SOLID DISPERSIONS: AN APPROACH TO ENHANCE SOLUBILITY OF POORLY SOLUBLE DRUGS

R. Santosh Kumar*, T. Naga Satya Yagnesh
GITAM Institute of Pharmacy, GITAM University, Rushikonda, Visakhapatnam, A.P 530045.

ARTICLE INFO
Article history
Received 04/10/2016
Available online
03/12/2016

Keywords
Solubility, Solid Dispersions, Fusion Method, Hot Melt Extrusion Method.

ABSTRACT
Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of hydrophobic drugs. By reducing drug particle size to the absolute minimum, and hence improving drug wettability, bioavailability may be significantly improved. Solid dispersion have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of hydrophobic drugs. Most of the newly invented chemical entities are poorly water soluble. As a result formulating them as oral solid dosage forms is a hurdle to the specialists. Many techniques have been exercised to improve oral bioavailability of drugs. Among several methods, solid dispersion has attracted attention of the researchers for previous 50 years. Different formulation strategies have been taken to prepare solid dispersions. It is evident that solid dispersions improve solubility of drug particles thus enhancing dissolution characteristics of drugs they increase the oral bioavailability. This article reviews the various preparation techniques for solid dispersions, carriers used in the formulation of solid dispersions and pharmaceutical applications of solid dispersions which can give an overall knowledge of enhancing the solubility of poorly soluble drugs.

Corresponding author
Dr. R. Santosh Kumar
GITAM Institute of Pharmacy,
GITAM University, Rushikonda,
Visakhapatnam, A.P 530045.
radasantosh@rediffmail.com

Please cite this article in press as Dr. R. Santosh Kumar et al. Solid Dispersions: an Approach to Enhance Solubility of Poorly Soluble Drugs. Indo American Journal of Pharmaceutical Research.2016:6(11).

Copy right © 2016 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.

www.iajpr.com
INTRODUCTION

The solubility of a drug is a key determinant of its oral bioavailability and permeability. Solubility [1-7] is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug may be expressed as parts, percentage, molarity, molality, volume fraction and mole fraction. Solubility is an important determinant in drug liberation and absorption and hence plays a key role in its bioavailability. For a drug to be absorbed, it must be present in the form of an aqueous solution at the site of absorption [8].

There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples such as griseofulvin, Digoxin, phenytoin, sulphathiazole and chloramphenicol come immediately to mind. Therefore formulation approaches are being explored to enhance bioavailability of poorly water-soluble drugs. One such formulation approach that has been shown to significantly enhance absorption of such drugs is to formulate solid dispersion. A review of new monograph (1992-1995) in European pharmacopoeia shows that more than 40% of the drug substances have aqueous solubility below 1mg/ml20 and the 32% have an aqueous solubility below 0.1mg/ml. Aqueous solubility of greater than 1 percent (1 g/100 ml) usually indicates that no potential problems in absorption resulting from the solubility characteristics of the compound need to be anticipated.

However, the 1 percent solubility limit is an arbitrary guideline and in no way represents a universal limitation in terms of solubility and absorption relationship [8] the higher dissolution rates of solid dispersions can be described to a number of factors which includes [9]

1. The formation of higher energy metastable states of the components as a function of the carrier system being used and the proportion of carriers present.
2. The reduction of particle size to nearly a molecular level. As the soluble carrier dissolves, the insoluble drug is exposed to dissolution medium as very fine particles leading to an increase in both surface area and solubilization for fast dissolution and absorption.
3. Formation of amorphous forms of drug and carriers. The presence of carrier may also prevent aggregation of fine drug particles, thereby providing a larger surface area for dissolution. The Wetting properties are also greatly increased due to the surfactant property of the polymer, resulting in decreased interfacial tension between the medium and the drug, hence higher dissolution rates.
4. The presence of carrier polymers also inhibits crystal growth of the drug which facilitates faster dissolution.
5. Co solvent effect on the drug by the water soluble carriers.
6. Intermolecular hydrogen bonds between drug and carrier.
7. Local solubilization effect of carrier at the diffusion layer. [10]

In the Biopharmaceutical Classification System (BCS) drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs. Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs.

Biopharmaceutical Classification System:

The BCS has proven to be an extremely useful guiding tool for the prediction of in vivo performance of drug substances and development of new drug delivery system to suit the performance of drug in the body, as also for the regulation of bioequivalence of drug product during scale up and post approval. The development of dosage form especially for prolonged release has been a challenge to formulation scientists because of many independent factors governing the absorption from the gastrointestinal tract. For this purpose, the drug substances are categorized into four classes based on their solubility parameter and permeability to biomembranes and such a classification system is called as a biopharmaceutical classification system[11] . The BCS serves as a guiding tool to improve the efficiency of drug development by proper selection of dosage form and bioequivalence tests, to recommend a class of immediate release (IR) solid dosage forms, for which bioequivalence may be assessed based on in vitro dissolution tests and to lay the effect of excipients on drug permeability.

Major boundaries used in BCS:

1. A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml water over a pH range 1 to 7.5.
2. A drug is considered highly permeable when the extent of absorption in humans is determined to be 90% of an administered dose, based on the mass balance or in comparison to an intravenous dose.
3. A drug product is considered to dissolve rapidly when 85% of the labeled amount of substance dissolves within 30 minutes, using USP apparatus I or II in a volume of 900ml buffer solution.

Characteristics of the Drugs under BCS [12, 13]:

Class I: High Permeability, High Solubility:

In-vivo these drugs behave like an oral solution having fast dissolution and rapid bioavailability. Since the dissolution and absorption of class I drugs is very fast, bioavailability and bioequivalence are unnecessary for the products of such drugs. These drugs are good candidates for controlled drug delivery if they qualify pharmacokinetically and pharmacodynamically for the purpose. Gastric emptying is often the rate governing parameter in this case.

Example:

Metoprolol, Diltiazem, Propanolol.

www.iajpr.com
Class II: High Permeability, Low Solubility:
Drugs belonging to this class have low solubility and high permeability, hence, the dissolution rate becomes the governing parameter for bioavailability. These are also suitable for controlled release development.
Example:
Atorvastatin calcium, Lovastatin, Felodipine.

Class III: Low Permeability, High Solubility:
Since absorption is permeation rate limited, bioavailability is independent of drug release from the dosage form. These drugs generally exhibit low bioavailability and permeability enhancement is generally required. These drugs are problematic for controlled release development.
Example:
Cimetidine, Neomycin, Captopril.

