Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 4, Suppl 3, 2012

Review Article

MECHANISM OF SOLUBILITY OF LIQUISOLID FORMULATION IN NON VOLATILE SOLVENT: A REVIEW

DONEY ALEX BABY*[1], SOUMYA SAROJ[1], SABITHA.M[2]

[1]M Pharm , Department of Pharmaceutics, [2]Principal, Amrita School of Pharmacy, AIMS Healthcare Campus, Kochi, India.
Email: alexdoney16@gmail.com

Received: 11 Feb 2012, Revised and Accepted: 3 April 2012

ABSTRACT

Solubility is one of the important parameter to obtain desired concentration of drug in systemic circulation. Liquisolid technique is one of the most promising techniques to achieve enhanced solubility of poorly soluble drugs. This approach is suitable for immediate or sustained release formulations and this depends upon the solubility of the drug in the non volatile solvents. Non volatile solvents enhance the solubility of water insoluble drugs by formation of micelles and act as dispersants. For immediate release liquisolid compacts, the selection of solvent is based on high drug solubility and for sustained release, solvents with least solubilising capacity is selected. The solubility of drug in non volatile solvents can be revealed by differential scanning calorimetry (DSC) and X- ray powder diffraction (XRPD). Since there are no specific non-volatile liquid vehicles used in the preparation of liquisolid compacts, different non aqueous solvents have been used as non-volatile liquid vehicles in the preparation of immediate release and sustained release liquisolid tablets with different drugs. So selection of non volatile solvent in liquisolid technique is important to obtain immediate or sustained release formulation.

Keywords: Dissolution rate enhancement, Liquisolid tablets, Non-volatile solvents, poorly soluble drugs.

INTRODUCTION

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response. [1] The solubility phenomenon is one of the least understood of all the physicochemical properties particularly with reference to pharmaceutical solutions. Therefore knowledge of solubility is important to the pharmacist as it permits in choosing the best solvent medium for a drug. The poor dissolution rates of water insoluble drugs are still a substantial problem confronting the pharmaceutical industry. A great number of new and possibly beneficial chemical entities do not reach the public merely because of their poor oral bioavailability due to inadequate dissolution. About 40% of the drug candidates identified via combinatorial screening programmes are poorly water soluble. Bioavailability of a drug depends upon the drug solubility in an aqueous environment and drug permeability through lipophilic membranes. Usually only solubilized drug molecules can be absorbed by the cellular membranes to subsequently reach the site of drug action. [2-4]

The use of poorly soluble drugs has a number of drawbacks such as increasing the dosage, administration frequency and the resultant occurrence of side effects. Furthermore, the rate-limiting step in the absorption process for poorly water-soluble drugs is the dissolution rate of such drugs in the gastro intestinal fluids rather than the rapidity of their diffusion across the gut wall; it is however, important to improve the oral bioavailability of poorly water soluble drugs by improving their dissolution rate and solubility. The dissolution rate is the rate limiting factor in drug absorption for class II (low solubility and high permeability) and class IV (low solubility and low permeability) drugs as defined in the Biopharmaceutics Classification System.[5-7]. Poorly soluble drugs are difficult to formulate using conventional techniques. Over the years, various techniques have been employed to enhance the dissolution profile and, in turn, the absorption efficiency and bioavailability of water insoluble drugs. Various techniques have been employed to formulate oral drug delivery system that would enhance the dissolution profile and in turn, the absorption efficiency of water insoluble drug such as micronization, adsorption onto high surface area carriers, lyophilization, co-grinding, formulation of inclusion complexes, solubilization by surfactants, solid dispersions, solid solutions, hydrotrophy, inclusion of the drug solution or liquid drug into soft gelatin capsules, and cosolvency. The most common method is to increase the drug surface area and there by dissolution rate by micronization. But, in practice, the effect of micronization is often disappointing, because it alters the drug flow property, especially when the drugs are encapsulated or tableted.[8-10].

