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Effect of dissolution rate by liquisolid compact approach: An overview

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ABSTRACT

In recent generations the limited solubility of drugs, which are challenging issue for industry during development of the ideal solid dosage unit. To overcome this consequence, liquisolid technique is a novel and promising approach. The technique is based upon the admixture of drug loaded solutions (or) liquid drug with appropriate carrier and coating materials. Addition of the additives improves the technique. The selection of non-toxic hydrophilic solvent, carrier, coating excipients and its ratios are independent of the individual chemical entities. Indirectly it leads to enhance the bioavailability. However, poorly soluble drugs with low dose chemical entities are more ideal to formulate in the above said technique.

Keywords*:* Poorly soluble drugs, Liquisolid, Non-Toxic Hydrophilic solvent, Carrier, Coating.

INTRODUCTION

Nowadays, the synthesis of poorly soluble drugs steadily increasing. At present 40% of the drugs in the development pipelines and approximately 60% of the drugs coming directly from synthesis are poorly soluble [1]. The increasing synthesis of new poorly soluble drugs candidates should adopt innovative formulation approach to reach a sufficiently high bioavailability after oral administration or at least to make available intravenously injectable form meanwhile it should pass dissolution test criteria as per official media prescribed. Various formulation approaches already established to enhance poorly soluble drugs, e.g. use of solvent mixtures, cyclodextrins. The principle limitation of all these approaches is that the drug needs to possess certain physicochemical properties or to 'fit' to the solubilising principle (e.g. having the right molecular size to fit into the cyclodextrine ring). Increasing the dissolution rate by reducing the

particle size of poorly water-soluble drugs has been the most popular practice for many decades [2].

Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Today, micronization of drugs is widely done by milling techniques using a jet mill, rotor stator, colloidal mill, and air attrition. With the aforementioned advantages, micronization has some limitations; micronization of sparingly or poorly soluble drugs is by no means a guarantee of better dissolution and absorption. A hydrophobic powder with small particle size leads to aggregation, making it difficult to disperse. The particles float on the dissolution medium because of entrapped air. It is difficult to remove or wet these particles. All these effects, in fact, reduce the rate of dissolution [3].

Consequently, the next step was taken to move from micronization to nanonisation that means producing drug nanocrystals. By definition drug nanocrystals are nanoparticles being composed of 100% drug without any matrix material, according to the definition of nanoparticles the mean particle size is below 1 mm (i.e. in the nanometre range, typically somewhere between 200 and 500 nm).Typically, the drug nanocrystals are generated in a liquid dispersion medium (e.g. by precipitation or a disintegration process). The obtained product from this process is a suspension of drug nanocrystals in a liquid stabilised by a surfactant or polymer (so-called 'nanosuspension'). In contrast to micronized powders the drug nanocrystals can be administered using very different administration routes. Oral administration is possible as a suspension. More patient convenient dosage forms can be produced by transferring the liquid nanosuspensions to solid dosage forms, i.e. tablets or pellets or granulate containing capsules. In addition, because of their small size the nanosuspensions can be injected parenterally, especially intravenously. Intravenous injection leads 'per definition' to a 100% bioavailability, but this technology is too economic [4]. In generic development cost of formulation will be high.

This paper focuses on the novel and promising technology of liquisolid compact effect on dissolution. It is feasible, low cost and capability to industrial production. From the historical point of view, liquisolid compacts were evolved from 'Powdered Solutions' which depended on preparing a true solution of the drug in a high boiling point, water-miscible solvent, which was carried out on the extensive surface of an inert carrier such as silica. Liquisolid system refers to formulations formed by conversion of liquid drugs, drug suspensions or drug solution in non-volatile solvents into dry, non-adherent, free-flowing and compressible powder mixtures by blending the suspension or solution with selected carriers and coating materials [5]. Due to significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release characteristics and, consequently, improved oral bioavailability. Since dissolution of a non-polar drug is often the rate limiting step in gastrointestinal absorption, better bioavailability of an orally administered water-insoluble drug is achieved when the drug is already in solution, thereby displaying enhanced dissolution rates. That is why soft gelatin elastic capsules containing solutions of such medications demonstrate higher bioavailability when compared to conventional oral solid dosage forms. A similar principle underlies the mechanism of drug delivery from liquisolid compacts and is chiefly responsible for the improved dissolution profiles exhibited by these preparations as shown in the ***figure 2***. In this case, even though the drug is in a solid dosage form, it is held within the powder substrate in solution or, in a solubilized, almost

molecularly dispersed state, which contributes to the enhanced drug dissolution properties [6 - 7].

