ISSN: 2321-3132

Review Article

International Journal of Chemistry and Pharmaceutical Sciences

www.pharmaresearchlibrary.com/ijcps

Solid Dispersion-A Strategy for Improving the Solubility of Lipophilic Drugs

Krishna Moorthy S.B,*[1] Sandeep. J[2], Rajalakshmi.R[1], Rubiya SK[1], Saddam hussain. SK[1]

[1]*Department of Pharmaceutics, Sree Vidyanikethan College of Pharmacy, A. Rangampet, Tirupathi, Andhra Pradesh, India. 517102.*

[2]*Department of Pharmaceutics, Sri Padmavathi School of Pharmacy, Tiruchanoor, Tirupathi, Andhra Pradesh, India. 517503.*

Received: 25 July 2014, Accepted: 29 August 2014, Published Online: 27 October 2014

Abstract

Improving oral bioavailability of drugs those given as solid dosage forms remains a challenge for the formulation scientists due to solubility problems. The dissolution rate could be the rate-limiting process in the absorption of a drug from a solid dosage form of relatively insoluble drugs. Therefore increase in dissolution of poorly soluble drugs by solid dispersion technique presents a challenge to the formulation scientists. Solid dispersion techniques have attracted considerable interest of improving the dissolution rate of highly lipophilic drugs thereby improving their bioavailability by reducing drug particle size, improving wettability and forming amorphous particles. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug. This review discusses the recent advances in the field of solid dispersion technology.

Keywords: Solid dispersions, solubility, dissolution rate, bioavailability, particle size.

Contents

***Corresponding author**
Krishna Moorthy S.B
Department of Pharmaceutics,
Sree Vidyanikethan College of Pharmacy,
A. Rangampet, Tirupathi, A.P, India-517102.
Manuscript ID: IJCPS2220

PAPER-QR CODE

1. Introduction

The enhancements of oral bioavailability of poorly water-soluble drugs often show poor bioavailability because of low and erratic levels of absorption. Drugs that undergo dissolution rate limited gastrointestinal absorption generally show improved dissolution and bio availability as a result of reduction in particle size. However, micronizing of drugs often leads to aggregation and agglomeration of particles, which results in poor wet ability. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution. The development of solid dispersions as a practically viable method to enhance bioavailability

of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubalization by cosolvents, and particle size reduction.

Chiou and Riegelman defined the term solid dispersion as "a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures". The term solid dispersion refers to the dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent, or the melting solvent method. Sekiguchi *et.al.* suggested that the drug was present in a eutectic mixture in a microcrystalline state, after few years Goldberg *et.al* reported that all drug in solid dispersion might not necessarily be presents in a microcrystalline state, a certain fraction of the drug might be molecular dispersion in the matrix, thereby forming a solid solution. Once the solid dispersion was exposed to aqueous media & the carrier dissolved, the drug was released as very fine, colloidal particles. Studies revealed 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 particle. 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. [1-5]

1.2 History

Solid dispersion technique was firstly demonstrated by Sekiguchi and Obi. They proposed the faster absorption of poorly water-soluble drugs such as sulfathiazole by the formation of eutectic mixture with a water-soluble and physiologically inert carries like urea. Upon exposure to aqueous fluids the active drug released into fluids is fine, dispersed particles because of fine dispersion of the drug in the solid eutectic mixture and the faster dissolution of the soluble matrix. The eutectic mixture contained 52 per cent w/w of sulfathiazole and 48 per cent w/w of urea. A solid dispersion technique has been used by various researchers who have reported encouraging results with different drugs. The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi (Sekiguchi, 1961). Technique for the preparation of solid dispersions, Lyophilization has also been thought of as a molecular mixing technique where the drug and carrier were co-dissolved in cyclohexanol, frozen and then sublimed under vacuum to obtain a lyophilized molecular dispersion (Lin, 1980).[5,6]

1.3 Types Of Solid Dispersion

1.3.1 Eutectic Mixtures

When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a co-melt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.

1.3.2 Solid Solutions

According to their miscibility two types of solid solution are

1.3.2.1 Continuous Solid Solutions

In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical literature to date.

1.3.2.2 Discontinuous Solid Solutions

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical phase diagram, show the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. Below a certain temperature, the mutual solubilities of the two components start to decrease. According to the way in which the solvate molecules are distributed in the solvendum, the two type of solid solution. They are

Substitutional Crystalline Solutions

A substitutional crystalline solid dispersion is a type of solid solutions which have a crystalline structure, in which the solute molecules substitute for solvent molecules in the crystal lattice. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules.

