SOLID DISPERSION- STRATEGY TO ENHANCE SOLUBILITY AND DISSOLUTION OF POORLY WATER SOLUBLE DRUGS

Ankush Kumar©, Kapil Kumar©
Global Institute of Pharmaceutical Education and Research, Kashipur, Uttarakhand, India

ABSTRACT
Improving oral bioavailability of drugs those given as solid dosage forms remains a challenge for the formulation scientists due to solubility problems. Over the years a variety of solubilization techniques have been studied and widely used, as maximum drugs are poorly water soluble in pharmaceutical field. The enhancement of dissolution rate and oral bioavailability is one of the greatest challenges in the development of poorly water soluble drugs. Solid dispersions have attracted many researchers as an efficient means of improving the dissolution rate and hence the bioavailability of a range of poorly water-soluble drugs. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug. Solid dispersion can form either a eutectic mixture or solid solution or glass solution or amorphous precipitation in a crystalline carrier or compound or complex formation. The focus of this review article is on the advantages, limitations, various methods of preparation and characterization of the solid dispersion.

Keywords: Bioavailability, eutectic mixture, solid dispersion, solubility, solubilization techniques.

INTRODUCTION
Oral drug delivery is the most popular, simplest and easiest way for drugs administration. When a drug is administered orally, it must dissolve in gastric and/or intestinal fluids in order to permeate the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Maximum drugs have poor solubility and permeability. Hence, pharmaceutical research that focuses on improving the oral bioavailability of active agents by enhancing solubility and dissolution rate of poorly water-soluble drugs. The term solid dispersion refers to a group of solid products consisting of a hydrophilic matrix and a hydrophobic drug. The matrix can be amorphous or crystalline in nature. Solid dispersion need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion. When the solid dispersion comes in contact of aqueous media, the carrier dissolves and the drug release as a fine colloidal particle, resulting enhanced surface area. This results in higher dissolution rate and bioavailability of poorly water soluble drugs. In addition, 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 submicron size. Solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs.

B.C.S categories

| Class | Solubility | Permeability |
|-------|------------|--------------|
| Class 1 | High Solubility | High Permeability |
| Class 2 | Low Solubility | High Permeability |
| Class 3 | High Solubility | Low Permeability |
| Class 4 | Low Solubility | Low Permeability |

The classification of drugs based on BCS is:

Class 1: High Solubility, High Permeability
Class 2: Low Solubility, High Permeability
Class 3: High Solubility, Low Permeability
Class 4: Low Solubility, Low Permeability

Advantages
1. Enhance solubility and bioavailability of poorly water soluble drugs.
2. Easy to produce.
3. Rapid dissolution rate, leads to increase in extent and rate of drug absorption.

Table 1: BCS Classification of drugs.
4. Transformation of liquid or gaseous form of drug in to solid form is possible.  
5. Avoiding polymorphic changes and the consequent bioavailability problems  
6. Easy to prepare rapid disintegration oral tablets by solid dispersion.  
7. Improve porosity of drug.  

Disadvantages  
The disadvantages of solid dispersion are enlisted below:  
1. Poor scale-up for the purpose of manufacturing.  
2. Polymers used in solid dispersion can absorb moisture and cause phase-separation, crystal growth and convert amorphous form into crystalline form. It may leads to decrease solubility and dissolution rate.  
3. Difficulty in pulverization and sifting because of their tacky and soft nature.  
4. It causes reproducibility of physicochemical characteristics.  
5. Poor stability of dosage form.  
6. Laborious and expensive method of preparation.  
7. Aggregation, agglomeration and air adsorption during formulation.  
8. Decrease in dissolution rate with aging.  

TYPES OF SOLID DISPERSION  
1. Eutectic mixtures  
Eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state. These systems are usually prepared by melt fusion method. When the eutectic mixture is exposed to water, the soluble carrier dissolves leaving the drug in a microcrystalline state which gets solubilized rapidly. The increase in surface area is mainly responsible for increased rate of dissolution. Examples of this type include phenacetin–phenobarbital, Chloramphenicol-urea, griseofulvin-succinic acid, and paracetamol-urea.  

