Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 21s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Insights of Different Solid Dispersion Techniques and Their Importance in Product Development

Priyanshu Tyagi[1], Sanjeev Kumar Chauhan[2]*, Surbhi Kamboj[3], Pragati Gupta[4], Richa Goel[5], Praveen K Dixit[6]

[1]Department of Pharmaceutics, KIET School of Pharmacy, KIET Group of Institutions, Ghaziabad, Delhi-NCR, Uttar Pradesh, INDIA.

[2]Department of Pharmaceutical Chemistry, KIET School of Pharmacy, KIET Group of Institutions, Ghaziabad, Delhi-NCR, Uttar Pradesh, INDIA.

[3]Department of Pharmacognosy, KIET School of Pharmacy, KIET Group of Institutions, Ghaziabad, Delhi-NCR, Uttar Pradesh, INDIA.

[4]Department of Pharmacology, KIET School of Pharmacy, KIET Group of Institutions, Ghaziabad, Delhi-NCR, Uttar Pradesh, INDIA.

***Corresponding Author:**

Mr. Sanjeev Kumar Chauhan

KIET School of Pharmacy, KIET Group of Institutions, Ghaziabad, Delhi-NCR, Uttar Pradesh

Email ID: sanjeevchauhan150@yahoo.com

Cite this paper as: Priyanshu Tyagi, Sanjeev Kumar Chauhan, Surbhi Kamboj, Pragati Gupta, Richa Goel, Praveen K Dixit, (2025). Insights of Different Solid Dispersion Techniques and Their Importance in Product Development. *Journal of Neonatal Surgery*, 14 (21s), 788-804.

ABSTRACT

One of the biggest and most significant challenges in the development of pharmaceutical is poor water solubility or bioavailability. Solid dispersions were introduced as a means of enhanced dissolution rates and consequent therapeutic effectiveness of poorly water-soluble biopharmaceutical classification system (BCS) Class II drugs by incorporating the drugs into hydrophilic carriers. In this review, we cover the core principles, benefits and recent developments in solid dispersion technology. It discusses different preparation approaches, like fusion, solvent evaporation, spray drying, hot-melt extrusion, and newer routines like supercritical fluid processing and electrospinning. Different strategies have their unique advantages including molecular-level distribution, enhanced solubility rate, and larger-scale production capabilities. The review also provides a historical perspective on Solid dispersion system development, from crystalline carriers to amorphous and controlled-release carriers and the four generations of solid dispersion systems. Here, we discuss challenges including recrystallization, thermodynamic instability, and phase separation and strategies to overcome these challenges. Additionally, enhanced characterization techniques like DSC, XRD, and SEM are explored for assessing the structural and dissolution characteristics of solid dispersions. Moreover, solid dispersion techniques are an essential method for increase the solubility of hydrophobic agents and improving the performance of newly developed or established pharmaceutical agents by advancing oral delivery systems. This review highlights their critical role in addressing solubility challenges and advancing the field of drug formulation.

***KEYWORD*:** *SOLID DISPERSION, SOLUBILITY, BIOAVAILABILITY, IMPROVEMENT, PHARMACEUTICAL, FORMULATIONS*.

1. INTRODUCTION

Oral delivery remains the most widely used and favored passage for drug delivery. For patients, swallowing medicine is a well-known and easy process, resulting in better patient compliance and better therapeutic effects compared to other delivery routes, especially, parenteral routes.1 When ingested orally, the active ingredient of a drug necessary first dissolved in stomach or succus entericus in order to be absorbed into the bloodstream.2 A drug's water-soluble nature and permeability within the membrane have a direct impact on bioavailability and are crucial for gastrointestinal absorption. Drugs with low membrane permeability may have poor absorption if the permeability is low, and drugs with insufficient aqueous solubility may not be absorbed due to slow dissolution.3 Scientists in the pharmaceutical sector have therefore created two broad strategies to increase pharmacologically active compounds' oral bioavailability, which act either by improving the permeability of drug compounds known to have low membrane permeability and/or by making poorly water-soluble medications more soluble and, hence, more rapidly soluble.4 The pharmaceutical literature describes other plan to improve the dissolution properties of slightly water-soluble drugs besides solid dispersions. These tactics involve size reduction, .

solubilization of medications in solvents, complexation with cyclodextrins, and the formation of salts.5 Despite their efficacy, each has significant hurdles, including poor drug solubility, a lack of low-cost and user-friendly solutions, and long preparation times. Conversely, solid dispersions, can be prepared using a variety of manufacturing methods and excipients, allowing more flexibility in creating oral delivery system for poorly water-soluble drugs that may have poor tolerability.6 As dissolution is the rate limiting factor in drug absorption, most studies on solid dispersion technologies

have either been on drugs that have high permeability into biological membranes, but poor water solubility. Increasing the rate of dissolution can enhance the drug's in vivo absorption. Class II drugs are defined by the Biopharmaceutical Classification System (BCS) as drugs characterized by high membrane permeation and low water solubility. Thus, the solid dispersion method has great potentiality for improving oral absorption and bioavailability of BCS Class II drugs.[7] Poor solubility of many recently approved drugs limits their therapeutic efficacy. Statistical studies suggest that near to 40% of newly identified chemical entities are water-insoluble in nature.[8] Unfortunately, solubility issues frequently cause many drugs with potential to fail in early development. Thus, the generation of novel strategies to overcome these solubility issues will be essential to maximizing the therapeutic value of these moieties.[9]

Solubility

The quantity of solute dissolved in a solvent is known as solubility, wherein an equilibrium is established between the solute within solution and/or any excess, undissolved solute at an equilibrium under certain temperature and/or pressure condition. "Solute" refers to the material that dissolves, "solvent" refers to the liquid that dissolves the solute, and "solution" refers to the combination that results.[10]

System for Classifying Biopharmaceuticals (BCS)

Amidon and colleagues came up with the first Biopharmaceutical Classification System in 1995. Their approach is to upgrade the bioavailability of Class II drugs by increase their solubility and dissolution rate in gastrointestinal fluids. For the drug release, due to the constraints in oral bioavailability for poorly soluble drugs in the disgestive tube, the release of the drug is the most critical and restrict factor. Optimising the release profile of these medications can increase drug consumption while reducing negative effects.[11,12] Based on publicly accessible data, the World Health Organization's (WHO) model list of absolutely required medications has been classified using a biopharmaceutical categorization system. Regretfully, only 61 of the 130 oral medications on the WHO list could be properly categorised. Among these, Class I drugs represent 84%, Class II drugs account for 17%, Class III drugs make up 49%, and Class IV drugs comprise 10%.[10]

Mechanisms of the Solid Dispersion Technique for Enhancing Drug Solubilization

The primary idea is to remove drug crystallinity entirely while dispersing a poorly soluble molecule into a hydrophilic polymeric carrier. The specifics of this are still not well understood.[13] The carrier Polymer dissolves in aqueous mediums, allowing the drug to be released in colloidal state particulates. This increases the surface area obtainable for dissolution leading to an improve in the bioavailability of the poorly soluble drugs. Decreasing the particle size and increasing the porosity of the drug enlarge the drug's solubility within the hydrophilic carrier, therefore increasing the dissolution rate. This approach has significant advantages. Recently, there has been adding of surfactants to formulations in order to increase functionality, although they can incite problems of recrystallization and thermodynamic instability. For that reason, surfactants are used to increase solubility and minimize the risk of recrystallization.[14]

Reasons behind the pharmaceutical industry's make use of the solid dispersion technique

The primary objectives of applying this strategy in the pharmaceutical industry are as follows:[15]

Improving solubility of drugs

Increasing stability of drugs

Disguising medications' disagreeable flavour

Getting the intended release profile

Depending on the Carrier Employed

Four generations of solid dispersions may be distinguished based on the carrier that is utilized :[18]

First generation: Crystalline materials were the first carriers utilised in solid dispersions, like sugars or urea.[19] A major limitation of these early carriers is their crystalline structure, which hinders drug release compared to the amorphous form, as they are thermodynamically stable.[20]

Second generation: Amorphous carriers, commonly in the form of polymers, are widely used in this generation.[21] Ethyl cellulose, hydroxypropyl methylcellulose (HPMC), and starch derivatives like cyclodextrins or hydroxypropyl cellulose are examples of polymers obtained from nature. On the other hand, synthetic polymers include polyethylene glycols (PEG), povidone, polyvinylpyrrolidone, and polymethacrylates.[22]

Third generation: Research has demonstrated that carriers with surfactant properties can enhance the dissolution profile. Consequently, the application of surfactant-based carriers – like Inulin, gelucire 44/14, compritol 888, ATO, inutec SP1, and

poloxamer 407 - has confirmed to be successful in boosting in vivo bioavailability and attaining a high degree of polymorphism purity.[23]

Fourth generation: Controlled-Release Solid Dispersion describes a system created for drugs which have a short biological half-life period along with poor water solubility. This system employs transporters that are insoluble or soluble in water. The principal aims of controlled release solid dispersions are to make better solubility and to prolong the release of the drug in a restrained.[24] Carriers which achieve this level of systematization include ethyl cellulose, hydroxypropyl cellulose, and other water-soluble polymers.

