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Review Article

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Attempts and outcomes of liquisolid technology: An updated chronological compilation of innovative ideas and adjuvants in the field

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Abstract

It has been observed that most of the chemical entities have high lipophilicity and poor aqueous solubility, which result in poor bioavailability. In order to improve the bioavailability, the release behavior of such drugs should be improved. Although there are numerous techniques to handle solubility related issue, but they are expensive due to involvement of complicated equipments, advanced manufacturing operations that includes multiple and tedious steps. The liquisolid technology or powder solution technology is a promising technique for modifying the release characteristics of active pharmaceutical ingredients. As the liquisolid technology uses similar production processes as followed to develop a conventional tablet, but this technology to improve the release rate of poorly water soluble drugs is simple and cost effective The core concept of the technique involves, liquids such as solution/dispersion of poorly soluble drugs in a non-volatile solvent that is transformed into free flowing and desirable compression characteristics. To develop a fast-release liquisolid formulation, high amount of liquid vehicle is required while more effective tableting excipients with high liquid adsorption are needed to reduce the weight of the tablet. Simultaneously, this technology also has the capability to sustain the drug release and allow the development of sustained release formulation with desirable release kinetics. The present work deals with the chronological compilation and briefing of all the reported researches which involved the concept of underlined technology by the use of common as well as novel excipients to modify the release behavior of therapeutically active compounds.

Keywords: Liquisolid technology, non-volatile solvent, carrier material, coating material, dissolution enhancement, liquisolid compact, sustained release

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Introduction

The pharmaceutical goal of developing any oral dosage form is to carry most of the active pharmaceutical ingredient to the blood and if the dosage form is in solid state the primary concern falls on the solubility of the drug in GIT (1). Overall estimate reveals that around 40% of the developed molecules exhibit poor water solubility, which lead to poor bioavailability and high dropout rate from the drug discovery and development process (2). On the other hand about 15% of the drug-like compounds and 40% of lead optimization compounds are insoluble at a concentration less than or equal to 20µg/ml. Such drugs tend to get eliminated from the gastrointestinal tract before they get fully dissolved as well as absorbed into the systemic circulation (3).

The solubility/dissolution of a drug substance can be mainly altered at two different levels, through material engineering of the drug substance or through formulation approaches (4). Several methods had been employed to enhance the dissolution of the drugs having low solubility, such as - salt formation (5), cosolvancy (6), complexation (7), micronization (8), melt sonocrystallization (9-10), lyophilization (11), steam-aided granulation (12), solubilization by surfactants (13), solid solution (14), inclusion of drug solution in soft gelatin capsule (15), are some of the major formulation tools which have been shown to enhance the dissolution characteristics of water-insoluble drugs. On the other hand various approaches have been attempted to improve the bioavailability of

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drugs, that comprise, the use of adjuvant like piperine in case of curcumin (16), formulation of liposomes, development of drug nanoparticles, the use of drug phospholipid complex (17), fabrication of structural analogues of the drug (18). Apart from this other approaches investigated are the use of self micro emulsifying drug delivery systems (19), design of drug-loaded PLGA nanoparticles (20), nanoemulsion (21), co grinding (22) and co crystallization (23).

Albeit, the above mentioned techniques have been proved as a promising technique for the solubility enhancement, but simultaneously they also possess some practical limitations. Hygroscopicity increases as a compound is formulated into a salt leading to solubility problem (24-25). Drug dissolution through co-solvents may precipitate on dilution with aqueous media. Solubilization by use of surfactants and co-solvents results in liquid formulations that are generally undesirable for commercialization as well as patient compliance. Fine particle size may lead to aggregation and agglomeration due to increased surface energy, consequently increment in the attraction power of Vanderwaals force acting between non polar molecules (26). In case of solubilization through complexation, if the ratio of complexing agent and drug increase there is a probability of toxicity and if the complexing agent is of high molecular weight, it will increase the dose size. Furthermore, release of drug from complexing agent is also sometime a big deal. In case of micellar solubilization, it may have palatability problems and toxic effects, if the concentration of surfactant is more. There is a chance of interaction among preservatives and surfactant(s) used. On the other hand if we consider the case of solid dispersions, few solid dispersion based commercial formulations are available; because of their poor physical characteristic for the long term stability of the dosage form. If prepared by using PEG and PVP (soft and tacky mass), causes difficulty in handling especially in capsule filling and tablet making process. Dispersions prepared by melting technique may give rise to stability problem. Moreover, if will become environmental and safety concern if large quantity of organic solvents are used in the preparation of solid dispersion. However, there is an approach of solubility enhancement which utilizes the concept of converting the liquid drug or poorly water-soluble solid drug dissolved in a suitable non volatile solvent into a dry looking, non adherent, free flowing and acceptably compactable powder by its simple admixture with selected carrier and coating material by applying fewer processing steps.

The method was firstly developed by Spireas *et al.*, in 1998 and the technique is coined as "Liquisolid Technology" in which the process of drying and evaporation is not involved in the preparation of dosage form i.e. "Liquisolid Tablets" or "Liquisolid Compacts" (27). Here the drug is held within the solution even though it is in the tableted on encapsulated form (28), that is the reason the technique is also called as "Powder Solution Technology". Particles with high surface area and having high adsorption properties can be used as a carrier material to adsorb/ absorb sufficient volume of drug solution/ liquid medication. More the moisture in the carrier material more will be the adhesion and poor will be the flow of the powder. As shown in figure 1, coating material is needed to circumvent the surface and maintain the flowability of the liquisolid system in order to make formulation dry looking, free flowing and acceptable pharmaco-technical properties to obtain a perfectly compressible "LiquiSolid System".

Classification of liquisolid system

A) Based on the formulation of powdered drug in liquid vehicle, liquisolid system(s) are termed as – i) Powdered drug solutions, ii) Powdered drug suspensions, iii) Powdered drug emulsions and iv) Powdered liquid drugs. Since the non volatile solvents are used to provide the drug solution or suspension, the liquid vehicle does not evaporate and thus, the drug is carried within the liquid state which in turn is dispersed throughout the final product (29).

