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REVIEW

Revealing facts behind spray dried solid dispersion technology used for solubility enhancement

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Abstract Poor solubility and bioavailability of an existing or newly synthesized drug always pose challenge in the development of efficient pharmaceutical formulation. Numerous technologies can be used to improve the solubility and among them amorphous solid dispersion based spray drying technology can be successfully useful for development of product from lab scale to commercial scale with a wide range of powder characteristics. Current review deals with the importance of spray drying technology in drug delivery, basically for solubility and bioavailability enhancement. Role of additives, selection of polymer, effect of process and formulation parameters, scale up optimization, and IVIVC have been covered to gain the interest of readers about the technology. Design of experiment (DoE) to optimize the spray drying process has been covered in the review. A lot more research work is required to evaluate spray drying as a technology for screening the right polymer

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for solid dispersion, especially to overcome the issue related to drug re-crystallization and to achieve a stable product both *in vitro* and *in vivo*. Based on the recent FDA recommendation, the need of the hour is also to adopt Quality by Design approach in the manufacturing process to carefully optimize the spray drying technology for its smooth transfer from lab scale to commercial scale.

Contents

1. Introduction

In recent times, many new chemical entities (NCEs) have been synthesized on the basis of structure of their target receptors using combinatorial chemistry, which results in the invention of very large molecules with greater degree of hydrophobicity. Their poor aqueous solubility may cause poor solubilization in the gastrointestinal tract with low and unpredictable bioavailability (Shukla et al., 2011). It is frequently documented that almost 40% of NCEs discovered by the pharmaceutical researchers are poorly soluble or lipophilic in nature (Giri et al., 2010). The solubility performance of drugs remains one of the most challenging qualities in formulation development and it results in challenge in targeted delivery of poorly water soluble drugs (Kumar et al., 2011). Solid dispersion is one of methods which involves dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting, dissolution in solvent or solvent evaporation method (Verma et al., 2011). Solid dispersion based spray drying technology is widely applied in pharmaceutical industry because it is simple, economic and advantageous (Patel and Patel, 2012; Hite et al., 2003; Mohanachandran et al., 2010). This review article covers an overview of spray drying technology, critical process parameters (CPPs) and their effect in final product quality, effect of various additives in spray drying, screening methodology for selection of suitable carrier polymer, scale up in spray drying and *in vitro–in vivo* correlation (IVIVC) of spray dried formulation. Quality by Design (QbD) is also an important aspect in optimization of the spray drying process parameters to assure the desirable reproducibility and quality of final product; therefore, it has also been covered under this review.

2. Various methods to overcome solubility issue

As shown in Table 1, various physical and chemical methods can be used to improve the solubility of poorly water soluble drugs. Particle size reduction is one of the physical methods to enhance solubility, but sometime decreasing the particle size may cause the agglomeration, which may retard the solubility and bioavailability during storage of final product. Presenting the compound as a molecular dispersion combines the benefits of a local increase in the solubility as well as stability of amorphous form of drug (Pouton, 2006; Leuner and Dressman, 2000). Selection of right carrier polymer is also vital to improve solubility and stability, so screening right excipient for solid dispersion technology has also been covered in the current review. As shown in Fig. 1, absorption of a BCS class II drug can be significantly improved by optimization of the formulation in such a way that it maintains class II drugs in a solubilized condition at the absorption site and due to that it gives a similar absorption profile like that of a class I molecules. For BCS class III and IV molecules, the permeability and absorption can be improved by means of chemical modification during the drug synthesis (Pouton, 2006).

Table 1 List of technologies to improve the solubility of poorly soluble drugs (Kumar et al., 2011; Patel and Patel, 2012; Leuner and Dressman, 2000).

Physical methods	Chemical modification
Particle size reduction (micronization or nanosuspensions)	Salt formation
Polymorphism	Prodrug approach
Change in crystal habit	
Complexation/solubilization (use of surfactants or use of cyclodextrines)	
Drug dispersion in carriers (solid dispersions)	

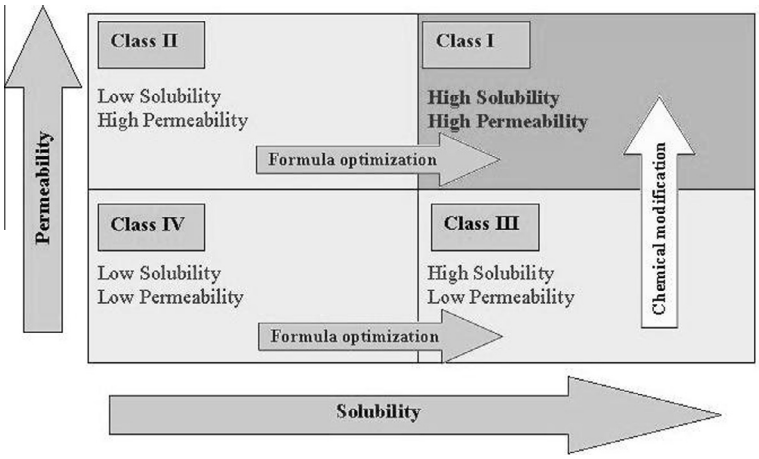


Figure 1 Bio pharmaceutics (BCS) classification (modified from Pouton, 2006).

