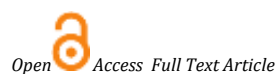


Available online on 15.11.2022 at <http://jddtonline.info>

# Journal of Drug Delivery and Therapeutics

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Review Article

## A Review of Various Manufacturing Approaches for Developing Amorphous Solid Dispersions

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### Article Info:



#### Article History:

Received 09 Sep 2022  
Reviewed 17 Oct 2022  
Accepted 28 Oct 2022  
Published 15 Nov 2022

### Cite this article as:

Konda KK, Dhoppalapudi S, A Review of Various Manufacturing Approaches for Developing Amorphous Solid Dispersions, Journal of Drug Delivery and Therapeutics. 2022; 12(6):189-200

DOI: <http://dx.doi.org/10.22270/jddt.v12i6.5787>

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### Abstract

In recent years amorphous solid dispersions (ASD) has gained a tremendous response for improving the solubility of poorly water-soluble drug substances. Despite the stability challenges, various ASD commercial products have been successfully launched into the market over the last two decades. Among various manufacturing approaches, hot melt extrusion (HME) and spray drying techniques have attracted industries attributing to their simple manufacturing processes. In addition, Kinetisol<sup>®</sup>, a solvent-free approach, is also being most widely investigated for developing ASDs since the thermal exposure time of the formulations is significantly less compared with the hot melt extrusion process. Kinetisol<sup>®</sup> can be employed for developing ASDs of thermolabile drug substances. Another solvent-based technique, electrospinning, is also employed for developing nanofibers-based ASD. However, much research is warranted for the electrospinning process before implementing it in commercial manufacturing. Various critical factors such as drug-polymer solubility, the solubility of the drug in the polymer, drug-polymer interactions, type of manufacturing process, and storage conditions need to be considered for developing a stable and robust ASD formulation. This review mainly focuses on the most advanced manufacturing technologies of ASDs, namely HME, spray drying, Kinetisol<sup>®</sup>, and electrospinning, along with a note on the various critical factors that affect the stability of ASD formulations.

**Keywords:** amorphous solid dispersions; hot melt extrusion; spray drying; Kinetisol<sup>®</sup>; electrospinning

## 1. Introduction

In recent years, the demand for pharmaceutical medications is increasing tremendously with the increasing patient population. Poor solubility of the drug substances and poor manufacturing technologies are affecting the products from getting into the market resulting in considerable losses in revenue for the pharmaceutical industries. Around 60-70 % of the new chemical entities are claimed to be poorly soluble, belonging to biological classification system (BCS) class II and IV, affecting oral bioavailability<sup>1-4</sup>. Improving the solubility of the drug substances is the primary prerequisite for successfully developing oral dosage forms. Among various routes of administration, the oral route is majorly preferred by the patient population due to its cost-effectiveness, self-administration, and no pain. Even developing sterile injectable formulations requires the drug wholly dissolved in a suitable carrier. However, oral dosage forms (capsules/tablets) have huge market demand and generate more revenue for the pharmaceutical industry when compared to sterile formulations. Developing sterile dosage forms requires huge capital compared to oral formulations<sup>5-7</sup>. Thus, developing oral formulations is the primary interest to the pharmaceutical industry.

Various approaches, such as self-emulsifying drug delivery systems, liposomes, pro-liposomes, cyclodextrin complexation, solid crystal suspension, salts, and co-crystals,

have been investigated to improve the solubility of drug substances. The underdeveloped manufacturing processes, use of solvents, and poor scaleup have limited the commercial viability of conventional approaches<sup>8-14</sup>. For the last two decades, amorphous solid dispersions (ASDs) have been most widely investigated for improving the solubility of drug substances. Various commercial products of ASDs developed by different manufacturing strategies have been launched into the market. Within the ASDs, the drug is dispersed in the amorphous state within a polymeric carrier. The amorphous drug has improved wettability, resulting in improved solubility and permeability of drug molecules across the biological membranes. However, the stability of amorphous drugs over crystalline drugs remains a significant limitation. Within ASDs, the drug exists in a high energy state, which is prone to recrystallization attributed to various factors such as miscibility, interactions, manufacturing process, and environmental conditions. In recent years various conventional and novel approaches have been investigated for developing ASDs<sup>15-22</sup>. Among various manufacturing techniques, hot melt extrusion (HME), spray drying, Kinetisol<sup>®</sup>, electrospinning, and fluid bed granulation have remarkably responded to developing ASDs. This review mainly focuses on the most advanced manufacturing technologies of ASDs, namely HME, spray drying, Kinetisol<sup>®</sup>, and electrospinning, along with a note on the various critical factors that affect the stability of ASD formulations.

## 2. Hot melt extrusion

In early 1930, the HME process was most widely employed in the plastic, rubber, and food industries. Later with the advancement in technology, the suitability of the HME process for developing various pharmaceutical formulations was investigated in the early 1980s<sup>23-25</sup>. Initially, single-screw extruders (SSE) were introduced into pharmaceuticals. However, SSEs have resulted in the non-homogeneous distribution of formulation components, raising the requirement for a twin screw (TSE) and multi-screw extruder (MSE). The implementation of TSE and MSE has overcome the limitation of non-homogeneous distribution. In today's world, HME is the most widely accepted process for developing ASDs of poorly water-soluble drug substances<sup>26-28</sup>. The schematic representation of hot melt extruder is shown in Figure 1.

