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"Amorphous Solid Dispersions: An Emerging Approach for Improving Solubility And Oral Bioavailability Of Poorly Water-Soluble Drugs"

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ABSTRACT :

Amorphous solid dispersions (ASDs) are widely used to improve the oral bioavailability and solubility of drug that are poorly soluble in water. ASDs have been produced using a variety of methods, and new ones are constantly being developed. An updated summary of manufacturing processes for creating ASDs is included in this review. Given that physical stability is a crucial quality attribute for ASDs, the effects of downstream processing, formulation, equipment, and process factors have been examined. In order to find appropriate manufacturing techniques that could help create ASDs with adequate physical stability, selection procedures are suggested.

Keywords: Amorphous solid dispersions, oral bioavailability, solubility, physical stability

INTRODUCTION

For orally administered drugs to be absorbed into the systemic circulation, solubilization is an essential prerequisite. Unfortunately, a significant portion of medications in the R&D pipeline (~90%) and those on the market (~40%) have poor water solubility. As a result, different formulation techniques have been used to address certain medications' solubility and/or dissolving issues. Formulating poorly water-soluble medications as ASDs can effectively increase their solubility and rate of dissolution. [1] One for APIs whose solubility cannot be improved by reducing their particle size, amorphous solid dispersions (ASDs) are the method of choice. ASDs are typically produced in industry using processes such as hot melt extrusion, spray drying, wet granulation, KinetiSol, and fluid bed coating. ASDs are also included a large range of dosage forms, including films, semi-solids, controlled drug release, nanoparticles, etc. [2, 3, 4] It can be prepared via hot melt extrusion. Since the energy needed to break the crystal lattice of crystalline pharmaceuticals is not needed to dissolve drugs in an amorphous state, the dissolution rate and transient solubility of the API in an amorphous state are significantly increased from a thermodynamic perspective. [5]

The production procedures, stability, solubility, and bioavailability of the ASDs are all impacted by the choice of polymer carriers. Therefore, the most important element influencing the development of ASD is the choice of polymer. Polyvinyl lactam polymers like polyvinylpyrrolidone, polyvinylpyrrolidone-vinyl acetate copolymer and Soluplus®, as well as cellulose derivatives like hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxy ethyl cellulose, Hypromellose acetate succinate (HPMCAS), hydroxypropyl methylcellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), and polymethacrylates (Eudragit® E, L, S) are commonly used in the formation of ASDs. Glass transition temperatures (Tg), hygroscopicity, degradation temperatures, and solubilization capacities are some of the physicochemical characteristics of these polymers that may contribute to the unique capabilities of the ASDs. [6,7]

ADVANTAGES AND SALIENT CHARACTERISTICS OF AMORPHOBIC SOLID DISPERSION [8]

- Acidic, basic, neutral, and Zwitterionic medications can all be affected by ASD.
- ASD reduces the amount of active medication needed to assess safety and efficacy.
- ASD speeds up the drug's absorption and rate of dissolution, perhaps leading to a rapid commencement of effect.
- Alternative routes are offered by ASD to enhance oral bioavailability.
- ASD offers faster onset, lower dosage, and enhanced oral bioavailability.
- It offers a platform for clinical research as well as support for toxicity studies.
- A small amount of medication in solid state can be distributed uniformly using ASD.

METHODS OF PREPARATION OF AMORPHOUS SOLID DISPERSION

a. Fusion method

The fusion method, also known as the melt method. This technique was first employed by Sekiguchi and Obi to create simple eutectic mixtures. Later, Leuner and Dressman (2000) referred to this process as the hot melt method. In this approach, the drug is melted along with a carrier, then the mixture is cooled and ground into a fine powder. Despite its advantages, the method has certain drawbacks, such as the requirement for high processing temperatures, which can potentially lead to drug degradation, and limited miscibility between the drug and carrier.[9] A physical mixture of a medication and a water-soluble carrier is prepared using the melting or fusion process, which involves heating the mixture until it melts. After that, the melted slurry is vigorously stirred in an ice bath to quickly solidify it. The final solid mass undergoes sieving, pulverization, and crushing. Appropriately, this has undergone numerous modifications, such as pouring the homogenous melt onto a stainless steel or ferrite plate in the form of a thin layer and cooling it with water or air flowing on the other side of the plate. Furthermore, it is frequently possible to achieve a super-saturation of a medication or solute in a system by quickly quenching the melt at a high temperature.[10]In these circumstances, the immediate solidification process stops the solute molecule in the solvent matrix.