Figure 1: Hypothetical phase diagram of eutectic mixture  

2. Solid solution  
These consist of a solid solute dissolved in a solid solvent. The particle size of the drug in the solid solution is reduced to its molecular size. Solid solutions are comparable to liquid solutions, consisting of just one phase irrespective of the number of components. These systems are generally prepared by solvent evaporation or co-precipitation method, in which solute and carrier are dissolved in a common volatile solvent such as alcohol. Solid solution differs from eutectic mixture in a way that the drug is precipitated out in an amorphous form in solid dispersion/solution while it is in crystalline form in eutectics. Solid solution can generally be classified according to the extent of miscibility between the two components or the crystalline structure of the solid solution as-  

i). Continuous Solid Solutions:  
In this system, the two components are miscible or soluble at solid state in all proportions. Although it is theoretically possible but no established solid solution of this kind has been shown to exhibit faster dissolution properties. The presence of a small amount of the soluble carrier in the crystalline lattice of the poorly soluble drugs may also produce a dissolution rate faster than the pure compound with similar particle size.

Figure 2: Hypothetical Phase Diagram of Continuous Solid Solution  

ii). Substitutional solid solution:  
In substitutional solid solution, the solute molecule substitutes for the solvent molecules in the crystal lattice of the solid solvent. It can form a continuous or discontinuous solid solution. The size of the solute and the solvent molecule should be as close as possible.

Figure 3: Substitutional solid solution  

iii). Discontinuous solid solution  
In contrast to the continuous solid solution, this system has only a limited solubility of a solute in a solid solvent. Each component is capable of dissolving the other component to a certain degree above the eutectic temperature.

Figure 4: Hypothetical phase diagram of discontinuous solid solution
IV. Interstitial solid solution
The solute (guest) molecule occupies the interstitial space of the solvent (host) lattice. It usually forms only a discontinuous (limited) solid solution. The size of the solute is critical in order to fit into the interstices. It was found that the apparent diameter of the solute molecules should be less than that of the solvent in order to obtain an extensive interstitial solid solution of metals. 19

3) Glass solution
It is a homogenous system in which a glassy or a vitreous carrier solubilized drug molecules in its matrix. By an abrupt quenching of the melt, the glassy or vitreous state is usually obtained. It is characterized by transparency andbrittleness below the glass transition temperature. On heating, it softens progressively without a sharp melting point 20.

4) Compound or complex formation
This system is characterized by complexation of two components in a binary system during solid dispersion preparation. Rate of dissolution and gastrointestinal absorption can be increased by the formation of a soluble complex with low association constant 21.

Table 2: Classification of carriers

| Carriers                  | Examples                                                                 |
|---------------------------|--------------------------------------------------------------------------|
| Polymers                  | polyvinylalchol, polyvinylpolypryridonide, polypyrrolidone, polyethylene glycols, hydroxypropyl cellulose |
| Surfactants               | Tweens, spans, polyoxyethylene stearates, poly (caprolactone)-b-poly (ethylene oxide) |
| Carbohydrates             | Lactose, sorbitol, mannitol, glucose, maltose, soluble starch, cyclodextrins, galactose, xylitol, galactomannan |
| Polyglycolized glycerides acids | Gelucire 44/14, gelucire 50./13, gelucire 62/05                           |
| Cyclodextrins             | Beta-cyclodextrins, hydroxypropyl-beta-cyclodextrins                     |
| Dendrimers                | Citric acid, succinic acid, phosphoric acid, starburst, polyamidoamine   |
| Superdisintegrants        | Sodium starch glycolate, croscarmellose sodium, cross-linked polyvinyl pyrrolidone, cross-linked alglin, gellan gum, xanthan gum, calcium silicate etc |
| Hydrotropes               | Sodium acetate, sodium citrate, sodium-o-hydroxyl benzoate, sodium-phydroxyl benzoate |

PREPARATION OF SOLID DISPERSIONS

1. Fusion method
First solid dispersions created for pharmaceutical application were prepared by the fusion method. It is also referred as the melt method only when the starting materials are in crystalline state. Drug and carrier mixture of eutectic composition is molten at temperature above its eutectic temperature. Then molten mass is solidified on an ice bath and pulverized to a powder. The solidification is often performed on stainless steel plates to facilitate rapid heat loss. A modification of the process involves spray congealing from a modified spray drier onto cold metal surfaces 22.

