IJBPAS, May, 2025, 14(5): 2426-2439

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

EXPLORING CUTTING-EDGE TOOLS AND TECHNIQUES FOR COMPREHENSIVE ANALYSIS OF AMORPHOUS SOLID DISPERSIONS

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Received 15th Nov. 2023; Revised 19th Dec. 2023; Accepted 8th June 2024; Available online 1st May 2025

https://doi.org/10.31032/IJBPAS/2025/14.5.8881

ABSTRACT

A major part in drug therapy is contributed by the oral route of drug administration which has a high turnover rate in the pharmaceutical research and development sector. Nevertheless, obtaining a dosage form with sufficient bioavailability for weakly water-soluble drugs, (BCS classes II and IV) presents considerable hurdles. To overcome the limited bioavailability of poorly soluble pharmaceuticals, amorphous solid dispersions (ASDs) are one of several potential techniques that will increase the pace and extent of dissolution. Various analytical methodologies are being utilized to investigate the efficacy of ASDSs in increasing the bioavailability of hydrophobic medicines when compared to standard drug delivery methods. It is regarded as a significant method of increasing an active medicinal ingredient's perceived solubility. Physical and chemical features of ASDs are complicated. As a result, effective characterization procedures are required for the creation of ASDs. This study focuses mostly on commonly used methodologies for identifying ASDs and examining their procedures, implementations, advantages, and downsides.

Keywords: ASDs, Bioavailability, Characterization, Dissolution, BCS

INTRODUCTION

In the current context, the efficiency of the drug development process has grown dramatically, resulting in the identification of a large number of novel compounds. A medication with high permeability is always recommended for the creation of a drug delivery system since it can easily pass biological membranes. Because of benefits such as convenience of administration, cost effectiveness, and patient compliance, oral drug delivery systems continue to dominate the market. Medicines intended for oral administration should have high permeability and solubility. Drugs are divided into four types based on their solubility and permeability characteristics.

BCS class II/IV drugs dissolve slowly, resulting in partial release from the dosage form and poor oral bioavailability. Around 90% of pipeline medicines created in pharmaceutical R&D are poorly soluble **[1]**. It is quite difficult to develop such novel APIs for oral administration. As a result, new technologies and strategies for improving medication solubility and dissolution are being developed in order to achieve higher bioavailability. Many innovative strategies have been developed to enable for the oral delivery of hydrophobic substances. Cocrystals, prodrugs, salts, amorphous solid dispersions (ASDs), and self-emulsifiers are among the strategies used **[2]**. The usage of ASDs is a common strategy in both academia and industry for improving the absorption and dissolving characteristics of hydrophobic compounds **[3]**. ASDs are more common in other formulation processes, such as drug or cosolvent emulsification. ASDs are often described as "molecular dispersion of one or more active components in a solid-state carrier generated by the melting process" **[4]**.

When ASD products acquire commercial attention, it will become a preferred method for enhancing hydrophobic drug candidates' in vivo solubility and bioavailability. Since ASDs are complex systems with intricate physical properties, multidimensional techniques of analysis are necessary to better understand the link between the required composition variables and processing methods and the in vivo activity of ASD. While ASD are generated with molecularly coupled excipients, there are several problems associated with the amorphous system, principally owing to intrinsic thermodynamic instability, which may result in nucleation, crystallization, precipitation, and relaxation. Among of the areas of interest in the characterization of ASDs are interactions such as phase separation during storage, drug-polymer interaction, physical stability estimate, and dissolution mechanism between the API and carrier system **[5]**. At various phases of

formulation development, commonly utilized characterization approaches incorporate a variety of analytical techniques.

Characterization of the solid-state characteristics of ASDs

Based on analytical processes, solid-state characterization approaches are divided into three **(Figure 1)** sections:

(1) microscopic and surface analysis techniques

(2) thermal analysis methods and

(3) spectroscopic methods.

