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Review Article

Solid dispersion: application and limitations

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Abstract

Solubility and dissolution rate are essential factors in the bioavailability of a drug. The drug must be well-soluble in water to have good bioavailability. Solid dispersion is among the most widely used and effective methods for increasing solubility and releasing inadequately water-soluble medications. Solid dispersion requires the choice of a suitable carrier for the right active pharmaceutical ingredients and the proper techniques for preparing solid dispersions. The reliable dispersion system is designed in various ways to achieve the goal and avoid the accompanying obstacles.

Keywords: solid dispersion, solubility, solvent evaporation, lyophilization, generation, methods

Introduction

During drug discovery and development, it is estimated that a 40% to 70% rate of new chemical entities are delayed or failed. The main reason behind this is biopharmaceutical properties. Poor pharmacokinetics Examples of challenges that can arise include low solubility, poor permeability, and inadequate absorption. Chemical stability [1]. In addition to permeability, Solubility and dissolution rate are essential factors in the bioavailability of a drug. There have always been pharmaceuticals whose solubility has been troubling in developing a formulation suitable for oral administration. The therapeutic effect of the formulation depends on the amount of the drug at the site of action, which depends on the bioavailability of the drug [2]. The drug must be well-soluble in water and have good permeability to have good bioavailability. Dissolution might be the stage that influences the rate at which therapeutic action is onset. Solubility is the amount of drug solute present in a given volume of the solvent system at a given temperature, pressure, and pH. [3]. Possible causes of inadequate oral bioavailability are typically [4].: 1. Aqueous solubility less than [2]. Poor dissolution: intrinsic dissolution rate less than 0.1 mg/cm^2/min [3]. High molecular weight (greater than 500 Daltons), self-association, and aggregate [4]. High crystal energy, The Biopharmaceutical Classification System (BCS) was developed in 1995 to classify drugs by absorption conductivity. Drugs, according to BCS, are classified into four groups based on solubility and permeability [5], as shown in Figure 1. The BCS is considered highly permeable if its absorption rate in humans is 90% or more of the administered dose. It is defined as a product with high solubility, the maximum dose that can be dissolved from pH 1 to 7.5 in 250 ml or less of an aqueous medium [6]. BCS links drug release in vitro to bioavailability in vivo. It is a beneficial method for in vitro-in vivo correlations (IVIVC) that satisfies the requirements of the physicochemical properties of a compound, such as solubility and permeability [6]. When the modified Noyes-Whitney equation is considered, some indications demonstrate how very poorly soluble drugs can reduce their limitations on oral availability by increasing their dissolution rate [7,8].

$$\frac{dc}{dt} = \frac{AD\,(Cs - C)}{h}$$

In this equation, C is the concentration of the drug in the solution at time t; Cs is the solubility of the drug in the dissolution medium; h, the thickness of the diffusion boundary, and the dissolution rate of dissolution are all variables. Low solubility is a problem for BCS class II and IV medicines. The primary difficulty is improving the solubility of BCS II and IV medications. Different approaches to expanding the dissolution/bioavailability of poorly soluble drugs are shown in Table 1. Due to the solubility challenge, the pharmaceutical industry has been compelled to investigate chemical, physical, and carrier-based procedures for increasing drug solubility. [9]. By changing the drug's molecular structure, additive or new chemical salt conjugates with distinct pharmacological and pharmacokinetic

characteristics can be created with different pharmacokinetic and pharmacological aspects. [10]. The solubility is enhanced because the physical technique decreases the size and increases the contact surface. [11]. Various formulation approaches to increase solubility include producing liquid systems based on lipid carriers and/or surfactants [9] or carrier-based solid formulations[11]. Each has its advantages and limitations. (SDs) are a promising technology Because of their appealing properties—including solubility, small particle size, high wettability, high porosity, and enhanced drug stability—solid dispersions. [12]. Increased solubility can be easily achieved through reliable distribution, yielding high precision. [13].

Aim

This article examines the history of solid dispersion technology, including its categorization, various preparation procedures, benefits, and drawbacks .Applications. This study also reviews the numerous medications for which This approach has been employed.

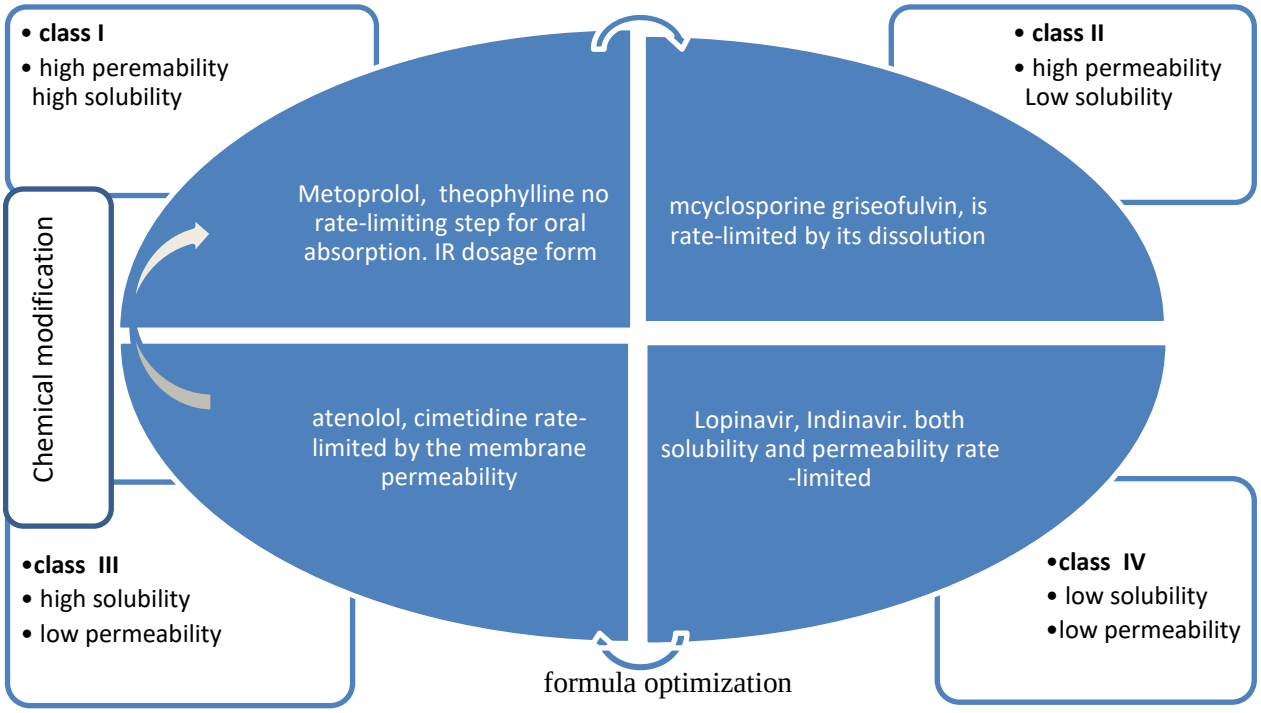

Figure 1: Biopharmaceuticals classification system. [14]

Table 1: Solubility enhancement techniques. [15,16,17]