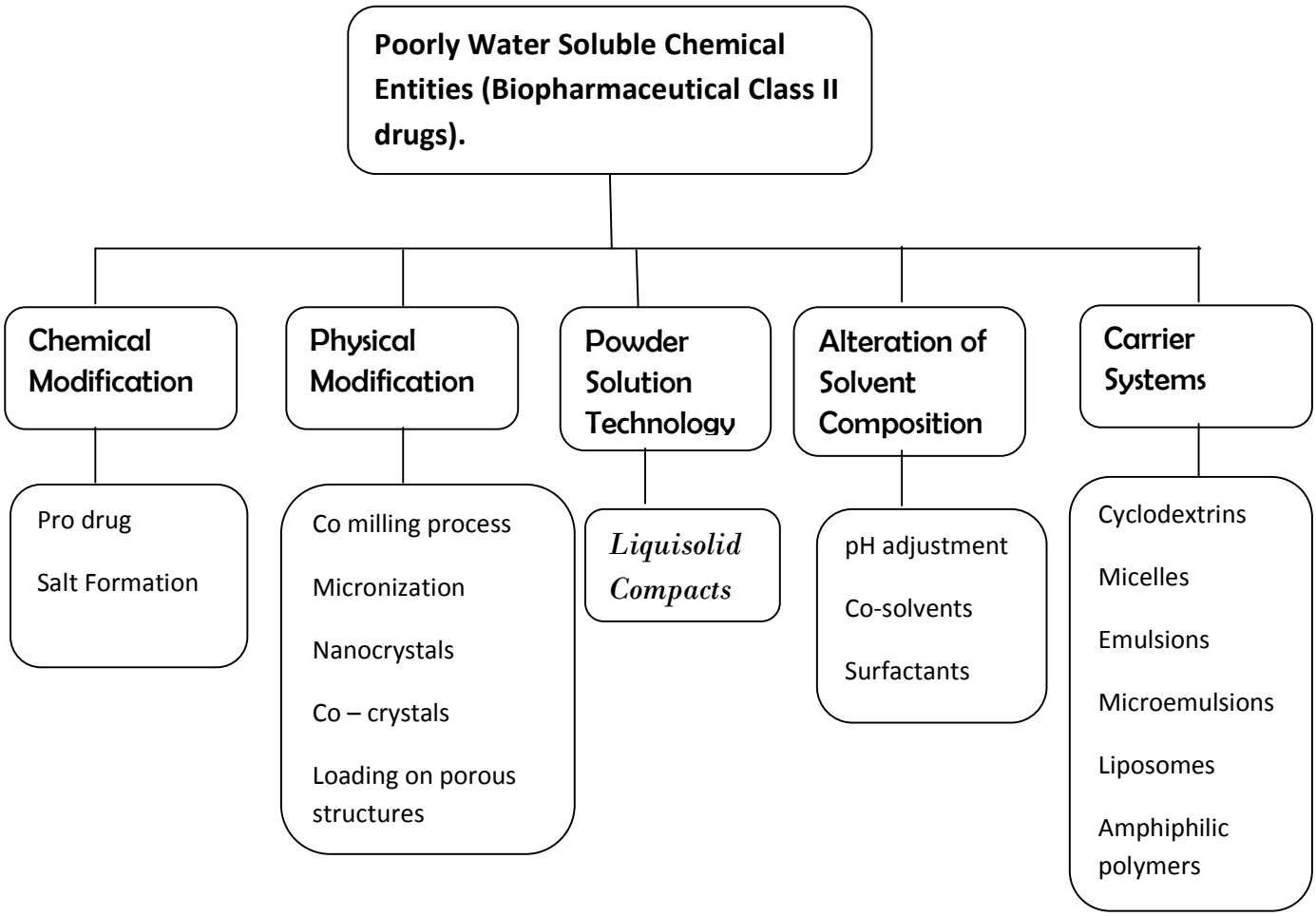

Figure 1: Various approaches to enhance the solubility of drugs

1.1. Liquisolid tablets advantages over the conventional tablets.

1) Liquisolid systems are low cost formulations than soft gelatin capsules.
2) Production of them is similar to that of conventional tablets.
3) Drug release can be modified using suitable formulation ingredients.
4) Drug can be molecularly dispersed in the formulation.
5) Capability of industrial production is also possible.
6) Enhanced bioavailability can be obtained as compared to conventional tablets.
7) Omit the process approaches like nanonisation, micronization techniques.
8) Differentiate the dosage form by admixture of colour into liquid vehicle.
9) To minimize excipients in formulation compare with other formulations like solid dispersions.

1.2. Basic theoretical aspect to formulate Liquisolid Compact

These studies are related to the flow and compression of formulation. The 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 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, where:

$$R = Q/q \qquad (1)$$

Which 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. :

$$L_f = W/Q \qquad (2)$$

It should be emphasized that 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 liquisolid systems are ensured and, in a way, built in during their manufacturing process via the (Φ – value) and **(Ψ** – number) concepts, respectively. These are introduced for fundamental properties of powders and are referred to as their flowable and compressible liquid-retention potentials, respectively [7].

