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Review on various techniques of solubility enhancement of poorly soluble drugs with special emphasis on solid dispersion

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ABSTRACT

A success of formulation depends on how efficiently it makes the drug available at the site of action. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules especially in oral formulation. But most of the time it becomes challenging to formulate poorly water soluble drugs. Therefore it is necessary to improve solubility of drug by various ways like salt formation, co-solvency, and addition of solublizing agent, micronization, and complexation. Although these techniques have commonly been used to increase dissolution rate of the drug, there are practical limitations with these techniques, the desired bioavailability enhancement may not always be achieved. One such formulation approach that has been shown to significantly enhance absorption of such drugs is to formulate/prepare solid dispersions.In this review we concentrated on improvement of the solubility of poorly water soluble drugs by preparing solid dispersion using various methods.

Key words: bioavailability, salt formation, co-solvency, solublizing agent, micronization, complexation, solid dispersion.

INTRODUCTION

Almost More than 90% drugs are orally administered. Drug absorption, sufficient & reproducible bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependant on Solubility of that compound in aqueous medium.

More than 90% of drugs are approved since 1995 have poor solubility. It is estimated that 40% of active new chemical entities (NCEs) identified in combinatorial screening programs employed by many pharmaceutical companies are poorly water soluble [1]. Drug absorption, sufficient and reproducible bioavailability and/or pharmacokinetic profile in humans are recognized today as one of the major challenges in oral delivery of new drug substances. Orally administered drugs on the Model list of Essential Medicines of the World Health Organization (WHO) are assigned BCS classifications on the basis of data available in the public domain. Of the 130 orally administered drugs on the WHO list, 61 could be classified with certainty. 84% of these belong to class I (highly soluble, highly permeable), 17% to class II (poorly soluble, highly permeable), 24 (39%) to class III (highly soluble, poorly permeable) and 6 (10%) to class IV (poorly soluble, poorly permeable). The rate and extent of absorption of class II & class IV compounds is highly dependent on the bioavailability which ultimately depends on solubility [2].

Due to this major reason Solubility enhancement is one of the important parameters which should be considered in formulation development of orally administered drug with poor aqueous solubility [3].Solubility is the characteristic physical property referring to the ability of a given substance, the solute, to dissolve in a solvent.

Solvent – The component which forms major constituent of a solution & is capable to dissolve another substance to form a uniformly disperse mixture at the molecular level [4].
Solute – A substance that present in small quantity & dissolves in solvent [4].
"The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature." In the other words, "solubility can also define as the ability of one substance to form a solution with another substance." [5]

Solubility Definitions [6], [7]

Table No 1

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

PROCESS OF SOLUBLISATION

The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute [8], the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion [9].

Figure no. 1

Step 1: Holes opens in the solvent

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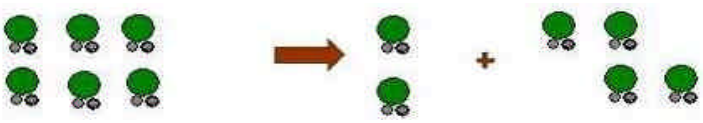
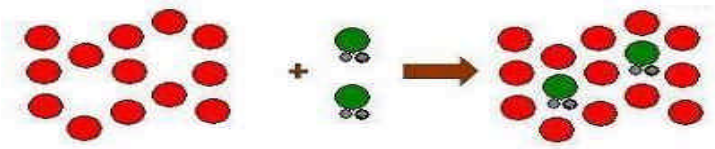
Step2: Molecules of the solid breaks away from the bulk



Step 3: The freed solid molecule is integrated into the hole in the solvent



FACTORS AFFECTING SOLUBILITY

The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system [8].

Particle Size:

The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent. The effect of particle size on solubility can be described by [9]

$$\log \frac{S}{S_0} = \frac{2\ \gamma\ V}{2.303\ R\ T\ r}$$

Where,
S is the solubility of infinitely large particles
$\mathbf{S_0}$ is the solubility of fine particles
V is molar volume
? is the surface tension of the solid
r is the radius of the fine particle
T absolute temp in degree kelvin
R universal gas constant

Temperature:

Generally, an increase in the temperature of the solution increases the solubility of a solid solute [10].

Pressure:

For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have practically no effect on solubility [8].

Nature of the solute and solvent:

While only 1 gram of lead (II) chloride can be dissolved in 100 grams of water at room temperature, 200 grams of zinc chloride can be dissolved. The great difference in the solubility's of these two substances is the result of differences in their natures [7].

Molecular size:

The larger the molecule or the higher its molecular weight the less soluble the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent [9].

Polarity:

Polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction. All molecules also have a type of intermolecular force much weaker than the other forces called London Dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives the non-polar solvent a chance to solvate the solute molecules [11].

Polymorphs:

The capacity for a substance to crystallize in more than one crystalline form is polymorphism. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called enantiotropic. If the system is monotropic, there is a transition point above the melting points of both polymorphs. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities. Generally the range of solubility differences between different polymorphs is only 2-3 folds due to relatively small differences in free energy [9].