b. Spray drying

Spray drying is a continuous and economically scalable drying method; it is one of the most used methods for producing ASDs. [11, 12] There are multiple processes in the spray drying process. Initially, a spray nozzle is used to pump the feed solution or suspension comprising the medication, polymer, and maybe additional additives into the drying chamber. the several kinds of widely used nozzles. Larger particles with improved flow characteristics can be produced using pressurized nozzles, which are also simple to scale up. Because it can enhance tablet consistency, compression, die filling, and powder flow, this is very beneficial for downstream processing. Using a pressured nozzle, sildenafil was spray-dried with poly (lactide-co-glycolide) to create ASD microparticulate (4e8 mm). [13] The drying capacity104, the kind of atomization nozzle, and the viscosity of the feed material all influence the feed pump selection. The solvent in the drying chamber evaporates when the nozzle's atomized droplets come into contact with the heated gas. Although the length of time particles stay in the drying chamber varies based on the equipment and process conditions, it typically lasts a few milliseconds. [14] Industrial spray dryers are capable of evaporating up to 400 kilograms of solvent per hour with a gas flow rate of up to 5000 kg/h84.

The heavier particles are extracted from the drying gas and gathered in the cyclone separator once the dried material has been transported there. The exhaust fumes are collected by a filter, which removes the finer particles. In certain situations, particles may scrape off and settle at the bottom of the drying chamber. [15] Mechanical brushes are another option, but they may cause more stress. The amount of solvent residue is one of the issues with spray drying.

As a result, secondary drying typically occurs after spray drying. By adjusting the formulation and process parameters84, ASD product features and performance can vary greatly. The feed rate and the input temperature are two manufacturing parameters of the critical processing variables. To get a uniform amorphous dispersion, these parameters must be optimized. The boiling point of the solvent(s) and the physical and chemical stability of the formulation's ingredients determine the inlet temperature. [16]

Advantage

1. **Good for Heat-Sensitive Drugs:** Uses lower temperatures compared to other methods like hot-melt extrusion.
2. **Uniform Particle Size:** Helps improve consistency and performance of the drug.
3. **Scalable and Widely Used:** Easily scaled from lab to industrial production.
4. **Customizable Formulations:** Flexible in terms of solvent, polymer, and processing conditions.
5. **Fast Solvent Removal:** Rapid drying minimizes drug degradation.

Disadvantages

1. **Requires Solvent Use:** Organic solvents are often used, which may be toxic and need proper handling and removal.
2. **Lower Drug Loading:** May require more polymer, which can increase the dose size.
3. **Physical Stability Issues:** Amorphous particles can absorb moisture and recrystallize over time if not properly stored.
4. **Possible Solvent Residue:** Incomplete drying can leave residual solvents, affecting safety and stability.

c. Solvent Evaporation

Tachibana and Nakamura used this technique for the first time in 1965. [17] Small quantities of drug and vector are dissolved in a common solvent in this procedure, which is followed by vaporization until a smooth, solventless film is left behind. The film is then dehydrated until it reaches a constant mass. " A key benefit of the solvent method is that it helps avoid thermal degradation of drugs or carriers, as organic solvents typically evaporate at relatively low temperatures**.** [18] For example, "The solvent evaporation method was used to prepare a solid dispersion of furosemide with eudragits".[19]

d. Freeze Drying (Lyophilization)