The **Ψ** number of powders may be determined using a new method termed the liquisolid compressibility (LSC) test or 'pactisity testing', which employs the recently proposed 'pactisity theories' to evaluate the compaction properties of the liquid: powder admixtures. Accordingly, the pactisity (Ω) or maximum crushing strength of the liquisolid compacts consisting of certain liquid and powder is inversely proportional to the liquid: solid weight ratio (*C*w) of the preparations. The desired compression properties of the finished liquisolid systems may be adjusted during pactisity testing according to the requirements of the individual target product and are, in essence, built in the magnitude of the determined numbers of the carrier (**Ψ**) and coating powders (Ψ).

The maximum amount of liquid loads on the carrier material, termed ''load factor" (L_f). The coating/carrier ratio (R) is important for determining the ''optimum flowable load factor" (L_f) which gives acceptable flowing powders and is characterised by the ratio between (W) and (Q), as shown in Eqs. 1 and 2.

$$L_f = \Phi_{CA} + \Phi_{CO}\,(1/R) \qquad (3)$$

Where, Φ_{CA} is the flowable liquid-retention potential of the carrier and Φ_{CO} is the flowable liquid-retention potential of the coating material.

The appropriate amounts of carrier and coating materials to produce acceptable flowing and compactible powders are calculated using Eqs. (1) and (3), based on the physical properties of powders termed ‘‘flowable liquid-retention potential” (Φ – value). The ratio (R) of the amount of carrier (Q) and coating (q) materials is closely related to the amount of liquid medication (W) [8].