B) Based on the formulation technique used, liquisolid systems may be classified into two categories which include i) Liquisolid compacts and ii) Liquisolid Microsystems. The term 'Liquisolid Compacts" refers to immediate or sustained release tablets or capsules prepared, combined with the inclusion of appropriate adjuvant required for tableting or encapsulation, such as lubricants and for rapid or sustained release action, such as disintegrants or binders, respectively. The term 'Liquisolid Microsystems" refers to capsules prepared by combining the drug with carrier and coating materials, combined with inclusion of an additive eg. PVP in the liquid medication wherein the resulting unit

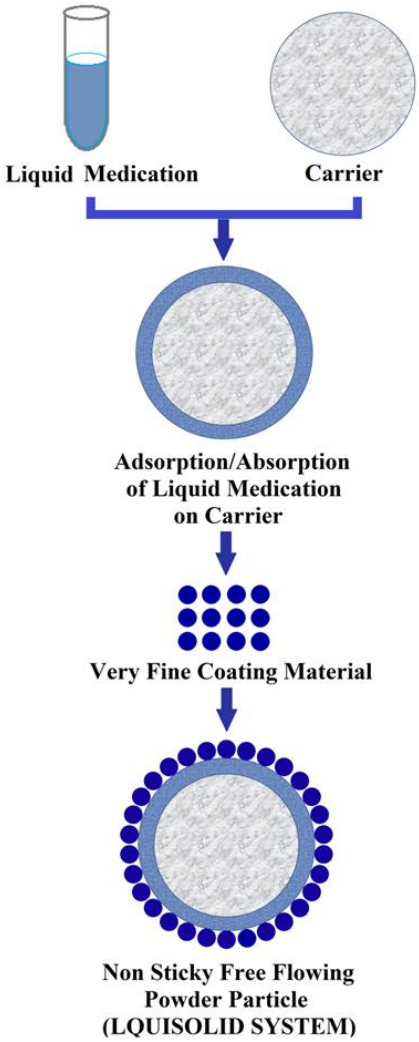

Figure 1 Core details involve in the development of liquisolid formulation

size may be as much as five times to that of liquisolid compacts (28).

Mechanisms of liquisolid technology

Three ways were proposed to increase dissolution of the drug from the liquisolid technology (27–28). Increased drug surface area is the first one. The drug within the liquisolid system is completely dissolved in the liquid vehicle and also located in the powder substrate still in a solubilized, molecularly dispersed state. Therefore, the surface area of drug available for release is much greater than that of drug particles within conventional tablets.

Secondly, sometimes the relatively small amount of liquid vehicle in a liquisolid compact is not sufficient to increase the overall solubility of the drug in the aqueous dissolution medium. However, at the solid/liquid interface between an individual liquisolid primary particle and the release medium, it is possible that the amount of liquid vehicle diffusing out of a single liquisolid particle together with the drug molecules might be sufficient to increase the aqueous solubility of the drug if the liquid vehicle acts as a co solvent.

The third approach will be due to the fact that the liquid vehicle can either act as surface active agent or has a low surface tension; wetting of the liquisolid primary particles is improved. Wettability of these systems has been demonstrated by measurement of contact angles.

Rationale of liquisolid system

The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and low medicine production costs. The bioavailability of poorly water soluble hydrophobic drugs (class II in biopharmaceutical classification system) is limited by their solubility and dissolution rate and for a drug to be absorbed into the systemic circulation following oral administration; the drug must be dissolved in the gastric fluids. The dissolution rate of these drugs can be improved by decreasing particle size, decreasing crystallinity, and/or increasing the surface area. Several studies have been carried out to increase the dissolution rate of drugs by decreasing the particle size, by creating nanoparticles and microparticles (29). Liquisolid technology evolved fulfilling all the necessary requirements for dissolution enhancement of poorly water soluble drugs. Mechanism behind enhanced solubility of insoluble drugs is expected to be increased wetting properties of drug particles by decreasing the interfacial tension between dissolution medium and the tablet surface (30) and increased surface area of the drug available for dissolution. Moreover, liquisolid technology had also been developed to formulate sustained release tablets successfully (31). Due to its simplicity, cost effectiveness and commercial viability with promising outcomes the technology has been exercised by numerous researchers. The objective of the present review is to briefly pen down all the research reports and compile in a chronological order, reported on various drugs to modify the solubility characteristics and pharmacokinetic behavior depending upon the excipients added.

Attempts and outcomes of technology: A chronological compilation

From initiation of the concept to 2007

As discussed above, initially the technique was adopted by Spireas and Sadu in the year 1998 when they formulated prednisolone as directly compressed tablets (DCT) and compared with liquisolid compacts (32). In the study, several liquisolid tablet formulations were prepared using a 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, compared to DCT. In the next consecutive year Spireas *et al.,* further explored the technology to study the effects on *in vitro* release properties of methyclothiazide (33). Liquisolid tablets of methyclothiazide containing a 5% w/w drug solution in polyethylene glycol 400 were assessed and compared to their commercial counterparts. It was observed that liquisolid tablets displayed significantly enhanced dissolution profiles compared to marketed products.

Further the technology was utilized by Khaled *et al.,* to evaluate the absorption characteristics of experimentally developed hydrochlorothiazide liquisolid tablets using six male beagle dogs (34). The drug was administered orally as a single dose (25mg) of commercial and liquisolid tablets, and pharmacokinetic parameters (post intravenous dosing) were reported for the first time. The results of the oral administration revealed statistically significant differences between the liquisolid and the commercial tablets in the AUC, C_{max} and the absolute bioavailability. On the other hand, no significant differences were observed between the two formulations with regard to the MRT, MAT, and K_a and the commonly expected intervals for bioequivalency, indicating greater bioavailability of the liquisolid tablets.

After the gap of four years Javadzadeh *et al.,* were exercised the technology to improve the dissolution rate of piroxicam (35). In the study, dissolution behaviour of piroxicam from liquisolid compacts was investigated in SGF, pH 1.2 and SIF, pH 7.2. Study involved the development of several liquisolid tablet formulations of piroxicam: tween 80 in different concentrations. The ratio of carrier i.e. microcrystalline cellulose (MCC) to coating material (silica) was kept constant in all formulations. The results showed that liquisolid compacts exhibited significantly higher drug release rates than conventional formulations (capsules and DCT). After exploring the technology for piroxicam, Javadzadeh *et al.* has further investigated the effect of technology on carbamazepine in the year 2007(30). In the study different liquisolid formulations of carbamazepine were prepared and loading factor was increased by adding PVP, HPMC and PEG 35000 to liquid medication. Liquisolid formulations containing PVP, exhibited higher dissolution rates in comparison

to DCT. An improvement in dissolution rate was observed with decreasing the ratio of MCC to silica from 20 to 10 while further decrease in the ratio of MCC: silica (10 to 5) resulted significant reduction in dissolution rate. On the other hand increased PVP concentration in liquid medication caused a dramatic increase in dissolution rate in initial 30min of dissolution.

Investigations reported in 2008

Another research on carabamazepine was come into lime light in 2008, with the object of improvement of dissolution rate of drug and to study the effect of enhanced dissolution on albino mice (36). In this study Avicel PH 102, and Aerosil 200 were used as the carrier and the coating materials, respectively, and explotab was used as disintegrant to prepare four tablet formulations. The dissolution patterns of liquisolid carmazepine tablets were comparable to Tegretol®. It has been observed that protection of male albino mice against the convulsion was lower in case of liquisolid tablets compared to Tegretol® suspension and tablets probably due to the precipitation of carbamazepine in the silica pores. A similar type of research was reported by El- Houssieny in the same year, in which repaglinide was selected to enhance the solubility using potentials of liquisolid technique (37). Famotidine, was also investigated *in vitro* and *in vivo* for the effect on dissolution and bioavailability using liquisolid technique in the same year (38). DSC and XRD simultaneously suggested the loss of drug crystallinity of upon liquisolid formulation which was further confirmed and validated by SEM that ensured the superiority of the technique. 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 $P < 0.05$.

