

LIQUISOLID TECHNIQUE FOR DISSOLUTION AND BIOAVAILABILITY ENHANCEMENT OF POORLY SOLUBLE DRUGS

INTRODUCTION

It is generally recognized that poor solubility of drugs is one of the most frequently encountered difficulties in the field of formulation scheme. Low solubility and subsequent unsatisfactory dissolution rate often compromise oral bioavailability.^[1] There are most therapeutic agents used to produce systemic effects by oral route that are the preferred way of administration owing to its several advantages and high patient compliance compared to other routes. However, poorly water-soluble drugs, when administered orally, have been shown to be slowly and unpredictably absorbed since their bioavailability is largely dependent on the dissolution process in gastrointestinal tract.^[2] The bioavailability of many poorly water-soluble drugs is limited by their dissolution rates, which are in turn controlled by the surface area that they present for dissolution.^[3]

It is one of the major challenges to synthesize any new molecule, which is pharmacologically active for the researchers and pharmaceutical companies.^[4] It may be necessary to increase the dose of a poorly soluble drug to obtain the efficacy required.^[5] Although pharmaceuticals have been able to overcome difficulties with very slightly soluble drugs, those with aqueous solubility of less than 0.1 mg/ml present some unique challenges. These strategies include using solubilization and surfactants, the use of polymorphic/ amorphous drug forms, the reduction of drug particle size, the complexation and the formation of solid drug dispersions.^[6]

The Biopharmaceutical Classification System (BCS)

The Biopharmaceutical classification system classifies drugs into four categories (Table 1.1), depending on their solubility and permeability characteristics.^[7]

Parameters affecting the dissolution of Class II

Factors important to dissolution can be identified from the following modification of the Noyes–Whitney equation:^[8]

$$\frac{dc}{dt} = \frac{DAKw/o}{Vh} \times (C_s - C_b) \quad \text{-----} \quad (1.1)$$

Where

A - Surface area of the drug D - Diffusion coefficient of the drug

h - Effective boundary layer thickness

C_s - Saturation concentration of the drug under the local gastrointestinal conditions

V - Volume of the fluid available to dissolve the drug

Kw/o - Water/oil partition coefficient of drug^[9]

Table 1. 1: Physical and physiological factors important to drug dissolution

Parameter	Physical factor	Physiological factor
Surface area	Particle size	Native surfactants
Diffusion coefficient	Molecular size	Viscosity of the luminal contents
Boundary Layer thickness	-	Motility patterns, Flow rates
Solubility	Hydrophilicity Crystal structure	pH, buffer capacity, bile, food components
Concentration of drug	-	Permeability
Volume of GI contents	-	Secretions, Administered

TECHNIQUES FOR SOLUBILITY ENHANCEMENT ^[10]**Liquisolid Technique**

Over the years, various techniques have been employed to enhance or retard the dissolution profile and, in turn, the absorption efficiency, reducing dosing frequency and bioavailability of water soluble and insoluble drugs and/or liquid lipophilic medications. ^[11] The use of water-soluble salts and polymorphic forms, the formation of water-soluble molecular complexes, drug micronization, solid dispersion, coprecipitation, lyophilization, microencapsulation, and inclusion of drug solutions or liquid drugs into soft gelatin capsules are some of the major formulation tools which have been shown to enhance the dissolution characteristics of water-insoluble drugs. ^[13] The use of water insoluble polymers, formation of matrix and formation of microspheres have been shown to retardation of dissolution profile, however, among them, the technique of “liquisolid compacts” is one of the most promising techniques. Liquisolid compacts are generally considered as acceptably flowing and compressible powdered forms of liquid medications that implies oily liquid drugs and solutions or suspensions of water insoluble solid drugs carried in suitable nonvolatile solvent systems termed the liquid vehicles. Using this new formulation technique, a liquid medication may be converted into a dry-looking, non-adherent, free flowing and readily compressible powder by a simple blending with selected powder excipients referred to as the carrier and coating materials. Various grades of cellulose, starch, lactose, etc., may be used as the carriers, whereas very fine particle size silica powders may be used as the coating (or covering) materials. ^[14]

Terminologies used in liquisolid technique**i. Liquisolid compacts**

The term “Liquisolid compacts” refers to immediate or sustained release tablets or capsules that are prepared by process under “Liquisolid system” combined with inclusion of appropriate adjuvants required for tableting or encapsulation.