A carrier intended to enhance the dissolution rate of a drug should meet the following criteria:
It must be both quick dissolving and soluble in water and has to dissolve automatically.
It does not have any pharmacological activity and is non-toxic.[16]
The emollient must possess a low melting point and must also be stable to heat.
Capability to dissolve is essential in many solvents.
To gain an enhanced solubility in water, then it would be better.
It must ideally be chemically compatible with the drug, enhancing its water solubility without forming a strong complex with it.[17]

Considering the arrangement of molecules

The following categories apply to solid dispersions :[25]

Solid dispersion classifications: Solid dispersions are categorized according to their molecular structure and the type of dispersion medium used. The primary classifications are eutectic mixtures, amorphous solid dispersions, solid solutions, and polymeric nanoparticle dispersions. These classifications significantly affect drug solubility, stability, and bioavailability, making them essential in drugs that aren't very soluble in water (Figure 1).

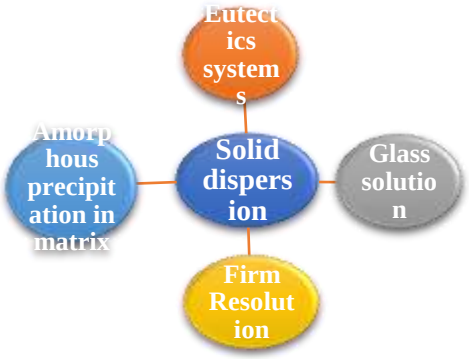

Fig 1: Shows the classification of solid dispersion.

Systems of Eutectics

This mixture is composed of two substances that are fully mixable in their liquid form, yet only marginally mixable in solid form. It is produced by quickly colling the molten combination of the two substances, leading to a product that is entirely mixable in the liquid phase but exhibits little solubility in the solid state. The physical combination of the two crystalline components is thermodynamically integrated into this system.[26]

Suspensions and Glass Solution

Glass suspensions are made up of precipitated particles that are dispersed within a glassy solvent, while glass solutions are uniform glassy systems where a solute is dissolved in a glass carrier. Common carriers used to create glass solutions and suspensions include compounds such as urea, citric acid, polyethylene glycol, polyvinylpyrrolidone, and sugars like dextrose, sucrose, and galactose.[26] These systems generally exhibits low lattice energy and do not have a specific melting point.

Firm Resolution

In this system, a uniform homogeneous phase is created when the two constituents solidified. In solid solutions, the size of the drug particles is lowered to the microscopic level. As a result, the solid solution dissolves more rapidly compared to a comparable eutectic mixture. The mobility of solvate molecules (whether substitutional, interstitial, or amorphous) or the degree of miscibility between the two compounds might affect whether the solution is continuous or discontinuous.[27]

Continuous Solid Solutions: In a continuous solid solution, all constituents are mixable, showing that a link between the two components is, in conceptual terms, higher compared with the bonding within each component alone. However, there have yet to be any reports of reliable solutions of this nature in the pharmaceutical industry.

Discontinuous Solid Solutions: Each component's solubility in the others is restricted in discontinuous solid solutions.[27]

Solid Substitutional Solutions: This type of solid solution occurs when there is a less than 15% size variance among the solute and solvent molecules.[28]

Solid Interstitial Solutions: The solute particles in interstitial solid solutions fill the spaces in the crystal lattice between the solvent molecules. Consequently, The solute molecule's diameter must be less than 0.59 times that of the solvent molecule.[29]

***Amorphous Precipitation in the Matrix of Crystals*:** Instead of the drug and the carrier co-crystallizing in a eutectic system, the drug can precipitate as an amorphous entity within the crystalline carrier. The elevated energy characteristic of the amorphous state of the drug frequently results in enhanced dissolution rates.[30]

Technique of Preparation

There is no generic method for magnify the solubility of poorly water-soluble drugs in strong dispersions. The selection of precise technique relies upon the factors which include the drug's dosage, molecular weight, and hydrophilic-hydrophobic stability. consequently, trial and error are regularly the best approach to decide the pleasant approach for improving the drug's solubility. Several strategies are to be had for preparing strong dispersions.[31]

Combination

The melt technique (fusion technique) was first presented in 1961 by Sekiguchi and Obi. In this approach, the drug and polymer are physically varied and, subsequently, heated until melted, cooled and solidified under vigorous mixing. This solid mass is then crushed, ground, and sieved to achieve required particle size. Although this approach is utilized extensively, it is restricted by the incompatibility of the drug and polymer at higher temperatures. Surfactants can be used to overcome this issue. Additionally, it is significant to ensure that the medication and the polymer remain thermally stable at the required melting temperatures, and that the fused mixture is resistant to phase separation and recrystallization.[32]

Hot Melt Extrusion (HME)

The HME technique is an innovation of the fusion process in which an extruder is used to properly combine the ingredients. The mixture of molten medication and polymer can be molded into implants, pellets, or oral dose forms by melt extrusion, in contrast to the conventional fusion process. But in order to use this method, the medication and polymer must melt completely into one another.[33,34] HME is a potent drug delivery technique that has expanded the range of substances that were previously thought to be unsuitable for use in pharmaceuticals throughout the last ten years. HME is useful for enabling targeted, modified, and prolonged medication release by increasing drug bioavailability.[35] It is an extremely effective method for creating solid molecular dispersions. Nonsteroidal anti-inflammatory medicines (NSAIDs) and paracetamol oral disintegrating tablets have been produced successfully using the HME technique.[36] Tablet compression was done after granulation with several low molecular weight polyethylene glycols (PEGs) for paracetamol. The medication release profile was improved by the HME granules. The USP 30 requirements for paracetamol tablets were met by tablets with 15% PEG, which released more than 80% of the medication in 30 minutes.[37]

Co-evaporation Co-precipitation Technique

The drug dissolves in an organic solvent, and the carrier dissolves in water after being carefully measured. The organic drug solution is combined with the aqueous carrier solution once both solutions have fully dissolved. After the solvents have evaporated, A pestle and mortar are used to crush, sift, and dry the mixture.[38]

Solvent Technique

The solvent approach generates a solid dispersion by dissolving the drug and polymer in a common solvent and then draining the solvent. By facilitating molecular-level mixing, this method enhances the final product's stability and solubility.[39,40] By reducing the possibility of thermal degradation—which can happen when low temperatures cause organic liquids to evaporate—this approach has a number of important advantages. When using this approach in simulations, there are two main obstacles to overcome.[41,42] The first obstacle is that the drug and polymer are difficult to dissolve inside the same solvent, particularly when their polarities are very different. Although surfactants can occasionally be added to increase solubility, their overuse in the finished formulation can lower the drug's loading capacity and result in problems if the body does not tolerate them. Production costs are further increased by the requirement to evaporate significant amounts of

solvent.[43,44] Phase separation, which can happen during solvent removal, is the second difficulty. Vacuum drying is frequently employed to counteract this, and in certain situations, a rotary evaporator is utilized to achieve quick drying. Higher drying temperatures have the potential to shorten the phase separation duration, but they can also increase the drug's and polymer's molecular mobility, which could unintentionally accelerate the process.[45-48] A study on furosemide, a medication with low permeability, bioavailability, and solubility, assessed methods to improve solubility and dissolution, including kneading, coprecipitation, and solvent evaporation. The results showed that all strategies improved solubility, with solvent evaporation proving to be the most successful. Physical mixing, kneading, solvent evaporation, and coprecipitation were ranked in order of effectiveness.[49]

Spray Drying

A common technique for producing solid medication dispersions is spray drying, which turns a liquid or solution into a dry powder. The method allows for the perfect control of crucial variables like particle size, shape, density, flow properties, and crystalline formations.[50] Rapid solvent evaporation throughout the spray drying process raises the solution's viscosity, which traps active ingredient inside the polymer matrix. Even if the medicine has reduced water solubility, it could be reduced to very tiny particles if it is dissolvable in the selected spray-drying solvent. However, the medication's elemental composition determines the properties of the final solid particles. Amorphous materials, crystalline structures, imperfect crystals, and metastable crystals are only a few of the forms that can be created by spray drying. Mahlin and Bergstrom's study[51] found that the chemical makeup of the drugs is more important in determining whether an amorphous state forms than the parameters of the method. The stability of these amorphous forms is, however, determined by the process conditions. Spray drying has emerged as the go-to solvent-based production method because of its cost-effectiveness, scalability, and capacity to generate continuous batches. It additionally permits remarkable control over the properties of the final powder.[52-54]

Technique of Supercritical Fluid (SCF)

