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Tool to Increase Solubility: Solid Dispersion

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Abstract

This review article focuses on the convenient and simplest method of solubility enhancement i.e., solid dispersion. As solubility is considered to be a major rate limiting factor for enhancing the bioavailability of a poorly soluble drug in human body, there arises the necessity of improving solubility. Solid dispersion is a method in which drug is entrapped inside a inert carrier molecule using methods like fusion, melt extrusion, solvent evaporation, etc. This article gives a detailed insight on the importance of BCS classification, process of solubilizaion, solubility enhancement methods, solid dispersion, methods of preparation, carriers and solvents used along with evaluation parameters.

Keywords: Solubility, solid dispersion, solubility, BCS

INTRODUCTION

Solubility is an intrinsic property of any dosage form, i.e. properties of active compound can be improved by internal modification i.e. by complexation of poorly soluble compounds with water soluble carrier. [1] On the other hand, dissolution is an extrinsic property of drug product, wherein properties or nature of active compound can be improved by external modification i.e. by size reduction, due to which effective surface area of active component will be increased and enables more contact with intestinal fluids for better absorption of drug. Solubility of drug product can be defined as both quantitatively and qualitatively. [2, 3, 4,5]

Quantitative solubility is defined as that milligram of solute particles required to make a saturated solution.

Qualitative solubility is defined as where two phases are mixed together to form a homogenous solution.

With the introduction of combinatorial chemistry and high throughput screening the properties of new developed active compound shifted towards higher molecular weight and lipophilicity of compound is increased, and this results in a decrease in aqueous solubility of compound.[2.4]

There are some aspects where active compound possesses low solubility.

- Active compound having five or more than five number of carbon atoms
- Value of log P is two or greater than two
- Molecular weight of compound is greater than 500 Daltons [3,5,6]

These above mentioned aspects are referred to as **Lipinski rule,** which demonstrate active compound as non-aqueous or poorly aqueous soluble. Solubility of drug substance can be altered on two levels either through material engineering of drug substance or through formulation approaches. Besides aqueous solubility, permeability is another critical aspect for oral bioavailability. [4, 6]

The Biopharmaceutical Classification System (BCS) was introduced in the mid 1990's to classify the drug substances with respect to their aqueous solubility and membrane permeability. Biopharmaceutics Classification System (BCS) has provided a mechanistic framework for understanding the concept of drug absorption in terms of permeability and solubility. [1,3]

BCS classification and solubility:[1,5]

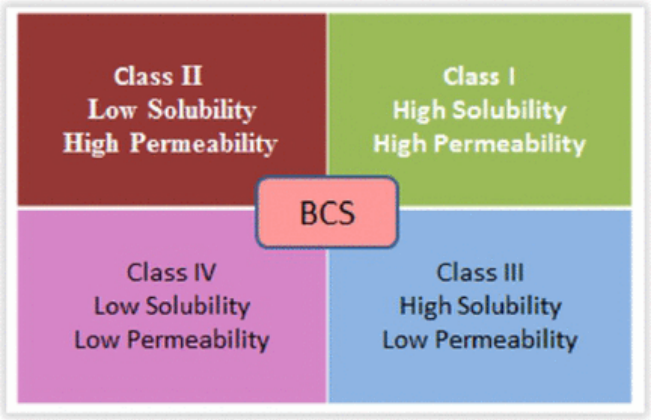


Fig. 1: BCS classification of drugs

Class Boundaries- [3, 5, 7]

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

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

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

Characteristics of the drugs under BCS- [3, 5, 7]

Class I: 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 .Gastric emptying is often the rate governing parameter in this case.

Class II: Drugs belonging to this class have low solubility and high permeability, hence, the dissolution rate becomes the governing parameter for bioavailability. These drugs exhibit variable bioavailability and need enhancement in the dissolution rate by different methods for improvement in bioavailability. These are also suitable for controlled release development.

Class III: Permeation through the intestinal membrane forms the rate-determining step for these drugs. 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.

Class IV: 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. These drugs are generally not suitable for oral drug delivery or else some special drug delivery technologies such as nanosuspensions will be needed.

