Review

A REVIEW ON SOLID DISPERSION

Parimita Kalita*, Aditya Bora

[1]Department of Pharmaceutical Science, Dibrugarh University. Dibrugarh.

[2] Girijananda Chowdhury Institute of Pharmaceutical Science, Azara.

Submitted on: 11.06.2014 Revised On: 02.08.2014 Accepted on: 10.08.2014

ABSTRACT

The oral route of administration is the mostly and easily used method of delivery due to convenience and ease of ingestion for many drugs it can be a tricky and inefficient mode of delivery for water-insoluble drug. There are some drugs which typically decreases dissolution rate limited absorption resulting in poor bioavailability of drugs when delivering via the oral route.Solid dispersion is a competent approach to deal with drugs that suffer from dissolution-limited absorption. This strategy has proven to improve the bioavailability by dispersing the hydrophobic drug as very fine particles within hydrophilic matrix that results in increased solubility with increased surface area available for dissolution.The review covers concise preface of solid dispersion highlighting various approaches for their preparation, Technology involved, selection of carriers and methods of characterization.

KEYWORDS: Solid dispersion; Dissolution; water insoluble drug.

Corresponding Author: Parimita kalita

E-mail id: parikalita1991@gmail.com

Indian Research Journal of Pharmacy and Science; 2(2014) 1-9;
Journal home page: https://www.irjps.in

INTRODUCTION

Aqueous solubility and poor dissolution of insoluble drugs always remains a problem to the pharmaceutical industry. Lipophillic molecules especially those belonging to the Biopharmaceutics Classification System (BCS) Class II and IV, dissolve slowly, poorly and irregularly, and hence poses serious drug delivery challenges like incomplete release from the dosage form, poor bioavailability etc.[1]

Various techniques are available to improve this characteristic such as solid dispersions, micronization, salt formation of drug and addition of surfactants. Solid dispersion technique is used to enhance the dissolution of a poorly water-soluble drug. Solid dispersions are one of the most successful techniques to improve dissolution rate of poorly water-soluble drugs .[2-5]Solid dispersions are molecular mixtures of poorly aqueous soluble solid drug with an inert hydrophilic carrier. Drug release profile from such mixtures is driven by the carrier properties. Studies revealed that drugs in solid dispersion need not necessarily exist in the micronized stat.[6] 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 release as a fine colloidal particles, resulting enhanced surface area, produces higher dissolution rate and bioavailability of poorly water-soluble drugs. Inaddition, in solid dispersion a portion of drug dissolves immediately to saturate gastro intestinal tract fluid and excess drug precipitates as fine colloidal particles or only globules of submicronsize [7].

1. SOLID DISPERSION: DEFINITION

Chiou and Reigelman first defined solid dispersion inn 1971 as “dispersion of one or more active ingredients inn an inert carrier or matrix at solid state prepared by fusion, solvent or melting solvent method”.

Dispersions prepared by fusion process are often termed as melts, e.g., nimesulide-PEG 4000 and those obtained by the solvent method are frequently referred to as co precipitates or co-evaporates, e.g., coprecipitates of furosemide cross povidone [8] .

1.1 MERITORIOUS FEATURES AND PITFALLS OF SOLID DISPERSION

The homogenous distributions of small amount ofdrug(s) at solid state, provided in solid dispersions tend to have numerous advantageous applicationsviz.

a) More acceptable to patients than solubilisation product, since solid dispersion rises to solidoral dosage forms instead of liquid assolubilisation products.
b) Enhancement of the active agent bioavailabilityto a desirable extent
c) Homogeneous distribution of small amount ofdrug at solid state is possible to attain.
d) Avoiding polymorphic changes and the consequent bioavailability problems
e) Transformation of liquid or gaseous form of drug in to solid form is possible

1.2 LIMITATION OF SOLID DISPERSION METHOD

Despite their numerous meritorious features, solid dispersions during formulation development have some limitations too, viz [9]

a) Reproducibility of its physico-chemical properties
b) Poor stability of dosage form.
c) Laborious and expensive method of preparation.
d) Aggregation, agglomeration and air adsorption during formulation.
e) Decrease in dissolution rate with aging ford.
f) Difficulty in pulverization and sifting because of their tacky and soft nature.

2. CARRIER USED IN THE PREPARATION OF SOLID DISPERSION

Table1: The various carries for solid dispersion are e enlisted in

Chemical class	Examples
Acids	Citric acid, Tartaric acid, Succinic acid
Sugars	Dextrose, Sorbitol, Sucrose,Maltose, Galactose, Xylit
Polymer material	Polyvinyl pyrolidone, PEG 4000,PEG-6000
Surfactant	Polyoxyethylene stearate, Deoxycholic acid
Miscellaneous	Pentaerythritol, Urea, Urethane.

