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Review Article

A REVIEW ON SOLIDS STATE OF CHARACTERIZATION METHOD IN PHARMACEUTICALS

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ABSTRACT

The solid form in pharmacy is generally classified into two types, i.e. stable and unstable amorphous solids. In addition, there are also several types of solids, such as disperse solids, solvates, hydrates, and nanoparticles. Comparing is done by several methods that have been used in general for solid characterization. Methods like X-Ray Diffraction (XRD), Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared (FTIR), Raman Spectroscopy (RS), Nuclear Magnetic Resonance (NMR), Density Measurement (DM), Thermal Analysis (TA), Supercritical Solvent (CSS), Supercritical Anti-Solvent (SAS) and Atomization Anti-Solvent (AAS) were used in general in solid-state characterization. The choice of method to be used depends on the desired information requirement of the solid. In general, the method used is more than one characterization technique for reached comprehensive analysis.

Keywords: Solid, Solid Characterization, Solvate, Solid Dispersion, Co-Crystal, Co-Amorf, Nanoparticle.

INTRODUCTION

The solid state in pharmacy is generally classified into two types: stable crystal and unstable amorphous. A crystal solid can be characterized using 3-dimensional imaging while the amorphous can be characterized by the atomic structure and distance between the molecules. Each molecule randomly differs in direction and conformation[1]. In addition to crystals and amorphous, there are several types of other solids, such as disperse solids, solvates, hydrates, and nanoparticles.

The importance of pharmaceutical solids in amorphous form is seen from the characteristics possessed such as favorable properties that have a higher solubility, rapid dissolution rate, and sometimes have better characteristics than the crystalline form. In addition, the amorphous form is also more unstable than the crystalline form and the amorphous form also has excess free energy which can increase its solubility. Some pharmaceutical drugs and excipients tend to be amorphous, and others require the prevention of crystalline formation to remain in the amorphous form[2].

In its development, the formulation of pharmaceutical products must optimize the chemical physicochemical properties of pharmaceutically active substances. Co-crystals are used to enhance the physicochemical characteristics of drugs such as solubility, dissolution, bioavailability, and stability of compounds in maintaining their therapeutic effects[3]. Physical modification aims to enlarge the particle surface area, increase solubility or wetting the powder, and improve API stability. Drugs that are poorly soluble in water formulated as amorphous, crystalline solids, or formulated with lipids to increase their solubility[4]. Crystal Engineering through co-crystallization is an approach to overcome drug-related problems. Co-crystals comprise more than two components of different crystalline materials (multicomponent). Where one component is API and the other component is conformer, as seen in Figure 1.

The various properties and interactions of conformers in both solid and liquid phases can be used to control the solubility of co-crystals. Other substances, such as polymorphs, salts, and amorphous solids have also been widely used to enhance the dissolving and bioavailability of drugs that are poorly soluble in water [3].

Drug administration through oral route is the most common and preferred route due to ease of administration, cost-effectiveness, and flexibility in design. However, if a given drug has a limited water solubility, it can cause poor bioavailability. Furthermore, low gastric pH and enzymatic activity may produce drugs delivered via oral route will be rapidly metabolized and degraded. Therefore, the solid dosage modification is needed to improve the solubility of a substance, which is a solid dispersion [5].

The solid dispersion is defined as a homogeneous mixture of one or more active ingredients in the matrix in the solid state. Solid dispersion is used to increase solubility of water-soluble oral drugs [6]. Increased solubility can be attributed to reduced particle size, reduction of agglomeration, changes in the physical state of the drug from crystalline to amorphous, and drug dispersion at the molecular level [7].

The solid dispersion is generally prepared by solvent addition method, which the drug and the carrier are dissolved in a solvent or using melting method, which the drug carrier mixture is prepared by melting / cooling. The disadvantage of this solvent method is the use of organic solvents with toxicity, safety hazards, and residual solvents as well as the possibility of deposition of the drug into various polymorphic forms, which have different solubility and bioavailability. PEG is widely used as a medium for solid dispersion because of low melting point, having the

ability to form solutions into solids quickly, low toxicity and low cost [8].

However, at higher drug concentrations, these drugs are often present in crystalline form in PEG dispersion or recrystallization over time, resulting in an unstable formulation. The use of solid dispersions to improve the solubility of drugs has been a focus of many studies [9].

