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Manufacturing of solid dispersions of poorly water soluble drugs by spray drying: Formulation and process considerations

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ABSTRACT

Spray drying is an efficient technology for solid dispersion manufacturing since it allows extreme rapid solvent evaporation leading to fast transformation of an API-carrier solution to solid API-carrier particles. Solvent evaporation kinetics certainly contribute to formation of amorphous solid dispersions, but also other factors like the interplay between the API, carrier and solvent, the solution state of the API, formulation parameters (*e.g.* feed concentration or solvent type) and process parameters (*e.g.* drying gas flow rate or solution spray rate) will influence the final physical structure of the obtained solid dispersion particles. This review presents an overview of the interplay between manufacturing process, formulation parameters, physical structure, and performance of the solid dispersions with respect to stability and drug release characteristics.

1. Introduction

Spray drying is a unit operation capable of transforming solutions or suspensions into a solid product. The first use of drying of products from an atomized liquid stream was already described in a patent from Percy in 1872 (Percy, 1872). Since then, a tremendous development of the spray drying process with the refinement in the hardware and equipment configuration and improved understanding of fluid dynamics has made it versatile technique operational in diverse industrial fields ranging from food and dairy processing, ceramics, paints, fertilizers, detergents and pharmaceutical industry (Fogler and Kleninschmidt, 1938). In the pharmaceutical field, spray drying is a well utilized unit operation employed for simple drying operations to particle engineering of bulk active pharmaceutical ingredients (API) and excipient and pulmonary formulations, granulation, encapsulation, *etc.* (Ré, 2006; Vehring, 2008). Besides, it is also used for processing vitamins and biopharmaceutical products such as peptides and proteins. One of the characteristics of a spray drying process is the very fast solvent evaporation. This makes it interesting with respect to preparation of amorphous solid dispersions. According to Chiou and Rielman (1971), a pharmaceutical solid dispersion is 'the dispersion of one or more active ingredients in an inert carrier matrix at solid state prepared by melting (fusion), solvent or melting solvent method'. Further, Corrigan, 1985, defined solid dispersions as products formed by converting a drug-carrier combination in fluid state to the solid state. Hydrophilic polymers are the most used carrier materials for the preparation of solid dispersions. The very fast solvent evaporation during spray drying leads to rapid viscosity increase and permits kinetic trapping of the API in the carrier matrix. Often a (supersaturated) molecular dispersion is the result of this process (Miller and Gil, 2012). Amorphous solid dispersions, soluble complexes, encapsulated systems, solid self emulsifying systems and nano-dispersions of poorly soluble drugs prepared by spray drying are primary solubilization strategies. In this review, we will discuss some fundamental aspects of spray drying and diverse aspects of spray dried formulations of poorly water soluble drugs with particular focus on amorphous solid dispersions, critical formulation and process variables, quality attributes of spray dried dispersions and feasibility studies for the development of spray dried dispersions.

2. Background of the spray drying process

The interested reader is referred to excellent reviews that have been published in recent years concerning the fundamentals of spray drying (Cal and Sollohub, 2010; Sollohub and Cal, 2010; Vehring et al., 2007; Celik and Wendel, 2007). In this part a brief summary is given to help the reader to understand the influence of process and formulation parameters on the quality of spray dried amorphous solid dispersions.

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The spray drying process consists of four basic stages: atomization of the liquid, mixing of the liquid with the drying gas, evaporation of the liquid and separation of the dried particles from the gas. The liquid solution or suspension is transported from the container to the nozzle entrance *via* a pump system. The solvent is mostly aqueous, but in case of solid dispersion preparation, organic solvents are mainly used. Hence appropriate equipment safeguards are mandatory.

Atomization transforms the liquid stream into fine droplets by applying a force. The high surface to volume ratio favors efficient and rapid drying of the droplets. Several types of atomization devices are available, depending on the type of energy that is involved: centrifugal energy, pressure energy, kinetic energy and vibrations. Centrifugal forces are generated in a rotary atomizer (disk or wheel type). Droplet size is in this case inversely proportional to the disk or wheel speed. The most commonly used types of nozzles are kinetic energy or pneumatic nozzles where the fluid stream is broken in small droplets by interaction with a second fluid, usually pressurized air. These nozzles are sometimes referred to as bi-fluid nozzles. The droplet size is determined by the ratio of the pressurized gas flow rate to that of the liquid. Also, density of the gas and the liquid as well as surface tension and viscosity of the liquid contribute to droplet size (Cal and Sollohub, 2010; Sollohub and Cal, 2010). Pressure nozzles generate fine droplets by pressurizing a liquid feed by a pump and forcing the liquid feed through the nozzle orifice. Inserts produce a rotary motion of the liquid inside the nozzle leading to the desired cone-shaped spray pattern. Droplet size is inversely proportional to the pressure applied and directly proportional to the feed rate. Ultrasonic nozzles have become the focus of increasing interest in recent years. Buchi developed a lab scale spray dryer based on vibration mesh spray technology which enables generation of very small and more uniformly sized droplets (Heng et al., 2011; Lee et al., 2011; Li et al., 2010a,b). Droplets are generated based on a piezoelectric driven actuator, vibrating a thin, perforated stainless steel membrane in a small spray cap. The spray mesh (membrane) features an array of micron-sized holes. The membrane vibrates and ejects millions of droplets through the holes, resulting in narrow droplet size distribution.

The liquid spray is subsequently mixed with the drying gas, often air or in some cases nitrogen. The drying gas needs to be conditioned to have the right temperature and humidity (ideally, the gas is also HEPA filtered), in order to exert its heat and mass transfer properties. Air dispersing systems (*e.g.* perforated plate) are used to introduce the drying gas into the drying chamber. The dimensions of the drying chamber may vary from a diameter to length ratio of 1–5 (or even higher) in case of pressure nozzles or bi-fluid nozzles tot 1–2 in case of rotary atomizers. Large droplets are most difficult to dry since they possess enough momentum to escape the gas whirl and are directed towards the chamber walls leading to deposits. Hence, consideration of the drying chamber dimensions is important for process optimization. The contact between the liquid spray and the drying gas is mostly established *via* a co-current design, which indicates that the gas flow and spray is in the same direction. Drying gas inlet and atomizer are positioned at the top of the drying chamber. This configuration leads to contact between the feed and the highest temperature drying gas, since the latter has not yet exchanged its heat with the surroundings. Of less importance is counter-current drying procedures in which the drying gas flows in opposite direction to the liquid spray, or systems that are a combination of both. Evaporative drying as in spray drying can be monitored/described using psychrometric charts providing information concerning properties like dry and wet bulb temperature, relative and absolute humidity and enthalpy of the drying gas and the relationships between them (*Mollier diagrams*). These charts are available for air–water systems, but unfortunately less available for organic solvents-air or nitrogen systems.

A particulate aerosol is formed when droplets are dried and transformed to solid particles. The last step in the spray drying process is the collection of the particles, hence separation of solid material from the drying gas stream. Particle collection is typically performed using a cyclone separator and/or bag filtration. The cyclone is very efficient to separate dispersed particles from the continuous gas phase based on density differences between the two phases. When the solid particles and the gas are subjected to an accelerating flow field, which occurs within a rotating vortex in the cyclone, there occurs a lag in velocity for the dense particles compared to the lower density medium. The most common type of cyclone used is the reverse-flow type in which a particle-air dispersion is introduced tangentially into the top part of the cyclone (cylinder-shaped part). The vortex that is produced by the high fluid velocity forces the particles to the walls of the cyclone and down to the conical section. At the end of the conical part, the gas stream reverses (inner vortex) and leaves the cyclone through the vortex finder. Large particles separate from the vortex and are collected, whereas smaller particles are entrained with the gas stream. Larger the acceleration in the cyclone, the smaller the particles that can be separated from the drying gas. Particles that cannot be separated can be collected using bag filters. The drying gas which is leaving the spray dryer must be filtered to avoid contamination.

In case of using organic solvents in the feed, inert drying gases are used (*e.g.* dry nitrogen) in combination with a closed-cycle set-up. A condenser unit is applied to recover the solvents and to avoid pollution of the environment. Often, after completion of the process, the particles are further post-dried in a vacuum oven.

Spray drying is a complicated process and understanding the interplay between process parameters on the one hand and formulation parameters on the other hand is crucial for the reproducible production of high quality material. Process parameters to consider during a spray drying process are: inlet temperature, drying gas properties (humidity, flow rate), feed rate, compressed air flow rate for a bi-fluid nozzle, pressure for a pressure nozzle, disk/wheel speed for a rotary atomizer. On the other hand, formulation parameters to consider are feed composition (API, carrier, solvent), solids content in the feed, solvent type, viscosity and surface tension of the drying solution. The impact these parameters have on the quality and performance of the resulting solid dispersions will be discussed in the following sections.

3. Spray drying of pure poorly water soluble drugs

Spray drying of poorly water soluble drugs is mainly aimed at generating amorphous materials. In addition, spray drying is also growing as a technique of choice for particle engineering (size reduction and thus increasing surface area) and as drying method for nanosuspensions to generate nanoparticle or nanocrystalline dispersions of poorly soluble drugs (Heng et al., 2011; Peltonen et al., 2010; Vehring, 2008). Although, amorphous forms are generally formulated as solid dispersions with polymeric carriers, spray dried amorphous forms of pure drug substances are also generated to understand their processability during feasibility studies and for the comparison of the amorphous state generated by other methods (Kim et al., 2008). Spray drying of poorly water soluble drugs is possible when they are soluble in a volatile organic solvent or mixtures of solvents. However, the solid state of the final product merely depends upon the chemical nature of the drug substance. It may result the amorphous form, partially crystalline mixtures, crystals with induced imperfection or metastable crystal forms (Corrigan, 1995). For example, spray drying of API like indomethacin and itraconazole generate completely vitrified forms with considerable stability while drug substances like naproxen show almost no amorphization upon spray drying (Mahlin et al.,

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2011). The ability of a pure drug substance to convert into its amorphous form depends upon its inherent glass forming ability dictated from its molecular structure and to a lesser extent on the preparation methods (Baird et al., 2012). Mahlin et al. (2011) tested for the propensity of amorphization of a set of sixteen poorly water soluble drugs with varying molecular structures and physicochemical properties by spray drying, melt-quenching and milling. With the processing conditions they tested, only half of the drug molecules could be amorphisized completely by spray drying. Next to manufacturability, the physical stability of metastable amorphous state is an important concern for the preservation of the delivery advantage in case of poorly water soluble drugs. The glass transition temperature (T_g) is a characteristic property associated with amorphous systems to discern its storage stability against recrystallization. The glassy state of amorphous form below T_g is less vulnerable to recrystallization as compared to the supercooled liquid state with higher mobility present above T_g. The translational and rotational motions of amorphous materials are assumed to be ceased for pharmaceutically relevant time scales at the characteristic temperature, often more than 50 °C below T_g, referred to as the Kauzmann temperature. Therefore, storage temperature of (T_g-50 °C) is expected to provide the physical stability of amorphous material for the desired storage duration (Corrigan et al., 2004). Recently, some researchers have shown an interest towards the use of coamorphous systems prepared by co-spray drying poorly water soluble API with poor glass forming ability like naproxen and that with the good glass forming ability like indomethacin, for the mutual dissolution rate enhancement and stabilization (Loebmann et al., 2011). Solubility of spray dried paclitaxel is markedly increased due to generation of the amorphous form in contrast to the dihydrate and anhydrate crystalline forms generated from precipitation and colloid formation (Pyo et al., 2007). The effect of counter ions on the physicochemical properties and stability of spray dried amorphous atorvastatin salts was recently published (Sonje et al., 2011). The bioavailability of spray dried atorvastatin calcium was markedly increased due to generation of the amorphous form and reduction of particle size (Kim et al., 2011). The surface energy, polar surface distribution and wettability of amorphous celecoxib prepared by spray drying are notably improved compared to the pure crystalline counterpart (Puri et al., 2010). In a recent publication, Grisedale et al. (2012), reported the completely amorphous state of pure salbutamol sulfate prepared by spray drying showing two T_gs upon thermal analysis which the authors believe to be due to the presence of higher plasticization of bulk fraction compared to the surface of the amorphous state by the moisture. Apart from amorphous form generation, one of recent studies mentions the utility of spray drying for co-crystal manufacturing of carbamazepine, with glutaric acid (Alhalaweh and Velaga, 2010). In contrast to the conventional solvent evaporation method that resulted into a mixture of phases, spray drying generated the pure co-crystal which is proposed by the authors to be mediated through glassy state or kinetically controlled.

4. Spray dried amorphous solid dispersions of poorly soluble drugs

In the last three decades, major strides towards the use of amorphous solid dispersions to tackle the oral bioavailability problems of poorly water soluble drugs have been observed (Van den Mooter, 2011). Among various methods of preparation of amorphous dispersions, spray drying stands at the frontier of the solvent based methods. The increasing trend to opt for the manufacture of spray dried dispersions (referred to as SDD henceforth) is attributable to the possibility of continuous manufacturing, ease of scalability and cost-effectiveness (Bikiaris, 2011; Srinarong et al., 2011). In this section, the potential carrier, solvent and additive systems often used to formulate binary or multi-component SDDs are discussed.

4.1. Carriers for manufacturing SDD of poorly soluble drugs

The ideal poorly soluble candidates to formulate as SDDs are identified by their physicochemical properties (*e.g.* melting point/enthalpy, solid state thermal stability, ionization constant, Hydrogen bond (H-bond) donating and/or accepting nature, solubility/interaction parameters, partition coefficient) other than solubility during preformulation studies and also by the desired downstream process (Miller and Gil, 2012). Thermolabile molecules are the suitable candidates for the manufacture of amorphous dispersion by solvent processes including spray drying over melt and melt plus solvent methods provided the sufficient solid state stability at processing temperatures namely outlet and cyclone temperature. The first requirement is indeed the appreciable solubility and solution state chemical stability of the API in one of the regularly used volatile organic solvent, if not in the solvent blends to project the viability of the process, up to the commercial scale. Next to the feasibility to spray dry, appreciable yield is a practical requirement for the analysis and performance testing. After selecting spray drying as the process for preparation amorphous solid dispersions of a poorly soluble drug, it is crucial to select the right carrier based on the chemical structure of the actives. Most of the carriers used for amorphous solid dispersion formulations are hydrophilic polymeric compounds that primarily serve as crystallization inhibitor by decreasing the molecular mobility (antiplasticization) of the amorphous form of a drug dispersed in the matrices and thus can sustain enhanced solubility by maintaining the supersaturation generated during *in vitro* dissolution and after oral administration in the gastrointestinal milieu (Bee and Rahman, 2010). In this context, the drug and accompanying polymeric excipient should certainly be soluble in a common volatile solvent or mixture of solvents to spray dry from a solution. Although a suspension of drug and polymer in a common solvent system can be spray dried, it can have several negative consequences in terms of homogeneity such as phase separation or partially crystalline dispersion and other physical properties of the final product. For the selection of a proper solvent system in case of acceptable solubility of drug and polymer in multiple spray drying solvents, the impact of solution state chemistry on the molecular, particulate and bulk level properties of the end product should be duly considered. The aspects of solvent selection for spray drying are discussed in the succeeding section.

By now, the most critical aspects to consider in the selection of suitable carriers for the development of physicochemically stable amorphous solid dispersions have been recognized as the molecular level understanding of the interaction between drug and polymeric carrier and their phase behavior in the resulting solid dispersion (Qian et al., 2010). The resistance of drug recrystallization from an amorphous solid dispersion is highest in case of molecular level homogeneity of drug–polymer mixing in the formulation (Paudel et al., 2010). This can be achieved at or below the thermodynamic solid solubility of a drug in the selected polymer. An API is expected to have higher solid solubility in the polymer with which there is possibility of stronger favorable intermolecular interaction such as intermolecular H-bonding, electrostatic, ionic or hydrophobic interactions. Having said this, the structure based excipient screening for a poorly water soluble drug molecule of known chemical structure can be the starting point for the formulation of solid dispersion (Van Eerdenbrugh and Taylor, 2011). One option to select polymers for formulating solid dispersions is done by comparing the solubility parameter of drug and polymer (Greenhalgh et al., 1999). The solubility parameter is proportional to the square root of the evaporation enthalpy of a substance which

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is further contributed by dispersive, polar and H-bonding interaction between molecules. Greenhalgh classified drug–polymer miscibility based on the difference between their solubility parameters which denotes that the difference should be <0.5 for the generation of homogenous dispersion. Although, the reliance on Greenhalgh's benchmarking is debated, it can certainly be informative for starting the initial screening studies. Furthermore, different thermodynamic mixing models such as Flory-Huggins (FH) lattice theory and Hildebrand regular solution theory have been tested for understanding the miscibility and phase (separation) behavior of a drug and a polymer in a solid dispersion. Nonetheless, due to the non-equilibrium rate of evaporation or solidification of the fluid state of drug polymer mixture (solution or melt) during the manufacturing process, the kinetic miscibility of a drug in a selected polymer in the amorphous solid dispersion prepared by energy intensive processes such as spray drying, hot melt extrusion or melt quenching is often far higher than the estimated thermodynamic solid solubility. There are ample information in literature on kinetic miscibility and equilibrium solid solubility between drug and polymer, and it is not the purpose of this review to discuss in that direction. The interested readers are suggested to consult references Marsac et al. (2009) and Sun et al. (2010) for details.

Shah et al. (2012) have recently published a concise set of different types of polymeric carriers commonly used to manufacture amorphous solid dispersion with their physicochemical properties. We present in Table 1 a more elaborate list of polymeric carriers of different chemical classes frequently used in formulating SDDs with their relevant information. Also examples of poorly soluble APIs with varying chemical category formulated as SDD with respective polymers are mentioned.

The advent of solvent methods like spray drying made it possible to formulate SDD from polymers that have a high melting temperature and hence not suitable through melting methods (Leuner and Dressman, 2000). However, with physicochemical constrains ranging from non-versatility in terms of pH dependent aqueous solubility, volatile organic solvent solubility to hygroscopicity of the existing list of polymers, there have been continuous surge and even some attempts to use the newer types of carriers for SDD formulation. Some of the new carriers are reported to show promising performance but the biocompatibility and toxicity issues are yet to be addressed. Fig. 1 shows the general trend in the use of common carriers for the preparation of binary and/or ternary SDDs of poorly water soluble drugs that are published over the years. Other than functional carrier acting as stabilizer of the amorphous drug phase, it is common practice to formulate SDD primarily as ternary systems with some additional component, most of time surfactant or excipients facilitating the downstream processes, such as glidant, binders or disintegrants. Below, the binary and ternary SDD systems of poorly water soluble drugs prepared using typical carriers belonging to different chemical classes are discussed with the focus on their physical structure and apparent solubility, wettability and in turn *in vitro* dissolution rate and/or bioavailability enhancement:

4.1.1. Cellulosic derivatives

Natural plant celluloses are unbranched polysaccharides in which monomer units (glucose) are connected by 1,4 glycosidic β-linkage. Pharmaceutical cellulosic excipients are mainly semi-synthetic–alkyl and/or hydroxyl alkyl substituted derivates of natural cellulose *viz.*, methyl cellulose (MC), ethyl cellulose (EC), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), *etc.* or the esters of these polymers such as cellulose acetate phthalate (CAP), HPMC phthalate (HPMC-P), HPMC acetate succinate (HPMC-AS). The physicochemical properties of these excipients widely vary with the degree of substitution.

