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Review

Melt Fusion Techniques for Solubility Enhancement: A Comparison of Hot Melt Extrusion and KinetiSol® Technologies

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Abstract: A successful candidate for oral drug delivery needs to possess adequate solubility and dissolution rate to elicit its therapeutic action. Extensive research is being carried out to enhance the solubility of poorly soluble drugs through a number of techniques involving polymeric and non-polymeric approaches. Non-polymeric approaches such as micronization and nanocrystals are successful in improving the apparent solubility of drugs, but the sustenance of solubility is not always possible. Amorphous solid dispersions (ASDs) lead to solubility enhancement as well as the maintenance of solubility with the assistance of polymers, thereby improving bioavailability. Spray drying, hot melt extrusion (HME), and KinetiSol® technologies are some of the techniques capable of manufacturing ASDs. Each of these techniques has its own advantages and disadvantages in terms of processing challenges and applicability in preparing ASDs. The latter two technologies are similar in being fusion and non-solvent techniques to improve solubility. This review compares both HME and KinetiSol® techniques regarding mechanism, equipment design, formulation, and process parameters involved and scalability.

Keywords: hot melt extrusion; KinetiSol®; fusion techniques; amorphous solid dispersions; solubility enhancement

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1. Introduction

The oral route of drug delivery remains the preferred route of drug delivery due to its high patient compliance, convenience, cost-effectiveness, low risk of microbial concerns, etc. [1]. Adequate solubility in the gastrointestinal tract (GIT) is a necessity for a drug designed for oral drug delivery to be available for drug absorption. However, more than 40% of active pharmaceutical ingredients (APIs) face solubility-related challenges leading to unpredictable in vivo performance [2]. Formulation development through the polymeric approach remains the only means for the improvement of solubility, which cannot be improved by non-polymeric approaches such as particle size reduction (micronization and nanonization) and supercritical fluid techniques, and chemical modification such as salt formation or crystal engineering. Moreover, non-polymeric approaches might be successful in improving the apparent solubility, but the maintenance of solubility is not always possible. This mechanism of enhancement and maintenance of solubility is best explained by the spring-parachute effect. The spring phase refers to supersaturation of drug in the solvent due to its high energy metastable state. Parachute phase refers to resistance to drug precipitation by polymers due to increased apparent solubility [3,4].

Solubility enhancement through amorphous solid dispersions (ASDs) has been widely recognized for poorly soluble drugs. The amorphous state of API has higher enthalpy and entropy leading to higher solubility in contrast to the crystalline state, which has lower

enthalpy and entropy [5]. The small drug particles in ASDs, due to their high energy, tend to recrystallize by agglomeration, which is prevented by polymers. The polymers used in ASDs, such as hydroxyl propyl methyl cellulose, polyvinyl pyrrolidone, and polyethylene glycol, are generally hydrophilic in nature and should have sufficient viscosity to form a rigid barrier between the drug particles [6]. ASDs are prepared using techniques such as spray drying, gas anti-solvent, and electrospinning, and fusion techniques such as hot melt extrusion (HME) and KinetiSol® [7].

HME and KinetiSol® technologies made their way into the pharmaceutical field from the plastic industry because of their capability to manufacture on a large scale and suitability to produce efficient formulations. HME has been used for decades in the pharmaceutical field and has also led to the commercialization of products such as KALETRA™, NORVIR™, ONMEL™, and NuvaRing® [8]. KinetiSol® is a relatively new technology owned by DisperSol Technologies that has become popular in the last decade and is used to overcome some of the challenges of product development using HME. This review compares two techniques with respect to the mechanism, equipment design, formulation, process parameters involved, scalability and case studies discussing the advantages of using KinetiSol® technology for developing ASD formulations.

2. Mechanism

Hot melt extrusion technology works by the simultaneous application of heat and shear on the ingredients to form extrudates with improved solubility characteristics. Heat energy is supplied by the barrel, which is differentiated into zones capable of being regulated at different temperatures by means of heating elements. Shear is a result of friction generated between the ingredients and the screw elements due to the rotation of the shaft. The shaft consists of several screw elements, which are morphologically and functionally organized to transfer material from one end to the other end of the barrel (Figure 1). The extrudates are further down processed by cooling and milling or cutting the extrudates based on the requirement [9].

