INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

REVIEW ON: SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUG

Sachin S. Gaikwad*, Rahul S. Mhalaskar, Yogesh D. Mahale, Nitin P. Jain
SND College of Pharmacy, Babhulgaon, Yeola, Dist-Nashik 423401 Maharashtra (INDIA).

ARTICLE INFO

Article history
Received 10/11/2014
Available online
30/11/2014

Keywords
Solubility,
Solid Dispersion,
BCS Classification.

ABSTRACT

Solubility is one of the important parameter to attain desired concentration of drug in systemic circulation for pharmacological response to be shown. It is vital to improve the solubility and dissolution rate for poorly soluble drugs since these drugs possess low absorption and bioavailability. About 40% of all new chemical entity has poor bioavailability. Increasing the bioavailability of poorly soluble drugs will be one of the biggest challenges for formulation scientists in the future. This review is intended to discuss thoroughly the various traditional novel techniques like sono crystallization, spray freezing in to liquid, pearl milling, solid dispersion, salt formation and pH adjustment etc. for solubility enhancement of hydrophobic drugs for oral pharmaceutical formulation and also tried to focus on the polymers used for to achieve solubility enhancement, process of Solubilization and factor affects on it. In this article we focused on, solubility of the drug is the most significant factor and prime requirement for to achieve good bioavaibility after the absorption of drug so it is most critical factor in the formulation development.

Corresponding author
Sachin S. Gaikwad
Department of Pharmaceutics,
SND College of Pharmacy, Babhulgaon,
Yeola, Dist-Nashik 423401 Maharashtra (INDIA),
sachingaikwad619@gmail.com
+91-9860070924

*Please cite this article in press as **Sachin S. Gaikwad** et al. Review on: Solubility Enhancement of Poorly Water Soluble Drug. Indo American Journal of Pharm Research.2014:4(11).*

Copy right © 2014 This is an Open Access article distributed under the terms of the Indo American journal of Pharmaceutical Research, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Therapeutic efficiency of a drug is not only depends upon the bioavailability but also the solubility of drug molecules. Drug solubility is the greatest concentration of the drug dissolved in the solvent under specific condition of temperature, pH and pressure. As solubility is an important determinant in drug liberation hence it plays a key function in its bioavailability. For absorption of any drug it must be present in the form of an aqueous solution at the site of absorption. About 40% of all new chemical entities have poor bioavailability. The bioavailability can be increased by changes in disintegration and dissolution. Aqueous solubility smaller than 1 µg/ml will definitely create a bioavailability problem and will affects the efficacy of the drug. There are number of methods through which aqueous solubility of the drug can be increased. Especially for class II substances according to the Bio pharmaceutics Classification System (BCS), the bioavailability may be improved by raising the solubility and dissolution rate of the drug in the gastro-intestinal fluids [1].

There are many approaches accessible and reported in literature to enhance the solubility of poorly water soluble drug. The techniques are selected on the basis of certain aspects such as property of drug under consideration, nature of excipients to be selected and nature of intended dosage form [2].

The difficulty is even more intense for drug such as intraconazole and carbamazepine as they are poorly soluble in both aqueous and organic media, and for drugs having a log p (The logarithm of the ratio of the concentrations of the un-ionized solute in the solvents is called log P) value of 2 Such drugs often have an erratic absorption profile and highly variable bioavailability because their performance is dissolution rate limited and is affected by the fed / fasted state of the patient.

There are successive two processes can be identified to describe the oral absorption of drugs from solid dosage forms:

• Dissolution of the drug *in vivo* to produce a solution and
• Transport of the dissolved drug across the gastrointestinal membrane.

Each process can be characterized by a rate constant. If the rate of dissolution of the drug is significantly slower than the rate of absorption, the dissolution of the drug becomes the rate-limiting step in the absorption process. Consequently, numerous attempts have been made to modify the dissolution characteristics of certain drugs in an effort to attain more rapid and more complete absorption. The particle size of the drug is having great importance in the transport from the gastrointestinal (GI) tract to the site of action by increasing the dissolution rate in the GI tract [3].

The techniques generally employed for solubilization of drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization and hydrotropy etc. Solubilization of poorly soluble drugs is a often encountered dispute in screening studies of new chemical entities as well as in formulation design and development. The solubility of a drug is represented through various concentration expressions such as parts, percentage, molarity, molality volume fraction mole fraction [4].

The Indian Pharmacopeia classified the solubility of drugs [5] in seven classes as listed in Table 1.

Table 1: IP Solubility criteria.

Descriptive term	Part of solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

BCS Classification: [6]

Class I-High Solubility, High Permeability

Class I drugs show a high absorption number and a high dissolution number. For those Class I compounds formulated as immediate release products, dissolution rate generally exceeds gastric emptying so, nearly 100% absorption can be predictable if at least 85% of a product dissolves inside 30 min of *in vitro* dissolution testing across a range of pH values accordingly, *in vivo* bioequivalence data are not necessary to assure product comparability.