SCF possess a unparalleled arrangement of liquid and gas characteristics. Specifically, they exhibit gas-like properties such as low viscosity, high diffusivity, and significant thermal conductivity, alongside solvent capabilities akin to liquids. This blend allows for enhanced mass transport, arising from the gas-like behavior, while still providing the benefits of a liquid solvent for dissolving drugs and polymers.[55] Carbon dioxide (CO2) is frequently employed just as a supercritical fluid, capable of acting as either a solvent or an antisolvent for these materials. In a process called Rapid Expansion of Supercritical Solutions (RESS)[56], a polymer and drug dissolved in supercritical CO2 are rapidly expelled through a nozzle into a region of lower pressure; the ensuing adiabatic expansion and rapid cooling of the CO2 results in the formation of drug particles with substantially reduced diameters. Supercritical fluid technologies offer a route to producing nanoparticulate suspensions with particle sizes ranging from 5 to 2000 nm. This environmentally conscious approach minimizes environmental impact by eliminating organic solvents and leaving only trace amounts of residual CO2 within the polymer matrix. The plasticizing and swelling capabilities of CO2 further enhance the process's appeal. However, the limited solubility of many therapeutic compounds in CO2 presents a significant challenge. To overcome this limitation and improve solubility, several specialized supercritical fluid-processing techniques have been created, including supercritical fluid-enhanced dispersion, gas antisolvent recrystallization, supercritical antisolvent processes, precipitation with a compressed antisolvent, and aerosol supercritical extraction systems.[57] The solubility of a drug in supercritical CO2 is a key factor affecting particle size in the RESS technique. Kim et al.[58] showcased this principle by producing ultrafine drug particles using only supercritical CO2, thus avoiding the need for organic solvents. Their experiment, which utilized orifice disks and capillary tubes for expansion, involved three drugs with varying solubilities in supercritical CO2: lidocaine, griseofulvin, and benzoic acid. Research into drug solubility in supercritical CO2, combined with studies on how operating conditions impact the physical characteristics of RESS-produced particles, indicated an inverse relationship between drug solubility and average particle diameter. Through response surface methodology, optimal conditions for minimizing particle size were determined to be 50°C, 17.7 MPa pressure, and a spray distance of 10 cm.[59]

Technique of Kneading

Within a glass container, a precisely calculated blend of a medication and carrier is moistened with a solvent and then extensively molded for a predetermined amount of time.[16] A pestle and mortar are used to grind the medication and polymer together during this kneading process, and the solvent—usually water or a hydroalcoholic mixture—is introduced gradually. By creating a slurry, the kneading motion lowers particle size and increases bioavailability. To guarantee homogeneity, the mixture is first dried before passing through a mesh screen.[60] The formation of cyclodextrin-satranidazole complexes resulted in a notable enhancement of their solubility after complexation.[61] Olmesartan medoxomil inclusion complexes were prepared into mouth-dissolving tablets in a different study by kneading the mixture. In addition to improving the tablets' solubility and dissolving, this method also increased their mechanical stability.[62] Using PVP K-30, efavirenz was processed by kneading as well as conventional solvent techniques. To examine both formulations, characterization methods like DSC, FT-IR, SEM, and XRD were used in conjunction with the dissolution profiles. Faster rates of dissolution were observed in solid dispersions based on kneading.[63] Etoricoxib-cyclodextrin complexes were prepared by Patel using the kneading process, and phase solubility investigations were performed to provide phase solubility diagrams. The solubility of these compounds

significantly increased.[64] The kneading complexation method also enhanced the solubility of mesulide.[65] One study evaluated azithromycin, a BCS class II medication, using physical characterization and melting point data. Azithromycin solid dispersions were made by solvent evaporation, kneading, and melting. According to the findings, kneading and melting techniques improved the drug's solubility more than solvent evaporation.[66]

Technique of Electrospinning

This method, which was created especially for use in the polymer sector, blends solid dispersion technology and nanotechnology. A liquid drug/polymer solution is exposed to a voltage between 5 and 30 kV. Submicron-diameter fibers are created when the applied electrical forces are greater than the solution's surface tension at the air-solution contact.[67] As the solvent evaporates the resulting fibers could be collected on a spinning mandrel or screen to create a woven material. The fiber diameter is influenced by several factors, including feeding rate, electric field intensity, surface tension, and the dielectric constant. This approach holds considerable promise due to its simplicity and cost-effectiveness in producing nanofibers and regulating drug release. In the future, it may be further explored for the creation of solid dispersions.[16] The technique's low cost and ease of implementation make it particularly advantageous. It has been demonstrated to effectively control the release of biomedical drugs and facilitate nanofiber fabrication. For example, electrospinning was used to produce a polyvinyl alcohol (PVA) and ketoprofen (1:1, w/w) nanofiber, which exhibited a remarkably higher dissolution rate compared to ketoprofen alone ($p < 0.05$). In another study, polyvinylpyrrolidone (PVP) was utilized as a carrier to combine amorphous forms of griseofulvin and indomethacin using electrospinning. This combination remained stable in a desiccator for up to eight months.[68]

Polymers Utilized in Solid Dispersion

Safety, kinetics, and thermodynamics are three important factors that determine whether polymeric carriers are suitable for the formation of solid dispersions. Polymeric carriers for solid dispersions must also be pharmacologically and chemically inert, as is a fixed requirement for each excipient included in pharmaceutical formulations. From a kinetic perspective, the polymer should hold the drug from crystallizing in the gastrointestinal tract, which is why generally recognized as safe (GRAS) carriers are preferred for these formulations.[69] Drugs that are weakly basic are especially vulnerable to precipitation because they mostly stay in their unionized form in the stomach.[70] Furthermore, by making it easier for the medication to be incorporated into micelles, a polymer with surfactant qualities might increase the drug's solubility. The advantages of keeping the medication in an elevated-energy amorphous form may be enhanced by this.[71,72] Deliquescent behavior is often shown by amorphous, hydrophilic polymers. The polymer is present in much greater amounts in solid dispersions with low drug loading, which is frequently the case. Phase separation caused by the devitrification of the amorphous phase poses a significant threat to the these systems' physical stability.[73] For amorphous dispersions to remain stable, thermodynamic considerations are also crucial. The polymer essential a high glass transition temperature (Tg) to preserve stability at room temperature and make less the possibility of Johri-Goldstein (JG) relaxations.[74-76] In order to create an amorphous solid dispersion, the formulation scientist needs to choose a polymer that has strong glass-forming qualities across a variety of chemicals. The evolution of a single-phase amorphous system requires high phase-solubility with the drug.[78] In order to keep the stability of the dispersion, the polymer should also possess a high potential for intermolecular interactions, specifically through hydrogen bonding (both as a donor and an acceptor). The polymer's phase-solubility and solubility in organic solvents are essential due to successful production of solid dispersions through melt and solvent-based methods, respectively, from a manufacturing standpoint.

Advanced Vinyl Pyrrolidone Devices

Polyvinylpyrrolidone, a water-soluble substance that was initially developed in 1939, is created when N-vinylpyrrolidone is polymerized. Derivatives of N-vinylpyrrolidone are categorized according to their crosslinking properties. PVP has grown in popularity as an excipient in the pharmaceutical sector over time.[79] Additionally, it was shown that N-vinylpyrrolidone could be crosslinked via the "popcorn polymerization" procedure at temperatures higher than 100°C when alkali hydroxide was present. In contrast to PVP, the crosslinked product, crospovidone, has unique physicochemical characteristics. Crospovidone is not commonly utilized in solid dispersions because of its crosslinking, which makes it insoluble in water.[80] A copolymer comprising N-vinylpyrrolidone and vinyl acetate was created in order to combine the beneficial qualities of both PVP and crospovidone. The polarity of this copolymer, called copovidone, lies in between that of crospovidone and PVP. A 6:4 copolymer of vinyl acetate and vinylpyrrolidone, copovidone has a number of advantageous physicochemical characteristics that make it perfect for use in formulations for solid dispersions.[81]

Pyrrolidone Poly Vinyl (PVP)

PVP is one of the popular polymeric carriers for formulations involving solid dispersion. The K values attributed to various classes of PVP polymers are influenced by the degree of polymerization, average molecular weight, and intrinsic viscosity.[82] Based on observations of viscosity, Fikentscher's formula is used to determine these K values. Since PVP is a hydrophilic polymer, it often occurs in an amorphous state and dissolves in ethanol, water, isopropyl alcohol, and chloroform.[83]

Copovidone

Copovidone is a copolymer of vinylpyrrolidone and vinyl acetate in a 6:4 ratio and is marketed under the brand names Plasdone S-630 (Ashland, USA) and Kollidon VA64 (BASF, Germany). It is a water-dilutable, amorphous polymer that is commonly in the pharmaceutical industry as a binder and film-forming agent.[84], and it was later repurposed by Abbott Laboratories for the growth of the solid dispersion formulation of the Lopinavir-Ritonavir combination, marketed as Kaletra85 Compared to PVP, copovidone has a much higher degradation temperature (approximately 230°C) than its glass transition temperature (approximately 100°C).[86] Its wide temperature range makes it ideal for use in hot melt extrusion (HME) processes, which allow for the production of solid dispersions including APIs with low and high melting points. Copovidone and APIs frequently combine to generate glassy, single-phase solutions. The water-soluble polymer dissolves alongside the molecularly distributed amorphous API in the solid dispersion, which is a crucial process by which dissolution is improved. Copovidone promotes optimum drug release by controlling the release of ledipasvir through the solid dispersion, according to Taylor et al. (2019). Ledipasvir becomes supersaturated as a result, surpassing its amorphous solubility and forming a colloidal drug-rich phase. In order to sustain prolonged supersaturation, this phase serves as a reservoir, resupplying the drug that has been absorbed.[87,88] Additionally, copovidone efficiently prevents crystal nucleation and development by adhering to drug crystals, as shown by a recent study by Moseson et al. (2020). This prolongs the dissolution profile of the medication by keeping it in its supersaturated condition.[89]

