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A Comprehensive Review of Formulation, Characterization, and Applications of Solid Dispersions in Drug Delivery

Noor Sabah Hazbar, Dr. Ahmed Najim Abood
Department of pharmaceuticals/ college of pharmacy/ unversity of Basrah, Basrah/Iraq

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Annotation: Many recently produced drug candidates still face formulation challenges due to low water solubility, which limits their oral bioavailability and therapeutic efficacy. A method that shows promise for increasing the solubility and the rate of dissolution of medications that are not very soluble in water is solid dispersion (SD) technology. To improve wettability, surface area, and dissolution kinetics, SDs can convert crystalline pharmaceuticals into amorphous forms with higher energy levels by dispersing the drug at the level of molecules or particles in an inert carrier matrix, usually a polymer. Solid dispersions are made employing various techniques, such as solvent evaporation, hot-melt extrusion, and spray drying. To solidify the amorphous state and prevent recrystallization, Poloxamers, PVP, PEGs, and Soluplus® are examples of polymers that are widely used. The latest developments in SD formulation are examined in this abstract.

Keywords: solid dispersion (SD), solubility enhancement, Drug delivery.

1. Introduction

In pharmaceutical development, poorly water-soluble medications are prevalent and it is very difficult problem. Drugs with poor solubility may have inadequate absorption and therapeutic efficacy. The druggability and clinical potency of poorly water-soluble medications have been affected by their low absorption, fast metabolism, decreased therapeutic efficacy, and decreased biosafety (1). Solubility can be quantitatively described as the necessary solute concentration in a solution at a specific temperature, pH and pressure. On the other hand, a material's solubility in

qualitative terms refers to its capacity to melt in a saturated solution at a particular temperature. According to the US Pharmacopoeia, solubility is the number of milliliters of solvent required to dissolve one gram of solute (2).

Drugs has been classified according to biopharmaceutical classification system(BCS) into four groups based on their water solubility, intestinal permeability. Class 1 include highly soluble and highly permeable drugs,

Class 11 for low soluble, highly permeable medications while class 111 involve highly soluble, low permeable drugs and lastly class 1V for low solubility, low permeability active pharmaceutical ingredients (3)

The modified Noyes-Whitney equation can provide some direction on how to increase a substance's oral bioavailability by speeding up the rate at which even very poorly soluble substances dissolve. The equation

dC/dt = AD (Cs - C)/h

where Cs is the compound's solubility in a dissolving medium, C represents the drug concentration in the medium at time t, D indicates compound's diffusion coefficient, A is the surface area available for dissolution, and h represent the diffusion boundary layer's thickness next to the dissolving compound's surface(4).

Table (1): USP and BP Solubility Standards (5)

Definition	Part of solvents required to dissolve One part of the solute
Very soluble	<1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000-10000
Practically insoluble	>10000

There are numerous approaches to improve the solubility include Particle size reduction, amorphous or polymorphous crystallinity alterations, and solid dispersion which are examples of physical-based approaches. chemical techniques, such as adjusting pH or forming complexes or salts, as well as hybrid techniques, including producing supercritical fluids or using various solubilizing agents(6)

2. Solid Dispersion

A solid dispersion is the solid state dispersion of one or more drugs in a matrix made of hydrophilic carriers (or a combination of carriers). Developing formulations to enhance the solubility and bioavailability profile of medications that don't dissolve well in water has been accomplished with success using SD technology(7). The drug may be present in SD in a molecular, amorphous, microcrystal, or colloidal state, depending on how it is prepared and formulated(8).

2.1 Mechanism Responsible for Solubility Enhancement in SD (9):

1. Smaller particles: The drug is released as tiny colloidal particles when the solid dispersion is exposed to watery liquids, causing the carrier to dissolve. For medications that are not very soluble in water, the larger surface area causes a quicker rate of dissolution.

2. Amorphous drug: Crystalline medications that have limited water solubility became more soluble as they converted into amorphous form. This is because no energy is required to break the crystal lattice in an amorphous phase during dissolution.