E.g. metoprolol, diltiazem, verapamil, propranolol

Class II -Low Solubility, High Permeability

Class II drugs have a high absorption number but a low dissolution number. *In vivo* drug dissolution is then a rate limiting step for absorption apart from at a very high dose number. The bioavailability of these products is likely to be dissolution-rate limited, for this reason, a correlation between *in vivo* bioavailability and *in vitro* dissolution rate may be observed.

e.g. Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedinpine

Class III – High Solubility, Low Permeability

In this class for drug absorption permeability is rate limiting step. These drugs show a high variation in the rate and amount of drug absorption. Dissolution will most likely occur very rapidly but absorption is permeability-rate limited so there has been some proposal that as extended as the test and reference formulations do not contain agents that can modify drug permeability or GI transit time, waiver criteria similar to those associated with Class I compounds may be appropriate.
e.g. Cimetidine, Acyclovir, Neomycin B, Captopril

Class IV- Low Solubility, Low Permeability

Those compounds have a poor bioavailability usually they are not well absorbed over the intestinal mucosa and a high variability is expected with very poor oral bioavailability. These compounds are not only difficult to dissolve but once dissolved, often show incomplete permeability across the GI mucosa. These drugs tend to be extremely tricky to formulate and can exhibit very large inter subject and intra subject variability.

Class boundaries:

***Highly Soluble*:**

When the highest dose strength is soluble in < 250 ml water over a pH range of 1 to 7.5 then drug substance is considered highly soluble

Highly Permeable:

When the extent of absorption in humans is determined to be > 90% of an administered dose then drug substance is considered highly permeable.

Rapidly Dissolving:

A drug product is considered to be rapidly dissolving when > 85% of the labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of < 900 ml buffer solutions.

Process of solubilization

The process of Solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion shown in figure 1. [7].

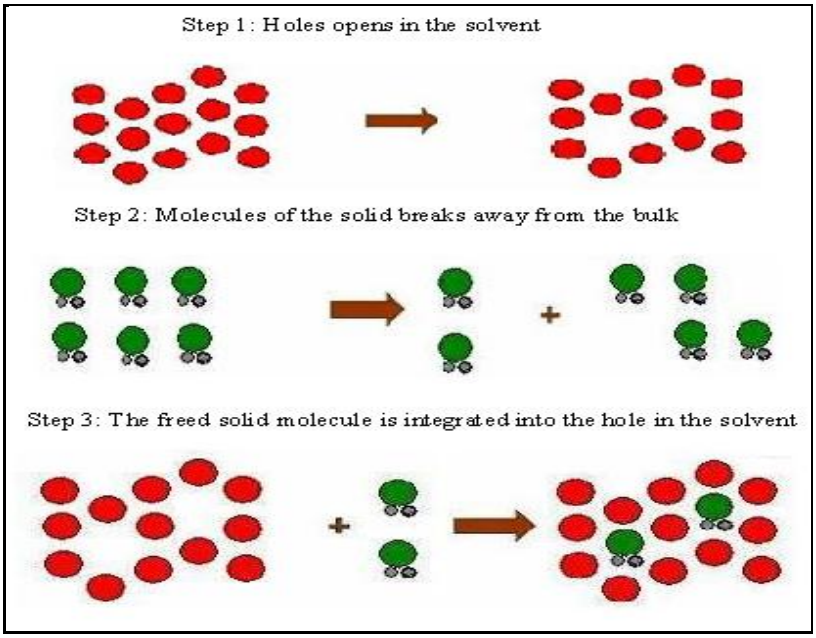

Figure 1: Steps of Solubilization.

Factor affecting solubilization:

Molecular size:

Increasing the particle size or its molecular weight of substance will decrease its solubility. Larger molecules are not easy to encircle with solvent molecules in order to solvate the substance. In the case of organic compounds the quantity of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent.

Temperature:

If the solution process absorbs energy then the temperature is increased as the solubility will be increased. If the solution process releases energy then the solubility will decrease with increasing temperature. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. For all gases, solubility decreases as the temperature of the solution increases.

Pressure:

For gaseous solutes, solubility is increases with the application of presser. For solids and liquid solutes, changes in pressure have nearly no effect on solubility.

Particle size:

The dimension of the solid element influences the solubility because particle size inversely proportional to the surface area. The larger surface area allows a greater interaction with the solvent. The effect of particle size on solubility can be describe by Eq.1

$$\log S/S_0 = 2\gamma V/2.303\ RTr \qquad \text{……Eq. 1}$$

Where, S is the solubility of infinitely large particles.

S_0 is the solubility of fine particles.

V is molar volume.

r is the radius of the fine particle.

Polymorphs:

The shape or habit of a crystal of a given substance may differ but the angles between the faces are forever constant. The ability 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. The two polymorphs cannot be transformed from one another without undergoing a phase transition. Polymorphs can differ in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities. Usually the range of solubility differences between different polymorphs is only 2-3 folds due to comparatively small differences in free energy [8].

***Rate of solution*:**

The rate of solution is determination of how fast substances dissolve in solvents. A various factors affecting rate of solution like-

***Size of the particles**:*

Breaking a solute into smaller pieces increases its surface area, when the total surface area of the solute particles is increased; the solute dissolves more rapidly because the action takes place only at the surface of each particle and hence increases its rate of solution.

***Temperature**:*

For liquids and solid solutes, rising the temperature not only increases the amount of solute that will dissolve but also increases the rate at which the solute will dissolve. For the gases reverse is true.

Amount of solute already dissolved:

When there is little solute previously in solution, dissolution takes place relatively rapidly. As the solution approaches the point where no solute can be dissolved, dissolution takes place more slowly.

***Stirring**:*

With liquid and solid solutes, stirring brings fresh portions of the solvent in contact with the solute, thereby increasing the rate of solution [7].

Methods of solubility enhancement:

There are various techniques available to improve the solubility of poorly soluble drugs.