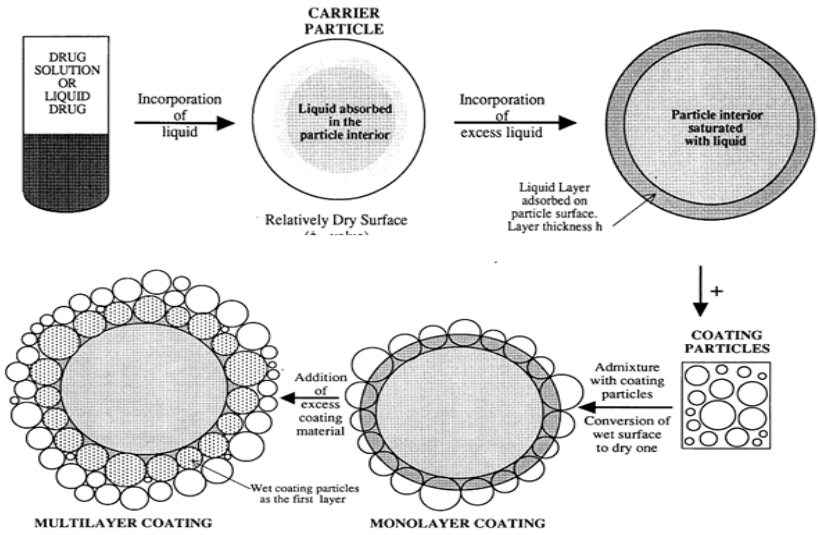

Figure 2: Mechanism represents formulation of liquisolid system

1. Formulation of Liquisolid Compacts

2.1. Selection of Solvent

To select the best non-volatile solvent for dissolving or suspending the drug in liquid medication, solubility studies of drug were carried out in different non-volatile solvents. Saturated solutions were prepared by adding excess drug to the vehicles and it was shaked on the shaker for 48h at 25◦C under constant vibration. After this period the solutions were filtered through a 0.45 µm Millipore filter, diluted with distilled water containing sodium lauryl sulphate (SLS) and analysed by UV-spectrophotometer at respected wavelength against blank sample (blank sample containing the same concentration of the specific solvent used without drug). Three determinations were carried out for each sample to calculate the solubility of drug [7, 9]. Some of the solvents mentioned can be incorporated to formulate Liquisolid compact viz. Poly ethylene glycol (PEG 200, 400, 600), Propylene Glycol, Polysorbate 80, Glycerol, Tweens, Spans, Polyoxyl 35 castor oil and poloxamer 181. The solvent should have the characteristic of a non – toxic and non –volatile solvent. The formulation liquisolid compacts should neither enhance the dissolution rates nor retard the dissolution rates of the drug it depends upon the selection of solvent and properties of the chemical entities. Prior to selection of solvent selection in the formulation there is need to check the saturation solubility with selected non- volatile solvents. From saturation solubility of solvent the one which has enhance rate of dissolution, the solvent with minimum solubility (least solubility) retards the rate of drug release [10].

2.2. Selection of Carriers and Coating Agents

In this approach the carrier play as a major role in obtaining the dry form of powder from the liquid medication. Each carrier has its unique property; selection of carrier will depend upon

liquid holding capacity, flow ability of powder and which, requires less compression force. Some example of carriers are like microcrystalline cellulose, lactose, di calcium phosphate etc.. Amorphous silica (200 nm) was ideal for coating of the formulation [10 - 11].

2.3. Role of Additive in Liquisolid Compact

Additive mixing was a major advantage in liquisolid compact; it can increase the loading factor. Additives with low viscosity grade polymers such as Hydroxyl propyl methyl cellulose (HMPC E3 LV), Polyvinyl Pyrrolidine (PVP K 25), Poly Ethylene Glycol (PEG 6000) etc., were suitable for enhancement of dissolution rate of drug. For extended release formulation, various grades of polymers can be used viz. Eudragit RS and RL, Guar gum, Xanthan gum Hydroxy Propyl Methyl Cellulose (HPMC K4M) etc., [10 - 12].

2.4. Role of Disintegrants in Liquisolid Compact

Disintegrants are indirectly effect the dissolution parameter since the immediate next step is dissolution. For fast disintegration super disintegrants can be chosen like Sodium starch glycolate, Crospovidone, Croscaramellose etc., [13 - 15].

3. Brief overview of existing formulations to produce Liquisolid Compact

3.1. Approach to Enhance Dissolution of Drug Release from its Immediate Release Tablets

In the liquisolid or powdered solution systems the drug might be in a solid form, it is held within the powder substrate in solution, or in a solubilized, almost molecularly dispersed state. Therefore, due to their significantly increased wetting properties and surface of drug available for dissolution, liquisolid compacts of water- insoluble substances may be expected to display enhanced drug release properties, and consequently, improved bioavailability [16].

Piroxicam is a poorly soluble, highly permeable drug and the rate of its oral absorption is often controlled by the dissolution rate in the gastrointestinal. The poor dissolution rate of water-insoluble drugs is still a major problem confronting the pharmaceutical industry. There are several techniques to enhance the dissolution of poorly soluble drugs. Among them, the technique of liquisolid compacts is a promising technique towards such a novel aim. The liquisolid compacts technique is the best alternative for the formulation of water- insoluble drugs, such as Piroxicam into rapid release tablets. In this study, the dissolution behaviour of Piroxicam from liquisolid compacts was investigated in simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 7.2). Several liquisolid tablets formulations containing various ratios of drug: Tween 80 (ranging from 10% to 50% w/w) was prepared. The ratio of microcrystalline cellulose (carrier) to silica (coating powder material) was kept constant in all formulations. The results showed that liquisolid compacts demonstrated significantly higher drug release rates than those of conventionally made (capsules and directly compressed tablets containing micronized Piroxicam). The higher dissolution rates displayed by liquisolid compacts may also imply enhanced oral bioavailability due to the increased wetting properties and surface of drug available for dissolution. The study states that, the liquisolid compacts of Piroxicam in which polysorbate 80 is the liquid vehicle, in different drug concentrations in their liquid medications, exhibit drug dissolution rates which are directly proportional to the fraction of the molecularly dispersed drug in their liquid medication. It can be concluded that liquisolid compacts technique can be a promising alternative for the formulation of water-insoluble drugs.