Solvate is a multicomponent crystal-shaped solid that is an active substance molecule as a host and a solvent molecule incorporated in a crystal lattice structure, commonly referred to as pseudo polymorphic [1]. The solvent will usually form a hydrogen bond or covalent bond with the molecule of the active substance in the crystal lattice [10]. Solvate is very often used in the pharmaceutical industry, although it has uncontrolled physicochemical properties. However, a solvent with the right solvent can improve physicochemical stability [11].

PREPARATION OF SOLIDS PREPARATIONS

Solid dispersion

The dispersion system can be interpreted as a system in which one of the substances is a dispersed phase to a substance or dispersing phase. The classification of dispersion systems in pharmaceuticals is carried out through dispersion medium, dispersed phase, and dispersed phase particle size. The classification of the three dispersion systems in the liquid medium is between the interactions between the dispersed phase and the dispersion medium. In the lyophilic system there is an affinity between the dispersed phase and the liquid medium. In the lyophobic system there is only attraction between the two phases, such as sulfur and magnesium stearate in the air. If the liquid is air, then use hydrophobic terminology. The group of this classification is a molecule, which has a hydrophobic and hydrophobic group, which is called amphiphil. This molecule in the form of colloidal size aggregates in the dispersion medium is called micelles, such as surfactants in the air. Of the various pharmaceutical dosage forms, liquid dispersion systems are the most complex systems. Production methods, formulation approaches, material selection, and environmental factors, as well as frequency, greatly influence variability, characteristics, and other variables. An example of a liquid dosage form is suspension which can be defined as a highly effective particle containing preparation which is freely distributed in a gift where the drug is very minimum proof of solubility [6, 12, 13].

Co-crystal

There are various methods that use to prepare solids such as solvent evaporation, vapor or solvent diffusion, an addition of anti-solvent, solid-state grinding, freeze-drying, spray-drying, melting, and quench-cooling, melt extrusion and mechanical activation (milling)[10]. In co-crystals, the most effective alternative is a solid-state grinding of two solids performed using a mortar and pestle [14]. There are new methods for producing solids with supercritical fluids, an example is the production of as indometacin-saccharin co-crystals [15] and on amorphous substances in modifying the solid-state properties of APIs [16], phase-mediated solvent transformation, and with the help of ultrasound

Co-amorphous

Co-amorphous pharmacy is a single phase amorphous type in a binary system that occurs between drug active substances (API) and other small solid or co-former molecular compounds (API2 or excipients) into new solids with different properties from its constituent compounds, co-amorphous pharmaceuticals have become one method alternatives for drug research and development, because of their advantages in improving solubility, mechanical properties, dissolution, stability or even bioavailability. Several methods can be applied in making coamorphous drugs, including cooling, solvent evaporation and milling-cryomilling. In this paper, the definition, preparation, physicochemical characterization and mechanism of coamorphous pharmaceutical formation are discussed. Comparison between coamorphous and solid dispersion or co-crystals is also presented[17, 18].

Salt

One conventional technique for increasing solubility is salt formation. Salt formation can occur when drug active substances (API) and compounds acting as ion counters are greater than 4 (pKa> 4). Molecular bonds in salt are ionic so that in the media the water will be easily ionized and dissolve quickly [19, 20].

Complexation

Freeze-drying is also called the lyophilization process, which is used to improve the stability of substances and the long stability of storage of an unstable substance. Freeze-drying has three stages: freezing, primary drying, and secondary drying. Freezing is an efficient step in which most of the solvents that water usually can be separated from the solute by ice formation. Furthermore, primary drying aims to select the temperature of the sufficient and hold the temperature always constant. The last stage is secondary drying which aims to reduce the residual water content to achieve optimal levels [21].

Spray-drying is changing the form of a substance from a liquid state to a dry particle shape by spraying the substance into a heat-draining medium. This process consists of three stages. First, atomize the liquid stream using the right device, then the subtle droplets will interact with the dryer gas at sufficient temperature to form a solid particle. In the final stages, the solid particles formed will be separated by the dryer gas by the appropriate means [22]. The milling process is one of the amorphous solid form preparation processes which aims to remove all impurities present in solid form [2].

Nanoparticle method

Preparation of the albumin nanoparticles became model A, B, and C with each treatment (Figure 2).

After that, the determination of the size and potential of the loading or unloading albumin zeta nanoparticles was determined by correlation spectroscopy (PCS) photographs using the Zetamaster analyzer system (Mervio Instruments, UK) [23].