Surfactants:

Conservative approach to solubilize a poorly soluble substance is to reduce the interfacial tension between the surface of solute and solvent for better wetting and salvation interaction. A wide variety of surfactants like polyglycolized glyceride, tweens, spans, polyoxyethylene stearates and synthetic block copolymers like poly (propylene oxide)-poly (ethylene oxide)- poly (propylene oxide) like poloxamers based micelles, Poly (beta-benzyl-L-aspartate)-b-poly (ethylene oxide), Poly (caprolactone)-b-poly (ethylene oxide) etc are very successful as excipient and carrier for dissolution enhancement. Improvement of drug solubility by using the amphiphilic surfactants is due to lowering surface tension between drug and solvent, improvement of wetting characteristics and micellar solubilization [9].

pH adjustment:

It is well documented that the influence of the changes in pH inside the gastrointestinal tract upon the bioavailability of pharmaceuticals. The absorption of drug is largely dependent upon diffusion, which vary with pH of the individual regions within the gastrointestinal tract, the pKa of the drug and permeability, which are not only moderated by the surface area of the region in which it is released, but also the regional pH effects upon drug ionization. By applying a pH change, poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water. While the significance of critical parameters like salt selection and pH adjustment has been stressed on pre-formulation, the use of pH altering excipients within drug delivery systems is also of significant utility. pH adjustment can in principle be used for both oral and parenteral administration. Because blood is a strong buffer, upon intravenous administration the poorly soluble drug may be precipitate with pH between 7.2 – 7.4. To assess the suitability of the approach, the buffer capacity and tolerability of the selected pH are important to consider. In the stomach the pH is around 1 to 2 and in the duodenum the pH is between 5-7.5, so upon oral administration the degree of solubility is also likely be influenced as the drug passes through the intestines. Solubilized excipients that boost environmental pH within a dosage form (tablet or capsule), to a range higher than pKa of weakly-acidic drugs increases the solubility of that drug, those excipients which act as alkalizing agents may increase the solubility of weakly basic drugs [9].

Salt formation:

Salt formation of poorly soluble drug candidates (weak acids and bases) has been a strategy for several decades to enhance solubility. It is an successful method in parenteral and other liquid formulations, as well as in solid dosage forms of approximately 300 new chemical entities approved by the FDA during the 12 years from 1995 to 2006 for marketing, 120 were in salt forms. In count, out of the 101 approved salts of basic drugs, 54 salts were prepared with hydrochloric acid, representing the hydrochloride was the predominant salt form the aqueous solubility of an acidic or basic drug as a function of pH dictates whether the compound will form suitable salts. The pH-solubility interrelationships also dictate what counter ions would be necessary to form salts, how easily the salts may dissociate into their free acid or base forms, what their dissolution behavior would be under different GI pH conditions, and whether solubility and dissolution rate of salts would be influenced by common ion. Several reviews have outlined general strategies and considerations for salt selection. For the salt formation drug should have ionizable groups that will assist salt formation. The criteria used to select counter ion is as follows:

a) There should be least difference of 2-3 pKa units between the drug and the counter ion.
b) Counter ion should decrease crystal lattice forces.
c) It must be FDA approved or should have sufficient toxicological data to support the selection of the counter ion.
d) This technique has tremendous capability to enhance dissolution rate but it is grasped with disadvantages like approval of salts is a tedious task and also not useful for neutral molecules [9].

Particle Size Reduction:

Micronization or nanonization is one of the most probable approaches to improve the bioavailability of lipophilic drugs by an increase in surface area and saturation solubility by means of reduction of the particle size to sub-micron level.

It is not possible to reduce particle size submicron level by the conventional milling techniques. Patented engineering processes have come up based on the principles of pearl milling high-pressure homogenization, solution enhanced dispersion by supercritical fluids (SEDS), rapid expansion from supercritical to aqueous solution (RESAS), spray freezing into liquid (SFL) and evaporative precipitation into aqueous solution (EPAS) [9].

Co-grinding/Co-micronization:

Co-grinding of a poorly water-soluble drug with water-soluble polymers like hydroxyl propyl methyl cellulose (HPMC), poly vinyl alcohol (PVA) etc in the presence of small amount of water is extremely effective to improve its apparent solubility with preservation of drug crystallinity to some level. However, energy added to decrease particle size results in increased Van der Waal's interactions and electrostatic magnetism between particles leading to reduce effective surface area due to agglomeration thus decreasing dissolution rate.

Co-micronization of drugs by using excipients like microcrystalline cellulose can be used as an option to reduce or remove cohesive and electrostatic forces. This approach increases apparent surface area available for drug dissolution by creating an ordered mixture, thereby causing a decrease in particle-particle agglomeration or by reducing Van der Waal's interactions. Increase in true surface area of the ordered powdered mixture is expected due to the inherent surface roughness and porosity of microcrystalline cellulose-Drug mixture

Following methods can be used for achieving Micronization:

- Jet milling
- Solid solution & eutectic mixtures
- Micro precipitation.
- Controlled crystallization
- Supercritical fluid technology
- Spray freezing into liquid
- Spray freeze dry (SFD)

Pearl Milling:

Based on pearl milling the drug micro particles are ground to nanoparticles (< 400 nm) in stuck between the moving milling pearls. The milling effectiveness is dependent on the properties of the drug, the medium and the stabilizer. rapamune, an immune suppressant agent, is the first FDA approved nanoparticle drug using Nano-Crystals technology developed by Elan Drug Delivery. Emend is another product containing 80 or 125 mg aprepitant formulated by this technique. In general the limitation of the pearl milling process is the introduction of contamination to the product from the grinding material, batch-to-batch variations and the danger of microbiological harms after milling in an aqueous environment.

