WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 9, 271-287. Review Article ISSN 2277–7105

SOLID DISPERSION: A REVIEW

Zaynab Nasikkar*[1], Sumit Tiwari[2], Radhika Vishwakarma[3], Pooja Tarmale[4], Nisha Verma[5] and Mallika Turerao[6]

[1]Department of Pharmaceutical Assistant Professor, Ideal College of Pharmacy and Research Kalyan -06 Maharashtra India.

[2,3,4,5,6]Student of Ideal College of Pharmacy and Research Kalyan -06, Maharashtra, India.

Article Received on
03 March 2024,

Revised on 24 March 2024,
Accepted on 14 April 2024

DOI: 10.20959/wjpr20249-32009

***Corresponding Author**
Zaynab Nasikkar
Department of Pharmaceutical Assistant Professor., Ideal College of Pharmacy and Research Kalyan -06 Maharashtra India.

ABSTRACT

Solid dispersion has sparked significant interest as an effective method to boost the dissolution rate and consequently the bioavailability of poorly water-soluble drugs. By employing water-soluble carriers, solid dispersions have effectively tackled issues linked to low solubility and improved dissolution. This technology underscores the importance of drug-polymer two-component systems, where the dispersion and stabilization of the drug are pivotal in formulation development. Despite the growing comprehension in recent years, commercial application remains limited. Various methods for preparing solid dispersions have been explored, with an emphasis on solubility, BCS classification, and carriers. The analysis also explores different types of solid dispersions based on the carrier employed and molecular arrangement, along with explanations of mechanisms and preparation techniques. Furthermore, it highlights recent technological advancements and offers insights into marketed drugs utilizing solid dispersion approaches.

KEYWORD: Solid dispersion, Drug solubility, Dissolution enhancement, Bioavailability, Polymer carriers, Hot-melt extrusion, Spray drying, Solvent evaporation.

INTRODUCTION

Solid dispersions have attracted considerable interest as an effective way to improve the dissolution rate and thus the bioavailability of several hydrophobic drugs. This article examines the different production methods of solid dispersion and summarizes recent

technology transfers. Different types of solid dispersions based on molecular arrangement are highlighted. Some practical aspects to consider when preparing solid dispersions, such as carrier selection and physicochemical characterization methods, are also discussed, as well as an understanding of the molecular arrangement of drugs in solid dispersions. Finally, the rationale for the limited commercialization and recent re-emergence of solid dispersions is reviewed.[1] Amorphous solid dispersions are an increasingly important formulation method for improving the dissolution rate and apparent solubility of poorly water-soluble compounds. Due to their complex physicochemical properties, versatile analytical methods are required to enable comprehensive characterization, and thermal techniques are widely used. Key parameters of interest that can affect product performance are glass transition temperature (Tg), drug molecular mobility, miscibility of drug and excipients, and rate and degree of drug crystallization. In addition to considering possible assumptions or limitations of different analytical approaches, it is important to evaluate what kind of information related to the aforementioned properties can be extracted from thermo analytical measurements. Although differential scanning calorimetry (DSC) is the most widely used thermo analytical technique used to characterize amorphous solid dispersions, there are many established and emerging techniques that have shown useful information. Full characterization of base material descriptors will ultimately lead to production of more durable solid dispersion products.[2] Oral administration is the most convenient and popular route of drug administration. From the patient's point of view, swallowing and taking the medicine is a convenient and familiar way of taking the medicine. As a result, oral medications are often more effective than alternative routes of administration, such as parenteral, according to patient observation and compliance. When an active substance is administered orally, it must first dissolve in the stomach and/or intestinal wall before it passes through the membranes of the gastrointestinal tract and enters the systemic circulation. Therefore, the water solubility and/or membrane permeability of a drug molecule are important factors in drug absorption from the gastrointestinal (GI) tract, leading to low drug bioavailability. As a result, the drug is poorly soluble in water.[3]

Solubility

Solubility is the property of a solid, liquid, or gaseous chemical Substance called solute to dissolve in a solid, liquid, or gaseous Solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent Used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is

measured as the saturation Concentration where adding more solute does not increase its Concentration in the solution.[1]

Types of Solubility

Absolute/Intrinsic solubility: The maximum amount of solute dissolved in a given solvent under slandered conditions of temperature, pressure and pH is called as absolute or intrinsic solubility. It is a static property. Saturated solubility: A maximum amount of solute dissolved in a given solvent up to its saturated level. Additional solute will not dissolve in solvent **TABLE 1.**

Description forms (solubility definition) Parts of solvent required for one part of solute Solubility range (mg/ml) Solubility assigned. **TABLE 2** gives BCS classification of various drugs.