Solubility enhancement techniques		
Physical modification	**Chemical modification**	**Miscellaneous**
-A smaller overall particle size	- Salt Formation	- Homogenization at High Pressure
1. Micronization	-The use of buffering agents	- Utilizing Hydrotropy
2. Complexation by use of nanosuspension	-A shift in the pH level	- The technique of solvent evaporation
- Alterations to the crystal structure	-Complexification	- Conversion of Polymers
- Dispersion of the drug in various carriers	1. Physical Mixture	- Supercritical fluid technique
1. The procedure is known as fusion melt	2. Technique of co-grinding	- Technique based on electrostatic spinning
2. The process of using a solvent	3. Process of kneading	- Spray freezing into liquid
3. Dropping technique	4. Neutralization	- Lyophilization method
4. The method is known as spray drying	5. The Process of Spray-Drying	- Evaporative precipitation into aqueous solution
5. Method of Irradiation using Microwaves	6. Technique of Irradiation using Microwaves	- Filling of capsules directly
6. lyophilization and freeze drying	- Soluble prodrug approach	
-Solubilization with the use of surfactants		

Solid solution:

The SD technique is widely used and effective for increasing solubility and releasing inadequate water-soluble medications. In 1960, Sekiguchi and Obi were the first to successfully demonstrate the solid dispersion method. To improve the bioavailability of drugs with poor water solubility, such as sulfathiazole, they suggested creating a eutectic combination with a water-soluble and physiologically inert carrier, like urea. This would allow the pharmaceuticals to be absorbed more quickly [18]. Due to the uniform medication distribution in the solid eutectic, the active ingredient released into fluids consists of tiny, scattered particles that showed in Fieger 2.

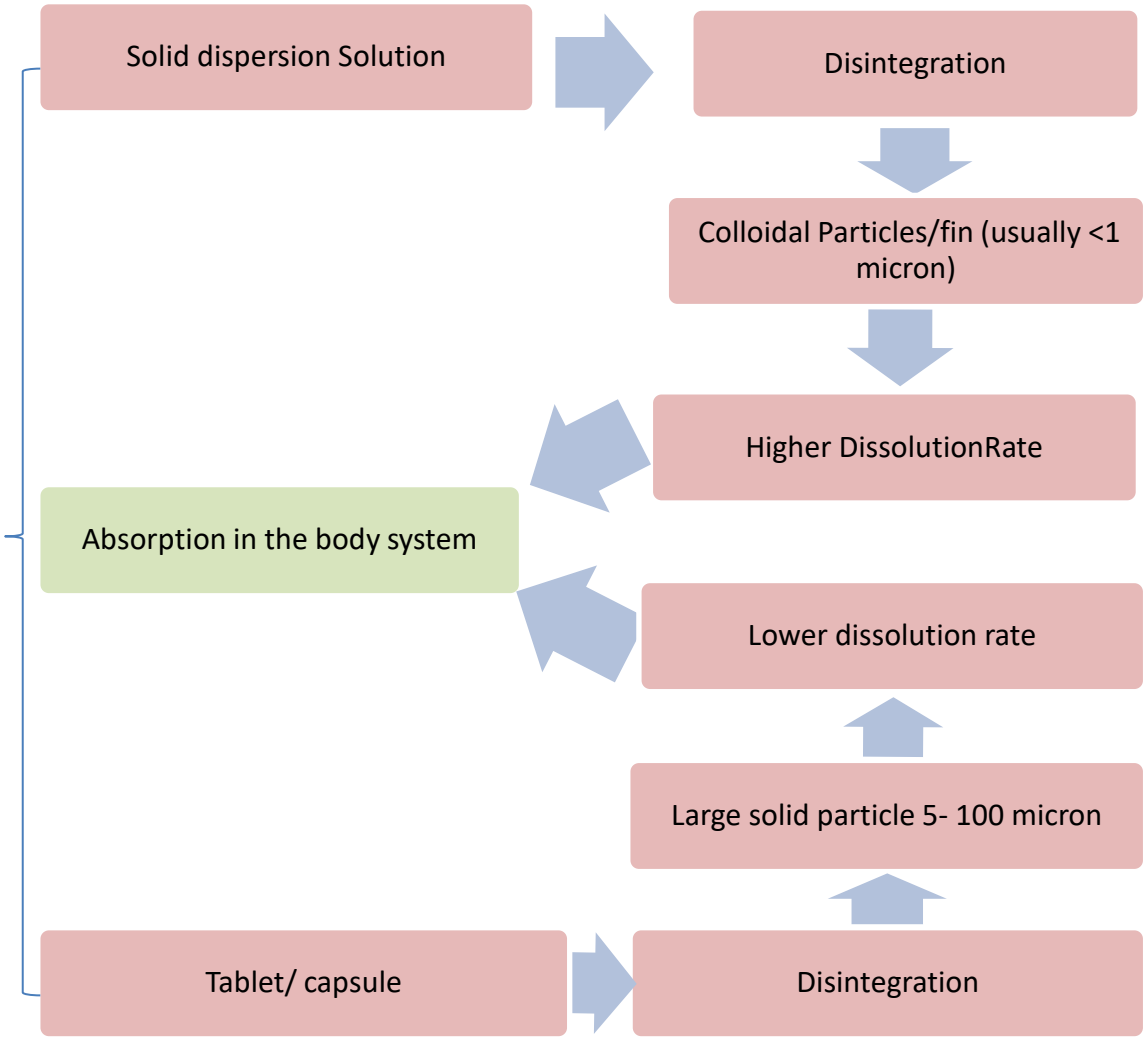

Figure 2: A schematic shows how solid dispersion improves the bioavailability of weakly soluble in-water drugs compared to a traditional tablet or capsule.

They are defined as "the dispersion of one or more active ingredients in an inert carrier matrix at solid-state produced via melting (fusion), solvent, or melting-solvent method" by Chiou and Riegelman, authors of a classic review. In his seminal work, Corrigan (1985) defined solid dosage forms as "products formed by converting a fluid drug-carrier combination to the solid state. "Chiou and Riegelman (1971) were the first to define these systems as 'solid dispersion' [19]. Patients are more therapeutically compliant with SD compared to other solubilization products. In contrast to the milling process or micronization, in which the particles of the size are confined to a range of 2-5 m, the SD effectively lowers the size of the particle, which in turn leads to an improvement in the medicament discharge. One further definition of further dispersion is "product formed by converting a fluid medicament-carrier combination to the solid-state." Therefore, the SD of medications satisfies the active agent bioavailability and solubility of a poor water solubility medication, which increases the medication's efficacy and decreases adverse effects. Physically stable SD are formed when solid dispersions are combined with high conformational entropy and low molecular mobility [20]. By using polymers that increase the physical strength of amorphous pharmaceuticals, it is possible to reduce molecular mobility [21]. To fabricate a commercially viable product, it is necessary to consider several essential factors. Once these things are considered, considering the variable parameters for the assessment and the variable production procedure, a concept demonstration is made. The technique has several disadvantages, including difficulties in scaling up to an industrial level, achieving consistent results when assessing physicochemical properties in a laboratory setting, and the Instability of the body. As SDs age, they lose crystallinity and dissolve more slowly.SD is unstable at room temperature and humidity due to its thermodynamic nature. These factors can increase the overall molecular mobility,