High- Pressure Homogenization:

Disso Cubes development involves dispersing a drug powder in an aqueous surfactant solution and passing through a high-pressure homogenizer, afterward nano suspensions are obtained. The cavitation force experienced is enough to break up drug from micro particles to nanoparticle. The particle size is dependent on the rigidity of the drug substance, the processing pressure and the number of cycles applied. The possible interesting features of Nano suspensions are:

- Increase in saturation solubility and dissolution rate of drug
- Increase in adhesive nature, thus resulting in enhanced bioavailability
- Increase the amorphous fraction in the particles, leading to a potential change in the crystalline structure and higher solubility
- Possibility of surface modification of nano-suspensions for site-specific delivery

Though, only fragile drug candidates might be broken up into nanoparticle by this method. A few points has to be careful, such as chemical instability of fragile drugs under the harsh production conditions, Ostwald ripening in long-term storage, toxicity of surfactants, redispersibility of the dried powder, batch-to-batch variation in crystallinity level and finally the difficulty of quality control and the stability of the partially amorphous nanosuspensions.

Solution Enhanced Dispersion by the Supercritical Fluids (SEDS):

The SEDS process was developed and patented by the University of Bradford. The use of a coaxial nozzle provide a means whereby the drug in the organic solvent solution mixes with the compressed fluid CO_2 (antisolvent) in the mixing chamber of the nozzle prior to dispersion, and flows into a particle-formation vessel via a restricted orifice. Such nozzle achieves solution breakup through the impaction of the solution by a higher velocity fluid. The high velocity fluid creates high frictional surface forces, causing the solution to disintegrate into droplets. A wide range of materials has been prepared as carriers of micro particles and nanoparticles using the SEDS process. A key step in the formation of nanoparticles is to enhance the mass transfer rate between the droplets and the antisolvent before the droplets coalesce to form bigger droplets. In another study, a significant decrease in the particle size is achieved by using the ultrasonic nozzle-based supercritical antisolvent process.

Rapid expansion from Supercritical to Aqueous Solution (RESAS):

This procedure induces fast nucleation of the supercritical fluid dissolve drugs and surfactants resulting in particle formation with a desirable size distribution in a extremely short time. The surfactants in the supercritical fluid stabilize the newly formed small particles and suppress any tendency of particle agglomeration or particle growth when spraying this solution (drug + surfactant + CO2) into an aqueous solution containing a second surface modifier. The low solubility of poorly water soluble drugs and surfactants in supercritical CO2 and the high pressure required for these processes restrict the utility of this technology in pharmaceutical industry.

Ultra-Rapid Freezing:

Ultra-rapid freezing is a novel, cryogenic technology that creates nano-structured drug particles with greatly enhanced surface area. The technology has the flexibility to produce particles of varying particle morphologies, based on control of the solvent system and process conditions. This process involves freezing a dissolved drug in a aqueous of anhydrous polymer water solution onto the surface of a cryogenic substrate with a thermal conductivity (k) between 10 and 20 W/(m K), collecting the frozen particles and removing the solvent, resulting in highly porous, agglomerated particles.

The polymer acts as a stabilizer acting as a crystal growth inhibitor. Because of rapid conductive heat transfer, resulting in high super-saturation and nucleation rates, the URF technology has the potential to create powders with superior physicochemical properties, similar to those produced by other rapid freezing technologies. As in other freezing technologies, the rapid freezing of the drug/polymer composition is decisive in preventing phase separation during freezing, allowing for the active to be molecularly dispersed with the polymer**.** As with controlled precipitation; this process uses pharmaceutically acceptable solvents, excipients and conventional process equipment making it fast and scalable.

Recrystallization of the drug is avoided by the inclusion of high glass-transition temperature (Tg) polymers such as PVP or HPMC. This technique is widely applicable to enhance in vivo absorption for the BCS class-II compounds.

Sono crystallization:

Sono crystallization is a novel particle engineering technique to improve solubility and dissolution of hydrophobic drugs and to study its effect on crystal properties of drug. Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed productively to reduce particle size by using ultrasound. Sono crystallization utilizes ultrasound power

characterized by a frequency range of 20–100 kHz for inducing crystallization. Most applications use ultrasound in the range 20 kHz-5 MHz [10].

Solvent Deposition/Evaporation:

In this method drug is dissolve in a solvent like methylene chloride to create a clear solution. The carrier is then discrete in the solution by stirring and the solvent is removed by evaporation under temperature and pressure. The resultant mass is then dehydrated, pulverized, and passed through a sieve. The Increase in the dissolution rate is ascribed to the reduced particle size of the drug deposited on the carrier and enhanced wettability of the particles brought about by the carrier [9].

Solid solutions/dispersions:

Solid dispersion is defined as a dispersion of one or more active ingredients in an inert carrier or matrix at solid state. It was initially introduced to overcome the low bioavailability of lipophilic drugs by forming of eutectic mixtures of drugs with water-soluble carriers. It was defined as the dispersion of one or more active ingredients in an inert carrier matrix in solid-state prepared by melting (fusion), solvent or melting-solvent method. The solubility of celecoxib, halofantrine, ritonavir can be improved by solid dispersion using suitable hydrophilic carriers [9, 11].

