REVIEW ARTICLE

Exploration of Mesoporous Silica-based Amorphous Solid Dispersions to Enhance Bioavailability

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Abstract

This research investigates using mesoporous silica-based amorphous solid dispersions (ASDs) to increase the bioavailability of poorly soluble drugs. Mesoporous silica is a valuable carrier for keeping active pharmaceutical ingredients (APIs) in their amorphous state, which improves solubility and dissolution rates. This is due to its vast surface area and tunable pore topologies. The development of supersaturated solutions upon interaction with aqueous media is one of the mechanisms driving this augmentation, as it considerably improves medication absorption. The study demonstrates a number of ASD preparation methods that help ensure even drug dispersion within the silica matrix, including spray drying and solvent evaporation. Scanning electron microscopy and differential scanning calorimetry are two characterization techniques used to evaluate the physicochemical characteristics of these formulations. Research both *in vivo* and *in vitro* show the research highlights various preparation techniques for ASDs, such as spray drying and solvent evaporation, which facilitate uniform drug distribution within the silica matrix. Characterization methods, including differential scanning calorimetry and scanning electron microscopy, are employed to assess the physicochemical properties of these formulations. *In vitro* and *in vivo* studies demonstrate that mesoporous silica prevents crystallization and enhances the pharmacokinetic profiles of APIs such as ritonavir and telmisartan. All things considered, the incorporation of mesoporous silica into ASD formulations offers a viable strategy for resolving the issues related to low-solubility medications, opening the door to more potent therapeutic uses. This investigation establishes the foundation for subsequent studies aimed at refining ASD formulations for an expanded array of poorly soluble chemicals.

Key words: Amorphous solid dispersions, bioavailability drug solubility, characterization techniques, mesoporous silica, supersaturation.

INTRODUCTION

The pharmaceutical industry has shown a great deal of interest in amorphous solid dispersions (ASDs) to increase the bioavailability of drugs that are not very soluble in water.[1] The utilization of mesoporous silica-based carriers, which offer an efficient platform for drug loading and release, is one of the promising strategies. Because of their large surface area, consistent pore size distribution, and stable amorphous structure, mesoporous silica materials are excellent choices for drug delivery system.[2] The current work aims to investigate the benefits of an amorphous formulation platform based on mesoporous silica over traditional spray-dried amorphous dispersions. The concept behind the application of mesoporous silica in formulations for ASD is to maintain the medication in an amorphous state, inhibiting crystallization and enhancing solubility.[3] Poorly soluble medications are molecularly distributed inside the mesoporous silica matrix of ASDs, thereby greatly increasing the rate of disintegration.

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Because the medication dissolves more easily, the circulatory system absorbs it more quickly, increasing bioavailability.[4]