ii. Liquisolid system

The term “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 a suitable nonvolatile solvent, in to dry, nonadherent, free flowing and compressible powder admixtures by blending with selected carrier and coating material.

iii. Liquid medication

The term “Liquid medication” includes liquid lipophilic drugs and drug suspensions or solutions of solid water insoluble drugs in a suitable nonvolatile system.

iv. Liquisolid microsystem

The term “Liquisolid microsystem” refers to capsules prepared by the process described under “Liquisolid technique” combined with the inclusion of an additive, e.g. polyvinylpyrrolidone (PVP), in the liquid medication.

v. Carrier material

The term “Carrier material” refers to a preferably porous material possessing sufficient absorption properties, which contributes in liquid absorption.

vi. Coating material

The term “Coating material” refers to a material possessing fine and highly adsorptive particles, such as various types of which contribute in covering the wet carrier particles and displaying a dry looking powder by adsorbing any excess liquid.

vii. Flowable liquid retention potential (Φ -value)

The term “Flowable liquid retention potential” of a powder material describes its ability to retain a specific amount of liquid while maintaining good flow properties. The Φ -value is defined as the

maximum weight of liquid that can be retained per unit weight of the powder material in order to produce an acceptably flowing liquid/powder admixture. [15]

Classification of Liquisolid system

A) Based on liquid medication

- a) Powdered drug solution
- b) Powdered drug suspension
- c) Powdered liquid drugs

B) Based on formulation technique

- a) Liquisolid Compacts
- b) Liquisolid Microsystems

Theoretical aspects of Liquisolid technique

In studies made by Spireas et al. in fundamental concerning flow and compression issues have been addressed with the use of the new formulation mathematical model of Liquisolid systems, which is based on the flowable (Φ -value) and compressible (Ψ -number) liquid retention potentials of the constituent powders. According to the above stated theories, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flow and compression properties. Depending on the excipient ratio (R) of the powder substrate given by equation 1.2,

$$R = Q/q \quad \text{-----} \quad (1.2)$$

Excipient ratio (R) is the fraction of the weights of the 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 load on the carrier material is not exceeded. Such a characteristic amount of liquid is termed the liquid load factor (L_f) and defined as the weight ratio of the liquid medication (W) and carrier powder (Q) in the system, i.e.:

$$L_f = W/Q \quad \text{-----} \quad (1.3)$$

The terms ‘acceptably flowing’ and ‘acceptably compressible’ imply preselected and desirable levels of flow and compaction which must be possessed by the final liquid: powder admixtures. Essentially, the acceptable flow and compaction characteristics of this systems are ensured in a way, built in during their manufacturing process via the Φ -value and Ψ -number concepts [16].

For powder substrate consisting of a certain carrier and coating powders mixed at various powder excipient ratios (R), there are specific maximum liquid load factors (L_f) which must be employed in order to produce acceptably flowing Liquisolid systems. Such liquid load factors based upon the Φ -value and Ψ -number can be calculated based upon following equations,

1) Based upon the Φ -value the optimum liquid load factor (${}^\Phi L_f$) can be derived by using,

$${}^\Phi L_f = \Phi + \phi (1/R) \quad \text{-----} \quad (1.4)$$

Where,

Φ - Flowable retention potential for carrier material. ϕ - Flowable retention potential for coating material.

R - Excipient ratio.

2) Similarly based upon the Ψ -number optimum liquid load (${}^\Psi L_f$) factor can be derived from,

$${}^\Psi L_f = \Psi + \psi (1/R) \quad \text{-----} \quad (1.5)$$

Where,

Ψ - Compressible retention potential for carrier material. ψ - Compressible retention potential for coating material.

R - Excipient ratio.

