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Advancements in Solubility Enhancement Through Liquisolid Compact Technology: A Comprehensive Review

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Abstract

The study examines Liquisolid Compact Technology as an innovative approach for improving the bioavailability and solubility of drugs that are poorly soluble in water. Liquisolid systems, comprising solid carriers and liquid drugs, offer advantages such as improved drug release and bioavailability, reduced manufacturing costs, and controlled drug delivery. The technique involves dissolving or suspending the drug in non-volatile solvents, adding carrier materials, super disintegrants, and coating materials, and then compressing the resulting mixture into tablets. Various evaluation methods, including DSC, FTIR, XRD, SEM, and angle of repose, assess the physical and chemical properties of Liquisolid formulations. The excipient ratio and liquid load factor play crucial roles in determining the compressibility and flow behavior of Liquisolid systems. Stability studies ensure the long-term efficacy of the formulations. In-vitro and in-vivo studies demonstrate the effectiveness of Liquisolid tablets in improving drug release and absorption rates, leading to enhanced bioavailability compared to conventional tablets. Overall, Liquisolid Compact Technology represents a promising strategy for addressing solubility issues and improving the therapeutic efficacy of poorly water-soluble drugs. The technique offers a versatile and cost-effective approach to pharmaceutical formulation, with potential applications in various therapeutic areas.

Keywords: Solubility, *in-vitro*, *in-vivo* studies, liquisolid technology, bioavailability

INTRODUCTION

The selection of the most suitable route is dependent upon parts related to the patient as well as the drug itself. The most common method for administering medicine is orally. Because oral therapy is less expensive and more patient-complied with, it is the recommended method. Over 70% of drugs that are commercially available are available in oral dose forms because of their adaptability and capacity to bypass pain [1].

Liquisolid Systems are compressible, free-flowing mixtures of pharmaceutical suspensions or solutions. Liquisolid consists of the terms “Solid” which belongs to a powdered form, and “Liqui” which belongs to drug solutions or suspensions [2].

A number of active pharmaceutical ingredients have been produced synthetically. About 40 to 60% newly developed drugs are having solubility issues [3]. Many active pharmaceutical ingredients have

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Table 1. Ingredients for manufacture of Liquisolid Compact [4, 5]

S.N.	Ingredients	Role of Ingredient	Examples
1	Drugs	Active Pharmaceutical Ingredient (API) is the biologically active component used to provide therapeutic action.	Pioglitazone, Celecoxib, Nebivolol Hydrochloride, Oxcarbazepine, Hydrochlorothiazide, etc.
2	Non-volatile oil	To dissolve the Active pharmaceutical ingredients	Polysorbate 20, Polysorbate 80, Propylene Glycol, Polyethylene Glycol -200/300/400/600, Cremophor ET (castor oil), etc.
3	Carrier	The ingredient in turning the mixture from a liquid into a dry powder is the carrier substance. It should possess satisfactory absorption properties for a liquid vehicle.	Ethyl cellulose, Microcrystalline cellulose (Avicel PH 102), Neusilin US2, etc.
4	Coat	It absorbs the excessive non-volatile solvent layer over the carrier particles. And displays a dry-looking, non-adherent, free flowing powder.	Amorphous silicon dioxide (Aerosil 200), Neusilin US2, Syloid 224FP, Mesoporous silica, Calcium silicate, Magnesium alumino meta silicates, etc.
5	Disintegrants	To disintegrate tablet	Sodium starch glycolate, Cross providone, sodium carscarmellose, pre gelatinized starch, etc.
6	Additives	Hardening agent, lubricant, binder, etc.	Stearic acid, Magnesium stearate, Polyvinylpyrrolidone (PVP), etc.

