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# Hydroxypropyl cellulose stabilizes amorphous solid dispersions of the poorly water soluble drug felodipine

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ABSTRACT

Overcoming the low oral bioavailability of many drugs due to their poor aqueous solubility is one of the major challenges in the pharmaceutical industry. The production of amorphous solid dispersions (ASDs) of these drugs using hydrophilic polymers may significantly improve their solubility. However, their storage stability and the stability of their supersaturated solutions in the gastrointestinal tract upon administration are unsolved problems. We have investigated the potential of a low viscosity grade of a cellulosic polymer, hydroxypropyl cellulose (HPC-SSL), and compared it with a commonly used vinyl polymer, polyvinylpyrrolidone vinyl acetate (PVP-VA), for stabilizing the ASDs of a poorly water soluble drug, felodipine. The ASDs were produced using hot melt mixing and stored under standard and accelerated stability conditions. The ASDs were characterized using differential scanning calorimetry, powder X-ray diffraction, and Fourier transform infrared spectroscopy. Drug dissolution and partitioning rates were evaluated using single- and biphasic dissolution studies. The ASDs displayed superior drug dissolution and partitioning as compared to the pure crystalline drug, which might be attributed to the formation of a drug–polymer molecular dispersion, amorphous conversion of the drug, and drug–polymer hydrogen bonding interactions. Late phase separation and early re-crystallization occurred at lower and higher storage temperatures, respectively, for HPC-SSL ASDs, whereas early phase separation, even at low storage temperatures, was noted for PVP-VA ASDs. Consequently, the partitioning rates for ASDs dispersed in HPC-SSL were greater than those of PVP-VA at lower and room temperature storage, whereas the performance of both of the ASDs was similar when stored at higher temperatures.



## 1. Introduction

Bioavailability is defined as the measurement of the rate and extent that a therapeutically active drug reaches the systemic circulation and becomes available at the site of action (Chiou, 2001). The pharmaceutical industry has been challenged by the low oral bioavailability of certain drugs for the last several decades. These compounds exhibit poor water solubility due to their hydrophobic nature, poor wettability, and highly ordered crystalline structure. The percentage of new chemical entities with poorly water soluble properties discovered by techniques such as high throughput screening and combinatorial chemistry is increasing (Timpe & Forschung, 2007; Vasconcelos, Sarmento, & Costa, 2007). The slower and incomplete dissolution of these promising active pharmaceutical ingredients (APIs) in the aqueous environment of the gastrointestinal tract results in their lower absorption and bioavailability. Hence, several researchers in the pharmaceutical industry and academia are trying various approaches such as particle size reduction, crystal habit modification, polymorphism, complexation or solubilization, solid dispersion in carriers, and prodrug and salt formation in order to improve the solubility of poorly water soluble drugs (Leuner & Dressman, 2000). Among these techniques, formulating solid dispersions of these drugs in hydrophilic polymers using hot melt mixing, melt extrusion, and solvent methods has gained in popularity due to often improved solubility and product performance (Vasconcelos et al., 2007). Continuous operation and the lack of need for organic solvents during hot melt extrusion processing provide economic and ecological advantages over solvent methods (Leuner and Dressman, 2000). Amorphous

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solid dispersions (ASDs) manufactured by mixing a molten mass of a drug–polymer mixture during melt mixing or hot melt extrusion enhance the solubility of drugs due to their transformation into a high energy, amorphous form and the formation of favorable drug–polymer interactions that may occur during the process (Maniruzzaman et al., 2012; Sarode, Sandhu, Shah, Malick, & Zia, 2012).