Table 1: Solubility Range.

Very soluble	<1	>1000	1000
Freely soluble	1 To 10	100-1000	100
Soluble	10-30	33-100	33
Sparingly soluble	30-100	10-33	10
Slightly soluble	100-1000	1-10	1
Very slightly soluble	1000-10000	0.1-1	0.1
Partially insoluble	>10000	<0.1	0.01

Table 2: Bcs Classification of Drugs.

Class	Permeability	Solubility	Example
Class 1	High	High	Propranolol, metoprolol.
Class 2	High	Low	Nifedipine, carbamazepine, azilsartan.
Class 3	Low	High	Metformin, cimetidine, insulin.
Class 4	Low	Low	Taxol, chlorthiazide, furosemide.

Methods of solubility enhancement of poor water soluble Drugs

There are several ways by which drug solubility and dissolution Rate can be enhanced, which can be categorized in to physical Modification, chemical modifications of the drug substance, and Other techniques.

Particle size reduction

The solubility of a drug is intrinsically Related to the particle size. Reduction of particle size of a drug by Various means such as jet mill, rotor stator colloidal mill, ball mill, Etc. leads to increase in surface area with enhanced dissolution. But Limitation of this process includes

thermal and physical stress on Drug product that leads to degradation. Other disadvantages include Limited opportunity to control important characteristics of final Product such as shape, size, morphology, surface properties, and Electrostatic charges. Also, amorphous region is thermodynamically Unstable and susceptible to recrystallization on in hot and humid Condition.[2]

Nanosuspension technology

Nanotechnology Technology Has Been developed as a promising candidate for effective delivery of Poor water-soluble drug. It is sub-micron colloidal dispersion of pure Particles of drugs, which is stabilized by surfactants for either topical or Oral use or parenteral or pulmonary administration. In nanosuspension, Particle size is usually less than one micron ranging between 200 And 600 nm. Media milling, high pressure homogenization in Water, high pressure homogenization in non-aqueous media and combination of precipitation and high pressure homogenization Are the various method of preparation of nanosuspension. Nanosuspension approaches have been employed for various drugs Including tarazepide, atovaquone, amphotericin B.[3]

Surfactant

The use of surfactant in enhancement of solubility of Poorly soluble drug has been employed successfully. Seedhar N et al., studied solubility improvement of enrofloxacine using a series of co-solvents and surfactants with solubility increase up to 26 times. Commonly used non-ionic surfactants are lauryl macro glycerides, Castor oil, di-fatty acid ester of low molecular weight polyethylene Glycol. Salt formation: Dissolution rate of particular salt is usually Different from that of parent compound. Sodium and potassium salt of week acid dissolve more rapidly than that of pure salt. Limitation of salt formation includes epigastric distress due to high alkalinity, Reactivity with atmospheric water and carbon dioxide leads to Precipitation, patient compliance.[4]

pH adjustment

Poor water soluble drug may potentially Dissolve in water by applying a pH change. To access the solubility of this approach, the buffer capacity and tolerability of the selected pH are important to consider. Solubilized excipients that increase environmental pH within the dosage form to a range higher than pKa of weekly acidic drugs increase the solubility of that drug, those excipients that act as alkalizing agents may increase the solubility of weekly basic drugs.[5]

Hydro trophy

Hydro trophy is a solubilization phenomenon in Which solubility of poorly water soluble drug is enhanced to many Folds by using sodium benzoate, urea, sodium citrate, and sodium Salicylate improve solubility of many Drugs, i.e., diazepam, griseofulvin, testosterone, progesterone, and 17-estradiol in presence of nicotinamide and related compounds.[6]

Classification of solid dispersion

A) Based on carrier used

The chosen carrier must fulfill several criteria to effectively enhance the dissolution rate of a drug. The material selected as a carrier should be:

- Freely water-soluble, possessing intrinsic quick-dissolving capabilities.
- Non-toxic and pharmacologically inert.
- Heat-stable with a low melting point during the melting process.
- Soluble in a wide range of solvents.
- Preferably capable of increasing the aqueous solubility of the drug.
  Ideally, capable of enhancing the drug's water solubility and chemically compatible with it, without forming a firmly bound complex.[7]
- **First Generation:** In this solid dispersions are formulated using crystalline carriers, with urea and sugars being among the earliest ones employed.[8] However, these carriers possess a disadvantage of thermodynamic instability, leading to a slower release of the drug. The first generation of solid dispersions utilizes crystalline carriers like urea and sugars, leading to the creation of thermodynamically stable crystalline solid dispersions. Regrettably, this stability inhibit the rapid release of the drug compared to amorphous carriers.[9]
- **Second generation:** In this solid dispersions are created using amorphous carriers instead of crystalline ones, where the drug is dispersed molecularly within the polymeric carrier. These carriers may consist of synthetic polymers like povidone, polyethylene glycols, and polymethacrylates, or natural polymers such as hydroxypropylmethylcellulose, ethyl cellulose, and starch derivatives like cyclodextrin. Second-generation solid dispersions utilize amorphous carriers, typically polymers, including synthetic ones like poly vinyl pyrrolidone (PVP), polyethylene glycols (PEG), ethyl cellulose, polymethacrylates, and natural polymers like hydroxylpropylmethylcellulose (HPMC), hydroxypropylcellulose, or starch derivatives like cyclodextrins.[10]

- **Third generation:** Demonstrations have confirmed that employing a carrier possessing surface-active agent properties can enhance dissolution profiles, leading to heightened bioavailability. Therefore, the use of surfactants such as poloxamer 407, compritol 888, ATO, inutec SP1, gelucire 44/14, and inulin as carriers has demonstrated effectiveness in achieving elevated purity levels of polymorphism and improving in vivo bioavailability. These solid dispersions frequently incorporate a surfactant carrier or a blend of amorphous polymers and surfactants as carriers, particularly advantageous for drugs with limited solubility. Third-generation solid dispersions have emerged to further refine dissolution profiles by employing carriers with surface activity or self-emulsifying properties. Surfactants including inulin, poloxamer 407, inutec SP1, compritol 888 ATO, and gelucire 44/14 have been singled out as effective carriers for attaining heightened polymorphic purity and enhanced in vivo bioavailability.[11]
- **Fourth Generation:** This type of dispersion is referred to as controlled-release solid dispersion, designed for poorly water-soluble drugs with a brief biological half-life. The carriers utilized are either water-soluble or insoluble in water. The primary objectives of controlled-release solid dispersion are enhancing solubility and prolonging drug release in a controlled manner. Water-soluble carriers employed in controlled-release solid dispersion encompass ethyl cellulose, Eudragit, hydroxypropyl cellulose, among others.[12]

B) Based on their molecular arrangements

The classification of solid dispersions can be divided into the following types:

1. Amorphous solid solutions

In a crystalline carrier, drugs may precipitate in an amorphous state, resulting in increased dissolution rates owing to the drug's elevated energy levels.[13] Rapid cooling of the drug-polymer fluid mixture can prevent drug crystallization, leading to the drug being trapped in its amorphous or "solidified-liquid" state, which increases the risk of converting into a more stable, less soluble crystalline form. Amorphous solid solutions disperse solute molecules irregularly within an amorphous solvent, thereby enhancing dissolution properties. Early investigations utilized carriers such as urea, sucrose, dextrose, and galactose while contemporary methods employ organic polymers like polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), and various cellulose derivatives. Polymer carriers, with their inherent amorphous polymer chain network, are especially prone to forming amorphous solid

solutions, with solute molecules potentially serving as plasticizers, thus lowering the polymer's glass transition temperature.[14]

2. Solid Solutions

A solid solution is a solid dispersion that mixes seamlessly in both its solid and fluid states, existing either as amorphous or crystalline forms. In amorphous solid solutions, the drug disperses molecularly within the carrier matrix, resulting in a notably increased dissolution rate due to its higher effective surface area. Crystalline solid solutions form when a crystalline drug is confined within a crystalline polymeric carrier. Similar to liquid solutions, solid solutions comprise a single phase, regardless of the components involved. They offer significant value for poorly water-soluble drugs when dissolved in carriers with good aqueous solubility, enhancing oral bioavailability. By reducing the drug's particle size to its molecular dimensions, the dissolution rate becomes reliant on the carrier's dissolution rate. Careful selection of the carrier can dramatically boost the drug's dissolution rate. In systems where two components crystallize together, they create a uniform, homogeneous phase. The drug's particle size is reduced to its molecular size within the solid solution, resulting in a quicker dissolution rate compared to eutectic mixtures. Solutions are categorized as continuous or discontinuous based on the degree of miscibility between the compounds or how the solvate molecules are distributed (substitutional, interstitial, or amorphous).[15,16]

Solid solutions can be classified based on their miscibility (continuous or discontinuous) and how solvate molecules are distributed within the solvent (substitutional, interstitial, or amorphous).[17]