HPMC (hypromellose) is the most used cellulosic stabilizer for the preparation of SDDs of poorly water soluble drugs alone or in combination with other polymers. It is a mixed poly alkoxy ether available in different grades with varying degree of methyl (16–30%) and/or hydroxypropyl (4–32%) substitutions of the hydroxyl groups of a cellulose monomer which makes it a physicochemically quite diverse family of polymer ranging from very high to low viscosity, solubility, surface activity, *etc.* (Leuner and Dressman, 2000). For example, HPMC 2906 denotes for the HPMC with average methyl and hydroxypropyl substitution of 29% and 6%, respectively. It is a water soluble polymer showing thermal gelation in aqueous solution. For SDD preparation, the insolubility in a range of volatile solvents (dichloromethane (DCM), acetone, methanol, *etc.*) necessitates the use of hydroalcoholic or binary mixture of organic solvent systems, mostly DCM with normal alcohols (Table 1). Since, the –OH of 2-hydroxypropyl group can act as a H-bond donor and –O– of methoxyl group weak H-bond, HPMC is preferably used to stabilize H-bonding accepting drugs in SDD (Bee and Rahman, 2010). The SDD of tolbutamide with HPMC prepared by atomizing solution in three and four fluid nozzles are completely amorphous compared to that prepared by spray drying the aqueous suspension of drug and polymer (Chen et al., 2004). The amorphous dispersions showed marked increase in the rate and extent of dissolution. Using chemical and structural analysis of the surface of the solid dispersion of two poorly soluble drug candidates prepared with HPMC by spray drying and roto-evaporation and subsequent contact angle measurements, Dahlberg et al. (2008) related the surface composition of the drug to the wettability of the solid dispersion during dissolution. The results from another study of Dahlberg et al. (2010a,b) reveal the role of drug–HPMC intermolecular interaction and the way the drug is fitted within the polymeric matrix in SDD on the wettability during dissolution. The incorporation of a hydrophobic drug in SDD decreases the surface hydrophilicity of HPMC compared to pure HPMC or that in physical mixture by redistributing the side groups of the polymer that are exposed to the air–water interface. It was evident from the NMR microimaging study published by the same group on HPMC based SDD that drug release during dissolution is dependent on the polymer mobilization rather than water ingress inside the tablet (Dahlberg et al., 2010a,b). The SDD of etravirine and HPMC provided the highest oral bioavailability enhancement when compared to cast films and pure amorphous drug owing to better mixing and drug distribution resulting from spray drying (Weuts et al., 2011). By monitoring the evolution of particle morphology and physicochemical properties of itraconazole-HPMC solid dispersion upon drying of acoustically levitated droplet from binary solvent mixtures, Wulsten et al. (2009) observed that the polymeric excipient specifically influence the drying rate correlating to the rate of skin formation during the process while the drug affects the final product morphology, mainly related to the differential solubility of drug and polymer in the solvent system. The solubility and dissolution rate enhancement of the poorly water soluble drug irbesartan from amorphous SDD prepared with HPMC E5 has been attributed to wetting, crystallization inhibiting and anti-plasticizing properties of the high T_g polymer (Boghra et al., 2011).

Next to HPMC, HPMC-AS, an ionizable polymer throughout a physiologically relevant pH range, is the most sought-after carrier for the preparation of amorphous SDD of poorly water soluble drugs (Friesen et al., 2008). It is randomly substituted cellulosic derivative with 12–28%, 4–23%, 2–16% and 4–28% mass content of methoxyl, hydroxypropyl, acetate and succinate functionality, respectively. HPMC-AS has higher versatility in formulating SDD over HPMC as it is readily soluble in common spray drying solvents such as methanol and acetone. A comprehensive study conducted on SDDs of more than 100 poorly water soluble drug candidates of Pfizer formulated with HPMC-AS published by Friesen et al. (2008) addresses various issues ranging from formulate-ability and processability, solid state characterization, understanding the phase

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Table 1
Overview of typical carriers for SDD preparation with their relevant properties and examples of co-spray dried APIs (only articles mentioning *in vitro* and/or *in vivo* studies are accounted).

Carriers	M.Wt (Range) (kDa)	T_g (T_m) (°C)	Solubility parameters $(cal/cm^3)^{1/2}$	Hygroscopicity (moisture at 75%RH/RT)	pH solubility	Commonly used solvents	Examples of poorly water soluble drugs loaded		
							Acid(s)	Neutral	Base(s)
Cellulosic derivatives: hydroxyl (ether)*									
HPMC 2910	10–1500	148.2–151.1	23.8	~10%	1–10	EtOH, MeOH, EtOH/DCM, water, DCM, MeOH/DCM, acetone and water	Valsartan (Yan et al., 2012), Ibuprofen (Park et al., 2009a,b), Tolubutamide (Chen et al., 2004)	Clopidogrel napadisilate (Kim et al., 2011), Nifedipine (Cilurzo et al., 2008)	Sibutramine base (Lim et al., 2010), Sibutramine (Li et al., 2010a,b), Itraconazole (Jung et al., 1999)
HPMCAS-MF	80	117.3–120	31.2	6–7%	>6.5	Ethyl acetate, acetone or MeOH, acetone/water, THF	Piroxicam (Jachowicz and Czech, 2008)		
HPMC-E5 (2906)	10–1500	152	–	–	1–10	Methyl acetate: MeOH	Irbesartan (Boghra et al., 2011)		
Na-CMC	90–700		–	–	–	Water	Flurbiprofen (Oh et al., 2011), Tacrolimus (Park et al., 2009a,b)		Roxithromycin (Biradar et al., 2006)
HPMC-P 55	10–1500	138	28	7–8%	>5.0	Acetone			
HPMC-AS HG	55–93	117.9–120	–	–	–	Acetone			Griseofulvin (Al-Obaidi and Buckton, 2009)
HPC (L-HPC)	50–1250	105 (220)				MeOH, Diluted ammonia solution	Valdecoxib (Ambike et al., 2004), Tolbutamide (Takeuchi et al., 1987)		
MCC	36	(260–270)				-		Bicalutamide (Li et al., 2011)	
Vinyl polymers: C=O group' and the N atom of the pyrrole ring*-PVP Carbonyl' &vinylacetate ester oxygen*-PVP/VA (OH of secondary alcohole)*-PVA									
PVP K 30	50	170–174	27.7	40%	1–10	EtOH, IPA/H_2O, water, MeOH, DCM, EtOH/water, MeOH/DCM, EtOH/acetone, IPA	Tolfenamic acid (Thybo et al., 2007), Lonidamine (Palmieri et al., 2002), andrographolide (Bothiraja et al., 2009a,b), Simvastatin (Ambike et al., 2005), progesterone/phenindione (Al-Obaidi et al., 2011), Curcumin (Paradkar et al., 2004), Ibuprofen (Xu et al., 2007), Probucol (Thybo et al., 2008a,b), valdecoxib (Ambike et al., 2004)	Hydrocortisone (Corrigan and Crean, 2002), Artemisinin (Sahoo et al., 2010)	Griseofulvin (Al-Obaidi et al., 2011)

Table 1 (*Continued*)

Carriers	M.Wt (Range) (kDa)	T_g (T_m) (°C)	Solubility parameters $(cal/cm^3)^{1/2}$	Hygroscopicity (moisture at 75%RH/RT)	pH solubility	Commonly used solvents	Examples of poorly water soluble drugs loaded		
							Acid(s)	Neutral	Base(s)
PVP K 25	28–34			35–40%	1–10	DCM, IPA	Ibuprofen (Xu et al., 2007)		
PVP-VA64	45–70	106.0–110.0		<10% (50% RH)	1–10	Acetone, Water/EtOH, DCM, Water, MeOH/DCM, IPA	Rebamipide (Tung et al., 2011), Ibuprofen (Xu et al., 2007)	Carbamazepine (Patterson et al., 2008)	Itraconazole Janssens et al., 2008a,b,c,d), Dipyridamole (Patterson et al., 2008)
PVP VA 37					1–10			Carbamazepine (Patterson et al., 2008)	Dipyridamole (Patterson et al., 2008)
Kollicoat IR	45					Water with or without HCl/ethanol, DCM	Celecoxib (Fouad et al., 2011), Ibuprofen (Xu et al., 2009)	Nitredipine (Wang et al., 2007)	Itraconazole (Janssens et al., 2009)
PVA 22000	20					Hydroalcoholic or DCM, water	Celecoxib (Fouad et al., 2011)	Nitrendipine (Wang et al., 2007)	
Lipidic carriers									
Gelucire 44/14		(44)		≈1% (<60% RH)		Water	Curcumin (Araújo et al., 2010)	Spironolactone (Yassin et al., 2009)	
Gelucire 50/13		(50)				MeOH, DCM	Etoricoxib (Shimpi et al., 2009), celecoxib Shimpi et al., 2009)		
Compritol 888 ATO						DCM	Etoricoxib (Chauhan et al., 2005)		
Sterotex K NF						DCM	Etoricoxib (Chauhan et al., 2005)		
Poly(ethylene oxide) & derivatives									
PEG 4000	2.6–3.8	(50–58)		<2.5%	1–14	DCM/MEOH, water, EtOH	Lonidamine (Palmieri et al., 2002)	Artemisinin (Sahoo et al., 2011), bendroflumethiazide (Corrigan et al., 2003)	
PEG6000	7.3–9.3	−22.71 (55–63)		<1%	1–14	DCM/MEOH, Hydroalcoholic or DCM, EtOH	Celecoxib (Fouad et al., 2011)	Oxazepam (Jachowicz et al., 1993)	Itraconazole (Janssens et al., 2008a,b,c,d)
PEG20,000	15–25	−41 (60–63)		NH		DCM/MEOH, DCM			Itraconazole (Janssens et al., 2008a,b,c,d)

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Table 1 (*Continued*)

Carriers	M.Wt (Range) (kDa)	T_g (T_m) (°C)	Solubility parameters $(cal/cm^3)^{1/2}$	Hygroscopicity (moisture at 75%RH/RT)	pH solubility	Commonly used solvents	Examples of poorly water soluble drugs loaded		
							Acid(s)	Neutral	Base(s)
Poloxamer 407	9.84–14.6					Water, DCM or acetone	Ibuprofen (Park et al., 2009a,b)		Sibutramine (Li et al., 2010a,b), griseofulvin (Wong et al., 2006)
Carbohydrates: hydroxyl (ether)*-dextrin									
Lactose	0.3423	(232)				Water	Bicalutamide (Li et al., 2011), Roxithromycin (Biradar et al., 2006)	Fenofibrate (Vogt et al., 2008)	
Arabia gum						Water	Bicalutamide (Li et al., 2011)		
Stevia-G						EtOH/H_2O	Flurbiprofen/Probucol (Uchiyama et al., 2010a,b), Indomethacin (Uchiyama et al., 2011)		
Glucosyl hesperidin						EtOH/H_2O	Flurbiprofen (Uchiyama et al., 2010a,b), Naringenin (Zhang et al., 2011a,b,c)		
(Meth)Acrylate polymers: hydroxyl of hydroxypropyl (Ester carbonyl)*-PHPMA, Carboxylic acid hydrogen*-PAA									
PHPMA (poly[N-(2-hydroxypropyl)methacrylate])	20	-				Acetone, acetone/water	Progesterone/phenindione (Al-Obaidi et al., 2011)		Griseofulvin (Al-Obaidi and Buckton, 2009), proges-terone/phenindione (Al-Obaidi et al., 2011)
Eudragit E 100	47	48	19.3			EtOH, DCM, IPA, Ethyl acetate, THF		Felodipine/carbamazepine (Nollenberger et al., 2009)	Itraconazole (Janssens et al., 2010;Jung et al., 1999)
NaPMM	135					Water			Nifedipine (Ciluzo et al., 2008)
Polyacrylic acid (PAA)	100	100–105 & 126				MeOH/DCM			Loperamide (Weuts et al., 2005a,b,c)
Carbopol 940	104.4	100–105							Piroxicam (Jachowicz and Czech, 2008)

*Proton donor (acceptor) functional groups, NH: not hygroscopic.

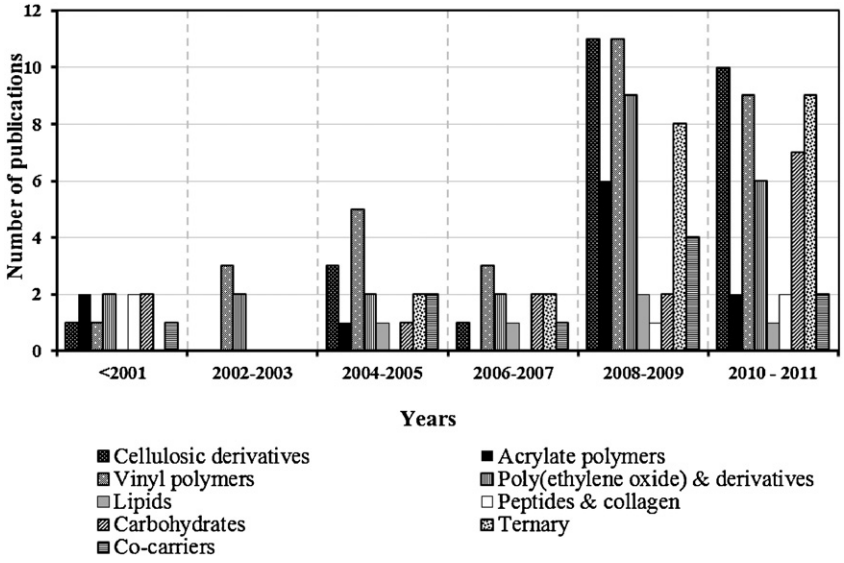

Fig. 1. Trend in the use of carriers in preparation of SDD showing improved *in vitro* and/or *in vivo* performance.

behavior and physical stability to *in vitro* performance testing and *in vivo* studies in healthy human volunteers. The study highlights several favorable properties of HPMC-AS to use as superior SDD carrier as compared to other cellulosic derivatives. Further, Curatolo et al. (2009) selected HPMC-AS as stabilizer for the preparation of amorphous SDD with several other poorly soluble developmental candidates of Pfizer based on a preliminary supersaturation screening in simulated intestinal media. Out of more than 40 small molecular and polymeric carriers tested, HPMC-AS was found to exhibit and sustain maximum supersaturation. The amphiphilic nature of HPMC-AS is shown to offer greater potential for intermolecular interaction with poorly water soluble drugs due to the presence of carboxylic ester moieties while the hydrophilic moiety will help in maintaining the colloidal nanostructure during the dissolution process. The improved dissolution rate of a developmental drug candidate, AMG 517, formulated as SDD with HPMC-AS at low drug loading, as compared to the SDD of same composition made with HPMC, is attributed to better wettability and water ingress during dissolution (Kennedy et al., 2008). Further, this effect has been explained to be due to the presence of the hydrophilic carboxyl function in HPMC-AS. The amorphous 1:1 SDD prepared of griseofulvin with HPMC-AS remains physically stable up to 19 months at 85% RH in contrast to the crystallized pure drug upon spray drying (Al-Obaidi and Buckton, 2009). The HPMC-AS based SDD approach has been applied in preparation of the solubility enhancing formulation of more than 400 poorly soluble drug candidates with 28 compounds being in clinical development (Arnum, 2010). With these processability and delivery benefits, *Bend Research* has been promoting HPMC-AS-SDDs as platform technology for testing and development of amorphous SDD of poorly soluble drug candidates (Arnum, 2010).

There have been occasional reports on the use of other cellulosic derivatives as carrier for SDD. The amorphous solid dispersions of griseofulvin prepared by coevaporation and of an antifungal drug candidate by spray drying using an enteric cellulosic ester, HPMC-phthalate ((HPMC-P), showed drastic increase in the dissolution rate compared to the pure drugs (Hasegawa et al., 1985; Kai et al., 1996). With the satisfactory results obtained during the small scale screening, Engers et al. (2010) prepared amorphous SDDs of itraconazole with HPMC-P at different scales *viz.*, 200 g and 1 kg cGMP batch. The amorphous SDD of itraconazole with HPMC-P displayed the best homogeneity (the narrowest T_g width) and the highest physical stability among the different stabilizers tested. Thermal analysis of X-ray amorphous SDD prepared at both scale confirmed compositional homogeneity (T_g position and width). The enhanced systemic availability in beagle dogs obtained upon oral administration of SDD filled in capsules confers the possibility of using such formulation to maximize the exposure in first in humans (FIH) studies. The cellulosic ether, hydroxypropyl cellulose (HPC), is also utilized for the preparation of amorphous SDD due its appreciable solubility in common spray drying solvents (Leuner and Dressman, 2000). The amorphous SDD prepared of valdecoxib with HPC with enhanced saturation solubility and dissolution rate remained stable up to 1 month whereas, although amorphous following spray drying, the pure drug completely recrystallized within 15 days (Ambike et al., 2004).

4.1.2. Vinyl polymers

Several vinyl polymeric excipients have been used as carriers for amorphous solid dispersion formulation of poorly soluble drugs prepared by different methods. The polymers from this family constitute the monomer unit with vinyl backbone with various types of substitutions and are synthesized from the respective alkene derivatives, mostly by free radical polymerization. Depending upon the chemistry of the side chains different vinyl polymers bear very different physicochemical properties. Commonly used vinyl polymeric carriers for amorphous solid dispersion formulation are linear and cross linked poly (N-vinylpyrrolidone) (PVP) and polyvinylpyrrolidone-co-vinyl acetate (PVP-VA).

Especially, PVP, a hydrophilic polymer of N-vinyl pyrrolidone (povidone), is very oftenly used carrier. Spray drying itself is the primary process for drying of most of PVP grades during manufacturing (Buhler, 2005). The solubility and chemical stability of PVP in a variety of spray drying solvents *viz.*, volatile alcohols, chlorinated hydrocarbon (DCM/chloroform), esters/ethers, *etc.*, has provided better versatility for its use in the preparation of amorphous SDD (Bee and Rahman, 2010). PVP with several viscosity average molecular weights ranges as low as 2400 Da (PVP K 12) to as high as 100 kDa (PVP K 90) has been used as carrier in amorphous SDD of poorly soluble drugs. PVP K 90 has very high viscosity in most of solvents rendering its use practically difficult in spray drying. Care should be taken in selecting PVP of certain average molecular weight range denoted by *K* values because the molecular weight distributions and type of end groups of PVP of the same *K* value can be dramatically different depending upon synthetic and other manufacturing procedures (Raith et al., 2002). The major

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concern with respect to the handleability, processability and storage conditions of PVP based SDD is related to the significant hygroscopicity of the polymer. Smaller molecular weight PVP, especially PVP K 12, can absorb moisture as high as its dry weight at elevated humidity. Although, the incorporation of a hydrophobic drug in amorphous SDD with PVP decreases the overall hygroscopicity compared to that of the pure polymer, the challenge posed due to the sorbed moisture by PVP on the physical stability of SDDs still remains (Rumondor and Taylor, 2009). The ability of the carbonyl moiety in 1-vinyl-2-pyrrolidinone group to act as H-bond acceptor lead to the formation of stronger stabilizing interactions in SDD with H-bond donating drugs (Bee and Rahman, 2010). The influence of PVP molecular weight on the increase in the dissolution rate and decrease in the recrystallization rate of drugs from SDD depends upon the nature of the drug (Buhler, 2005). Also, drug to polymer ratio is very crucial factor that determines the phase structure of PVP based SDDs. For example, in case of SDD prepared of hydroflumethiazide with PVP, the coexistence of both amorphous drug and an amorphous drug-PVP complex is reported at low PVP content (Corrigan and Holohan, 1984). PVP/VA is a random copolymer of 1-vinyl 2-pyrrolidone and vinyl acetate that is the next frequently used carrier for SDD of poorly soluble drugs belonging to vinyl polymer group. The ratio of vinyl pyrrolidone to vinyl acetate in the widely used PVP-VA is 6:4 although the use of PVP-VA with 3:7 has also been reported (Patterson et al., 2008). Other commercially available PVP/VA also constitutes 5:5 and 7:3 ratio of vinylpyrrolidone: vinyl acetate. With increasing molar fraction of vinyl acetate monomer in PVP/VA copolymer series, there is a decreasing trend of T_g, hydrophilicity, hygroscopicity, solubility parameter and propensity of H-bonding. Further, the appreciable solubility and chemical stability in a wider range of spray drying solvents and the slight surface activity of PVP-VA are desirable properties in terms of processability. In SDD systems, both monomer units have capability of accepting H-bonds from different types of H-bond donor groups of drugs favoring the solubilization and stabilization. However, the decrease in drug–polymer miscibility and hence the physical stability of SDD prepared of some drugs like carbamazepine and dipyridamole with PVP/VA has been shown with the increase of acetate fraction in the copolymer (Patterson et al., 2008).