lower the glass transition temperature (Tg), or disturb interactions between the drug and carrier. These all promote phase separation and crystallization of SD, reducing its solubility and dissolving rate [22]. The SD method frequently experiences problems with phase separation and drug stability. The recrystallization of the drug from a supersaturated solution and the incompatibility of the drug with the solvent are possible explanations. Polarity and temperature dependence of supersaturation are two factors that contribute to this mismatch. Products including NorvirVR, IncivekVR, and RezulinVR (all from the Abbott Laboratories in Chicago, Illinois) were taken off the market. The medicine recrystallized (changes in crystallinity resulted in a lower dissolving rate) from a supersaturation solution as it aged, which explains why it was taken off the market. Avoiding problems requires a solid grounding in the physicochemical properties of the medication, solvent, and matrix. Pharmaceutical [23] The engineering discipline comprises different dispersion systems. There are three primary categories of dispersion: colloidal (nanoparticles), coarse (suspensions), and molecular (correct solution, liquid, or solid-state). Suspensions are the most common type of dispersion. "dispersion" does not refer to the formation of covalent bonds; instead, it describes the reversible aggregation of two or more substances through the interaction of hydrogen bonds, van der Waals bonds, physical entanglement, and hydrophobic contact, [24]. By dispersing the drug in another material, it is feasible to quickly dissolve it and bypass the intermolecular force between the drug's molecules. This technique prevents the formation of drug crystals and makes it possible to achieve molecular dispersion of a drug with poor solubility in a hydrophilic polymeric carrier. [25]. The SD no longer acts as a barrier to the success of its applications in the real world. As a pharmaceutical intermediary for the production of various dosage forms, such as capsules, pills, and granules, or as a finished pharmaceutical product comparable to pellets generated via a single granulation process on a fluidized bed, SD can be utilized in both capacities. [26]. Strong dispersal This method is most successful when applied to medications with low glass transition temperature, high hygroscopicity, and low viscosity [27].

Carriers:

It is crucial in SD formation; Carriers are shown in Table 2. A wide variety of physicochemical factors can influence the process of making SDs. When developing SD, the characteristics, including molecular weight carrier, pore volume, type(amorphous, crystalline, semi-crystalline) carrier, Micrometric properties, specific surface area, carrier concentration, and transport hygroscopicity,y have been taken into account. These factors significantly impact the drug's soluble, dissolvable states, absorption, and SD stability [28]. SD carrier excipients are categorized as polymeric, low-molecular-weight, and surfactant carriers [29]. The following conditions must be met for a vehicle to optimize a drug dissolution rate: Rapid dissolution is characteristic of water-soluble substances and water-insoluble in carriers used to produce sustained release solid dispersion. Nontoxic and inactive from a pharmacological standpoint, temperature resistance for the melting procedure, Solubility in an assortment of solvents, rather than enhancing the medicine's aqueous solubility. Only make weakly linked complexes with the drug that is chemically compatible with it [30]. It was an attempt to use low-molecular-weight carriers like urea, saccharides, and organic acids. The medicine and liquid used set High standards for these carrier excipients. Polymeric carriers have a higher molecular weight than carriers with a low molecular weight., allowing for greater drug dispersibility and recrystallization inhibition. PEG, PVP, PVPVA, HPMC, and hydroxypropyl cellulose (HPC) are examples of polymers utilized in commercial formulations [31]. A high glass transition temperature is essential for a suitable carrier to get sufficient kinetic stability in supersaturated glass solutions. Functional groups that are either donors or acceptors of hydrogen bonds are also helpful since specific interactions make it easier for the solid drug to dissolve in its carrier. These interactions also seem to play a significant role in stopping a medication from separating into phases and crystallizing from a glass solution [32,33]. Polymeric carriers without surfactants have insufficient absorption-enhancing effects for poorly permeable pharmaceuticals, which only require dispersibility. Pages with surfactants can help the body absorb drugs better by interacting with the absorptive epithelium and stopping drug efflux transporters.

Table 2: **Carrier Excipients** [34]

Nature used carriers	Example	Comment
Sugars	Dextrose, Mannitol, Glucose, Lactose, Sorbitol, Sucrose	Possess the ability to influence drug absorption compatible with thermosensitive medications.
Organic acid	Tartaric acid, succinic acid, phosphoric acid, and Succinic acid.	Water solubility is compatible with the melt method. Not applicable for acid-labile API.
Polymer	polyvinyl pyrrolidone (PVP),PEG400, Poloxamer 188, PVP K30, B-cyclodextrin, Eudragit L100 sodium salt,	Able to inhibit recrystallization.
Surfactant	Pluronic F68, Tween 80, Gelucire 44/14, vitamin E TPGS, docusate sodium, polyoxyethylene stearate, sodium lauryl sulfate.	Capable of enhancing drug dissolution and absorption.
hydrotropy	Sodium acetate, Sodium benzoate, resorcinol, ascorbic acid, sodium citrate	compatible with thermosensitive medications

Classification of solid dispersion:

Solid dispersions were first classified by Chiou and Riegelman, who separated them into six different types: glass solutions and glass suspensions; solid solutions, simple eutectic mixtures, amorphous precipitations in a crystalline carrier; compound or complex formation; and combinations of the above five types.[19]. Table 3 displays the molecular and physical configurations of API. Such as active pharmaceutical ingredients (API) scattered as crystalline particles, API dispersed as amorphous groups, or API molecularly dispersed within the carrier. [25]. This classification was used for a significant amount of time and had widespread acceptance and citation. Nevertheless, several adjustments to the classification system have been made during the past several years. Proposed. Vasconcelos et al., who also classified solid dispersions into three generations35, accounted for recent advancements in the solid dispersion approach. Furthermore, it modified this categorization by including control release solid dispersion, as Table 3 displays API's molecular and physical configurations. Such as active pharmaceutical ingredients (API) scattered as crystalline particles, API dispersed as amorphous groups, or API molecularly dispersed within the carrier. Fourth generation[36]. Solid dispersions can be divided into crystalline solid dispersions and amorphous solid dispersions, depending on the physical condition of the carrier, which may be crystalline or amorphous. Solid dispersions can also be classified into four generations, as shown in Figure 3:

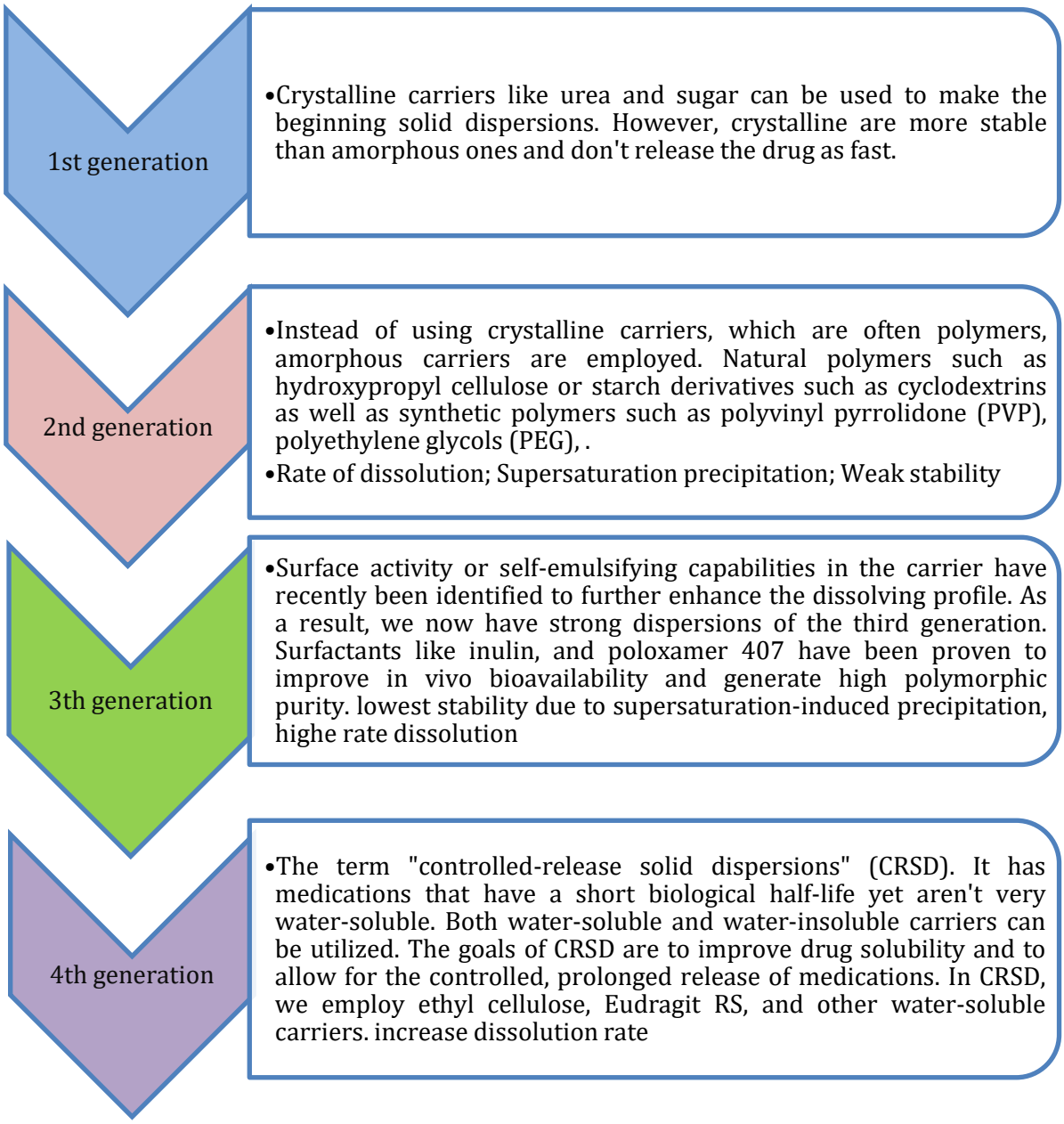

Figure 3: Generations of solid dispersion [37,38,29,39,40]

Table 3: Classification of Active Pharmaceutical Ingredients and Carriers by Physical State and Molecular Structure.

Class	The physical and molecular arrangement of API
Crystalline-Crystalline	Dispersion of crystalline API in a crystalline carrier
Crystalline- Amorphous	Dispersion of crystalline API in an amorphous carrier
Amorphous -Crystalline	Dispersion of Amorphous API in crystallin carrier
Amorphous -Amorphous	Dispersion of Amorphous API in an amorphous carrier
Molecularly dispersed-Crystalline	Dispersion API molecularly in crystallin carrier
Molecularly dispersed Amorphous.	Dispersion API molecularly in an amorphous carrier

Techniques/Methods for Solid Dispersion:

Methods for preparing solid dispersions: The reliable dispersion system is designed in various ways. These procedures are listed below.

1- Kneading technique.

2- Lyophilization.

3- Melt Agglomeration technique.

5- Melting method.

4- Electrospinning method.

6- Spray drying method.

7- Melt extrusion method.

8-Supercritical fluid technology

9 -Melting solvent method.

10 Solvent method.

Solvent method:

Solvent evaporation is one of the most often utilized procedures in the pharmaceutical business for enhancing the solubility of poorly water-soluble medicines. This method was developed specifically for heat-unstable components instead of opposed to melting, in which the medication and carrier are mixed using solvent rather than heat. Therefore, this method enables using pages with very high melting points. [41]. The basic principle of this method is to dissolve the drug and carrier in a volatile solvent so that they combine evenly. The solvent evaporates to achieve SD while the mixture is constantly stirred. The next step is to crush and sift the solid SD. In 1965, Tachibana and Nakamura were the first to use this strategy. The primary advantage of this method is that it prevents drug and carrier degradation due to the low temperature required for evaporation. Due to the low evaporation temperature, this method is beneficial for preserving the medication's and carrier's integrity. [42]. This approach has many disadvantages, including The increased expense of preparation, The difficulty in extracting the liquid solvent completely, The potential negative impact of solvent traces on chemical stability, Choosing a common volatile solvent, The challenge of replicating crystal form and supersaturation of the solute in the solid system is only possible in a system with very viscous characteristics [43]. This method has been used to enhance the solubility of many medicines, including tectorigenin [44], flurbiprofen [45], azithromycin [46], cilostazol [47], piroxicam [48], ticagrelor [49], indomethacin [50], abietic acid [51], loratadine [52]

Fusion/ melting technique:

The medication and the carrier are combined and melted at a temperature above their eutectic point in this procedure. Then, other methods are used to cool or solidify the liquid, such as spreading it out on stainless steel sheets exposed to air conditioning, placing a Petri dish in a desiccator filled with water, shaking an ice bath, or submerging the container in liquid nitrogen. After extraction, the solid is broken down, sieved, diced, and crushed. High-temperature fusion poses a risk of drug and carrier degradation. Fusion at high temperatures can cause the loss of volatile drugs or carriers. To avoid this issue, the physical mixture can be heated in a sealed container or melted under a vacuum or inert gas such as nitrogen. [53]. The advantage of this method is that no solvent is necessary, and it is simple and economical. Sekiguchi and Obi first used the dissolve technique in 1961 [38]. This method has been used to enhance the solubility of many medicines, such as Sulfathiazole [38], clotrimazole [54], albendazole [55], tacrolimus [56], fenofibrate [57], paclitaxel [58], manidipine [59], olanzapine [60], furosemide [61].

Lyophilization:

Alternative to solvent evaporation, lyophilization dissolves the drug and carrier. Lyophilized molecular dispersion is created by freezing the solution in liquid nitrogen. This approach has often employed the drug and carrier, dissolved in a common solvent and thermolabile compounds unstable in aqueous solutions but stable in dry form for lengthy storage [62]. This method has enhanced the solubility of many medicines, such as Nifedipine and sulfamethoxazole [63], celecoxib [64], meloxicam [65], and docetaxel [66].

Supercritical fluid technology SCF:

It exceeds its temperature and pressure thresholds. Vapour and liquid in equilibrium are essential at the highest possible temperature and pressure. SCF solidifies insoluble material/polymer with medication to improve solubility. It outperforms spray drying, hot melt, etc. Because SCFs are midway between liquid and gas [67,68], it is possible to fine-tune the mixture of structures needed for product processing. SCF processing, long utilized in the food sector, has been adapted for medical purposes. Most solvents are carbon dioxide, The liquid that is used the most. It is cost-effective, safe, and ecologically friendly. SCFs appeal in clinical research because they have low operating conditions (temperature and pressure) [69]., nitrous oxide, ethylene, and propylene. Drug particles scattered in the SCF can be recycled into smaller particles. Due to their flexibility and precision, SCF techniques can gradually create medication particles below micron levels. SCF methods can make nanosuspensions of 5-2,000nm particles. Nektar Therapeutics and Lavipharm use SCF technology to reduce particle size and enhance melt [70,71]. By lowering the melting temperature of the dispersed active

ingredient, supercritical fluids reduce the melt dispersion process temperature. The solubility of the lighter component (dense gas) in the developing phase (heavier part) is the cause of this depression [72]. This method has been used in drugs such as irbesartan [73], apigenin [74], carbamazepine [75], glibenclamide [76],.

