

## SOLID DISPERSIONS: RESUSCITATING ORAL DELIVERY OF HYDROPHOBIC DRUGS

RUCHI AGRAWAL<sup>1\*</sup>, ABID RAZA<sup>2</sup>, OM PRAKASH PATEL<sup>2</sup><sup>1</sup>Department of Pharmaceutics, Krupanidhi College of Pharmacy, Bengaluru - 560 035, Karnataka, India. <sup>2</sup>Student, Krupanidhi College of Pharmacy, Bengaluru - 560 035, Karnataka, India. Email: ruchi.kcp@gmail.com

Received: 25 September 2018, Revised and Accepted: 24 November 2018

## ABSTRACT

**Objective:** This review article explores solid dispersions (SDs) as one of the suitable approaches to formulate poorly water-soluble drugs. The objective of this review on SD techniques is to explore their utility as a feasible, simple, and economically viable method for augmentation of dissolution of hydrophobic drugs.

**Methods:** Various types of SDs are classified and compared. Use of surfactants to stabilize the SDs and their potential advantages and disadvantages has been discussed. Different techniques for preparing and evaluating SDs are appraised along with discussions on scalability and industrial production. Review of the current research on SD along with future trends is also offered.

**Results:** Based on the various researches, SDs offer an efficient means of improving bioavailability while concurrently contributing to lower toxicity and dose-reduction.

**Conclusion:** Solid-dispersions have been and continue to be one of the key technologies for solving the issue of poor solubility for newer hydrophobic molecules which are being discovered. This would give a new lease of life for such drugs enabling them to be delivered in an effective way.

**Keywords:** Amorphous, Dissolution rate, Hydrophobic drugs, Solid dispersions, Solubility enhancement.

© 2019 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) DOI: <http://dx.doi.org/10.22159/ajpcr.2019.v12i3.29948>

## INTRODUCTION

Active pharmaceutical ingredients (APIs) have been classified on the basis of their water solubility and permeability through the intestinal mucosa as per the biopharmaceutical classification system (BCS) [1]. The chief factors which affect absorption of APIs through intestinal mucosa after oral administration are their rate of dissolution, solubility, and permeability. The challenge lies with APIs belonging to BCS Class II or Class IV. In general, the rate limiting step for absorption of the drugs in these classes is the low dissolution velocity emerging from low solubility.

Nearly, more than 90% of drugs are orally administered. The bioavailability of APIs is directly related to their solubility or rate of dissolution in water and/or biological fluids which are primarily aqueous in nature. Nearly, one-third of all under development new drugs/chemical entities are poorly water-soluble and are, therefore, difficult to formulate. Hydrophobic drugs often encounter problems such as poor absorption which may lead to inadequate and mutable bioavailability. Hydrophobic APIs will display absorption kinetics based on the rate-limiting step of dissolution, and those APIs with insufficient permeability will demonstrate permeation - rate limited absorption kinetics [1]. Noyes-Whitney equation suggests that the aqueous solubility of an API is directly related to its rate of dissolution and consequently it is a significant variable that regulates the rate of dissolution and thereby the absorption [2].

To increase their solubility, numerous methodologies have been suggested such as alterations in physical form. These include a decrease in particle size to micrometers/nanometers and use of complexing agents, cosolvents, solubilizers, and surfactants. In addition, modification of crystal habit has been suggested which includes changing it to a more soluble polymorphic form or changing the crystalline form to an amorphous form solid dispersion (SD). Further, drug dispersion in hydrophilic carriers, formulation of lipid-based dosage forms and

chemical modifications such as changes in pH and alteration in the salt form have also been suggested.

In this review, the description of SDs as a simple and cost-effective tool for dissolution enhancement has been discussed.

## SDS

SDs are solid state systems where one or more APIs are mixed intimately with an inert substance which can be a hydrophilic polymer(s) or matrix forming agents [3]. The nature of the carrier can be crystalline or amorphous. The augmentation in the rate of dissolution of APIs made into SDs is credited to following reasons [4]:

- Molecular dispersions result in the reduction of particle size and increase in surface area.
- Conversion of crystalline APIs into amorphous systems results in the enhancement of the rate of dissolution. This is attributed to the lack of energy requirements during the dissolution process to break up the amorphous structure, unlike the organized crystalline state.
- Increase in wetting properties due to a decrease in interfacial tension, in case of carriers with surface activity.
- In contrast to APIs, SDs exhibit increased porosity.
- Hydrogen bonding effect among APIs and the carrier results in the cosolvent effect.

