Review Article

Preparation and Characterisation of Pharmaceutical Solids – A Review

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ABSTRACT

Pharmaceutical solids are pharmaceutical drugs in solid form, either crystalline or amorphous depending on the atom arrangements. This review paper briefly focuses on the preparation of pharmaceutical solids in both forms and also about the characterization techniques. Preparation techniques include conventional techniques as well as the advanced techniques that have been coming up such as Mechanical micronization, Particle size reduction by novel particle engineering, Solid lipid nanoparticles and many other methods. A number of characteristic techniques are tabulated for amorphous as well as crystallized solids and the related information on those techniques is also stated. Dependence of solids on various hygroscopic properties and molecular mobility is also dealt with. Lastly, there is a dim focus on the advancements occurring in the pharmaceutical industry governing these solids.

Keywords: Pharmaceutical solids, nanoparticles, micronization.

INTRODUCTION

The study of solid state chemistry of pharmaceutical solids focuses on all disciplines right from drug discovery to successful marketing. A clear understanding of the molecular structure can lead to a better design and control of drug performance. Moreover, interest in the subject of pharmaceutical solids stems in the part from FDA's substance guideline that states "appropriate" analytical procedures to be used to detect polymorphic, hydrated or amorphous forms of the drug substance. These guidelines suggest the importance of controlling the crystal form of the drug, its bioavailability, etc.

Pharmaceuticals are substances that are supplied to our bodies when the normal functioning of the system is disrupted. They can be in various forms like solids (tablets, capsules) or liquids (syrups). Pharmaceutical solids deal with pharmaceuticals in solid form. The solid phase is classified based on the order of molecular packing in two main forms – crystalline and amorphous. Crystalline phase has a regular arrangement throughout and it has both short as well as long range order while in amorphous solids the range is limited only to the neighbouring atoms. They also have additional molecular conformation compared to amorphous solids which are conformationally more flexible. Crystalline pharmaceutical solids are further classified into polymorphs, hydrates/ solvates and co-crystals. Polymorphism is the ability of one pharmaceutical solid to exist in multiple crystalline forms; solvatomorphism is phenomenon where the pharmaceutical solid is linked with solvent molecules (if water is the solvent molecule then it is called "hydrates") whereas co crystals are a completely fresh topic of discussion compared to the other forms. It is either defined as a mixed crystal that contains two different molecules, or as a consequence of a molecular recognition even between different molecular species.

Amorphous Pharmaceutical Solids

Amorphous solids are of added importance compared to their crystalline counterparts in aspects of solubility, dissolution rates, stability and occurrence. Amorphous solids are said to have a higher solubility range comparatively and to some extent it is even experimentally proved. Due to their minute particle nature, they have the advantage of easily getting dissolved in many solvents. Studies on indomethacin and ritonavir proved that amorphous forms had higher solubility rates compared to their crystalline forms, although not as high as expected from thermodynamic data[1]. Higher stability in amorphous states has experimentally been shown by Pikal et al by working on insulin[2].

Preparation of Amorphous Pharmaceutical Solids

Amorphous solids are generally prepared by three main processes: freeze-drying, spray drying and by milling or processing.

Freeze drying or lyophilisation is a technique known to improve stability and long term storage stability of labile drugs. In order to design an optimum freeze drying process it is first required to know how to apply critical formulation properties like collapse temperature, stability and properties of excipients used. This process involves three main steps: freezing, primary drying and secondary drying. In freezing, most of the solvents are evaporated hence leading to an increase in the concentration of the solute. Primary stage is the ice sublimation state and is considered the longest stage. In the final stage, water is

desorbed from the final product[3,4]. Freeze drying designs by manometric temperature measurement was carried out in order to develop an "expert system" that will allow the development of an optimised freeze drying process during a single laboratory experiment. Experiments carried out showed that this technique is comparatively better and does meet the required expectations[5].