Mechanism of drug release from SD:

The dissolution rate of a pharmaceutically active agent prepared by solid dispersion technique after oral administration in tablets, capsules, etc., will indicate its eventual success. One of the best ways to make poor soluble drugs more soluble is by transforming crystalline medicine into an amorphous structure. Maintaining a supersaturated state and stabilizing an amorphous form are two of the most important aspects of solid dispersion formulations. A problem with solid dispersions is the precipitation of supersaturated medications, which reduces their bioavailability [77]. The stability and solubility of the drug in the medium are improved by supersaturating drug delivery systems and particle size reduction, such as solid dispersion, and a spring-like action is observed due to the increased dissolving rate of the medication. The dissolving rate decreases during the supersaturation phase due to drug precipitation. Furthermore, when precipitation inhibitors are introduced to reduce aggregation, a parachute-like effect is observed in the dissolving profile of medicines in such a system. [78]. Two significant mechanisms mediate the release of medication from SDs. The drug was released after (1) drug-controlled release in the first mechanism and (2) carrier-controlled release in the second. Due to its hydrophilic characteristics, the designed drug carrier matrix readily dissolves or absorbs water. A concentrated gel layer or carrier layer may form in some cases. Because of the high viscosity of this gel matrix, drug diffusion is complicated when the medication dissolves. It is a rate-limiting stage in which the carrier is distributed into the bulk phase. After interaction with the dissolution media, the sparingly soluble or insoluble medication is released into the concentrated layer and released intact. The release profile is also affected by particle size, drug solubility, and polymorphism [78].

Evaluation of physicochemical properties of solid dispersion [79]:

Study of Phase Solubility

It is carried out in the presence of a polymer (carrier) using a shaking vessel. Higuchi and Connors primarily conduct it. The drug is dissolved in 25 ml of a polymer solution containing 1%, 2%, 3%, 4%, and 5%. The sample is placed in an orbital flask agitator at 37 °C 0.5 °C for 48 hours. The model is then filtered and analyzed with a UV spectrophotometer to ascertain the drug's concentration.

study of Saturation Solubility

In excess quantities, drug and solid dispersion batches are added to 25 ml of distilled water until it becomes supersaturated. The sample is then deposited in an orbital flask shaker at 37 °C0.5 °C for 48 hours. The model is then filtered through Whatman-filtered paper and analyzed by UV spectrophotometer to determine the substance concentration.

Drug content

A UV spectrophotometer determines drug content by dissolving a known amount of solid dispersion in a solvent and then analyzing the solution. The following equation is used to calculate % drug loading and % entrapment efficiency:

% Drug loading = (Weight of drug in solid dispersion powder) / (Weight of solid dispersion powder) X 100

Solid dispersions Characterization:

There are numerous methods for contributing data on the physical characteristics of solid dispersion systems**.** The enhanced dissolution of inadequately water-soluble pharmaceuticals in solid dispersions can be demonstrated using standard dissolution techniques. Other attributes of solid dispersions should be evaluated, including the drug–carrier interaction, the physical states of medicines, and the chemical stability of drugs. As a result, numerous instrumental and analytical techniques are used to confirm these properties. The crystalline condition and degree of pharmaceuticals are uniquely characterized. Indirectly, the quantity of amorphous narcotics can be deduced from the sample's degree of crystallinity [79].

Drug-carrier miscibility

Differential scanning calorimetry, hot-stage microscopy, and Raman Spectroscopic and FT-IR spectroscopy.

Drug carrier interactions

Raman spectroscopy, FT-IR spectroscopy, Solid-state NMR

Physical Composition

Atomic force microscopy, Raman microscopy, dynamic vapour sorption, surface characteristics, scanning electron microscopy, surface area analysis, and Inverse gas chromatography.

Amorphous content Studies

polarized light optical microscopy, powder X-ray diffraction, humidity stage microscopy, hot-stage microscopy, DSC (MTDSC),

stability

isothermal calorimetry, Humidity studies, saturated solubility study, DSC (Tg, Temperature recrystallization),

Enhancement of dissolution

dissolution, dissolution in media of biological relevance. Intrinsic dissolution, dynamic solubility,

Thermal Analysis Approaches:

Thermal analysis is a collection of methods in which a substance is put into a controlled temperature program to measure a physical attribute as a function of temperature. The technique will provide helpful data on the physical and chemical processes in SD and the carriers and stability of the medicine, which may be used to determine the best processing and preparation settings for SD formulation [80]**.**

X-Ray Diffraction (XRD):

This technique calculates a sample's XRD (or reflection) intensity of a sample as a function of the diffraction angles. The diffraction technique helps identify compounds and the formation of complexes. As complexes' spectrum or lattice parameters are notably different from those of purified components, the inability of dispersion systems to distinguish between amorphous precipitation and molecular dispersion if the lattice parameters of the solvent component are not altered is the primary challenge when employing the diffraction technique [81]**.**

Differential scanning calorimetry (DSC):

Determining the heat flow and temperature associated with substance transitions as a function of time and temperature is a thermal process. Using DSC, we can define the melting temperatures of various substances and monitor and analyze their thermal behaviour. DSC allows for the quantitative

observation of energy-consuming or energy-producing processes. It is commonly believed that interactions between pharmaceuticals and polymers alter the exothermic and endothermic peaks. DSC is the most reliable thermoanalytical technique for determining chemical transitions' temperature and heat flux. DSC permits the evaluation and monitoring of melting temperatures and the investigation of the thermal behaviour of various compounds. DSC can be used to observe quantitatively the methods by which energy is produced or required. Interactions between medications and carriers modify the exothermic and endothermic maxima [82]. DSC is also a common technique for determining the quantity of crystalline material. In DSC, samples are continuously heated, and the required energy is measured. DSC can observe the temperatures at which thermal events occur. Thermodynamic processes include transforming glass to rubber, (re)crystallization, dissolution, and degradation. In addition, it is possible to quantify melting and (re)crystallization energies. The melting point can be used to determine the number of crystallized substances. [83].

Fourier Transformed Infrared (FTIR) spectroscopy:

Infrared spectroscopy (IR) can detect variations in the energy distribution of drug-matrix interactions. Sharp vibrational bands signify crystalline structure. FTIR was used in purified material to detect crystallinity ranging from 1% to 99.9% [21].

Applications of solid dispersion[84]:

The following are the most critical applications of the solid dispersion technique in formulating pharmaceutically active compounds.

- Formulation of a sustained-release dosage form
- Decreased systemic inactivation of drugs such as morphine and progesterone.
- It increases the solubility of inadequately soluble medications and, as a result, the dissolution rate, thereby enhancing dissolution, which improves the absorption and bioavailability of the drug.
- To stabilize problematic pharmaceuticals against various decomposition processes, including hydrolysis, oxidation, etc.
- To reduce the side effects of medications.
- They mask the unpleasant flavour and odour of narcotics.
- To avoid undesirable incompatibilities.
- To accomplish a uniform distribution of a limited number of solid-form pharmaceuticals.

Solid-liquid dosage (up to 10 percent) or gases.

Table 4: Examples of commercially available products that utilize the solid dispersion technique in their production.

Drug	Company
Nifedipine	Elan Corp, Ireland
Cesamet® Nabilone	Lilly, USA
Cesamet® Nabilone	Valeant Pharmaceuticals, Canada
Certican® Everolimus	Novartis, Switzweland
Gris-PEG® Griseofulvin	Novartis, Switzweland
Gris-PEG® Griseofulvin	VIP Pharma, Denmark
Fenoglide® Fenofibrate	LifeCycle Pharma, Denmark
Nivadil® Nivaldipine	Fujisawa Pharmaceuticals Co., Ltd
Nimotop® Nimodipine	Bayer
Torcetrapib® Torcetrapib	Pfizer, USA
Ibuprofen® Ibuprofen	Germany
Incivek® Telaprevir	Vertex
Sporanox® Itraconazole	Janssen Pharmaceutica, Belgium
Onmel® Itraconazole	Stiefel
Prograf® Tacrolimus	Fujisawa Pharmaceuticals Co., Ltd
Cymbalta® Duloxetine	Lilly, USA
Noxafil® Posaconazole	Merck
LCP-Tacro® Tacrolimus	LifeCycle Pharma, Denmark
Intelence® Etravirine	Tibotec, Yardley, PA
Incivo® Etravirine	Janssen Pharmaceutica, Belgium
Rezulin® Troglitazone	Pfizer, USA
Isoptin SRE-240® Verapamil	Germany
Isoptin SR-E® Verapamil	Abbott Laboratories, USA
Crestor® Rosuvastatin	AstraZeneca

Conclusion:

Solid dispersion is a valuable technique for achieving better or controlled release profiles of pharmaceutically active compounds; the method is fast, simple, and cost-effective in many cases and could provide a solution for poorly soluble compounds.

