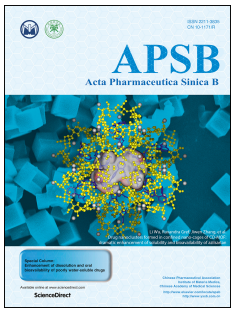
Journal Pre-proof



Pharmaceutical amorphous solid dispersion: A review of manufacturing strategies

Sonal V. Bhujbal, Biplob Mitra, Uday Jain, Yuchuan Gong, Anjali Agrawal, Shyam Karki, Lynne Taylor, Sumit Kumar, Qi Zhou

PII: S2211-3835(21)00180-5

DOI: https://doi.org/10.1016/j.apsb.2021.05.014

Reference: APSB 1102

To appear in: *Acta Pharmaceutica Sinica B*

Received Date: 5 February 2021

Revised Date: 2 April 2021

Accepted Date: 13 May 2021

Please cite this article as: Bhujbal SV, Mitra B, Jain U, Gong Y, Agrawal A, Karki S, Taylor L, Kumar S, Zhou Q, Pharmaceutical amorphous solid dispersion: A review of manufacturing strategies, *Acta Pharmaceutica Sinica B*, https://doi.org/10.1016/j.apsb.2021.05.014.

REVIEW

Pharmaceutical amorphous solid dispersion: A review of manufacturing strategies

Bhujbal Sonal V.[a], Mitra Biplob[b], Jain Uday[c], Gong Yuchuan[b], Agrawal Anjali[b], Karki Shyam[b], Taylor Lynne[a], Kumar Sumit[b,*], Zhou Qi (Tony)[a,*]

[a]*Department of Industrial and Physical Pharmacy, College of Pharmacy, Purdue University, West Lafayette, IN 47907, USA*

[b]*Oral Product Development, Bristol Myers Squibb, Summit, NJ 07901, USA*

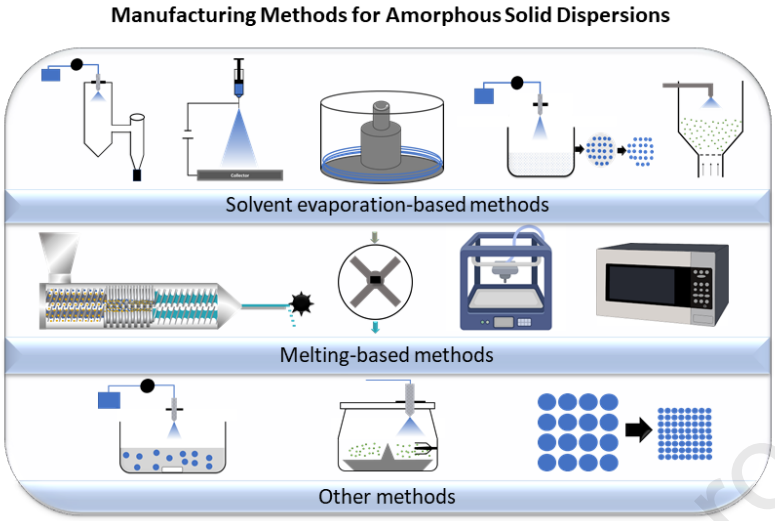
[c]*Material Science and Engineering, Bristol Myers Squibb, Summit, NJ 07901, USA*

Received 7 February 2021; received in revised form 5 April 2021; accepted 13 April 2021

*Corresponding authors. Tel.: +1 765 4960707 (Zhou Qi (Tony); +1 217 4167234 (Kumar Sumit).

E-mail addresses: tonyzhou@purdue.edu (Zhou Qi (Tony), sumit.kumar@bms.com (Kumar Sumit).

Running title: Manufacturing strategies for pharmaceutical amorphous solid dispersion



The review provides an updated overview of amorphous solid dispersion (ASD) manufacturing techniques. The impact of manufacturing variables of each method and downstream processing on the critical physical stability of ASDs are discussed.

Abbreviations: ASES, aerosol solvent extraction system; ASDs, amorphous solid dispersions; CAP, cellulose acetate phthalate; CO_2, carbon dioxide; $scCO_2$, supercritical CO_2; CSG, continuous-spray granulation; EPAS, evaporative aqueous solution precipitation; Eudragit®, polymethacrylates derivatives; FDM, fused deposition modeling; GAS, gas antisolvent; T_g, glass transition temperature; HME, hot-melt extrusion; HPC, hydroxypropyl cellulose; HPMC, hydroxypropyl methylcellulose; HPMCAS, hydroxypropyl methylcellulose acetate succinate; HPMCP, hypromellose phthalate; PCA, precipitation with compressed fluid antisolvent; SAS, supercritical antisolvent; PGSS, precipitation from gas-saturated solutions; PLGA, poly(lactic-*co*-glycolic acid; PVP, polyvinylpyrrolidone; PVPVA, polyvinylpyrrolidone/vinyl acetate; RESS, rapid expansion of a supercritical solution; SCFs, supercritical fluids; SEDS, solution-enhanced dispersion by SCF; SLS, selective laser sintering; Soluplus®,polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer; USC, ultrasound compaction; 3DP, three-dimensional printing

Abstract Amorphous solid dispersions (ASDs) are popular for enhancing the solubility and bioavailability of poorly water-soluble drugs. Various approaches have been employed to produce ASDs and novel techniques are emerging. This review provides an updated overview of manufacturing techniques for preparing ASDs. As physical stability is a critical quality attribute for ASD, the impact of formulation, equipment, and process variables, together with the downstream processing on physical stability of ASDs have been discussed. Selection strategies are proposed to identify suitable manufacturing methods, which may aid in the development of ASDs with satisfactory physical stability.

KEY WORDS Amorphous solid dispersions; Stability; Drug delivery; Manufacturing; Solvent evaporation; Melting process; Co-precipitation; Downstream processing; Selection criteria

1. Introduction

1.1 Amorphous solid dispersions (ASDs) for oral drug delivery

Drug solubilization is an essential step for orally administered medications to be absorbed systemically. Unfortunately, a large percentage of marketed drugs (~40%) and those in the R&D pipeline (~90%) are poorly water-soluble[1-3]. Therefore, various formulation strategies have been employed to overcome the solubility and/or dissolution challenges of these drugs[4,5]. Drug solubility and dissolution rate of poorly water-soluble drugs can be successfully improved by

formulating them as ASDs[6-11]. ASD is a solid dispersion in which the active ingredient is dispersed within an excipient matrix in a substantially amorphous form[12]. The amorphous state of the drug in ASDs is critical for increasing their solubility[13,14]. With the drug in an amorphous form, no energy is required to break the drug crystal lattice. For this reason, relative to the crystalline form, the amorphous form of many poorly water-soluble drugs can achieve substantially higher apparent solubility and markedly faster dissolution[15]. ASDs are also known to result in higher membrane flux due to a higher supersaturation[16] and thus, improve bioavailability[17,18]. ASDs also have a higher wettability due to the presence of hydrophilic polymers[7].

Based on formulation composition, solid dispersions are classified as first, second, or third generation[19]. Solid dispersions prepared using crystalline carriers are the first generation. Their drug release rate is generally slower than the other two generations of solid dispersions[20]. ASDs, which consist of an amorphous drug in combination with an amorphous polymer, constitute the second generation[7,21]. ASD formulations could also contain additional excipients, such as additional polymer and/or surfactants to further enhance drug release and stability[22]. Such ASDs are known as the third generation. Due to their solubility and dissolution advantages, ASD formulations have drawn increasing interest over the last decade, in both academia[21,23-29] and industry. Table 1 summarizes the US Food and Drug Administration (FDA)-approved pharmaceutical products based on ASDs[28,30]. There has been an increase in the number of ASDs under development and reaching the market over the last decade[7,22]. Currently, there are numerous methods available for ASD preparation, each of which has its advantages as well as limitations. This review aims to discuss the different manufacturing approaches to preparing ASDs.

Table 1 Examples of FDA-approved products that are based on amorphous solid dispersions.

Trade name	Chemical name	Manufacturing technique	Company	Year of Approval
Cesamet®	Nabilone	Solvent evaporation	Meda Pharmaceuticals	1985
Isoptin® SR	Verapamil	Melt extrusion	Ranbaxy	1987

			Laboratories	
Sporanox®	Itraconazole	Fluid bed bead layering	Janssen	1992
Prograf®	Tacrolimus	Spray drying	Astellas Pharma	1994
NuvaRing®	Etonogestrel/Ethinyl Estradiol	Melt extrusion	Merck	2001
Kaletra®	Lopinavir/Ritonavir	Melt extrusion	AbbVie	2007
Intelence®	Etravirine	Spray drying	Janssen	2008
Modigraf®	Tacrolimus	Spray drying	Astellas Pharma	2009
Zortress®	Everolimus	Spray drying	Novartis	2010
Norvir® Tablet	Ritonavir	Melt extrusion	AbbVie	2010
Onmel®	Itraconazole	Melt extrusion	Merz Pharma	2010
Incivek®	Telaprevir	Spray drying	Vertex	2011
Zelboraf®	Vemurafenib	Solvent/anti-solvent precipitation	Roche	2011
Kalydeco®	Ivacaftor	Spray drying	Vertex	2012
Noxafil®	Posaconazole	Melt extrusion	Merck	2013
Astagraf XL®	Tacrolimus	Wet granulation	Astellas Pharma	2013
Belsomra®	Suvorexant	Melt extrusion	Merck	2014
Harvoni®	Ledipasvir/Sofosbuvir	Spray drying	Gilead Sciences	2014
Viekira XR™	Dasabuvir/Ombitasvir/Paritaprevir/ Ritonavir	Melt extrusion	AbbVie	2014
Epclusa®	Sofosbuvir/Velpatasvir	Spray drying	Gilead Sciences	2016
Orkambi®	Lumacaftor/Ivacaftor	Spray drying	Vertex	2016
Venclexta®	Venetoclax	Melt extrusion	AbbVie	2016
Zepatier®	Elbasvir/Grazoprevir	Spray drying	Merck	2016
Stivarga®	Regorafenib	-	Bayer	2017
Mavyret™	Glecaprevir/Pibrentasvir	Melt extrusion	AbbVie	2017
Lynparza®	Olaparib	Melt extrusion	AstraZeneca	2018

Orilissa®	Elagolix	Wet granulation	AbbVie	2018
Erleada®	Apalutamide	Spray drying	Janssen	2018
Trikafta®	Elexacaftor (Crystalline)/Ivacaftor/Tezacaftor	Spray drying	Vertex	2019
Symdeko®	Tezacaftor/Ivacaftor and Ivacaftor	Spray drying	Vertex	2019
Braftovi®	Encorafenib	Melt extrusion	Pfizer	2020
Oriahnn™	Elagolix/estradiol/norethindrone acetate	Melt extrusion	AbbVie	2020

1.2 Physical stability challenges of ASDs

Below the melting point, the liquid/amorphous form of a drug has higher free energy than the crystalline form, hence there is a thermodynamic drive for crystallization. The solid-state physical instabilities associated with ASDs include amorphous-amorphous phase separation (AAPS) and/or the conversion of the amorphous drug to a crystalline form (crystallization), both of which negate the solubility advantage of ASDs. AAPS is a phenomenon wherein distinct drug-rich and polymer-rich amorphous phases are formed throughout the ASD matrix, which initially consisted of molecularly mixed drug and polymer[31]. These drug-rich phases are more prone to crystallization due to the reduction in the inhibitory effect of the polymer. Therefore, the drug within an ASD system exhibiting AAPS crystallizes faster than a drug within a completely miscible system. Since AAPS and the subsequent decrease in the inhibitory effect of the polymer occur prior to crystallization, increasing the polymer concentration in the ASD does not necessarily lead to improved stability to crystallization. This is contrary to the trend typically observed for ASDs that remain miscible[32]. Janssens et al.[33] demonstrated a varying degree of drug-polymer miscibility in itraconazole/ Eudragit® E100 solid dispersions prepared by film casting and spray drying. The miscibility limit for itraconazole into Eudragit® E100 was 15% when prepared by film casting and 27.5% when prepared by spray drying. This highlighted the influence of processing parameters such as solvent evaporation rate on AAPS[33]. Exposure of ASDs to moisture upon storage can also result in AAPS[32].

Crystallization, in general, can be viewed as consisting of two steps, viz. nucleation and crystal growth. Nucleation is the formation of small nuclei where the term nucleus refers to the minimum amount of a new crystalline phase that is capable of independent existence. Nucleation

is then followed by nuclei crystal growth[34,35]. An ideal manufacturing process should be able to produce homogenous ASDs which can retain their amorphous form for the required duration of time. In the following discussions, 'stability' of an ASD would refer to the solid-state physical stability of the ASD—particularly its tendency not to crystallize unless otherwise specified.

Ideally, the molecularly dispersed polymer in an ASD offers protection against drug crystallization by altering the thermodynamics and kinetics of the system. The ease of drug crystallization from its amorphous state depends on the driving force for crystallization. This force is governed by the free energy difference between the amorphous and crystalline states and the molecular interactions. The presence of functional groups that are either hydrogen bond donors or acceptors results in energetically favorable drug-polymer intermolecular interactions. These interactions, together with a higher entropy result in lower chemical potential of the drug in a miscible drug–polymer ASD system than that of a pure amorphous drug. This lowered drug chemical potential translates to a reduction in the thermodynamic driving force for the drug to convert to its crystalline form[36-38]. However, since the drug in the ASD is often supersaturated, it is also important to reduce the mobility of the drug molecules to delay phase separation and crystallization. A viscous polymer matrix can help provide this kinetic stabilization[39]. Hence, although the glass transition temperature (T_g) of the amorphous drug is usually lower than that of the polymer, an ASD system would typically have a T_g somewhere between the T_g of the drug and the polymer. This increase in T_g increases the kinetic barrier to crystallization[40,41]. This is also the primary reason for the 'T_g –50 °C' rule. According to this rule, the molecular mobility of an amorphous solid becomes negligible 50 °C below its T_g[42]. Therefore, a polymer with high T_g is generally crucial for an ASD. When the drug-polymer system is miscible and contains drug amounts lower than the saturation solubility of the drug in the polymer, the ASD will be thermodynamically stable. Therefore, amorphous formulations benefit from the presence of a

polymeric carrier, which serves as an amorphous form stabilizer. Also, because a majority of polymers used for ASD preparation are hydrophilic, they enhance drug dissolution by increasing formulation wettability[43]. Further, in some drug loading regimens, the dissolution of the drug is controlled by the dissolution of the polymer[44]. The polymer properties for generating successful ASDs have been comprehensively reviewed in the past[45,46] along with a description of approaches and methods for a rational polymer selection[23]. Briefly, besides an acceptable toxicological profile, a polymer capable of generating a homogenous dispersion with a single amorphous drug-polymer phase is preferred. For this, the polymer should provide a certain degree of drug solubility and kinetic stabilization[38]. The typically-used polymers for ASDs are often utilized across different manufacturing platforms and include povidone derivatives such as polyvinylpyrrolidone (PVP) and polyvinylpyrrolidone/vinyl acetate (PVPVA)[47], polymethacrylates derivatives (Eudragit® series)[48-50], hydroxypropyl methylcellulose (HPMC)[51], hydroxypropyl methylcellulose acetate succinate (HPMCAS)[52], and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®)[53]. Their T_g and solubility in organic solvents have been listed in

Table ***2***.

Table 2 Commonly used polymers for ASD preparation.

Polymer	T_g (°C)	Solubility in solvents
Hydroxypropyl methylcellulose	175–185	Water, ethanol:dichloromethane (1:1, 2:1), methyl acetate:methanol (1:1)
Hydroxypropyl methylcellulose acetate succinate	100–110	Caustic water, acetone, methanol, dichloromethane, chloroform
Hydroxypropyl methylcellulose phthalate	133–137	Water, acetone, ethyl acetate, methyl ethyl ketone, ethanol:dichloromethane (1:1) methanol, dichloromethane, tetrahydrofuran

Polyvinylpyrrolidone	175–180	Water, acetone, ethanol, methanol, ethyl acetate, methyl ethyl ketone, dichloromethane, tetrahydrofuran
Polyvinylpyrrolidone/vinyl acetate	70–110	Water, acetone, ethanol, methanol, ethyl acetate, methyl ethyl ketone, dichloromethane, tetrahydrofuran
Polymethacrylates derivatives (Eudragit®-L100, S100)	>150	Water (only L100), acetone, ethanol, methanol, ethanol:dichloromethane (1:1)
Cellulose acetate phthalate	160–170	Acetone, ethyl acetate, methyl ethyl ketone
Soluplus®	72	water, acetone, ethanol, methanol, dichloromethane

Additives such as secondary stabilizers or surfactants are often added to ASDs to augment the product. The inclusion of surfactants can favor nanodroplet formation[54]. The formation of nanodroplets increases apparent drug solubility[55,56]. However, surfactants can cause drug leaching from ASDs and enhance nucleation, promoting drug crystallization during dissolution[49,57,58]. Therefore, the impact on ASD stability is an important selection criterion for surfactant. Since the choice of excipients could have a significant effect on ASD stability as well as other material properties that affect processing, formulation optimization is crucial before downstream processing of ASDs. However, despite the selection of an optimal formulation, exposure of ASDs to thermal, environmental humidity, and mechanical stresses during manufacturing, storage, and dissolution have been known to cause issues of instability[32,59-62]. As the temperature increases, there could be a large increase in molecular mobility in the ASD that can accelerate phase separation and crystallization of the drug[63]. Ambient humidity can introduce moisture into the hygroscopic ASD systems. Moisture reduces the system T_g and causes a plasticizing effect which increases the molecular mobility of ASD and the risk of crystallization. Absorbed water can also potentially disrupt the drug-polymer interactions by competing with hydrophilic polymers for hydrogen bond formation[64]. For certain ASD systems, excess moisture can also reduce the drug-polymer solubility[65,66]. During the formulation process, mechanical stress such as grinding, crushing, or compressing can promote deformation-induced molecular mobility in ASDs[67,68]. In fact, the generation and maintenance of an amorphous drug form remains a primary challenge associated with many ASD systems and is a limiting factor for their wider application[69-73]. Therefore, while reviewing ASD preparation methods, it is important to

also focus on the impact of manufacturing variables on the physical stability of ASDs. Common factors affecting ASD stability are listed in

Table **3**. The impact of parameters of specific manufacturing processes is discussed in their relevant sections.

Table 3 General factors impacting the stability of amorphous solid dispersions.

Factor (Increase)	Stability	Cause	Ref.
Glass transition temperature (T_g)	Increases	Antiplasticization effect by polymers	74
Molecular mobility	Decreases	Molecular mobility is directly responsible for drug recrystallization	75
Configurational entropy	Increases	Low configurational entropy will favor crystallization	76
Configurational enthalpy	Decreases	The greater thermodynamic driving force for crystallization causes an increased rate of nucleation	77
Drug chemical potential	Decreases	Systems with lower drug chemical potential are generally more stable	78
Humidity, mechanical stress, and temperature	Decreases	These factors can significantly increase molecular mobility and may plasticize the material	79
Polymer concentration	Increases	Kinetic stabilization	11
Surfactant concentration	Decreases	Enhance nucleation, accelerate solution-mediated crystallization	57

2. Manufacturing methods for preparing amorphous solid dispersions

ASDs can be manufactured by several methods but the underlying principle for their formation is the same. Firstly, the lattice structure of a crystalline drug is broken and converted into a liquid state by applying heat or dissolving it in a solvent. The system is then rapidly cooled (if using heat) or dried (if using solvent), causing it to fall out of the equilibrium at the T_g. This results in the generation of a solid drug in an amorphous state. To generate an amorphous state, the liquefied drug should be cooled or dried at a sufficiently fast rate. ASD manufacturing methods can be broadly classified into solvent-based methods and melting or fusion methods. Solvent evaporation-based methods include spray drying (SD), electrospraying, and rotary evaporation, wherein the drug and polymer are dissolved in a solvent which is then evaporated to form an ASD[7,80]. These are suitable methods for thermolabile drugs. In melting methods, the physical mixture of the drug and the polymer is melted and solidified rapidly to form the ASD[81]. Although some of the methods to produce ASDs have been well-established, researchers have made consistent efforts over the past decade to further improve and understand them. In addition, novel manufacturing techniques are constantly emerging. Therefore, the purpose of this review is to provide an updated overview of manufacturing techniques for ASDs.

Different manufacturing processes will generate ASD products with different physical and functional properties[53,82]. Therefore, an adequate understanding of manufacturing processes and their impact on product properties is crucial for obtaining a successful ASD product. To aid the development of robust ASDs, we will discuss the impact of formulation, equipment, and process variables together with downstream processing on the critical physical stability of ASDs for each method. In addition, the advantages and limitations of each of the processes have been evaluated. Lastly, in consideration of the several variables mentioned above, selection strategies have been proposed to identify suitable manufacturing methods.

2.1 Solvent evaporation-based methods

The solvent evaporation processes for preparing ASDs essentially involve drug–polymer dissolution in organic solvent systems and their subsequent evaporation. Aqueous solvents can also be used in conjunction with organic systems to enhance polymer solubility, and/or reduce the extent of organic solvent usage. Amorphous drug–polymer dispersion is generated by rapidly evaporating the solvent from the drug–polymer solution. Because organic solvent evaporation is

usually performed at temperatures well below the drug melting point, solvent evaporation is particularly suitable for thermolabile formulation systems[83].

An important consideration when developing an ASD using a solvent evaporation process is the choice of a solvent system. The most challenging aspect of this method is obtaining a solvent system that can solubilize the drug–polymer system and be compatible with the formulation[84], and has a low residue in the product. Poor or partial solubility of the constituents may lead to longer processing times and non-homogenous ASDs. In order to obtain the desired solvent parameters, often a combination of solvents is used. In such cases, azeotrope forming solvents such as water with ethanol (95.5%, *w*/*w*) or isopropanol (87.7%, *w*/*w*) are preferred. This is because binary solvents with different evaporation rates can cause a variable degree of supersaturation that can result in rapid precipitation of selective components at some point in the evaporation process. Such an event generates a strong potential for phase separation[85]. Similarly, significant differences in the solubility of components can result in a faster rate of drying and selective precipitation of the component with lower solubility on the droplet surface[86,87]. This in turn could further affect ASD stability. The solvent should not affect the physical or chemical stability of the formulation constituents during the manufacturing process before being evaporated from the system. The amount of residual solvent(s) in the final ASD products must be within the acceptable values of the International Council for Harmonization Q3C(R6) guideline[88,89]. This guideline defines three different classes of solvents: Classes I, II, and III. Of these, the Class I solvents are to be avoided and Class III are the most preferable. However, Class II solvents can also be used to a limited extent if Class III solvents fail to provide adequate manufacturing conditions. Adequate removal of the residual solvent from the final product is particularly crucial when toxic organic solvents have been employed[90,91]. Therefore, ASD preparation by solvent evaporation-based method is usually followed by secondary drying[92-95]. Other important considerations for a solvent-evaporation based method are operator exposure to harmful organic solvents and the environmental impact of solvent waste.

Additional important solvent properties include drying efficiency, combustibility, viscosity, and toxicity[96]. The drying efficiency is governed by the extent of heat and mass transfer which in turn depends on heat supply and solvent vapor removal. Thus, in order to obtain adequate drying efficiency, solvent parameters affecting its evaporation rate such as vapor pressure, boiling point, specific heat, the heat of vaporization, and viscosity need to be assessed[84]. A high feed solution

viscosity can also cause sticking of the solution to the processing equipment, which can result in low product yields[97]. Typical solvents used for solvent evaporation methods are water[98], alcohols (methanol, ethanol or isopropanol)[98,99] or other organic solvents such as dichloromethane[100], acetone[101], ethyl acetate[99], and methyl ethyl ketone[99] (Table 4).

There are several methods based on the principle of solvent evaporation like spray drying, electrospraying, fluidized bed drying, supercritical fluid methods, spray freeze-drying, as well as many laboratory-scale methods. Each method has unique processing procedures and parameters, which may impact ASD product properties. Small changes in the processing conditions can lead to substantial differences in product characteristics and performance[36]. Therefore, a fundamental understanding of different processes is essential for selecting the most appropriate manufacturing method.

Table 4 Commonly used solvents for ASD preparation.

Solvent	Boiling point (°C)	Solubility in water (g/100 g)	Density (at 25 °C, g/mL)	Viscosity (at 25 °C, cP)	Dielectric constant	ICH Class (limit ppm)
Acetone	56.2	Miscible	1.049	0.295	20.7	Class 3
Butanone	79.6	29	0.805	0.4	18.51	Class 3
Butyl acetate	126.1	0.68	0.882	0.685	5.07	Class 3
Chloroform	61.7	0.795	1.498	0.536	4.81	Class 2 (60)
Dichloromethane	39.6	1.32	1.326	0.413	9.08	Class 2 (600)
Dimethyl acetamide	165	Miscible	0.937	0.92	37.78	Class 2 (1090)
Dimethyl formamide	153	Miscible	0.944	0.97	36.7	Class 2 (880)

Dimethyl sulfoxide	189	25.3	1.092	1.987	47	Class 3
Ethanol	78.5	Miscible	0.789	1.04	24.6	Class 3
Ethyl acetate	77	8.7	0.895	0.428	6	Class 3
Glycerin	290	Miscible	1.261	954	42.5	–
Isopropanol	82.6	Miscible	0.786	1.96	18.2	Class 3
Methanol	64.6	Miscible	0.791	0.543	32.6	Class 2 (3000)
Tetrahydrofuran	66	Miscible	0.889	0.48	7.52	Class 2 (720)
Water	100	–	0.998	1	78.5	–

–, not applicable.

2.1.1 Spray drying

Spray drying is one of the widely used processes for manufacturing ASDs[102,103] because it is a continuous and commercially scalable drying process[104]. The schematic set-up of the process is presented in Figure 1a. The spray drying process constitutes several steps. First, the feed solution/suspension containing the drug and the polymer (and possibly other additives) is pumped into the drying chamber through a spray-nozzle. The different types of commonly used nozzles are shown in Fig. 1 (b, c, d). The two-fluid nozzle has been the most commonly used nozzle for preparing spray-dried ASDs, particularly on a laboratory-scale[105]. The energy required to atomize the liquid is primarily provided by a gas. Liquid fed into the nozzle under low pressure can be mixed either internally or externally with the gas[106]. Another widely used nozzle in the pharmaceutical industry is the pressurized nozzle[107,108], which solely uses the feed liquid pressure for atomization. The potential energy of the liquid is converted into kinetic energy within the pressure-swirl nozzle. Due to internal instability as well as instability arising from the interaction with the surrounding air, the annular liquid lamella disintegrates[109]. The pressure-swirl nozzle does not atomize highly viscous liquids effectively[110]. A higher solution viscosity decreases the swirl intensity and leads to a higher liquid throughput as the cross-sectional area of

the liquid increases[105]. Pressurized nozzles provide the ability to produce larger particles with better flow properties and are easy to scale-up. This is particularly advantageous for downstream processing, as it can improve powder flow, die filling, compression, and tablet uniformity. Sildenafil was spray-dried with poly(lactide-*co*-glycolide) using a pressurized nozzle to form microparticulates (4–8 μm) of ASDs[111]. No significant changes in physicochemical properties or *in vitro* drug release were observed during a scaled-up manufacturing process using the same procedure.