3.0 Preparation of Solid Dispersions

A. Fusion method

The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline. Therefore, the more general term fusion method is preferred. The first solid dispersions created for pharmaceutical applications were prepared by the fusion method. The dispersion consisted of sulfathiazole and urea as a matrix, which was melted using a physical mixture at the eutectic composition, followed by a cooling step The eutectic composition was chosen to obtain simultaneous crystallization of drug and matrix during cooling. This procedure resulted in solid dispersions of type I. Poly (ethylene glycol) (PEG) is a hydrophilic polymer often used to prepare solid dispersions with the fusion method. This often results in solid dispersions of type III since many drugs are incorporated as separate molecules in the helical structure present in a crystalline PEG. The helices are aligned in orderly fashion, illustrating that PEG easily crystallizes. Another polymer frequently applied as a matrix in the fusion method is poly (vinyl pyrollidone) PVP. PVP, supplied in the amorphous state, is heated to above its *Tg* (glass transition temperature).

The drug has to fuse with or dissolve in the rubbery matrix, which is subsequently cooled to vitrify the solid dispersion. When PVP is used as matrix, solid dispersions of type V or VI are obtained.

The mode of incorporation of the drug depends on the PVP-drug miscibility and the preparation procedure. Grinding is required to obtain the solid dispersion as powder that is easy to handle. Although frequently applied, the fusion method has serious limitation. Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature. When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture, which results in an inhomogeneous solid dispersion.

This can be prevented by using surfactants. Secondly, a problem can arise during cooling when the drug-matrix miscibility changes. In this case phase separation can occur. Indeed, it was observed that when the mixture was slowly cooled, crystalline drug occurred, whereas fast cooling yielded amorphous solid dispersions. Thirdly, degradation of the drug and or matrix can occur during heating to temperatures necessary to fuse matrix and drug.

For example, to melt a sugar matrix of galactose a temperature of 169°C was required and in order to get the glassy PVP in the rubbery state a temperature of about 170°C is required. Poly ethylene glycols melt at around 70°C and are therefore often used for the preparation of solid dispersions with the fusion method[10].

B. Hot melt extrusion

Melt extrusion is essentially the same as the fusion method except that intense mixing of the

components is induced by the extruder. When compared to melting in a vessel, the product stability and dissolution are similar, but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding.[11]

Types of solvent technique

The choice of solvent and its removal rate are critical to the quality of the dispersion. Depending upon the method of evaporation, there are various types of techniques.

A. 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.[12]

Advantages

- Ability to work with temperature sensitive APIs.

Drawbacks

- Added costs associated with the use and consumption of the organic solvents.
- Requirement of unit operation for residual solvent removal.

B. Freeze drying

To overcome the disadvantages of the above discussed techniques and to obtain a much faster dissolution rate, freeze drying technique has been proposed. The drug and the carrier are dissolved in a common solvent, which is immersed in liquid nitrogen until it is fully frozen then; the frozen solution is further lyophilized. The instance includes that a solid dispersion of tenoxicam with skimmed milk, prepared using freeze drying showed 23-fold increase in solubility with respect to the plain drug.

Advantages

- Risk of phase separation is minimized as soon as the solution is vitrified.
- Offers the potential to customize the size of the particle to make them suitable for further processing.

Drawbacks

- The tablets are very fragile.
- The manufacturing process is very expensive.

C. Solvent melt technique

To overcome the problems associated with fusion technique, a blend of fusion and solvent evaporation method has also been proposed. In this technique, the drug is dissolved in an organic solvent and mixed with the melted carrier. The solvent is then evaporated and the resultant product is pulverized to the desired size.[13]

D. Supercritical fluid methods

Supercritical fluid methods are mostly applied with carbon dioxide (CO2), which is used as either a solvent for drug and matrix or as an anti-solvent. When supercritical CO2 is used as solvent, matrix and drug are dissolved and sprayed through a

nozzle, into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO2 is considered environmentally friendly, this technique is referred to as 'solvent free'. The technique is known as Rapid Expansion of Supercritical Solution (RESS). However, the application of this technique is very limited, because the solubility in CO2 of most pharmaceutical compounds is very low (<0.01wt-%) and decreases with increasing polarity. Therefore, scaling up this process to kilogram-scale

