive ensuing in a unit size that may be as much as five times less than that of a liquisolid compact.

Carrier: Coating Material Ratio (R): It is the ratio between the quantities of carrier (Q) and coating materials (q) present in the formulation. It is represented as:

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

Carrier material: These are as porous substance possessing adequate absorption properties. Various grades of microcrystalline cellulose (MCC) such as pH101, and 200, Avicel® RTM 105, Avicel® pH 102 granular Microcrystalline cellulose (MCC) grade, Avicel ® pH 200
coarse granular MCC grade, experimental grade of granular amorphous cellulose, starch, lactose used as carrier materials. Starch 1500, Silica possessing large surface areas and MCC of fine particle size granular grades produced good flow properties and compression properties resulting in good tablets.

Coating Material: It is a substance possessing fine and highly adsorptive particles. These are flow-enhancing, very fine 10 nm to 5,000 nm in diameter, highly adsorptive coating particles
e. g: silica of various grades like Cab-O-Sil M5, Aerosil 200,Syloid244FP etc., contributes in covering the wet carrier particles and displaying a dry-looking powder by adsorbing
any excess liquid.[12-15]

Hydrophobic carrier: Eudragit RL and RS[15], HPMC K4M[16] etc, for sustained release.

Liquid load factor (Lf): It is the ratio of the amount of liquid medication (W) over the quantity of carrier material(Q) in the system. The ratio can be calculated with this equation:

$$L_f = \frac{W}{Q}$$

Super disintegrants: Sodium starch glycolate[17] Explotab13, Pumogel, Crosspovidone,[18] Sodium croscarmellose,[19,20] Pre gelatinized starch.[21]

Non-Volatile solvents: preferably water-miscible, Inert high boiling point and not highly viscous organic solvent systems
e.g. propylene glycol, liquid polyethylene glycols, N, N dimethylacetamide, polysorbates, glycerin, fixed oils etc., are most suitable as vehicles.[22]

Designing of Liquisolid Systems
Before designing the liquisolid, the preformulation studies should be performed first, these include
1. Determination of drug in different non-volatile solvents
2. Determination of angle of slide
3. Determination of flowable liquid retention potential (Ø value)
4. Calculation of liquid load factor (Lf)
5. Liquid solid compressability test (LSC)

The flowability and compressibility of liquisolid compacts are addressed concurrently in the new formulation mathematical model of liquisolid systems, which was used to calculate the appropriate quantities of the carrier and coating materials required to produce acceptably flowing and compressible powders based on new fundamental powder properties called the flowable liquid retention potential (Φ -value) and compressible liquid retention potential (Ψ - number) of the constituent powders.[23,24]

Determination of drug in different non-volatile solvents:
These are carried by preparing saturated solutions of drug in non-volatile solvents, and analyzing them spectrophotometrically.[25] Saturated solutions are prepared by adding excess of drug to vehicles and shaking them on shaker for specific time period under steady vibration. After this, the solutions are filtered and analyzed spectrophotometrically.

Determination of angle of slide: The required amount of carrier is weighed and placed at one of a metal plate with a polished surface and it is gradually raised till the plate becomes angular to the horizontal at which powder is about to slide.[26] It was used to measure the flow properties of powders. The angle of 33° is optimum for flow of powders.

Determination of liquid flowable liquid retention potential (Φ): It is defined as the maximum weight of liquid that can be retained per unit powder material in order to produce and acceptably flowing liquid/powder admixture.
This Φ –value of powders may be determined using a new procedure, the liquisolid flowability (LSF) test. The Ø value was used to calculate excipients quantities. Equation for this
is as follows:
Lf= **Ø** + Ø (1 / *R*)

Where **Ø** and Ø are the constant Ø values of carrier and coating materials, respectively. By calculating Lf and W, we can calculate the amount of Q and q required for liquisolid systems.[27]

Calculation of liquid load factor (Lf): It is defined as the ratio of weight of liquid medication (w) to weight of carrier material (Q). Different concentrations of nonvolatile solvents are taken and the drug is dissolved and the carrier coating material is added and blended.[28]

Lf=W/Q
W=ratio of weight of liquid medication
Q= weight of carrier material
The liquid load factor that ensures acceptable Flowability (Lf), and can be measured by:

Lf= (1/R)

Liquisolid compressability test (LSC): It was developed to determine Ψ values and involves steps such as preparing carrier coating material admixture systems,[29] preparing several uniform liquid/powder admixtures to tablets, determining average hardness, measuring of average liquid content of crushed tablets, as well as determining plasticity, sponge index and Ψ value
and Lf.