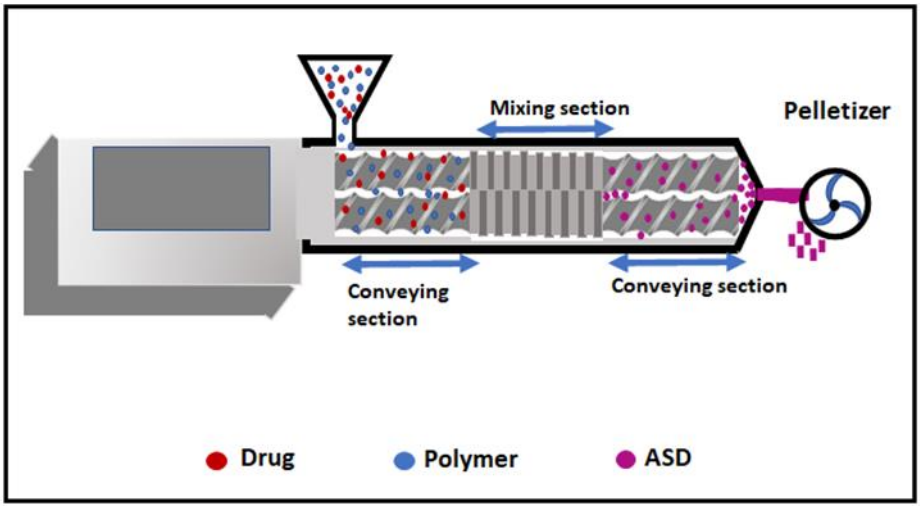

Figure 1. Schematic presentation of ASD preparation through HME technology.

KinetiSol® technology resembles HME technology in being a heat energy-based fusion method to formulate products with enhanced solubility. However, unlike the HME technology that relies on an external supply of heat energy, KinetiSol® technology involves the generation of heat energy by mechanical forces and frictional forces between the ingredients and the processor. KinetiSol® processor consists of a centrally aligned rotating shaft in a cylindrical chamber. The central rotating shaft has a set of blades extending towards the cylindrical chamber. The temperature inside the processor is monitored by a probe present outside the cylindrical chamber (Figure 2). The loading and unloading of the materials into

and out of the processor is through the doors in the cylindrical chamber. After the addition of ingredients in the processor, the process is initiated by the rotation of blades rubbing the materials against themselves or against the processor, leading to heat energy formation. The rotation speed of blades is at much higher rates compared to the rotation speed of the shaft with screw elements in the case of HME. The materials are ejected after the process is completed which is generally quenched with the help of a pneumatic press to increase the surface area. Finally, the quenched product is sized to a suitable particle size based on the desired attributes. The processing time involved with KinetiSol® technology is also relatively less compared to the processing time for HME [10].

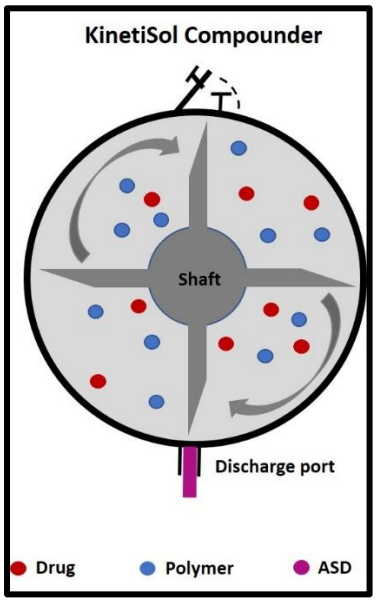

Figure 2. Preparation of ASD through KinetiSol® technology.

At the molecular level, both techniques result in the conversion of the solid materials into a molten liquid state and uniformly dispersing the drug in the hydrophilic carrier to form amorphous solid dispersion. Quench cooling the fused product will arrest the movement of the dispersed drug molecules in the hydrophilic matrix [11].