Interstitial Crystalline Solid Solutions

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

1.3.3 Amorphous Solid Solutions

In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Using griseofulvin in citric acid, Chiou and Riegelman were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carriers urea and sugars such as sucrose, dextrose and galactose, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol and various cellulose derivatives have been utilized for this purpose.

1.3.4 Glass Solutions and Glass Suspensions

A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent. The term glass can be used to describe either a pure chemical or a mixture of chemicals in a glassy or vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency & brittleness below the glass transition temperature. [7-15]

1.4 Selection of Carriers

The properties of the carrier have a profound influence on the dissolution characteristics of the dispersed drug. A carrier ought to meet the following prerequisites for being suitable for increasing the dissolution rate of a drug. It should be

a. Freely water soluble with rapid dissolution properties
b. Nontoxic and pharmacologically inert
c. Heat stable with a low melting point for the melt method
d. Soluble in a variety of solvents
e. Preferably enhancing the aqueous solubility of the drug
f. Chemically compatible with the drug
g. Forming only weakly bounded complex with the drug

1.4.1 First generation carriers

Example: Crystalline carriers: Urea, Sugars, Organic acids.

1.4.2 Second generation carriers

Example: Fully synthetic polymers include povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates.
Natural product based polymers are mainly composed by cellulose derivatives, such as
hydroxypropylmethylcellulose (HPMC), ethylcellulose or hydroxypropylcellulose or starch derivates, like cyclodextrins.

1.4.3 Third generation carriers

Example: Surface active self emulsifying carriers: Poloxamer 408, Tween 80, and Gelucire 44/1425. [16-20]

2. Techniques Involved In Preparation of Solid Dispersions

2.1 Solvent Evaporation Method

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 removed at room temperature, obtained mass is dried in a desiccator over anhydrous calcium chloride for 1-2 days depending on the removal rate of solvent at room temperature. The product is crushed, pulverized & sieved through a suitable mesh number sieve.

The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented, because of the relatively low temperatures required for the evaporation of organic solvents.

a. However, some disadvantages are associated with this method such as
b. The higher cost of preparation.
c. The difficulty in completely removing liquid solvent.
d. The possible adverse effect of traces of the solvent on the chemical stability
e. The selection of a common volatile solvent

2.2 Fusion /Melting Method: It involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. However many substances, either drugs or carriers, may decompose or evaporates during the fusion process which employs high temperature. Some of the means to overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier.

Advantages

1. The main advantage of direct melting method is its simplicity and economy.
2. In addition melting under vacuum or blanket of an inert gas such as nitrogen may be employed to prevent oxidation of drug or carrier.

Disadvantages

The method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature.

2.3 Hot Melt Extrusion: Hot-melt extrusion (HME) technique represents a novel application of polymer processing technology to prepare pharmaceutical dosage forms. The process involves embedding a drug in a polymer while

shaping the composite material to form a pharmaceutical product. This technique is same as the fusion method. The only difference is that in this method, intense mixing of the components is induced by the extruder. High shear forces results in to the high local temperature in the extruder and that can be problematic for the heat sensitive materials.

There are some advantages over the conventional fusion method

a. This technique offers the potential to shape the heated the drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms
b. It also offers the possibility of continuous production, which makes it suitable for large scale production.
c. It is a fast, simple, continuous, solvent free process requiring fewer processing steps than traditional tabletting techniques.
d. When used as a molding technique, there are no requirements for compressibility of the materials used in the formulation

2.4 Spray drying

Manufacture of milk powder was one of the first applications of spray drying when the method was developed in 1920. This method consists of dissolving or suspending the drug and carrier, then spraying it in to a stream of heated air flow to remove the solvent. Spray drying usually yields drug in the amorphous state, however sometimes the drug may have (partially) crystallized during processing.

Advantages

a. Ability to work with temperature sensitive APIs.
b. Tremendous formulation flexibility from the wide variety of solvents, polymers and adjuvants that can be employed.
c. Enhancement in performance that can be obtained by mixing the API and polymer at the molecular level in solution and then freezing this morphology in place through rapid solvent removal.