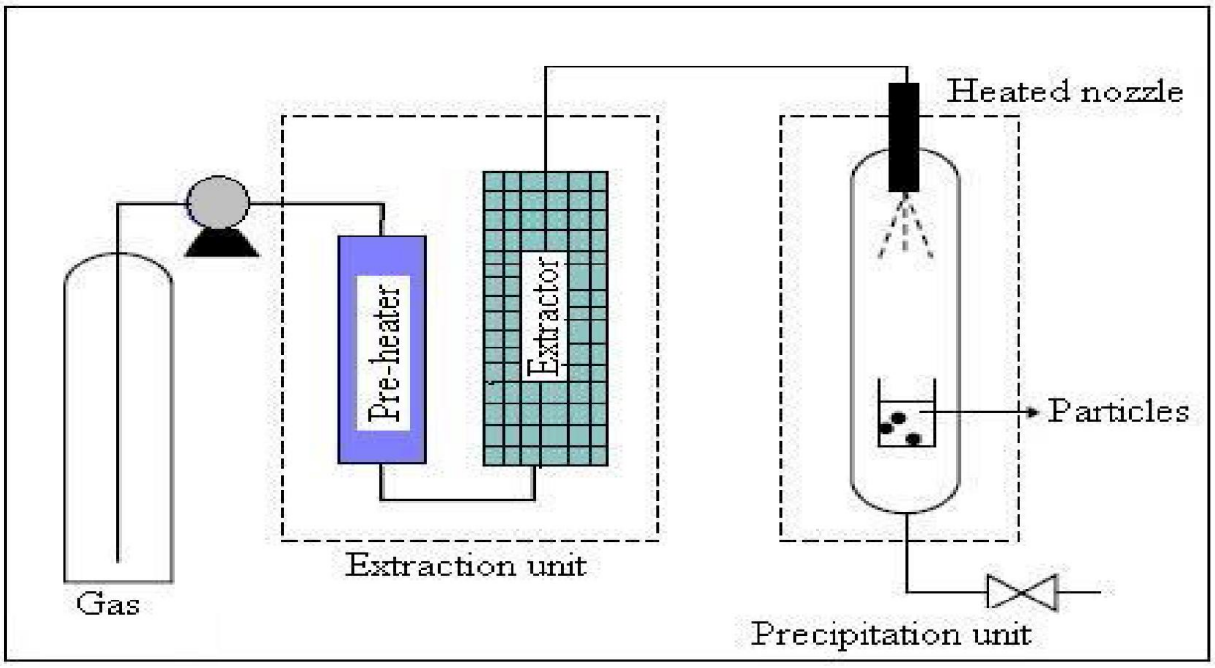

Fig1: schematic diagram of RESS apparatus on supercritical fluid method.