The choice of the feed pump depends on the feed material viscosity, the type of atomization nozzle, and the drying capacity[104]. The droplets atomized by the nozzle come in contact with the heated gas, which causes evaporation of the solvent in the drying chamber. The duration of particle residence in the drying chamber will vary depending on the equipment and process parameters, however, it is usually in the range of a few milliseconds[112,113]. Industrial spray dryers are equipped to have a gas flow rate as high as 5000 kg/h that can result in a solvent evaporation capacity of up to 400 kg/h[84]. The dried material is carried to the cyclone separator, where the heavier particles are separated from the drying gas and collected[114]. The finer particles are removed with the exhaust gases which are collected *via* a filter. Particles can deposit at the bottom of the drying chamber in some cases and may be scraped. Scraping can be done with the aid of vibratory devices, and/or compressed air[115]. Although mechanical brushes can also be used, they might result in additional stresses[45,116-118]. One of the concerns in using spray drying is the amount of residual solvent. Therefore, spray drying is usually followed by secondary drying.

ASD product characteristics and performance can vary significantly by fine-tuning the formulation and process parameters[84]. Relevant manufacturing parameters are shown in Figure 1a[119-121]. Of these, two of the crucial processing variables are the inlet temperature and the feed rate. Optimization of these factors is essential to obtain a homogenous amorphous dispersion. Selection of the inlet temperature is dictated by the physical and chemical stability of formulation constituents and the boiling point of the solvent(s)[122]. An operating and processing space for generating stable ASDs is shown in Figure 2[123]. During rapid solvent evaporation from the atomized droplet, if the surface film formed is permeable, a porous particle is formed. A hollow particle with a thicker shell is formed if the initial film is impermeable[124,125]. Slower rates of evaporation can provide adequate time for molecular rearrangement. This can cause phase separation or even crystallization. The extent of phase separation/crystallization is dependent

upon the strength of the drug-polymer interactions[126]. Studies have shown that the extent of drug-polymer miscibility varies depending on the location in the spray dryer from which it has been collected[127]. Naproxen-PVP-VA ASDs collected from the cyclone of the (Pro-C-epT Micro) spray dryer showed the narrow glass transition width, indicating a higher degree of drug-polymer miscibility relative to the ASDs sampled from the collector[127].

Recently, solvent composition during spray drying has also been shown to have a significant impact on ASDs despite the complete solubilization of drug and polymer in the selected solvent system. In their work, Li et al.[85] found that water addition to the solvent system can lead to phase separation of ASDs during spray drying even for an initially one-phase feed solution. For the investigated ritonavir–PVPVA system, phase separation appeared to be subtle at a 25% drug loading with the co-solvents of water and methanol (10:90 ratio). However, a significant reduction in drug release rate was noted for this batch. Both experimental and modeling results indicated that the extent of phase separation increased when a higher amount of water (60:40 water-methanol ratio) was added to the spray solvent. When comparing systems prepared from the same solvent composition but with varying drug-loads, higher-drug loaded ASDs were more prone to phase separation than the low-drug-loading system. However, the impact of phase separation on drug release rates of high-drug loaded ASDs was minimal, likely due to the already compromised release often seen at high drug loadings[85]. A change in the co-solvent ratio has also been shown to alter the surface composition of spray-dried ASDs, likely due to the varying evaporation and diffusion kinetics[128,129]. These observations are particularly significant, considering a higher surface ratio of drug to polymer is known to result in an increased tendency of the amorphous drug to recrystallize[130]. For an in-depth reading regarding the fundamentals of ASD particle engineering by spray drying, readers are referred to some previously published reviews[84,102,124,131].

The solubility of the drug and excipients in the feed solvent limits the output of a traditional spray drying process. If the solubility of the solute and excipient in the solvent is very different, spray-dried ASDs obtained from such solutions are often not homogeneous[128,129,132-134]. Recently, modified spray drying techniques have been developed for ASD production in which the aqueous, organic, or combination feed solution is heated by a heat exchanger before being atomized and spray-dried[135,136]. This process generally leads to spray-dried ASDs that are more homogeneous[136]. The increase in temperature of the feed solution increases the solubility of the

drug and other excipients. Such temperature increase of feed solution can reduce its viscosity and enable improved uniformity of atomization[136]. In addition, this modification allows for the rapid evaporation of the solvent and shorter times of particle solidification than conventional spray drying[136]. However, operation safety and formulation stability concerns must be carefully evaluated before employing this method for preparing ASDs.

Spray drying has some limitations. A major concern in spray-dried ASDs is solvent residue[137,138]. The low bulk density ASD powder prepared by this method often needs densification to improve its flow properties for further processing into the final dosage forms. Additionally, adhesion of the material to the equipment walls reduces product yield which can be a limiting factor early in development where the developers have a limited amount of the active ingredient, especially for those expensive drugs. Adding silicon dioxide into the feed has been shown to increase bulk density, and therefore the recovery of ASD product[139,140]. Nevertheless, spray drying remains one of the most popular methods due to its applicability to a wide variety of compounds and its ability to obtain a product with a high drug load and the desired particle properties by fine-tuning multiple processing variables. For example, albendazole was found to be degrading up to 97.4% during hot-melt extrusion, despite the precautions of earlier forced chemical and thermal degradation tests[141]. However, no degradation was seen for spray-dried ASDs. The capability of spray drying to prepare high drug-loaded indomethacin-PVP ASDs was compared with co-milling and supercritical anti-solvent process in another report[142]. The spray drying method could prepare stable formulations up to a higher drug load (80%, *w*/*w*) relative to the other processes (60%, *w*/*w*)[142]. In a very short timeframe, spray drying can generate particles with a size range from nano- to micro-meter scales. Nanoparticles of celecoxib-phospholipoid E80 and trehalose were prepared *via* spray drying[143]. Microspheres (3–10 μm) of caffeine ASDs were generated when it was spray-dried with poly(lactic-*co*-glycolic acid) and polylactic acid[144]. It is also a process that can be scaled up from laboratory to industrial manufacturing. For example, Sawicki et al.[98] showed that spray drying is more suited to scale-up than freeze-drying. For a Phase 1 clinical trial of docetaxel or paclitaxel, spray drying was a method of choice over freeze-drying since the values of both saturation solubility and precipitation onset time of spray-dried ASDs were either similar or better to the freeze-dried ASD[98].

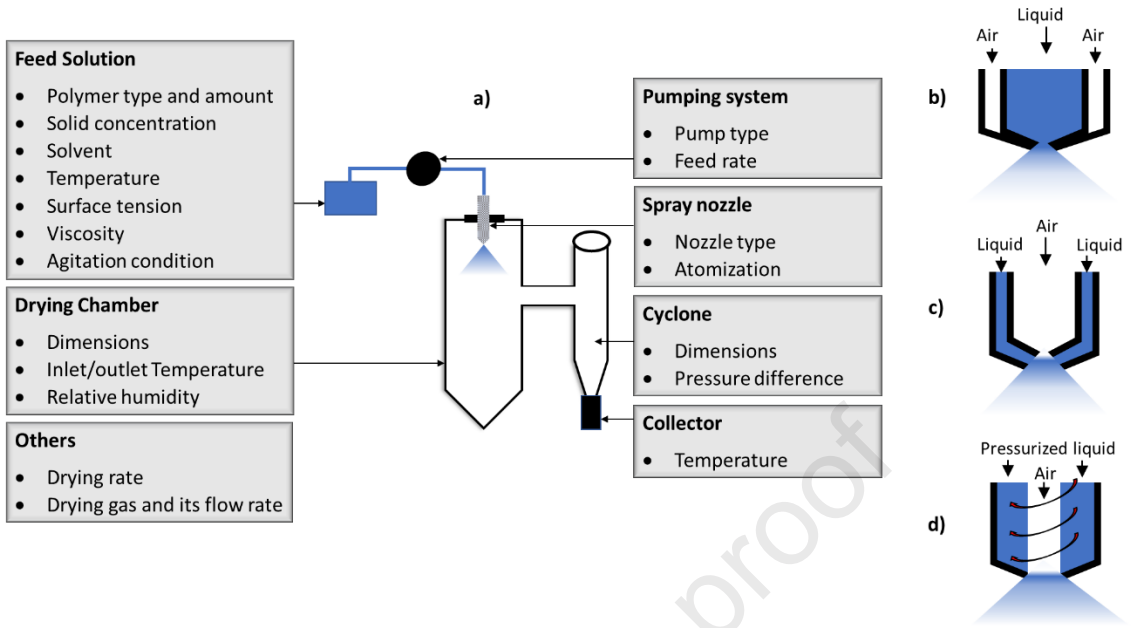


Figure 1 A schematic of (a) spray dryer set-up and the manufacturing variables affecting product properties and performance; (b) external mixing two-fluid nozzle; (c) internal mixing two-fluid nozzle; (d) pressure-swirl nozzle.

2.1.2 Figure 2. **Spray drying design space for generating stable ASDs.** *Electrospraying*

In electrospraying, electrical forces atomize feed solution (containing drug and other additives) into small droplets in the range of a few nanometers or micrometers. Similar to spray drying, the rapid rate of solvent evaporation contributes to the formation of the amorphous drug state within the ASD. With atomization of the drug-containing solvent and rapid drying, the method is somewhat similar to that of spray drying[124,125,137]. However, one of the key advantages of electrospraying over spray drying and many other techniques is its capability to produce small particles, with a narrow particle size distribution[145-147]. The 'free-fall' of the droplets with subsequent rapid solvent evaporation allows for minimal to no agglomeration of the electrosprayed particles[148]. This technique additionally offers adaptability with basic equipment designs to generate particles with the desired size, shape, and morphology[149,150].

The standard electrospraying set-up is comprised of 4 significant parts: a siphoning system (usually a pump), a spray nozzle set-up with a variable high voltage, and a grounded substrate[151].

The electrically conductive feed is pumped gradually into the spray nozzle, which has an applied electrical potential difference. When the feed solution is ejected from the nozzle, at an adequately high applied voltage, the free charges on the solution surface create an electrical pressure. This results in the generation of the 'Taylor cone', where the meniscus at the nozzle tip is shaped like a cone (Fig. 3)[152]. The solution at the tip of the cone has a high free charge and is pulled away rapidly towards the collector, forming a highly charged solution jet[151]. During the flight to the collector, solvent evaporation on the primary droplet surfaces causes them to shrink. This increases charge concentration causing the droplet to undergo Coulomb fission and break into even smaller droplets[151]. These nano- or micro-sized droplets allow for instant solvent evaporation so that only solidified particles reach the grounded substrate[153,154]. Several studies have also used an additional assembly of a corona neutralizer. The neutralizer is placed opposite to or concentrically around the nozzle and is used to prevent further Coulomb fission and disruption of charged droplets to obtain monodispersed particles[155-161]. Besides the Taylor cone-jet mode, many other electrospraying modes can be achieved by adjusting the electrical potential. However, the Taylor-cone mode, which emits a steady stream of microscopic jet and breaks up periodically into uniformly sized droplets is the preferred mode for the generation of monodisperse particles.

For electrospraying, the processing conditions are optimized such that the solution kinetic energy and surface tension are overcome by the electrostatic repulsion, allowing the jet to break into smaller droplets[151]. However, if the kinetic energy in the Taylor cone and the surface tension exceeds the electrostatic repulsion, usually due to the presence of high molecular weight polymers, the charged solution jet will not break into droplets[162]. This forms fine polymeric fibers (instead of particles) with their diameter ranging from a couple of nanometers to a few micrometers[163]. This process is known as electrospinning. Although ASDs can be prepared using electrospinning[164-167], electrospraying is preferred due to its ability to generate spherical and monodisperse particles with better flow characteristics relative to electrospun fibers.

Bohr et al.[168,169] formulated celecoxib-poly(lactic-*co*-glycolic acid) (PLGA) microspheres of ASDs with electrospraying. Not only was the drug release from ASDs faster than that of a pure crystalline drug, but optimization of electrospraying allowed for varying ASD properties like particle size and porosity which helped alter drug release profiles. Yu et al.[170] prepared ketoprofen-PVP ASD nanoparticles using electrospraying with drug-polymer ratios of 1:10,

2:10, and 5:10. Almost complete drug release was achieved for all the ratios within 1 min at a 50 mg drug dose in phosphate buffer solution. Similar rapid release (<1 min) was exhibited for acetaminophen/PVP K25 prepared by electrospraying[171]. Electrospraying can also be useful for preparing ASDs of drugs that are poorly soluble in common solvents or have a high melting point, which makes using traditional heat or solvent-based methods challenging. For instance, quercetin is one such drug with a high melting point of 326 °C. Li et al.[172] formulated a quercetin-PVP ASD by electrospraying their dimethylacetamide and ethanol-based solution, which exhibited rapid release (<10 s) and 10-fold higher permeation rates across porcine sublingual mucosae than crystalline quercetin.

Although there are studies indicating successful ASD formation by electrospraying, there are also reports highlighting the complexity of electrospraying in preparing ASDs. When clarithromycin ASDs were prepared by electrospraying, Mohammadi et al.[173] observed an incomplete amorphization of the drug. Similarly, even though the -Eudragit® L100 ASDs prepared by Zhang et al.[174] had a significantly enhanced drug release, incomplete amorphization (<5% crystallization) was observed in the formulation. Besides the nature of the drug[175,176], ambient pressure is one of the factors that results in incomplete amorphization during electrospraying. For example, Nyström et al.[157,158,177] reported the varying effect of ambient pressure on drug amorphization during electrospraying. Electrospraying the solutions of budesonide and piroxicam at low pressure (0.3 bar) led to powders exhibiting higher degree of amorphization compared to solutions electrosprayed at atmospheric pressure. On the other hand, indomethacin solutions electrosprayed at lowered pressure (0.3 bar) prompted the formation of more crystalline drug than that produced at atmospheric pressure.

An important parameter impacting the crystallinity of eletrosprayed solids is the electrical field, especially for dipolar compounds. Increased interaction of the compound dipole moments with a strong electrical field, can cause molecular rearrangements that promote crystallization[178]. Also, it is important for the feed solution to have sufficient conductivity[179,180] and low viscosity so that the solution jet can be broken into smaller droplets[181,182]. Figure 3 shows some other equipment and process variables that can affect the drug amorphization during electrospraying.

Since even a small trace of crystalline phase can induce subsequent crystallization of the ASD, residual crystallinity is a parameter that needs to be monitored while manufacturing ASDs, especially *via* electrospraying. Although there is some advancement in scale-up approaches of

electrospraying like multi-spray nozzle[183], nozzle-free[184], and high-speed electrospinning[167], the use of electrospinning for ASD preparation is restricted due to its low production rates and complex process design. For in-depth reading regarding the fundamentals of electrospraying, readers can refer to some previously published reviews[151-154,185].

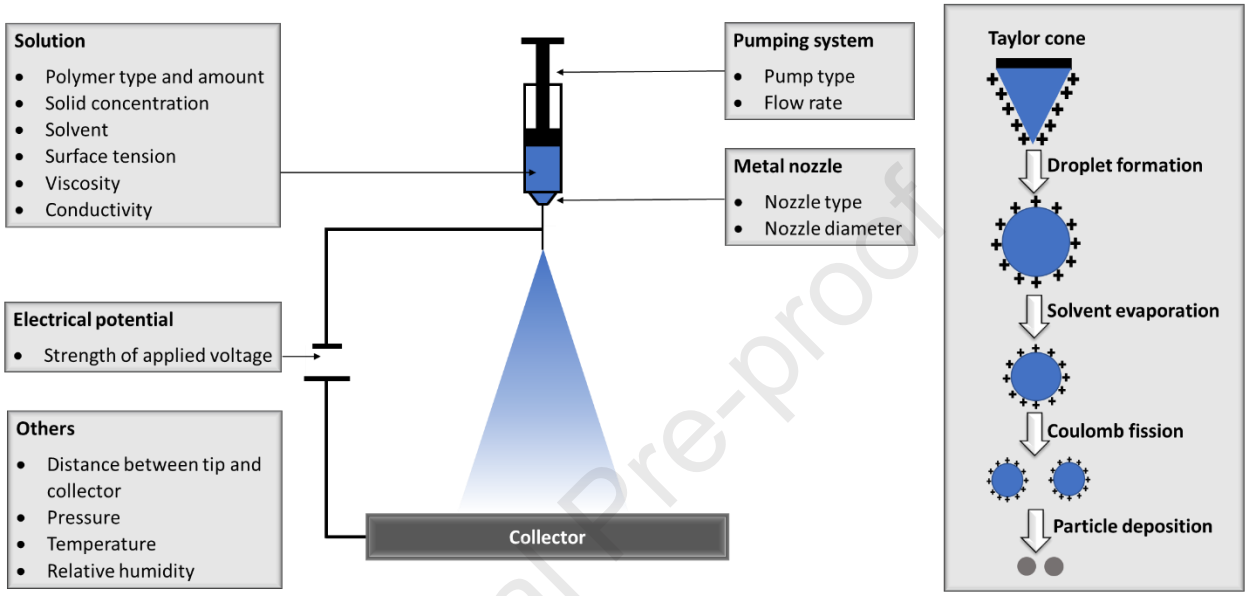


Figure 3 Formulation and process variables of electrospraying affecting ASD performance (left diagram) and the mechanism of particle formation by electrospraying (right diagram).

2.1.3 *Fluidized bed technology*

Fluid bed technology is used for various pharmaceutical unit operations including granulation (fluidized bed granulator), coating (fluidized bed coater), drying (fluidized bed dryer), and cooling[186-188]. Along similar lines, fluidized bed coaters and granulators are also used to manufacture ASDs[189,190]. For ASD preparation, the drug-polymer solutions are sprayed onto inert excipient cores, with the solvent evaporation and ASDs layering occurring simultaneously. The organic solvent can be recovered and recycled[191]. This method has been used to formulate both controlled- and immediate-release solid dispersions[192,193]. Direct formation of ASD granules by this method reduces additional downstream processing steps, which aids in avoiding potential stability issues during these processes[45,194]. In addition, such granules allow an additional coating of suitable excipients which can control the release profiles or enhance the ASD stability[195]. For example, indomethacin–PVP ASDs prepared by coating onto sugar spheres were further coated with various polymers to achieve the desired drug release and diffusion rates[194].

Based on the nozzle location, there are four types of setups available for fluidization as shown in Figure 4[196]. In both the bottom and tangential spray process, the drying air and feed solution are introduced in the same direction. This presents a more controlled particle movement and allows for a uniform ASD coating. Therefore, these two configurations are usually the preferred fluid bed technology methods to prepare ASDs[197]. The typical formulation and process parameters of fluidized bed manufacturing which affect product properties are shown in Figure 4[198]. Dipyridamole controlled release ASD pellets were formulated by Beten et al.[192] using the bottom spray fluidized bed process. When Ho et al.[193] prepared nifedipine-HPMC ASDs by layering them on sugar spheres using a fluidized bed coater, they observed varying rates of drug release with varying drug-polymer ratios. Similarly, Sun et al.[199] employed a fluidized bed coating method to prepare silymarin-PVPP ASDs. Additionally, Zhang et al.[200] demonstrated the success of this process to prepare ASDs at low air temperatures of <30 °C for thermolabile drugs. This technique was also utilized to produce wax-based (floating) ASD pellets which gave a sustained release for 12 h[201]. The wax-based core was coated with protocatechuic acid and ethylcellulose solution in a single-step fluidized bed coating method. Fluid bed layering has also been used to prepare an amorphous complex of drug and cyclodextrins to enhance the drug dissolution profile[202]. For ASD preparation, fluid bed layering can be challenging on a larger scale due to stickiness of the material and over-agglomeration; though there are still a few marketed products manufactured using the fluid bed process[203,204], probably because the fluidized bed offers a one-step granulation-coating-drying approach with the possibility of relatively lower operating temperatures than spray drying.

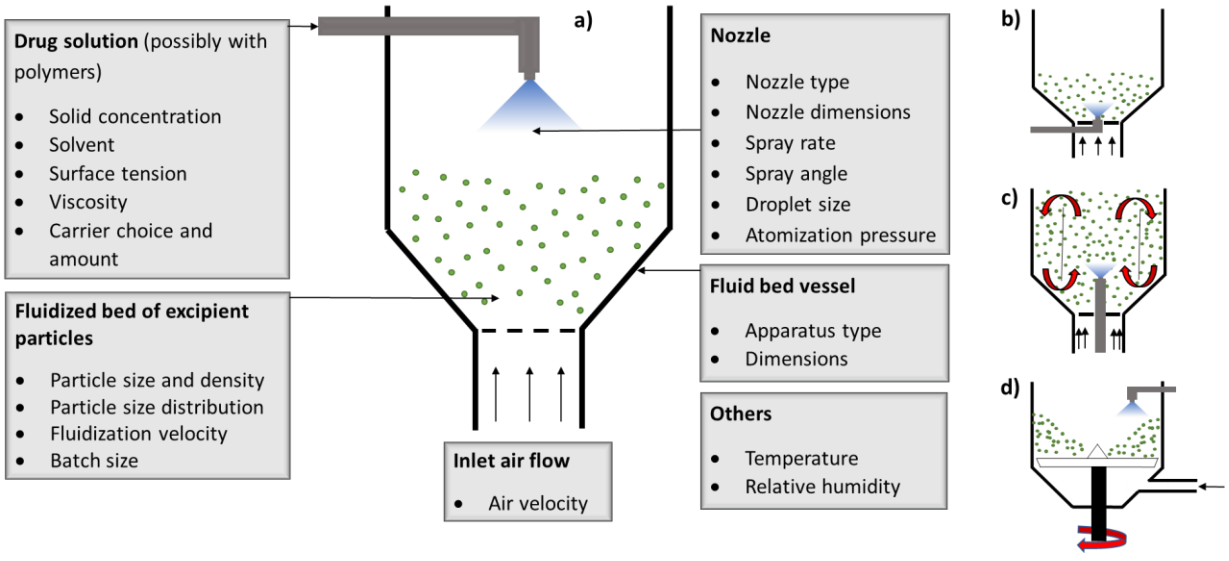


Figure 4 Fluidized bed manufacturing variables affecting product properties and the different types of fluidized bed dryers (a) top spray; (b) bottom spray; (c) Wurster; (d) tangential or side rotor spray.

2.1.4 Supercritical fluids

Supercritical fluids (SCFs) have also been used to produce ASDs. SCFs are simply gases that simultaneously present gaseous and liquid state properties under specific pressure and temperature conditions[205-207]. The liquid property of SCFs is useful for drug-polymer solubilization whereas the gaseous property aids in solid diffusion and solvent evaporation[206]. Although theoretically nearly all gases can be SCFs, practically only a few are used due to the limitation of attainable temperature and pressure conditions. In fact, >98% of all SCF applications have been developed with carbon dioxide (CO_2)[205]. This is because CO_2 has a low critical temperature (31 °C) and pressure (7.4 MPa), making it easier to achieve adequate conditions for an SCF process. In addition, it is non-flammable, reusable, non-toxic, and inexpensive[206,208,209]. Another gas used as an SCF in the pharmaceutical industry is trifluoromethane[209]. The major advantage of SCF-based methods is that they are relatively greener in nature and have lower production costs compared to other solvent-evaporation processes. The solvent evaporation process can also be controlled more by adjusting the temperature and pressure conditions. The low viscosity of SCFs result in a high diffusivity and rapid solvent evaporation with faster and higher yields[210]. Drawbacks of using SCF-based methods for ASD preparation include the difficulty in removing residual organic solvents (if used), and the high capital investment[205].

SCF-based processes can be divided into three groups[206]. The first includes processes that use SCFs as solvents. An example of such a process is the rapid expansion of a supercritical solution (RESS). In RESS the drug and polymer/s are dissolved in an SCF and the SCF is then rapidly expanded by sudden decompression. This is usually done by passing the SCF solution through an orifice at low pressure[210]. RESS is an advantageous single-step process requiring minimal to no organic solvent. However, a typical issue with this process is particle agglomeration. Many poorly water-soluble compounds have inadequate solubility in SCFs under moderate conditions of temperature (<60 °C) and pressure (<300 bar)[206,210]. Cosolvents such as methanol can be

added to CO_2 to aid drug solubility. However, this necessitates an additional step for removing the residual solvent which increases process complexity and expense[211-213].

The second group consists of processes that use SCFs as antisolvents. In these processes, the drug-polymer system is solubilized in an organic solvent and then mixed with an SCF which acts as an antisolvent. The solubilization capability of the organic solvent reduces as SCF is being added to the organic solvent. Thus, the new liquid mixture now becomes supersaturated with respect to the drug (and the polymer) causing them to precipitate as ASDs. To successfully produce an ASD by this method, the drug and polymer should possess high solubility in the selected organic solvent and limited/no solubility in the SCF. Also, the selected organic solvent should be miscible with the selected SCF (antisolvent). The precipitated particles are subsequently filtered. There are different techniques that have the same underlying principle but differ in the mixing method of the solvent and antisolvent[206,210]. The examples include precipitation with compressed fluid antisolvent (PCA), supercritical antisolvent (SAS) precipitation, aerosol solvent extraction system (ASES), gas antisolvent (GAS) precipitation, and solution-enhanced dispersion by SCF (SEDS). For the PCA method, the organic solvent solution is introduced *via* capillaries into the controlled chamber containing the SCF[214], whereas in SAS the solvent solution is introduced *via* a nozzle[215,216]. These methods have been applied to provide ASDs on an industrial-scale[217]. Atorvastatin[218], megestrol acetate[219], and valsartan[220] are ASDs produced by the SAS approach and have exhibited improved solubility and bioavailability. Indomethacin[221], cefdinir[222], and glycyrrhizic acid ASDs[223] produced by this process have shown enhanced solubility whereby the formulated powder also exhibited uniform particle size. Glibenclamide ASDs prepared by the SAS were shown to have similar solubility as those prepared by solvent evaporation using a rotary evaporator[208]. A recent study further demonstrated improved permeability of zidovudine-poly(L-lactic acid) solid dispersions relative to the pure crystalline drug when tested in an *ex vivo* everted rat intestinal sac model[224]. The observed effect was attributed to the enhanced poly(L-lactic acid) (polymer) plasticization which increased the extent of drug diffusion in the polymer matrix. In the ASES method, the organic solvent solution and SCF are sprayed at the same time (using different nozzles) into the chamber[216]. Itraconazole-HPMC ASD particles (100–500 nm) produced by ASES showed >609-fold increase in the amount of drug released during dissolution compared to the pure crystalline

drug. Also, the bioavailability of ASDs as determined in rat models was similar to that of the marketed ASD drug product Sporanox®[225].

As an alternative to the above methods, the SCF can be added to the organic solution in the GAS technique[206,226]. A key unique feature of this method is that the SCF can be used as an antisolvent in the supercritical condition for the entire time of processing. The pressure applied varies continually from 1 Bar to the final pressure. With an increase in pressure, the concentration of the gas employed increases, causing the ASD to precipitate. Compared to other SCF methods, GAS is a slow process that can allow for molecular rearrangement and is therefore not ideal for ASDs. SEDS, another process of the second group uses a unique patented nozzle that allows SCF to function both as an antisolvent and a dispersing agent for the organic solution[227]. Thus, the organic solution and SCF are atomized simultaneously[228]. There are two types of a nozzle in the SEDS: one with two channels (one each for SCF and organic solution) and another with three channels. The nozzle with three channels provides more choices in operating variables. For example, one channel can be for the organic solution with a drug, a second for polymer in aqueous solution, and a third for SCF[229]. Puerarin microparticles produced by SEDS were amorphous whereas the ones prepared by GAS were crystalline[230], likely due to the slow process of GAS.