In the similar year Javadzadeh *et al.* exposed another face of the coin by utilizing the liquisolid technique as a new approach to sustain propranolol hydrochloride release from tablet matrices (31). In the study, propranolol hydrochloride was dispersed in polysorbate 80 and a binary mixture of carrier–coating materials Eudragit RL or RS (carrier) and silica (coating material) was added to the liquid medication. Liquisolid tablets of propranolol HCl showed greater retardation properties in comparison with conventional matrix tablets. In continuation with numerous researchers, Gubbi and Jarag have also reported the use of liquisolid technique for enhancement of dissolution properties of bromhexine hydrochloride and compared with DCT (39). Different liquisolid formulations were developed using Avicel PH102 (carrier), Aerosil® 200 (coating material) and Explotab (disintegrant). It has been reported that the drug release rates of liquisolid formulations were distinctly higher as compared to DCT, which show significant effect of liquisolid technique on increasing the dissolution.

Factors affecting liquisolid system development

On analyzing the summarized reports mentioned above and reviewing the core phenomenon as well as the structural components of liquisolid technology – the initial step started with the absorption/ adsorption of liquid medication (solution of drug in selected nonvolatile solvent) into/onto the carrier material (Figure 2). The role of nonvolatile solvents in enhancement of dissolution behavior can be easily observed by analyzing the obtained dissolution data, but the burden of further increment in these pharmaceutical parameters, falls on nature and type of carrier material used. All the carrier material opted by numerous scientists were porous, highly hygroscopic and hydrophilic in nature. As a principle, liquid medication firstly gets adsorbed onto the surface of the carrier material, followed by absorption of adsorbed liquid medication through available pores that may result in disintegration of liquisolid formulation. On contact with dissolution media liquisolid formulation disintegrate rapidly due to faster wetting of the formulation and resulted in immediate collapse of the structure (40 – 41). Thus the process of dissolution can be attributed to the above discussed three mechanisms - (a) movement of dissolution media through pores of the carrier material, (b) movement of dissolution media by solubilisation of carrier material towards the core, and (c) dissolution/diffusion/transfer of dissolved drug molecules in the bulk (42).

According to Sharma & Pathak the increment in drug concentration in liquid portion resulted in amount of drug beyond the solubility limit, thus by decreasing the fraction of dissolved drug in non-volatile solvent the release rate decreases (43). Interestingly, a remarkable

Figure 2 Schematic representation and step wise details of liquisolid technology

difference in dissolution behavior of drug from liquisolid formulation was observed when compared to the saturation solubility of drug in nonvolatile solvents alone. This indicates that the drug release from liquisolid formulation is not only dependent on the solubility in the nonvolatile solvent albeit, there may be some other factors like physical or chemical interaction between drug, solvent used to prepare liquid medication, carrier as well as coating material that played a significant role in the enhancement of the dissolution. A similar explanation was also given by Abdou and his coworker which express that the rate of drug dissolution may be dependent on the physicochemical properties of the drug including-solubility and crystalline state such as polymorphism, state of hydration, solvation and complexation (44). But in case of liquisolid systems, the increase in surface area of the drug resulting from the adsorption on to the surface of carrier material plays a highly significant role.

Investigations reported in 2009

An investigation was carried out by Javadzadeh *et al.* in the year 2009 to study the effect of some commercial grades of MCC on flowability, compressibility, and dissolution profile of piroxicam liquisolid formulations

(45). For this means, several formulations were prepared using various grades of MCC as carrier. Propylene glycol (non volatile solvent), silica (coating material) and sodium starch glycolate (disintegrant) were used to develop the formulations. The results showed that among all the evaluated grades of MCC, formulations containing MCC PH 101 and 102 showed better tablet properties, while better flowability was observed with MCC PH 101. In continuation Yadav and Yadav have reported a study to improve the solubility and dissolution of indomethacin by liquisolid and compaction granulation technique (46). Indomethacin was dispersed in PEG 400, while MCC PH102 and dibasic calcium phosphate were used as carrier(s), HPMC as coating material and sodium starch glycolate and crosscarmellose sodium were used as disintegrants. Parallely granules were prepared by compaction technique with the same excipients excluding non volatile liquid vehicle (PEG 400). The obtained liquisolid system displayed enhanced solubility and *in vitro* dissolution profiles due to increased wetting property and surface of drug available for dissolution in comparison to granules obtained from compaction technique and physical mixture. In the same year the technology was also practicized by Tiong and Elkordy, who deals with the effects of liquisolid formulations on dissolution of naproxen (47). This study was designed to evaluate the effects of different formulation variables like type of non-volatile liquid vehicles and drug concentrations, on drug dissolution rates. The liquisolid tablets were formulated with three different liquid vehicles - Cremophor EL, Synperonic PE/L61 and PEG 400 at two different drug concentrations, 20%w/w and 40%w/w. In the study Avice PH102 was used as carrier, Cab-o-sil M-5 as a coating material and maize starch as a disintegrant. *In vitro* drug dissolution profiles were studied and compared with the DCT, in SGF, pH 1.2 and SIF, pH 7.2 in absence of enzyme. 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. Stability studies showed that the dissolution property of formulation prepared with Cremophor® EL was negligibly affected by aging; while DSC revealed that drug particles in liquisolid formulations were completely in solubilize state.

Investigations reported in 2010

The approach of liquisolid technology was also investigated for aceclofenac by Yadav *et al.*, in the year 2010 (48). The objectives of study were to formulate and evaluate orodispersible liquisolid compacts using various non volatile solvents and to study the effect of mode of superdisintegrant addition on rate of dissolution. Liquisolid compacts were prepared by dispersing aceclofenac in PG, PEG 400 and Tween 80, individually in a ratio of 1:1 to drug followed by the addition of diluents, superdisintegrants (Cross carmelose Sodium, Cross povidone and Sodium starch glycolate) in different ways and different combinations. It was observed that all the liquisolid compacts get rapidly disintegrated within 3min with enhanced dissolution properties over the DCT of aceclofenac. Among all developed formulations, liquisolid compact containing tween 80 along with cross carmelose sodium showed highest dissolution rate. Another study was carried out by Gubbi and his coworkers aiming the enhancement of atorvastatin calcium by application of the liquisolid technique (49). Avicel PH102, Aerosil® 200 and Explotab were employed as carrier, coating material and disintegrant, respectively. On analysis XRPD study confirmed the formation of a solid solution inside the compact matrix. The liquisolid compact demonstrated better dissolution and bioavailability compared with the DCT of atorvastatin calcium. During similar span of time a research was reported by Pardhi *et al.*, in which the *in vitro* dissolution property of carvedilol was improved by exploring the potential of liquisolid system (50). Avicel PH102, Aerosil 200 and sodium starch glycolate were employed as carrier, coating material and disintegrant, respectively. It was reported that the drug release rates of liquisolid compacts were distinctly higher as compared to DCT that showed significant benefit of iquisolid compact in increasing wetting properties and surface area of drug available for dissolution.