Table 1: Solubility Enhancement Methods [8,9,10,30,45]

Method	Drugs for which increased dissolution and absorption is reported
I. Methods which increases the solubility of the drug	
1. Buffering the pH of the Microenvironment	Buffered Aspirin, Theophylline, Sulphamethoxazole and Clotrimazole
2.Use of Salts of Weak Acids and Weak Bases	Sodium Potassium and calcium salts of p-aminosalicylic acid, sodium tolbutamide, tetracycline hydrochloride
3. Use of Solvents and Hydrates	Ampicillin anhydrate, Theophylline, caffeine
4. Use of selected Polymeric forms	Novobiocin, chloramphenicol palmitate and succinyl sulphathiazonel
5.Inclusion Complex	Cyclodextrin- inclusion complexes
6. Prodrug Approach	Prodrugs of ampicillin ie. pivampicillin, Hetacillin
7. Complexation	Benzocaine-caffeine complex, digitoxin hydroquinone complex
8. Use of Surfactants	Hydrocortsone-tween 80, amphoterecin-B biosurfactants (sodium cholate), tolubutamide tween 20 And tween 80
II. Methods which increase the surface area of the drug	
1. Micronization (Particle Size Reduction to Increase Surface Area)	Greiseofulvin, digoxin, phenacetin and Sulphadiazine
2. Use of Surfactant (to increase effective surface area by facilitating proper wetting).	Phenacetin
3. Solvent Deposition (dispersion of poorly soluble drug in a solid matrix of water soluble carrier).	Oxyphenbutazone, prednisolone, tolbutamide, indomethacine, phenylbutazone and hydrochlorothiazide.
4. Solid Dispersions (dispersion of poorlysoluble drug in a solid matrix of water soluble carrier).	Griseofulvin-PVP, reserpine-PVP, tolbutamidepolythyleneglycoletc.

Among various techniques to overcome the solubility issue, several researchers reported that the formulation of liquisolid tablets is one of the most promising techniques for promoting drug dissolution. [11-18] 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 microcrystalline cellulose. In such systems, the drug existed in a molecular dispersion state of subdivision. Also, these systems were free flowing, non-adherent, dry looking powders. Liquid compacts are acceptably flowing and compressible powdered forms of liquid medications. The term "liquisolid medication" implies oily liquid drugs and solutions or suspensions of water-insoluble solid drugs carried in suitable nonvolatile solvent systems. Using this new formulation technique, a liquid medication may be converted into a dry looking, non-adherent, free flowing and compressible powder by a simple blending with selected powder excipients referred to as the carrier and coating materials.

Table 2: Different exicipents used in Liquisolid system [31-33]

Carrier used in liquisolid system	Liquid vehicle	Coating agent
Microcrystalline cellulose	PEG	Colloidal silicon dioxide
Avicel pH 101	PG	Aerosil 200
Avicel pH102	Polysorbate	Syloid
Lactose	Cremophor® EL	
Starch	Synperonic® PE/L 81	

Liquisolid compacts of poorly soluble drugs containing a drug solution or drug suspension in a solubilising vehicle show enhanced drug release due to

1. An increased surface area of the solubilized drug in a non volatile solvent will increase its aqueous solubility.
2. A reduction of contact angle for the drug particles.
3. Increased dielectric constant of glycols which reduce the force of attraction between oppositely charged ions.
4. Capability of solvating molecules and ions to form hydrogen bonds through dipole interaction increases the drug solubility.[19]

Accordingly, this improved drug release may result in a higher drug absorption in the gastrointestinal tract and thus, an improved oral bioavailability.[20]