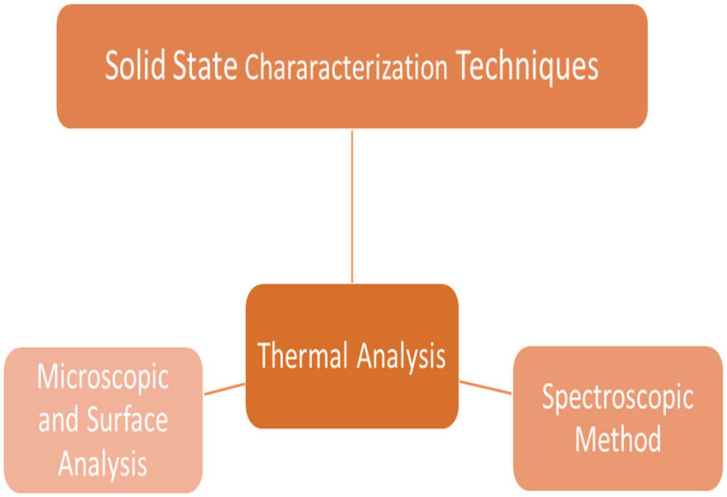

Figure 1: Techniques for characterization of ASD

1. Microscopic & Surface Analysis

Characterization of the solid state using microscopic methods demonstrates the interaction of molecular solids with optical/electronic sources, revealing morphology. It is a non-destructive and quick approach for measuring surface characteristics, glass transition, thermal behavior, particle morphology, crystallinity, dissolving behavior, and particle size in tiny sample sizes **[6]**.

Scanning Electron Microscopy (SEM)

A scanning electron microscope is commonly used in pharmaceutical formulation development and quality control to assess particle condition, property, and shape in ASDs. It's also employed in the quantitative study of ASDs **[7]**. Collisions between electrons and samples generate a variety of complicated reflecting signals, such as Auger electrons, unique X-ray secondary electrons (SE), and back-scattered electrons (BSE), which are detected by a variety of detectors. SEM is useful for monitoring changes in sample

morphology following dissolution **[8]**. *Bruce et al.* utilized SEM to analyze the initiation of crystallization depending on the sample surface modifications. This approach illustrates the crystallinity of bulk ASDs and also provides additional data for analysis through X-Ray diffraction **[9]**. *Ye et al.* analyzed morphology and distribution of the drug (efavirenz) in solid dispersion utilizing SEM. The size was roughly 20 μm, as well as the drug distribution was found to be uniform **[10]**.

Transmission Electron Microscopy (TEM)

Transmission electron microscopy (TEM) is a useful tool for identifying ASDs. It provides real-space pictures and develops electron diffraction patterns, which are used to characterize the crystallinity of medicinal compounds in ASDs **[11]**. Ricarte *et al*. detected 3% crystallinity in hydroxypropyl methylcellulose acetate succinate (HPMCAS) dependent spray-dried ASD using TEM, which was less than the lowest detection limit of wide-angle X-ray scattering **[12]**. TEM + EDX are employed early in formulation development to evaluate polymer and medication interactions in ASDs **[13]**.

Atomic force microscopy (AFM)

Atomic force microscopy is a technique for examining or measuring surface topography in three dimensions with sub-nanoscale precision. It is a high-resolution kind of probe microscopy. AFM may be used to study a variety of materials, regardless of conductivity or opacity **[14]**. The data is collected by contacting the surface with a sharp tip probe **[15]**. AFM may be used to visualize sample properties such as particular separation rates dependent on mixture, surface evolution, and underlying de-mixing processes in molecules. AFM can measure four mechanical properties: height, stiffness, force of adhesion, and friction. A combination of all these results provides an overall assessment of the subject. In a study *Lamm et al*, prepared ASDs by using hot melt extrusion and further characterized the sample by combining MDSC and AFM techniques to examine the morphology and phase behavior. The result revealed that sample processed in high RPM (Rotation per minute) show single phase and low RPM result separation in phase **[16]**.

X-ray photoelectron spectroscopy (XPS)

X-ray photoelectron spectroscopy is commonly utilized in quantitative surface composition studies of ASDs, which allows for rapid screening of solid dispersion systems. Based on the atomic concentration, it assesses the sample's surface chemical composition. Every element has some binding energy, and XPS analyses the chemical bonding energy change to investigate the drug-polymer interaction in ASD. Irradiating the material with an X-ray beam causes the emission of core electrons

with some kinetic energy. An energy analyzer detects the released electron, which produces a photoemission peak. Essentially, XPS demonstrates sensitivity in identifying the degree of protonation by calculating changes/shifts in an atom's binding energy **[17]**. Song *et al*. investigated the acid-base interaction of excipients and drugs. By evaluating the change in binding energy of nitrogen atoms, XPS was utilized to determine the protonation of the nitrogen atom present in the medication **[18]**.

X-ray diffraction

For assessing a solid-state pharmaceutical formulation, X-ray diffraction is the primary method employed to study the crystalline nature. Based on the peak and intensity, it can distinguish between the crystalline and amorphous phases as well as determine the kind of crystallinity in the sample **[19]**.