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References:

1. Sheetal Z Godse MS, Patil, Swapnil M Kothavade RBS. Techniques for solubility enhancement of Hydrophobic drugs : A Review. J Adv Pharm Educ Res. 2013;3(4):403-414.

2. Administration USF and D. The Biopharmaceutics Classification System (BCS) Guidance. US Food Drug Adm Drug Eval Res. Published online 2019.

3. Pitani L. Solubility Enhancement of Model Compounds. Published online 2017.

4. Jagtap S, Magdum C, Jadge D, Jagtap R. Solubility enhancement technique: a review. J Pharm Sci Res. 2018;10(9):2205-2211.

5. Dahan A, Miller JM, Amidon GL. Prediction of solubility and permeability class membership: provisional BCS classification of the world's top oral drugs. AAPS J. 2009;11:740-746. https://doi.org/10.1208/s12248-009-9144-x PMid:19876745 PMCid:PMC2782078

6. Kuchekar AB, Gawade A, Boldhane S. Hydrotropic Solubilization: An Emerging Approach. J Drug Deliv Ther. 2021;11(1-s):200-206. doi:10.22270/jddt.v11i1-s.4724 https://doi.org/10.22270/jddt.v11i1-s.4724

7. Noyes AA, Whitney WR. The rate of solution of solid substances in their own solutions. J Am Chem Soc. 1897;19(12):930-934. https://doi.org/10.1021/ja02086a003

8. Nernst W. Theorie der Reaktionsgeschwindigkeit in heterogenen Systemen. Zeitschrift für Phys Chemie. 1904;47(1):52-55. https://doi.org/10.1515/zpch-1904-4704

9. Vasconcelos T, Marques S, das Neves J, Sarmento B. Amorphous solid dispersions: Rational selection of a manufacturing process. Adv Drug Deliv Rev. 2016;100:85-101. https://doi.org/10.1016/j.addr.2016.01.012 PMid:26826438

10. Seo JH, Park JB, Choi WK, et al. Improved oral absorption of cilostazol via sulfonate salt formation with mesylate and besylate. Drug Des Devel Ther. 2015;9:3961. https://doi.org/10.2147/DDDT.S87687 PMid:26251575 PMCid:PMC4524531

11. R Serrano D, H Gallagher K, Marie Healy A. Emerging nanonisation technologies: tailoring crystalline versus amorphous nanomaterials. Curr Top Med Chem. 2015;15(22):2327-2340. https://doi.org/10.2174/1568026615666150605122917 PMid:26043733

12. Kumar Sarangi M. "Solid Dispersion - a Novel Approach for Enhancement of Bioavailability of Poorly Soluble Drugs in Oral Drug Delivery System." Glob J Pharm Pharm Sci. 2017;3(2). https://doi.org/10.19080/GJPPS.2017.03.555608

13. Bhowmik D, G.Harish, S.Duraivel, Kumar BP, Raghuvanshi V, Kumar KPS. Solid Dispersion - A Approach To Enhance The Dissolution Rate of Poorly Water Soluble Drugs. Pharma Innov J. 2013;1(12):24-38. https://www.thepharmajournal.com/archives/?year=2013&vol=1&issue=12&ArticleId=104

14. Wu CY, Benet LZ. Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. Pharm Res. 2005;22:11-23. https://doi.org/10.1007/s11095-004-9004-4 PMid:15771225

15. Gulia R, Singh S, Sharma N, Arora S. Hydrotropic solid dispersions: A robust application to undertake solubility challenges. Plant Arch. 2020;20:3279-3284.

16. Kapadiya N, Singhvi I, Mehta K, Karwani G, Dhrubo JS. Hydrotropy: A promising tool for solubility enhancement: A review. Int J Drug Dev Res. 2011;3(2):26-33.

17. Arunachalam A, Karthikeyan M, Kishore K, Pottabathula HP, Sethuraman S, Hutoshkumar SA. Solid Dispersions. Curr Pharma Res. 2010;1(1). https://doi.org/10.33786/JCPR.2010.v01i01.016

18. Singh S, Baghel RS, Yadav L. A review on solid dispersion. Int J Pharm life Sci. 2011;2(9).

19. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci. 1971;60(9):1281-1302. https://doi.org/10.1002/jps.2600600902 PMid:4935981

20. Zhou D, Grant DJW, Zhang GGZ, Law D, Schmitt EA. A calorimetric investigation of thermodynamic andmolecular mobility contributions to the physical stability of two pharmaceutical glasses. J Pharm Sci. 2007;96(1):71-83. https://doi.org/10.1002/jps.20633 PMid:17031846

21. Taylor LS, Zografi G. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. Pharm Res. 1997;14:1691-1698. https://doi.org/10.1023/A:1012167410376 PMid:9453055

22. Pokharkar VB, Mandpe LP, Padamwar MN, Ambike AA, Mahadik KR, Paradkar A. Development, characterization and stabilization of amorphous form of a low Tg drug. Powder Technol. 2006;167(1):20-25. https://doi.org/10.1016/j.powtec.2006.05.012

23. Alshehri S, Imam SS, Hussain A, et al. Potential of solid dispersions to enhance solubility, bioavailability, and therapeutic efficacy of poorly water-soluble drugs: newer formulation techniques, current marketed scenario and patents. Drug Deliv. 2020;27(1):1625-1643. https://doi.org/10.1080/10717544.2020.1846638 PMid:33207947 PMCid:PMC7737680

24. Zhang X, Sun N, Wu B, Lu Y, Guan T, Wu W. Physical characterization of lansoprazole/PVP solid dispersion prepared by fluid-bed coating technique. Powder Technol. 2008;182(3):480-485. https://doi.org/10.1016/j.powtec.2007.07.011

25. Meng F, Gala U, Chauhan H. Classification of solid dispersions: correlation to (i) stability and solubility (ii) preparation and characterization techniques. Drug Dev Ind Pharm. 2015;41(9):1401-1415. https://doi.org/10.3109/03639045.2015.1018274 PMid:25853292

26. Vo CLN, Park C, Lee BJ. Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs. Eur J Pharm Biopharm. 2013;85(3):799-813. https://doi.org/10.1016/j.ejpb.2013.09.007 PMid:24056053

27. Zhang X, Xing H, Zhao Y, Ma Z. Pharmaceutical dispersion techniques for dissolution and bioavailability enhancement of poorly water-soluble drugs. Pharmaceutics. 2018;10(3).

https://doi.org/10.3390/pharmaceutics10030074 PMid:29937483 PMCid:PMC6161168

28. Van Duong T, Van den Mooter G. The role of the carrier in the formulation of pharmaceutical solid dispersions. Part II: amorphous carriers. Expert Opin Drug Deliv. 2016;13(12):1681-1694. https://doi.org/10.1080/17425247.2016.1198769 PMid:27267583

29. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today. 2007;12(23-24):1068-1075. https://doi.org/10.1016/j.drudis.2007.09.005 PMid:18061887