The third group includes methods that use SCFs as solutes, including precipitation from gas-saturated solutions (PGSS). It utilizes the ability of supercritical CO_2 ($scCO_2$) to diffuse into organic compounds like polymers. When $scCO_2$ diffuses into the polymer, it lowers polymer T_g and viscosity. In the PGSS process, the drug-polymer physical mixtures are first introduced into SCF. Elevated pressure and SCF cause the mixture to melt. This non-viscous solution is sprayed into a receiving chamber with controlled pressure. Due to rapid decompression, SCF escapes the solid matrix, and ASDs are formed. This method is particularly suitable for materials like PVP and PLGA which easily absorb SCF. PGSS is an advantageous SCF-based process since it does not require organic solvents and usually operates at low pressures with lower gas consumption relative to other processes such as RESS. Composite solid dispersions of fenofibrate and stearoyl macrogol-32 glycerides (Gelucire®) have been prepared using PGSS by Pestieau et al.[231] Biphasic dissolution of the formulation indicated a significantly higher concentration of the drug in the aqueous (0.1 mol/L HCl) as well as organic (octanol) layer relative to the physical mixture. In another study, progesterone solid dispersions were prepared with PGSS[232]. Amongst

the tested variables, a yield of 94.7% and the highest extent of progesterone dissolution after 20 min (85.6%) was observed for lower progesterone-to-excipient ratio (1:10) and process values of higher pressure (186 bar), higher temperature (60 °C), and a longer processing time (30 min).

SCFs have also been used as processing aids in combination with melt extrusion (usually in RESS or PGSS mode)[233]. A schematic for the selection of an appropriate SCF-based process for ASD preparation is shown in Figure 5. Among SCF-based processes, SAS-based processes are generally favored for ASD preparation due to easier scale-up and more tunable variables[234]. Besides the formulation composition (discussed in previous methods), the key variables that affect product attributes in the SCF-based methods are pre-expansion conditions (temperature and pressure of vessel), nozzle type (atomization, dimension) and angle of impact of the jet stream, feed rate of solution, flow rate of the SCF, and final drying/extraction time[234].

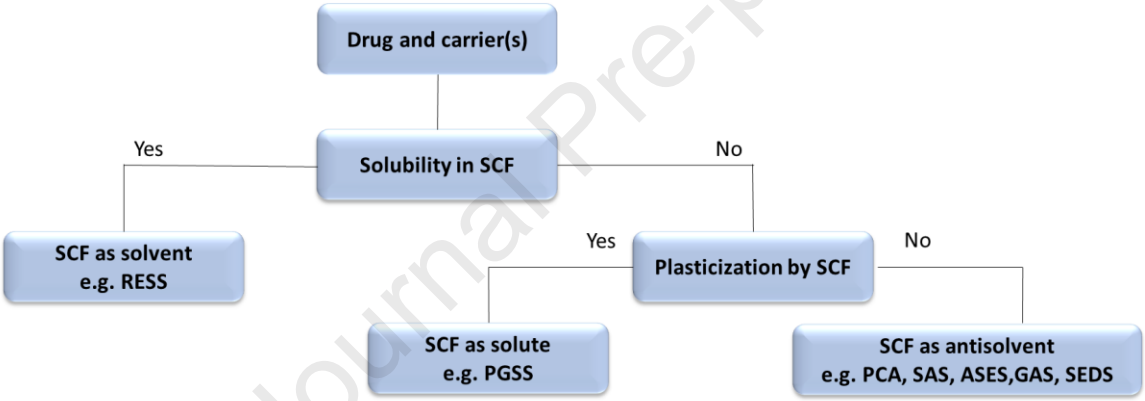


Figure 5 Schematic for selection of SCF-based process for ASD preparation.

2.1.5 Spray-freeze-drying

Spray-freeze-drying is one of the cryogenic technology for preparing ASD powders (Figure 6)[235,236]. During the spray-freeze-drying process, the feed solution or suspension comprising of the drug, polymer, and possibly other excipients are atomized and sprayed directly into a cryogenic liquid[237,238]. The frozen particles are then transferred to a freeze-dryer to generate a flowable ASD powder. This process can be further categorized depending on the type of injection devices (capillary, rotary, pneumatic, ultrasonic, two-fluid/three fluid nozzle), location of the nozzle, and the composition of the cryogenic liquid (liquid nitrogen, liquid argon,

compressed CO_2)[207]. However, generally, spray-freeze-dried powders are amorphous and porous, which results in a high surface area and a high dissolution rate[239-244]. Also, relative to spray drying, spray-freeze-drying offers a higher control over particle size, compatibility with more excipients, less thermal stress, and a higher yield[245]. The spray-freeze-drying process has been successfully used to enhance the dissolution and bioavailability of poorly soluble drugs like carbamazepine[239,240], and danazol[241,243,244,246-248]. He et al.[249] demonstrated that this technology could be employed for producing stable and free-flowing baicalein powers that could not be obtained by a conventional solvent evaporation method (*i.e.*, rotavapor). Pluronic F68 was used as a carrier and inhibited baicalein from crystallizing. In comparison with the ASDs prepared by rotary evaporation, the spray-freeze-dried ASDs exhibited significantly enhanced baicalein dissolution rate and improved oral bioavailability in rats[249], likely as a result of their porous structure and higher specific surface area.

Since spray-freeze-drying is a combination of spraying and freeze-drying processes, the manufacturing considerations for preparing stable ASD systems using this method are a combination of those two as well (discussed in their respective sections). Nevertheless, an important distinction is the solvents used for preparing the feed solution. Spray drying solvents may have a high ratio of organic components. However, for spray-freeze-drying, it is preferable that the feed solution have a low organic component since freeze-drying usually does not permit high organic solvent content. Another concern with spray-freeze-drying is that the porous and low-density structures of the ASDs may make them fragile and difficult for secondary processing.

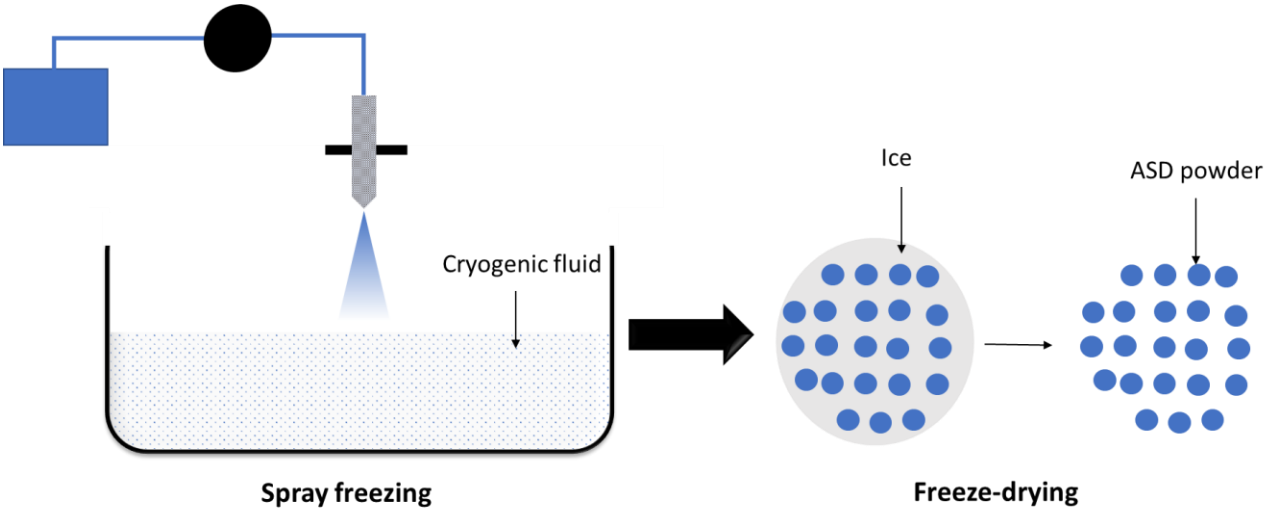


Figure 6 Preparation of ASDs by spray-freeze-drying. The feed solution is atomized and sprayed directly into a cryogenic liquid and the frozen particles are subsequently transferred to a freeze-dryer to generate dried ASD powder.

2.1.6 Other solvent-based methods

Solvent casting is a commonly used laboratory process for preparing ASDs[250-253]. A drug–polymer solution (mostly organic) is spread onto a substrate and then the solvent is evaporated at room temperature under normal pressure[254]. The solvent evaporation can also be sped up using a hot plate[255] or by placing it in an oven (at low temperatures and pressure) and followed by cooling[250]. The films that form are usually milled to obtain powders. However, this method is limited to drugs that can be solubilized in solvents with low boiling points like ethanol, chloroform, dichloromethane, or their mixtures[256-258]. Also, it might be challenging to completely evaporate the residual solvent.

Solvent evaporation using a rotary evaporator is another frequently used process for a small-scale ASD preparation[48,259]. In this process, the drug–polymer solution, typically using an organic solvent, is evaporated under vacuum and at slightly elevated temperatures. Simultaneous application of vacuum and heat increases the rate of solvent evaporation and allows the use of a solvent with higher boiling points if required. In the rotary evaporator process, solvents like tetrahydrofuran or dimethylformamide that could not be used in a solvent casting process can be used. The final product is collected from the flask and, if necessary, can be further milled.

Sandhu et al.[123] reported rotating jet-spinning as an alternative to electrospinning for ASD production with particles in the nano- or micro-meter size range. The typical set-up consists of a rotating reservoir containing drug-polymer solutions attached to a motor (Figure 7). The reservoir can either be perforated, or equipped with a side nozzle, or possibly placed over metal plates with perforations for ejecting the solution. The drug-polymer solution is placed into a preheated or room temperature rotating metal container (spinning reservoir) which rotates at high speed (generally in the range of 2000–13,000 rpm). When the reservoir is rotated (about its axis) at a rate that overcomes the capillary and centrifugal forces, the solution jet is ejected from a side nozzle/perforations on the reservoir or a gap between metal plates holding the reservoir[260]. This jet is propelled along a long spiral trajectory extended by the centrifugal forces. This generates a higher surface area. Solvent evaporation also occurs during this step. The solvent evaporation

rate is dependent upon the solvent diffusion coefficient in the polymer[261]. Relative to solvent evaporation methods like spray drying or electrospinning, challenges posed by this method include its lower ability to remove the residual organic solvent(s) to a satisfactory level, and the necessity of a batch mode[262]. Further study on the scale-up capability of this method for producing ASDs is warranted for the feasibility of industrial manufacturing[262].

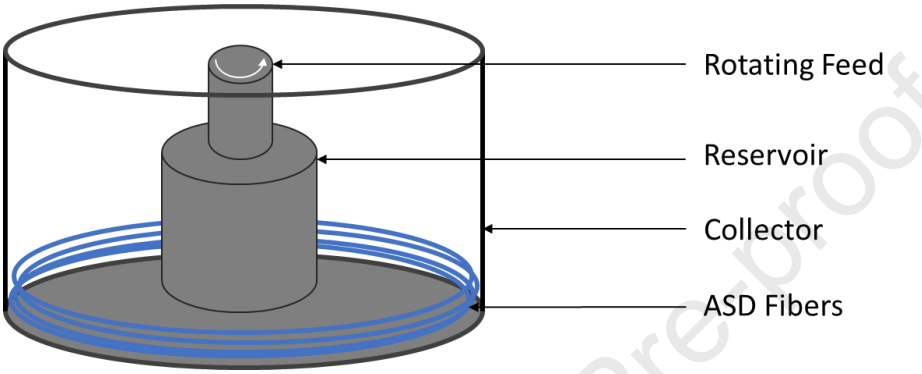


Figure 7 A typical set-up of the rotating jet-spinning process. The reservoir containing feed solution is rotated such that the solution jet is ejected with a higher surface area, resulting in rapid solvent evaporation.

2.2 Melting-based methods

In melt-based methods, the formulation components are heated to form dispersions, followed by cooling. Solvent avoidance is a significant benefit of the melting techniques[263]. However, a major drawback of these methods is that the high temperatures may induce drug degradation[84]. Melting methods also require sufficient solubility/miscibility of drugs in the polymer melt, which can be very difficult for certain molecules to achieve[7,264,265].

An efficient ASD production by melting depends on the operational as well as compositional variables. The use of a polymer in the production of an ASD is of course to stabilize the amorphous form, but it is also important for processing because the polymer provides a molten medium for drug solubilization or dispersion. Therefore, the polymers used in melting processes are usually polymers or waxes with a low melting point or T_g[52,266]. Commonly used carriers include PVP[52], PVPVA[267-269], cellulose esters and acrylates[47,52], and polymethacrylate derivatives[268]. There are some commercial polymers specifically designed for melting processes

such as HPMCAS[270-272], Soluplus®[273,274], and Affinisol® HPMC HME (modified HPMC)[275]. These carriers can also be used in combination to achieve improved amorphization, stability, dissolution, and bioavailability[47,276].

Sufficient plasticization is essential to form an ASD during the melting process. Although the drug itself can provide some plasticizing effect[277], additional plasticizers can be added to aid the mixing of drug and polymer. Melting-based ASD preparation processes are also often characterized by high shear stress, which can be reduced by the incorporation of a plasticizer[265]. Plasticizers reduce the viscosity of the mixture and therefore can lower the processing temperature. Some examples of frequently used plasticizers are D-α-tocopheryl[270,278], poloxamers[273,279], low molecular-weight poly(ethylene glycol)s (PEGs)[265], and surfactants[280,281]. Plasticizer selection is dependent on its intended formulation functionality, such as lowering the processing temperature or lowering the melt viscosity. Added plasticizers that remain in the product, can affect its properties and performance (physicochemical stability, dissolution, T_g, hygroscopicity, or appearance). In addition, conventional plasticizers are used in a concentration range of 5%–30%, *w*/*w*[282,283] which increases the total weight of the formulation and may result in large, unacceptable dosage forms. Therefore, an ideal plasticizer should be capable of providing the desired plasticizing effect and then be removed from the formulation to mitigate its possible negative effects before final processing. For this reason, $scCO_2$, low boiling solvents, or reagents that can evaporate or sublime are being used[123,233,284].

2.2.1 Hot-melt extrusion (HME)

For commercial-scale production, only two types of melting processes are available, hot-melt extrusion (HME) and melt agglomeration (discussed later in the 'Granulation' subsection). HME, and especially the twin-screw melt extrusion with Meltrex™ as a representative example, is one of the most widely used techniques for producing ASDs[263,265,285]. The drug and the polymer are mixed, melted, dispersed, and then extruded under specific processing conditions[265,286]. Figure 8 shows the HME process, which can be divided theoretically into five steps, namely: feeding, melting and plasticizing, mixing/kneading and conveying, discharging, and cooling for further downstream processing. Important parts of a hot-melt extruder include a feed hopper, barrel, extrusion screws, torque sensors, heating-cooling system and dies.

The HME equipment has a flexible design, which enables processes to be tailored to achieve the desired outcomes and to accommodate varying raw materials, by adjusting the modular

design elements, namely the screws and barrels[287]. It is also possible to apply HME technology to drugs liable to oxidation and hydrolysis by excluding oxygen and moisture from the mixture[265,287,288]. The barrels can be flanged together or linked *via* internal tie rods. The most critical component of the extruder is the screw, which determines the quality and quantity (per unit time) of the extruded material[52,287]. Based on the screw configuration, the process may be categorized into single-screw or twin-screw extrusion. A twin-screw provides many benefits over the single screw model, with decreased drug residence time in the extruder and facilitated continuous mass flow with better mixing[278,289]. It can also be designed with two separate hoppers, both of which can vary in temperature over a wide range and are equipped with the self-cleaning function[265,266,290]. In addition, twin-screw extruders can limit thermal stress on the materials by reducing the 'non-motion' and preventing localized overheating[265,266]. It also presents easier feeding of materials and less propensity to overheat[288].

Depending on the desired shear level and operating speed, two screws can be designed in different configurations[52,291] of co-rotating (rotating in the same direction) or counter-rotating (rotating in the opposite direction), depending on the desired mixing intensity. Co-rotating screws are usually used in pharmaceutical manufacturing because they generate relatively lower shear forces than the counter-rotating[266]. Nakamichi et al.[289] demonstrated that the physicochemical properties of the extruded material were substantially impacted by the machine operating conditions. The study reported that since the kneading screws kept the material in the machine for a prolonged period under shear, stable ASDs exhibiting super-saturation upon dissolution could be prepared irrespective of changes in operating conditions such as the rate of revolution of the screws (20–100 rpm) and the amount of water (0%–50%) introduced in the feed[289]. When the kneading screws were detached from the screws and only the feed screw elements were used for ASD preparation, the extent of amorphization and dissolution profiles of the extruded material was substantially impacted by the machine operating conditions. Although partial crystallinity was observed in all the batches, the extent of crystallinity decreased with a reduction in rotation rate and amount of water. Slow screw rotation and the addition of a sufficient amount of water to the mixture increased the rate of dissolution of the drug, although no super-saturation occurred in any of the batches tested[289].

The kneading paddles play a vital role in drug amorphization. Verhoeven et al.[292] reported that at least one kneading zone was necessary for the homogeneous distribution of metoprolol tartrate in

ethyl cellulose matrices, even though the homogeneity of distribution and drug release rate were not significantly altered by the number of kneading zones or their location along the extruder barrel. The impact of screw configuration on the dissolution behavior was studied by Liu et al.[293] with indomethacin-Eudragit® EPO ASDs. They observed that indomethacin dissolution into the polymer melt was accelerated by the kneading blocks. Adequate shear stress, shear rate and mean residence time (which is linked to lower screw speed and feeding rate), are required to ensure complete drug amorphization[263,266,294,295]. However, excessively high shear stress, shear rate, and residence times pose the risk of material degradation.

The molten mass can be conveyed to the dies of a variety of shapes and sizes depending on the desired product properties. For example, the production of films[296] and patches[297] use flat dies, whereas pelletization and spheronization use circular dies[298,299]. Injection molding can also be utilized to fill the molten drug-polymer mass into molds[233,300]. Tablets, granules, capsules, or ear inserts can be produced in these molds[263,265,295,301]. After cooling at room temperature, the resulting product is collected and can be further milled to obtain the required particle sizes[265,302]. Apart from these important variables, other parameters such as temperature, die geometry, barrel design, and screw speed can also impact the final product properties[265]. Recent work has shown that the degassing process can remove volatile substances and subsequent air bubbles, which facilitates consistent production of extrudates with improved cross-sectional uniformity[303]. In order to reduce torque during screw rotation, certain minimum temperatures capable of plasticizing the material are required in HME[263,265]. Material flow properties are also critical to ensure a consistent feed rate from the hopper. For poorly flowing material, flow aids such as spray-dried mannitol, maltodextrin, and colloidal silica[123] can be used. As some of these flow aids are crystalline, the miscibility of the drug in the polymer may be affected, further complicating the solid-state and chemical analysis.

HME is continuous, single-step, solvent-free, and capable of scaling up[263]. The HME method can be equipped with on-line and in-line quality-control analysis such as near-infrared, Raman, and dielectric spectroscopies[304], which facilitate quality by design and continuous manufacturing. Some drawbacks include the higher energy usage and exclusion of thermolabile compounds[263,266,305]. Changes in the design of the equipment (*e.g.*, presence of kneading elements), as well as the addition of plasticizers, can lead to a reduction in processing

temperatures and/or residence time, and thus minimize the potential of thermal degradation of drugs during the processing[265].

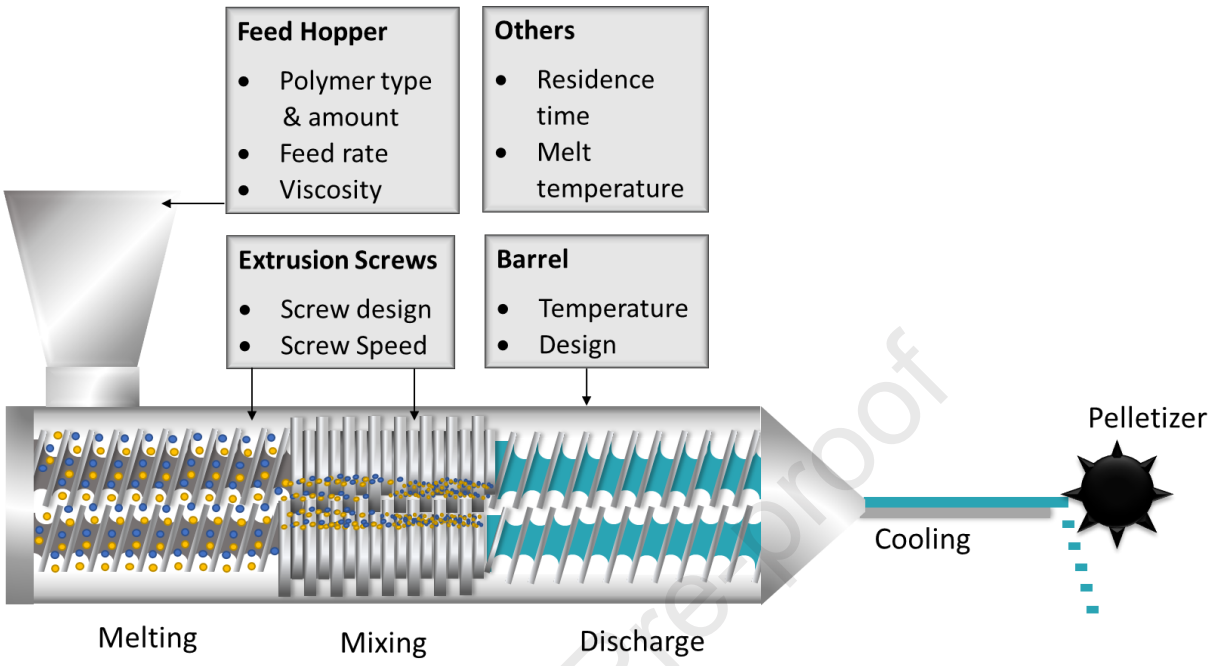


Figure 8 Twin-screw hot-melt extrusion and the associated manufacturing variables impacting product properties.

2.2.2 *KinetiSol®*

KinetiSol® is a modern fusion-based method that uses high shear force combined with heat to melt the drug-polymer blend and generate an ASD[306]. A rapid temperature rise is generated by the combined mechanical forces involved in the process. This creates a molten mass that is immediately quenched and processed further. The schematic representation of KinetiSol® technology is shown in Figure 9. A series of paddles rotating in a cylindrical vessel and shaft with high-speed mixing blades produce a large amount of frictional and shear energy[307]. This mechanical force results in the generation of heat, and the material temperature increases without applying external heating. Computer software controls the real-time temperature of the composition inside the KinetiSol® chamber, and the molten mass is quickly ejected from the processing vessel upon reaching the user-defined temperature endpoint. The entire process duration is normally <20 s, and the material is generally exposed to high temperatures for <5 s before the product is discharged and cooled[308]. The method is designed to operate in a batch

mode at a laboratory-scale, whereas it can be run semi-continuously at an industrial-scale with output as high as 1000 kg/h[309,310].

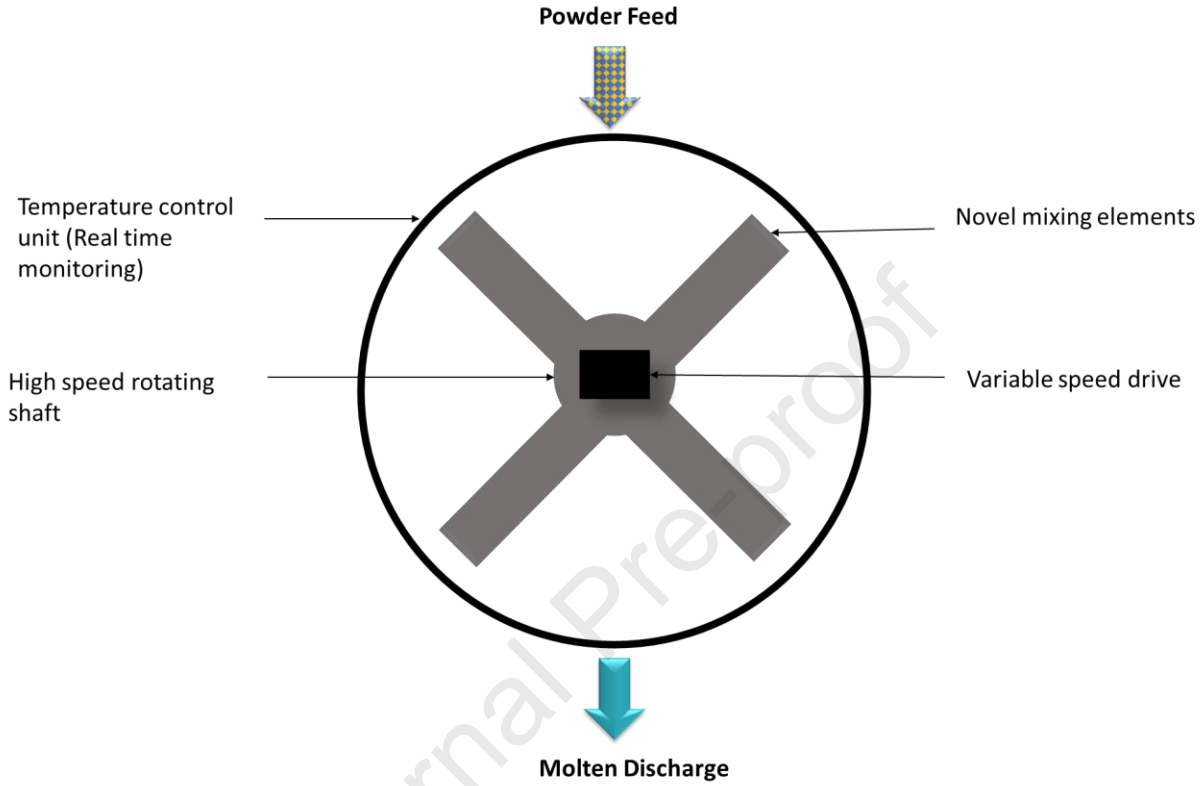


Figure 9 Schematic of KinetiSol® technology. Mechanical forces involved in the process result in a rapid temperature increase. This creates a molten mass which is immediately quenched to generate ASDs.

Being a short process in which desired temperature is reached within seconds, and material is ejected rapidly when the target temperature is reached, it lowers the exposure of the material to thermal stress, which is beneficial to ASD regarding degradation. Hydrocortisone-HMPC and -PVPVA matrices were found to be chemically 'preserved' during KinetiSol® processing (160 °C, <30 s); while heating the mixture at higher temperatures of >180 °C reduced drug potency due to decomposition[311]. Griseofulvin ASDs prepared with this method did not exhibit any sign of crystallinity or increased impurity, even after storage at 40 °C and 43% relative humidity (RH) for 6 months[309]. The utilization of heat generated by the process (with no added external heating) in KinetiSol® makes it one of the few methods applicable to drugs with high melting points as well as low solubility in organic solvents. This also enables the elimination of plasticizers and

reduces the risk of extended heat exposure[312]. Even viscous polymers (*e.g.*, PVP K30, PVP K90, HPMC K15 M) can be applied in KinetiSol® processing without the aid of plasticizers.

Another benefit of KinetiSol® is that it permits high drug loading without high torque and degradation, unlike other thermal processes[306]. Itraconazole dispersion with Methocel E50LV was prepared using KinetiSol® at a temperature range below the drug melting point without excessive shear[312]. T_g values of itraconazole-Eudragit® L100-55 ASDs prepared by KinetiSol® (at 1:2 ratio) were higher than those prepared using other thermal techniques, suggesting improved stability. This improved stability was attributed to the ability of KinetiSol® to offer a short processing time of < 10 s, a processing temperature lower than the polymer degradation temperature, and the use of low torque (even without plasticizers)[306].