Class IV: Low Permeability, Low Solubility:
Drugs of this class exhibit poor and variable bioavailability. The overall bioavailability is governed by several factors such as rate of dissolution, intestinal permeability, gastric emptying, and so on.
Example:
Hydrochlorothiazide, Tobromycin, Furosamide. [14]

Various approaches of Solubility Enhancement [15]:
Enhancement of bioavailability of poorly water-soluble drug remains one of the most challenging aspects of drug development. Various approaches have been suggested to enhance the solubility which includes:
a) pH Control
b) Co-solvency
c) Solubilization
d) Complexation
e) Particle size reduction
f) Hydrotrophy
g) Solid dispersion
An approach enlisted from to have been reported to have one or more problems however, solid dispersions is mainly considered as one of the most emerging techniques to enhance solubility of poorly water soluble drugs.

pH Control:
Poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water by applying a pH change. Upon intravenous administration the poorly soluble drug may be precipitate because blood is a strong buffer with pH between 7.2 – 7.4.

Advantages
• Simple to produce and fast track.
• Simple to formulate and analyze.
• Simple to produce and fast track.
• Uses small quantities of compound, amenable to high through put evaluations.

Disadvantages
• Risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble.
• Tolerability and toxicity (local and systemic) related with the use of a non physiological pH and extreme pHs.
• As with all solubilized and dissolved systems, a dissolved drug in an aqueous environment is frequently less stable chemically compared to formulations crystalline solid. The selected pH may accelerate hydrolysis or catalyze other degradation mechanisms.

Co-Solvency:
The solubility of a poorly water soluble drug can be increased frequently by the addition of a water miscible solvent in which the drug has good solubility known as co-solvents.

Advantages
Simple and rapid to formulate and produce.

Disadvantages
• As with all excipients, the toxicity and tolerability related with the level of solvent administered has to be considered.
• Uncontrolled precipitation occurs upon dilution with aqueous media.
• As with all solubilized forms, the chemical stability of the insoluble drug is worse than in a crystalline state.
Co-Solvent Products:
Nimodipine Intravenous Injection (Nimotop, Bayer) and Digoxin Elixir Pediatric (Lanoxin, GSK) are examples of co-solvent formulations.

Particle Size Reduction:
The bioavailability intrinsically related to drug particle size. By reducing particle size, increased surface area improves the dissolution properties. Particle size reduction, it is done by milling techniques using jet mill, rotor stator colloid mills etc.

Advantages:
- Liquid forms can be rapidly developed for early stage testing (pre-clinical) that can be converted into solids for later clinical development.
- Low excipients to drug ratios are required.
- Formulations are generally well tolerated provided that strong surfactants are not required for stabilization.
- Crystal forms are chemically and physically more stable than amorphous particles.

Disadvantages:
- 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.
- Development of sterile intravenous formulations is more challenging.

Complexation:
Complexation of drugs with cyclodextrins has been used to enhance aqueous solubility and drug stability. Cyclodextrin of pharmaceutical relevance contain 6, 7 or 8 dextrose molecules (α, β, γ-cyclodextrin) 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. Derivatives of β-cyclodextrin with increased water solubility (e.g. hydroxypropyl cyclodextrin HP-β-CD) are most commonly used in pharmaceutical formulation.

Examples of poorly soluble compounds that use Complexation are:
- α-cyclodextrin- PGE1 (Controlled hypotension during surgery), Cefotiamhexetil (Antibiotics)
- β-cyclodextrin- PGE2 (Induction of labour), Piroxicam (Anti inflammatory, Analgesic)
- γ-cyclodextrin- OP-1206 (Buerger’s disease)
- HPβ-cyclodextrin- Hydrocortisone (Mouth wash against gingivitis, etc.), Itraconazole (Esophageal candidiosis)
- HPγ-cyclodextrin- Diclofenac Na (Non-steroid anti-inflammatory)
- Methyl β-cyclodextrin- Chloramphenicol (Eye drop, Antibiotic agent).

Hydrotropy:
Hydrotropy is a solubilization process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to “salt in” the solute and those salts that decrease solubility “salt out” the solute. Several salts with large anions or cations that are themselves very soluble in water result in “salting in” of non electrolytes called “hydrotropic salts” a phenomenon known as “hydrotropism”.

Advantages:
- 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.

Solid Dispersion:
The term ‘solid dispersion’ has been defined as the technique whereby the drug is dispersed in a biologically inert matrix, to enhancing oral bioavailability. Solid dispersion was firstly introduced to overcome the low bioavailability of lipophilic drugs by forming of eutectic mixtures of drugs with water-soluble carriers. More than 500 papers have been published on the subject and various materials are employed as drug carriers [16]. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcome the limitations of previous approaches such as salt formation, solubilization by co solvents, and particle size reduction. It has been reported that drugs in solid dispersion need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs. In addition, in solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size.

www.iajpr.com
The dosage form can be developed and prepared by using small amounts of drug substances in early stages of the drug development process, the system might have an advantage over such other commonly used bioavailability enhancement techniques as micronization of drugs and soft gelatin encapsulation. Single or combination of carriers is essential for development of solid dispersion [17].

A number of theories have been proposed by which the dissolution rate is improved. These are

**Particle Size Reduction and Reduced Agglomeration**

Size reduction has been classically considered a result of eutectic or solid solution formation, it is worth noting that this mechanism suggests an intrinsic link between solid state structure and release. Similarly it has been suggested that the presentation of particles to the dissolution medium as physically separate entities may reduce aggregation. In addition, many of the carriers used for solid dispersions may have some wetting properties, hence it is reasonable to suggest that improved wetting may lead to reduced agglomeration and hence increased surface area [18].

**Dissolution Rate of the Drug**

Again, many of the carriers used may increase the solubility of the drug dissolving surface. Similarly, the carrier and drug may form a soluble complex, although the evidence for this occurring with other carriers is weaker.

**The advantageous properties of Solid Dispersions [19]**

**Particle Size:**

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers.

**Wettability:**

A strong contribution to the enhancement of drug solubility is related to the drug Wettability improvement verified in solid dispersions. It was observed that even carriers without any surface activity, such as urea improved drug Wettability [20]. Carriers with surface activity such as cholic acid and bile salts when used can significantly increase the Wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

**Porosity:**

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore, result in a higher dissolution rate [21]. The increased porosity of solid dispersion particles also hastens the drug release profile.