30. Kaushik R, Budhwar V, Kaushik D. An Overview on Recent Patents and Technologies on Solid Dispersion. Recent Pat Drug Deliv Formul. 2020;14(1):63-74. https://doi.org/10.2174/1872211314666200117094406 PMid:31951172 PMCid:PMC7569281

31. Swain RP, Subudhi BB. Effect of semicrystalline polymers on self-emulsifying solid dispersions of nateglinide: in vitro and in vivo evaluation. Drug Dev Ind Pharm. 2018;44(1):56-65. https://doi.org/10.1080/03639045.2017.1371739 PMid:28845687

32. Marsac PJ, Shamblin SL, Taylor LS. Theoretical and practical approaches for prediction of drug-polymer miscibility and solubility. Pharm Res. 2006;23:2417-2426. https://doi.org/10.1007/s11095-006-9063-9 PMid:16933098

33. Matsumoto T, Zografi G. Physical properties of solid molecular dispersions of indomethacin with poly (vinylpyrrolidone) and poly (vinylpyrrolidone-co-vinyl-acetate) in relation to indomethacin crystallization. Pharm Res. 1999;16:1722-1728. https://doi.org/10.1023/A:1018906132279 PMid:10571278

34. Sun N, Zhang X, Lu Y, Wu W. In vitro evaluation and pharmacokinetics in dogs of solid dispersion pellets containing Silybum marianum extract prepared by fluid-bed coating. Planta Med. 2008;74(02):126-132. https://doi.org/10.1055/s-2008-1034294 PMid:18240100

35. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today. 2007;12(23-24):1068-1075. https://doi.org/10.1016/j.drudis.2007.09.005 PMid:18061887

36. Vo CLN, Park C, Lee BJ. Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs. Eur J Pharm Biopharm. 2013;85(3 PART B):799-813. https://doi.org/10.1016/j.ejpb.2013.09.007 PMid:24056053

37. Sekiguchi K, Obi N, Ueda Y. Studies on Absorption of Eutectic Mixture. II. Absorption of fused Conglomerates of Chloramphenicol and Urea in Rabbits. Chem Pharm Bull. 1964;12(2):134-144. https://doi.org/10.1248/cpb.12.134 PMid:14126741

38. Sekiguchi K, Obi N. Studies on Absorption of Eutectic Mixture. I. A Comparison of the Behavior of Eutectic Mixture of Sulfathiazole and that of Ordinary Sulfathiazole in Man. Chem Pharm Bull. 1961;9(11):866-872. https://doi.org/10.1248/cpb.9.866

39. Kaur N, Gupta RC. To quantify the luteolin content from the aerial parts of Heteropogon contortus (L.) Beauv.(spear grass) through High-performance thin-layer chromatography. Asian J Pharm Clin Res. 2018;11(1):191-194. https://doi.org/10.22159/ajpcr.2018.v11i1.22116

40. Vo CL, Park C, Lee B. European Journal of Pharmaceutics and Biopharmaceutics Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs. Eur J Pharm Biopharm. 2013;85:799-813. https://doi.org/10.1016/j.ejpb.2013.09.007 PMid:24056053

41. Saharan V, Kukkar V, Kataria M, Gera M, Choudhury PK. Dissolution enhancement of drugs. Part I: technologies and effect of carriers. Int J Heal Res. 2009;2(2). https://doi.org/10.4314/ijhr.v2i2.55401

42. Hülsmann S, Backensfeld T, Keitel S, Bodmeier R. Melt extrusion-an alternative method for enhancing the dissolution rate of 17β-estradiol hemihydrate. Eur J Pharm Biopharm. 2000;49(3):237-242. https://doi.org/10.1016/S0939-6411(00)00077-1 PMid:10799815

43. Jatwani S, Rana AC, Singh G, Aggarwal G. An overview on solubility enhancement techniques for poorly soluble drugs and solid dispersion as an eminent strategic approach. Int J Pharm Sci Res. 2012;3(4):942. https://doi.org/10.1002/chin.201313244

44. Shuai S, Yue S, Huang Q, et al. Preparation, characterization and in vitro/vivo evaluation of tectorigenin solid dispersion with improved dissolution and bioavailability. Eur J Drug Metab Pharmacokinet. 2016;41:413-422. https://doi.org/10.1007/s13318-015-0265-6 PMid:25669445

45. Daravath B, Tadikonda RR, Vemula SK. Formulation and pharmacokinetics of gelucire solid dispersions of flurbiprofen. Drug Dev Ind Pharm. 2015;41(8):1254-1262. https://doi.org/10.3109/03639045.2014.940963 PMid:25039470

46. Dhapte V, Mehta P. Advances in hydrotropic solutions: An updated review. St Petersbg Polytech Univ J Phys Math. 2015;1(4):424-435. https://doi.org/10.1016/j.spjpm.2015.12.006

47. Mustapha O, Kim KS, Shafique S, et al. Comparison of three different types of cilostazol-loaded solid dispersion: Physicochemical characterization and pharmacokinetics in rats. Colloids Surfaces B Biointerfaces. 2017;154:89-95. https://doi.org/10.1016/j.colsurfb.2017.03.017 PMid:28324691

48. Al-Hamidi H, Obeidat WM, Nokhodchi A. The dissolution enhancement of piroxicam in its physical mixtures and solid dispersion formulations using gluconolactone and glucosamine hydrochloride as potential carriers. Pharm Dev Technol. 2015;20(1):74-83. https://doi.org/10.3109/10837450.2013.871029 PMid:24392858

49. Kim SJ, Lee HK, Na YG, et al. A novel composition of ticagrelor by solid dispersion technique for increasing solubility and intestinal permeability. Int J Pharm. 2019;555:11-18. https://doi.org/10.1016/j.ijpharm.2018.11.038 PMid:30448313

50. Zhang W, Zhang C ning, He Y, et al. Factors affecting the dissolution of indomethacin solid dispersions. Aaps Pharmscitech. 2017;18:3258-3273. https://doi.org/10.1208/s12249-017-0813-2 PMid:28584898

51. Crucitti VC, Migneco LM, Piozzi A, et al. Intermolecular interaction and solid state characterization of abietic acid/chitosan solid dispersions possessing antimicrobial and antioxidant properties. Eur J Pharm Biopharm. 2018;125:114-123. https://doi.org/10.1016/j.ejpb.2018.01.012 PMid:29366926

52. Frizon F, de Oliveira Eloy J, Donaduzzi CM, Mitsui ML, Marchetti JM. Dissolution rate enhancement of loratadine in polyvinylpyrrolidone K-30 solid dispersions by solvent methods. Powder Technol. 2013;235:532-539. https://doi.org/10.1016/j.powtec.2012.10.019

53. Khuspe PR, Kokate K, Mandhare T, Otari K, Katiyar P. THE COMPREHENSIVE REVIEW ON SOLID DISPERSION TECHNOLOGY. Published online 2017.