Although the solubility of poorly water soluble drugs can be enhanced by formulating ASDs, the resulting high energy amorphous form is thermodynamically unstable (Kawakami & Pikal, 2005). Re-crystallization of a drug and/or phase separation of a drug–polymer molecular dispersion may occur during ASD storage due to enhanced molecular motions in the amorphous substance (Marsac et al., 2010; Rumondor & Taylor, 2009). Furthermore, a drug may undergo chemical degradation during ASD manufacture, as well as due to increased molecular mobility induced by higher temperature and humidity conditions during storage (Sarode, Sandhu, Shah, Malick, & Zia, 2013; Yoshioka & Aso, 2007). These deleterious effects can significantly reduce the performance aspects of ASDs in terms of enhancing drug solubility and compromising product shelf life. In addition to the storage instability issue, ASDs also suffer from a problem of supersaturation induced precipitation during dissolution in the gastrointestinal tract (Guzman et al., 2007; Warren, Benameur, Porter, & Pouton, 2010). Very high supersaturation levels attained during dissolution may surpass the drug's critical nucleation concentration and trigger rapid nucleation and/or crystal growth (Cao, 2004). A competition won by precipitation over absorption in the supersaturated solutions of a drug in the gastrointestinal tract leads to substantially low bioavailability (Bevernage, Brouwers, Annaert, & Augustijns, 2012). These phenomena may be moderated by the careful selection of appropriate formulation polymers. Several hydrophilic polymers with various backbones and functional groups and amorphous characteristics have been investigated in melt processes in order to enhance drug storage stability as well as to prevent nucleation and/or growth in the supersaturated solutions that occur in the gastrointestinal tract upon product administration (Warren et al., 2010; Wyttenbach et al., 2013). These polymers can restrict the molecular motions due to their high glass transition temperature as well as due to drug–polymer interactions (Wegiel, Mauer, Edgar, & Taylor, 2013). Furthermore, the nucleation and/or crystal growth in the aqueous environment during dissolution can be moderated or inhibited due to drug–polymer interactions and polymer induced viscosity and surface activity in supersaturated solutions (Ilevbare, Liu, Edgar, & Taylor, 2012). Ideally, an improvement in the solubility while maintaining an optimum dissolution rate by using a polymer in order to attain supersaturation below the critical nucleation concentration may prevent the initiation of nucleation and thus enhance oral absorption of the drug significantly (Sarode, Wang, Obara, & Worthen, 2014).

Several cellulose polymers such as hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), hydroxypropyl methylcellulose acetate succinate (HPMCAS), carboxymethylcellulose acetate butyrate (CMCAB), and cellulose acetate phthalate (CAPhth) have been investigated in order to improve the solubility of poorly water soluble drugs, increase the storage stability of the ASDs, and inhibit nucleation and/or crystal growth in supersaturated solutions (Ilevbare et al., 2012; Li, Harich, Wegiel, Taylor, & Edgar, 2013; Li, Konecke, et al., 2013; Li, Wegiel, Taylor, & Edgar, 2013; Obara, Tanno, & Sarode, 2013; Sarode, Obara, et al., 2014). Among these tested polymers is HPC, a cellulosic polymer in which some of the hydroxyl groups in the repeating sugar units are hydroxypropylated using propylene oxide. The relatively high glass transition temperature of HPC may promote stability and restrict drug diffusion and recrystallization during storage while, at the same time, the melt viscosity of the polymer make it suitable for hot melt extrusion processing (Paradkar, Kelly, Coates, & York, 2009). The hydroxyl groups of this polymer may interact with the carbonyl groups of drugs via hydrogen bonding and improve stability in the solid state. In addition, these interactions, along with viscosity and surface activity imparted by the polymer to the supersaturated solution in the aqueous environment, may inhibit precipitation (Sarode et al., 2013; Warren et al., 2010). A combination of both hydrophobic and hydrophilic moieties of HPC may provide an optimum drug dissolution rate to an ASD in order to maintain the supersaturation of a drug below critical concentration for nucleation and thus enhance drug absorption (Ilevbare et al., 2012).

In this manuscript we have investigated the potential of a low viscosity grade of cellulosic polymer, HPC-SSL, in comparison with a vinyl acetate-substituted, polyvinylpyrrolidone polymer, PVP-VA, for their relative utility in melt mixing and in stabilizing ASDs of a poorly water soluble drug, felodipine (FLD). The storage stability of the ASDs, including that of the drug itself, has been studied under various controlled temperatures and humidity conditions. Drug dissolution experiments assessing ASDs of poorly water soluble drugs using biphasic dissolution media have gained in popularity (Heigoldt, Sommer, Daniels, & Wagner, 2010; Phillips, Pygall, Cooper, & Mann, 2012a, 2012b; Shi, Gao, Gong, & Ping, 2010). These biphasic dissolution studies may better simulate the in vivo environment, wherein the concentration gradient is maintained due to constant removal of the dissolved drug because of partitioning into a solvent that more closely reflects some of the properties of lipid membranes in the gastrointestinal tract. Accordingly, the performance of the melt mixed ASDs produced in this study has been evaluated using both single- and biphasic dissolution studies. We hypothesized that the cellulosic backbone of low-viscosity HPC-SSL may better stabilize the amorphous drug as compared to the vinyl backbone of PVP-VA during storage and may prevent phase separation and/or re-crystallization of the drug in the solid state.