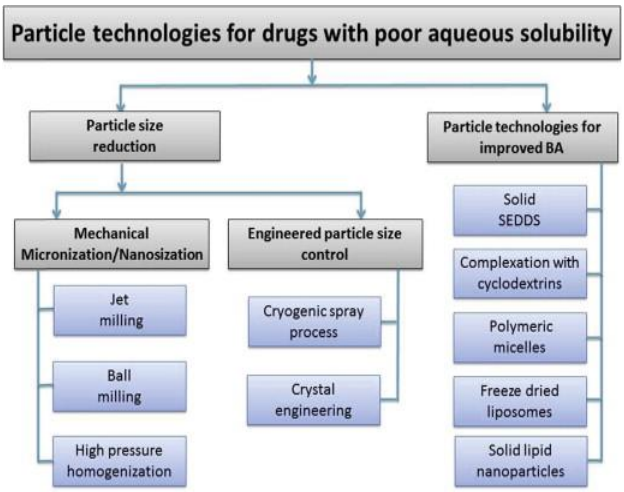
A spray-dried dispersion is a single-phase, amorphous molecular dispersion of a drug in a polymer matrix. It is a solid solution with the compound molecularly "dissolved" in a solid matrix. As the name suggests, SDDs are obtained by dissolving drug and polymer in an organic solvent and then spray-drying the solution. The formulation and process conditions are chosen so that the solvent quickly evaporates from the droplets, allowing insufficient time for phase separation or crystallization[6,7]. The advantage of spray drying process is that alongside formation of amorphous solid, the drying of the substance is also achieved. It is highly advantageous as it helps in modification of size, crystal habit, polymorphism and moisture content. Apart from these, there are benefits of increased bioavailability, improved drug compressibility, complex formation and encapsulation[8]. There is a technique called Bend's spray dried dispersion (SSD) which combines with the normal spray drying technique to offer solutions to approximately 60% of compounds that have poor solubility[9]. Spray drying has led to improvements in the pharmaceutical particle engineering as well.

In milling, the crystalline solids formed are broken down into smaller pieces. The smaller pieces could either be amorphous or microcrystalline solids. Physical transformations taking place in this process have a direct influence on the stability and solubility of the compounds. The best technique for amorphization by this process is keeping the temperature below T_g[10]. The process of grinding pharmaceutical solids has been reviewed by Bruno et al[11].

The ultimate aim of the conventional methods as well as the novel methods of preparation of these solids is better solubility, better bioactivity and stability. The following table reviews on particle technology as a means to develop drugs with lesser water solubility issues. The processing and applications are beautifully explained by Hovione[12-14].

CHARACTERISATION

The characterisation technique of amorphous solids varies from that of crystalline solids due to structural variations. As in crystalline solids, molecular level structural elucidations like diffraction and spectroscopic methods is not possible in the case of amorphous solids. So on what basis can they be then classified? The answer to this is structural mobility and changes. As the most important characteristic feature of an amorphous solid is its T_g, it is mandatory to characterise the solids based on it. Hence, techniques related to this and used include Raman spectroscopy (RS), Solid State Nuclear Magnetic Resonance (ssNMR) or Fourier transform infrared spectroscopy (FT-IR) ; differential scanning calorimetry (DSC) and XRPD.



Particle technologies, methods involved and examples were reviewed by Khadka et al[15].

The prior ones probe the samples at molecular levels while the latter ones are used for directly obtaining intermolecular information at particulate level. Recent studies show that terahertz pulsed spectroscopy (TPS), second harmonic generation (SHG) and 14N nuclear quadruple resonance (NQR)[16] can also be used in order to investigate particulate properties.

Several types of information can be obtained from the physical characterisation of the amorphous solids. These include structural information, thermodynamic properties, changes occurring when amorphous solids crystallise and also about the carious multi-component substances that are present in the amorphous solid[17].

Structural Information obtained helps in understanding whether the solid is truly amorphous or not. Johari et al used calorimetry to distinguish between amorphous and microcrystalline solids. A two-step calorimetric test was able to do what the usual diffractograms couldn't[18]. Similarly degree of crystallinity, micro heterogeneity and polymorphism present in the amorphous solid can be seen through the knowledge obtained from the structure.

Thermodynamics

Thermodynamically, amorphous solids are said to possess excess properties with respect to their crystalline counterparts. Theoretically, these excess properties can be calculated from heat capacities over a specific temperature range. The stored internal energy means that the form is unstable. This excess energy is removed either through crystallization or by irreversible relaxation processes. The best way through which these energy features can be best visualised are by a schematic representation of enthalpy (or volume) variations as a function of temperature. The slope represents heat capacity[19].