SOLID CHARACTERIZATION

From several types of solids obtained various methods of characterization that can be used, including:

Powder X-ray diffraction (PXRD)

One rapid analytical technique is primarily used for the identification of phase crystalline materials and can provide information about cell dimensions. The analyzed material was finely ground and homogenized. This method is one of the most widely used methods of solid characterization. This technique is also used to verify the shape of amorphous structures [10]. In addition, XRD techniques can also determine the degree of crystallinity of a solid form, in which the co-crystalline atoms cause the X-rays to diffract in certain directions. X-ray diffraction (XRD) is one of the most important non-destructive tools for

analyzing all types of matter - from liquids to powders and crystals. From research to production and engineering, XRD is an indispensable method for material characterization and quality control [2, 24–26].

Differential Scanning Colorimetry (DSC)

DSC is a thermal analysis technique that measures the energy absorbed or emitted by the sample as a function of time or temperature. When thermal transitions occur in the sample, the DSC provides a measurement of the calorimetry of the transition energy from a certain temperature [27]. This technique is used to distinguish amorphous forms with microcrystals based on the absence of glass transitions when the analysis with XRD technique fails. Preferably the amorphous form observed with XRD is also supported by this DSC technique [2, 10].

Fourier transform infrared spectrophotometer (FTIR)

FTIR is used to examine the possibility of hydrogen bond formation between API and polymer. FTIR is used to observe molecular interactions using electromagnetic radiation [12]. This technique shows the level of solid characteristics based on the capacity of different absorption bands [28]. The IR spectrum can provide information about the hydrogen bonds in the structure because in the formation of co-crystals is based on the hydrogen bond interaction between 2 or more different molecular groups as well as a single component in the solid state.

In another journal it was said, a fourier transform infrared spectrophotometer (FT-IR) analysis was performed on a spectrophotometer (Bruker Optics). FT-IR was used to characterize functional groups of ZnO and ZnO nanoparticles - PVA composite particles [29].

Scanning electron microscopy (SEM)

Particle size and morphology are examined by scanning electron microscopy (SEM). SEM is a technique that can be used for morphological analysis and particle size, but this technique has significant errors and biases static values related to orientation and agglomeration of particles that are difficult to control and minimize so that analytical support is required by other techniques [16, 30].
In other journals focusing on characterizing the size and distribution of ZnO nanoparticles in the polymer matrix has also been confirmed that results using SEM show good adhesion between the surfaces of ZnO nanoparticles with PVA matrices defined by the modification of the organic surface of ZnO nanoparticles [29, 31].

BET analysis

This technique is used to determine the surface area of a solid area determined by N2 adsorption using the Surface Area Analyzer [16].

Nucleo magnetic resonance analysis (NMR)

The NMR technique is very widely used in the characterization of solid forms. This technique is one of the amorphous quantification methods contained in solid form [5].

Fourier Transform Raman spectroscopy (FT-Raman)

It is a spectroscopic method that observes the vibrations, rotations and low-frequency modes of the system. This method is used to identify molecules based on changes in molecular and environmental conformations [5]. Raman spectroscopy can also be used to identify or characterize and estimate the purity of co-crystalline phases resulting from AAS and SAS techniques [15].

Density measurement

One alternative technique for knowing the characteristics of pharmaceutical substances is to determine the density of a solid. The amorphous form generally has a lower density when compared to crystals [5]. The density of pure amorphous compounds can be obtained by using a helium pycnometer [10].

Co-crystallization with supercritical solvent (CSS)

The CSS technique is a method that uses a supercritical CO_2 solvent in co-crystalline production. SCF-CO (supercritical fluid) acts as a solvent medium for molecular interactions and thus nucleation and co-crystalline growth with new stoichiometry or crystal structures. In this technique, supercritical CO_2 dissolves pure solids placed inside stainless steel vessels and depressurization leads to saturation and co-crystalline formation. So in its application, the pure component must have an ideal solubility in supercritical CO_2 [15].

Thermal analysis

The thermal properties can be characterized by DSC and TGA. Data analysis was performed using thermal analysis software. In general, the heating rate of 100C / min is used in the 30-3000C temperature range for DSC and TGA. DSC analysis is performed using an open pan configuration. Modulated DSC is done at Q100 at 30C / min from 35 to 300^0C in an open aluminum pan with $1,00^0$C every 60 seconds. Modulated DSC is done using a pan with lid (not wrinkled) [32].

Co-crystallization using supercritical anti-solvent (SAS) and atomization and anti-solvent (AAS)

The SAS technique is based on the solvent contact of the solute being attracted in a conventional liquid solvent with SCF. After mixing and passing through the nozzle, supercritical fluid saturates the liquid droplets, reduces their dissolvability, and simultaneously extracts the solvent, causing the deposition of the solute by its anti-solvent effect. In this technique, the liquid solvent must be fully mixed with SCF and with the soluble substances in the mixture.

