Trends in Applied Sciences Research

ISSN 1819-3579

Academic
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Trends in Applied Sciences Research 7 (8): 596-619, 2012
ISSN 1819-3579 / DOI: 10.3923/tasr.2012.596.619

An Exhaustive Review on Solubility Enhancement for Hydrophobic Compounds by Possible Applications of Novel Techniques

[1]Rakesh Tiwle, [1]Ajazuddin, [1]Tapan Kumar Giri, [1]Dulal Krishna Tripathi, [2]Vishal Jain and [1]Amit Alexander

[1]Rungta College of Pharmaceutical Sciences and Research, Kohka-Kurud Road, Bhilai, Chhattisgarh, India
[2]University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur, Chhattisgarh, India

Corresponding Author: Amit Alexander, Rungta College of Pharmaceutical Sciences and Research, Kohka-Kurud Road, Bhilai, Chhattisgarh, India Tel: 09907333846

ABSTRACT

The combinatorial chemistry and high throughput screening increases the solubility of poorly water soluble compounds. The most challenging task in development of a formulation is the solubility of drug, availability at the site of action and stability of drug. Aqueous solubility of any therapeutically active substance is a key property as it governs dissolution, absorption and thus the *in vivo* efficacy. Among all newly discovered chemical entities about 40% drugs are lipophilic and these drugs are rejected by the pharmaceutical industry and will never benefit a patient because of its poor bioavailability due to low water solubility and/or cell membrane permeability. Drug efficacy can be severely limited by poor aqueous solubility and some drugs also show side effects due to their poor solubility. Therefore, drug release profiles are exhibited by such formulations for poorly soluble drugs to improve the solubility of such poorly soluble drugs. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of drugs which are weakly acidic and basic show poor aqueous solubihty hence various methods like, salt formation, co-solvency, micronization, addition of agent, solid dispersion, complexation etc., are some of the vital approaches routinely employed to enhance the solubility of poorly soluble drugs. This article reviews various methods used for improving the solubility of hydrophobic drugs and improve the drug release profiles which are exhibited by such formulations for poorly soluble drugs.

Key words: Solubility, bioavailability, salt formation, co-solvency, solubilizing agent, micronization, solid dispersion

INTRODUCTION

The combinatorial screening programs employed by the pharmaceutical companies identified that about 40% of active New Chemical Entities (NCEs) are poorly water soluble. The two major obstacles in developing a therapeutic agent are Solubility and stability (Seedher and Sharma, 2007). Since 1995, more than 90% of drugs are approved as hydrophobic having poor solubility. A maximum amount of solute dissolved in a given solvent at a specified temperature defined as solubility (Patil *et al*., 2011). The substance which is to be dissolved is known as solute and the fluid (medium) in which the solute to be dissolve is known as solvent and the process of dissolving solute into solvent is called as solution. Descriptive terms for solubility are shown in (Table 1)

Table 1: Solubility definitions (Rodier *et al.*, 2005)

Definition	Parts of solvent required for one part of solute
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10.000
Insoluble	>10,000

Table 2: Biopharmaceutical classification system (BCS) (Malpani *et al.*, 2009)

Drng belongs (%)	Class	Category	Examples	Reference
84	1	Highly soluble, high permeable	Metropol	Klein and Dressman (2006)
17	2	Poor soluble, high permeable	Glibenclamide	Lim *et al.* (2010)
39	3	High soluble, poor permeable	Cimetidine	Jantratid *et al.* (2006)
10	4	Poor soluble, poor permeable	Hydrochlorothiaze	Kim *et al.* (2011)

(Beringer, 2005). The poorly soluble agent have low water solubility hence they low bioavailability and absorption (Heimbach *et al.*, 2007; Nourani *et al.*, 2008; Vahedi, 2012). There are various techniques and formulations have been employed to overcome these limitations. Although, existing strategies such as complexing drugs by using Cyclodextrins (Vyas *et al.*, 2008; Zhixun *et al.*, 2006; Sangshetti *et al.*, 2008) conjugation to dendrimers (Gupta *et al.*, 2006), salt formation of ionizable drugs (Serajuddin, 2007) and the use of co-solvents (Akers, 2002; Strickley, 2004) have been shown to improve drug solubility. The World Health Organization (WHO) have classified BCS classification on the basis of data as 130 orally administer drug from which according to WHO list 61 could be classified as poorly soluble drug (Al Omari *et al.*, 2009) (Table 2). Biopharmaceutical Classification System (BCS) many drugs belongs to Biopharmaceutics Classification System (BCS) class II (high permeability, low solubility) or IV (Low permeability, Low solubility) (Amidon *et al.*, 1995; Porter and Charman, 2001). For the BCS class II drugs, the oral absorption is limited by the solubility or dissolution in gastrointestinal (GI) tract.

Solubilisation process: The breaking of inter-ionic or intermolecular bonds in the solute occurs mainly in the method of solubilisation. In solubilisation method the solvent provide space for the solute, interaction between solvent and the solute molecule or ion (Fig. 1).

FACTORS AFFECTING SOLUBILITY

Polymorphs: Absorption and bioavailability can also be enhanced by polymorphs as defined as the greater the solubility of the metastable form Blagden *et al.* (2007) and Ajazuddin *et al.* (2011). Polymorphs can vary in melting point. Since, the melting point of the solid is related to solubility, the capacity for a substance to crystallize in more than one crystalline form is polymorphism. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called enantiotropy. If the system is monotropic, there is a transition point above the melting points of both polymorphs. So, polymorphs will have different solubility (Worthen, 2006; Noorizadeh and Farmany, 2011).

Particle size: The solubility of crystalline solids gets affected by particle size it is well describe in the documented (Hammond *et al.*, 2007; Wu and Nancollas, 1998; Mosharraf and Nystrom, 1995).