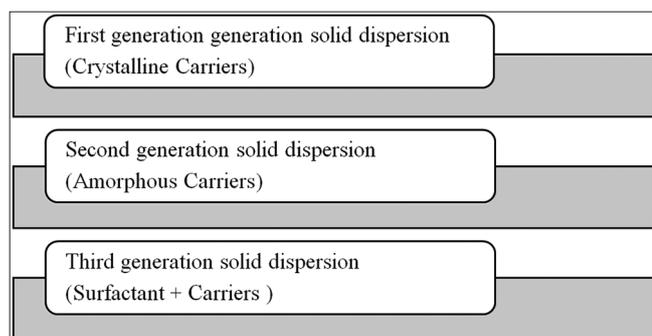
Categorization of SDs.

## Based on the carriers used

This is depicted in Fig. 1.

## First generation SDs

Carriers which are crystalline in nature are mixed with APIs to make SDs. Urea and sugar were amongst the first carriers used for the formulation of SDs [5]. However, such SDs have the serious drawback of having crystalline structures which are thermodynamically stable and, therefore, have greater energy needs for the disruption of the system



**Fig. 1: Categorization of solid dispersions based on carriers employed**

into solution. This adversely affects the release of a drug at a faster rate. Kalaiselvan *et al.* formulated SDs of albendazole to using crystalline carriers such as urea, polyethylene glycol (PEG) 6000, and poloxamer 407 and achieved significant improvement in the dissolution profile of albendazole [6].

#### Second generation SDs

Amorphous carriers are the excipients of choice to formulate these SDs. Some of them include synthetic polymers such as hydroxypropyl methyl cellulose, ethyl cellulose, polymethacrylates, polyethylene oxides, polyvinylpyrrolidone (PVP), and naturally derived polymers such as starch derivatives like cyclodextrins. These result in an amorphous product which is thermodynamically less stable and releases drugs at a faster rate compared to their crystalline counterparts. Sharma and Jain have prepared SDs of carvedilol with amorphous carrier PVP K 30 using the solvent evaporation method [7].

#### Third generation SDs

To prepare these SDs, usually, a surfactant or a blend of polymers or a blend of surfactants and polymers are employed as carriers which exhibit self-emulsifying properties. Surfactants such as inulin, glyceryl behenate, and poloxamer 407 have been used as carriers in many preparations to enhance the dissolution profile of a drug. They are advantageous as the presence of surfactants prevents recrystallization and additionally enhances wettability and hence the dissolution rate. Patel and Joshi evaluated surfactants and their combinations as effective carriers in preparation of SDs [8].

### Based on solid-state structure

#### Eutectic mixtures

A physical blend of two or more components that tends to reduce melting points when mixed in certain proportions leading to the formation of a mix that has melting point lower than the individual components is called a eutectic mixture. This was first used in context with SDs by Sekiguchi and Obi in 1961 [5]. In SDs composed of a eutectic blend, the API and the carrier are present as fine particles. This leads to an enormous increase in surface area and the enhancement rate of dissolution of the API. Sulfathiazole is known to be first formulated by this technique with urea as a carrier [3].

#### Solid solution

The SDs which are miscible in liquid, as well as the solid state, are termed as solid solutions. Based on the degree of miscibility of the API and the carrier, solid solutions are of two types; continuous and discontinuous solid solutions. In continuous solid solutions, the two components are miscible in the solid state in all proportions, whereas, in discontinuous solid solutions, the components are immiscible at intermediate composition, but miscible at the extreme of composition.

On the basis of the molecular size of the two components, the solid solutions are classified as substitutional and interstitial. In

substitutional solid solutions, the solute molecules substitute the solvent molecules in the crystal lattice. While in the interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. Examples include solid solutions of methyltestosterone, hydrocortisone acetate in the matrix of PEG 6000 [9].

In 1965, Goldberg *et al.* elucidated the advantages of solid solutions as compared to eutectic mixtures [10]. He mentioned that release of the drug is faster from solid solutions as the dissolution process does not consume the energy needed to disrupt the crystalline forms.