3. High porosity particles: It has been discovered that particles in solid dispersion have high porosity, which speeds up the drug release profile. The carrier characteristics determine the rise in porosity; reticular particles are smaller and less porous than linear polymers.

4. Particles with enhanced wettability: It has been demonstrated that increasing drug wettability significantly affects drug solubility in solid dispersion. Surface-active carriers, such bile salt and cholic acid, can significantly improve the medication's wettability and dissolving profile.

2.2 Solid Dispersion Classification

A-Solid Dispersion Classification Based on Solid Structure:

2.2.1 Eutectic Mixtures

Eutectic mixtures are created when a drug and polymer are miscible when molten, but crystallize as two separate substances with very little miscibility when cooled(9)

The melting point of the dispersion in a eutectic mixture is lower than the melting points of the drug and carrier. The term "eutectic point" refers to the precise composition of a eutectic mixture containing tiny crystals of two components at which the drug crystallizes out. The rate of breakdown and oral absorption of weakly water-soluble medications is often improved by small particle size, which increases specific surface area(10)

2.2.2 Solid Solution

Like liquid solutions, solid solutions can create a single phase system, regardless of how many components they include. However, such a system cannot develop until the two solid components combine together at the same time. In solid solutions, the drug product's particle size is decreased to molecular dimensions. **There are two categories of solid solutions based on miscibility**

1-continuous Solid Solutions

The components of continuous solid solutions are miscible in all proportions, meaning that their bonding strength is greater compared to that of their individual bonds.

2-Discontinuous Solid Solutions

in these solutions, each component's solubility in the other component is naturally restricted

And according to the distribution of solvate molecules in the solvent:

1-Substitutional Solid Solution

in which the solvent molecule in the solid solvent's crystal lattice is replaced by the solute molecule.

2-Interstitial Solid Solutions

The interstitial gaps between the solvent molecules in the crystal lattice are filled by the dissolved molecules(11)

2.2.3 Glass Solutions and Suspensions

Solutes dissolve in a glass carrier to form homogenous glassy systems known as glass solutions. Mixtures of precipitated particles suspended in a glass solvent are known as glass suspensions. A "glass" is a pure chemical or a mixture of them in their glassy condition exist just below glass transition temperature(12).

2.2.4 Amorphous Precipitation in Crystalline Matrix

this is comparable to simple eutectic mixtures, the only distinction is that the drug precipitates out in an amorphous form, example include Sulfathiazole in crystalline urea(13).

B- Solid Dispersion Classified According to The Carrier Type (14)**,** (15), (10):

The physical condition of the carrier and the API are used to categorize SDs into fifth generations as seen in fig.1

