

REVIEW ON LIQUISOLID COMPACT TECHNOLOGY

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ABSTRACT

Liquisolid compacts were used to formulate water insoluble drugs in non volatile solvents and convert into acceptable flowing compressible powders by blending with selected powder excipients. By using this method dissolution rate and bioavailability of BCS class-II drugs can be increased. About 40-50% drugs available marketed water insoluble drugs. It is challenge to industry to increase solubility of unit dosage forms to overcome this liquid solid compact technology is best suitable one. On this study the pre compressible parameters like porosity, corsaldity index, flow behavior, power bed hydrophilicity, saturate solubility. Post compressibility parameters like uniformity, weight variation, hardness, friability, wet ability, time. In this we can use

carrier (microcrystalline cellulose, starch, and lactose), coating materials (silica gel), and disintegrating agents. In this we can do flourier transform infra red spectroscopy, differential scanning calorimeters (DSC), and differential scanning thermometer, x-ray diffraction. It could promise strategy in improvising dissolution of poor water soluble drugs and formulating immediate release solid dosage forms.

KEY WORDS: Liquisolid compacts, Bioavailability, Poorly soluble drugs, Dissolution rate.

INTRODUCTION

Solubility of drugs is a major factor in the design of pharmaceutical formulations lead to variable oral bioavailability. Dissolution is an important factor for absorption of drugs especially in case of water insoluble or poorly soluble drugs. The rate limiting step for most of the pharmaceutical formulations is dissolution. Various methods used to increase the solubility of poorly water soluble drugs are solid dispersions, inclusion complexes with β -cyclodextrins, micronization, and eutectic mixtures and spray drying technique (Sharma *et al*

2010). The new developed technique by Spire as liquisolid system improves the dissolution properties of water insoluble or poorly soluble drugs. The term 'liqui-solid systems' (LS) is a powdered form of liquid drug formulated by converting liquid lipophilic drug or drug suspension or solution of water-insoluble solid drug in suitable non-volatile solvent systems, into dry looking, non-adherent, free-flowing and readily compressible powdered mixtures by blending with selected carrier and coating materials (Saharan, V.A. Kukkar *et al* 2009). Various grades of cellulose, starch, lactose, etc. are used as the carriers, whereas very fine silica powder is used as the coating (or covering) material. The good flow and compression properties of Liqui-solid may be attributed due to large surface area of silica and fine particle size of avicel. Hence, Liqui-solid compacts containing water-insoluble drugs expected to display enhanced dissolution characteristics and consequently improved oral bioavailability. The *in vitro* drug dissolution rates of such preparations were compared to those of conventionally prepared directly compressed tablets using a USP-II apparatus. Liquid lipophilic drugs (e.g. Chlorpheniramine and Clofibrate) or solid drugs (e.g., prednisone, Prednisolone, hydrocortisone, theophylline, Polythiazide and Spironolactone) dissolved in non volatile, high-boiling point solvent systems (e.g., polyethylene and polypropylene glycols, glycerin, N,N-dimethyl acetamide, various oils) have been formulated in powdered solutions by admixture with various carriers (e.g., cellulose) and coating materials (e.g., silica). This technique has been reported to produce improved dissolution profiles as compared to the commercially available products (Saharan, V.A. Kukkar *et al* 2009). Liao proposed mathematical expressions for the calculation of the amount of excipients needed for powdered solution formulations. Enhanced dissolution characteristics and consequently improved oral bioavailability. The *in vitro* drug dissolution rates of such preparations were compared to those of conventionally prepared directly compressed tablets using a USP-II apparatus. The Biopharmaceutical Classification System (BCS) groups poorly soluble compounds as Class II, compounds which feature poor solubility, high permeability and Class IV, compounds which feature poor solubility and poor permeability respectively. Aqueous solubility of a drug can be a critical limitation to its oral absorption. Lipophilic molecules, especially those belonging to the biopharmaceutical classification system (BCS) class II and IV, dissolve slowly, poorly and irregularly, and hence pose serious delivery challenges, like incomplete release from the dosage form, poor bioavailability, increased food effect, and high inter-patient variability. 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. Various techniques have been employed to formulate oral drug

delivery system that would enhance the dissolution profile and in turn, the absorption efficiency of water insoluble drug such as micronization, adsorption onto high surface area carriers, lyophilization, co-grinding, formulation of inclusion complexes, solubilization by surfactants, solid dispersions, solid solutions, hydro trophy, inclusion of the drug solution or liquid drug into soft gelatin capsules, and co solvency and liquisolid compact technology(Sharma *et al* 2010).