- **Continuous solid dispersions:** Continuous solid solutions allow components to mix in all proportions, indicating stronger bonding between them compared to individual molecules. However, despite this potential bonding advantage, such solid solutions have not been documented in pharmaceutical literature.[18,19]
- **Discontinuous solid dispersions:** Discontinuous solid solutions exhibit restricted solubility of each component within the other, illustrated in Fig. 2, where regions of true solid solutions are presented. Below a specific temperature, mutual solubility's decline. Goldberg et al. propose using the term "solid solution" exclusively when mutual solubility surpasses 5%. The feasibility of employing it as a dosage form strategy hinges on mutual solubility's and drug component dosage, with practical limitations on tablet or capsule mass. Increased drug solubility in the carrier permits larger doses.[17]

- **Substitutional solid solutions:** In crystalline classical solid solutions, solute molecules can either take the place of solvent molecules within the crystal lattice or fit into the spaces between solvent molecules. Substitution happens when the size variation between solute and solvent molecules is roughly 15% or less.[20]
- **Interstitial solid solutions**: In interstitial solid solutions, dissolved molecules occupy the spaces between solvent molecules in the crystal lattice. Like substitutional crystalline solid solutions, relative molecular size is crucial for classification. Solute molecules must have a diameter ≤ 0.59 of the solvent molecule's diameter, and their volume should be < 20% of the solvent. Thus, the solute molecule diameter should be < 0.59 times that of the solvent molecule, allowing them to fill the gaps between solvent molecules in the lattice.[21]

C) **Eutectic Mixtures:** A eutectic mixture is formed by combining two compounds that are fully miscible in liquid form but only partially miscible in solid form. This mixture is created through rapid solidification of the fused melt, ensuring complete liquid compatibility and minimal solid-solid solubility. Eutectic mixtures play a vital role in improving the bioavailability of poorly soluble compounds, typically comprising a slightly soluble drug and a highly water-soluble carrier. Upon dissolution in an aqueous solution, the carrier dissolves quickly, releasing fine drug crystals, thereby enhancing dissolution rates and overall bioavailability.[22,23]

D) **Glass Solutions:** Glass solutions are made when a substance dissolves in a glass-like material, creating a smooth mixture. Glass suspensions, on the other hand, have tiny particles suspended in the glass. These materials have a melting point that's not very clear. Examples of substances that can create glass solutions and suspensions include polyethylene glycol (PEG), urea, citric acid, PVP (polyvinylpyrrolidone), and sugars like dextrose, sucrose, and galactose. The glassy state, which is clear and easily breakable when cold, can describe either a single substance or a mix of them.[15]

Fusion Method

The melt method, often referred to as the fusion method, was proposed by Sekiguchi and Obi in 1961.[24] Drug and polymer are physically combined and heated to a molten slurry, which is cooled and solidified while being vigorously stirred. The solid mass is ground, pulverised, then sieved to get the appropriate particle size.[25] This has appropriately undergone several changes in order to pour the homogeneous melt onto a surface in the shape of a thin layer. Either a stainless steel plate or a ferrite plate, and it is cooled by water or air flowing on its

other side. In addition, fast quenching a melt at a high temperature can frequently result in a super-saturation of a solute or medication in a system. In these circumstances, the immediate solidification process stops the solute molecule in the solvent matrix. For simple eutectic mixes, the quenching process produces a significantly finer dispersion of crystallites.[26] There are a number of disadvantages to using this method to create solid dispersions, despite its widespread use. One of these disadvantages is that the medication and polymer are not miscible at the heating temperature. Surfactants, however, can be utilised to get around this problem. Lower manufacturing temperatures are preferred since drugs and polymers need to be thermally stable at melting temperatures. Furthermore, the fused combination ought to be immune to phase separation and recrystallization.[25] The solubility of anticancer medications that are poorly soluble has also been improved by the melting approach. For instance, an SD was made using the melting process utilising PEG 4000 and mannitol as the carriers in order to increase the solubility of prednisolone.[25]

Hot melt extrusion

The hot-melt extrusion method is a contemporary variation of the fusion process wherein the components are intensely mixed by the extruder. Melt extrusion provides an alternative to the conventional fusion process in that the molten drug-polymer combination may be shaped into pellets, implants, or oral dosage forms.[28] Nevertheless, for this approach to work, the medication and the polymer must be completely miscible while they are melted. Phase diagrams for solubility parameters may be utilised to logically choose the suitable polymer and forecast miscibility.[29]

In the past ten years, hot-melt extrusion has emerged as a successful drug delivery method and has begun to accommodate compounds that were previously thought to be unsuitable for use as pharmaceuticals. It has been demonstrated that hot-melt extrusion, an effective technique for producing solid molecular dispersions, can result in targeted, modified, and prolonged drug administration after increased drug bioavailability.[30] Using the hot-melt extrusion process, nonsteroidal anti-inflammatory medicines (NSAID) and paracetamol were made into orally disintegrating tablets.[31]

Co Precipitation

In order to prepare solid dispersions, the medication must first be dissolved in an appropriate liquid solvent. The drug solution is then added directly to the polyethylene glycol melt and

allowed to evaporate until a clear, solvent-free film is left behind. To maintain a consistent weight, the film is further dried.