3. Solid dispersion technology

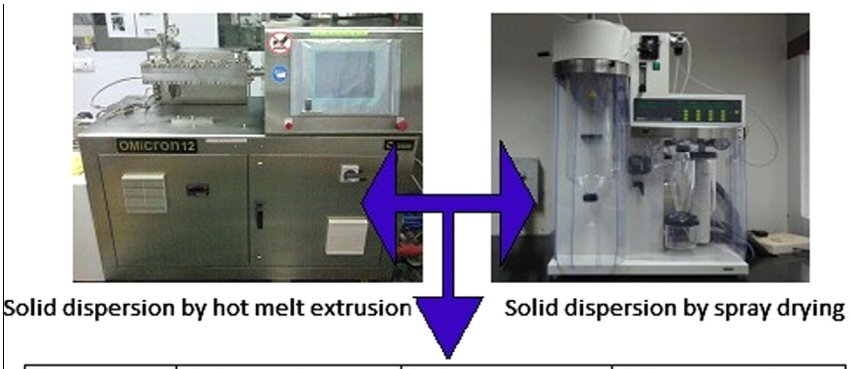
Solid dispersion is defined as the dispersion of one or more active ingredients in an inert excipient or matrix (carrier), where the active ingredients could exist in finely crystalline, solubilized or amorphous state (Sareen et al., 2012; Kapoor et al., 2012). Solid dispersion consists of two or more than two components, generally a carrier polymer and drug along with stabilizing agent (and/or surfactant or other additives). The most important role of the added polymer in solid dispersion is to reduce the molecular mobility of the drug to avoid the phase separation and re-crystallization of drug during storage. The increase in solubility of the drug in solid dispersion is mainly because drug remains in amorphous form which is associated with a higher energy state as compared to crystalline counterpart and due to that it required very less external energy to dissolve (Duarte et al., 2011). Additionally, formation of small particle size with better porosity, wettability and surface area are the main reasons for the improvement in bioavailability (Vasconcelos et al., 2007).

There are basically two types of solid dispersion systems: crystalline and amorphous solid dispersions (Dhirendra et al., 2009; Calahan, 2011). Former system contains the crystalline drug dispersed within a crystalline or semi-crystalline carrier. Later system contains a carrier which is amorphous rather than crystalline, and it can be additionally classified into solid crystalline suspension, solid glassy suspension, and solid glassy solution (Baird and Taylor, 2012). As shown in Fig. 2, solid glassy solutions containing drug and carrier are homogeneous and molecularly dispersed with each other in single homogeneous phase and in differential scanning calorimetry (DSC), it shows single glass transition temperature (Tg) peak. Solid glassy solution is the best system to achieve solubility enhancement with good thermal and physical stability. Two phase blends also known as solid glassy suspensions contain drug in partially miscible state with the carrier and are more prone to undergo phase separation during storage. Solid crystalline suspension contains polymer in amorphous phase while drug in crystalline phase and in DSC it shows one Tg peak for polymer and one melting peak for drug which indicates no miscibility between drug and the polymer. To accomplish the substantial stability of solid dispersion, pharmaceutically suitable carriers like polymers, surfactants and stabilizers are added into the formulation, usually at high concentrations to reduce the molecular mobility and re-crystallization of drug (Baird and Taylor, 2012).

4. Screening of polymer in solid dispersion technology

With the aim to accomplish the desired solubility and stability of amorphous form of drugs, selection of right polymer(s) or carrier(s) is required in the initial stage of formulation development. Excipient screening or selection would be time-consuming and requires an extra labor with consumption of a large amount of drug. In the early phase of lead optimization and candidate selection, large numbers of hydrophobic compounds are synthesized in very small quantities and, therefore well efficient polymer screening method is required which consumes minimum amount of drug (Dai et al., 2008; Ghebremeskel et al., 2007).

Dai and co-workers have developed experimentation approaches to rapidly identify a solubility-enhancing polymer that improved the bioavailability of a poorly water-soluble



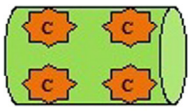
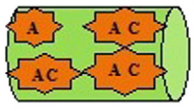
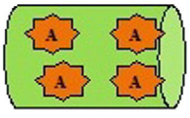
Extrudate or dispersion type	Solid crystalline suspension	Solid glassy suspension	Solid glassy solution
Polymer phase	Amorphous	Amorphous	Amorphous
Drug phase	Crystalline	Amorphous	Amorphous
In DSC it will shows	Two peak: One for drug Melting (Tm) and one for polymer Tg	Two Tg peak	Single Tg peak
Appearance of extrudes is	Opaque	Translucent	Transparent
Interpretation is	Not ideal for solubility enhancement but ok for modified release and taste masking.	Solubility enhancement occurred initially but maybe failed in stability due to drug recrystallization.	Ideal for solubility enhancement without any drug recrystallization during stability.
Image			

Figure 2 Types of solid dispersion.

compound. In the experiments, the lead compound and a panel of excipients were dissolved in common organic solvent like *n*-propanol and distributed into the wells of a 96-well micro titer plate by a TECAN (innovative liquid handling workstation) robot. After solvent evaporation, the dried formulations were further diluted with an aqueous buffer and incubated for 24 h and the solubilization capacity of the excipients was analyzed by HPLC (Dai et al., 2007). Moreover, the optimized formulation can be scaled up and developed using various methods like hot melt extrusion or spray drying to compare the actual solubility and screening experimental solubility (Shanbhag et al., 2008). Barillaro and co-workers have also evaluated total 108 experiments containing 7 different polymers and 5 different surfactants to study the dissolution property of phenytoin (Barillaro et al., 2008). Similarly, Mansky and team have also developed in house and well efficient screening method to identify lipid and semisolid formulations for low soluble compounds (Masky et al., 2007). The limitation of all the above mentioned methods is that it requires consumption of drug and requires extra labor for analytical study to identify suitable polymer. So, various pharmaceutical companies, service provider and excipient manufacturer companies are working on various novel approaches for improving solubility of poorly soluble drugs using solid dispersion technology (Arnum, 2012).