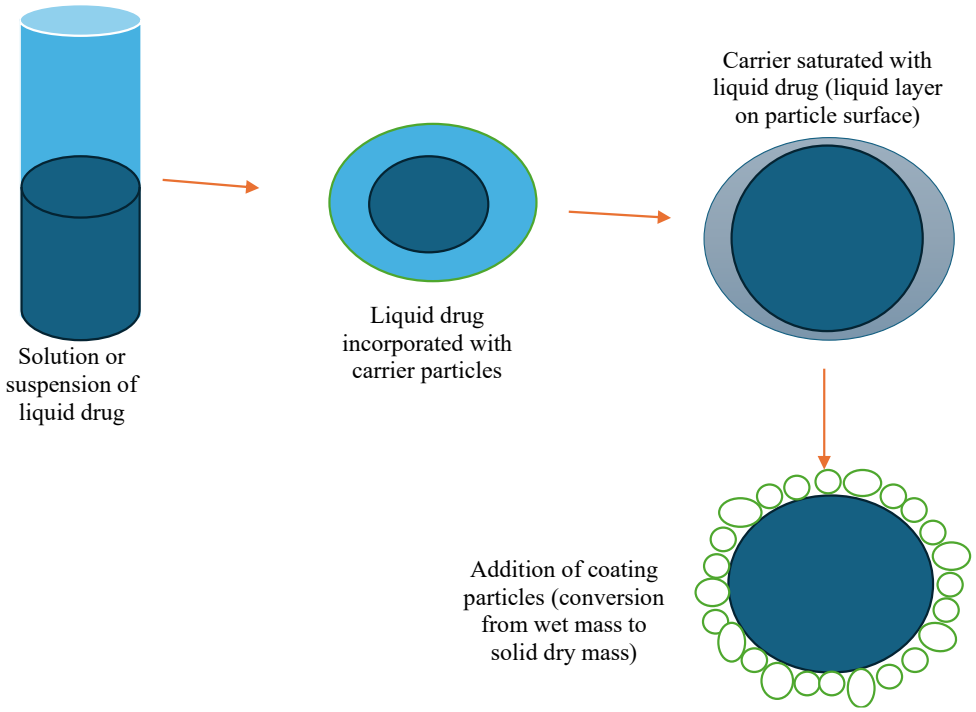

Figure 1. Diagram of liquisolid compact technology [13].

solubility problems in Gasto-intestinal tract including API like Lansoprazole, Azithromycin, Loperamide, Duloxetine, etc. (Table 1) [4, 5].

Liquisolid Compact System is defined as the dry, non-adherent, free-flowing and compressible powder mixture developed from liquid drug. The liquid drug or the solution or suspension of poorly soluble drugs using the non-volatile solvents that are mixed-up with carrier and coat materials and develop the final product as dispersible phase which is used to manufacture granules and tablets, etc. [6].

Liquisolid tablet was formulated of drugs like Ibuprofen [7], Pioglitazone [8], Celecoxib [9], Nebivolol Hydrochloride [10], Oxcarbazepine [11], Hydrochlorothiazide [12], etc. (Figure 1) [13].

Types of Liquisolid Compact [6]

- Powdered drug suspension,
- Powdered drug emulsion,
- Powdered drug solution, and
- Powdered liquid drugs.

Advantages [13]

1. It belongs to biopharmaceutical class II, in which drugs have high permeability and less solubility; that is why it can be converted into Liquisolid systems.
2. When a drug which is insoluble in water, administered orally, that drug in liquid state increases its bioavailability and improves its drug release *in-vitro* and *in-vivo*.
3. It helps in the enhancement of bioavailability of hydrophobic drugs, like, pantoprazole, hydrochlorothiazide, carvedilol, etc.
4. Liquisolid compact is used for controlling drug delivery.
5. Liquisolid systems reduce pH influence on the dissolution rate of poorly soluble drugs in GI Track.
6. Liquisolid compact has low manufacturing costs than soft gelatin capsules.

Disadvantages [13]

1. If drugs solutions are utilized, one of the drawbacks or restrictions of Liquisolid compact is that the drug must have a high solubility in non-volatile liquid carriers.
2. There is restriction to formulation of high amounts of poorly water-soluble drugs (such as flutamide and carbamazepine) in the "Liquisolid system".
3. To produce dry powder with an appropriate flowability and compressibility, drugs need a lot of liquid vehicle, carrier, and coating material. For ease of application, this may increase the mass of each tablet over its maximum limit.

