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Study the Effect of Liquid Solid Compact Technology on Drug's Pharmacokinetic and Pharmacodynamic Behaviour

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Abstract
Water solubility and bioavailability of drugs are the major challenges in the therapeutic field today. Low solubility of drugs often affects bioavailability, which is a key determinant of drug efficacy and release. The 40% of new active ingredients have high molecular weight, which in turn increases the lipophilicity of the drug and reduces the drug's solubility in water. Better solubility of the drug leads to better bioavailability, and reduce dose frequency which further reduces toxicity. This review focuses on utilization of new technique i.e. Liquisolid technology, and its impact on the drug's pharmacokinetic and pharmacodynamics behavior. This study discusses how the liquisolid technology increases the solubility and the drug release patterns during drug formulation design and its impact on human organs and tissues. With the advancement in technology it is observed that most of the BCS Class II and IV drugs possess high lipophilic character which in response affects the solubility and thus bioavailability of the drug. Liquisolid technology is cost effective as the production process is similar to the production of conventional tablets. This technique can effectively improve the poor dissolution characteristics and can also improve the drug release patterns. Numerous drugs have been undergone this process for the solubility enhancement, such as Valsartan, Propranol Hydrochloride, Naproxen, Glibenclamide, Carbamazepine, and Endomethazine. Powder solution technology is thought to be a viable option for improving drug solubility and may play a key role in the development of oral formulations for future generations.

Keywords
Lipophilicity; dissolution characteristics; conventional; BCS Class.

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INTRODUCTION:
BCS class II and IV drugs face many challenging problems in the development of pharmaceutical product due to their low dissolution and solubility rates. It is understood that an active therapeutic component of any solid dosage form must be first dissolved before gastrointestinal absorption is possible. These drugs are lipophilic and are having

poor dissolution rate in the GIT tract which in turn affects the absorption of the drug in systemic blood circulation (1) For the drug having very-low aqueous solubility, the rate determining step is dissolution, which is the main parameter to determine the absorption rate and a major problem to produce them into a suitable dosage form which can exert optimum therapeutic effects (2). Various approaches were employed to improve the solubility of drugs .08with poor solubility, like micronization, conversion of crystalline state into amorphous state, using surfactants, complexation, and usage of organic solvent in solid dispersions also faces challenging problems due to environmental, poor physicochemical characteristics of drug formulation and safety problems. To overcome these shortcomings a technique surface solid dispersion were introduced, but there is again a hurdle in formulation development that lies with the use of solvents. Therefore it is necessary to find the solvent that is suitable to dissolve the drug into the selected carrier, which is a difficult process (3). Thus, recent novel technique i.e. liquisolid technology has been applied. Liquid solid compact technology is the novel technique that has been extensively used for increasing the solubility of drug. The liquid solid technology improves the dissolution characteristics of less water soluble drugs. This technology is used to disperse solid liquid medication of lipophilic drugs in an organic solvent into non-adherent, dry or free flowing powders. The compressible powders having optimum porosity are prepared by physically blending the medication using optimum concentration of the carrier and coating material. Due to this phenomenon there will be a significant rise in wettability and the available surface area of drug for dissolution. To get desired concentration of drug in the systemic circulation formulation scientist have to focus on receiving the desired concentration of drug, selection of additive or excipients like solvent, glidant, disintegrant and lubricant are to be judicially utilized to achieve an optimized compressible blend or desired dosage form (4,5).