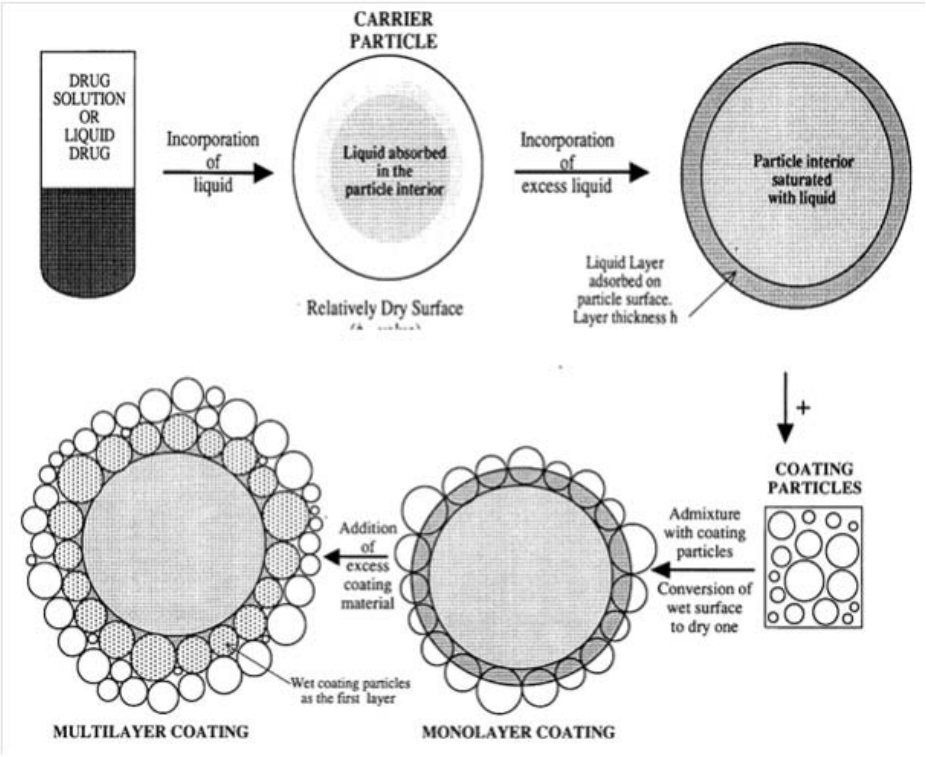

Fig. 1: Schematic representation of Liquisolid systems [46]

Mechanism of solubility enhancemement by non volatile solvents used in liquisolid system

Non-aqueous solvents have been used in oral, parentral, subcutaneous or intramuscular pharmaceutical formulations to dissolve water-insoluble drugs. In recent years, the need for these vehicles was increased since the drug discovery process has yielded many poorly water-soluble drugs. Besides, preparations containing embolic materials dissolved in undiluted non-aqueous water-miscible solvents have been proposed for the intravascular treatment of aneurysms, arteriovenous malformations, or tumors. These organic solvents, regarded as chemically and biologically inert, may show pharmacological and toxicological effects.

Therefore, knowledge of tolerance and activity of non-aqueous solvents is essential before they can be administered, especially when given undiluted.[21]

Surfactants are commonly used in liquisolid preparation. Surfactants are amphiphilic molecule having a polar head and a non polar, hydrophobic part usually called as tail. The head group can be of ionic or non ionic and termed as ionic and non ionic surfactant. Solubilizing effect of surfactants is mainly due to the formation of micelles in which hydrophobic part will aggregate and it is core surrounded by the polar head groups and it is well distributed in aqueous phase. The concentration at which micelle formed is called critical micelle concentration (CMC). Micelles are usually in nanometric size so they exist clear and transparent. The CMC for most of the surfactants is very low. 10^{-5} mol/L for non ionic surfactants and due to the electrostatic repulsion between the ionic head groups, ionic surfactants have CMC values of 10^{-3} mol/L. The strong hydrogen bond formed by the water molecule, which expel the hydrophobic parts is the driving force for the formation of micelles.

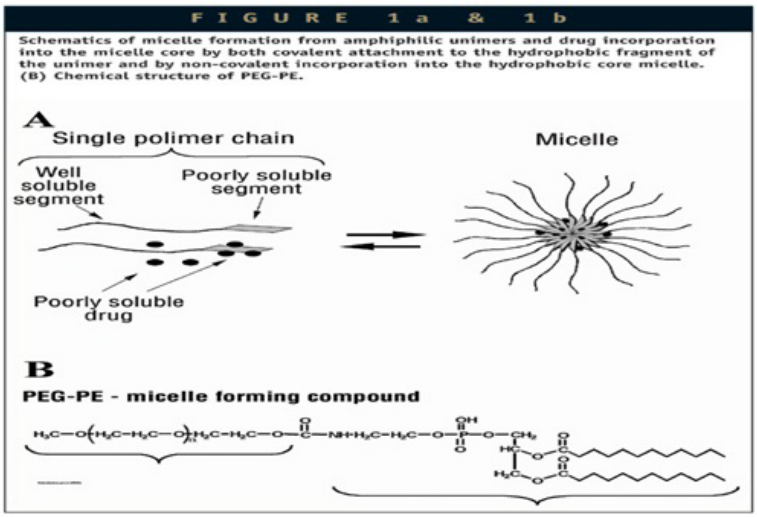

Fig. 2: Schematics of micelle formation by non volatile solvent [47]

Due to the amphiphilic nature of surfactants, it can acts as dispersants. Dispersants means it can stabilize very small particle of insoluble substances. The non-polar tail part will adsorb onto the non-polar surface of water insoluble particle and the polar head will point away from it into the aqueous phase. The ionic surfactants posses electrostatic charge which will be repelled by other particles in system and in non-ionic surfactants, the hydrophilic parts will form hydrophilic layer around the particle which prevent particle-particle attraction and stabilize the aqueous dispersion.[22] Solvents which are successfully used in liquisolid system are given below