Hughey et al.[312] conducted a design of experiment matrix to examine the effect of KinetiSol® process variables on drug stability. Meloxicam-Soluplus® ASDs were prepared at varying processing temperatures (110–140 °C) and processing speeds (2250–3000 rpm). The results indicated that the residence time was inversely related to process speed; when the processing speed was increased from 2250 to 3000 rpm, the residence time decreased from 22 s to less than 3 s. No definite relationship between the processing speed and drug degradation was observed. Ejection temperature and degradation, however, were found to be correlated. The samples ejected at 110 and 118 °C showed a drug content of >95%, but when the ejection temperature was raised above 125 °C it decreased to <90%, and further decreased to 79% when the ejection temperature was raised to >140 °C.

Similar effects of KinetiSol® processing conditions have been reported on the stability of ritonavir-PVPVA ASDs[308]. The processing time was decreased, but the amount of impurity increased with an increase in mechanical energy (processing speed), indicating that exceeding the mechanical energy over a certain limit can result in drug degradation. Of important note was that even though the ejection temperature was maintained at 80-100 °C, which was far below the drug degradation temperature of 160 °C, a high processing speed of 2000 rpm still caused the drug to degrade. The above case studies illustrate the capacity of KinetiSol® for generating ASDs after adequate process optimization.

2.2.3 *Three-dimensional (3D) printing*

Three-dimensional printing (3DP) is a relatively innovative technology that can transform 3D computer models into physical objects by additive manufacturing[313,314]. The significance and

relevance of 3DP for pharmaceutical applications have been discussed in depth elsewhere[315-322]. It is a technique to manufacture customized medicines for patients[323] by delivering multiple drugs[324-327] with varying print settings, allowing for better control over the drug dissolution kinetics[328-331]. There are several techniques and variations in 3DP, such as material jetting, binder jetting, and material extrusion[332]. The most widely used technology in the pharmaceutical sector is material extrusion and fused deposition modeling (FDM)[333,334]. *In vivo* experiments in animals as well as humans have demonstrated good tolerance of FDM 3D printed formulations[335-337].

For ASD preparation, 3DP has often been used in conjunction with HME[338]. HME + FDM 3DP involves heating a drug–polymer mix and extruding it with the HME technique, followed by 3DP, and cooling-solidification of the molten mass into the desired form on the build plate[339,340]. Although many polymers have been studied for HME + FDM 3DP[341], hydroxypropyl cellulose (HPC) remains the most commonly used one due to its suitable properties of particle size, viscosity, and T_g which allow for ease of extrusion, shape retention, and dimensional accuracy while generating a stable product[323,342-344]. Friability of the tablets greatly depends on the particle size of the employed polymer with smaller polymer particles improving the friability, whereas disintegration time and dissolution properties mainly depend on the viscosity of the employed polymers[345]. The polymers with higher viscosity usually lead to slower disintegration and dissolution[345]. One obvious drawback of FDM 3DP is the need for drug dispersions to be prepared by HME, which increases the probability of thermal drug degradation[346,347]. Another significant downside is the constraint on the use of excipients and drugs because they need to generate filaments with the necessary mechanical and physical characteristics for a successful 3DP[348,349]. Nowadays many 3DP studies in pharmaceutical applications have focused on the selection and optimization of excipient filaments appropriate for 3DP. The drug loading potential of the process is typically limited since a significant amount of polymer is required to impart adequate rheological properties to the extrudate. Therefore, the possibility of eliminating the HME step in FDM 3DP would be of great value in pharmaceutical product development[316]. In the plastics industry, direct pellet extrusion, a new 3DP material extrusion process, has recently been introduced as a possible alternative to FDM 3DP[350]. This technology uses a single screw extruder with a printer nozzle to directly print material in the form of pellets/powder. Since this technology does not require the preparation of filaments using HME, it may potentially permit the extrusion of mixtures which, due to the insufficient mechanical properties of the filaments,

would not be printed by conventional FDM (*e.g.*, being too brittle or too flexible). Similar technology was employed by Goyanes et al.[351] to prepare cylindrical 'printlets' or 3D printed tablets of ASDs. This new, single-step 3DP technique was used to prepare itraconazole ASD printlets directly from powdered materials using four different grades of HPC (HPC-UL, SSL, SL, and L). All the generated printlets exhibited acceptable mechanical and physical characteristics complying to pharmacopeial limits. In addition, no drug degradation was detected in the printlets and they exhibited a sustained drug release profile with drug concentrations exceeding the crystalline drug solubility. This research demonstrated the ability of this technology to resolve one of the major drawbacks of HME FDM 3DP, *i.e.*, the need for filament preparation by HME.

Recently another single-step 3DP process, selective laser sintering (SLS), was used to produce ritonavir–copovidone ASDs[352]. A complete conversion of the crystalline drug to its amorphous form was obtained as a function of laser-assisted selective fusion. In this study, powder flow properties, surface temperature, chamber temperature, laser speed, and hatch spacing were found to be crucial for successful ASD formation[352]. Moreover, ritonavir in the SLS 3D printed tablets exhibited a 20-fold increase in solubility relative to the crystalline drug. These novel, single-step technologies could be advantageous for the preparation of ASDs for preclinical studies where the quantity of drugs is limited or the use of traditional HME is challenging.

2.2.4 Microwave heating

Microwave-induced *in situ* amorphization is being investigated, wherein the crystalline drug in the final dosage form is amorphized *in situ* inside the final dosage type using a microwave oven[353]. Several experiments have demonstrated the feasibility of using microwaves to prepare ASDs. Doreth et al.[354] obtained indomethacin–PVP ASDs generated *in situ* by microwave heating. The indomethacin-PVP ASDs exhibited no microwave-induced drug degradation and the dissolution rate of the microwaved amorphous tablets was 6-fold higher than that of the physical mixture containing crystalline indomethacin-PVP[354].

The microwave-induced amorphization process consists of three main steps. First, preparing the drug-polymer physical mixture. Second, inducing drug amorphization with continuous or intermittent microwave heating. The last step is cooling, followed by possible pulverizing and sieving. In order to achieve a higher degree of drug amorphization, the formulation should be

optimized such that the drugs have high solubility in the polymer, and the polymers can be melted or softened at relatively low temperatures[355-357]. To date, only a few polymers have been studied for this technology, with a primary focus on PVP K12. Therefore, it is important to identify more potential carriers to be used with the microwave heating method to expand its applicability in pharmaceutical applications.

High input of microwave energy is needed for the amorphization[354] because unlike water, polymers and drug molecules are weak absorbers of microwave[358,359]. Usually, the following two techniques are applied to generate sufficient heat: i) convective heating, *i.e.*, a microwave absorbing reactor or a sample holder is heated and this heat is then indirectly transferred to the sample[353,360-370]; and ii) The addition of microwave absorbing solvent[371] or solvent slurry[372,373] to the drug-polymer solution mix and followed by solvent evaporation due to heating. For example, Moneghini et al.[353] placed the physical mixture of ibuprofen and PVP-VA in a glass sample holder, and materials were heated due to the convective heating from glass, whereas Abreu-Villela et al.[372] manufactured ASDs by microwaving suspensions prepared by adding defined amounts of water to the drug-polymer physical mixture.

The microwave heating time is typically <15 min, which has a relatively short exposure time to heat and thus potentially shields drug degradation[374-376]. The potential of the microwave heating method is its applicability to introduce drug amorphization in the final dosage form without downstream processing[354,377-379]. Of a particular note, such *in situ* amorphization process by microwave heating can take place in the final dosage form. Doreth et al.[354] demonstrated an *in situ* amorphization process where a drug can be amorphized within its final dosage form (tablets) through microwave irradiation. The authors also noted that increasing moisture content resulted in a higher fraction of amorphous drug. For the tablets in which the absorbed water evaporated rapidly from the surface after storage, the microwaves could not be absorbed, leaving a shell of the crystalline drug at the surface. In regard to the drug chemical stability, there is potential for drug degradation during microwave processing due to the microwave energy applied[376]. But even before microwaving, the presence of absorbed water, which is a prerequisite for facilitating *in situ* amorphization by microwave irradiation, can potentially lead to drug hydrolysis and degradation. A potential explanation why Doreth et al.[354] did not detect drug degradation during their *in situ* amorphization process may be due to the short storage time (RT and 54% RH for two weeks) prior to microwaving at 1000 W for 90 s. It is possible that long-term storage can

have a substantial effect on the drug stability profile, especially considering the large quantity of absorbed water (approx. 10%) present in such systems. Therefore, it is important to perform more systematic studies to evaluate the drug degradation propensity during formation as well as storage of ASDs prepared by microwave heating. There are presently only a few other publications on microwave-induced *in situ* amorphization in the final dosage form[377-379].

2.2.5 Other melt-based methods

On a laboratory-scale, ASDs can be produced by the melt-quench method, where formulation ingredients are melted, and followed by a natural or forced rapid cooling[380]. A water bath[381] or a hot plate[382] can be used to melt the formulation components while the molten mass can then be solidified either by allowing it to cool naturally to room temperature[383-385] or by immersing in an ice bath[386-388] or liquid nitrogen[389]. However, during early drug discovery and development of ASD formulations there is a limited amount of drug to work with. Therefore, a high throughput method that can prepare ASDs in small batches is particularly useful and efficient. Guo et al.[390] proposed a novel acoustic fusion method, which can provide a fast process with only a small amount of drugs. In this method, a Labram resonant acoustic mixer was used for acoustic fusion. The heating metal plate attached to the mixer was preheated to 80–160 °C and 10 mg of solid load (2 mg drug and 8 mg polymer) was filled into each glass vial of the 24-vial plate. The vials were then sealed and placed in the acoustic fusion heating block. The powder was mixed at an intensity of 50–80 G. The heating/mixing time varied between 15–60 min depending on the formulation. The samples were then removed and cooled to room temperature, which resulted in a dense glassy solid. The batch size limit for this process can vary from 10 mg to 2000 mg depending on the powder density. Torcetrapib, itraconazole and lopinavir of ASDs were prepared using a variety of polymer systems, including HPMCAS (L, M, and H), copovidone, Soluplus®, Vitamin-E TPGS, Kolliphor EL, and Eudragit®[390]. These ASDs demonstrated significantly higher drug solubility compared to the crystalline form. Thus, this approach can be used to prepare and optimize ASDs during early screening.

Another potential method for early-stage pre-clinical investigations of ASDs is ultrasonic-assisted or ultrasound compaction (USC). USC is a modified tableting process that provides heat, pressure, and shear to melt the powders during compaction with ultrasonic energy. The USC method is a relatively new fusion-based technique in pharmaceutical research[391-398]. Fini et al.[395]

pioneered the use of USC for drug amorphization. In this earlier study, the effectiveness of USC in preparing indomethacin and β-cyclodextrin SDs was examined[395]. Indomethacin melted during processing and eventually was dispersed in β-cyclodextrin. Due to the presence of amorphous indomethacin, the USC formulations displayed enhanced dissolution properties over the physical mixture or kneaded compositions. Sancin et al.[393] also prepared a ketoprofen–Eudragit® S100 ASD system sing USC. The findings showed that the dispersed ketoprofen crystallized at a much lower rate (>6 months) than the pure ketoprofen produced using USC (<1 day). Similarly, Fini et al.[394] prepared PVP-based indomethacin systems using USC. The use of a PVP matrix allowed a faster dissolution rate than the formulations prepared with β-cyclodextrin. Fini et al.[392] also investigated PEG-based compositions of indomethacin prepared by USC. It was hypothesized that, due to the low melting point of the material, the USC process would soften or melt each material, enabling a solid dispersion to be formed inside the die cavity. However, despite the observed increased dissolution rate, the formulations prepared by USC were not able to reach the dissolution rate of the ASD control samples prepared by the melt-quench method, suggesting, incomplete amorphization[392]. This is perhaps the reason for the observed increase in indomethacin dissolution rate with an increase in the input of ultrasonic energy, suggesting that higher energy input leads to a higher extent of amorphization[392].

When monitoring the USC process, Ueda et al.[391] noted changes in both the punch position and the die pressure with respect to the phase transition process of the polymer. Their study inferred that a sudden increase in the pressure on the lower punch can detect the optimum ultrasound energy for complete transformation. This is why the polymer as well as system T_g are important considerations during the USC process.

The primary advantages of using this method are the low quantities of material required and elimination of downstream processing. However, a crucial limitation of this method is the incomplete amorphization of the drug due to the lack of distributive mixing with ultrasonic energy. The product may show some inhomogeneity, and phase separation or presence of a small amount of crystalline phase which can be detrimental to the stability of an ASD system, as discussed in the earlier sections. For wider applicability of this method, more in-depth studies are required to understand the requisite physicochemical properties of the drug and the polymer, stability of the materials during and after processing, as well the method reproducibility[399].

2.3 Others miscellaneous techniques

2.3.1 Granulation

Preparation of ASDs by the granulation approach enables the direct generation of ASD granules with a reduced number of manufacturing unit operations and minimized cost for investing in new equipment[400,401]. Depending on the nature of the binder fluid, granulation can be categorized into solvent evaporation or melting process categories. Several granulation techniques can be utilized to produce ASDs including fluidized bed granulation, tumbling granulation, and mixing granulation[190,402-407]. Figure 10 shows the commonly used high-speed granulator and the associated manufacturing variables affecting ASD properties.

The principle of granulation for ASD preparation by solvent evaporation is the same as discussed in the fluidized bed technique section earlier (fluidized bed granulators). In this case, the binder usually consists of a drug dissolved in appropriate solvent(s) which is then added to the remaining excipients of the formulation. There are several examples in the literature which have utilized solvent evaporation-based granulation for the successful preparation of ASDs[190,402,403,406,408,409]. In addition, if it is critical to avoid drug exposure to the organic and/or aqueous solvents, the process of melt agglomeration can be employed wherein a molten mass of the drug and the polymer serves as a binder for forming granules[405,410]. This further reduces the drying steps associated with the solvent-based wet granulation process. Melt agglomeration also employs standard granulation equipment such as high shear granulators[411,412] and fluidized bed granulators[81,413]. The melted drug-polymer mass serves as a binding liquid for granulation, ensuring sufficient homogeneity. Polymers for melt agglomeration can be liquids such as PEG 300 and caprylocaproyl macrogol-8 glycerides (Labrasol®) or semi-solids like stearoyl polyoxyl-32 glycerides (Gelucire® 50/13)[411,414]. Solid polymers with low melting temperature/T_g, such as PEG (3000[412] and 6000[81] grades) and poloxamer 188[412,415] can also be used. However, similar to other melting processes, the use of high temperatures limits its application to thermally sensitive drugs. The limited choice in carriers is another drawback of this method because high T_g polymers are not suitable[405].

A modified method of granulation is thermal adhesion granulation (TAG)[416]. This process can be loosely considered as a combination of solvent- and melt-based processes. In TAG, little to no solvent is added to the drug and excipient mixture relative to the traditional wet granulation methods. The mixture is heated (30–130 °C) to promote the formation of the adhesive binder,

and then mixed by tumble rotation until granules are formed. Drying is not needed in most instances because little to no solvent is added in the process. Following cooling, granules of the specific particle size can be collected by sieving. The method imparts good flow properties and binding ability to granules to form tablets with low friability and sufficient hardness[416]. Lin et al.[417] converted hydrophilic polymers such as PVP and HPMC into the matrix materials while processing them with other diluents using TAG. Chen et al.[404] developed cilostazol ASDs by TAG using two adsorbents dibasic calcium phosphate anhydrous (Fujicalin®) and microcrystalline cellulose (Microcel®) for granule formation.

However, a major drawback of TAG is that it is challenging to formulate tablets of high-dose drugs since it necessitates the use of a larger amount of other excipients for inert core[418]. To overcome this challenge, Theismann et al.[419] developed an alternative process of spray granulation capable of preparing high drug-loading (80%, *w*/*w*) nicotinamide (NAM) granules by wet extrusion and spheronization. However, it would be a challenge to employ this method for stable ASD preparation due to the higher extent of water/solvent exposure. Continuous-spray granulation (CSG) may overcome the above limitations in solvent exposure[420]. This is a one-step method generating granules from solution or suspension. In the CSG method, the solution or suspension containing the drug and polymer (and possibly other excipients) is spray-dried generating small particles. These are then further layered by continuous spray. A typical set-up for CSG is a kind of a combination of spray dryer and fluid bed granulator. It consists of a two-fluid spray nozzle which is placed vertically at the bottom of the drying chamber. Additional air nozzles are present on the inside wall of the drying chamber which remove adhered powder off and maintain a continuous flowable state of the particles during drying/layering. Recently, Tanaka et al.[420] prepared ASD granules of rebamipide and PVPVA using a continuous-spray granulator. Dense and smooth granules with satisfactory physical stability (20 °C/75% RH for up to 6 months) and improved dissolution properties relative to the pure crystalline drug were obtained with the optimized polymer concentration.

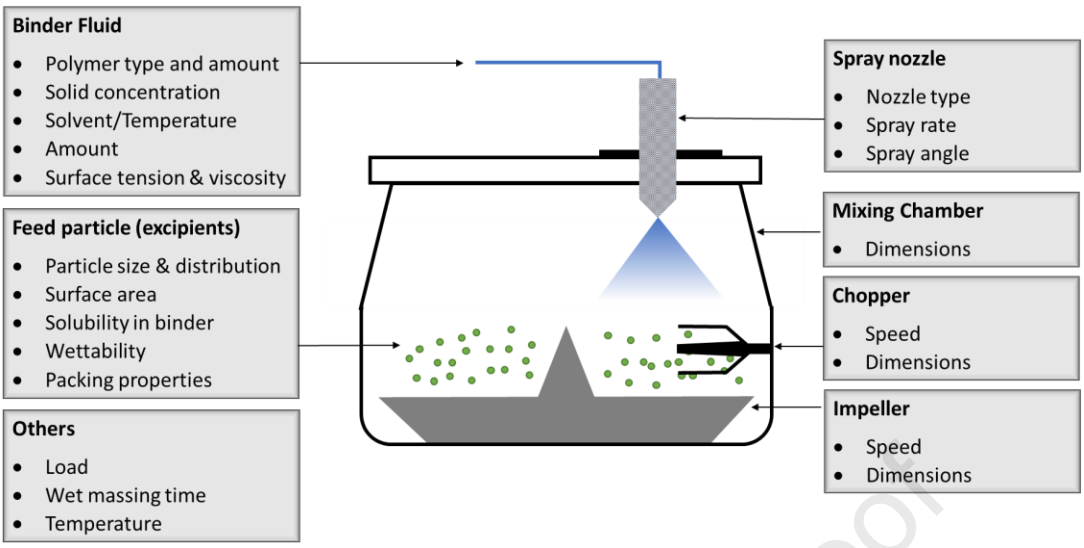


Figure 10 Preparation of ASDs using a high-speed mixer granulator. Molten drug–polymer mass can be added in the form of binder into the excipient mixture to form granules (melt agglomeration). Depending on the availability of suitable solvent system, alternate route includes using an organic feed solution as a binder fluid.

2.3.2 Co-precipitation

Antisolvent co-precipitation is another widely employed approach to produce ASDs[44,421,422] at both small-scale[423-428] and industrial-scale[18]. Compared to the spray-dried ASDs, the ASDs produced by the solvent exchange process have a larger particle size and often do not need further densification. These result in a superior compaction profile, limiting the need for added excipients such as compaction aids[123]. In addition, it is possible to maximize drug loading as high as 70% for certain compounds[123].

Co-precipitation amorphize drugs by the rapid precipitation of the ASD in the anti-solvent. The low processing temperatures circumvent the stability issues for the thermal-liable drugs. The co-precipitation process, as shown in Figure 11, begins with the dissolution of the drug and an ionic polymer in the nonvolatile solvents that are usually dimethylacetamide, dimethylformamide, or dimethylsulfoxide. The solution is then transferred gradually into a pH-controlled and chilled anti-solvent (usually water). It is crucial that both the drug and the polymer are insoluble in anti-solvent and that the common solvent is miscible with the anti-solvent to cause rapid co-precipitation[423]. An additional condition for the anti-solvent environment is that in the precipitated suspension state, the drug-polymer ASD remains in an

amorphous state, *i.e.*, the T_g of the amorphous composite is above the precipitation temperature as plasticized by the anti-solvent environment. After the controlled co-precipitation process, the precipitated wet solid mass can still contain a relatively significant amount of the organic solvent, which needs further removal. The organic solvent is generally removed by washing the solid precipitate with appropriate aqueous solvent until the residual organic solvent is <0.1%, *w*/*w*[10]. The washing is followed by a drying process to remove the aqueous solvent from the precipitate with the forced-air oven or fluid bed dryer.

Commonly used polymers for this process are HPMCAS (L, M, H grades), cellulose acetate phthalate (CAP), cellulose acetate butyrate, polyvinyl phthalate, hypromellose phthalate (HPMCP), and polymethacrylates derivatives/Eudragit® (L100–55, L100, S-100, and EPO grades)[123]. The use of low temperature, low solvent/antisolvent ratio, and adequate shear helps in improving the operational efficiency of co-precipitation. The time required for drug transition between the two solvents must be less than that associated with drug diffusion and crystallization in the solvent. The method therefore can benefit from agitation which rapidly mixes the solvent and antisolvent[429]. Rotor-stator devices are often incorporated into the co-precipitation process for adequate mixing. The introduction of higher shear often provides greater volumetric efficiency and enables the formation of more homogenous products[429]. Other process variables that need to be monitored and optimized for preparing a stable ASD are shown in Figure 12.

In order to generate ASD, many variations of solvent-mediated precipitation have been explored, *e.g.*, evaporative aqueous solution precipitation (EPAS), flash nanoprecipitation, and controlled precipitation. In EPAS, the drug–polymer solution is atomized into a heated aqueous solution, where the heated antisolvent evaporates the solvent (generally dichloromethane)[430]. However, this method is limited to low boiling solvents such as dichloromethane that can be readily evaporated due to the use of heated aqueous fluid as an antisolvent. Also, since this process occurs at elevated temperatures, it may not be ideal for ASD stability, particularly for the thermal-liable compounds. A modification to the EPAS process is controlled precipitation, which involves in-line extraction of solvent by vacuum distillation[431]. The controlled precipitation method also utilizes solvents with low boiling points such as methanol. Mann et al.[432] used a slightly altered co-precipitation system in which nonionic polymers were used and the precipitation was induced by organic antisolvents as opposed to pH modified aqueous antisolvents. The integration of surfactants into these ASDs was also possible due to the use of

aqueous solvents. Moreover, using solvents and antisolvents with relatively lower boiling points makes the downstream isolation and drying of the precipitates easier.

A major limitation of the co-precipitation method is that due to pH-dependent solubility and stability, some pH sensitive compounds may not have sufficient time for adequate precipitation in the anti-solvent. Furthermore, heat and moisture may cause stability concerns during the washing and drying processes.

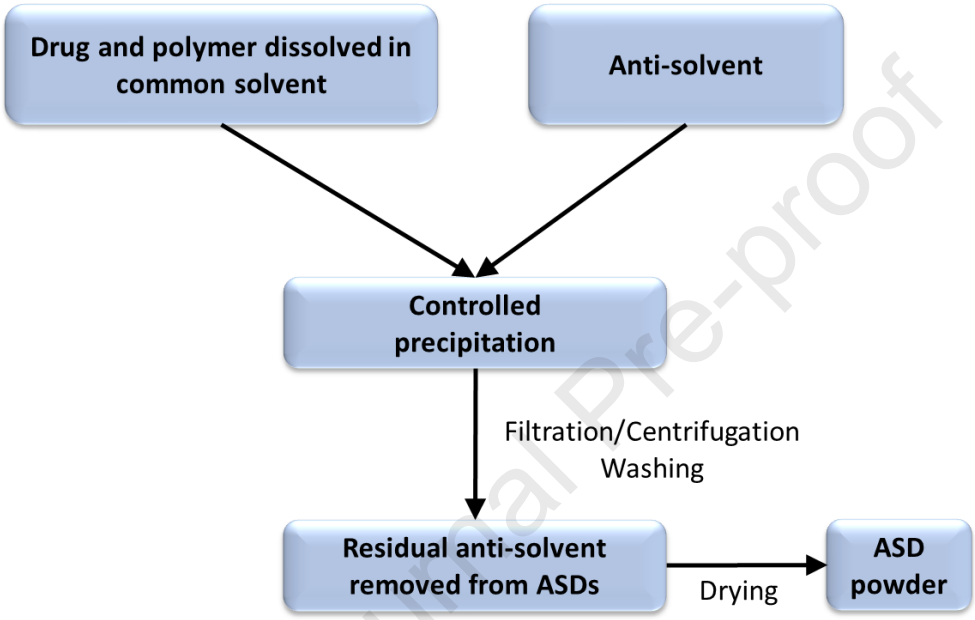


Figure 11 Schematic of co-precipitation process to prepare ASDs.

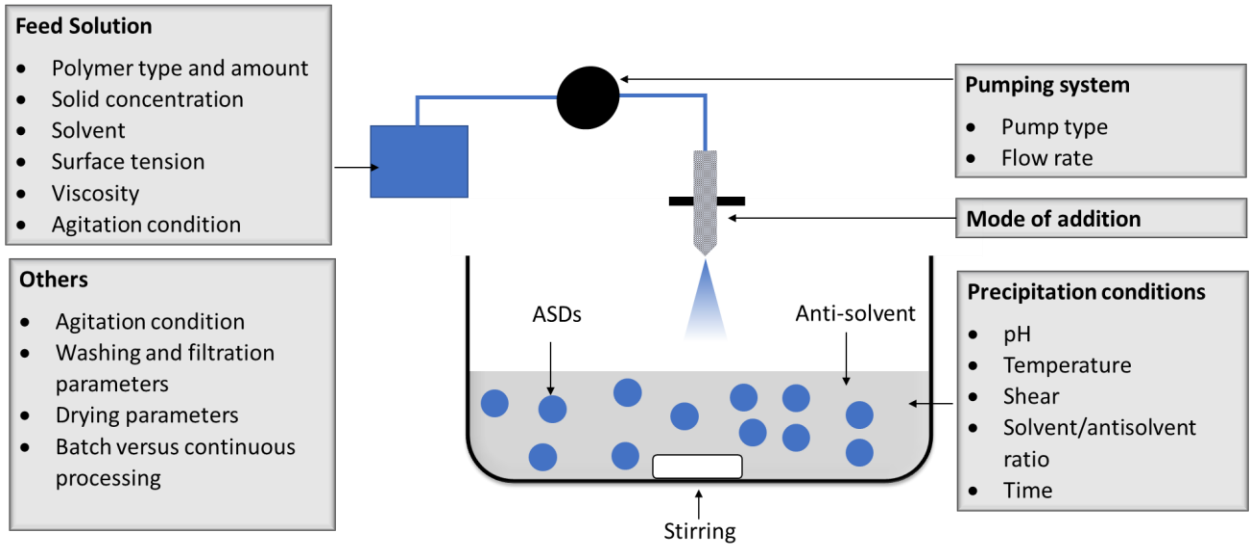


Figure 12 Co-precipitation and its processing variables for preparing ASDs.

2.3.3 Milling-based methods

On a laboratory-scale, milling/cryogrinding has been employed for preparing ASDs of certain compounds[433-439]. The reduction in particle size has long been known to decrease crystallinity and achieve amorphization[440-442]. A partially amorphous anti-inflammatory product has been manufactured using SoluMatrix®, a technique that entails dry milling the crystalline drug with a hydrophilic carrier[443]. However, the method is not widely popular in the pharmaceutical industry[433] as there is often a risk of residual crystallinity, which can act as a seed and induce nucleation/crystallization during the shelf life, even with some stabilizers (*e.g.*, magnesium aluminometasilicate, crospovidone, sugar)[441,442].