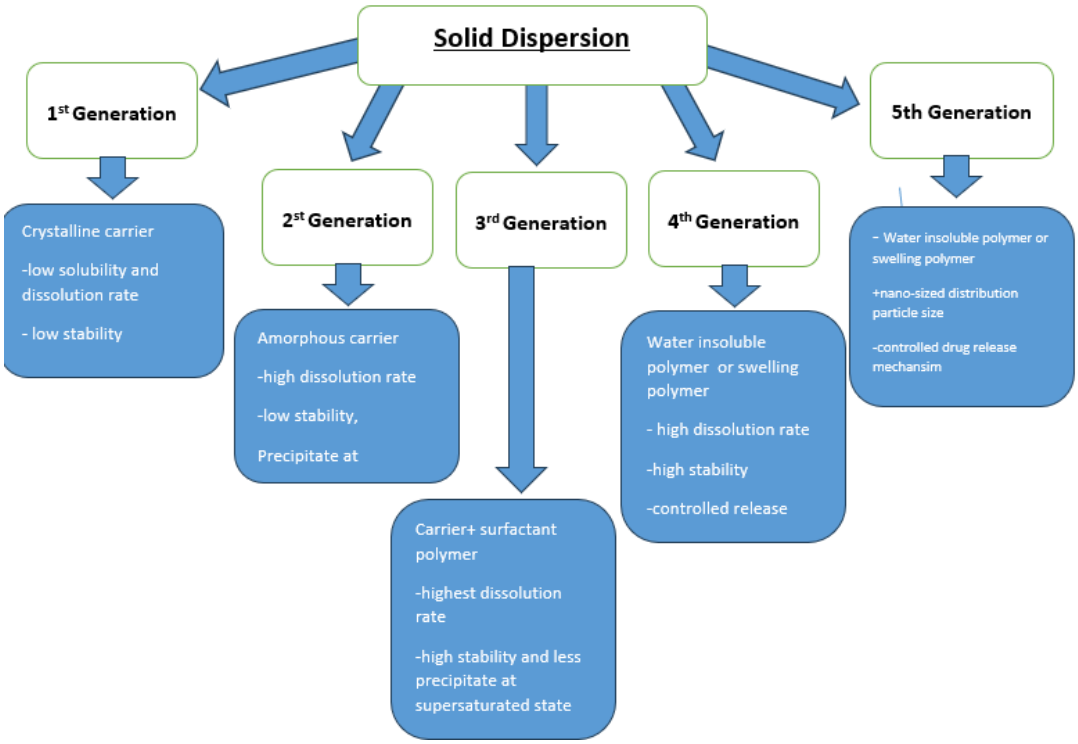

Fig.1 Classification of SD based on carrier used and its properties

2.2.5 First Generation

This type of solid dispersions is created by dispersing crystalline drug in a crystalline carrier such as lactose or urea to create a eutectic or monotectic combination. Sugars and urea are two examples of crystalline carriers that are employed. Due to its ability to dissolve in water and a variety of organic solvents, urea is frequently utilized and it work effectively for SD prepared by solvent-based methods.

How ever, This kind forms a crystalline SD that is unstable with reduced solubility and dissolution rate(15).

2.2.6 Second Generation

These include amorphous carriers such as cellulose derivatives, PVP, and PEG. Due to their thermodynamic stability, second generation solid dispersions (SD) were found to be more effective than first generation SD. High viscosity polymers can be used to prevent drug recrystallization throughout the manufacture, storage, and dissolving processes. Furthermore, using a polymer with a high viscosity can slow down the pace at which a drug dissolves in an aqueous media. Drug precipitation and recrystallization, which impact in vitro or in vivo drug release, are the main issues with second generation solid dispersions.

2.2.7 Third Generation SD

Third generation SDs, which are made up of carriers with emulsifying or surface activity, can enhance the drug's dissolving profile. Precipitation and recrystallization issues can be resolved by using a certain kind of carrier . In addition to improving the drug's dissolving profile, the use of surfactants or emulsifiers increases the drug's chemical and physical stability in solid dispersion. These carriers include, for instance, poloxamer , Gelucir, and inulin

2.2.8 Forth Generation

Controlled release solid dispersions (CRSD) are another name for these kinds of dispersions. It contains a medication that has a limited biological half-life and is poorly soluble in water. Either water-soluble or water-insoluble carriers are employed.The two goals of CRSD are to improve the drug's solubility and provide regulated prolonged release. Ethyl cellulose, Eudragit RS, Eudragit RL, HPC, and other water-soluble carriers are utilized in CRSD.

2.2.9 Fifth generation SD

This type of SD have been observed more frequently lately. Such SDs are created through the development of structures at the nano and micron sizes to improve the end product's functionality.

2.3 Advantages of SDs

The following pharmaceutical benefits are provided by the solid dispersions approach (16), (17), (10):

1. The solid dispersion approach can help maximize the solubility & bioavailability of APIs that are not very soluble in water.
2. It is more applicable and simpler to make.
3. It causes a drug's absorption to increase in both extent and rate, which results in a quick rate of disintegration.
4. Drug transformation from liquid to solid form.
5. cover up unpleasant taste.
6. Reduced particle size.
7. Enhancing particles' wettability.
8. Drugs are delivered as supersaturated solutions, which are thought to be metastable polymorphic forms.
9. offering the drug in an amorphous form.
10. creating controlled release dosage form.