Powder X-ray diffraction is a typical technique used to determine the crystalline structure of organic, inorganic, and polymeric materials. Because PXRD may be utilized on bulk samples, it can be used to determine the crystallinity of an ASDs batch **[20]**. Takeuchi *et al*. investigated the correlativity of terahertz time-domain spectroscopy and PXRD on time-dependent changes in nifedipine ASDs **[21]**. The results show that THz-TDS can replace PXRD when compared using linear regression. Current research indicates that PXRD can be coupled with other approaches to improve sensitivity. Additionally, PXRD can now act under changeable temperature and humidity, which are non-ambient settings, and can offer information on changes in the kinetics of amorphous medicines in ASDs **[22]**.

Polarized light microscopy (PLM) and hot-stage polarized light microscopy (HSPLM)

PLM plays a crucial role in analyzing the material under microscope while investigating the solid-state characteristics of ASDs. PLM requires relatively little time to analyze the amorphous condition of the medication or sample. It also gives some extra information that may be compared to other characterization approaches **[23]**. Each substance has its unique optical property when evaluated under polarized light, and each optical property has a different characterization under crossed polarizer **[24]**. Hot-stage polarized light microscopy (HSPLM) is a method that combines microscopic and thermal examination. It provides intelligent views as well as extensive data analysis. It is utilized to assess the stability of ASD, drug-polymer miscibility, and thermal behavior of the sample using DSC **[25]**. PLM has a benefit over XRD in that it is sensitive enough to study tiny crystals and nuclei found in ASDs.

2. Thermal Analysis Techniques

The thermal technique of analysis is often used to characterize ASD depending on temperature. Thermal analysis is often used to assess changes in sample temperature or to monitor endothermic and exothermic activities. This section will go through the various thermal characterization methodologies for ASDs.

Differential scanning calorimetry (DSC)

DSC is typically employed for analysis when two identical thermocouples are symmetrically positioned outside the pan. This enables quantitative investigation of heat flow and determination of area below the heat flow curve. DSC detects thermal transitions such as melting point, glass transition, recrystallization, and polymorphic form alteration when heated **[26]**. There are two types of DSC approaches: heat flux DSC and power consumption DSC. Heat flux is a more powerful and user-friendly approach than power consumption. DSC cannot quantify weak or overlapping transitions, hence Modulated DSC was developed to alleviate this shortcoming. MDSC gives an advantage over DSC by applying temperature perturbation at set intervals on two samples with two distinct linear heating rates. Maesac *et al*. coupled HSPLM and MDSC in research to evaluate the kinetic and thermodynamic properties of an amorphous sample. Nifedipine requires a substantially higher thermodynamic driving power and configurational Gibbs-free energy than Felodipine **[27]**.

Thermogravimetric analysis (TGA)

TGA is a popular yet old method of thermal analysis. It entails determining the thermal stability and amount of volatile component in the material by measuring the change in weight of the sample when heated at a constant pace in an inert atmosphere. Several elements react when inert gas passes over them, and gas by-products are formed. These by-products are eliminated, and the difference in residual mass is measured. This information about the sample is used to estimate the temperature window in the hot-melt extrusion process, which is employed for ASD development **[28]**. TGA is also utilised to analyse the sample's evaporation pattern during spray-drying methods, because drying kinetics affect the surface chemistry and crystalline structure of spray-dried ASDs **[29]**. TGA is frequently integrated with other spectroscopic detection technologies to enable the molecular identification of volatile matter extracted from materials using gas chromatography or infrared spectroscopy.

3.Spectroscopic technique

Spectroscopy is the study of how electromagnetic radiation interacts with matter (drug-polymer in the case of ASDs), and the change depends on the wavelength and frequency of radiation. It is mostly utilised to look into changes in a complex

system's molecules and atoms. The three different forms of alterations brought on by electromagnetic radiation are electronic, vibrational, and nuclear transitions. Depending on the circumstances, spectroscopy can be used to examine changes at both the macro and nanoscales. In the production and quality control processes, spectroscopic methods are frequently used.

Solid-state Nuclear Magnetic Resonance (NMR)

NMR is frequently used to characterise solids, liquids, and gases. An established technique for gathering molecular-level information on ASDs is solid state NMR. NMR is used to identify, quantify, clarify the structure of, and study the molecular dynamics of the material. For the investigation of ASD dynamics such as degree of crystallinity, polymer-drug interaction, miscibility, and tendency to crystallisation, solid state NMR is an independent, non-destructive approach **[30-32]**.

Raman spectroscopy

Raman spectroscopy and infrared spectroscopy both depend on changes in a compound's polarizability and dipole moment while in vibrational motion, respectively. In Raman, molecules are the target of a laser beam that collides with them. Light is scattered and energy is gained or lost during collision. A detector that is precise at the molecular level is used to gauge the intensity of scattered light. Confocal Raman microscopy is a new technique that combines microscopic examination with Raman spectroscopy and uses light with a shorter wavelength for characterisation **[33, 34]**.