With the liquisolid technology, a liquid may be transformed into a free flowing, readily compressible and apparently dry powder 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 (Saharan, V.A. Kukkar *et al* 2009).

The most promising and new technique for promoting dissolution is the formation of liquisolid tablets 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 (Sharma *et al* 2010).

Theory of Liquid Solid Systems

A powder can retain only limited amounts of liquid while maintaining acceptable flow and compression properties. To calculate the required amounts of powder excipients and coating materials) a mathematical approach for the formulation of liqui-solid systems has been developed by Spireas (Spiras S, Bolton SM *et al* 2000). This approach is based on the flowable (Φ - value) and compressible (Ψ -number) liquid retention potential introducing constants for each powder/liquid combination. The Φ -value of a powder represents the maximum amount of a given non-volatile liquid that can be retained inside its bulk [w/w] while maintaining acceptable flow ability. The flow ability may be determined from the powder flow or by measurement of the angle of repose. The Ψ -number of a powder is defined as the maximum amount of liquid the powder can retain inside its bulk [w/w] while maintaining acceptable compact ability resulting in compacts of sufficient hardness with no liquid leaking out during compression. The compact ability may be determined by the so-called “plasticity” which describes the maximum (plateau) crushing strength of a one-gram tablet compacted at sufficiently high compression forces. The terms “acceptable flow and compression properties” imply the desired and thus preselected flow and compaction properties which must be met by the final liqui-solid formulation (Saharan, V.A. Kukkar *et al*

2009). Depending on the excipient ratio (R) of the powder substrate an acceptably flowing and compressible liquid-solid system can be obtained only if a maximum liquid load on the carrier material is not exceeded. This liquid/carrier ratio is termed liquid load factor L_f [w/w] and is defined as the weight ratio of the liquid formulation (W) and the carrier material (Q) in the system (Spiras S, Bolton SM *et al* 2000):

$$L_f = W/Q \text{----- (1)}$$

' R ' represents the ratio between the weights of the carrier.

(Q) And the coating (q) material present in the formulation:

$$R = Q/q \text{----- (2)}$$

The liquid load factor that ensures acceptable flow ability.

(L_f) can be determined by:

$$L_f = \Phi + \phi \cdot (1/R) \text{----- (3)}$$

Where Φ and ϕ are the Φ -values of the carrier and coating material, respectively. Similarly, the liquid load factor for production of liquid-solid systems with acceptable compact ability.

(ΨL_f) can be determined by:

$$\Psi L_f = \Psi + \psi \cdot (1/R) \text{----- (4)}$$

Where Ψ and ψ are the Ψ -numbers of the carrier and coating material, respectively.

Therefore, the optimum liquid load factor (L_o) required to obtain acceptably flowing and compressible liquid-solid systems are equal to either ΦL for ΨL_f , whichever represents the lower value. As soon as the optimum liquid load factor is determined, the appropriate quantities of carrier (Q_o) and coating (q_o) material required to convert a given amount of liquid formulation (W) into an acceptably flowing and compressible liquid-solid system may be calculated as follows:

$$Q_0 = W/L_o \text{----- (5) And } q_0 = Q_0/R \text{----- (6)}$$

The validity and applicability of the above mentioned principles have been tested and verified by producing liquid-solid compacts possessing acceptable flow and compaction properties.

Mechanisms of Enhanced Drug Release from Liquid-Solid Systems

Several mechanisms of enhanced drug release have been postulated for liquid-solid 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 wet ability of the drug

particles. Formation of a complex between the drug and excipients or any changes in crystalline of the drug could be ruled out using DSC and XRPD measurements (Fahmy RH, Kassem MA *et al* 2008).

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 (Fahmy RH, Kassem MA *et al* 2008).

b. Increased aqueous solubility of the drug

In addition to the first mechanism of drug release enhancement it is expected that C_s , the solubility of the drug, might be increased with liquisolid systems. In fact, the relatively small amount of liquid vehicle in a liquisolid compact 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 cosolvent (Charman SA *et al* 2003).