3. Formulation Aspects

3.1. Active Ingredients

APIs are processed through hot fusion technologies to improve the solubility, which is achieved by dispersing the API in a hydrophilic environment. HME and KinetiSol® technologies are the choices for APIs with organic solvent-related solubility or compatibility issues to form amorphous solid dispersion. However, certain APIs cannot be processed using HME due to the high melting point of API or lead to thermal degradation on prolonged exposure to heat. Such APIs can also be processed through KinetiSol® due to lesser processing times (5–20 s) associated with it in comparison to the long processing times involved with HME. Moreover, KinetiSol® technology is capable of manufacturing ASDs well below the melting point of the API unlike HME where the processing temperature is generally above the melting point of the API [12]. The only limitation for KinetiSol® technology is the APIs (Merck investigational drug, CP-448,187) which are prone to degrade when subjected to shear are not suitable candidates [13–15].

3.2. Polymers

The polymers used for preparing amorphous solid dispersions through HME and KinetiSol® are characteristically hydrophilic and able to form a rigid barrier between the dispersed API particles. Drug–polymer phase diagrams are helpful in the preliminary se-

lection of suitable polymer and % drug load to prepare stable amorphous solid dispersions. An ideal amorphous solid dispersion will lead to maintenance of spring-parachute pattern release of the drug under in vitro and in vivo conditions.

High-molecular weight (HMW) and viscous polymers are preferred to low-molecular weight (LMW) in the preparation of ASD because of their greater ability to prevent the movement of drug particles, resulting in precipitation. However, processing HMW polymers through HME is challenging due to the torque limitations that an extruder can offer. KinetiSol® technology has demonstrated that even HMW polymers such as HPMC E50, HPMC E4M, and PVP K90 can be successfully processed to prepare ASDs [16].

3.3. Additives and Processing Aids

In addition to the polymer, certain additives such as surfactants and stabilizers that improve the stability or solubility characteristics of the ASDs are also included in the formulation. Processing aids such as plasticizers in the case of HME and lubricants in the case of KinetiSol® may also be included to improve the processability. Some examples of plasticizers used in HME are triethyl citrate, stearyl alcohol, polyethylene glycols, propylene glycol, glycerol monostearate, and triacetin and an example of lubricant used in KinetiSol® is sodium stearyl fumarate [17–22].

The purpose of plasticizers in HME is to facilitate processability by reducing the glass transition temperature of the processing materials. However, low glass transition temperature has also a deteriorating effect on the stability of the systems by enabling recrystallization due to the molecular motion of the drug in the matrix of the polymer. KinetiSol® improves processability without the aid of plasticizers in certain cases, enhancing the stability of solid dispersions. Table 1 lists the comparison of few formulation and technical aspects of both the techniques [23].

Table 1. A comparison of hot melt extrusion and KinetiSol® techniques.

Technique	Hot Melt Extrusion	KinetiSol®	References
Mechanism	Thermal fusion	Thermal fusion	[10]
API constraint	APIs sensitive to prolonged exposure to heat High melting point	APIs sensitive to shear	[12,13]
Polymers	Mostly hydrophilic	Mostly hydrophilic	[16]
Processing aid	Need for plasticizer in the case of high-melting-point APIs	Need for lubricant to improve processability	[17,18]
Processing time	Varies from minutes tohours	Seconds	[12,13]

4. Process Parameters Involved in HME and KinetiSol®

Though both HME and KinetiSol® technologies work on a similar principle, the effect of process parameters on the characteristics of the product is different due to the equipment design and their mechanism. The process variables involved with each of the processes can be categorized into independent variables and dependent variables. The independent process variables dealing with HME are temperature, screw configuration, screw speed, feed rate, and length of the extruder, whereas the independent variables involving KinetiSol® are shaft rotation speed and time. The dependent variables in the HME process are (a) residence time, which is influenced by feed rate, screw speed, and length of the extruder; and (b) specific energy, which depends on feed rate, temperature, and screw speed. The temperature in KinetiSol® is a dependent variable that is affected by shaft rotation speed [24,25].