For a liquid medication incorporated into a given powder substrate consisting of certain carrier and coating materials (e.g. microcrystalline cellulose and silica) blended at a specific excipient ratio (R), there exists an optimum liquid load factor, L_0 , required to produce acceptably flowing and, simultaneously, acceptably compressible Liquisolid preparations. The L_0 value required at a given powder excipient ratio for any system is equal to either its ${}^\Phi L_f$ or ${}^\Psi L_f$ value, whichever is less; thus:

$$LO = {}^\Phi L_f \quad \text{When, } {}^\Phi L_f < {}^\Psi L_f \quad \text{-----} \quad (1.6)$$

Or

$$LO = {}^\Psi L_f \quad \text{When, } {}^\Phi L_f > {}^\Psi L_f \quad \text{-----} \quad (1.7)$$

Optimum liquid load factor of a given excipient ratio system is established, the appropriate quantities of carrier (Q_0) and coating (q_0) powder materials required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible Liquisolid system, may be calculated as follows:

$$Q_0 = W / L_0 \quad \text{-----} \quad (1.8)$$

$$Q_0 = Q_0 / R \quad \text{-----} \quad (1.9)$$

The minimum carrier quantity (Q_{\min}) and maximum coating quantity (q_{\max}) required to produce an acceptably flowing and compressible Liquisolid compacts unit possessing minimum weight (U_{\min}) and containing W of liquid may be assessed using following relation,

$$Q_{\min} = W / L_{\max} \quad \text{-----} \quad (1.10)$$

$$q_{\max} = Q_{\min} / R_{\min} \quad \text{-----} \quad (1.11)$$

In terms of producing compacts of realistic unit size, the practical substance of the Liquisolid formulation desired to be prepared may be assessed by predicting unit dose weight U_w using equation 1.10. This can be done as long as weight W of the liquid medication (to be included in a single Liquisolid formulation) and the desired excipient ratio (R) of the formulation have been selected leading to the determination of the required optimum load factor (L_0). The minimum possible unit dose weight (U_{\min}) which can be produced by the carrier: coating system may also be predicted using equation 1.10, having selected the weight W of the liquid medication (per unit dose) and having determined the minimum excipient ratio (R_{\min}) of the powder system and its corresponding maximum load factor L_{\max} required to yield a Flowable and compressible Liquisolid system.^[17]

$$U_w = W + W (1 + 1/R) (LO) \quad \text{-----} \quad (1.11)$$

$$U_{\min} = W + W (1 + 1/R_{\min}) (1 / L_{\max}) \quad \text{-----} \quad (1.12)$$

Powdered solution technology

A more recent technique, entitled “powdered solution technology”, has been applied to prepare water soluble or water insoluble drugs into rapid release or sustained release solid dosage forms. The concept of powdered solutions enables one to convert drug solutions or liquid drugs into acceptably flowing powders by a simple admixture with selected powder excipients.^[18]

Method of Preparation of Liquisolid system

The preparation of Liquisolid system is based on equations no. 1.2 to 1.13.

- i. **Selection and preparation of drug solution:** If a solid water-insoluble drug is formulated, the drug is dissolved or suspended in a non-volatile solvent or vehicle. (% w/w concentration).
- ii. **Selection of Carrier and Coating materials:** The carrier and coating materials to be incorporated in the Liquisolid formulation are selected on the basis of, the characteristic excipient or carrier: coating ratio R_{\min} (w/w) and the Flowable liquid retention potential (Φ -value) and compressible liquid retention potential (Ψ -number) are determined by using Liquisolid flowability test (LSF) and Liquisolid compressibility test (LSC) respectively.
- iii. The desired excipient or carrier: coating ratio R , where $R > R_{\min}$, of the carrier: coating combination to be included in the liquisolid system is selected. If minimum unit dose weight (U_{\min}) is desired, the excipient ratio of the formulation must be selected to be equal to R_{\min} which is the characteristic minimum excipient ratio of the carrier: coating system used.
- iv. Selected amounts (W) of the resulting hot liquid medications were incorporated into calculated quantities of carrier and coating materials.
- v. **Determination of Liquid load factor:** The optimum liquid load factor (LO) required yielding an acceptable flowing and compressible Liquisolid system is assessed by using equation 1.9-1.12.^[19]

Mixing process

The mixing procedure was conducted in three stages. During the first stage, the system was blended at an approximate mixing rate of one rpm in order to consistently distribute the liquid medication into the powder. In the second stage, the liquid/powder admixture was