Rate of solution:

The rate of solution is a measure of how fast substances dissolve in solvents.

NEED OF SOLUBILITY ENHANCEMENT

The better characterization of biochemical targets increasingly drives drug development; these targets are generally cell-based and access to them in these models is relatively straightforward. This has led to the widely discussed proliferation of highly active compounds that have physicochemical characteristics that are poorly suited to delivery to a whole organism: at the head of this list of undesirable characteristics is poor water solubility [12].

According to recent estimates, nearly 40% of new chemical entities are rejected because of poor solubility i.e. biopharmaceutical properties. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules.

Bioavailability – is measurement of the extent of therapeutically active drug that reaches systemic circulation & is available at the site of action. It is one of the essential tools in pharmacokinetics, as bioavailability must be considered when calculating dosages for non intravenous routes of administration[13].

Poor aqueous solubility is caused by two main factors [14]
1) High lipophilicity and
2) Strong intermolecular interactions which make the solubilisation of the solid energetically costly.

Solubility of active pharmaceutical ingredients (APIs) has always been a concern for formulators, since inadequate aqueous solubility may hamper development of products and limit bioavailability of oral products. Solubility plays an essential role in drug disposition, since the maximum rate of passive drug transport across a biological membrane, the main pathway for drug absorption, is the product of permeability and solubility. Among the five key physicochemical screens in early compound screening, **pKa, solubility, permeability, stability** and **lipophilicity,** poor solubility tops of the list of undesirable compound properties. Compounds with insufficient solubility carry a higher risk of failure during discovery and development since insufficient solubility may compromise other properties, influence both pharmacokinetic and pharmacodynamic properties of the compound, and finally may affect the ability of the compound to develop as API [14]. Currently only 8% of new drug candidates have both high solubility and permeability.

TECHNIQUES TO OVERCOME POOR SOLUBITY

The description of a technology as **'solubility enhancing'** can be misleading, since although the phenomenon of super-saturation is real, the techniques used do not increase the solubility of insoluble compounds. More accurately, they present the drug in a form which is optimal to its absorption, given its solubility limitations. It is also important to be aware that water solubility also requires the specification of **temperature and pH**; many important drugs only exhibit aqueous solubility under certain physiological conditions, and these need to be met at the site of absorption [8].

This article focuses on the technologies that have arisen to meet the challenge posed by insoluble compounds and the ways in which these technologies have made a difference. The techniques that are used to overcome poor drug solubility are discussed under following major headings [9],[12].

I. Chemical Modifications :

1.Salt Formation
2.Co-crystallization
3.Co-solvency
4.Hydrotropic

5.Solublizing agent
6.Nanotechnology

II. Physical Modifications :

1.Particle size reduction
a.Micronization
b.Nanosuspension

2.Modification of the crystal habit
a.Polymorphs
b.Pseudopolymorphs

3.Complexation
a.Use of complexing agents

4.Solubilization by surfactants:
a.Microemulsions
b.Self microemulsifying drug delivery system

5.Drug dispersion in carriers
a.Solid dispersions
b.Solid solutions

I. CHEMICAL MODIFICATIONS

1. Salt Formation : is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. Acidic or basic drug converted into salt having more solubility than respective drug. Ex. Aspirin, Theophylline, Barbiturates[7].

2. Co-crystallisation : new approach available for the enhancement of drug solubility is through the application of the co-crystals, it is also referred as molecular complexes. A Co-crystals may be defined as crystalline material that consist of two or more molecular (& electrical neutral) species held together by non-covalent forces. It can be prepared by evaporation of a heteromeric solution or by grinding the components together or by sublimation, growth from the melt & slurry preparation. It is increasingly important as an alternative to salt formation, particularly for neutral compounds[9].

3. Co-slvent : It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs. Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent. Solvent used to increase solubility known as cosolvent. It is also commonly referred to as solvent blending[8],[15].

4. Hydrotropy : It designate to increase in solubility in water due to presence of large amount of additives.It improves solubility by complexation involving weak interaction between hydrophobic agents (Sodium benzoate, sodium alginate, urea) & solute. Ex. Sublimation of Theophylline with Sodium acetate & Sodium alginate[7].

5. Solublising Agents : The solubility of poorly soluble drug can also be improved by various solubilizing materials. Ex. PEG 400 is improving the solubility of hydrochlorthiazide[8].

6. Nanotechnology Approaches : Nanotechnology will be used to improve drugs that currently have poor solubility[7]. Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometers (nm) or less. For many new chemical entities of very low solubility, oral bioavailability enhancement by micronisation is not sufficient because micronised product has very low effective surface area for dissolution and next step taken was nanonisation[16].

II. PHYSICAL MODIFICATIONS

1. Particle Size Reduction : The techniques of size reduction using various milling processes are well established and these practices are a standard part of formulation development[8]. This can be done mainly by Micronization & Nanosuspension[9]. As particle size decreases, surface area of particle increases resulting in increase in solubility. Sometimes Sonocrystallisation technique is also used for particle size reduction [17],[18].