HME is a single-step continuous manufacturing process requiring a controlled feeding of the physical mixture into the barrel. The barrel of corotating or counter-rotating screws imparts distributive and dispersive mixing along with the mechanical shear onto the processing material. The screw configuration mainly consists of conveying and mixing elements and can be customized as required. The primary purpose of conveying elements is to convey the material between the mixing zones and has no mixing property. The mixing elements impart mechanical shear onto the processing materials and possess no conveying property<sup>29,30</sup>. The mixing elements can be configured at 0°, 30°, 60°, and 90° offset angles. With the increasing angle, the amount of shear imparted onto the material will increase, and the residence of material inside the barrel decreases. The material inside the barrel gets exposed to mechanical and thermal energy greater than the lattice energy of the drug crystals resulting in the formation of amorphous solid dispersions. The molten mass inside the barrel gets conveyed all along the length of the barrel and is pumped out as cylindrical filaments through a die nozzle connected at the discharge point<sup>31-33</sup>. The collected extrudates can be cut into pellets, milled, encapsulated, or compressed into tablets using suitable diluents. Various process parameters involved in the extrusion process are feed rate, screw speed, barrel and die temperature, process torque, and melt pressure.

To date, various researchers have explored the suitability of the HME process for developing ASDs of BCS class II and IV drug substances in the form of immediate release, modified release, delayer release, chronotherapeutic, colon targeting, gastroretentive, and taste masking formulations. In addition, the ASD filaments of the HME process can also be utilized as feedstock material for fabricating patient-centric dosage forms using fused deposition modeling (FDM) three-dimensional (3D) printing<sup>34-39</sup>. The FDM 3D printing process provides the flexibility of altering the dose, size, shape, and release profiles of medications for the different age groups of the patient population, depending on the stage of the disease condition. The extruder can also be employed to manufacture granules, referred to as twin screw granulation (TSG). Depending on the physical state of the binder, the TSG process is further categorized as twin-screw melt granulation (TSMG), twin screw wet granulation (TSWG), and twin-screw dry granulation (TSDG)<sup>40-44</sup>. The process of HME has gained a lot of commercial viability, making it suitable for establishing a single-step continuous manufacturing line by employing suitable process analytical technology (PAT) tools. The PAT tools continuously monitors, controls, and preserves the quality of the product. Though HME is most widely employed for manufacturing commercial products, a few limitations, such as high processing temperature, poor stability, poor compressibility of milled extrudates, and low drug loading, remained unaddressed<sup>45-49</sup>. A few case studies where HME has

been recently investigated for developing ASDs are further discussed below.

As mentioned earlier, the milled extrudates of HME exhibit poor compressibility attributed to their glassy nature. Saurabh M Mishra et al. (2022)<sup>50</sup> investigated the effect of milling techniques on the compressibility of milled extrudates and the performance of the compressed tablets. ASDs of itraconazole were prepared using hypromellose acetate succinate (HPMCAS) as a polymeric carrier by HME. The formulations were prepared for a drug load of 20 %w/w. The extrudates were sized manually using a pelletizer and a chill roller attached to a flaker. The sized extrudates were milled at different speeds using different-sized screens. The milled extrudates were compressed into tablets of hydroxypropyl cellulose, microcrystalline cellulose PH 102, and silicon dioxide. The size technique has resulted in varied particle size distribution, which has eventually influenced the compressibility of milled extrudates and the performance of tablets. Among all the investigated sizing techniques, the extrudates processed using a chill roller has resulted in superior compressibility. This shows the importance of the sizing and milling process for developing tablets of milled extrudates.

Alex Mathers et al., (2022)<sup>51</sup> investigated the effect of glass forming ability (GFA) of the drug on the stability of ASDs. The ASDs of two drug substances, one with good GFA (indomethacin) and the other with poor GFA (naproxen), were developed using polyvinyl alcohol (PVA) as a polymeric carrier. The ASDs with 30, 40, and 50 %w/w of drug load was developed and investigated for their stability. The formulations of indomethacin possessing good GFA properties were stable for 24 months at ambient conditions, whereas the formulations of naproxen recrystallized, attributing to poor GFA. This shows the importance of evaluating the properties of drugs that play an essential role in developing stable ASD formulations.

Wenling Fan et al., (2019)<sup>52</sup> investigated the effect of the ball milling process on developing ASDs for high melting point drug substances by the HME process. Resveratrol with a melting point of 253 C was selected as a model drug and Eudragit EPO as a polymeric carrier. The ASDs were prepared by extruding the physical mixture of drug and polymer (1:1 ratio) using the HME process. In addition, the ASDs were also developed by milling the physical mixture (1:1 ratio of drug and polymer) in a ball mill at varied residence times, followed by extrusion through an HME. Among the investigated approaches, the co-processed formulations (ball mill and HME) have successfully converted a high melting point drug into an amorphous form compared to the formulations developed using HME alone. This shows the importance of the HME process with conventional techniques to develop the ASDs of drug substances with high melting points.

Bhupendra Raj Giri et al., (2021)<sup>53</sup> developed pH-modulated solid dispersions of telmisartan using soluplus as a polymeric carrier and sodium carbonate as an alkalizer. The formulations were developed using the HME process with a drug load between 10 - 60 %w/w and sodium carbonate between 0 - 10 %w/w. The saturation solubility studies conducted for the drug molecule have resulted in the pH-dependent solubility of telmisartan. Telmisartan possesses a high melting point of 270 °C. The formulations were extruded at 150-160 °C of barrel temperature, preserving the crystallinity of the drug substances within the extrudates. The solubility of sodium carbonate, when brought in contact with the dissolution media, has resulted in a micro pH environment favoring the amorphization and solubility of the drug, thereby resulting in improved dissolution profiles. The formulations of

HME were found to be superior and stable at accelerated storage conditions when compared with the commercial formulation (MICARDIS 40 mg tablets). This shows the role of alkalizers or acidifiers in improving the solubility of drug

substances by preserving the crystallinity and improving the stability of the formulations. Various other recent advancements that have been investigated using HME technology for developing ASDs are detailed in Table 1.