General Procedure for Liquisolid Tablets: The liquisolid tablet preparation method involves, first a mathematically calculated amount of pure drug weighed and dissolved in the suitable amount of solvent in a molecularly dispersed state. For attaining good flow properties trial and
error methods were used i.e. changing the carrier: coating material ratio from 50:1 to 5:1 ratios according to new mathematical model expressions proposed by Liao.[30] This liquid medication is poured on the suitable amount of carrier material. The liquid medication is absorbed into the
carrier material internally and externally and then a suitable disintegrant was added to this material. Finally, coating material was added for dry looking, adherent to the carrier material for achieving good compression properties. Liquid medication is incorporated into carrier material which has a porous surface and closely matted fibers in its interior as cellulose.[23] Both absorption and adsorption take place, i.e., the liquid absorbed into the interior of the particles is captured by its internal structure and after saturation of this process, adsorption of the liquid onto the internal and external surface of the porous

carrier particles occurs.[30] Excipients possessing fine and highly adsorptive particles such as various types of amorphous silicon dioxide (silica) are most suitable for this step. Before compression or

encapsulation, various ingredients such as lubricants disintegrants or Polymers, and binders (as shown in Fig. 3), may be mixed with the finished liquisolid systems to produce liquisolid compacts in the dosage form of tablets or capsules.[31-33]

Evaluation of liquisolid systems

Flow behavior: The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to reduce high dose variations.[34] Angle of repose, Carr's index and Haunser's ratio were used in order to ensure the flow properties of the liquisolid systems.[35]

Pre compression studies of the prepared liquisolid Powder systems: In order to ensure the suitability of the selected excipients, Fourier Transform Infra Red Spectroscopy, Differential scanning Calorimetry, X-ray Diffraction and Scanning Electron Microscope studies are to be performed. In addition, flowability studies are also to be carried out to select the optimal formulae for compression, prior to the compression of the powders the dosage forms such as into tablets and capsules.

Fourier Transform Infra Red Spectroscopy (FT-IR):FT-IR spectra of prepared melt granules are recorded on FTIR-8400 spectrophotometer. Potassium bromide (KBr) pellet method is employed and background spectrum is collected under identical situation. Each spectrum is derived from single average scans collected in the region 400 - 4000cm-1 at spectral resolution of 2cm-2 and ratio against background interferrogram. Spectra are analyzed by software.[23]

Differential scanning calorimetry (DSC): Differential scanning calorimetry (DSC) is performed in order to assess the thermotropic properties and the thermal behaviors of the drug, excipients used in the formulation of the liquisolid system. Complete disappearance of characteristic peaks of drug indicates the formation of drug solution in the liquisolid powdered system, i.e., the drug is molecularly dispersed within the liquisolid matrix.[23,36-37]

X-ray diffraction (XRD): For the characterization of crystalline state, X-ray diffraction(XRD) patterns are determined for physical mixture of drug and excipients used in formulation and for the prepared liquisolid compacts.[38]Absence of constructive

specific peaks of the drug in the liquisolid compacts in X-ray diffractogram specify that drug has almost entirely converted from crystalline to amorphous or solubilized form. Such lack of crystallinity in the liquisolid system was understood to be as a result of drug solubilization in the liquid vehicle i.e., the drug has formed a solid solution within the carrier matrix.This amorphization or solubilization of drug in the liquisolid compacts it may contribute to the consequent improvement in the apparent solubility and enhancement of dissolution rate of the drug.

Scanning electron microscopy (SEM): Scanning electron microscopy (SEM) is utilized to assess the morphological characteristics of the raw materials and the drug-carrier systems.[39]

Contact angle measurement: For assessment of wettability, contact angle of liquisolid tablets is measured according to the imaging method. The commonly used method is to measure contact angle directly for a drop of liquid resting on a plane surface of the solid, the so-called imaging method. A saturated solution of the drug in dissolution media is prepared and a drop of this solution is put on the surface of tablets. The contact angles are calculated by measuring the height and diameter of sphere drop on the tablet.[38]

***In vitro* dissolution studies:**Works of many researchers revealed that technique of liquisolid compacts could be a promising alternative for formulation of water-insoluble drugs. This technique of liquisolid compacts has been successfully employed to improve the *in-vitro*

release of poorly water soluble drugs as hydrocortisone,[12] Prednisolone[27] Carbamazepine[37] Piroxicam.[15,38,40] Also several water insoluble drugs nifedipine, gemfibrozil, and ibuprofen, have shown higher bioavailability in rats as compared to their commercial counterparts.

In vivo evaluation **of liquisolid systems:**This liquisolid technology is a promising tool for the enhancement of drug release of poorly soluble drugs. The absorption characteristics of Hydroclorothiazide liquisolid compacts in comparison with commercial tablets were studied in beagle dogs. Significant differences in the area under the plasma concentration-time curve, the peak plasma concentration and the absolute bioavailability of the liquisolid and the commercial tablets were observed.However, for the mean residence time, the mean absorption time, and the rate of absorption no significant differences were found. The absolute bioavailability of the drug from liquisolid compacts was 15% higher than that from the commercial formulation.[41]

Liquisolid technique is a potential alternative for formulation of water-insoluble/soluble drugs. The enhanced rate of drug dissolution from liquisolid tablets is probably due to an increase in wetting properties and surface area of drug particles obtainable for dissolution. Rapid disintegration rates are experimentally compared to conventional tablets. Hence liquisolid compacts show improved release rates and greater bioavailability. By this technique, sustained drug delivery systems were also be developed for the water soluble drugs in which hydrophobic non-volatile solvents are used as vehicles Alteration of formulation by use of definite agent's source it control the release of drugs from the liquisolid tablets.

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