Prednisolone, a very slightly water soluble glucocorticoid, formulated in directly compressed tablets and liquisolid compacts, were studied at different dissolution conditions. According to the new formulation method of liquisolid compacts, liquid medications such as solutions or suspensions of water insoluble drugs in suitable non-volatile liquid vehicles can be converted into acceptably flowing and compressible powders by blending with selected powder excipients. It has been speculated that such systems exhibit enhanced release profiles due to the increased wetting properties and surface of drug available for dissolution. In this study, the potential of liquisolid systems to improve the dissolution properties of water-insoluble agents was investigated using prednisolone as the model drug. Several liquisolid tablet formulations were prepared using a new mathematical model to calculate the appropriate quantities of powder and liquid ingredients required to produce acceptably flowing and compressible admixtures. Liquisolid compacts demonstrated significantly higher drug release rates, in different dissolution media and volumes, compared to tablets prepared by the direct compression method. It was also observed that the drug dissolution rate from liquisolid tablets was independent of the volume of dissolution medium, in contrast to the plain tablets which exhibited declining drug release patterns with decreasing dissolution volumes [17].

Carbamazepine, 5H-dibenzazepine-5-carboxamide, is a sodium channel blocker that has been in routine use in the treatment of epilepsy and trigeminal neuralgia for over 40 years. Carbamazepine (CBZ) is considered a first line drug in the treatment of Epilepsy. It is practically insoluble in water. The oral absorption of CBZ is slow, erratic and unpredictable in humans owing to slow dissolution. Many studies were done in trial to improve the bioavailability of Carbamazepine. This agent belongs to class II drugs that its bioavailability is limited by its poor dissolution rate in GI. In fact, its solubility and dissolution rate are key factors in its bioavailability. Different liquisolid formulations of carbamazepine were accomplished by dissolving the drug in the non-toxic hydrophilic liquids, and adsorbing the solution onto the surface of silica. In order to reduce the amounts of carrier and aerosil in liquisolid formulations, some namely additives Polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC) and polyethylene glycol (PEG 35000) were added to liquid medication to increase loading factor. The effects of various ratios of carrier to coating material, PVP concentration, effect of aging and type of the carrier on dissolution rate of liquisolid compacts were studied.

The results showed that the drug loading factor was increased significantly in the presence of additives. Liquisolid formulations containing PVP as additive, exhibited significantly higher drug dissolution rates compared to the compacts prepared by the direct compression technique. It was shown that microcrystalline cellulose had more liquid retention potential in comparison with lactose, and the formulations containing microcrystalline cellulose as carrier, showed higher dissolution rate. By decreasing the ratio of microcrystalline cellulose to silica from 20 to 10, an improvement in dissolution rate was observed. Further decrease in the ratio of microcrystalline cellulose: silica from 10 to 5 resulted in a significant reduction in dissolution rate. Increasing of PVP concentration in liquid medication caused a dramatic increase in dissolution rate at first 30 min. The prepared tablets showed good wettability, rapid disintegration, and acceptable dissolution rate comparable to the generic product. Better pharmacological activity could possibly be obtained had CBZ concentration been lower to avoid possible precipitation into the silica pores [12].