Poly Ethylene Glycol

PEG is a polymer of ethylene oxide. PEGs are liquids or low-melting solids, depending on their molecular weights. PEGs can be manufactured by polymerization of ethylene oxide. PEG with different molecular weights are used in different applications and have different physical properties, (e.g., viscosity), due to chain length effects, their chemical properties are nearly identical and also have different melting points. Their hydrophilic-lipophilic balance (HLB) values range from 8 – 19 depending on chain length. Lower-molecular-weight PEGs are also available as pure oligomers, referred to as monodisperse, uniform or discrete. It is coupled to hydrophobic molecules to produce non-ionic surfactants due the hydrogen bonding. PEG is used as an excipient in pharmaceutical products. Lower-molecular-weight variants are used as solvents in oral liquids and soft capsules whereas solid variants are used as ointment bases, tablet binders, film coatings, and lubricants. Drugs such as carbamazepine, fenofibrate, glibenclamide, polythiazide, indomethacin etc are successfully formulated into liquisolid system with polyethylene glycol.[23-25]

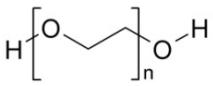

Fig. 3: General structure of Poly Ethylene Glycol

Propylene Glycol

Propylene glycol, also called 1,2-propanediol or propane-1,2-diol, is an organic compound (a diol or double alcohol) with formula $C_3H_8O_2$ or HO-CH_2-CHOH-CH_3. It is a colorless, nearly odorless, clear, viscous liquid with a faintly sweet taste, hygroscopic and miscible with water, acetone, and chloroform. Propylene glycol is produced from propylene oxide. It is having HLB value of 11-13.The acute oral toxicity of propylene glycol is very low, and large quantities only cause perceptible health damage in humans; prolonged contact with propylene glycol is essentially non-irritating to the skin. Since propylene glycol has low toxicity and being biodegradable it is used for many applications. It is used as a solvent in many pharmaceuticals, including oral, injectables and topical formulations. It is also used as humectants, emulsification agent, moisturizer etc. Propylene glycol is successfully used as non volatile solvent in liquisolid preparation of drugs such as bromhexine hydrochloride, famotidine, prednisalone etc.[26]

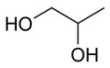

Fig. 4: Structure of Propylene Glycol

Polysorbate

Polysorbates are a class of emulsifiers used in some pharmaceuticals and food preparation. They are often used in cosmetics to solubilize essential oils into water-based products. Polysorbates are oily liquids derived from PEG-elated sorbitan (a derivative of sorbitol) esterified with fatty acids. Polysorbates are available in different varieties according to the presence of oxyethylene -(CH_2CH_2O)- groups found in the molecule, example Polysorbate 20 , Polysorbate 40 , Polysorbate 60, Polysorbate 80. Their HLB values range from 14– 20 depending on chain length. Polysorbates are used in pharmaceuticals as an excipient and it is also used as surfactant for enhancement of drug solubility. Enhanced dissolution for piroxicam is achieved by formulating liquisolid system with polysorbate80.[27]

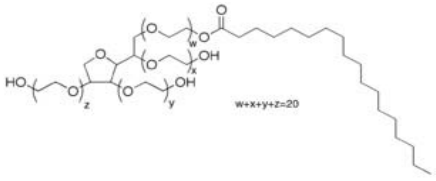

Fig. 5: General structure of Poly Sorbate

Cremophor EL

Cremophor EL is a non-ionic solubilizer and emulsifier obtained by the reaction between ethylene oxide and castor oil in a molar ratio of 35 moles to 1 mole. The main component of Cremophor EL is glycerol-polyethylene glycolricinoleate, which, together with fatty acid esters of polyethylene glycol, represents the hydrophobic part of the product. The smaller, hydrophilic part consists of polyethylene glycols and ethoxylated glycerol. It appeared as a pale yellow, oily liquid having characteristic odour. The hydrophilic-lipophilic balance (HLB) lies between 12 and 14.it is used as a solubilizer and emulsifier in pharmaceutical industry. The degree to which the hydrophobic substance is distributed in the liquid depends largely on its properties and on the amount of Cremophor EL used. Toxicological studies revealed that it is safe to use. Liquisolid system of naproxen formulated with cremophor EL shows better release than other non volatile solvents.[28]

Synperonic PE/L61

Synperonic PE/L61 is a non ionic surfactant of block copolymer of polyethylene and polypropylene glycol. It is used in the manufacture of liquisolid preparation as a solubilizer for poorly soluble drug. Synperonic PE/L61 possess higher dissolution for furosemide.[29-30]

Nonvolatile solvents used for water insoluble drugs in liquisolid system to obtain immediate release compacts

Accordingly, there is no single non-volatile liquid vehicle which is suitable for a wide range of hydrophobic drugs in formulating liquisolid tablets. Various non aqueous solvents used in liquisolid preparation with different drugs are given below.