5. Background of spray drying technology

Spray drying technology can be defined as a unit operation in which a liquid stream (solution, suspension or emulsion) is constantly divided into very fine droplet (by a process known as atomization) into a glass compartment where they come in contact with hot gas and get dried into fine particles, which are further separated from the drying gas using a cyclone or a bag-filter (Paudel et al., 2012). Spray driers can operate in open cycle mode for aqueous based or in closed-loop mode for organic based system. Spray drying is a moderate drying technique (where gentle temperatures and little exposure times are used as compared to other solid dispersion technology like melt extrusion) that yields powder with reasonable particle size (Patel et al., 2009; Vehring, 2008). Moreover, the fast drying process within few seconds or milliseconds is also important to prevent phase separation between the drug and polymer components (Duarte et al., 2011).

6. Selection of carrier polymer in spray drying based solid dispersion technology

Selection of carrier in spray drying has a significant effect on stability of amorphous form of drug during *in vitro* and *in vivo*

condition. There are numerous factors which need to be evaluated before carrier polymer selection like: glass transition temperature (Tg) of polymer, nature of polymer (anionic/cationic) and presence of functional group, hygroscopicity of polymer, solubility in common organic solvent, thermal stability, etc. Some polymers work as a wetting agent to solubilize the released drug, whereas others will also help to stabilize the supersaturated drug solution (Mooter, 2011). The existence of useful moieties like hydrogen donors or acceptors is a surplus advantage which helps to inhibit crystallization of a drug from a glass solution. Generally physical instability or nucleation occurs below Tg of polymer due to higher molecular mobility, so polymer with higher Tg value is usually preferred in solid dispersion to improve shelf life of final formulation (Vasconcelos et al., 2007; Mooter, 2011). Polymers can boost the physical stability of system by increasing the Tg of miscible mixtures and for that it should be also molecularly miscible with drug (Vasconcelos et al., 2007). There are numerous carriers like enteric polymers, hydrophilic polymers, amphiphilic polymers and surfactants are used in spray drying technology and is highlighted in Table 3. Kanno and Taylor (2006) have evaluated three different carrier polymers mainly poly(vinylpyrrolidone) (PVP), hydroxypropyl methylcellulose (HPMC) and hydroxypropyl methylcellulose acetate succinate (HPMCAS) for solubility enhancement of Felodipine via the solvent evaporation method. They have observed that HPMCAS was found to sustain the highest level of supersaturation for the maximum length of time during both dissolution and solution crystallization experiments, whereas PVP was found to be the least effective crystallization inhibitor. They have concluded that HPMCAS and HPMC were most effective at inhibiting growth rates while PVP was much less effective (Kanno and Taylor, 2006). So, the role of polymer is not only to stabilize drug against crystallization in the solid state but it should also improve the dissolution profile by inhibiting crystallization from the supersaturated solution generated by dissolution of the amorphous material.

7. Critical process and formulation parameters in spray drying technology

Table 2 and Figs. 3 and 4 show effect of critical process and formulation parameters like spray rate, outlet temperature, solid concentration, atomization rate, etc., on the product characteristics of spray drying technology. These parameters in detail have been discussed below.

7.1. Selection of solvent(s) and feed rate for spray drying technology

In order to make uniform and stable solid dispersions, the choice of solvent should be selected very carefully for solvent based spray dryer because spray dryers are generally sized based on their evaporative capability for a particular solvent. In general, lower boiling solvents are very easy to evaporate and it results in higher solid production yield (Paudel et al., 2012). Drug dissolution rates can be greatly influenced by drug concentration in the feed solution, the choice of polymer, choice of surfactant and the ratio of polymer/surfactant/drug (Huntington, 2004). Feed solution can be a reactive system and must be evaluated in terms of impurity levels over a number of days due to possible chemical reaction of drug with solvents and additives (Wu et al., 2011; Paudel and Mooter, 2012). Solvent selection should be carried out on the basis of following criteria like: boiling point, solubility of drug and polymer and toxicity of solvent on the basis of ICH classification (like class III solvents are more selected as compared to class I solvent due to less toxicity potential) (ICH, 2011a,b). In Tables 3 and 4 possible carriers as well as commonly used solvents for spray drying technology have been enlisted (ICH, 2011a,b; Mahapatra et al., 2012; Shi et al., 2012; Hugo et al., 2013).

Table 2 Critical process parameters (CPP) and their influence in spray drying process (modified from Behera et al., 2010, Buchi Technical Documents).

