Review Article

Amorphous solid dispersion method for improving oral bioavailability of poorly water-soluble drugs

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ABSTRACT

Amorphous solid dispersions are one of the most promising strategies to improve the oral bioavailability of sparingly water-soluble drugs. Drug particle size reduction improved the drug wettability and bioavailability significantly. Poorly soluble drugs may benefit from formulation approaches that overcome poor solubility and dissolution rate limited bioavailability. The solubility of a compound in the amorphous form is higher than the more stable crystalline form because the Gibbs free energy is higher. In addition, glasses or amorphous forms are kinetically trapped high energy disordered materials that lack the periodicity of crystals but behave mechanically as solids. Lipophilic molecules, especially those belonging to the biopharmaceutics classification system (BCS) class II and IV, dissolve slowly, like incomplete release from the dosage form, poor bioavailability, increased food effect, and high inter-patient variability. Hence, several formulation approaches can be taken to improve the solubility and dissolution of poorly water-soluble compounds, such as formulating the API in an amorphous form. Amorphous solid dispersions of poorly water-soluble drugs with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution. This review is mainly focus on advantages, methods of preparation, and characterization of the amorphous solid dispersion.

1. Introduction

In 1961, Sekiguchi and Obi[1] first proposed the utilization of solid dispersions to increase the dissolution and oral absorption of poorly water-soluble drugs, it was first used by Mayersohn and Gibaldi (1966).[2] In 1971 Chiou and Riegelman defined solid dispersion as "the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method".[3] The biopharmaceutical classification system (BCS) categorizes oral medications into four groups on the basis of their solubility and permeability characteristics.[4] The use of pro-drugs, salt formation, and micronization, preparation of solid dispersions with soluble polymers or conversion of the crystalline drug to the amorphous form have all been suggested and used. The drug can be dispersed molecularly in

amorphous particles (clusters) or in crystalline particles.[5] The amorphous state is characterized by the absence of the long-range, three-dimensional molecular order characteristic of the crystalline state. From a practical standpoint, an amorphous material can be obtained in two ways: (i) by cooling the molten liquid until the molecular mobility is "frozen in," thus producing the glass and (ii) by gradually inducing defects in the crystal until the amorphous form is attained.

At industrial scale amorphous solid dispersions can be prepared by processes such as fusion method, rapid solvent evaporation method (spray drying, vacuum drying, freeze drying) and spray congealing method. However, they may not be amenable to conventional dosage form manufacturing processes due to the typical soft, tacky nature and sensitivity to stress as a trigger for instability. The salient features for design of solid dispersions would include judicious selection of carrier, drug-carrier ratio and understanding the drug release mechanism from matrix. The thermal, chemical and mechanical stress applied during processing can spontaneously induce the recrystallization process. In the changing paradigm of drug discovery, amorphization of drug provides an attractive option for overcoming solubility limitations for 'difficult to deliver' drugs. Accompanied with a molecular level understanding of amorphous systems, we can design systems with predictable stability and performance. Of these approaches, amorphous materials are attractive as they are broadly applicable and fit the generic criteria established for good formulation approaches.[6]

2. Salient features and advantages of amorphous solid dispersion (ASD)

- ASD is broadly applicable to acidic, basic, neutral, and zwitterionic drugs.[7]
- Minimize API (active drug) requirements necessary to evaluate efficacy and safety.[8]
- Minimize resources required to manufacture preclinical supply.
- Investigate alternate pathways to improve bioavailability.
- Rapid dissolution and absorption of drug, which may produce quick onset of action.[9]
- Improve exposure (increase bioavailability, more rapid onset, and decrease dose). Support toxicology studies and Clinical tool.[10,11]
- Commercial product and masking of unpleasant taste and smell of drugs.[12]
- Improvement of drug release from ointment creams and gels. To avoid undesirable incompatibilities.[13] To obtain a homogeneous distribution of a small amount of drug in solid state.
- To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.[14]

3. Characterization

The characterization of amorphous solids differs from that for crystalline solids. It is customary to characterize an amorphous material both below and above the glass transition temperature, i.e., both as the frozen solid and as the supercooled viscous liquid. The physical characterization of amorphous solids utilizes a wide range of techniques and offers several types of information.[15]

3.1. Powder X-ray diffraction

Powder X-ray diffraction can be used to qualitatively detect material with long-range order.[16] Sharper diffraction peaks indicate more crystalline material. Diffraction techniques are perhaps the most definitive method of detecting and quantifying molecular order in any system, and conventional, wide-angle and small-angle diffraction techniques have all been used to study order in systems of pharmaceutical relevance.[17] Conventional X-ray powder diffraction, also known as PXRD can be used to quantify noncrystalline material down to levels of 5% and with temperature and environmental control can also be used to follow the kinetics of phase transformation. Small-angle X-ray measurements have been used to study structural (density) changes in polymers in the glassy state upon annealing, and neutron scattering is gaining wider use in the characterization of short-range two-dimensional order in amorphous materials.[18]