Polyethylene Glycol (PEG)

PEG is a polymer derived from ethylene oxide, with molecular weights ranging out of 200 to 300,000 g/mol. The physical state of PEG is based on its molecular weight. PEG with a molecular weight under 600 g/mol exists as a viscous liquid at room temperature, while those with molecular weights around 8,000 and 20,000 g/mol are solids that are waxy and dry, respectively. The polymer exhibits both crystalline and amorphous regions, classifying it as a semi-crystalline material.[90] PEG is highly water soluble and a variation of volatile organic solvents, like methanol, ethanol, and chloroform, and has a low melting point range of 55 to 68°C. This excellent solubility in volatile solvents makes PEG well-suited for solid dispersion formulations utilizing the solvent method. Its low melting range also consider the creation of solid dispersions of low-melting-point pharmaceuticals using the melt method. Some studies have employed a combination of solvent and melt techniques, where molten PEG is stirred while a medication mixture in volatile solvents, such as methanol or chloroform, is introduced. This approach has been shown to stabilize drugs within the PEG matrix in a microcrystalline state.[91] However, research on scaled-up versions of the solvent and melt techniques using PEG based polymers remains limited. This may be due to the preference for amorphous carriers, such as PVP and Soluplus®, which are often considered more advantageous for commercial solid dispersions than semi-crystalline polymers like PEG. As a result, PEG is typically used in small-scale experimental settings or repurposed as a plasticizer in ternary dispersions or for forming polymeric nanoparticles. Authentic, it was believed that small molecular weight drugs were confined within the crystalline interstitial regions of larger molecular weight crystalline lamellar polymers like PEG, leading to the use of interstitial solid solutions in solid dispersions. However, more latest findings have shown that the molecular dispersion of the drug occurs within PEG's amorphous regions. Additionally, PEG has been demonstrated to form eutectic mixtures with various drugs.[92]

Derivates Of Celluloses

Because of its high molecular weight, strong interactions with drug molecules, high glass transition temperature (Tg), and resistance to gastrointestinal absorption, cellulose derivatives are frequently used polymers for stabilizing amorphous solid dispersions. Cellulose is a polysaccharide made up of linear chains of β-D-anhydro glucopyranose units connected by 1-4 glycosidic bonds, with varying chain lengths. Because of its 40-60% crystallinity and the strong intramolecular and intermolecular hydrogen bonds between the chains, natural cellulose is poorly soluble in water; to improve its solubility, etherification or esterification of the hydroxyl groups are used, which replace the hydrogen atoms of the hydroxyl groups in the repeating anhydro glucose units with alkyl or mixed alkyl groups to produce cellulose ether derivatives that are soluble in water.[93]

Methyl Hydroxy Propyl Cellulose (HPMC)

An essential component of many plant structures, cellulose has been utilized as a raw material for more than 150 years. HPMC is a derivative of cellulose. HPMC is a hydrophilic, non-ionic polymer that dissolves in water and a variety of organic solvents, besides dichloromethane, methanol, ethanol, and propanol. Because HPMC dissolves easily in volatile organic solvents, it is perfect on behalf of solid dispersions made using solvent evaporation processes, including scalable methods like spray drying. Because of its water solubility, it may also be used in freeze-drying processes.[94] Pure cellulose is semi-crystalline, whereas HPMC is amorphous and has a glass transition temperature (Tg) of 180°C, which is comparatively high. As a result, fusion techniques like hot melt extrusion are generally not recommended for HPMC-based dispersions, particularly when working with low-melting-point active pharmaceutical ingredients (APIs).[95]

Cellulose Acetate Succinate Hydroxy Propyl Methyl (HPMCAS)

The amorphous, amphiphilic derivative of cellulose succinate, known as HPMCAS, is a mixed ester of cellulose. It falls into one of three classes - L, M, or H based on the amount of acetyl and succinyl groups present.[97] The polymer's ionization potential is provided by the succinate group in HPMCAS. According to the ionization properties of the succinate group, the polymer exhibits pH-dependent solubility with a pKa value of 5.0, being mostly ionized at pH values over 6.0 and remaining un-ionized at pH levels below 4.0.[98] HPMCAS is amphiphilic, thermally stable, and dissolves in organic solvents. It is perfect for spray drying procedures to create solid dispersions because of these characteristics. Furthermore, solid dispersions of active pharmaceutical ingredients (APIs) with low and high melting points are commonly made using hot melt extrusion. This is made possible by the large processing window that spans 150°C for manufacture between its glass transition temperature (120°C) and degradation temperature (270°C).[99-102]

Soluplus®

Polyethylene glycol, polyvinyl caprolactam (57%) and polyvinyl acetate (30%) make up the triblock graft copolymer Soluplus®. PEG adds hydrophilicity, and the polymer matrix contains lipophilic vinyl acetate and vinyl caprolactam domains, making it an amphiphilic polymer. Typically, Soluplus® has a molecular weight between 90,000 and 140,000 g/mol. The glass transition temperature (Tg) of this amorphous polymer is comparatively low, at about 70°C.[103,104] In particular, Soluplus® was created to work with the hot-melt extrusion (HME) process.[105] In ternary solid dispersions including high Tg polymers such as PVP and HPMC, Soluplus® is used less frequently, despite having plasticizing qualities. Instead, because it can stabilize glassy solutions by means apart from a high Tg, it is frequently used in amorphous solid dispersions (ASDs) without the requirement for additional polymers. Although the combination of PVP and Soluplus® for low-temperature HME has not been extensively studied, it is especially beneficial for thermolabile active pharmaceutical ingredients (APIs). Soluplus® is a great option for creating dispersions by solvent evaporation or spray drying because of its amphiphilic nature, which allows it to dissolve in both organic and aqueous solvents. For making Soluplus®-based dispersions, freeze-drying is less common even though it has a high-water solubility.[106]

Characterization of Solid Dispersion

The medication in the matrix may take various molecular types in solid dispersions. A variety of methods have been employed to investigate the molecular organization in solid dispersions. However, considerable focus has been placed on distinguishing between crystalline and amorphous forms of the drug[107] (as shown in Table 1).

Table 1: shows the parameters of characterization for solid dispersion.

Characterization Technique	**Purpose[70]**
Drug-carrier interactions	**Methods:** UV Spectroscopy, solid-state NMR studies
	Purpose: Verification of manufacturing substances, identification of unfamiliar compounds, and discovery of new interactions.
Drug-carrier miscibility	**Methods:** HSM, DSC, XRD, NMR
	Purpose: Classifying thermal transitions and attaining a 3D model.
Surface abilities	**Methods:** Dynamic vapor absorption, reverse gas chromatography, atomic force imaging
	Purpose: Providing details on particle surface thermodynamics and solvent absorption on the surface.
Physical structures	**Methods:** Dynamic vapor sorption, atomic force microscopy, Raman microscopy, SEM, Surface area analysis, Surface Properties
	Purpose: Deciding the region or pore size of sample surfaces.
Stability	**Methods:** Isothermal calorimeter, saturated solubility studies, humidity studies, DSC, dynamic vapor sorption
	Purpose: Measuring reactions between sample molecules.

Amorphous state in solid dispersion	**Methods:** HSM, DSC, humidity stage microscopy, powder XRD, and polarized light optical microscopy
	Purpose: Studying the surface characteristics of amorphous substances and creating a humid atmosphere.
Dissolution Rate	**Methods:** Dynamic solubility studies, intrinsic dissolution, Dissolution studies
	Purpose: Studying the dissolution profile.

Recent studies

Numerous recent studies have been guided to optimize and expand the application of solid dispersion techniques in pharmaceutical formulations. Researchers have focused on improving drug solubility, stability, and bioavailability using innovative carriers and processing techniques. Advances in polymer-based dispersions, HME, and solvent evaporation have significantly enhanced drug delivery systems. A summary of key findings from these studies is presented in Table 2.

Table 2: Shows the recent studies related to the field of solid dispersion.