S. No	CPP	Significance in spray drying process
1	High aspirator rate	1. Due to more drying energy the outlet gas temperature may increase 2. Residual moisture in the final product may decrease 3. Offers more and uniform separation of particles in the cyclone
2	High solid content or high viscosity	1. Less liquid to vaporize and increase exhaust temperature 2. Due to more solid in a drop may increase the particle size 3. Produces bigger particles, which are easier to separate and increases yield 4. Decreases the moisture level in final product
3	High drying gas humidity	1. Moist particles may adhere into the glassware and decreases process yield 2. Might increase the humidity in final product
4	High feed rate	1. Decreases the outlet temperature 2. Increases the droplet size and subsequently particle size 3. Increases the moisture level in the final product
5	High spray gas flow	1. Decreases the outlet temperature 2. Produces smaller droplets from nozzle and parallel particle size decreases
6	High inlet temperature	1. It increases the outlet temperature proportionally 2. Increases the yield and gives less sticky product
7	Use of organic solvent	1. Use of organic solvent generates smaller particles due to lower surface tension

Critical process parameters in spray drying technology

Process parameters	Formulation parameter
Inlet temp	Feed composition (API/carrier/ solvents)
Drying gas properties like humidity	% w/w solid content in spray solution
Solution/ suspension feed rate	Type of solvent (organic/ hydroalchoholic/ aqueous)
Pump pressure for pressure nozzle	Viscosity of spray solution
Compressed air flow	Surface tension of spray solution
Disk/wheel speed for rotary atomizer	
Actuator speed/design	
Outlet and cyclone temperature	

Figure 3 Critical process and formulation variables in spray drying technology.

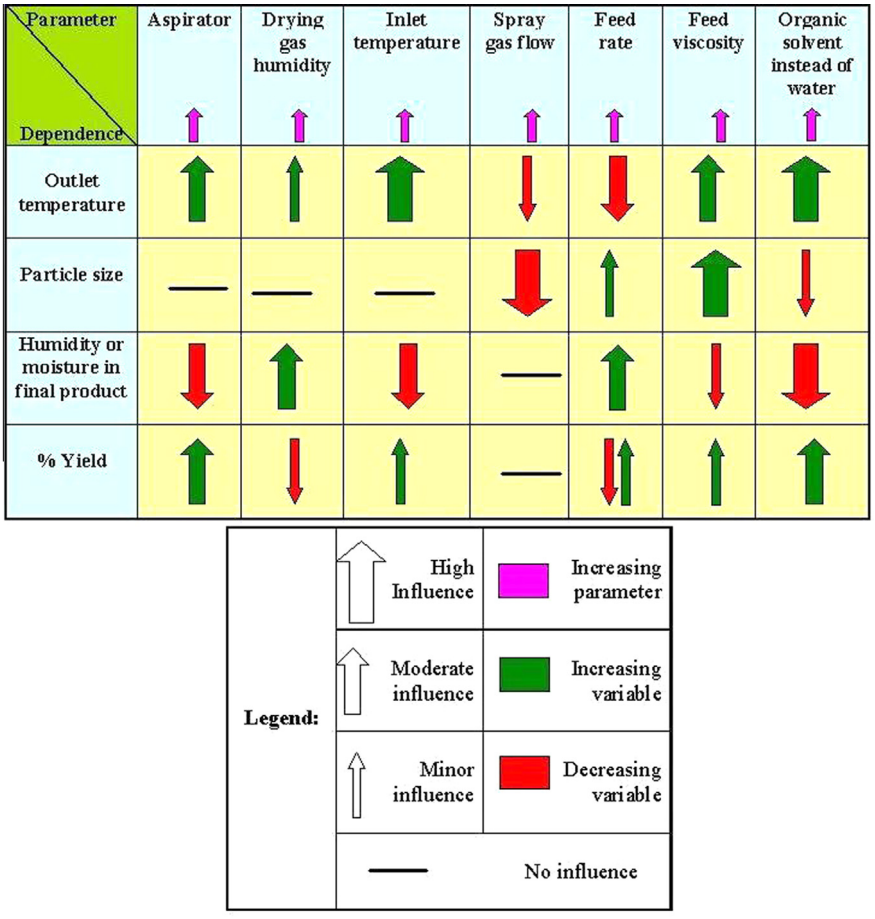


Figure 4 Effect of process parameters in final product characteristics (modified from Behera et al., 2010, Buchi Technical Documents).

Table 3 List of carriers used for solid dispersion technology (Duarte et al., 2011; Mahapatra et al., 2012; Shi et al., 2012).

Type of carrier	Examples
Enteric polymer	Methacrylate polymers (Eudragit® E PO/100, Eudragit® RLPO, Eudragit® L100, Eudragit® S100), Hydroxypropyl methyl cellulose phthalate (HPMCP), Cellulose acetyate phthalate (CAP)
Hydrophilic polymers	Starch, Sodium Carboxymethyl cellulose, Sodium alginate, Polyethylene glycol (PEG), Polyvinyl pyrollidone (PVP), Hydroxy propyl methyl cellulose (HPMC), Polyvinyl alcohol (PVA), β-Cyclodextrin, Mannitol, Chitosan, Carrageenan
Surfactant	Polyethylene – polypropylene glycol, lecithin, bile salt, Lauroyl polyoxyl-32 glycerides
Amphiphilic polymers	Polyethylene oxides (PEO)/Polypropylene glycol (PPG) copolymers, PEG-modified starches, Vinyl acetate/vinylpyrrolidone random copolymers, Polyacrylic acid and Polyacrylates

Table 4 List of commonly used solvents in spray drying technology (ICH, 2011a,b; Hugo et al., 2013).