Poorly water soluble drugs with varying degree of glass forming ability have been successfully formulated as physically stable amorphous SDD with PVP and PVP-VA showing superior physicochemical properties, *in vitro* dissolution rates and/or *in vivo* performance (Table 1). Weuts et al. (2004, 2005a,b,c) studied the influence of the chemical structure of loperamide and two structurally related compounds (representing an interacting and non interacting structural fragment of loperamide) on the phase behavior and the physical stability of SDDs prepared with PVP K-30 and PVP/VA 64. All dispersions prepared with intact loperamide completely vitrify whereas amorphous SDD of structural analogues are only possible in presence of higher amount of polymer. Further, physical stability studies performed at elevated humidity reveal the apparent crystallization induction from the SDD prepared from molecules not interacting with the polymer in contrast to the molecularly interacting fragment. But, SDD of loperamide which itself has no H-bonding interaction with the polymers is less susceptible to crystallization. Overall, this proves the importance of the inherent glass forming ability of a drug in combination with the H-bonding intermolecular interactions with polymer for molecular miscibility and physical stabilization of SDDs. The dissolution of SDD of probucol and PVP K-30 with different drug:polymer ratio has been attributed to amorphization, crystallization inhibition and particle size reduction of the drug in SDD (Thybo et al., 2008a,b). As reported in the case of a poorly soluble drug candidate, along with the amorphous state, the smaller crystallites of the drug dispersed in SDD matrices have the capability to form intermolecular H-bonds with PVP leading to apparent hydrophilization of drug (Tobyn et al., 2009). However, the crystal form in partially crystalline SDDs (PVP content < 50%) was characterized to be the ethanolate. The surface composition study of Dahlberg et al. (2008) on amorphous SDD of two hydrophobic drugs with PVP K 30 revealed that the higher amount of drug with higher hydrophobicity tends to migrate to the surface and therefore to lower the drug loading within the SDD matrix. Furthermore, the surface composition and contact angle of these amorphous solid dispersions were highly dependent of evaporation rate in the different processing methods employed *viz.*, spray drying and rotary evaporation. However, no marked difference in water contact angle and hence wettability of the powders were observed for dispersions with varying surface composition, in contrast to HPMC based dispersion. As mentioned above for the case of HPMC based dispersion, the levitated droplet drying of itraconazole-PVP/VA 64 from DCM:EtOH mixture reveals that polymer plays the major role towards the drying rate, the droplet surface temperature profile observed in the falling part of the drying curve and also the starting time for the constant drying rate phase of the droplet (Wulsten et al., 2009). Occasionally, the miscibility and physical stability of PVP based SDDs have been compared with the solid dispersions prepared by different methods. Dontireddy and Crean (2011) have shown that amorphous dispersions of hydrocortisone with PVP prepared from an aqueous ethanolic solution by freeze drying resulted in higher dissolution rate before and after exposure to 40 °C/75% RH compared to the same system prepared by spray drying. Recently, amorphous SDD of sulfa drugs prepared with PVP has been shown to have comparable phase behavior as that of respective solid dispersions prepared by milling (Caron et al., 2011). Apart from these vinyl derivatives, poly (vinyl alcohol) (Fouad et al., 2011) or its substituted derivative (Orienti et al., 2002) and substituted polyvinylacetal (Jung et al., 1999) have rarely been used as the carrier for SDD.

4.1.3. (Meth)acrylate polymers

Poly(meth)acrylate polymers for pharmaceutical application, commonly available under tradename Eudragit®, are synthetic polymers containing varying ratio of two to three different methacrylate monomers *viz.*, methacrylic acid, methacrylic acid esters and dimethylaminoethyl methacrylate. With a different ratio of monomers, these polymers show firm pH dependent aqueous solubility making them suitable matrix and/or coating agents for targeted release/delivery systems (Table 1). Also, due to the appreciable solubility of these polymers in a wide range of volatile organic solvents, they are carriers of choice for the formulation of amorphous solid dispersions of poorly soluble drugs by solvent processes, specifically for targeting regional absorption in the GI tract. The glassy methacrylate polymer, Eudragit E100, polymerized from three monomers (dimethylaminoethyl methacrylate, methacrylate methylester, and methacrylate butylester in 2:1:1 ratio) has been used as carrier for the preparation of amorphous solid dispersions of various poorly soluble drugs by solvent methods (Table 1). The protonation of tertiary amino group of Eudragit E100 in acidic microenvironment can stabilize the amorphous state of drugs through ionic interaction in SDD that is stronger than H-bonding interactions. Amorphous SDD of itraconazole prepared with Eudragit E is shown to exhibit higher apparent solubility enhancement compared to that prepared with other pH independent polymers while tablets manufactured from this Eudragit based SDD of itraconazole presented the highest improvement of dissolution rate (Jung et al., 1999). Janssens et al. (2010) found the kinetic miscibility of itraconazole in Eudragit E 100 for SDD to be four times higher than the thermodynamic amorphous miscibility of drug in the polymer. Conversely, the solid state miscibility enhancement of the drug in the polymer is only two times the equilibrium

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amorphous miscibility for the formulation prepared by film casting. The equilibrium drug release from and physical stability of amorphous SDD of furosemide with water insoluble acrylic resins (Eudragit RL 100 and RS 100) are dependent upon the drug to quaternary ammonium ratio (Otsuka et al., 1993). The amorphous low drug loaded SDD of carbamazepine with Eudragit E 100 improved the dissolution rate several folds compared to the pure crystalline drug or physical mixture. Moreover, the spray dried formulation outperformed the equivalent dispersions prepared by melt extrusion (Nollenberger et al., 2009). An investigation on amorphous SDD of the basic drug loperamide with polyacrylic acid has revealed the formation of organic salt between drug-carrier leading to the elevation of T_g and hence increased physical stability and dissolution rate (Weuts et al., 2005a,b,c). In addition to spray drying, other solvent processes such as film casting and rotary solvent evaporation have been occasionally used to prepare the solid dispersions of several poorly soluble drugs (nifedipine, griesofulvin, spironolactone) with enteric (meth)acrylate copolymers composed up of methacrylic acid and methyl acrylate (Eudragit L 100 and S 100) or ethyl acrylate (Eudragit L 100-55) monomers (Hasegawa et al., 1985).

4.1.4. Poly (ethylene oxide) polymers and derivatives

Polyethylene glycols (PEGs) are the most used carrier for the formulation of SDD from this group. They are highly hydrophilic semicrystalline polymers built up of ethylene oxide monomers. Lower molecular weight PEG (<600 Da) are viscous fluid and efficient vehicle or solubilizing agent for drug administration. Depending upon molecular weight range, PEGs exists as vaseline like (800–1500 Da), waxy (2000–6000) or hard brittle solid (>20,000 Da) form at room temperature (Leuner and Dressman, 2000). The semicrystalline solid PEGs are composed of an amorphous fraction having very low T_g spread over the surface of low melting lamellar crystals with twice-folded, once-folded or fully extended modifications, of which the latter show the highest melting temperature and accordingly thermodynamic stability (Weuts et al., 2005a,b,c). Due to their low melting temperature, biocompatibility and solubility in a wide range of aqueous and nonaqueous solvents, PEGs (1500–20,000 Da) have long been utilized as the carrier for the preparation of solid dispersion of poorly soluble drugs by melting methods and/or solvent methods. The hygroscopicity of PEG decreases with the increase in molecular weight. Depending upon the drug loading, the nature of drug–polymer interactions as well as the preparation methods and processing conditions, the drug molecules are homogenously mixed in the amorphous state, in the form of eutectic or monotectic mixture or phase separated amorphous/partially crystalline forms in PEG based solid dispersion, wherein PEG molecules exist as lamellar crystalline forms (Zhu et al., 2012). Only two publications have reported the complete amorphous state of PEG in solid dispersion (Corrigan et al., 2003; Law et al., 2001). Moreover, PEG has been shown to solidify separately during co-spray drying with materials like lactose wherein the extent of crystallization of the latter during the process increases with the increase in PEG content and the decrease in PEG molecular weight (Mosén et al., 2006). The SDD of bendroflumethiazide/PEG4000 showed superior dissolution performance and insignificant drug degradation as compared to the higher degradation observed in corresponding dispersions prepared by the melting method (Corrigan et al., 2003). However, incorporation of PEG resulted into poorer physical and chemical stability leading to recrystallization of drug and degradation of PEG during storage. Similarly, progression of recrystallization of loperamide from the partially amorphous state was observed along with the eutectic form in SDD with PEG 6000 resulting into a drop in dissolution rate upon exposure at elevated temperature and humidity (Weuts et al., 2005a,b,c). This was explained by unfolding of PEG from SDD upon exposure to the stressed condition, hence decreasing the ability to prevent drug recrystallization. Due to the lower T_g, there would be potential driving force for recrystallization from the amorphous dispersion of drug in PEG fraction, upon storage at stress condition. The authors believe that the physical state of drug and carrier in PEG based SDD of drugs like loperamide is not of significant importance. Rather, the solubility enhancement of drugs formulated as semicrystalline dispersion of PEG can be attributed to the increased wettability, localized micro-environmental solubilization and reduction of dispersed crystallites size. The aqueous solubility and *in vivo* oral bioavailability of lonidamide was markedly enhanced when formulated as SDD with higher amount of PEG 4000 (Palmieri et al., 2002). Recently, Fouad et al. (2011) have shown that the increased *in vitro* dissolution of celecoxib from SDD with PEG 6000 is due to the formation of intermolecular H-bonding of drug with polymer in the formulation leading to the increase in overall hydrophilicity and wetting. The SDD of a developmental Bristol Meyers Squib (BMS) compound with PEG 8000 resulted by the partially crystalline dispersion wherein the crystalline portions of drug were found to be dispersed in nano-size (Qian et al., 2007). Likewise, increased dissolution rate of a poorly water soluble anti-malarial drug, artemisinin, from the SDD dispersion with PEG 4000 prepared using a three fluid nozzle (Sahoo et al., 2011) has been attributed the generation of increased amount of amorphous fraction in the formulation as compared to that generated upon spray drying the pure drug.

Through recent publications including that from our group, a graft copolymer of ethylene glycol (EG) and vinyl alcohol (VA), Kollicoat IR, has been proposed as a novel potential carrier for solid dispersion (Guns et al., 2010; Janssens et al., 2007). Generally used as film coating material, this semicrystalline polymer constitutes highly plasticizing PEG fraction (25%) with subzero T_g/lower melting temperature and PVA fraction (75%) characterized by T_g of approximately 45 °C/higher melting temperature (Table 1). Spray drying is reported to result in complete amorphization of the PVA fraction of Kollicoat without the change in PEG fraction (Guns et al., 2010). The lower solubility of Kollicoat in relatively nonaqueous volatile solvents necessitates the use of aqueous cosolvent systems for spray drying applications (Janssens et al., 2007). The test performed with different types of plasticizers pointed towards the possible incorporation of drugs in one or both amorphous fractions of the copolymer (Guns et al., 2010). A study published by Janssens et al. (2009) on cosolvent spray drying has shown generation of SDD with higher drug–polymer miscibility and therefore higher dissolution performance by mixing an itraconazole solution with an acidic solution of Kollicoat IR in a ternary solvent, prior to atomization rather than during atomization. Guns et al. (2011) have reported encouraging solid state kinetic miscibility of miconazole with Kollicoat IR prepared by spray drying the solution that was prepared by mixing the preheated ethanolic solution of drug with boiled aqueous solution of polymer. The authors believe that the improvement in miscibility of SDD resulting from preheated solutions as compared to that from untreated ones is due to the breaking of internal H-bonding within polymer upon heating which promotes the formation of drug–polymer stabilizing interactions. Likewise, SDD of omeprazole with Kollicoat IR demonstrates marked improvement in dissolution performance due to the amorphization of drug (El-Badry, 2010; E.L-Badry et al., 2010). Amorphous solid dispersions prepared by pulse combustion drying of an aqueous suspension of ibuprofen and Kollicoat IR displayed more than eight times higher equilibrium drug release (Xu et al., 2009). The details on pulse combustion drying are discussed in Section 6.2. Furthermore, the enhancement of dissolution rate of celecoxib SDD with Kollicoat IR has been attributed to the formation of intermolecular H-bonding between drug and polymer along with particle size reduction of the dispersed drug (Fouad et al., 2011).

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The amphiphilic-nonionic triblock copolymer surfactant comprising hydrophobic central poly (propylene) connected with the hydrophilic poly (ethylene oxide), commonly known as poloxamer, is frequently used as a solubility enhancing adjuvant in preparation of ternary SDD, especially for wettability enhancement of the resulting powder. This is covered in more detail in the section on ternary dispersions. These polymers form micelles at a critical concentration and temperature which is dependent upon the molecular weight of hydrophobic chain and weight fraction of the hydrophilic chain (Schmolka, 1991). Also, solid dispersions prepared from poloxamers with a higher fraction of poly (ethylene oxide) chains are reported to provide improved solubility. Although poloxamers based binary solid dispersions are mostly prepared by melting methods, few cases have been reported where poloxamer has been employed to generate binary SDD of poorly water soluble drugs. Owing to the wetting characteristics of the polymeric surfactant, the griesofulvin/poloxamer 407 microcrystalline particles generated by spray drying exhibit significantly higher *in vitro* dissolution rate and oral bioavailability in rats compared to the spray dried pure drug or a physical mixture (Wong et al., 2006). Yin et al., 2005 reported that the enhancement in dissolution and *in vivo* performance in dogs of BMS-347070 SDD with pluronics F127 is due to the formation of a nanocrystalline dispersion of drug in the polymeric matrix leading to the tremendous increase in surface area and wettability. The mechanistic investigation on the same SDD system by Qian et al. (2007) revealed that crystallization of the poly (propylene oxide) block of the polymer might induce the nano-confinement of the crystallizing drug from the low T_g glass solution (15–26 °C) of the drug with the poly (ethylene) fraction hence leading to the generation of a nanocrystalline dispersion.

4.1.5. Carbohydrates

Classical crystalline dispersions of poorly soluble drugs have been prepared with different types of crystalline sugars due to their hydrophilic nature and water solubility. The major drawbacks of these carriers are their poor solubility in commonly used organic volatile solvents, lower T_g (stickiness) and high melting temperature rendering them difficult to process through both solvent and melting methods. Wide varieties of sugar derivatives and process modifications have been tested for the development of SDD over the years. The first attempt to prepare SDD with carbohydrates was published by Kawashima et al. (1975). SDD of salicylic acid were prepared with acacia gum leading to significant amorphization of the drug as well as improvement of the wetting properties. The heat of solution of SDD was found to be inversely proportional to the amount of amorphous content in the product leading to 50% enhancement of the apparent solubility of the drug. Spray drying of an aqueous solution of tolbutamide and a disintegrant, pregelatinized corn starch, resulted into particles with a starch core which was coated by small drug crystals (Takeuchi et al., 1987). The drug dissolution rate from these particles was found to be significantly enhanced owing to the ease of diffusion of smaller particles from the surface of the swelling disintegrant. Spray and freeze drying from a hydroalcoholic solution containing Δ^9-tetrahydrocannabinol, a pharmacological agent having poor water solubility and chemical stability, with an oligofructose (inulin) was attempted to enhance the dissolution rate and more preferably the drug's chemical stability (van Drooge et al., 2004). Upon exposure to elevated temperature and/or humidity, the drug in the solid dispersion was markedly protected from degradation compared to the pure drug. Van den Mooter et al. (2006) showed the use of an alkyl isocyanate substituted inulin derivative, inutec SP1, as a potential carrier for SDD. Despite the generation of a phase separated system made up of glassy and crystalline API and amorphous polymer, a significant improvement in dissolution rate of itraconazole was observed compared to that of pure amorphous drug or physical mixtures with the polymer. Chitosan, a glucosamine polysaccharide, has been used for the generation of spray dried microparticles of the poorly water soluble oxacarbazepine with reduced particle size and increased wettability (Rane et al., 2007). The spray dried microparticles of rifampicin with mannitol is reported to show better aerosol performance as well as lung deposition (Mizoe et al., 2008). Likewise, the spray dried microparticles of artemisinin with maltodextrin generated by optimized formulation and process condition remarkably improved the dissolution rate of the drug resulting from significant reduction of crystallinity (Sahoo et al., 2009). In recent years, some non toxic plant derived glycosides have gained attention towards the use as the carriers for the SDD development. Uchiyama et al. (2010a,b) have shown the applicability of transglycosylated *stevia* (Stevia-G) and α-glycosyl hesperidin (Hsp-G) as novel carriers for the preparation of SDD for solubility and dissolution rate enhancement of flurbiprofen and probucol. The enhancement of *in vitro* dissolution rate and *oral* bioavailability (in rat) of flurbiprofen from SDD was found higher with Hsp-G over Stevia-G while the opposite was observed in case of probucol. Both amorphous and amphiphilic glycosides showed slight surface activity and the authors proposed that higher solubilization could be yielded by selecting the glycoside carrier based on the structure of drugs in view of the interaction propensity and the extent of amorphization (Uchiyama et al., 2010a,b). Detailed spectroscopic characterization of SDD of flurbiprofen and narigenin with Hsp-G and colloidal characterization of the feed solution carried out by Zhang et al. (2011a,b,c), revealed that the hydrophobic drugs are entrapped within the hydrophobic aglycone core of glycoside micelles and held by intermolecular interaction while spray drying facilitates the solubilization. The oral bioavailability and aqueous solubility of flurbiprofen is increased several times from the SDD prepared with cycloamylose (Baek et al., 2011). A novel glycosidic carrier, rubusoside, showed encouraging dissolution rate enhancement of curcumin when formulated as SDD (Zhang et al., 2011a,b,c).

4.1.6. Peptides and collagen

Few publications are available on the use of peptides and gelatin as single carrier for the preparation of SDD of poorly water soluble drugs. Due to the potential solubilization capacity and stabilizing interaction with drugs in solution, similar behavior can be expected in solid dispersions with these carriers. However, the limited solubility in different spray drying solvents and chemical instability during processing remains an issue of these thermolabile carriers for using them in SDD. The SDD of the poorly water soluble oxazepam prepared with a collagen hydrolysate, gelita collagel, showed a six fold increase in dissolution rate of the drug compared to the pure crystalline drug because of the complete amorphization at higher collagel content (Jachowicz et al., 1993). To solve the difficulty in tabletting of the electrostatic SDD powder, ternary SDDs of oxazepam, collagel and lactose were prepared wherein the dissolution rate enhancement was still sustained due to the complete amorphous state of drug over the wide composition range (Jachowicz and Nürnberg, 1997). Very recently, a plant derived hexaconta-peptide with major content of glutamine, arginine and glycine, "moringa coagulant", has been used as the carrier for the formulation of SDD of ibuprofen, meloxicam and felodipine (Bhende and Jadhav, 2012). All drugs were vitrified to more than 85% in SDD with drug-carrier H-bonding being the additional factor for stabilization and enhancement of dissolution.