HYPOTHESIS:

The compression and flow of liquid present liquisolid system are expressed simultaneously in mathematically model of liquisolid system (6)

$$\text{Excipients Ratio (R)} = \frac{\text{Weight of carrier (Q)}}{\text{Coating material (q)}}$$

$$\text{Liquid Load Factor (Lf)} = \frac{\text{Weight of liquid medication (W)}}{\text{Weight of the carrier powder (Q)}}$$

The excipients ratio (R) of powders and the liquid load factors (Lf) of pharmaceutical formulation are related as follows:

$$\Phi Lf = \Phi + \Phi\,(1/R)$$

IMPORTANCE OF SOLUBILITY ENHANCEMENT:

Solubility is the major determinant parameter to obtain desired concentration of drug release in blood circulation in order to achieve desired pharmacological/ therapeutic response. Hydrophobic drugs (poorly water soluble) requires high dose of drug to achieve desired therapeutic plasma concentrations after drug delivery. Decreased solubility causes the chief problems in the development of new chemical entities, like **(7)**

1. Toxicity
2. Poor patient compliance
3. Narrow therapeutic window

NEED OF SOLUBILITY ENCHANCEMENT:

Poor aqueous solubility of drug is mainly due to two factors i.e. High lipophilicity, and strong intermolecular interaction. Drug absorption takes place in the gastrointestinal tract and it can be limited by a various factors, like low aqueous solubility of drug and poor membrane permeability (8). To achieve maximum drug concentration in the systemic circulation the drug needs to get solubilized in the gastrointestinal fluid then only it can get absorbed in the systemic circulation and becomes bioavailable to our body. Hence, there are two areas of pharmaceutical research to treat the difficulties in development of new drug that focuses on enhancing solubility and dissolution characteristic of drug, enhancing permeability of hydrophobic drugs (9). For the research scientific formulators solubility is the main problem in the production of pharmaceutical drug as if any drug is having inadequate aqueous solubility then it may affect its oral bioavailability (8). Mechanism of Liquisolid compact that enhances the Drug release: (10)

There are three main mechanisms that have been postulated:

1. Enhanced surface area of the drug
2. Enhanced wetting properties
3. Increased Aqueous solubility

Effective Surface Area

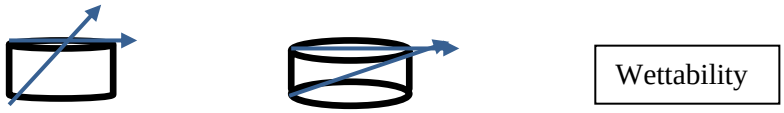
Liquisolid system is composed of drug entirely dissolved in the non-volatile vehicle/solvent and available in solubilized form as a molecular dispersion. Consequently the effective surface area of the drug is more in comparison to the drug particles present in directly compressed tablets. If there is elevation in the level of drug release then it results in exceeding the solubility limits which means increased part of insolubilized form of drug is present in the non-volatile vehicle which will further reduce or decrease the drug release rate.

Aqueous Solubility

As indicated by the drug release enhancement mechanism, it is understand that the medication solvency may be improved by shaping as liquisolid frameworks. Non-volatile solvent in an exceedingly liquisolid compact isn't sufficient to strengthen the general dissolvability of the medication inside the liquid medium. Nevertheless, within the solid-liquid interface between unharness medium and along these lines the essential liquisolid molecule, it's even potential that fluid vehicle distributive out of one liquisolid molecule related to the drug entities is adequate to reinforce the liquid solubility of the drug.

Wetting Properties

The liquid vehicle possess activity of a surface active agent and possess small surface tension hence wetting of the primary liquisolid particles is enhanced. Wetting property of these systems can be explained by water rising times and make contact with angles conjointly drug surface assimilation on carrier particles which can increase the effective extent, that in response improves the contact of drug and wettability.



SOLUBILITY ENHANCEMENT BY LIQUISOLID TECHNIQUE ON VARIOUS DRUGS

Lumefantrine: Lumefantrine is an antimalarial drug effective in the treatment of resistant *Plasmodium falciparum*. Lumefantrine is a member of BCS Class IV drugs which mean it is having low solubility and permeability. Amreen khan and Shikha Aggarwal formulated a liquisolid capsule by using drug solution and suspension method to overcome the problem of solubility. Lumefantrine is present in the formulation as molecular dispersion. Their study shows that this drug have no significant change in their organoleptic properties after being formulated as liquisolid compact but the formulation is having good stability. Dissolution studies shows that due to liquisolid formulations drug improves the poor dissolution characteristics and solubility profile as compared to pure drug (11).