Drawbacks

a. Added costs associated with the use and consumption of the organic solvents.
b. Requirement of unit operation for residual

2.5 Adsorption on insoluble carriers

These dispersions are also referred to as surface solid dispersions. In this method, the support material is suspended in a solution of the drug followed by evaporation of the solvent. The resulting material contains the drug in a "molecularly micronized" state on the surface of the carrier. Here, adsorbents maintain the concentration gradient (Cs-Ct), to its maximum, thus increasing the dissolution rate.

Alternative Strategies: There are certain other approaches also those may be used for the preparation of solid dispersion as given as follows:

2.6 Supercritical fluid technology (SCF):

SCF techniques can be adopted for the preparation of solvent free solid dispersion dosage forms to enhance the solubility of poorly soluble compounds. Super critical fluid is the one where substances existing as a single fluid phase above their critical temperature and pressure. Methodology includes a very fine dispersion of hydrophobic drug in the hydrophilic carrier. Carbon dioxide is the most commonly used SCF because it is chemically inert, non toxic and non flammable.

2.7 Co-precipitation method:

In this method, while during constant stirring, a non solvent is added drop wise to the drug and carrier solution and the drug and carrier are co-precipitated to get micro particles, and then this microparticle suspension is filtered and dried.

2.8 Electrostatic Spinning Method:

This technology is used in polymer industry wherein it combines solid solution/dispersion technology with nanotechnology. In this process, a potential between 5 and 30 kV is applied on the liquid stream of a drug/polymer solution. And as when the electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameter are formed. After evaporating the solvent, the formed fibers can be collected on a screen.

2.9 Dropping method:

The dropping method was developed by Bülau and Ulrich (1977) to facilitate the crystallization of different chemicals. This method is a new procedure for producing round particles from melted solid dispersions. Methodology includes that the solid dispersion of a melted drug–carrier mixture is dropped onto a cooling plate, where it get solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. As viscosity is highly temperature dependent, it is very important to adjust the temperature so that, when the melt is dropped onto the plate, it solidifies into a spherical shape. The dropping method does not use organic solvents and therefore has none of the problems associated with solvent evaporation.

2.10 Spin-coated films: It is a new process to prepare solid dispersion by the solvent evaporation method, which consists of dissolving drug and carrier in a common solvent that is dropped on to a clean substrate highly spinned.

Solvent is evaporated during spinning. This process is indicated to moisture sensitive drug since it is performed under dry condition. [21-33]

3. Characterization

A number of techniques can be employed to identify the physical nature of the solid dispersions. No single method however, can furnish the complete information and hence a rational combination of the methods is preferred

3.1 Thermodynamic methods

In this analysis, the phase diagrams of eutectic and solid solution systems give the value of heats of fusion, entropies and partial pressures at various compositions that helps to determine the solubility gap below the solid-liquid equilibrium temperature.

3.1.1 Physical appearance

Includes visual inspection of solid dispersions.

3.1.2 Aqueous solubility studies

It was carried out to determine solubility drug alone in aqueous medium and also in presence of carriers .This was done by dissolving excess drug in different flasks containing different
concentration of carrier in distilled water. The flasks were shaken thoroughly for 6 hours and kept aside for 24hours.The suspensions were filtered, diluted suitably and absorbance was measured at suitable wavelength.

3.1.3 Percent Practical Yield

Percentage practical yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. SDs were collected and weighed to determine practical yield (PY) from the following equation

$$\%\ Practical\ yield = \frac{Practical\ mass\ (solid\ dispersion)}{Theoratical\ mass\ (drug + carriers)} \times 100$$

3.1.4 Drug content

In this method definite amount of solid dispersion is taken and dissolved in a suitable solvent in which drug is freely soluble, then after appropriate dilution concentration are measured by UV Spectrophotometry.

3.1.5 Dissolution Studies: Dissolution studies are the most significant evaluation parameter for any solid dosage form. Dissolution study is carried out to determine the rate and extent of dissolution. The dissolution studies of solid dispersion were performed in 500ml at 37ºC by the USP- II paddle apparatus at 75 rpm. Drug was dispersed in medium. Aliquots of 5 ml from the dissolution medium were withdrawn at different time interval and replenished by an equal volume of fresh dissolution medium. The samples were filtered through whattman filter paper and analyzed for drug contents by measuring the absorbance at suitable wavelength using Shimadzu 1700 UV/visible Spectrophotometer.

3.2 Significant properties of solid dispersion

There are certain parameters that are given below when successfully controlled, can produce improvements in bioavailability.