4.1.7. Spray dried lipidic formulations and solid self emulsifying systems

Gelucire is the most used lipid carrier for the preparation of SDD of poorly water soluble drugs. Gelucire grades differ based

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on their HLB value ranging 1–18 and melting point 33–70 °C. HLB values govern the mechanism of drug release. The mechanisms of drug release from Gelucire with high HLB value are diffusion and erosion. For low HLB values the release could be either simple diffusion or complex release kinetics (Aınaoui and Vergnaud, 1998; Chauhan et al., 2005). Gelucire 44/14 and 50/13 are the most commonly used polyglycolized glycerides grades as a carrier in solid dispersions (Table 1). Spray drying is not the optimal strategy to prepare lipid containing solid dispersions. Lipidic carriers have very poor powder flowability with sticky and tacky nature due to their low melting point (Shimpi et al., 2009). They are usually used as a carrier in solid dispersions in combination with glidants. However, good glidants like Aerosil®200 are hydrophobic and can also affect drug release profile. Therefore creating a balance between flowability and drug release is pivotal during downstream processing of these formulations. It is generally advocated that a solid dispersion with the lowest possible composition of lipidic carriers with acceptable drug release profile is easy to optimize. Moreover, combining Gelucire with high melting point lipids can subdue this problem. Gelucire 44/14, a surfactant comprised of a mixture of glyceride and PEG 1500 esters of long-chain fatty acids, at low composition showed acceptable drug release and pharmacotechnological properties (Araújo et al., 2010). Due to low melting point of Gelucire, inlet temperature has to be set at low values during spray drying which leads to incomplete amorphization and rather facilitate rapid crystallization. Shimpi et al. (2009) reported that spray drying followed by melt granulation with Gelucire improved the stability of the solid dispersion due to amorphization of crystalline traces. Hydrogen bonding ability and immobilization of the API in lipid matrix are responsible for the stability in lipid containing solid dispersions. In case of etoricoxib hydrogen bonding ability is the more dominant stabilization mechanism unlike celecoxib. Spray drying was also described as a preferable method of preparation for solid lipidic formulations using other carriers than Gelucire. Cyclosporine A in lipidic vehicle (Lauroglycol 90, Sefsol 218, sunfat GDC-N and Capryol 90) with surfactants (SLS, Cremophore RH40) and carriers (PVP, PEG) were spray dried to generate solid lipidic formulation to improve oral bioavailability (Ambühl et al., 2010).

Due to promising successes, self emulsifying drug delivery (SEDD) systems have been used to improve bioavailability of poorly water soluble drugs (Singh et al., 2011). SEDDs have been marketed as liquid or encapsulated dosage forms which have a drawback due to high production cost, patient preference, incompatibility with soft gelatin capsules, stability and storage related problems like tendency of precipitation of drug and/or excipients at lower temperature (Balakrishnan et al., 2009; Yi et al., 2008). Solid SNEDDs/SMEDDs could be a possible strategy to overcome these problems. Spray drying can be used to remove the water phase from the emulsion which contains lipidic vehicles and surfactants in the carrier (hydrophobic or hydrophilic) containing aqueous external phase. Hydrophobic carriers like silicon dioxide and magnesium stearate were able to enhance both drug release and bioavailability from solid SNEDDs of flurbiprofen. Spray drying of liquid SNEDDs could result in the formation of solid dispersions. Kang et al., 2011; Yi et al., 2008 also showed that spray drying of liquid SNEDDs of flurbiprofen in PVA, Na-CMC and HP-β-CD led to either a solid dispersion or microcapsules. An acceptable solid SNEDDS with minimum degree of agglomeration and regular particle shape was developed for nimodipine using dextran 40 as bulk forming agent (carrier). Therefore, much attention is required to select appropriate carriers for spray drying of liquid SEDDs based on their effect on crystalline properties, dissolution and bioavailability of the solid SEDDs. The success of spray dried emulsion is measured by its reconstitution property and comparative bioavailability with the liquid SEDDs.

4.1.8. Co-carrier systems

Lately, the concepts of using multiple stabilizers in amorphous solid dispersions have been initiated by virtue of utilizing multi-mechanistic solubilization or stabilization of the amorphous state in SDD. Most of carriers discussed in this section are different than surfactant, glidant or disintegrant (*covered in succeeding section*) as each of them has one or multiple roles for amorphization during spray drying or stabilization of the final amorphous solid solution product. The use of two carriers together for the preparation of SDD should be weighed in terms of risk to benefit ratio as various features like solubility in organic solvents, binary and or ternary interactions in feed solution can build diverse quality in the final product. Cilurzo et al. (2007) have shown that the loading of nitroflurbiprofen in the blend of PVP (K 25 or 30)/polyaminomethacrylate (PAMA) by spray drying leads to significant increase in drug release rate in aqueous environment compared to the binary drug polymer system. The binary polymer blends showing solid state immiscibility throughout the whole composition range are highly plasticized by the loaded drug through H-bonding and compatibilized by water molecules during dissolution and thus assisting the maintenance of supersaturation generated during the process. Janssens et al. (2008a,b,c,d) attempted to decrease the crystallinity of PEG 6000 to the least by forming co-spray dried blend with HPMC. However, the incorporation of itraconazole by forming ternary SDD led to phase separation which in turns induces recrystallization of either drug or PEG and hence reduction of the dissolution performance in comparison to that of HPMC based binary dispersion. The improvement in the drug release is only achieved upon addition of PEG from ternary SDD provided itraconazole is highly amorphous. Due to the decrease in miscibility of PEG with HPMC as a function of PEG chain length, the ternary SDDs prepared with high MW PEGs (10,000, 20,000 Da) displayed increased recrystallization of drug owing to the phase separation as compared to the low MW PEGs (2000, 6000 Da) (Janssens et al., 2008a,b,c,d). Al-Obaidi et al. (2009, 2011) implemented an approach of preparing ternary SDDs of proton accepting drugs such as griseofulvin, progesterone or phenindione and a proton acceptor polymer, PVP, with an additional polymer having both H-bond accepting and donating properties, poly [2-hydroxypropyl methacrylate] (PHPMA), wherein the later acts as a linker to establish ternary H-bonding. Thus, the immiscible binary SDDs (API-PVP) are converted to a miscible system upon formulation into the ternary SDDs. This resulted into marked increase in the physical stability against recrystallization of amorphous drugs from these ternary SDDs. Furthermore, the authors found that addition of PHPMA can also cooperatively strengthen the existing H-bonding between griseofulvin with a proton donor polymer, HPMC-AS in ternary SDD (Al-Obaidi and Buckton, 2009). In comparison to binary SDD with HPMC-AS, a noticeable improvement in physical stability in ternary SDD was observed with minor impact in dissolution. The amorphous ternary SDD consisting of felodipine, Eudragit E100 and Eudragit NE 30D (10:85:5) significantly enhanced and further sustained the *in vitro* dissolution rate of the drug (Nollenberger et al., 2009). The combination of the two polymers in SDD is proposed to generate a high initial drug release rate due to the hydrophilic Eudragit E100 which is further stabilized due to the hindrance posed against precipitation by the finely dispersed Eudragit NE 30 D in the medium. Huang et al. (2011) prepared nifedipine solid dispersions with binary polymer systems, EC and Eudragit RL. The higher molecular dispersibility of drug found in the ternary system was attributed to the synergistic effect of the two carriers wherein stronger drug–polymer interactions by Eudragit and matrix rigidity by EC is balanced. The combination of pH-dependent polymers such as HPMC-AS along with other carrier is reported to facilitate regional recrystallization inhibition of drugs in the GIT (Bittorf et al., 2009a,b). Recently, a novel dual-polymer spray

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drying approach, named as solumerization, has been promoted for the preparation of SDD of poorly water soluble drugs with wide physicochemical and structural diversity, including a hydrophilic polymer (sodium carboxymethylcellulose and chitosan, for example) and an amphiphilic polymeric carrier (PEG and Poloxamer, for example) (Mark Mitchnick et al., 2011). The nanocrystalline SDD formulated with this platform technology showed appreciable improvement of *in vitro*/*in vivo* performance owing to the melting point depression of drug crystals and homogeneous dispersion of drug particles into the polymer matrix (Shi et al., 2012; Zalcenstein, 2010).

4.1.9. Ternary SDD systems

The trend of solid dispersion development is shifting towards the addition of a third or even more components on top of the primary polymeric carrier or stabilizer for the desired post-processability especially through improvement of particulate and bulk level properties. Plasticizers are regularly applied for the preparation of solid dispersions by hot melt extrusion with high T_g polymers (Ghebremeskel et al., 2007). The compilation of various ternary SDD with functional adjuvants published over the years is listed in Table 2. The most used additives are a variety of surfactants for the subsequent ease of solubilization mediated by improvement in powder wettability, glidants/drying agents for improved powder flow, disintegrants, pH modifiers and complexing agents. The competing effects of the added functional excipients in feed solutions can induce solubility gaps, changes the solution state interactions between drug-stabilizer and solvent, and changes in the mode and rate of particle formation by altering the solvent evaporation rate. This, in turn, can have several serious consequences in terms of the particulate level properties such as particle size, shape and morphology to physical structure such as surface chemistry, miscibility, relative crystallinity and moreover physical stability of ternary SDD when compared to the simpler binary SDDs. Despite the ubiquitous publications focusing on the use of functional excipients in ternary SDD, the literature information presenting the understanding of these interplay of aforementioned aspects is rare. As a primary step towards the understanding for multi-component solid dispersion development, Yoo et al. (2009) investigated the correlation between amorphous miscibility, crystallinity and physical stability of twenty four binary dispersions prepared (by solvent evaporation or spray drying) from the combination of four amorphous carriers (PVP, PVP/VA, Eudragit E100 and Eudragit L) with six crystalline additives (SLS, TPGS, meglumine, tartaric acid, citric acid and tromethamine). Among eight amorphous dispersions generated, four constituting the strong acid–base ionic interaction between additive-carrier pair exhibited the best miscibility and physical stability under acceralated conditions. Besides, stronger H-bonding and/or the similarity in solubility parameter ($\Delta\delta \leq 2.8$) and hydrophobicity ($\Delta \mathrm{Log}\, P \leq 1.7$) between the mixing components were found to be the determining factors contributing the miscibility and physical stability. Janssens et al. (2008a,b,c,d) reported that in spite of the absence of molecular mixing or interaction of itraconazole or PVP/VA 64 with inutec SP1 throughout the ternary compositions of SDD, the dissolution rate of drug from ternary SDD was found better as compared to that from binary SDD without inutec SP1. The latter being a surface active polymer enhances solubilization through increased wettability. Also, the presence of another surfactant, TPGS (d-alpha-tocopheryl polyethylene glycol) 1000 has been shown to enhance initial dissolution rate of itraconazole from the ternary SDD with PVP/VA 64, despite solid state phase separation into amorphous and crystalline clusters induced by the surfactant (Janssens et al., 2008a,b,c,d). The retardation of dissolution performance after 1 h was attributed to the crystal growth and precipitation of itraconazole crystals initiated by TPGS surface activity. The disintegration time of tablets prepared from the amorphous SDD of a poorly water soluble drug, UC 781, with PVP/VA and TPGS 1000 was drastically accelerated (4 min) resulting to 90% drug release (Goddeeris et al., 2008). Thermal analysis of this dispersion evidenced the eutectic behavior in SDD with the drug becoming finely dispersed in the polymeric matrices.

Considering the superior physical stability of crystalline dispersions over amorphous dispersions, many recent publications mention the addition of surfactants in drug-polymeric carriers to generate ternary SDDs with unchanged or micro/nano drug crystallites that are finely dispersed in stabilizer matrices with surfactant adsorption leading to increased hydrophilicity and wettability (Li et al., 2010a,b; Oh et al., 2011; Park et al., 2009a,b; Yan et al., 2012). Further, the use of components like L-arginine or meglumine to form ternary SDDs systems have been shown to generate amorphous salts of drugs with the additives and hence increase of physical stability due to T_g elevation (Gupta and Bansal, 2005; Patel et al., 2012). The addition of adsorbent like Aerosil® 200 as drying aid to form ternary dispersions has been reported to improve the flow property during spray drying of low T_g simvastatin with PVP (Ambike et al., 2005). In the same way, the use of colloidal silica or lactose can avoid electrostatic interactions of the resultant powders with the spray dryer wall, leading to increased yield as well as improved post processability (Araújo et al., 2010; Jachowicz and Nürnberg, 1997; Kim et al., 2011. Hydrophilic additives like Aerosil are also believed to act as buffer to protect SDD from moisture (Pokharkar et al., 2006).

4.2. Solvent systems for SDD preparation

Selection of an adequate solvent system is an equally important prerequisite for the generation of amorphous SDD of the desired phase structure and physicochemical attributes. The first indispensable condition is indeed to find out a common solvent (s) system to solubilize all feed components *viz.*, API, carrier and other additives. The primary criteria for the selection of spray drying solvent system include (i) high solubility of drug and carrier in the selected solvent (>50 mg/ml), (ii) the generation of a feed solution with acceptable viscosity, (iii) low toxicity (ICHQ3(R5), 2011 class 2 and 3 solvents), (iv) high volatility for the ease of solvent evaporation during droplet drying, (v) appreciable chemical stability of feed components in the selected solvent and (vi) non-combustive in spray drying environment (Miller and Gil, 2012).

Some relevant physical properties of the common spray drying solvents are depicted in Table 3. The relative volatility of the solvent should be primarily taken into account for spray drying to obtain sufficient yield of SDDs with desired rheological properties and targeted residual solvent limit. Enthalpy of vaporization provides important information that can be helpful in controlling the outlet temperature and energy consumption by the spray dryer. Other solvent properties like viscosity and surface tension are determining factors for the feed atomization during spray drying. Furthermore, they can provide important information on the solution state interaction among drug-carrier and solvent. Dielectric constant and polarizability are the polarity scales of a solvent; the higher the values, the more polar the solvent is. Sometimes, these properties of a solvent are correlated with the phase structure in resulting SDD from feed solution prepared from them. For example, solid dispersions of dihydroartemisinin prepared with PVP using different solvents led to a different extent of amorphization and hence different level of equilibrium solubility enhancement (Ansari and Sunderland, 2008). The solvents with higher dielectric constant and dipole moment resulted into solid dispersions with higher amorphous content thus exhibiting higher equilibrium solubility. As mentioned in the carrier selection section, solubility parameter can be an estimable guide for the spray solvent selection too. It can also provide an estimate for the solubility gap between drug

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Table 2
Examples of ternary SDDs with API, carrier (s), solvent (s) and additives with their functions.

Drug	Solvent (s)	Carrier (s)	Functional excipients	Purpose (s)	References
Sibutramine base	EtOH	HPMC	citric acid	pH modifier	Lim et al. (2010)
Clopidogrel napadisilate	EtOH/DCM	HPMC	colloidal Silica	Glidant/antiadherant	Kim et al. (2011)
Valsartan*	Water (suspension)	HPMC	SLS	Surfactant	Yan et al. (2012)
Flurbiprofen*	–	Na-CMC	Tween 80	Surfactant	Oh et al. (2011)
Sibutramine	Water	HPMC & poloxamer	Citric acid	pH modifier	Li et al. (2010a,b)
Cyclosporin A	EtOH/Water (1:1)	Dextrin	SLS	Surfactant	Lee et al. (2001)
Ibuprofen	Water	HPMC	Poloxamer	Surfactant	Park et al. (2009a,b)
Itraconazole*	water (suspension)	PVP	poloxamer/citric acid	Surfactant/pH modifier	Park et al. (2010)
Rebamipide	EtOH/DCM	PVP-VA64	l-lysine	pH modifier	Tung et al. (2011)
Itraconazole	DCM (suspension)	PVPVA 64	Inutec SP1	Surfactant	Janssens et al. (2008a,b,c,d)
Celecoxib	–	PVP	Meglumine	pH modifier	Gupta and Bansal (2005)
Curcumin	Water (suspension)	Gelucire 44/14,	Collodial silicon dioxide	Drying aid/glidant/anti-adherant	Araújo et al. (2010))
Nitrendipine	Water (suspension)	PVP/PVA	Aerosil/Sylysia and Tween 80	Glidant/anti-adherant and surfactants	Wang et al. (2007)
Tacrolimus	Water (suspension)	CMC-Na	SLS/citric acid	Surfactant/pH modifier	Park et al. (2009a,b)
Tolbutamide	Dil. ammonia solution	L-HPC	Pregelatinized corn starch	Disintegrants	Takeuchi et al. (1987)
Tenoxicam	EtOH/DCM	Optionally with PVP	L-Arginine	pH modifier	Patel et al. (2012)
Cefuroxime axetil	–	Gelucire 50/13 or PVP	Aerosil 200 (with Gelucire)	Glidant/anti-adherant	Dhumal et al. (2009)
Carvedilol	DCM	PVP	Aerosil® 200	Glidant/anti-adherant	Pokharkar et al. (2006)
Itraconazole	DCM	PVPVA 64	TPGS 1000	Surfactant	Janssens et al. (2008a,b,c,d)
Ibipinabant	DCM and EtOH	PVP	SLS	SLS	Leane et al. (2012)
Simvastatin	DCM	PVP	Aerosil 200	Glidant/anti-adherant	Ambike et al. (2005)

and carrier in the feed solution. The Kamlet-Taft (KT) parameter is a traditionally used scale for getting insight into the possibility of having H-bond donor and acceptor pairs alongwith the strength of H-bonding in solution (Kamlet et al., 1983). Solvents with the higher α value, H-bond donor acidity, are protic solvents like normal alcohols that can efficiently disperse polymer or drug molecules with stronger H-bond acceptor functionality in solution. In contrast, protophilic solvents with higher H-bond acceptor value (β) are suitable for drug and/or polymer with stronger H-bond donor groups. The readers are referred to a recent article by Paudel and Van den Mooter (2012) for the further discussion on the relevance of these properties on the physicochemical properties of SDD from different solvent combinations.

The trend observed in the use of diverse spray drying solvents is illustrated by the bar diagrams depicted in Fig. 2. Although ICH classification categories DCM in class two, it happened to be the solvent of choice due to the highest volatility among spray drying solvents and appreciable solubilizing power to wide diversity of API and polymers. With the better understanding gained on solvent effect on product qualities over the years, the paradigm is shifting towards the use of volatile alcohols or hydroalcoholic systems for the preparation of SDD. The other benefit besides the (eco) toxicological reason on using solvent mixtures is reported as an opportunity of particle engineering by varying solvent composition in the feed solution.

Most of poorly water soluble API and polymeric carriers show acceptable solubility in a range of organic solvents or mixtures. However, the growing structural complexity of the molecules entering drug discovery and development program render them insoluble not only in water but also in several spray drying solvents.

Table 3
ICH limit for the residual content and some relevant physical properties of spray drying solvents.