Another research was reported by Akinlade *et al.* that deal with the development of liquisolid systems to improve the dissolution of furosemide exploring some novel excipients in the area of liquisolid technology (51). Several liquisolid formulations were prepared using Avicel PH101 and Cab-O-Sil® M-5 as carrier and coating materials, respectively.

Polyoxyethylene- polyoxypropylene-polyoxyethylene block copolymer; 1, 2, 3-propanetriol, homopolymer, (9Z) – 9 - octadecenoate and PEG 400 were used as non- volatile water-miscible liquid vehicles (Table 1). Results showed that all the developed formulations containing Synperonic® PE/L 81 exhibited higher drug release in water (pH 6.4 – 6.6) as compared to acidic pH (pH 1.2).

While on the other hand formulations containing PEG 400 displayed lower drug release, in comparison to conventional tablets. In the subsequent research Emmadi *et al.*, has utilized the potentials of liquisolid technology to improve the meloxicam dissolution rate followed by the evaluation of *in vitro* and *in vivo* performance (52).

Table 1 List of various non volatile solvents used to prepare liquid medication for development of suitable liquisolid formulation(s)

No	Non volatile solvent	Trade name	References
1.	Glycerine	Glycerol	(27, 61, 64)
2.	Olive oil	----	(102)
3.	Soyabean Oil	----	(102)
4.	Propane-1,2-diol	Propylene Glycol	(36, 38, 39, 49, 79)
5.	Poly *(ethylene glycol)*	PEG	(64, 103 – 104)
6.	*Poly(ethylene glycol) 200*	PEG 200	(30, 34, 60)
7.	*Poly(ethylene glycol) 300*	PEG 300	(105)
8.	*Poly(ethylene glycol) 400*	PEG 400	(33, 39, 49, 71, 106 – 107)
9.	*Poly(ethylene glycol) 600*	PEG 600	(84, 108 – 109)
10.	Polysorbate 20	Tween 20	(110)
11.	Polysorbate 40	Tween 40	(110)
12.	Polysorbate 60	Tween 60	(110)
13.	Polysorbate 80	Tween 80	(80, 82, 84, 103 – 104, 110-112)
14.	Poloxamer 181	Synperonic® PE/L 61	(47)
15.	Polyoxyethylene-polyoxypropylene block copolymer	Synperonic® PE/L 81	(51)
16.	Polyoxyl 35 castor oil	Cremophor® EL	(47)
17.	N,N-dimethylacetamide	----	(113)
18.	Propylene glycol monocaprylate	Capryol™ 90	(85)
19.	Polyethylene glycol (15)-hydroxystearate	Solutol® HS-15	(85)
20.	Polyvinyl acetate stabilized with polyvinyl pyrrolidone and sodium lauryl sulfate	Kollicoat® SR 30 D	(85)
21.	Propylene glycol monolaurate (type 1)	Lauroglycol® FCC	(114)
22.	Glyceryl monolinoleate	Maisine® 35-1	(114)
23.	PEG-35 castor oil	Kolliphor® EL	(114)
24.	Diethylene glycol monoethyl ether	Transcutol® HP	(82)
25.	Capryl capryol polyoxy glycerides	Labrasol®	(82)
26.	1,2,3-propanetriol homopolymer (9Z)-9-octadecenoate	Caprol® PGE-860	(51)
27.	Castor Oil Derivative	Acrysol® EL 135	(65)
28.	Liquid Paraffin	----	(98)

The possible interaction between meloxicam and excipients was studied by DSC and XRD, which revealed that there was a loss of drug crystallinity and exist in molecularly dispersed state, which contributed to the enhanced drug dissolution. After *in vivo* evaluation, analgesic and anti inflammatory response of optimized liquisolid compact in Swiss albino mice and Wistar rats was found to be superior compared to the marketed formulation.

The next study (53) was an extension of the previous work reported by El-Houssieny *et al.* (37). Repaglinide containing optimized liquisolid formulation was orally administered to rabbits and and compare with marketed tablets (Novonorm® 2mg). Oral glucose tolerance tests (OGTT), area under the curve (AUC) and insulin levels were studied along with the efficacy and safety of new formula. The blood glucose level, insulin, kidney and liver function was also studied using different dose of the drug (0.5, 1, and 2mg). Researchers reported that the relative bioavailability of repaglinide from liquisolid compact was found to be increased significantly in comparison to that of the Novonorm®. The commercial formula increased insulin levels upto 3.52% (insignificant) while the liquisolid formulation increased the insulin level significantly with a percent change of 37.6%. Glucose tolerance test showed that the blood glucose level was decreased significantly after the administration of commercial formulation (18.1%) while in groups treated with the new formulation the decrease in levels was highly significant ($p < 0.01$) with a percent change of 29.98%.

In continuation, the next study was aimed to improve the dissolution properties of rofecoxib. The dissolution studies of rofecoxib liquisolid tablets were carried out and compared with commercial product. The researchers reported that the formulated liquisolid systems exhibited significant enhancement of the dissolution profiles as compared to commercial product (54).

Nokhodchi *et al.*, has also developed a sustain release matrix tablet using liquisolid technology (55). The tablets were prepared with silica–Eudragit RL or RS followed by the compaction of the mixture. The effect of the type of non volatile solvent and the concentration of HPMC on drug release was investigated. A comparative study of liquisolid tablets and conventional tablets showed that most of liquisolid formulations were better in terms sustainment of drug release and it was revealed that by changing the type of cosolvent the desirable release profile can be achieved to produce zero-order release kinetics for less water soluble drugs such as theophylline.

Basis of excipients selection

As discussed earlier the major concern of the technology deals with the selection of suitable carrier and coating material which is mainly responsible for loading of liquid medication. The liquid medication, which can be a liquid drug in its original form, a drug suspension in a solvent, or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material (Figure 1). Once the carrier is saturated with liquid, a liquid layer is start forming on the surface of the particle that resulted in a moist/sticky blend. On addition of the dry coating material which physically exist in a very fine powder, instantly adsorb/absorb the fine layer of the drug solution over the carrier particle (56) and thus, a dry looking, free flowing, and compressible powder is obtained (Figure 2). As mentioned in previously discussed studies, various forms of microcrystalline cellulose (MCC/ Avicel PH101/ Avicel PH102) are used as carrier material and amorphous silicon dioxide is used as the coating material in most of the cases (Table 2). Application of liquisolid technique to poorly water soluble drugs; containing a drug solution/suspension in a suitable non volatile vehicle provide enhanced drug release due to increased surface area of the drug, that lead to increased solubility and improved wettability of the drug particles (57). The liquisolid technology may also be used to prolong drug release (58). According to the principle, sustained release dosage form leads to desirable therapeutic plasma levels which are maintained throughout the therapy. It has been reported that by using hydrophobic carriers such as Eudragit® RL and RS instead of hydrophilic carriers or by addition of a matrix forming polymer such as HPMC, sustained release formulations can be developed. The enhancement in solubility/release characteristics has been successfully applied to low dose poorly soluble drugs by liquisolid technology (32 – 33) however, the technology is limited for the formulation of high dose poorly soluble drug. Defining the core concept of the technology the rate of drug release is directly