In our recent publication we demonstrated that improving and controlling the drug dissolution rate in order to achieve supersaturation below the critical nucleation concentration in order to obtain higher partitioning of poorly water soluble drugs into the organic phase during biphasic dissolution may be a more useful approach for attempting to predict enhancement in their oral absorption (Sarode, Wang, et al., 2014). In this investigation we found that although the highest supersaturation of FLD was attained using Eudragit® EPO and HPMCAS-LF with better nucleation and crystal growth inhibition using the latter during single phase dissolution, higher partitioning of the drug into the organic phase during biphasic dissolution was achieved using HPMC and PVP-VA by maintaining supersaturation below critical nucleation concentration. We hypothesized that, like PVP-VA and HPMC, a similar improvement in drug solubility along with an optimum dissolution rate might also be obtained using HPC-SSL as the polymeric carrier in ASDs, and might also lead to supersaturation while preventing nucleation in order to achieve higher partitioning of FLD. In addition, the impact of exposure to the storage stability conditions on ASD characteristics and attaining supersaturated levels in the aqueous medium and subsequent partitioning into the organic phase during biphasic dissolution has been investigated.

## 2. Experimental

### 2.1. Chemicals

The poorly water soluble, non-ionic dihydropyridine drug FLD was purchased from Ria International (East Hanover, NJ). The cellulosic polymer HPC-SSL was supplied by Nisso America, Inc. (New York, NY). The polyvinylpyrrolidone polymer Kollidon®

**Table 1**
Physicochemical properties of the polymers. Data as supplied by the manufacturers.

| Polymer | Physicochemical properties | | | | |
|---|---|---|---|---|---|
| | Backbone | Molecular substitution | Pyrrolidone:acetate ratio | Molecular weight | $T_g/T_m$[a] (°C) |
| HPC-SSL | Cellulosic | 3.24 | NA | Average 40,000 | −25 to 0/180–220 |
| PVP-VA | Polyvinyl | NA | 6:4 | 45,000–70,000 | 107/NA |

[a] $T_m$ is applicable for semi-crystalline HPC-SSL.

VA-64 (PVP-VA) was obtained from BASF Corporation (Florham Park, NJ). The physicochemical properties of the polymers are listed in Table 1. All other chemicals and reagents used were of analytical grade and were obtained from Fisher Scientific (Fair Lawn, NJ).

### 2.2. Preparation of physical mixtures

The drug was gently mixed with the polymers using a glass mortar and a pestle for 5 min at a 30:70 drug–polymer w/w ratio to prepare 45 g each of the corresponding physical mixtures (PMs). These PMs were then transferred to amber colored glass bottles and further mixed in a Turbula mixer (Willy A Bachofen, Basel, Switzerland) for 15 min to prepare homogenous PMs.

### 2.3. Manufacturing of ASDs using hot melt mixing (HMM)

A three-piece hot melt mixer with roller blades (C.W. Brabender Instruments, Inc., Hackensack, NJ, USA) was used to manufacture the ASDs. About 40 g of the corresponding PM was fed into the hot melt mixer and mixed at 150 °C and 150 rpm for 3 min. The resulting ASDs were then milled using a twin-blade rotary mill and the size fraction of 250–420 μm was obtained by sieving between US mesh nos. 40 and 60. These ASDs were stored in a desiccator at 5 °C and 0% relative humidity (RH) for further analysis.

### 2.4. Stability studies

Formulation stability studies were performed at serial temperatures in sealed glass humidity chambers. A saturated sodium chloride (NaCl) salt solution with excess un-dissolved NaCl was prepared using distilled water and chemically pure NaCl. This solution with excess un-dissolved NaCl was enclosed in three sealed glass chambers to maintain 75 ± 1% RH w/w and the chambers were then kept and allowed to equilibrate at 5, 25, and 40 °C. The ASDs were stored in these chambers in sealed HDPE bottles specially designed to allow water vapor exchange into and out of the bottles. The sample containers were pulled after 3, 6, 9, and 12 weeks and the ASDs were collected. The ASDs that aggregated after absorbing moisture were gently separated and screened through US mesh no. 45. All stability samples were thoroughly dried in a vacuum desiccator for 24 h at room temperature and then stored in a desiccator at 5 °C and 0% RH until further analysis.