Solvent	ICH limit (ppm)[a]	B.P. (°C)[b]	ΔH_v (kJ/mol)[c]	P (hPa)[d]	η (mPa s)[b]	γ (mJ/m^2)[b]	ε[e]	δ (cal/cm^3)$^{1/2}$[e]	μ (D)[b]	Kamlet taft (KT) parameter[e]	
										α	β
Water	Na	100.0	40.7	17.5	0.89	71.90	78.4	23.4	1.84	1.17	0.47
Methanol	3000	64.7	35.3	128	0.54	22.10	32.6	14.5	1.60	0.98	0.66
Ethanol	Na	78.3	38.7	59	1.08	22.00	24.3	12.7	1.70	0.86	0.75
Isopropanol	-	82.3	45.7	44	2.07	18.30	18.3	11.4	1.66	0.76	0.84
DCM	600	39.8	28.0	475	0.42	27.20	8.9	9.7	1.60	0.13	0.10
Acetone	Class 3	56.3	29.1	240	0.30	22.68	20.7	9.6	2.70	0.08	0.43
Methyl ethyl ketone	Class 3	79.6	31.2	105	0.40	23.04	18.5	9.3	2.76	-	-
Dioxane	380	101.3	38.0	41	1.26	33.00	2.2	10.0	0.40	0.00	0.37
Tetrahydrofurane	720	66.0	26.9	200	0.46	26.40	7.5	9.1	1.60	0.00	0.55
Ethyl acetate	Class 3	77.1	31.9	97	0.43	23.20	6.0	9.0	1.78	0.00	0.45
Chloroform	60	61.2	30.8	210	0.54	26.60	4.7	9.3	1.01	0.20	0.10
Acetonitrile	410	81.6	33.8	97	0.34	28.45	37.5	11.9	-	3.44	-

B.P.: boiling point, ΔH_v: enthalpy of vaporization, P: vapor pressure at 20 °C, η: viscosity at 25 °C, γ: surface tension at 25 °C, ε: dielectric constant, δ: total solubility parameter, μ: dipole moment, α: KT hydrogen bond donor (acidity), β: hydrogen bond acceptor (basicity).

[a] ICHQ3(R5) (2011).
[b] http://www.trimen.pl/witek/ciecze/old_liquids.html (accessed on 2012.04.27).
[c] http://www.umsl.edu/~chickosj/JSCPUBS/vap2003.pdf (accessed on 2012.04.27).
[d] http://murov.info/orgsolvents.htm (accessed on 2012.04.27).
[e] Malavolta et al. (2002).

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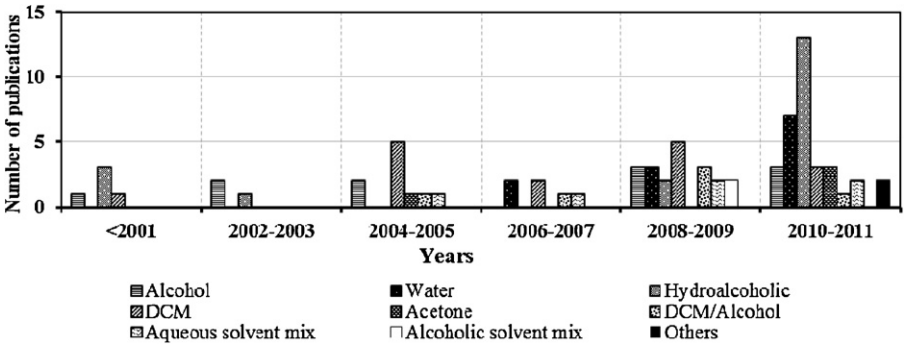

Fig. 2. Trend in the use of spray drying solvents (only articles mentioning *in vitro* and/or *in vivo* are accounted).

This necessitates the rigorous exercise in selecting the optimal solvent system for SDD manufacturing. Provided multiple choices, the spray drying solvent is widely considered as one of the most important variables for pharmaceutical particle engineering to prepare tailor made products in terms of size distribution, morphology and surface composition/topography and eventually drug release from the spray dried products (Nandiyanto and Okuyama, 2011). Beyond the eminent impact on the particulate and bulk properties, the recent concern has been driven towards the understanding of the spray drying solvent on the phase structure and therefore *in vitro*/*in vivo* performance and/or physical stability of amorphous SDDs (Al-Obaidi et al., 2009; Paudel and Van den Mooter, 2012). The solubility of API in the selected solvent can have an influence on the drug loading efficiency and hence release behavior of spray-dried particles. The use of solvent wherein the drug remains (partially) undissolved can result in remaining drug particles which possibly will not be enclosed in the spray-dried microspheres and if they will, they cause an inhomogeneous drug distribution in the microspheres, far from the often ambitioned molecular dispersion of the API in the polymeric matrix.

The influence of solvent selection on particle architecture can be explained by looking at the particle formation process. Solvent evaporation rate and solvent power will determine the hardening of the droplet and hence particle formation, thereby influencing its structure and bulk density. Particle formation in spray drying and more precisely the distribution of the components in spray-dried materials has been described in detail by Vehring et al. (2007). These authors emphasized the use of the Peclet number (*Pe*) to predict compound distribution during the particle formation process (Eq. (1)).

$$Pe_i = \frac{\kappa}{8D_i} \tag{1}$$

In Eq. (1), the evaporation rate is represented by K and D_i stands for the diffusion coefficient of solute *i*. The combination of these parameters will determine particle morphology and drug distribution in the particle, which is hence clearly influenced by the solvent selected, its evaporation rate and the distribution coefficient of the compounds in this solvent (Rizi et al., 2011).

Solvent selection has an influence on particle morphology and associated density through the solvent's evaporation rate. For a given feed concentration, a lower solvent evaporation rate (and thus lower *Pe*) allows the droplet surface to recede during the evaporation process, resulting in limited void spaces, denser particles and hence a higher bulk density of these microspheres. More rapid evaporation (higher *Pe*) and therefore faster solute deposition occurs in solvents which require low quantities of thermal energy to effect vaporization (solvents having a low boiling point) or in which the polymer has a low solubility. Consequently the solidification point will be reached faster, resulting in an increase in void volume and porosity. Shell formation will be likely due to the enrichment of solute at the droplet surface. Solvent can also have influence on the feed component distribution through the differential diffusion coefficient during droplet drying and hence affect the physical structure of the final SDD. With a constant evaporation rate, a lower diffusion coefficient (and thus higher *Pe*) implies that the diffusional movement of the compound is slow compared to speed of the receding droplet surface, resulting in an enrichment of the compound at the droplet surface, leading towards shell formation. Compounds with a higher diffusion coefficient (and hence lower *Pe*) can follow the shrinkage of the droplet surface and will be distributed homogeneously throughout the particle. For immiscible compounds, the differences in diffusion coefficient will have an influence on their phase distribution: the compound with the lowest diffusion will most likely be situated at the microsphere surface (in the case that none of the compounds possesses surface activity). The diffusion coefficient of feed components can be correlated with various feed parameters using the Stokes Einstein equation (Eq. (2))

$$D = \frac{K_B T}{6\pi\eta r} \tag{2}$$

where D is the diffusion coefficient, r the globular radius, T the absolute temperature and η the viscosity of the solution. K_B is the Boltzmann constant. The diffusion coefficient is inversely related to the medium viscosity and hydrodynamic radius of the diffusing feed component during droplet drying. Viscosity of a polymer solution depends on the polymer concentration and molecular weight and is specific for a certain solvent/polymer pair. This specificity lies in the polymer dispersivity in a chosen solvent and non-covalent interaction between polymer–solvent accompanied by the cooperative influence of the drug. This in turn influences the viscosity by altering the polymer conformation in solution. When interactions occur between solvent and polymer, the polymer chain will exist in an expanded state and will increase the solution's viscosity (Bodmeier and McGinity, 1988). In contrast, the viscometric data from Molyneux and Frank (1961) shows that the cross-linking H-bonding interaction between non-ionic cosolutes and PVP eventually contract the polymeric chain in aqueous solution.

Moreover, the interplay between solvent evaporation rate and polymer solubility will influence the final particle size. With high evaporation rate and/or low polymer solubility, solidification of the droplet surface will be fast resulting in large particles. A slow evaporation rate and/or high polymer solubility will evoke slow shrinking of the droplets with a slower solidification rate (low *Pe*) whereby smaller but denser particles will be formed (Rizi et al., 2011).

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Table 4
Overview of the particle characteristics influenced by solvents selection and their corresponding solvent-dependent attributes/phenomena.

Particle characteristics	Solvent-dependent parameters
Particle morphology	Evaporation rate, diffusion coefficient
Particle density	Evaporation rate, diffusion coefficient
Compound distribution	Diffusion coefficient, solubility
Encapsulation efficiency	Solubility (difference)
Particle yield	Particle density, residual solvent, particle size
Release kinetics	Particle morphology, density, solid dispersion type
Residual solvent	Particle density
Particle size	Viscosity feed solution, evaporation rate/ polymer solubility
Mass Median Aerodynamic Diameter (MMAD)	Evaporation rate, solubility
API/polymer miscibility and stability	API/polymer/solvent interactions

Another important product quality influenced by solvent properties is the amount of residual solvent retained in the SDD. During the evaporation process the solvent removal rate will be dictated by the ratio between the boiling temperature of the solvent and the inlet temperature of the spray dryer. A high ratio will be translated into a slower solvent evaporation and a higher amount of residual solvent. The foremost precaution related to solvent retention in SDD is indeed the toxicity issues of these solvents. As mentioned in Table 2, various solvents classified by ICH are allowed below a certain limit in the final product based on their toxicity (ICHQ3(R5), 2011). In physicochemical perspectives, the residual solvent present will plasticize amorphous SDD hence lowers T_g of the SDD that can potentially lead to physical instability. The residual solvent has also direct impact on the SDD particle density. During secondary drying of SDD products, denser particles markedly impede the solvent evaporation. Bain et al. (1999) additionally showed that retention of solvent was in parallel to solvency power of the individual solvents and thus determined by polymer–solvent interactions. Table 4 summarizes the different particle (formation) properties influenced by spray drying solvent Different authors described the benefits of using solvent mixtures, comprising increased drug–polymer miscibility, improved dissolution kinetics and enhanced stability. The pharmacotechnological properties of powders can also be improved by using appropriate solvent blends for spraying liquid. Using non-volatile or high boiling point solvents in solvent mixtures can also improve powder derived properties like density, particle size and ultimately flowability. Spray drying of VX-90 from a solution which contains a cellulosic polymer and surfactant in a solvent blend of a high boiling solvent such as glacial acetic acid, DMSO, DMF and water resulted in a solid dispersion with larger particle size, higher density and improved flowability (Bittorf et al., 2009a,b). Janssens et al. (2009) reported an increased polymer–drug miscibility when spray drying from a ternary solvent mixture. Al-Obaidi et al. (2009) described drastic changes in morphology, stability and dissolution properties when changing a binary solvent mixture. The authors related these differences to conformational variations of the polymers in the feed solution. Paudel and Van den Mooter (2012) observed an improved miscibility and physical stability of solid dispersions spray dried from binary solvent mixtures. Again changes in the conformation of the polymer in solution were found to be responsible, and indicated changes in polymer–solvent interactions. To summarize, the driving force behind the observed advantages in these studies lies in altering the solvent–solute interactions. Changes in these interactions, introduced by the use of a different solvent or a solvent mixture, resulted in different mixing behavior and thermal characteristics of the spray-dried materials. A difference in solvent–solute interactions will result in an altered T_g. A higher T_g reflects increased interactions between API and polymer and/or less interaction between API/polymer and solvent and hence a lower solubility in the solvent (Janssens et al., 2009; Paudel and Van den Mooter, 2012).

5. Critical spray drying variables and quality attributes of SDD

The current era of *quality by design* (QbD) conceptualization of the industrial manufacturing processes including pharmaceuticals in hyphenation with process analytical technology (PAT) offer various opportunities of exploiting the knowledge space of precursor material properties and design space of underlying process variables for the development of a robust process as well as the desired quality attributes of the end products (ICHQ8(R2), 2009; Nagy and Meszena, 2009). Plethora of information available on the use of QbD in pharmaceutical spray drying are directed towards the built-in particulate or bulk level properties of the final product (Baldinger et al., 2011; Lebrun et al., 2012). Nonetheless, there is paucity in literature information on the investigation of the impact of various formulation and/or processing variables of SDD on the final product quality. Few studies on SDDs attempted to relate the formulation and process variables on the yield, particulate/bulk properties or other derived properties therefrom of the obtained product that are important for the downstream product development process. In spite of copious information on the significant impact of evaporation rate on the characteristics of the generated supramolecular structures in spray dried composites of food and dairy products, it is surprising that the pharmaceutical literature as such is silent on aspects of the nano to mesoscopic phase structures like homogeneity, amorphous miscibility, crystallinity, surface energy, hygroscopicity and on the physical stability of high energy amorphous SDDs resulted from the interplay of various process and formulation variables. The non-exhaustive information on multivariate relationship of SDD quality attributes with formulation and process variable are discussed here.

5.1. Feed solution properties

Understanding solution chemistry and control of the feed solution properties play a determining role on powder characteristics *viz.*, porosity, particle size/shape/morphology (distribution), surface charge/stickiness, volatile (residual solvent/moisture) content as well as phase homogeneity and surface/bulk energy of the resulting SDD (Baldinger et al., 2011; Wang and Langrish, 2009). These outputs on the one hand affect several derived properties like powder flow (Carr index), bulk/tap density, tablettability, *etc.* and on the other hand determine the *in vitro* dissolution rate and/or *in vivo* performance, hygroscopicity, stressed and/or long term physical stability (structural relaxation, phase separation and/or recrystallization rate) (Gonnissen et al., 2007, 2008). Additionally, final yield, experimental throughput and drying capacity can be notably affected (Maury et al., 2005). Some critical feed solution properties and their contribution on various phenomena and quality attributes of the final formulation are illustrated in Fig. 3.

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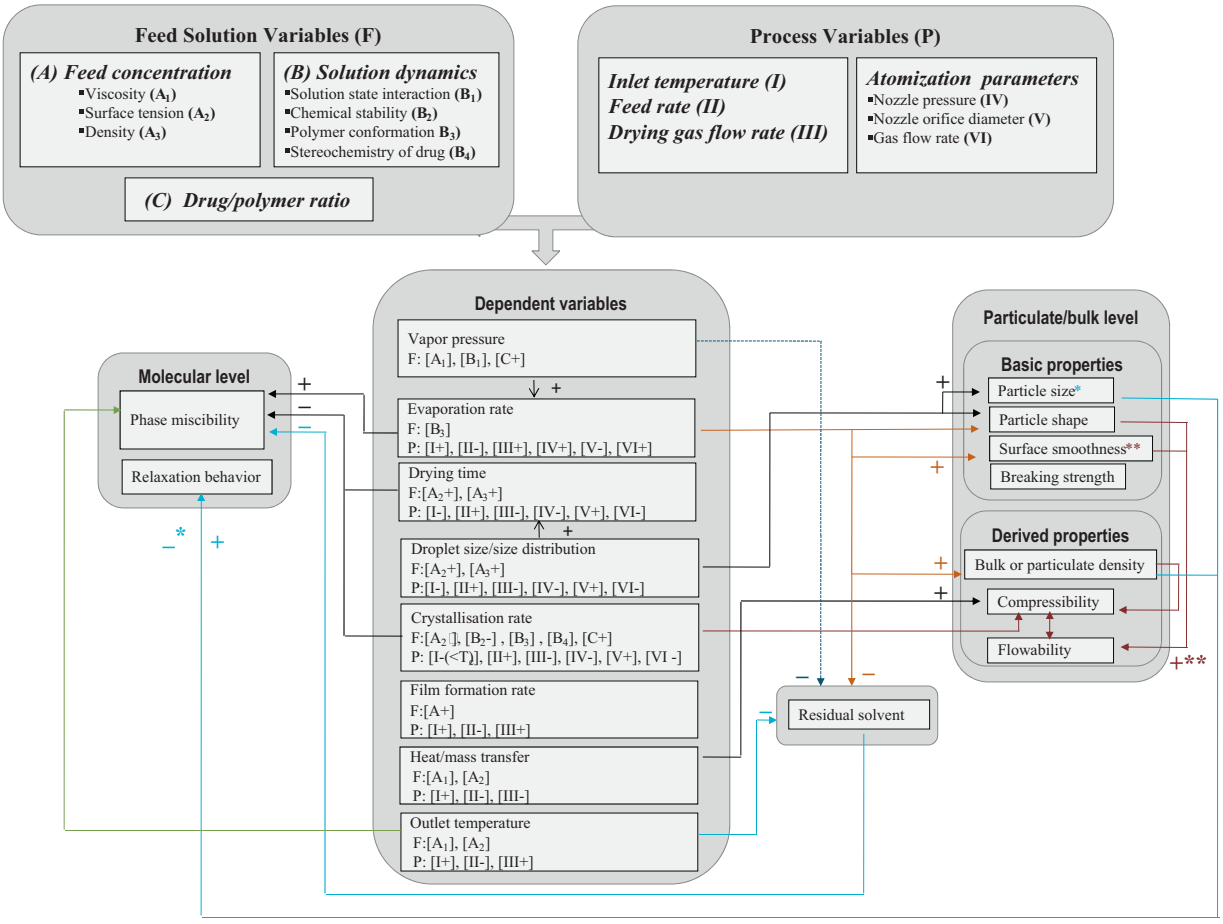

Fig. 3. A flowchart illustrating the influence of feed solution and process variables on underlying processes during spray drying and thereby on the molecular and particulate/bulk level properties of the SDD [(+): directly related, (−): inversely related, T_c: crystallization temperature and no notation (+ or −): variables can have a direct or an inverse relation with the effects).