5. Physical Properties of ASDs Prepared Using HME and KinetiSol®

The ASDs prepared by both HME and KinetiSol® technologies tend to have improved solubility due to their low specific area but are dense and have a non-porous nature. Further downstream processing may be necessary if the ASDs need to be compressed into tablets or

encapsulated into capsules. In either case of tableting or encapsulation, the ASDs need to be milled using equipment such as a hammer mill, air-jet mill, or conical mill. The selection of milling equipment should consider the glass transition temperature of polymer and the melting point of API as heat generated during milling might result in precipitation of drug. In such cases, the cryo-milling of the extrudates could be the possible solution to prevent precipitation. Both the techniques result in high density extrudates which suffer from poor compaction properties creating issues during compression. In such cases, blending milled ASDs with highly compressible excipients, such as spray dried lactose, microcrystalline cellulose, and compressible starch, can improve compressibility [13,25].

6. Scalability

Hot melt extruders are available in various sizes, which vary in the screw diameter capable of processing from a few grams to tons per hour. The scale-up for the HME process is based on several approaches that involve volume, specific mechanical energy, and heat transfer coefficient. With the pharmaceutical application of KinetiSol® technology being relatively new compared to hot melt extrusion, the KinetiSol® equipment is not available to manufacture ASDs on a large scale. To date, the KinetiSol® equipment is capable of manufacturing only from a few grams to hundreds of kilos per hour. On the other hand, all the KinetiSol® processers are geometrically similar, avoiding the need for extensive development activities to scale up the process [24,25].

7. Case Studies

The poor intrinsic water solubility of crystalline APIs hinders their use in the drug development due to the bioavailability-associated complications of the formulations. Converting the crystalline API into amorphous form by forming the dispersion of API in a polymer is one of the most reliable methods to improve the solubility. The crystalline API and polymer can be stabilized into an amorphous solid dispersion (ASD) by different processing techniques, such as hot melt extrusion, KinetiSol®, spray drying, and micro-precipitation [26,27]. Each of these techniques have unique advantages in developing ASD formulations. Below are a few case studies utilizing KinetiSol® Dispersing (KSD) technology in development of ASD formulations that could not be developed or faced shortcomings when developed through other technologies, such as HME and the solvent-controlled co-precipitation technique.

Deferasirox, an iron chelator, is currently marketed as Exjade® and Jadenu® for the treatment of iron overload. Exjade® is a tablet for oral suspension, approved by FDA in 2005, but has patient compliance issues due to its unpalatability [28]. To overcome this issue, Jadenu®, a film-coated tablet formulation, was developed, which was approved by the FDA in 2015. However, it was observed that, in certain patients, deferasirox suffers from intra-patient variability due to absorption, first-pass metabolism, intestinal transit time, lipid solubility, and differences in transporter activity. A new formulation to enhance bioavailability, DST-0509, was developed using KSD technology to counter inter-patient variability issues due to absorption. DST-0509 is currently in the phase II clinical stage. The phase I studies have provided evidence for the superior bioavailability of DST-0509 over Exjade® and Jadenu® [29,30].

Abiraterone is a poor water-soluble anticancer drug that has a high melting point (227.85 °C) and low solubility in organic solvents, making it difficult to formulate as an ASD using HME or spray drying techniques. Hence, Gala et al. utilized KSD to prepare ASDs to improve the solubility. Different ASDs were prepared from either polymers or oligomer (binary ASDs) or a combination of polymer and oligomer (tertiary ASDs). Hydroxy propyl methylcellulose (HPMC E3 and HPMC E5), polyvinyl pyrrolidone (PVP 30), and polyvinyl acetate phthalate (PVAP) were the polymers and hydroxyl propyl cyclodextrin β (HPβCD) was the oligomer studied in the case of binary ASDs. Hydroxypropyl methylcellulose (HPMC E15 and HPMC E50), polyvinyl pyrrolidone (PVP K90), sodium carboxymethyl cellulose (Na CMC), and hydroxypropyl methylcellulose acetate succinate (HPMCAS 126G,