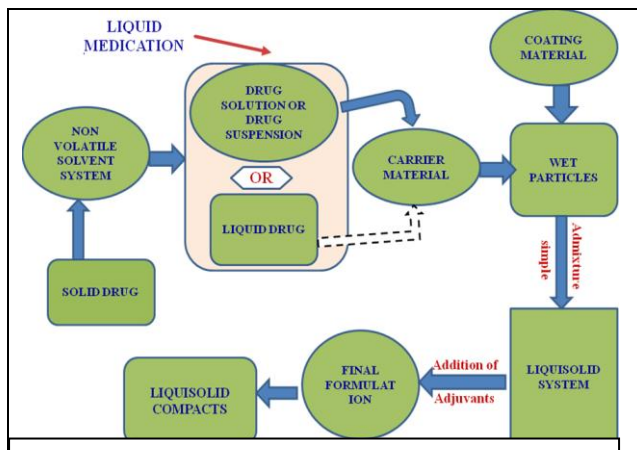


Figure 1.1: Method of preparation of liquisolid compacts

Mechanism involved in designing of Liquisolid

Liquisolid hypothesis that, if a liquid is incorporated into a material which has a porous surface and closely matted fibers in its interior, e.g., cellulose, both absorption and adsorption take place. The liquid is initially absorbed in the interior of the particles by its internal structure and after the saturation of process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particle occurs. It represents the generalized “total liquid retention potential” or “holding capacity” of the sorbent. The coating material, which possesses high adsorptive properties and large specific surface area, gives the Liquisolid system the desirable flow characteristics. [21]

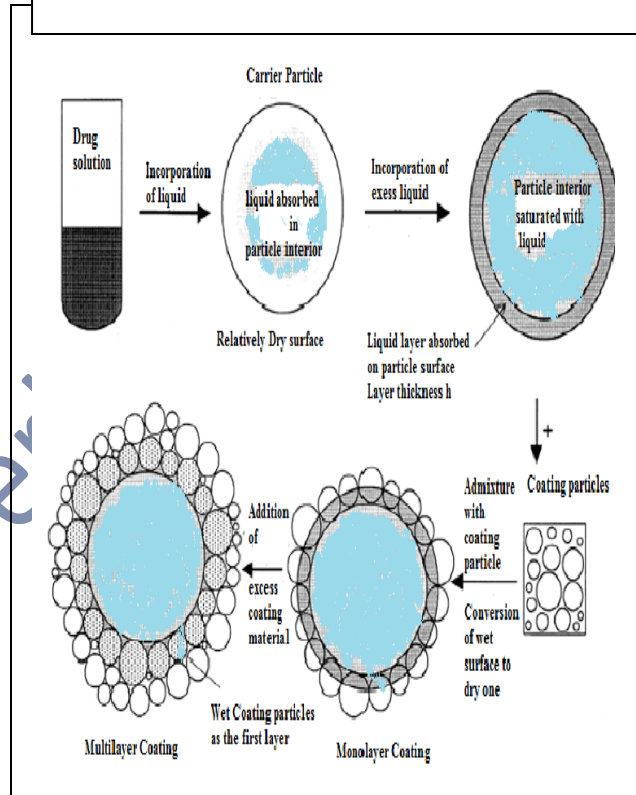


Figure 1.2: Mechanism representing formulation of liquisolid system

Advantages

1. A great number of slightly and very slightly water soluble and practically water insoluble drugs can be formulated in to Liquisolid system. Production cost of Liquisolid system is lower than that of soft gelatin capsule, as production of Liquisolid system is similar to that of conventional tablets.
2. Optimized sustained release Liquisolid tablets or capsules of water-insoluble drugs reveal surprisingly constant dissolution rates compared to conventional expensive tablets.

Complexation

Inclusion complexes are formed by the insertion of the nonpolar region of one molecule into the cavity of molecule or group of molecule. Cyclodextrins (CDs) used as complexation agents. The natural and most employed cyclodextrins are crystalline, homogeneous, non-hygroscopic substances. They are biocompatible, non-toxic in a wide range of concentration, relatively inexpensive and produced naturally

by enzyme degradation of starch.^[23] The most notable feature of cyclodextrins is their ability to form solid inclusion complexes. Complex formation is a dimensional fit between host cavity and guest molecule. The lipophilic cavity of cyclodextrin molecules provides a microenvironment into which appropriately sized non-polar moieties can enter to form inclusion complexes. No covalent bonds are broken or formed during formation of the inclusion complex.^[24]

Kneading method

It is one of the methods used in formation of complex between drug and β - cyclodextrin.^[25]