Cefixime: Oral capsules of cefixime were formulated by liquisolid technique after mixing the drug with non-volatile solvent in various concentrations. This is followed by their addition to different proportions of carrier: coating material. This study focuses on comparing the drug release profile of the optimum formula to that of the marketed cefixime capsules.

This work has shown that liquisolid system is a prom ising technique to enhance thesolubility and dissolu tionof cefixime from its capsules and can therefore i ncrease its absorption and oral bioavailability (12).

Risperidone: Risperidone is Associate in nursing tranquillizer employed in the treatment of dementia praecox, emotional disturbance, and autism. With the help of liquisolid technology, we are able to improve the flow characteristics and hardness character of the formulation by neutering the proportion of carrier and coating materials. Further, a 23 factorial design is used and liquisolid compact is developed mistreatment Neusilin and Fugicalin. The In vitro drug unharness from liquisolid compact make up my mind in 0.1N HCl and also the optimized formulation was then any compared with pure drug and marketed product. The studies showed that the liquisolid tablets provide higher drug release profile than both the pure drug and marketed product, due to increased wettability of drug. Thus, Liquisolid compact technology is employed as better alternative and it obtains increased dissolution rate of risperidone that considerably improves the oral bioavailability (13).

Olmesartan medoxomil: Olmesartan medoxomil is an Angiotensin Type II Receptor Blocker or an antihypertensive agent generally administered orally. It is extremely hydrophobic drug with 26% absolute bioavailability. The solubility of lipophilic drug is still a main concern confronting the pharma industry. Various dissolution studies for liquisolid

compacts and marketed formulations were performed, and it was observed that the liquisolid compacts with 80% w/w of Acrysol EL 135 to the drug exhibited enhanced drug release rates than the conventional tablets (14).

Carvedilol: Carvedilol is a β-blocker and belongs to BCS class II drug, helps in the treatment of high blood pressure and cardiac failure. Liquisolid technology helps in improving the dissolution behavior of carvedilol by improving its physical properties. The formulation containing drug dissolved in PEG 400, with Avicel 101 as carrier and Aerosil as coating material has shown 98.4% drug release within 20 min which is better than marketed product (CARCA 12.5mg, Intas). The physicochemical properties of formulation and drug excipient interactions are evaluated by performing DSC and X-RD studies. The resultant liquisolid compact of carvedilol shows improved dissolution and increased drug release profile. (15)

Curcumin: Curcumin is a BCS Class IV drug, having antioxidant activity and also possess free radical scavenger properties. Curcumin has potency against various disease like cough, rheumatism and hepatic disorders, Alzheimer disease, diabetes, anorexia but due to its very low solubility and permeability it became unable to formulate a dosage form in order to achieve maximum therapeutic effect. . Optimized formulation is prepared by using 5% drug in PEG 400, with Avicel 101 as carrier and Aerosil as coating material in 3:1 shows that drug release rate is high due to the curcumin solubilization. Due to the use of high amount of PEG400 the dosage form gets easily solubilized as there is increase in wettability and effective surface area of the compound available for dissolution media. Thus the resultant liquisolid formulation of curcumin showed improved dissolution and increased drug release profile and the technique can be used effectively for the poorly soluble drugs (16).