2. Freeze-drying method: This method consists of dissolving the drug and carrier in a common solvent, which is immersed in liquid nitrogen until it is fully frozen. Then, the frozen solution is further lyophilized. An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. Furthermore the risk of phase separation is minimized as soon as the solution is vitrified 23.

3. Spray-drying: This method consists of dissolving or suspending the drug and carrier, then spraying it into a stream of heated air flow to remove the solvent. Due to the large specific surface area offered by the droplets, the solvent rapidly evaporates and the solid dispersion is formed within seconds, which may be fast enough to prevent phase separation 24.

4. Dropping method: It is a new procedure for producing round particles from melted solid dispersions. This method does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation. A solid dispersion of a melted drug carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. This method also avoids the pulverization and compressibility difficulties 25.

5. Solvent evaporation method: The solvent evaporation method consists of the solubilization of the drug and carrier in a volatile solvent that is later evaporated such as ethanol, chloroform, mixture of ethanol and dichloromethane. The solvent evaporation process uses organic solvents, the agent to intimately mix the drug and carrier molecules. Vacuum evaporation may be used for solvent removal at low temperature and also at a controlled rate. More rapid removal of the solvent may be accomplished by freeze-drying. The difficulties in selecting a common solvent to both drug and carrier may be overcome by using an azeotropic mixture of solvent in water 26.


6. Supercritical fluid methods

In this method carbon dioxide is used as an anti-solvent for the solute but as a solvent with respect to the organic solvent. In these technique drug and carrier are dissolved in a common solvent leads to particle formation vessel through a nozzle using carbon dioxide.

In addition the ability of carbon dioxide to plasticize and swell polymers can also be exploited and the process can be carried out near room temperature. Moreover, supercritical fluids are used to lower the temperature of melt dispersion process by reducing the melting temperature of dispersed active agent. The temperature condition used in this process is fairly mild (35-75°C), which allows handling of heat sensitive biomolecules, such as enzymes and proteins. The use of this method reduces residual solvent content, particle size without any degradation.

7. Co-precipitation method

In this method non-solvent is added drop wise to the drug and carrier solution, under constant stirring. In the course of the non-solvent addition, the drug and carrier are co-precipitated to form micro particles. At the end, the resulted micro particle suspension is filtered and dried.

8. Hot melt extrusion method: In this method extruder is utilized for intense mixing of components. The components of the extruder are barrel, hopper, a kneading screw, heating jacket, and a die. Physical mixture of both the carrier and drug is introduced into the hopper then passed through screw and finally it is extruded from the die. The product produced by this method can easily be handled because any shape can be adopted.

CHARACTERIZATION

1. Microscopic Methods

These methods are used to determine size and observe morphology of solid dispersion. In scanning electron microscopy sample coated by gold or palladium -using vacuum evaporator examined at accelerating voltage with suitable magnification.

2. Spectroscopic methods

a. FTIR spectroscopy

This is used to check interaction between drug and carrier used in formulation of solid dispersion. Appearance and disappearance of peak indicate interaction between two compound and degradation of drug.

b. UV visible Spectroscopy

Spectra of pure drug and dispersed drug are scanned. Calculation of molar extinction provides evidence of any decomposition.

c. X-ray diffraction spectroscopy

This is used to study quantitatively the concentration of crystalline compound in mixture. It is efficient tool in studying physical nature of solid dispersion. Intensity of X-ray diffraction (or reflected) from sample is measured as function of diffraction angle. Compound or complex formation can be detected by change in spectra of pure drug.

3. Thermal Methods

These methods include exposure of sample to different temperature condition. Studying physicochemical interaction between drug and carrier is based on principle of change in thermal energy as function of temperature.

a. Thaw Melting Method

In this method samples are frozen heated and suddenly converted from solid state to liquid state. Thaw point and melting point can be noted. A limitation of this method is that it depends upon subjective observation, therefore not highly reproducible.

b. Cooling curve Methods

In this method prepared physical mixtures are heated and homogeneous melt temperature of each mixture is noted. Limitations of this method include time consuming process, it requires relatively large amount of sample and not suitable for heat sensitive material.

c. Differential Thermal Analysis (DTA)

In this study the temperature difference that develops between a sample and an inert reference material is measured, at identical heat treatments. Phase transitions or chemical reactions can be followed by absorption or evolution of heat.

d. Differential Scanning Calorimetry (DSC)

This technique it is used to observe fusion and crystallization events, glass transition temperatures, oxidation, as well as other chemical reactions.