Polyethylene glycol 6000 may include liquid substances up to a weight percentage of 5–10% (w/w) without significantly losing its solid characteristics. The chosen solvent or medicine that has been dissolved might not mix well with the polyethylene glycol melt. Also, the drug's polymorphic form, which precipitates as a solid dispersion, may be impacted by the liquid solvent utilised. This process has special benefits over solvent evaporation and fusing techniques. Practically speaking, it is only applicable to medications having modest therapeutic doses, such as less than 50 mg.[33]

Solvent method

When the medication and carrier are dissolved in a volatile solvent, the solvent evaporation technique is an easy approach to create solid dispersions. Evaporation of the solvent follows. The drug and carrier were originally dissolved in a common solvent by Tachibani and Nakamara (1965), who then used a vacuum to evaporate the solvent to create a solid solution.[34] This method's main benefit is that it prevents the thermal destruction of drugs and polymers, which happens frequently when organic solvents evaporate at low temperatures. However, there are two challenges that simulation scientists must overcome when applying this approach.[35]

However, there are two challenges that scientists must overcome when using this approach for mulation.[36] The first problem is to mix the drug and the polymer in a single solvent, which can be difficult if there are significant polarity differences. Surfactants are occasionally created to help with drug delivery or polymer solubility in specific solvents. Nevertheless, their final dose form often contains a considerable number of them, which lowers drug capacity for loading and may cause problems if the body does not take them well. Furthermore, the need to evaporate a significant portion of the solvent makes this approach costly.[37]

Spray drying method

Spray-drying is a formulation technique in which a heated gas stream (usually air) atomizes, sprays and dries a combination of excipients, usually a polymeric dispersion, including a medication, in a chamber.[38] This method has many benefits, including being appropriate for thermolabile chemicals since it allows for quick solvent evaporation and subsequent chamber

temperature lowering because the heat inlet gas comes into contact with the high humidity incoming sample.[39] One popular processing technique for making solid medication dispersions is spray drying. It is employed for the one-step conversion of a liquid or solution into a dry powder. Powders with the necessary size, shape, density, flow properties, and crystalline forms can be produced using this technology, which enables more exact control over process variables.[40] The fast evaporation of the solvent during spray drying causes a sharp rise in viscosity and traps the drug molecules in the polymer matrix. If drugs are soluble in specific spray drying solvents, they can be spray-dried into incredibly small particles even while their water solubility is limited.[41]

One of the most popular methods for evaporating solvents and producing solid dispersions is spray-drying. To eliminate the solvent, it entails dissolving or suspending the medication and carrier and then spraying it into a stream of hot air flow.[42]

Supercritical fluid

SCFs can be used as an antisolvent, such as gas antisolvent (GAS) and supercritical antisolvent (SAS), or as a solvent, such as rapid expansion from supercritical solution (RESS). Carbon dioxide is employed as an antisolvent for the solute in the supercritical fluid antisolvent technique. Because of its low temperature and pressure, supercritical carbon dioxide has many benefits and is a popular choice for processing heat-labile medications. The non-toxicity, non-flammability, and affordability of carbon dioxide as a supercritical fluid are other appealing qualities. Even though a tiny amount of carbon dioxide is trapped inside the polymer, it is still easy to remove from polymeric materials and does not endanger consumers.[43]

Supercritical fluids exhibit properties of both a liquid and a gas. Under supercritical circumstances, materials display characteristics of a liquid solvent as well as gas-like viscosity, diffusivity, and thermal conductivity. The fluids' mass transport characteristics are significantly improved by the gas-like qualities, even though the solvent properties are beneficial for drug/polymer solubilization.[44] Supercritical carbon dioxide (CO2) is most frequently utilised in this manner, either as an antisolvent or as a drug and polymer solvent. Through the use of a nozzle, the medication and polymer are dissolved in supercritical CO2 and shot into a low-pressure area, causing rapid cooling and adiabatic CO2 expansion. This method therefore makes it possible to create medication particles that are substantially

smaller in size. The standard term for this technology is the rapid expansion of supercritical solutions (RESS).[45]