Method of solid dispersions:

Hot melt method (fusion method):

In this method, the physical mixture of a drug and a water-soluble carrier was heated directly until it melted. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized, and sieved, which can be compressed into tablets with the help of tabletting agents. The melting point of a binary system is dependent upon its composition, i.e., the selection of the carrier and the weight fraction of the drug in the system.

An important requisite for the formation of solid dispersion by the hot melt method is the miscibility of the drug and the carrier in the molten form. Another important requisite is the thermo stability of the drug and carrier.

Solvent Evaporation Method:

Tachibana and Nakumara were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic β-carotene in the highly water soluble carrier polyvinyl pyrrolidone.

The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents. However, some disadvantages associated with this method are the higher cost of preparation, the difficulty in completely removing liquid solvent, the possible adverse effect of the supposedly negligible amount of the solvent on the chemical stability of the drug, the selection of a common volatile solvent, and the difficulty of reproducing crystal forms [7].

Hot melt extrusion:

Hot melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. High shear forces resulting in high local temperature in the extruder is a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can adapted to the next processing step without grinding [7].

Characterization of solid dispersion:

Solid dispersion can be characterized with several analytical methods. FT-IR Spectroscopy, scanning electron microscopy (SEM), X-ray diffraction, dissolution rate determination and thermal analysis methods like thermo-microscopic method, differential thermal analysis (DTA), and differential scanning colorimetry (DSC) can be employed for solid dispersion evaluation [11].

Co-evaporate System / Co-precipitation:

Weak basic drugs like prochlor perazine maleate contain good solubility in acidic pH but in alkaline pH solubility is significantly reduced and when a conventional formulation containing weak base is given orally precipitation of poorly soluble free base occurs within formulation in intestinal fluid. Precipitated drug is no longer capable of release from formulation leading to decrease in bioavailability of drug. This problem can be solved by use of co-evaporate system which incorporates a carrier with solubilizing effect in alkaline intestinal fluid which may operate in the microenvironment, immediately surrounding the drug particle and polymers for controlling the dissolution rate to formulate dosage forms ensuring maximum bioavailability with controlled release of weak base [9].

Inclusion Complexes:

Cyclodextrins are a group of cyclic oligosaccharides obtained from enzymatic degradation of starch. The three major cyclodextrins α, ß, and γ-CD are composed of six, seven, and eight D-(+) -glucopyranose units. These agents have a torus structure with primary and secondary hydroxyl groups orientated outwards. Consequently, cyclodextrins have a hydrophilic exterior and a hydrophobic internal cavity. CD and their derivatives have been employed as complexing agents to increase water solubility, dissolution rate and bioavailability of lipophilic drugs for oral or parenteral delivery [9].

Supercritical fluid method:

A supercritical fluid (SCF) procedure allows the micronization of drug particles inside sub-micron levels. Supercritical fluids are fluids whose temperature and pressure are superior than critical temperature (Tc) and critical pressure (Tp). At near-critical temperature, SCFs are highly compressible, allowing reasonable changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely decide its solvent power. Once the drug particles are solubilised within SCF, they may be recrystallised at greatly reduced particle size. Carbon dioxide and water are the most usually used supercritical fluids. The SCF process can create nanoparticulate suspensions of particles 5–2,000 nm in diameter. e.g. enhancing water solubility of etraconazole with water soluble polymer HPMC by using supercritical fluid processing [10, 12].

Drug dispersion in carriers:

The term "solid dispersions" refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, often prepared by the melting method, solvent method, or fusion solvent-method. Novel additional preparation techniques have included rapid precipitation by freeze drying and by means of supercritical fluids and spray drying, often in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion. The most commonly used hydrophilic carriers for solid dispersions include polyvinyl pyrrolidone, polyethylene glycols, and plasdone-S630. Many times surfactants may also use in the formation of solid dispersion. Surfactants like Tween-80, docusate sodium, Myrj-52, Pluronic-F68 poloxamer and sodium lauryl Sulphate used.

Table 2: List of solubility enhanced drug [13-41]