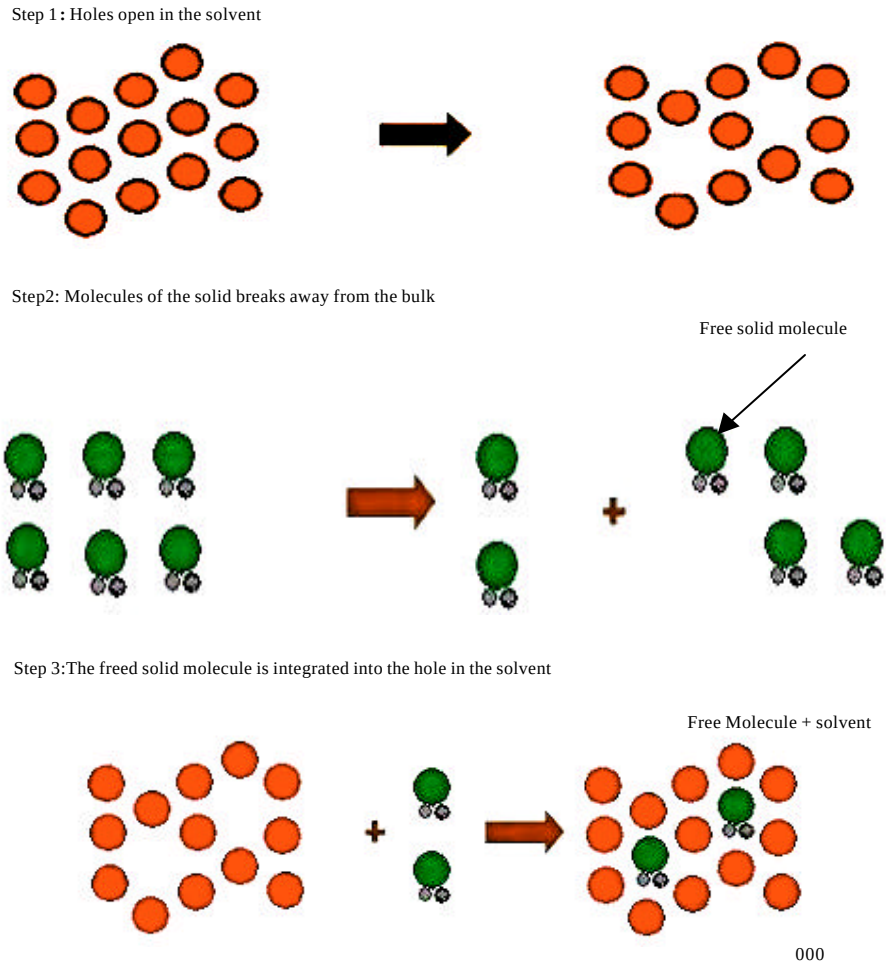

Fig. 1: Solubilisation process (Dabbagh and Taghipour, 2007; Sangshetti *et al*., 2008)

By reducing the particle size, the solubility of crystalline drugs can be increased to submicron levels, but the effect of solubility is trifling if the particle size is not reduced below 10 μm. The effect of particle size on solubility can be described by Chaumeil (1998):

$$\text{Log}\frac{s}{so} = \frac{2\gamma v}{2.303RT\gamma}$$

Where:
S : The solubility of infinitely large particles
So : The solubility of fine particles
V : Molar volume
g : The surface tension of the solid
γ : The radius of the fine particle

Pressures: An increase in pressure increases solubility for gaseous solute. While decreases in pressure for solids and liquid solutes, changes in pressure have practically no effect on its solubility

(Ain *et al.*, 2009). There are various approaches to improve the solubility or to increase the available surface area for dissolution. These can be altered or modified by following the methods of Leaner and Dressman (2000).

Temperature: Solubility changes with the temperature. It is demonstrated by Pore and Kuchekar (2011), in solubilisation process energy get absorbs then the temperature will increased and their solubility will increases. If the temperature will increases enhance solubility decrease. A few solid solutes are less soluble in warm solutions (Lindenberg *et al.*, 2004). The solubility of gases deceases with the increasing temperature.

METHOD FOR SOLUBILITY ENHANCEMENT

Physical modifications

Particle size reduction

Micronization: Surface area for dissolution can be increases by Micronization (Kawashima *et al.*, 1975). Micronisation increases the dissolution rate of drug through increased surface area but does not enhanced equilibrium solubility. The increase in bioavailability after micronization of drugs, e.g., by jet or ball milling Example, danazol (Liversidge and Cundy, 1995), progesterone (Hargrove *et al.*, 1989), or dioxin (Jounela *et al.*, 1975).

Nanosuspension: Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilized by the surfactants. (www.expresspharmapulse.com). Nanosuspensions in aqueous or non-aqueous vehicles can be produced by bottom-up (e.g., precipitation) or top-down (e.g., wet milling) processes (Rainbow, 2004; Douroumis and Fahr, 2006). High pressure homogenizers such as the piston gap homogenizer have proved to be a highly successful technology in nanosuspension formation.

Homogenization: Homogenization the required technique is used to reduce the globule size of a coarse emulsion (Amit *et al.*, 2011), globule size is less than 100-200 nm (Davis *et al.*, 1974). Brownian movement prevents creaming because of small globule size which also promotes good physical stability (Floyd, 1999; Chattopadhyay *et al.*, 2011). There are so many method used to improve the dissolution of hydrophobic drugs. High-Pressure Homogenization (HPH) has been mostly used to reduce the particle size (Uchiyama *et al.*, 2011; Grau *et al.*, 2000). For example processing highly concentrated suspensions (Muller *et al.*, 2001) and preparing emulsions (Tian *et al.*, 2007). HPH has lot of advantages over other milling techniques as it is very simple, time saving and an organic solvent-free process. Therefore, HPH can be used to enhance the solubility of hydrophobic drugs such as PLH for which usage of organic solvents is limited (Al-Haj and Rasedee, 2009; Ajazuddin and Saraf, 2010b). This method having some advantages for Production of Solid Lipid Nanoparticles (SLNs) (Bhoyar *et al.*, 2012; Ajazuddin and Saraf, 2010a). The objective of this study was to investigate solid lipid nanoparticles using Carbopol gel as gelling agent containing triamcinolone acetonide acetate (glucocorticoid compound) for transdermal iontophoretic delivery Solid Lipid Nanoparticles (SLN) (Mehnert and Mader, 2001; Muller *et al.*, 2001) have been introduced to the literature as a carrier system for poorly water soluble pharmaceutical drugs (Ugazio *et al.*, 2002; Westesen *et al.*, 1997; Lokhande *et al.*, 2006; Nourani *et al.*, 2008) and cosmetic active ingredients.