2. Modification of Crystal Habit: Polymorphism is the ability of an element or compound to crystallize in more then one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability. Similarly amorphous form of drug is always more suited than crystalline form due to higher energy associated & increase in surface area. Order for dissolution of different solid forms of drug[19],

Amorphous >Metastable polymorph >Stable polymorph

3. Complexation : Complexation is the association between two or more molecules to form a non bonded entity with a well defined stichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions[7,12]. Examples of complexing agents are; chelates-EDTA, EGTA, molecular complexes- polymers, inclusion complexes-cyclodextrins[20],[21].

4. Solublisation By Surfactents : Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or nonionic. When small polar molecules are added they can accumulate in the hydrophobic core of the micelles[20]. This process of solubilization is very important in industrial and biological processes. The presence of surfactants may lower the surface tension but increases solubility of drug within an organic solvent[22].
This article focuses on the technologies that have arisen to meet the challenge posed by insoluble compounds but here special emphasis given on solid dispersion. Although salt formation, partical size reduction, etc. have commonly been used to increase dissolution rate of the drug[23], there are practical limitation with these techniques the desired bioavailability enhancement may not always be achieved. 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/prepare solid dispersion. Solid dispersion of an amorphous drug in a polymer matrix has been demonstrated to be an effective tool for solubility and subsequently, bioavailability enhancement [24].

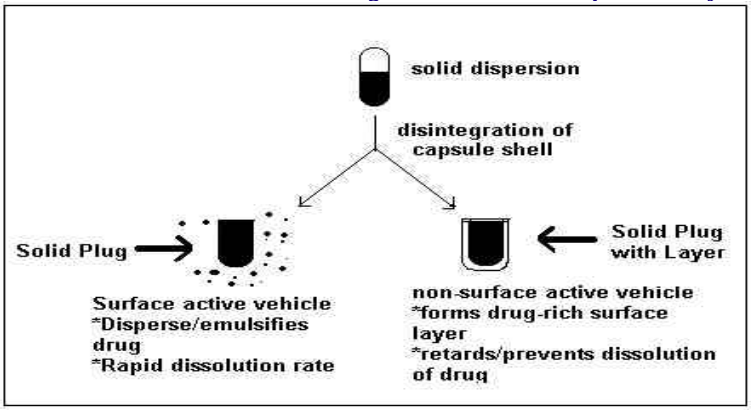
SOLID DISPERSION

Solid dispersion, a concept firstly introduced by Sekiguchi & Obi. The term "solid dispersions" refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method, or fusion solvent-method. However, the definition can now be broadened to include certain nanoparticles, microcapsules, microspheres and other dispersion of the drug in polymers prepared by using any one of the process. Sekiguchi and Obi 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 presented in a microcrystalline state, a certain fraction of the drug might be molecular dispersion in the matrix, thereby forming a solid solution[6]. Once the solid dispersion was exposed to aqueous media & the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high[24].

The commercial use of such systems has been limited primarily because of manufacturing problems with solid dispersion systems may be overcome by using surface active and self-emulsifying carriers. The carriers are melted at elevated temperatures and the drugs are dissolved in molten carriers.

Carriers for Solid Dispersions[9]
1.Acids – Citric Acid, Tartaric Acid, Succinic Acid.
2.Sugars – Sucrose, Dextrose, Sorbitol, Maltose, Galactose, Xylitol.
3.Polymeric Materials – Polyvinylpyrollidone, PEG 4000 & 6000, Carboxymythyl cellulose, Hydroxypropylvcellulose, Guar gum, Xanthan gum, Sodium Alginate, Dextrin, Cyclodextrin.
4.Surfactants – Polyoxyethylene stearate, poloxamer, Deoxycholic acid, Tweens and Spans, Gelucire 44/14, Vitamine E TPGS NF
5.Miscellenous – Urea, Urethane, Hydroxyalkyl Xanthene, Pentaerythritol
Surface-active agents are substances that at low concentrations adsorb onto the surfaces or interfaces of a system and alter the surface or interfacial free energy and the surface and the interfacial tension. Surface-active agents have a characteristic structure, possessing both polar (hydrophilic) and non-polar (hydrophobic) regions in the same molecule. The surface active carriers are said to be amphipathic in nature.

The advantage of a surface-active carrier over a non-surface-active one in the dissolution of drug from a capsule formulation is shown schematically in Figure no 2



A schematic representation of the comparative dissolution of a poorly water-soluble drug from surface-active versus non surface-active vehicle[25].

This is an effective method for increasing the dissolution rate of poorly soluble drugs, hence, improving their bioavailability. When 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 dispersion 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 [25].