Solubility:[2,4,8]

Solubility is defined as the phenomenon of dissolution of solute in solvent to give a homogenous system. Dissolution is defined as the transfer of molecules or ions from a solid state into solution. Solubility may be stated in units of concentration, molality, mole fraction, mole ratio, and other units. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for showing pharmacological response. [4, 7]. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Low aqueous solubility is the major problem with formulation development of new chemical entities. Poorly waters soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Most of drugs are weakly acidic and weakly basic with poor aqueous solubility. [8,9,10]

Table 1: Expression of Solubility

Descriptive terms	Relative amounts of solvents to dissolve 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000-10,000
Insoluble or practically insoluble	More than 10,000

Dissolution theory: [8.9,10,11]

Modified Noyes-Whitney equation gives some hints as to how the dissolution rate of a very poorly soluble compound might be improved to maximize the oral bioavailability:

$$\frac{dC}{dt} = \frac{DAKo/w(Cs - Cb)}{Vh}$$

Where, dC/dt = rate of dissolution

A = surface area available for dissolution

D = diffusion co-efficient of the compound

Ko/w = partition coefficient of the drug

Cs = solubility of compound in dissolution medium

Cb = concentration of drug in medium at time 't'

h = thickness of diffusion boundary layer adjacent to the surface of the dissolving compound.

V= volume of dissolution medium

According to the above modified Noyes-Whitney equation, dissolution rate can be enhanced by the following methods:[5.8.11]

1. Increasing the surface area available for dissolution by-
   - Decreasing the particle size of drug.
   - Optimizing the wetting characteristics of compound surface.
2. Decreasing the boundary layer thickness.
3. Ensuring sink condition for dissolution.
4. Improving apparent solubility of drug under physiologically relevant conditions.

Among the above four approaches, the most attractive option for increasing the release rate is the improvement of the solubility through various formulation approaches.

Methods of solubility enhancement: [,912,13]

A] Physical modification

A) Particle size reduction
   i. Micronization
   ii. Sonocrystallization
   iii. Nano-suspension
   iv. Super critical fluid process

B) Modification of crystal habit
   i. Polymorphism
   ii. Pseudo polymorphism

C) Drug dispersed in carriers
   i. Eutectic mixtures
   ii. Solid dispersion

D) Complexation
   i. Using complexing agents

E) Solubilization by surfactants
   i. Micro emulsions

F) Chemical modification
   i. Change in pH
   ii. Use of buffer
   iii. Derivatization

G) Other methods
   i. Co-crystallization
   ii. Co-solvency
   iii. Hydrotrophy
   iv. Solubilizing agents
   v. Selective adsorption on insoluble carrier
   vi. Solvent deposition
   vii. Using soluble prodrug
   viii. Functional polymer technology

Solid dispersions: [5,7,8,14,15]

Solid dispersion is defined as dispersion of one or more active ingredients (hydrophobic) in an inert carrier (hydrophilic) or matrix at solid state are prepared by using different methods such as the melting (fusion), solvent evaporation and melting-solvent method. The solid dispersions may also be called solid-state dispersions. Solid dispersion is an effective way of improving the dissolution rate of poorly water soluble drugs and hence its bioavailability. The water soluble carriers used in preparation of solid dispersion enhance the dissolution rate of the poorly water soluble drug.

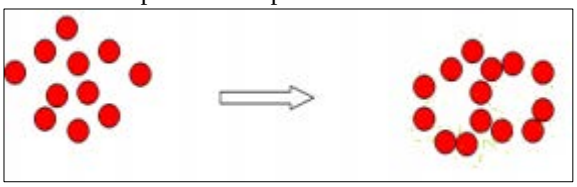
The drugs which are having poor water solubility they often show poor oral bioavailability due to the low levels of absorption. Drugs that undergo dissolution rate limited absorption, their dissolution rate can be enhanced by micronisation or size reduction but this leads to aggregation of particles which leads to poor wettability. Various other approaches for increasing the bioavailability of poorly water soluble drugs include salt formation, solubilisation using a co-solvent, complexation with cyclodextrin and particle size reduction; all these approaches have various limitations. Development of solid dispersions of poorly bioavailable drugs overcame the drawbacks of the previous approaches.

When the solid dispersion comes in contact with the aqueous medium, the inert carrier dissolves and the drug is released, the increased surface area produces a higher dissolution rate thus increasing the bioavailability of the poorly soluble drug.

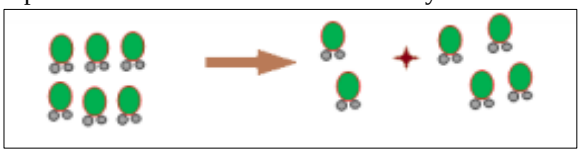
Process of solubilisation: [5, 7]

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

Step 1: Holes opens in the solvent



Step 2: Molecule of the solid breaks away from the bulk



Step 3: The feed of solid molecule is integrated into the hole in Solvent.