List of solvents	Boiling point (°C)	Dielectric constant	Solubility in water (g/100 g)	Density (g/ml)	ICH limit (ppm)
Acetone	56.2	20.7	Miscible	1.049	Class 3
Chloroform	61.7	4.81	0.795	1.498	60
Methanol	64.6	32.6	Miscible	0.791	3000
Methylene chloride	39.8	9.08	1.32	1.326	600
Ethanol	78.5	24.6	Miscible		Class 3
Dimethyl formamide (DMF)	153	36.7	Miscible	0.944	880
Dimethyl sulfoxide (DMSO)	189	47	25.3	1.092	Class 3
Glycerin	290	42.5	Miscible	1.261	–
Ethyl acetate	77	6	8.7	0.895	Class 3
Water	100	78.54	–	0.998	–

Dielectric constant of solvent is also one of the important criteria for suitable solvent selection in spray drying process because solubility of solute into solvent is dependent on the dielectric constant of the medium. In simple terms, the energy required to separate two oppositely charged bodies is inversely proportional to the dielectric constant of the medium (Behera et al., 2010). The addition of a co-solvent can increase the solubility of hydrophobic molecules by reducing the dielectric constant of the solvent. Moreover, water is a good solvent for polar molecules due to its high dielectric constant (Behera et al., 2010). Jouyban et al. (2004) had developed a simple computational method for calculating dielectric constants of solvent mixtures based on Redlich–Kister extension. They found that the model can be applied to the experimental dielectric constant of binary and ternary solvent mixtures at fixed and/or various temperatures and it showed accurate results. Moreover, changes in dielectric constant of the medium have a dominant effect on the solubility of the ionizable drug mainly as higher dielectric constant can cause more ionization of the drug and results in more solubilization (Fakhree et al., 2010).

In one of the research work, Al-obaidi et al. (2011) had evaluated two different solvents' combination for griseofulvin–PVP based spray drying technology. They observed that solid dispersion prepared from acetone/methanol (150/150) showed smaller size particles as compared to acetone/water (185/85) solvent mixture. The viscosity of the spray drying solution was lower for acetone–methanol (0.554 cP) than for acetone–water (1.39 cP) and from that it would be anticipated that a dispersion resulting from the less viscous solution had a quicker rate of evaporation and gives small particle size. Likewise, Harjunen et al. (2002) have studied the effect of ethanol to water ratio in feed solution and they found that lactose spray dried from pure ethanol was 100% crystalline while lactose spray dried from pure water was 100% amorphous.

Esposito et al. (2005) have observed that low feed rate gives a better result in terms of morphology of prednisolone microparticles like moisture level, small particle size and good flow property. Rattes and Oliveira (2007) have also found that slower dissolution is obtained at higher feed rate and is partly due to the increase in the diameter of the atomized drops at high feed flow rate which generates a bigger particle with lower total surface area. So, physicochemical characteristics of spray dried powder are significantly affected on the basis of selection of solvent, viscosity of feed solution, concentration of solid in feed solution, feed rate, and to some extent by solution surface tension.

7.2. Role of feed atomization on spray dried product characteristics

The aim of atomizer is to break down bulk liquid feed concentrate into fine droplets in order to provide a very large surface, to facilitate solvent evaporation and particle separations. Atomizer is appropriately fitted in the drying assembly along with feed inlet to allow uniform mixing between feed solutions and drying gas. The most common atomizers used in pharmaceutical industry are two-fluid nozzles (pneumatic atomization), pressure nozzles (hydraulic atomization), rotary

atomizers (rotating wheel atomization) and ultrasonic atomizer (Rattes and Oliveira, 2007; Bittner and Kissel, 1999; Cal and Sollohub, 2010). The choice of atomizer depends upon the properties of the feed and the dried product specification.

Current research scenario is much more focused toward the use of four fluid spray nozzle in spray drying process to overcome the necessity of using common solvents for two drugs. In one of the studies, Mizoe et al. (2007) have used 4-fluid spray nozzle containing spray drier for preparing drug-containing microparticles of poorly water-soluble drugs ethenzamide (EZ) and flurbiprofen (FP). They found that the 4-fluid nozzle atomizer can overcome the problems of using a common solvent for two drugs as it has two liquid and two gas passages, which allows drug and carrier to be dissolved in separate solvents. Similarly, Chen and co-workers have prepared amorphous solid dispersion by separately passing drug and polymer solutions all the way through four-fluid nozzle and observed better performance in terms of effective distribution of particles in lungs with enhanced absorption characteristics as compared to the microparticles prepared from a single solution (Chen et al., 2008).

The particle size distribution obtained after traditional spray drying process is not well controlled. So, in order to control the particle size and morphology electro hydro-dynamic or electro-spraying (EHD) atomization is generally used in spray drying process (Lastow et al., 2007). In the EHD based atomization method, feed solution is first pumped through a nozzle and the nozzle is applied with a high potential difference. The electrical field formed causes the jet emitted from the nozzle to disintegrate into mono dispersed droplets in the micrometer range (Kuang et al., 2012). Recently, Kuang and co-workers have studied about changing the voltage applied to the electrodes on the particle size. They observed that particles fabricated at a much lower voltage were of smaller diameter than particles fabricated at higher voltage. EHD is also used to produce fine particles of a complex structure which are hard to obtain by other means (Ciach, 2007). So, electro spraying process has a unique advantage to produce a narrow size distribution under the influence of electrical forces which makes it more suitable for many pharmaceutical applications (Yurteri et al., 2010).

7.3. Effect of inlet/outlet temperatures on final product characteristics

Outlet air temperature is one of the most critical parameters which exclusively affects the product morphology like particle size, surface roughness, density, stickiness of particles, residual solvent or moisture levels, product yield, etc. After performing spray drying process, secondary drying of powder is generally required to remove the excess residual solvent because, presence of solvents may plasticize the solid dispersion by increasing molecular mobility and it results in the development of crystal growth. Spray drying process carried out at a lower outlet temperature gives a product with high residual solvent levels and poor flow property (Alexander and King, 1985; Littringer et al., 2012; Maury et al., 2005a,b).