Synergism effect

Synergistic effect of nonvolatile solvents like PEG-400 and cyclodextrin may have effect on the solubility of drug. Beta cyclodextrin was used as a type of cyclodextrins. PEG-400 used in an attempt to improve the aqueous solubility of drug. The aqueous solubility of a drug improved significantly by the addition of PEG-400 and β - cyclodextrin. The theoretical solubility was calculated by adding the solubilities in the individual systems. The observed solubility value was higher than the theoretical values. The effect of synergism was significant in 5% to 50% PEG-400 containing beta cyclodextrin.^[26]

BIOAVAILABILITY

Bioavailability is defined as the rate and extent (amount) of absorption of unchanged drug from its dosage form. It is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. A drug with poor bioavailability is one with poor aqueous solubility, slow dissolution rate in biological fluids, poor stability of dissolved drug at physiological pH, poor permeation through biomembrane, extensive presystemic metabolism. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities.^[27]

Techniques for improving bioavailability

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the methods to improve the solubility includes Physical modifications Chemical Modifications formulation based novel drug delivery system and inhibition of P-glycoprotein efflux. Inhibition of P-glycoprotein efflux by using P-glycoprotein inhibitors, surfactants, dendrimers.^[28] To improve the systemic availability of the drug is to deliver it by alternative routes of administration such as parenteral, nasal, vaginal, rectal or transdermal. However, improvement of the oral bioavailability of the drug is the most realistic approach, as it is the most preferred and convenient route of administration.^[29]

FORMULATION OF LIQUISOLID SYSTEM^[30]

Preparation of complex with beta cyclodextrin Kneading method

Preparation of complex of drug with beta cyclodextrin done by:

First the cyclodextrin is added to the mortar; further small quantity of 50% ethanol is added while triturating to get slurry like consistency. Then slowly drug is incorporated into the slurry and trituration is further continued for 30 minutes. Slurry is then air dried at 25⁰C for 1 hrs, pulverized and passed through sieve No. 80 and stored.

Solubility studies of complex and synergism effect with different ratios

The complex of drug and beta cyclodextrin Complex was taken in different mass ratios. after that complex was taken in liquid vehicle for studying the synergism effect.

Determination of angle of slide for various excipients

10 gram of powder excipients were weighed accurately and placed at one end of an aluminum metal plate with a polished surface. This end was raised gradually until the plate made an angle with the horizontal at which the powder was about to slide. This angle θ represented the angle of slide. It was taken as a measure for the flow characters of powders. An angle of slide corresponding to 33⁰ corresponded to optimal flow properties.

PRECOMPRESSION STUDY^[31]

Flow properties of the Liquisolid system

Flow properties of the Liquisolid systems were estimated by determining the angle of repose, Carr's Compressibility index (CCI), and Hausner's ratio (HR). Angle of repose was measured according to the fixed funnel and free standing cone method. A funnel with the end of the stem cut perpendicular to the axis of symmetry is secured with its tip 2 cm height, H , above a graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the conical pile so formed just reaches the tip of the funnel. The radius of heap was calculated and tangent of the angle of repose was given by:

$$\theta = \tan^{-1}(H/R) \quad \text{-----} \quad (6.9)$$

Where, θ is the angle of repose, H is height of pile and R is radius of pile.

The Bulk density and Tap densities were determined for the calculation of Hausner's ratio (HR) and Carr's Compressibility Index. (CCI). It was determined by following equation,

$$CCI = \frac{(TD - BD)}{TD} \times 100 \quad \text{-----} \quad (6.10)$$

$$HR = \left(\frac{TD}{BD} \right) \quad \text{-----} \quad (6.12)$$

Where, TD and BD are tapped density and bulk density respectively.

POST COMPRESSION STUDY^[32]

Evaluation of liquisolid compacts

Weight variation test^[33]

Twenty tablets from each formulation were selected at random and average weight was determined. Then the individual tablets were weighed and were compared with average weight. Not more than 2 of individual weight deviate by more than percentage (refer table 1.2), while none deviates by more than twice that percentage.

Table 1.2: Uniformity of weight

Dosage form	Average weight	% deviation
Uncoated and film coated tablets	80 mg or less	10
	> 80mg and less than 250 mg	7.5
	250 mg or more	5

Hardness test^[34]

After preparation of matrices, primary micromeritic properties are measured like, Tablet thickness, diameter, weight & hardness. Thickness & diameter is measured by using vernier caliper, hardness is determined by using Monsanto hardness tester. Tablet hardness is defined as the force required breaking a tablet in a diametric compression force. It is also known as tablet crushing strength. The hardness tester used in the study was Monsanto Hardness Tester, which applies the force to the tablet diametrically with the help of an in built spring. The tester was initially adjusted to zero.