2.4 Disadvantages of SDs (18), (19)

1. Their main drawbacks are their instability. As they age, they exhibit changes in crystallinity and a slower rate of dissolution.
2. Solid dispersions are more negatively impacted by temperature and moisture than physical mixes.
3. Handling become tough due to sticky condition.
4. A significant amount of carrier is necessary to accomplish good dissolution.
5. Reproducibility of physicochemical properties.
6. Its challenging to produce SD in a dosage form.

3. Formulation Techniques of SD

3.1 Solvent Evaporation Approach

This approach involves dissolving drugs and polymers in organic solvent systems, followed by their evaporation. It is also possible to increase polymer solubility and/or decrease the amount of organic solvents utilized by combining aqueous solvents with organic systems. The solvent is quickly evaporated from the drug-polymer solution to create an amorphous drug-polymer

dispersion.(16) The primary benefit is that because organic solvents need a low temperature to evaporate, the drug or carrier can be kept from thermal decomposition.(17) Finding a solvent system that is compatible with the formulation, has a minimal residue in the final product, and can solubilize the drug-polymer system is the most difficult part of this process. poor or partial solubility of the component could result in non-homogenous ASDs and solubility of the component could result in non-homogenous ASDs and prolonged processing periods(16).

3.2 Melting Method

Melt-based techniques involve heating the formulation ingredients to create dispersions and then cooling them. One important advantage of the melting procedures is the avoidance of solvents. The possibility of drug deterioration due to the high temperatures is a significant disadvantage of these techniques. Additionally, medications must be sufficiently soluble or miscible in the polymer melt for melting techniques to work, which can be extremely challenging for some compounds to do(16).

3.3 Kneading Method

In this technique the carrier is turning into paste by adding small amount of solvent, next the drug is added and kneaded thoroughly for a specific amount of time. After kneading, the mixture is dried and, if required, sieved(18).

3.4 Hot Melt –Extrusion

The hot-melted extrusion method is a newer modification of the fusion method in which the extruder causes strong mixing of the components. The molten drug-polymer mixture can be shaped into implants, pellets, or oral dosage forms in contrast to the conventional fusion approach. The advantages of this technique includes reduced processing steps as it is straightforward, continuous, and effective method and there is no need to dry items or compress materials, additionally its produce molecular level dispersion and a consistent distribution of tiny drug particles in the polymer matrix. lastly This method is appropriate for large-scale production since it is allow for continuous manufacturing(19). Special equipment is needed to develop the dosage form from solid dispersions, which limits the use of the extrusion method(20).

3.5 Spray Drying

In this procedure the API and the polymer are first dissolved or suspended in a typical organic solvent and the solution is then atomized into tiny droplets by pumping it through a nozzle.

After the moist gas and these tiny droplets travel through a drying chamber, The granules of dry powder are sorted within a cyclone cluster. Ultimately The item gets dropped into the gathering vessel. Benefits include quick drying, compatibility with heat-sensitive drugs, and the ability to create particles with precise size and shape.

Drawbacks include: Possible residual solvents, therefore, careful monitoring of process conditions is necessary(8)

3.6 Lyophilization(freeze-drying)

In this method the medicine and carrier have been dissolved in a solvent and frozen, the solvent is then sublimated under vacuum in order to remove it.