Name of Drug	Polymers Used	Investigation
Atenelol	Polyethylene glycol 6000 (PEG 6000)	Mahajan A. et al.
Olmesartan medoxomil	Poly ethylene glycol 4000 (PEG 4000), HPMC K4, HPMC K100, Poloxamer-407.	Hasan A. et al.
Mefenamic Acid,	HPMC	Kumar S. et al.
Diclofenac Sodium	PEG4000, PEG6000,and co-solvents PEG200, PEG400	Khan MA. et al.
Celecoxib	PEG 400, Ethanol	Lingam M. et al.
Indomethacin	Hydroxy propyl methylcellulose (HPMC), Kollicoatir, chitosan, Polyvinyl pyrrolidone.	Yadav VB. et al.
Raloxifene	Polyvinyl pyrrolidone, Hydroxy propyl methyl Cellulose (HPMC) Hydroxy propyl cellulose.	Rai VK. et al.
Flutamide	Prostatic carcinoma	Dixit M. et al.
Tinidazole	Polyethylene glycols (PEG 4000,Hydroxypropyl Methyl cellulose (HPMC 5cps), And cyclodextrin.	Chhaprel P. et al.
Clonazepam	Polyethylene glycol 6000 (PEG- 6000),Kollicoat IR, Kollidon VA 64, and Poloxomer	Minhaz A. et al.
*K*etoprofen	Ketoprofen Gelucire 44/14, PVP K30	Nagar G. et al.
Glipizide	Polyvinyl Pyrrolidone (PVP K30), Polyethylene glycol (PEG 6000). Kneading, Skimmed Milk	Rote H. et al.
Steviol Glycosides rebaudioside	cyclodextrin	Mani U. et al.
Fluconazole	Oleic acid, Dimethyl sulfoxide	Shivhare UD. et al.
Ibuprofen	PEG 6000, PVP K 30.	Hasnain MS. et al.
Meloxicam	Polyvinyl pyrrolidone (pvp) Poly ethylene glycol (peg6000).	Jafar M. et al.
Prednisolone	PEG 6000	Milani P. et al.
Aceclofenac	Polyethylene glycol (PEG 6000). Polyvinyl Pyrrolidone (PVP K30),	Kumar T. et al.
Theophylline	HPMC	Jayakumar.C.et al
Cefixime	wherein natural	Reddy SA. et al.
Etoricoxib	poloxamer-407	Kulthe VV. et al.
Telmisartan	PVP K30 aerosil 200	Lakshmi K. et al.
Nimesulide	PVP K-40, PEG 4000, PEG-6000	Gunturu S. et al.
Irbesartan	(polyvinyl pyrrolidone, PVP, and hydroxypropyl methylcellulose, HPMC)	ChawlaG. et al.
Cyclodextrins	PEG 4000	Kumar SK. et al.
Bicalutamide	Povidone K 30, Poloxamer 407	shrikant MV. et al.
Escitalopram Oxalate	Polyvinyl alcohol and Urea	Nirav SP. et al.

Alprazolam	polyethylene glycol-6000 (PEG-6000) and polyvinylpyrrolidone-K30 (PVP-K30)	Roul LK. et al.
Piroxicam	Dimyristoyl phosphatidyl glycerol (DMPG)	Mirza S. et al.
Glimepiride	Poloxamer 188 and Poloxamer 407	Wagh VT. et al.
Amisulpride	β-cyclodextrin, microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate,	Murli KT. et al.

Carriers for Solubility Enhancement:

Carriers, which are soluble and dissolve in water at a fast rate, are widely used in pharmaceutical formulations to enhance solubility and dissolution of drugs. Various carriers are used for solubility enhancement listed mentioned in the table 3 [42].

Table 3: List of carriers used for solubility enhancement.

Category	Examples of carrier
Polymeric materials	Povidone (PVP), polyethylene glycol (PEG), cyclodextrin, hydroxypropyl methyl cellulose, methyl cellulose, hydroxy ethyl cellulose, hydroxy propyl cellulose.
Acid	Citric acid, succinic acid.
Miscellaneous	Microcrystalline cellulose, dicalcium phosphate, silica gel, sodium chloride.
Hydrotrops	Urea, sodium acetate, nicotinamide, sodium benzoate, sodium salicylate, sodium-o-hydroxy benzoate.
Sugars	Dextrose, sucrose, galactose, sorbitol, maltose, mannitol, lactose.
Surfactants	Deoxycholic acid, tweens, spans, polyoxyethylene stearate, renex, poloxamer 188.
Insoluble or enteric polymer	Eudragit L100, Eudragit S100, Eudragit RL, Eudragit RS, Hydroxy propyl methyl cellulose phthalate.

Advantages & disadvantages [12, 43]:

Advantages:

Complexation:

Complexing agent such as hydroxyl propyl beta cyclodextrin and sulfobutyl beta cyclodextrin are less toxic compared to other solubilizing agent such as surfactants and co-solvents.

Melt extrusion:

- The pre-concentrates are relatively easy to manufacture.
- Well-developed micro-emulsion pre-concentrates are not normally dependent upon digestion for drug release. Therefore, optimal bioavailability and reproducibility can be also being expected without co-administration of food (i.e. the fasted state).

Particle size reduction:

- Liquid forms can be rapidly developed for early stage testing (pre-clinical) that can development.
- Typically, low excipients to drug ratios are required.
- Formulations are generally well tolerated provided that strong surfactants are not required for stabilisation.

Hydrotropy:

- Hydrotropy is suggested to be superior to other solubilization method, such as miscibility, micellar solubilization, co-solvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification
- It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.

pH adjustment:

- Simple to formulate and analyze.
- Simple to produce and fast track.

Solid Dispersions:

- *Particles with reduced particle size:* Dispersions, as solid dispersion, represent the last state on particle size reduction, and after inert carrier or matrix dissolution the drug is molecularly dispersed in the dissolution medium. A high surface area is formed which results an increased dissolution rate and further improved the bioavailability of the poorly water-soluble drug.
- *Particles with improved wetability:* The solubility enhancement of the drug is related to the drug wetability improvement verified in solid dispersion.

- *Particles with higher porosity*: Particles in solid dispersions have been found to have a higher degree of porosity and the increase in porosity also depends on the properties of the carrier. More porous nature of the particle results higher dissolution rate.
- *Drugs in amorphous state:* Water-soluble crystalline drugs, when in the amorphous state tend to have higher degree of solubility. Drug in its amorphous state shows higher drug release because no energy is required to break up the crystal lattice during the dissolution process.