In the AAS technique, SCF increases the atomization of the solution, with different properties in the crystallization of the anti-solvent and the crystallization of spray-drying. Below and the same temperature, CO2, and N2 show the different diversity and different levels of different conditions in density[26]. The summary of characterization of solid preparation has been presented in table 1.

Table 1: Method of Solid Characterization

Types of solid preparation	Solvate	Solid Dispersion	Co-crystal	Co-amorphous	Nanoparticle
SCXRD	X		X	X	
PXRD	X	X	X	X	X
SAS			X		
Thermal	X		X	X	
2DF	X				
DSC	X	X	X	X	
TA	X		X		
FTIR		X	X	X	X
PSD					
SEM	X		X	X	
BET					X
NMR			X	X	
FTIR-RAMAN			X		
DM					
Microscopy				X	

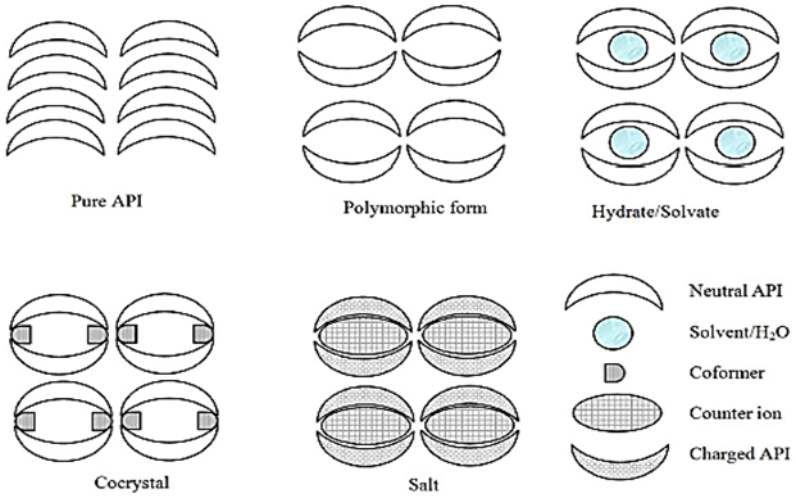

Figure 1: Schematics of salt, co-crystal, and polymorphism

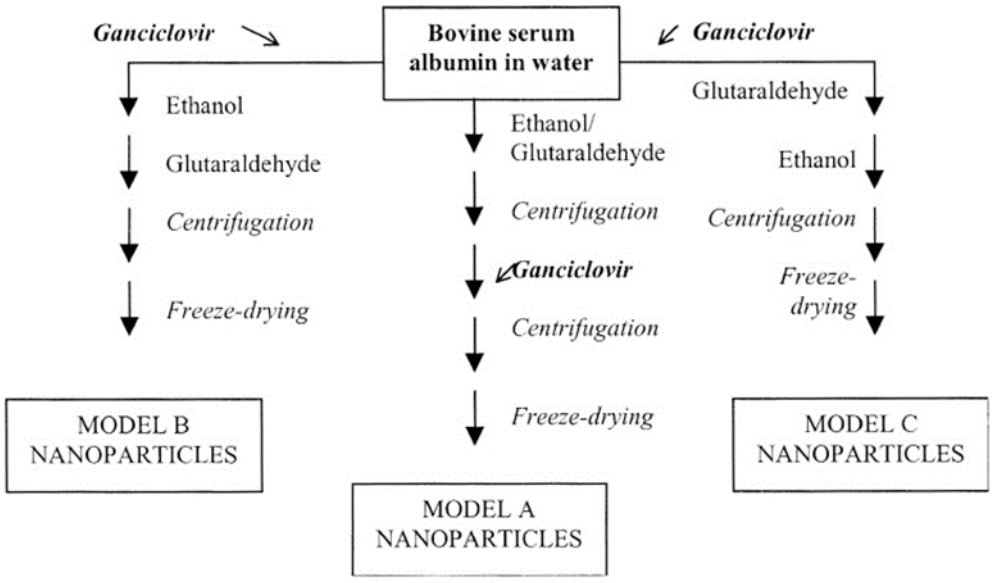

Figure 2: Preparation of the albumin nanoparticles

CONCLUSION

There are various characterization techniques that can be used to characterize pharmaceutical solids. But the choice of method to be used depends on the desired information requirement of the solid. In general, the characterization of a solid is carried out by a combination technique that is at least the method employed by more than one characterization technique.

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