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Thermal processing of a poorly water-soluble drug substance exhibiting a high melting point: The utility of KinetiSol® Dispersing

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ABSTRACT

Poorly water-soluble drug substances that exhibit high melting points are often difficult to successfully process by fusion-based techniques. The purpose of this study was to identify a suitable polymer system for meloxicam (MLX), a high melting point class II BCS compound, and investigate thermal processing techniques for the preparation of chemically stable single phase solid dispersions. Thermal and solution based screening techniques were utilized to screen hydrophilic polymers suitable for immediate release formulations. Results of the screening studies demonstrated that Soluplus®(SOL) provided the highest degree of miscibility and solubility enhancement. A hot-melt extrusion feasibility study demonstrated that high temperatures and extended residence times were required in order to render compositions amorphous, causing significant degradation of MLX. A design of experiments (DOE) was conducted on the KinetiSol® Dispersing (KSD) process to evaluate the effect of processing conditions on the chemical stability and amorphous character of MLX. The study demonstrated that ejection temperature significantly impacted MLX stability. All samples prepared by KSD were substantially amorphous. Dissolution analysis of the KSD processed solid dispersions showed increased dissolution rates and extent of supersaturation over the marketed generic MLX tablets.

1. Introduction

With the introduction of high-throughput screening to the pharmaceutical industry, the number of newly synthesized chemical entities exhibiting poor water-solubility characteristics has increased dramatically (Lipinski, 2000, 2002). In most cases these drug substances exist in a thermodynamically stable crystalline state, often resulting in poor oral bioavailability. When amorphous, a drug substance is in a high free energy and entropy state and is capable of exhibiting apparent solubilities many times greater than that of its crystalline form (Hancock and Parks, 2000; Janssens and Van den Mooter, 2009). This improvement in apparent solubility often results in increased oral bioavailability for drugs where absorption is not limited by permeability. However, apparent solubility is transient in nature and without stabilization solubility will ultimately decrease to that of the most thermodynamically stable form. Similarly, amorphous solids are inherently unstable in that the drug substance may revert to the thermodynamically stable crystalline state during processing or storage (Hancock et al., 1995).

An increasingly popular method of enhancing apparent solubility values and kinetically stabilizing the amorphous form of a drug substance is through the manufacture of single phase solid dispersions, also termed solid solutions, in polymeric matrices. The use of amorphous polymers in solid dispersion systems was first described by Tachibana et al. in 1965 (Leuner and Dressman, 2000; Tachibana and Nakamura, 1965). The ability of a polymer system to provide solubility enhancement properties is dependent on the drug substance and may be experimentally determined (Vandecruys et al., 2007). While semi-crystalline polymers may be used for this purpose, amorphous polymers are frequently used due to their inherent physical stability and dissolution properties. Solid dispersion systems such as these have been extensively studied and have been shown to significantly improve oral bioavailability (Ambike et al., 2005; DiNunzio et al., 2008, 2010c,d).

Single phase solid dispersions may be prepared by solvent-based methods such as spray-drying and lyophilization or fusion-based techniques such as hot-melt extrusion (HME) (Breitenbach, 2002; Curatolo et al., 2009; Friesen et al., 2008; Six et al., 2003; Verreck et al., 2003). While fusion-based techniques such as HME do not require the use of organic solvents, degradation of the drug substance due to high processing temperatures is a concern (DiNunzio et al., 2010a; Follonier et al., 1994; Hughey et al., 2010; Repka et al., 1999, 2003).

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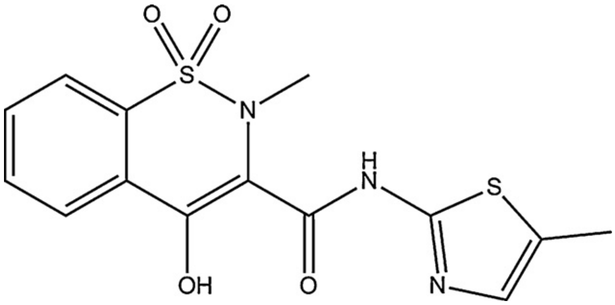

Fig. 1. Chemical structure of meloxicam.

For thermally stable drug substances and polymers, HME may be conducted at temperatures above the melting temperature of the drug substance. This scenario is ideal as it does not require high shear rates to render drug substances amorphous. However, this can result in a multi-phase system if the components do not exhibit miscibility. Processing temperatures below that of the drug's melting point are also possible provided that there is adequate shear input to render the drug substance amorphous (Chokski et al., 2005; Liu et al., 2010; Qi et al., 2008). If processing occurs at temperatures much less than the melting point of the drug substance, reasonable residence times may not be sufficient to solubilize the drug substance. In these cases, increasing specific shear input or processing temperature can facilitate the solubilization process. However, the HME process is somewhat limited in the amount of shear that can be imparted to the melt. Furthermore, elevated temperatures can cause decomposition of the polymer system or drug substance.

KinetiSol® Dispersing (KSD) has emerged as a novel fusion-based processing technique that is capable of imparting high rates of shear into compositions. In this processing technique, paddles within a cylindrical chamber containing raw materials rapidly rotate, generating all heat energy through a combination of shear and friction. Temperatures within the chamber rapidly increase from room temperature to the desired ejection temperature, allowing for minimal thermal exposure. The technique has been previously utilized to prepare single phase solid dispersions of itraconazole in hypromellose, a highly viscous water-soluble polymer (DiNunzio et al., 2010c,d). Similarly, the KSD process has been utilized to prepare plasticizer-free compositions of Eudragit® L100-55 and other advanced solid dispersions (DiNunzio et al., 2010b,d). The ability of KSD to successfully process compositions such as these can be attributed to its high torque output and rates of shear.

Meloxicam (MLX) is a widely used non-steroidal anti-inflammatory drug (NSAID) with its structure depicted in Fig. 1. The weak acid form of MLX is characterized as having solubility values of 12 μg/mL and 0.9 μg/mL in water and 0.1 N HCl, respectively with reported pK_a values of 1.09 and 4.18 (Luger et al., 1996; Seedher and Bhatia, 2003). Having a high permeability, MLX is classified as a class II BCS compound. The melting point of MLX is reported to be approximately 270 °C, indicating that HME may not be a suitable processing technique for the preparation of amorphous compositions (Bashiri-Shahroodi et al., 2008).