Mass et al. (2011) have prepared 15% aqueous solution of mannitol and spray dried it at 3 different temperatures i.e. 60 °C, 90 °C and 120 °C (M60, M90, and M120). They observed that at 60 °C outlet temperature, mannitol particles were more spherical without inside void spaces or hole formation as compared to particles dried at 90 °C and 120 °C. They concluded that due to lower internal pressure applied by the evaporating liquid at 60 °C than at 90 °C and 120 °C, giving the vapor sufficient time to escape without rupturing the solid shell (Mass et al., 2011). Likewise, Paramita and co-workers have also found that spray-dried powders at higher outlet temperatures give higher percentages of hollow particles (Paramita et al., 2010).

8. Effect of various formulation additives on product characteristics

The development of solid dispersion is shifting toward the addition of a third or even more components along with polymeric carrier (so called as ternary solid dispersion) to stabilize the amorphous form of drug during storage. The most commonly used adjuvants are surfactants or co-solvents that are added in the solid dispersion to improve the dissolution and physical stability of drug by improving the wettability and minimize the crystallization of drug during storage. Apart from surfactant, glidants/drying agents are also added during spray drying process to improve the flow property and yield of the powder and to minimize sticking tendency of particle in spray drying chamber. Some other additives can also be added in spray drying process like disintegrants, pH modifiers, salt former, complexing agents, etc. (Mahdjoub et al., 2003; Aejaz et al., 2010; Shinde et al., 2011; Maghraby and Alomrani, 2011; Rahmati et al., 2013).

8.1. Effect of silica on product characteristics

The use of colloidal silica can minimize the electrostatic charge generation between powders with the spray dryer wall, leading to increased yield as well as improved flow property of powder. Moreover, porous silica also works as adsorbents (which gives more surface area) and plays a significant role in solubility enhancement (Mahajan et al., 2012). Planinsek et al. (2011) have developed solid dispersion containing porous silica and observed that porous silica plays a significant role in solubility enhancements. Pokharkar and team have also accomplished that the stability of solid dispersion was significantly improved due to the addition of Aerosil® 200 (Pokharkar et al., 2006). Ambike and team have also found that silica was playing a significant role in the improvement of flow property and stability of low glass transition temperature (Tg) drug like Simvastatin (Ambike et al., 2005). Similarly, Chauhan et al., 2005 have prepared spray dried solid dispersion in the presence of Aerosil® 200 as adsorbents and found improvement in dissolution rate (even after 3 months storage) as well as bioavailability. Numerous other research works have also been reported about improvement in dissolution, process yield and stability after addition of silica in spray drying feed solution (Martins et al., 2011; Takeuchi et al., 2005; Shen et al., 2011).

8.2. Effect of lactose on product characteristics

Makai et al. (2008) have evaluated the effects of lactose on the surface properties of microparticles prepared by a spray-drying

method. In this work, they compared three different formulations of untreated microcrystals, alginate-based spray-dried microparticles and alginate-based lactose containing spray-dried microparticles of trandolapril. They observed faster dissolution for the sample containing lactose in comparison to those samples containing alginate or alginate and lactose. Moreover, they concluded that the application of lactose caused a marked increase in the surface polarity of the particles which helps to increase the solubilization potential of drug.

9. Effect of stabilizer on product characteristics

The amorphous form of drug has the highest free energy and entropy which results in superior molecular motion compared to the crystalline state (leading to higher apparent solubility and dissolution rate). High internal energy and molecular mobility of amorphous materials are also accountable for crystallization during storage and it can be minimized by the addition of suitable and proper concentration of stabilizer (Yu, 2001; Laitinen et al., 2012). So, stabilization of amorphous form of drug during storage is more important to improve the dissolution and *in vivo* efficacy of developed formulation. In various research studies, scientists have used different stabilizers or surfactants along with drug-polymer mixtures to improve the stability of solid dispersion. Beck et al. (2013) have recently used non-ionic surfactant Pluronic F127 as a stabilizer for the HPMC based solid dispersion. They observed that the addition of Pluronic F127 along with HPMC results in controlling initial growth and suppression of agglomeration and the optimal formulation results in faster and higher extent of dissolution than a poorly stabilized suspension.

10. Scale-up in spray drying

Spray dryers in the pharmaceutical industry are available in a wide range of scales: from lab scale to commercial scale which is capable of handling several tons of material per day (Gil et al., 2010). Comparison of spray dryer at laboratory, pilot and commercial scales is shown in Table 5 (Thybo et al., 2008; Gohel, 2009).

Proper optimization of process parameters using factorial design is a very powerful tool to support the scale-up of spray drying process to achieve the desired powder characteristics at a larger scale. The use of process simulation tool can also give robust processes, faster development at a lower cost and high product quality (Dobry et al., 2009). Influence of four main parameters like as inlet temperature, feed flow rate, atomization gas flow rate and solid concentration in feed solution should be evaluated properly in the lab scale development. The effects need to be determined in terms of particle size, morphology, residual solvent, crystallinity, yield and stability. In order to accomplish the uniform particle size in production scale, atomization gas flow and feed rate also need to be optimized (like high atomization gas flow and low feed rate give smaller particles in production scale spray dryer) (Thybo et al., 2008). Selection of suitable nozzle type depends on the target quality attributes and properties of feed solution. In most pharmaceutical applications, pressure nozzles are preferred then two-fluid nozzles, because they provide powders with a narrow particle size distribution. In the literature, it was also reported that the lab scale atomizers are typically two-fluid nozzle, which are replaced by a pressure nozzle in the commercial scale to control the particle size (Arpagaus and Schwatzbach, 2008; Schwatzbach, 2010).