Infrared spectroscopy

The IR spectroscopic technique analyses the absolute frequency (vibrational) at which the molecule absorbs the radiation as a result of a change in its dipole moment. These substances are also known as IR active substances. To move from the ground state to the exited state, the sample or molecule must absorb a precise frequency of radiation. The qualities of the sample are the basis for IR absorption, which aids in analysing the structure and interactions. Drug polymer interaction can be studied via IR spectroscopy by observing changes in peak form and frequency. By analysing the drug distribution pattern in the polymer matrix, FTIR can be used to identify ASD stability and molecular interactions **[35, 36]**. FTIR is favoured over alternative technologies because specimens may be assessed quickly, painlessly, and relatively accurately in a variety of physiological conditions. Despite recent advances in hardware, software, and other characterization approaches, FTIR is still a valuable tool for assessing ASDs.

Latest techniques

There are several latest techniques that can be investigated for the characterization of ASDs. Some of them are discussed in this section.

Terahertz spectroscopy

The frequency of this non-destructive technique ranges from 0.1 to 20 THz. It can look at physical phenomena like rotational and vibrational transitions in molecules, low-energy torsional modes in condensed-phase media, and low-energy transitions in electronic samples **[37]**. Over the past few years, it has received significant attention in the field of medicinal science. Free electron lasers, narrowband quantum cascade lasers, synchrotrons, and broadband production from ultrafast pulsed lasers are among sources that can produce terahertz radiation. Time-resolved THz (TRTS), THz time-domain (THz-TDS), and THz emission spectroscopy (TES) are the three different forms of THz spectroscopy **[38]**.

Terahertz spectroscopy can be used to track and monitor ASD recrystallization. The terahertz region of the spectrum contains a large number of molecule rotational and vibrational modes. When performing the investigation using in-situ temperature-dependent terahertz spectroscopy, the distinctive spectrum shifts that occur at high temperatures provide crucial insights regarding the relaxation and crystallisation process **[39]**.

Dielectric spectroscopy

The foundation of dielectric spectroscopy (DS) is the reaction of the material to an electric field. The detection of molecular movement across a large temperature range is made possible by dipoles with sufficient mobility, which also react to an externally applied electric field and have a very short relaxation time (10-3-109 seconds) **[40]**. It is becoming more and more well-liked as a useful technique for characterising pharmaceuticals and investigating the complexity of the material system **[41]**. Dielectric spectroscopy, a method that can measure both cooperative and non-cooperative particle motion, has been especially used to monitor intramolecular and molecular movement. The dielectric response data, which is based on wavelength, time, and temperature of ASDs, might be analysed using a variety of methods. To determine the physical stability of the ASDs, molecular mobility and crystallisation can be investigated using ASDS **[42]**.

X-ray microtopography

It is a 3D X-ray micro computed (MC) imaging technique used for material analysis and imaging. In contrast to X-ray diffraction, which produces a 3D image of the material based on the electron density of each sample, X-Ray MC produces a 3D image of the material from the ordered organisation of atoms. When the material is illuminated, the detector gathers a magnified

projection image based on the hundreds of angular reflections the material receives as it rotates. Using X-Ray MC spectroscopy, the internal structure and thickness of a spray-dried sample can be evaluated in ASD analysis **[43, 44]**.

It is challenging to distinguish between samples with the same signal reduction coefficient, such as crystalline and amorphous materials. Synchrotron radiation, which helps to improve the contrast of phase, can help to solve this issue **[45]**.

CONCLUSION

The rational development of ASDs is ensured by their wide variety of characterisation tools and techniques, but it is necessary to create efficient analytical techniques that can investigate and gauge the stability of ASDs at the molecular level. Although there are many technologies available, a qualitative and quantitative study of ASDs is necessary to assess the stability and performance more accurately. The methods covered above enable us to ascertain the molecular stability and thermodynamic behaviour of ASDs, such as the glass transition, the interaction of polymer and drug, and molecular mobility. The choice of the manufacturing procedure that is practical for creating ASDs is heavily influenced by data from characterisation techniques. Significant advancements have been made in the characterisation of ASDs over the past ten years. The fundamental analytical methods frequently employed for characterising ASDs were summarised in this review paper. We also looked at some of the earlier research projects that characterise ASDs using different methods. Scientists are motivated to contribute proportionally to delivering poorly soluble drugs with high bioavailability because of emerging sensitive methodologies and instruments.

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