MESOPOROUSSILICA

The medication compound load into mesoporous silicon (MS) has been viewed as a unique and promising approach to standard ways of developing amorphous formulations in recent decades. Drug molecules can be effectively trapped in mesopores by MS materials, preventing recrystallization. Their unique nanoscale mesopores with large pore volumes and surface areas are responsible for this. Because of this, pharmaceuticals that are amorphous and trapped in mesopores can produce drug supersaturation in aqueous environments and accelerate the rate of dissolution, which results in a higher bioavailability than when the drug is in its crystalline form. Consequently, there has been a lot of interest in MS materials as effective delivery systems for medicinal compounds that are poorly soluble in water. Numerous fields, including optics, sensing, drug delivery, and catalysis, employ mesoporous silica.[5]. The ligands used in the examined mesopores remove heavy metals from waste fluxes. There are two ways to use mesoporous silica synthesis: Creating liquid-crystal templates and constructing cooperative self-assembly processes. The basis of this synthesis process is the interplay of organic templates.[6] Mesoporous silica nanoparticles can have their shape and functionality adjusted through a variety of synthetic approaches. With an emphasis on experimental techniques, we explain how various synthesis conditions, pore-swelling agents, and templating can alter the pore topology and size of the mesopore system. Furthermore, we demonstrate how co-condensation techniques using silane coupling agents can functionalize the mesoporous nanoparticles, with a focus on the spatially selective anchoring of various molecular functionalities within the nanoparticles. We go over ways to modify the mesoporous particles' pore walls, such as adding redox-sensitive sulfide linkages or making mesoporous organosilica that are autofluorescent and contain curcumin. Morphological characteristics like size have a significant impact on the effectiveness of targeted medication delivery applications. The ultimate goal is to enable safer, more convenient administration methods that are also more effective and patient friendly by lowering drug concentrations and dosage frequencies. Personalized medicine may be made possible by nanotechnology and a variety of techniques that lead to maintained medication action. Apart from these advantages, there exist evident business benefits including the potential to restructure medications that have not reached the clinic because of their poor solubility or severe side effects. It has been proposed that a variety of nanodevices could improve the medication delivery landscape. Surprisingly few medicine formulations based on nanotechnology have made it to the clinic, despite enormous expectations and intensive research efforts over the past few decades. The scientific community has recently focused a significant deal of attention on mesoporous silica with regular geometries because of their significance and enormous promise in real-world applications such as sensing, adsorption, catalysis, separation, medicine, ecology, and nanotechnology. In particular, immobilization of the associated functional groups in the mesopores is frequently necessary for applications. Modification of these mesoporous silica is necessary to obtain desired uses.[7]

Properties of mesoporous silica

Due to its many specific characteristics, mesoporous silica is an extremely adaptable material that finds use in a wide range of scientific and industrial applications. Reaching up to 1000 m^2/g, its high surface area is one of its most remarkable features. Because it offers a large number of active sites for interactions, its large surface area improves its efficacy in adsorption, catalysis, and drug delivery applications. Moreover, the "adjustable pore size" of mesoporous silica, which normally ranges from 2 to 50 nanometers, enables exact control over its chemical and physical characteristics.[8] Apart from its thermal and structural characteristics, mesoporous silica is also biocompatible, indicating that it is safe for use in biological applications. Because of this, its porous network may be loaded with therapeutic agents and released in a regulated way, making it a great option for drug delivery systems. Because of its extraordinary adsorption properties, which come from being porous, it can also capture and store a wide range of molecules, gasses, or toxins.[9] This property makes it helpful for environmental applications such as cleaning up air or water of pollutants. Mesoporous silica is considered to have a high surface area, configurable pore size, thermal and chemical stability, and biocompatibility.[10]

ASD

Therapeutic materials that lack crystalline structure are solid-state and lack a clear intermolecular arrangement are known as amorphous products. As a result, they have low thermodynamic stability. For molecular dissolution to occur in a conventional crystalline structure, the solubility/dissolution process must first shatter the crystal structure.[11] The use of amorphous active pharmaceutical ingredients (APIs), or APIs, in different formulations, has gained popularity in recent years, particularly after it was discovered that their crystalline versions have extremely low aqueous solubility. This frequently results in insufficient oral bioavailability and dissolution rates.[12] When compared to crystal forms, amorphous forms typically show higher levels of supersaturation in aqueous fluids, which results in higher apparent solubility. A constant problem in drug research, poor water solubility of APIs is increasingly common in novel therapeutic candidates. Therefore, it would be beneficial to use sophisticated formulation techniques to increase the apparent solubility and/or dissolution rate of weakly soluble APIs.[13] A single issue with creating an ASD is that the

medication and the polymer are combined and diffused at the molecular level, which makes precise characterization more challenging. Fortunately, recently developed characterization approaches offer quantitative and qualitative data on the characterization of ASDs.[2] The best way to characterize ASDs is to use a variety of methods to look at their physicochemical characteristics at various developmental stages. A potential reason for this could be that ASDs are more complex structures than typical medication formulations: ASDs if formed under such conditions, are either unstable or cannot be manufactured.[14] ASDs have been defined in a variety of ways, frequently using underlying physicochemical characteristics (such as being eutectic), the presence or lack of crystallinity, or the system's thermodynamic versus kinetic stability. Nonetheless, the following definition has gained traction when discussing pharmaceutical medication delivery. Amorphous pharmaceutical ingredients (APIs) are primarily embedded in solid matrixes made of polymers, which are known as ASDs. It has been demonstrated that using ASDs for oral drug delivery improves both *in vivo* bioavailability in animals and *in vitro* performance.[15]