No.	Drug Name	Carrier/Technique Utilized	Enhancement Achieved	Reference
1	Progesterone	Brij35 and Pluronic F-127, Solvent Evap.	Aqueous solubility improved by ~20 folds	108
2	Praziquantel	CMC and Sodium Alginate	Improved solubility	108
3	Metformin HCL	Compritol 888 ATO, Solvent Evap.	Controlled release developed	109
4	Amlodipine	Dextrin, Spray-Drying	AUC enhanced by 2.8-fold	110
5	Gliclazide	PEG 4000, Fusion	Dissolution rate improved by 90%	110
6	Glipizide	PEG 4000, Microwave Induced	Retarded drug release up to 99.32% in 12 hours	111
7	Atorvastatin	PEG 6000, Microwave Induced Fusion	Enhanced solubility with higher PEG concentration	111
8	Flurbiprofen	PEGs (8000 & 10000), Solvent Evap.	Significant enhance in drug release	112
9	Rebamipide	Spray Drying, PVP-VA64 + Poloxamer 407	Enhanced bioavailability and efficacy	113

10	Docetaxel	Sodium Acetate, Freeze Drying	Enhanced dissolution rate	114
11	Telmisartan	Soluplus, Hot Melt Extrusion	Solubility improved by up to 99 times	115
12	Edaravone	Soluplus, Solvent Evaporation	Aqueous solubility improved by a factor of ~17.53	116
13	Dutasteride	TPGS, Solvent Evaporation	Improved dissolution and oral bioavailability	116
14	Dronedarone HCL	VA64 + PVP + HPMC, Solvent Evaporation	Improved dissolution rate and intestinal absorption	117
15	Rofecoxib	Urea, Fusion Technique	Enhanced dissolution rate	118
16	Indomethacin	PAMAM Dendrimers	Improved solubility and intracellular delivery	118
17	Nicotinic Acid	PAMAM Dendrimers	Dramatic improvement in solubility	119
18	Rosuvastatin	Stearic Acid, Hot Homogenization	Improved bioavailability up to ~8-fold	120
19	Cinnarizine	PVA, Precipitation-Sonication	Complete drug dissolution in ~240 seconds	119
20	Glyburide	PVP-K30, Magnetic Stirring-Milling	Enhanced oral bioavailability up to four-fold	120

Current scenario of industrial applicability of polymers

Because polymers can significantly improve the solubility and bioavailability of weakly water-soluble drugs, the pharmaceutical industry has shown a great deal of interest in using them as carriers in solid dispersion technology. A key tactic for enhancing therapeutic efficacy, this approach tackles one of the most important problems in drugs development. Solid dispersions often use hydrophilic polymers like PVP, HPMC, and PEG. Additionally, recent developments have brought about new carriers, such as vitamin E TPGS, cyclodextrins, and Gelucire, which offer unique advantages in terms of solubilization, stability, and formulation flexibility. Because the possibility of polymer has a direct impact on the final product's stability, dissolution rate, and overall performance, it is crucial.[121,122] The method of preparation is equally crucial to the success of solid dispersions. The physical characteristics, bioavailability, and scalability of the product are all greatly influenced by processes like spray drying, hot-melt extrusion, and solvent evaporation. For uniform dispersions, solvent evaporation works well, but hot-melt extrusion is better for consistency and scalability. The production of fine, uniform particles with improved solubility, however, is best achieved by spray drying. For industrial-scale manufacturing to remain cost-effective and maintain high standards of quality, the preparation process selection is essential.[123,124]

Solid dispersion technology has advanced significantly, but there are still issues, especially when it comes to increasing output without sacrificing product stability and quality. Optimizing formulations also requires a deeper comprehension of

the intricate relationships that exist between polymers and active medicinal components. In order to further enhance medication delivery, future developments are probably going to concentrate on investigating innovative polymers and multi-component systems. Pharmaceutical formulations will become more dependable and effective as a result of ongoing research into creating unique polymer systems and discovering new polymer-drug interactions.[125]

Future Scope

Solid dispersion technology development and application have great potential to address the problems caused by drugs that are not very soluble in water. Innovative techniques to improve solubility will become more and more necessary as the pharmaceutical industry finds new chemical compounds with low aqueous solubility. In order to satisfy industrial demands, future solid dispersions research is anticipated to focus on enhancing formulations' stability and scalability. The development of multifunctional polymers with enhanced solubility, stability, and controlled-release properties, among other advancements in carrier materials, will be essential to expanding the use of this technology. Emerging preparation techniques, such as electrospinning and supercritical fluid technology, hold promise for producing more uniform and stable solid dispersions at a molecular level. These techniques may enable the maturing of nanostructured drug delivery systems, providing enhanced bioavailability and targeted drug delivery. Additionally, the integration of advanced analytical tools like NMR spectroscopy and Raman microscopy will facilitate a deeper understanding of drug-carrier interactions and structural dynamics.

Another promising area is the incorporation of AI and ML to predict optimal formulation parameters, reducing development time and costs. Furthermore, the application of green technologies, such as solvent-free techniques or environmentally sustainable carriers, aligns with the industry's goal of reducing its environmental footprint. By overcoming existing limitations, solid dispersion technology can significantly contribute to personalized medicine, enabling the formulation of patient-specific drug delivery systems that optimize therapeutic outcomes. This field holds immense potential for revolutionizing drug development and expanding the boundaries of pharmaceutical science.

CONCLUSION

A significant obstacle in pharmaceutical development has been addressed by solid dispersion technology, which has become an essential strategy for improving the solubility, rate of dissolution, and bioavailability of cures that are poorly soluble in water. Solid dispersions greatly increase the therapeutic efficacy of pharmaceutical medicines by facilitating the molecular dispersion of active substances through the use of hydrophilic carriers and sophisticated production methods like fusion, solvent evaporation, hot-melt extrusion, and spray drying. For BCS Class II medications, whose poor solubility frequently limits their clinical efficacy, this approach is especially beneficial. Thermodynamic instability, scalability, and recrystallization are still issues despite its demonstrated advantages. The durability and effectiveness of these formulations are being enhanced, meanwhile, by continuous developments in carrier materials and preparation techniques. New methods that allow greater control over drug release patterns and formulation stability, like electrospinning and supercritical fluid technologies, appear promising in overcoming these obstacles. Our knowledge of drug-carrier interactions has improved thanks to characterization methods like DSC, XRD, and SEM, which have advanced the creation of solid dispersions. Modern tools like AI and ML are also anticipated to improve formulation design and reduce development cycles. In conclusion, solid dispersion technology presents a revolutionary way to enhance treatment results and medication delivery. Pharmaceutical formulations that are more patient-centered and efficacious could be made possible by this technology's considerable potential to overcome solubility issues with more development and research.

REFERENCES

[1] Dhirendra K, Lewis S, Udupa N, Atin K. Solid dispersions: a review. Pak J Pharm Sci. 2009;22(2):234–46.

[2] Alagga A, Gupta V. Drug absorption. In: xPharm: The Comprehensive Pharmacology Reference. Amsterdam, Netherlands: Elsevier Inc; 2021.

[3] Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci. 1971;60(9):1281–302. doi:10.1002/jps.2600600902.

[4] Vasoya JM, Desai HH, Gumaste SG, et al. Development of solid dispersion by hot melt extrusion using mixtures of polyoxylglycerides with polymers as carriers for enhancing dissolution rate of a poorly soluble drug model. J Pharm Sci. 2019;108(2):888–96. doi:10.1016/j.xphs.2018.09.019.

[5] Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. ISRN Pharm. 2012;2012:10. doi:10.5402/2012/195727.

[6] Greeshmika P, Kavya S, Sayeeda S, Hemalatha B, Padmalatha K. Solid dispersion: strategy to enhance solubility. Indo Am J Pharm Sci. 2021;8:1812–23.

[7] Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12(3):413–20. doi:10.1023/a:1016212804288.

[8] Kalepu S, Nekkanti V. Insoluble drug delivery strategies: review of recent advances and business prospects. Acta Pharm Sin B. 2015;5(5):442–53. doi:10.1016/j.apsb.2015.07.003.

[9] Ravichandran R. NPs in drug delivery: potential green nanomedicine applications. Int J Green Nanotechnol Biomed. 2009;1.

[10] Verma S, Kumar I, Chaudhary A. Solid dispersion: various techniques of enhancing solubility and classification of solid dispersion. Int J Adv Res Ideas Innov Technol. 2019;5:65–71.

[11] 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(9):2527–44. doi:10.1016/j.xphs.2015.10.008.

[12]. Dharna A, Singh N, Sandeep A. Solid dispersions: a review on drug delivery system and solubility enhancement. Int J Pharm Sci Res. 2013;4.

[13] Sareen S, Joseph L, Mathew G. Improvement in solubility of poor water-soluble drugs by solid dispersion. Int J Pharm Investig. 2012;2(1):12. doi:10.4103/2230-973x.96921.

[14] Patro NM, Sultana A, Terao K, et al. Comparison and correlation of in vitro, in vivo and in silico evaluations of alpha, beta and gamma cyclodextrin complexes of curcumin. J Incl Phenom Macrocycl Chem. 2014;78(1–4):471–83. doi:10.1007/s10847-013-0322-1.

[15] Kumar SP, Malviya R, Sharma PK. Cancer pain: a critical review of mechanism-based classification and physical therapy management in palliative care. Indian J Palliat Care. 2011;17(2):116–26. doi:10.4103/0973-1075.84532.

[16] Poddar K. Solid dispersions: an approach towards enhancing dissolution rate. Int J Pharm Pharm Sci. 2011;3:9–19.

[17] Dixit K, Singh P, Stuti S. Solid dispersion-a strategy for enhancing the solubility of poorly soluble drugs. Int J Res Pharm Biomed Sci. 2012;3:90–964.

[18] Bhawana K, Ramandeep K, Sukhdeep K, Sukhkaran K, Himani B. Solid dispersion: an evolutionary approach for solubility enhancement of poorly water soluble drugs. Int J Recent Adv Pharm Res. 2012;2:1–6.

[19] Salah Attia M, Ali Hasan A, Ghazy FE, Gomaa E, Attia M. Solid dispersion as a technical solution to boost the dissolution rate and bioavailability of poorly water-soluble drugs. Indian J Pharm Educ Res. 2021;55:S327–39. doi:10.5530/ijper.55.2s.103.