Components/Materials Used to Prepare of Liquisolid Compact [4]

- *Active pharmaceutical ingredients*
  - The drugs which belong to BCS class II and IV, and have low solubility, are suitable candidates for the formulation of Liquisolid compact.
- *Nonvolatile solvents*
  - Its organic solvent systems are not very viscous, and it has a high boiling point, making it inert.
  - Liquid vehicles used in Liquisolid system should be safe.
  - Nonvolatile liquids can be found to serve binding action inside the formulation.
- *Carrier material*
  - The carrier used should be spongy in character.
  - The carriers that are used in Liquisolid systems should have a porous surface since they are very good at absorbing liquids.
  - It should possess satisfactory absorption properties for a liquid vehicle.
  - Carrier and Coating materials should hold a limited quantity of liquid.
  - The primary ingredient in turning the medicine from a liquid into a dry powder is the carrier substance.
  - The carrier must have to preserve both compressibility and flowability.
- *Coat material*
  - Coating materials are extremely thin, highly adsorptive coating particles that improve flow.
  - Their qualities should be excellent and very adsorptive in nature.
  - Coat material covers the wet carrier particles.
  - It absorbs the surplus layer of nonvolatile solvent from the carrier particles.
  - It displays a free-flowing powder and non-adherent powder that seems dry.
  - Typically, they are materials that are coarse powdered, which aid in covering the particles.
- *Disintegrants*
  - Super disintegrants have an influence on drug release.

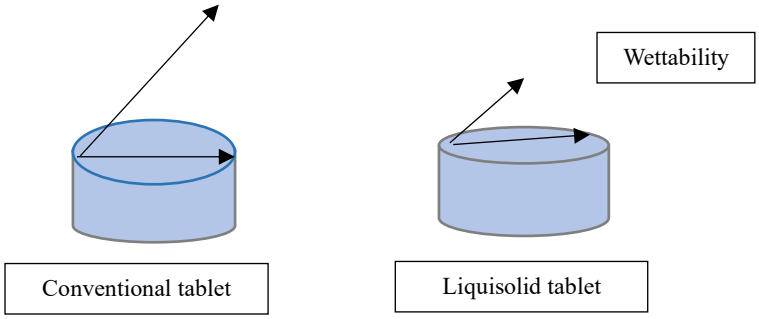

Figure 2. Difference between Depiction of the contact angle of conventional and Liquisolid tablets [5].

- It increases the wettability as well as solubility of drug.
- Disintegrants are used in Liquisolid compact system for disintegration of the tablet (Figure 2).

PROCESS OF MANUFACTURE LIQUISOLID COMPACT [15]

- The API/Drugs dissolve or suspend in the nonvolatile solvents until homogenous drug solution is obtained.
- Nonvolatile solvents used, depending on drug dissolution are: Polysorbate 20, Polysorbate 80, Polyethylene glycol 200/300/400/600, Glycerin, etc.
- In this mixture, add carrier material. Carrier material also works as absorbance material. With continuous triturate using mortar pestle or blend mixture in blending machine rotation is set for 1 rotation for 1 sec. Do the process for 1 min and obtain homogenous distribution.
- Then add sodium starch glycolate, Cross povidone, Pre-gelatinized starch, etc. which are used as super Disintegrants.
- And continuously triturate using mortar pestle.
- Then in that mixture add coating material. The very small, highly adsorptive coating particles that make up coating materials help to cover the wet carrier particles by absorbing the excess non-volatile solvent layer over them. As a result, it forms a powder that looks dry, is non-adherent, and flows smoothly.
- The dry, non-adherent, and free flowing powder is used for the encapsulation, pellets, or tablet (Figure 3).

Theory of Liquisolid Systems [16]

Spires introduced the mathematical model of Liquisolid compact systems on the basis of good flow behavior and compressibility of formulation.

Excipient Ratio (ER)

This excipient ratio is dependent on the liquid carrier. Compressibility and flowability of a liquid system can only be achieved when the liquid load on the carrier material is below the specified limit.

Excipient ratio (ER) is known as the ratio of weight of carrier agent (Ca) to the coating agent (Co):

$$ER=Ca/Co \quad (1)$$

Excipient ratio is a critical parameter in Liquisolid system. It can represent the maximum load that can be retained on the carrier material without the acceptable liquid to powder percentage ratio range between the 2 and 52%.

Liquid Load Factor (LF)

The liquid load factor is represented as the optimal liquid that can be incorporated into the liquid system. The liquid load factor is typically expressed as a percentage of the total formulation weight.