Electrospinning method

For application in the polymer sector, this technology integrates nanotechnology and solid dispersion technology. This method involves applying a voltage of 5 to 30 kV to a liquid stream containing a drug/polymer solution. When electrical pressures are greater than the drug/polymer solution's surface tension at an air contact, submicron-diameter fibres are created.[46] The produced fibres can be gathered on a mandrel as the solvent evaporates, or they can be gathered on a screen to create a woven fabric. The fibre diameter is influenced by the following factors: feeding rate, surface tension, dielectric constant, and electric field strength. It has great potential because it is the most straightforward and affordable method of creating nanofibers and regulating the release of medications. This method may be applied in the future to create solid dispersions.[47] Solid fibres are created by the electrospinning technique, which involves delivering a melt or polymeric fluid stream via a millimeter-scale nozzle. A conducting capillary attached to a reservoir holding a polymeric solution and a conductive collective screen were subjected to an electric field during this procedure.[48]

Kneading method

A solvent is used to fully knead a mixture of precisely weighed drug and carriers in a glass. This process takes some time.[49] The medication and polymers are triiturated in a pestle and mortar while the liquid which might be water or a hydroalcoholic mixture is added dropwise in the kneading procedure. Due to the kneading action, this causes a slurry to form and the size of the particles to decrease, increasing the bioavailability. After that, the mixture is dried and put through a mesh screen to ensure that all of the components are uniform.[50] Solid dispersions created using the kneading method have been seen to dissolve at a faster rate. Phase solubility investigations were carried out for each material in order to create the phase solubility diagram. This method's inclusion complexes demonstrated a markedly higher solubility.[51]

Drawbacks of Solid dispersion

1. Not commonly used as a commercial product because of the conversion of the amorphous drug into the less soluble crystalline form since the exposure to moisture during storage and consequently increased drug mobility can lead to phase separation and instability.
2. Large scale production is limited due to expensive preparation methods.

3. Reproducibility cannot be guaranteed.
4. Incorporation SDs into some dosage forms is challenging.

REFERENCE

1. Ruba Malkawi, 1 Walla I. Malkawi, 2 Yahia Al-Mahmoud,1 and Jawad Tawalbeh3, Current Trends on Solid Dispersions: Past, Present, and Future Advances in Pharmacological and Pharmaceutical Sciences, 2022; ID5916013: 17.
2. K. Dhirendra, S Lewis, N Udupa, K Atin Solid dispersions: a review Pakistan journal of pharmaceutical sciences, 2009; 22(2).
3. SS Shinde, SS Patil, FI Mevekari, AS Satpute International Journal of Advances in Pharmaceutical Sciences, 2010; 1(3).
4. Jaskirat Singh, Manpreet Walia, SL Harikumar Journal of drug delivery and Therapeutics, 2013; 3(5): 148-155.
5. Rahul M Patil, Ajim H Maniyar, Mangesh T Kale, Anup M Akarte, Dheeraj T Baviskar Cheminform, 2012; 43(23).
6. Christian Leuner, Jennifer Dressman European journal of Pharmaceutics and Biopharmaceutics, 2000; 50(1): 47-60.
7. K. Dixit, P. Singh, and S. Stuti, "*Solid dispersion-a strategy For improving the solubility of poorly soluble drugs*," International Journal of Research in Pharmaceutical and BioMedical Sciences, 2012; 3: 90–964.
8. Kiran Singh Sharma, Jagannath Sahoo, Seema Agrawal, Asha Kumari "*Solid dispersions: a technology for improving Bioavailability*" Journal of Analytical & Pharmaceutical Research, 2019; 8(4).
9. Singh N, Sarangi M. Solid Dispersion – a Novel Approach for Enhancement of Bioavailability of Poorly Soluble Drugs in Oral Drug Delivery System. Glob J Pharmaceu Sci., 2017; 3(2): 555608. DOI: 10.19080/GJPPS.2017.03.555608
10. P. Ganesan, R. Soundararajan, U. Shanmugam, and V. Ramu, "Development, characterization and solubility Enhancement of comparative dissolution study of second generation of solid dispersions and microspheres for poorly Water soluble drug," Asian Journal of Pharmaceutical Science, 2015; 10(5): 433–441.
11. P. P. Mande, S. S. Bachhav, and P. V. Devarajan, "Bioenhanced advanced third generation solid dispersion of Tadalafil: repurposing with improved therapy in pyelone Phritis," Asian Journal of Pharmaceutical Sciences, 2017; 12(6): 569–579.