**Amorphous State:**

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process [22]. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution and it is speculated that, if drugs precipitant.

**Disadvantages:**

The limitations of this technology have been a drawback for the commercialization of solid dispersions, the limitations include

1. Laborious and expensive methods of preparation,
2. Reproducibility of physicochemical characteristics,
3. Difficulty in incorporating into formulation of dosage forms,

**Carriers in Solid Dispersion**

Carriers, which are soluble and dissolve in water at a fast rate, are widely used in pharmaceutical formulations to enhance dissolution of drugs.

**Ideal Properties of a Carrier for Solid Dispersions:**

- High water solubility, improves wettability and enhances dissolution
- High glass transition point (Tg) and improve stability
- Minimal water uptake (reduces Tg)
- Soluble in common solvent with drug (solvent evaporation technique)
- Relatively low melting point (melting process)
- Capable of forming a solid solution with the drug
- Good compressibility index and flow index
- Ability to protect drug from moisture

The carriers which have been reported in literature are described in detail below.
Polyethylene Glycol:

Polyethylene glycols (PEGs) are polymers of ethylene oxide, with a molecular weight (MW) usually falling in the range 200 ± 3,000,000. Their solubility in water is generally good, but decreases with MW. A particular advantage of PEGs for the formation of solid dispersions is that they also have good solubility in many organic solvents. The melting point of the PEGs of interest lies under 65°C in every case (e.g. the m.p. of PEG 1000 is 30-40°C, the m.p. of PEG 4000 is 50-58°C and the m.p. of PEG 20,000 is 60-63°C) [23].

If a PEG with too low a MW is used, this can lead to a product with a sticky consistency that is difficult to formulate into a pharmaceutically acceptable product [24].

Ozkan et al. [25] reported increasing solubility of etodolac with PEG 6000 as a carrier by melting method. Similarly Dehghan and Jafar [26] studied meloxicam solid dispersions prepared by physical mixing, co-grinding and kneading methods with PEG 6000. The enhanced dissolution rate of meloxicam by solid dispersion technique may be due to increased Wettability and hydrophilic nature of carrier.

Further drugs which exhibit elevated release rates when formulated as PEG 6000 solid dispersions include ofloxacin [27], silymerin [28], gliclazide [29], dapsone [30], mebendazole [31], Cisapride [32], Nitrendipine [33], oxazepam [34], valdecocixib [35], isosorbide dinitrate [36], zolpidem [37], piroxicam [38], fenofibrate [39], glibenclamide [40], ketoprofen [41]. PEGs with higher MW have also been used with success e.g. products containing PEG 8000 [42] and PEG 10,000 [43] showed enhanced dissolution rates compared to the pure drug.

Poly Vinyl Pyrrolidone:

Polymerization of vinylpyrrolidone leads to polyvinylpyrrolidone (PVP) of molecular weights ranging from 250 to 3,000,000. These can be classified according to the K value [44]. Due to their good solubility in a wide variety of organic solvents, they are particularly suitable for the preparation of solid dispersions by the solvent method. Similarly to the PEGs, PVPs have good water solubility and can improve the Wettability of the dispersed compound in many cases. Improved wetting and thereby an improved dissolution rate from a solid dispersion in PVP has been demonstrated for flufenamic acid [45]. The chain length of the PVP has a very significant influence on the dissolution rate of the dispersed drug from the solid dispersion. The aqueous solubility of the PVPs becomes poorer and viscosity lowers with increasing chain length.

Solid dispersions of praziquantel (PZQ) containing varying concentrations of PVP with different MW (3000, 11,000 and 34,000) were prepared. The solubility of PZQ in the co precipitate was greater when PVP of a smaller molecular weight was used [46]. An enhancement of 6.15-fold in dissolution rate of ipriflavone (IP) solid dispersion [47] was noted with PVP K-30 as that of IP alone and 40 fold increase with piroxicam [48] when PVP K 17 is used.

Further drugs which exhibit elevated release rates when formulated as PVP solid dispersions include diflunisal [49], nifedipine [50], tanshinone [51], cefuroxime axetil [52], flunarizine [53], daidzein [54], nitrendipine [55], ketoprofen [56], bicalutamide [57], quercetin [58], and lansoprazole. [59]

Urea:

In one of the first bioavailability studies of solid dispersions, it was shown that sulphathiazole was better absorbed in rabbits when given as a eutectic with urea [60]. Similarly, Goldberg et al. [61] reported faster dissolution rates of chloramphenicol when prepared with urea as the carrier. Although urea is not often used as a carrier these days, it has been recently shown that the dissolution rate of the poorly soluble compound ofloxacin can be improved by more than threefold by incorporating it in co evaporation with urea [62]. In the case of Rofecoxib [63] the release rate from urea dispersions was faster than from other carriers studied, including PEG 4000. A increase in the dissolution rate of piroxicam [64] has also been achieved with urea; however, in this case PEG 4000 was far more efficient. Maheshwari [65] reported solubility enhancement by using urea as a hydrotropic agent. Verma investigated increased dissolution of flurbiprofen with urea and xylitol. [66]

Sugars:

Lactose is useful as a carrier for the production of solid dispersions of drugs having a primary amide group in their structures like carbamezapine or ethenzamide prepared by melting and rapid cooling showed marked increase in dissolution same results were shown in study with naproxen [67, 68].

Chitosan, a derivative of the polysaccharide chitin which is formed by deacetylation at the N position, has also been used as a carrier in solid dispersions. Both Chitosan and its salt form, Chitosan glutamate, were able to improve the release of nifedipine by a factor of two to three compared to the drug powder [69]. In solid dispersion with 1:1 ratio ofloxacin to Chitosan, showed as the best carrier for drug release [70]. Similar results were found with fenofibrate [71], oxazepam [72] and miconazole. [73]

Mannitol, which has a melting point of 165-168°C and decomposes only above 250°C, can be employed in some cases to prepare dispersions by the hot melt method. Improved release characteristics have been reported for sorbitol dispersions of several compounds, including nitrofurantoin [74], prednisolone [75], ofloxacin [76] and uresodeoxycholic acid [77]. In most of these cases, other carriers produced better results. Interestingly, nitrofurantoin showed better release from sorbitol than mannitol dispersions. Indeed, a dispersion of prednisolone in sorbitol released the drug faster than all other carriers tested, including PEG, PVP, urea and mannitol. [78]
Emulsifiers:

The release behaviour of many drugs can also be improved through the use of emulsifying agents. Two mechanisms are possible here: improvement of wetting characteristics and solubilization of the drug. Owing to their potential toxicity problems, such as damage to mucosal surfaces, they are used in combination with another carrier. For example, the enhanced release of mefenamic acid from solid dispersions, using PEG 6000 with tween 20 [79].