Particle Technology	Method	Example Drugs
Mechanical micronization	Jet milling	*Cilostazol* *Ibuprofen*
	Ball milling	*Danazol* *Carbamazepine, Dypyridamole, Indomethacin*
	High pressure homogenization (HPH)	*Prednisolone, Carbamazepine* *Nifedipine*
Particle size reduction by novel particle engineering	Cryogenic spraying process/spray freezing into liquid	*Danazol* *Carbamazepine*
	Crystal engineering	*Glibenclamide* *Febantel, Itrazonazole*
Solid SEDDS technology	Spray drying, *in situ* salt formation, solidification with polymers	*Nimodipine* *Flurbiprofen* *Dexibuprofen* *Docetaxel* *Crucumin* *Meloxicam* *Fenofibrate* *Ibuprofen*
Complexation with cyclodextrins	Freeze-drying, vacuum evaporation, kneading	*Praziquantel* *Bifonazole, Clotrimazole* *Celecoxib*
Polymeric micelles	Dialysis, freeze-drying	*Paclitaxel* *Etoposide, Docetaxel, 17-AAG* *Amphotericin B*
Freeze–dried liposomes	Freeze-drying	*Sirolomus (Rapamycin)* *Paclitaxel*
Solid lipid nanoparticles	HPH, solvent emulsification-evaporation/diffusion	*All trans-retinoic acid* *Tretinoin*

Due to higher Gibbs free energy than crystalline solids, amorphous solids have higher apparent solubility and faster dissolution rates, which in turn lead to higher bioavailability for drugs that exhibit dissolution-rate limited Absorption (classified according to the Biopharmaceutical Classification System (BSC) as Class II drugs)[20]. However, due to excess entropy, enthalpy and free energy that account for better solubility, the amorphous state is inherently unstable and recrystallization may occur.

Changes

When right conditions are applied there is a possibility to convert amorphous solids into crystals or undergo structural relaxation owing to their instability.

Multiple Component System

The final pharmaceutical may contain either the active substance or the excipient in the amorphous state or both in the amorphous and crystalline state.

Characterisation Techniques

Raman Spectroscopy

Raman spectroscopy is a spectroscopic method that is used to observe vibrational, rotational and the low frequency modes in a system. It is used in order to identify molecules. It examines the properties of the molecule itself and the changes occurring in the solid state properties of the substance are inferred from the changes occurring in the molecular conformation and molecular environment. This is a result of the difference in packing conditions of the molecule and can be studied from the fine changes observed in the peak positions[21]. A brief review on this technique, its applications and other related contents has been done by Ying and Chrurch[22]. Recently it has been used to distinguish between different amorphous forms of the same substance. Karmwar et al worked on indomethacin and simvastatin to show this[23, 24]. Raman spectroscopy was also used to study and quantify disorder in a substance[25]. However in contrast to this, Boetker et al found that it was unable to distinguish between the amorphous forms of amlopodine[26].

Solid State Nuclear Magnetic Resonance (Ssnmr)

Solid-state NMR is widely used in pharmaceutical analysis for the characterization of active pharmaceutical ingredients, drug products, and excipients. The sensitivity of solid-state NMR spectra to molecular structure and the experimental flexibility of the technique provide many incentives for applications to increasingly complex systems. Lefort et al studied ssNMR and DSC methods for

quantifying the amount of amorphous content in solid forms of trehalose[27]. Tran et al studied the ability of ssNMR to characterise the structure of solid dispersions[28]. An overall review of the technique and its several applications in the pharmaceuticals is given by Berendt et al[29].

Differential Scanning Calorimetry (DSC)

Along with quantification of the amorphous content, DSC is also used for investigating the phase behaviour of pharmaceutical solids[30]. For detection of amorphous nature generally employed DSC techniques include conventional DSC; modulated temperature DSC (MTDSC) [31] or high-speed DSC(HSDSC)[32]. DSC is also used for the characterization of amorphous solids that have a weak glass transition temperature[33].

X ray Power Difraction (XRPD)

This technique also controls the phase transformation as well as quantification of the amorphous nature. XRPD is one of the most used quantification techniques because of its simplicity and also as it measures periodicities of atoms in the powder sample[34]. Quantification of amorphous material by XRPD can be achieved by three ways: measuring the characteristic crystalline peak intensities, measuring the intensity of characteristic region of amorphous scattering and by measuring the integrated peak areas of the principal crystalline peaks[35]. X-ray amorphous powder diffraction patterns of microcrystalline cellulose, indomethacin, and piroxicam done resulted in the assignment of structures in each of the system examined[36].