Table 2 Pharmacotechnical details of various carrier/coating materials used in liquisolid technology

No.	Common name	Trade name	Synonym/ INCI names	Particle size (µm)	Bulk density (g/c.c.)	Application in liquisolid technology	Approximate specific surface area [BET (m^2/g)]
1.	Microcrystalline cellulose	Avicel® Avicel® PH101 Avicel® PH102 Avicel® PH105 Avicel® PH200	MCC, Cellulose gel	50 50 100 20 180	0.26 – 0.31 0.26 – 0.31 0.28 – 0.33 0.20 – 0.30 0.29 – 0.36	Carrier	1.00 1.07 1.10 0.90 0.41
2.	Spherically granulated dicalcium phosphate anhydrous	Fujicalin®	DCPA	115	0.46	Carrier	36 - 42
3.	Calcium silicate	Florite®	Calcium metasilicate, calcium silicon oxide, silicon calcium oxide	75	0.16 – 0.22	Carrier	142 – 149
4.	Amoprhous magnesium alumino metasilicate	Neusilin®	Fine ultra light granule of magnesium aluminometasilicate	60 - 120	0.15 - 0.33	Carrier	300
5.	Colloidal silica	Aerosil®200	Hydrophilic fumed silica	12 -30nm	0.30	Coating material	200 -225
6.	Copolymer of ethylacrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium group	Eudragit RL Eudragit RS	Acrylates, Ammonium methacrylate copolymer	At least 90% < 0.30	0.42 0.50	Carrier, Release retardant	340 415
7.	Fumed silica	Cab-o-Sil M-5	Hydrophilic fumed silica, untreated fumed silica	0.2 – 0.3	3.0 lb/ft^3	Coating material	175 – 225
8.	Insoluble polyvinyl pyrrolidone	Kollidon® CL SF	Crospovidone	10-30	0.10 – 0.16	Coating material, Superdisintegrant, Release retardant	3

Continue...

9.	Hydroxy propyl methyl cellulose	HPMC-E15 HPMC-E4M HPMC K100M	---- ---- ----	80-100 80-100 80-100	0.16 0.20 0.42	Carrier, Coating material, Release retardant	240 280 220
14.	Magnesium carbonate	Destab	Carbonic acid (magnesium salt)	7 - 43	0.207–0.56	Carrier	18.2
15.	Sodium starch glycolate	Explotab	Primojel	<106	0.81	Superdisintegrant	0.185
17.	linked Cross-sodium carbo xymethyl cellulose	Croscarmellose Sodium	Akucell	85	0.52	Superdisintegrant	140
19.	Lactose	Spray dried lactose	Lactopress spray dried	32	0.57 – 0.62	Carrier	240
20.	D-Glucitol	Sorbitol	Sorbitab	<125	0.448	Hydrophilic material, Sweetening agent	0.220
21.	Starch	Amidon	Melojel	2 - 32	0.45 – 0.58	Carrier, Disintegrant	0.40–0.54

proportional to the fraction of molecularly dispersed drug in the non volatile solvent (27, 32). Thus, a higher drug dose requires a large volume of non volatile solvent to obtain a faster drug release. As a definite amount of powder can adsorb/absorb a limited volume of non volatile solvent maintaining acceptable flow and compression properties, high amounts of carrier and coating materials are needed in case of large volume of liquid medication. This result in increase in tablet weight ultimately leads to formation of bulky tablet. So a primary requirement is to minimize tablet weight and to increase the liquid adsorption capacity either by adding binding agents to the liquid medication or by using a carrier and coating material(s) with a high specific surface area (SSA). Higher the SSA of the carrier, higher will be the liquid load factor. It has been reported that the liquid adsorption capacity of the experimental grade granular cellulose that exhibit the SSA of 24.22 m^2/g is higher than that of microcrystalline cellulose (Table 2); Avicel PH102 (SSA = 1.10 m^2/g) and Avicel PH 101 (SSA = 1.07 m^2/g) which have been frequently used in studies (56). This is to be highlighted that the physicochemical characteristics (polarity, viscosity, chemical structure and lipophilicity) of the liquid used for solubilizing/suspending the drug cannot be ignored that could also affect the adsorption capacity of the carrier and coating materials. Consequently, the liquid adsorption capacity of a blend of carrier and coating material is not only dependent on their SSA, but also dependent on the respective non volatile solvent used (36).

Investigations reported in 2011

A study has been carried out by Hentzschel *et al.*, to investigate some novel porous tableting excipients with a high SSA with regard to their capacity of liquid adsorption while maintaining acceptable flow and tableting properties (59). Liquisolid compacts containing the liquid drug tocopherol acetate (TA) and various excipients were developed. The effect of liquid drug content on the flowability and compression characteristics of the liquisolid powder blends was investigated. It has been traced out that the liquid adsorption capacity of the blend is dependent on the SSA of the excipients used. Fujicalin® and especially

Neusilin® are more effective carrier materials in terms of liquid adsorption capacity in comparison to Avicel®, which is frequently used carrier for liquisolid systems. Moreover, Florite® and Neusilin® turned out to be more efficient coating materials than the commonly used Aerosil® due to better tableting properties. The finding of the research suggested that if Neusilin® is used as carrier and coating material instead of Avicel® (carrier material) and Aerosil® (coating material), the tocopherol acetate adsorption capacity is increased by a factor of 7. The technique was further applied by Mahajan *et al.*, aimed to prepare immediate release liquisolid tablets of glipizide (60) using Avicel PH102 and Aerosil® 200 and to evaluate treated gellan gum as disintegrant to increase dissolution rate of glipizide. The dissolution patterns of glipizide liquisolid tablets were compared with their commercial counterparts which revealed that all the glipizide liquisolid tablets exhibits higher dissolution rates in comparison to marketed tablets. It was found that dissolution rates increases with increase in the concentration of non volatile solvent, while maximum drug release was achieved by formulations containing polyethylene glycol 400 (PEG 400).

A well known water insoluble drug indomethacin was also investigated by Saeedi *et al.* for enhancement of dissolution rate (61). The results showed that the liquisolid formulations exhibited significantly higher drug dissolution rates in comparison to DCT. It was reported that enhanced dissolution rate of indomethacin through liquisolid tablets was probably due to increase in the wetting properties and surface area of drug particles available for dissolution which indicated that, the fraction of molecularly dispersed drug (*FM*) in the liquid medication of liquisolid systems was directly proportional to the indomethacin dissolution rate (*DR*). Another research was carried out by Kasture *et al.*, who investigated lansoprazole (62), which shows high inter-subject variation of bioavailability and the rate of its oral absorption is often controlled by the dissolution rate in the intestine. On detail analysis researchers concluded that the enhanced drug release profiles was due to increased wetting properties and surface of drug available for dissolution obtained in case of liquisolid tablets. Boghra *et al.*, has also exercised the technology for improvement of the dissolution and bioavailability of simvastatin (63). The liquisolid tablets of simvastatin were prepared by using various ratio of Avicel PH102 to Cab-O-Sil M5 using PEG 400 as non volatile solvent. The dissolution profile of simvastatin tablets were determined and compared with a commercial product. Liquisolid tablets showed more than 90% release within 45 minutes.