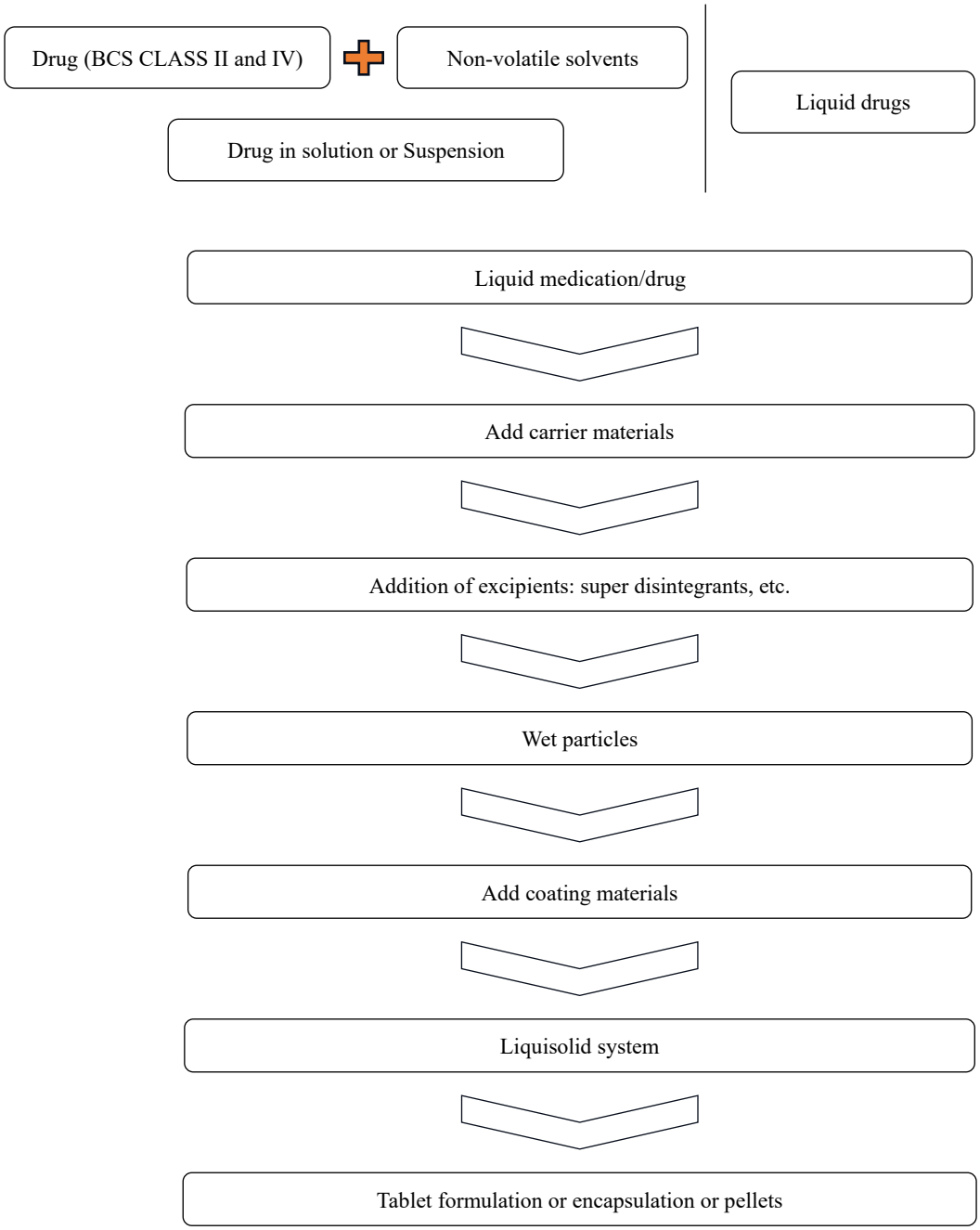

Figure 3. Preparation and formulation of liquisolid [14].

This is given by liquid load factor (LF) which is a ratio of weight of liquid formulation (W) to carrier material (Ca):

$$LF=W/C \quad (2)$$

Similarly, to create liquisolid systems with appropriate compatibility, the liquid load factor (ΨLf) can be found using:

- *Adequate flow behavior (ϕLF):*
  Adequate flow behavior is attained by this liquid load factor (LF);

  $$\phi LF=Ca+Co.(1/ER) \quad (3)$$

  Here Ca and Co are the values for the carrier and coating material.