3.2.1 Particle size reduction

Solid dispersion represents the last state of the size reduction. It includes the principle of drug release by creating a mixture of poorly water soluble drug and highly soluble carriers, and after dissolution of carrier, the drug get molecularly dispersed in dissolution medium.

3.2.2 Wettability: Carriers having surface activity like cholic acid and bile salts, when used, can significantly increase the wettability properties of drug. Recently, in third generation solid dispersion surfactants have been included that is the emerging technique.

3.2.3 Higher porosity: Solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore, result in a higher dissolution rate.

3.3.4 Amorphous state of drug particles: Drug particles in amorphous state have higher solubility.

3.3.5 Approaches for avoiding drug recrystallisation

Recrystallisation is the major disadvantage of solid dispersions, as we are using amorphous drug particles and they are thermodynamically instable and have the tendency to change to a more stable state. Several polymers are being used for improving the physical stability of the amorphous drugs by increasing the Tg of the miscible mixture.

3.3 Thermal Analysis

3.3.1 Thermo-microscopic Methods

This is a visual method of analysis using a polarized microscope with a hot stage to determine the thaw And melting points of solids. The method is advantageous as small amount of sample is required And direct observation of the changes taking place in the sample through the thaw and melts stages. The Technique has been used to support DTA or DSC measurement. It gives information about the phase diagram of binary systems.

3.3.2 FT-IR Spectroscopy: FT-IR spectroscopy used to study the possibility of an interaction between drug and polymer in solid state. Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of

interactions between drug and matrix. Infra red studies was carried out to rule out interaction between drug and carrier used in formulation of solid dispersion by potassium bromide disc method using Infra red spectrophotometer.

3.3.3 Differential Scanning Colorimetry (DSC)

In DSC, both the sample and reference materials are subjected to linear heating, but both are maintained at the same temperature. Here change in temperature is not recorded, but the heat flow into the system is recorded which is required to maintain isothermal conditions. The method is useful to study the behaviour of crystallization and melting and deriving phase diagrams of solid dispersions.

3.3.4 Scanning Electron Microscopy

It usually gives primary information of system and tells about the amorphous or crystalline nature of solid dispersions. The application of the electron microscope technique, however, usually limited to chemicals with high resolution.

3.3.5 Differential thermal analysis (DTA)

This is an effective thermal method for studying the phase equilibria of pure substance or solid mixture. Differential heat changes that accompany physical and chemical changes are recorded as a function of temperature as the substance is heated at uniform rate. In addition to thawing and melting, polymorphic transition, evaporation, sublimation, desolvation and other types of changes such as decomposition of the sample can be detected. The method has been used routinely to identify different types of solid dispersion. The greatest advantage of using this technique is in constructing phase diagram of high reproducibility; a higher temperature range is permitted, greater resolution realest. A sample size of less than 1 mg can be used.

3.3.6 X-ray diffraction (XRD)

In this analytical tool, intensity of x-ray reflection is measured which is a function of diffraction method. The diffraction method is very important and efficient tool in studying the physical nature of solid dispersion which has been used in crystal structure studies in two different ways

1. Single crystal x-ray crystallography dealing with the determination of bond angle and inter atomic distances.
2. Power x-ray diffraction dealing with the study of crystal lattice parameter, where the x-ray diffraction intensity from a sample is measured as a function of diffraction angles. Thus, changes in diffraction pattern indicate changes in crystal structure. The relationship between wavelength, of the x-ray, the angle of diffraction, θ, and the distance between each set of atomic planes of crystal lattice, d, is given by equation: $M\lambda=2d \sin \theta$, where M represent the order of diffraction. [34-40].

Table No: 1 List of Carrires Used In Solid Dispersions

S. No	Chemical Class	Examples
1	Acids	Citric acid, Tartaric acid, Succnic Acid
2	Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol
3	Polymer Material	Polyvinyl pyrolidone, PEG 4000, PEG 6000, Sodium alginate, Carboxy methylcellulose, Guar gum, Xanthan gum, Methyl cellulose
4	Surfactant	Polyoxyethylene stearate, Polaxamer, Deoxycholic acid, Tweens and Spans, Gelucire 44/14, Vitamin E TPGS NF
5	Miscellaneous	Pentaerythritol, Urea, Urethane, Hydroxylakyl xanthenes