HPMCAS 716G, and HPMCAS 912G) were studied in the case of tertiary ASDs. The processing temperature was 160 °C and blade RPM of 4000–6000, followed by the quench cooling of the product. The study provided evidence of the short-chain oligomer and long-chain polymer processing ability via KinetiSol® technology. The ASDs were added with extra granular excipients and further compressed into tablets with a target hardness of 8–12 KP. The DSC and XRD studies revealed the amorphous nature of the API in all formulations. A small peak was observed in the XRD diffractogram of ASDs prepared from polymers HPMC E3 and E5. It was ascertained that the peak was not due to the crystalline drug but due to the presence of NaCl in the polymers HPMC E3 and HPMC E5. All the polymer based binary ASD formulations (HPMC E3, HPMC E5, and PVP K30) showed improvement in dissolution compared to neat API due to the amorphization of API, except formulations based on PVAP. The low dissolution of PVAP-based ASDs was because of the degradation of the ionizable groups of PVAP at the processing conditions, resulting in decreased solubility. The formulations with HPβCD showed a dramatic increase in dissolution due to the capacity of HPβCD to form inclusion complexes with the hydrophobic groups of API. Although a good spring effect was observed with HPβCD formulations, the saturation levels were not maintained throughout the dissolution studies. Of the tertiary ASDs, the ASD with HPβCD and HPMCAS 126G showed the highest super saturation levels of API. n-vivo studies in beagle dogs demonstrated a significant improvement in the pharmacokinetics of ASDs prepared through KSD compared to generic abiraterone tablets [31]. The formulation of Abireterone, DST-2970, is currently in Phase I clinical trials [32].

James C DiNunzio et al. studied the physicochemical characteristics, dissolution, and bioavailability of solid dispersions prepared from itraconazole and hypromellose through HME and KSD technologies. The processing time was relatively shorter for KSD (below 15 s) when compared to over 300 s of process time required for HME process. The characterization studies were performed by modulated differential scanning calorimetry (DSC) and X-ray diffraction (XRD) revealed the successful formation of amorphous solid dispersions by KSD. The DSC studies exhibited a single glass transition temperature (T_g) of the formulations prepared by KSD, while the formulations produced by HME exhibited two T_gs. The single T_g of KSD formulations indicates the complete miscibility of API and polymer and demonstrated a better mixing ability and homogeneity produced by KSD. The results from XRD spectra were confirmed by the absence of characteristic peaks, indicating complete amorphization. The dissolution studies performed under non-sink conditions showed the increased rate of dissolution for formulations processed by both KSD and HME, indicating the improvement in solubility of poorly soluble itraconazole. The improved solubility of itraconazole was also reflected in bioavailability studies conducted in Sprague Dawley rats. The bioavailability studies showed the enhanced area under the curve (AUC) for formulations produced by both KSD and HME compared to crystalline itraconazole. These results indicate the improvement in the bioavailability of itraconazole by KSD technology compared to crystalline API and also has relatively shorter processing time and better process efficiency compared to the HME technique [33].

High-viscous polymers pose processing challenges in the preparation of ASDs due to the lack of required plasticity for processing by HME and the inability to form droplets during spray drying. Keen et al. (2018) demonstrated the ability of KSD to process two high-molecular-weight grades of HPMC (HPMC E50M and HPMC E4M) by preparing ASDs of itraconazole and further compressing into tablets. The API was blended with the polymer at a ratio of 2:3 and processed to a target temperature of 140 °C to ensure the solubility of itraconazole in the polymer. The selection of process temperature of 140 °C (below the melting point of itraconazole 169 °C) was based on the T_g of polymer grades and ratio of API/polymer. After 4 s of processing time at 2200 RPM of process speed, the temperature was rapidly raised to achieve the target temperature in order to eject the product from the equipment. DSC and XRD studies revealed the amorphous nature of API in the formulations produced. The T_g of the formulations prepared using HPMC E50M and

HPMC E4M were detected as 72.5 °C and 83.4 °C in DSC studies, respectively. The higher T_g of the ASDs prepared from high molecular weight polymers restricts the molecular mobility/rotation during storage, resulting in improved stability. The in vitro release studies reveal the improved solubility of itraconazole in the ASDs prepared using HPMC E50 and HPMC E4M compared to the commercially marketed itraconazole tablets (Onmel®). The in vivo studies conducted in beagle dogs demonstrated prolonged absorption phase due to the high viscosity of the formulations compared to marketed formulation [34].