### Based on the miscibility of drug and carrier

#### Immiscibility in fluid phase

In certain cases, where API and carriers are immiscible in their fluid phase, they may not demonstrate the desired miscibility even on solidification. Enhancement in dissolution rate of these type of drugs can be done through alteration in the morphology of the APIs and/or carriers due to changes in physical structure. The rate of solidification and the rate of crystal formation are the critical parameters that govern whether crystalline or amorphous SDs are formed.

#### Miscibility in the fluid phase

As both drugs and polymers are miscible in a fluid state, phase separation is expected (i.e., may or may not) during solidification, thereby influencing the structure of SD.

### Methods for preparation of SD

The various methods are classified in Fig. 2.

#### Kneading technique

This is a simple method where drug and the polymer (carrier) are mixed in a predetermined ratio and kneaded with the solvent resulting in the formation of a paste formed that is dried and sieved.

SDs of indomethacin with lactose monohydrate and different polymers -polyethylene oxide - 6000, hypromellose, PVP, and  $\beta$  cyclodextrins - were prepared through the kneading method. A significant improvement in the dissolution and flow properties over raw indomethacin was observed [11]. This technique was successfully employed to augment the rate of dissolution of the hydrophobic drug, meloxicam using poloxamer 188 [12].

#### Melting/fusion technique

This involves melting of the carrier and the addition of the drug into the melted carrier with continuous mixing. The drug melts inside the heated carrier, and a homogenous melt mass is obtained [13]. The fused mass is cooled rapidly and kept in desiccating chamber for the predetermined time. The solidified mass is grinded, milled, and sieved. Revaprazan-loaded SDs were prepared using hydroxypropylmethylcellulose which resulted in a significant enhancement of its dissolution property [14]. The method shows the benefits of being simple and economical and does not require any sophisticated instrumentation. However, its application is restricted to the combination of drug and carrier where both have nearly the same melting point and are stable at temperatures near their melting points. The cooling speed and temperature of the drugs and carriers are critical factors in obtaining a homogenous product.

#### Solvent evaporation method

The method involves choosing a solvent that has the capacity to dissolve drugs as well as the carriers. The API and the carrier are dissolved in the least possible volume of solvent with continuous stirring in two different containers. The drug solution is added to the carrier solution with continuous stirring. The solution is then evaporated under reduced pressure to yield dry product [15]. The dried mass is crushed and sieved and stored in desiccators. This method has the advantage over the melting method that the drug is not exposed to higher temperature. This method was employed to prepare SD of carbamazepine using PVP combined

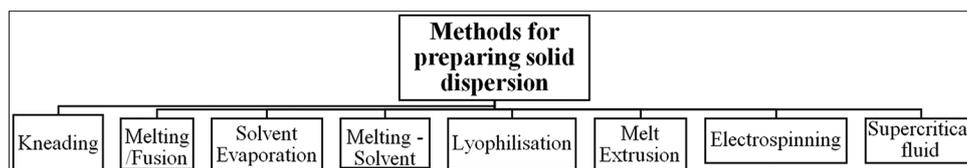


Fig. 2: Various methods for preparing solid dispersions

with either Gelucire 44/14 or Vitamin E TPGS. The SDs showed higher dissolution rate as compared to pure carbamazepine [16].

#### Sometimes, a combination of melting and solvent method can be employed

In this case, the API is dissolved in a solvent in which it is freely soluble, the carrier is melted, and the API solution is added into the melt of the solid carrier. This blend is finally evaporated to yield a clear solvent-free film. The drying of the film is continued until it attains a constant weight. This technique has the benefits of melting technique as well as solvent evaporation methods. This method is particularly useful for drugs that are thermolabile or have high melting points, but it is not suitable for drugs with a low therapeutic dose (below 50 mg).

#### Lyophilization method

This method is generally used as an alternate to the solvent evaporation method. Similar to the solvent evaporation method, this method also involves the choice of a common solvent in which the drug and the carrier are dissolved in a predetermined ratio. The solution containing the drug and the carrier is frozen and subjected to lyophilization where the frozen mass directly sublimates, and a porous SD is obtained. This is advantageous over solvent evaporation as it offers minimal thermal stress and chances of phase separation while the solvent is being removed. Dissolution enhancement of glyburide was achieved using this technique using different grades of PEGs as polymers [17]. SD of efavirenz - PVP K-30 produced through the lyophilization technique resulted in significant solubility enhancement of efavirenz [18].