An increase in 7 fold in solubility observed when solid dispersions of nitrendipine were prepared by using a melting method with PEG 6000 and polysorbate 80 as carriers [80]. The fenofibrate solid dispersion tablets prepared by kneadind method using PEG 4,000 and sodium lauryl sulfate has showed increased release [81]. Shokri and Azami proved the effect of anionic (SLS), cationic (CTAB) and nonionic (Miry 52) surfactants as carriers on enhanced dissolution rate of oxazepam. Surfactants are suitable carriers for low dose and very low water soluble drugs. [82]

Kwon and Kim [83] suggested Pluronic F 127 polymeric micelles could improve the oral bioavailability of genistein. Badry and Fathy used Pluronic F 98 for dissolution enhancement of piroxicam [84]. Similar results like increased solubility and enhanced bioavailability have been showed by nifedipine and 5b-[85, 86]

Chen et al. improved the dissolution and bioavailability of ABT-963, a poorly water-soluble compound by preparing solid dispersion using Pluronic F-68 as a carrier by evaporation and hot melt method. [87]

The grades of Gelucire® is denoted by different number like 44/14 and 13, in that first digit denotes the melting point of carrier and second digit denote HLB value of carrier. Gelucire® 44/14 is a mixture of glyceryl and PEG-1500 ester of long-chain fatty acid and is official in European pharmacopoeia as a lauryl macrogolglycerides. [88]

Dordunoo et al. [89] studied the effect of Gelucire® 44/14 for improving the solubility of temazepam in comparison with various poly ethylene glycol and shown large increase in its water solubility. Enhanced dissolution was observed with lornoxicam [90], tiaprofenic acid [91], and thio-carboxanilide UC-781 [92] and carbamazepine [93] when Gelucire 44/14 is used as surfactant alone and with other carriers.

Like other surfactants, they enhance the wetting and solubility of many lipophilic substances, leading to an increase in the dissolution rate. Stoll et al. [94] Likewise, the release of hydrocortisone can be enhanced by formulation as a solid dispersion in cholesterol and various cholesterol esters. [95]

Polyacrylates and Polymethacrylates:

In pharmaceuticals they are mostly used in coatings to modify the release of the drug from the dosage form. Commonly they are referred by the trade name Eudragit [96]. Among the eudragits eudragit E is often used to improve the release rate since it is soluble in buffer solutions at pH values up to 5 and swells at higher pH values, while eudragit L can be used when it is desirable to avoid release in the stomach. Jun and Jeong observed improved dissolution of atorvastatin calcium with eudragit E100 as a carrier. [97]

Cellulose Derivatives:

Celluloses are naturally occurring polysaccharides that are ubiquitous in the plant kingdom. They consist of high molecular weight unbranched chains, in which the saccharide units are linked by β-1, 4-glycoside bonds. By appropriate alkylation, the cellulose can be derivatized to form methyl- (MC), hydroxypropyl (HPC), hydroxypropylmethyl (HPMC) and many other semi-synthetic types of cellulose. A further possibility for derivatization is the esterification of the cellulose to form compounds such as cellulose acetate phthalate (CAP) and hydroxypropylmethylcellulose phthalate (HPMCP). [98]

Suspension formulated employing paracetamol-HPMC solid dispersions gave highest improvement in the dissolution rate and dissolution efficiency of paracetamol [99]. Other drugs which exhibit faster release from solid dispersion in HPMC include the poorly soluble weak acids nilvadipine [100] and bendipidine [101], Carbamezapine [102] and Cisapride [103]. Yuasa et al. [104] carried out extensive studies of the influence of the chain length and proportion of HPC in the solid dispersion on the release behaviour of flurbiprofen. The release rate improved as the proportion of HPC was increased and when lower molecular weight HPCs was used as the carrier.
Table 1: Based on their Molecular Arrangement, 6 Different Types of Solid Dispersions can be Distinguished.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Solid dispersion type</th>
<th>Matrix *</th>
<th>Drug **</th>
<th>Remarks</th>
<th>No. of phases</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Eutectics</td>
<td>C</td>
<td>C</td>
<td>The first type of solid dispersion Prepared</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
<td>Amorphous precipitations in crystalline matrix</td>
<td>C</td>
<td>A</td>
<td>Rarely encountered</td>
<td>2</td>
</tr>
<tr>
<td>III</td>
<td>Solid solutions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continuous solid solutions</td>
<td>C</td>
<td>M</td>
<td>Miscible at all composition, never prepared</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Discontinuous solid solutions</td>
<td>C</td>
<td>M</td>
<td>Partially miscible, 2 phases even though drug is molecularly dispersed.</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Substitutional solid solutions</td>
<td>C</td>
<td>M</td>
<td>Molecular diameter of drug (Solute) differs less than 15% from the 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.</td>
<td>1 or 2</td>
</tr>
<tr>
<td></td>
<td>Interstitial solid solutions</td>
<td>C</td>
<td>M</td>
<td>Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous. Example: Drug in helicalinterstitial spaces of PEG.</td>
<td>2</td>
</tr>
<tr>
<td>IV</td>
<td>Glass suspension</td>
<td>A</td>
<td>C</td>
<td>Particle size of dispersed phase dependent on cooling/ evaporation rate. Obtained after crystallization of drug in amorphous matrix.</td>
<td>2</td>
</tr>
<tr>
<td>V</td>
<td>Glass suspension</td>
<td>A</td>
<td>A</td>
<td>Particle size of dispersed phase dependent on cooling/evaporation rate. Much solid dispersion is of this type.</td>
<td>2</td>
</tr>
<tr>
<td>VI.</td>
<td>Glass solution</td>
<td>A</td>
<td>M</td>
<td>Requires miscibility or solid solubility, complex formation or upon fast cooling or evaporation during preparation, many Examples especially with PVP.</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

*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.