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 (fig 3). Wet ability of these systems has been demonstrated by measurement of contact angles and water rising times⁴⁴. Many poorly soluble drugs have been formulated as liquisolid systems showing enhanced drug release. Different liquid vehicles, carrier and coating materials were used to formulate these drug delivery systems.

General Procedure for Preparation of Liquisolid Compact 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. 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 (Fahmy RH, Kassem MA *et al* 2008). 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 (Charman SA *et al* 2003). 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.1), may be mixed with the finished liquid systems to produce liquid compacts in the dosage form of tablets or capsules.

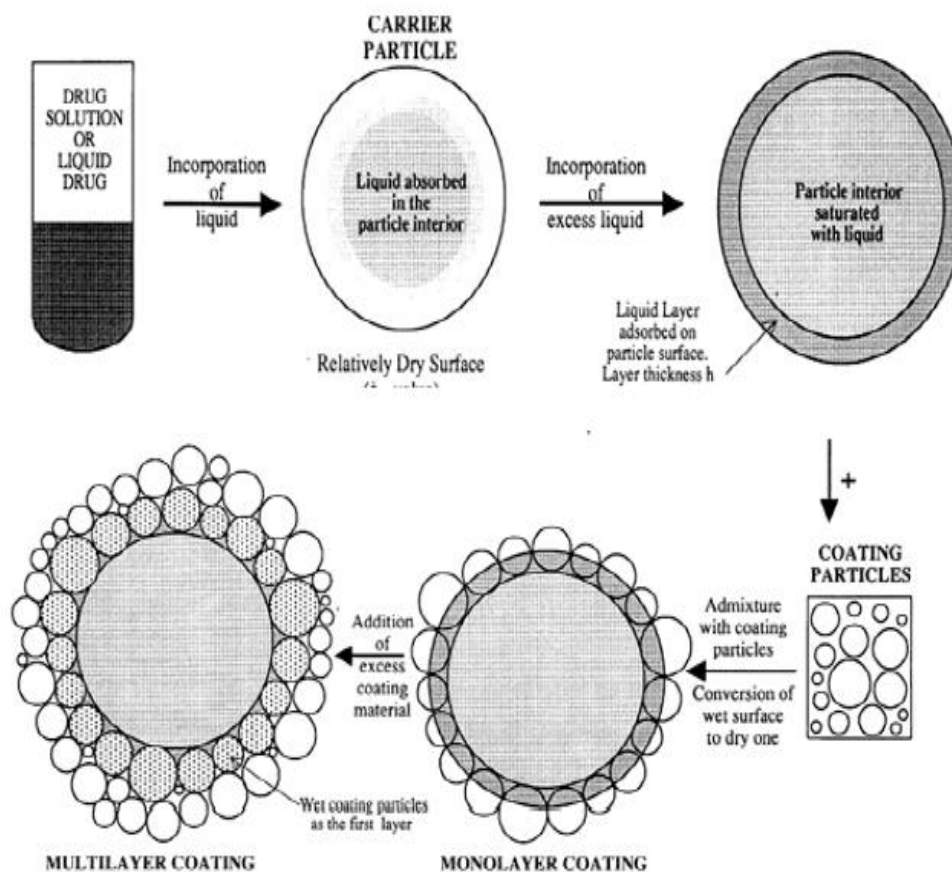
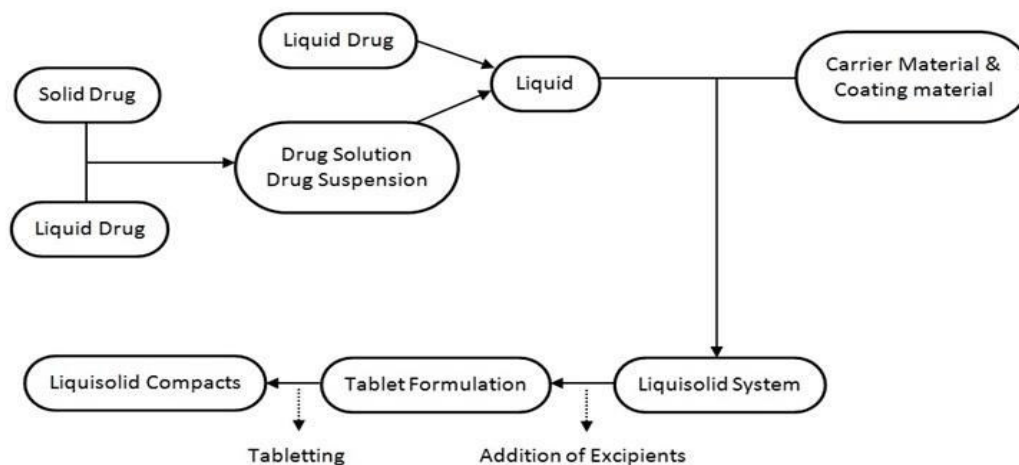


FIG 1: Theoretical model of powdered solutions.