#### Melt extrusion method

This method employs a corotating twin screw extruder. Here, the drug and the carrier are mixed together at their melting temperatures and the mix is extruded at a high rotational speed. Three processes, namely melting, homogenizing and then extrusion takes place simultaneously, and the product is shaped as desirable solid dosage form.

This technique involves a very brief exposure of the drug-carrier mix to an elevated temperature for a period of about one min. This enables even thermolabile drugs to be processed without being degraded. SD formulation of antiulcer drug *lafutidine* was successfully formulated using hot melt extrusion (HME) technique, and it was demonstrated that the SD of *lafutidine* performed better with immediate drug release as compared with pure *lafutidine* [19]. Agrawal *et al.* developed SDs using HME technology with a scale up from mini scale to clinical scale [20].

#### Electrospinning method

This method involves preparation of solid fibers by passing drug carrier melt or drug carrier blend in a fluid state through nozzles of millimeter scale. A strong electrostatic field is applied over a capillary which is attached to vessel which contains the aforesaid drug-carrier fluid blend or melts. This method is advantageous as it can yield fibres in nano range, and it is simple and economical to perform. Researchers have made successful attempts to produce SDs of *ketoprofen* as nanofibers using PVP as the carrier [21]. Similarly, SDs of hydrophobic API *piroxicam* were prepared using hypromellose and nanofibers were produced using the electrospinning method [22].

#### Supercritical fluid method

This method uses the principle of precipitating out drug-carrier blends to form a common solvent using carbon dioxide as an anti-solvent. This approach is beneficial as it gives products in the micron to submicron

range. In addition, it offers multiple advantages including the fact that supercritical carbon dioxide can be removed and that carbon dioxide is non-toxic and safe for patients even if some traces are left behind. *Itraconazole* was formulated into SD using supercritical fluid technique using hypromellose, Pluronic F-127, and L-ascorbic acid [23]. Similar attempts were made by researchers for poorly soluble API *cefuroxime axetil* using hypromellose and polyvinyl pyrrolidone as carriers [24].

#### Evaluation of SD

The evaluation is carried out by studying the effect on the dissolution rate of drug after being formulated into SDs. In addition, solid-state characterization of the SDs must be done and compared with that of pure drug. The details of these evaluation tests are discussed below.

#### Comparative dissolution rate studies

This is done by comparing the *in vitro* dissolution release profiles of the marketed product or pure drug, the physical mixture of drug and polymer used in SD and the SD itself. For immediate release products, a model-independent approach can be followed which involves calculation of difference factor ( $f_1$ ) and similarity factor ( $f_2$ ) between two dissolution profiles following dissolution method [25]. Dissolution conditions can be chosen based on the specifications recommended in the United States Food and Drug Administration (US FDA) database or official books.

#### Solid state characterization

This is performed by employing the following techniques:

- Differential scanning calorimetry (DSC)
- X-ray diffraction study (XRD)
- Scanning electron microscopy (SEM).
- Diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS)
- Residual solvent content determination
- Effect of aging.

#### DSC

DSC is done to comprehend the thermal behavior of the product [26]. This includes heating of samples at a predetermined rate which is mostly 10°C/min, till their melting point. The height of endothermic peak and heat of fusion is studied, and the physical mixture and the pure drug are compared. Any reduction in endothermic peak suggests partial conversion of the crystalline drug into amorphous and the complete disappearance of endothermic peak suggests total conversion of the drug from crystalline to amorphous form. This polymorphic transition is favorable as it leads to faster dissolution rate due to reduced energy requirement for breaking the disordered molecular structure in the amorphous product as compared to the highly ordered lattice in the crystalline product.

#### X-ray powder diffraction (XRPD)

XRD is a critical tool used for the study of crystal structures and atomic spacing [27]. The scattering of X-rays from atoms produces a diffraction pattern that is characteristic of their arrangement. Monochromatic X-rays are produced by the cathode ray tube is focused toward the powder sample. The rays are diffracted which are characteristic of the crystal structure of powder sample. These diffracted rays are sensed and counted. Physical characterization of SD is done by studying the absence of peak of crystallinity.