Different Methods of Preparation of Solid Dispersion:
Several approaches have been attempted for the preparation of solid dispersion, to improve the solubility and dissolution characteristics of poorly water-soluble drugs which include:

a) Spray drying  
b) Fusion method  
c) Solvent evaporation  
d) Hot-melt extrusion  
e) Particle size reduction  
f) Supercritical fluid (SCF) processes.  
g) Kneading  
h) Inclusion Complexes  
i) Direct Capsule filling  
j) Electrostatic Spinning Method  
k) Surface-active Carriers

(a) Spray Dry :-
Today, spray drying finds great utility in pharmaceutical industry because of the rapid drying and specific characteristics such as particle size and shape of the final product. In addition, it is simple and cost effective, as it is 30-50 times less expensive than freeze-drying. An established method is initiated by atomizing suspensions or solutions into fine droplets followed by a drying process. The solvent-based process uses organic solvent to dissolve and intimately disperse the drug and carrier molecule [105]. In this method drug & carrier is dissolved in a volatile organic solvent with help of magnetic stirrer to get a clear solution and solvent is evaporated at 400°C under reduced pressure by using vacuum evaporator, obtained mass is dried in a dessicator over anhydrous calcium chloride for 1-2 days depending on the removal rate of solvent. The product is crushed, pulverized & sieved through a suitable mesh number sieve.
Limitations:
Preparation of solid dispersions by conventional spray drying has been found problematic. The sticky and tacky mass is obtained by a conventional spray drying technique. Problem related with organic solvent limit this technology. [106]

(b) Fusion Method:
The fusion process is technically the less difficult method of preparing dispersions provided the drug and carrier are miscible in the molten state. This process employs melting of the mixture of the drug and carrier in metallic vessel heated in an oil bath, immediately after fusion, the sample are poured onto a metallic plate which is kept at ice bath. [107]

Limitation:
Thermal instability and immiscibility have resulted in development of the fusion solvent method which is particularly useful for drugs with high melting points or which is thermolabile.

(c) Solvent Method:
This method involves two steps:
1. The preparation of a solution containing both matrix material and drug.
2. The removal of solvent(s) resulting in formation of a solid dispersion.

Using the solvent method, the pharmaceutical engineer faces two challenges
1. The first challenge is to mix both drug and matrix in one solution, which is difficult when they differ significantly in polarity. To minimize the drug particle size in the solid dispersion, the drug and matrix have to be dispersed in the solvent as fine as possible preferably drug and matrix material are in the dissolved state in one solution.
2. The second challenge in the solvent method is to prevent phase separation, e.g. crystallization of either drug or matrix, during removal of the solvent(s). Drying at high temperatures speeds up the process and reduces the time available for phase separation. On the other hand, at high temperatures the molecular mobility of drug and matrix remains high, favoring phase separation (e.g., crystallization).

<table>
<thead>
<tr>
<th>S.No</th>
<th>Solvents</th>
<th>Melting Point (°C)</th>
<th>Boiling Point (°C)</th>
<th>Vapour Pressure at 25°C (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Water</td>
<td>0</td>
<td>100</td>
<td>3.16</td>
</tr>
<tr>
<td>2</td>
<td>Methanol</td>
<td>-93.9</td>
<td>65</td>
<td>16.9</td>
</tr>
<tr>
<td>3</td>
<td>Ethanol</td>
<td>-117</td>
<td>78.5</td>
<td>5.79</td>
</tr>
<tr>
<td>4</td>
<td>1-propanol</td>
<td>-85.8</td>
<td>97.4</td>
<td>2.27</td>
</tr>
<tr>
<td>5</td>
<td>2-propanol</td>
<td>-127</td>
<td>82.4</td>
<td>5.85</td>
</tr>
<tr>
<td>6</td>
<td>Chloroform</td>
<td>-63</td>
<td>62</td>
<td>26.1</td>
</tr>
<tr>
<td>7</td>
<td>Dimethylsulphoxide (DMSO)</td>
<td>19</td>
<td>189</td>
<td>0.08</td>
</tr>
<tr>
<td>8</td>
<td>Acetic acid</td>
<td>17</td>
<td>118</td>
<td>1.64</td>
</tr>
<tr>
<td>9</td>
<td>1,4-dioxane</td>
<td>12</td>
<td>102</td>
<td>4.92</td>
</tr>
<tr>
<td>10</td>
<td>2-methyl-2-propanol (TBA)</td>
<td>25</td>
<td>82</td>
<td>5.49</td>
</tr>
</tbody>
</table>

(d) Hot-Melt Extrusion:
The extruding method was originally designed as an extraction / casting method for polymer alloys in plastic industry, is now used to process cereals and functionalize food materials, such as tissue products from animal proteins. Hot melt extrusion approach represent the advantageous mean of preparation of SD(s) by using the twin-screw hot melt extruder where only thermo stable components are relevant. The effect of screw revolution speed and water content on the preparation of SD(s) should be investigated, since these parameters have profound impact on the quality of SD(s). In addition, high screw speed –high feed rate processes in comparison with low screw speed–low feed rate processes caused an increase in extrudate radius and porosity and decrease in mechanical strength and drug release rate from the matrix attributed to the expansion promoted under certain extrusion conditions. [107]

Limitations:
The disadvantages are few and mainly relate to negative effects of shear force.

(e) Particle Size Reduction:
The bioavailability of low solubility drugs is often intrinsically related to drug particle size. By reducing particle size, the increased surface area may improve the dissolution properties of the drug to allow a wider range of formulation approaches and delivery technologies. The critical parameters of comminution are well-known to the industry, thus permitting an efficient, reproducible and economic means of particle size reduction.
Limitations:

Particle size reduction, whether via traditional micronization or novel nanosizing methods, may not be applicable to all poorly soluble compounds, most notably high dose drug products and those compounds with higher melting points.

(f) Supercritical Fluid (SCF) Processes:

This technology has been introduced in the late 1980s and early 1990s, and experimental proofs of concept are abundant in the scientific literature for a plethora of model compounds from very different areas such as drugs and pharmaceutical compounds, polymers and biopolymers, explosives and energy materials, superconductors and catalyst precursor’s dyes and biomolecules such as proteins and peptides. These methods use SCFs either as solvent: Rapid expansion from supercritical solution (RESS) or antisolvent: gas antisolvent (GAS), supercritical antisolvent (SAS), and solution enhanced dispersion by supercritical fluids (SEDS) and/or dispersing fluid: GAS, SEDS, particles from gas-saturated solution (PGSS). Conventional methods, i.e. spray drying, solvent evaporation and hot melt method often result in low yield, high residual solvent content or thermal degradation of the active substance. [108]

(g) Kneading:

In this method a mixture of drug and carrier is wetted with water and kneaded thoroughly for 30 minutes in a glass mortar. The paste is dried under vacuum for 24 hours. Dried powder is passed through sieve no. 60 and stored in a dessicator. Solid dispersion involving PVP and valdecoxib were prepared by kneading technique.