3. Downstream processing

It is clear from the discussion so far that variations in manufacturing techniques have a substantial impact on ASD properties such as particle size, particle porosity, and density, flowability, tabletability, and stability. However, it is important to note that these properties are not only linked with the manufacturing process but also to the formulation composition. Obviously, even slight changes in the process parameters and formulation can alter these physicochemical properties. During the development of a specific ASD product, the process parameters need to be carefully evaluated and optimized to obtain an optimal product. In many cases, downstream processing is necessary to obtain such desired properties.

During the downstream processing of ASDs, there is often a risk of drug crystallization, especially during operations that expose the ASDs to moisture, thermal or mechanical stress[59,60,68,386,444,445]. The crystallization of a drug from the ASD during transport and storage due to the mechanical activation by grinding, crushing, or even scratching has also been discussed by Német et al.[68]. Therefore, ideal ASDs require minimal downstream unit operations. However, in reality, certain downstream processes might be inevitable. Depending on the manufacturing method, the ASDs obtained can be in the form of a fine powder, granule, extrudate, or fiber. Processes like spray drying, electrospraying, super-critical fluid technology, cryogrinding, and milling usually generate fine ASD powders that require further densification (or granulation) to enhance their density and flow properties for efficiently manufacturing their final dosage forms[446-448]. For ASDs, dry granulation and direct compaction are usually preferred over wet

granulation due to the moisture sensitivity of ASDs. Fu et al.[449] observed that the amorphous drug is more inclined to crystallize in a tablet prepared from a wet granulated method than in tablets prepared by direct compression. Leane et al.[444] also noted a significantly higher crystallinity in the tablets with roller-compacted granules, in contrast to directly compressed tablets under accelerated storage conditions (40 °C/75% RH).

HME generates extrudates (usually spaghetti-shaped) while processes like electrospinning and rotating-jet spinning result in ASD fibers, which need to be milled into granules. The granules of ASDs can be further combined with additives such as disintegrants, flow aids, compression aids, lubricants, etc. for efficient encapsulation or tableting[450]. HME granules, however, usually have limited compaction properties due to the reduced porosity of the extrudates and the ductile properties of the polymers used. Recently, two types of post-die melt extrudate processing milling techniques were evaluated for itraconazole-HPMC ASDs, *viz.* hammer mill and air classifier mill[450]. The product was prepared by using the hammer mill melted at higher mill loadings. In contrast, this problem did not emerge when an air classifier mill was used. The addition of an elastic substance (*e.g.*, carrageenan or polyglycolic glyceride) has been shown to prevent an amorphous drug from crystallization during compression and storage[59,451], possibly due to the cushioning effect of elastic materials. However, the addition of elastic substances during compression can generate other undesirable effects on product properties and performance such as physicochemical stability, dissolution, T_g, hygroscopicity, or appearance.

Large surface area can contribute to the lower stability of amorphous drug because T_g of ASD is typically lower on the surface than in the bulk particle region[452,453]. Increased crystallization rates are often noticed on the particle surface because of greater molecular mobility[454]. Coating celecoxib-PVP ASDs prepared by the fluidized bed (Wurster) process with coating excipients (PVA, inulin, and polyvinyl acetate were tested) formed a barrier layer[455]. This led to lower molecular mobility at the surface and increased protection against moisture. Figure 13 shows a schematic of possible downstream processes to prepare a solid dosage form of an ASD (tablet/capsule).

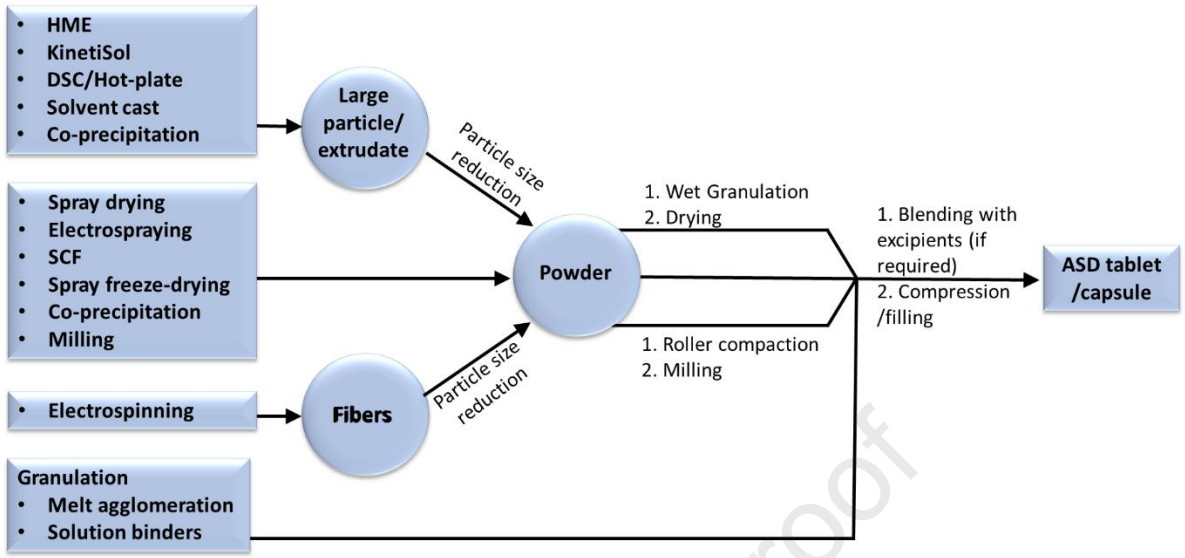


Figure 13 A schematic of downstream processing routes to prepare ASD solid dosage forms.

4. Selection criteria of an ASD manufacturing method

Besides the drug thermal stability and solubility, other important considerations for selecting a manufacturing method are batch size (scale), and equipment availability. If the drug can melt <150 °C without degradation, melting methods can be considered. Amongst melting methods, if the purpose of preparation is screening, even DSC pans can be used for ASD preparation by melt-quenching. For a larger laboratory-scale batch, melt-quenching by using a hot-plate/oil bath can be considered. However, a molten mass with a viscosity of >300cP may make ASD processing with these methods challenging. In such cases, HME or solvent evaporation techniques can be considered.

The key factors to consider when choosing a solvent evaporation-based manufacturing method are the properties of the organic solvents used to solubilize the drug and polymer(s). For a screening study, if the boiling point of the solvent/s is <50 °C, the solvent cast method can be used. For solvent/s boiling at higher temperatures or for a larger batch, rotavapor or spray drying can be the choice. For intermediate or industrial-scale production, the choice of processes for ASD preparation is limited. This is because, at a larger scale, additional criteria such as the process efficiency, process yield, particle properties, and if applicable, solvent toxicity, environmental impact, the safety of the operator, and flammability/explosion risk need to be considered. Based on formulation properties, a straightforward method selection decision tree for preparing ASDs is shown in Figure 14.

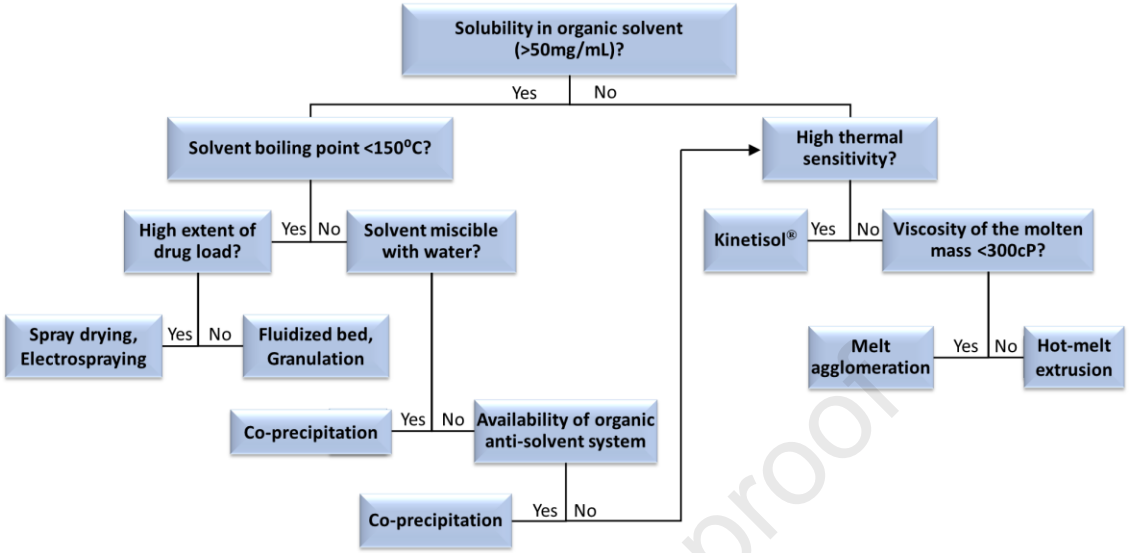


Figure 14 A method selection decision tree with the commonly used manufacturing processes for preparing ASDs[30].

5. Conclusions

A successful development of amorphous solid dispersion formulations depends on three primary factors: active pharmaceutical ingredient properties, stabilizing polymer, and processing technology. Polymers provide the basic and essential foundation for a stable drug amorphization and the process supplies the energy required to transform the system to an amorphous form. The effectiveness of the process is critical to generate, capture, and preserve the amorphous form. The success of these processes is dependent on the processing time and the supersaturation conditions that are being generated during the formation of the solid dispersion.

Despite the discovery of solid dispersions in the early 1960s, the application of the solid dispersion concept to solve solubility challenges had been limited for several decades partly due to the lack of commercially viable processing technologies. However, the past two decades have seen remarkable progress in developing pharmaceutical ASD products as our understanding of ASD systems and their manufacturing technologies have evolved considerably, leading to several commercial products in addition to numerous in development. Spray drying and HME have become the mainstay of ASD preparation in the pharmaceutical industry, while newer

methods are constantly being added into the toolbox that promise to improve the quality, productivity, and/or better performance of the products.

Acknowledgments

This work was supported, in whole or in part, by the Bill & Melinda Gates Foundation [No.OPP1159809, USA]. Qi (Tony) Zhou and Sonal Bhujbal are also supported by the National Institute of Allergy and Infectious Diseases of the National Institute of Health under Award (No. R01AI132681, USA). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Health. The authors would like to thank Bristol Myers Squibb and Oral Product Development for supporting this work as a part of Sonal Bhujbal's summer internship. The Bristol Myers Squibb authors acknowledge that one or more patent applications, related to the work disclosed in this paper, may be planned, pending, and/or has been granted.

Author contributions

Sonal Bhujbal, Qi (Tony) Zhou, Sumit Kumar, Biplob Mitra, and Uday Jain were responsible for the conception and design of the review. Sonal Bhujbal wrote the manuscript. Tony (Qi) Zhou, Sumit Kumar, Biplob Mitra, Uday Jain, Yuchuan Gong, Lynne Taylor, Anjali Agrawal, and Shyam Karki supervised and revised the manuscript. All of the authors have read and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Babu NJ, Nangia A. Solubility advantage of amorphous drugs and pharmaceutical cocrystals. *Cryst Growth Des* 2011;**11**:2662-79
2. Benet LZ, Broccatelli F, Oprea TI. BDDCS applied to over 900 drugs. *AAPS J* 2011;**13**:519-47
3. Ku MS. Use of the biopharmaceutical classification system in early drug development. *AAPS J* 2008;**10**:208-12
4. Jatwani S, Rana AC, Singh G, Aggarwal G. An overview on solubility enhancement techniques for poorly soluble drugs and solid dispersion as an eminent strategic approach. *Int J Pharm Sci Res* 2012;**3**:942
5. Di L, Fish PV, Mano T. Bridging solubility between drug discovery and development. *Drug DiscovToday* 2012;**17**:486-95
6. Brough C, Williams R. Amorphous solid dispersions and nano-crystal technologies for poorly water-soluble drug delivery. *Int J Pharm* 2013;**453**:157-66
7. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. *Drug DiscovToday* 2007;**12**:1068-75
8. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. *Eur J Pharm Biopharm* 2000;**50**:47-60
9. Serajuddin AT, Thakur AB, Ghoshal RN, Fakes MG, Ranadive SA, Morris KR, et al. Selection of solid dosage form composition through drug–excipient compatibility testing. *J Pharm Sci* 1999;**88**:696-704
10. Shah N, Sandhu H, Choi DS, Chokshi H, Malick AW. Amorphous solid dispersions. In: Rathbone MJ, editors. New York City, US: Springer, 2014.
11. Van den Mooter G. The use of amorphous solid dispersions: a formulation strategy to overcome poor solubility and dissolution rate. *Drug Discov Today Technol* 2012;**9**:e79-e85
12. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. *J Pharm Sci* 1971;**60**:1281-302
13. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. *J Pharm Sci* 1997;**86**:1-12
14. Newman A, Hastedt JE, Yazdanian M, editors. New directions in pharmaceutical amorphous materials and amorphous solid dispersions, a tribute to Professor George Zografi. Proceedings of the Land O'Lakes Conference at the University of Wisconsin-Madison in June 201; Downloaded from link.springer.com. Springer; 201715. Vaka SRK, Bommana MM, Desai D, Djordjevic J, Phuapradit W, Shah N. Excipients for amorphous solid dispersions. In: Shah N, Sandhu H, Choi DS, Chokshi H, Malick AW, editors. *Amorphous solid dispersions.* New York City, US: Springer, 2014, p. 123-61.16. Miller JM, Beig A, Carr RA, Spence JK, Dahan A. A win–win solution in oral delivery of lipophilic drugs: supersaturation *via* amorphous solid dispersions increases apparent solubility without sacrifice of intestinal membrane permeability. *Mol Pharm* 2012;**9**:2009-16
17. Newman A, Knipp G, Zografi G. Assessing the performance of amorphous solid dispersions. *J Pharm Sci* 2012;**101**:1355-77

18. Shah N, Iyer RM, Mair HJ, Choi DS, Tian H, Diodone R, et al. Improved human bioavailability of vemurafenib, a practically insoluble drug, using an amorphous polymer- stabilized solid dispersion prepared by a solvent- controlled coprecipitation process. *J Pharm Sci* 2013;**102**:967-81
19. Tekade AR, Yadav JN. A review on solid dispersion and carriers used therein forsolubility enhancement of poorly water soluble drugs. *Adv Pharm Bull* 2020;**10**:359-69
20. Kim KT, Lee JY, Lee MY, Song CK, Choi J, Kim D-D. Solid dispersions as a drug delivery system. *Int J Pharm Investig* 2011;**41**:125-42
21. Bindhani S, Mohapatra S. Recent approaches of solid dispersion: a new concept toward oral bioavailability. *Asian J Pharm Clin Res* 2018;**11**:72-8
22. Vo CL-N, Park C, Lee B-J. Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs. *Eur J Pharm Biopharm* 2013;**85**:799-813
23. Baghel S, Cathcart H, O'Reilly NJ. Polymeric amorphous solid dispersions: a review of amorphization, crystallization, stabilization, solid-state characterization, and aqueous solubilization of biopharmaceutical classification system class II drugs. *J Pharm Sci* 2016;**105**:2527-44
24. Schittny A, Huwyler J, Puchkov M. Mechanisms of increased bioavailability through amorphous solid dispersions: a review. *Drug Deliv* 2020;**27**:110-27
25. Arunachalam A, Karthikeyan M, Konam K, Prasad PH, Sethuraman S, Ashutoshkumar S. Solid dispersions: a review. *J Curr Pharm Res* 2010;**1**:82
26. Ma X, Williams III RO. Characterization of amorphous solid dispersions: an update. *J Drug Deliv Sci Technol* 2019;**50**:113-24
27. Pandi P, Bulusu R, Kommineni N, Khan W, Singh M. Amorphous solid dispersions: an update for preparation, characterization, mechanism on bioavailability, stability, regulatory considerations and marketed products. *Int J Pharm* 2020:119560
28. Jermain SV, Brough C, Williams III RO. Amorphous solid dispersions and nanocrystal technologies for poorly water-soluble drug delivery–An update. *Int J Pharm* 2018;**535**:379-92
29. Singh G, Kaur L, Gupta G, Sharma S. Enhancement of the solubility of poorly water soluble drugs through solid dispersion: a comprehensive review. *Indian J Pharm Sci* 2017;**79**:674-87
30. Vasconcelos T, Marques S, das Neves J, Sarmento B. Amorphous solid dispersions: Rational selection of a manufacturing process. *Adv Drug Del Rev* 2016;**100**:85-101
31. Rumondor AC, Jackson MJ, Taylor LS, Design. Effects of moisture on the growth rate of felodipine crystals in the presence and absence of polymers. *Cryst Growth* 2009;**10**:747-53
32. Rumondor AC, Stanford LA, Taylor LS. Effects of polymer type and storage relative humidity on the kinetics of felodipine crystallization from amorphous solid dispersions. *Pharm Res* 2009;**26**:2599
33. Janssens S, De Zeure A, Paudel A, Van Humbeeck J, Rombaut P, Van den Mooter G. Influence of preparation methods on solid state supersaturation of amorphous solid dispersions: a case study with itraconazole and eudragit e100. *Pharm Res* 2010;**27**:775-85
34. Mullin JW. Crystallization. Amsterdam, Netherlands: Elsevier, 2001.
35. Shamblin SL, Zografi G. The effects of absorbed water on the properties of amorphous mixtures containing sucrose. *Pharm Res* 1999;**16**:1119-24

36. Taylor LS, Zografi G. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. *Pharm Res* 1997;**14**:1691-98
37. Khougaz K, Clas SD. Crystallization inhibition in solid dispersions of MK- 0591 and poly (vinylpyrrolidone) polymers. *J Pharm Sci* 2000;**89**:1325-34
38. Marsac PJ, Shamblin SL, Taylor LS. Theoretical and practical approaches for prediction of drug–polymer miscibility and solubility. *Pharm Res* 2006;**23**:2417
39. Aso Y, Yoshioka S. Molecular mobility of nifedipine–PVP and phenobarbital–PVP solid dispersions as measured by 13C- NMR spin- lattice relaxation time. *J Pharm Sci* 2006;**95**:318-25
40. Hancock BC, Zografi G. The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids. *Pharm Res* 1994;**11**:471-77
41. Van den Mooter G, Wuyts M, Blaton N, Busson R, Grobet P, Augustijns P, et al. Physical stabilisation of amorphous ketoconazole in solid dispersions with polyvinylpyrrolidone K25. *Eur J Pharm Sci* 2001;**12**:261-69
42. Yoshioka M, Hancock BC, Zografi G. Crystallization of indomethacin from the amorphous state below and above its glass transition temperature. *J Pharm Sci* 1994;**83**:1700-05
43. Konno H, Handa T, Alonzo DE, Taylor LS. Effect of polymer type on the dissolution profile of amorphous solid dispersions containing felodipine. *Eur J Pharm Biopharm* 2008;**70**:493-99
44. Simonelli A, Mehta S, Higuchi W. Dissolution rates of high energy polyvinylpyrrolidone (PVP)- sulfathiazole coprecipitates. *J Pharm Sci* 1969;**58**:538-49
45. Ayenew Z, Paudel A, Van den Mooter G. Can compression induce demixing in amorphous solid dispersions? A case study of naproxen–PVP K25. *Eur J Pharm Biopharm* 2012;**81**:207-13
46. Janssens S, Van den Mooter G. Physical chemistry of solid dispersions. *J Pharm Pharmacol* 2009;**61**:1571-86
47. Janssens S, De Armas HN, Roberts CJ, Van den Mooter G. Characterization of ternary solid dispersions of itraconazole, PEG 6000, and HPMC 2910 E5. *J Pharm Sci* 2008;**97**:2110-20
48. Gangurde AB, Kundaikar HS, Javeer SD, Jaiswar DR, Degani MS, Amin PD. Enhanced solubility and dissolution of curcumin by a hydrophilic polymer solid dispersion and its insilico molecular modeling studies. *J Drug Deliv Sci Technol* 2015;**29**:226-37
49. Chen J, Ormes JD, Higgins JD, Taylor LS. Impact of surfactants on the crystallization of aqueous suspensions of celecoxib amorphous solid dispersion spray dried particles. *Mol Pharm* 2015;**12**:533-41
50. Marasini N, Tran TH, Poudel BK, Cho HJ, Choi YK, Chi S-C, et al. Fabrication and evaluation of pH-modulated solid dispersion for telmisartan by spray-drying technique. *Int J Pharm* 2013;**441**:424-32
51. Paidi SK, Jena SK, Ahuja BK, Devasari N, Suresh S. Preparation, *in- vitro* and *in- vivo* evaluation of spray- dried ternary solid dispersion of biopharmaceutics classification system class II model drug. *J Pharm Pharmacol* 2015;**67**:616-29
52. Morott JT, Pimparade M, Park J-B, Worley CP, Majumdar S, Lian Z, et al. The effects of screw configuration and polymeric carriers on hot-melt extruded taste-masked formulations incorporated into orally disintegrating tablets. *J Pharm Sci* 2015;**104**:124-34

53. Homayouni A, Sadeghi F, Nokhodchi A, Varshosaz J, Garekani HA. Preparation and characterization of celecoxib dispersions in Soluplus®: comparison of spray drying and conventional methods. *Iranian J Pharm Res* 2015;**14**:35
54. Harmon P, Galipeau K, Xu W, Brown C, Wuelfing WP. Mechanism of dissolution-induced nanoparticle formation from a copovidone-based amorphous solid dispersion. *Mol Pharm* 2016;**13**:1467-81
55. Ilevbare GA, Taylor LS. Liquid–liquid phase separation in highly supersaturated aqueous solutions of poorly water-soluble drugs: implications for solubility enhancing formulations. *Cryst Growth Des* 2013;**13**:1497-509
56. Frank KJ, Westedt U, Rosenblatt KM, Hölig P, Rosenberg J, Mägerlein M, et al. What is the mechanism behind increased permeation rate of a poorly soluble drug from aqueous dispersions of an amorphous solid dispersion?. *J Pharm Sci* 2014;**103**:1779-86
57. Canselier J, Lin C, Gabas N, Tanori J, Pezron I, Clausse D. Surfactant effects in crystallization: nucleation and crystal habit of γ-aminobutyric acid. In: Ottewill RH, Rennie AR, editors. *Trends in colloid and interface science VIII*. New York City, US: Springer, 1994, p. 174-78.
58. Rodríguez- Hornedo N, Murphy D. Surfactant- facilitated crystallization of dihydrate carbamazepine during dissolution of anhydrous polymorph. *J Pharm Sci* 2004;**93**:449-60
59. Dhumal RS, Shimpi SL, Paradkar AR. Development of spray-dried co-precipitate of amorphous celecoxib containing storage and compression stabilizers. *Acta Pharm* 2007;**57**:287-300
60. Suzuki H, Sunada H. Some factors influencing the dissolution of solid dispersions with nicotinamide and hydroxypropylmethylcellulose as combined carriers. *Chem Pharm Bull* 1998;**46**:1015-20
61. Alonzo DE, Gao Y, Zhou D, Mo H, Zhang GG, Taylor LS. Dissolution and precipitation behavior of amorphous solid dispersions. *J Pharm Sci* 2011;**100**:3316-31
62. Luebbert C, Sadowski G. Moisture-induced phase separation and recrystallization in amorphous solid dispersions. *Int J Pharm* 2017;**532**:635-46
63. Lin X, Hu Y, Liu L, Su L, Li N, Yu J, et al. Physical stability of amorphous solid dispersions: A physicochemical perspective with thermodynamic, kinetic and environmental aspects. *Pharm Res* 2018;**35**:125
64. Xie T, Taylor LS. Effect of temperature and moisture on the physical stability of binary and ternary amorphous solid dispersions of celecoxib. *J Pharm Sci* 2017;**106**:100-10
65. Lehmkemper K, Kyerematen SO, Heinzerling O, Degenhardt M, Sadowski G. Impact of polymer type and relative humidity on the long-term physical stability of amorphous solid dispersions. *Mol Pharm* 2017;**14**:4374-86
66. Marsac PJ, Konno H, Rumondor AC, Taylor LS. Recrystallization of nifedipine and felodipine from amorphous molecular level solid dispersions containing poly (vinylpyrrolidone) and sorbed water. *Pharm Res* 2008;**25**:647-56
67. Yang Z, Nollenberger K, Albers J, Qi S. Molecular implications of drug–polymer solubility in understanding the destabilization of solid dispersions by milling. *Mol Pharm* 2014;**11**:2453-65
68. Német Z, Sztatisz J, Demeter Á. Polymorph transitions of bicalutamide: a remarkable example of mechanical activation. *J Pharm Sci* 2008;**97**:3222-32
69. Zhang Z, Dong L, Guo J, Li L, Tian B, Zhao Q, et al. Prediction of the physical stability of amorphous solid dispersions: Relationship of aging and phase separation with the

thermodynamic and kinetic models along with characterization techniques. *Expert Opin Drug Del* 2020
70. LaFountaine JS, McGinity JW, Williams RO. Challenges and strategies in thermal processing of amorphous solid dispersions: a review. *AAPS PharmSciTech* 2016;**17**:43-55
71. He Y, Ho C. Amorphous solid dispersions: utilization and challenges in drug discovery and development. *J Pharm Sci* 2015;**104**:3237-58
72. Qian F, Huang J, Hussain MA. Drug–polymer solubility and miscibility: stability consideration and practical challenges in amorphous solid dispersion development. *J Pharm Sci* 2010;**99**:2941-47
73. Rahman Z, Siddiqui A, Gupta A, Khan M. Regulatory considerations in development of amorphous solid dispersions. In: Shah N, Sandhu H, Choi DS, Chokshi H, Malick AW, editors. *Amorphous solid dispersions*. New York City, US: Springer, 2014, p. 545-63.
74. Li J, Zhao J, Tao L, Wang J, Waknis V, Pan D, et al. The effect of polymeric excipients on the physical properties and performance of amorphous dispersions: part I, free volume and glass transition. *Pharm Res* 2015;**32**:500-15
75. Nunes TG, Viciosa MT, Correia NlT, Danede F, Nunes RG, Diogo HP. A stable amorphous statin: solid-state NMR and dielectric studies on dynamic heterogeneity of simvastatin. *Mol Pharm* 2014;**11**:727-37
76. Graeser KA, Patterson JE, Zeitler JA, Gordon KC, Rades T. Correlating thermodynamic and kinetic parameters with amorphous stability. *Eur J Pharm Sci* 2009;**37**:492-98
77. Marsac PJ, Konno H, Taylor LS. A comparison of the physical stability of amorphous felodipine and nifedipine systems. *Pharm Res* 2006;**23**:2306-16
78. Guo Z, Lu M, Li Y, Pang H, Lin L, Liu X, et al. The utilization of drug–polymer interactions for improving the chemical stability of hot- melt extruded solid dispersions. *J Pharm Pharmacol* 2014;**66**:285-96
79. Sarode AL, Sandhu H, Shah N, Malick W, Zia H. Hot melt extrusion for amorphous solid dispersions: temperature and moisture activated drug–polymer interactions for enhanced stability. *Mol Pharm* 2013;**10**:3665-75
80. Sóti PL, Bocz K, Pataki H, Eke Z, Farkas A, Verreck G, et al. Comparison of spray drying, electroblowing and electrospinning for preparation of Eudragit E and itraconazole solid dispersions. *Int J Pharm* 2015;**494**:23-30
81. Passerini N, Calogerà G, Albertini B, Rodriguez L. Melt granulation of pharmaceutical powders: a comparison of high-shear mixer and fluidised bed processes. *Int J Pharm* 2010;**391**:177-86
82. Potter C, Tian Y, Walker G, McCoy C, Hornsby P, Donnelly C, et al. Novel supercritical carbon dioxide impregnation technique for the production of amorphous solid drug dispersions: a comparison to hot melt extrusion. *Mol Pharm* 2015;**12**:1377-90
83. Won D-H, Kim M-S, Lee S, Park J-S, Hwang S-J. Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical anti-solvent precipitation process. *Int J Pharm* 2005;**301**:199-208
84. Paudel A, Worku ZA, Meeus J, Guns S, Van den Mooter G. Manufacturing of solid dispersions of poorly water soluble drugs by spray drying: formulation and process considerations. *Int J Pharm* 2013;**453**:253-84
85. Li N, Cape JL, Mankani BR, Zemlyanov DY, Shepard KB, Morgen MM, et al. Water-induced phase separation of spray dried amorphous solid dispersions. *Mol Pharm* 2020