Piroxicam is a poorly soluble, highly permeable drug. Oral absorption of drug in GI depends upon the solubility of the drug in gastrointestinal fluid. Since it is a water insoluble drug its dissolution rate is less. The liquisolid compact technique is the best alternative for the formulation of water- insoluble drugs, such as Piroxicam into rapid release tablets. In this study, drug solubility is carried out in different solvents such as SGF, SIF and the Tween 80. Results show that the solubility of piroxicam was markedly increased by the presence of Tween 80. The dissolution study of liquisolid tablets prepared with tween 80 as liquid vehicle demonstrated significantly higher drug release rates than those of conventionally made tablets. 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.[31]

Prednisolone, a very slightly water soluble glucocorticoid, formulated in directly compressed tablets and liquisolid compacts, were studied at different dissolution conditions. .The solubility study of prednisolone in water, propylene glycol, polyethylene glycol 400, glycerin and polysorbate 80 were carried out. Results shows that Prednisolone has more solubility in propylene glycol when compared to other liquid vehicle. The dissolution study of liquisolid tablets prepared with propylene glycol as liquid vehicle showed a significantly higher release rates than those of directly compressed counter parts. Higher dissolution of prednisolone is attributed due to increased surface of the molecularly dispersed prednisolone in the liquisolid tablets.[32]

Naproxen is a non-steroidal anti-inflammatory drug which is practically insoluble in water. The study reported the effects of different 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, Synperonic PE/L61 and poly ethylene glycol 400 at two drug concentrations, 20%w/w and 40%w/w. The solubility study of naproxen in different non volatile solvents such as Cremophor EL, Synperonic PE/L61, PEG400 and distilled water were carried out. Naproxen is more soluble in cremophor EL and PEG 400. 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 (pH7.2) without 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. Enhancement of dissolution of naproxen is due to molecular dispersion of drug particles in a nonvolatile hydrophilic liquid vehicle, which in turn increase the wetting properties and surface area of drug particles, and hence improve the dissolution profiles and the oral bioavailability of the drug.[33]

Poor water solubility of Famotidine is its rate limiting step in the absorption of the drug from the gastro intestinal tract. Here propylene glycol is used as a liquid vehicle and all the tested liquisolid tablet formulations showed higher drug dissolution rates than the conventional directly compressed tables. Higher dissolution of the liquisolid formulation is because famotidine exists in a state of molecular dispersion, in propylene glycol, which increases the surface area for dissolution of the drug particle.[34]

Atorvastatin calcium (ATR) is a BCS class II drug used as a lipid lowering agent by acting as HMGCoA reductase inhibitor. Solubility studies were carried out with different solvents such as distilled water, propylene glycol and PEG400 for selecting a proper liquid solvent. The study showed that drug is more soluble in propylene glycol than other solvents. The in vitro dissolution study confirmed enhanced drug release from liquisolid compacts prepared with propylene glycol compared with directly compressed counterparts and this was independent of the type and volume of the dissolution medium. The improvement in oral bioavailability was confirmed by estimating the pharmacokinetic parameters in vivo in rabbits.[35]

The anti diabetic agent, Glipizide exhibits poor aqueous solubility. Glipizide belongs to class II of the biopharmaceutics classification system. To find out the best non-volatile solvent for dissolving or suspending Glipizide for liquid formulation, solubility studies of Glipizide were carried out in different nonvolatile solvents, i.e. PG, PEG 200, PEG 400, gastric fluid (pH 1.2) and phosphate buffer (pH 7.4). The results showed that Glipizide had more solubility in PEG400. Liquisolid tablets containing PEG 400 as liquid vehicle produces higher dissolution rates as compared to other liquisolid tablets containing PG and PEG 200 as liquid vehicle of the same drug concentration. The wetability of the compacts by the dissolution media is one of the proposed mechanisms to explain the enhanced dissolution rate of Glipizide from liquisolid tablets.[36]