Disadvantages:

Particle size reduction

- Due to the high surface charge on discrete small particles, there is a strong tendency for particle agglomeration.
- Developing a solid dosage form with a high pay load without encouraging agglomeration may be technically challenging.
- Technically, development of sterile intravenous formulations is even more challenging.

pH adjustment

- Hazard for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble. Intravenously this may lead to emboli, orally it may cause unpredictability.
- As with all solubilized and dissolved systems, a dissolved drug in an aqueous environment is often less steady chemically compared to formulations crystalline solid. The chosen pH may accelerate hydrolysis or catalyze

Solid Dispersions

The major disadvantages of SDs are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate on ageing. By absorbing moisture, phase separation, crystal growth or a change from metastable crystalline form to stable form can take place which leads to the reduction of drug solubility. Moisture and temperature have more of deteriorating effect on solid dispersions than on physical mixtures. Sometimes it is tricky to handle because of tackiness.

Summary and conclusion:

In this article we concluded that, solubility of the drug is the most significant factor and prime requirement for to achieve good bioavaibility after the absorption of drug so it is most critical factor in the formulation development.

There are number of methods and techniques available to improve the solubility and enhance bio availability we had tried to discuss all these methods in this script. But Solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs. In recent years, a great deal of knowledge has been accumulated about solid dispersion technology, but other methods like micronization, complexation, and pro-drugs concepts also useful in pharmaceutical operations. The deep study is required to prevent the limitation of any method. We gather the list of drug (Table 2.)Whose solubility was enhanced by using one of above methods, also tried to focus on the polymers used and carrier for (Table 3.) to achieve solubility enhancement.

ACKNOWLEDGEMENT

The authors are grateful to SND College of Pharmacy, Yeola, Nashik, India, for providing necessary library facilities to carry out this work. The authors like to thank to Dr. Vikas Patil for their help in improving the quality of this article.

Authors' Statements

Competing Interests

The authors declare no conflict of interest

REFERENCES

1) Ahmad Z., Maurya N., Mishra K., Khan I., Solubility enhancement of poorly water soluble drugs: a review, International Journal of Pharmacy and Technology 2011; 2:1:807-23.
2) Kumar A., Sahoo K., Padhee K., Singh P., Satapathy A., Pathak N., Review on solubility enhancement techniques for hydrophobic drugs, International journal of comprehensive pharmacy 2011; 3:3:1-7.
3) Kumar P., Singh C., Study on solubility enhancement methods for poorly water soluble drugs, American Journal of Pharmacological Sciences 2013; 1:4: 67-73.
4) Vemula V., Lagishetty V., Lingala S., Solubility enhancement techniques, International Journal of Pharmaceutical Sciences Review and Research 2010; 5:1: 41-51.
5) Indian Pharmacopoeia, Controller of Publication, Govt. of India, Ministry of Health and Family Welfare, New Delhi, 2007.p. 143.
6) Reddy B., Karunakar A., Biopharmaceutics classification system: a regulatory approach, Dissolution Technologies 2011; 31-37.
7) Chaudhary A., Nagaich U., Gulati N., Sharma V., Khosa R., Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review, Journal of Advanced Pharmacy Education and Research 2012; 2:1: 32-67.
8) Reddy N., Reddy A., Kavitha K., Kumar R., et al. Review on: better solubility enhancement of poorly water soluble drugs, International Journal of Inventions in Pharmaceutical Sciences 2013; 1:4: 267-73.