In the similar year Lakshmi *et al.*, has attempted a research with the aim of increasing the solubility of a poorly water soluble drug, valsartan (64). Two techniques namely liquisolid technology and solid dispersion by kneading method were parallely used to enhance the solubility. Liquisolid compacts prepared by non volatile solvents (PG, PEG and glycerine) exhibited maximum release in case of the formulations prepared by using PG among all the batches. Solid dispersion by kneading method was another approach attempted to improve the solubility using PVP K 30, PEG 6000 and mannitol as carrier in different ratio(s). The dissolution rate of drug using solid dispersion kneading method with mannitol was found maximun in a ratio of 1:3. It was concluded that the liquisolid compacts were superior in enhancing the solubility of valsartan as compared to traditional solid dispersions.

A similar pattern for selection and comparison of various excipients had been followed by Siloji *et al.* for the formulation and comparative evaluation of telmisartan liquisolid compacts (65). Liquisolid technology and solid dispersion by fusion method were simultaneously utilized for solubility enhancement. Liquisolid compacts were prepared individually by using tween 80, transcutol HP, Acrysol EL 135 and PEG 400 as non volatile solvent. Avicel PH102, spray dried lactose were used as carrier and Aerosil® 200 as a coating materials. Results showed that the dissolution rate of the telmisartan was increased in transcutol HP containing formulation. On comparison liquisolids system were found better in terms of drug release than the solid dispersion prepared with poloxamer 407 as a hydrophilic carrier.

Investigations reported in 2012

In the next research two different groups of researchers parallely explored the potentials of liquisolid technology for the drug griseofulvin in year 2012 (66 – 67). The investigation carried out by Hentzschel *et al.*, deals with the use of potential of hydrophilic aerogel formulations and liquisolid systems to improve the

release of griseofulvin, as model drug. The *in vitro* release rate of this drug formulated as directly compressed tablets containing crystalline griseofulvin was compared to aerogel tablets with the drug adsorbed onto hydrophilic silica aerogel and to liquisolid compacts containing the drug dissolved in PEG 300. The conventionally used carrier and coating materials in liquisolid systems Avicel® (carrier) and Aerosil® (coating material) were replaced with Neusilin®, an amorphous magnesium aluminometasilicate with high specific surface area (Table 2) to potentiate the adsorption of liquid medication. Comparative analysis showed that the aerogel tablets exhibited faster drug release than DCT, while in case of liquisolid compacts the release rate increased with increased fraction of dissolved drug in the non volatile solvents. It could be shown that Neusilin® with its sevenfold higher liquid adsorption capacity than the traditional excipients produced liquisolid tablets remarkably of lower weights.

Elkordy and his coworkers explored the technique for enhancement as well as for the sustainment of hydrophobic drug, griseofulvin (67). Fast dissolving tablets were prepared using three different non-ionic surfactants (Cremophor® EL, Synperonic® PE/L61 and Capryol TM 90), on the contrary Kollicoat®SR 30D was used for the development of SR tablets of grieseofulvin. Avicel® PH102 and Cab-O-Sil® M5 were used as carrier and coating materials, respectively. *In vitro* evaluation of all the fast release liquisolid formulations showed higher percentage drug dissolution efficiency (%DE) than conventional directly compacted tablets. Among all the fast release liquisolid tablets, formulations which contain Cremophor® EL showed the best dissolution enhancement with %DE of 90%, in comparison to conventional tablets (23%); DSC thermograms suggested the loss of griseofulvin crystallinity. On the contrary Kollicoat® SR 30D retarded the drug release even in the presence of hydrophilic carrier and the obtained DSC thermograms reveals that only small fraction of the drug was present in the molecular state within the system, consequently exhibited sustained release of gresiofulvin.

As reported by Elkordy *et al.*, for the release retardation of gresiofulvin using different non volatile solvent (67), the approach of sustaining the drug release using the concept of liquisolid technique was also attempted by Elkhodairy *et al.* for diltiazem hydrochloride using release retarding polymers (68). Ethyl cellulose, HPMC and Sterotex were used separately in the study as release retardants in the first method of preparation and as carriers in the second method. The second method involved the addition of the carrier-coating materials to the liquid medication prepared using PG under continuous stirring, while in the third method blending of dispersed medication in Tween 20 to the mixture of carrier and coating materials was done. Formulations containing HPMC prepared by the different techniques showed promising retardation of the drug, followed by formulations containing EC, while Sterotex showed the least release-retardation effect. In the same year, Thadkala *et al.* investigated nimesulide for enhancement of dissolution characteristics (69). Several liquisolid tablets formulations were prepared using PEG-400 as non volatile solvent, MCC, HPMC-E15 and starch were used as carrier(s) and nano sized silica gel was used as coating materials. It was found that formulated liquisolid tablets were superior in terms of drug release rate in comparison to compressed tablets, while formulation containing MCC exhibited highest dissolution among all the developed liquisolid tablets. Parallely another group of researchers have also attempted a research on nimesulide by applying liquisolid technology (70). The researchers observed enhancement of dissolution rate, absorption efficiency and bioavailability of nimesulide. Nimesulide liquisolid tablets were prepared by using PEG-400 as liquid vehicle; MCC, HPMC-E15 and starch were used as carriers and silica gel as coating material in different ratios.

As published by Pardhi *et al.*, in the year 2010 (50), one more research was published on the same drug (carvediol) in the year 2012, by Burra and Reddy (71). During formulation the hardness of the formulation was achieved by changing the ratio of Avicel® PH200 and Aerosil® from 20:1 to 5:1. Developed liquisolid formulations exhibited higher dissolution rates in the range of 90-99.9%, when compared to commercial product (CARCA®12.5 mg) within 20min. DSC and XRD confirmed the amorphization of the crystalline drug, and the transition occurs because the drug is in solution form. As of other drugs sodium salt of diclofenac was also considered for enhancement of solubility by Vajir *et al.* (72). Several formulations of

liquisolid compacts with different drug concentrations (40% to 60% w/w) and different R values (5 to 15) were prepared using Avicel® and Aerosil® as carrier and coating material and propylene glycol was used as a nonvolatile solvent. Liquisolid compacts demonstrated significantly higher drug release rates than the pure drug.

To set up a new trend in the field of development of liquisolid compacts, statistical approach was utilized by Vittal and his coworker for formulation and optimization of ketoprofen liquisolid compacts by Box Behnken Design (73). On evaluation optimized formulation yielded the response values, which were found very close to the predicted values, which proved that statistical approach is a useful tool for development and optimization of liquisolid formulations. In the next research El-Hammadi and Awad had proposed a study with a hypothesis that formulation of loratadine using liquisolid compacts technique may reduce the effect of pH on drug dissolution behavior (74). Several liquisolid tablet formulations containing various concentrations of drug in propylene glycol (5%, 10%, and 20% w/w) were prepared. The dissolution behavior of loratadine from liquisolid compacts was investigated in various dissolution media at different pH (pH 1.2, 2.5, and 5). The results showed that the drug release rates produced by liquisolid compacts were significantly higher and less affected by pH variation compared with DCT and commercial (Clarityn®) tablets.