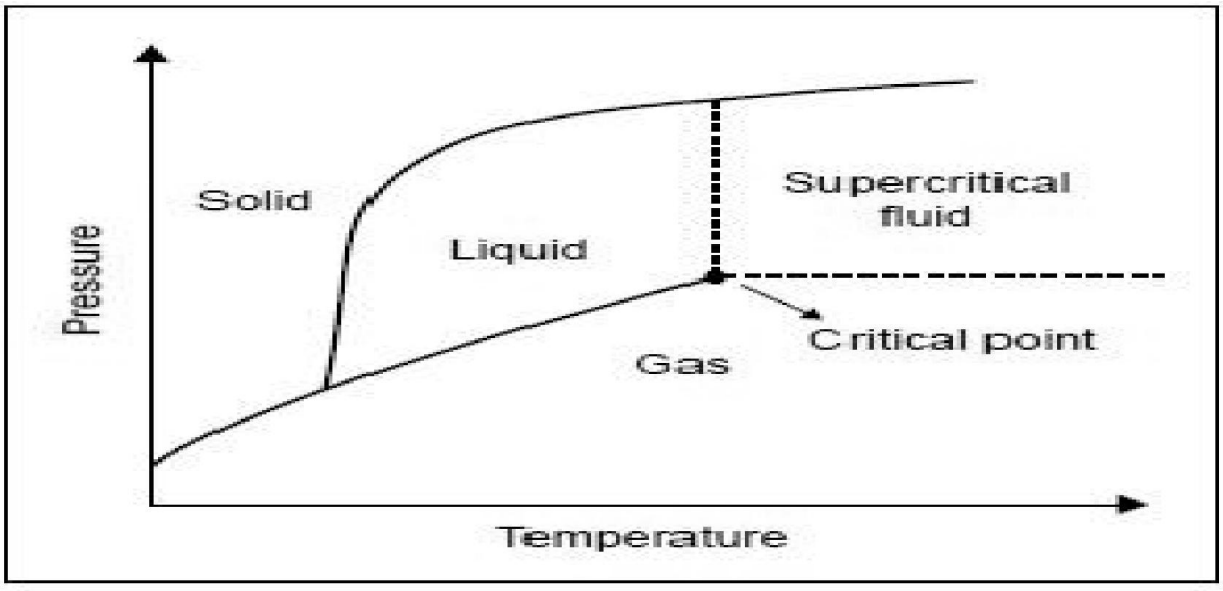

Fig 2: Supercritical region of a hypothetical compound (Indicated by the dotted lines)

Although generally labelled as solvent-free, all these supercritical fluid methods use organic solvents to dissolve drug and matrix and exploit the low solubility of pharmaceutical compounds in CO2. In fact, these techniques represent alternative methods to remove solvents from a solution containing typically a drug and a polymer. Moneghini and co-workers (2001) reported their method as solvent-free, but they dissolved PEG and carbamazepine in acetone.

They used a technique that is called the Gas-Anti-Solvent technique (GAS) or Precipitation from Gas Saturated Solutions (PGSS). The solution is brought into contact with compressed CO2. The conditions are chosen so that CO2 is completely miscible with the solution under supercritical conditions, whereas drug and matrix will precipitate upon expansion of the solution. When the volume of the solution expands the solvent strength (i.e. the ability to dissolve the drug) decreases. This results in precipitation of matrix and drug.

Since this technique is often applied with PEG as matrix, this technique results in formation of a solid dispersion with a crystalline matrix (Sethia and Squillante, 2002). The second type of precipitation technique involves the spraying of a solution containing drug and matrix through a nozzle into a vessel that contains a liquid or supercritical anti-solvent. The supercritical anti-solvent rapidly penetrates into the droplets, in which drug and matrix become supersaturated, crystallize and form particles. The general term for this process is Precipitation with Compressed Anti-Solvent (PCA). More specific examples of PCA are Supercritical Ant solvent (SAS) when supercritical CO2 is used, or Aerosol Solvent Extraction System (ASES), and Solution Enhanced Dispersion by Supercritical fluids (SEDS). However, as with the other solvent techniques described in the previous section, the critical step in these precipitation techniques might be the dissolution of drug and matrix in one solution. The use of water is limited, because the water solubility in compressed CO2 is limited. Usually organic solvents like dichloromethane or methanol have to be applied to dissolve both drug and matrix[14].

Advantages

- Dissolving power of the SCF is controlled by pressure and/or temperature
- SCF is easily recoverable from the extract due to its volatility
- Non-toxic solvents leave no harmful residue
- High boiling components are extracted at relatively low temperatures
- Thermally labile compounds can be extracted with minimal damage as low temperatures can be employed by the extraction
- Non-inflammable and inexpensive technique

Drawbacks

- Elevated pressure required
- Compression of solvent requires elaborate recycling measures to reduce energy costs
- High capital investment for equipment.

E. Co-evaporates

This techniques, drug and copolymer are dissolved separately in same organic solvent and then these two solutions are mixed with further evaporation of solvent under either vacuum or using flash evaporation to give evaporates. Co-evaporates have mainly been employed for dermatological products, e.g., co-evaporates of hydrocortisone acetate-PVP

and betamethasone dipropionate-PVP, both of which showed improved ceutaneous penetration[15]

F. Co-precipitates

Co-precipitates are produced by adding a nonsolvent with agitation to a drug and polymer mixture in an organic solvent. The co-precipitates are later filtered and dried.[16]

4.0 Characterization of solid dispersion

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.

4.1. Thermal Analysis

4.1.1. 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 melt stages. The technique has been used to support DTA or DSC measurement. It gives information about the phase diagram of binary systems [17].

4.1.2. Differential thermal analysis (DTA)

This is an effective thermal method for studying the phase equilibriam 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.

4.1.3. 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.

4.2. 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.[18]

a) Single crystal x-ray crystallography dealing with the determination of bond angle and inter atomic distances.

b) 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 changesin 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 represents the order of diffraction .

4.3. 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.

4.4. Dissolution rate determination

The method involves comparing the in vitro dissolution rates of the solute component from a constant- surface tablet made from molecular dispersion (i.e., solid or glass solution) with a physical mixture of the same chemical composition.The technique is simple to perform. It tells whether the solid dispersion has improved the dissolution rate or not. The degree of crystallinity can also be studied if it is carried out under standard conditions.