Wet milling: Active drug in the presence of surfactant is defragmented by milling (Aulton, 2002). Other technique involves the spraying of a drug solution in a volatile organic solvent into a heated aqueous solution. Rapid solvent evaporation produces drug precipitation in the presence of surfactants.

MODIFICATION OF THE CRYSTAL HABIT (Hite *et al*., 2003)

Polymorphs: Polymorphism is the ability of compound to crystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability etc Generally, the anhydrous form of drug has greater solubility than the hydrates. This is because the hydrates are already in interaction with water and therefore, have less energy for crystal breakup in comparison to the anhydrites (i.e., thermodynamically higher energy state) for further interaction with water (Hammond *et al*., 2007; Chattopadhyay *et al*., 2011).

DRUG DISPERSION IN CARRIERS

Solid dispersion technique: The concept of solid dispersions was given by Sekiguchi and Obi (1961) who investigated the generation and dissolution performance of eutectic melts of a sulfonamide drug and a water-soluble carrier in the early 1960s (Tapas *et al*., 2011; Giri *et al*., 2010; Zhixun *et al*., 2006). Many of the drugs belongs to these techniques; can be categorized as class II according to the Biopharmaceutical Classification System (BCS). These drugs are poorly water soluble but once they are dissolved they get easily absorbed through the gastro-intestinal membrane. One of the approaches to enhance the dissolution rate is the use of solid dispersion. Some marketed formulation of solid dispersion shown in (Table 3).

Definition of solid dispersions: The two different components, generally a hydrophilic matrix and a hydrophobic drug mainly consist of solid dispersion (Chiou and Riegelman, 1971). These matrix are either crystalline or amorphous. In both particle (amorphous particles or crystalline particles) the drug can be dispersed molecularly (Ajazuddin *et al*., 2011). Solid dispersion is describing the most promising method to improve the oral bioavailability of hydrophobic drugs by preparing Lipid Nano Spheres (LNSs) (Amarji *et al*., 2007). There are different approaches which can be used for increasing the dissolution hydrophobic drugs of t he as given in the figure Fig. 2. That describes the approaches to Increase solubility/Dissolution (Verma, 2011; Patidar *et al*., 2010).

Table 3: Marketed formulation of solid dispersion (Patel *et al*., 2010)

Drug name	Brand name	Company name
Nelfinavir	Viracept	Agouron pharmaceuticals
Ritonavir	Norvir	Abbott laboratories
Amprenavir	Agenerase	GlaxoSmithKline
Calcitriol	Rocaltrol	Roche
Cyclosporine	A/I neural	Novartis
Indomethacin	Indomethacin	Eisai.co

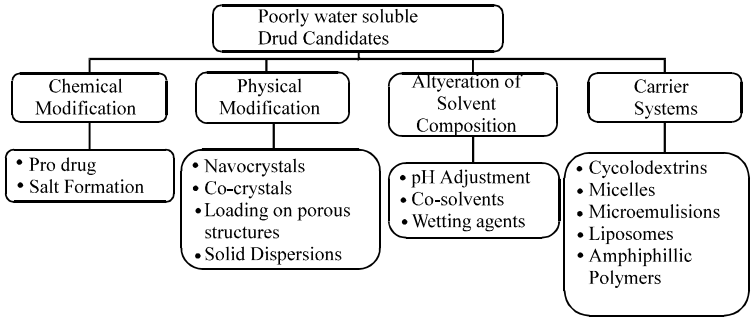

Fig. 2: Approaches to increase solubility/dissolution (Verma, 2011)

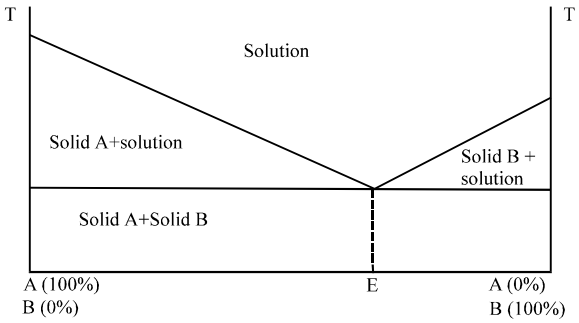

Fig. 3: Phase diagram of a simple eutectic mixture with negligible solid solubility, (Sharma *et al.*, 2009).T A: M.P. of solid A (in °C), T B: M.P. of solid B (in °C), TE: Eutectic point

Categories of solid dispersions

Simple eutectic mixtures: The two components which are completely miscible in a liquid state but only to a very limited extent in the solid state forms a simple eutectic mixture (Fig. 3) (Sharma *et al.*, 2009). When, a composition E with a mixture of A and B is cooled, at first A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out while after that when composition E is further cooled one component starts to crystallize out before the others (Goldberg *et al.*, 1966). Solid eutectic mixtures are usually prepared by rapid cooling of a co-melt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug. Where T A-M.P. of solid A (in °C), T B-M.P. of solid B (in °C), TE-Eutectic Point.

Solid solution: Solid solutions of a poorly water soluble drug dissolved in a carrier with relatively good aqueous solubility are of particular interest as a means of improving oral bioavailability (Leaner and Dressman, 2000). Two components crystallize together in homogenous one phase system. Particle size of drug in solid solution is reduced to its molecular size. Solid solutions shows faster dissolution rate than eutectic mixtures. Solid solutions can be divided in two types, according to their miscibility (continuous versus discontinuous solid solutions) or, according to the way in which the solvate molecules are distributed in the solvendum (substitutional, interstitial or amorphous).

Miscibility types

Continuous: The continuous solid solution consists of totally miscible components both in liquid and solid state (Giri *et al*., 2010). The pure components in a solid state lattice energy as compare to continuous solid solution it is due to the higher heteromolecular bonding than the homomolecular one in a continuous solid solution (Fig. 4) shows the hypothetical phase diagram of a continuous solid solution.