3.2. Differential scanning calorimetry (DSC)

Frequently used technique to detect the amount of crystalline material is differential scanning calorimetry (DSC).[19] In DSC, samples are heated with a constant heating rate and the amount of energy necessary for that is detected. With DSC the temperatures at which thermal events occur can be detected. Thermal events can be a glass to rubber transition, (re)crystallization, melting or degradation. Furthermore, the melting- and (re)crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material.[20]

3.3. Solid state NMR (ss-NMR)

High-resolution 13C ss-NMR spectra are obtained using proton decoupling and magic angle spinning (MAS) and sensitivity enhancement is achieved by cross-polarization (CP). 13C ss-NMR has the advantage of being a nondestructive test method that provides information about the structure of the material. Like in any other one-dimensional NMR method, it is possible to relate straightforwardly the integral of the CPMAS NMR signal to the number of 13C atoms involved, provided relaxation rates, Hartmann–Hahn conditions and cross-polarization rates are properly investigated for each species in the sample.[21] In cases where the reference spectra of the individual constituents are unavailable, quantitative estimation of defects, amorphous contents, or mixed phases by NMR can be done based on the comparison of the integrated intensity of two separate lines in the spectrum. A crystallinity index for microcrystalline cellulose was determined in the following way:

$$CrI \ 1/4 \ a = a/(a+b)$$

Where 'a' is the integration of peaks between 86 and 93 ppm and 'b' is the integration of peaks between 80 and 86 ppm.

However, this type of analysis can sometimes be tricky especially if the two lines under scope are overlapping and cannot be easily deconvoluted. These difficulties can be overcome by resorting to other independent measurements like T1 or T1r relaxation times of 1H or 13C, relying on the expected difference in the mobility of amorphous and crystalline regions.

3.4. Temperature modulated differential scanning calorimetry (TMDSC)

In MTDSC, a sinusoidal wave modulation is superimposed over the conventional linear (or isothermal) heating or cooling temperature program. MTDSC is based on the same theory as conventional DSC, in which the heat flow signal is a combination of the specimen heat capacity Cp, t (heat-rate dependent component) and of any temperature dependent, often irreversible, 'kinetic' component.[22] Quantification of amorphous content of a sample using MTDSC is based on the measurement of heat capacity jump associated with the amorphous phase glass transition by preparing a calibration curve based on the heat capacity jumps of physical mixtures of known crystallinity.

$$Cp = K\,(Cp)\frac{AmpMHF}{AmpMHR}$$

Where K (Cp) is the heat capacity constant, AmpMHF and AmpMHR are the amplitudes of modulated heat flow and heat rate, respectively.

$$K(Cp) = \frac{Cp,\ theoretical}{Cp,\ measured}$$

However, for precise heat capacity measurements several points like the thickness of the sample bed in sample pan, the thermal contact resistance between the sample and the sample pan, and the thermal contact resistance between the sample pan and the base plate of the apparatus have to be considered in order to get reliable results.

3.5. Inverse gas chromatography (IGC)

IGC is a vapor sorption technique in which the powder is packed in a column and known vapors (usually at infinite dilution in a carrier gas) are injected. From the retention times of the probes it is possible to assess the surface nature of the material in the column.[23] IGC is a highly sensitive technique and has been used to determine the specific energies of adsorption of polar probes DGSP A, which can then be used to calculate the basic/acidic parameter ratio KD/KA. This parameter describes the acidic and basic nature of the powder surface and can be correlated with crystallinity.[24] Values of KD/KA of greater than 1 mean a basic nature on the surface of a solid and values of less than 1 mean an acidic nature.

3.6. Dynamic vapor sorption (DVS)

Water sorption or gravimetric techniques have been extensively used in the study of many amorphous and partially amorphous powders.[24] It is a useful method for standardizing the amorphous content either as a single component or in combination.[21] Dynamic vapor sorption (DVS) is based on the concept of exploitation of crystallization of amorphous materials with changes in humidity, with consequent expulsion of water. Extent of water sorption and desorption is related to the amorphous content of the sample. DVS works simply by detecting the crystallization response for the amorphous material, with little or no interfering response from the crystalline component.[25] The gravimetric studies are usually conducted in a humidity-controlled microbalance system. The sample is loaded on one side of a single or twin pan balance, and the system is programmed for measurement of sorption and desorption at particular humidity and temperature. However, the moisture sorption isotherms cannot be used as such for the quantification of amorphous content as the moisture absorbed by the amorphous regions as well as that adsorbed onto the surface will contribute to the total water adsorbed by the sample.