The use of solid dispersions has been studied extensively. Despite all the advantages, the commercial use of solid dispersions has been very limited, primarily due to the manufacturing difficulties and stability problems. A significant problem with the systems is the present difficulties in the formulation development and subsequent scaling-up. Thermo sensitive drugs and carriers may be destabilized during the melting or solvent-facilitated melting process since high melting temperatures are usually applied. The pre-formulation pulverization of the melting/ congealed slabs is more challenging because they are usually semisolid and waxy in nature and difficult to micronize. It's also difficult to scale up the formulation of solid dispersion. The soft and tacky properties of solid dispersion powders result in poor flow ability, mixing property and compressibility, which may complicate the operations and render poor reproducibility of physicochemical properties of final products. Although the solvent method does not have the problems associated with the melting method, The problem in the evaporation process is that it is hard to remove the solvent from the co precipitates to an acceptable level because the co precipitates become more and more viscous during the "drying" process, which prevents further evaporation of the residual solvent Lately, several innovations in solid dispersion technique have offered a number of interesting opportunities to solve these problems. However, problems associated with the miscibility and thermo stability of molten drugs and carriers limit the application of this technique.

Mechanism Of Increased Dissolution Rate By Solid dispersion [26]:

1.Reduction in particle size.
2.Solublization effect (use of carriers).
3.Increased wettability and dispersibility by carriers
4.Formation of metastable dispersion with reduced lattice energy for faster dissolution.
5.Ex. Dissolution energy for furesamide is 17Kcal/mol while Dissolution energy for 1:2 furesamide:PVP co-precipitate is 7.3Kcal/mol.

Advantages and Disadvantages of solid dispersion[26] :

Advantages - Increase in dissolution rate & extent of absorption and reduction in Pre systemic metabolism. Transformation of liquid form of drug into solid form. **Ex.** Clofibrate & benzyl benzoate incorporated into PEG-6000 to give solid dispersion also avoidance of polymorphic changes so no bioavailability problems (as in case of nabilone & PVP dispersions.

Disadvantages – major problem is instability**.** There is change in crystallanity & decrease in dissolution rate with aging. **Ex.** Crystallization of ritonavir from supersaturated solution in solid dispersion system (main reason for withdrawal of ritonvir capsules [Norvir, Abbott] from market.)

Moisture & Temperature increases deteriorating effect on solid Dispersion than physical mixtures.

CLASSIFICATION OF SOLID DISPERSION

Chiou & Reigalman classified solid dispersion as follows [27];

1.Simple Eutectic Mixtures
2.Solid Solutions
3.Glass Solution & Glass Suspension
4.Amorphous precipitation In Crystalline Carrier
5.Compound Or Complex Formation
6.Combination Of Previous Five Types(usually combination of 2-3 methods)

1. Simple Eutectic Mixtures:

It is prepared by rapid solidification of fused melt of two components that show complete liquid miscibility but negligible solid-solid solution. Thermodynamically it is intimately blended mixture of two crystalline components [27].

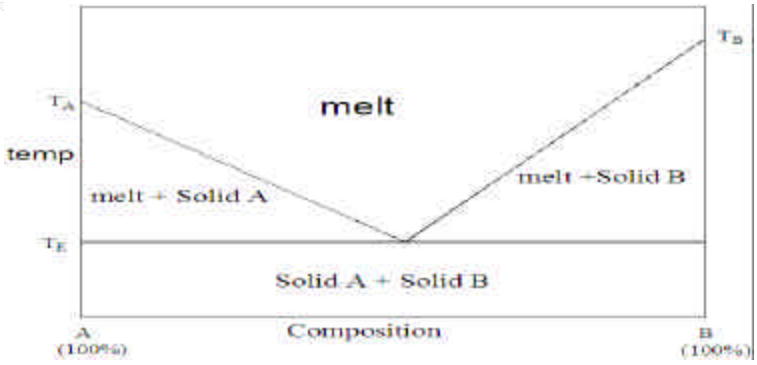


Figure no 3

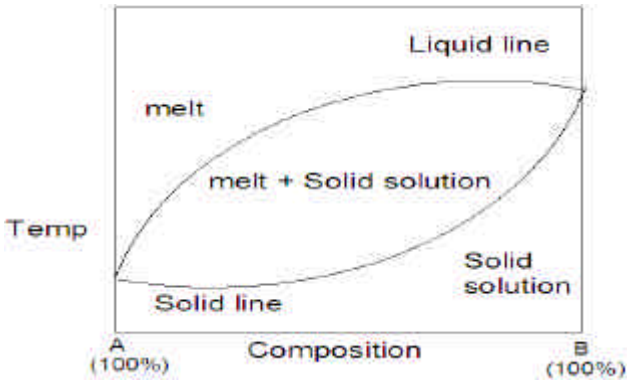
Ex. Chloremphenicol-urea; Paracetamol-urea; Griseofulvin & Tolbutamide-PEG 2000.