### 2.5. Differential scanning calorimetry

Thermal analysis was performed using differential scanning calorimetry (DSC). Samples of the PMs and initial and stability samples (6–8 mg each) of the ASDs were hermetically sealed in aluminum pans and subjected to heat-cool-heat cycling using a Q DSC (TA Instruments, New Castle, DE, USA). The heating rate was 10 °C/min and the cooling rate was 50 °C/min. The range of temperatures evaluated was −50 to 200 °C. The DSC plots were interpreted using TA Universal Analysis software.

### 2.6. Powder X-ray diffraction

Powder X-ray diffraction (PXRD) of the PMs and initial and stability samples of the ASDs was performed using a Rigaku Ultima IV XRD system. The samples were analyzed using Cu $K\alpha$ radiation at 40 kV and 44 mA. The X-ray pattern was collected in the angular range of $1 < 2\theta < 45^\circ$ in the step scan mode with a step width of 0.02° and a scan rate of 1°/min.

### 2.7. HPLC analysis

Mixing at high temperatures during HMM processing and adverse storage conditions during stability analysis could lead to chemical degradation of an incorporated drug. Hence, HPLC analysis of the ASD samples was performed using a LaChrom Elite system (Hitachi High-Tech) in order to determine FLD content and chemical degradation. A Waters Symmetry C18 (3.9 mm × 150 mm, 5 μm) column was used for the analysis with a mobile phase containing acetonitrile and water in the ratio of 80:20 v/v at a flow rate of 1 ml/min. The injection volume was 20 μl and the run time was 5 min. The retention time for FLD was 2.3 min. FLD concentrations in the ASD samples were determined based upon linear concentration versus area under the curve (AUC) plots generated at 360 nm.

### 2.8. Fourier transform infrared spectroscopy (FT-IR)

Pellets of the PMs and initial and stability samples of the ASDs for FT-IR analysis were prepared using a Smart accessory. The samples were analyzed by an FTIR analyzer (Nicolet 380, Thermo Scientific) and the IR plots were obtained using Omnic software.

### 2.9. Dissolution studies

The dissolution studies were carried out using a USP dissolution apparatus type II (LID-8D, Vanguard Pharmaceutical Machinery Inc., TX, USA). Single phase dissolution experiments of ASDs were performed at 37 ± 0.5 °C and 50 rpm in 700 ml aqueous medium comprising 50 mM phosphate buffer (pH 6.8). For biphasic dissolution of the ASDs, 700 ml of aqueous medium (as described above) was equilibrated with 200 ml of *n*-octanol as the organic phase for 2 h at 37 ± 0.5 °C and 50 rpm. Both single and biphasic dissolution experiments were carried out under non-sink conditions with respect to the aqueous medium. One hundred milligram ASD samples, equivalent to 30 mg of the active drug, were loaded into fresh size 0 gelatin capsules with sinkers that were then dropped into the dissolution medium for either single or biphasic dissolution. Serial dissolution samples collected from the aqueous phase were filtered using 0.22 μm syringe filters (MCE membrane), whereas samples withdrawn from the organic phase were used as is. These dissolution samples from the aqueous and organic phases were transferred to UV 96 well plates (Costar®) and analyzed using a SpectraMax M2 UV detector (Molecular Devices, PA, USA). Drug concentrations were determined based upon linear concentration versus absorbance plots generated at 360 nm.

## 3. Results and discussion

### 3.1. Characterization of the ASDs

During the formulation of ASDs, the amorphous transformation of a crystalline drug, its molecular dispersion into the polymer matrix, and interactions between the drug and the polymer are all important for improving in the solubility and dissolution rate of poorly water soluble drugs. These solid state characteristics of ASDs may be variable and unpredictable, and the drug – in this case FLD, a di-ester – may degrade chemically during melt mixing formulation and storage due to exposure to high temperature and humidity. Hence, DSC was performed in order to determine the amorphous nature and phase characteristics of the ASDs, whereas PXRD was carried out in order to confirm the amorphous or crystalline nature of the drug. The chemical stability of FLD was determined using HPLC and drug–polymer interactions were investigated using FT-IR analysis.