The utility of amorphous MLX to improve dissolution performance has been studied extensively (Bashiri-Shahroodi et al., 2008; Dehghan and Jafar, 2006; El-Badry and Fathy, 2006; Ghareeb et al., 2009; Kumar and Mishra, 2006; Shenoy and Pandey, 2008). El-Badry et al. found that polyvinylpyrrollidone based matrices of MLX prepared by lypholization and solvent evaporation techniques exhibited dissolution rates and extents much greater than unprocessed MLX (El-Badry and Fathy, 2006). Similarly, Ghareeb et al. found that dispersions of MLX in polaxamer-based matrices prepared by a solvent-based kneading technique improved the dissolution rate and extent of MLX (Ghareeb et al., 2009).

Solid dispersions of MLX prepared by HME have not been previously reported which may be due in part to its thermal instability. It was hypothesized that the KSD processing method would successfully render compositions amorphous while maintaining chemical stability due to rapid processing times. In this study, three polymer systems were screened for miscibility with MLX and their extent of solubility enhancement in solution. Once a suitable polymer was selected, thermal processing studies utilizing HME and KSD were conducted to evaluate the suitability of each. A design of experiments (DOE) was conducted to evaluate the effect of KSD processing conditions on amorphous character and recovery of MLX in the preparation of dissolution enhanced dosage forms.

2. Materials and methods

Kollidon® 30 (polyvinylpyrollidone) (PVP), Kollidon® VA 64 (PVPVA) a vinylpyrrolidone–vinylacetate copolymer and Soluplus®(SOL), a polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer were kindly donated by BASF Corporation (Florham Park, NJ). Weight average molecular weights of PVP, PVPVA and SOL are 50,000 g/mol, 65,000 g/mol, 118,000 g/mol, respectively. Meloxicam (MLX) was purchased from Aurobindo Pharma Ltd. (Ameerpet, India). Generic MLX tablets (15 mg) (Zydus Pharmaceuticals, Princeton, NJ) were purchased from the Department of University Health Services at The University of Texas at Austin (Austin, TX). High performance liquid chromatography (HPLC) grade methanol was purchased from Fisher Scientific (Pittsburgh, PA). All other chemicals were of ACS grade or higher.

2.1. *KinetiSol® Dispersing*

KinetiSol® Dispersing (KSD) activities were conducted on a lab scale pharmaceutical compounder designed and manufactured by DisperSol Technologies, L.L.C. (Austin, TX), as previously described (DiNunzio et al., 2010a,b,c,d; Hughey et al., 2010). Binary mixtures of polymer and meloxicam (50 g total) were mixed by hand for 1-min in a low density polyethylene bag prior to being placed in the KSD processing chamber. Once processing began, an automated computer control module was utilized to monitor real-time paddle rotational speed, amperage, and product temperature. Immediately after the desired product temperature was reached (ejection temperature), the molten dispersion was ejected into a stainless steel product container and rapidly quenched between two chilled plates. Compositions were immediately milled using a Laboratory L1A Fitzmill (Fitzpatrick Inc., Elmhurst, IN) equipped with a 0.020-in. screen at 9000 rpm and passed through a 60-mesh (250 μm) screen prior to characterization. Processing conditions and real-time data graphs are outlined in Section 3.

2.2. *Hot-melt extrusion*

A HAAKE Minilab II Microcompounder (Thermo Electron Corporation, Newington, NH) equipped with 5/14 mm conical screws and a 2-mm circular die was utilized for hot-melt extrusion (HME) studies. Binary mixtures of polymer and meloxicam (50 g total) were mixed by hand for 1-min in a low density polyethylene bag prior to being manually fed into the extruder hopper. The extruder was operated in flush and recirculate modes, as described in subsequent sections. Extrudates were cooled to room temperature by convective cooling and immediately milled with a Laboratory L1A Fitzmill equipped with a 0.020-in. screen at 9000 rpm and passed through a 60-mesh (250 μm) screen prior to characterization. Actual HME processing conditions are outlined in Section 3.

2.3. Hot-stage microscopy

The miscibility of MLX in each polymer system was evaluated by hot-stage microscopy (HSM). Solutions of polymers were prepared by dissolving SOL and PVPVA in acetone while PVP was dissolved in methanol. Resulting solutions were pipetted onto glass microscope slides and placed in a desiccator at room temperature for 24 h. Meloxicam powder was dispersed over the dried polymeric films and placed on a FP82HT hot stage (Mettler Toledo, Columbus, OH). An Olympus BX60 microscope (Olympus Corp., Center Valley, PA) equipped with an Insight QE camera (Diagnostic Instruments Inc., Sterling Heights, MI) captured images prior to heating, after 15 min at 175 °C and after an additional 15 min at 200 °C.

2.4. Thermogravimetric analysis

A PerkinElmer Thermogravimetric Analyzer (Norwalk, CT) was utilized to evaluate the thermal stability of MLX, each polymer system and combinations thereof. Prior to analysis, moisture was removed from samples by placing bulk samples under vacuum in a desiccator for 48 h. Approximately 10 mg of each desiccated raw material was weighed into separate 40 μL aluminum pans. Sample pans were placed in the chamber and equilibrated at 50 °C under a constant flow of nitrogen (65 mL min^{-1}). Once equilibrated, sample mass was monitored as the temperature was increased from 50 °C to 350 °C at a rate of 10 °C/min.

2.5. X-ray powder diffraction

Milled dispersions, unprocessed MLX and unprocessed polymers were placed on an aluminum sample holder suitable for X-ray powder diffraction (XRPD) analysis. A Philips Model 1710 X-ray diffractometer (Philips Electronic Instruments Inc., Mahwah, NJ) operating at 40 kV and 30 mA was used to determine the presence of crystallinity in processed compositions. Samples were scanned over a 2θ range of 5–50° with a step size of 0.05° and a dwell time of 3 s.

2.6. High performance liquid chromatography

High performance liquid chromatography (HPLC) was used to analyze MLX content in solubility screening and recovery analysis samples. A Waters 717 autosampler (Waters Corporation, Milford, MA) was utilized to inject 35 μL samples onto a Phenomenex® Luna 5 μm C18(2), 150 mm × 4.6 mm column (Phenomenex®, Torrance, CA). The aqueous mobile phase consisted of a 0.1% (w/v) monobasic potassium phosphate aqueous solution, adjusted to pH 6.0 while the organic phase was HPLC grade methanol. The total mobile phase flow rate throughout the gradient method was 1.00 mL min^{-1}. A Waters 2996 photodiode array detector, extracting at 362 nm, quantified the amount of meloxicam in each sample. The retention time of MLX was approximately 8.5 min. All analyses maintained linearity ($R^2 \geq 0.999$) in the range tested and a relative standard deviation of less than 2.0%. Empower version 5.0 was utilized to process all chromatography data.