ASD benefits

An important consideration in drug formulation is increasing the bioavailability and solubility of drugs that are not very water-soluble. ASDs provide a considerable benefit in this regard. ASDs preserve the medication in its amorphous state, which is more soluble than its crystalline equivalent, by distributing it in a polymer matrix. This method improves the drug's therapeutic efficacy by facilitating better absorption in the body. Furthermore, ASDs minimize unwanted effects by enabling lower therapeutic dosages to produce the desired results. In addition, they provide customization options based on the characteristics of the medicine by providing freedom in the selection of excipients and production processes.[16] ASD is a solid dispersion in which an excipient matrix contains an active component that is primarily scattered amorphously. To make the medication more soluble in ASDs its amorphous form is essential. As the substance is amorphous, no energy is needed to shatter its crystal lattice. As a result, many weakly soluble in water drugs can achieve markedly faster dissolution and substantially higher apparent solubility in their amorphous form as compared to their crystalline form. In addition, ASDs have been shown to increase supersaturation, which raises membrane flux and increases bioavailability. A.S.D.s' increased wettability is also a result of the hydrophilic polymers they contain. Solid dispersions are categorized as first, second, or third generation based on the composition of the formulation. Glass-forming ability and low-crystallization tendency, or ASD, can be evaluated by experimental and computational approaches.[17] The use of experimental and in-silicon miscibility prediction methods for polymer excipient screening is described. Reviewed are enhanced methods for polymer screening that need less drug material as well as ASD's scalability from workbench to marketplace. There is additional discussion of preclinical animal selection, *in vitro* assessments, and the application of preclinical findings to clinical investigations. Understanding how polymeric improves the amorphous phase's stability in the solid form and how ASD increases bioavailability has advanced made it easier to apply ASD in a variety of contexts, from preclinical research to commercialization and discovery research.[18] Although making up the majority of therapeutic candidates in development, poorly soluble candidates typically have the greatest attrition rates because of their poor bioavailability. Drug distribution in the form of ASDs is one possible remedy. The increased interest in ASD research over the past few decades is shown by a recent analysis of patent and literature review. There has been an exponential rise in articles and patents in both academia and industry. Different definitions of ASDs have been proposed; these definitions frequently consider underlying physicochemical features. Nonetheless, the following definition has gained traction when discussing pharmaceutical medication delivery. ASDs are frequently employed in the development of novel therapeutic solutions to accelerate and enhance dissolution, hence boosting the absorption of less soluble substances. These systems consist of a polymer matrix stabilizing an amorphous active medicinal component to give increased stability. The preparation and characterization processes of ASDs were covered in this review, with a focus on comprehending and forecasting stability. Reasonable polymer selection, preparation methods, their benefits and drawbacks, and polymeric ASDs' characterization have all been covered. According to the International Council for Harmonisation recommendations, stability aspects have been defined as relying on the choice of polymers and ASD. ASDs are frequently employed in the development of novel therapeutic solutions to accelerate and enhance dissolution, hence boosting the bioavailability of poorly soluble substances.[19] These systems are made up of a polymermatrix that increases stability by stabilizing an amorphous API. This review focused on understanding and forecasting stability while covering the preparation and characterization stages of ASDs. Reasonable polymer selection, advantages and disadvantages of preparation techniques, and characterization of polymeric ASDs have all been discussed. Stability aspects are stated by the ICH recommendations depending on the polymer selection and ASD preparation methods. A method that increases bioavailability was also considered. ASDs are widely used in the development of innovative medicinal solutions to improve and accelerate dissolving while increasing the bioavailability of poorly soluble compounds. These systems consist of a polymer matrix that stabilizes an amorphous active medicinal component, hence increasing stability. This review covered the preparation and characterization stages of ASD with an emphasis on understanding and forecasting stability. The benefits and drawbacks of preparation methods, rational polymer selection, and characterization of every aspect of every aspect of polymeric amorphous solid dispersions have been discussed as been discussed. The ICH guidelines suggest that stability factors depend on the polymer choice

and ASD preparation techniques. The process that enhances bioavailability was also taken into account.[20]