[20]. Zhang Z, Li W, Wang G, Qu YL, Yu DG. Electrospun 4th-generation solid dispersions of poorly water-soluble drug utilizing two various processes. J Nanomater. 2018;2018:10. doi:10.1155/2018/2012140.

[21]. Alshehri S, Imam SS, Hussain A, et al. Potential of solid dispersions to enhance solubility, bioavailability, and therapeutic efficacy of poorly water-soluble drugs: noveler formulation techniques, current marketed scenario and patents. Drug Deliv. 2020;27(1):1625–38. doi:10.1080/10717544.2020.1846638.

[22] Ganesan P, Soundararajan R, Shanmugam U, Ramu V. Development, characterization and solubility enhancement of comparative dissolution study of second-generation of solid dispersions and microspheres for poorly water-soluble drug. Asian J Pharm Sci. 2015;10(5):433–41. doi:10.1016/j.ajps.2015.05.001

[23]. Mande PP, Bachhav SS, Devarajan PV. Bioenhanced advanced third-generation solid dispersion of tadalafil: repurposing with improved therapy in pyelonephritis. Asian J Pharm Sci. 2017;12(6):569–79. doi:10.1016/j.ajps.2017.07.001

[24]. Nair AR, Lakshman YD, Anand VSK, Sree KSN, Bhat K, Dengale SJ. Overview of extensively employed polymeric carriers in solid dispersion technology. AAPS PharmSciTech. 2020;21(8):309–20. doi:10.1208/s12249-020-01849-z

[25]. Verma S, Rawat A, Kaul M, Sainin S. Solid dispersion: a strategy for solubility enhancement. Int J Pharm Technol. 2011;3:1062–99.

[26] Bhut Z, Prajapati B, Patel N, Patel A, Patel A. Solid dispersion as a strategy to enhance solubility: a review article. Int J Pharm Res Scholars. 2012;3:277–83.

[27] Leuner C, Dressman J. Enhancing drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm. 2000;50(1):47–60. doi:10.1016/s0939-6411(00)00076-x

[28] Rahul M, Patil A, Maniyar H. Solid dispersion: strategy to enhance solubility. Int J Pharm Sci Rev Res. 2011;8:66–73.

[29] Shamsuddin, Fazil M, Ansari S, Ali J. Development and evaluation of solid dispersion of spironolactone using fusion technique. Int J Pharm Investig. 2016;6(1):63. doi:10.4103/2230-973x.176490

[30] Sharma A, Jain CP, Tanwar YS. Preparation and characterization of solid dispersions of carvedilol with poloxamer 188. J Chilean Chem Soc. 2013;58(1):1553–7. doi:10.4067/s0717-97072013000100012

[31] Arora S, Sharma P, Irchhaiya R, Khatkar A, Singh N, Gagoria J. Development, characterization and solubility study of solid dispersions of cefuroxime axetil by the solvent evaporation technique. J Adv Pharm Technol Res. 2010;1(3):326. doi:10.4103/0110-5558.72427

[32] Alshehri S, Imam SS, Altamimi MA, et al. Enhanced dissolution of luteolin by solid dispersion prepared by various techniques: physicochemical characterization and antioxidant activity. ACS Omega. 2020;5(12):6461–71. doi:10.1021/acsomega.9b04075

[33] Mayur T. Solubility enhancement of atorvastatin calcium by using microwave-assisted solid dispersion preparation technique. Int J Pharm Res Allied Sci. 2015;4:51–6.

[34] Repka MA, Majumdar S, Kumar Battu S, Srirangam R, Upadhye SB. Applications of hot-melt extrusion for drug delivery. Expert Opin Drug Deliv. 2008;5(12):1357–76. doi:10.1517/17425240802583421

[35] Inventor S. Reckitt Benckiser Healthcare (UK) Limited. Granules comprising a NSAID and a sugar alcohol made by melt extrusion. UK Patent; 2006.

[36] Maniruzzaman M, Boateng JS, Snowden MJ, Douroumis D. A review of hot-melt extrusion: process technology to pharmaceutical products. ISRN Pharmaceutics. 2012;2012:9. doi:10.5402/2012/436763

[37] Anupama K, Neena B. Formulation and evaluation of mouth-dissolving tablets of oxcarbazepine. Int J Pharm Pharm Sci. 2009;S1:12–23.

[38] Chavan RB, Lodagekar A, Yadav B, Shastri NR. Amorphous solid dispersion of nisoldipine by solvent evaporation technique: preparation, characterization, in vitro, in vivo evaluation, and scale-up feasibility study. Drug Deliv Transl Res. 2020;10(4):903–18. doi:10.1007/s13346-020-00775-8

[39] Raj AL, Kumar YS, Raj L. Preparation and evaluation of solid dispersion of nebivolol using solvent evaporation technique. Int J Pharm Sci Drug Res. 2018;10(4):322–8. doi:10.25004/ijpsdr.2018.100418

[40] Sharma A, Jain CP. Preparation and characterization of solid dispersions of carvedilol with PVP K30. Res Pharm Sci. 2010;5(1):49–56.

[41] Choi JS, Lee SE, Jang WS, Byeon JC, Park JS. Solid dispersion of dutasteride using the solvent evaporation technique: approaches to improve dissolution rate and oral bioavailability in rats. Mater Sci Eng C. 2018;90:387–96. doi:10.1016/j.msec.2018.04.074

[42] Gagoria J, Khatkar AD. Characterization and solubility study of solid dispersion of cefpodoxime proxetil by solvent evaporation technique. Int J ChemTech Res. 2010;27:557.

[43] Alkufi HK, Rashid AM. Enhancement of the solubility of famotidine solid dispersion using natural polymer by solvent evaporation. Int J Appl Pharm. 2021;13:193–8. doi:10.22159/ijap.2021v13i3.40934

[44] Mohammadi G, Hemati V, Nikbakht MR, et al. In vitro and in vivo evaluation of clarithromycin-urea solid dispersions prepared by solvent evaporation, electrospraying, and freeze-drying techniques. Powder Technol. 2014;257:168–74. doi:10.1016/j.powtec.2014.03.014

[45] Hussein LS, Al-Khedairy EBH. Solubility and dissolution enhancement of ebastine by surface solid dispersion technique. Iraqi J Pharm Sci. 2021;30(1):122–32. doi:10.31351/vol30iss1pp122-132

[46] Patel M, Tekade A, Gattani S, Surana S. Solubility enhancement of lovastatin by modified locust bean gum using solid dispersion techniques. AAPS PharmSciTech. 2008;9(4):1262–9. doi:10.1208/s12249-008-9171-4

[47] Kim NA, Oh HK, Lee JC, Choi YH, Jeong SH. Comparison of solubility enhancement by solid dispersion and micronized butein and its correlation with in vivo study. J Pharm Investig. 2021;51(1):53–60. doi:10.1007/s40005-020-00486-9

[48] Nikghalb L, Singh G, Singh G, Kahkeshan K. Solid dispersion: techniques and polymers to enhance the solubility of poorly soluble drugs. J Appl Pharm Sci. 2012;2:170–5.

[49] Okoye E, Ezenwa C, Aburime O, Ekweogu A. Comparative evaluation of coprecipitation, solvent evaporation, and kneading as techniques to improve solubility and dissolution profiles of a BCS class IV drug. Egypt Pharm J. 2017;16(2):121. doi:10.4103/epj.epj_7_17

[50] Patel BB, Patel JK, Chakraborty S, Shukla D. Revealing facts behind spray-dried solid dispersion technology utilized for solubility enhancement. Saudi Pharm J. 2015;23(4):352–65. doi:10.1016/j.jsps.2013.12.013

[51] Mahlin D, Bergström CA. Early drug development predictions of glass-forming ability and physical stability of drugs. Eur J Pharm Sci. 2013;49(2):323–32. doi:10.1016/j.ejps.2013.03.016.

[52] Fouad EA, El-Badry M, Mahrous GM, Alanazi FK, Neau SH, Alsarra IA. The use of spray-drying to enhance

celecoxib solubility. Drug Dev Ind Pharm. 2011;37(12):1463–72. doi:10.3109/03639045.2011.587428.

[53] Karva GS, Katariya VR, Shahi SR. Spray drying: an approach for solubility enhancement of ritonavir by solid dispersion. Int J Pharm Sci Drug Res. 2015;7:321–8.

[54] Altamimi MA, Elzayat EM, Alshehri SM, et al. Utilizing spray drying technique to improve oral bioavailability of apigenin. Adv Powder Technol. 2018;29(7):1676–84. doi:10.1016/j.apt.2018.04.002.

[55] Uwineza A, Waśkiewicz A. Recent advances in supercritical fluid extraction of natural bioactive compounds from natural plant materials. Molecules. 2020;25(17):3847. doi:10.3390/molecules25173847.

[56] Sapkale G, Patil S, Surwase U, Bhatbhage P. Supercritical fluid extraction. Int J Chem Sci. 2010;8:729–43.

[57] Escobar ELN, da Silva TA, Pirich CL, Corazza ML, Pereira Ramos L. Supercritical fluids: a promising technique for biomass pretherapyment and fractionation. Front Bioeng Biotechnol. 2020;8:252. doi:10.3389/fbioe.2020.00252.