Valsartan: Valsartan is angiotensin receptor blocker (ARBs) which is used in treatment of heart failure and high blood pressure. Valsartan liquisolid tablet was prepared by using Propylene Glycol as non-volatile vehicle, Avicel PH102 (carrier) and Aerosil 200 (coating material). Liquisolid tablet of valsartan when compared with marketed product shows that the dissolution efficiency of the drug at 15 min has increased from 13.58% for marketed product to liquisolid formulation having 29.47% drug release. (17)

Rofecoxib: Rofecoxib is a COX-2 selective nonsteroidal anti-inflammatory drug (NSAID), helpful in treating dysmenorrhea, osteoarthritis, migraine, rheumatoid arthritis. Liquisolid tablets of rofecoxib were produced by dispersing the drug in PEG 600 and the admixture of magnesium oxide and microcrystalline cellulose-silica added to the mixture. Ac-Di-Sol® and magnesium stearate was also mixed for a period 10 minutes. Incorporation of 10% Cab-O-Sil® and 5% magnesium oxide helps in improving both compressibility and flow-ability thus change flow-ability from bad flow to satisfactory flow. (18)

Fenofibrate: Fenofibrate is a BCS Class II drug, help in decreasing the elevated plasma levels of triglycerides, LDL and total cholesterol. It is used to treat the patients having abnormal blood lipid levels. Calculated quantities of fenofibrate in propylene glycol (non-volatile solvent) in different concentration (10%, 20% and 30%), carrier and coating materials were taken and formulated as a liquisolid tablet. In vitro dissolution study was done and compared with liquisolid formulation at 10min and 30min. Liquisolid formulation of fenofibrate at various concentrations at 10-30 min. shows greater drug release rate as compared to conventional product. All the various formulation shows more than 89.182% drug release at 45 min. which is way more less in marketed products. (19)

Loperamide: Loperamide is an opioid agonist and acts on μ-opioid receptors thus used for treatment of various diarrheal conditions. It belongs to BCS Class II which means water solubility is very low thus there is need for the enhancement of the dissolution characteristics. Liquisolid formulation of Loperamide was developed by using Propylene glycol (PG) as an organic solvent, Avicel pH 102 (carrier), Aerosil (coating material) and Sodium Starch Glycolate (superdisintegrant). The dissolution profile of Loperamide at 15 min was enhanced from 54.57% for marketed product to 86.81% for the tablets prepared by liquisolid compact technique. (20)

Clonazepam: Clonazepam is an anti-convulsant and help in enhancing the activity of GABA receptors. A suspension was formulated by dispersing the drug in Propylene glycol (non-volatile solvent) which increases the wetting property and surface area of the drug thus enhanced dissolution efficiency of the drug. Liquisolid tablet shows 90.27% drug release at 15 min. which is greater as compared to marketed product. (21)

Propranolol Hydrochloride: Propranolol Hydrochloride is a β-Adrenergic blocking agent having antihypertensive and antiarrhythmic properties. Molecular dispersion of Propranolol Hydrochloride dispersed is prepared by dissolving the drug in Poly-sorbate 80 and a physical admixture of carrier and coating material was used to prepare liquisolid medication. The resultant liquisolid

formulation containing Eudragit shows greater retardation properties and enhanced drug release as compared to conventional matrix tablets. (22)

Famotidine: Famotidine belongs to BCS Class III drug thus the oral absorption and bioavailability is limited because the intestinal permeability is low. It is used in the treatment of ulcers in stomach and intestine. Optimized amount of drug is dissolved in PEG 400, with Avicel 101 as carrier and Aerosil as coating material and used to prepare liquisolid tablet. The liquisolid powder is then finally blended with Explotab (sodium starch glycollate) which enhances the flow-ability and compressibility of the formulation. This optimal formula shows drug release of 78.36 % in 10 minutes which is 39% more than directly compressed tablet. (23)

Repaglinide: Repaglinide Liquisolid compact was orally administered to rabbits and blood samples were collected which is then further used to determine the pharmacokinetic behavior of repaglinide, which then evaluated by a comparing pharmacokinetic parameters of marketed tablets (Novonorm 2 mg). Insulin level in the marketed tablet possess insignificantly increased level (3.52% change) while the new LSC formula enhanced the insulin level with change of 37.6%. Glucose tolerance test also confirms that the blood glucose level decreases significantly after the marketed product (percent change, 18.1%) while in groups treated with the LSC formulation the decrease was significantly high with change of 29.98%. Furthermore, the new repaglinide Liquisolid Compact formulation reduces blood glucose levels more than the marketed product. (24)