Diameter and thickness

Diameter and thickness was performed by using digital vernier caliper. Results for all the batches of liquisolid compacts were reported.

Friability test^[35]

Friability test is performed to assess the effect of friction and shock that may often cause tablet to chip, cap, or break. Friabilator was used for the purpose. Compressed tablets should not lose more than 1% of their weight. It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed

($W_{initial}$) and transferred into Friabilator. The Friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by,

$$F = \frac{W_{Initial} - W_{Final}}{W_{initial}} \times 100 \quad \text{-----} \quad (6.13)$$

In vitro dissolution study ^[36]

The various compacts were subjected to dissolution test using USP Type II Apparatus.

Differential Scanning Calorimetry (DSC) ^[37]

Thermograms of the samples were recorded on a DSC. Thermal behavior of the samples was investigated under a scanning rate of 10°C/min, covering a temperature range of 30–300°C.

Powder-X Ray Diffraction (P-XRD)

X-ray diffractograms of liquisolid formulations were performed by using Philips Analytical. The cross section of samples was exposed to X-ray radiation.

FTIR Study

FTIR is an important tool to analyze the purity of the drug. FTIR spectrum shows the fundamental peaks corresponding to the chemical nature of the drug and excipients. FTIR studies were carried out in order to determine any possible interaction among drug and other excipients; it was carried out by FTIR spectrophotometer.

IN VIVO STUDIES

In-vivo studies of solid formulations ^[38]

Bioavailability studies of prepared solid formulations

The bioavailability studies were performed for the prepared formulation containing herbal inhibitors like piperine. Female rabbit was selected as experimental model having weight 1.5 to 2.5 kg. The blood serum concentration of drug was determined along with AUC, C_{max} , and T_{max} .

Experimental layout

Study Protocol

Healthy adult albino rabbits were used for the study of pharmacokinetic parameter and were divided into 4 groups namely control, test 1, test 2 and standard. Animals were used repeatedly by keeping washout period for complete removal of drug from body. All animals were taken care of under ethical consideration as per the guidelines.

Drug administration and sampling

The animals were required to be kept on standard supplemented diet and water for one week prior to experiment and maintained on it thereafter. For study, albino rabbits were randomly assigned to four groups on body weight basis. Group 1 was serve as normal control (water), Group 2 was serve as positive control (standard drug), group 3 and 4 was treated with the liquisolid formulation and experiment was repeated for study by keeping washout period between of 8 days. The steps involved in drug administration and sampling as,

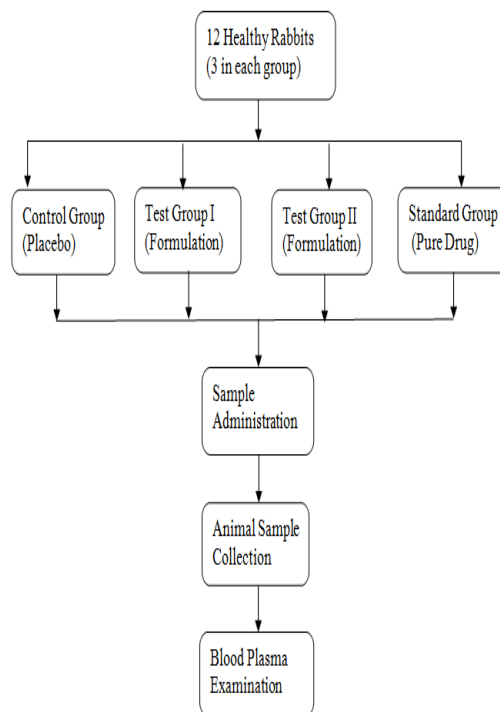


Figure 1.3: Process flow of bioavailability

study by taking rabbit as model

Procedure for animal experimental work

The parameters were selected for the experimental work:

The sample for dose was prepared with gum acacia suspension for required animal dose. Prepared solid formulation of physical mixture was administered as a single oral dose to rabbit through oral feeding needle and 2 ml of water was again given over the dose.

The blood sample of rabbit was collected via ear marginal vein puncture, for that 1ml insulin syringe was used. 1 ml blood sample was collected while in each withdrawal.