2.7. Solubility enhancement study

Approximately 10 mg of MLX was weighed into 60 separate culture tubes. Polymers (PVP, PVPVA or SOL) were incorporated into the culture tubes such that concentrations of 0%, 0.1%, 0.3% or 0.9% ($n = 3$ for each individual system) would be obtained with the addition of 10 mL of deionized water or 0.1 N HCl. Once the appropriate media was added, the culture tubes were sonicated for 90 min which resulted in excess MLX suspended in solutions of PVP, PVPVA or SOL. Culture tubes containing SOL exhibited a Tyndall effect that became more prevalent as polymer concentration was increased. Samples were shaken at room temperature on a Lab-Line Orbit Environ-Shaker (Lab-Line, Melrose Park, IL) at 100 rpm for 72 h. Suspension pH values were recorded and aliquots were filtered through Whatman 0.45 μm PVDF filters (Whatman, Piscataway, NJ) and analyzed by high performance liquid chromatography to determine equilibrium solubility values.

2.8. MLX recovery testing

High performance liquid chromatography was used to determine MLX recovery values in prepared compositions. Milled dispersions were accurately weighed to 100.0 ± 3 mg and placed in 100-mL volumetric flasks. Approximately 75 mL of a 50:50:5 mixture of methanol:water:1 N NaOH diluent was added to the flasks which were then subjected to 2 min of sonication. Once brought to volume and mixed, samples were filtered through 25 mm 0.2 μm PVDF filters (Whatman, Piscataway, NJ) and transferred to 1 mL vials (VWR International, West Chester, PA) for HPLC analysis. MLX assay values were adjusted for the recorded sample weight and compared to a known standard containing 10.0 ± 0.10 mg in 100 mL of the diluent described above.

2.9. Dissolution analysis

Dissolution analysis of KSD processed compositions was performed in 900 mL of water and 0.1 N HCl according to the USP 34 Apparatus II (paddle) method at 50 rpm. A VK 7000 dissolution apparatus (Vankel Technology Group, Cary, NC) equipped with a VK 8000 autosampler was utilized for the analysis. Milled dispersions and tablets were weighed such that each vessel contained 15 mg of MLX. All materials studied rapidly dispersed in the dissolution vessel and did not exhibit coning. During analysis, samples were taken at 5, 10, 15, 20, 30, 45, 60, 90, and 120 min without media replacement. Each sample was immediately diluted at a 1:1 ratio with a 50:50:5 mixture of methanol:water:1 N NaOH to prevent the precipitation of MLX. Samples were transferred to a 96-well plate reader and analyzed by UV–vis spectrophotometry at 362 nm.

2.10. Statistical analysis

The design of experiments (DOE) and subsequent statistical analyses were conducted with MINITAB Release 14 software (Minitab Inc., State College, PA). In ANOVA analyses, a value of $p \leq 0.05$ was used as the criteria for statistical significance.

3. Results and discussion

3.1. Thermal based polymer screening studies

Thermogravimetric analysis is a tool often utilized by pharmaceutical scientists to screen formulation components for thermal degradation. This technique is particularly useful for drug substances or polymers that are candidates for thermal processing methods. In this study, TGA was conducted on MLX and three water soluble polymers: SOL, PVPVA and PVP, as illustrated in Fig. 2.

Crystalline MLX was found to exhibit thermal stability at temperatures below its melting point of 270 °C, after which rapid weight loss due to degradation occurred. Further inspection of Fig. 2 showed that SOL and PVPVA began to exhibit mass loss at temperatures greater than 300 °C, while PVP began to decompose at temperatures as low as 175 °C. While TGA is a useful tool in many cases, it should be noted that this technique can lead to false positive results as thermal degradation can occur without a measureable loss in mass. Without taking other factors into consideration, results of the TGA study could lead one to believe that a

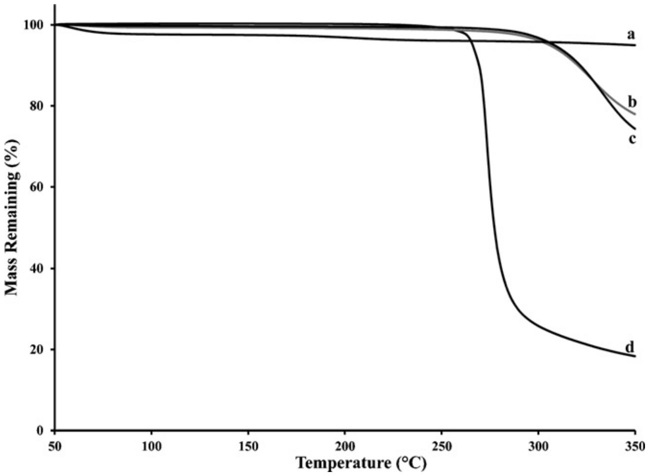

Fig. 2. Thermogravimetric analysis of (a) PVP, (b) SOL, (c) PVPVA and (d) unprocessed crystalline MLX.

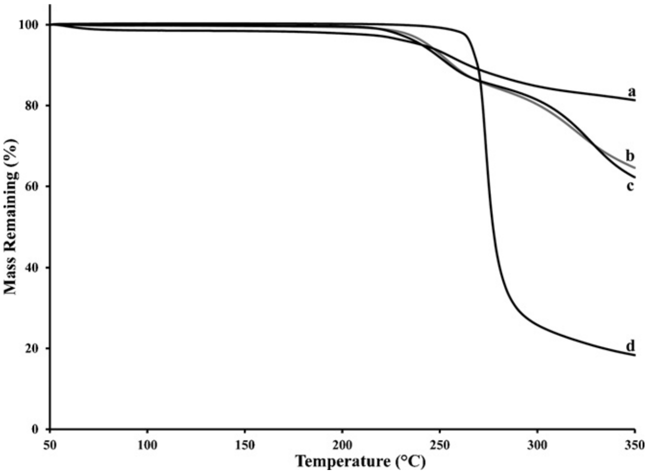

Fig. 3. Thermogravimetric analysis of 1:3 physical mixtures of (a) MLX:PVP, (b) MLX:SOL, (c) MLX:PVPVA and (d) unprocessed crystalline MLX.

processing temperature in the range of 270 °C, the reported melting point of MLX, would be suitable for PVPVA and SOL matrices. However, Kolter et al. described the maximum HME processing temperature of PVPVA and SOL as being below 200 °C (Kolter et al., 2010). The researchers described these polymers as browning at temperatures above 200 °C, indicating a thermal decomposition mechanism that is not observed by TGA. It should also be noted that the authors did not characterize PVP (Kollidon®30) due to its propensity to degrade at elevated temperatures.