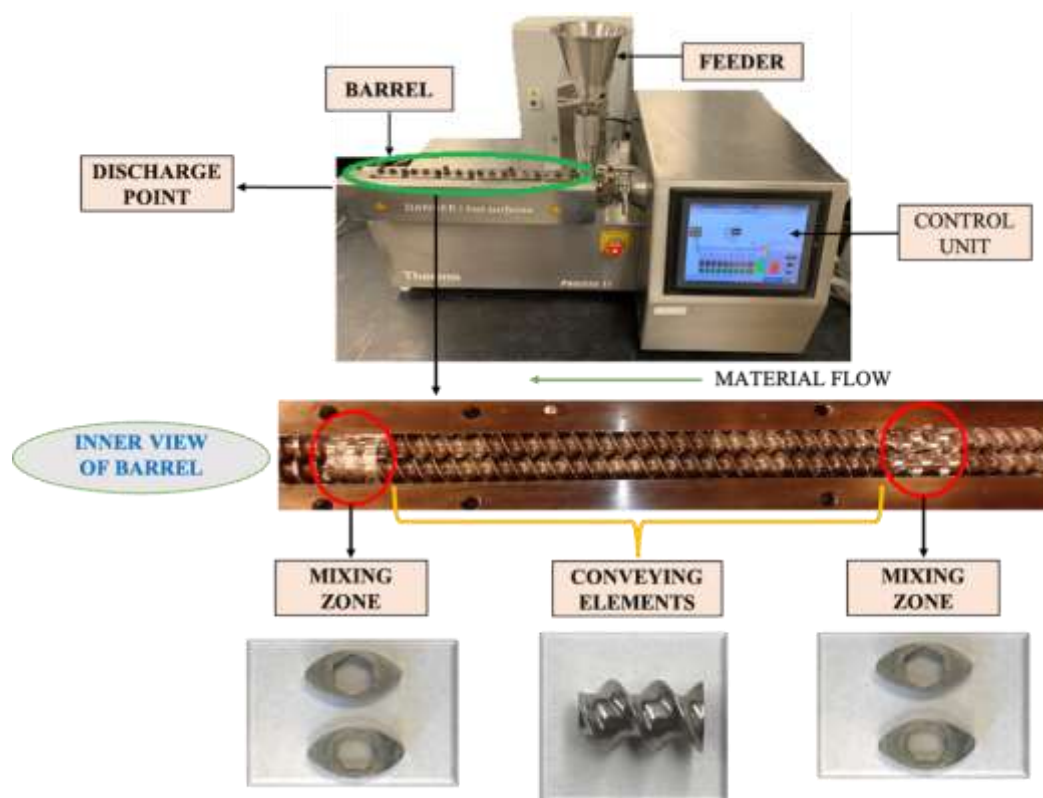


Figure 1: The schematic representation of hot melt extruder.

Table 1: Various formulations investigated by the HME process for developing ASDs of poorly water-soluble drug substances.

Drug Substance	Polymers	Extrusion Temperature (°C)	Research outcomes	Ref
Indomethacin Naproxen Ibuprofen	Eudragit E	65 - 120	High drug loadings of 60 -70 %w/w were achieved. The formulations were stable at high humidity conditions of 95 %RH with no recrystallization of the drug	54
Indomethacin Itraconazole Griseofulvin	Eudragit EPO Eudragit L-100-55 Eudragit L-100 HPMCAS-LF HPMCAS-MF Pharmacoat 603 Kollidon® VA64	N/A	Among all the investigated formulations the drug substances which has the capability to form interactions with the polymer has resulted in faster dissolution profiles and maintained supersaturated state with no recrystallization.	55
Carbamazepine	Soluplus Kollidon® VA 64 HPMC E5	160	Cocrystals of carbamazepine - nicotinamide were developed by reducing the processing temperature and preventing the degradation of carbamazepine at its melting point of 190 C	56
Azithromycin	Eudragit RL PO	150	Taste masking of bitter drug Azithromycin was achieved and the formation of interactions between drug and polymer improved the stability of ASD.	57
Itraconazole	HPMCAS LG	160	Addition of hydrophilic additive (Vitamin E TPGS) improved the processing conditions and also improved the release profiles of the formulations in an acidic environment. In addition, the supersaturated state of the amorphous drug was maintained due to the surfactant property of vitamin E TPGS.	58