Terahertz Pulsed Spectroscopy (TPS)

Terahertz pulsed spectroscopy (TPS) is a novel technique for the physical characterization of pharmaceutical drug material and final solid dosage form, utilizing spectral information in the far infrared region of the electromagnetic spectrum. Terahertz radiation lies between the IR and microwave regions of electromagnetic spectrum and can be defined as having a frequency of between 0.1 and 3 THz, corresponding to 3.3–100/cm. While responses from infrared and NIR spectroscopes are due to intermolecular vibrations and hydrogen bonding, the results from terahertz regime probes lattice vibrations and also low energy hydrogen bonding. As a result modes in terahertz region are directly affected by the changes in intermolecular bonding and so the spectra of different solid-state forms of the same compound may show more pronounced spectral changes in the terahertz regime than in the IR or NIR region. For the quantification purpose, distinct peaks showed crystallinity while no peaks showed presence of amorphous nature[37]. Zeitler et al reviewed the development and performance of pharmaceutical applications of this technology and also compared with other tools for physical characterisation[38].

Atomic Pairwise Distribution

This is a method to analyse the local structure based on the total scattering pattern from the crystalline, nanocrystalline quasi crystalline or amorphous materials[39,40]. It has recently been applied in the pharmaceutical field to study short and long range order amorphous glassy materials.

Solution Calorimetry

Solution calorimetry works by dissolving the solid material in a solvent and measuring the temperature rise or fall in the solvent as a result of dissolution. Since crystalline and amorphous solutions have different heats of solution, this technique can be used to quantify the amorphicity. Evaluation of lactose by this technique demonstrated that solution calorimetry is a rapid and simple method for the determination of amorphous content[41].

Microcalorimetry

Micro calorimetry is based on principles of heat conduction. The process involves maintaining the sample and a reference at a constant temperature in a suitable chamber in the instrument. This technique offers much potential as an assay for amorphous content. This is demonstrated by Gaisford in his research work[42].

Density Measurements

Crystalline materials in general have higher density than their amorphous counterparts because the atoms in the crystal lattice are located at a minimum possible distance from each other. An increase in lattice disorder (decreasing crystallinity) usually results in an increase in volume and therefore a decrease in density. Changes in crystallinity should therefore be accompanied by gradual, progressive changes in density[43]. Hence, different density measurement techniques can be used to detect levels of amorphous phase in crystalline pharmaceuticals[44], or to determine sample crystallinity. Therefore, density measurements can also be used as an alternative technique to determine the solid state of pharmaceuticals.

Dissolution Tests

Dissolution rate depends on the molecular mobility of the solid. As the molecular mobility of amorphous solids is much higher than crystalline solids, they have an added advantage in this method. The amount dissolved is used to quantify crystallinity in case of amorphous solid dispersions[45]. But this technique has the disadvantage of devitrification in the dissolution fluid[46].

Thermodynamics and Glass Transition Temperature

Glass transition temperature of an amorphous pharmaceutical solid is a critical physical property which can dramatically influence its chemical stability, physical stability, and viscoelastic properties. Transition of amorphous solids occurs usually from a highly under cooled liquid state or by slow cooling techniques. As long

as crystallization can be avoided the relevant thermodynamic properties of the metastable glassy and undercooled liquid phases can be measured below and above the glass transition temperature, respectively[47].

Effect of composition on T_g

There are two fundamental relations for the effect of composition on T_g, one arising from the entropy continuity condition (at Tg) and the other from the volume continuity condition[48].

Relationship between T_g and water content

Bancock et al concluded from their research that water acts as a potent plasticizer for amorphous solids based on experimenting with the T_g values[49].

Relationship between T_g and molecular mobility

Studies on various samples of indomethacin, poly (vinyl pyrrolidone) (PVP) and sucrose showed that there existed very high molecular mobility above T_g and low levels below T_g[50]. Molecular mobility as a function of temperature and humidity were also studied on indomethacin[51]. The quantity and the molecular mobility of mobile water in lyophilized formulations was shown to affect the T_g of lyophilized formulations, which in turn governs their stability[52].

Crystalline Pharmacetical Solids

A crystalline solid or a crystal is a substance which has a highly ordered structure arranged in a definite geometric form. Interfacial angles and symmetry form the basic characteristic property of crystals. There are seven basic crystal systems namely cubic, orthorhombic, tetragonal, monoclinic, triclinic, hexagonal and rhombohedral. Bravais showed that there are only 14 different ways by which similar points can be arranged in a three dimensional space[53].