Discontinuous solid solutions: Discontinuous solid solutions, the miscibility or solubility of one component is restricted in other (Fig. 5) shows a typical phase diagram of a discontinuous solid solution. α and β shows the regions of true solid solutions. The region labeled β is a solid solution of B in A that is component A would be regarded as the solvent and B as the solute. Similarly the region labeled β is a solid solution of A in B (Goldberg *et al*., 1965).

The way in which the solvate molecules are distributed in the solvendum

Substitutional crystalline solid solutions: A substitution crystalline solid dispersion is a type of solid solutions which is having a crystalline structure, in that the solute molecules substitute for solvent molecules in the crystal lattice. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules (Fig. 6) Substitutional solid solution.

Interstitial crystalline solid solutions: In interstitial solid solutions, dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In the case of interstitial crystalline solid solutions, the solute

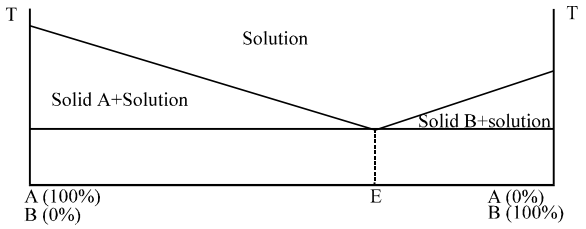

Fig. 4: Hypothetical phase diagram of a continuous solid solution (Giri *et al*., 2010)

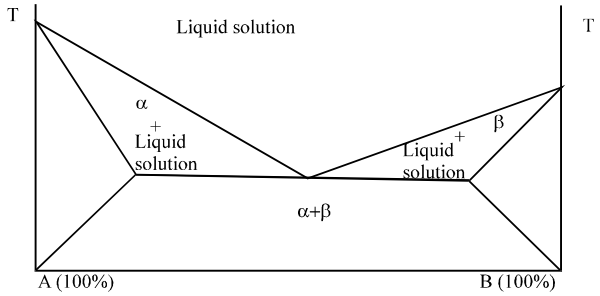

Fig. 5: Hypothetical phase diagram of a discontinuous solid solution (Goldberg *et al*., 1965)

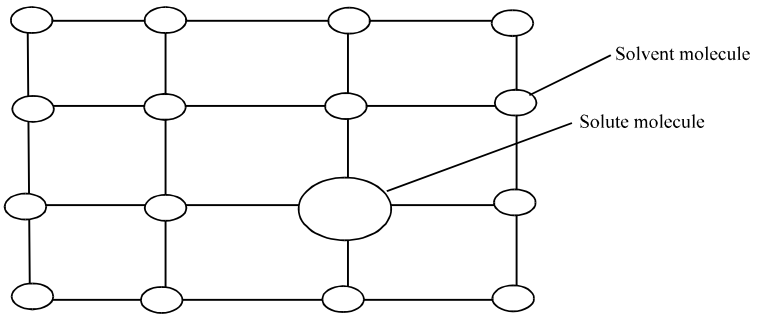

Fig. 6: Substitutional solid solution (Maski *et al*., 2009)

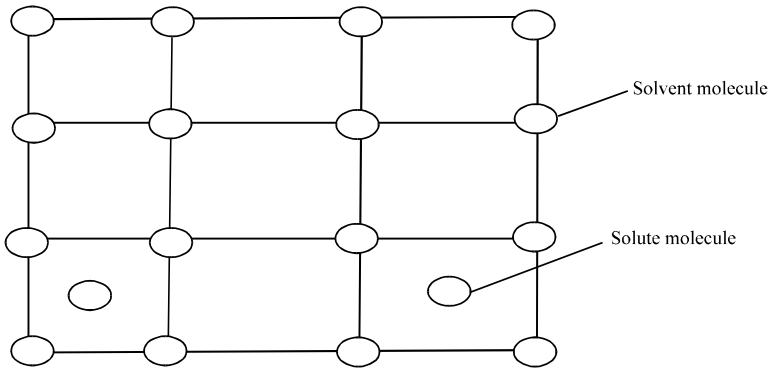

Fig. 7: Interstitial solid solution

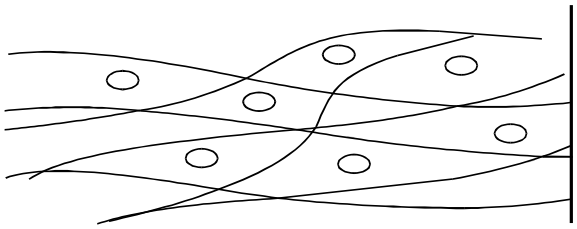

Fig. 8: Amorphous solid solution (Suryawanshi *et al*., 2010)

molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter Furthermore, the volume of the solute molecules should be less than 20% of the solvent (Fig. 7) Interstitial solid solution.

Amorphous solid solution: It is demonstrated, that drug with propensity to super cooling has more tendency to solidify as an amorphous form in presence of carrier (Nikhil, 2010). This is quite similar to simple eutectic mixtures but only difference is that drug is precipitated out in an amorphous form. Ex. Precipitation of sulfathiazole in crystalline urea (Fig. 8), amorphous solid solution (Table 4) and classification of Solid Dispersions according to Molecular arrangement (Gavali *et al*., 2011).

Table 4: Classification of solid dispersions according to molecular arrangement (Sonpal *et al*., 2011)

Solid dispersion type	Matrix	Drug	Remarks	No. of Phases	References
Eutectics	C*	C**	The first type of solid dispersions prepared	2	Chiou and Riegelman (1971)
Amorphous Precipitations in crystalline matrix	C*	A**	Rarely encountered	2	and Breitenbach *et al*. (2002)
Solid solutions					Mullins and Macek (1960)
Continuous solid Solutions	C*	M**	Miscible at all compositions, never prepared	1	and Goldberg *et al*. (1965)
Discontinuons solid solutions	C*	M**	Partially miscible, 2 phases even though drug is molecularly dispersed	2	Sekiguchi and Obi (1961)
Substitutional solid solutions	C*	M**	Molecular diameter of drug (solute) differs less than 15% from matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinuous: 2 phases even though drug is molecularly dispersed	1 or 2	Rastogi and Varma (1956) and Wilcox *et al*. (1964)
Interstitial solid Solutions	C*	M**	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuons Example: Drug in helical interstitial spaces of PEG	2	Chiou and Riegelman (1971) Chiou and Riegelman (1969)
Glass suspension	A*	C**	Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	2	Chiou and Riegelman (1971) and Sarkari *et al*. (2002)
Glass suspension	A*	A**	Particle size of dispersed phase dependent on cooling/evaporation rate much solid dispersion are of this type	2	Chiou and Riegelman (1971) and Sarkari *et al*. (2002)
Glass solution	A*	M**	Requires miscibility/solid solubility, complex formation or upon fast cooling/evaporation duriug preparation, many (recent) examples especially with PVP	1	Simonelli *et al*. (1969)