The detection is based on Bragg's law which says that radiation of wavelength  $\lambda$  incident on a series of planes with periodic spacing  $d$  will be diffracted through an angle  $\theta$  where,

$$n\lambda = 2 \sin\theta$$

#### SEM

SEM technique enables the study of sample's surface topography and composition [28]. In this technique, the double-sided carbon tape is attached on aluminum stubs, and powder sample is sprinkled onto the tape. The aluminum stubs are positioned in the vacuum chamber, and the morphological portrayal and surface characteristic of the sample are studied using the electron beam.

#### DRIFTS

Drug carrier interaction studies can be performed through this technique. This is done using an FTIR spectrometer equipped with a diffuse reflectance attachment and a data station [29]. This involves preparation of KBr pellets after mixing it with the sample to be analyzed and scanning it at a wavelength range from 4000 to 400  $\text{cm}^{-1}$ . The spectra obtained are characteristic of the atomic arrangement in molecules. If the characteristic peaks of the drug and polymer are present in SD, it indicates that the drug and the polymer do not have any chemical interaction and will not alter each other's stability.

#### Residual solvent content determination

This is required where organic solvents are being used for the preparation of SD to ensure that they are present in quantities lower than their toxicity levels [30]. This is achieved using Karl Fischer titration and thermal gravimetric analysis.

#### Aging effect

The SD is stored at 30°C/65% RH for 3 months, and the dissolution rate profile is performed to see the effect of aging in drug release. DSC and XRPD studies are performed and compared with the freshly prepared product to observe any change in the crystal structure.

#### Scalability and industrial applications

SDs have been reported to have drawbacks with respect to their large-scale preparation due to the onerous processes of preparation involving careful and subtle adjustments during their developmental stages. Furthermore, concerns about the stability of the API within its vehicle are a major issue which impacts the shelf-life of the product. However, on the positive side, efforts to overcome these hurdles have yielded promising results. The techniques to improve industrial application, scalability along with stability are discussed below:

#### Capsugel® technology

It was innovated by bend research as a pioneering technology which employed a spray-dried dispersion (SDD) method [31]. It presented a single-phase, amorphous molecular dispersion of API in a polymeric matrix where the API is molecularly dissolved within a solid mass. SDDs were acquired by adding API and polymer to an organic solvent and then spray-dried. The process parameters were selected in such a way so as to ensure that the solvent evaporated rapidly from the globules, permitting inadequate time for phase separation or crystal formation. SDDs have revealed enduring stability supplementing their established results in solubility enhancement, simplistic scale-up, and admirable manufacturing capability. Expiration dates extending beyond 2 years have been reliably exhibited with SDDs. Manufacturability has been consistently exhibited at levels ranging from milligrams up to tons.

#### Free flowing sugar coated bead

It is a novel technique which yielded APIs dispersed within a polymeric solution which is dried, and then coated with sugar solution to form free-flowing particles [32]. Such an oral dosage form is largely devoid of any residue of methylene chloride. The method consists of making a working solution made up of an alcohol, a strong acid, API, a water-soluble polymer, and water. Itraconazole-coated particles have been successfully formulated using this technique.

#### HME

HME is enormously adaptable for making industrial-scale SD [33]. The chief benefit is that solvents are not needed. This circumvents the possibility of any residual solvent which may hamper stability and shelf life. For example, in research work, miconazole SDs were prepared by HME. Miconazole was dissolved with the PEG portion of the copolymer or was yielded as crystals in the identical or a dissimilar polymorph as the starting substance. The kinetic miscibility was found to be greater for the HME-SDs produced from solutions that were pre-heated in comparison with the spray-dried formulations. Furthermore, greater amount of drug was incorporated into HME-SD than the spray-dried product [34].

#### Filling of semi-SDs into hard capsules

Semi-SDs are often tacky and pose a problem of handling and storage. Stability problems are also seen in such formulations. A facile remedy for this problem is the direct filling of the liquid/semisolid melt of SD into hard capsules. Once filled by means of mechanical and automated filling devices such as dosators, the melt solidifies into the capsules. This circumvents the additional process of pulverization of the hardened mass, which speeds up production as well as reduces the chances of changes in the crystallinity of the SD on grinding. For example, in a research work, SDs of sparingly water-soluble drug amlodipine besylate were prepared and converted into a semisolid mass [35]. This mass was then filled in hard gelatin capsules. The results showed improved dissolution with a shortening of the lag time which meant a subsequent improvement in bioavailability.