4. Dissolution Studies

Carried out at physiological temperature by using type II USP dissolution apparatus. Dissolution profile of solid dispersion or compressed tablet made from solid dispersion is determined by comparison between dissolution profile of pure drug, physical mixture and solid dispersion gives idea about dissolution rate. Effect of different carrier and their different proportion on dissolution rate of solid dispersion is main characterization tool.

APPLICATIONS OF SOLID DISPERSIONS

Solid dispersion technique has following applications

1. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.

2. To obtain a homogeneous distribution of a small amount of drug in solid state.

3. To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerisation, photo oxidation and other decomposition procedures.

4. To reduce side effect of certain drugs.

5. Masking of unpleasant taste and smell of drugs.

6. Improvement of drug release from ointment, creams and gels.
CONCLUSION

Solubility plays an important role for a drug formulation and its therapeutic efficacy. Hence, enhancing of solubility and bioavailability is the major challenge for the researchers. Solid dispersion technique is one of the major techniques to enhance the solubility of drug. It is a promising technique for the enhancement of bioavailability of poorly aqueous soluble drugs. It aims at improving the dissolution and absorption of drugs by various methods like fusion, solvent evaporation, freeze drying etc. A major focus on the future will become the identification of new surface active carriers and self emulsifying carriers for solid dispersion. So, the commercial development of this technique is necessary. For it further research is necessary for the better implementation of solid dispersion technology on industrial scale.