T_A – M.P. of solid A (in ^{0}C)
T_B – M.P. of solid B (in ^{0}C)
T_E – Eutectic Point

2. Solid Solution:

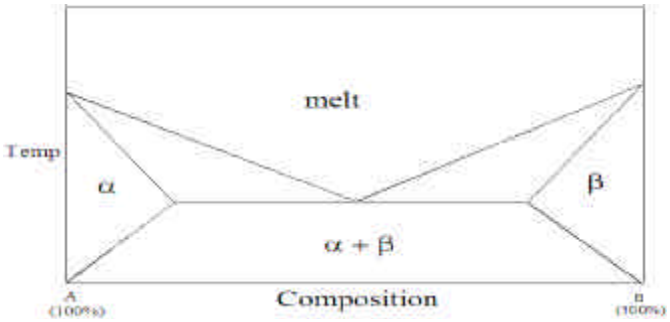
Two components crystallize together in homogenous one phase system. Particle size of drug in solid solution is reduced to its molecular size [27].
Solid solutions shows faster dissolution rate than eutectic mixtures.
Classification of solid solutions, according to extent of miscibility of two components;
a) Continuous Solid Solution – Two solids miscible in solid state in all proportions

Figure no. 4



b) Discontinuous Solid Solutions – Exist at extremes of composition

Figure no 5

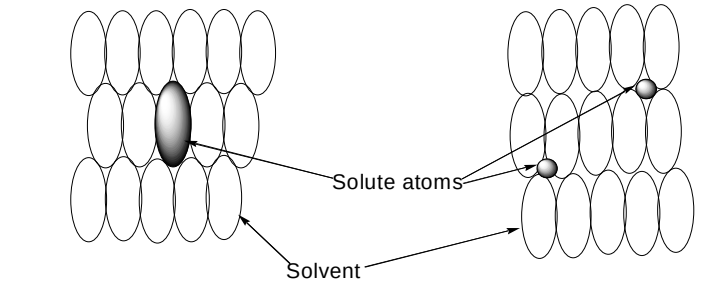


According to criterion of molecular size of two components;

a) Substitutional Solid solution – Here Substitution of solvent molecule by solute molecule in crystal lattice. Molecular size should not differ by 15% <
Ex. Anthracene-Acenapthacene, Ammonium-potassium thiocynate.

b) Interstitial Solid solutions – In this solute (guest) molecule occupies interstitial space in solvent (host) lattice. Solute molecule diameter should be less than 0.59 times than that of solvent. Owing to their large molecular size polymers favors formation of interstitial solid solution.
Ex. Solid solution of digoxin, prednisolone acetate in matrix of PEG 600.

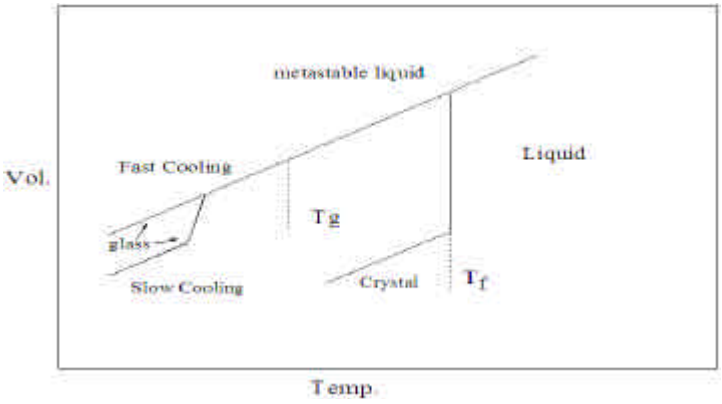
Figure no. 6



a) Substitutional Solid solution b) Interstitial Solid solutions

3. Glass Solution & Suspensions:
Glass solutions are homogeneous glassy system in which solute dissolves in glass carrier. Glass suspensions are mixture in which precipitated particles are suspended in glass solvent. Different characteristics of glassy state are transparency, brittleness below the glass transition temperature. Lattice energy (barrier to rapid dissolution) is much lower in glass solution & suspension [27].
Ex. Carriers for glass solution and suspension – citric acid, sugars (dextrose, sucrose, galactose), PVP, PEG, urea.

Figure no.7 -Volume changes associated with cooling of melt.



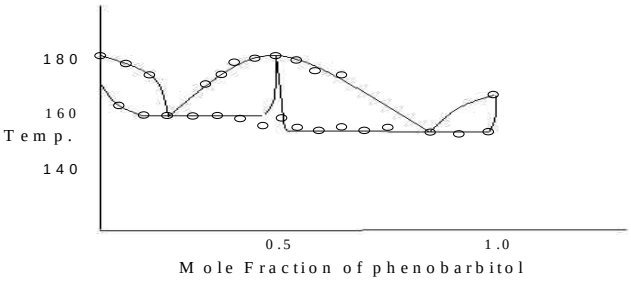
T_g – glass transition temp.
T_f – M.P. of material

4. Amorphous Precipitation In Crystalline Carrier:

It is postulated that drug with propensity to super cooling has more tendency to solidify as an amorphous form in presence of carrier. This is similar to simple eutectic mixtures but only difference is that drug is precipitated out in an amorphous form [27] (while in simple eutectic mixtures drug is precipitated in crystalline form).
Ex. Precipitation of sulfathiazole in crystalline urea.

5. Compound or Complex Formation:
In this formation molecular compound by two substances takes place. Molecular Compound is Present at the maximum in the phase diagram. But it is difficult generalize the influence of complex formation on dissolution because of following [27];
Complex between digoxin-hydroquinone – increase in dissolution rate
Insoluble complex between phenobarbital-PEG – decrease in dissolution rate.
Ex. Quinine-phenobarbital system showing molecular compound formation.