54. Madgulkar A, Bandivadekar M, Shid T, Rao S. Sugars as solid dispersion carrier to improve solubility and dissolution of the BCS class II drug: clotrimazole. Drug Dev Ind Pharm. 2016;42(1):28-38. https://doi.org/10.3109/03639045.2015.1024683 PMid:25874729

55. de los Santos CJJ, Pérez-Martínez JI, Gómez-Pantoja ME, Moyano JR. Enhancement of albendazole dissolution properties using solid dispersions with Gelucire 50/13 and PEG 15000. J Drug Deliv Sci Technol. 2017;42:261-272. https://doi.org/10.1016/j.jddst.2017.03.030

56. Xu H, Liu L, Li X, Ma J, Liu R, Wang S. Extended tacrolimus release via the combination of lipid-based solid dispersion and HPMC hydrogel matrix tablets. Asian J Pharm Sci. 2019;14(4):445-454. https://doi.org/10.1016/j.ajps.2018.08.001 PMid:32104473 PMCid:PMC7032121

57. Karolewicz B, Gajda M, Pluta J, Górniak A. Dissolution study and thermal analysis of fenofibrate-Pluronic F127 solid dispersions. J Therm Anal Calorim. 2016;125:751-757. https://doi.org/10.1007/s10973-015-5013-2

58. Shen Y, Lu F, Hou J, Shen Y, Guo S. Incorporation of paclitaxel solid dispersions with poloxamer188 or polyethylene glycol to tune drug release from poly (ϵ-caprolactone) films. Drug Dev Ind Pharm. 2013;39(8):1187-1196. https://doi.org/10.3109/03639045.2012.704042 PMid:22803692

59. Chamsai B, Limmatvapirat S, Sungthongjeen S, Sriamornsak P. Enhancement of solubility and oral bioavailability of manidipine by formation of ternary solid dispersion with d-α-tocopherol polyethylene glycol 1000 succinate and copovidone. Drug Dev Ind Pharm. 2017;43(12):2064-2075. https://doi.org/10.1080/03639045.2017.1371731 PMid:28836855

60. Krishnamoorthy V, Prasad VPR. Physicochemical characterization and in vitro dissolution behavior of olanzapine-mannitol solid dispersions. Brazilian J Pharm Sci. 2012;48:243-255. https://doi.org/10.1590/S1984-82502012000200008

61. Prasad R, Radhakrishnan P, Singh SK, Verma PRP. Furosemide-Soluplus® Solid Dispersion: Development and Characterization. Recent Pat Drug Deliv Formul. 2017;11(3):211-220. https://doi.org/10.2174/1872211311666171129120020 PMid:29189186

62. Betageri G V, Makarla KR. Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques. Int J Pharm. 1995;126(1-2):155-160. https://doi.org/10.1016/0378-5173(95)04114-1

63. Altamimi MA, Neau SH. Investigation of the in vitro performance difference of drug-Soluplus® and drug-PEG 6000 dispersions when prepared using spray drying or lyophilization. Saudi Pharm J. 2017;25(3):419-439. https://doi.org/10.1016/j.jsps.2016.09.013 PMid:28344498 PMCid:PMC5357108

64. Jacobsen AC, Elvang PA, Bauer-Brandl A, Brandl M. A dynamic in vitro permeation study on solid mono-and diacyl-phospholipid dispersions of celecoxib. Eur J Pharm Sci. 2019;127:199-207. https://doi.org/10.1016/j.ejps.2018.11.003 PMid:30408522

65. Suzuki H, Yakushiji K, Matsunaga S, et al. Amorphous solid dispersion of meloxicam enhanced oral absorption in rats with impaired gastric motility. J Pharm Sci. 2018;107(1):446-452. https://doi.org/10.1016/j.xphs.2017.05.023 PMid:28551427

66. Ngo AN, Thomas D, Murowchick J, Ayon NJ, Jaiswal A, Youan BBC. Engineering fast dissolving sodium acetate mediated crystalline solid dispersion of docetaxel. Int J Pharm. 2018;545(1-2):329-341. https://doi.org/10.1016/j.ijpharm.2018.04.045 PMid:29689368

67. Phillips EM, Stella VJ. Rapid expansion from supercritical solutions: application to pharmaceutical processes. Int J Pharm. 1993;94(1-3):1-10. https://doi.org/10.1016/0378-5173(93)90002-W

68. Nikolai P, Rabiyat B, Aslan A, Ilmutdin A. Supercritical CO 2: Properties and technological applications-a review. J Therm Sci. 2019;28:394-430. https://doi.org/10.1007/s11630-019-1118-4

69. Rantakylä M. Particle Production by Supercritical Antisolvent Processing Techniques. Helsinki University of Technology; 2004.

70. Manna L, Banchero M, Sola D, Ferri A, Ronchetti S, Sicardi S. Impregnation of PVP microparticles with ketoprofen in the presence of supercritical CO2. J Supercrit Fluids. 2007;42(3):378-384. https://doi.org/10.1016/j.supflu.2006.12.002

71. Martin TM, Bandi N, Shulz R, Roberts CB, Kompella UB. Preparation of budesonide and budesonide-PLA microparticles using supercritical fluid precipitation technology. AAPS PharmSciTech. 2002;3:16-26. https://doi.org/10.1208/pt030318 PMid:12916933 PMCid:PMC2784047

72. 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;131:53-59. https://doi.org/10.1016/j.molliq.2006.08.026

73. Adeli E. The use of supercritical anti-solvent (SAS) technique for preparation of Irbesartan-Pluronic® F-127 nanoparticles to improve the drug dissolution. Powder Technol. 2016;298:65-72. https://doi.org/10.1016/j.powtec.2016.05.004

74. Zhang J, Huang Y, Liu D, Gao Y, Qian S. Preparation of apigenin nanocrystals using supercritical antisolvent process for dissolution and bioavailability enhancement. Eur J Pharm Sci. 2013;48(4-5):740-747. https://doi.org/10.1016/j.ejps.2012.12.026 PMid:23305994

75. Moneghini M, Kikic I, Voinovich D, Perissutti B, Filipović-Grčić J. Processing of carbamazepine-PEG 4000 solid dispersions with supercritical carbon dioxide: preparation, characterisation, and in vitro dissolution. Int J Pharm. 2001;222(1):129-138. https://doi.org/10.1016/S0378-5173(01)00711-6 PMid:11404039

76. Tabbakhian M, Hasanzadeh F, Tavakoli N, Jamshidian Z. Dissolution enhancement of glibenclamide by solid dispersion: solvent evaporation versus a supercritical fluid-based solvent-antisolvent technique. Res Pharm Sci. 2014;9(5):337.

77. Teja SB, Patil SP, Shete G, Patel S, Bansal AK. Drug-excipient behavior in polymeric amorphous solid dispersions. J Excipients Food Chem. 2016;4(3).

78. Craig DQM. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int J Pharm. 2002;231(2):131-144. https://doi.org/10.1016/S0378-5173(01)00891-2 PMid:11755266

79. Kumar R, Singh A, Salwan R, Bhanot R, Rahar S, Dhawan RK. An informative review on solid dispersion. GSC Biol Pharm Sci. 2023;22(1):114-121. https://doi.org/10.4103/jpbs.jpbs_432_22 PMid:37654356 PMCid:PMC10466630

80. Shah B, Kakumanu VK, Bansal AK. Analytical techniques for quantification of amorphous/crystalline phases in pharmaceutical solids. J Pharm Sci. 2006;95(8):1641-1665. https://doi.org/10.1002/jps.20644 PMid:16802362

81. Patel A, Jain RK, Jain V, Khangar PK. Formulation and Evaluation of Sustained Release Solid Dispersed Nifedipine Microcapsules. Asian J Dental Health Sci [Internet]. 2022 Nov. 22 [cited 2024 Feb. 8];2(3):12-8. https://doi.org/10.22270/ajdhs.v2i3.21

82. Berndl G, Degenhardt M, Mägerlein M, Dispersyn G. Itraconazole compositions with improved bioavailability. Published online October 6, 2015.

83. Kerc J, Srcic S. Thermal analysis of glassy pharmaceuticals. Thermochim Acta. 1995;248:81-95. https://doi.org/10.1016/0040-6031(94)01949-H

84. Kumar B. Solid dispersion-a review. PharmaTutor. 2017;5(2):24-29