The DSC and PXRD plots for the FLD: HPC-SSL systems are shown in Fig. 1a and b, respectively. An endotherm starting at ~125 °C in the PM of FLD (melting point 145 °C) with HPC-SSL represents a depressed melting point for the drug in the presence of the polymer and also confirms the crystalline nature of the drug in the PM (Fig. 1a). Such an endotherm was not detected in the corresponding initial ASD, suggesting amorphous conversion of the drug after HMM processing. Moreover, no other thermal event was detected in the initial ASD, which indicates formation of a single phase system. Similar thermograms were obtained for the stability samples stored at 5 and 25 °C for 3 weeks, suggesting no significant phase separation or re-crystallization of the drug during storage. In contrast, the stability sample stored at 40 °C for 3 weeks depicted two endotherms: a glass transition endotherm between 85 and 100 °C; and a second melting endotherm starting at ~125 °C, which can be attributed to phase separation and FLD re-crystallization, respectively. Upon longer storage, the samples stored at 5 and 25 °C exhibited phase separation, whereas the sample stored at 40 °C eventually showed re-crystallization of the entire drug. This was determined from DSC thermograms obtained for 12 week stability samples. Glass transition endotherms were detected between 115 and 135 °C for the samples stored at 5 and 25 °C, whereas only a melting endotherm was observed at ~125 °C for the sample stored at 40 °C (Fig. 1a). The amorphous nature of FLD in the initial ASD and the ones stored at 5 and 25 °C, as well as its crystalline nature in the PM and the ASDs stored at 40 °C, were confirmed using PXRD. For instance, the sharp diffraction peaks for crystalline FLD were detected in the PXRD plots for only its PM and the ASDs stored at 40 °C (Fig. 1b). Thus, it can be determined that late phase separation and early re-crystallization occurred at lower and higher storage temperatures, respectively, for the FLD:HPC-SSL system.

Although the ASDs of FLD formulated by HMM using PVP-VA did not show any re-crystallization of FLD during storage, early phase separation was detected for this system, in contrast to the FLD:HPC-SSL system. The absence of a melting endotherm in the DSC thermograms and of sharp diffraction peaks in the PXRD plots for both the initial and the stability samples of the ASDs confirms the non-crystalline nature of the drug initially as well as over the stability testing period (Fig. 2). The single glass transition endotherm observed between 75 and 85 °C for the initial ASD indicates formation of a one phase system, whereas several endothermic events detected for all of the stability samples, even including those stored at lower temperatures (5 and 25 °C) for only 3 weeks indicates early phase separation (Fig. 2a). Interestingly, a sharp endotherm, unlike a glass transition endotherm, was detected between 70 and 85 °C (near the $T_g$ of the FLD:PVP-VA solid solution) for the ASD sample stored at 40 °C for 3 weeks (Fig. 2a). Since no diffraction peaks were detected during PXRD analysis, the possible formation of a polymorph of FLD in this sample might be ruled out (Fig. 2b). Instead, these data correlate well with the results reported by Marsac et al. (2010) and Rumondor and Taylor (2009) where they depicted a similar sharp apparent melting endotherm near $T_g$ in the thermograms of FLD ASDs manufactured using various polymers such as PVP, PVP-VA, and HPMCAS after storage for a shorter period of time. Often, stress may be built into the amorphous material as a result of processing, handling or thermal history. Subsequently, a sharp endotherm is detected during a DSC cycle when such material is heated through its $T_g$ as the molecules transform from a rigid to a flexible structure and thus can move to relieve the stress. Hence, this apparent melting endotherm near $T_g$ was attributed to the relaxation of stress built into this stability sample as a result of higher temperature (40 °C) conditioning for a shorter period of time. Eventually, phase separation occurred for the ASDs stored at 40 °C, which was confirmed by the detection of multiple glass transition endotherms in the thermograms of these samples (Fig. 2a). Since the storage humidity level was approximately 75% RH for all of the samples, it can be inferred that initially and for up to 3 weeks, the phase characteristics of the ASDs were more dependent upon temperature rather than humidity. Hence, it can be deduced that a rigid amorphous phase was formed initially and the process of phase separation started late for the ASDs stored at 40 °C, whereas early phase separation occurred for the FLD:PVP-VA system stored at 5 and 25 °C.

As determined by HPLC, the drug was chemically stable after HMM processing as well as over the entire stability study for both FLD:HPC-SSL and FLD:PVP-VA systems. Neither a reduction in the drug AUC nor the development of degradation peaks was observed in the chromatograms of either the initial or the stability samples of the ASDs manufactured using either polymer. Furthermore, HPLC assays based upon linear concentration versus AUC plots revealed that the percent recovery of FLD in triplicate samples of all of the ASDs was between 95 and 105% of the theoretical concentration, confirming the important characteristics of both chemical stability and homogeneous content uniformity of FLD throughout the ASDs.