Figure no. 8



SOLID DISPERSION – METHODS OF PREPARATION [28]

A. Melt/Cool Method:
a. Melting Solvent Method
b. Hot stage extrusion

B. Solvent Evaporation:
a. Hot Plate Drying
b. Vacuum drying
c. Slow evaporation at low temperature
d. Rotary evaporation
e. Spray drying
f. Freeze drying
g. Spin drying
h. Fluid bed coating

C. Co-precipitation
a. Addition of an anti-solvent
D. Dropping method

A. MELT/COOL METHOD
This method involves following techniques;

Hot Melt Extrusion:
Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971. Hot melt extrusion has in recent years gained wide acceptance as a method of choice for the preparation of solid dispersions. The hot-melt extrusion process is highly dependent on the physicochemical properties of the compounds and their miscibility in the molten state. There is a potential that the API, the polymer or both may degrade if excessively high temperature is needed in the melt extrusion process, especially when the melting point of the API is high. This report details a novel method where the API was first converted to an amorphous form by solvent evaporation and then melt-extruded with a suitable polymer at a drug load of at least 20% w/w. By this means, melt extrusion could be performed much below the melting temperature of the drug

substance It has been reported that melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipients. The process has been useful in the preparation of solid dispersions in a single step[29].

The amorphous melt extrusion formulations showed higher bioavailability than formulations containing the crystalline API. There was no conversion of amorphous solid to its crystalline form during accelerated stability testing of dosage forms.

Melting Solvent Method :
In 1978, Francois and Jones further developed the solid dispersion method by directly filling hard gelatin capsules with semisolid materials as a melt, which solidified at room temperature. Chatham reported the possibility of preparing PEG-based solid dispersions by filling drug–PEG melts into hard gelatin capsules. A drug is first dissolved in a suitable liquid solvent and then this solution is incorporated into the melt of polyethylene glycol, obtainable below 70C without removing the liquid solvent. The selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also polymorphic form of the drug precipitated in the solid dispersion may get affected by the liquid solvent used[30].

B. SOLVENT EVAPORATION
This method works best for water insoluble drugs. The solvent evaporation method provides good encapsulation efficiency and produces amorphous form of compound, which gave better solubility and dissolution than its crystalline form. Like required quantity of drug dissolved in suitable solvent (like Methanol for nitrezepam), then added to polymer by stirring & melted into water-bath (50-60^{0}c). This mixture was kept in water-bath until solvent gets evaporated. Afterward it was cooled to room temperature & pass through sieves as per requirement [31].
This Process involves, active ingredient dissolved or dispersed in solution of the polymer in a suitable water-immiscible & volatile organic Solvent. This solution or dispersion is emulsified in an aqueous medium to form micro droplets. The organic solvent then diffuses into the aqueous phase and evaporates at the water/air interface. The micro droplets solidify and solid, free-flowing microspheres are obtained after complete organic solvent evaporation, filtration and drying. Many variables can influence the preparation and properties of microspheres [32].
Many different methods (including spray- and freeze-drying) have been used to remove organic solvents from solid dispersions. Simonelli et al.5 evaporated the ethanolic solvent with a steam bath and removed the residual solvent by applying reduced pressure. Chiou and Riegelman dried an ethanolic solution of griseofulvin and PEG 6000 in an oil bath at 115 °C until ethanol bubbles were no longer formed. The viscous mass was then solidified by cooling it in a stream of cold air [28].

Removal of organic solvents such as chloroform from large masses of material may be difficult because the solid dispersions are usually amorphous and may be viscous and waxy. Additional problems may be residual solvent, the cost of recovering the solvents and the further processing (such as pulverization and sifting) of the solidified product [28].

Fluid bed Coating:
Kennedy and Niebergall described a hot-melt fluid-bed method whereby nonpareils could be coated with PEGs with molecular weights between 1450 and 4600. It is fundamentally based on the process of solvent evaporation and simultaneous coprecipitation of drugs and carriers. The fluid-bed coating technique and the conventional solvent method both involve the process of dissolving drugs and carriers in an organic solvent. The difference between the two methods is that the fluid-bed is employed as a means of removing large quantity of solvent and the fluid-bed coating is traditionally used to perform functional coating around drug-loaded cores of tablets or pellets. The fluid-bed coating is more advantageous than the conventional solvent method when it is used for the preparation of solid dispersions on non-pareil core pellets. The deposition of solid dispersion on core pellets is a one-step process, thus preventing many problems associated with the traditional solvent method [33].

Ex. The dissolution of the PVP/Silymarin solid dispersions was enhanced greatly at PVP/Silymarin ratios of over 4/1 and a coating weight gain of about 100%.