12. A. R. Nair, Y. D. Lakshman, V. S. K. Anand, K. S. N. Sree, K. Bhat, and S. J. Dengale, "Overview of extensively Employed polymeric carriers in solid dispersion technology," AAPS PharmSciTech, 2020; 21(8): 309–320.
13. S. Verma, A. Rawat, M. Kaul, and S. Sainin, "Solid dispersion: A strategy for solubility enhancement," International Journal Of Pharmacy and Technology, 2011; 3: 1062–1099.
14. W.L. Chiou, S. Riegelman, Pharmaceutical applications of solid Dispersion systems, J. Pharm. Sci., 1971; 60: 1281-1302.
15. Z. Bhut, B. Prajapati, N. Patel, A. Patel, and A. Patel, "Solid Dispersion as a strategy to enhance solubility: a review article," International Journal for Pharmaceutical Research Scholars, 2012; 3: 277–283.
16. A.H. Goldberg, M. Gibaldi, J.L. Kanig, 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: 1145-1148.
17. C. Leuner, J. Dressman "Improving drug solubility for oral delivery using solid dispersions" European Journal of Pharmaceutics and Biopharmaceutics, 2000; 50: 47-60.
18. C. Leuner and J. Dressman, "Improving drug solubility for Oral delivery using solid dispersions," European Journal of Pharmaceutics and Biopharmaceutics, 2000; 50(1): 47–60.
19. M. Rahul, A. Patil, and H. Maniyar, "Solid diperstion: Strategy to enhance solubility," International Journal of Pharmaceutical Sciences Review and Research, 2011; 8: 66–73.
20. R.E. Reed-Hill, Physical Metallurgy Principles, Van-Nostrand, Prin-Cetown, NJ, 1964.
21. K. Sekiguchi, N. Obi, Studies on absorption of eutectic mixtures. I.A comparison of the behavior of eutectic mixtures of sulphathazole and that of ordinary sulphathiazole in man, Chem. Pharm. Bull., 1961; 9: 866-872.
22. A.H. Goldberg, M. Gibaldi, J.L. Kanig, Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and Eutectic mixtures II ± experimental evaluation of a eutectic mixture: Urea-acetaminophen system, J. Pharm. Sci., 1966; 55: 482-487.
23. Ruba Malkawi, 1 Walla I. Malkawi, 2 Yahia Al-Mahmoud, 1 and Jawad Tawalbeh 3, "Current Trends on Solid Dispersions: Past, Present, and Future" Advances in Pharmacological and Pharmaceutical Sciences, 2022; 5916013.
24. S. Baghel, H. Cathcart, and N. J. O'Reilly, "Polymeric amorphous solid dispersions: a review of amorphization, crystallization, stabilization, solid-state characterization, and aqueous solubilization of biopharmaceutical classification system class II drugs," Journal of Pharmaceutical Sciences, 2016; 105(9): 2527–2544.

25. Goldberg, A., Gibaldi, M., and Kanig, L., Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II experimental evaluation of a eutectic mixture: urea-acetaminophen system, J. Pharmaceut. Sci., 1996; 55: 482-487.
26. Palanisamy M., Khanam J. Solid dispersion of prednisolone: Solid state characterization and improvement of dissolution profile. *Drug Dev. Ind. Pharm.,* 2011; 37: 373–386. doi: 10.3109/03639045.2010.513984
27. S. Baghel, H. Cathcart, and N. J. O'Reilly, "Polymeric amorphous solid dispersions: a review of amorphization, crystallization, stabilization, solid-state characterization, and aqueous solubilization of biopharmaceutical classification system class II drugs," Journal of Pharmaceutical Sciences, 2016; 105(9): 2527–2544.
28. M. A. Repka, S. Majumdar, S. Kumar Battu, R. Srirangam, and S. B. Upadhye, "Applications of hot-melt extrusion for drug delivery," Expert Opinion on Drug Delivery, 2008; 5(12): 1357–1376.
29. Inventor S. Reckitt Benckiser Healthcare (UK) Limited, "Granules comprising a NSAID and a sugar alcohol made by melt extrusion," UK patent, 2006.
30. M. Maniruzzaman, J. S. Boateng, M. J. Snowden, and D. Douroumis, "A review of hot-melt extrusion: process technology to pharmaceutical products," ISRN Pharmaceutics, 2012; 436763: 9.
31. Goldberg, A., Gibaldi, M., and Kanig, L., Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II experimental evaluation of a eutectic mixture: urea-acetaminophen system, J. Pharmaceut. Sci., 1996; 55: 482-487.
32. L. Nikghalb, G. Singh, G. Singh, and K. Kahkeshan, "Solid dispersion: methods and polymers to increase the solubility of poorly soluble drugs," Journal of Applied Pharmaceutical Science, 2012; 2: 170–175.
33. L. Nikghalb, G. Singh, G. Singh, and K. Kahkeshan, "Solid dispersion: methods and polymers to increase the solubility of poorly soluble drugs," Journal of Applied Pharmaceutical Science, 2012; 2: 170–175.
34. A. Sharma and C. P. Jain, "Preparation and characterization of solid dispersions of carvedilol with PVP K30," Research in Pharmaceutical Sciences, 2010; 5(1): 49–56.
35. C. Encina, G. Márquez-Ruiz, F. Holgado, B. Giménez, C. Vergara, P. Robert, Effect of Spray-drying with organic solvents on the encapsulation, release and stability of fish Oil, Food Chem., 2018; 263: 283–291.