Limitations:

This method cannot be applied to all poorly water soluble drugs. [109]

(h) Inclusion Complexes:

The improvement in solubilization ability within these water soluble polymer/drug-included CD aggregates requires less cyclodextrin to solubilise the same amount of drug, reducing the volume constraints present for non-aggregated CDs and increasing the range of delivery technologies available. Drug-CD complexes are commonly formed through either supersaturating a CD solution with drug and mildly agitating the solution for an extended period of time, or adding a mass of drug to a CD and solvent slurry and ‘kneading’ to produce a paste which is then dried and sieved.

Limitations:

This method is not applicable to all poorly water soluble drugs.

(i) Direct Capsule Filling:

The filling of semisolid materials into hard gelatin capsules as melts, which solidify at room temperature, was first done in 1978. It was not until much later that the potential application of the technique for solid dispersions was fully realized. For example, the filling of hard gelatin capsules has been feasible in molten dispersions of triamterene-PEG 1500 using a Zanasi LZ 64 capsule filling machine (Zanasi Co, Bologna, Italy).

(j) Electrostatic Spinning Method:

Electro spinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape (commonly known as Taylor’s cone). This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest, the cheapest. This technique can be utilized for the preparation of solid dispersions in future.

(k) Surface-Active carriers:

A surface-active carrier may be preferable in almost all cases for the solid dispersion of poorly water-soluble drugs. The surface active and self-emulsifying carriers for solid dispersion of poorly water-soluble drugs have been of great interest in recent years. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, and solubilization, detergency, enhanced oil recovery and corrosion inhibition.

Surfactants have also been reported to cause salvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of Characterization of Solid Dispersion.

Differential Scanning Calorimetry (DSC):

The transition from amorphous solid to crystalline solid results in an exothermic peak in the DSC signal. As the temperature increases the sample eventually reaches its crystallographically in equivalent sites in a unit cell.
Water Vapor Sorption:

Water vapor sorption can be used to discriminate between amorphous and crystalline material when the Hygroscopicity is different. The method requires accurate data of the hygroscopicity of both crystalline and completely amorphous samples.

Table 1: Recent Work Done on Enhancement of Solubility and Dissolution Rate of Poorly Soluble Drugs.