Furosemide, 4-chloro-2-[(furan-2-ylmethyl)amino]-5-sulfamoylbenzoic acid, is a drug with a diuretic action which is used in the treatment of oedema of pulmonary, cardiac or hepatic origin as well as in the treatment of hypertension and in the chronic treatment of cardiac infarction. The major problem associated with the formulation and effectiveness of the furosemide is its variable oral absorption of about 11–90% due to insufficient aqueous solubility at gastrointestinal pH, thus making solubility the rate-determining step in the gastric absorption of furosemide [18]. Therefore, liquisolid system has the ability to improve the dissolution properties of poorly water soluble drugs. Liquisolid compacts are flowing and compactable powdered forms of liquid medications.

Several liquisolid tablets were prepared using microcrystalline cellulose and fumed silica as the carrier and coating materials, respectively. Polyoxyethylene- polyoxypropylene-polyoxyethylene block copolymer (Synperonic® PE/L 81); 1, 2, 3-propanetriol, homopolymer, (9Z)-9-octadecenoate (Caprol® PGE-860) and polyethylene glycol 400 (PEG 400) were used as non-volatile water-miscible liquid vehicles. The liquid loading factors for such liquid vehicles were calculated to obtain the optimum amounts of carrier and coating materials necessary to produce acceptable flowing and compactible powder admixtures viable to produce compacts. The ratio of carrier to coating material was kept constant in all formulations at 20 to 1. The *In-vitro* release characteristics of the drug from tablets formulated by direct compression (as reference) and liquisolid technique were studied in two different dissolution media. The results showed that all formulations exhibited higher percentage of drug dissolved in water (pH 6.4–6.6) compared to that at acidic medium (pH 1.2). Liquisolid compacts containing Synperonic® PE/L 81 demonstrated higher release rate at the different pH values. Formulations with PEG 400 displayed lower drug release rate, compared to conventional and liquisolid tablets [19].

The potential of liquisolid systems to improve the dissolution properties of a water-insoluble agent (indomethacin) was investigated. In this study, different formulations of liquisolid tablets using different co-solvents (non-volatile solvents) were prepared and the effect of aging on the dissolution behaviour of indomethacin liquisolid compacts was investigated. Dissolution test was carried out at two different pH, 1.2 and 7.2, to simulate the stomach or intestine fluid, respectively. The results showed that liquisolid formulations exhibited significantly higher drug dissolution rates at pH 1.2 and 7.2 compared to compacts prepared by the direct compression technique. The enhanced rate of indomethacin dissolution from liquisolid tablets was probably due to an increase in wetting properties and surface area of drug particles available for dissolution. In order to investigate the effect of aging on the hardness and dissolution rate of liquisolid compacts, the formulations were stored at 25^0C/75% relative humidity for a period of 12 months. Liquisolid compacts containing propylene glycol as vehicle produced higher dissolution rates in comparison with liquisolid compacts containing PEG 400 or Tween 80 of the same concentration. Liquisolid formulations were designed to contain liquid medications in powdered form, thereby possessing mechanisms of drug delivery similar to those of soft gelatin capsule preparations containing liquids. The results showed that the liquisolid technique could be a promising alternative technique to increase the dissolution of water insoluble drugs. It states that effect of aging had no significant effects on dissolution profile of indomethacin liquisolid tablets [20].

Naproxen, non-steroidal anti-inflammatory drug, is a weak acid (pKa = 4.15) which is practically insoluble in water in a solid dosage form. This study was designed to evaluate the effects of different formulation variables, i.e. type of non-volatile liquid vehicles and drug concentrations, on drug dissolution rates. The liquisolid tablets were formulated with three different liquid vehicles, namely Cremophor EL (polyoxyl 35 castor oil), Synperonic PE/L61 (poloxamer 181, polyoxyethylene–polyoxypropylene copolymer) and poly ethylene glycol 400 (PEG400) at two drug concentrations, 20%w/w and 40%w/w. Avicel (microcrystalline cellulose) was used as a carrier material, Cab-o-sil (silica) as a coating material and maize starch as a disintegrant. In vitro drug dissolution profiles of the liquisolid formulations were studied and compared with conventional formulation, in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.2) without enzyme. Stability studies were carried out to evaluate the stability of the tablets under humid conditions. It was found that liquisolid tablets formulated with Cremophor EL at drug concentration of 20%w/w produced high dissolution profile with acceptable tablet properties. The stability studies showed that the dissolution profiles of liquisolid tablets prepared with Cremophor EL were not affected by ageing significantly [8].