Differential scanning calorimetry (DSC) is a tool that may be utilized to measure the extent of miscibility between a drug substance and a polymer matrix through melting point depression (Forster et al., 2001). When 1:3 MLX:polymer physical mixtures were heated in crimped aluminum pans, the resulting thermograms showed that decomposition of one or more substances occurred at temperatures above 200 °C in each case (data not presented). Thermograms of pure polymer and raw drug substance did not show signs of decomposition. It was hypothesized that the observed degradation was that of molecularly dispersed or amorphous MLX as dissolution within polymer systems occurred. This phenomenon occurred at temperatures much lower than 270 °C, the reported melting temperature of MLX. In previous work conducted by Hughey et al., it was found that the thermally labile drug substance being studied decomposed at a temperature much lower than predicted by TGA when in the presence of molten polymers due to the formation of amorphous drug (Hughey et al., 2010). In order to further characterize the observed degradation in the present study, 1:3 physical mixtures of MLX:polymer were prepared and analyzed by TGA. Inspection of Fig. 3 confirmed that without shear input or mixing, degradation of MLX:polymer blends occurred at temperatures lower than predicted. It was found that degradation of MLX in the presence of PVPVA and SOL occurred at a higher rate than when in the presence of PVP. This finding is likely due to a low molecular mobility within the high viscosity of the PVP system, effectively reducing the amount of solubilized (amorphous) MLX relative to molten mixtures containing PVPA or SOL. With intensive mixing and high rates of shear, it is expected that the onset of MLX degradation would occur at even lower temperatures than predicted by TGA. This finding clearly demonstrated that the ability to process MLX by fusion processing techniques would be limited by thermal degradation.

Hot-stage microscopy (HSM) was utilized to visually observe the onset and extent of MLX dissolution into each polymer as a qualitative analysis of miscibility and alternative to DSC analysis. Reflected light images under magnification are shown in Fig. 4.

As expected, MLX did not undergo a phase transformation in the absence of polymer at the temperature range studied due to its high melting point. Further inspection of Fig. 4 showed that dissolution of MLX into PVP was not observed at the temperature range studied, either due to immiscibility or high viscosity of the polymer. Extensive solubilization of MLX in PVPVA and SOL was observed at temperatures as low as 175 °C. These findings correlated well with results of the TGA study of physical mixtures that showed higher rates of MLX degradation in PVPVA and SOL matrices due to the formation of amorphous MLX at elevated temperatures.

Based on results of the TGA and HSM studies, it was clear that PVPVA and SOL were capable of solubilizing MLX at temperatures well below the crystalline melting point of MLX. However, TGA studies indicated that thermal processing techniques may cause decomposition of MLX to occur at relatively low temperatures.

3.2. *Solution based polymer screening studies*

When identifying a polymeric carrier for solid dispersion applications, it is important to identify one that provides a high degree of supersaturation of poorly water-soluble drug substances (Vandecruys et al., 2007). In order to identify the most suitable water-soluble polymer for amorphous dispersions of MLX, a polymer solution screening study was conducted. In this study, the ability of PVP, PVPVA and SOL to supersaturate MLX was evaluated and compared to controls in deionized water and 0.1 N HCl.

Analysis of the control containing water showed that the water solubility of MLX was approximately 14.1 μg/mL, in close agreement with the reported value of 12.0 μg/mL (Seedher and Bhatia, 2003). In unbuffered water, the solubility of MLX was significantly reduced in the presence of PVP and PVPVA, as shown in Fig. 5. This effect became more apparent as the polymer concentration was increased from 0.1% to 0.3%. Further inspection of Fig. 5 demonstrated that the addition of these polymers caused the suspension pH to decrease, which effectively reduced the solubility of MLX, a weak acid. Similarly, as the concentration of SOL was increased from 0.1% to 0.3%, the suspension pH was found to decrease. However, unlike PVP and PVPVA, increased concentrations of SOL resulted in a statistically significant increase in MLX solubility. Specifically, at a concentration of 0.9%, the solubility of MLX was found to be enhanced by 2-fold. This solubility enhancement can be attributed to the micellar solubilization properties of SOL, as evidenced by an observed Tyndall effect that became more apparent as concentration increased. The critical micelle