Figure 1.4: Blood sample collection of rabbit by ear marginal vein puncture

Blood sample processing

1. The collected blood sample was processed through centrifugation at 5000 rpm for 15 min.
2. Supernatant clear serum sample was separated with the help of micropipette in graduated plastic tube having cap.
3. The volume of serum sample was further diluted up to 1 ml with optimized mobile phase i.e. methanol: water (80:20 v/v).
4. Precipitation of proteins was separated by again centrifugation with 5000 rpm for 15 min. The obtained supernatant was separated with the help of micropipette.
5. The clear supernatant was again filtered with 0.42 micron Whatmann syringe filter and finally used the HPLC analysis using DAD detector.

STABILITY STUDY ^[39]

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. FDA and ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use. The formulation were wrapped in aluminum foil, and then placed in amber colored bottle.

CONCLUSION

Liquisolid technique can be optimized for the production of immediate release of drug. Simplicity, low cost and capability of industrial production are some of the advantages of this technique. The complex of drug and beta cyclodextrin was successfully prepared by kneading method. Complex was taken which shows synergetic effect and enhances solubility drug. The results showed that maximum drug can be incorporated with dissolution enhancement compared with conventional formulation. Hence, this liquisolid technique with two way approach of solubility and bioavailability enhancement may found as key aspect in oral formulations. Liquisolid technique can successfully be employed to enhance the solubility and dissolution properties.

REFERENCES

1. Aulton, M E. *Pharmaceutics: The science of dosage form design*, 2nd edition, London: Churchill Livingstone; 113-138, 2002.
2. Ansel, H.C. Allen, L.V. Popovich, N.G. *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Lippincott Williams and Wilkins, Philadelphia, 1999, 7th, 60-63.
3. Bajaj, H. Bisht, S. Yadav, M. Singh, V. *Bioavailability enhancement.*, *International Journal of Pharma and Bio Sciences.*, 2(2),2011
4. Briggs, A. R., *Process for preparing powder blends*. Patent US 3721725, 1973.
5. Pinnamaneni, S. Das, N.G. and Das, SK. *Formulation approaches for orally administered lipophilic drugs*, *Pharmazie*, 57, 291-300,2002.
6. Mehta, M.U. *AAPS/FDA, Biopharmaceutics Classification System: Implementation Challenges and Extension Opportunities*. September 2002, Arlington, VA, 25-27.
7. Amidon, G.L. Lennerna, S H. Shah, V.P. Crison, J.R., *A theoretical basis for a biopharmaceutical drug classification: The correlation of in Pharvitro drug product dissolution and in vivo bioavailability*. *Pharm. Res.* 12, 413–420,1995.
8. Blagden, N. Gavan, P .T. York, P. *Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates*.*Adv. Drug Del. Rev*, 59(30), 617-630, 2007
9. Noyes, A.A. Whitney ,W.R. *The rate of dissolution of solid substances in their own solutions*. *J Am Chem Soc*, 19, 930–934, 1987
10. Thakkar, H. Patel, B. ,*Techniques for oral bioavailability enhancement of drugs*, *International Journal of Pharmaceutical Sciences Review and Research*,203, 4(3) , 2010.
11. Spireas, S.S.,*Liquisolid systems and methods of preparing same*. 2000 United State Patent no 6423339, July 23 2002.
12. Spireas, S.S. Sadu, S. *Enhancement of prednisolone dissolution properties using Liquisolid compacts*. *Int. J. Pharm*, 166,177-188, 1998.
13. Spireas, S.S. Sadu S. Grover R. *In-vitro release evaluation of hydrocortisone Liquisolid tablets*, *J. Pharm. Sci.*,87 (7), 867-872, 2000 b.
14. Spireas, S. Bolton, S. *Sustained-release liquisolid compacts*. 25th International Symposium on Controlled Release of Bioactive Materials, Nevada, USA,138-139, 1998.
15. Spireas, S.S. *Liquisolid systems and methods of preparing same*. United State Patent no 642, 3339, July 23, 2000.
16. Spireas, S.S. *Liquisolid system and method of preparing same*. United State Patent no 6096337, August 1st, 2000.
17. Spireas, S. Bolton, S. *Sustained-release liquisolid compacts*. 25th International Symposium on Controlled Release of Bioactive Materials, Nevada, USA,138-139, 1998.
18. Spireas, S.S. Wang T, Grover, R. *Effect of powder substrate on the dissolution properties of Methyclothiazide Liquisolid compacts*. *Drug. Dev. Ind. Pharm*, 25, 163–168, 1999.
19. Spireas, S.S. *Liquisolid system and method of preparing same*. United State Patent no 6096337, August 1st, 2000.
20. Spireas, S.S.,*Liquisolid systems and methods of preparing same*. 2000 United State Patent no 6423339, July 23 2002.
21. Spireas, S.S. Sadu S., *Enhancement of prednisolone dissolution properties using Liquisolid compacts*, *Int. J. Pharm.* 166 (1998) 177-188
22. Spireas, S.S. Wang T, Grover, R. *Effect of powder substrate on the dissolution properties of Methyclothiazide Liquisolid compacts*. *Drug. Dev. Ind. Pharm*, 25, 163–168, 1999.
23. Uekama, K. Hirayama, F. and Irie, T. *Cyclodextrin Drug Carrier Systems*. *Chem. Rev*, 98, 2045 - 2076, 1998.
24. Erem, M. Bochot, B. Murat, S. Dominique, B. Hincal, A. *Non-surfactant nanospheres of progesterone inclusion complexes with amphiphilic β -cyclodextrins*, *Int J Pharm*, 251,143- 153,2003
25. Nandi, I. Bateson, M. Bari, M. and Joshi, H. *Synergistic Effect of PEG-400 and Cyclodextrin to Enhance Solubility of Progesterone*, *AAPS Pharm SciTech* ;4(1)2003-04
26. Nandi, I. Bateson, M. Bari, M. and Joshi, H. *Synergistic Effect of PEG-400 and Cyclodextrin to Enhance Solubility of Progesterone*, *AAPS Pharm SciTech* ;4(1)2003-04