3.2. Approach to Sustained Release of Drug from its Dosage Unit

Development of sustained release oral dosage forms is beneficial for optimal therapy in terms of efficacy, safety and patient compliance. Ideally, a controlled release dosage form will provide therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval. To achieve this aim, several methods have been developed such as preparation of salt form of drug, coating with special materials and incorporation of drugs into hydrophobic carriers. Liquisolid technique is a new and promising method that can change the dissolution rate of drugs [10].

Propranolol hydrochloride is a β - adrenergic blocking agent, i.e. a competitive inhibitor of the effects of catecholamines at β - adrenergic receptor sites. It is widely used in therapeutics for its antihypertensive and antiarrhythmic properties. Furthermore, it has a short elimination half-life of 3 h, which makes it a suitable candidate to be delivered at a controlled rate [21, 22].

It is suggested here that liquisolid technique has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems. In the present study, propranolol hydrochloride was dispersed in polysorbate 80 as the liquid vehicle. The liquid vehicle selected on the basis of least solubility of liquid vehicle. Then a binary mixture of carrier - coating materials (Eudragit RL or RS as the carrier and silica as the coating material) was added to the liquid medication under continuous mixing in a mortar. The effect of drug concentration, loading factor, thermal treating and aging on release profile of propranolol hydrochloride from liquisolid compacts were investigated at two pH values (1.2 and 6.8). Tablets were prepared by liquisolid technique showed greater retardation properties in comparison with conventional matrix tablets. The results also showed that wet granulation had remarkable impact on release rate of propranolol HCl from liquisolid compacts, reducing the release rate of drug from liquisolid compacts. The kinetics studies revealed that most of the liquisolid formulations followed the zero-order release pattern [10].

3.4. Bio - availability assessment

Bio availability assessment is required for liquisolid technique. Because it was proved that enhancing the drug releases form the dosage form by determination of *In – vitro* release studies. So, this parameter should establish for determination of the efficacy of the formulation [23].

Repaglinide is a novel post prandial glucose regulator for the treatment of type 2 diabetes mellitus. It helps to control blood sugar by stimulating release of insulin from the pancreatic β-cells. Repaglinide is rapidly absorbed from the gastrointestinal tract after oral administration. This study was designed to determine the bioavailability and biological activity of liquisolid compact formula of repaglinide and its effect on glucose tolerance in rabbits. This study is an extension of the previous enhancement of dissolution properties of repaglinide using liquisolid compacts. The development and validation of a High Performance Liquid Chromatography (HPLC) assay for the determination of repaglinide concentration in rabbit plasma for pharmacokinetic studies is described. Repaglinide optimizing formula was orally administered to rabbits and blood samples were used to determine the pharmacokinetic parameters of repaglinide, which were compared to pharmacokinetic parameters of marketed tablets (Novonorm 2 mg). Also, to investigate the biological activity of this new formula, in comparison with the commercial product, Oral Glucose Tolerance Tests (OGTT), area under the curve and insulin levels were studied. Moreover, we studied the efficacy and safety of this new formula in several potencies (0.5, 1, and 2 mg) and blood glucose, insulin, kidney and liver functions [24].

The relative bioavailability of repaglinide from its liquisolid compact formula was found to be increased significantly in comparison to that of the marketed tablet. In regard to urea and creatinine, no significant change was recorded after the administration of the commercial and the three potencies of the new formulation compared with the control group. Similarly, in liver function tests (serum glutamic pyruvic transaminase, SGPT), there were no changes observed in its level. Regarding insulin levels, the commercial formula increased insulin levels insignificantly (3.52% change) while the new formula increased the insulin level significantly with a percent change of 37.6%. The results of the glucose tolerance test showed that the blood glucose level was decreased significantly after the commercial drug (percent change, 18.1%) while in groups treated with the new formulation the decrease was highly significant ($p < 0.01$) with a percent change of 29.98%. The change in area under the curve for blood glucose was significantly higher in the commercial drug plus glucose load than in the new formulation plus glucose load group ($p < 0.05$) in the periods of 30-45 min and 45-60 min. Furthermore, the new repaglinide formulation significantly decreased blood glucose levels more than the commercial formula [24].