Candesartan Cilexitil: It is an Angiotensin II receptor antagonist and used in the treating hypertension. It is the member of BCS Class II drugs thus hydrophobic in nature. The drug release rate of candesartan cilexetil from liquisolid tablet is higher than the marketed tablet. The dissolution efficiency of Candesartan cilexetil after 30 min. reach at 101.44% while conventional tablet exert only 35.81% drug release and even after 60 min. the rate of drug release form conventional tablet reaches 59.33%. (25)

Table No. 1: Examples of other drugs with improve bioavailability

S.No.	Name of drug	Year	Change in dissolution/bioavailability	Author	REF NO
1	Lumefantrine	2018	The Dissolution rate of liquisolid formulation was significantly higher than the pure drug	Khan A.,Agarwal S.	5
2	Cefixime	2018	The Dissolution rate of liquisolid formulation was significantly higher than the pure drug	Zainab H.M	6
3	Resperidone	2015	The Dissolution rate of liquisolid formulation was significantly higher than the pure drug	Shamili K., Santhesh PRB	7
4	Olmesartan	2013	The Dissolution rate of liquisolid formulation was significantly higher than the pure drug	Shailaish T.B., Hitesh H.B	8
5	Carvidelol	2013	The Dissolution rate of liquisolid formulation was significantly higher than the pure drug	Sandhya P., Khanam S.	9
6	Curcumin	2012	The Dissolution rate of liquisolid formulation was significantly higher than the pure drug	Shailendra S S., Pritesh P	10
7	Valsartan	2012	The Dissolution rate of liquisolid formulation was significantly higher than the pure drug	Naveen c., Shastri N	11
8	Fenofibrate	2014	The Dissolution rate of liquisolid formulation was significantly higher than the pure drug	Tejas P.	12
9	Loperamide	2016	The Dissolution rate of liquisolid formulation was significantly higher than the pure drug	Kambham V.	13
10	Clonazepam	2014	The Dissolution rate of liquisolid formulation was significantly higher than the pure drug	Sanka K	14
11	Propranolol	2008	The Dissolution rate of liquisolid formulation was significantly higher than the pure drug	Javedzadeh Y	15
12	Famotidine	2008	The Dissolution rate of liquisolid formulation was significantly higher than the pure drug	Raina H.F	16

CONCLUSION:

Liquisolid technology is the best technology because of economical, formulation development identical to older marketed tablets, and increased dissolution rate. It converts liquid hydrophobic drugs or solid drugs into dry, non-adherent and acceptably free

flowing powders. In this technique formulators can easily modify the drug release can using different formulation ingredients in suitable concentrations. As it works on principle of molecular dispersion so molecularly dispersed drugs can results in enhancing the bioavailability, proved from clinical trial studies.

FUTURE ADVANCEMENTS:

For the improvement of solubility and its enhancement or sustaining the drug release, various approaches are available today; but those techniques are having very high formulation cost, complicated machinery, technologies, IPR concerns, and new advanced preparation methods. However, this liquisolid technology helps in overcoming all shortcomings. Liquisolid compact is administered orally, thus it possess great patient compliance. Varied carriers and coating materials are incorporated in this technique and very cost-effective. The authors suggests that vast research must be done for obtaining information about different sources and grades of carrier and coating materials, and their varied particle sizes and their effect on solubility and absorption of the drug. In case of sustained release dosage forms, the use of various carriers must be evaluated and it has capacity to evaluating the effect of various disintegrants and superdisintegrants, surface active agent, preservatives on dissolution characteristics of the formulation. In future, liquisolid technology will give a feasible alternative to conventional dosage forms.

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CONFLICT OF INTEREST:

We have no any conflict of Interest to declare if a journal prints unsigned editorials.

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