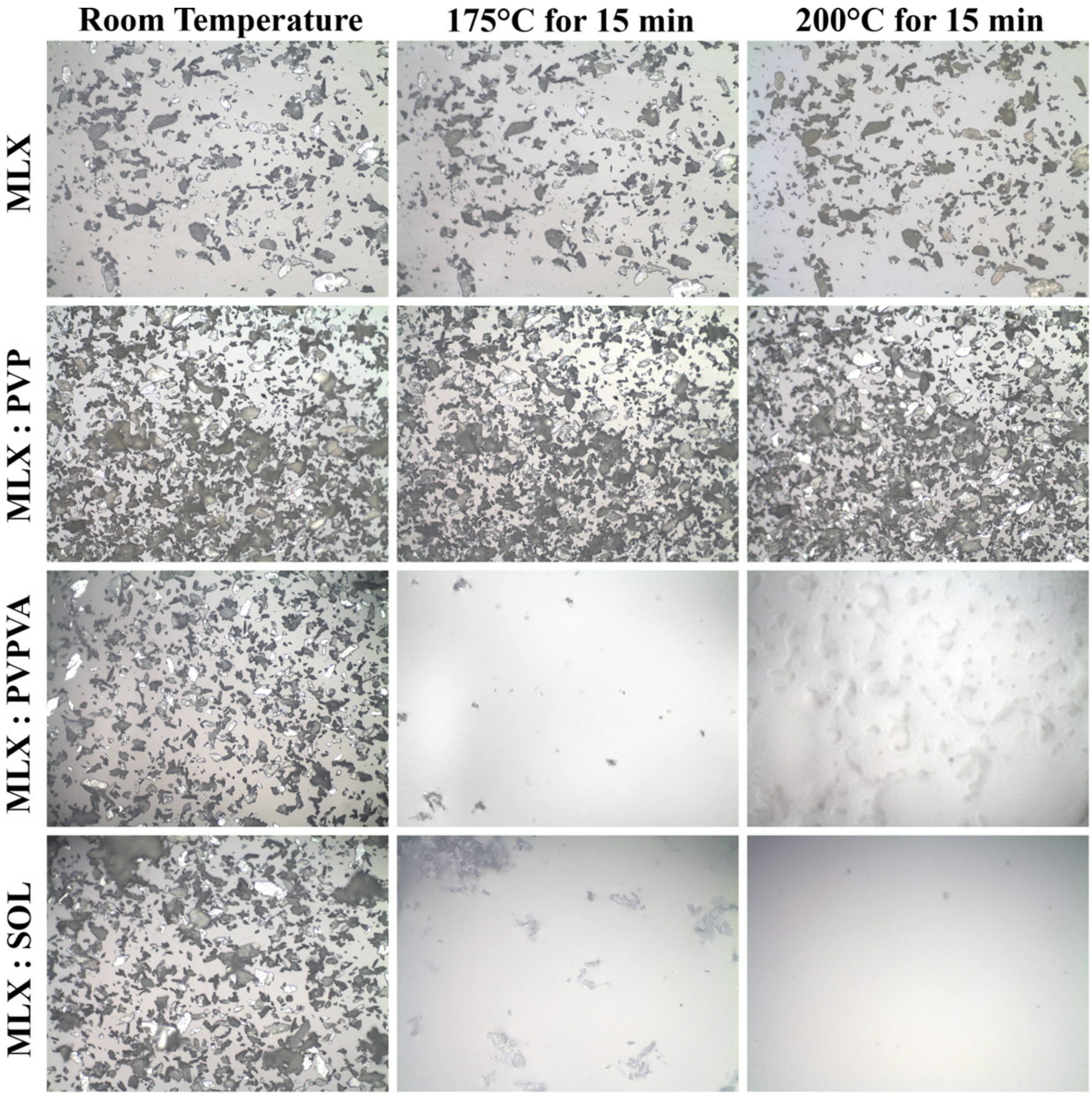

Fig. 4. Hot stage microscopy images of MLX in the presence of PVP, PVPVA, and SOL.

concentration of (CMC) of SOL is 7 μg/mL, which was achieved at even the lowest SOL concentration studied (BASF, 2010).

The equilibrium solubility of MLX in 0.1 N HCl was found to be 0.7 μg/mL which is significantly less than the measured water solubility. The addition of each polymer system did not lower the pH of 0.1 N HCl systems further due to a buffer effect. However, the equilibrium solubility of MLX did not increase by a significant amount in the presence of PVP and PVPVA, as shown in Fig. 5. As the concentration of SOL was increased, the solubility of MLX increased to approximately 10 μg/mL, a 15-fold improvement.

Solution based screening studies demonstrated that SOL provided the greatest degree of supersaturation in water and in 0.1 N HCl mediums at all polymer concentrations studied Based on this observation and thermal screening results, SOL was chosen as the matrix polymer for subsequent studies. A MLX:SOL ratio of 1:9 was utilized based on the required MLX dose of 15 mg.

3.3. Hot-melt extrusion

Hot-stage microscopy images demonstrated that SOL solubilized MLX at temperatures as low as 175 °C. This finding indicated that thermal processing could take place well below the melting

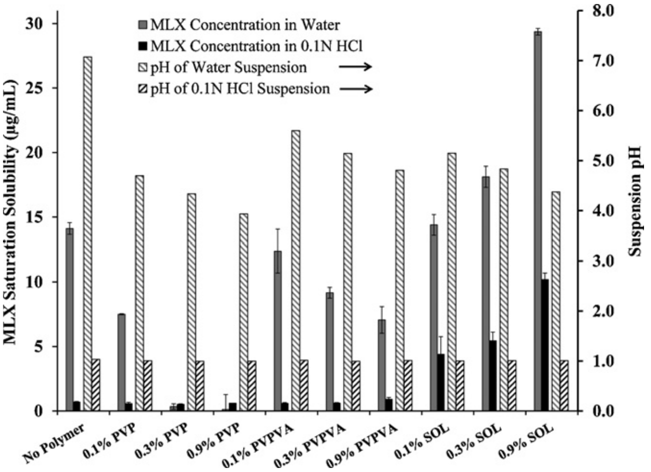

Fig. 5. Solubility of crystalline MLX and resulting pH values in the presence of PVP, PVPVA, and SOL at polymer concentrations of 0%, 0.1%, 0.3% and 0.9%.

Table 1
Hot-melt extrusion processing conditions.

Temperature (°C)	Screw speed (rpm)	Recirculation time (min)	MLX recovery (%)
160	100	0	94.8 ± 4.1
175	100	0	90.6 ± 2.4
175	100	2	87.1 ± 3.2

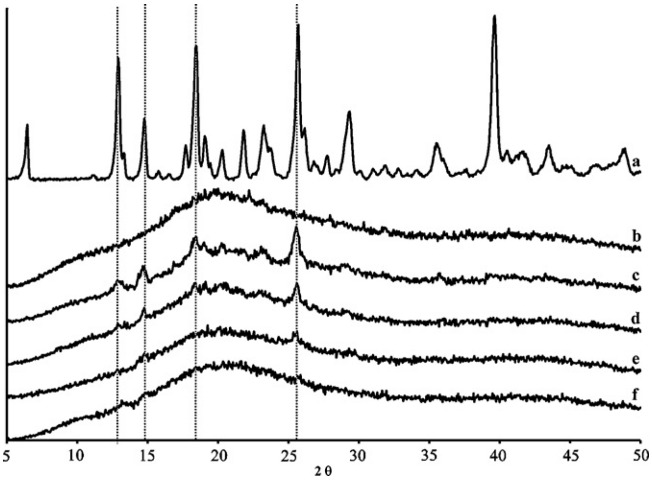

Fig. 6. XRPD profiles of (a) MLX, (b) SOL, (c) 1:9 MLX:SOL physical mixture, 1:9 MLX:SOL HME compositions processed at (d) 160 °C with no recirculation, (e) 175 °C with no recirculation, and (f) 175 °C with 2 min recirculation.

point of MLX. A study investigating the feasibility of processing 1:9 compositions of MLX:SOL by HME was conducted. Processing conditions and resulting MLX assay values are presented in Table 1. Initial attempts to extrude compositions at 160 °C without recirculation resulted in completely opaque compositions, indicating the presence of crystalline MLX. Extrusion temperature was increased to 175 °C in an effort to form an amorphous composition. When extruding at this temperature without recirculation the extrudate appeared translucent with darkening, indicating low levels of MLX crystallinity and degradation. As the recirculation time was increased to 2 min at 175 °C, compositions became glassy but were significantly darker than the composition prepared without recirculation, indicating additional decomposition.