Intermolecular interactions such as hydrogen bonding between the drug and the polymers were characterized by FT-IR analysis. Hydrogen bonding occurs between a hydrogen bond donor and a hydrogen bond acceptor. As shown in Fig. 3a, FLD has a hydrogen bond donor (the NH group) as well as hydrogen bond acceptors (primarily the C=O groups). The OH groups of HPC-SSL can act as hydrogen bond donors (Fig. 3b), and it is possible that the ether groups of HPC-SSL could act as hydrogen bond acceptors. The C=O groups of PVP-VA are hydrogen bond acceptors (Fig. 3c). In both the crystalline and the amorphous forms of FLD, it has been shown that the NH groups of FLD forms hydrogen bonds with FLD C=O groups (Kestur & Taylor, 2010). In the case of ASDs, the hydrogen bonding may most likely occur between the OH groups of HPC-SSL and the C=O groups of FLD, whereas the NH group of FLD may form hydrogen bonds with the C=O groups of PVP-VA. The FT-IR spectra of the FLD:HPC-SSL system are shown in Fig. 4. The peaks at ~1620, 1644, 1688 and 1700 $cm^{-1}$ represent C=C ring stretching, NH bending, hydrogen bonded C=O stretching, and non-hydrogen bonded C=O stretching, respectively, in the pure crystalline drug. These peaks can also be seen in the PM, suggesting the presence of the reported drug–drug hydrogen bonded, crystalline form of FLD. A significant peak broadening of the C=O stretching vibrations of FLD was detected in the initial ASDs as compared to the PM, which suggests the occurrence of significant drug–polymer hydrogen bonding as a result of the HMM process. The spectrum of ASD stored at 40 °C for 12 weeks almost superimposes with that of the PM, which indicates complete breaking of drug–polymer hydrogen bonds, the formation of drug–drug hydrogen bonds, and re-crystallization of the drug, as previously demonstrated in the DSC and PXRD analyses. However, the ASD stored at 25 °C for

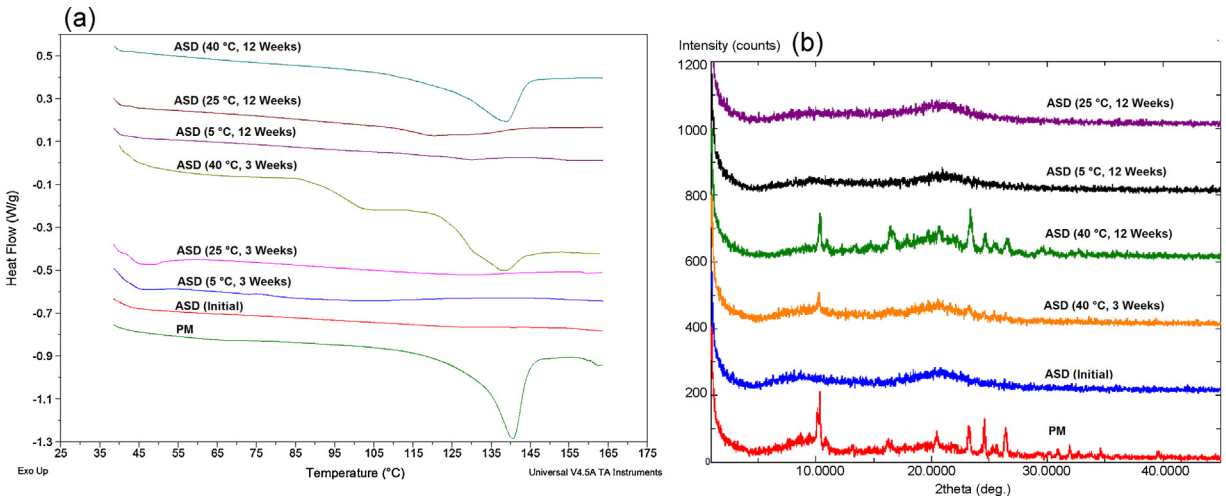


**Fig. 1.** DSC (a) and PXRD (b) plots of FLD:HPC-SSL PMs and ASDs, where late phase separation and early re-crystallization occurred at lower and higher storage temperatures, respectively.