Table 2: List of Poor Water Soluble Drugs, Category & Solubility Profile

S.No	Drugs	Category	Solubility profile
1	Ibuprofen	Anti-inflammatory, analgesic	Ibuprofen is only very slightly soluble in water. Less than 1 mg of ibuprofen dissolves in 1 ml water (< 1 mg/ml). However, it is much more soluble in alcohol/water mixtures.
2	Furosemide	Diuretics	Soluble in acetone, sparingly soluble ethanol (95%),slightly soluble in ether.
3	Gliclazide	Anti diabetic	Spairingly soluble in dichloromethane, slightly soluble in ethanol 95%.
4	Aceclofenac	Anti-inflammatory, analgesic	Practically insoluble in water; freely soluble in acetone; soluble in ethanol (95 per cent).
5	Ketoprofen	Anti-inflammatory, analgesic	Freely soluble in ethanol 95 % , chloroform, and ether
6	Morphine	NSAIDS	Soluble in water, Freely soluble in hot water, More soluble in hot ethanol.
7	Nimodipine	Calcium channel blocker	Poor water soluble drug.
8	Ofloxacin	Antibiotic	Soluble in ethanol and chloroform, Insoluble in ether.

4. Applications of Solid Dispersion in Pharma Industries

The application of solid dispersions for increasing drug bioavailability is by no means a new field of pharmaceutical research. In their early paper on the use of solid dispersions, Chiou and Riegelman observed that, "It is believed that this relatively new field of pharmaceutical techniques and principles will play an important role in increasing dissolution, absorption and therapeutic efficacy of drugs in future dosage forms." Apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored. It is possible that such a technique be used:

a. To obtain a homogeneous distribution of a small amount of drug in solid state.
b. To stabilize the unstable drug.
c. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
d. To formulate a fast release primary dose in a sustained released dosage form.
e. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
f. To reduce pre systemic inactivation of drugs like morphine and progesterone.
g. Polymorphs in a given system can be converted into is amorphous, solid solution, eutectic or molecular addition compound. [41-42]

5. Challenging Future For Solid Dispersion Technique

Since solid dispersions were introduced in 1961, an immense amount of research has been done in this area. However, very few solid dispersion systems have been marketed. Ritonavir capsules (Norvir, Abbott) has been withdrawn temporarily from the market because of crystallization. Various issues that impeded the commercial development of solid dispersions includes

(a) Difficulty to control physicochemical properties,
(b) Difficulty in delivering solid dispersion formulations as tablet or capsule dosage forms
(c) Inability to scale bench top formulations to manufacturing- sized batches and
(d) Physical and chemical instability of the drug and/or the formulation itself. [43]

6. Marketed Products

a. Gris-PEG, a griseofulvin-PEG fusion method solid dispersion, was manufactured initially by Dorsey / Sandoz and reached the market in the mid- 1970s.Gris-PEG was developed as tablet product, and this led to two USP monographs for griseofulvin tablets. Griseofulvin solid dispersiontablets are currently marketed by a number of manufacturers and contain corn starch, lactose, magnesium stearate, PEG, and sodium lauryl sulfate as inactive ingredients.
b. Cesamet, a nabilone-PVP solvent method solid dispersion manufactured by Eli Lilly and Co. Has been marketed internationally since 1982. Eli Lilly discontinued marketing Cesamet contains PVP and corn starch as inactive ingredients and is presented as a capsule product.
c. Solid dispersion formulation of Troglitazone (Rezulin) is marketed by Parke-Davis.
d. Solid Solutions of lopinavir and ritonavir in polyvinylpyrrolidone-vinyl acetate. copolymer
e. successfully enabled a reformulation of "Kaletra" (Abbott Laboratories, Abbott Park, IL). In addition to reducing the dosage burden from six softgel capsules to four tablets, tablets made with the solid solutions eliminate the need for refrigeration.
f. Sporanox" (Janssen Pharmaceutica, Titusville, NJ) is a solid dispersion of itraconazole in
g. hypromellose that has been layered onto sugar spheres.
h. The most recently approved product is the nonnucleoside reverse transcriptase inhibitor
i. "Intelence" (Tibotec, Yardley, PA), an amorphous, spray-dried solid dispersion of etravirine, hypromellose, and microcrystalline cellulose. [44]

7. Conclusion

Solubility is a most important parameter for the oral bio availability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the *in vivo* absorption of drug. Currently only 8% of new drug candidates have both high solubility and permeability. Because of solubility problem of many drugs the bio availability of them gets affected and hence solubility enhancement becomes necessary. Solid dispersion technology is one of the possible modes that increase the solubility of poorly soluble drugs**.**

8. References

1. Sekiguchi. K., and Obi N., Studies on Absorption of Eutectic Mixture. II. Absorption of Fused Conglomerates of Chloramphenicol and Urea in Rabbits. Chem. Pharm. Bull., 1964, vol 12(2): 134–144.
2. Sekiguchi, K. and Obi, N., (1961) Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. Chem. Pharm. Bull,**1961**, vol 9(1): 866–872.