5.1.1. Feed composition

As mentioned in the preceding sections (4 and 5), the rational selection of a suitable carrier, solvent and other possible additives in the right ratio is the foremost step in the development of a SDD of poorly water soluble drugs with the desired phase homogeneity and miscibility. Indeed, solid solubility is primarily the limiting factor for deciding the drug to polymer ratio to obtain homogenous amorphous SDD under the applied processing condition. The solubility difference among drug, carrier and other additives in a feed solution (solvent) leads to a different degree of saturation/supersaturation of these components (Wang and Langrish, 2009). This would expectedly influence several underlying phenomena during droplet drying (Fig. 4). Moreover, the excessive gap in temperature dependent solubility between solute components can potentially induce radial demixing during particle formation as an insoluble component starts precipitating earlier at the shrinking droplet surface. According to Raoult's law, the partial vapor pressure of the solvent in the feed solution is directly influenced by the solute content which has direct impact on the solvent evaporation rate. More specifically, the polymer content in the feed solution greatly modulates the vapor pressure as polymers are reported to show an immense composition dependent intermolecular interaction with solvents (Al-Obaidi et al., 2009; Bercea et al., 2009a,b). The outer skin formation during droplet drying and hence the retardation of evaporation rate is highly dependent on the solution concentration of carrier having film forming properties like PVP (Kiil, 2011). The other latent feed solution properties that can be altered with the variation in drug to polymer ratio are viscosity, surface tension, specific gravity, pH, *etc.* This would impact the droplet size (distribution) during spray drying and in turn the rate of solvent removal. The rate of core to surface transport of solvent and then evaporation from a droplet surface decrease with the increase in feed viscosity due to higher fraction and/or molecular weight of polymer present in solution (Wu et al., 2011). Also, breakup length of liquid jet during atomization increases with increasing feed viscosity resulting into larger droplets. The shift in rheological regime of feed solution from Newtonian to non-Newtonian can drastically change the spray rate, droplet size (distribution) and density. As shown by Cilurzo et al. (2007) the viscometry of multi-component feed solution provides a handful of information on different solute–solute and solute–solvent interactions. Paudel and Van den Mooter (2012) observed the marked difference in overall solvent evaporation rate from naproxen-PVP solutions containing same total solute content but different drug to polymer ratio. The solution state properties such as polymer diffusion coefficient and solute–solvent supramolecular interactions are drastically altered with the different drug to polymer ratio. Besides, it is well known, especially from polymer literature, that the influence of composition on non-covalent interactions (dispersive, polar, H-bonding) in metastable solutions is governed by specific ternary interaction attributes among two solutes and solvent rather than binary parameters (Bercea et al., 2009a,b). Therefore, polymer folding/unfolding and dispersed state of drug in solution (monomer or multimer) as a function of composition are key attributes for the unique solid state structure in SDD (Paudel and Van den Mooter, 2012). These facts imply the utmost

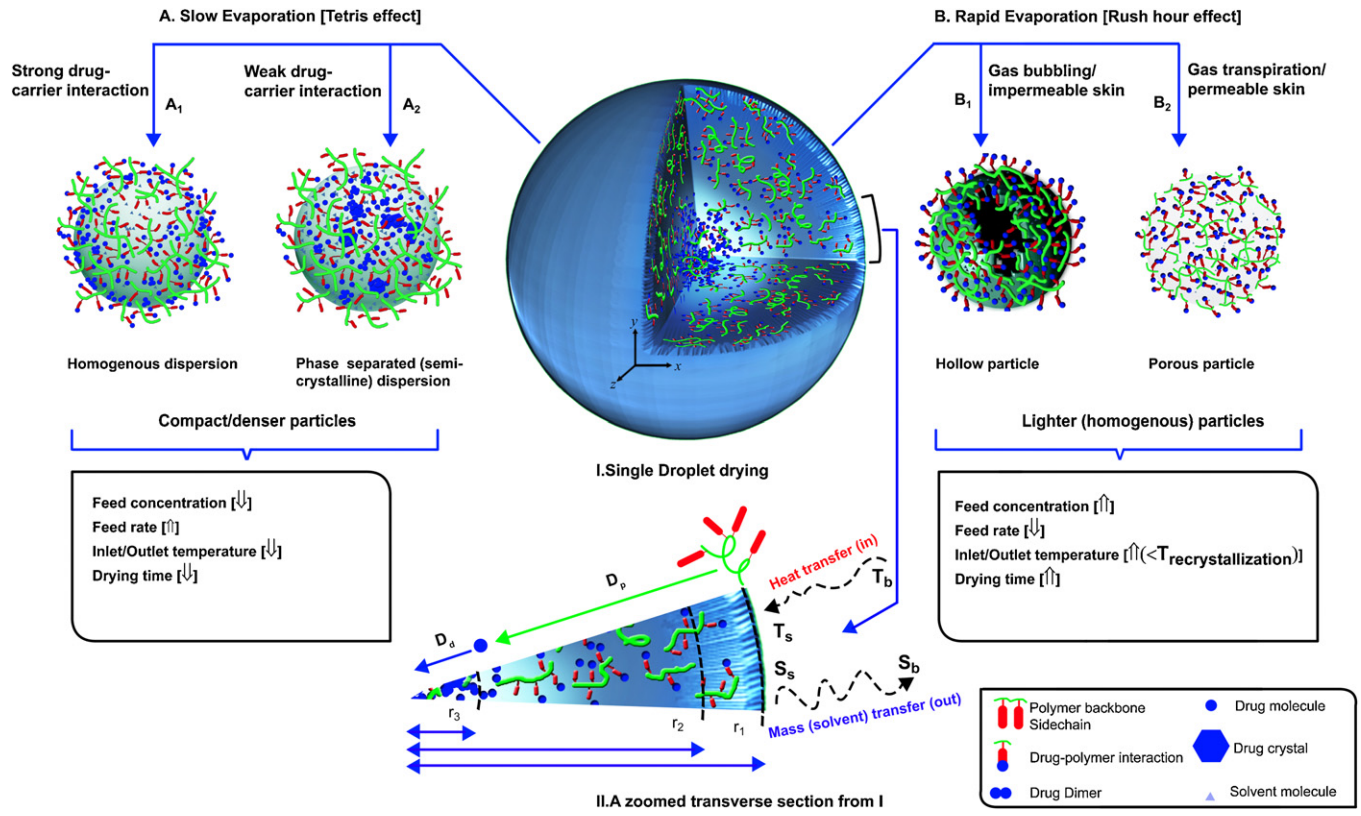

Fig. 4. I. A representation of a single droplet drying phenomenon of drug-carrier feed solution during spray drying. **II**. A zoomed section of a drying droplet displaying spatial distribution of the drying components; where $\mathbf{r_1}$: radius of initial droplet, $\mathbf{r_2}$: radius of the receding solvent font containing bulky polymer and drug–polymer interaction systems and $\mathbf{r_3}$: radius of the droplet core concentrated with fast diffusing smaller molecular weight API, diffusion coefficient of drug ($\mathbf{D_d}$) ≫ diffusion coefficient of polymer (**Dp**), Temperature at droplet surface ($\mathbf{T_s}$) ≤ Temperature of bulk drying gas ($\mathbf{T_b}$) and Solvent vapor around droplet surface ($\mathbf{S_s}$) > Solvent vapor in bulk drying gas ($\mathbf{S_b}$). **A.** slow evaporation process where the drying process provides enough time for conformational alteration and/or stacking of molecules (effect analogous to Tetris- a tiling game) generating dense particle with higher residual solvent content; $\mathbf{A_1}$: homogenous dispersion resulted from crystallization inhibition and stronger drug–polymer interaction (therefore surface hydorphobization) and $\mathbf{A_2}$: weaker drug–polymer interaction and efficient stacking of drug molecules (therefore partial nucleation/recrystallization). **B.** Rapid evaporation leading to skin formation and fast diffusion of feed components (rush hour effect) without sufficient time for ordering of drug molecules for nucleation/recrystallization; $\mathbf{B_1}$: impermeable film formation resulting into expansion of entrapped solvent vapor thus formation of hollow dry particles and $\mathbf{B_2}$: solvent vapor transpiration from permeable film formed at surface thus resulting into porous dry particles (⇑: high, ⇓: low).
Refer the article by Marin et al. (2011) for the explanation of Tetris effect and rush hour effect.

importance of composition dependent solution dynamics in predicting the phase behavior of the resulting SDD.

The figurative illustrations of different non-mutually exclusive phenomena occurring during droplet drying of a drug-carrier binary solution are presented in Fig. 4. Although a droplet drying process only lasts for fractions of a second, differential time dependent migration of dissolved solids, *viz.*, drug, polymer and other additives (surface activity also, if applicable) are to be explicitly accounted for, on top of the solvent evaporation process, for predicting the phase behavior of the resulting SDD particles. For a simple depiction, effect of solvent evaporation rate on the evolving structure in SDD particles can be understood with two kinds of analogies (Marin et al., 2011). The first type, "rush hour effect" is used to explain the rapid solvent evaporation condition wherein the fast diffusion is followed by turbulent mixing of the components without getting time for reorganization or ordering, hence low possibility of recrystallization. The second is "Tetris effect" that occurs during slow solvent evaporation which provides sufficient time for molecular stacking or reorganization, like tiling effect observed in Tetris game, hence facilitating phase separation or the worst to nucleation/recrystallization. The rate of diffusive transport of drug, carrier and additives during particle formation can vary several orders of magnitude as a result of differences in their physicochemical properties. For example, usually drug molecules of smaller size diffuse several orders of magnitude faster than bulky polymer molecules (Al-Obaidi et al., 2009). At a given drug: carrier composition, the large difference between the *Pe* values (Eq. (1)) of drug and carrier could mediate phase separation of components in the final SDD due to their different diffusional velocities (Vehring, 2008). The composition and T_g within SDD particles is reported to vary radially with the surface bearing the carrier rich fraction (Adhikari et al., 2003). Furthermore, the addition of other excipients can further induce anomalies in droplet drying behavior (Wang and Langrish, 2009). The addition of surfactants is reported to result in increased particle size (Sollohub and Cal, 2010). Specifically, surfactants or carriers with surface activity tend to move towards the liquid-air interface during drying (Millqvist-Fureby et al., 1999) which may result into a surfactant rich and plasticized surface zone prone to recrystallization. The content of surfactants should be properly optimized considering their subsequent effect during dissolution of SDD particles. Critical micelle concentration (CMC) and hydrophilic–lipophilic balance (HLB) values of surfactants are to be taken into account. Low levels of surfactants may render insufficient wetting while high levels will solubilize fines and accelerate early nucleation and crystal growth (Biradar et al., 2006). The increase in the fraction of Aerosil 200 in the spray dried ternary microparticles made up of carbamazepine-Gelucire-Aerosil is reported to decrease the solubility and increase the hygroscopicity of the product (Martins et al., 2012). Therefore, due concern is required regarding relationships

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between feed composition and properties built in the resulting SDD particles.

5.1.2. Feed concentration

Concentrated feeds, especially coarser colloids to nanosuspensions of crystalline drugs dispersed in a carrier results into the generation of submicron range crystals finely dissipated in carrier matrices. Typical feed concentration used for the preparation of amorphous pharmaceutical solid dispersion preparation ranges from 10 to 20% (w/v) (Miller and Gil, 2012). Apparently, feed concentration is directly proportional to *Pe* and hence inversely related to the evaporation time. The solute content of feed solution in principle affects the ternary relation among viscosity–temperature–concentration during droplet drying. For a feed solution with fixed composition, even the total solute content can largely influence several properties of the resultant spray dried amorphous particles (Alexander and Judson King, 1985). With increasing feed concentration, higher drop in evaporation rate and hence drying is expected compared to pure solvent or dilute solution. The diffusivity ratio between feed solution components can alter markedly with the change in feed concentration (Kim et al., 2003). This is because in dilute solutions the drug is present as monomer while at higher concentration some drugs are able to form multimers or undergo polycondensation (Tomasko and Timko, 1999). Likewise, polymer chains are more solvated/extended in dilute solution but become coiled or folded at higher concentration leading to the formation of SDDs with more voids, *i.e.* less density (Paudel and Van den Mooter, 2012). The amorphous SDDs of griseofulvin-PHPMA-PVP prepared using lower feed concentrations were shown to display a slower structural relaxation which in turn should have lower molecular mobility (Al-Obaidi et al., 2009). The authors believe that higher extent of non-covalent interaction between drug and polymer can be expected in the dilute feed solution due to the less entanglement of polymer chain. These concentration dependent changes in drug species and polymer architecture in feed solution can also change the solution state supramolecular interactions among drug-carrier and solvent (Rizi et al., 2011). Spray drying from feed solutions with increasing concentration led to the generation of a higher fraction of the metastable polymorph III of phenobarbitone (Corrigan et al., 1983). The more explorative investigation on the effect of feed concentration on the phase structure and physical stability of amorphous SDD is certainly an interesting topic for future research. At particle level, lower solute content in feed solution typically generates spherical and smaller particles. Generally, the smaller particles generated from dilute solutions are highly electrostatic with increased wall adhering tendency (Murtomaa et al., 2004). The increased hygroscopicity due to the higher effective surface area (smaller particle size) of amorphous solid dispersions prepared from dilute feed solutions led to the decrease in physical stability despite of their slower relaxation behavior (Al-Obaidi et al., 2009). In contrast, larger particles are generated from concentrated and hence viscous solutions due to the formation of larger droplets (Littringer et al., 2012; Rizi et al., 2011). It is well known that the geometric mean diameter of spray dried particles is directly proportional to the feed concentration. Additionally, it is reported that a concentrated feed solution may also lead to the formation of hollow spray dried particles with rough surface, higher porosity and bulk density (Littringer et al., 2012). The feed concentration effect on the surface morphology depends upon the chemical nature of feed solution components (Paramita et al., 2010a,b). The effect of solute concentration on the droplet size is less pronounced at higher settings of spray drying process parameters (Littringer et al., 2012). However, feed concentration is precisely controlled sometimes down to 1–2% (w/v), for inhalation formulations where varying other parameters does not result into the appropriate aerodynamic radius of the spray dried particles (Miller and Gil, 2012). The increase in feed concentration of phospholipids for pulmonary delivery tends to increase crystallinity of the spray dried particles (Alves and Santana, 2004).

5.1.3. Feed solution stability

It is very important to determine the time dependent change in feed solution to ensure the consistency of feed solution during spray drying period particularly in terms of chemical stability in solution. A large volume of feed solution might reside hours before being charged into the drying chamber in spray drying processes at large scale. Any reactive combinations among the drug substance, polymeric carrier, additives and spray drying solvent should be potentially avoided. The time dependent alternation of solution chemistry of the feed solution should be duly investigated. Metastable solutions can undergo precipitation due to nucleation and crystal growth of drug or clouding or jellying of polymer with time (Lindfors et al., 2008). Interestingly, time dependent stereo-oscillating behavior has been reported in the aqueous and non-aqueous solutions of some class of drugs, like that belonging to aryl acetic acid class of non-steroidal anti-inflammatory drugs (NSAIDs) (Sajewicz et al., 2010). The prior knowledge and monitoring of these aspects of the feed solution is important because stereo-selective drug–polymer interaction and nucleation/crystallization kinetics of different isomers of chiral drug molecules like nitredipine (Miyazaki et al., 2011) and NSAIDs like naproxen, ibuprofen, ketoprofen, *etc.* has been reported in their respective solid dispersion (Ivanov and Tsokeva, 2009). Conversely, time dependent coiling, molecular aggregation, folding or the conformational change of tactic or atactic macromolecular carrier can bring difference in drug–polymer–solvent interaction which consecutively can alter the structure of the final SDD. The feed solution temperature has to be properly controlled as the mere change can sometimes result into very noticeable variation in the properties of the final product. Sometimes feed solution is intentionally heated to increase feed concentration (Engers et al., 2010) or to aid drug–polymer H-bonding for the drug–polymer miscibility in resulting SDD (Guns et al., 2011). However, in case of spray dried phospholipid particles intended for pulmonary delivery application, the increase in feed solution temperature led to the increase in overall crystallinity of the product (Alves and Santana, 2004). The increase in feed temperature is reported to produce higher fraction of hollow particles with wall thickness directly related with the feed temperature for spray dried microencapsulated products (Paramita et al., 2010a,b).

5.2. Process parameters

A large number of pharmaceutical publications emphasize the influence of processing parameters on the particulate and bulk properties of spray dried products (Baldinger et al., 2011). The excipient performance of spray dried lactose with diverse rheological and mechanical properties resulting from varying morphology, sphericity, powder flowability and crystallinity when prepared using different processing parameters has been extensively studied (Chiou et al., 2007; Langrish, 2007, 2008). In this way, spray drying process parameters have been thoroughly explored for particle engineering of pharmaceutical materials including excipients. Some predictive models correlating product quality and spray drying conditions have been proposed (Patel and Chen, 2005). However, there is almost no theoretical as well as experimental information in pharmaceutical literature dealing with the impact of different processing parameters on the phase structures as well as particulate and derived properties of the resulting SDD. An excellent review providing a systemic flowchart on the spray drying process development for manufacturing SDD of poorly water

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soluble drugs has been published by Dobry et al. (2009). Based on the little information available from reported cases and processes exhibiting analogous situations, a cause-effect scheme is presented in Fig. 3 to illustrate the influence of processing conditions on various phenomena during droplet formation/drying and on the various properties of the resulting SDDs. Accordingly, existing case studies on the process-mediated structural development of spray dried poorly water soluble drugs and their solid dispersions have been presented here with particular emphasis on the phase structure of resulting SDD.

5.2.1. Feed flow rate

The feed rate is the foremost parameter to start with for attaining the balance between throughput and proper drying considering the drying capacity of a particular spray drier set up (Miller and Gil, 2012). Apart from the atomization pattern and droplet size (distribution), feed rate primarily governs the time period a particle remains in the drying chamber, conveyer, cyclone and bag filters during the spray drying operation. As feed rate directly affects the saturation degree of exiting gas, it influences the outlet temperature at the given drying set up. Therefore the upper limit of flow rate for a given feed solution is set to attain sufficient drying of the particles before they hit the spray dryer wall (Vehring, 2008). Recently, it was shown that size and crystallinity of spray dried artemisinin-maltodextrin microparticles decrease with the increase of feed flow rate (Sahoo et al., 2009). Surprisingly, the aqueous solubility enhancement of the drug was found to be inversely proportional to the feed rate. Higher feed rate also decreased the breaking strength of materials like mannitol (Littringer et al., 2012).

5.2.2. Inlet and outlet temperature

The temperature of the drying gas encountering the droplets of the atomized feed is considered as the most important determinant of the internal structure of the resulting spray dried particles. Next to feed solution development and feed rate setting, optimization of inlet temperature is crucial to maintain sufficient P_e value and to attain the targeted outlet temperature. Having direct impact on solvent evaporation kinetics from the drying droplet, it is a primary process variable responsible for the development of the unique phase structure and controlling the level of residual content and bulk/particulate level properties of the final product. There is abundant literature information on the evaluation of various quality attributes such as amorphicity, flowability, particle size morphology, *etc.* of spray dried lactose, mannitol and other excipients as a function of inlet temperature (Chiou et al., 2007; Elversson and Millqvist-Fureby, 2005). However, such studies on amorphous state of poorly water soluble drugs and their solid dispersions prepared by spray drying are again limited. The striking differences in thermal properties and molecular behavior for the amorphous states of some poorly water soluble drugs generated by spray drying at different inlet temperatures was demonstrated earlier. Yamaguchi et al. (1992) published an interesting article showing the correlation of morphology, dissolution rate, physical stability and thermal properties of a spray dried amorphous poorly water soluble macrolide antibiotic (T_g = 102 °C) as a function of inlet temperatures (50–160 °C). All spray dried powders except that prepared at 50 °C were completely amorphous with consistent T_g. The morphologically distinct amorphous state generated at inlet temperatures between T_g and recrystallization temperature showed the highest stability when stored at 40 °C/75% RH and the highest rate and extent of dissolution. Likewise, a significant difference in intermolecular interaction, T_g and hygroscopic stability of amorphous furosemide prepared by spray drying at 50 °C and 150 °C has been reported (Matsuda et al., 1992). The amorphous sample prepared at lower inlet temperature displayed lower T_g (44 °C) and complete absence of intermolecular interaction where as that prepared at higher temperature showed higher T_g (54 °C) as well as the partial retention of intermolecular interaction of the crystalline state. This explains for the observation of higher physical stability of the amorphous form prepared at higher inlet temperature compared to that of sample prepared at lower temperature. The inverse relationship between spray drying inlet temperature (60–200 °C) and the crystallinity in spray dried ursodeoxycholic acid has been reported (Ueno et al., 1998). The crystallinity drastically decreases up to the sample prepared at 180 °C. The extent of disruption of intermolecular H-bonding and hence hygroscopicity of the sample increased with inlet temperature employed. Ohta and Buckton (2005) have shown the difference in the short range order and energetics of particle surface as the reason for the diverse recrystallization tendency and hygroscopicity of two amorphous materials of cefditoren pivoxil prepared by two different inlet temperatures having identical T_g. Despite similar moisture sorption behavior and physical state at lower RH, the sample obtained by spray drying at lower inlet temperature showed recrystallization and higher moisture uptake compared to that prepared at higher temperature which resists crystallization with comparatively lower water uptake at higher RH. Very recently, Gad et al. (2012), showed that the morphology and solid state of spray dried para-aminosalicylic acid particles prepared from aqueous ethanolic solution (90% ethanol v/v) in presence of varying concentration of ammonium carbonate is markedly dependent on the inlet temperature. At lower inlet temperature, a novel solvated complex with stiochiometry of; PAS: ammonia: water, 2:1:0.5 resulted while at higher temperature pure para-aminosalicylic acid was obtained. Spray drying in presence of ammonium carbonate resulted into the successful production of nanoporous microparticles having favorable properties for dry powder inhalation delivery.