27. Bajaj, H. Bisht, S. Yadav, M. Singh, V. Bioavailability enhancement., International Journal of Pharma and Bio Sciences., 2(2),2011.
28. Chaumeil, J C. Micronization: a method of improving the bioavailability of poorly soluble drugs. Apr, 20(3), 211-5, 1998.
29. Sing, A. Duggal, S. Piperine –Advances in Pharmacology; International Journal of Pharmaceutical Sciences and Nanotechnology; 2 (3) ,2009.
30. Steele, D.F. Tobyn, M.J. Staniforth, J.N. The mechanical properties of compacts of microcrystalline cellulose and silicified microcrystalline cellulose. Int. J. Pharm. 2000, 200, 67-
31. Kothari, S.H. Bankar, G.S., Vijay Kumar., Comparative evaluation of powder and mechanical properties of low crystallinity cellulose, microcrystalline celluloses and powdered cellulose. Int. J. Pharm.232, 69-80,2002.
32. Mehta, M.U. AAPS/FDA Workshop on Biopharmaceutics Classification System: Implementation Challenges and Extension Opportunities. September 2002, Arlington, VA, 25-27.
33. Khaled, K.A. Formulation and evaluation of hydrochlorothiazide Liquisolid tablets. Saudi Pharm J, 6, 39-46, 1988.
34. Kapsi, S.G. , Processing factors in development of solid solution formulation of itraconazole for enhancement of drug dissolution and bioavailability. Int. J. Pharm, 229, 193-203, 2001.
35. Ansel, H.C. Allen, L.V. Popovich, N.G. Pharmaceutical Dosage Forms and Drug Delivery Systems, Lippincott Williams and Wilkins, Philadelphia, 1999, 7th, 60-63.
36. Amidon, G.L. Lennerna, S H. Shah, V.P. Crison, J.R., A theoretical basis for a biopharmaceutical drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res. 12, 413-420,1995.
37. Indrayanto, G. Mugihardjo, A. Handayani, R. Compatibility study between famotidine and some excipients using differential scanning calorimetry. Drug Dev. Ind. Pharm, 20 (5), 911-920, 1994
38. Chaumeil, J C. Micronization: a method of improving the bioavailability of poorly soluble drugs. Apr, 20(3), 211-5, 1998.
39. Patel, H. Bhat, R. S.Balamuralidhara, V. Pramod Kumar, T.M. Comparison of stability testing requirements of ICH with other International Regulatory Agencies. Pharmatimes, 2011 43(9), 21-24.