## Spray drying

In recent years spray drying has been most widely investigated for developing ASDs of poorly water-soluble drug substances. This approach is advantageous for processing thermal sensitive and high melting point drug substances. Though spray drying involves a supply of heated gas, the contact time of the particles with the heated gas is much less (seconds) when compared with the HME process. The spray drying process mainly involves spraying of formulation solution or suspension using a nozzle into the drying chamber supplied with a heated gas. The dried particles are carried into a cyclone separator and filter, where the particles are separated from the gas. A schematic representation of the spray drying system is shown in Figure 2. The spray drying process remains expensive compared with HME since it requires high amounts of solvent for the feed material preparation<sup>59-63</sup>. It also requires a specialized collection unit for the recovery of solvents. The size of particles mainly depends on the spray nozzle and atomization pressure. The smaller the particle size, the more the solvent evaporation will be attributed to the improved surface area. However, utmost care needs to be taken since the process involves the use of solvents and thermal energy, which might result in an explosion. The spherical morphology of the particles results in improved flow behavior of the formulations. The feed rate and the type of pump mainly depend on the viscosity of the feed solution to be sprayed. The higher the drug concentration, the faster the drying time since less solvent will be incorporated. Spray drying can also be employed for taste masking of bitter drugs, modified release formulations, and manufacturing of inhalation formulations. It can also be used for manufacturing sterile formulations with an improved shelf life over liquid intravenous formulations<sup>64-66</sup>. A few case studies are discussed in which the spray drying approach was employed for developing ASDs of poorly water-soluble drug substances.

Emilia Sawicki et al., (2016)<sup>67</sup> developed ASDs of combination drugs paclitaxel and docetaxel by spray drying approach. A combination of ethanol and water (75: 25 v/v) was used as a solvent carrier, and the process was carried out at an inlet-outlet temperature of 100 - 65 °C. The feed solution was prepared by dissolving polyvinyl pyrrolidone K30 and sodium dodecyl sulfate (SDS) in a 9:1 w/w of ratio. The feed solution was studied at a wide range of concentrations (62.5 - 175 mg/mL). The process was carried out using nitrogen as drying

gas, with a 12 mL/min feed rate and nozzle of dimensions 0.7/1.5 mm. The drug load was maintained at 9.1% for all the investigated formulations. It was noticed that with increasing solute content, particles' size increased (4.8 to 7.7 microns). Interestingly the spray-dried particle has resulted in poor flow behavior; however, the particles have exhibited superior compressibility properties in the presence of lactose as a diluent. The compressed tablets have improved drug release profiles and were found stable for 24 months at ambient conditions.

Surendra Poudel et al., (2021)<sup>68</sup> developed pH-modulated ASD of candesartan cilexetil using polyvinyl pyrrolidone K30 as a polymeric carrier and sodium carbonate as an alkaliizer. The solution of formulation components was prepared using methanol and water in a 1:2 ratio. The solution was sprayed at 3.5 mL/min through a nozzle of 0.4 mm, maintaining the inlet-outlet temperatures at 120 - 70 °C. Among all the investigated formulations, the formulation with the lowest amount of polymeric carrier resulted in greater drug solubility where the ratio of drug - alkaliizer was found to be 1:1. The conversion of the drug into amorphous was confirmed by differential scanning calorimetry (DSC) and x-ray diffraction (XRD) analysis. The developed ASD was stable for four weeks at accelerated and 12 weeks at long-term conditions.

Alyssa Ekdahl et al., (2019)<sup>69</sup> investigated the effect of spray drying parameters on particle size distribution, flow properties, and compressibility. ASDs of felodipine with 20% drug load was developed using Kollidon® VA 64 as a polymeric carrier dissolved in acetone. The concentration of the drug and polymer was maintained at a 1:4 mass ratio. Following spray drying, the formulations were further dried in an oven for 2-3 days to remove a trace amount of solvent. The spray drying process was carried out at an inlet temperature between 72 - 184 °C with a liquid flow rate of 110 - 188 mL/min. The solid content was maintained at 2.0 % for the two-fluid nozzle and 20% for the pressure swirl nozzle. The size of the particles for all the investigated formulations ranged between 4 - 115 microns. Irrespective of the processing conditions, all the formulations have resulted in superior flow and compressibility. A list of commonly used solvents for developing ASDs by spray drying approach is shown in Table 2.

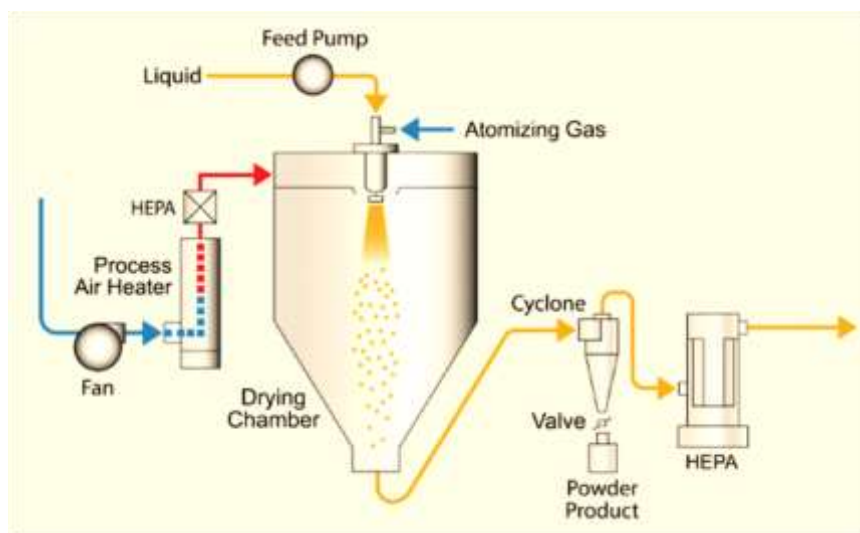


Figure 2: A schematic representation of spray drying process.

Table 2: Commonly used solvents for developing ASDs by spray drying approach.