9) Thorat Y., Gonjari D., Hosmani A., Solubility enhancement techniques: a review on conventional and novel approaches, International journal pharmaceutical science and research 2011; 2;10: 2501-13.
10) Zaheer A., Naveen M., Mishra K., Khan I., Solubility enhancement of poorly water soluble drugs: a review, International Journal of Pharmacy and Technology 2011; 3:1: 807-23.
11) Wairkar S., Gaud R., Solid dispersions: solubility enhancement technique for poorly soluble drugs, International Journal of Research in Pharmaceutical and Biomedical Sciences 2013; 4:3: 847-54.
12) Kumar M., Manjula B., A Review and enhancement on solubility techniques, Universal journal of pharmacy 2013;2:2: 27-36.
13) Mahajan A, Singh S, Kaur S, Aggrwal A., Studies on solubility enhancement and In-vitro dissolution profile of poorly water soluble drug atenolol using solid dispersion technique, International journal of research in pharmaceutical science, 2013; 4:3: 344-49.
14) Hasan A., Jayalakshmi J., Enhancement of solubility and dissolution rate of olmesartan medoxomilby solid dispersion technique. Journal of current chemical and pharmaceutical scinces 2013; 3:2: 123-34.
15) Kumar S., Parkash C., Kumar P., Singh S., Application of some novel techniques for solubility enhancement of mefenamic acid a poorly water soluble drug, International Journal of Pharmaceutical Sciences and Drug Research 2009;1:3:164-71.
16) Khan M., Enhancement of solubility of poorly water soluble drugs diclofenac sodium by mixed solvency approach, International Journal of Research and Development in Pharmacy and Life Sciences 2013; 2:5: 580-82.
17) Lingam M., Venkateswarlu V., Enhancement of solubility and dissolution rate of poorly water soluble drug using cosolvancy and solid dispersion techniques, International journal pharmaceutical sciences and nanotechnology 2012; 1:4: 349-56.
18) Rai V., Singh R., Sharma M., Agarwal A., Gupta A., Solubility enhancement of poorly water-soluble drug (Raloxifene Hydrochloride) by using different hydrophilic binders in solid dosage form, International journal of comprehensive pharmacy 2010; 3:5:1-5.
19) Dixit M., Kini A., Parthasarthi K., Shivakumar G., A novel technique to enhancing the solubility and dissolution of flutamide using freeze drying, Turk journal pharmacy science 2012; 9:2: 139-50.
20) Chhaprel P.,Talesara A., Jain A., Solubility enhancement of poorly water soluble drug using spray drying technique, International Journal of Pharmaceutical Studies and Research 2012; 3:2: 1-5.
21) Minhaz A., Rahman M., Ahsan Q. Chowdhury M., Dissolution enhancement of poorly soluble drug by solvent evaporation method using hydrophilic polymer: a solid dispersion technique, International Journal of Pharmaceutical and Life Sciences 2012; 1:2: 1-18.
22) Nagar G., Luhadiya A., Agrawal S., Dubey P., Solubility enhancement of a poorly aqueous soluble drug ketoprofen using solid dispersion technique, Pelagia Research Library 2011:2:4: 67-73.
23) Rote H., Thakare V., Tekade B., Zope R., Chaudhari R., Patil V., Solubility enhancement of glipizide using solid dispersion technique, World Journal of Pharmaceutical research 2011; 1:4: 1096-115.
24) Upreti M., Strassburger K., Wu S., Prakash I., Solubility enhancement of steviol glycosides and characterization of their inclusion complexes with gamma-cyclodextrin, International Journal of Molecular Sciences 2011; 12:2: 7529-53.
25) Shivhare U., Mathur V., Nanhe S., permeation enhancement of poorly water soluble drug flucanozole, Journal of drug delivery research 2013;2:2: 1-6.
26) Jafar M., Dehghan M., Shareef A., Enhancement of dissolution andanti-inflammatory effect of meloxicam using solid dispersions, International Journal of Applied Pharmaceutics 2010; 2:1: 22-27.
27) Milani P, Nezhadi S., Jalali M., Studies on dissolution enhancement of prednisolone, a poorly water-soluble drug by solid dispersion technique, Advanced Pharmaceutical Bulletin 2011; 1:1: 48-53.
28) Kumar T., Gupta V., Jain A., Pandey A., Enhancement of solubility of aceclofenac by using different solubilization technique, International Journal of Pharmacy and Life Sciences 2011;2:3: 620-24.
29) Jayakumar C., Morais A., Gandhi N., Solubility enhancement of theophylline drug using different solubilization techniques, International Journal of Pharmaceutical and Clinical Science 2012:2:1: 7-10.
30) Reddy S., Rangaraju D., Kant A., Shankraiah M., et al. Solubility and dissolution enhancement of cefixime using natural polymer by solid dispersion technique, International journal of research in pharmacy and chemistry 2011;1:2: 283-88.
31) Kulthe V., Chaudhari P., Solubility enhancement of etoricoxibby solid dispersions prepared by spray drying technique, Indian Journal of Pharmaceutical Education and Research 2011;45:3: 248-258.
32) Lakshmi K., Kumar P., Kaza R. Dissolution enhancement of telmisartan by surface solid dispersion technology. International Journal of Innovative Pharmaceutical Research.2012; 3:4:247-51.
33) Gunturu S., Amaravadi D., Preparation and evaluation of solid dispersions of nimesulide, International Journal of Pharmacy 2012; 2:4: 777-85.
34) Chawla G., Bansal K., Improved dissolution of a poorly water soluble drug in solid dispersions with polymeric and non-polymeric hydrophilic additives, Acta Pharm 2008;58: 257–274.
35) Kumar S., Sushma M., Prasanna R., dissolution enhancement of poorly soluble drugs by using complexation technique – A Review, Journal of pharmceuticals science and reaserch 2013:5:5: 120 – 24.
36) Shrikant M., Murali G., Sunil S., Murthy K., In- vitro dissoluation rate of poorly water soluble non-steroidal antiadrogen agent, Bicalutamide, with hydrophilic carriears, Journal of scientific and industrial research 2010; 69: 629-34.
37) Nirav S., Patel J., Dissolution enhancement of anti-depressant escitalopram oxalate by solid dispersion technique.journal of current pharmaceutical research 2012; 9:1: 26-32.

38) Roul L., Manna N., Parhi R., Sahoo S., Dissolution rate enhancement of alprazolam by solid dispersion, Indian journal of pharmaceutical education and research 2012; 46:1: 38-44.
39) Mirza S., Miroshnyk I., Muhammad H., Brauch J., Muhammad H., Enhanced dissolution and oral bioavailability of piroxicam formulations: modulating effect of phospholipids, Pharmaceutics 2010; 2: 339-50.
40) Wagh V., Jagtap V., Shaikh T.. Nandedkar S., Formulation and evaluation of glimepiride solid dispersion tablets for their solubility enhancement, Journal of Advanced Scientific Research 2012; 3:4: 36-41.
41) Murali K., Patel V., Valluru R., Hiremath J., Prathapreddy D., Solubility enhancement of amisulpride by solid dispersion technique and preparation of fast dissolving tablets, Indo American Journal of Pharmaceutical Research 2012;1:5:616-28.
42) Patel C., Asija R., Asija S., Different methods of enhancement of solubilization and bioavailability of poorly soluble drugs: a recent review, Pharmatutor-ART-1424.http://www.pharmatutor.org/articles/different-methods-enhancement-solubilization-bioavailability-poorly-soluble-drugs-review
43) Bajaj H., Bisht S., Yadav M., Singh V., Bioavailability enhancement: a review, International Journal of Pharma and Bio Sciences 2011; 2:2: 202 –16.

5487847845**1141124**