In another study, itraconazole ASDs were prepared by KSD technology using high viscous polyvinyl alcohol (PVA). The process temperature of 170 °C was selected based on the melting point of itraconazole and the process was executed at 2800 RPM. Two different studies were carried out; one for the selection of an optimal grade of PVA and another for the optimal drug load to form stable ASDs. To determine the optimal grade of PVA, formulations with 20% drug load were prepared with different hydrolyzed grades of PVA (4-38, 4-88, 4-75, and 4-98) with the slight adjustment of the process parameters. The in vitro release studies showed that the release was dependent on the hydrolyzed grade of the polymer and also the interaction between non-ionic PVA (which has high density of H bond donor sites) and basic itraconazole. In vivo studies showed that the PVA 4-88 formulation exhibited a greater maximum concentration (C_{max}) and AUC compared to Onmel®. In order to select optimal drug load, ASDs were prepared at different concentrations (10% *w*/*w*, 20% *w*/*w*, 30% *w*/*w*, 40% *w*/*w*, and 50% *w*/*w*) of itraconazole in PVA 4-88. The ASDs were subjected to dissolution studies under non-sink dissolution studies. The dissolution results under acid conditions showed that the 20% *w*/*w* drug load had the highest dissolution followed by 30% *w*/*w*, 40% *w*/*w*, 10% *w*/*w*, and 50% *w*/*w*, but in basic pH, the dissolution of ASDs followed a typical order, which is a decrease in drug release with an increase in drug load. It was inferred that the aberration in drug release of 10% *w*/*w* drug-loaded ASD might be due to the improper mixing of viscous PVA hydrogel loaded with the drug. Based on the performance and size of final dosage form, the ASD with 30% *w*/*w* drug load was considered optimal [35,36].

A study was conducted by Jermain S.V. et al. to compare the performance of ASDs of a weakly basic drug prepared using anionic polymer (hypromellose acetate succinate MMP grade) processed by orthogonal techniques, Spray drying, and KinetiSol®. BI 667 was used as model drug and has a pKa of 2.4 and shows pH-dependent solubility (76 µg/mL in 0.01 N HCl and 32 µg/mL in pH 6.8 phosphate buffer). ASD was prepared by processing the drug and polymer in a KinetiSol® formulator at 4500 RPM to reach a temperature of 160 °C. The molten mass was subsequently quench cooled and milled. ASD was also prepared through the spray drying technique by dissolving the drug and polymer in an acetone–water mixture and spray drying the mixture using the Büchi mini spray dryer B-290. The spray dried material was slugged and milled to obtain the required particle size. The same drug to polymer ratio of 1:2 was used in preparing both the ASD techniques. The impact of processing technology on the physicochemical characteristics, in vitro drug release in acidic and neutral media, and the in vivo oral bioavailability were evaluated. The results from the in vitro drug release and in vivo studies in beagle dogs indicated an improved bioavailability by four times of the drug in the case of formulations prepared using KSD compared to ASD prepared using spray drying. The higher bioavailability of the drug with ASD prepared with the KSD technique is due to the increased supersaturation drug levels in the neutral media compared to ASD prepared through spray drying [13].