The common crystalline forms for a drug substance are polymorphs, solvates or hydrates. Since these differ in crystal packing, there is a significant difference in their physical properties like density, hardness, melting point, thermodynamic properties, colour, etc [54]. The difference in the physical properties has an impact on the processing of drug substances[55] while differences in solubility lead to implications on the absorption of active drug from its dosage form[56].

Crystallization is a major technological process for particle formation in pharmaceutical industry and, in addition, plays an important role in defining the stability and drug release properties of the final dosage forms. Solution crystallization is widely used for manufacturing bioactive drug substances and formulation excipients during final and intermediate stages of purification and separation. Over 90% of all the pharmaceuticals are in particulate, especially crystalline form[57]. The significance of crystallisation mechanisms and kinetics in directing crystallization pathways of pharmaceutical solids and factors affecting the formation of crystals has been reviewed by various researchers [58,59].

Crystallization Process

Although the influence of the crystallization process on the properties of dosage forms and products is well documented, particle information and crystallization have been regarded as a 'low tech' area of chemical production and hence a few methods have been reported.

A number of factors, such as solvent composition, Degree of saturation, temperature, additives, pH, etc. influence the crystallisation process.

The composition of the solvent used is known to influence crystallization either directly or by influencing the temperature at which the crystallization is initiated. For example, in the mannitol system, the α-polymorph is formed by evaporation of 100% ethanol while the β-polymorph is formed by crystallization from aqueous ethanol[60].

Degree of super saturation affected crystallisation was showed by Sudo by using isopropyl alcohol. It was seen that there occurred spontaneous crystallisation[61].

Temperature can have a very significant effect on the polymorph produced. Studies by Kitamura on the crystallization of L-glutamic acid showed that at 45^0C the α-form nucleates slowly resulting in β-form growth, whereas at 25^0C the α-form nucleates rapidly cause α-form growth[62].

The effect of additives on crystallization has been of interest for many years. Early work has indicated that polymeric additives could prevent the crystallization of certain phases. Significantly, studies in recent years by Lahav and co-workers have shown that additives (as little as 0.03%) can inhibit nucleation and crystal growth of a stable polymorph, thus favouring the growth of a metastable polymorph. They also showed that it is possible to design crystal nucleation inhibitors to control polymorphism[63].

Crystallisation is a crucial process in the pharmaceutical industry. Three main areas of crystallisation include: 1) nucleation, 2) production and scale up of novel solid forms, 3) continuous processing. This is in detail reviewed by Chen et al and was published as part of the crystal growth and design 10^{th} anniversary perspective[64].

Characterisation of Crystalline Solids

Different forms of solid results in the variation of properties with respect to stability, dissolution, bioavailability, etc[65]. Various analytical methods are being currently used to characterize the crystalline form of the drug during the various steps of processing and development. Some of the methods are as described below.

Single Crystal X-Ray Diffractometry

Single crystal X-Ray diffractometry is a non-destructive analytical technique which provides detailed information about the internal lattice of crystalline substances, including unit cell dimensions, bond length, bond angles, and details of screen ordering. The fundamental principles and working are explained by Dutrow et al[66].

Vibrational Spectroscopy

Vibrational spectroscopy contains information about the motions of the functional groups present in the solid and is often site-specific in nature. Infrared absorption and raman scattering techniques come under this.

Infrared spectroscopic techniques reflect significant spectral differences between crystalline and amorphous phases and hence are used to quantify the crystalline content. Infrared procedures for measuring the crystalline content are based on the study of the peak measurement[67]. Fourier-Transform Raman Spectroscopy (FTRS) is active when there is a change in polarizability during vibration [68]. FTRS is advantageous compared to IR due to the following reasons: (i) minimal sample preparation, thereby preventing the likelihood of inducing any phase changes; (ii) rapid collection of data; (iii) non-destructiveness; and (iv) minimum interference of water with the vibrational modes from most drugs [69].

The process and technique in detail of these have been reviewed by Birju et al[70].

Nuclear Magnetic Resonance Spectrometry

NMR has the advantage of bulk analysis of the sample. As with most of the other reports, these are used in the investigation of pharmaceutical polymorphs and performed in conjugation with other analytical techniques. Differences in polymorphic forms of benoxaprofein, nabilione, and pseudo polymorphic forms of cefazolin were reported through this technique[71].