86. Bercea M, Eckelt J, Morariu S, Wolf BA. Islands of immiscibility for solutions of compatible polymers in a common solvent: experiment and theory. *Macromolecules* 2009;**42**:3620-26
87. Bercea M, Eckelt J, Wolf BA. Vapor pressures of polymer solutions and the modeling of their composition dependence. *Ind Eng Chem Res* 2009;**48**:4603-06
88. Yue H, Nicholson SJ, Young JD, Hsieh D, Ketner RJ, Hall RG, et al. Development of a control strategy for benzene impurity in HPMCAS-stabilized spray-dried dispersion drug products using a science-based and risk-based approach. *Pharm Res* 2015;**32**:2636-48
89. Harmonization ICf. International Council for Harmonization. Q3C impurities: residual solvents R6: FDA, 2019.
90. Pouton CW. Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. *Eur J Pharm Sci* 2006;**29**:278-87
91. Dhirendra K, Lewis S, Udupa N, Atin K. Solid dispersions: a review. *Pak J Pharm Sci* 2009;**22**
92. Dobry DE, Settell DM, Baumann JM. Spray Drying and Scale- Up. In: Newman A, ed. *Pharmaceutical amorphous solid dispersions*. Hoboken, US: Wiley, 2010, p. 1-26.
93. Dobry DE, Ketner RJ, Lyon DK, Mullin JM, inventors; Bend Research Inc, assignee. Drying of drug-containing particles. United States patent US No. 8,834,929. 2014 Sep 16.
94. Ray RJ, Newbold DD, Beyerinck RA, Dobry DE, Grove KD, inventors; Bend Research Inc, assignee. Drying of drug-containing particles. United States patent US No. 8,834,929. 2016 Feb 23.
95. Shepard KB, Dower AM, Ekdahl AM, Morgen MM, Baumann JM, Vodak DT. Solvent-Assisted Secondary Drying of Spray-Dried Polymers. *Pharm Res* 2020;**37**:1-11
96. Miller DA, Gil M. Spray-drying technology. In: Williams III RO, Watts AB, Miller DA, editors. Formulating poorly water soluble drugs. New York City, US: Springer, 2012, p. 363-442.
97. Tonon RV, Brabet C, Hubinger MD. Influence of process conditions on the physicochemical properties of açai (Euterpe oleraceae Mart.) powder produced by spray drying. *J Food Eng* 2008;**88**:411-18
98. Sawicki E, Beijnen JH, Schellens JH, Nuijen B. Pharmaceutical development of an oral tablet formulation containing a spray dried amorphous solid dispersion of docetaxel or paclitaxel. *Int J Pharm* 2016;**511**:765-73
99. Nežić I, Sander A, Meštrović E, Čavužić D. Production of stable amorphous form by means of spray drying. *Part Sci Technol* 2019;**37**:632-42
100. Ohyagi N, Ueda K, Higashi K, Yamamoto K, Kawakami K, Moribe K. Synergetic role of hypromellose and methacrylic acid copolymer in the dissolution improvement of amorphous solid dispersions. *J Pharm Sci* 2017;**106**:1042-50
101. Kim J-S, Kim M-S, Park HJ, Jin S-J, Lee S, Hwang S-J. Physicochemical properties and oral bioavailability of amorphous atorvastatin hemi-calcium using spray-drying and SAS process. *Int J Pharm* 2008;**359**:211-19
102. Singh A, Van den Mooter G. Spray drying formulation of amorphous solid dispersions. *Adv Drug Del Rev* 2016;**100**:27-50
103. Ogawa N, Hiramatsu T, Suzuki R, Okamoto R, Shibagaki K, Fujita K, et al. Improvement in the water solubility of drugs with a solid dispersion system by spray drying and hot-

melt extrusion with using the amphiphilic polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer and d-mannitol. *Eur J Pharm Sci* 2018;**111**:205-14
104. Mujumdar AS. Handbook of industrial drying, revised and expanded. Boca Raton, US: CRC Press, 1995.
105. Bayvel LP, Orzechowski Z. *Liquid atomization*. Boca Raton, US: CRC Press, 1993.
106. Lefebvre AH, McDonell VG. Atomization and sprays. Boca Raton, US: CRC press, 2017.
107. Beyerinck RA, Deibele HL, Dobry DE, Ray RJ, Settell DM, Spence KR, inventors; Pfizer Inc, assignee. Method for making homogeneous spray-dried solid amorphous drug dispersions utilizing modified spray-drying apparatus. United States patent US No. 6,763,607. 2004 Jul 20.
108. Beyerinck RA, Ray RJ, Dobry DE, Settell DM, inventors; Bend Research Inc, assignee. Method for making homogeneous spray-dried solid amorphous drug dispersions using pressure nozzles. United States patent US No. 7,780,988. 2010 Aug 24.
109. Wang X, Lefebvre A. Mean drop sizes from pressure-swirl nozzles. *J Propul Power* 1987;**3**:11-18
110. Stähle P, Schuchmann HP, Gaukel V. Performance and efficiency of pressure- swirl and twin- fluid nozzles spraying food liquids with varying viscosity. *J Food Process Eng* 2017;**40**:e12317
111. Beck-Broichsitter M, Bohr A, Aragão-Santiago L, Klingl A, Kissel T. Formulation and process considerations for the design of sildenafil-loaded polymeric microparticles by vibrational spray-drying. *Pharm Dev Technol* 2017;**22**:691-98
112. Oakley DE. Spray dryer modeling in theory and practice. *Drying Technol* 2004;**22**:1371-402
113. Zbicinski I, Strumillo C, Delag A. Drying kinetics and particle residence time in spray drying. *Drying Technol* 2002;**20**:1751-68
114. Hoekstra AJ. Gas flow field and collection efficiency of cyclone separators. *TU Delft, Ph. D. Thesis, Delft University of Technology* 2000
115. Cal K, Sollohub K. Spray drying technique. I: Hardware and process parameters. *J Pharm Sci* 2010;**99**:575-86
116. Ayenew Z, Paudel A, Rombaut P, Van den Mooter G. Effect of compression on non-isothermal crystallization behaviour of amorphous indomethacin. *Pharm Res* 2012;**29**:2489-98
117. Singh A, De Bisschop C, Schut H, Van Humbeeck J, Van Den Mooter G. Compression effects on the phase behaviour of miconazole-poly (1-vinylpyrrolidone-*co*-vinyl acetate) solid dispersions—role of pressure, dwell time, and preparation method. *J Pharm Sci* 2015;**104**:3366-76
118. Singh A, Van Humbeeck J, Van den Mooter G. A new twist in the old story-can compression induce mixing of phase separated solid dispersions? A case study of spray-dried miconazole-PVP VA64 solid dispersions. *Pharm Res* 2014;**31**:3191-200
119. Gu B, Linehan B, Tseng Y-C. Optimization of the Büchi B-90 spray drying process using central composite design for preparation of solid dispersions. *Int J Pharm* 2015;**491**:208-17
120. Thybo P, Hovgaard L, Lindeløv JS, Brask A, Andersen SK. Scaling up the spray drying process from pilot to production scale using an atomized droplet size criterion. *Pharm Res* 2008;**25**:1610-20

121. Dobry DE, Settell DM, Baumann JM, Ray RJ, Graham LJ, Beyerinck RA. A model-based methodology for spray-drying process development. *J Pharm Innov* 2009;**4**:133-42
122. Ohta M, Buckton G. A study of the differences between two amorphous spray-dried samples of cefditoren pivoxil which exhibited different physical stabilities. *Int J Pharm* 2005;**289**:31-38
123. Sandhu H, Shah N, Chokshi H, Malick AW. Overview of amorphous solid dispersion technologies. In: Shah N, Sandhu H, Choi DS, Chokshi H, Malick AW, editors. Amorphous Solid Dispersions. New York City, US: Springer, 2014, p. 91-122.
124. Vehring R. Pharmaceutical particle engineering *via* spray drying. *Pharm Res* 2008;**25**:999-1022
125. Vehring R, Foss WR, Lechuga-Ballesteros D. Particle formation in spray drying. *J Aerosol Sci* 2007;**38**:728-46
126. Marin AG, Gelderblom H, Lohse D, Snoeijer JH. Order-to-disorder transition in ring-shaped colloidal stains. *Phys Rev Lett* 2011;**107**:085502
127. Worku ZA, Aarts J, Singh A, Van den Mooter G. Drug–polymer miscibility across a spray dryer: A case study of naproxen and miconazole solid dispersions. *Mol Pharm* 2014;**11**:1094-101
128. Bhujbal SV, Zemlyanov DY, Cavallaro A, Mangal S, Taylor LS, Zhou QT. Qualitative and quantitative characterization of composition heterogeneity on the surface of spray dried amorphous solid dispersion particles by an advanced surface analysis platform with high surface sensitivity and superior spatial resolution. *Mol Pharm* 2018;**15**:2045-53
129. Bhardwaj V, Trasi NS, Zemlyanov DY, Taylor LS. Surface area normalized dissolution to study differences in itraconazole-copovidone solid dispersions prepared by spray-drying and hot melt extrusion. *Int J Pharm* 2018;**540**:106-19
130. Wu T, Sun Y, Li N, de Villiers MM, Yu L. Inhibiting surface crystallization of amorphous indomethacin by nanocoating. *Langmuir* 2007;**23**:5148-53
131. Kemp IC. Fundamentals of energy analysis of dryers. *Modern drying technology* 2012;**4**:1-46
132. Shetty N, Ahn P, Park H, Bhujbal SV, Zemlyanov D, Cavallaro A, et al. Improved physical stability and aerosolization of inhalable amorphous ciprofloxacin powder formulations by incorporating synergistic colistin. *Mol Pharm* 2018;**15**:4004-20
133. Wang W, Zhou QT, Sun S-P, Denman JA, Gengenbach TR, Barraud N, et al. Effects of surface composition on the aerosolisation and dissolution of inhaled antibiotic combination powders consisting of colistin and rifampicin. *AAPS J* 2016;**18**:372-84
134. Zhou QT, Loh ZH, Yu J, Sun S-p, Gengenbach T, Denman JA, et al. How much surface coating of hydrophobic azithromycin is sufficient to prevent moisture-induced decrease in aerosolisation of hygroscopic amorphous colistin powder?. *AAPS J* 2016;**18**:1213-24
135. Kolter K, Schoenherr M, Ascherl H, inventors; assignee. Production of solid solutions based on poorly-soluble active substances by a short-term heating and rapid drying. United States patent application US No. 11/916,074. 2008 Oct 9.
136. Friesen DT, Newbold DD, Baumann JM, Dubose DB, Millard DL, inventors; Bend Research Inc, assignee. High-temperature spray drying process and apparatus. United States patent US No. 9,248,584. 2016 Feb 2.
137. Smeets A, Koekoekx R, Clasen C, Van den Mooter G. Amorphous solid dispersions of darunavir: Comparison between spray drying and electrospraying. *Eur J Pharm Biopharm* 2018;**130**:96-107

138. Ziaee A, Albadarin AB, Padrela L, Faucher A, O'Reilly E, Walker G. Spray drying ternary amorphous solid dispersions of ibuprofen–an investigation into critical formulation and processing parameters. *Eur J Pharm Biopharm* 2017;**120**:43-51
139. Tran DT, Majerová D, Veselý M, Kulaviak L, Ruzicka MC, Zámostný P. On the mechanism of colloidal silica action to improve flow properties of pharmaceutical excipients. *Int J Pharm* 2019;**556**:383-94
140. Lee Y-C, McNevin M, Ikeda C, Chouzouri G, Moser J, Harris D, et al. Combination of colloidal silicon dioxide with spray-dried solid dispersion to facilitate discharge from an agitated dryer. *AAPS PharmSciTech* 2019;**20**:1-7
141. Hengsawas Surasarang S, Keen JM, Huang S, Zhang F, McGinity JW, Williams III RO. Hot melt extrusion *versus* spray drying: hot melt extrusion degrades albendazole. *Drug Dev Ind Pharm* 2017;**43**:797-811
142. Lim RTY, Ong CK, Cheng S, Ng WK. Amorphization of crystalline active pharmaceutical ingredients *via* formulation technologies. *Powder Technol* 2017;**311**:175-84
143. Fong SYK, Ibisogly A, Bauer-Brandl A. Solubility enhancement of BCS Class II drug by solid phospholipid dispersions: spray drying *versus* freeze-drying. *Int J Pharm* 2015;**496**:382-91
144. Sóti PL, Nagy ZK, Serneels G, Vajna B, Farkas A, Van der Gucht F, et al. Preparation and comparison of spray dried and electrospun bioresorbable drug delivery systems. *Eur Polym J* 2015;**68**:671-79
145. Chen D-R, Pui DY, Kaufman SL. Electrospraying of conducting liquids for monodisperse aerosol generation in the 4 nm to 1.8 μm diameter range. *J Aerosol Sci* 1995;**26**:963-77
146. Hogan Jr CJ, Biswas P. Narrow size distribution nanoparticle production by electrospray processing of ferritin. *J Aerosol Sci* 2008;**39**:432-40
147. De Juan L, De La Mora JF. Charge and size distributions of electrospray drops. *J Colloid Interface Sci* 1997;**186**:280-93
148. Boel E, Koekoekx R, Dedroog S, Babkin I, Vetrano MR, Clasen C, et al. Unraveling particle formation: from single droplet drying to spray drying and electrospraying. *Pharmaceutics* 2020;**12**:625
149. Kivikero N, Murtomaa M, Ingelbeen B, Antikainen O, Räsänen E, Mannermaa J-P, et al. Microscale granulation in a fluid bed powder processor using electrostatic atomisation. *Eur J Pharm Biopharm* 2009;**71**:130-37
150. Ho H, Lee J. PEG/PLA core/shell particles from coaxial electrohydrodynamic spray drying. *Macromol Res* 2011;**19**:815-21
151. Nguyen DN, Clasen C, Van den Mooter G. Pharmaceutical applications of electrospraying. *J Pharm Sci* 2016;**105**:2601-20
152. Yurteri CU, Hartman RP, Marijnissen JC. Producing pharmaceutical particles *via* electrospraying with an emphasis on nano and nano structured particles—a review. *KONA Powder Part. J* 2010;**28**:91-115
153. Jaworek A. Micro-and nanoparticle production by electrospraying. *Powder Technol* 2007;**176**:18-35
154. Jaworek A, Sobczyk AT. Electrospraying route to nanotechnology: An overview. *J Electrostatics* 2008;**66**:197-219
155. Xie J, Marijnissen JC, Wang CH. Microparticles developed by electrohydrodynamic atomization for the local delivery of anticancer drug to treat C6 glioma *in vitro*. *Biomaterials* 2006;**27**:3321-32

156. Ciach T. Microencapsulation of drugs by electro-hydro-dynamic atomization. *Int J Pharm* 2006;**324**:51-55
157. Nyström M, Roine J, Murtomaa M, Sankaran RM, Santos HA, Salonen J. Solid state transformations in consequence of electrospraying–a novel polymorphic form of piroxicam. *Eur J Pharm Biopharm* 2015;**89**:182-89
158. Nyström M, Murtomaa M, Salonen J. Fabrication and characterization of drug particles produced by electrospraying into reduced pressure. *J Electrostatics* 2010;**68**:42-48
159. Davies LA, Hannavy K, Davies N, Pirrie A, Coffee RA, Hyde SC, et al. Electrohydrodynamic comminution: a novel technique for the aerosolisation of plasmid DNA. *Pharm Res* 2005;**22**:1294-304
160. Ijsebaert JC, Geerse KB, Marijnissen JC, Lammers J-WJ, Zanen P. Electro-hydrodynamic atomization of drug solutions for inhalation purposes. *J Appl Physiol* 2001;**91**:2735-41
161. Xie J, Lim LK, Phua Y, Hua J, Wang CH. Electrohydrodynamic atomization for biodegradable polymeric particle production. *J Colloid Interface Sci* 2006;**302**:103-12
162. Kessick R, Fenn J, Tepper G. The use of AC potentials in electrospraying and electrospinning processes. *Polymer* 2004;**45**:2981-84
163. Collins G, Federici J, Imura Y, Catalani LH. Charge generation, charge transport, and residual charge in the electrospinning of polymers: A review of issues and complications. *J Appl Phys* 2012;**111**:044701
164. Verreck G, Chun I, Peeters J, Rosenblatt J, Brewster ME. Preparation and characterization of nanofibers containing amorphous drug dispersions generated by electrostatic spinning. *Pharm Res* 2003;**20**:810-17
165. Nagy ZK, Balogh A, Vajna B, Farkas A, Patyi G, Kramarics Á, et al. Comparison of electrospun and extruded Soluplus®-based solid dosage forms of improved dissolution. *J Pharm Sci* 2012;**101**:322-32
166. Yu DG, Shen XX, Branford-White C, White K, Zhu LM, Bligh SA. Oral fast-dissolving drug delivery membranes prepared from electrospun polyvinylpyrrolidone ultrafine fibers. *Nanotechnology* 2009;**20**:055104
167. Nagy ZK, Balogh A, Démuth B, Pataki H, Vigh T, Szabó B, et al. High speed electrospinning for scaled-up production of amorphous solid dispersion of itraconazole. *Int J Pharm* 2015;**480**:137-42
168. Bohr A, Kristensen J, Stride E, Dyas M, Edirisinghe M. Preparation of microspheres containing low solubility drug compound by electrohydrodynamic spraying. *Int J Pharm* 2011;**412**:59-67
169. Bohr A, Kristensen J, Dyas M, Edirisinghe M, Stride E. Release profile and characteristics of electrosprayed particles for oral delivery of a practically insoluble drug. *J R Soc Interface* 2012;**9**:2437-49
170. Yu DG, Williams GR, Wang X, Yang JH, Li XY, Qian W, et al. Polymer-based nanoparticulate solid dispersions prepared by a modified electrospraying process. *J Biomed Sci Eng* 2011;**4**:741
171. Yu DG, Xu Y, Luo JQ, Zhao JS, Teng L, Kuang QK, et al. Oral rapid-dissolving polymeric nanoparticles of acetaminophen fabricated using electrospraying. *Adv Mat Res* 2014;**898**:283-87
172. Li C, Yu D-G, Williams GR, Wang Z-H. Fast-dissolving core-shell composite microparticles of quercetin fabricated using a coaxial electrospray process. *PLoS One* 2014;**9**:e92106

173. Mohammadi G, Hemati V, Nikbakht M-R, Mirzaee S, Fattahi A, Ghanbari K, et al. In vitro and *in vivo* evaluation of clarithromycin–urea solid dispersions prepared by solvent evaporation, electrospraying and freeze drying methods. *Powder Technol* 2014;**257**:168-74
174. Zhang S, Kawakami K, Yamamoto M, Masaoka Y, Kataoka M, Yamashita S, et al. Coaxial electrospray formulations for improving oral absorption of a poorly water-soluble drug. *Mol Pharm* 2011;**8**:807-13
175. Baird JA, Van Eerdenbrugh B, Taylor LS. A classification system to assess the crystallization tendency of organic molecules from undercooled melts. *J Pharm Sci* 2010;**99**:3787-806
176. Van Eerdenbrugh B, Baird JA, Taylor LS. Crystallization tendency of active pharmaceutical ingredients following rapid solvent evaporation—classification and comparison with crystallization tendency from under cooled melts. *J Pharm Sci* 2010;**99**:3826-38
177. Nyström M, Murtomaa M, Salonen J. Fabrication of amorphous pharmaceutical materials by electrospraying into reduced pressure. *J Electrostatics* 2011;**69**:351-56
178. Ziabicki A, Jarecki L. Crystal nucleation in an electric field. *Macromolecular Symposia* 1996;**104**:65-87.
179. Bohr A, Yang M, Baldursdóttir S, Kristensen J, Dyas M, Stride E, et al. Particle formation and characteristics of Celecoxib-loaded poly (lactic-*co*-glycolic acid) microparticles prepared in different solvents using electrospraying. *Polymer* 2012;**53**:3220-29
180. Bohr A, Wan F, Kristensen J, Dyas M, Stride E, Baldursdottír S, et al. Pharmaceutical microparticle engineering with electrospraying: the role of mixed solvent systems in particle formation and characteristics. *J Mater Sci Mater Med* 2015;**26**:61
181. Gupta P, Elkins C, Long TE, Wilkes GL. Electrospinning of linear homopolymers of poly (methyl methacrylate): exploring relationships between fiber formation, viscosity, molecular weight and concentration in a good solvent. *Polymer* 2005;**46**:4799-810
182. Palangetic L, Reddy NK, Srinivasan S, Cohen RE, McKinley GH, Clasen C. Dispersity and spinnability: Why highly polydisperse polymer solutions are desirable for electrospinning. *Polymer* 2014;**55**:4920-31
183. Theron S, Yarin A, Zussman E, Kroll E. Multiple jets in electrospinning: experiment and modeling. *Polymer* 2005;**46**:2889-99
184. Lu B, Wang Y, Liu Y, Duan H, Zhou J, Zhang Z, et al. Superhigh- throughput needleless electrospinning using a rotary cone as spinneret. *small* 2010;**6**:1612-16
185. Bock N, Dargaville TR, Woodruff MA. Electrospraying of polymers with therapeutic molecules: state of the art. *Prog Polym Sci* 2012;**37**:1510-51
186. Tamrakar A, Ramachandran R. CFD–DEM–PBM coupled model development and validation of a 3D top-spray fluidized bed wet granulation process. *Comput Chem Eng* 2019;**125**:249-70
187. Wentzlaff M, Senz V, Seidlitz A. Evaluation of the suitability of a fluidized bed process for the coating of drug-eluting stents. *Eur J Pharm Biopharm* 2019;**139**:85-92
188. Rajabi-Siahboomi AR. Overview of multiparticulate systems for oral drug delivery. In: Rajabi-Siahboomi A, Ed. *Multiparticulate drug delivery*. New York City, US: Springer, 2017, p. 1-4.
189. Kallakunta V, Sarabau S, Tiwari R. Multiple Unit Particle Systems (MUPS), a Versatile Strategy for Controlled Drug delivery: Focus on Formulation and Process Concerns. *J Formulation Sci Bioavailability* 2017;**1**:106

190. Kwon HJ, Heo EJ, Kim YH, Kim S, Hwang YH, Byun JM, et al. Development and evaluation of poorly water-soluble celecoxib as solid dispersions containing nonionic surfactants using fluidized-bed granulation. *Pharmaceutics* 2019;**11**:136
191. Nandi A, Cheng A, Billingham JF, inventors; Praxair Technology Inc, assignee. System and method for solvent recovery in a batch fluidized bed process. United States patent US No. 8,973,283. 2015 Mar 10.
192. Beten DB, Amighi K, Moës AJ. Preparation of controlled-release coevaporates of dipyridamole by loading neutral pellets in a fluidized-bed coating system. *Pharm Res* 1995;**12**:1269-72
193. Ho H-O, Su H-L, Tsai T, Sheu M-T. The preparation and characterization of solid dispersions on pellets using a fluidized-bed system. *Int J Pharm* 1996;**139**:223-29
194. Dereymaker A, Scurr DJ, Steer ED, Roberts CJ, Van den Mooter G. Controlling the release of indomethacin from glass solutions layered with a rate controlling membrane using fluid-bed processing. Part 1: Surface and cross-sectional chemical analysis. *Mol Pharm* 2017;**14**:959-73
195. Varum FJ, Veiga F, Sousa JS, Basit AW. Mucoadhesive platforms for targeted delivery to the colon. *Int J Pharm* 2011;**420**:11-19
196. Dybdahl Hede P. Fluid bed particle processing. Frederiksberg, Denmark: BookBoon, 2006.
197. Mendonsa N, Almutairy B, Kallakunta VR, Sarabu S, Thipsay P, Bandari S, et al. Manufacturing strategies to develop amorphous solid dispersions: An overview. *J Drug Deliv Sci Technol* 2019;**55**:101459
198. Guignon B, Regalado E, Duquenoy A, Dumoulin E. Helping to choose operating parameters for a coating fluid bed process. *Powder Technol* 2003;**130**:193-98
199. Sun N, Wei X, Wu B, Chen J, Lu Y, Wu W. Enhanced dissolution of silymarin/polyvinylpyrrolidone solid dispersion pellets prepared by a one-step fluid-bed coating technique. *Powder Technol* 2008;**182**:72-80
200. Zhang X, Sun N, Wu B, Lu Y, Guan T, Wu W. Physical characterization of lansoprazole/PVP solid dispersion prepared by fluid-bed coating technique. *Powder Technol* 2008;**182**:480-85
201. Yan H-X, Zhang S-S, He J-H, Liu J-P. Application of ethyl cellulose, microcrystalline cellulose and octadecanol for wax based floating solid dispersion pellets. *Carbohydr Polym* 2016;**148**:143-52
202. Lu Y, Zhang X, Lai J, Yin Z, Wu W. Physical characterization of meloxicam-*β*-cyclodextrin inclusion complex pellets prepared by a fluid-bed coating method. *Particuology* 2009;**7**:1-8
203. Narayan P, Porter III WW, Brackhagen M, Tucker C. Polymers and surfactants. *Pharmaceutical Sciences Encyclopedia: Drug Discovery, Development, and Manufacturing* 2010:1-43
204. Gilis PM, De Conde VF, Vandecruys RP, inventors; Janssen Pharmaceutica NV, assignee. Beads having a core coated with an antifungal and a polymer. United States patent US No. 5,633,015. 1997 May 27.
205. Srinarong P, de Waard H, Frijlink HW, Hinrichs WL. Improved dissolution behavior of lipophilic drugs by solid dispersions: the production process as starting point for formulation considerations. *Expert Opin Drug Del* 2011;**8**:1121-40
206. Pasquali I, Bettini R, Giordano F. Supercritical fluid technologies: an innovative approach for manipulating the solid-state of pharmaceuticals. *Adv Drug Del Rev* 2008;**60**:399-410