11. Characterization of amorphous solid dispersion after spray drying process

Conversion of API from amorphous to crystalline form during storage may result in solubility retardation. So, determination of glass transition temperature of carrier, molecular mobility of the drug and the rate and extent of drug crystallization, etc., need to be evaluated accurately to study the effect of storage on solubility of drug. A wide range of thermal analytical techniques can be used for characterization of solid dispersion and among it, differential scanning calorimetry (DSC) is generally available in many industrial and academic laboratories (Baird and Taylor, 2012; Leuner and Dressman, 2000; Paradkar et al., 2004). A modest factor like presence of moisture in DSC instruments can also affect the Tg of solid dispersion which was previously reported by Crowley and Zografi

Table 5 Comparison of spray dryer at laboratory, pilot and commercial scales (Thybo et al., 2008; Gohel, 2009).

Parameter	Lab scale	Pilot scale	Commercial scale
Drying gas	Nitrogen/air		
Type of feed	Aqueous/organic solutions, suspensions or emulsions		
Fit for injectables?	Yes	Yes	Yes
Atomization devices	Two-fluid nozzle	Two-fluid nozzle, pressure nozzle	Two-fluid nozzle, pressure nozzle
Nominal drying gas flow (kg/h)	40	80	1250
Feed flow rate (kg/h)	2.5	45	45–60
Outlet temperature (°C)	40–65	40–65	40–65
Evaporating capacity (kg water/h)	1	6	90
Typical batch scale (kg)	0.01–0.500	0.2–20	10–1000

(2002), as they have evaluated the absorption of moisture by various solid dispersions and concluded that Tg was strongly depressed by absorption of moisture. Kanno and Taylor (2006) have also studied the plasticizing effect of the moisture and they observed that in the absence of moisture, the Tg of solid dispersion was increased toward the direction of the Tg of the pure polymer. While, in the presence of moisture, the Tg values of the dispersions were lower, which clearly indicate that the presence of moisture enhances the molecular mobility of polymer and reduces the Tg value in PVP based solid dispersion. Some other thermal analytical techniques like X-ray diffractometry (XRD), hot stage microscopy (HSM) and NMR are used for identification of crystalline structure in solid dispersion. In XRD spectra, crystalline form of drug usually shows sharp peaks as specific 2θ angles while amorphous form shows a halo peak and so both polymorphic forms can be easily differentiated from each other. Similarly, presence of single Tg peak of polymer without sharp melting peak of drug in DSC spectra for solid dispersion indicates that degree of crystallinity is considerably reduced and the drug is present in amorphous form (Bhinse, 2011).

12. Quality by Design (QbD) in spray drying

QbD can be defined as to design a process in such a way that the final product meets all the predefined specifications and achieves desirable quality attributes. In recent times, there is an increasing demand from regulatory authorities to implement QbD and design of experiment (DoE) methodology in product development stage. Objective behind this initiative is to understand the manufacturing processes together to achieve final product within predefined excellence (Lebrun et al., 2012). International Conference on Harmonization (ICH) has published guidelines that "the aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provides scientific understanding to support the establishment of the design space, specifications, and manufacturing controls". So, identification of critical quality attributes (CQA) and critical process parameters (CPP) in spray drying is more needed to study the effect of their variation on the quality of final product. FDA's process analytical technology (PAT) initiative is also one of the collaborative efforts and the aim of PAT is similar in line with QbD to assure high product quality through timely measurements of critical quality and performance attributes of raw materials, in-process materials and final products (Yu et al., 2004).

By considering the complexity of spray drying process, optimization of spray drying process parameters is quite challenging to achieve the desirable product. In one of the research work, Amaro et al. (2011) have applied 2^4 factorial DoE and studied various CPPs like inlet temperature, gas flow rate, feed solution flow rate and feed concentration. They have evaluated resulting powders in terms of yield, particle size (PS), residual solvent content (RSC), specific surface area and outlet temperature as CQA. They observed that the yield was increased with a decrease in gas flow and it remains unchanged with respect to increasing or decreasing the inlet temperature. Similar observation was also further supported by Buchi documents that lower gas flow reduces atomization energy and produces larger particles. Baldinger et al. (2012) had recently illustrated the influence of CPP on CQA of spray-dried powders by applying DoE and found that the full factorial design proved to be unsuitable due to the non-linear influence of factors while the composite face-centered design improved the quality of the models and showed both linear and non-linear influence of the parameters on the outcomes.

Prinn et al. (2002) and Maltesen et al. (2008) have found that feed solution concentration has the higher impact than gas flow rate on process yield. Büchi technical data also demonstrated that gas flow and feed solution concentration have a largest influence on the resulting particle size. Lower gas flow reduces atomization energy and producing larger particles (Stahl et al., 2002). Maury et al. (2005a,b) have shown that the powder yield was increased at higher process temperatures, due to improved droplet drying and reduced droplet/particle deposition on the walls of the drying chamber. Particle size is also one of the most important CQA in spray drying process and there are a number of reports indicating that as gas flow decreases and feed concentration increases larger particles are produced (Stahl et al., 2002; Al-Asheh et al., 2003; Tajber et al., 2009).