The anti asthmatic agent, Bromhexine hydrochloride (BXH) exhibits poor aqueous solubility. To find out the best non-volatile solvent for dissolving or suspending Bromhexine in liquid medication, solubility studies of Bromhexine hydrochloride were carried out in different nonvolatile solvents, i.e. distilled water, PG and PEG 400. The results show that Bromhexine hydrochloride had more solubility in Propylene glycol. Since the Liquisolid compacts contain a solution of the drug in Propylene glycol and PEG 400, the drug surface available for dissolution is tremendously increased. The relatively poorer dissolution properties of the liquisolid prepared with PEG400 may be mainly attributed to the lower solubility of BXH in PEG 400 compared to those in propylene glycol. Liquisolid compact of BXH made in propylene glycol showed better dissolution rate than BXH with PEG 400 based upon solubility and molecular fraction (*F*M) of the drug in their liquid medication.[37]

Nonvolatile solvents used for water soluble drugs in liquisolid system to obtain sustained release

Propranolol hydrochloride is an anti hypertensive drug having a short elimination half-life of 3 h and freely soluble drug, which makes it a suitable candidate to be delivered at a controlled rate. Here hydrophobic carriers such as Eudragit RL and RS are used instead of hydrophilic carries in liquisolid systems. Solubility studies of Propranolol hydrochloride were carried out in five different nonvolatile solvents i.e. PEG 200, PEG 400, glycerin, polysorbate80 and propylene glycol (PG). The results showed that the drug had more solubility in propylene glycol and least solublibility in polysorbate80. To achieve sustained release, polysorbate 80 was selected as liquid vehicle. Dissolution study profiles showed that liquisolid compacts show greater retardation properties in comparison with conventional matrix tablets. The mechanism of prolonged release is likely to be a more efficient in encapsulation of drug particles by the hydrophobic polymers. Due

to the plasticizer effect of polysorbate 80, it can reduce the glass transition temperature (Tg) of polymers and impart flexibility. The plasticizers affect the intermolecular bonding between polymer chains, thereby increasing flexibility Therefore, reduction of *T*g of the polymer might be the reason for the prolonged release of liquisolid tablets.[38]

Table 3: Different liquid vehicles, carrier and coating materials and with different liquid load factor used in Liquisolid system. [39-45]

Drug	Liquid vehicle	Carrier & coating material	Liquid load factor
Piroxicam	Polysorbate 80	MCC & Colloidal silicon dioxide	0.200 - 0.225
Famotidine	Propylene glycol	Avicel ph102& aerosol 200	0.225
Rofecoxib	PEG600	Avicel ph101 & Cab-O-Sil M-5	0.225 - 0.275
Bromhexine	PG	Avicel ph102& aerosol 200	0.235- 0.253
Glipizide	PEG400	Avicel ph102& aerosol 200	0.280 - 0.300
Naproxen	Cremophor® EL	Avicel ph102& aerosol 200	0.315
Atorvastatin	PG	Avicel ph102& aerosol 200	0.230- 0.250
Prednisolone	PG	Avicel ph200 & Cab-O-SilM-5	0.225 - 0.250
Carbamazepine	PG	Avicel ph102& aerosol 200	0.250 & 0.470
Furosemide	Synperonic® PE/L 81	Avicel ph101 & Cab-O-Sil M-5	0.274
Fenofibrate	PG	Avicel ph102& aerosol 200	0.226- 0.270

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, non adherent, free-flowing and compressible powder mixtures by blending the suspension or solution with selected carriers and coating agents. The liquisolid tablets dosage form showed significantly greater extent of absorption in GIT due to their solubility and dissolution improvement in various non-volatile solvents. The non volatile solvents also play a key role in design of sustained release systems by using hydrophobic carriers instead of hydrophilic carriers in liquisolid systems. Therefore, these formulations have great scope as a technique to enhance the solubility of a poorly soluble drug.