A*: Matrix in the amorphous state, C*: Matrix in the crystalline state, A**: Drug dispersed as amorphous clusters in the matrix, C**: Drug dispersed as crystalline particles in the matrix, M**: Drug molecularly dispersed throughout the matrix

Glass solutions: Solute dissolves in glass carrier to form a homogeneous glassy system is known as glass solutions (Swarbrick, 2006; Kim *et al*., 2010). Glass suspensions are mixture in which precipitated particles are suspended in glass solvent. Different characteristics of glassy state are brittleness, transparency below the glass transition temperature. Lattice energy (barrier to rapid dissolution) is much lower in glass solution and suspension. Ex-Carriers for glass solution and suspension-citric acid, sugars (dextrose, sucrose and galactose), PVP, PEG and urea (British Pharmacopoeia, 2007; Van Drooge *et al*., 2004) (Table 4) Different carriers used for the preparation of solid dispersion (Naveen *et al*., 2010) (Fig. 9) Schematic picture of the variation of enthalpy (or volume) with temperature. TG-glass transition temp, T f-M.P. of material.

METHODS OF PREPARATION OF SOLID DISPERSIONS

Hot melt method: A process of transferring a powder blend of drug and carrier by a rotating screw, through the heated barrel of an extruder and pressing the melt through a die into a product of uniform shape is known as Hot-Melt Extrusion (HME) or fusion method (McGinity and

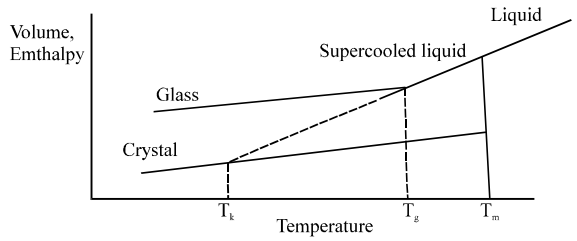

Fig. 9: Schematic picture of the variation of enthalpy (or volume) with temperature (Shujun *et al.*, 2006) Tag: Glass transition temp, To: M.P. of material

Zhang, 2003). HME was first introduced in the plastics industry in the mid-nineteenth century to apply polymeric insulation coatings to wires (Crowley *et al.*, 2007). First applications of HME were realized as a manufacturing tool in the pharmaceutical industry (Chaudhuri, 2007).

Solvent evaporation method: The process which involve solubilization of drug and carrier in a volatile solvent which is later evaporated is termed as Solvent Evaporation Method (SEM). (Hasegawa *et al.*, 1985; Lloyd *et al.*, 1999; Lima *et al.*, 2008). In this method, the thermal decomposition of drugs or carriers can be prevented, since organic solvent evaporation occurs at low temperature (Won *et al.*, 2005; Gupta *et al.*, 2008; Singh *et al.*, 2011). Solvent evaporation method is popularly used for preparation of microsphere because of its simplicity, fast processing and reproducibihty with minimum controllable process variables that can be easily implemented at the industrial level. Many studies have been done on solid dispersions of Meloxicam (Chokshi and Hossein, 2004; Leila *et al.*, 2011), Naproxen and (Mullins and Macek, 1960), by solvent evaporation techniques.

Fusion method: A method in which a molten mixture of drug and carrier are cooled to solidification, is called as fusion method it is also called as solvent method in which precipitation of drug and carrier from a common solvent occur. Paracetamol solid dispersion with PEG 8000 was prepared by melt fusion method (Khan *et al.*, 2011).

Melting solvent method: This involves dissolution of drug in a minimum amount of an organic solvent, which is then added to the molten carrier (Chiou and Riegelman, 1969; Gupta and Moorthy, 2007). Melting solvent method (melt evaporation) method is used to prepare spironolactone-polyethylene glycol 6000 solid dispersion without removing the solvent. They mention that 5-10% (w/w) of liquid compound could be incorporated into polyethylene glycol 6000 without significant loss of its solid property (Table 5). Some resent patent on solubility enhancement using solid dispersion technique (Schroeder, 2009; Ajazuddin and Saraf, 2011) has been shown in Table 5.

COMPLEXATION

Cyclodextrins (CD) is a group of cyclic oligosaccharides, known for their ability to form inclusion complexes with a variety of organic molecules (Saenger *et al.*, 1984; Khan *et al.*, 2001) Complexation by Cyclodextrins, especially the most commonly available β-Cyclodextrins, is widely

Table 5: Some resent patent on solubility enhancement using solid dispersion technique (Schroeder, 2009)

Patent No.	Author name	Abstract	References
200090143423	Rudolf Schroeder, Tanja Heitmann	A solid dispersion prodnct comprising at least one N-aryl urea-based pharmaceutically active agent or an agent of related structural type is obtained	Schroeder (2009)
69546043	Guitard, patric	They invent oral pharmaceutical composition comprising a macrolide in solid dispersion	Guitard (2005)
6753330	Takano *et al*. toshio	Their invention provide a solid dispersion composition containing Hpmc-3-one 2-benzyl- 5-(4-chlorophenyl)-6-[4-(methylthio) phenyl]-2 H-pyridazin and PE PPG	Takano (2004)
6677362	Barbara, ink, rainer Richter, Friedreich	A novel solid pharmaceutical dispersion that improves the bioavailability of poorly water soluble drugs is produced by combining the drug with a polymer carrier such as polyvinyl pyrrolidone	Barbara (2004)
5456923	Nakamichi, Izumi, Kouichi	They perform solid dispersion by employing twin-screw extruder technique	Nakamichi (1995)