36. Laura Modica De Mohaca Bahijja Raimi-Abrahamb, Roberto Caruanac, Giammona Gaetanod Mariano Licciardi Multicomponent solid dispersion a new generation of solid dispersion Journal of Drug Delivery Science and Technology, 2020; 57: 101750.
37. A. Paudel, Z.A. Worku, J. Meeus, S. Guns, G. Van Den Mooter, Manufacturing of Solid dispersions of poorly water soluble drugs by spray drying: formulation and Process considerations, Int. J. Pharm., 2013; 453: 253–284.
38. M.A. Augustin, Y. Hemar, Nano- and micro-structured assemblies for encapsulation Of food ingredients, Chem. Soc. Rev., 2009; 38: 902–912.
39. B. B. Patel, J. K. Patel, S. Chakraborty, and D. Shukla,"Revealing facts behind spray dried solid dispersion technology used for solubility enhancement," Saudi Pharmaceuticals Journal, 2015; 23(4): 352–365.
40. Mooter G, Evaluation of Inutec SP1 as a new carrier in the formulation of solid dispersions for poorly soluble drugs, Int. J. Pharm., 2006; 316: 1–6.
41. Drooge DJV, Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques, Int. J. Pharm., 2006; 310: 220–229.
42. Dohrn R, Bertakis E, Behrend O, Voutsas E, Tassios D. Melting Point depression by using supercritical CO2 for a novel melt Dispersion micronization process. J Mol Liq., 2007; 131: 53-9.
43. A. Uwineza and A. Waskiewicz, "Recent advances in supercritical fluid extraction of natural bioactive compounds From natural plant materials," Molecules, 2020; 25.
44. E. L. N. Escobar, T. A. da Silva, C. L. Pirich, M. L. Corazza, and L. Pereira Ramos, "Supercritical fluids: a promising Technique for biomass pretreatment and fractionation," Frontiers in Bioengineering and Biotechnology, 2020; 8(252): 34.
45. Rahul M. Patil*, Ajim H. Maniyar, Mangesh T. Kale, Anup M. Akarte, Dheeraj T. Baviskar SOLID DISPERSION: STRATEGY TO ENHANCE SOLUBILITY, May – June, 2011; 8(2): 012.
46. Ruba Malkawi, 1 Walla I. Malkawi, 2 Yahia Al-Mahmoud,1 and Jawad Tawalbeh3, Current Trends on Solid Dispersions: Past, Present, and Future Advances in Pharmacological and Pharmaceutical Sciences, 2022; ID5916013: 17.
47. K. Poddar, "Solid dispersions: an approach towards enhancing dissolution rate," International Journal of Pharmacy and Pharmaceutical Sciences, 2011; 3: 9–19.
48. S. Baboota, M. Dhaliwal, and K. Kohli, "Physicochemical characterization, in vitro dissolution behavior, and pharmacodynamic studies of rofecoxib-cyclodextrin inclusion

compounds preparation and properties of rofecoxib hydroxypropyl β-cyclodextrin inclusion complex: a technical note," AAPS PharmSciTech, 2005; 6(1): E83–E90.

49. H. M. Patel, B. N. Suhagia, S. A. Shah, I. S. Rathod, and V. K. Parmar, "Preparation and characterization of etoricoxib-β-cyclodextrin complexes prepared by the kneading method," Acta Pharmaceutica, 2007; 57(3): 351–359.
50. A. Kumar, P. Globale, S. K. Sahoo et al., "Review on solubility enhancement techniques for hydrophobic drugs," International journal of comprehensive pharmacy, 2011; 3: 1–7.
51. V. Patel, R. Patel, H. Shah, S. Purohit, M. Pawar, and A. Pathan, "Solubility enhancement of azithromycin by solid dispersion technique using mannitol and β-cyclodextrin,"Act Scientific Pharmaceutical Sciences, 2021; 5(4): 48–54.