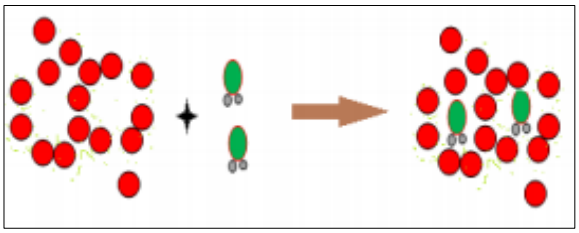


Fig. 2: Process of solubilisation

Types of solid dispersions:[5, 6,9]

1. On the basis of carrier used- Solid dispersions can be classified into three generations:

a. First generation: Using crystalline carriers such as urea and sugars, first generation solid dispersions were prepared which were the first carriers to be employed in solid dispersions. They have the demerits of forming crystalline solid dispersions and did not release the drug as quickly as amorphous ones.

b. Second generation: Second generation solid dispersions include amorphous carriers instead of crystalline carriers which are usually polymers. These polymers include synthetic polymers such as povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates as well as natural products based polymers such as hydroxylpropylmethyl-cellulose (HPMC), ethyl cellulose, and hydroxypropylcellulose or starch derivatives like cyclodextrins.

c. Third generation: Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties. Therefore, third generation solid dispersions appeared.

2. On the basis of their molecular arrangement

Advantages of solid dispersion: [4,9,12,13]

a) Solid dispersion technique is useful to enhance solubility and bioavailability of poorly water soluble drugs.
b) It is easier to produce and is more applicable
c) It leads to increase in extent and rate absorption of a drug, hence rapid dissolution rate occurs
d) Transformation of liquid form of drug into solid form.
e) Control of various parameters like molecular weight, composition, particle porosity and wettability can enhance the bioavailability of poorly water soluble drugs.
f) It is easier to produce rapid disintegration oral tablets by solid dispersion.
g) It is used to mask the bitter taste of drug and improve drug dissolution.
h) It is used to improve porosity of drug.
i) Particles with reduced particle
j) No energy is required to break up the crystal lattice of a drug during dissolution process and drug solubility and wettability may be increased by surrounding hydrophilic carriers.

Disadvantage of solid dispersion: [4,9,12,13]

a) It leads to the poor scale-up for the purpose of manufacturing.
b) The polymers used in solid dispersion can absorb moisture and cause phase-separation, crystal growth and convert amorphous form into crystalline form. Thus result in decrease solubility and dissolution rate.
c) It is laborious method of preparation.
d) Difficulty in incorporating into formulation of dosage forms.

Applications of solid dispersion: [4,9,12,13,15]

The Solid dispersion systems were shown to provide the bio available oral dosage forms for the anti-cancer drugs, which could be substituted for the standard injections to improve the patient compliance & comfort.

a) Solid dispersion also act as the functional carriers that offer the added benefit of the targeting the release of the highly soluble forms of the poorly water soluble drugs for absorption to an optimum site.

b) The solid dispersion systems were also found to reduce the food effects on the drug absorption, thus by increasing the convenience of the drug therapy as it is the need for some drugs to be taken with food was eliminated.
c) The solid dispersion formulations were demonstrated to accelerate the onset of action for the drugs such as NSAIDS [non-steroidal anti-inflammatory drugs] where immediate action is crucial in relieving acute pain and inflammation.
d) The improved absorption efficiency was demonstrated for the solid dispersion systems that allows for the reduction in the content of the active agent per dose thus it decreases the cost associated with these drug therapies.
e) The dry powder formulation consisting of the solid dispersion for use as inhalation is prepared in improving the immunosuppressive therapy in the lung transplant patients. Many problems can be avoided which includes use of local anesthesia & irritating solvents.

Selection of a Carrier: A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug: [3,7,10,15]

a) Freely water-soluble with intrinsic rapid dissolution properties.
b) Non-toxic and pharmacologically inert.
c) Heat stable with a low melting point for the melt method.
d) Soluble in a variety of solvents.
e) Able to preferably increase the aqueous solubility of the drug and
f) Chemically compatible with the drug and not form a strongly bonded complex with the drug.