To contribute the efforts in same field, a group of researchers have developed liquisolid compacts of nifedipine (75). Different formulations were prepared by using PEG-400 and PG, MCC and Aerosil and characterized for different quality control tests to comply with pharmacopoeial limits. It was found that liquisolid tablets exhibited significantly higher drug release rates than conventional tablets and PEG 400 was found to be better in comparison to PG for enhancing the dissolution rate. Chella and his team mates have reported a research on improvement of dissolution rate of valsartan (76). Initially liquisolid compacts were prepared using PG as non volatile solvent, Avicel PH102 as carrier and Aerosil 200 as the coating material. On analyzing the dissolution data it was found that the dissolution efficiency of valsartan at 15min was increased from 4.02% (pure valsartan) and 13.58% (commercial product) to 29.47% exhibited by liquisolid formulation. Another research was carried by Singh and his team mates, with the aim to investigate the use of liquisolid technique in improving the dissolution of glyburide (77). The stability studies showed no effect of ageing significantly, as f_2 value found between aged and fresh samples was 51.92. The liquisolid tablets prepared with PVP showed a remarkably improved dissolution rate in comparison with DCT and other formulations.

Investigations reported in 2013

In the next consecutive year Kankudte et al., have developed liquisolid tablets in order to study, the potential of liquisolid systems to improve the dissolution properties aceclofenac (78). The *in vitro* release pattern of liquisolid tablets and DCT were studied using USP-II apparatus. Different liquisolid tablets were prepared using Avicel PH102, Aerosil 200 and sodium starch glycolate were as carrier, coating material and disintegrant, respectively. Liquisolid tablets demonstrated significantly higher drug release rates in dissolution media compared to DCT. This was due to an increase in wetting properties and surface of drug available for dissolution.

Kaur *et al.*, have investigate the drug for enhancement in dissolution property and bioavailability (79) of amlodipine. In the study PG, Avicel PH – 101 and Aerosil was used to develop the formulations. On detail analysis it was reported that the enhancement in dissolution rate of amlodipine was observed due to significant reduction in crystallinity. Another research was carried out by Sayyad *et al.*, (80) on candesartan cilexetil, an angiotensin-II receptor antagonist used for the treatment of hypertension, having the half life of 5.1h with 15-40% bioavailability. The liquisolid tablets were formulated using Tween 80, MCC and silica along with sodium starch glycolate used as a superdisintegrant. 3^2 full factorial design was utilized to formulate various liquisolid powder systems. All prepared liquisolid formulations were showed higher drug dissolution than the conventional, DCT. Another research deals with the aim of improving the dissolution properties of Efaverinz by liquisolid technique was reported by Bodakunta *et al.* (81). *In vitro* drug release showed a good increment in dissolution rate of Efaverinz. Researchers concluded that PEG 400, PG,

Tween 80 could be economic substitutes for dissolution enhancement.

Khanfar and his team mates have reported an investigation on formulation factors affecting the release of ezetimibe from different liquisolid compacts (82). All liquisolid compacts had expressed faster dissolution profiles compared with that of conventional formula. It was concluded that the dissolution rate was affected by the drug concentration, solubility of the drug in the liquid vehicle and type of carrier. In addition, the presence of the liquid vehicle has been found to affect the mechanical properties of the liquisolid formulations also.

In the same year Kumar *et al.*, have developed the liquisolid extended release formulations of mefenamic acid using HPMC K100M as release retardant, while Avicel PH102 and Aerosil® 200 were employed as carrier and coating materials (83). From the results it was concluded that the formulations which contain higher amount of Aerosil® 200 and HPMC K100M showed better release retardation as compared to other formulations containing less concentrations. Further, Kapure *et al.* has presented their research on solubility enhancement of rosuvastatin calcium by formulation of liquisolid compacts which was studied for *in vitro* release characteristics at different dissolution conditions and compared with DCT (84). In year 2013 Elkordy *et al.* have attempted another research on spironolactone release from liquisolid formulations (85). In the study three non-volatile liquids Capryol™ 90, Synperonic® PE/L61 in combination with Solutol® HS-15 at a ratio of 1:1, and Kollicoat® SR 30 D were used. Liquisolid powder formulations formulated with a combination of Synperonic® PE/L61–Solutol®HS-15 showed highest dissolution characteristics. In another research trimetazidine di hydrochloride a water soluble drug, was investigated by Pavani *et al.*, by dispersing in polsorbate-80. Binary mixtures of carrier (Ethyl cellulose, Eudragit L-100 and RS-100) and aerosil as coating material was individually added to the liquid medication under continuous stirring (86). Trimetazidine di hydrochloride tablets prepared by liquisolid technique showed statistically significant difference ($p < 0.05$) in drug retardation, when compared with marketed tablets.

Investigations reported in 2014

Sanka *et al.*, has also explored the technology in 2014 and attempted to improve the oral delivery of BCS class II drug clonazepam (87) by formulating into a novel liquisolid powder compacts (LSPCs). The LSPCs were formulated using PG as non volatile solvent. LSPCs of clonazepam formulated with PG at optimum drug concentration produced high dissolution profile with acceptable tablet properties. DSC and XRD indicated conversion of crystalline to amorphous form of the clonazepam. Further the permeation studies carried out in isolated rat intestine revealed that potential of LSPCs for enhanced permeation of clonazepam across rat intestinal barrier. The similar changes in dissolution behavior was also observed by Reddy *et al.*, who have tested the technology for candesartan liquisolid tablets prepared by using PEG -400 and PG as non volatile liquid vehicles along with Avicel PH102, Aerosil 200 as carrier and coating materials, croscarmellose sodium as super disintegrant (88).

Furthermore, Adibkia and his co-worker (89), investigated the effect of type of solvent on release behavior of diltiazem hydrochloride. The results showed that diltiazem HCl had lowest solubility in polysorbate 20 while the highest amount was devoted to polysorbate 80 and PG. It was recorded that the type of nonvolatile solvent and its physicochemical characteristics as well as solubility of the drug in the applied solvent have an important role on the drug release behavior liquisolid compacts. Jyothi *et al.* had enhanced the dissolution rate of glyburide by preparing different formulations using different vehicles and carriers and aerosil as coating material (90). *In vitro* dissolution profiles of the liquisolid formulations were studied and compared with conventional formulation in 0.1N HCl. It was found that liquisolid tablets formulated with PEG 400 and Avicel PH102 produced high dissolution profile and showed significantly higher drug release rates than conventional tablets. In the same year two different teams of researchers have attempted the technology by development of fast dissolving tablets of lamotrigine (91 - 92), and exhibited better *in vitro* dissolution profile of in comparison to marketed one. The *in vitro* dissolution property of lornoxicam was also improved by exploring the potential of liquisolid technology using two non solvents, by Srivastava *et al.* (93). Different compacts were prepared using Avicel PH102, Aerosil 200 and Explotab, PEG 400 and PG were employed as carrier, coating material, disintegrant and non volatile solvent respectively. The *in vitro* release pattern of LS

compacts and DCT were studied and the drug release rates of LS compacts were found distinctly higher as compared to DCT, which show significant benefit of LS in increasing wetting properties and surface area of drug available for dissolution.