REFERENCES

1. Youn YS. Improved intestinal delivery of salmon calcitonin by Lys18- amine specific PEylation: Stability, permeability, pharmakoherin behavior and in vivo hypocalcemic efficacy. J Contr Rel 2006; 334–342. https://doi.org/10.1016/j.jconrel.2006.06.007
2. Ohara T. Dissolution mechanism of poorly water-soluble drug from extended release solid dispersion system with ethylcellulose and hydroxypropylmethylcellulose. Int J Pharm 2003; 302; 95–102. https://doi.org/10.1016/j.ijpharm.2005.06.019
3. Dhananjay S Saindane, et al. Enhancing drug solubility and oral bioavailability using solid dispersions a review. Int J Biopharm 2011; 2(1); 22-30.
4. Dixit AK, Singh RP, Singh S. Solid dispersion - a strategy for improving the solubility of poorly soluble drugs. Int J of Res Pharm Biom Sci 2012; 3 (2), 963-965. https://doi.org/10.15406/djdrus.2007.09.005
5. Singh S, Singh RB, Yadav L. A review on solid dispersion, Int J Pharm J Life Sci 2011; 2(9), 1093. https://doi.org/10.13040/IJPSR.0975-5232.46.2094-05
6. Hasegawa S. Effects of water content in physical mixture and heating temperature on crystallinity of troglitazone-PVP K30 solid dispersions prepared by closed melting method. Int J Pharm 2003; 302; 103–112. https://doi.org/10.1016/j.ijpharm.2005.06.021
7. Lloyd GR. A calorimetric investigation into the interaction between paracetamol and polyethylene glycol 4000 in physical mixes and solid dispersions. Eur J Pharm Biopharm 2003; 48; 59–65. https://doi.org/10.1016/S0939-6411(99)00223-3
8. Rodier E. A three step supercritical process to improve the dissolution rate of Eflulcinamide. Eur J Pharm Sci 2005; 26: 184–193.https://doi.org/10.1016/j.ejps.2005.05.011
9. Yoshihashi Y. Estimation of physical stability of amorphous solid dispersion using differential scanning calorimetry. J Therm Anal Meth 2006; 85: 689-692. https://doi.org/10.1007/s10973-006-7653-8
10. Mohanachandran PS, Sindhumo PG, Kiran TS. Enhancement of solubility and dissolution rate: an overview. Int J Comp Pharm 2010; 4: 1-10.
11. Jain R K, Sharma D K, Jain S, Kumar S and Dua J S. Studies on solid dispersions of nimesulide with pregelatinized starch. Biosc Biotechnol Res Asia 2006; 151-153.
12. Tanaka N, Imai K, Okimoto K, Ueda S, Rinta Ibuki Y T, Higaki, Kimura T. Development of novel sustained-release system, disintegrationcontrolled matrix tablet with solid dispersion granules of nilvadipine, solid dispersion technique – a review. J Pharm Res 2010; 3(9): 2314-2321. https://doi.org/10.1016/j.jcril.2005.08.024
13. Baghel S, Cathcart H, Reilly NJO. Polymeric Amorphous Solid Dispersions: A review of amorphization, crystallization, stabilization, solid-state characterization, and aqueous solubilization of biopharmaceutical classification system class ii drugs. J Pharm Sci 2016; 105: 2527-2544.http://doi.org/10.1016/j.xphs.2015.10.008
14. Kakumanu VK, Bansal AK. Supercritical fluid technology in pharmaceutical research. CIRPS. 2003; 83(4):8-12. https://doi.org/10.3109/10837450.2012.726998
15. Won DH. Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical anti solvent precipitation process. Int J Pharm 2005; 301; 199–208. https://doi.org/10.1016/j.ijpharm.2005.05.017
16. Yadav B, Tanwar YS. Development, characterization and in vitro evaluation of flurbiprofen solid dispersions using polyethylene glycol as carrier. J App Pharm Sci 2016; 6 (04): 060-066 https://doi.org/10.7324/JAPS.2016.60408
17. Kamalakannan V, Puratchikody A, Masilamani K and Senthulnathan B: Solubility enhancement of poorly soluble drugs by solid dispersion technique – a review. J Pharm Res 2010; 3: 2314-2321.
18. Tiwari R, Tiwari G, Srivastava B and Rai AK: Solid Dispersions: An overview to modify bioavailability of poorly water soluble drugs. Int J Pharm Tech Res 2009; 1: 1338-1349.
19. Sultana S, Saifuddin Ahmm. Review article: Solid dispersion currently practiced in pharmaceutical field. Int J Adv Res Tech 2016; 5(3): 170.
20. Sawicki E, Schellens JHM, Beijnen JH, Nuijen B. Pharmaceutical development of an amorphous solid dispersion formulation of elacridar hydrochloride for proof-of-concept clinical studies. Drug Dev Ind Pharm 2017; 43(4): 584-594. https://doi.org/10.1080/036001945.2016.1279401
21. Robert CI, Armas HN, Janssen S: Characterization of ternary solid dispersion of intracranazole PEG 6000. J Pharm Sci 2008; 97: 2110-2120. https://doi.org/10.1002/jps.21128
22. Roul LK, Manna NK, Parhi RN, Sahoo S, P Suresh, Dissolution rate enhancement of Alprazolam by Solid dispersion. Int J Pharm Ed Res 2010; 55-60.
23. Arunachalam A, Karthikeyan M, Kothari K, Prasad PH, Sethuraman S, Kumar A. Solid dispersions: a review. Curr Pharm Res 2010; 1(1): 82-90. https://doi.org/10.22270/ujpr.v2i1.RW4
24. Huang J. Nifedipine solid dispersion in microparticles of ammonio methacrylate copolymer and ethylcellulose binary blend for controlled drug delivery: Effect of drug loading on release kinetics. Int J Pharm 2006; 319: 44-54. https://doi.org/10.1016/j.ijpharm.2006.03.035
25. Nagesamy DV, Sangeetha S. Solid dispersions-A review. Int J Pharm Res 2008; 1: 5-12.
26. Cassidy OE, Rouchotas C. Comparison of surface modification and solid dispersion techniques for drug dissolution. Int J Pharm 2000; 195 (2): 1–6. https://doi.org/10.1016/S0168-7777(00)00159-6
27. Chawla V, Bansal AK. Improved dissolution of poorly water soluble drug in solid dispersions with polymeric and non polymeric hydrophilic additives. Acta Pharm 2008; 58: 257-274.https://doi.org/10.2478/v1007-008-0016-1
28. Kataria MK, Bhandari A. Biopharmaceuticals drug disposition classification system: an extension of biopharmaceutics classification system. Int J Pharm 2012; 3(3): 5-10.