Table 2: Carriers used in solid dispersion

S. No.	Category	Carriers
1	Sugars	Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose
2	Acids	Citric acid, succinic acid
3	Polymeric materials	Polyvinyl pyrrolidine (PVP), polyethylene glycol (PEG), hydroxypropyl methyl cellulose (HPMC), methyl cellulose (MC), hydroxy ethyl cellulose, cyclodextrin, hydroxy propyl cellulose, pectin, galactomannan
4	Insoluble or enteric polymer	Hydroxy propyl methyl cellulose phthalate (HPMCP), eudragitL100, eudragit E100, eudragit RL, eudragit RS
5	Surfactants	Polyoxyethylene stearate, poloxamer 188, deoxycholic acid, tweens, spans
6	Miscellaneous	Pentaerythritol, pentaerythrityl tetraacetate, urea, urethane, hydroxy alkyl xanthins

Generations of Carriers: [4,8,12]

a) First generation carriers: Example: Crystalline carriers: Urea, Sugars, Organic acids.
b) 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.
c) Third generation carriers: Example: Surface active self-emulsifying carriers: Poloxamer 408, Tween 80, and Gelucire 44/14.

Selection of Solvents: [7,10,11,12]

Solvent to be included for the formulation of solid dispersion should have the following criteria:

a) Both drug and carrier must be dissolved.
b) Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane. Ethanol can be used as alternative as it is less toxic.
c) Water based systems are preferred.
d) Surfactants are used to create carrier drug solutions but as they can reduce glass transition temperature, so care must be taken.

Table 3: Solvents used in solid dispersion

Solvent	Melting Point(°C)	Boiling Point(°C)	Vapour pressure at 25°C (pka)
Water	0	100	3.16
Methanol	-93.9	65	16.9
Ethanol	-117	78.5	5.79
Chloroform	-63	62	26.1
DMSO	19	189	0.08
Acetic acid	17	118	1.64

Methods of Preparation of Solid Dispersions: [12,14,15]

1. Melting Method (Fusion Method)-

The melting or fusion method 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 icebath 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.

2. Melt Extrusion Method-

This method is same as the melt method where polymer processing technology is applied and intense mixing of drug/carrier mix is done with a twin-screw extruder. The

process involves embedding a drug in a polymer while shaping the composite material to form a pharmaceutical product. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder.

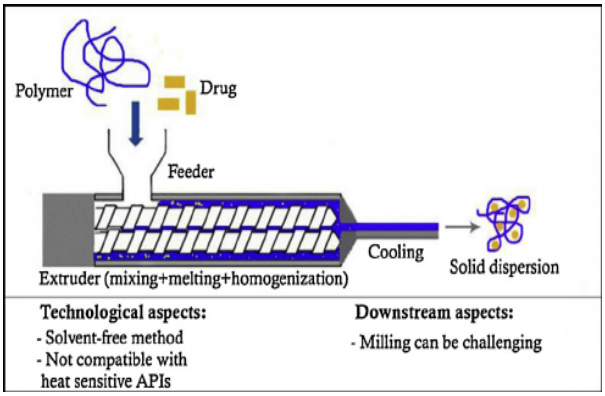


Fig. 3: Melt extrusion method

3. Solvent Evaporation Method-

The first step is formation of solution containing physical mixture of the drug and carrier dissolved in a common solvent and second step involve the removal of solvent resulting the formation of solid dispersion. The product is crushed, pulverized & sieved through a suitable mesh number sieve. An important requirement for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent.

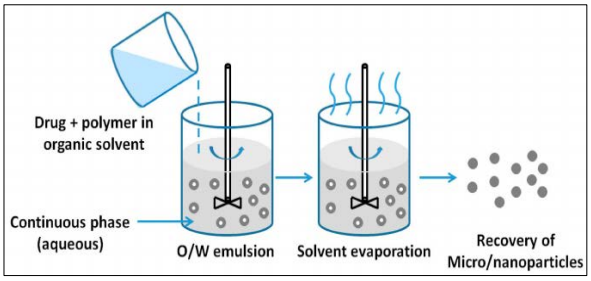


Fig. 4: Solvent evaporation method

4. Melting Solvent Method (Melt Evaporation)-

Here the solid dispersions are prepared by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5 –10% w/w of liquid compounds can be incorporated into polymer without significant loss of its solid property. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polymer. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg.