4.5. 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.

4.6. 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.

CONCLUSION

The review provides various methodologies of using solid dispersions, and discusses as to why, when, and how to develop them. Proper selection of formulation method and carriers play important role in solubility enhancement of poorly water soluble drugs. Improved understanding of physical stability of solid dispersions is the main driver for increasing future relevance of solid dispersions. With further expansion in polymer science and a greater perceptive of biopharmaceutical properties prevailing dosage form selection, solid dispersions technique will be widely applied to develop oral dosage form of poorly water-soluble drugs With further expansion in polymer science and a greater perceptive of biopharmaceutical properties prevailing dosage form selection, solid dispersions technique will be widely applied to develop oral dosage form of poorly water-soluble drugs. 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. 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.

REFERENCE

1. Chawla G., Bansal. A.K.., Improved dissolution of a poorly water soluble drug in solid dispersion with polymeric and nonpolymeric hydrophillic additives. Acta Pharma. 2008; 58:257-274.

2. Shahroodi A.B., Nassab P.R., Revesz P.S., Preparation of a solid dispersion by a dropping method to improve the rate of dissolution of

meloxicam. Drug. Dev. Ind.Pharm. 2008; 34: 781-788.

3. Leuner. C., Dressnan. J., Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. 2000; 50: 47-60.

4. Streubel. A., Siepmann. J., Bodmeier. R., Drug delivery to the upper small intestine window using gastroretentive technologies. Curr. Opin. Pharmacol. 2006; 6: 501-508.

5. Konno. H., Handa. T., Alonzo D.E., Taylor L.S., Effect of polymer type on the dissolution profile of amorphous solid dispersion containing felodipine. Eur. J. Pharm. Biopharm. 2008; 70: 493-499.

6.Vasconcelos T.F., Sarmento B., Costa P.,Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discovery Today. 2007; 12: 1068-1075.

7. Karanth. H., Shenoy.V.S., Murthy.RR., Industrially feasible alternative approaches in the manufacture of solid dispersion; A technical report. A A P S Pharmscitech. 2006; 7:E1-E8

8.Chiou.W.L., Riegelman.S., Pharmaceutical application of solid dispersion. J Pharm Sci.1971; 60:1281-1302.

9. Vasconcelos. T., Sarmanto. B., Costa. P., Solid dispersion as strategy to improve oral bioavailability of poorly water soluble drugs. J Pharm Sci. 2007; 12:1068-1075.

10. Subrahmaniam, B., Rajewski. R.A., and Snavely. K., (1997) Pharmaceutical processing with supercritical carbon di oxide.J.Pharma.sci 86(8) 885-890.

11. Sharma. D.K., Joshi. S.B., Solubility enhancement strategies for poorly water soluble drug in solid dispersion: A Review. Asian Journal of Pharmaceutics. 2007; 1:9-19

12. Ambike. A.A., Mahadik. K.R., Paradkar. A., Spray dried amorphous solid dispersions of a low Tg drug: *In vitro* and invivo evaluations. Pharm Res. 2005; 22:990–998.

13. Takayama. K., Nambu. N., Naka. T., Factor affecting the dissolution of ketoprofen from Solid dispersion in various water solublepolymers. Chem Pharm Bull. 1982;

14. Muhrer. G.U., Meie.r F., Fusaro. S., Mazzotti . M., Use of compressed gas precipitation to enhance the dissolution behavior of a poorly water-soluble drug: Generation of drug microparticles and drug-polymer solid dispersion. Int J Pham. 2006; 308:69-83.

15. Jarmer. D.J., Lengsfeld. C.S., Anseth. K.S., Randolph. T.W., Supercritical fluid crystallization of griseofulvin: Crystal habit modification with a selective growth inhibitor. Pharm Sci. 2005; 94:2688–2702.

16. Edwards. A.D., Shekunov. B.Y., Kordikowski. A., Forbes. R.T., Yor. P., Crystallization of pure anhydrous polymorphs of carbamezapine by solution enhanced dispersion with Supercritical fluids (SEDS). J Pharm Sci. 2001; 90:1115–1124.

17. Morita. M., Hisrota. S., Correlation studies between thermal and dissolution rate constant of cimitidine drug and tablet. Chem Pharm Bull. 1985; 33:2091.

18. Vidyadhara. S., Babu. P.S., Swapnasundari. P., Rani. M.T., Solid Dispersion: An approach to improve sold formulation development. Pharma Bioworld 2004; 70-7.

Conflict of Interest Reported: Nil; Source of Funding: None Reported