ASD challenges

This method improves the drug's therapeutic efficacy by facilitating better absorption in the body. Furthermore, ASDs minimize unwanted effects by enabling lower therapeutic dosages to produce the desired results. In addition, they provide customization options based on the characteristics of the medicine by providing freedom in the selection of excipients and production processes.[21]

Nanoparticles

Nanoparticle-based drug delivery techniques offer a number of advantages for increasing the bioavailability of poorly soluble drugs. By decreasing the drug's particle size to the nanometer range, nanoparticles increase the drug's surface area-to-volume ratio and accelerate its solubility and dissolution rates. In addition, the drug's interaction with biological membranes is improved by the small size of the nanoparticles, improving absorption and bioavailability. Memetic material, proteins, peptides, anticancer drugs, and genetic material can all be loaded onto mesoporous nanoparticles of silicon (MSNs), an adaptable drug delivery platform. Because of their surface functionalization, pore shape, and tuneable particle size, MSNs are thought to be promising drug carriers. As a result, MSNs offer chances for their practical application in numerous domains. We cover both traditional and cutting-edge MSN synthesis techniques in this review, along with their uses in medication delivery, gatekeepers, and biosensors.[22] Furthermore, the state of research on internalization processes, cytotoxicity, and biocompatibility is reported. The development of these modern multifunctional materials is currently opening up a wide range of study disciplines to innovative solutions. In this way, the previously unreachable selectivity of recent biomedical research advancements is creating opportunities for tailored treatments and diagnostic techniques in the future.

The production of devices that can establish a close connected with the biological world is made possible by powerful advancements in the preparation and characterization processes of nanotechnology products. This fact indicates precise control over the release of therapeutic agents and raises the possibility of improving the therapeutic action's specificity as well as the possibility of reevaluating some of the more potent medications for various diseases that were abandoned because of their low tolerance.[23]

Co crystal

Co-crystals were discovered in 1844, but their composition was not completely clarified until 1958. In 1963, Lawton and Lopez came up with the phrase "co-crystal." Massive crystalline supramolecular complexes with several constituents belonging to the same crystal lattice interact with the food and according to the drug administration, co-crystals are made of non-ionic interactions and are in a neutral state.[24] Co-crystals can be roughly categorized into two primary groups: molecular co-crystals and ionic co-crystals. Two or more distinct neutral components joined by hydrogen or halogen bonds form molecular co-crystals. On the other hand, coordination bonds or charge-assisted hydrogen bonds are responsible for maintaining an ionic co-crystal if it possesses at least one ionic component. Co-crystal has created a cutting-edge technique for modifying the physicochemical characteristics of medicinal compounds through the use of crystal engineering. Co-crystals are single-phase, crystalline solids made up of two or more distinct ionic and/or molecular components. These substances are neither solvates nor simple salts, and they usually have a stoichiometric ratio. Crystals are formed by non-covalent interactions such as halogen bonding, van der Waals forces, hydrogen bonds, and π-π interactions.[25] The primary interaction A pharmaceutical cocrystal is a chemical compound that is formed when a medicine and a conformer, or excipient, are approved by pharmaceutical companies. Typically, the conformers consist of chemicals that dissolve in water, such as saccharin, coffee, nicotinamide, and carboxylic acids. Among the drug forms with high thermodynamic energy are salts, amorphous systems, and co-crystals of medications including highly soluble coformers because of the supersaturation, drugs in these formulations should have a higher kinetic solubility in the gastrointestinal fluid. When the concentration of drug molecules in solution exceeds the equilibrium solubility of the drug's thermodynamically stable state, supersaturation takes place. Since a supersaturated drug solution is thermodynamically unstable, the stable form of the drug crystallizes out of it. The change causes the concentration to drop quickly to the stable form's solubility level.[26] The pharmaceutical industry uses crystallization techniques extensively to extract, separate, and purify drug leads from natural resources. Nutraceuticals can be transformed from their amorphous form into a lot more thermodynamically stable, highly soluble molecule with a much higher % purity by crystallizing. The purity, size, and shape distribution of the crystal lattice all affect an API's solubility, bioavailability, and shelf life. Over the years, pharmaceutical crystallization has undergone significant development. At the moment, some of the frequently anticipated pharmaceutical crystals are co-crystals, polymorphs, salts, hydrates, and solvates. The creation and application of cocrystals, salts, and other molecular complexes of an API have become common procedures in the pharmaceutical business over time, and government organizations have already released a number of formal guidelines for the sector. Salts are defined as compounds that result from replacing part or all of the acid hydrogen of an acid with a metal or a radical acting like a metal; an ionic or electrovalent crystalline solid. Cocrystals