29. Wagh MP, Patel JS. Biopharmaceutical classification system scientific basis for biowave extensions. Int J Pharm Sci 2010; 2(1): 12-19. https://doi.org/10.1023/A:1016473601633

30. Dash V, Kesari A. Role of biopharmaceutical classification system in drug development program. J Curr Pharm Res 2011; 5(1): 28-31. https://doi.org/10.1208/s12248-008-9020-0

31. Shamsuddin, Fazil M, Ansari SH, Ali J. Atorvastatin solid dispersion for bioavailability enhancement. J Adv Pharm Tech Res 2016; 7(1): 22-26. https://doi.org/10.4103/2231-4040.169873

32. Singh S, Singh R, Yadav L. A Review on solid dispersion, Int J Life sci. 2011; 2(9): 1078-1095.

33. Karanth H, Shenoy VS, Murthy RR. Industrially feasible alternative approaches in the manufacture of the solid dispersion: A technical report. AAPS Pharm Sci Tech 2006; 7 (4): E1-E8. https://doi.org/10.1023/e:psb.0000022886.71598.2f

34. Sriamornsak P, Kontong S, Weerapol Y, Nunthanid J, Sunghthonjeen S, Limmatvapirat S. Manufacture of ternary solid dispersions composed of nifedipine, eudragit and adsorbent. Adv Mat Res 2011; 317–319: 185-188. https://doi.org/10.4028/www.scientific.net/AMR.317-319.185

35. Ahire BR, Rane B R, Pawar SP. Solubility enhancement of poorly water soluble drug by solid dispersion technique. Int J Pharm Tech Res 2010; 2(3): 2007-2015.

36. Kapoor B, Kour R, Kour S, Behl H, Kour S. Solid dispersion an evolutionary approach for solubility enhancement of poorly water soluble drug. Int J Rec Adv Pharm Res 2010; 2(2): 1-16. https://doi.org/10.22270/ijopr.v2i1.R3

37. Najmuddin M, Tousif K, Mohsin AG, Shelar S, Patel V. Enhancement of dissolution rate of ketoconazol by solid dispersion. Int J Pharm Sci 2010; 2(3): 132-36.

38. Alam KM, Jali R, Zaman N, Islam ASM. Study of Dissolution improvement of various poorly water soluble drugs by solid dispersion mixing with HPMC 6CPS and PEG 6000. J Pharm Sci Tech 2011; 3 (6): 613-627.

39. Ludadiya A, Agrawal S, Jain P, Dubey PK. A Review on Solid Dispersion. Int J Adv Res Pharm Bio 2012; 1(2): 281-91.

40. Chauhan B. Preparation and evaluation of glibenclamide polyglycolized glycodies solid dispersions with silicon dioxide by spray drying technique. Eur J Pharm Sci 2005; 26: 219–230. https://doi.org/10.1016/j.ejps.2005.06.005

41. Kawabataa Y, Wadah K, Nakatanib M, Yamadaa S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications. Int J Pharm 2011; 420:1-10. https://doi.org/10.1016/j.ijpharm.2011.08.032

42. Singh G, Pai RS, Devi VK. Effects of the Eudragit and Drug coat on the release behaviour of poorly soluble drug by solid dispersion technique. Int J Pharm Sci Res 2011; 2(4):816-24. https://doi.org/10.13040/IJPSR.0975-8232.2(4).816-24

43. Lalitha Y, Lakshmi PK. Enhancement of dissolution of nifedipine by surface solid dispersion technique. Int J Pharm Sci 2011; 3(3):41-46.

44. Kushwaha A. Solid dispersion a promising novel approach for improving the solubility of poorly soluble drugs. Int J Pharm Sci Res 2011; 2(8):2021-2030.

45. Usman Mohammed Jajere, Achadu AE. Fabrication and characterization of ezetimibe solid dispersion for solubility enhancement. Universal J Pharm Res 2017; 2(1): 12-16. https://doi.org/10.22270/ujpr.v2i1.R3