Solvent	Boiling point (°C)	Density (g/mL)	Viscosity (cP)	ICH Class
Acetone	57.0	1.10	0.28	III
Butanone	80.0	0.81	0.39	III
Butyl acetate	126.0	0.90	0.70	III
Dichloromethane	40.0	1.33	0.45	II
Dimethyl acetamide	163.0	1.00	0.90	II
Dimethyl formamide	150.0	0.90	0.95	II
Ethanol	79.0	0.80	1.00	III
Glycerin	289.0	1.30	950.00	N/A
Isopropyl alcohol	83.0	0.80	2.00	III
Methanol	65.0	0.80	0.55	II
Water	100.0	1.00	1.00	N/A

### 3. Kinetisol®

In recent years, Kinetisol® technology has been more rapidly investigated for developing ASDs of poorly water-soluble drug substances. This approach is advantageous when compared with HME and the spray drying process. The process utilizes the heat generated by mechanical shear generated by the rotating paddles inside the chamber and requires no external heat supply. The material gets exposed to the generated thermal energy and transforms into a molten state. The entire operation completes in less than 30 seconds and the formulation is exposed to high temperature for less than 5 seconds, making the process suitable for thermolabile drug substances. Once the process reaches the end point, the material gets cooled and ejected from the system. The process requires no solvent and external thermal energy, which is advantageous over other manufacturing techniques such as HME and spray drying<sup>70-72</sup>. The major process parameters involved in the Kinetisol® process are the speed of the blades, temperature (pre-set), and time. The temperature is a pre-defined parameter, and once the set temperature is reached inside the chamber, the sample is rapidly ejected. With the increasing speed of the blades, the temperature inside the chamber increases. The speed of the blades mainly depends on the viscosity of the formulation composition, where lower speeds are suitable for low viscous materials and high viscous materials require higher speeds<sup>16,73-75</sup>. The schematic representation of the Kinetisol® instrument is shown in Figure 3.

James C. Dinunzio et al., (2010)<sup>76</sup> investigated the role of the manufacturing process in preserving the stability of the temperature-sensitive drug hydrocortisone. The ASDs of hydrocortisone was developed using Kollidon® VA 64 and HPMC E3 as polymeric carriers using HME and Kinetisol® techniques. The ASD formulations developed by Kinetisol® at 160 °C were stable compared to the formulations developed by HME at 180 °C. The drug's potency within the formulations was reduced with increasing processing temperatures of HME. The conversion of the drug to an amorphous form was confirmed by XRD analysis. This shows the importance of selecting the manufacturing process based on the physicochemical properties of the drug substance.

In another research, James C. Dinunzio et al. (2010)<sup>77</sup> investigated the effect of triethyl citrate (TEC) on the stability

of ASDs developed by HME and Kinetisol® techniques. Itraconazole was selected as the model drug, whereas Eudragit L100-55 and Carbomer 974P were polymeric carriers. All the formulations were investigated for 33.0 %w/w of drug load. The process of HME was carried at 130 °C of barrel temperature, whereas the ejection temperature for Kinetisol® was between 158 - 177 °C. The formulations of HME with plasticizer have resulted in a low glass transition temperature of 54 °C. In contrast, the ASD formulations developed by Kinetisol® without plasticizer have resulted in a glass transition of 101 °C. The formulations of HME with plasticizer have resulted in recrystallization of the drug upon storage at accelerated conditions. In comparison, the formulations of Kinetisol® without plasticizer were found to be stable. This shows the suitability of the Kinetisol® process for developing plasticizer-free ASD formulations and improving the stability by maintaining high glass transition.

Justin R. Hughey et al., (2011)<sup>78</sup> has investigated the effect of the manufacturing process on the purity of ASDs developed by HME and Kinetisol® techniques. Meloxicam was selected as a high melting point model drug, and Soluplus was selected as a suitable polymeric carrier based on preliminary characterization. The ASD formulations developed by HME at 160-175 °C have resulted in a purity of 87 - 94 %. Whereas the formulations developed by Kinetisol® at 110 °C of ejection temperature have resulted in 97.7 % purity at 2625 rpm of paddle speed attributing to the short residence time of exposure.

Urvi Gala et al., (2020)<sup>79</sup>, for the first time, investigated the suitability of the Kinetisol® technique for developing oligomer (cyclodextrin) based ASD formulations of abiraterone in the presence of HPMC E3, HPMC E5, Kollidon® 30, hydroxypropyl β cyclodextrin (HPBC), and polyvinyl acetate phthalate polymers. Drug load was maintained at 10% for all the investigated polymers. The Kinetisol® process was carried at 4000 - 6000 rpm of paddle speed with an ejection temperature of 160 °C. Among all the investigated formulations, the ASD comprising HPBC has resulted in the maximum amount of drug release. This shows the suitability of the Kinetisol® technique for developing cyclodextrin complexation for poorly soluble drug substances. Additionally, a few case studies related to the development of ASDs by the Kinetisol® approach are discussed in Table 3.