C. CO-PRECIPITATION
Co-precipitation is a recognised technique for increasing the dissolution of poorly water soluble drugs, so as to consequently improve bioavailability. Co-precipitation techniques employ the use or solvents of an organic solvent to dissolve and intimately disperse the drug and carrier molecules as herein before described[29]. Separation of the drug and carrier from the solvent on precipitation can rely on the solubility properties of either the drug or carrier**.**

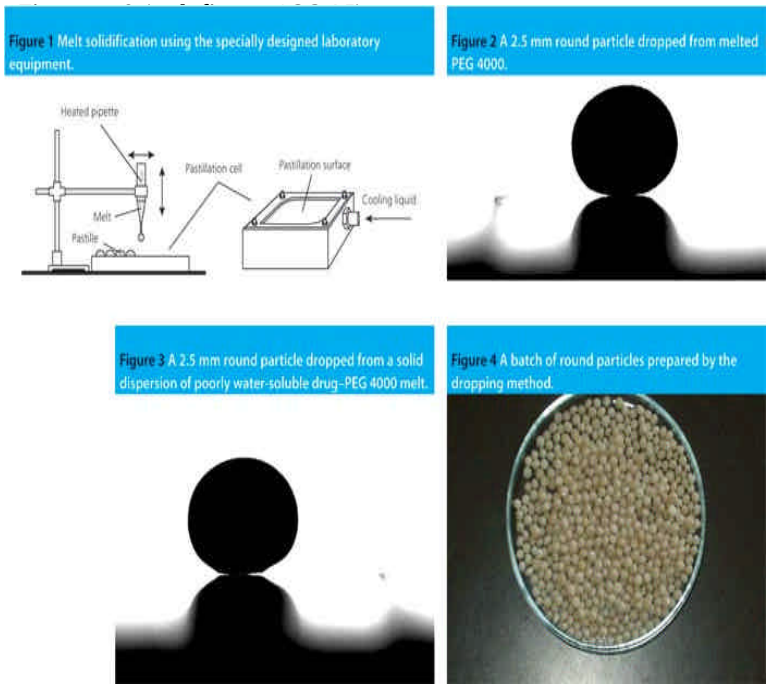
The required quantity of polymer and the drug were mixed and then solvent was added to obtain clear solution. The Solution was first dried under vacuum at room temperature and kept inside incubator(37^{0}c) for 12 hrs. Finally it was passed through sieves (as per requirement)[34].

By Addition of Anti-solvent :
Simonelli et al, Journal of Pharmaceutical Sciences, Vol. 58, No. 5, May 1969, describes a co-precipitation process wherein sulfathiazole is dissolved in sodium hydroxide, followed by addition of polyvinylpyrrolidone; hydrochloric acid is then added to effect co-precipitation. This process is based on co-precipitation employing the solubility of the drug at different pH values. In general terms, problems which can be associated with known co-precipitation techniques can include excess solvent usage, identifying carrier/drug combinations which can be effectively precipitated and enhance bioavailability, the use of heat to effect solution which may detrimentally affect the drug[35]. Co-precipitation techniques are however attractive for the preparation of solid dispersions, in that less solvents and heat are employed when compared to techniques such as co-evaporation and solvent removal may therefore be facilitated.

D. DROPPING METHOD

The dropping method, developed by Ulrich et al.12 to facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions. This technique may overcome some of the difficulties inherent in the other methods.

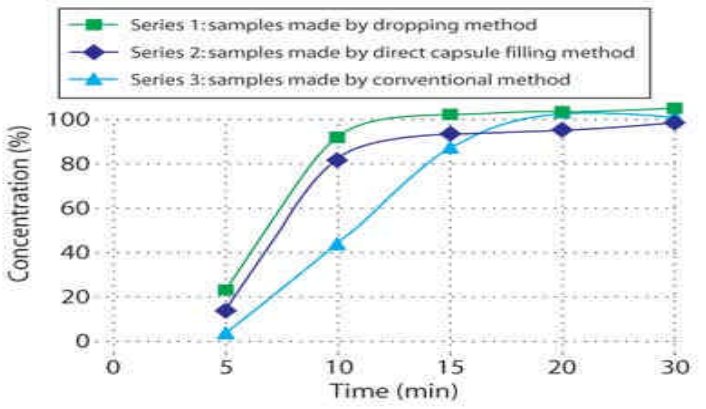
Laboratory-scale preparation.- A solid dispersion of a melted drug– carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles (Figure 1). The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. Because 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 to a spherical shape [28].



Figures 2 and 3 in Figure no 9 show samples of round particles made by the dropping method. The round particle in Figure 2 is made from melted PEG 4000 alone (Fluka AG, Buchs, Switzerland), which solidifies at room temperature. The use of carriers that solidify at room temperature may aid the dropping process. Figure 3 shows a round particle dropped from a solid dispersion of a melted drug–carrier mixture, and Figure 4 shows a batch of round particles prepared at labora-

tory scale by the equipment illustrated in Figure 1. The particles, dropped at 58 °C onto a stainless steel plate, have a diameter of 2.5 mm (60.13 mm). The temperature of the plate was adjusted to room temperature (20 °C 61 °C). Stainless steel was chosen because of its optimal surface energy (30.17 mN/m), which results in the formation of round particles.