REFERENCE

5. Shinde AJ. Solubilization of poorly soluble drugs: A review, available at http://www.pharmainfo.net/reviews/solubilization - poorly-soluble-drugs-review (2007).
6. Sharma A and Jain C.P., Techniques to enhance solubility of poorly soluble drugs: a reviewJournal of Global Pharma Technology. 2010; 2 (2): 18-28.
7. Bittner B., Mountfield R.J. Intravenous administration of poorly soluble new drug entities in early drug discovery: the potential impact of formulation on pharmacokinetic parameters. Current Opin.Drug Discov. Develop. 2002; 5:59–71.
8. Bittner B., Mountfield R.J. Formulations and related activities for the oral administration of poorly water soluble compounds in early discovery animal studies. Pharm. Ind. 2002; 64: 800–807.
9. Amidon G.L., Lennernas H., Shah V.P., Crison J.R. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and invivo bioavailability. Pharm. Res. 1995;12(3):413-20.
10. Lindenberg M., Kopp S., Dressman J.B. Classification of orally administered drugs on the World Health Organization model list of essential medicines according to the biopharmaceutics classification system. Eur. J. Pharm. Biopharm.2004; 58(2):265-78.
11. G.L. Amidon, H. Lennernas, J.R. Crison, A theoretical basis for biopharmaceutics drugs classification: the correlation of in-vitro drug product dissolution and in-vivo bioavailability, Pharm. Res.1999; 12 : 413–420.
12. Saharan, V.A, Kukkar, V, Kataria M., Gera M, Choudhury, P.K. Dissolution enhancement of drugs. Part I: technologies and effect of carriers. Int. J. Health Res. 2009; 2: 107-124.
13. Saharan, V.A, Kukkar V, Kataria M., Gera M, Choudhury P.K. Dissolution enhancement of drugs. Part II: effect of carriers. Int. J. Health Res.2009; 2: 207-223.
14. Mohanachandran P S P. G Sindhumol and T. S Kiran, enhancement of solubility and dissolution rate: an overview Pharmacie Globale (IJCP); 2010, 4 (11):1-10
15. Amrit B. karmarkar , Indrajeet D. gonjari, Avinash H. Hosmani, Pandurang N. Dhabale, Satish B. Bhise. Dissolution Rate Enhancement of Fenofibrate using Liquisolid Tablet Technique. Lat. Am. J. Pharm. 2009;28 (2): 219-25.
16. Vijay kumar Nagabandi, T.Ramarao,K.N.Jayaveera. LIQUISOLID Compacts: A Novel Approach to Enhance Bioavailability of Poorly Soluble Drugs. International Journal of Pharmacy and Biological Sciences.2011;1(3):89-102.
17. Ajit S. Kulkarni, Nagesh H. Aloorkar, Madhav S. Mane and Jayashree B. Gaja. Liquisolid Systems. International Journal of Pharmaceutical Sciences and Nanotechnology . 2010;3(1):795-802.
18. Bindu MB, Kusum B and David Banji. Novel strategies for poorly water soluble drugs. International Journal of Pharmaceutical Sciences Review and Research. 2010; 4(3):76-84.
19. Spireas SS. Theoretical and practical aspects of Liquisolid compacts, PhD Thesis, St. John's University, New York. 1993.
20. S. Spireas,C.I. Jarowski, B.D. Rohera. Powdered solution technology: principles and mechanism. Pharm Res. 1992; 9:1351–1358
21. Javadzadeh, Y., Jafari-Navimipour, B., Nokhodchi, A. Liquisolid technique for dissolution rate enhancement of a high dose waterinsoluble drug carbamazepine. Int. J. Pharm.2007; 341: 26-34.
22. Spiras S, Wang T, Grover R. Effect of powder substrate on the dissolution properties of methchrothiazide Liquisolid compacts. Drug Dev Ind Pharm. 1999; 25: 163–168
23. Alfred Martin, James Swarbrick, Arthur Cammarata. Solubility and distribution phenomena. Physical pharmacy. 2007; 212-222.
24. Betty Ann Hoener, leslie Z Benet. Factors influencing drug absorption and drug availability. Gilbert .S.Banker, Christopher .T . Rhodes. Modern pharmaceutics.2002.93-99.
25. Florence Mottu, Alexandre Laurent, Daniel A. Rüfenacht and Eric Doelker. Organic Solvents for Pharmaceutical Parenterals and Embolic Liquids: A Review of Toxicity Data.PDA J Pharm Sci Technol. 2000; 54:456-469.
26. Thomas reintjes. Solubility enhancement with BASF pharma polymers. Solubilizer comendium: available at http:// http://www.pharma-ingredients.basf.com/ October 2011.
27. 23.French AC, Thompson AL, Davis BG. High-purity discrete PEG-oligomer crystals allow structural insight. Angew Chem Int Ed Engl. 2009;48(7):1248-52.
28. Di Palma JA. A randomized, multicenter comparison of polyethylene glycol laxative and tegaserod in treatment of patients with chronic constipation. Am J Gastroenterol. 2007; 102(9):1964-71.
29. Andersen F Alan, Final report on the safety assessment of PEG-2, -3, -5, -10, -15, and -20 Cocamine, international journal of toxicology,1999; 18: 43-50.
30. Janusz Szajewski, MD, Warsaw Poison Control Centre (August, 1991). "Propylene glycol (PIM 443)". IPCS INChem. Retrieved July 2, 2009.