Table 6: List of complexing agents

Types	Examples
Inorganic	I_B^-
Coordination	Hexamine cobalt (III) chloride
Chelates	EDTA, EGTA
Metal-olefin	Ferrocene
Inclusion	Cyclodextrins, choleic acid
Molecular complexes	Polymers

used to increase the solubility of drug molecules which have limited solubilities in water (Abou-Auda *et al*., 2006). Cyclodextrins Can also be used to prevent drug-drug interaction, it Convert liquid drug in to microcrystalline powders, decreases volatility, modify gastrointestinal or ocular irritation and mask of objectionable taste or odor of drug. Cyclodextrins of pharmaceutical relevance contain 6, 7 or 8 dextrose molecules (α, β, γ-Cyclodextrins) bound in a 1, 4-configuration to form rings of various diameters. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form noncovalent inclusion complexes resulting in increased aqueous solubility and chemical stability. Complexation is occurring between two or more molecules to form a nonbonded entity with a well defined stoichiometry. Complexation relies weak forces such as London forces, hydrogen bonding and hydrophobic interactions. The Inclusion complexes can induce modification of the physicochemical properties of the guest molecules, particularly in terms of water solubility and solution stability (Lyng *et al*., 2004). Complex Formation by Cyclodextrins shown in Fig. 10 (Khan *et al*., 2001). Different method are used to prepare inclusion complexes of a variety of drugs in order to improve their solubility and dissolution rate. E.g., Co-precipitation, kneading and solid dispersion methods (Shujun *et al*., 2006). There are many types of complexing agents and a partial list can be found in Table 6.

SOLUBILISATION BY SURFACTANTS

Surfactants are known to play a vital role in pharmacy because it have an ability to increase the solubility of poorly soluble drug in water (Gharaei-Fathabad, 2011; Moghaddam and

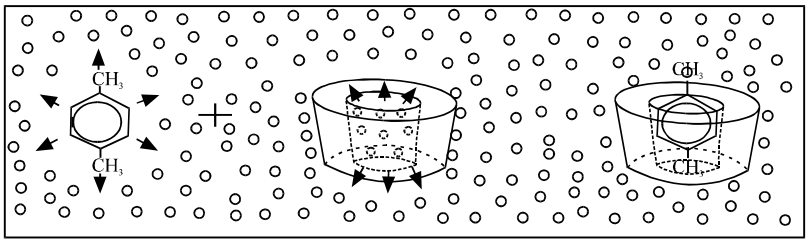

Fig. 10: Complex Formation by Cyclodextrins (Kawashima *et al*., 1975)

Moghaddam, 2011). One of important property of surfactants is the formation of colloidal-sized clusters in solutions, called as micelles which is having a particular significance in pharmacy. Surfactant having the characteristic property of reducing the interfacial and surface tension using the same mechanism as chemical surfactant. Surfactants are the molecules with distinct no Polar Regions (Emara *et al*., 2002). Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be cationic, anionic, nonionic or zwitterionic. When small polar molecules are added they can accumulate in the hydrophobic core of the micelles. This technique of solubilization is very important in biological and industrial processes (Gavali *et al*., 2011). This work was investigated to develop the carvedilol tablets, allowing fast, reproducible and complete drug dissolution, by using surfactant.

Microemulsions: The concept of microemulsion was first introduced by Hoar and Schulman (1943). A monodispersion spherical droplets consisting of oil, surfactant, co-surfactant and aqueous phase, which is optically isotropic and thermodynamically stable with a droplet diameter within the range of 10-100 nm is defined as 'microemulsion (Tenjarla, 1999; Yazdani and Hadianfard, 2012). Microemulsions could enhance the potential solubilization of hydrophobic drugs (Yin *et al*., 2009; Alexander *et al*., 2011a). Amongst the various drug delivery systems, the microemulsion system is considered as an ideal alternative for the oral delivery of lipophilic drug.

Self micro emulsifying drug delivery systems: For the improving solubility, dissolution and oral absorption of hydrophobic drugs 'self- micro emulsifying drug delivery systems' (SMEDDS) have been preferred (Breitenbach *et al*., 2002; Cui *et al*., 2005). SMEDDS is a isotropic mixtures of an oil, surfactant, co surfactant or (solubilizer) and drug. The basic principle of this system is its ability to form fine oil-in-water (o/w) microemulsions under gentle agitation following dilution by aqueous phases.

Self emulsifying drug delivery systems (SEDDS): An isotropic mixture of oils, surfactants, along with co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) micro emulsions upon moderate mixing of these ingredients in aqueous media, such as GI (Gastro Intestinal) fluids is termed as Self Emulsifying Drug Delivery Systems (SEDDS) (Agrawal *et al*., 2012). It is the most useful technology to improve the rate and extent of this poorly water soluble drug. SEDDS is a mixture of oil, surfactant and if necessary a solubiliser. Self emulsification is initiated under gentle agitation following contact with aqueous phase and forms

a thermodynamically stable o/w microemulsion with particle diameter of 100 nm or less. They are reputed to improve the oral bioavailability of poorly water soluble drug (Obitte *et al.*, 2008; Ajazuddin and Saraf, 2010b).

CHEMICAL MODIFICATIONS (Rytting *et al.*, 2005)

Salt formation: For enhancement solubility and dissolution rates of acidic and basic drugs salt formation is the most common and effective method (Serajuddin, 2007). Salts of acidic and basic drugs have, in general, higher solubility than their corresponding acid or base forms. Salt formation to enhance the aqueous solubility is the most preferred approach for the development of liquid formulations for parenteral administration (Sweetana and Akers, 1996; Lakade and Bhalekar, 2010).

Co-crystallization: The crystalline material that consists of two or more molecular and electrical neutral species held together by non-covalent forces is termed as co-crystallization' (Masuda *et al.*, 2012). The non-ionizable drugs can be form due to the co crystal, which cannot undergo in salt formation (Childs *et al.*, 2007). By the addition, for ionizable drugs, the number of suitable co crystal formers can exceed the number of suitable salt formers. For example, the ionizable drug piroxicam has more than 50 reported co crystal formers (Tran *et al.*, 2010).