207. Yang W, Owens DE, Williams RO. Pharmaceutical cryogenic technologies. In: Williams RO, Watts AB, Miller DA, editors. *Formulating poorly water soluble drugs*. New York City, US: Springer, 2012, p. 443-500.
208. Tabbakhian M, Hasanzadeh F, Tavakoli N, Jamshidian Z. Dissolution enhancement of glibenclamide by solid dispersion: solvent evaporation *versus* a supercritical fluid-based solvent-antisolvent technique. *Res Pharm Sci* 2014;**9**:337
209. Yin X, Daintree LS, Ding S, Ledger DM, Wang B, Zhao W, et al. Itraconazole solid dispersion prepared by a supercritical fluid technique: preparation, *in vitro* characterization, and bioavailability in beagle dogs. *Drug Des Devel Ther* 2015;**9**:2801
210. Girotra P, Singh SK, Nagpal K. Supercritical fluid technology: a promising approach in pharmaceutical research. *Pharm Dev Technol* 2013;**18**:22-38
211. Sanganwar GP, Gupta RB. Dissolution-rate enhancement of fenofibrate by adsorption onto silica using supercritical carbon dioxide. *Int J Pharm* 2008;**360**:213-18
212. Mishima K, Honjo M, Sharmin T, Ito S, Kawakami R, Kato T, et al. Gas-saturated solution process to obtain microcomposite particles of alpha lipoic acid/hydrogenated colza oil in supercritical carbon dioxide. *Pharm Dev Technol* 2016;**21**:737-48
213. Jiang Q, Li Y, Fu Q, Geng Y, Zhao J, Ma P, et al. *In-vitro* and *in-vivo* study of amorphous spironolactone prepared by adsorption method using supercritical CO2. *Drug Dev Ind Pharm* 2015;**41**:201-06
214. Dixon DJ, Johnston KP, Bodmeier RA. Polymeric materials formed by precipitation with a compressed fluid antisolvent. *AIChE Journal* 1993;**39**:127-39
215. Reverchon E. Supercritical antisolvent precipitation of micro-and nano-particles. *J Supercrit Fluids* 1999;**15**:1-21
216. York P, Kompella UB, Shekunov BY. *Supercritical fluid technology for drug product development*. Boca Raton, US: CRC Press, 2004.
217. Jung J, Clavier JY, Perrut M, editors. Gram to kilogram scale-up of supercritical anti-solvent process. Proceedings of the 6th International Symposium on Supercritical Fluids at Versailles, on April 28, 2003. Downloaded from www.futurechemtech.com.
218. Kim MS, Jin SJ, Kim JS, Park HJ, Song HS, Neubert RH, et al. Preparation, characterization and *in vivo* evaluation of amorphous atorvastatin calcium nanoparticles using supercritical antisolvent (SAS) process. *Eur J Pharm Biopharm* 2008;**69**:454-65
219. Ha E-S, Kim J-S, Baek I-h, Yoo J-W, Jung Y, Moon HR, et al. Development of megestrol acetate solid dispersion nanoparticles for enhanced oral delivery by using a supercritical antisolvent process. *Drug Des Devel Ther* 2015;**9**:4269
220. Kim M-S, Baek I-h. Fabrication and evaluation of valsartan–polymer–surfactant composite nanoparticles by using the supercritical antisolvent process. *Int J Nanomedicine* 2014;**9**:5167
221. Gong K, Viboonkiat R, Rehman I, Buckton G, Darr J. Formation and characterization of porous indomethacin- PVP coprecipitates prepared using solvent- free supercritical fluid processing. *J Pharm Sci* 2005;**94**:2583-90
222. Park J, Park HJ, Cho W, Cha KH, Kang YS, Hwang SJ. Preparation and pharmaceutical characterization of amorphous cefdinir using spray-drying and SAS-process. *Int J Pharm* 2010;**396**:239-45
223. Sui X, Wei W, Yang L, Zu Y, Zhao C, Zhang L, et al. Preparation, characterization and *in vivo* assessment of the bioavailability of glycyrrhizic acid microparticles by supercritical anti-solvent process. *Int J Pharm* 2012;**423**:471-79

224. Yoshida VM, Balcão VM, Vila MM, Júnior JMO, Aranha N, Chaud MV, et al. Zidovudine-poly (L-lactic acid) solid dispersions with improved intestinal permeability prepared by supercritical antisolvent process. *J Pharm Sci* 2015;**104**:1691-700
225. Lee S, Nam K, Kim MS, Jun SW, Park J-S, Woo JS, et al. Preparation and characterization of solid dispersions of itraconazole by using aerosol solvent extraction system for improvement in drug solubility and bioavailability. *Arch Pharm Res* 2005;**28**:866-74
226. Muhrer G, Meier U, Fusaro F, Albano S, Mazzotti M. Use of compressed gas precipitation to enhance the dissolution behavior of a poorly water-soluble drug: Generation of drug microparticles and drug–polymer solid dispersions. *Int J Pharm* 2006;**308**:69-83
227. Hanna M, York P, inventors; University of Bradford, assignee. Method and apparatus for the formation of particles. United States patent US No. 5,851,453. 1998 Dec 22.
228. Ghaderi R, Artursson P, Carlfors J. A new method for preparing biodegradable microparticles and entrapment of hydrocortisone in DL-PLG microparticles using supercritical fluids. *Eur J Pharm Sci* 2000;**10**:1-9
229. Beach S, Latham D, Sidgwick C, Hanna M, York P. Control of the physical form of salmeterol xinafoate. *Org Process Res Dev* 1999;**3**:370-76
230. Li Y, Yang DJ, Chen SL, Chen SB, Chan ASC. Process parameters and morphology in puerarin, phospholipids and their complex microparticles generation by supercritical antisolvent precipitation. *Int J Pharm* 2008;**359**:35-45
231. Pestieau A, Krier F, Lebrun P, Evrard B. Optimization of a PGSS process for a fenofibrate lipid-based solid dispersion formulation. 2015
232. Falconer JR, Wen J, Zargar- Shoshtari S, Chen JJ, Mohammed F, Chan J, et al. The effects of supercritical carbon dioxide processing on progesterone dispersion systems: a multivariate study. *AAPS PharmSciTech* 2012;**13**:1255-65
233. Verreck G, Decorte A, Heymans K, Adriaensen J, Cleeren D, Jacobs A, et al. The effect of pressurized carbon dioxide as a temporary plasticizer and foaming agent on the hot stage extrusion process and extrudate properties of solid dispersions of itraconazole with PVP-VA 64. *Eur J Pharm Sci* 2005;**26**:349-58
234. Sheth P, Sandhu H. Amorphous solid dispersion using supercritical fluid technology. In: Shah N, Sandhu H, Choi DS, Chokshi H, Malick AW, editors. *Amorphous solid dispersions.* New York City, US: Springer, 2014, p. 579-91.
235. Wang Z, Finlay W, Peppler M, Sweeney L. Powder formation by atmospheric spray-freeze-drying. *Powder Technol* 2006;**170**:45-52
236. Leuenberger H. Spray freeze-drying–the process of choice for low water soluble drugs?. *J Nanopart Res* 2002;**4**:111-19
237. Maa Y-F, Nguyen P-A, inventors; Genentech Inc, assignee. Method of spray freeze drying proteins for pharmaceutical administration. United States patent US No. 6,284,282. 2001 Sep 4.
238. Williams III RO, Johnston KP, Young TJ, Rogers TL, Barron MK, Yu Z, et al., inventors; University of Texas System, assignee. Process for production of nanoparticles and microparticles by spray freezing into liquid. United States patent US No. 6,862,890. 2005 Mar 8.
239. Hu J, Rogers TL, Brown J, Young T, Johnston KP, Williams Iii RO. Improvement of dissolution rates of poorly water soluble APIs using novel spray freezing into liquid technology. *Pharm Res* 2002;**19**:1278-84

240. Hu J, Johnston KP, Williams III RO. Spray freezing into liquid (SFL) particle engineering technology to enhance dissolution of poorly water soluble drugs: organic solvent *versus* organic/aqueous co-solvent systems. *Eur J Pharm Sci* 2003;**20**:295-303
241. Hu J, Johnston KP, Williams III RO. Rapid dissolving high potency danazol powders produced by spray freezing into liquid process. *Int J Pharm* 2004;**271**:145-54
242. Hu J, Johnston KP, Williams III RO. Stable amorphous danazol nanostructured powders with rapid dissolution rates produced by spray freezing into liquid. *Drug Dev Ind Pharm* 2004;**30**:695-704
243. Rogers TL, Overhoff KA, Shah P, Santiago P, Yacaman MJ, Johnston KP, et al. Micronized powders of a poorly water soluble drug produced by a spray-freezing into liquid-emulsion process. *Eur J Pharm Biopharm* 2003;**55**:161-72
244. Rogers TL, Johnston KP, Williams III RO. Physical stability of micronized powders produced by spray-freezing into liquid (SFL) to enhance the dissolution of an insoluble drug. *Pharm Dev Technol* 2003;**8**:187-97
245. Maa YF, Ameri M, Shu C, Payne LG, Chen D. Influenza vaccine powder formulation development: spray- freeze- drying and stability evaluation. *J Pharm Sci* 2004;**93**:1912-23
246. Rogers TL, Hu J, Yu Z, Johnston KP, Williams III RO. A novel particle engineering technology: spray-freezing into liquid. *Int J Pharm* 2002;**242**:93-100
247. Rogers TL, Nelsen AC, Hu J, Brown JN, Sarkari M, Young TJ, et al. A novel particle engineering technology to enhance dissolution of poorly water soluble drugs: spray-freezing into liquid. *Eur J Pharm Biopharm* 2002;**54**:271-80
248. Vaughn JM, McConville JT, Crisp MT, Johnston KP, Williams III RO. Supersaturation produces high bioavailability of amorphous danazol particles formed by evaporative precipitation into aqueous solution and spray freezing into liquid technologies. *Drug Dev Ind Pharm* 2006;**32**:559-67
249. He X, Pei L, Tong HH, Zheng Y. Comparison of spray freeze drying and the solvent evaporation method for preparing solid dispersions of baicalein with Pluronic F68 to improve dissolution and oral bioavailability. *AAPS PharmSciTech* 2011;**12**:104-13
250. Vasconcelos T, Marques S, Sarmento B. Development of a resveratrol solid dispersion with soluplus®. Proceedings of the 2nd Annual Meeting & Exposition of the Controlled Release Society at Edinburgh, Scotland on July 2015. Downloaded from www.researchgate.net.
251. Engers D, Teng J, Jimenez-Novoa J, Gent P, Hossack S, Campbell C, et al. A solid-state approach to enable early development compounds: selection and animsal bioavailability studies of an itraconazole amorphous solid dispersion. *J Pharm Sci* 2010;**99**:3901-22
252. Shanbhag A, Rabel S, Nauka E, Casadevall G, Shivanand P, Eichenbaum G, et al. Method for screening of solid dispersion formulations of low-solubility compounds—miniaturization and automation of solvent casting and dissolution testing. *Int J Pharm* 2008;**351**:209-18
253. Shi C, Tong Q, Fang J, Wang C, Wu J, Wang W. Preparation, characterization and *in vivo* studies of amorphous solid dispersion of berberine with hydrogenated phosphatidylcholine. *Eur J Pharm Sci* 2015;**74**:11-17
254. Lloyd G, Craig D, Smith A. A calorimetric investigation into the interaction between paracetamol and polyethlene glycol 4000 in physical mixes and solid dispersions. *Eur J Pharm Biopharm* 1999;**48**:59-65

255. Desai J, Alexander K, Riga A. Characterization of polymeric dispersions of dimenhydrinate in ethyl cellulose for controlled release. *Int J Pharm* 2006;**308**:115-23
256. Karavas E, Ktistis G, Xenakis A, Georgarakis E. Effect of hydrogen bonding interactions on the release mechanism of felodipine from nanodispersions with polyvinylpyrrolidone. *Eur J Pharm Biopharm* 2006;**63**:103-14
257. Majerik V, Charbit G, Badens E, Horváth G, Szokonya L, Bosc N, et al. Bioavailability enhancement of an active substance by supercritical antisolvent precipitation. *J Supercrit Fluids* 2007;**40**:101-10
258. Tanaka N, Imai K, Okimoto K, Ueda S, Tokunaga Y, Ibuki R, et al. Development of novel sustained-release system, disintegration-controlled matrix tablet (DCMT) with solid dispersion granules of nilvadipine (II): *in vivo* evaluation. *J Control Release* 2006;**112**:51-56
259. Sinha S, Ali M, Baboota S, Ahuja A, Kumar A, Ali J. Solid dispersion as an approach for bioavailability enhancement of poorly water-soluble drug ritonavir. *AAPS PharmSciTech* 2010;**11**:518-27
260. Badrossamay MR, Balachandran K, Capulli AK, Golecki HM, Agarwal A, Goss JA, et al. Engineering hybrid polymer-protein super-aligned nanofibers *via* rotary jet spinning. *Biomaterials* 2014;**35**:3188-97
261. Mellado P, McIlwee HA, Badrossamay MR, Goss JA, Mahadevan L, Kit Parker K. A simple model for nanofiber formation by rotary jet-spinning. *Appl Phys Lett* 2011;**99**:203107
262. Marano S, Barker SA, Raimi-Abraham BT, Missaghi S, Rajabi-Siahboomi A, Craig DQ. Development of micro-fibrous solid dispersions of poorly water-soluble drugs in sucrose using temperature-controlled centrifugal spinning. *Eur J Pharm Biopharm* 2016;**103**:84-94
263. Repka MA, Shah S, Lu J, Maddineni S, Morott J, Patwardhan K, et al. Melt extrusion: process to product. *Expert Opin Drug Del* 2012;**9**:105-25
264. Huang Y, Dai W-G. Fundamental aspects of solid dispersion technology for poorly soluble drugs. *Acta Pharm Sin B* 2014;**4**:18-25
265. Patil H, Tiwari RV, Repka MA. Hot-melt extrusion: from theory to application in pharmaceutical formulation. *AAPS PharmSciTech* 2016;**17**:20-42
266. Crowley MM, Zhang F, Repka MA, Thumma S, Upadhye SB, Kumar Battu S, et al. Pharmaceutical applications of hot-melt extrusion: part I. *Drug Dev Ind Pharm* 2007;**33**:909-26
267. Li X, Jiang C, Pan L, Zhang H, Hu L, Li T, et al. Effects of preparing techniques and aging on dissolution behavior of the solid dispersions of NF/Soluplus/Kollidon SR: identification and classification by a combined analysis by FT-IR spectroscopy and computational approaches. *Drug Dev Ind Pharm* 2015;**41**:2-14
268. Yang Z, Nollenberger K, Albers J, Craig D, Qi S. Microstructure of an immiscible polymer blend and its stabilization effect on amorphous solid dispersions. *Mol Pharm* 2013;**10**:2767-80
269. Sakai T, Thommes M. Investigation into mixing capability and solid dispersion preparation using the DSM X plore P harma M icro E xtruder. *J Pharm Pharmacol* 2014;**66**:218-31
270. Lang B, Liu S, McGinity JW, Williams III RO. Effect of hydrophilic additives on the dissolution and pharmacokinetic properties of itraconazole-enteric polymer hot-melt extruded amorphous solid dispersions. *Drug Dev Ind Pharm* 2016;**42**:429-45

271. Agrawal AM, Dudhedia MS, Patel AD, Raikes MS. Characterization and performance assessment of solid dispersions prepared by hot melt extrusion and spray drying process. *Int J Pharm* 2013;**457**:71-81
272. Sotthivirat S, McKelvey C, Moser J, Rege B, Xu W, Zhang D. Development of amorphous solid dispersion formulations of a poorly water-soluble drug, MK-0364. *Int J Pharm* 2013;**452**:73-81
273. Fule R, Amin P. Development and evaluation of lafutidine solid dispersion *via* hot melt extrusion: Investigating drug-polymer miscibility with advanced characterisation. *Asian J Pharm Sci* 2014;**9**:92-106
274. Liu X, Lu M, Guo Z, Huang L, Feng X, Wu C. Improving the chemical stability of amorphous solid dispersion with cocrystal technique by hot melt extrusion. *Pharm Res* 2012;**29**:806-17
275. Huang S, O'Donnell KP, Keen JM, Rickard MA, McGinity JW, Williams RO. A new extrudable form of hypromellose: AFFINISOL™ HPMC HME. *AAPS PharmSciTech* 2016;**17**:106-19
276. Sakurai A, Sakai T, Sako K, Maitani Y. Polymer combination increased both physical stability and oral absorption of solid dispersions containing a low glass transition temperature drug: physicochemical characterization and *in vivo* study. *Chem Pharm Bull* 2012;**60**:459-64
277. Zhu Y, Shah NH, Malick AW, Infeld MH, McGinity JW. Solid-state plasticization of an acrylic polymer with chlorpheniramine maleate and triethyl citrate. *Int J Pharm* 2002;**241**:301-10
278. Lee JY, Kang WS, Piao J, Yoon IS, Kim DD, Cho HJ. Soluplus®/TPGS-based solid dispersions prepared by hot-melt extrusion equipped with twin-screw systems for enhancing oral bioavailability of valsartan. *Drug Des Devel Ther* 2015;**9**:2745
279. Djuris J, Ioannis N, Ibric S, Djuric Z, Kachrimanis K. Effect of composition in the development of carbamazepine hot- melt extruded solid dispersions by application of mixture experimental design. *J Pharm Pharmacol* 2014;**66**:232-43
280. Ghebremeskel AN, Vemavarapu C, Lodaya M. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: stability testing of selected solid dispersions. *Pharm Res* 2006;**23**:1928-36
281. Ghebremeskel AN, Vemavarapu C, Lodaya M. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: selection of polymer–surfactant combinations using solubility parameters and testing the processability. *Int J Pharm* 2007;**328**:119-29
282. McGinity JW, Zhang F, Koleng J, Repka M. Hot-melt extrusion as a pharmaceutical process. *Am Pharm Rev* 2001;**4**:25-37
283. Repka MA, Gerding TG, Repka SL, McGinity JW. Influence of plasticizers and drugs on the physical-mechanical properties of hydroxypropylcellulose films prepared by hot melt extrusion. *Drug Dev Ind Pharm* 1999;**25**:625-33
284. Verreck G, Decorte A, Heymans K, Adriaensen J, Liu D, Tomasko DL, et al. The effect of supercritical CO2 as a reversible plasticizer and foaming agent on the hot stage extrusion of itraconazole with EC 20 cps. *J Supercrit Fluids* 2007;**40**:153-62
285. Berndl G, Rosenberg J, Liepold B, Breitenbach J, Reinhold U, Alani L, et al., Inventors; Abbott Laboratories, Assignee. Solid pharmaceutical dosage form. United States patent US No. 8,025,899. 2011 Sep 27.

286. Shah S, Maddineni S, Lu J, Repka MA. Melt extrusion with poorly soluble drugs. *Int J Pharm* 2013;**453**:233-52
287. Breitenbach J. Melt extrusion: from process to drug delivery technology. *Eur J Pharm Biopharm* 2002;**54**:107-17
288. Wilson M, Williams MA, Jones DS, Andrews GP. Hot-melt extrusion technology and pharmaceutical application. *Ther Deliv* 2012;**3**:787-97
289. Nakamichi K, Nakano T, Yasuura H, Izumi S, Kawashima Y. The role of the kneading paddle and the effects of screw revolution speed and water content on the preparation of solid dispersions using a twin-screw extruder. *Int J Pharm* 2002;**241**:203-11
290. Breitenbach J, Lewis J. Two concepts, one technology: controlled release and solid dispersion with meltrex. *Modified-release drug deliv tech* 2003;**125**
291. Teixeira C, Covas J, Stützle T, Gaspar-Cunha A. Multi-objective ant colony optimization for the twin-screw configuration problem. *Engineering Optimization* 2012;**44**:351-71
292. Verhoeven E, De Beer T, Van den Mooter G, Remon JP, Vervaet C. Influence of formulation and process parameters on the release characteristics of ethylcellulose sustained-release mini-matrices produced by hot-melt extrusion. *Eur J Pharm Biopharm* 2008;**69**:312-19
293. Liu H, Wang P, Zhang X, Shen F, Gogos CG. Effects of extrusion process parameters on the dissolution behavior of indomethacin in Eudragit® E PO solid dispersions. *Int J Pharm* 2010;**383**:161-69
294. Tiwari RV, Patil H, Repka MA. Contribution of hot-melt extrusion technology to advance drug delivery in the 21st century. *Expert Opin Drug Del* 2016;**13**:451-64
295. Mishra M. Handbook of encapsulation and controlled release. Boca Raton, US: CRC press, 2015.
296. Trey SM, Wicks DA, Mididoddi PK, Repka MA. Delivery of itraconazole from extruded HPC films. *Drug Dev Ind Pharm* 2007;**33**:727-35
297. Palem CR, Kumar Battu S, Maddineni S, Gannu R, Repka MA, Yamsani MR. Oral transmucosal delivery of domperidone from immediate release films produced *via* hot-melt extrusion technology. *Pharm Dev Technol* 2013;**18**:186-95
298. Dumpa NR, Sarabu S, Bandari S, Zhang F, Repka MA. Chronotherapeutic drug delivery of ketoprofen and ibuprofen for improved treatment of early morning stiffness in arthritis using hot-melt extrusion technology. *AAPS PharmSciTech* 2018;**19**:2700-09
299. Young CR, Koleng JJ, McGinity JW. Production of spherical pellets by a hot-melt extrusion and spheronization process. *Int J Pharm* 2002;**242**:87-92
300. Andrews GP, Jones DS, Diak OA, McCoy CP, Watts AB, McGinity JW. The manufacture and characterisation of hot-melt extruded enteric tablets. *Eur J Pharm Biopharm* 2008;**69**:264-73
301. Quinten T, Gonnissen Y, Adriaens E, De Beer T, Cnudde V, Masschaele B, et al. Development of injection moulded matrix tablets based on mixtures of ethylcellulose and low-substituted hydroxypropylcellulose. *Eur J Pharm Sci* 2009;**37**:207-16
302. Stanković M, Frijlink HW, Hinrichs WL. Polymeric formulations for drug release prepared by hot melt extrusion: application and characterization. *Drug DiscovToday* 2015;**20**:812-23
303. Alshahrani SM, Morott JT, Alshetaili AS, Tiwari RV, Majumdar S, Repka MA. Influence of degassing on hot-melt extrusion process. *Eur J Pharm Sci* 2015;**80**:43-52

304. Alig I, Fischer D, Lellinger D, Steinhoff B. Combination of NIR, Raman, Ultrasonic and Dielectric Spectroscopy for In- Line Monitoring of the Extrusion Process. *Macromolecular symposia* 2005;**230**:51-58
305. Repka MA, Battu SK, Upadhye SB, Thumma S, Crowley MM, Zhang F, et al. Pharmaceutical applications of hot-melt extrusion: Part II. *Drug Dev Ind Pharm* 2007;**33**:1043-57
306. Ellenberger DJ, Miller DA, Williams RO. Expanding the application and formulation space of amorphous solid dispersions with KinetiSol®: a review. *AAPS PharmSciTech* 2018;**19**:1933-56
307. Keen JM, McGinity JW, Williams III RO. Enhancing bioavailability through thermal processing. *Int J Pharm* 2013;**450**:185-96
308. LaFountaine JS, Jermain SV, Prasad LK, Brough C, Miller DA, Lubda D, et al. Enabling thermal processing of ritonavir–polyvinyl alcohol amorphous solid dispersions by KinetiSol® dispersing. *Eur J Pharm Biopharm* 2016;**101**:72-81
309. LaFountaine JS, Prasad LK, Brough C, Miller DA, McGinity JW, Williams RO. Thermal processing of PVP-and HPMC-based amorphous solid dispersions. *AAPS PharmSciTech* 2016;**17**:120-32
310. Miller DA, Keen JM. KinetiSol®-based amorphous solid dispersions. Amorphous Solid Dispersions: Springer, 2014, p. 567-77.
311. DiNunzio JC, Brough C, Hughey JR, Miller DA, Williams III RO, McGinity JW. Fusion production of solid dispersions containing a heat-sensitive active ingredient by hot melt extrusion and Kinetisol® dispersing. *Eur J Pharm Biopharm* 2010;**74**:340-51
312. Hughey JR, Keen JM, Miller DA, Brough C, McGinity JW. Preparation and characterization of fusion processed solid dispersions containing a viscous thermally labile polymeric carrier. *Int J Pharm* 2012;**438**:11-19
313. Basit AW, Gaisford S. 3D printing of pharmaceuticals. In: Basit A, Gaisford S, editors. New York City, US: Springer, 2018.
314. Barnatt C. 3D printing. Scotts Valley, US: CreateSpace Independent Publishing Platform, 2016.
315. Alhnan MA, Okwuosa TC, Sadia M, Wan K-W, Ahmed W, Arafat B. Emergence of 3D printed dosage forms: opportunities and challenges. *Pharm Res* 2016;**33**:1817-32
316. Awad A, Trenfield SJ, Gaisford S, Basit AW. 3D printed medicines: A new branch of digital healthcare. *Int J Pharm* 2018;**548**:586-96
317. Goole J, Amighi K. 3D printing in pharmaceutics: A new tool for designing customized drug delivery systems. *Int J Pharm* 2016;**499**:376-94
318. Palo M, Holländer J, Suominen J, Yliruusi J, Sandler N. 3D printed drug delivery devices: perspectives and technical challenges. *Expert Rev Med Devices* 2017;**14**:685-96
319. Trenfield SJ, Awad A, Goyanes A, Gaisford S, Basit AW. 3D printing pharmaceuticals: drug development to frontline care. *Trends Pharmacol Sci* 2018;**39**:440-51
320. Trenfield SJ, Goyanes A, Telford R, Wilsdon D, Rowland M, Gaisford S, et al. 3D printed drug products: Non-destructive dose verification using a rapid point-and-shoot approach. *Int J Pharm* 2018;**549**:283-92
321. Trenfield SJ, Tan HX, Awad A, Buanz A, Gaisford S, Basit AW, et al. Track-and-trace: Novel anti-counterfeit measures for 3D printed personalized drug products using smart material inks. *Int J Pharm* 2019;**567**:118443

322. Zema L, Melocchi A, Maroni A, Gazzaniga A. Three-dimensional printing of medicinal products and the challenge of personalized therapy. *J Pharm Sci* 2017;**106**:1697-705
323. Pietrzak K, Isreb A, Alhnan MA. A flexible-dose dispenser for immediate and extended release 3D printed tablets. *Eur J Pharm Biopharm* 2015;**96**:380-87
324. Awad A, Fina F, Trenfield SJ, Patel P, Goyanes A, Gaisford S, et al. 3D printed pellets (miniprintlets): A novel, multi-drug, controlled release platform technology. *Pharmaceutics* 2019;**11**:148
325. Khaled SA, Burley JC, Alexander MR, Yang J, Roberts CJ. 3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles. *J Control Release* 2015;**217**:308-14
326. Khaled SA, Burley JC, Alexander MR, Yang J, Roberts CJ. 3D printing of tablets containing multiple drugs with defined release profiles. *Int J Pharm* 2015;**494**:643-50
327. Robles-Martinez P, Xu X, Trenfield SJ, Awad A, Goyanes A, Telford R, et al. 3D printing of a multi-layered polypill containing six drugs using a novel stereolithographic method. *Pharmaceutics* 2019;**11**:274
328. Fina F, Goyanes A, Madla CM, Awad A, Trenfield SJ, Kuek JM, et al. 3D printing of drug-loaded gyroid lattices using selective laser sintering. *Int J Pharm* 2018;**547**:44-52
329. Fina F, Madla CM, Goyanes A, Zhang J, Gaisford S, Basit AW. Fabricating 3D printed orally disintegrating printlets using selective laser sintering. *Int J Pharm* 2018;**541**:101-07
330. Goyanes A, Wang J, Buanz A, Martínez-Pacheco R, Telford R, Gaisford S, et al. 3D printing of medicines: engineering novel oral devices with unique design and drug release characteristics. *Mol Pharm* 2015;**12**:4077-84
331. Martinez PR, Goyanes A, Basit AW, Gaisford S. Influence of geometry on the drug release profiles of stereolithographic (SLA) 3D-printed tablets. *AAPS PharmSciTech* 2018;**19**:3355-61
332. Madla CM, Trenfield SJ, Goyanes A, Gaisford S, Basit AW. 3D printing technologies, implementation and regulation: An overview. In: Basit A, Gaisford S, editors. 3D printing of pharmaceuticals. New York City, US: Springer, 2018, p. 21-40.
333. Goyanes A, Martinez PR, Buanz A, Basit AW, Gaisford S. Effect of geometry on drug release from 3D printed tablets. *Int J Pharm* 2015;**494**:657-63
334. Awad A, Trenfield SJ, Goyanes A, Gaisford S, Basit AW. Reshaping drug development using 3D printing. *Drug DiscovToday* 2018;**23**:1547-55
335. Goyanes A, Fernández-Ferreiro A, Majeed A, Gomez-Lado N, Awad A, Luaces-Rodríguez A, et al. PET/CT imaging of 3D printed devices in the gastrointestinal tract of rodents. *Int J Pharm* 2018;**536**:158-64
336. Genina N, Boetker JP, Colombo S, Harmankaya N, Rantanen J, Bohr A. Anti-tuberculosis drug combination for controlled oral delivery using 3D printed compartmental dosage forms: From drug product design to *in vivo* testing. *J Control Release* 2017;**268**:40-48
337. Arafat B, Qinna N, Cieszynska M, Forbes RT, Alhnan MA. Tailored on demand anti-coagulant dosing: An *in vitro* and *in vivo* evaluation of 3D printed purpose-designed oral dosage forms. *Eur J Pharm Biopharm* 2018;**128**:282-89
338. Tan DK, Maniruzzaman M, Nokhodchi A. Advanced pharmaceutical applications of hot-melt extrusion coupled with fused deposition modelling (FDM) 3D printing for personalised drug delivery. *Pharmaceutics* 2018;**10**:203