These substantial influences of inlet temperature on physical state and properties reported for the spray dried amorphous state of pure drug evidently points towards the possibility of more prominent effect discernable in miscibility, surface properties and physical stability of multi-component SDDs. This broadcasts an open opportunity for the exploration of the interplay between the processing temperature and material properties to yield SDDs with tunable physicochemical properties and physical stability. A screening study based on solution casting recently published by Wu et al. (2011), evidenced the highest influence of solvent evaporation temperature over the formulation composition and polymer molecular weight for the retardation of the crystal nucleation from a piroxicam-PVP solid dispersion. The upper inlet temperature for amorphous SDD manufacturing is constrained by the phase separation of the product while the lower extreme should consider the avoidance of residual solvent and plasticization of the system. Itraconazole crystallinity in spray dried microparticles of mannitol increased with inlet temperature (Duret et al., 2012) while in spray dried artemisinin-maltodextrin microparticles drug crystallinity decreased with increase of inlet temperature leading to the proportional increase in drug solubility (Sahoo et al., 2009). The higher inlet temperature resulted into the higher fraction of larger particles in both cases owing to the higher droplet formation and agglomeration. It is of common knowledge that higher inlet temperature result in the spray dried materials with larger particle size and hollow core. During spray drying at higher temperature, hot/fast particle formation occurs with the temperature at drying gas-droplet interface equivalent to or more than solvent boiling temperature wherein the vapor pressure built in by the solvent keep the surface smoother. In case of spray drying at lower temperature (slow/cold), shrinking of particle leads to the rough surface topography (Dobry et al., 2009). Higher inlet temperature generates dry particles with reduced residual solvent content but with higher hygroscopicity due to the activated surface.

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Next to inlet temperature, outlet temperature is also an important process parameter to get the desired product quality. For formulation like amorphous composites, it is of prime importance in relation to physical stability issue as this is practically the highest temperature to which the solidified product may be heated during spray drying. Outlet temperature of drying gas is the derived process parameter dependent upon inlet temperature, drying gas flow rate and enthalpy of evaporation of solvent in feed (Cal and Sollohub, 2010). The overall process efficiency of spray drying is highly dependent on the ratio of inlet to outlet temperature (Sollohub and Cal, 2010). For spray dried lactose, the degree of crystallinity was found sharply higher when dried inside the insulated chamber at higher outlet temperature compared to the non-insulated condition (Islam and Langrish, 2010a,b). Spray-drying at lower outlet temperature (<boiling point of solvent) will produce a powder with a higher residual solvent level that may have direct consequence on the long-term physical stability of the final SDD. However, the secondary drying of SDD is commonly carried out to remove residual solvents and moisture remained within the particle interstices. Feeding the preheated solution into the drying chamber set at lower inlet temperature and the drying gas set at relatively high flow rate to achieve (outlet temperature-T_g of exiting SDD) <20 °C is reported to reduce final residual solvent content while still maintaining or improving the product homogeneity (Beyerinck et al., 2005a,b,c). The development of the spray drying operating space for SDD is typically based on tuning other parameters to obtain the target outlet temperature by generating a contour of drying gas flow rate per unit feed rate as a function of inlet temperature (Dobry et al., 2009). Selection of outlet temperature should primarily account for physical (T_g) and chemical (thermal degradation) stability aspects of the resulting SDD. Further, right selection of outlet temperature is made to avoid stickiness on the dryer walls (>T_g) and to obtain acceptable yields (Patterson et al., 2007, 2008). Outlet temperature is considered as the key parameter influencing the morphology, surface properties and crystallinity of various spray dried excipients *viz.*, lactose, mannitol, *etc.* (Littringer et al., 2012) and inhalation products formulated therefrom (Maas et al., 2011). The yield of ternary SDD of carbamazepine was increased with the increase in outlet temperature owing to the decrease of particle stickiness (Martins et al., 2012). Thybo et al. (2008a,b) observed the influence of outlet temperature on the morphology and residual solvent content of the acetaminophen-PVP amorphous SDD at pilot scale and on the particle size at production scale. SDDs with drug: polymer ratio of 1:2 prepared at lower outlet temperature setting led to rougher surface topography whereas smoother particles were yielded at higher outlet temperature. The SDD with higher polymer content (1:9) resulted into rougher particles regardless of outlet temperature. However, the SDD particles generated at higher outlet temperature on production scale were remarkably larger compared to those prepared at low outlet temperature. The authors attribute the variation in the outlet temperature to the difference in the temperature profile and particle residence time inside the drying zone operated at the different scales. Therefore, the influence of outlet temperatures on the physical stability of the amorphous SDD and other characteristics that are important for secondary dosage development should be carefully evaluated.

5.2.3. Drying and atomization gas type and flow rate

Selection of proper drying as well as atomization gas type and flow rate for spray drying ensures efficient drying capacity of a process with built-in product attributes. Other than for optimization of specific drying capacity of a spray dryer, *i.e.* the mass ratio of drying gas flow rate to feed rate, drying gas is generally considered as the idle parameter in relation to the product properties. Slower rate of charging drying gas into the drying chamber leads to the higher span of drying particles on the chamber which reduces the residual solvent content while higher drying gas flow rate tends to the reduction of particle size due to the higher gas-particle attrition (Wang et al., 2009). On the other hand, for a given nozzle orifice, the nozzle flow rate directly controls the droplet size and distribution during atomization. Generally dehumidified air is used as the drying/atomization gas for most of aqueous feed for the preparation of SDD (Miller and Gil, 2012). Inert gases like nitrogen or helium are recommended for the non-aqueous feed, especially for the feed containing oxidatively labile species at higher temperature settings. Spray drying of Δ^9-tetrahydrocannabinol with inulin using air led to the purple coloration of the yielded particles with the significant extent of degradation detected (van Drooge et al., 2004). Switching drying gas from air to nitrogen markedly improved the chemical stability of drug during spray drying. Recently, Islam and Langrish have shown the impact of atomization and drying gas type on the crystallization behavior of spray-dried products (Islam and Langrish, 2010a,b). The crystallinity of the resulting spray dried lactose powder was found in the order of drying and atomization gas of nitrogen > air > carbon dioxide. Expectedly, the surface morphology of the spray dried particles with higher crystallinity was rough and edged. This signifies that the selection of drying and atomization gas type based on the thermal conductivities and density can add an additional degree of freedom for particle engineering.

5.2.4. Types of atomization nozzles

With the optimized setting of feed concentration, feed rate, inlet temperature, atomization and drying gas (type) flow rate, the atomization efficiency primarily relies on the selection of type, orientation and size of the atomization device. The descriptions on the types of atomization devices and product properties of the particles obtained therefrom are detailed in Section 2 of this review. Mostly, bifluid nozzles are used to prepare pharmaceutical solid dispersions (Sollohub and Cal, 2010). The selection of atomization nozzle type is important to consider in view of the subsequent scale up of the process to yield the matching droplet size distribution and evaporation profiles. Most of times, particle size distribution of the product is the main response to select the atomization parameters and nozzle types. Pressure nozzles are getting recent concern for the generation of larger droplets and thereby the larger SDD particles of granular size that can be processed directly (without granulation step) for the manufacturing of tablets (Beyerinck et al., 2010; Dobry et al., 2009). In such cases, the special dryer configuration to generate “organized plug flow” of the drying gas for the efficient drying of larger droplets has been suggested (Beyerinck et al., 2005a,b,c). However, the use of this type of nozzle has been debated for viscous feeds, especially the non-Newtonian fluids (Cal and Sollohub, 2010). Incorporation of pressure nozzle, a diffuser plate and a drying chamber extension by improving flow of drying gas and increasing drying time were also claimed to enhance homogeneity of amorphous solid dispersions (Beyerinck et al., 2005a,b,c). Atomization is often considered as one of the most important issues in up-scaling the spray drying process. Thybo et al. (2008a,b) prepared amorphous SDD of acetaminophen with PVP at pilot scale and production scale using bifluid nozzle with liquid orifice-atomization gas cap diameter of 1 mm–2 mm and 4 mm–10 mm, respectively. Despite of different droplet-drying gas mixing efficiency and droplet residence time distribution at two scales, no differences were observed on the homogeneity of the dispersion. The flow of compressed air that is supplied through the nozzle simultaneously with the feed governs the droplet size (distribution).

In recent years, increasing interest has been witnessed towards the use of four-fluid nozzle for the preparation of SDD. This is intended for feeding separately prepared drug solutions in organic solvents and carrier solutions in water charged into a same

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atomization nozzle and thus overcoming the problem related to the common solvent requirement for the components with diverse solubility behavior. The nano-sizing of partially soluble bioactive based on spray drying using dual nozzles spray drying technique and ionic solution capable of forming precipitate upon contact has been patented wherein both anionic and cationic solutions are supplied through different channels of nozzle and form water soluble salt when they are in contact at the tip of the nozzle (Chow and Sun, 2010). SDD of tolbutamide-HPMC prepared by separately feeding drug and polymer solution through a four-fluid nozzle was found to be completely amorphous compared to the partially crystalline dispersion by spray drying the equivalent feed composition (Chen et al., 2004). The ternary SDD of acetaminophen-chitosan-HPMCP for controlled release application was successfully prepared by simultaneously passing feed solutions prepared at different pH through a separate channel into the nozzle (Chen et al., 2006). The lactose and mannitol based spray dried microparticles of ethenzamide and flurbiprofen prepared by four fluid nozzle showed significant enhancement of *in vitro* dissolution and *in vivo* performance (Mizoe et al., 2007). The spray dried amorphous SDD of salbutamol sulfate-eudragit (RL and RS) intended for sustained release prepared by separately passing drug and polymer solutions through four-fluid nozzle showed better performance compared to that prepared from a single solution (Chen et al., 2008). The improvement in aerosol performance and pulmonary retention was observed for spray dried rifampicin-PLGA-mannitol nanoparticles prepared using a four-fluid nozzle compared to rifampicin-PLGA microparticles (Mizoe et al., 2008; Ohashi et al., 2009). The operation of a four-fluid nozzle at pilot scale to produce spray dried microparticles of artemisinin-maltodextrin has been reported (Sahoo et al., 2009). The SDD of artemisinin with PVP and PEG has also been prepared using four-fluid nozzle (Sahoo et al., 2010, 2011).

6. Emerging techniques

6.1. Electrospray drying

The pursuit of spray drying with versatile processability of thermolabile and viscous feed solution for amorphous dispersion generation procreate electrospray drying in which solvent evaporation from the atomized droplets takes place using an electric field at ambient temperature and pressure. Originally designed to spray dry protein formulation, growing interest is observed also for preparing amorphous dispersions and nanoparticles of poorly water soluble drugs. The interested readers are referred to go through the recent articles by Peltonen et al. (2010) and Heng et al. (2011) for more details on the working principle and application of this technique. The fourth generation spray dryer of Buchi®, nano-spray dryer B-90, is a commercialized electrospray dryer. In brief, the feed solutions are passed through piezoelectrically vibrating fine mesh to generate fine aerosol accompanied by laminar flow of drying air resulting into particles of nanometer range that are collected at the grounded electrode (Lee et al., 2011). In another type of electrospraying process, a feed solution is passed at slower rate through a metal capillary supplied with a strong electric field which is exposed to the droplets generated at the capillary tip. A Taylor cone is formed due to the continuous Columbic combustion of the charged droplets. The homogenous ternary nanoparticles of naproxen-PVP-triasterin prepared by electrospray drying showed improved release of the drug due to self-assembly during dissolution (Yu et al., 2011a). Yu et al. (2011b), also showed the facile formation of amorphous ketoprofen-PVP Nanoparticulate solid dispersions by electrospray drying that were shown to exhibit markedly improved dissolution rate. The particle size of nanoparticles is shown to gradually decrease with the increase in drug content. Zhang et al. (2011a,b,c) prepared core-shell structures of griseofulvin-Eudragit L 100 by electrospray drying. The polymer solution in ethanol and the drug solution in chloroform were separately syringed to the coaxial nozzle (inside or outside) which is supplied with 25 kV electric potential. The solution passed through the inner channel formed the core of the particle while that passed through the outer channel formed the shell. The completely amorphous electrospray dried nanoparticles with drug at core significantly improved the *in vitro* drug release as well as *in vivo* plasma concentration profile in rats whereas the nanoparticles containing the polymeric core and nanocrystalline drug coverage at surface showed a performance compared to that of the physical mixture. Feed solution conductivity and viscosity are considered as the most important parameters for electrospray drying (Zhang et al., 2011a,b,c). The electrospray dried PLGA nanoparticles loaded with amorphous celecoxib showed burst release followed by the sustained release profile which was overall higher than that of the crystalline drug (Bohr et al., 2011, 2012). Further, the same group investigated the influence of process parameters such as flow rate, solute concentration and drug loading, on the physicochemical properties of and the drug-release profile from the electrospray dried celecoxib loaded PLGA amorphous microspheres (Bohr et al., 2012). It was found that the internal porosity of the particles increased with increasing solvent concentration. The alteration in release profile was directly related to the influence of the process parameters on the size and porosity of microsphere particles.

6.2. Pulse-combustion drying

The recent applications of pulse-combustion drying have appreciated its use as an instant and efficient solvent evaporation method for the preparation of amorphous solid dispersions of poorly water soluble drugs (Bikiaris, 2011). Originally utilized for processing large volume chemicals, the use of this technique has also been reported to agrochemicals, fine-chemicals and pharmaceutical products including antibiotics, vitamins and excipients (Ozer et al., 1993). The detailed description on the functioning and instrumentation is available in literature (Kudra, 2008). Continuous ultrasonic shock waves mediated by the explosion of air-fuel (generally alkanes like propane) mixing followed by ignition on the pulse engine of the dryer, aid the drying of droplets generated by the atomizer. The instantaneous exposure of feed droplets to very high temperatures (200–300 °C) and tremendous turbulence generated are claimed to provide better heat and mass transfer, drying efficiency and lower cost of operation as compared to conventional spray dryers. Therefore, a complete evaporation of solvent takes place without harm to the material. The ternary solid dispersion of nitredipine-Aerosil-tween 80 prepared by drying aqueous suspension at 60 °C using Hypulcon pulse combustion dryer showed the formation of physically stable amorphous and smaller spherical particle with narrow size distribution compared to the equivalent dispersion prepared by conventional spray drying with comparable dissolution profile (Wang et al., 2007). Furthermore, amorphous solid dispersions of ibuprofen with different PVP grades (K 25, K 30 and cross linked) and PVP/VA 64 by drying an aqueous suspension in Hypolcon pulse combustion dryer showed particles of half the diameter of that prepared by spray drying (Xu et al., 2007). Also, the drug dissolution rate from dispersions prepared by pulse combustion drying was improved markedly compared to that prepared by spray drying. Similar superior performance of amorphous dispersions of ibuprofen-Kollicoat IR prepared by pulse combustion drying compared to the respective dispersion prepared by spray drying is reported by the same group (Xu et al., 2009). These results, indeed forecast the future viability and growth of pulse combustion drying as a green and cost effective process of amorphous

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Table 5
Relevant physicochemical properties of API, carrier and solvent in selecting carrier and solvent for spray drying.

Drug	Carrier	Solvent
Fragility (T_m/T_g), fusion enthalpy	Molecular weight, T_g	B.P., partial vapor pressure
Thermal/solution stability	Hydrophilicity, viscosity	Polarity, dielectric constant
Solubility in organic solvents	Solubility in organic solvents	Polarizability
pH-solubility/stability profile	pH-solubility/ionizability	Viscosity, surface tension, density
Log *P*, p*Ka*	Hygroscopicity at various RH	Evaporation enthalpy
H-bond donor/acceptor	H-bond donor/acceptor	H-bond donor/acceptor
Solubility parameter	Solubility parameter	Solubility parameter
Computed solid solubility in range of polymers	Achievable aqueous supersaturation of drug	Co-solvency, azeotropic composition with cosolvents

solid dispersion preparation from aqueous system. Nonetheless, further exploration and understanding of critical process variables are warranted for the successful application.

7. Miniaturized formulation screening for the development of amorphous SDD

As discussed in preceding sections, the product quality of amorphous spray dried solid dispersions ranging from solvent content, compositional homogeneity and physical stability to various physical characteristics such as morphology, particle density, flow properties, compressibility, *etc.* hugely rely on formulation and process variables. In this section, roadmap strategies for the initial carrier, adjuvant and solvent selection at the minimal scale are discussed.

Based on the physicochemical information of API (Table 5), a suitable carrier and solvent can be preliminarily selected for initial screening studies (Shah et al., 2012). The ternary Bagley plots (the plot of H-bonding *versus* total solubility parameter) drawn using solubility parameters of drug, carrier and solvent can provide the ternary solution miscibility and interaction potential in the feed solution (Albers et al., 2011).

The flowchart presented in Fig. 5 provides a roadmap for the formulation screening and feed solution characterization for the development of amorphous SDD. Several miniaturized techniques (low to high throughput) for the screening of polymers for amorphous drug stabilization (SPADS) are reported in literature (Shah et al., 2012; Vandecruys et al., 2007). Most of published carrier selection techniques rely on the phase solubility or supersaturation studies (Janssens et al., 2008a,b,c,d) and more recently amorphous film formation of drug and polymers at several ratios by casting solutions prepared in a common solvent and micro-dissolution test performed on them, sometimes with 96-well plate format (Mansky et al., 2007; Shah et al., 2012). The phase behavior and quasi-equilibrium solid solubility limit obtained from film characterization in hyphenation with FH based computations provide a rough estimate on the degree of solid state supersaturation, an important predictor of physical stability, that would be achieved in the subsequent spray dried formulation (Janssens et al., 2010; Nair et al., 2001; Weuts et al., 2011). Therefore the composition from below solid solubility exhibiting homogenous film formation can be declared safer for amorphous SDD development. However, as discussed in the solvent section, the solvent dependence of such phase behavior should be duly considered to avoid over/under estimation (Ansari and Sunderland, 2008). Consequently, a comprehensive solution-state characterization of feed solution would be helpful to decide the fate of miscibility in the resulting SDDs therefrom (Fig. 5). Additionally, the evaluation of films prepared at different solution concentration can provide information on the impact of solution equilibrium between monomer/multimer of drug and folded/extended polymeric chains. Also, attention should be given for the film characterization as analytical results of small portion of heterogeneous films may not represent the intact phase structure (unpublished data). After the selection of a suitable carrier, solvent and binary feed composition/concentration, screening tests to study the effect of other additives such as surfactant and/or drying agents on the feed solution interactions and thereby resulting solid state of dispersions should be carried out (Shanbhag et al., 2008; Yoo et al., 2009).

8. Spray drying process-indicating preliminary experiments

The spray drying process development during preclinical stage is always confronted by the inequity between the limited amount of API available and risk of insufficient yield of the spray dried product for subsequent characterization and performance testing. Furthermore, selection of spray drying conditions and process parameters on a trial and error basis during the starting phase can potentially result in phase behavior and particulate/bulk level properties of SDD that are seldom reproduced in larger scale. Although, the applications of computational fluid dynamics (CFD) in the process development for the desired product structure for various scale of food and dairy spray drying operations have been repeatedly published, the success of the same in pharmaceutical spray drying, especially for SDD products, has yet to be achieved (Dobry, 2011; Patel and Chen, 2005; Wang and Langrish, 2009). Here, we discuss various possible offline and online experiments that can partially provide guidance for selection of spray drying process parameter subsequent to feed selection and characterization, with special focus on the physical structure of the solid dispersion. The assessment flowchart displaying various steps is illustrated in Fig. 5.