Co-solvent: Non-aqueous co-solvent systems have been evaluated for their potential use in the freeze-drying of pharmaceutical products. Co-solvents have been reported to affect the rate of the organic phase partitioning into the external aqueous phase and thus, influence the physicochemical properties and release kinetics of PLGA microspheres (Rudra *et al.*, 2011; Singh *et al.*, 2011).

Hydrotropic: For drug aqueous solubility 'hydrotropic' solubilization is an important technique (Shibata *et al.*, 2009). Since 1916, New berg, was first suggested the term hydrotropic which is used to designate anionic organic salts which, at high concentrations, considerably increase the aqueous solubility of poorly soluble solutes. Hydrotropes dissolved in water which can produce high degree solubility enhancement of hydrophobic drugs (Trana *et al.*, 2011). For enhancement of aqueous solubihty of hydrophobic drugs 'hydrotropic agents' have been found to be more effective and hence can play important role for improving the oral bioavailability (Maheshwari and Jagwani, 2011; Alexander *et al.*, 2011b) (Table 7). Hydrotropic is a molecular phenomenon where by adding a second solute (the hydrotropic) results in an increase in the aqueous solubility of poorly soluble solutes (Nidhi *et al.*, 2011) (Table 8) provide the example of some drug which Enhance the solubility by using various technique.

Table 7: Hydrotropic is a molecular phenomenon where by adding a second solute results in an increase in the aqueous solubility of poorly soluble solutes (Bobe *et al.*, 2011)

Drug	Hydrotropic agent
Cefprozil	Potassium acetate, sodium acetate
Paracetamol, diclofenac sodium	Sodium acetate urea
Theophylline	Sodium salicate
Salicylic acid	Ibuprofen sodium, sodium salicate
Furosemide	Ibuprofen sodium
Chlorpropamide gatifloxacin	Sodium salicylate

Table 8: Example of some drug which Enhance the solubility by this technique

Drug	Polymer	Drug delivery	Method	Solubility+ drug profile	Use	Dose	Conclusion	References
Roxithromycin	β-CD PEG, PVP, sugar	Oral	Solid dispersion	0.018 mg mL^{-1} T½ = 12 h Bioavabilaity = 50%	Antibacterial	150-300 mg	70% increases	Venkatesh *et al.* (2009)
Paracetamol	HPβ-CD	Oral	Inclusion complexes	13.69 mg mL^{-1}	Analgesic	10 mg	Solubility 82.14 mg mL^{-1}	Aejaz *et al.*(2010)
Acyclovir	PEG 6000 PVP K-30, β-CD, HP β-CD	Oral	Inclusion and solvent method	12.84 mg mL^{-1} T ½ = 3-5 h	Anti-viral	200 mg	Increase in presence of peg-6000	Meera *et al.* (2010)
Glipizide	Polaxamer 188,407	Oral	SD kneading method	0.004 mg mL^{-1}	Hypoglycemic	5-15 mg	4.01 mg mL^{-1}	Chaudhary (2010)
Olanzepine	2HP β-CD	Oral	Inclusion method	13.13 µg mL^{-1}	Antipsychotic	2.5-10 mg	22.97 µg mL^{-1}	Sethi (2011)
Nimisulide	β-CD	Oral	Inclusion complexes	2.25 µg mL^{-1}	NSAID	100 mg tab	D+β-cd(1:2) = 30.50 µg mL^{-1}	Deepthi (2009)
Alprazolam	PEG-600 PVP k-30	Oral	Solvent evaporation	0.064 mg mL^{-1}	Sedative hypnotic	0.75-3.0 mg	85% increases	Badawi *et al.* (2011)
Fenofibrate	Polaxamer 407, PEG-6000	Oral	Fnsion method	Poorly soluble T ½ = 20 h	Hypolidemic	200 mg	95% increases	Patel *et al.*(2010)
Aceclofenac	PVP k 30 HPMC Aerosil 200	Oral	Solvent evaporation method	14 µg mL^{-1}	NSAID	200 mg	85% increases	Shinde *et al.* (2010) and Siddiqui *et al.*(2005)
Glibenclamide	Poloxamer 407 Polyethyleneglycol 4000	Oral	Solvent evaporation method	Poorly water soluble	Blood glncose level lowering	5-15 mg	Increases	Manimaran *et al.*(2010)
Atorvastatin	Urea, Poloxamer-407, citric acid, mannitol	Oral	Hot-melt method solvent evaporation method	0.21 mg mL^{-1} bioavailability 14%	Hyperlipidemia	20 mg	Methanol 10 µ mL^{-1}	Bobe *et al.* (2011)
Tenoxicam	Poloxamer 127	Oral	Solid dispersions	Poorly water soluble	Anti inflammatory	20 mg	Increases in presence of polaxamer	Saritha and Shastri (2010)
Ibrofen	Peg-6000 tween-80 sls gelncire	Oral	Solid dispersion	0.1 mg mL^{-1}	NSAID	200 mg	PH6 = 2.325 g L^{-1}	Ali (2006)
Diacerein	β-CD	Oral	Solid inclnsion complexes	0.01 mg mL^{-1}	Osteoarthritis	200 mg	Increase in presence of β-cyclo dextrin 299.5 moL^{-1}	Maski *et al.* (2009)
Ibuprofen	Peg-6000 tween 80 Sls gelncire	Oral	Solid dispersions	0.1 mg mL^{-1}	NSAID	200, 400 600 mg	Solubility increased up to 50%.	Nitin *et al.* (2009)
Amoxycillin trihydrate	Gum karaya	Oral	Solid dispersion solvent evaporation method	3430 mg L^{-1} poorly water soluble	Anti-microbial	100 mg	The concentration of gum increases,	Biswas and Subhasis (2011)
Bicalutamide	L-arginine; cyclodextrin	Oral	Inclusion complexes kneading method	Poor aqueons solubility (5 mg L^{-1})	Prostate cancer	50 mg tab	Solubility of complex was increased by 91%.	Pandya *et al.* (2008)
Itraconazole	Eudragit PEG HPMC	Oral	Solid dispersions	Poorly water-soluble T1/2 = 30-60 h	Anti-fungal	200 mg	Solubility 254.592.1 mg mL^{-1}	Lee *et al.* (2005)
Naproxen	HPMC	OraL	Roller compacted powder mixtures	45 mg mL^{-1} T ½ = 12-16 h	NSAID	250 mg	Solubility increases 50 mg mL^{-1}	Mura *et al.* (2005)
Carvedilol	Acetone	Oral	Solid dispersion particles	10.4 g 100 mL in acetone T1/2 = 2-8 h	Hypertension	25 mg	Increases in surface 27.1 average pore diameter (nm)	Swamy *et al.*(2010)