Benefits include producing porous and amorphous solids with improved solubility and being appropriate for thermolabile medications.

their limitation: More expensive to produce; time and energy-consuming(21)

3.7 Co-preciptation Method

In this technique the drug and polymer are dissolved in the same solvent, and the solid dispersion is then precipitated using an antisolvent(22)

3.8 Kinetisol

Its a new technology that was brought to the pharmaceutical manufacturing from the plastics industry to improve the solubility of drugs that are not very water soluble . This fusion-based method quickly turns drug-polymer mixtures into a molten state by using shear and frictional energy. To create a single-phase ASD system, Kinetisol® quickly and completely combines the API with its excipient carrier(s) at the molecular level concurrent with the change to a molten state(23)

3.9 Electrospining

In this process The drug-containing polymer solution is treated with a high voltage electric field which lead to evaporation of the solvent rapidly and formation of fine fibers that solidify into a solid dispersion. The dissolving performance is enhanced by the improvement in surface-to-volume ratio that results from the production of electrospun drug–polymer matrices. Furthermore, a rapid evaporation rate and a high degree of mixing between the polymer and the API—both of which are challenging to achieve through powder blending—allow for the creation of physically stable amorphous solid dispersions(24).

4. Carriers and polymers used in SD

4.1 Selection of The Carrier

The physicochemical properties of the API and the processing facts should be considered while choosing the polymer since it effect on SD formation ,stability, drug dissolution and absorption(25). These are the standards for choosing a carrier (29), (30):

1. should be inert pharmacologically and chemically and considered safe
2. The polymer should be able to prevent medications from precipitating into their crystalline forms in the gastrointestinal (GI) environment.
3. To ensure that the produced dispersion is stable at room temperature, the polymer needs to have a high glass transition temperature (Tg).
4. the polymer should have good solubility in organic solvents
5. should have high glass-forming ability when formulating ASD since it can effectively stabilize drugs in their amorphous state.
6. must have good solubility and compatibility with the drug being formulated
7. In case of melting methods, Polymers need to have thermoplastic properties and thermally stable , possess minimal hygroscopicity and pseudoplastic behavior

4.2 Common Used Polymers in SD

4.2.1 Polyethylene Glycol (PEG)

PEG is a synthetic polymer made up of polymerization of ethylene glycol(26), typically have a molecular weight (M.wt) between 200 D and 300,000 D those with M.wt range from 1500-20000 D used in production of SD. their viscosity increase as their M.wt rise for instance the PEG with M.wt up to 600 D are fluids while those with M.wt range from 800-1500 D have vaseline like texture , from 2000-6000 D being waxy and lastly those with M.wt of 20000 D and higher develop hard crystals at room temperature. Their benefits for SDs include their high solubility in water and in a wide range of solvents that are organic in nature. The relevant PEGs' melting points is always below 65 ˚C. additionally They have the potential to increase compound wettability and solubilize some compounds. their disadvantage comprise toxicity—particularly that of low molecular weight PEGs, which exhibits somewhat higher toxicity than those of higher molecular weight—as well as stability issues during the hot melt technique(27).

4.2.2 Polyvinylpyrrolidone (PVP)

It is a fabricated homopolymer that's soluble in water produced from the polymerization process among the monomer N-vinyl-2-pyrrolidone(28). PVP is basically pH-stable, colorless, resistant to temperature changes, and chemically inert, among other special physical and chemical characteristics. Different K-values, such as K12 (3100–5700 Daltons), K17 (7900–10,800 Daltons), K25 (23,000–32,000 Daltons), K30 (35,000–51,000 Daltons), and K90 (900,000–1,300,000 Daltons), are used to identify the different molecular weight PVPs(29).

Because PVPs have a high glass transition temperature (Tg), they are used in the hot melt method to prepare solid dispersions. They are also primarily appropriate for the solvent method because of their exceptional solubility in a range of organic solvents. The PVPs' water solubility decreases as chain length increases, and their significantly increased viscosity at a given concentration is another drawback of high MW PVPs(27).

4.2.3 Poloxamers

Poloxamers, which are triblock copolymers depending on poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) (PEO-PPO-PEO), are also marketed under the brand name Pluronic® have the capacity to solubilize various substances. Therefore they have been used to produce SDs(30).