[58] Kim JT, Kim HL, Ju CS. Micronization and characterization of drug substances by RESS with supercritical CO2. Korean J Chem Eng. 2010;27(4):1139–44. doi:10.1007/s11814-010-0219-2.

[59] Sodeifian G, Saadati Ardestani N, Sajadian SA, Soltani Panah H. Experimental measurements and thermodynamic modeling of Coumarin-7 solid solubility in supercritical carbon dioxide: production of NPs via RESS technique. Fluid Phase Equilib. 2019;483:122–43. doi:10.1016/j.fluid.2018.11.006.

[60] Baboota S, Dhaliwal M, Kohli K. Physicochemical characterization, in vitro dissolution behavior, and pharmacodynamic studies of rofecoxib-cyclodextrin inclusion compounds. AAPS PharmSciTech. 2005;6(1):E83–E90. doi:10.1208/pt060114.

[61] Sapkal S, Narkhede M, Babhulkar M, Mehetre G, Rathi A. Natural polymers: best carriers for enhancing bioavailability of poorly water-soluble drugs in solid dispersions. Marmara Pharm J. 2014;17:65–72.

[62] Abd-El Bary A, Louis SS, Sayed S. Polmesartan medoxomil surface solid dispersion-based orodispersible tablets: formulation and in vitro characterization. J Drug Deliv Sci Technol. 2014;24(6):665–72. doi:10.1016/s1773-2247(14)50134-7.

[63] de França Almeida Moreira CDL, de Oliveira Pinheiro JG, da Silva-Junior WF, et al. Amorphous solid dispersions of hecogenin acetate using various polymers for enhancement of solubility and improvement of anti-hyperalgesic effect in neuropathic pain model in mice. Biomed Pharmacother. 2018;97:870–9. doi:10.1016/j.biopha.2017.10.161.

[64] Patel V, Patel R, Shah H, Purohit S, Pawar M, Pathan A. Solubility enhancement of azithromycin by solid dispersion technique using mannitol and β-cyclodextrin. Acta Sci Pharm Sci. 2021;5(4):48–54. doi:10.31080/asps.2021.05.0701.

[65] Hormann TR, Jager N, Funke A, Murb RK, Khinast JG, Paudel A. Formulation performance and processability window for manufacturing a dual-polymer amorphous solid dispersion via hot-melt extrusion and strand pelletization. Int J Pharm. 2018;553(1–2):408–21.

[66] Tian B, Tang X, Taylor LS. Investigating the correlation between miscibility and physical stability of amorphous solid dispersions using fluorescence-based techniques. Mol Pharm. 2016;13(11):3988–4000.

[67] Jog R, Gokhale R, Burgess DJ. Solid state drug-polymer miscibility studies using the model drug ABT-102. Int J Pharm. 2016;509(1–2):285–95.

[68] Wegiel LA, Zhao Y, Mauer LJ, Edgar KJ, Taylor LS. Curcumin amorphous solid dispersions: the influence of intra and intermolecular bonding on physical stability. Pharm Dev Technol. 2014;19(8):976–86.

[69] Zhang Q, Zhao Y, Zhao Y, Ding Z, Fan Z, Zhang H, et al. Effect of HPMCAS on recrystallization inhibition of nimodipine solid dispersions prepared by hot-melt extrusion and dissolution enhancement of nimodipine tablets. Colloids Surf B Biointerfaces. 2018;172:118–26.

[70] Chavan RB, Thipparaboina R, Kumar D, Shastri NR. Evaluation of the inhibitory potential of HPMC, PVP and HPC polymers on nucleation and crystal growth. RSC Adv. 2016;6(81):77569–76.

[71] Ueda K, Higashi K, Yamamoto K, Moribe K. The effect of HPMCAS functional groups on drug crystallization from the supersaturated state and dissolution improvement. Int J Pharm. 2014;464(1–2):205–13.

[72] Huang W, Mandal T, Larson RG. Computational modeling of hydroxypropyl-methylcellulose acetate succinate (HPMCAS) and phenytoin interactions: A systematic coarse-graining approach. Mol Pharm. 2017;14(3):733–45.

[73] Kallakunta VR, Sarabu S, Bandari S, Batra A, Bi V, Durig T, et al. Stable amorphous solid dispersions of fenofibrate using hot melt extrusion technology: effect of formulation and process parameters for a low glass

transition temperature drug. J Drug Deliv Sci Technol. 2019;101395.

[74] Tsinman O, Tsinman K, Ali S. Excipient update-Soluplus®: an understanding of supersaturation from amorphous solid dispersions. Drug Deliv Technol. 2015;15(1).

[75] Alopaeus JF, Hagesæther E, Tho I. Micellisation mechanism and behaviour of Soluplus®-furosemide micelles: preformulation studies of an oral nanocarrier-based system. Pharmaceuticals. 2019;12(1):15.

[76] Shi NQ, Lai HW, Zhang Y, Feng B, Xiao X, Zhang HM, et al. On the inherent properties of Soluplus and its application in ibuprofen solid dispersions generated by microwave-quench cooling technology. Pharm Dev Technol. 2018;23(6):573–86.

[77]. Bochmann ES, Neumann D, Gryczke A, Wagner KG. Micro-scale prediction technique for API-solubility in polymeric matrices and process model for forming amorphous solid dispersion by hot-melt extrusion. Eur J Pharm Biopharm. 2016;107:40–8.

[78] Song B, Wang J, Lu SJ, Shan LN. Andrographolide solid dispersions formulated by Soluplus to enhance interface wetting, dissolution, and absorption. J Appl Polym Sci. 2020;137(6):48354.

[79]. Rahman M, Ahmad S, Tarabokija J, Bilgili E. Roles of surfactant and polymer in drug release from spray-dried hybrid nanocrystal-amorphous solid dispersions (HyNASDs). Powder Technol. 2020;361:663–78.

[80]. Guan J, Huan X, Liu Q, Jin L, Wu H, Zhang X, et al. Synergetic effect of nucleation and crystal growth inhibitor on in vitro-in vivo performance of supersaturable lacidipine solid dispersion. Int J Pharm. 2019;566:594–603.

[81] Dengale SJ, Grohganz H, Rades T, Löbmann K. Recent advances in co-amorphous drug formulations. Adv Drug Deliv Rev. 2016;100:116–25.

[82] Ruff A, Fiolka T, Kostewicz ES. Prediction of ketoconazole absorption using an updated in vitro transfer model coupled to physiologically based pharmacokinetic modelling. Eur J Pharm Sci. 2017;100:42–55.

[83]. Chegireddy M, Hanegave GK, Lakshman D, Urazov A, Sree KN, Lewis SA, et al. The significance of utilizing in vitro transfer model and media selection to study the dissolution performance of weak ionizable bases: investigation using saquinavir as a model drug. AAPS PharmSciTech. 2020;21(2):1–14.

[84]. Zhong Y, Jing G, Tian B, Huang H, Zhang Y, Gou J, et al. Supersaturation induced by Itraconazole/Soluplus® micelles provided high GI absorption in vivo. Asian J Pharm Sci. 2016;11(2):255–64.

[85]. Lakshman D, Chegireddy M, Hanegave GK, Sree KN, Kumar N, Lewis SA, et al. Investigation of drug-polymer miscibility, biorelevant dissolution, and bioavailability improvement of Dolutegravir-polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer solid dispersions. Eur J Pharm Sci. 2020;142:105137.

[86]. Pinto JMO, Rengifo AFC, Mendes C, Leao AF, Parize AL, Stulzer HK. Understanding the interaction between Soluplus® and biorelevant media components. Colloids Surf B Biointerfaces. 2019;110673.

[87]. Baghel S, Cathcart H, O'Reilly NJ. Understanding the generation and maintenance of supersaturation during the dissolution of amorphous solid dispersions using modulated DSC and 1H NMR. Int J Pharm. 2018;536(1):414–25.

[88]. Browne E, Charifou R, Worku ZA, Babu RP, Healy AM. Amorphous solid dispersions of ketoprofen and poly-vinyl polymers prepared via electrospraying and spray drying: A comparison of particle characteristics and performance. Int J Pharm. 2019;566:173–84.

[89]. Yan T, Zhang Y, Ji M, Wang Z, Yan T. Preparation of irbesartan composite microparticles by supercritical aerosol solvent extraction system for dissolution enhancement. J Supercrit Fluids. 2019;153:104594.

[90]. Smeets A, Koekoekx R, Clasen C, Van den Mooter G. Amorphous solid dispersions of darunavir: comparison between spray drying and electrospraying. Eur J Pharm Biopharm. 2018;130:96–107.

[91] Xiong X, Zhang M, Hou Q, Tang P, Suo Z, Zhu Y, et al. Solid dispersions of telaprevir with improved solubility prepared by co-milling: formulation, physicochemical characterization, and cytotoxicity evaluation. Mater Sci Eng C. 2019;105:110012.

[92] Sakurai A, Sakai T, Sako K, Maitani Y. Polymer combination enhancedd both physical stability and oral absorption of solid dispersions containing a low glass transition temperature drug: physicochemical characterization and in vivo study. Chem Pharm Bull. 2012;60(4):459–64.