Results of the HME processing study showed that as temperature or recirculation time increased the percent MLX recovered decreased significantly. Inspection of HPLC chromatograms confirmed that MLX related impurities increased proportionally as extrusion temperature and recirculation time increased. These findings correlated well with visual observations, demonstrating that MLX is prone to degradation at temperatures much lower than predicted by TGA.

In order to access MLX crystallinity in the HME processed compositions, an XRPD analysis was conducted. Diffractograms, presented in Fig. 6 demonstrate that MLX has strong characteristic peaks at 2θ values of 12.9°, 14.8°, 18.4° and 25.7° that are readily apparent in the 1:9 MLX:SOL physical mixture. Further analysis of Fig. 6 clearly showed the presence of crystalline MLX in HME compositions processed without recirculation. As the recirculation time increased to 2 min, effectively increasing cumulative thermal exposure, MLX crystallinity decreased to very low but detectable levels.

Attempts were made to utilize modulated differential scanning calorimetry (mDSC) in order to evaluate the number of phases present in processed compositions and to provide a secondary confirmation that crystalline MLX was not present. However, this was complicated by both the thermal instability of MLX and the propensity of MLX to dissolve into SOL during first scan heating. During the mDSC analyses, degradation of MLX resulted in an erratic thermogram in which glass transition temperatures could not be extracted (data not shown). However, in the present case, an amorphous system is formed through melting point depression. That is, the polymer system acts as a viscous solvent that dissolves drug particles under intensive mixing (Liu et al., 2010). Therefore, compositions prepared in this manner would be predicted to form single phase solid dispersions provided that they are shown to be amorphous by a method such as XRPD analysis. However, without a secondary method of analysis, the number of phases cannot be determined with certainty.

The HME study demonstrated that in order to achieve complete conversion of crystalline MLX to an amorphous form, a relatively long mixing time was required which resulted in decomposition of MLX. In order to understand the factors that can control the MLX dissolution rate into a molten polymer, it is useful to refer to the Noyes–Whitney equation which is based on Fick's first law (Hintz and Johnson, 1989; Liu et al., 2010). While intended to describe the dissolution rate of drug particles in an aqueous environment, there are parallels to the system described above that allow one to understand the factors influencing drug dissolution into a molten polymer. Inspection of the equation shows that the dissolution rate of a drug particle is inversely proportional to the thickness of its boundary layer, h, and is proportional to the solubility of the drug substance in the dissolving medium, C_s:

$$\frac{dM}{dt} = \frac{-3DM^{2/3}m_i{}^{1/3}}{\rho h r_i}\left[C_s - \frac{n(m_i - M)}{V}\right]$$

where M is the particle mass, t is time, m_i and r_i are the initial single particle mass and radius, n is the total number of particles, V is the total volume of the mixture, D is the diffusion coefficient and ρ is the drug particle density.

Generally speaking, the solubility of a drug substance in a dissolving medium decreases as the temperature of the system is decreased. Similarly, in a molten drug:polymer system, the solubility of a drug substance would be expected to decrease as the difference between processing temperature and the melting point of the drug substance increases. In the case of a high melting point compound such as MLX, this difference may be very large which can result in a low solubility value, hindering dissolution of the drug into the polymer system. Therefore, drug solubility within the polymer may be relatively low even at high processing temperatures which may result in incomplete drug dissolution in the barrel residence time in an HME process. In the case of MLX, increasing processing temperature or barrel residence time is not an option due to thermal instability.

As alluded to previously, another potential method of increasing the dissolution rate of a drug into a molten drug:polymer system is to decrease the boundary layer thickness of the dissolving particle. In HME processing, the boundary layer thickness may be decreased by increasing specific shear input. This may be accomplished by increasing the number of distributive and dispersive mixing elements in a modular screw design or by increasing screw speeds. However, there are limitations to the amount of shear that can be imparted to a melt with the HME process and it may not be possible to reduce the boundary layer thickness sufficiently. While the addition of aggressive mixing elements can increase rates of shear to an acceptable level, they often increase barrel residence time which can result in degradation of the drug substance.

As demonstrated in this study, MLX was not rendered amorphous in a processing time that allowed for the formation of an amorphous system without decomposition. Increasing the processing temperature, which in effect increases C_s, and barrel residence time by recirculation allowed for substantial drug dissolution

Table 2
KSD processing conditions of batches produced for factorial DOE.

Pattern	Processing speed (rpm)	Ejection temperature (°C)	MLX assay (%)
−−	2250	110	97.7 ± 0.9
−+	2250	140	84.9 ± 0.5
00	2625	125	89.0 ± 3.4
+−	3000	110	98.6 ± 0.9
++	3000	140	81.5 ± 0.6

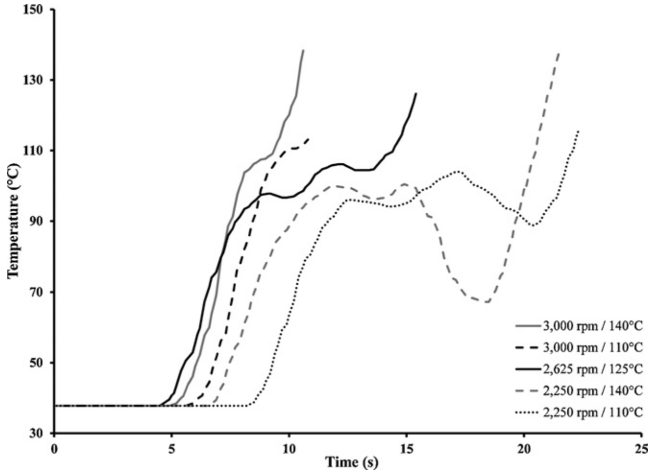

Fig. 7. KSD temperature processing profiles of compositions prepared for the factorial DOE.

within the polymer. However extensive degradation of MLX was observed as evidenced by low MLX recovery values.

3.4. *KinetiSol® Dispersing*

KinetiSol® Dispersing is a high shear processing method that has been previously utilized to rapidly process amorphous compositions of chemically unstable drug substances (DiNunzio et al., 2010a; Hughey et al., 2010). In this processing technique, solid dispersions are prepared in less than 30 s and are exposed to elevated temperatures for a fraction of that time. It was hypothesized that increased rates of shear and short processing times inherent to the KSD process would allow for high melting point compounds such as MLX to be rapidly rendered amorphous with minimal decomposition.