3. Chiou, W.L., and Rielman, S., (1971). Pharmaceutical application of solid dispersion system. J. Pharm. Sci., **1971**, vol.60: 1281-1302.
4. Dhirendra k, solid dispersions: a review, pak. j. pharm. sci., **2009**, vol.22(2): 234-246.
5. K. Punitha, Daisy Chella Kumari , V.Venkatesh Kumarc , S. Suresh Kumar, Enhancement of solubility of Rosiglitazone through solid dispersion technique: *in-vitro* and *in-vivo* permeation study analysis, Der Pharma Chemica, **2010**, vol.2(5): 190-200
6. Sekiguchi, K., and Obi, N., (**1964**). Studies on Absorption of Eutectic Mixture. II. Absorption of Fused Conglomerates of Chloramphenicol and Urea in Rabbits. Chem. Pharm. Bull.,1964, vol 12(2): 134–144.
7. Goldberg, A.H., Gibaldi, M., and Kanig, J.L.,(**1965**). Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures I theoretical considerations and discussion of the literature. J. Pharm. Sci, **1965**, vol 54(2): 1145-1148.
8. Chiou, W.L., and Riegelman, S., (1969). Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. J. Pharm. Sci, **1969**, vol 58(4): 1505-1510.
9. Vasconcelos, T.F., Sarmento, B., and Costa, P., (**2007**). Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug discovery today, **2007**, vol 12(1): 1069-1070.
10. Sekiguchi, K., and Obi, N., Studies on Absorption of Eutectic Mixture. II. Absorption of Fused Conglomerates of Chloramphenicol and Urea in Rabbits. Chem. Pharm. Bull, **1964**, vol 12: 134–144
11. Sekiguchi, K. and Obi, N., Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. Chem. Pharm. Bull, **1961**, vol 9: 866–872.
12. Levy, G., (1963). Effect of particle size on dissolution and gastrointestinal absorption rates of pharmaceuticals. Am. J. Pharm. Sci, **1963**, vol 135: 78–92.
13. Kaning, J.L., Properties of Fused Mannitol in Compressed Tablets. J. Pharm. Sci, **1964**, vol 53: 188– 192.
14. Goldberg, A.H., et al. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. IV. Chloramphenicol– urea system. J. Pharm. Sci, **1966**, vol 55: 581–583.
15. D. M. Patel, R. R. Shah: Studies on release profile of Piroxicam solid dispersion; Indian Journal of Pharmaceutical Sciences, **2003**, vol 65: 264-266.
16. Sharma D, Soni M, Kumar S and Gupta GD. Solubility Enhancement -Eminent Role in Poorly Soluble Drugs. Research Journal of Pharmacy and Technology, **2009**, Vol 2(2): 220-224.
17. Vasconcelos TF, Sarmento B and Costa P. Solid dispersion as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discovery Today, **2007**, Vol. 12: 1068-1075.
18. Kamalakkannan V, Puratchikody A, Masilamani K and Senthilnathan B, Solubility enhancement of poorly soluble drugs by solid dispersion technique – A review. Journal of Pharmacy Research, **2010**, Vol. 3: 2314-2321.
19. Patidar Kalpana et al. Drug Invention Today, **2010**, Vol.2(7):349-357.
20. Ansel C. Howard, Allen V. Loyd, Popovich A. Nicholas, Pharmacetical dosage forms and drug delivery systems, 7 th edition, **2000**; 248-252.
21. Patidar Kalpana et al. Solid Dispersion: Approaches, Technology involved, Unmet need & Challenges in Drug Invention Today, **2010**, vol 2(7): 349-357.
22. Karanth H, Shenoy VS, Murthy RR. Industrially Feasible Alternative Approaches in the Manufacture of Solid Dispersions: A Technical Report. AAPS Pharm Sci Tech. **2006**; E1-E8.
23. Mohanachandran PS, Sindhumo PG and Kiran TS. Enhancement of solubility and dissolution rate: an overview. International Journal of Comprehensive Pharmacy, 2010, Vol. 4(2): 1-10.
24. Khadilkar M., Avari J and GudsookarV. R: Solid dispersions of Ketoprofen; the Eastern pharmacist, **1997**, vol 40:129-131.
25. Kuchekar B.S. and Yadav A.V: Studies on solid dispersion of Paracetamol; The Eastern Pharmacist, **1995**, vol 38: 149.
26. D. M. Patel, R. R. Shah: Studies on release profile of Piroxicam solid dispersion; Indian Journal of Pharmaceutical Sciences, **2003**, vol 65:264-266.
27. M Gopalrao, R. Suneetha: Improvement in dissolution of poorly soluble Naproxen; Indian Journal of Pharmaceutical Sciences, **2005**, vol 67(1):26-29.
28. M. M. Soniwala, P. R. Patel: Studies on dissolution profile of Rofecoxib by formulating solid dispersions; Indian Journal of Pharmaceutical Sciences, **2005**, vol 67(1): 61-65.
29. Aggarwal S, Gupta GD and Chaudhary S. Solid dispersion as an eminent strategic approach in solubility enhancement of poorly soluble drugs. International Journal of Pharmaceutical Sciences and Research, **2010**, Vol 1(1): 1-13.
30. Shahroodi AB, Nassab PR and Révész PS. Preparation of a Solid Dispersion by a Dropping Method to Improve the Rate of Dissolution of Meloxicam. Drug Development and Industrial Pharmacy, **2008**, Vol 34: 781–788.