The following table gives the analytical techniques used and the information that is obtained from the techniques[71.]

Analytical techniques	Information
MOLECULAR LEVEL SPECTROSCOPHY	
Mid-IR (Fourier transformed infrared (FT-IR)/diffused reflectance infrared transmission spectroscopy (DRIFTS)/attenuated total reflectance.	- Intramolecular vibrations, H-bonding Polymorphic forms: unique bands, peak shifting Amorphous form: broadening of peaks - Complementary to Raman spectroscopy - Spatial chemical information with imaging setups
Raman Spectroscopy	- Intramolecular vibrations Polymorphic forms: unique bands, peak shifting Amorphous form: broadening of peaks - Complementary to IR spectroscopy -Spatial chemical information with imaging setups
Near infrared (NIR)	- Overtones and combinations of vibrations in the mid-IR region - Sensitive to different water states -Spatial chemical information with imaging setups
Solid-state nuclear magnetic resonance (ss-NMR)	- Nuclei and chemical environment within a molecule - Molecular dynamics - Interactions; drug–drug or drug–excipients
PARTICULATE LEVEL SPECTROSCOPY	
Terahertz pulsed spectroscopy (TPS)	- Intramolecular and lattice vibrations (phonon modes) Polymorphic forms: unique peaks Amorphous form: no spectral features
X-ray Powder X-ray diffraction (PXRD)	- Structural information from 5 to 90◦2 Polymorphic forms: unique diffraction peaks Amorphous form: no peaks, broad halo - Degree of crystallinity - Combine with PDF to yield more structural information (i.e., differences between amorphous states and/or nanocrystalline drug)
Single crystal X-ray diffraction (SCXRD)	See PXRD -Traditionally used to solve crystal Structures
Small angle X-ray scattering (SAXS)	- Structural information from 0.01 to 3◦2
Thermoanalytical and gravimetric analyses Differential scanning calorimetry (DSC)	-Thermal events; glass transition temperature (Tg), crystallization temperature (Tc) and melting temperature (Tm), heat capacity, heat of fusion/transition/ crystallization - Interactions; drug–drug or drug–excipient - See DSC

Modulated temperature differential scanning calorimetry (MTDSC)	- Separation into reversing and non-reversing heat flow (i.e., more information available)
Thermogravimetric analysis (TGA)/dynamic vapour sorption (DVS)	-Transitions involving either a gain or a loss of mass - Decomposition temperature - Use in conjunction with Karl Fischer Titration
Isothermal microcalorimetry (IMC)	- Heat change in a reaction, e.g., enthalpy relaxation of amorphous material (direct measurement), heat of crystallization.
Solution calorimetry (SC)	- Heat change in a reaction, e.g., heat of solution (main), heat of wetting, heat capacity of liquids, heat capacity of solids (mixture method)

BULK LEVEL SPECTOSCOPY	
Karl Fischer titration	- Water content (adsorbed or hydrate) - Use in conjunction with TGA/DVS
Brunauer, Emmett and Teller (BET) method	- Surface area of the samples (the BET equation is an extension of the Langmuir equation, for multilayer adsorption)
Density (gas pycnometer)	- True density of the sample by dividing the known mass with the measured volume

A through summary of the process and the spectroscopic methods involved in the characterisation of the solid state are given by Bugay[73].

Properties

By drawing a theoretical link between order of water molecules in hydrates and shape of the isotherm obtained, it was proved that different models on non-stoichiometric hydrates can fit many experimental situations and is in a good agreement with qualitative assessments of the order of hydrates [74, 75].

CONCLUSION

At present, the pharmaceutical and healthcare industries are moving through a period of unparalleled change. Major multinational pharmaceutical companies are restructuring, consolidating, merging and more importantly critically assessing their competitiveness to ensure constant growth in an ever-more demanding market where the cost of developing novel products is continuously increasing. The pharmaceutical manufacturing processes currently in existence for the production of solid oral dosage forms are associated with significant disadvantages and in many instances provide many processing problems. Therefore, it is well accepted that there is an increasing need for alternative processes to dramatically improve powder processing, and more importantly to ensure that acceptable, reproducible solid dosage forms can be manufactured. Consequently, pharmaceutical companies are beginning to invest in innovative processes capable of producing solid dosage forms that better meet the needs of the patient while providing efficient manufacturing operations [76-78].

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