Rotational speed and ejection temperature were identified as the critical parameters in the KSD process that can affect the chemical stability and physical state of a drug substance. A 2-level full factorial DOE, presented in Table 2, was conducted to evaluate the effect of these two processing variables on MLX recovery and crystallinity of the prepared solid dispersions. The studied levels represent a wide range of processing conditions that may offer certain advantages.

Characteristic of compositions prepared by KSD, relatively rapid cycle times were observed, which in effect minimized thermal exposure. Processing profiles of the compositions prepared for the DOE are presented in Fig. 7. Compositions prepared at 3000 rpm were ejected from the compounder within 10 s, with exposure to temperatures above 100 °C for less than 3 s. Residence time within the processing chamber increased to as high as 22 s when compositions were processed at 2250 rpm due to a reduction in thermal energy input. All processing curves are characterized as having an inflection point that becomes more apparent as the processing speed is decreased. This can be attributed to a kinetic event related to the glass transition temperature of the polymer. In an optimized process, ejection would take place during the temperature inflection to avoid excessive thermal energy input.

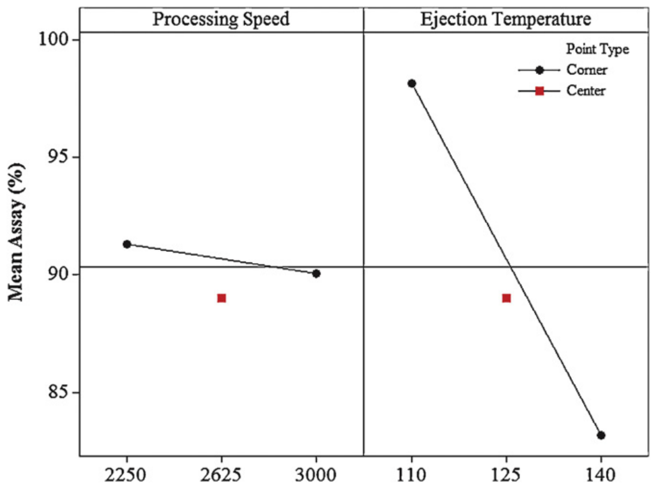

Fig. 8. Effect of processing speed and ejection temperature on MLX recovery (data means). Surface plot demonstrating the effect of KSD processing speed and ejection temperature on the assay value of MLX.

A wide range of MLX recovery values were obtained from the DOE, as detailed in Table 2. Examination of MLX recovery values presented in Table 2 showed that compositions ejected at 110 °C exhibited assay values above 95% while those ejected at 140 °C exhibited recovery values of less than 85%. Further analysis of the main effects (from data means), illustrated in Fig. 8 confirmed that ejection temperature provided a statistically significant impact on MLX recovery ($p = 0.014$). Processing speed, which affects residence time within the processing chamber did not significantly impact MLX recovery ($p = 0.915$). Similarly, a significant interaction between processing speed and ejection temperature was not observed ($p = 0.387$). This finding indicated that degradation of MLX occurs at a threshold temperature located above the observed inflection points where all processing curves exhibit a similar slope.

The ability to render compositions amorphous is essential to the successful development of solid dispersions. Based on results of the HSM and HME studies, SOL exhibited an ability to act as a solvent for MLX at temperatures well below its melting point. The amorphous character of compositions prepared in the DOE was assessed by XRPD analysis as DSC analysis was not practical, due in part to thermal instability and solubility of MLX within the polymer system. Results of the XRPD study are presented in Fig. 9. All compositions were characterized as exhibiting an amorphous halo with no detected crystallinity which indicated that MLX was in an amorphous state. As previously discussed, XRPD is not capable of distinguishing the number of phases but due to the mechanism of solubilization and supporting XRPD data, compositions would be predicted to be single phase systems.

While amorphous solid dispersions were prepared at all conditions studied, only those prepared with low ejection temperatures exhibited suitable MLX recovery values. Results of the factorial DOE indicated that degradation of MLX in KSD processed compositions was a function of temperature. To further evaluate this finding, a study was designed to investigate the effect of various ejection temperatures between 110 °C and 140 °C on MLX recovery at a constant processing speed of 2625 rpm. Similar to previous MLX compositions prepared by KSD, all processing profiles exhibited a similar slope after their respective inflection points as illustrated in Fig. 10. Resulting MLX recovery values are detailed in Table 3. As the ejection temperature was increased from 110 °C to 118 °C there was no significant change in MLX degradation ($p = 0.941$). However,

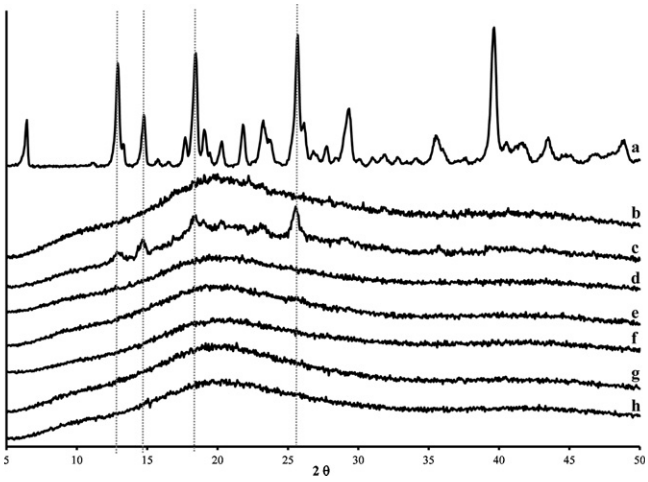

Fig. 9. XRPD profiles of (a) MLX, (b) SOL, (c) 1:9 MLX:SOL physical mixture, 1:9 MLX:SOL KSD compositions processed at (d) 3000 rpm/140 °C, (e) 3000 rpm/110 °C, (f) 2625 rpm/125 °C, (g) 2250 rpm/140 °C, and (h) 2250 rpm/110 °C.