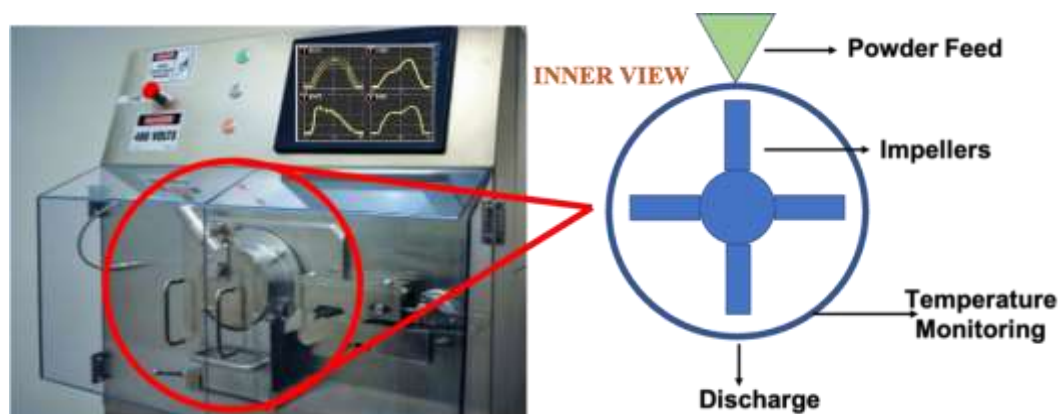


Figure 3: A detailed schematic representation of Kinetisol<sup>®</sup> process setup.

Table 3: A detailed overview of the investigations for developing ASDs by Kinetisol<sup>®</sup> approach

Drug	Polymer	API Melting point (°C)	Paddle Speed (RPM)	Ejection Temperature (°C)	Ref
Meloxicam	Kollidon <sup>®</sup> VA64	256	3250	130	80
Ritonavir	Kollidon <sup>®</sup> VA64 Polyvinyl alcohol	120	1000-2000	80-100	81
Vermurafenib	HPMCAS-LMP	272	2400	180	82
Abiraterone	Hydroxypropyl- $\beta$ -cyclodextrin	223	500-7000	150-180	79
Itraconazole	HPMC	169	2200	140	83

#### 4. Electrospinning

The name “Electrospinning” indicates the process requires electrical field application. The electrospinning process can be employed to develop nanofibers less than 100 nm. The nanofibers provide the advantage of improved surface area. It is a solvent-based approach, where the solution of the drug and polymer is injected through the orifice of a needle (spinneret) with the help of an injection pump<sup>19,84,85</sup>. An electrical field is created between the needle and the sample collector using a high-voltage power supply. When the electric field energy exceeds the surface tension, the solution droplet at the needle tip gets distorted and forms the Taylor cone. The Taylor cone travels as thin nano-scale fibers and coils on top of the rotating collector drum. This approach requires no external heat, and the solvent gets evaporated during the travel of nanofibers from the tip of the needle to the collector drum or plate. The quality of the nanofibers is influenced by the viscosity of the solution, feed rate, size of the needle, voltage, and distance between the needle tip and collector. The commercial viability of this technique to produce large-scale ASDs remains questionable since this process requires a low feed rate of solution<sup>86-88</sup>. Though single needle and high-speed electrospinning have been investigated for scaling the process, the throughput remains low for the batch quantities required at the commercial scale. A detailed overview of electrospinning process is shown in Figure 4.

Zsombor et al., (2015)<sup>89</sup> investigated the advantage of the electrospinning technique over spray drying and film casting techniques. The ASDs of itraconazole were developed using Kollidon<sup>®</sup> VA 64 as a polymeric carrier. The nanofibers were developed using single-needle electrospinning and high-speed electrospinning approaches. For the single-needle electrospinning approach, an electric potential of 30 kV was 15 cm of distance between the needle and the collector. The solution feed rate was maintained at 20 mL/h. In contrast, the

high-speed electrospinning was run at 1500 mL/h of feed rate with 40,000 rpm collector speed and 50 kV of electric potential. The distance between the needle and the collector was 35 cm. The solution was prepared using dichloromethane and ethanol in a 2:1 ratio. All the investigated formulation has an identical ratio of drug and polymer (6:4 ratio). Among all the investigated approaches, the formulations developed by electrospinning and spray drying have converted the drug into an amorphous form. However, the performance of electrospinning formulations was found to be superior, where fast drug release profiles were achieved over spray-dried formulations.

Demuth et al., (2017)<sup>90</sup> investigated the suitability of electrospinning nanofibers for the compression of tablets. The ASD nanofibers of itraconazole were developed using Kollidon<sup>®</sup> VA 64 as a polymeric carrier and a combination of dichloromethane and ethanol (2:1) as a solvent carrier. The high-speed electrospinning process was carried at 1500 mL/h of feed rate with 50 kV of voltage and 40,000 rpm spinneret speed. The collected nanofibers were compressed into tablets using microcrystalline cellulose, mannitol, Kollidon<sup>®</sup> CL, Aerosil, and magnesium stearate. The milled nanofibers have exhibited superior compressibility with 76.25 %w/w of extra granular materials. The tablets exhibited negligible friability (<0.1%), and the tensile strength was found to be 1.94 N/mm<sup>2</sup> with a disintegration time of 6 minutes. This shows the suitability of ASD nanofibers for developing tablet formulations.

B. Demuth et al., (2015)<sup>91</sup> investigated the stability of ASDs developed by single-needle and high-speed electrospinning technologies when stored in long-term and accelerated conditions. Itraconazole was employed as a model drug, and the ASDs were prepared using Kollidon<sup>®</sup> VA64 and HPMC 2910. The polymer Kollidon<sup>®</sup> VA 64 cannot form interactions with the drug substance. The polymer HPMC has the ability to

form interactions. The solutions were prepared using dichloromethane and ethanol in a 2:1 ratio. For the single-needle electrospinning approach, an electric potential of 30 kV was 15 cm of distance between the needle and the collector. The solution feed rate was maintained at 20 mL/h. The high-speed electrospinning was run at 1500 mL/h of feed rate with 40,000 rpm collector speed and 50 kV of electric potential. The distance between the needle and the collector was 35 cm. Among all the investigated formulations, the formulations of HPMC were found to be stable at accelerated conditions for 12 months with no observations of drug recrystallization. This shows the importance of screening polymeric carriers and the role of drug-polymer interactions in preserving the stability of ASDs.