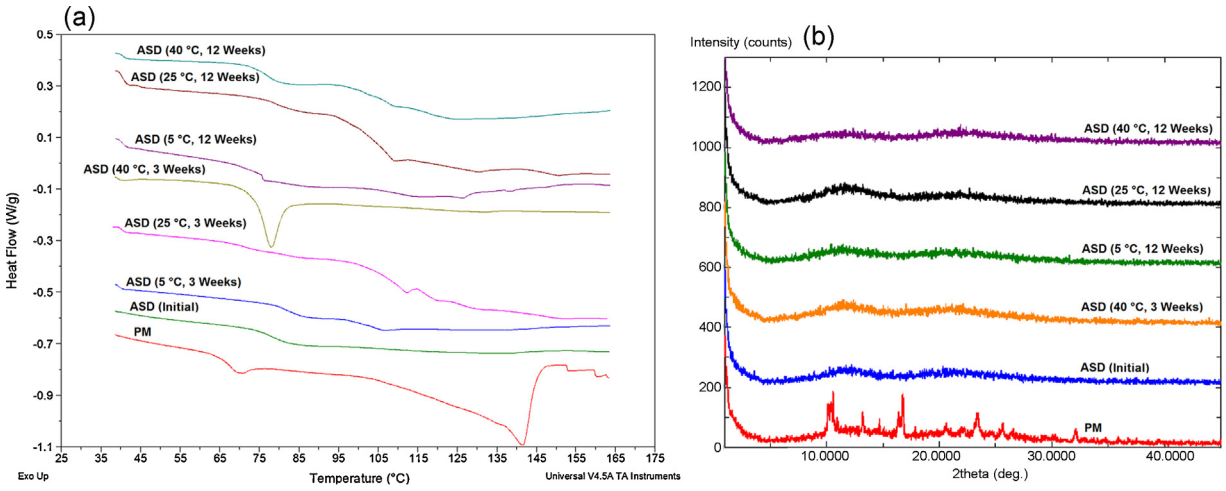


**Fig. 2.** DSC (a) and PXRD (b) plots of FLD:PVP-VA PMs and ASDs, where early phase separation but no re-crystallization was detected.

12 weeks exhibited a spectrum similar to the initial ASD, perhaps due to remaining hydrogen bonds between the drug and the polymer in a partially phase separated system. In the case of FLD:PVP-VA system, the peaks of the FT-IR spectrum of FLD were overlapped by the strong peaks of C=O stretching vibrations of the polymer (Fig. 5). These peaks of carbonyl stretching vibrations of PVP-VA in the initial ASD sample were broader as compared to the corresponding PM suggesting the formation of hydrogen bonds between the polymer and the drug. The spectrum of the partially phase-separated ASD sample stored at 40 °C for 12 weeks did not show a significant difference as compared to that of the initial sample. Thus, it can be inferred that hydrogen bond formation occurred for both FLD:HPC-SSL and FLD:PVP-VA systems during HMM processing. Although the drug–polymer hydrogen bonds were broken with the accompanying formation of drug–drug hydrogen bonding in re-crystallized systems, hydrogen bonding between the drug and the polymer was still present in partially miscible, phase separated amorphous systems.

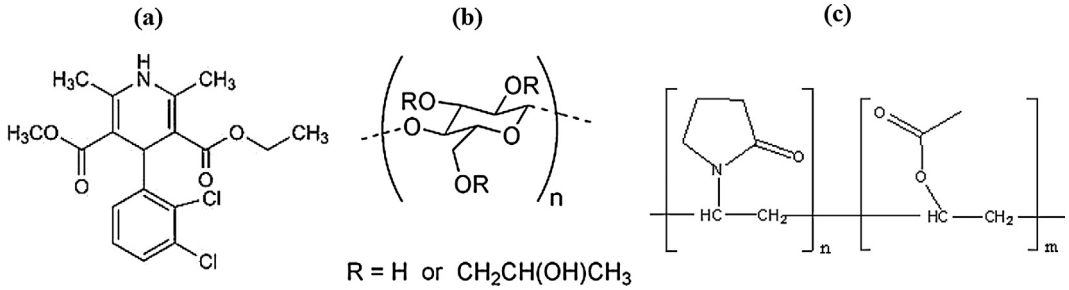


**Fig. 3.** Chemical structures of (a) FLD, (b) HPC-SSL, and (c) PVP-VA, where the NH and C=O groups of the drug, OH group of HPC-SSL, and C=O group of PVP-VA can participate in hydrogen bonding interactions.