5. Alternative Methods-

i. **Physical Mixture Method:** The physical mixtures were prepared by weighing the calculated amount of drug and carriers and then mixing them in a glass mortar by triturating. The resultant physical mixtures were passed through 44-mesh sieve and stored in desiccators until used for further studies.

ii. **Co-Grinding Method:** The calculated amounts of drug and carriers where weighed and mixed together with one ml of water. The damp mass obtained was passed through a 44- mesh sieve; the resultant granules were dispersed in Petri dishes and dried at 60°C under vacuum, until a constant weight was obtained. The granules obtained were stored in desiccators until used for further studies.

iii. **Kneading method:** A mixture of accurately weighed drug and carrier is wetted with solvent and kneaded thoroughly for some time in a glass mortar. The paste formed is dried and sieved.

iv. **Supercritical fluid methods-** Supercritical fluid methods are mostly applied with carbon dioxide (CO_2), which is used as either a solvent for drug and matrix or as an antisolvent. This technique consists of dissolving the drug and the carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO_2. When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel. This technique does not require the use of organic solvent and since CO_2 is considered environmentally friendly, this technique is referred to as 'solvent free'. This technique is also known as Rapid Expansion of Supercritical Solution (RESS).

Evaluation of solid dispersion:[4,6,8,13,15]

1) Determination of Percentage yield-

The yield of the final solid dispersion of all ratios was calculated by using the final weight of solid dispersion after drying and the initial weight of drug and polymer used for preparation of solid dispersion. The following formula is used for calculation of percent practical yield-

$$\%\ \boldsymbol{Practical\ yield} = \frac{\boldsymbol{Weight\ of\ solid\ dispersion}}{\boldsymbol{Theoretical\ weight\ (Drug + carrier)}} \times \mathbf{100}$$

2) Determination of drug content of prepared solid dispersions-

The percentage drug content in solid dispersion was estimated by dissolving quantities equivalent to 10mg of solid dispersion in 10ml methanol, centrifuged for 10min and filtered through 0.45µm membrane filter, appropriately diluted with distilled water and the UV absorbance were recorded at 241nm by using UV-visible spectrophotometer. The percentage drug content was calculated using the following formula-

$$\%\ \boldsymbol{Drug\ content} = \frac{\boldsymbol{Actual\ amount\ of\ drug\ in\ solid\ dispersion}}{\boldsymbol{Theoretical\ amount\ of\ drug\ in\ solid\ dispersion}} \times \mathbf{100}$$

3) Determination of saturation solubility of prepared solid dispersions-

Excess amount of solid dispersions were added to 250ml conical flasks containing 25ml of distilled water. The sealed flasks were shaken for 24hrs at 37±0.5ºC. Then, aliquots were filtered through whatmann filter paper. The concentration of Carvedilol was determined by UV spectrophotometer at 241nm. Saturation solubility study was also performed in 1.2pH phosphate buffer and 6.8pH buffers.

4) FTIR study of solid dispersion-

Infrared spectra of solid dispersion powder was obtained using FTIR spectrometer in the range of 4000-400cm^{-1}. This was done to study about the compatibility between drug and polymers in the solid dispersion.

5) Differential Scanning Calorimetry (DSC) study of solid dispersion-

DSC was performed to characterize thermal changes in the melting behavior of Carvedilol with polymers present in solid dispersion. DSC study also reveals whether the drug is in crystalline or in amorphous form. The study of prepared solid dispersion were carried out using thermal analyzer. DSC studies were carried out using thermal analyzer (TA SDT-2790). The samples were hermetically sealed in an aluminum pan and heated at constant rate of 10^{0}C/min over a temperature range of 30-300^{0}C. Inert atmosphere was maintained by purging nitrogen gas at a flow of 10ml/min.

6) Scanning Electron Microscopy (SEM) study of solid dispersion-

SEM of optimized solid dispersion batch was carried out using JSM 6360, JEOL India Pvt. Ltd. to study the morphological characteristics of the solid dispersion.

7) *In-vitro* dissolution studies of solid dispersion systems-

Dissolution study under gastric conditions, intended to select the solid dispersion system with superior dissolution properties to be incorporated into the formulation of immediate release tablet, were performed using the USP dissolution apparatus II at 50 rpm. At appropriate intervals, samples from the dissolution medium were withdrawn, filtered, and concentrations were determined spectrophotometrically at 241nm. The dissolution studies were conducted in triplicate and the cumulative % drug release was plotted against time.

CONCLUSION

Solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs. In recent years, a great deal of knowledge has been accumulated about solid dispersion technology, but their commercial application is limited. Various methods have been tried recently to overcome the limitation and make the preparation practically feasible. The problems involved in incorporating into formulation of dosage forms have been gradually resolved with the advent of alternative strategies. These include methods like spraying on sugar beads and direct capsule filling. Although there are some hurdles like scale up and manufacturing cost to overcome, there lies a great promise that solid dispersion technology will hasten the drug release profile of poorly water soluble drugs.

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