<table>
<thead>
<tr>
<th>S No</th>
<th>Name of the drug</th>
<th>Category</th>
<th>Reason for formulation into SD</th>
<th>Technique used</th>
<th>Super disintegrate used</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nimesulide</td>
<td>Non-steroidal, anti-inflammatory drug</td>
<td>It is a highly water insoluble drug, exhibited poor dissolution, poor absorption, so increase the solubility by prepare SDs.</td>
<td>Fusion method</td>
<td>PoloxamerPF-127, PEG4000, citric acid, pvp, urea &amp; mannitol</td>
<td>Efficiency of carriers Poloxamer PF 127 &gt; PEG4000 &gt; PVP &gt; Citric Acid &gt; Mannitol</td>
<td>The solid dispersions improved the dissolution characteristics of Nimesulide.</td>
</tr>
<tr>
<td>2</td>
<td>Carbamazepine</td>
<td>Anti convulsant</td>
<td>Drug has poor solubility, increase solubility by prepare a SDs</td>
<td>Fusion method (or) solvent method</td>
<td>PEG4000, PEG6000, mannitol, citric acid, urea, ethanol, PVP 44000, tween 20,60.</td>
<td>The solid dispersions technique had shown as a successful approach to improve the dissolution rate of Carbamazepine.</td>
<td>The nature and the amount of the carrier used played an important role in the enhancement of the dissolution rate and increase in the dissolution rate would provide the rapid onset of action after the drug is taken orally.</td>
</tr>
<tr>
<td>3</td>
<td>Itraconazole</td>
<td>Anti fungal agent</td>
<td>It is a poor aqueous solubility, so enhancement in the dissolution rate of ITR was observed with all the SDs</td>
<td>Solvent method</td>
<td>PVP, HPMC, HPC</td>
<td>The dissolution rates of Itraconazole can be enhanced by using PVC, HPMC, and HPC. These dispersions can be formulated into tablets which give higher dissolution rates.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Glipizide</td>
<td>Oral hypoglycemic agent</td>
<td>It is practically insoluble drug in water, by prepare SDs with water soluble carriers increase the dissolution rates.</td>
<td>Solvent method</td>
<td>PVP, PEG</td>
<td>A maximum increase in dissolution rate was obtained with weight ratio for Glipizide is 1:7 (Drug: PEG) and Glipizide:PVP solid dispersion with a weight ratio of 1:5 (Drug: PVP) though PVP dispersions showed faster dissolution at low polymer level in comparison with that of PEG dispersions, PEG dispersions are more suitable for formulation development as PVP is more hygroscopic.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Meloxicam</td>
<td>Non-steroidal anti inflammatory</td>
<td>It is poor aqueous solubility, when prepared SDs enhance solubility</td>
<td>Solvent evaporation technique</td>
<td>Cyclodextrin, PEG4000, PEG10000</td>
<td>β-cyclodextrin increases the solubility, but lesser than PEG 8000, whereas Lutrol F-127 delays in...</td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Drug Name</td>
<td>Class/Action</td>
<td>Techniques Used</td>
<td>Excipients/Active Ingredient</td>
<td>Description</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>-------------------</td>
<td>-------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Sulphamethoxazole</td>
<td>Antibacterial agent</td>
<td>Solid dispersion technique can be used to increase the dissolution and absorption of insoluble drugs</td>
<td>mannitol</td>
<td>Improve the solubility and bio-availability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Albendazole</td>
<td></td>
<td>Enhance the dissolution rate</td>
<td>Melting and melt solvent evaporation technique</td>
<td>Improve the solubility and bio-availability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Terbinafine</td>
<td>β-Adergenic Agonist Broncho dilator</td>
<td>To improve the solubility and bio-availability</td>
<td>PVP k30</td>
<td>The addition of PVP K30 to terbinafine HCl improved its dissolution rate by the mechanisms of solubilization and wetting. PVP K30 rich micro-environment formed at the surface of drug crystals enhanced dissolution rate compared with physical mixtures.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Furosemide</td>
<td>Loop Diuretic</td>
<td>Enhance the dissolution properties of the drug</td>
<td>Sodium starch glycolate</td>
<td>This study showed that the dissolution rate of Furosemide can be enhanced considerably by formulating in it as a solid dispersion in SSG using a kneading method. Incorporation of Superdisintegrants in the solid dispersions played a critical role in dissolution enhancement. It may be feasible to prepare suitable formulations of Furosemide solid dispersions as fast dissolving tablets.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Indomethacin</td>
<td>Non-steroidal anti-inflammatory drug</td>
<td>Fusion and mold method</td>
<td>PEG, HPMC</td>
<td>The Liquisolid compact can be a promising alternative for formulation of water insoluble drugs. The higher dissolution rates are displayed using this technology due to wetting property. Liquosolid compacts of Indomethacin in different drug concentrations in liquid medications exhibit the drug dissolution rates which are which is directly proportional to the fraction of molecularly dispersed drug in the liquid medication.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Olanzapine</td>
<td>Antipsychotic</td>
<td>Enhance the aqueous solubility of olanzapine</td>
<td>SSG, PGS (pre gelatinised starch)</td>
<td>The method used to formulate solid dispersion of olanzapine was found to be suitable and reproducible in nature.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug</td>
<td>Category</td>
<td>Methodology</td>
<td>Polymer/Carrier</td>
<td>Dissolution Rate/Effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-------------</td>
<td>-----------------</td>
<td>------------------------------</td>
<td>--------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Glipizide</td>
<td>Oral hypoglycemic agent</td>
<td>Kneading method (poloxamer 407, poloxamer 188)</td>
<td>Dissolution rate increased by kneading method with use of PXM than the physical mixtures. PXM 188 showed faster release than PXM 407 without any drug carrier interactions and enhanced dissolution efficiency.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Gliclazide</td>
<td>Oral hypoglycemic agent</td>
<td>Fusion method (or) melting method (PEG 4000)</td>
<td>The present work shows that the dissolution rate of Gliclazide from solid dispersions with PEG 4000 improved to more than 90% compared to the pure drug. Increase in its solubility was observed as the concentration of PVP K 30 increased.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Curcumine</td>
<td>Anti-inflammatory, anti bacterial, anticancer</td>
<td>PVP k30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Indomethacin</td>
<td>Non-steroidal anti inflammatory drug</td>
<td>Hot melting method (PEG4000, Gelucire 50/13)</td>
<td>The Liquisolid compact can be a promising alternative for formulation of water insoluble drugs. The higher dissolution rates are displayed using this technology due to wetting property. Liquisolid compacts of Indomethacin in different drug concentrations in liquid medications exhibit the drug dissolution rates which are which is directly proportional to the fraction of molecularly dispersed drug in the liquid medication. Among different formulations of SDs, SD containing drug is to polymer ratio 1:4 gave the best dissolution profile and dissolution efficiency and among tablet formulations, formulations containing 5% Crosscarmellose sodium gives best disintegration and dissolution profiles compared with other formulations. As the</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Drug Name</td>
<td>Type</td>
<td>Method Description</td>
<td>Excipients</td>
<td>Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>---------------</td>
<td>------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>-----------------------------</td>
<td>------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Azithromycin</td>
<td>Antibiotic</td>
<td>To increase the solubility and dissolution rate of azithromycin by preparation of its solid dispersions</td>
<td>Urea</td>
<td>Dissolution rate and solubility were higher than those of the intact drug.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Aceclofenac</td>
<td>NSAID</td>
<td>Improvement in dissolution rate of aceclofenac from solid dispersion</td>
<td>Gelucire 14/44</td>
<td>Enhancement of dissolution rate and bioavailability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Flurbiprofen</td>
<td>NSAID</td>
<td>Solid dispersion techniques used to improve dissolution and bioavailability of poorly water soluble drugs</td>
<td>PVPK25, PVPK30, PVPK29-30, &amp; PEG 6000</td>
<td>Water insoluble drugs can be easily overcome by solid dispersion having hydrophilic carriers.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Celecoxib</td>
<td>NSAID</td>
<td>Solid dispersion techniques used to improve dissolution and bioavailability of several insoluble drugs</td>
<td>Polyethylene glycol 6000</td>
<td>The solid dispersions of celecoxib was prepared to improve the solubility and dissolution rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Acyclovir</td>
<td>Antiviral</td>
<td>The solubility and dissolution rate of acyclovir by preparing SDs with various water soluble polymers</td>
<td>Lactose, mannitol, urea</td>
<td>A significant increase in the dissolution rate of solid dispersions as compare with pure acyclovir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Mefenamic acid</td>
<td>NSAID</td>
<td>Improve the therapeutic performance of acyclovir through enhancing its solubility and dissolution rate by solid dispersions and inclusion Complexation</td>
<td>Polyethylene glycol 6000, poly vinylpyrrolidone K 30</td>
<td>These preparations shows higher solubility and dissolution rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Efavirenz</td>
<td>Antiviral</td>
<td>Solid dispersions are improve the oral bioavailability of poorly water soluble drugs</td>
<td>Mannitol, PVP</td>
<td>Enhance the solubility, dissolution rate, dissolution efficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Dr. R. Santosh Kumar et al.</td>
<td>Vol 6, Issue 11, 2016.</td>
<td>ISSN NO: 2231-6876</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Drug</td>
<td>Category</td>
<td>Description</td>
<td>Method</td>
<td>Carrier</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>------</td>
<td>----------</td>
<td>-------------</td>
<td>--------</td>
<td>---------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Etoricoxib</td>
<td>Non-Steroidal Anti-Inflammatory</td>
<td>The solubility of poorly water soluble drugs improved by fused – sugar dispersions</td>
<td>Solvent evaporation</td>
<td>PVP K 30-Poloxamer 407</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Furosemide</td>
<td>Loop Diuretic</td>
<td>To improve solubility and dissolution rate of a poorly water soluble drug by solid dispersion technique</td>
<td>Solvent evaporation method</td>
<td>Eudragit RL 100, RS 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Metformin hydrochloride</td>
<td>Anti hyperglycemic agent</td>
<td>Solid dispersions have been used to improve the dissolution properties and bioavailability of drugs that are poorly soluble in water</td>
<td>Solvent evaporation method, &amp; closed melt method</td>
<td>Glycerol-Behenate, Compritol 888,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Diclofenac sodium</td>
<td>Non-Steroidal Anti-Inflammatory</td>
<td>Solid dispersion technology is used to increasing the dissolution rate and total bioavailability of poorly water soluble drugs</td>
<td>Carboxymethyl cellulose, Sodium Starch Glycolate, Cross linked Povidone, Ac-Di-Sol Polyethylene glycol400, Propylene glycol, glycerol, and ethanol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Enrofloxacin</td>
<td>Antibiotic</td>
<td>The enhancement of solubility of enrofloxacin is use of co-solvent technique</td>
<td>Solvent evaporation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Celecoxib</td>
<td>Non-steroidal anti-inflamm</td>
<td>The solubility and dissolution rate of Celecoxib enhanced by Complexation with β-dispersion and PEGylated product improved dissolution rate when compared with physical mixtures. Thus the dissolution rate of a poorly water soluble drug can be increased by using hydrophilic carriers such as PEG than PEGylation technology.</td>
<td>Solvent evaporation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sublimation technique would be an effective alternative approach compared with the use of more expensive adjuvant in the formulation of fast dissolving tablets with improved drug dissolution.