Vemurafenib, marketed as Zelboraf, is prescribed for the treatment of late-stage melanoma. Vemurafenib has a low aqueous solubility of <2 µg/mL. It also has low solubility in organic solvents and a high melting point, leading to processing challenges for preparing ASDs using spray drying and HME techniques. Hence, the solubility of vemurafenib in Zelboraf is improved by a solvent-controlled coprecipitation technique to prepare micro-precipitated bulk powder (MBP) or ASD. KinetiSol® technique is also suitable to prepare ASDs that cannot be prepared using HME and spray drying. A comparative study of vemurafenib ASDs processed by MBP and KinetiSol® was conducted by employing

polymer HPMCAS-L. The KinetiSol® process was carried out with 30% drug load and a processing conditions of 180 °C and 2400 RPM. The DSC and XRD studies revealed the amorphous nature of formulation produced by both MBP and KinetiSol®. The chemical analysis showed minimum or no degradation of vemurafeb (purity 0.1% less than neat API) in both the processes. The in vitro release studies showed a significant improvement in solubility in formulations prepared by MBP and KinetiSol® compared to neat API. However, the KinetiSol® formulations maintained higher saturation levels compared to MBP. The results of the in vitro and in vivo studies indicated a better dissolution and improved bioavailability by approximately three times for the formulation processed by KinetiSol® compared to the MBP formulation. The reason for the improved bioavailability is the difference in the porosity of the formulations prepared from MBP and KinetiSol®. The morphology of the particles produced by KinetiSol® were dense and uniform compared to the porous nature (i.e., a high surface area) of the particles produced by MBP. Interestingly, the MBP formulation, though having a higher surface area due to its porous nature, was not successful in fluid exchange between dissolved drug within the particles and the bulk medium. The dissolved drug, after reaching saturated or super-saturated levels within the particles, resulted in the precipitation of drug. In vivo studies in Sprague Dawley rats also showed the superior performance of KinetiSol® formulations compared to MBP formulations. The KinetiSol® formulation showed a higher C_{max} and also prolonged absorption, which can be correlated to the physico-chemical properties of the formulations that further affected the rate of precipitation of the formulations prepared by both techniques [37].

Hughey et al. developed ASD of Meloxicam, a BCS class II drug by using Soluplus®. Experiments were performed to observe the effect of process variables on the stability of the drug. Process conditions of 110–140 °C and RPM 2250–3000 RPM were studied. A correlation was observed between ejection temperature, residence time, and process RPM. Residence time was reduced from 22 s to <3 s when the process RPM was increased from 2250 to 3000. The reduction in the processing time facilitated the minimum exposure of the product to a higher temperature. There was an inverse relation observed with increased process temperature and drug degradation. The product ejected at 110 °C and 118 °C had an assay >95%; however, when the ejection temperature was raised to over 125 °C, the assay dropped to <90% and further reduced to 79% at an ejection temperature of 140 °C. These results demonstrated that the degradation might have started between the process temperature of 118 °C and 125 °C, indicating the importance of bracketing safe processing conditions, which is crucial for the stability of the formulations. The formulated solid dispersions showed a profile with the significant improvement of dissolution (~7 folds) in 0.1 N HCl and deionized water [38].

Homogeneity issues often can arise when dealing with low API loading in the formulations. KSD technology can be applied successfully to produce homogeneous ASDs of potent APIs. Meloxicam, a BCS class II non-steroidal anti-inflammatory, was processed by KSD with different drug loads of API loading of 1%, 5%, and 10% w/w. The processing time was under 40 s. The milled product was evaluated for blend homogeneity and content uniformity to study the homogeneity. Energy-dispersive X-ray spectroscopy combined with scanning electron microscopy (SEM/EDS) was utilized to further map the distribution of the drug in the drug–polymer matrix. It was observed that the relative standard deviation of the assay was less than 2.0% in the samples collected for blend uniformity studies. The images from SEM/EDS indicates that there were no hot spots or absence of drug in the matrix, and the drug was uniformly distributed in the matrix. Additionally, Raman spectroscopy confirmed the amorphous nature of the solid dispersions and NMR studies demonstrated the miscibility of the polymer and API at all drug loads [12].