Jana Becelaere et al., (2022)<sup>92</sup> developed high drug-loaded ASDs of flubendazole (55 % drug loading) by electrospinning

approach. The solutions of the drug and polymer (2-phenyl-2-oxazoline) are prepared in formic acid. The electrospinning process was carried out at 0.1 mL/h of feed rate and a 20 cm distance between the needle and the collector. A 20-27 kV voltage was applied to the needle, and -5 kV was applied to the collector. The conversion of the drug to an amorphous form was confirmed by scanning electron microscopy and XRD analysis. The formation of interactions between drug and polymer was investigated using Fourier transform infrared spectroscopy (FTIR). The formulations with a high drug loading of 55 %w/w were stable, with no drug recrystallization attributed to the drug-polymer interactions. This shows the importance of drug-polymer interactions in preserving the stability of formulations. An overview of the investigations for developing ASDs by electrospinning technique is tabulated in Table 4.

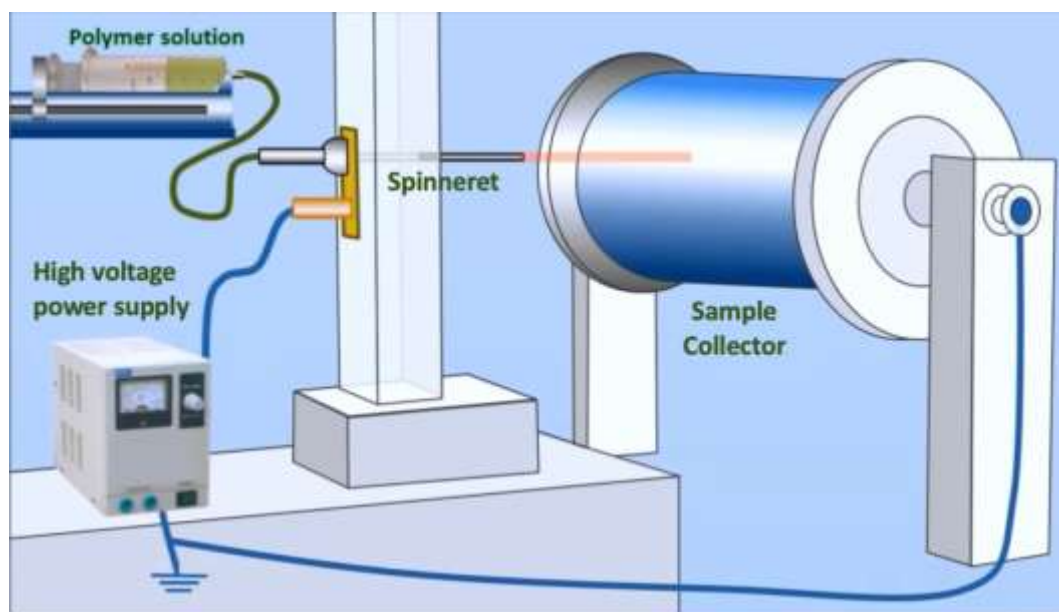


Figure 4: A detailed overview of electrospinning process.

Table 4: An overview of the investigations for developing ASDs by electrospinning technique

Drug	Polymer	Solvent	Electrospinning Parameters	Reference
Meloxicam	Eudragit	Dimethylformamide; tetrahydrofuran; ethanol	Speed: N/A Voltage: 20-30 kV Distance: 25 cm Flow rate: 3-6 mL/h Spinneret: 0.8 mm	93
Carvedilol	Kollidon® VA 64	Ethanol	Speed: 35,000 rpm Voltage: 35 kV Distance: 35 cm Flow rate: 750 mL/h Spinneret: N/A	94
Spirolactone	Kollidon® VA 64	Dichloromethane; ethanol	Speed: 40,000 rpm Voltage: 40 kV Distance: N/A Flow rate: 300-600 mL/h Spinneret: 330 microns	95
Itraconazole	Kollidon® VA 64	Dichloromethane; ethanol	Speed: 40,000 rpm Voltage: 50 kV Distance: N/A Flow rate: 1500 mL/h Spinneret: N/A	96



## 5. Critical aspects for developing ASDs

Since the drug substance within the ASDs exists in a high-energy state, the molecules always tend to recrystallize, affecting the stability and performance of the formulation. Recrystallization of drugs results in reduced solubility and bioavailability. Thus, protecting and preserving the stability of ASDs throughout the product's shelf life is the primary requirement of ASDs. Many factors must be considered during the screening of excipients, the selection of the manufacturing process, and storage conditions for developing a stable and robust formulation. Among various factors, a few of the significant aspects that need to be considered are drug-polymer miscibility, the solubility of the drug in polymer, the glass transition temperature of the amorphous system, drug-polymer interactions, and environmental conditions<sup>21,74,97,98</sup>. Various factors that influence the stability of ASDs is shown in Figure 5.