Schematic Diagram Representing Preparation of Lquisolid Compacts

Figure 2: schematic diagram representing preparation of lquisolid compacts

Components of Lquisolid Copact Formulations

Lquisolid compact mainly includes

1. Non volatile solvent
2. Disintegrants
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(Charman SA *et al* 2003). The non volatile solvent acts as a binding agent in the lquisolid formulation Various non-volatile solvents for the formulation of lquisolid systems include Polyethylene glycol 200 and 400, glycerin, Polysorbate 80 and propylene glycol.

2. Disintegrant

Superdisintegrants increases the rate of drug release, water solubility and wet ability of lquisolid granules. Mostly superdisintegrants like sodium starch glycolate and croscopolidone.9.

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 flow ability. These include grades of microcrystalline cellulose such as avicel PH 102 and avicel PH 200, 20.

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 flow ability. Coating material includes silica (Cab-O-Sil) M520, 35, Aerosil 20030, Syloid, 244FP 20, 35 etc.

Examples of some drugs that can be incorporated into liquisolid systems

1. Chlorpheniramine
2. Digoxin
3. Nifedipine
4. Clofibrate
5. Gemfibrozil
6. Etoposide
7. Carbamazepine
8. Hydrochlorothiazide
9. Methyclothiazide
10. Spironolactone
11. Hydrocortisone
12. Piroxicam
13. Indomethacin
14. Ibuprofen

Pre-Compression Studies of the Liquid Solid System

Flow Properties of the Liqui-Solid System

The flow properties of the liqui-solid systems were estimated by determining the angle of repose, Carr's index, and Hausner's ratio.

Angle of repose

The angle of repose physical mixtures of liqui-solid compacts were determined by fixed funnel method. The accurately weighed physical mixtures of liqui-solid compacts were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through the funnel freely into the surface. The height and diameter of the powder cone was measured and angle of repose was calculated (Smirnova I, Suttiruengwong S *et al* 2004).

Tan $\theta = h/r$

Where, θ is the angle of repose, h is the height in cms, r is the radius in cms. Values for angle of repose $\leq 30^\circ$ usually indicate a free flowing material and angles $\geq 40^\circ$ suggest a poorly flowing material. 25- 30 showing excellent flow properties, 31-35 showing good flow properties, 36-40 showing fair flow properties, 41-45 showing passable flow properties (Charman SA *et al* 2003).

Bulk Density

The loose bulk density and tapped density were determined by using bulk density apparatus. Apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. The bulk density was calculated using the formula:

$D_b = M/V_b$ Where, M is the mass of powder

V_b is bulk volume of powder

Tapped Density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density was calculated using the.

Formula:

$D_t = M/V_t$ Where, M is the mass of powder

V_t is tapped volume of powder

Carr's Index (%)

The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of material because all of these can influence the observed compressibility index. The simplest way for measurement of free flow

of powder is Carr's Index, a indication of the ease with which a material can be induced to flow is given by Carr's index (CI) which is calculated as follows (Smirnova I, Suttiruengwong S *et al* 2004):

$$\text{CI (\%)} = [(\text{Tapped density} - \text{Bulk density}) / \text{Tapped density}] \times 100$$

The value below 15% indicates a powder with usually gives rise to good flow characteristics, where as above 25% indicates poor flow ability.

Hausner's Ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner's Ratio} = \text{Tapped density } (\rho_t) / \text{Bulk density } (\rho_b)$$

Where ρ_t is tapped density and ρ_b is bulk density. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones, between 1.25 to 1.5 showing moderate flow properties and more than 1.5 poor flow.

Post Compression Studies of Liqui-Solid Compacts

Weight Variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation three batches were calculated. It passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance (Smirnova I, Suttiruengwong S *et al* 2004).