It is concluded that solid dispersions of Furosemide can be obtained by solvent evaporation technique with Eudragit RL-100 as the carrier. The S.D exhibits better profile than the dissolution marketed formulations.

Solid dispersions for controlled release of Metformin were developed by using Compritol.

Solvent evaporation method was helpful than closed melting method. Ac-Di-Sol was found to be better for the formulation of fast dissolving tablets of Diclofenac sodium, when compared to other Superdisintegrants used in the study. Ionic surfactants are better than non-ionic surfactants.

All the co solvents were found to increase the dissolution rate of drug and the amount of drug dissolved increased with increase in concentration of the co-solvent in each case the values were highest in ethanol followed by glycerol and propylene glycol. The dispersions with mannitol (1:5) by fusion method showed faster dissolution rate as
The formulation of inclusion complexes of atenolol with HPβ-CD to improve its aqueous solubility and dissolution rate, and the bioavailability of Atenolol. Complex prepared with HPβ-CD by co-precipitation method exhibited greatest enhancement in solubility and fastest dissolution of Atenolol.

**Pharmaceutical Applications of Solid Dispersion:**

The pharmaceutical applications of solid dispersions technique are numerous. They may be employed:
1. To enhance the absorption of drug;
2. To obtain a homogeneous distribution of a small amount of drug in solid state;
3. To stabilize unstable drugs and protect against decomposition by processes such as hydrolysis, oxidation, racemization, photo oxidation etc;
4. To dispense liquid or gaseous compounds;
5. To formulate a fast release priming dose in a sustained release dosage form;
6. To formulate sustained release preparation of soluble drugs by dispersing the drug in poorly soluble or insoluble carrier.

**CONCLUSION**

The emerging pharmaceutical scenario of drug discovery has shifted the major portion of newer drugs from hydrophilicity to lipophilicity. In consequence, a large number of drugs in the development pipeline are poorly water soluble presenting significant challenges to formulation scientists. Amorphous solid dispersions have provided an attractive alternative for overcoming solubility limitations. The solid dispersion method is one of the effective approaches to achieve the goal of solubility enhancement of poorly water-soluble drugs. The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Dissolution of drug is the rate determining step for oral absorption of drugs which can subsequently affect the in vivo absorption of drug. So to improve the aqueous solubility of the drugs, many techniques have been adopted since decades and solid dispersion is one of those techniques. Use of solid dispersions for the development of the release rate and oral bioavailability of poorly water soluble drugs, by careful choice of the carrier it is also feasible to delay or slow down the release pattern of a drug by formulating it into solid dispersion.

**Recent Advances and Future Trends:**

Solid dispersion has great potential both for increasing the bioavailability of drug and developing controlled release preparations. Thus, to solve bioavailability issues with respect to poorly water-soluble drugs, solid dispersion technology has grown rapidly. The dosage form can be developed and prepared using small amounts of drugs substances in early stages of the drug development process, the system might have an advantage over such other commonly used bioavailability enhancement techniques as micronization of drugs and soft gelatin encapsulation. The review is recommended for future review.

**Abbreviations List**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Abbreviation</th>
<th>Expansion of abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>PEG</td>
<td>Polyethylene glycol</td>
</tr>
<tr>
<td>2.</td>
<td>M.W</td>
<td>Molecular Weight</td>
</tr>
<tr>
<td>3.</td>
<td>M.P</td>
<td>Melting Point</td>
</tr>
<tr>
<td>4.</td>
<td>PVP</td>
<td>Poly Vinyl Pyrrolidone</td>
</tr>
<tr>
<td>5.</td>
<td>PZA</td>
<td>Praziquantel</td>
</tr>
<tr>
<td>6.</td>
<td>M.C</td>
<td>Methyl cellulose</td>
</tr>
<tr>
<td>7.</td>
<td>HPC</td>
<td>Hydroxypropyl cellulose</td>
</tr>
<tr>
<td>8.</td>
<td>HPMC</td>
<td>Hydroxypropyl methyl cellulose</td>
</tr>
<tr>
<td>9.</td>
<td>CAP</td>
<td>Cellulose acetate phthalate</td>
</tr>
<tr>
<td>10.</td>
<td>HPMCP</td>
<td>Hydroxy propyl cellulose phthalate</td>
</tr>
<tr>
<td>11.</td>
<td>T&lt;sub&gt;g&lt;/sub&gt;</td>
<td>Glass transition point</td>
</tr>
<tr>
<td>12.</td>
<td>KP&lt;sub&gt;a&lt;/sub&gt;</td>
<td>Kilo Pascal</td>
</tr>
<tr>
<td>13.</td>
<td>DMSO</td>
<td>Dimethyl sulphoxide</td>
</tr>
<tr>
<td>14.</td>
<td>SD</td>
<td>Solid dispersion</td>
</tr>
<tr>
<td>15.</td>
<td>RESS</td>
<td>Rapid expansion from supercritical solution</td>
</tr>
<tr>
<td>16.</td>
<td>GAS</td>
<td>Gas antisolvent</td>
</tr>
<tr>
<td>17.</td>
<td>SAS</td>
<td>Supercritical antisolvent</td>
</tr>
<tr>
<td>18.</td>
<td>SEDS</td>
<td>Solution enhanced dispersion by supercritical fluids</td>
</tr>
</tbody>
</table>
REFERENCES