339. Vithani K, Goyanes A, Jannin V, Basit AW, Gaisford S, Boyd BJ. An overview of 3D printing technologies for soft materials and potential opportunities for lipid-based drug delivery systems. *Pharm Res* 2019;**36**:4
340. Alhijjaj M, Belton P, Qi S. An investigation into the use of polymer blends to improve the printability of and regulate drug release from pharmaceutical solid dispersions prepared *via* fused deposition modeling (FDM) 3D printing. *Eur J Pharm Biopharm* 2016;**108**:111-25
341. Melocchi A, Parietti F, Maroni A, Foppoli A, Gazzaniga A, Zema L. Hot-melt extruded filaments based on pharmaceutical grade polymers for 3D printing by fused deposition modeling. *Int J Pharm* 2016;**509**:255-63
342. Arafat B, Wojsz M, Isreb A, Forbes RT, Isreb M, Ahmed W, et al. Tablet fragmentation without a disintegrant: A novel design approach for accelerating disintegration and drug release from 3D printed cellulosic tablets. *Eur J Pharm Sci* 2018;**118**:191-99
343. Buanz AB, Saunders MH, Basit AW, Gaisford S. Preparation of personalized-dose salbutamol sulphate oral films with thermal ink-jet printing. *Pharm Res* 2011;**28**:2386
344. Kolakovic R, Viitala T, Ihalainen P, Genina N, Peltonen J, Sandler N. Printing technologies in fabrication of drug delivery systems. *Expert Opin Drug Del* 2013;**10**:1711-23
345. Infanger S, Haemmerli A, Iliev S, Baier A, Stoyanov E, Quodbach J. Powder bed 3D-printing of highly loaded drug delivery devices with hydroxypropyl cellulose as solid binder. *Int J Pharm* 2019;**555**:198-206
346. Goyanes A, Fina F, Martorana A, Sedough D, Gaisford S, Basit AW. Development of modified release 3D printed tablets (printlets) with pharmaceutical excipients using additive manufacturing. *Int J Pharm* 2017;**527**:21-30
347. Goyanes A, Det-Amornrat U, Wang J, Basit AW, Gaisford S. 3D scanning and 3D printing as innovative technologies for fabricating personalized topical drug delivery systems. *J Control Release* 2016;**234**:41-48
348. Goyanes A, Buanz AB, Hatton GB, Gaisford S, Basit AW. 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. *Eur J Pharm Biopharm* 2015;**89**:157-62
349. Fuenmayor E, Forde M, Healy AV, Devine DM, Lyons JG, McConville C, et al. Material considerations for fused-filament fabrication of solid dosage forms. *Pharmaceutics* 2018;**10**:44
350. Liu X, Chi B, Jiao Z, Tan J, Liu F, Yang W. A large- scale double- stage- screw 3 D printer for fused deposition of plastic pellets. *J Appl Polym Sci* 2017;**134**:45147
351. Goyanes A, Allahham N, Trenfield SJ, Stoyanov E, Gaisford S, Basit AW. Direct powder extrusion 3D printing: Fabrication of drug products using a novel single-step process. *Int J Pharm* 2019;**567**:118471
352. Davis Jr DA, Thakkar R, Su Y, Williams III RO, Maniruzzaman M. Selective Laser Sintering 3-Dimensional Printing as a Single Step Process to Prepare Amorphous Solid Dispersion Dosage Forms for Improved Solubility and Dissolution rate. *J Pharm Sci* 2020 Available from: https://doi.org/10.1016/j.xphs.2020.11.012.
353. Moneghini M, Bellich B, Baxa P, Princivalle F. Microwave generated solid dispersions containing ibuprofen. *Int J Pharm* 2008;**361**:125-30
354. Doreth M, Hussein MA, Priemel PA, Grohganz H, Holm R, de Diego HL, et al. Amorphization within the tablet: Using microwave irradiation to form a glass solution *in situ*. *Int J Pharm* 2017;**519**:343-51

355. Hempel N-J, Knopp MM, Berthelsen R, Löbmann K. Convection-induced *vs.* microwave radiation-induced *in situ* drug amorphization. *Molecules* 2020;**25**:1068
356. Hempel N-J, Knopp MM, Berthelsen R, Zeitler JA, Löbmann K. The influence of drug and polymer particle size on the *in situ* amorphization using microwave irradiation. *Eur J Pharm Biopharm* 2020;**149**:77-84
357. Serajuddin AT. Solid dispersion of poorly water- soluble drugs: Early promises, subsequent problems, and recent breakthroughs. *J Pharm Sci* 1999;**88**:1058-66
358. Bergese P, Colombo I, Gervasoni D, Depero L. Microwave generated nanocomposites for making insoluble drugs soluble. *Materials Science and Engineering: C* 2003;**23**:791-95
359. Wong T. Use of microwave in processing of drug delivery systems. *Curr Drug Del* 2008;**5**:77-84
360. Waters LJ, Bedford S, Parkes GM. Controlled microwave processing applied to the pharmaceutical formulation of ibuprofen. *AAPS PharmSciTech* 2011;**12**:1038-43
361. Moneghini M, Zingone G, De Zordi N. Influence of the microwave technology on the physical–chemical properties of solid dispersion with Nimesulide. *Powder Technol* 2009;**195**:259-63
362. Maurya D, Belgamwar V, Tekade A. Microwave induced solubility enhancement of poorly water soluble atorvastatin calcium. *J Pharm Pharmacol* 2010;**62**:1599-606
363. Moneghini M, De Zordi N, Solinas D, Macchiavelli S, Princivalle F. Characterization of solid dispersions of itraconazole and vitamin E TPGS prepared by microwave technology. *Future Med Chem* 2010;**2**:237-46
364. Zawar LR, Bari SB. Preparation, characterization and *in vivo* evaluation of antihyperglycemic activity of microwave generated repaglinide solid dispersion. *Chem Pharm Bull* 2012;**60**:482-87
365. Patil PH, Belgamwar VS, Patil PR, Surana SJ. Enhancement of solubility and dissolution rate of poorly water soluble raloxifene using microwave induced fusion method. *Braz J Pharm Sci* 2013;**49**:571-78
366. Zawar L, Bari S. Microwave induced solid dispersion as a novel technique for enhancing dissolution rate of repaglinide. *Adv Pharmacol Pharm* 2013;**1**:95-101
367. Sonawane R, Bonde P, Chatap V, Bari S, Zawar L. Preparation and Characterization of Microwave-assisted Candesartan Cilexetil Solid Dispersions. *Res Rev J Pharm Sci* 2013;**4**:9-19
368. Shi N-Q, Lai H-W, Zhang Y, Feng B, Xiao X, Zhang H-M, et al. On the inherent properties of Soluplus and its application in ibuprofen solid dispersions generated by microwave-quench cooling technology. *Pharm Dev Technol* 2018;**23**:573-86
369. Alshehri S, Shakeel F, Ibrahim M, Elzayat E, Altamimi M, Shazly G, et al. Influence of the microwave technology on solid dispersions of mefenamic acid and flufenamic acid. *PLoS One* 2017;**12**:e0182011
370. Alshehri S, Imam SS, Altamimi MA, Hussain A, Shakeel F, Elzayat E, et al. Enhanced dissolution of luteolin by solid dispersion prepared by different methods: Physicochemical characterization and antioxidant activity. *ACS omega* 2020;**5**:6461-71
371. Radacsi N, Stefanidis GD, Szabó-Révész P, Ambrus R. Analysis of niflumic acid prepared by rapid microwave-assisted evaporation. *J Pharm Biomed Anal* 2014;**98**:16-21
372. Abreu-Villela R, Adler C, Caraballo I, Kuentz M. Electron microscopy/energy dispersive X-ray spectroscopy of drug distribution in solid dispersions and interpretation by multifractal geometry. *J Pharm Biomed Anal* 2018;**150**:241-47

373. Otsuka M, Maeno Y, Fukami T, Inoue M, Tagami T, Ozeki T. Solid dispersions of efonidipine hydrochloride ethanolate with improved physicochemical and pharmacokinetic properties prepared with microwave treatment. *Eur J Pharm Biopharm* 2016;**108**:25-31
374. Papadimitriou SA, Bikiaris D, Avgoustakis K. Microwave- induced enhancement of the dissolution rate of poorly water- soluble tibolone from poly (ethylene glycol) solid dispersions. *J Appl Polym Sci* 2008;**108**:1249-58
375. Barba AA, Dalmoro A, d'Amore M. Microwave assisted drying of cellulose derivative (HPMC) granular solids. *Powder Technol* 2013;**237**:581-85
376. Sridhar I, Doshi A, Joshi B, Wankhede V, Doshi J. Solid dispersions: an approach to enhance solubility of poorly water soluble drug. *J Sci Innov Res* 2013;**2**:685-94
377. Zhang J, Thakkar R, Zhang Y, Maniruzzaman M. Microwave induced dielectric heating for the on-demand development of indomethacin amorphous solid dispersion tablets. *J Drug Deliv Sci Technol* 2020:102109
378. Edinger M, Knopp MM, Kerdoncuff H, Rantanen J, Rades T, Löbmann K. Quantification of microwave-induced amorphization of celecoxib in PVP tablets using transmission Raman spectroscopy. *Eur J Pharm Sci* 2018;**117**:62-67
379. Doreth M, Löbmann K, Priemel P, Grohganz H, Taylor R, Holm R, et al. Influence of PVP molecular weight on the microwave assisted *in situ* amorphization of indomethacin. *Eur J Pharm Biopharm* 2018;**122**:62-69
380. Shalaev EY, Lu Q, Shalaeva M, Zografi G. Acid-catalyzed inversion of sucrose in the amorphous state at very low levels of residual water. *Pharm Res* 2000;**17**:366-70
381. Vasconcelos T, Costa P. Development of a rapid dissolving ibuprofen solid dispersion. *Pharm. Res* 2007;**16**:676-81
382. Shergill M, Patel M, Khan S, Bashir A, McConville C. Development and characterisation of sustained release solid dispersion oral tablets containing the poorly water soluble drug disulfiram. *Int J Pharm* 2016;**497**:3-11
383. Chiou WL, Riegelman S. Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. *J Pharm Sci* 1969;**58**:1505-10
384. Vippagunta SR, Wang Z, Hornung S, Krill SL. Factors affecting the formation of eutectic solid dispersions and their dissolution behavior. *J Pharm Sci* 2007;**96**:294-304
385. Gunawan L, Johari G, Shanker RM. Structural relaxation of acetaminophen glass. *Pharm Res* 2006;**23**:967-79
386. Pokharkar VB, Mandpe LP, Padamwar MN, Ambike AA, Mahadik KR, Paradkar A. Development, characterization and stabilization of amorphous form of a low Tg drug. *Powder Technol* 2006;**167**:20-25
387. Sekiguchi K, Obi N, Ueda Y. Studies on absorption of eutectic mixture. II. Absorption of fused conglomerates of chloramphenicol and urea in rabbits. *Chem Pharm Bull* 1964;**12**:134-44
388. Timko RJ, Lordi NG. Thermal characterization of citric acid solid dispersions with benzoic acid and phenobarbital. *J Pharm Sci* 1979;**68**:601-05
389. Nagapudi K, Jona J. Amorphous active pharmaceutical ingredients in preclinical studies: preparation, characterization, and formulation. *Curr Bioact Compd* 2008;**4**:213-24
390. Guo Z, Boyce C, Rhodes T, Liu L, Salituro GM, Lee KJ, et al. A novel method for preparing stabilized amorphous solid dispersion drug formulations using acoustic fusion. *Int J Pharm* 2020:120026

391. Ueda H, Kawai A, Hayashi T, Ida Y, Kakemi M, Tozuka Y. Process monitoring of ultrasound compaction as a small-scale heating process. *Eur J Pharm Sci* 2013;**49**:829-35
392. Fini A, Rodriguez L, Cavallari C, Albertini B, Passerini N. Ultrasound-compacted and spray-congealed indomethacin/polyethyleneglycol systems. *Int J Pharm* 2002;**247**:11-22
393. Sancin P, Caputo O, Cavallari C, Passerini N, Rodriguez L, Cini M, et al. Effects of ultrasound-assisted compaction on Ketoprofen/Eudragit® S100 Mixtures. *Eur J Pharm Sci* 1999;**7**:207-13
394. Fini A, Holgado MA, Rodriguez L, Cavallari C. Ultrasound- compacted indomethacin/polyvinylpyrrolidone systems: Effect of compaction process on particle morphology and dissolution behavior. *J Pharm Sci* 2002;**91**:1880-90
395. Fini A, Fernández- Hervás M, Holgado M, Rodriguez L, Cavallari C, Passerini N, et al. Fractal analysis of *β*- cyclodextrin–indomethacin particles compacted by ultrasound. *J Pharm Sci* 1997;**86**:1303-09
396. Caraballo I, Millán M, Fini A, Rodriguez L, Cavallari C. Percolation thresholds in ultrasound compacted tablets. *J Control Release* 2000;**69**:345-55
397. Rodriguez L, Cini M, Cavallari C, Passerini N, Saettone MF, Fini A, et al. Evaluation of theophylline tablets compacted by means of a novel ultrasound-assisted apparatus. *Int J Pharm* 1998;**170**:201-08
398. Matsuoka S-i. Effects of ultrasonic vibration on the compaction molding of polymeric powders. *J Mater Process Technol* 1994;**40**:443-50
399. Hughey JR, McGinity JW. Emerging technologies to increase the bioavailability of poorly water-soluble drugs. In: Williams III RO, Watts AB, Miller DA, editors. *Formulating poorly water soluble drugs*. New York City, US: Springer, 2012, p. 569-602.
400. Parikh DM. Handbook of pharmaceutical granulation technology: CRC Press, 2016.
401. Hirai N, Ishikawa K, Takahashi K. Improvement of the agitation granulation method to prepare granules containing a high content of a very hygroscopic drug. *J Pharm Pharmacol* 2006;**58**:1437-41
402. Cho CS, Shin TH, Lim JL, Moon KY, Kim DK, Choi YW. Stability-enhanced solid dispersion formulation of amorphous raloxifene hydrochloride. *Korean J Chem Eng* 2010;**27**:1906-09
403. Jang DJ, Kim ST, Lee K, Oh E. Improved bioavailability and antiasthmatic efficacy of poorly soluble curcumin-solid dispersion granules obtained using fluid bed granulation. *Bio-medical materials and engineering* 2014;**24**:413-29
404. Chen YC, Ho HO, Chiou JD, Sheu MT. Physical and dissolution characterization of cilostazol solid dispersions prepared by hot melt granulation (HMG) and thermal adhesion granulation (TAG) methods. *Int J Pharm* 2014;**473**:458-68
405. Shanmugam S. Granulation techniques and technologies: recent progresses. *BioImpacts: BI* 2015;**5**:55
406. Fujimoto Y, Hirai N, Takatani-Nakase T, Takahashi K. Novel tablet formulation of amorphous indomethacin using wet granulation with a high-speed mixer granulator combined with porous calcium silicate. *J Drug Deliv Sci Technol* 2016;**33**:51-57
407. Hansuld E, Briens L. A review of monitoring methods for pharmaceutical wet granulation. *Int J Pharm* 2014;**472**:192-201
408. Trasi NS, Bhujbal SV, Zemlyanov DY, Zhou QT, Taylor LS. Physical stability and release properties of lumefantrine amorphous solid dispersion granules prepared by a simple

solvent evaporation approach. *Int J Pharm X* 2020 Available from: https://doi.org/10.1016/j.ijpx.2020.100052.
409. Trasi NS, Bhujbal SV, Zhou QT, Taylor LS. Amorphous solid dispersion formation *via* solvent granulation–A case study with ritonavir and lopinavir. *Int J Pharm X* 2019;**1**:100035
410. Kowalski J, Kalb O, Joshi YM, Serajuddin AT. Application of melt granulation technology to enhance stability of a moisture sensitive immediate-release drug product. *Int J Pharm* 2009;**381**:56-61
411. Seo A, Holm P, Kristensen HG, Schæfer T. The preparation of agglomerates containing solid dispersions of diazepam by melt agglomeration in a high shear mixer. *Int J Pharm* 2003;**259**:161-71
412. Vilhelmsen T, Eliasen H, Schæfer T. Effect of a melt agglomeration process on agglomerates containing solid dispersions. *Int J Pharm* 2005;**303**:132-42
413. Aleksić I, Đuriš J, Ilić I, Ibrić S, Parojčić J, Srčič S. In silico modeling of *in situ* fluidized bed melt granulation. *Int J Pharm* 2014;**466**:21-30
414. Gupta MK, Goldman D, Bogner RH, Tseng Y-C. Enhanced drug dissolution and bulk properties of solid dispersions granulated with a surface adsorbent. *Pharm Dev Technol* 2001;**6**:563-72
415. Passerini N, Albertini B, González-Rodríguez ML, Cavallari C, Rodriguez L. Preparation and characterisation of ibuprofen–poloxamer 188 granules obtained by melt granulation. *Eur J Pharm Sci* 2002;**15**:71-78
416. Yeh TS, Yeh DH, inventors; Wei Ming Pharmaceutical Mfg Co. Ltd., assignee. Process for the preparation of direct tabletting formulations and aids. United States patent US No. 6,761,905. 2004 Jul 13.
417. Lin HL, Ho HO, Chen CC, Yeh TS, Sheu MT. Process and formulation characterizations of the thermal adhesion granulation (TAG) process for improving granular properties. *Int J Pharm* 2008;**357**:206-12
418. Kimura S-i, Uchida S, Kanada K, Namiki N. Effect of granule properties on rough mouth feel and palatability of orally disintegrating tablets. *Int J Pharm* 2015;**484**:156-62
419. Theismann E-M, K Keppler J, Owen M, Schwarz K, Schlindwein W. Modelling the Effect of Process Parameters on the Wet Extrusion and Spheronisation of High-Loaded Nicotinamide Pellets Using a Quality by Design Approach. *Pharmaceutics* 2019;**11**:154
420. Tanaka R, Hattori Y, Horie Y, Kamada H, Nagato T, Otsuka M. Characterization of Amorphous Solid Dispersion of Pharmaceutical Compound with pH-Dependent Solubility Prepared by Continuous-Spray Granulator. *Pharmaceutics* 2019;**11**:159
421. Sekikawa H, Fujiwara J, Naganuma T, Nakano M, Arita T. Dissolution behaviors and gastrointestinal absorption of phenytoin in phenytoin-polyvinylpyrrolidone coprecipitate. *Chem Pharm Bull* 1978;**26**:3033-39
422. Schenck L, Lowinger M, Troup GM, Li L, McKelvey C. Achieving a hot melt extrusion design space for the production of solid solutions. In: am Ende MT, am Ende DJ, editors. Chemical engineering in the pharmaceutical industry: drug product design, development, and modeling. Hoboken, US: Wiley, 2019, p. 469-87.
423. Sertsou G, Butler J, Scott A, Hempenstall J, Rades T. Factors affecting incorporation of drug into solid solution with HPMCP during solvent change co-precipitation. *Int J Pharm* 2002;**245**:99-108

424. Hu Q, Choi DS, Chokshi H, Shah N, Sandhu H. Highly efficient miniaturized coprecipitation screening (MiCoS) for amorphous solid dispersion formulation development. *Int J Pharm* 2013;**450**:53-62
425. Dong Z, Chatterji A, Sandhu H, Choi DS, Chokshi H, Shah N. Evaluation of solid state properties of solid dispersions prepared by hot-melt extrusion and solvent co-precipitation. *Int J Pharm* 2008;**355**:141-49
426. Sertsou G, Butler J, Hempenstall J, Rades T. Solvent change co- precipitation with hydroxypropyl methylcellulose phthalate to improve dissolution characteristics of a poorly water- soluble drug. *J Pharm Pharmacol* 2002;**54**:1041-47
427. Zhou H, Wang W, Hu H, Ni X, Ni S, Xu Y, et al. Co-precipitation of calcium carbonate and curcumin in an ethanol medium as a novel approach for curcumin dissolution enhancement. *J Drug Deliv Sci Technol* 2019;**51**:397-402
428. Bhujbal SV, Pathak VV, Zemlyanov DY, Taylor LS, Zhou QT. Physical stability and dissolution of lumefantrine amorphous solid dispersions produced by spray anti-solvent precipitation. *J Pharm Sci* 2020 Available from: https://doi.org/1016/j.xphs.2020.12.033.
429. D'Addio SM, Prud'homme RK. Controlling drug nanoparticle formation by rapid precipitation. *Adv Drug Del Rev* 2011;**63**:417-26
430. Vaughn JM, Gao X, Yacaman M-J, Johnston KP, Williams III RO. Comparison of powder produced by evaporative precipitation into aqueous solution (EPAS) and spray freezing into liquid (SFL) technologies using novel Z-contrast STEM and complimentary techniques. *Eur J Pharm Biopharm* 2005;**60**:81-89
431. Meng F, Meckel J, Zhang F. Investigation of itraconazole ternary amorphous solid dispersions based on povidone and Carbopol. *Eur J Pharm Sci* 2017;**106**:413-21
432. Mann AK, Schenck L, Koynov A, Rumondor AC, Jin X, Marota M, et al. Producing amorphous solid dispersions *via* co-precipitation and spray drying: impact to physicochemical and biopharmaceutical properties. *J Pharm Sci* 2018;**107**:183-91
433. Dedroog S, Huygens C, Van den Mooter G. Chemically identical but physically different: A comparison of spray drying, hot melt extrusion and cryo-milling for the formulation of high drug loaded amorphous solid dispersions of naproxen. *Eur J Pharm Biopharm* 2019;**135**:1-12
434. Caron V, Hu Y, Tajber L, Erxleben A, Corrigan OI, McArdle P, et al. Amorphous solid dispersions of sulfonamide/Soluplus® and sulfonamide/PVP prepared by ball milling. *AAPS PharmSciTech* 2013;**14**:464-74
435. Nowak P, Krupa A, Kubat K, Węgrzyn A, Harańczyk H, Ciułkowska A, et al. Water vapour sorption in tadalafil-Soluplus co-milled amorphous solid dispersions. *Powder Technol* 2019;**346**:373-84
436. Descamps M, Willart J. Perspectives on the amorphisation/milling relationship in pharmaceutical materials. *Adv Drug Del Rev* 2016;**100**:51-66
437. Krupa A, Descamps M, Willart J-F, Jachowicz R, Danède F. High energy ball milling and supercritical carbon dioxide impregnation as co-processing methods to improve dissolution of tadalafil. *Eur J Pharm Sci* 2016;**95**:130-37
438. Willart J, Descamps M. Solid state amorphization of pharmaceuticals. *Mol Pharm* 2008;**5**:905-20
439. Willart J-F, Carpentier L, Danède F, Descamps M. Solid-state vitrification of crystalline griseofulvin by mechanical milling. *J Pharm Sci* 2012;**101**:1570-77

440. Mura P, Cirri M, Faucci M, Ginès-Dorado J, Bettinetti G. Investigation of the effects of grinding and co-grinding on physicochemical properties of glisentide. *J Pharm Biomed Anal* 2002;**30**:227-37
441. Gupta MK, Vanwert A, Bogner RH. Formation of physically stable amorphous drugs by milling with Neusilin. *J Pharm Sci* 2003;**92**:536-51
442. Gupta MK, Tseng Y-C, Goldman D, Bogner RH. Hydrogen bonding with adsorbent during storage governs drug dissolution from solid-dispersion granules. *Pharm Res* 2002;**19**:1663-72
443. iCeutica's SoluMatrix Technology. SoluMatrix™ Technology, Access Date Dec 07, 2020. Secondary iCeutica's SoluMatrix Technology. SoluMatrix™ Technology, Access Date Dec 07, 2020. Available from: http://www.iceutica.com/products/products.php#page-pain-inflammation.
444. Leane MM, Sinclair W, Qian F, Haddadin R, Brown A, Tobyn M, et al. Formulation and process design for a solid dosage form containing a spray-dried amorphous dispersion of ibipinabant. *Pharm Dev Technol* 2013;**18**:359-66
445. Chauhan B, Shimpi S, Paradkar A. Preparation and evaluation of glibenclamide-polyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique. *Eur J Pharm Sci* 2005;**26**:219-30
446. Mitchell SA, Reynolds TD, Dasbach TP. A compaction process to enhance dissolution of poorly water-soluble drugs using hydroxypropyl methylcellulose. *Int J Pharm* 2003;**250**:3-11
447. Giri TK, Jana P, Sa B. Rapidly disintegrating fast release tablets of diazepam using solid dispersion: development and evaluation. *J Sci Ind Res* 2008;**67**:436-39
448. Kiran T, Shastri N, Ramakrishna S, Sadanandam M. Surface solid dispersion of glimepiride for enhancement of dissolution rate. *Int J Pharm Tech Res* 2009;**1**:822-31
449. Fu J, Xu L, Wang X, Zhang S, Tao X, Zhao X, et al. Nimodipine (NM) tablets with high dissolution containing NM solid dispersions prepared by hot-melt extrusion. *Drug Dev Ind Pharm* 2011;**37**:934-44
450. Démuth B, Nagy ZK, Balogh A, Vigh T, Marosi G, Verreck G, et al. Downstream processing of polymer-based amorphous solid dispersions to generate tablet formulations. *Int J Pharm* 2015;**486**:268-86
451. Shimpi S, Mahadik K, Takada K, Paradkar A. Application of polyglycolized glycerides in protection of amorphous form of etoricoxib during compression. *Chem Pharm Bull* 2007;**55**:1448-51
452. Sharp J, Forrest JA. Free surfaces cause reductions in the glass transition temperature of thin polystyrene films. *Phys Rev Lett* 2003;**91**:235701
453. Tisato K, Keiji T, Atsushi T. Study of the surface glass transition behaviour of amorphous polymer film by scanning-force microscopy and surface spectroscopy. *Polymer* 1998;**39**:4665-73
454. Jukes PC, Das A, Durell M, Trolley D, Higgins AM, Geoghegan M, et al. Kinetics of surface crystallization in thin films of poly (ethylene terephthalate). *Macromolecules* 2005;**38**:2315-20
455. Puri V, Dantuluri AK, Bansal AK. Barrier coated drug layered particles for enhanced performance of amorphous solid dispersion dosage form. *J Pharm Sci* 2012;**101**:342-53