Heat and mass are transferred to and from the product being prepared during the freeze-drying process. This method was put out as substitute for solvent evaporation. In order to create a lyophilized molecular dispersion, the drug and carrier are co-dissolved in a shared solvent, frozen, then sublimed. This process is known as lyophilization. [20]

e. Electro Spinning

In this, solid fibres are created from a polymeric fluid stream solution. In this procedure, a conducting capillary attached to a reservoir holding a polymer melt or solution and a conductive collection screen is subjected to a strong electrostatic field. Charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape (also called Taylor's cone) when the electrostatic field strength is increased to but not beyond a critical value. When the critical threshold is not exceeded, a charged polymer jet is emitted from the tip of the cone, serving to discharge the accumulated surface charge on the hanging drop. The electrostatic force then carries the charged jet that was ejected to the collection screen. As the charged jet travels

toward the collection screen, it thins due to the columbic repulsion force. As the charged jet dries, the rise in viscosity limits the thinning down of the jet. This method has a lot of promise for managing the usage of biomedicine and creating nanofibers. Since it's the most straightforward and affordable method. [21,22]

Advantages

- This technique holds great promise for fabricating nanofibers and regulating the release of pharmaceutical agents. It is one of the simplest and most cost-effective processes.
- In the future, it may also be applied to the development of solid dispersions.

Disadvantages

- Less economical for all the drugs and carrier.

f. Supercritical Fluid (SCF) Technology

Supercritical fluid (SCF) technology emerged in the late 1980s and early 1990s. It enables the production of formulations with narrow particle size distributions typically in the micro- or nanoscale without the need for conventional solvents. Interestingly, the use of SCFs for particle formation was first reported by Hannay and Hogarth in 1897. [23] A substance enters the supercritical state when both its temperature and pressure exceed the critical point. In solid dispersion techniques, SCFs can function either as solvents or antisolvents, depending on the process design. SCF's basic concept is to dissolve the drug and carrier in a supercritical solvent, like CO2, and then spray the mixture into a lower pressure expansion vessel via a nozzle. The rapid expansion leads to swift nucleation of the dissolved drug and carrier, facilitating the fast formation of solid dispersion particles with an appropriate size distribution. SCF can currently be performed in a variety of ways, such as solution enhanced dispersion by gas antisolvent (GAS), [24] rapid expansion from supercritical solution (RESS), [25] SCF (SEDS)[26] and supercritical antisolvent (SAS). In the RESS (Rapid Expansion of Supercritical Solutions) process, the drug and carrier are first dissolved in a supercritical fluid, then rapidly sprayed through an atomizer into a low-pressure expansion chamber, resulting in the formation of a solid dispersion. One advantage of this approach is that it can lower the quantity of organic solvent required to make the solid dispersion. Carbon dioxide (CO_2) is an ideal solvent for SCF technology in the preparation of solid dispersions of poorly soluble drugs, owing to its low critical temperature (31.04 °C) and pressure (7.38 MPa), along with its non-toxic and non-flammable nature. [27,28] The optimal ratio was one to one between the drug and the carrier. To improve the solubility and bioavailability of apigenin, a different study used the SAS technique to create apigenin nanocrystals. [29]

According to the findings, the final formulation's Cmax and AUC increased 3.6 and 3.4 times, respectively, in comparison to the medicine alone, suggesting improved BA. In drug research, the SCF approach shows promise for increasing the solubility and bioavailability (BA) of medications with low water solubility. One disadvantage of this approach is that most drugs are insoluble in CO2.

Advantages

- Rapid penetration of the supercritical anti solvent into the droplets causes the drug and matrix to become supersaturated, solidify, and form particles.
- This method is commonly referred to as precipitation with compressed anti-oven. More particular instances of PCA include solution enhanced dispersion by supercritical fluids, Supercritical Anti Solvent when supercritical CO2 is utilized, and Aerosol Solvent Extraction System.