KSD technology can also be used to improve the API load of formulations without affecting the formulation performance. Norvir® is an antiviral tablet containing 15% w/w of Ritonavir API processed through HME technology. The large tablet size and low API load are the limitations of HME-processed Norvir®. The extensive degradation of melt-extruded ritonavir is another limitation. API (Ritonavir) load can be increased to

30% w/w and the mass of the tablet can be reduced by 45% with KSD technology. The in vivo pharmacokinetics and permeation rate of Ritonavir tablets produced by KSD were equivalent to Norvir® [39].

In another study, Lafountaine et al. reported the effect of processing conditions on the stability of ritonavir solid dispersion. Ritonavir solid dispersions were produced using the polymers PVA 4-88 and PVP VA64. The process was performed at different processing speed of 1000–2000 RPM. The additional mechanical energy (process RPM) reduced the process time; however, an increase in impurity content was observed. From the results, it was evident that the mechanical energy above certain proportion could cause the drug degradation. Though the ejection temperature (80–100 °C) was much below the degradation temperature (160 °C) of the API, the API degradation was evident at the high process speed of 2000 RPM. To confirm the results, a placebo batch was manufactured to confirm that the degraded product was the API and not polymer. These results emphasized the importance of processing conditions as the processing conditions directly affected the stability of API. This suggests that the processing conditions need to be specifically tailored based on the type of API and polymer in the formulation [40].

DiNunzio et al. studied the effect of HME and KSD techniques on the potency of a heat-sensitive drug, hydrocortisone. Kollidon VA64 and hydroxypropyl methyl cellulose E3 were used as polymers to prepare ASDs. Thermogravimetric analysis (TGA) was used to determine the thermal stability as hydrocortisone exhibits a change in weight upon degradation. Studies indicated that ASDs prepared using HPMC E3 on KSD were able to be processed at 160 °C and 180 °C and had potencies of 91.9% and 83.0%, respectively, but HPMC E3 could be processed on HME only at 180 °C and led to a potency of only 75.0%. Extrudates prepared using Kollidon VA64 resulted in decreased potency with increasing residence time. This can result in decreased potencies with scale-up from smaller to larger extruder, but the same was not be observed with KSD as the residence time remained the same during the scale-up [41]. A list of the APIs investigated in the case studies and their challenges are listed in Table 2.

Table 2. List of challenges that were resolved by KinetiSol® technology in the preparation of ASDs.

Challenge	API/Polymer	Reference
Variable bioavailability	Deferasirox	[27–29]
High melting point and low solubility of API in organic solvents	Abiraterone	[31]
High viscous polymers	HPMC E50M, HPMC E4M, PVA	[34]
Drug solubility in neutral media	Investigational drug, BI 667	[13]
Drug loading	Vemurafenib	[37]
Drug uniformity	Meloxicam	[38]
Drug stability	Ritonavir	[40]
Drug stability	Hydrocortisone	[41]

8. Conclusions

As a high proportion of drug molecules in the development pipeline face solubility issues, there is a need for new technologies that can improve solubility and thereby address bioavailability issues. Several process techniques are currently being invented to find solutions to the solubility issues of the APIs. Hot melt extrusion and KinetiSol® techniques are similar in terms of being solvent-free and melt-fusion techniques, but differ in their principle of working. Hot melt extrusion technology has been established in the pharmaceutical industry with a number of products either commercialized or in the development phase. Hot melt extrusion technology has also gained attention by regulatory agencies as being a continuous process that has the ability to maintain consistency in quality compared to a batch process. On the other hand, KinetiSol® is a relatively a novel technique that is capable of resolving unique issues associated with process development. KinetiSol® technique is especially useful in APIs that have a poor solubility in organic solvents and

are susceptible to degradation upon a prolonged exposure to heat. This review helped to provide an idea of the unique advantages that KinetiSol® can offer in the preparation of ASDs, potentially shaping the future of drug product development.

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Abbreviations

GIT	Gastrointestinal tract
ASDs	Amorphous Solid Dispersions
HME	Hot Melt Extrusion
API	Active Pharmaceutical Ingredient
HMW	High-Molecular Weight
LMW	Low-Molecular Weight

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