The poloxamers are class of surface-active substances and it is extensively employed in the drug industry. Propylene oxide and ethylene oxide are sequentially polymerized to produce these polymers. The characteristics of the resulting polymers vary greatly because blocks of different molecular weights can be combined. These are typically white, waxy granules that flow freely and are essentially tasteless and odorless. In the presence of metal ions, alkalis, and acids, pluronic aqueous solutions are extremely stable. The poloxamers have become a desirable molecule in formulation procedures because of their facile solubility in aqueous, polar, and non-polar organic solvents(31)

4.2.4 Soluplus®(SOL)

It is Polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol(32). A novel water-soluble graft copolymer made up of both lipophilic and hydrophilic components that invented by BASF Corporation. By forming micelles, this amphiphilic polymer can dissolve several medications over the critical micelle concentration (CMC). Yet below CMC, SOL is utilized to prevent drug precipitation through inhibiting drug nucleation, crystal creation and offer steric stabilization in a supersaturated state. Several SOL-based formulations that were created using the SD approach show promise for increasing drug solubility(33). This polymer provides excellent capabilities for the solubilization of BCS class II medicines and It is recognized as belonging to the fourth generation of solid dispersion due to its dual nature mentioned above(34)

5. Methods for Characterization of SD

5.1 Fourier Transform Infrared Spectroscopy (FTIR)

IR is a useful tool for identifying changes in the energy distribution of drug-matrix interactions. Sharp bands of vibration are a sign of crystallinity. Crystallinity in pure material ranged from 1 to 99%, which was precisely detected using the FTIR. It can be serves to track alterations in the bonding between functional groups(35).

5.2 Differential Scanning Calorimetry (DSC)

DSC is a thermal analysis used for Determining the temperature and heat flow associated with substance transitions as a function of temperature and time. We can monitor and investigate the thermal behavior of different substances, as well as determine melting temperatures, with the use of DSC. With the aid of DSC, processes that involve the production or consumption of energy can be quantitatively observed. Changes in the exothermic and endothermic peaks are typically

attributed to interactions between medicines and polymers. A glass-to-rubber transition, (re)crystallization, melting, or deterioration are examples of thermal phenomena(35).

5.3 Scanning Electron Microscopy (SEM)

High-resolution imaging is provided by scanning electron microscopy (SEM), which gives precise and in-depth information about the morphology and surface properties of materials(36).

5.4 Powder X-ray Diffraction(PXRD)

A practical method for examining the crystal structures of organic, inorganic, and polymeric materials is powder X-ray diffraction. Atoms and repeating units are arranged differently in each crystal. These atoms are exposed to X-ray radiation, which produces a sequence of different peaks that are utilized to clearly distinguish the crystalline components. XRD can differentiate between two materials based on their distinct molecular structures, even if their chemical compositions are identical.

PXRD has become a popular analytical method in both industry and academics due to its ability to quickly perform measurements on pharmaceutical powders(37).

5.5 Solubility and In Vitro Dissolution Test

The shak flask method is used to determine the equilibrium solubility at a specific pH and temperature. This approach involves adding an excess of the compound to a particular medium and shaking it at a set time, usually 24 hours or more. The presence of undissolved material serves as confirmation of saturation. A sample for analysis can be obtained once the slurry has been filtered. The sample is frequently diluted to avoid

crystallization. The quantity of solute present in the sample is ascertained using a suitable technique that depends on the concentration and the type of solute or solvent.

Typical techniques are:

- ✓ Visible and ultraviolet spectroscopy
- ✓ Chromatographic technique
- ✓ Volumetric and gravimetric(38).

In vitro dissolution testing is crucial for process control and quality assurance, determining the product's stability and release characteristics over time, and supporting regulatory decisions (such as determining whether minor formulation changes or changes in the manufacturing site have an impact on performance). As a predictor of the formulation's in vivo performance, the dissolving test has also been extensively studied over the last 20 years(39).