8.1. Solvent evaporation

The preparation and characterization of films by rapid solvent evaporation at variable temperature can give the upper and lower inlet temperature constrains for spray drying a particular feed solution system. In a study of Wu et al. (2011) the piroxicam solutions with PVP (K 25, 64, 90) at different weight ratio in acetone-methanol cosolvent system were used to prepare films by solvent evaporation at various controlled temperatures (30–70 °C). The solvent evaporation rate was thermogravimetrically measured at different temperatures. The authors proposed that the channel formation at the surface due to folding of PVP mediated by the inhomogeneous viscosity distribution at lower temperature led to higher crystallization of drug compared to less or no crystallization at higher temperature. However, one should carefully interpret the evaporation rate from the mixture of solvents with different volatility as discontinuous change in the rate is expected with the time progression (Paudel and Van den Mooter, 2012). The possible use of azeotropic composition is suggested to in case of cosolvent spray drying (Miller and Gil, 2012). Moreover, this miniaturized evaporation studies can be extended using different drying gases with varying flow rates to have more comprehensive information. Provided the initial evaporation rate and diffusion coefficient of solution components (mainly depends upon polymeric solvation

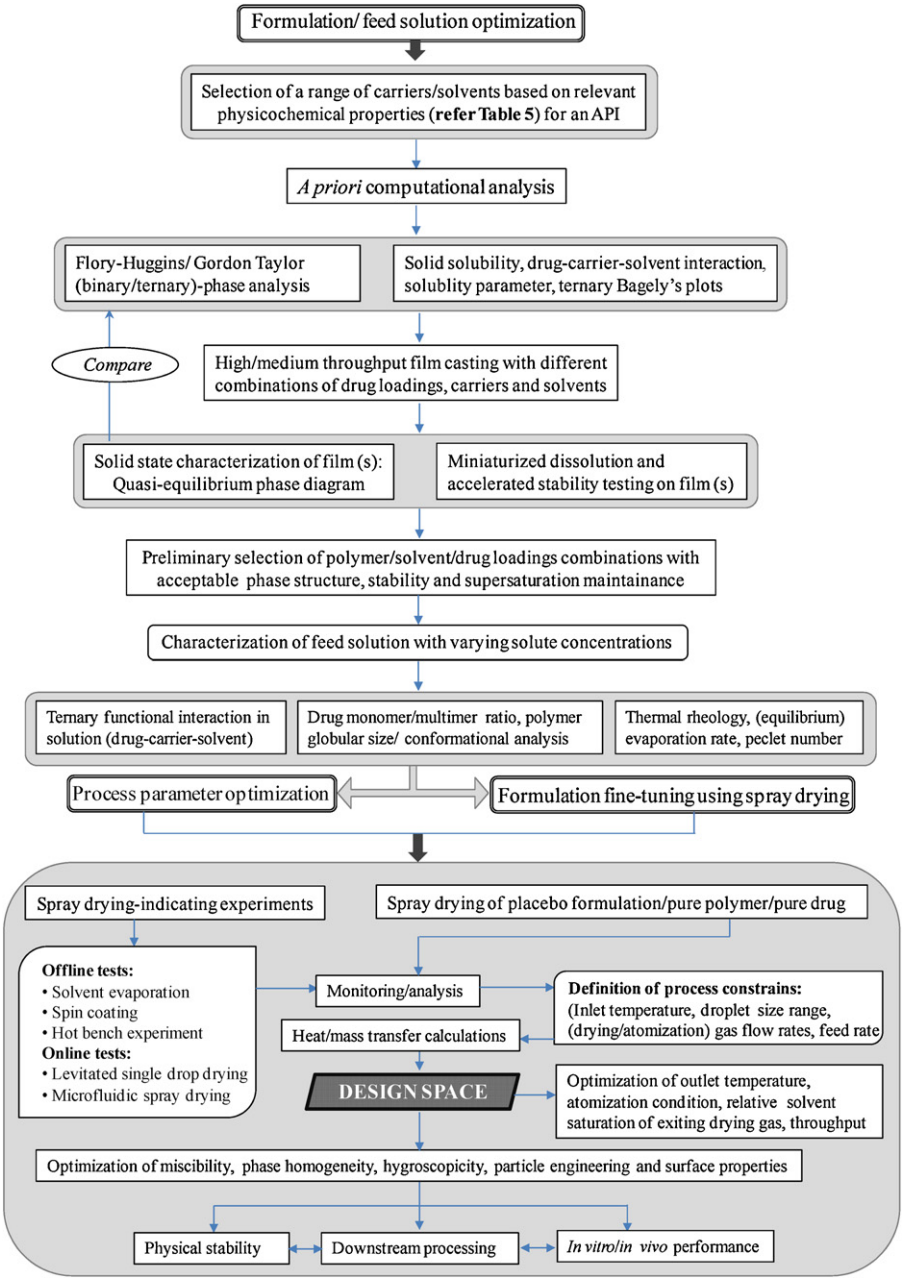

Fig. 5. A generic roadmap for the development of a spray dried dispersion of a poorly water soluble API.

and globular size), the *Pe* number for a system can be estimated which in fact provides the idea on ratio of the droplet shrinking rate (solvent evaporation rate) to the diffusion rate of solute flux towards the center (Rizi et al., 2011).

8.2. Spin coating

Spin coating using a small quantity of API with intended spray drying solvent at temperature relevant to spray drying has been proposed to be predictive for the miscibility, solid state supersaturation and stability of SDD (Konno and Taylor, 2006). Lee and Lee (2003) utilized rapid solvent evaporation method based on the solution spin coating of different poorly water soluble drug–polymer–solvent combinations on silicon wafer chip for the screening of suitable carriers and right (amorphous) composition. The patent assigned to Lee (2003) on spin coating of a wide diversity of drugs, polymers and solvents combinations at different composition/concentration and temperature range between subambient to solvent boiling point, proposes this methodology to identify the processing condition for preparation of solid dispersions by solvent methods. The data obtained from varying spinning speed and time along with processing temperature can certainly provide the tentative information on the effect of rigorous turbulence on phase structure during spray drying.

8.3. Hot bench experiment

Dobry et al. (2009) has recommended the use of hot bench experiments as an offline method for determining the range of outlet temperatures for spray drying, which in fact can be used to optimize the inlet temperature. This is a simple method wherein SDD powders obtained from preliminary run or films from formulation screening are spread onto a metallic plate heated up to the temperatures targeted to the spray drying process and any changes

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occurring are observed/analyzed for the time scale of the spray drying operation. The results can provide alerts on the possible risk of in-process agglomeration, degradation, melting, sticking or phase transition (separation and or/crystallization) of amorphous SDD particles during passage from drying chamber outlet or residing inside the cyclone at the elevated temperature. Additionally, selecting outlet temperature based on this offline experiment can improve the yield of SDD due to the less wall deposit. The authors have also cited the model of Oakley (2004) to use a cooling assembly surrounding the drying chamber outlet to reduce the hot spots.

8.4. Levitated single-droplet drying

Originally rooted from protein crystallization techniques, acoustically levitated single droplet drying is a containerless drying wherein a single droplet, freely suspended in space at the nodal point of harmonic wave generated by two acoustic transducers mounted vertically, is dried with the aid of heated drying gas (Leiterer et al., 2008). The use of this technique is increasing in pharmaceutical application especially for optimizing manufacturing conditions for amorphous forms by spray drying or congealing (Benmore and Weber, 2011; Weber et al., 2012). Wulsten et al. (2009) were the first to apply levitated-droplet drying to monitor drying of a single droplet of itraconazole and PVPVA 64 or HPMC solutions prepared in DCM: ethanol mixture of different compositions. The progression of surface temperature and reduction of vertical and horizontal diameter of the droplet was monitored, followed by the microscopic analysis of resultant particles. The solvent composition and polymer dependence of particle evolution and drying kinetics obtained in this experiment has already been discussed in the previous sections. Furthermore, various phases temporally progressing *in situ* with the solvent evaporation from the droplet can be monitored by online techniques mounted with the levitator such as FT-Raman spectroscopy, synchrotron X-ray diffractometry and image velocimetry (Radnik et al., 2011). This technique certainly has potential to dictate more real time situation of solvent evaporation kinetics and structural evolution during spray drying, although the actual conditions in the spray dryer such as droplet velocity as well as heat, mass, momentum transfer is hard to mimic (Dobry et al., 2009). Recently, GEA Niro has promoted a platform technology with the name DRYING KINETICS ANALYZER™ for product oriented spray drying method development that is based on acoustically levitated single droplet drying (http://www.niro.com/niro/cmsdoc.nsf/webdoc/ndkw7a4jmy (accessed on 2012.04.27)). The online measurement of size (distribution), density and velocity of droplets formed during spray drying at various scale can be performed by flux-sensitive phase doppler velocimetry or high speed CCD camera (Dobry et al., 2009).

8.5. Microfluidic spray dryer

A recent article from Thiele et al. (2011) has shown the potential of a disposable microfluidic spray dryer fabricated by lithographing on plasma-bonded poly (dimethylsiloxane) chip for the preparation of amorphous SDD of danazole with PVP or drug nanocrystals (>100 nm) using a limited amount of API. The drying air flow rate and other process parameters for spray drying were set with the aid of CFD calculations to prevent wall deformation of the set up. Using a three-fluid inlet, the drug solution in isopropanol and aqueous PVP solution were pumped through a separate channel into the stream of pressurized drying air passing through the third inlet at room temperature. Danazole turned completely amorphous in a solid dispersion prepared with high PVP content while high drug content resulted into the nanocrystalline dispersion of drug in PVP. The particle diameter increased with the increase of drying air pressure or the distance between spray cone and collector. The authors believe that with the simpler inexpensive chip design process and flexibility in geometry, very little amount of API can be used for the miniaturized SDD formulation process that can be directly collected in vials or sample holders for subsequent characterizations avoiding waste.

9. *In vitro* performance on SDD

The huge research flow towards the exploration of amorphous solid dispersions as a universal strategy for the enhancement of aqueous solubility, dissolution rate and oral bioavailability of poorly water soluble drugs has necessitated the deconvolution of multiple events simultaneously undergoing during the drug release process. Recently, the attention towards the investigation of dissolution behavior of amorphous formulation in terms of drug release, recrystallization, and polymer mobilization has been initiated (Alonzo et al., 2011). Depending upon the carrier used, drug release from amorphous dispersions has been proposed as drug controlled or carrier controlled (Craig, 2002). The readers are referred to a comprehensive review on the various aspects of *in vitro* and *in vivo* performance testing of amorphous solid dispersion recently published by Newman et al. (2012). Most of dissolution tests of SDD rely on the USP II compendial method with some of reports on scaled-down version for the limited amount of API and formulation supply during preclinical development. Several miniaturized supersaturated dissolution testing ranging from micro-centrifugation to semi-permeable membrane or biphasic octanol–water partitioning methods have been used for amorphous SDD powders prepared at small quantity (Miller and Gil, 2012).

The potential phase transitions during dissolution from amorphous solid dispersion are solid state phase transition and solution mediated phase transformation predominantly recrystallization into native crystal form or polymorph/hydrate of different size (Alonzo et al., 2011). For amorphous SDD this can be the consequence of multi-factorial interplay of initial compositional homogeneity, particle size, agglomeration, supersaturation, wetting and also the strength of drug–polymer interaction and the effect of dissolution media on it (Karavas et al., 2007). Generally, increased wettability/particle surface hydrophilization by polymeric dispersant in amorphous SDD is translated as one of the reasons for the dissolution enhancement of the drug. However, few articles provide the surface composition and/or wettability data supporting their hypotheses (Dahlberg et al., 2010a,b; Puri et al., 2010). This could be due to the inherent difficulty in measuring interfacial tension and complexity of surface characterization of the SDD particles (Lindfors et al., 2008). The variation in compression force applied for making compact can alter the contact angle by several degrees. The discussions presented in the previous sections on the dependence of evaporation rate and the physicochemical properties of drug and carrier on wetting and surface enrichment of SDD highlight the need of further exploration on the relation of these attributes with the various feed solution chemistry and processing parameters employed for spray drying (Dahlberg, 2010). The improvement of dissolution rate from SDD powder may not be always sustained in the final dosage form. Puri et al. (2011) have shown that the alteration of PVP functionality due to the stabilizing solid state intermolecular interaction with celecoxib in celecoxib-meglumine-PVP ternary amorphous SDD causes atypical increase in cohesivity *via* water mediated H-bonding resulting into solid mass agglomeration during dissolution from amorphous SDD filled in hard gelatin capsules. Leaching of meglumine into the dissolution medium leads to hydrophobization of PVP that promotes the formation of a non-dispersing plug during dissolution. This problem could be solved by formulating barrier coated

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particles of an amorphous solid dispersion layered onto microcrystalline cellulose (MCC) using hydrophobic polymers (Puri et al., 2012). There are still several open questions about the release behavior of the amorphous SDD in the *in vitro* medium that can be rooted from the differential molecular chaos introduced in the system by processing parameters and rate of solvent evaporation during processing.

10. Downstream processing and stability considerations of SDD formulations

Regardless of method of preparations employed, certain level of physicochemical vulnerability and several post processing related hurdles are guaranteed for amorphous solid dispersions. Considering oral administration as a primary delivery route for drugs processed as amorphous SDD, several molecular to particulate/bulk level properties from tablet or capsule manufacturability viewpoint is desired for SDD powders. The physical stability of amorphous SDD generally prepared using hydrophilic and often hygroscopic polymers are highly moisture sensitive (Rumondor and Taylor, 2009). The hygroscopic behavior of amorphous SDD poses problems in terms of initial collection and handleability to poor rheological properties of powder. Designated as special formulations, amorphous SDDs deserve appropriate physical chemical stability testing protocols followed by proper packaging and storage conditions. Surprisingly, harsher conditions equivalent to ICH acceralated and long term stability testing protocols for normal drug products have been found widely employed for developmental stability assessment of amorphous SDD formulations (Bothiraja et al., 2009a,b; Dontireddy and Crean, 2011). Cui et al. (2006) performed the physical stability assessment following ICH protocol *viz.*, 25 °C/60%RH and 40 °C/75%RH (both open and closed containers) on the pure amorphous form and ternary amorphous solid dispersion of an investigational compound, VX-950, with PVP and SLS prepared by spray drying and solvent evaporation. All dispersions remained amorphous up to two months except pure drug and SDD wherein recrystallization was attested from one month. Physical stability failure should not alone be considered as the rejection criterion for amorphous SDD prepared with particular carrier system, provided the superior *in vitro*/*in vivo* performance of the same (Miller and Gil, 2012). Further attempts by the formulation process optimization and/or process modification can lead to improved stability. It is of common knowledge that molecular mobility and thus the recrystallization kinetics in an amorphous system are several orders of magnitude larger at the surface as compared to that in bulk of the particle (Wu et al., 2007; Zhu et al., 2008). Indeed, ratio of surface to bulk relaxation reliably depends upon the SDD particle size as it varies the surface to volume ratio of a particulate (Lubach et al., 2007). Ke et al. (2012) has recently shown a striking process dependent molecular mobility for indomethacin-PVP amorphous solid dispersions despite all of them showing same glass transition profile. The molecular mobility and hence the physical stability was in the order of melt quenched > spray dried > ball milled amorphous dispersions. In contrast, the surface relaxation time was in the order of spray dried >melt quenched > ball milled dispersions indicating their differential surface energies. Similar types of differences in surface behavior can be expected with the diverse surface chemistry/enrichment of amorphous SDDs that can be obtained from various combinations of formulation and/or processing parameters (Dahlberg, 2010). Surface protections (against recrystallization) of amorphous systems have been an effective amorphous stabilization strategy (Wu et al., 2007). In special case of amorphous SDD, the product development strategy based on the water insoluble polymeric barrier coating of amorphous SDD of celecoxib-PVP-meglumine layered on MCC applied by Puri et al., 2012 showed marked reduction against the deleterious effect of moisture on physical stability (recrystallization rate).

The dosage form development aspect of amorphous SDD is an uncharted field that warrants further research. The compression step during tableting of amorphous SDD can be liable for the physical stability of drug in the resulting product. Compression induced drug–polymer demixing has recently been shown by Ayenew et al. (2012) for metastable compositions of spray dried amorphous SDD of naproxen/PVP. The impact of deformation on the relaxation behavior of amorphous solids could be markedly different depending upon their method of preparation. Deformation of aged polymethyl methacrylate has been reported to generate a state as freshly melt cooled sample, bearing high molecular mobility and energy state (Lee and Ediger, 2010; Lee et al., 2009). However, the relaxation of freeze dried sugars was facilitated by compression due to their relative higher bulk volume (Imamura et al., 2011). Likewise, compression of amorphous SDD can potentially result in similar relaxation behavior as observed for freeze dried product due to shortening of relaxation segments after deformation.

The impact of filler materials and product manufacturing steps to the phase structure and subsequently the physical stability of the final dosage form is yet another unexplored area. Dhumal et al. (2007) have shown that the superior physical stability against drug recrystallization from tablets prepared from amorphous SDD of celecoxib with PVP and carrageenan as compared to binary SDD with PVP only and corresponding binary or ternary physical mixtures could be attributed to the synergistic effects of cushioning action provided by the viscoelastic carrageenan and H-bonding interaction between celecoxib and PVP. Shimpi et al. (2007) mention the advantage of tablettability at low pressure and elastic recovery behavior of Gelucire on inhibition of polymorphic transformation of during compression of ternary amorphous SDD of etoricoxib-PVP-Gelucire. Very recently, Leane et al. (2012) published a study that focuses on the impact of the unit operations (granulation/compression/coating) and excipients used during the process on the physical stability of tablets/capsules prepared from ternary amorphous SDD of ibipinabant-PVP-SLS. Striking effects of filler/coating materials type on the physical stability of amorphous drug in dosage form and therefore on *in vitro* release profile were observed when stored at 40 °C/75%RH (closed) conditions for 3 months. The crystallinity after the latter storage condition and time in the tablets containing different diluents was in the order of mannitol > lactose+ MCC > lactose > MCC. Tablet depth profiling analysis revealed the PVP enrichment at the surface upon compression which would increase overall hygroscopicity upon exposure to the humidity. Other than differential extent of moisture-induced immiscibility in presence of different fillers, the authors believe that the mechanical protection against fracture or surface perturbations of amorphous SDD during compression by plastically deforming MCC could be the reason for the stabilization as compared to other excipients like mannitol or lactose having poor compressibility. Further, the physical stability of the MCC containing dosage forms of amorphous SDD *viz.*, tablets prepared by compressing roller compacted granules or powder blends without granulation or capsule filled with powder blends was compared. Indeed, highest crystallinity was observed for tablets prepared from stress intensive route *i.e.* roller compaction followed by simpler manufacturing routes. Also, barrier coated tablets surprisingly exhibited higher crystallinity, more pronounced in those prepared by roller compacted granules, as compared to uncoated tablets which the authors believe is due to the seeding by nuclei generated during the coating process itself. Novel alternative coating processes using organic coating at lower temperature that can overcome the possible exposure to stress condition (moisture/heat) is desired for preventing process induced transformation from amorphous SDD (Mizuno et al., 2005). On top of these physical stability

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aspects, chemical drug-excipient incompatibility between amorphous drug in SDD and adjuvant(s) added for product development should be reviewed. This is because the drug-excipient compatibility data generated during preformulation studies are mostly based upon the crystalline drug which could underestimate the behavior of higher energy amorphous state of drug in SDD.

11. Future perspectives

Spray drying is a time-tested manufacturing process for amorphous solid dispersion of poorly water soluble drugs. The understanding on the influence of complex interplay of various formulation and process variables on the molecular to particulate/bulk level properties of spray dried dispersions is the current need in this field. The improvement of existing CFD models to imply in the drying of feed solution containing poorly water soluble API, polymer and additives can further support the robust process development and subsequent scale up with the desired product properties. The transformation of the knowledge on solution chemistry and droplet drying kinetics from polymer chemistry, chemical engineering and allied disciplines will prove helpful in understanding the structural evolution of phase structures in SDD. Further, the exploration on the emerging applications of surrogate drying techniques such as electrospray drying and pulse combustion drying in manufacturing spray dried dispersions could be viable alternatives to spray drying. Additionally, production processes of amorphous SDD requiring less/no further downstream steps for product development would add an additional dimension in this research.

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