In continuation to other researchers Iizhar and Bhavani, had studied the effect of excipients dissolution of liquisolid compacts of nateglinide (94). The results indicate that liquisolid based tablets showed greater disintegration and dissolution rate. It might be due to the presence of PEG-400 as it showed the enhancement in the solubility of nateglinide. In the next research Manish *et al.*, had developed liquisolid formulations of poorly water soluble drug nilvadipine (95). Liquisolid formulations showed better flowability, compressibility, improved solubility and dissolution behavior as well as rapid disintegration was observed compared to conventional tablets. The use of non-volatile solvent in the formulation causes increased wettability of water insoluble drugs and ensures molecular dispersion of drug in the formulation. Further Suliman *et al.*, had attempted a research in which norfloxacin was selected as a model hydrophobic drug which showed the unique drug release pattern from liquisolid formulations prepared with PEG 200 and Synperonic PE/L-61as non-volatile liquid vehicles (96). The dissolution profiles were evaluated and compared to counterpart conventional norfloxacin tablets. The results indicated that the percentage of norfloxacin release in acetate buffer, pH 4.0 is higher than in distilled water. Moreover, Synperonic PE/L-61 liquisolid tablets showed higher dissolution profiles than PEG 200 liquisolid tablets, although the solubility of norfloxacin in PEG 200 was much higher than in Synperonic PE/L-61. Srinivas *et al.* had also improved the solubility and dissolution rate of piroxicam by using liquisolid technique (97). Solubility is increased by using non-volatile solvents such as PEG 400, Labrosol, Span 20 and Tween 80 individually and in combination followed by blending with MCC and Aerosil.

Investigation reported in 2015

Pathuri *et al.*, have prepared the liquisolid compacts of amlodipine besylate having improved solubility and the dissolution profile (98). The amlodipine loaded liquid-solid compacts were developed using various grades of MCC (PH101, PH102, PH 200) as carrier, Aerosil as coating material and PG, Tween 80, PEG 400, Liquid paraffin as non-volatile solvents. The formulation shows %CDR of approximate 98% which was greater than marketed conventional tablets of amlodipine besylate (83%). On the other hand Ansari *et al.*, attempted dissolution enhancement of domperidone maleate by preparing fast dissolving tablets using liquisolid technique (99). The purpose of the investigation was to increase the solubility and dissolution rate of domperidone maleate by applying combination approach of liquisolid compacts and fast dissolving tablets by direct compression method. Superdisinegrants used were crospovidone, croscarmellose sodium and sodium starch glycolate, while PG, PEG 200 & 400 were used as liquid vehicles and Avicel PH 102, Aerosil-200 as a carrier and coating material, respectively. Developed formulations showed 95.5 % drug release within 30 min. In the next research (100) liquisolid technique and solid dispersion formation two approaches have been utilized for enhancement of dissolution rate of hydrochlorothiazide. Three formulations of hydrochlorothiazide were prepared by liquisolid technique using MCC as carrier and Aerosil as coating material along with water, PEG 400 and Tween 60 were used as non volatile solvents. Solid dispersions of hydrochlorothiazide were prepared by solvent fusion method using PEG-4000 as carrier polymer. The results obtained indicated that liquisolid compact formulations were more effective in terms of enhance dissolution rate compared with solid dispersion technique.

Current reports on liquisolid technology

In 2016 a study was conducted by Pezzini *et al.*, on feasibility of liquisolid pellets of felodipine (101). The effects of Kollidon®CL-SF as a coating and disintegrating material and the type of non-volatile solvent, PEG 400 or Cremophor®EL, was analyzed on dissolution behavior. Results showed Cremophor®EL was found more effective in comparison to PEG 400 due to the formation of softer and more porous structures. The amount of Kollidon®CL-SF also showed remarkable positive effect on the drug dissolution characteristics. The study consists of an innovation and expansion of the current liquisolid technology since the literature did not describe so far the development of liquisolid pellets and the use of

Kollidon®CL-SF as a coating material in liquisolid formulations.

Recently a research has been reported by Sharma and Pathak who investigated the molecular mechanism involved in solubility and bioavailability enhancement of curcumin (43). Drug loaded liquisolid systems were prepared using different vehicles (PEG 200, PEG 400 and Tween 80) at different concentrations in vehicle (40, 50, 60 and 70% w/w). The carrier (MCC PH102) to coat (Aerosil®) ratio was 20 in all formulations. It was found that LTs exhibited higher %CDR than the DCT. To assess the mechanism of enhanced solubility the optimized formulation was characterized by XRD, DSC, SEM and FTIR. In depth analysis revealed the formation of new strong hydrogen bonds because of the chemical interaction among curcumin, MCC PH102 and Aerosil®. The mechanism has been established that the newly formed strong hydrogen bonds were responsible for the cleavage of weaker hydrogen bonds that played an important role in enhancing the solubility/release of drug. *Ex-vivo* permeation of curcumin liquisolid tablet through goat gastrointestinal mucosa was significantly ($P < 0.05$) enhanced and its oral bioavailability was increased 18.6-fold in New Zealand rabbits. *In vitro* cytotoxicity (IC_{50}) of optimized formulation towards NCL 87 cancer cells substantiating its anticancer efficacy.

As noticed the underlined technique is a potential alternative for formulation of water-insoluble as well as water soluble drugs. Summarized reports revealed that enhanced rate of drug dissolution from liquisolid tablets is mainly due to increase in wetting properties and surface area of drug particles obtainable for dissolution. By this technique, sustained drug delivery systems were also developed for the water soluble drugs in which hydrophobic non-volatile solvents are used as vehicles with suitable coating material. Thus, a constant plasma level will be acheived, which is maintained throughout the dosing interval.

Conclusion

The review discussed the advantages of the liquisolid technology in formulation of poorly water soluble drugs with enhanced dissolution and slowing the release of highly water soluble drugs. In the present time there are numerous methods which have been described to improve the solubility and bioavailability of drugs. Among all the techniques in current practice, liquisolid technology is the most promising approach for improvement in solubility and improving the bio-availability of practically water insoluble drugs. Classic formulation strategies often fail to achieve the desired results as it is an effective technology in terms of production capability and low cost of manufacturing. The technology can also be considered for the purpose of retarding the drug release of highly water soluble drug by considering right excipients. Moreover, as the route of administration of this type of formulation is the oral route, the patient compliance for the final products obtained by the liquisolid technology will be high.

Conflict of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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