#### CONCLUSION

The paradigm shift occurring in the pharmaceutical industry worldwide is the refocusing of efforts and financial resources into the development of formerly neglected poorly water-soluble drugs for oral drug delivery. SD has been one of the key technologies driving this shift. As newer hydrophobic molecules are discovered, instead of being discarded in the pipeline they are being given a new lease of life through innovative technologies as SDs. The synthesis of better excipients, polymers, and surfactants will offer many new avenues for the progress and development of better and novel SDs. With newer strategies employed, and with a deeper understanding of the molecular and thermodynamic architecture, more stable, viable, effective, and feasible SDs can be prepared.

#### ACKNOWLEDGMENT

Authors express their sincere thanks to The Management, Krupanidhi Group of Institutions for supporting the work through Krupanidhi Research Incubator Centre program under Krupanidhi College of Pharmacy and Accendere: CL Educate Ltd. Authors also extend sincere gratitude to Dr. Arshad Bashir Khan, Professor Krupanidhi College of Pharmacy, for his expert guidance and contribution toward the manuscript.

#### AUTHORS' CONTRIBUTIONS

Mrs. Ruchi Agrawal, contributed 46%, Mr. Abid Raza contributed 34% and Mr. Om Prakash Patel contributed 20% toward the preparation of the manuscript of this review article.

#### CONFLICTS OF INTEREST

All the authors declare that they have no conflicts of interest.

#### REFERENCES

1. Shekhawat PB, Pokharkar VB. Understanding peroral absorption: Regulatory aspects and contemporary approaches to tackling solubility and permeability hurdles. *Acta Pharm Sin B* 2017;7:260-80.
2. Hassan HA, Charoo NA, Ali AA, Alkhatem SS. Establishment of a bioequivalence-indicating dissolution specification for candesartan cilexetil tablets using a convolution model. *Dissolution Technol*