Thickness

The thickness of liqui-solid tablets was determined by using Digital micrometer. Ten individual tablets from each batch were used and the results averaged.

Hardness: The hardness of the tablets was determined by using Monsanto hardness tester. Five individual tablets from each batch were and results averaged.

Friability

The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min. Percentage friability was calculated using the following equation.

$$\text{Friability} = ([\text{WO} - \text{W}] / \text{WO}) \times 100$$

Where, WO = Weight of the tablet at time zero before revolution.

W = Weight of the tablet after 100 revolutions.

Disintegration Test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets Apparatus was run for 10 minutes and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

In-vitro Release

Drug release from liqui-solid tablets was determined by using dissolution test United States Pharmacopoeia (USP) type II (paddle). 5ml aliquots of dissolution media were withdrawn each time at suitable time intervals (5, 10, 15, 20, 25, 30, 45 and 60 minutes.) and replaced with fresh medium. After withdrawing, samples were filtered and analyzed after appropriate dilution by appropriate analytical method. The concentration was calculated using standard calibration curve (Smirnova I, Suttiruengwong S *et al* 2004).

Differential scanning calorimetry

This is prerequisite to know if any possible interaction present between the excipients and the drug used in the formulation. The characteristic peak in the DSC thermo gram belongs to a drug absent that indicates that the drug is present in molecularly dispersed in this system.

X- ray diffraction

To get justification that the drug is in the solubilized state or converted into amorphous form because of disappearance of characteristic peaks belongs to drug and their by appearance of peaks which belongs to carrier is absorbed.

Scanning electron microscopy

This study confirms that there are any crystals present, or else drug is present in The solubilized form by absence of crystals of drug

Applications of Liquisolid Compacts

Following are few important applications of liquid-solid compacts:

Rapid release rates are obtained in liqui-solid formulations

1. These can be efficiently used for water insoluble solid drugs or liquid lipophilic drugs.

2. Sustained release of drugs which are water soluble drugs such as propranolol hydrochloride has been obtained by the use of this technique.
3. Solubility and dissolution enhancement.
4. Designing of controlled release tablets.
5. Application in probiotics.

Advantages of Liquisolid Systems

- a. Number of water-insoluble solid drugs can be formulated into liquisolid systems.
- b. Can be applied to formulate liquid medications such as oily liquid drugs.
- c. Better availability of an orally administered water insoluble drug.
- d. Lower production cost than that of soft gelatin capsules
- e. Production of liquisolid systems is similar to that of conventional tablets.
- f. Can be used for formulation of liquid oily drugs
- g. Exhibits enhanced in-vitro and in-vivo drug release as compared to commercial counterparts, including soft gelatin capsule preparations.
- h. Can be used in controlled drug delivery.
- i. Drug release can be modified using suitable formulation ingredients
- j. Drug can be molecularly dispersed in the formulation.
- k. Capability of industrial production is also possible.
- l. Enhanced bioavailability can be obtained as compared to conventional tablets.

Limitations

1. Not applicable for the formulation of high dose insoluble drugs.
2. 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.
3. Acceptable compression properties may not be achieved since during compression liquid drug may be squeezed out of the liquid-solid tablet resulting in tablets of unsatisfactory hardness 21.
4. 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.

CONCLUSION

Various methods are known to various improve water solubility and drug release, among which the liquisolid technology is one of the most promising approaches. With this

technology liquids such as solutions or suspensions of poorly soluble drugs in a non-volatile liquid vehicle are converted into acceptably flowing and compressible powders by simple physical blending with selected excipients named the carrier and the coating material. As highest drug release rates are observed with liquisolid compacts containing a drug solution as liquid portion, liquisolid compacts may be optimized by selection of the liquid vehicle and the carrier and coating materials. The addition of disintegrants may further accelerate drug release from liquisolid compacts. The liquisolid technology may also be used for the preparation of sustained release formulations with zero order release pattern. Thus, a constant plasma level will be reached, which is maintained throughout the dosing interval. For sustained release liquisolid compacts, the selection and the concentration of the excipients such as liquid vehicle, retarding agent (matrix forming material) as well as carrier and coating material play an important role. The liquisolid approach is a promising technology because of the simple manufacturing process, low production costs and the possibility of industrial manufacture due to the good flow and compaction properties of liquisolid formulations.

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