Disadvantages

- Typically, both the medication and matrix must be dissolved using more expensive organic solvents such dichloromethane or methanol.

g. Co-Precipitation

By dissolving the carrier in the solvent and then adding the medication while stirring to form a uniform mixture, this method produces a solution. Water is then added dropwise to the homogeneous mixture to produce precipitation. After that, the precipitate is filtered and dried. including utilizing HPMC E15LV as the carrier and a variety of methods, such as co-precipitation, spray-drying, and kneading, to prepare a silymarin solid dispersion. The silymarin solid dispersion made by co-precipitation showed a significantly ($p < 0.05$) higher solubility than the other two methods. [30]

h. Melt Agglomeration Process

This method, in which the binder serves as a carrier, has been utilized to create solid dispersions. Additionally, solid dispersions can be created by either heating the excipient, drug, and binder to a temperature above the melting point of the binder (a process called "melt-in") or by spraying a drug dispersion in molten binder onto the heated excipient (a process called "spray-on") using a high shear mixer.

Because the temperature can be more easily controlled and a higher binder content can be added to the agglomerates, the rotary processor may be better than the high melt agglomeration.

When preparing a solid dispersion by melt agglomeration, the impact of the type of binder, the manufacturing process, and the particle size are crucial factors. Because of the immersion process of agglomeration formation and growth, it has been discovered that the melt-in method yields higher dissolution rates than the spray-on method using PEG 3000, poloxamer 188, and gelucire 50/13. Additionally, the melt-in process produces a uniform medication distribution in the agglomeration. While tiny particles promote total adherence to the material to bowl immediately after melting due to their dispersion and coalescence, larger particles cause agglomerates to densify.

PHYSICAL STABILITY CHALLENGES OF AMORPHOUS SOLID DISPERSIONS

- There is a thermodynamic force for crystallization since a drug's liquid or amorphous form has a higher free energy below the melting point than its crystalline form. Amorphous-amorphous phase separation (AAPS) and/or crystallization—the process by which an amorphous substance transforms into a crystalline form—are examples of solid-state physical stabilities linked to ASDs that counteract the solubility advantage of ASDs. [31]

- AAPS can also arise from exposing ASDs to moisture while they are being stored. [32]
- Moisture can be introduced into hygroscopic ASD systems by ambient humidity. By reducing the system Tg and creating a plasticizing action, moisture enhances the molecular mobility of ASD and increases the probability of crystallization. Absorbing water may potentially disrupt drug-polymer interactions because it competes with hydrophilic polymers for the creation of hydrogen bonds. In certain ASD systems, too much moisture can also make the drug-polymer less soluble. [33,34]
- Mechanical stressors like grinding, crushing, or com pressing might encourage deformation-induced molecular mobility in ASDs during the formulation process. [35]
- One of the key problems with many ASD systems is still the creation and upkeep of an amorphous drug form, which restricts their expanded use. [36, 37] Therefore, it's crucial to consider how manufacturing variables affect the physical stability of ASDs while examining ASD preparation techniques.

FUTURE PROSPECTS OF AMORPHOUS SOLID DISPERSIONS

Solid dispersions have several benefits, but their application in commercial dosage forms for poorly water-soluble medications has been constrained by problems with formulation, stability, scale up, reproducibility, and preparation. However, the availability of surface-active and self-emulsifying carriers with comparatively low melting temperatures has made successful development possible in recent years. Hard gelatin capsules are used to hold the medicine and carrier due to their easier production process, increased dissolving rate, and higher bioavailability. The discovery of novel surface-active and self-emulsifying carriers for amorphous solid dispersion would be one of the main areas of study. The development of extended-release dosage forms, the physical and chemical stability of the drug and carrier in amorphous solid dispersion, and the identification of vehicles or excipients that would slow or stop the crystallization of pharmaceuticals from super-saturated systems would be the other main focus. [38]

CONCLUSION

Drugs that don't dissolve well in water can be made more soluble and easier to absorb via amorphous solid dispersions. The medicine remains in an amorphous, or non-crystalline, state when combined with a unique polymer, which facilitates its quicker absorption by the body. ASDs are now more dependable and simpler to manufacture thanks to recent developments in novel polymers, enhanced manufacturing techniques (such as hot-melt extrusion and spray drying), and computer-based tools. Additionally, researchers are working on eco-friendly procedures, personalized medicine, and improved methods for predicting how a drug will act in the body. To put it briefly, ASDs are a useful and developing pharmaceutical technology that aids in the conversion of poorly soluble medications into efficient therapies.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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