6. Applications of SD

1. It was shown that the SD system could provide bioavailable oral dosage forms for anti-cancer drugs, which might be used to improve patient comfort and compliance by replacing traditional injections
2. Solid dispersion is a functional carrier with the added benefit of guiding the release of highly soluble versions of weakly water soluble medications for optimal absorption at the appropriate site.
3. Solid dispersion systems minimized the need for certain prescriptions to be taken with food, by reducing the effect of food on drug absorption, as a result the drug treatment became more convenient.
4. It has been demonstrated that solid dispersion formulations can speed up the onset of action for pharmaceuticals such as NSAIDS [non-steroidal anti-inflammatory drugs], where quick action is crucial in lowering acute pain and inflammation.

5. The improved absorption efficiency of solid dispersion systems allows for a reduction in the amount of active agent needed per dose, lowering the cost of these medication regimens.
6. In order to improve immunosuppressive therapy for lung transplant recipients, the solid dispersion is prepared as a dry powder formulation for inhalation. Many problems can be avoided, including the use of local anesthetic and irritating solvents(40).

7. Challenges and Prospects

7.1 Physical Stability and Recrystallization

Amorphous materials are thermodynamically metastable solids that have molecules instructed in short order with greater solubility and free energy than their crystalline counterparts that have three dimensional arrangement and less solubility, When a drug is available in an amorphous form, SD can ultimately increase its bioavailability. The choice of an appropriate polymer carrier aids in improving the drug's solubility, rate of dissolution, and physical stability in the solid state. However, despite all of these advantages, the main drawback of amorphous material is its low chemical and physical stability and converts easily to the more stable crystalline form which frequently causes problems for the product's development and marketing(41).

The amorphous drug crystallize in two steps: Nucleation, the first stage, takes place at a cooler temperature, whereas crystal formation, the stage two, needs a greater temperature. polymeric excipients can slow down the rate of nucleation, via, lowering the concentration of free medication for the development of seeds or nuclei,, improve aqueous solubility and prevent the precipitation of the dissolved drug Additionally, polymers make the solution more viscous, which could change how frequently atoms or molecules move across the nucleus' surface. Furthermore, because of their huge, difficult, and soft arrangements, large M.wts, and capacity to be present in multiple configurations, they possess an entropy of configuration that is adequately high . These significantly diminish the free energy of the SD, which in turn reduces the likelihood of drug recrystallization. another mechanism by which polymer stabilize SD its by exert antiplasticization effect which is phenomena that increases the value of the Tg, there by increasing The required free energy for the amorphous substance to transform into its crystallized state(42). The drug molecules could bond with the polymer molecules through a variety of weak forces, including hydrophobic, ionic, electrostatic, van der Waals forces, and H-bonding that contribute to the stabilization of SD(43).

7.2 Scale Up and Industrial Translation

With careful control of key process parameters, spray drying and hot-melt extrusion can be used to scale up solid dispersions from bench to commercial production. Successful industrial translation is supported by the use of Quality-by-Design principles, trustworthy modeling tools, and comprehensive stability assessments. HME is a leader in commercial ASD products because of its many advantages, which include solvent-free processing, small equipment, continuous operation, and green manufacturing(44).

8. Conclusion

Solid dispersions are a potent and adaptable method for improving the oral bioavailability, solubility, and rate of dissolution of medications that are not highly water soluble. Significant progress has been achieved in formulation methods, carrier selection, and analytical characterization tools over the past few decades, leading to dispersion systems that are more stable and effective. Modern methods like hot-melt extrusion and spray drying have increased the usefulness of solid dispersions in both industrial and scientific contexts, whereas polymers are essential for maintaining the drug's amorphous form and avoiding recrystallization.

There are still issues in spite of these developments, especially with regard to reproducibility, scale-up, and long-term physical stability. To enhance formulation conditions, create performance prediction models, and better understand drug–polymer interactions, more research

is needed. Solid dispersion systems are anticipated to become more and more important in the creation of pharmaceutical products of the next generation, particularly for Category II and IV of the Biopharmaceutics Classification System (BCS) medications, as a result of continued innovation and greater mechanistic understanding.

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Ethics Information

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Data Availability

The article contains all the relevant details.

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