Table 8: Continue

Drug	Polymer	Drug delivery	Method	Solubility+ drng profile	Use	Dose	Conclnsion	Reference
Oridonin	PVP K17	Oral	Anti-solvent techni	0.75 g L^{-1} bioavailability 26.4-fold	Carcinoma	50 mg	0.5-1 mL min^{-1}	Gokturk and Var (2011)
Sibutramine	HPMC 2910	Oral	Solid dispersion	Solubility 0.01 mg mL^{-1}	Obesity	10 mg	4.99±0.31 (mg mL^{-1})	Lim *et al.* (2010)
Tacrohmns	HP-β-CD	Oral	Solvent-evaporation method, solvent-wetting method	0.67±0.19 μg mL^{-1} T1/2= 12-13 h	Immune supppresants	10 mg	0.7 μg mL^{-1},solubility increases	Tsaoa *et al.*(2010)
Carbamazepine	Glnco samine hydrochloride	Oral	Solid dispersion particles	Solubility 8.54±0.15 mg 100 mL	Osteoarthritis	20 mg	2:1 (acetone-water) 8.20±0.50 mg/100 mL	Al-Hamidia *et al.*(2010)
Itraconazole	Poloxamer 188, PVP HPMC, eudragit	Oral	Solid dispersions	Low water solubility T1/2 = 30-60 h	Antifungal agent	200 mg	141.4-146.9 fold increases	Jung *et al.* (1999)
Felodipine	Poloxamer 188 poloxamer 407	Oral	Super critical anti-solvent precipi-tation.	0.5 μg m^{-1} in water	Cardio vascular	5-10 mg	35-110 μg mL^{-1}	Won *et al.* (2005)
Nifedipine	PVA HPMC	Oral	Cogrinding method	11 mg L^{-1}	Anti angina	5-20 mg	417 μg mL^{-1}	Sugimoto *et al.* (1998)
Oxaprozin	Chitosan methy lated β-cyclo dextrin	Oral	Phase solubility studies	0.2g/100 mL at 20°C	NSAID	600 mg	0.324 mg mL^{-1},	Maestrelli *et al.* (2011)
Glyburide	SLS HPMC	Oral	Nano-suspension.	4.4± 0.70 μg mL^{-1} in water	Blood glucose level lowering	5-15 mg	24.56± 0.35 μg mL^{-1} in 10% sls	Singh *et al.* (2011)
Mebenda zole	L-HPC	Oral	Solid dispersion	Low aqueons solu-bility	Anthel-mintics	200 mg	3.80-fold	Jain *et al.* (2010)
Losartan potassium	Poloxamer 188 MCC, poly ethylene glycol,	Oral	SD granules	Poorly soluble in gastric flnid T1/2=6-9 h	Angio tensin antagonist	50 mg	pH 1.2 (gastric flnid) = 400 μg mL^{-1} pH6.8 (intestinal flnid).253 mg mL^{-1}	Garcia-Rodriguez *et al.* (2011)
Griseofulvin	Corn starch; processed starch;	Oral	Solid dispersion, roll mixing;	Poorly water soluble	Anti fungal	125 mg	15-fold and 30-45-fold higher,	Saito *et al.* (2002)
Gliclazide	PVP K-30 HPMC E4	Oral	Solid dispersion	0.004 mg mL^{-1}	hypoglycemic	5-15 mg	solubility increased 4.01 mg mL^{-1}	Ingle *et al.* (2011)
Loper-amide	PEG600	Oral	Solid dispersions by spray drying	1 mg/100 mL	Diarrhoea	2-4 mg	Enhanced solubility by PEG	Hasegawa *et al.* (2005) and Lolodi (2011)
Indomethacin	Cros PVP	Oral	SD with an extruder or kneader	8.5 μg mL^{-1} T1/2 = 2-5 h	NSAID	25 mg	30 μg mL^{-1} four-fold increase solubility	Yusuk (2009)
Isradipine	PVP fumaric, citric and malic acid	Oral	Solid dispersions	6.98± 0.01 μg mL^{-1} in water	Hyper-tension	2.5 mg	Solubility increases 316.22±2.44 μg mL^{-1}	Planinsek *et al.* (2011)
Carvedilol	β-CyD	Oral	Inclusion-complex	0.1 mg mL^{-1} 37°C	Hyper-tension	25 mg	carvedilol +β-CD and forms a complex and increase solubility.	Wen *et al.* (2004)
Bromazepam,	β-CD β-HP-CD	Oral	Inclusion complexes	water insoluble	NSAID	60 mg	Solubility increase.presence of β-CD and β-HP-CD	Emara *et al.* (2002)
Aceclofenac	Hydro philic carrier, Aerosil 200,	Oral	Solvent evaporation method	14 μg mL^{-1}		200 mg	85% increas Drug+ hpmc+ aerosil	Furqan *et al.* (2011)

CONCLUSION

The stability of the drug, its solubility and availability at the site of action, is very important particularly when the formulation is intended for oral administration. Solubihty and dissolution can be subsequently affecting the *in vivo* absorption of drug. So, it is very important to improve the aqueous solubility drugs. By reviewing this article we conclude that, solubility is a most important parameter for the oral bioavailability of hydrophobic. Solubility is also the basic requirement for the formulation and development of different dosage form of different drugs. Solubility can be enhanced by many techniques and number of folds increase in solubility is reported too. Because due to the solubility and stability problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It is now possible that to increase the solubility of hydrophobic drugs with the help of various techniques as mentioned above.

ACKNOWLEDGEMENT

The authors would like to acknowledge the assistance provided by the Library of "Rugnta College of Pharmaceutical Sciences and Research, Kohka-kurud Road, Bhiali, C.G. (India) for collection of literature.

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