- *Satisfactory compatibility (ψLf):*
  Satisfactory compatibility for a Liquisolid system can also be determined as:

  ψLF=Co+Ca.(1/ER) (4)

  Where, Co and Ca are numbers for the coating material and carrier.

To achieve a satisfactory compressibility and flow behavior of the system, the ideal liquid load factor must be reached. Liquid load factor is measured, enough coating agent (Co) and carrier required for the liquid formulation to convert into a compactable, free flowing system can be calculated as:

Ca=W/Lo (For calculating carrier material) (5)

or

Co=Co/ER (For calculating coating material) (6)

Evaluation of Powder Mixture

The powder mixture properties can be evaluated as follows.

Differential Scanning Calorimetry (DSC) [5]

This thermoanalytical method measures the variation in the amount of heat required to raise a sample's temperature relative to a standard as a function of temperature. Throughout the experiment, the sample and standard are kept at almost the same temperature. DSC is used to test whether pure drug and excipients used in the Liquisolid process are compatible. The drugs are molecularly spread throughout the system if the typical peak for the drug is absent from the DSC thermogram, indicating that the drug is in solution in the Liquisolid formulation. Using a nitrogen environment with a flow rate of 100 mm/min, 5 mg of the sample was enclosed in the aluminium pans and heated at a rate of 10°/min, spanning a temperature range of 50 to 250°.

Fourier Transformed Infrared Spectroscopy [5]

FTIR spectra can be used to track changes in the stretching or vibrational bands of important functional groups to identify drug-excipient interactions. The KBr pressed pellet method is utilized to make pellets. The resulting pellets were stored in the infrared chamber, and a Bruker FTIR spectrophotometer fitted with Opus software was used to capture the mixes' infrared spectra.

X Ray Diffraction (XRD) [5]

The technique is mostly used for characterizing and identifying substances according to their diffraction pattern. XRD patterns are generated for the manufactured liquisolid compacts and the physical mixture of drug and excipients used in formulation in order to characterize the crystalline state.

Scanning Electron Microscopy [5]

The presence or absence of the drug's crystal form or that of the excipients in the formulation is shown by scanning electron microscopy. If the drug's SEM image indicates that it is not crystallized, it means that the drug is completely dissolved into the carrier system at this time.

Angle of Repose [17]

The angle of repose had been determined by use of the fixed funnel method. A piece of graph paper was set on a horizontal platform, and a glass funnel was securely attached with its tip at a predetermined height (H) above it. Until the conical pile's apex contacted the funnel's tip, powder was poured through it. To calculate the angle of repose, the following formula was utilized (Table 2):

$$Tan\ \theta = \frac{h}{r} \text{ or } \theta = Tan^{-1}\frac{h}{r}$$

Where, θ is the angle of repose, h is the height of heap, and r is the radius of the heap circle.

Table 2. Flow properties and corresponding angle of response.

Flowability	Angle of repose (°)
Excellent	25–30
Good	31–35
Fair-aid not needed	36–40
Passable-must agitate	41–45
Poor-must agitate, vibrate	46–65
Very poor	56–65
Very, very poor	>66

Bulk Density [17]

By carefully pouring a known quantity of powder sample through a glass funnel into a graduated measuring cylinder, the bulk density of the powder was obtained. The sample's volume was measured and recorded. The bulk density was calculated using a particular formula:

$B_d = W/V_b$

Where, B_d= Bulk density, W= Mass of the powder, and B= Bulk volume of the powder.

Tapped Density [17]

The powder sample was carefully poured into the graduated measuring cylinder using a glass funnel. The initial powder volume was recorded, and the sample was tapped until no more volume decline was observed. The volume difference as a percentage was also recorded as a percentage, ensuring it did not exceed 2%. The following formula was used to determine the tapped density of the samples based on the volume occupied by them post tapping:

$D_t = W/T$

Where, T_d= tapped density, W=Mass of the powder, and T= Tapped volume of the powder.