Drug-polymer miscibility and drug solubility within the polymer are the major prerequisites for developing ASDs. Since ASDs are one-phase systems (homogeneous), the drug and polymer need to be miscible with each other. Few drugs might be miscible with the polymers up to higher drug loads of 30 %w/w, and few drugs are poorly miscible and resulted in very low drug loadings of 5-10 %ww. Thus screening of miscible polymers is of utmost importance for developing stable formulations with high drug loadings<sup>17,19,99,100</sup>. A miscible system can be characterized using differential scanning calorimetry, where a single glass transition temperature indicates a single-phase miscible system. With increasing drug load, a decreasing trend in the melting point of active substance also indicates miscibility of the drug with the polymer. The decreasing trend of melting peaks is also called "melting point depression." In addition, developing the ASDs with a drug load greater than the solubility of the drug within the polymer results in phase separation and recrystallization of the drug, affecting the quality of the product. Hot-stage microscopy can be employed to determine the solubility of the

drug within the polymer<sup>17,56</sup>. The formation of drug-polymer interactions favors the stability of ASDs. Formations of interactions between the drug and polymer will inhibit the molecular mobility of amorphous drug thereby prevents its recrystallization.

Since the ASDs are one-phase systems, they possess a single glass transition temperature. At the glass transition temperature, the ASD exists in a rubber state where the mobility of dispersed amorphous drugs remains high. Maintaining a high glass transition temperature for the amorphous systems is one of the most essential criteria for preserving the stability of the formulations. The storage temperature needs to be 20-30 C lower than the glass transition temperature of the single-phase amorphous system. In addition, the ASDs need to be protected from environmental moisture<sup>101-103</sup>. The absorbed moisture acts as a plasticizer, lowering the amorphous system's glass transition temperature. Thus, the storage conditions play an essential role in preserving stability. In addition to the above-discussed critical aspects, the manufacturing process selection also plays a vital role in developing a robust ASD formulation. Among various manufacturing techniques, hot melt extrusion is a solvent-free technique referred to as the "Green Technique." However, the HME process is unsuitable for thermolabile active substances<sup>19,104,105</sup>. A short residence time of the formulation inside the extruder barrel needs to be maintained since exposure to higher process temperatures results in the degradation and generation of impurities. For thermolabile substances, employing the Kinetisol® approach is beneficial since the exposure time of the formulation material for high temperatures remains as low as 5 seconds. In the case of spray drying and electrospinning approach, the ASD formulations need to be thoroughly dried and free of any trace amount of solvents since it results in toxicity and acts as a plasticizer resulting in reduced glass transition and stability of the formulation<sup>106,107</sup>. Thus, utmost care needs to be taken while selecting the manufacturing process for developing ASD formulations.

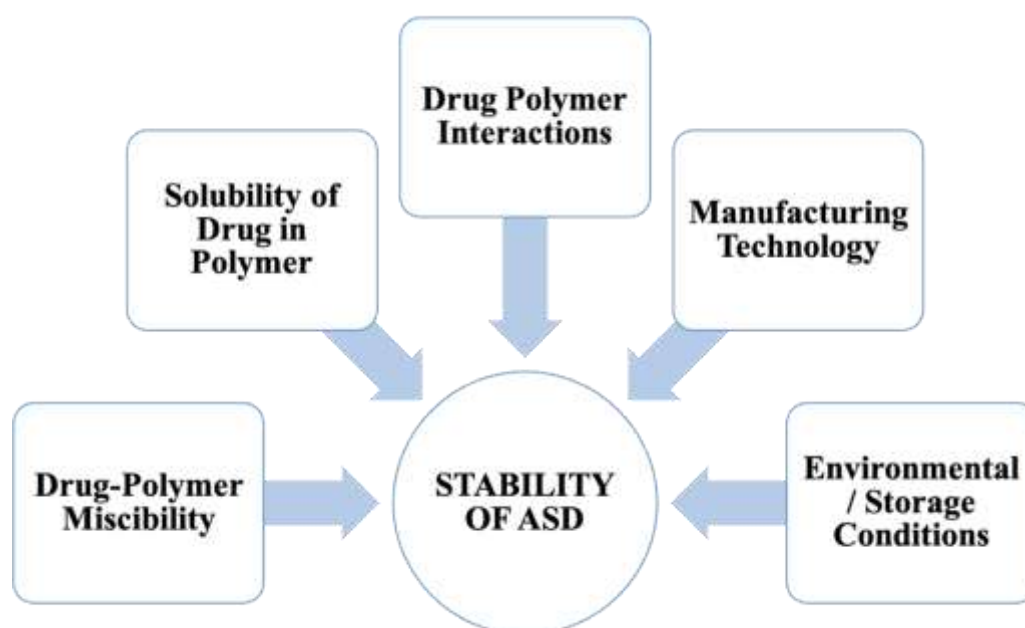


Figure 5: A detailed overview of various critical factors that affects the stability of amorphous solid dispersions.



## 6. Conclusion

Over the last two decades, the ASD approach has gained a tremendous response over many other approaches for improving the solubility and bioavailability of poorly water-soluble drug substances. Among various manufacturing technologies, HME has attracted people from academics, industries, and regulatory bodies. The HME technique is a single-step manufacturing process, requires no solvent, and is suitable for establishing a single-step continuous manufacturing line by mounting appropriate PAT tools for monitoring and controlling the quality of the formulation. Though spray drying is a single-step continuous manufacturing process, it is not economical and requires a vast quantity of solvent and special recovery systems. Kinetisol® is advantageous over HME and spray drying processes since it is also suitable for thermolabile drug substances and requires no solvent. Like the spray drying process, electrospinning requires more solvent and time for manufacturing nanofibers based ASDs. Despite the disadvantages associated with the manufacturing technologies, there is still a requirement for addressing the issues of low drug loadings, poor compressibility, and stability of ASDs.

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