Famotidine is indicated for active and maintenance therapy of various types of ulcers and hyper secretory conditions. The mechanism of action, pharmacological effects, site of action, and clinical uses are the same as for the other H_2-receptor antagonists, but on equimolar bases, famotidine is reported to be about 7.5 and 20 times more potent than ranitidine and cimetidine, respectively, in inhibiting gastric acid secretion. However, famotidine is relatively free of side effects despite its high potency. Although famotidine reportedly undergoes minimal first-pass metabolism and its oral bioavailability in man has been reported to be low and variable, ranging from 40% to 50% due to its poor aqueous solubility, high polarity, and gastric degradation Since for poorly water-soluble drugs (like famotidine) the dissolution rate is often the rate-limiting step

for bioavailability, and the dissolution rate is a function of the solubility and the surface area of the drug, thus, dissolution rate will increase if the solubility of the drug is increased, and it will also increase with an increase in the surface area of the drug [16].

The purpose of this study was to improve famotidine dissolution through its formulation into liquisolid systems and then to investigate the *In - vitro* and *In - vivo* performance of the prepared liquisolid tablets. All the tested liquisolid tablet formulations showed higher drug dissolution rates (DR) than the conventional, directly compressed tables. In addition, the selected optimal formula released 78.36% of its content during the first 10 min which is 39% higher than that of the directly compressed tablets. Further, the bioavailability study indicated that the prepared optimal liquisolid formula did not differ significantly from the marketed famotidine tablets concerning C_{max}, t_{max}, and $AUC_{(0–8)}$ at $P < 0.05$ by statistical analysis (ANOVA) [16].

The anticonvulsant activity of Carbamazepine (CBZ) in liquisolid tablets as well as marketed tablets and suspension was determined using the maximal electroshock method. Male albino mice, weighing 20–25 mg, were fasted overnight and divided into four groups, each consisting of six animals. CBZ, supplied from the different above products to mice in a dose of 35 mg/kg body weight. Maximal electroshock seizure (MES) was induced using an electrical simulator with ear electrodes to deliver stimuli. An electrical stimulus (50 mA, 60 Hz) was delivered for 0.2 s to the animal after 60 min of drug administration. The animals were restrained by hand and released at the moment of stimulation in order to permit the observation of the entire seizure. Absence of hind limb tonic extensor component indicated that the drug received could prevent MES spread. The results were expressed as percentage of the animals protected [11].

4. Evaluations

4.1. Determination compatibility studies

Differential scanning calorimetry (DSC) and Fourier transform infrared were used to investigate physicochemical interaction between drug and the excipients. The results reveal the compatibility of the formulation [7 - 10].

4.2. Determination of morphology

X-ray crystallography and DSC were used to investigate the formation of any complex between drug and excipients or any crystallinity changes during the manufacturing process which was further confirmed by Scanning electron photomicrograph (SEM) indicating the existence of morphology (***Figure.3***) of the system containing famotidine [16].

Figure 3: Scanning electron photomicrograph (SEM) of A) Pure drug Famotidine

B) Liquisolid formulation of Famotidine

4.3. Pre Compression Evaluations

The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to get a uniform feed as well as reproducible filling of tablet dies, otherwise, high dose variations will occur. In order to ensure the flow properties of the liquisolid systems that will be selected to be compressed into tablets and further evaluated, angle of repose measurements, Carr's index and Hausner's ratios were adopted [7 - 9, 16 - 17].

4.4. Post compression Evaluations

a) Content of uniformity
b) Hardness
c) Weight variation
d) Friability
e) Disintegration
f) *In - vitro* dissolution studies

These are should be in the official limits prescribed by official pharmacopoeias [5 - 9, 10 - 16].

CONCLUSION

In conclusion, liquisolid compact refers to formulations formed by conversion of solid state to liquid state, drug suspensions or drug solution in non-volatile solvents into dry, nonadherent, free-flowing and compressible powder mixtures by blending the suspension or solution with selected carriers and coating agents. The formed liquisolid tablets dosage form showed significantly greater extent of absorption due to their solubility and dissolution improvement. The technique is also used to design sustained release systems by using hydrophobic carriers instead of hydrophilic carries in liquisolid systems. Therefore, this formulation of the drug has the potential to be considered for human study in order to be manufactured on a large scale.

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