31. Sharma DK, Joshi SB. Solubility enhancement strategies for poorly water soluble drug in solid dispersion: A Review. Asian Journal of Pharmaceutics. **2007**, vol 1(3): 9-19.
32. Ambike AA, Mahadik KR, Paradkar A. Spraydried amorphous solid dispersions of simvastatin, a low Tg drug: In vitro and in vivo evaluations. Pharm Res. **2005**, vol 22: 990– 998.
33. Vasconcelos T, Sarmanto B, Costa P. Solid dispersion as strategy to improve oral bioavailability of poorly water soluble drugs. J Pharm Sci. **2007**, vol 12(4):1068-1075.
34. Vasconcelos TF, Sarmento B and Costa P. Solid dispersion as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discovery Today, **2007**, Vol. 12(2):1068-1075.
35. Chiou WL, Riegelman S. Pharmaceutical application of solid dispersion. J Pharm Sci. **1971**, vol 60:1281-1302
36. Ahuja S, Scypinski S. Handbook of modern pharmaceutical analysis. Academic press. **2005**, vol 3(3); 247.
37. Vemula VR, LagishettyV and Lingala S. Solubility enhancement techniques. International Journal of Pharmaceutical Sciences Review and Research, **2010**, Vol. 5(2): 41-51.
38. Costa P, Lobo JMS. Modelling and comparison of dissolution profiles. Eur J Pharm Sci, **2001**, vol. 13: 123-33.
39. V.Kamalakkannan et al. Solubility enhancement of poorly soluble drugs by soliddispersion technique – A review Journal of Pharmacy Research, **2010**, 3(9): 2314-2321.
40. Rajesh Kaza, Y. Prasanna Raju1 and R. Nagaraju, Dissolution enhancement of valsartan using natural polymers by solid dispersion technique, Der Pharmacia Lettre, **2013**, vol.5(2):126-134
41. Vemula VR, LagishettyV and Lingala S, Solubility enhancement techniques.International Journal of Pharmaceutical Sciences Review and Research, **2010**, Vol. 5(2): 41-51.
42. V.Kamalakkannan et al. Solubility enhancement of poorly soluble drugs by solid dispersion technique – A review Journal of Pharmacy Research, **2010**, vol.3(9): 2314-2321
43. Kamalakkannan V, Puratchikody A, Masilamani K and Senthilnathan B, Solubility enhancement of poorly soluble drugs by solid dispersion technique – A review. Journal of Pharmacy Research, **2010**, Vol. 3: 2314-2321
44. Breitenbach J, Magerlein M. Melt Extruded Molecular Dispersion. In: Sellassie IG, Martin C, editors Pharmaceutical Extrusion Technology. Informa Health care, **2003**: 246.
45. URL:http://www.pharmtech.findpharma.c om/pharmtech/article/529177.