Figure 5 Comparison of dissolution rates of solid dispersions produced by three methods.



The results are shown in Figure 5. Samples in Series 1 are solid dispersions made by the dropping method, Series 2 shows those made by direct capsule filling and Series 3 those made by a conventional (pestle and mortar) melting method. The results of the dissolution tests show that the solid dispersions made by the dropping method have better drug-release properties than those produced by the other two methods, particularly during the first 20 min. This shows that using the dropping method not only simplifies the manufacturing process, but also gives a higher dissolution rate.

Advantages of the dropping method - The dropping method does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation. The method also avoids the pulverization, sifting and compressibility difficulties encountered with the other melt methods.

Disadvantages of the dropping method. - Only thermo stable drugs can be used and the physical instability of solid dispersions is a further challenge [28].

RECENT ADVANCES & APPLICATION

. Serrajuddin particularly emphasize on self emulsifying system. Commercial development of drug products based on solid dispersion by advances in filling solid dispersion directly into hard gelatin capsule and availability of surface active agent and self emulsifying agent. For ease manufacturing carrier must be amenable to liquid filling into hard gelatin capsules as melts. Melting temperature should not exceed 70^0c (because maximum acceptable temperature for hard gelatin capsule is 70^0c). There are two new surface active carriers for increment of bioavailability [36];

1)Gelucire 44/14 (Gattfosse corp. France) – it is mixture of glycerol & PEG-1500 esters of long chain fatty acid(lauryl monoglycerides). [44 is M.P. while 14 is HLB value).

2) Vitamin E TPGS NF (Eastman, Kingsport, TN).

Serrajuddin also showed that appropriate combination of polysorbate 80 & PEG acts as good self emulsifying system [36]. More recently, solid dispersion explored with insoluble carrier material and formulation of sustain release products.

Hasegawa, Nakagawa & Sugimoto prepared sustained release dosage forms of Nifedepine by forming solid dispersion with anionic polymers like, HPMC phthalate, methacrylic acid methyl ester co-polymers [36].

In solid dispersion of Nifedepine it is amorphous in nature and practically insoluble in gastric fluid (pH 1.2) but rapidly dissolves in intestinal fluid (ph 6.8) [Super saturation phenomenon]. And these dispersions are stable for 6 months under accelerated condition. Similar results for digoxin & dipyridamole are obtained, but additionally its chemical stability in acidic condition increases.

The solid dispersion technique is one of greatly useful idea in pharmaceutical field and is usually used to improve the dissolution properties and bioavailability of poorly water-soluble drugs by dispersing them into water-soluble carriers. An application of the solid dispersion method to the controlled release of an extremely high water-soluble medicine (oxprenolol hydrochloride, OXP) by polymer blending technique. Here Water-insoluble ethylcellulose (EC) and water-soluble hydroxypropylcelluloce (HPC) were used as polymer carriers [36].

- Fassihi, Parker & Pourkvoos used combination of hydrophilic & lipophillic polymers to control release rate [36].
  Ex. Solid dispersion of Theophylline by fusion method using various ratios of PEG-600, ethyl cellulose & acrylic methacrylic esters.
- Takahashi, Nambu & Nagi showed that co-precipitate of water soluble drug (Thiridazone hydrochloride) with pectin can be used as sustain release preparation[36].
- Novel approach by Yang & Swarbick to prepare sustain release solid dispersion Dapsone by using less soluble derivatives of drug as carrier [36].

MARKETED PREPARATIONS OF SOLID DISPERSION

1) Solid dispersion of VALDECOXIB (NSAID) using PVP by Solvent Evaporation method [37].

2) Solid dispersion of TERBINAFINE HYDROCHLORIDE (synthetic allyl amine derivative, broad spectrum antifungal activity when used orally/topically) using polyvinyl pyrollidone K30 by Solvent Evaporation method[38].

3) Surface Solid Dispersion Of GLIMEPIRIDE (third generation sulphonylurea, antidiabetic drug which stimulates insulin release) using crospovidone, pregelatinised starch, croscarmellose sodium and Avicel PH 101 by Solvent Evaporation method [39].

CONCLUSION

A drug administered in solution form is immediately available for absorption and efficiently absorbed than the same amount of drug administered in a tablet or capsule form. Solubility is a most important parameter for the oral bioavailability 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 bioavailability of them gets affected and hence solubility enhancement becomes necessary. Although salt formation, partical size reduction, etc. have commonly been used to increase dissolution rate of the drug, there are practical limitation with these techniques the desired bioavailability enhancement may not always be achieved. Therefore formulation approaches are being explored to enhance bioavailability of poorly water-soluble drugs. Solid dispersion is mainly used to mask the taste of the drug substances, and to prepare rapid disintegration oral tablets. Solid dispersion has also been used to produce sustained-release microspheres using tedious methods such as water-in-oil emulsions. Above Review shows that, it is now possible that to increase the solubility of poorly soluble drugs with the help of Solid Dispersion Technique effectively. Also this method is practically simple & less tedius than other methods.

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