Compressibility Index and Hausner Ratio [17]

The compressibility index and the closely related Hausner ratio may now be used to forecast powder flow qualities quickly and easily, as a result, the compressibility index has been proposed as an indirect measure of bulk density, size, shape, cohesiveness, surface area, and moisture content of materials, all of which can affect the apparent compressibility index. The Hausner ratio and compressibility index of the powder are determined by measuring both its bulk density and its tapped density (Table 3) [18].

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where, I= Compressibility index, D_t= Tapped density of the powder, D_b= Bulk density of the powder, and Hausner ratio= D_t/D_b.

Table 3. Scale flowability [18].

Compressibility index (%)	Flow character	Hausner ratio
<10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
<38	Very, very poor	>1.60

EVALUATION OF LIQUISOLID TABLETS [5]

Weight Variation Test

20 tablets of each formulation type were weighed separately on an electronic balance; the average weight of the tablets was determined, and the weight of each tablet was added to the average value to get the weight deviation (Indian Pharmacopeia, 2014) (Table 4) [19].

Friability Test

The strength of a tablet is measured by its friability. The following method was utilized to assess the friability using the Roche friabilator (Meta Lab, Mumbai). This test applies the total impact of shock abrasion on many tablets using a plastic chamber that rotates at a speed of 25 rpm and lowers the tablets 6 in each time. A sample of six pre-weighed medications was placed inside the Roche Friabilator, which was then operated for 100 revolutions, or 4 min. After that, the pills were weighed again and given a dusting. It is widely accepted that a weight reduction of less than 1% is acceptable. Percent friability (% F) was calculated as follows (Indian pharmacopoeia 2014):

$$\text{Percentage of Friability} = \frac{\text{Initial weight}-\text{inal weight}}{\text{Initial weight}} \times 100$$

Hardness Test

For each formulation, the hardness of the tablets determines how resistant they are to breaking, shipping, handling, and storage conditions before use. Six pills were tested for hardness using a hardness tester (Monsanto, Mumbai). The tablet was held along its diametric axis between the tester's two jaws. The reading at this moment should be 0 kg/cm^3. Then the knob was turned again and again until the tablet cracked. At this point, the value was recorded.

Wetting Time

A tiny petri dish equipped with enough water was filled with a piece of tissue paper that had been folded twice and placed in it. The duration needed for the tablet to become completely wet was measured while it was resting on paper.

Water Absorption Ratio (R)

The tablet's weight (Wb) was recorded before it was put in the petri dish. We removed the wetted medicine and measured the weight (Wa). We next calculated the water absorption ratio using the following equation:

$$R = 100 \times \frac{(\text{Wa}-\text{Wb})}{\text{Wb}}$$

Where, Wb= Tablet weights before absorption, and Wa= Tablet weights after water absorption.

In vitro Release

Liquisolid tablet *in vitro* release is accomplished at 37±2°C using a USP II device. During these studies many researchers observed that if the drug concentration is low in liquid formulation, then rapid drug release can be expected from the formulation. Liquisolid tablet *in vitro* release rates that are higher will also have better absorption rates, which raises the drug's bioavailability.

Table 4. Specifications for tablets [19].

S.N.	Average weight of tablet	Percentage deviation permit
1	130 mg or less	10%
2	More than 130 mg but less that mg	7.5%
3	324 mg or more	5%

In vivo Study

By using this liquisolid technology, drugs that are poorly soluble can release their contents more effectively. Liquisolid compacts' absorption properties were examined in beagle dogs and compared to those of commercial tablets. Variations were noted between the commercial tablets and the area under the plasma concentration time curve, peak plasma concentration, and absolute bioavailability. There were no appreciable differences seen in the absorption rate, mean residence time, or mean absorption time. The absolute bioavailability was 15% higher than that from the commercial formulation.

Stability Studies

The drug content is determined by charging up the crystals of the drug to accelerate the stability conditions according to ICH guidelines Q1 R2. After certain amounts of time, samples are collected. After that, these samples are examined with an infrared spectrophotometer.

CONCLUSION

Liquisolid compact technique is novel technique for the formulation of water-insoluble solid and liquid drugs. Liquisolid techniques are used for increase in dissolution rate of the drug on the site of action. The reason for the higher rate of drugs dissolution for liquisolid tablets is most likely to be an increase in the wetting characteristics and surface area of the drug substance available for dissolution. When compared to traditional tablets, rapid disintegration rates are observed; this results in improved release rates and increased bioavailability.

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