- 2015;22:36-43.
3. Chiou WL, Riegelmant S. Pharmaceutical sciences pharmaceutical applications of solid. *J Pharm Sci* 1971;60:1281-302.
  4. Baghel S, Cathcart H, O'Reilly NJ. 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;105:2527-44.
  5. Sekiguchi K, Obi N. Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. *Chem Pharm Bull* 1961;9:866-72.
  6. Kalaiselvan R, Mohanta G, Manna P, Manavalan R. Studies on mechanism of enhanced dissolution of albendazole solid dispersions with crystalline carriers. *Indian J Pharm Sci* 2006;68:599.
  7. Sharma A, Jain CP. Preparation and characterization of solid dispersions of carvedilol with PVP K30. *Res Pharm Sci* 2010;5:49-56.
  8. Patel AR, Joshi VY. Evaluation of SLS: APG mixed surfactant systems as carrier for solid dispersion. *AAPS PharmSciTech* 2008;9:583-90.
  9. Chiou WL, Riegelman S. Increased dissolution rates of water-insoluble cardiac glycosides and steroids via solid dispersions in polyethylene glycol 6000. *J Pharm Sci* 1971;60:1569-71.
  10. Goldberg AH, Gibaldi M, Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. I. Theoretical considerations and discussion of the literature. *J Pharm Sci* 1965;54:1145-8.
  11. Singh MC, Sayyad AB, De Sawant S. Review on various techniques of solubility enhancement of poorly soluble drugs with special emphasis on solid dispersion. *J Pharm Res* 2010;3:2494.
  12. Ghareeb MM, Abdulrasool AA, Hussein AA, Noordin MI. Kneading technique for preparation of binary solid dispersion of meloxicam with poloxamer 188. *AAPS PharmSciTech* 2009;10:1206-15.
  13. Yadav S, Veena M, Srinivas M. Solid dispersion technique to enhance the solubility and dissolution rate of aripiprazole by fusion method. *Int J Pharm Pharm Sci* 2016;8:187-92.
  14. Park JH, Kim DS, Mustapha O, Yousaf AM, Kim JS, Kim DW, et al. Comparison of a revaprazan-loaded solid dispersion, solid SNEDDS and inclusion compound: Physicochemical characterisation and pharmacokinetics. *Colloids Surf B Biointerfaces* 2018;162:420-6.
  15. Ayoub M, Hasan A, El Nahas H, Ghazy FE. Enhancing oral bioavailability of carvedilol using solid dispersion technique. *Int J Pharm Pharm Sci* 2016;8:193-9.
  16. Sethia S, Squillante E. Solid dispersion of carbamazepine in PVP K30 by conventional solvent evaporation and supercritical methods. *Int J Pharm* 2004;272:1-10.
  17. Betageri GV, Makarla KR. Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques. *Int J Pharm* 1995;126:155-60.
  18. Fitriani L, Haqi A, Zaini E. Preparation and characterization of solid dispersion freeze-dried efavirenz-polyvinylpyrrolidone K-30. *J Adv Pharm Technol Res* 2016;7:105-9.
  19. Fule R, Amin P. Development and evaluation of lafutidine solid dispersion via hot melt extrusion: Investigating drug-polymer miscibility with advanced characterisation. *Asian J Pharm Sci* 2014;9:92-106.
  20. Agrawal AM, Dudhedia MS, Zimny E. Hot melt extrusion: Development of an amorphous solid dispersion for an insoluble drug from mini-scale to clinical scale. *AAPS PharmSciTech* 2016;17:133-47.
  21. Nagy ZK, Balogh A, D emuth B, Pataki H, Vigh T, Szab o B, et al. High speed electrospinning for scaled-up production of amorphous solid dispersion of itraconazole. *Int J Pharm* 2015;480:137-42.
  22. Paaver U, Hein am aki J, Laidm ae I, Lust A, Kozlova J, Sillaste E, et al. Electrospun nanofibers as a potential controlled-release solid dispersion system for poorly water-soluble drugs. *Int J Pharm* 2015;479:252-60.
  23. Yin X, Daintree LS, Ding S, Ledger DM, Wang B, Zhao W, et al. Itraconazole solid dispersion prepared by a supercritical fluid technique: Preparation, *in vitro* characterization, and bioavailability in beagle dogs. *Drug Des Devel Ther* 2015;9:2801-10.
  24. Jun SW, Kim MS, Jo GH, Lee S, Woo JS, Park JS, et al. Cefuroxime axetil solid dispersions prepared using solution enhanced dispersion by supercritical fluids. *J Pharm Pharmacol* 2005;57:1529-37.
  25. Administration USD of H and HSF and D, (CDER) C for DE and R. Guidance for Industry Dissolution Testing of Immediate Release Solid Oral Dosage Forms; 1997. Available from: <http://www.fda.gov/downloads/Drugs/./Guidances/ucm070246.pdf>.
  26. Kodre KV, Attarde SR, Yendhe PR, Patil RY, Barge VU. Differential scanning calorimetry: A review. *Res Rev J Pharm Anal* 2014;3:11-22.
  27. Kang F, Iwashita N. X-ray powder diffraction. In: *Materials Science and Engineering of Carbon*. Oxford, UK: Butterworth-Heinemann; 2016. p. 7-25.
  28. Carter M, Shieh J, Carter M, Shieh J. Microscopy. In: *Guide to Research Techniques in Neuroscience*. Ch. 5. Burlington, MA: Academic Press; 2015. p. 117-44.
  29. Mitchell MB. Fundamentals and applications of diffuse reflectance infrared fourier transform (DRIFT) spectroscopy. *Adv Chem* 1993;236:351-75.
  30. Grodowska K, Parczewski A. Analytical methods for residual solvents determination in pharmaceutical products. *Acta Pol Pharm* 2010;67:13-26.
  31. Spray-Dried Dispersion (SDD) Technology/Capsugel. Available from: <https://www.capsugel.com/biopharmaceutical-technologies/spray-dried-dispersion>.
  32. Namburi RR, Kerr JE. Oral Itraconazole Formulations and Methods of Making the Same. US6663897B2; 2001.
  33. Crowley MM, Zhang F, Repka MA, Thumma S, Upadhye SB, Battu SK, et al. Pharmaceutical applications of hot-melt extrusion: Part I. *Drug Dev Ind Pharm* 2007;33:909-26.
  34. Guns S, Dereymaker A, Kayaert P, Mathot V, Martens JA, Van den Mooter G, et al. Comparison between hot-melt extrusion and spray-drying for manufacturing solid dispersions of the graft copolymer of ethylene glycol and vinylalcohol. *Pharm Res* 2011;28:673-82.
  35. Tyagi VK, Singh D, Pathak K. Semisolid matrix-filled hard gelatin capsules for rapid dissolution of amlodipine besilate: Development and assessment. *J Adv Pharm Technol Res* 2013;4:42-9.