Residual solvent content is also one of the important evaluation parameters in spray drying process as residual solvent work as plasticizer to reduce the Tg and may convert amorphous form of dug to crystalline form during storage. Amaro et al. (2011) have recently shown that with increasing inlet temperature, more energy is supplied to the drying chamber leading to more efficient solvent removal from the droplets which reduces residual solvent in the powder. Maury and team have observed that high feed rate generates more solvent vapor and reduces the exhaust temperature leading to a less efficient drying, hence higher residual solvent content (Maury et al., 2005a,b). So, in order to achieve higher yield with less residual solvent content, high outlet temperature is required.

Another important evaluation parameter in spray drying process is the porosity and specific surface area (SSA) of microparticles (Amaro et al., 2011). Porous microparticles have potential advantages over non-porous materials as they have less inter-particulate attractive forces with better flow characteristics, and exhibit smaller aerodynamic diameters than their geometric diameters, facilitating greater deposition in the lower pulmonary region, with improved efficiency (Healy et al., 2008; Papelis et al., 2003). Amaro et al. (2011) have shown that three major CPPs have a negative effects i.e. inlet temperature, feed rate and feed concentration, indicating that when any of these factors decrease, particles with higher surface area are produced. One major CPP has a positive coefficient i.e. gas flow, giving particles with higher surface area at higher levels. Cabral-Marques and Almeida (2009) have also developed and characterized a beclomethasone:γ-cyclodextrin complex and optimized the variables on the spray-drying process to obtain a powder with the most suitable characteristics for lung delivery. All of above research work highlights the complexity of process and interaction of spray drying process parameters in the final quality of product. So, proper design of experimental is required in spray drying process to achieve powders with desirable characteristics, i.e. high yield, uniform particle size, high surface area and low residual solvent.

13. *In vitro–in vivo correlation* (IVIVC) of spray dried formulation

After preparing amorphous solid dispersion by spray drying technology, *in vitro* dissolution as well as animal or human *in vivo* absorption study is required for complete understanding. Poddar et al. (2011) have prepared solid dispersion of ritonavir using polyvinyl pyrollidone vinyl acetate as a carrier polymer for solubility enhancement. During *in vitro* dissolution analysis, they observed that 95% of drug was released in 25 min from solid dispersion while only 20% of drug was released in 60 min from physical mixture. *In vivo* bioavailability results showed AUC (t-8 h) value of 59.62 μg/ml h for solid dispersion compared with that of pure drug which was 8.08 μg/ml h. This result suggested that the absorption rate of solid dispersion was remarkably higher than pure drug and they concluded that prepared solid dispersion could significantly improve both the dissolution rate and bioavailability of ritonavir.

Patel et al. (2010) have prepared the solid dispersion of fenofibrate with poloxamer 407 using spray drying technology. The spray dried particles were characterized for the *in vitro* dissolution studies and *in vivo* absorption studies and the results showed that the dissolution rate and oral bioavailability of the spray dried fenofibrate/poloxamer 407 particles were significantly increased as compared to pure drug. They concluded that improved particle wetting in the presence of the hydrophilic surfactant (as evidenced by contact angle measurements) seems to be the most important determinant for *in vivo* oral bioavailability. Muttil et al. (2007) have prepared biodegradable and inhalable microparticles containing anti-tuberculosis drugs using spray drying technology. During *in vivo* studies they found that drug concentrations in macrophages were ~20 times higher when microparticles were inhaled rather than drug solutions administered. Naikwade et al. (2009) have investigated the *in vivo* efficacy of budesonide (BUD) microparticles for pulmonary administration and found that developed formulations had extended half-life (14 h) compared to conventional formulation (9 h) with one to four-fold improved systemic bioavailability with excellent lung deposition.

14. Conclusion

The new molecules synthesized by various pharmaceutical companies or even existing molecules from certain therapeutic classes turn out to be of low aqueous soluble in most cases. So, there is a need for a formulator to find a solution though different formulation designs and among it amorphous solid dispersion approach has proven to overcome such solubility issues of BCS class II and IV molecules. Out of various technologies to generate solid dispersion/solution, the spray drying method is constantly gaining attention due to its ease of processing thermo labile compounds, its flexibility in terms of wide application range and the ease on process control to achieve final powder characteristics in terms of particle size distribution, flow property, porosity, yield, etc. Major challenge for formulation scientist in spray drying technology is to accomplish a long term stability of amorphous form of drug. In order to achieve a long term stability, selection of right polymeric carrier is required which can form a molecular solid glassy solution by decreasing the molecular mobility of the drug and due to that it reduces the re-crystallization of drug during storage. A deep insight into the critical process parameters of the spray drying technology is important to obtain the desired product quality. Carrier polymer is a critical component in spray drying process because it not only increases the solubility of poorly water soluble drug but also plays a vital role in minimizing the crystallization of drug during storage. Moreover, a proper understanding of various thermo analytical methods like DSC and XRD is also very important to understand the desired solid state characteristics of solid dispersions.

Moreover, spray drying process involves interactions between various formulation variables (like feed concentration, solvent type, type of polymer) and process conditions (drying gas flow rate, feed rate, outlet temperature, atomization rate) which can significantly influence the particle characteristics (yield, particle size, residual solvent content, flow property, surface area and release profile) of the solid dispersion. Based on the recent FDA and ICH product development guidelines, Quality by Design (QbD) should also be adopted in spray drying formulation development to achieve the product within predefined quality specification. By considering the complexity of spray drying process, factorial design models can also be put together to optimize the CPP which can produce a powder with suitable characteristics, i.e. high process yield, maximum dissolution, uniform particle size with low residual moisture content. It is also important to understand the factors influencing scale up of spray drying process for easy commercialization.

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