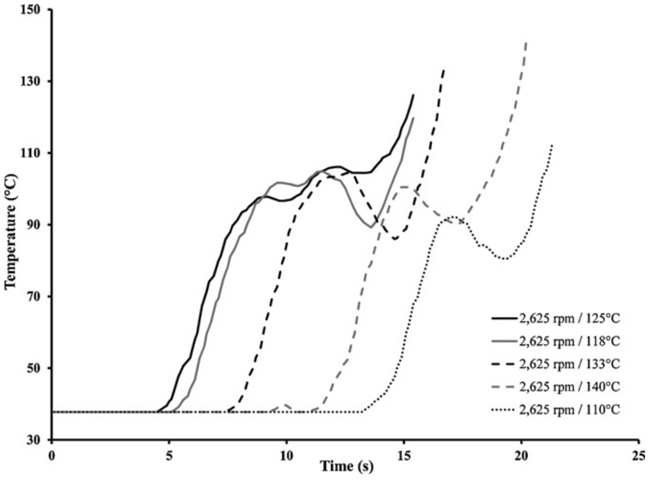

Fig. 10. KSD temperature processing profiles of compositions prepared to study the effect of temperature on MLX recovery.

increasing the ejection temperature to 125 °C resulted in a statistically significant increase in MLX degradation ($p = 0.009$). Inspection of HPLC chromatograms confirmed that impurity levels increased as the ejection temperature was changed from 118 °C to 125 °C. While a further ejection temperature increase to 133 °C did not result in additional degradation ($p = 0.975$), a further increase to 140 °C did cause significantly more degradation of MLX ($p = 0.012$). This trend clearly demonstrated that the onset of MLX degradation occurred at a temperature between 118 °C and 125 °C. Provided that thermal processing occurs at temperatures below 118 °C, KSD processing is an acceptable manufacturing technique for this particular system. The ability of the KSD process to successfully process combinations such as this is primarily due its high torque output which allows for low temperature processing relative to HME processing (Table 3).

Table 3
KSD processing conditions of batches produced for ejection temperature study.

Processing speed (rpm)	Ejection temperature (°C)	MLX assay (%)
2625	110	97.7 ± 1.3
2625	118	97.7 ± 1.2
2625	125	89.0 ± 3.4
2625	133	88.6 ± 1.6
2625	140	79.3 ± 3.3

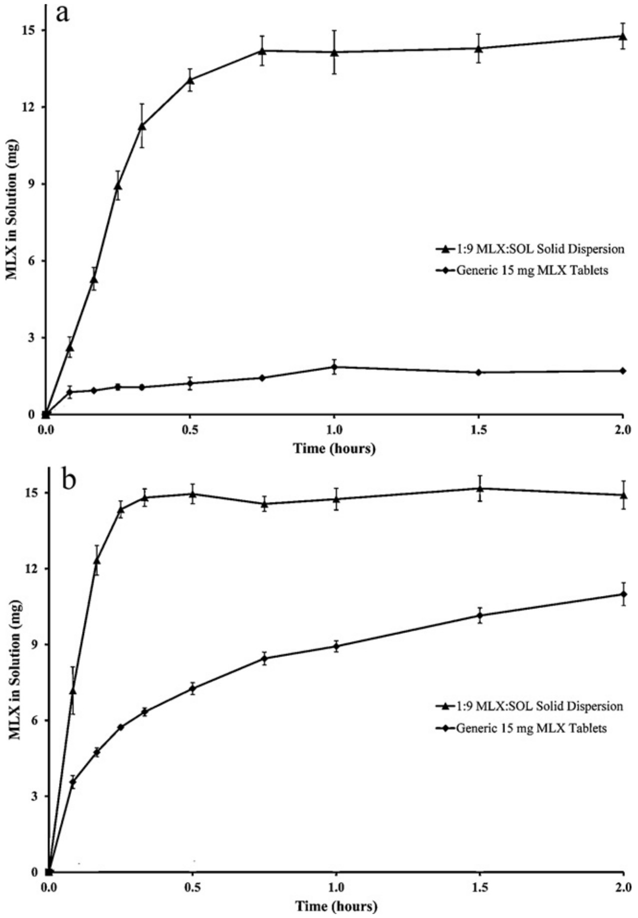

Fig. 11. Dissolution profiles of 1:9 MLX:SOL amorphous solid dispersions containing 15 mg MLX and 15 mg MLX generic tablets in (a) 0.1 N HCl and (b) deionized water ($n = 6$).

3.5. Dissolution characterization

It is reasonable to assume that an oral composition containing 15 mg of MLX, capable of supersaturating the dissolving medium, would produce a sufficient concentration of dissolved drug to allow for increased drug absorption and a more rapid therapeutic benefit. In order to assess the dissolution rate enhancement of MLX solid dispersions, a non-sink dissolution analysis was conducted. As a comparator, dissolution analysis was also conducted on commercially available generic MLX tablets (15 mg). Results of the dissolution analysis in 0.1 N HCl and deionized water are presented in Fig. 11a and b, respectively. Inspection of the drug release profiles revealed that the dissolution rate and extent of the solid dispersion system was much higher than that of the marketed 15 mg MLX tablet. In 0.1 N HCl, the marketed dosage form exhibited minimal release (<2 mg) while the solid dispersion exhibited rapid and complete release (~15 mg) within the 2 h testing period. Further inspection of Fig. 11a revealed that MLX in the marketed dosage form reached a concentration that was 2-fold greater than the equilibrium solubility of MLX. This could potentially be due to the presence of a higher energy form of MLX created during a manufacturing unit operation (i.e., milling, granulation, etc.). Another possible explanation is the presence of sodium citrate in the tablet which could, in effect, increase microenvironment pH and result in a higher aqueous solubility. In deionized water, the solid dispersion showed complete dissolution (∼15 mg) within 20 min whereas approximately half (∼6 mg) of the MLX in the marketed dosage form had solubilized.

4. Conclusions

Proper polymer carrier selection is an important aspect in the formulation of single phase solid dispersions containing high melting point drug substances. It is important to select a carrier that adequately solubilizes the drug substance at temperatures much lower than its melting point while also providing dissolution enhancement properties. As demonstrated in this study, residence times typical of the HME process were not sufficient to render compositions completely amorphous. However, extending residence times to facilitate the formation of amorphous MLX caused degradation of the drug substance. The effect of KSD processing conditions on the chemical stability and amorphous character of MLX was also studied. The KSD process provided acceptable MLX recovery values and amorphous character at temperatures much lower than required for HME processing. DOE results demonstrated that the KSD ejection temperature significantly impacted MLX recovery values. Further investigation of this finding clearly showed that KSD processing of MLX:SOL systems was possible at temperatures below 118 °C, which cannot be accomplished by the more traditional hot-melt extrusion manufacturing technique. Through proper selection of the carrier polymer and careful selection of processing parameters, it is possible to produce chemically stable amorphous solid dispersions of high melting point compounds by KSD processing.

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