3.7. Dissolution calorimetry

Dissolution calorimetry measures the energy of dissolution, which is dependent on the crystallinity of the sample. Usually, dissolution of crystalline material is endothermic, whereas dissolution of amorphous material is exothermic.

3.8. Confocal Raman spectroscopy

Confocal Raman spectroscopy is used to measure the homogeneity of the solid mixture. It is described that a standard deviation in drug content smaller than 10% was indicative of homogeneous distribution.[26] Because of the pixel size of 2 μm^3, uncertainty remains about the presence of nano-sized amorphous drug particles.

4. Methods of preparation of amorphous solid dispersion

4.1. Fusion method

The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline. Melting method was first used to prepare simple eutectic mixtures by Sekiguchi and Obi Leuner and Dressman (2000) used to describe melting method as hot melt method. This method consists of melting the drug within the carrier followed by cooling and pulverization of the obtained product. The process has got some limitations like, use of high temperature and chance of degradation of drug during melting, incomplete miscibility between drug and carrier.[27] The melting or fusion method is the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature.[28] Under such conditions, the solute molecule is arrested in the solvent matrix

by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures.

4.2. Ball milling

The drugs were ball milled in a mixer mill (Glen Creston Ltd., Loughborough, UK) using a 25 mL chamber for 120 min at 2% w/v with 2–12 mm diameter and 6–7 mm diameter stainless steel ball bearings.[29] The samples were milled at 17.5/s.1.

4.3. Solvent evaporation method

Solvent evaporation method is a simple way to produce amorphous solid dispersions where the drug and carrier is solubilized in a volatile solvent.[30] The first step in the solvent method is the preparation of a solution containing both matrix material and drug. The second step involves the removal of solvent(s) resulting in formation of a solid dispersion.[30] Mixing at the molecular level is preferred, because this leads to optimal dissolution properties. Using the solvent method, the pharmaceutical engineer faces two challenges.[31] The first challenge is to mix both drug and matrix in one solution, which is difficult when they differ significantly in polarity. To minimize the drug particle size in the solid dispersion, the drug and matrix have to be dispersed in the solvent as fine as possible preferably drug and matrix material are in the dissolved state in one solution. The second challenge in the solvent method is to prevent phase separation, e.g. crystallization of either drug or matrix, during removal of the solvent(s).

4.4. Hot melt extrusion

Melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. When compared to melting in a vessel, the product stability and dissolution are similar, but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms.[32] The theoretical approach to understanding the melt extrusion process is therefore, generally presented by dividing the process of flow into four sections are Feeding of the extruder, Conveying of mass (mixing and reduction of particle size), Flow through the die, Exit from the die and down-stream processing.

4.5. Lyophilization technique

Lyophilization involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophilization has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.[33]

4.6. Supercritical fluid methods

The supercritical fluid antisolvent techniques, carbon dioxide are used as an antisolvent for the solute but as a solvent with respect to the organic solvent. Different acronyms were used by various authors to denote micronization processes: aerosol solvent extraction system, precipitation with a compressed fluid antisolvent, gas antisolvent, and solution enhanced dispersion by supercritical fluids, and supercritical antisolvent. The SAS process involves the spraying of the solution composed of the solute and of the organic solvent into a continuous supercritical phase flowing concurrently. Use of supercritical carbon dioxide is advantageous as it is much easier to remove from the polymeric materials when the process is complete, even though a small amount of carbon dioxide remains trapped inside the polymer; it poses no danger to the patient. This technique does not require the use of organic solvents and since CO_2 is considered environmentally friendly, this technique is referred to as 'solvent free'.[34] The technique is known as rapid expansion of supercritical solution (RESS).

5. Conclusion

Amorphous solid dispersion is widely used for the preparation of oral poorly water-soluble drugs. This review is mainly explains the preparative methods of dispersion and the characterization. Amorphous solids are minimizes the various disadvantages of the oral drug delivery system. Solubility enhancement of the drugs remains one of the most challenging aspects of drug development in the pharmaceutical field. Various methods are developed for enhancing the solubility and dissolution of the drugs. The amorphous solid dispersion is the one of the most effective approaches to achieve the goal of solubility enhancement of poorly water-soluble drugs. Various methods described for preparation of ASD in lab scale and industrial scale.

Conflicts of interest

All authors have none to declare.

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