are crystallized one-phase materials made up of two or more different molecular and/or ionic compounds, usually in a stoichiometric ratio that are neither solvates.[27]

Spray

An effective and popular method for increasing medication solubility and bioavailability is sprinkling. Using this technique, a medication suspension or solution is sprayed into a heated drying chamber. Where the solvent quickly evaporates and leaves behind tiny drug particles. ASDs, which are distinguished from their crystalline counterparts by their increased solubility, can be created using spray drying. The medication is distributed in a polymer matrix in ASDs created by spray drying, which aids in keeping the drug in its amorphous form. Because of its larger free energy, the amorphous form dissolves more quickly and has better solubility. For medications that are sensitive to heat, spray drying is especially helpful because it may be done at comparatively low temperatures by modifying the drying conditions.[28] Scalability is a key benefit of spray drying, as it may be applied to both large- and small-scale industrial production and development. Furthermore, the procedure can be adjusted to generate particles. The pharmaceutical industry continues to have serious concerns about the low and inconsistent oral bioavailability of poorly water-soluble medications. By employing low-melting hydrophilic excipients, spray congealing is a newly developed technique for producing solid dispersions that improve the bioavailability of poorly soluble medications. The primary benefits are the lack of solvents and the ability to produce spherical free-flowing microparticles (MPs) using a reasonably priced, straightforward, one-step procedure. The goal of this review is to provide a comprehensive description of the physicochemical properties, composition, structure, and characterization methods of spray-congealed formulations. In addition, the impact of these characteristics on the MPs' solubility and dissolution enhancement ability is investigated.[29] Spray drying is a scalable, energy-intensive, and continuous drying method. In a very short amount of time, the procedure can produce narrowly distributed nano-to-micron-sized particles. Spray dryers can be thought of as solid-state transforming reactors in the context of this review, where the crystalline starting material is transformed into an amorphous result. Over 140 years ago, the first patent for the spray drying process was issued, describing it as a procedure for spray drying thermodynamics. The final product properties in the spray drying process are determined by the temporal and spatial factors of heat and mass transmission. The creation of a sizable surface area across which heat and mass transfer occur is the primary effect of atomization. Amorphous SDs have been created using a variety of drug-processing techniques, including electrostatic spinning, spray drying, hot melt extrusion (HME), Kinetisol®, and supercritical fluid technology. The final product's characteristics determine which of these approaches to use. For example, due to its many advantages over alternative approaches, HME has lately been the preferred way for developing SDs. HME technology can be used to develop medications that are poorly soluble in water because one of its benefits is that it does not require the use of solvents.[30]

CONCLUSION

The exploration of mesoporous silica-based ASDs offers a promising approach to enhancing the bioavailability of poorly water-soluble drugs. Mesoporous silica, with its large surface area and tunable pore structure, allows for improved drug dissolution by stabilizing drugs in their amorphous form, which typically has higher solubility than the crystalline form. This stabilization also helps prevent recrystallization, maintaining the amorphous state and ensuring sustained solubility. In addition, mesoporous silica provides versatility in drug-loading methods, making it adaptable to various pharmaceutical compounds.

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