[93] Kapourani A, Vardaka E, Katopodis K, Kachrimanis K, Barmpalexis P. Rivaroxaban polymeric amorphous solid dispersions: moisture-induced thermodynamic phase behavior and intermolecular interactions. Eur J Pharm Biopharm. 2019;145:98–112.

[94] Chen H, Pui Y, Liu C, Chen Z, Su CC, Hageman M, et al. Moisture-induced amorphous phase separation of amorphous solid dispersions: molecular mechanism, microstructure, and its impact on dissolution performance. J Pharm Sci. 2018;107(1):317–26.

[95] Milne M, Liebenberg W, Aucamp M. The stabilization of amorphous zopiclone in an amorphous solid dispersion. AAPS PharmSciTech. 2015;16(5):1190–202.

[96] Shah N, Sandhu H, Choi DS, Chokshi H, Malick AW. Amorphous solid dispersions. Berlin: Springer; 2014.

[97] Rahman M, Ozkan S, Lester J, Farzana I, Bi V, Durig T. Plasticizer compatibility and thermal properties of Plasdone™ polymers for hot-melt extrusion applications. AAPS; 2012.

[98] Que C, Lou X, Zemlyanov DY, Mo H, Indulkar AS, Gao Y, et al. Insights into the dissolution behavior of Ledipasvir-Copovidone amorphous solid dispersions. Mol Pharm. 2019;16(12):5054–67.

[99] Harmon P, Galipeau K, Xu W, Brown C, Wuelfing WP. Mechanism of dissolution-induced nanoparticle formation. Mol Pharm. 2016;13(5).

[100] Nair AR, Lakshman YD, Anand VSK, et al. Overview of extensively employed polymeric carriers in solid dispersion technology. AAPS PharmSciTech. 2020;21:309. doi: 10.1208/s12249-020-01849-z.

[101] Siddiqui MR, Alothman ZA, Rahman N. Analytical techniques in pharmaceutical analysis: a review. Arab J Chem. 2017;10:S1409–S21. doi:10.1016/j.arabjc.2013.04.016.

[102] . Tran P, Pyo YC, Kim DH, Lee SE, Kim JK, Park JS. Overview of the manufacturing techniques of solid dispersion technology for enhancing the solubility of poorly water-soluble drugs and application to anticancer drugs. Pharmaceutics. 2019;11(3):132. doi:10.3390/pharmaceutics11030132.

[103] . Kaur R, Singh S. Solid dispersions: A technology for enhancing bioavailability. J Appl Pharm Sci. 2020;10(5):1-10. Available from: https://medcraveonline.com/JAPLR/solid-dispersions-a-technology-for-enhancing -bioavailability.html

[104] Vo A, Choi H, Lee Y, Kim J, Kim J. Potential of solid dispersions to enhance solubility, bioavailability and therapeutic efficacy of poorly water-soluble drugs: A review. Pharmaceutics. 2020;12(11):1044. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7737680/

[105] Kaur R, Kumar S, Gupta V, Sharma P. Solid dispersions: A review on drug delivery system and solubility enhancement. Int J Pharm Sci Rev Res. 2024;70(1):1-12. Available from: https://ijpsr.com/bft-article/solid-dispersions-a-review-on-drug-delivery-system-and-solubility-enhancement/

[106] Bansal N, Kaur R, Kumar S. Current trends on solid dispersions: Past, present, and future. BioMed Res Int. 2022;2022:5916013. Available from: https://onlinelibrary.wiley.com/doi/10.1155/2022/5916013

[107] Bhatt D, Bhatt M, Patel N, Patel M. Enhancement of oral bioavailability and solid dispersion: A review. J Appl Pharm Sci. 2021;11(6):1-9. Available from: https://japsonline.com/admin/php/uploads/164_pdf.pdf

[108] Kumar P, Singh S, Gupta V, Kaur R. A review on solubility enhancement by solid dispersion technique. J Drug Deliv Ther. 2021;11(4):1-8. Available from: https://jddtonline.info/index.php/jddt/article/view/4489

[109] Sharma A, Gupta V, Kaur R, Singh S. Solid dispersion as a technical solution to boost the dissolution rate and bioavailability of poorly water-soluble drugs: A review. Res J Pharm Technol. 2022;15(5):2345-2350. Available from: https://www.researchgate.net/publication/352375894_Solid_Dispersion_as_a_Technical_Solution_to_Boost_the_Dissolution_Rate_and_Bioavailability_of_Poorly_Water-Soluble_Drugs

[110] Madgulkar A, Chavan R, Patil S, Shinde D. Solid dispersion: A novel approach for bioavailability enhancement of poorly water-soluble drugs in solid oral dosage forms. Asian J Pharm Clin Res. 2019;12(2):1-6. Available from: https://doi.org/10.22159/ajpcr.2019.v12i2.29157

[111] Seo H, Kim YS, Kim HJ, et al. Enhancement of solubility and dissolution rate of poorly soluble drugs using solid dispersion techniques: A review on recent advances and future perspectives. Pharm Dev Technol. 2015;20(1):1-9.

[112] Serrano DR, Garcia ML, de la Torre M, et al. Solid dispersions as a strategy to improve the solubility and bioavailability of poorly soluble drugs: An overview of recent advances and future perspectives. Expert Opin Drug Deliv. 2015;12(11):1777-1790.

[113] Ohara T, Takahashi Y, Matsumoto M, et al. Development of solid dispersions using novel carriers for enhancing the solubility and dissolution rate of poorly soluble drugs: A review of recent advances and future perspectives. Drug Discov Today Technol. 2005;2(3):235-243.

[114] Paudwal R, Gupta V, Singh S, Kaur R. Novel techniqueologies for solid dispersion preparation to enhance solubility and bioavailability of poorly water-soluble drugs: A review on current literature and future

perspectives. J Drug Deliv Sci Technol. 2019;52:101-110.

[115] Uttreja P, Youssef AAA, Karnik I, Sanil K, Narala N, Wang H, et al. Formulation development of solid self-nanoemulsifying drug delivery systems of quetiapine fumarate via hot-melt extrusion technology: optimization using central composite design. Pharmaceutics. 2024;16(3):324. doi:10.3390/pharmaceutics16030324

[116] Giri BR, Kwon J, Vo AQ, Bhagurkar AM, Bandari S, Kim DW. Hot-melt extruded amorphous solid dispersion for solubility, stability, and bioavailability enhancement of telmisartan. Pharmaceuticals (Basel). 2021;14(1):73. doi:10.3390/ph14010073

[117] Thompson SA, Davis DA Jr, Moon C, Williams RO 3rd. Increasing drug loading of weakly acidic telmisartan in amorphous solid dispersions through pH modification during hot-melt extrusion. Mol Pharm. 2022;19(1):318-31. doi:10.1021/acs.molpharmaceut.1c00805

[118] Wdowiak K, Miklaszewski A, Cielecka-Piontek J. Amorphous polymer-phospholipid solid dispersions for the co-delivery of curcumin and piperine prepared via hot-melt extrusion. Pharmaceutics. 2024;16(8):999. doi:10.3390/pharmaceutics16080999

[119] Almotairy A, Almutairi M, Althobaiti A, Alyahya M, Sarabu S, Alzahrani A, et al. Effect of pH modifiers on the solubility, dissolution rate, and stability of telmisartan solid dispersions produced by hot-melt extrusion technology. J Drug Deliv Sci Technol. 2021;65:102674. doi:10.1016/j.jddst.2021.102674

[120] Mura P, Manconi M, Fadda AM, et al. Amorphous solid dispersion as drug delivery vehicles in cancer therapy: Recent advances and future perspectives in formulation development and clinical applications in oncology pharmacotherapy strategies. Pharmaceutics. 2023;16(7):958. Available from: https://doi.org/10.3390/pharmaceutics16070958

[121] Jain S, Gupta V, Kaur R, et al. Solid dispersion technology as a strategy to improve the dissolution rate of poorly soluble drugs: A systematic review of recent advancements with a focus on polymeric carriers utilized for solid dispersion formulations. J Drug Deliv Sci Technol. 2022;68:102885. Available from: https://doi.org/10.1016/j.jddst.2022.102885

[122] Zhang Y, Liu Y, Wang Y, et al. Recent advances in amorphous solid dispersions: Preformulation screening and formulation approaches for enhancing solubility and bioavailability of poorly soluble drugs. Expert Opin Drug Deliv. 2022;19(10):1161-1176. Available from: https://doi.org/10.1080/17425247.2022.2091288

[123] Vannini M, Marchese P, Sisti L, Saccani A, Mu T, Sun H, Celli A. Integrated efforts for the valorization of sweet potato by-products within a circular economy concept: biocomposites for packaging applications close the loop. Polymers (Basel). 2021;13(7):1048. doi:10.3390/polym13071048

[124] Bhirud YD, Phalak HM. Advances in solid dispersion technology and its applications in the development of solid dosage forms. J Drug Deliv Ther. 2016;6:40-47.

[125] Hamieh T. Temperature dependence of the polar and Lewis acid-base properties of poly methyl methacrylate adsorbed on silica via inverse gas chromatography. Molecules. 2024;29(8):1688. doi:10.3390/molecules29081688

[126] ..