31. Steele RH, Limaye S, Cleland B, Chow J, Suranyi MG.Hypersensitivity reactions to the polysorbate contained in recombinant erythropoietin and darbepoietin. Nephrology Carlton.2005;10 (3): 317–20.
32. Technical leaflet: Cremophor EL (1997) BASF Fine Chem. John A. Fields, Andrew Wingham, Frances Hartog and Vincent Daniels. Finding Substitute Surfactants for Synperonic N .Journal of the American Institute for Conservation .2004;43(1): 55-73
33. Khamkar Ganesh S. Self micro emulsifying drug delivery system (smeed) o/w microemulsion for bcs class II drugs: An approach to enhance an oral bioavailability. Int J Pharm Pharm Sci. 2011; 3: 1-3.
34. S. S. Spireas, S. Sadu. Enhancement of prednisolone dissolution properties using liquisolid compacts. Int. J.Pharm., 1998, 166: 177-188.
35. Nokhodchi, A, Javadzadeh,Y, Siahi-Shadbad, M.R., and Barzegar-jalali, M., Enhancement of dissolution rate of piroxicam using liquisolid compacts. IlFarmco.2005; 60:361-365
36. N. Tiong, A.A. Elkordy. Effects of liquisolid formulations on dissolution of naproxen. Eur J Pharm Biopharm. 2009, 73:373-384
37. Fahmy, R.H., Kassem, M.A. Enhancement of famotidine dissolution rate through liquisolid tablets formulation: in vitro and in vivo evaluation. Eur. J. Pharm. Biopharm.2008; 69: 993-1003.
38. Sanjeev Raghavendra Gubbi, Ravindra Jarag. Formulation and characterization of atorvastatin calcium liquisolid compacts, Asian Journal of Pharmaceutical Sciences .2010,;5 (2): 50-60
39. Hitendra S. Mahajan, Manoj R. Dhamne, Surendra G. Gattani,Ashwini D. Rasal and Hannan T. Shaikh. Enhanced Dissolution Rate of Glipizide by a Liquisolid Technique. International Journal of Pharmaceutical Sciences and Nanotechnology.2011;3(4):1205-1213
40. Sanjeev Gubbi, Ravindra Jarag .Liquisolid Technique for Enhancement of Dissolution Properties ofBromhexine Hydrochloride.Research J. Pharm. and Tech.2009;.2 (2):382-386.
41. Y. Javadzadeh, Musaajrezaei L, Nokhodchi A., Liquisolid technique as a new approach to sustain propranolol hydrochloride release from tablet matrices. International Journal of Pharmaceutics .2008;362 : 102–108.
42. Karmarkar, A.B, Gonjari, I.D, Hosmani, A.H, Dhabale, P.N, Bhise, S.B. Liquisolid tablets: a novel approach for drug delivery. Int. J. Health Res.2009; 2: 45-50.
43. Nokhodchi, A, Javadzadeh Y, Siahi-Shadbad, M, Barzegar-Jalali M. The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug indomethacin from liquisolid compacts. J. Pharm. Pharm. Sci. 2005;8: 18-25.
44. Yadav V.B, Yadav, A.V. Improvement of solubility and dissolution of indomethacin by liquisolid and compaction granulation technique. J. Pharm. Sci. & Res.2009; 1: 44-51.
45. Khalid M. El-Say, Ahmed M. Samy, Mohamed I. Fetouh. formulation and evaluation of rofecoxib liquisolid tablets. International Journal of Pharmaceutical Sciences Review and Research.2010; 3(1),135-142.
46. Amal A. Elkordy, Babatunde Akinlade,Ebtessam A. Essa , Sahar Elhagar. Liquisolid Systems to Improve the Dissolution of Furosemide. Sci Pharm. 2010; 78: 325–344.
47. Ali Nokhodchi, Roya Aliakbar, Sandip Desai, Yousef Javadzadeh. Liquisolid compacts: the effect of co solvent and HPMC on theophylline release.colloids and surfaces B:Biointerfaces.2010;79:262-269.
48. M.Najmuddin, Tousif Khan, Mohsin AA, S.Shelar, Vishal Patel, Enhancement of dissolution rate of Ketoconazole by Solid Dispersion Technique. Int J Pharm Pharm Sci. 2010; 2(3): 132-136.
49. K. Kavitha, Kotha N. S. Lova Raju, N.S Ganesh, B. Ramesh.Effect of dissolution rate by liquisolid compact approach: An Overview. Der Pharmacia Lettre. 2011; 3(1):71-83.
50. Vladimir Torchilin.Polymeric Immunomicelles: Carriers of Choice for Targeted Delivery of Water-Insoluble Pharmaceuticals. Drug development and delivery.2004;4(3).