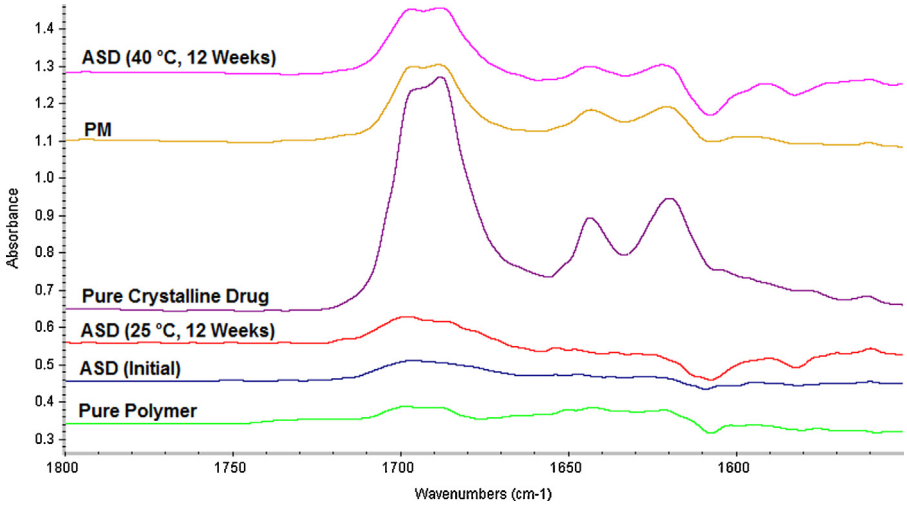


**Fig. 4.** FTIR plots of FLD:HPC-SSL system, where peak broadening of C=O stretching vibrations of FLD in the ASDs suggests hydrogen bonding.

### 3.2. Drug dissolution and partitioning

An improvement in the aqueous dissolution rate and extent is a critical performance aspect of an ASD of a poorly water soluble drug. In addition, an increase in the organic partitioning rate and extent of the drug may be useful for better understanding the influence of the ASD formulation on potential bioavailability enhancement. The dissolution and partitioning profiles for the initial ASD samples of FLD during single- and biphasic dissolution studies are shown in Fig. 6. The ASDs formulated using both the polymers depicted higher dissolution concentrations for FLD as compared to the pure crystalline drug sample, with HPC-SSL showing slightly higher dissolution rate and extent than that of PVP-VA (Fig. 6a). Although the ASDs can achieve supersaturation above the equilibrium solubility of a poorly soluble drug, nucleation can practically occur if a critical supersaturation is attained during the dissolution process. A critical supersaturation concentration was not attained over a period of 5 h using either of these non-ionic polymers and hence no precipitation of the dissolved drug was detected during single phase dissolution studies. Although *n*-octanol is considered to be practically immiscible with water, it does show very slight solubility in water (0.05% w/w), and may act as a surfactant or co-solvent in the aqueous phase. Since both the aqueous and organic phases were equilibrated for 2 h at 37 ± 0.5 °C and 50 rpm before each biphasic dissolution experiment, it was suspected that the dissolution rate for pure crystalline drug sample as well as the ASDs could be higher during biphasic dissolution as compared to their corresponding single phase dissolution study due to the potential co-solvent and surfactant properties of *n*-octanol dissolved in the aqueous phase. In addition, it was anticipated that the dissolution rate in the aqueous phase during biphasic dissolution could have controlled the partitioning rate of the drug from the aqueous to the organic phase. As shown in Fig. 6b, the partitioning rate and extent of FLD into the organic phase were similar for its ASDs manufactured using both HPC-SSL and PVP-VA, and these were both higher than that of the pure crystalline drug sample. Such an enhancement in dissolution as well as partitioning of FLD using ASDs can be attributed to the amorphous transformation of the drug as well as drug–polymer hydrogen bonding interactions formed during the HMM process.

The phase separation and/or re-crystallization of a drug in the ASDs that occurred due to temperature and/or humidity exposure might be expected to adversely affect its dissolution and subsequent partitioning. The partitioning profiles for the ASDs stored at various temperatures and 75% RH are shown in Fig. 7. As compared to the initial ASDs, the partitioning rate and extent were reduced for the stability samples, likely due to phase separation and/or FLD re-crystallization. This reduction was dependent on both time and temperature for the FLD:HPC-SSL system. For instance, the

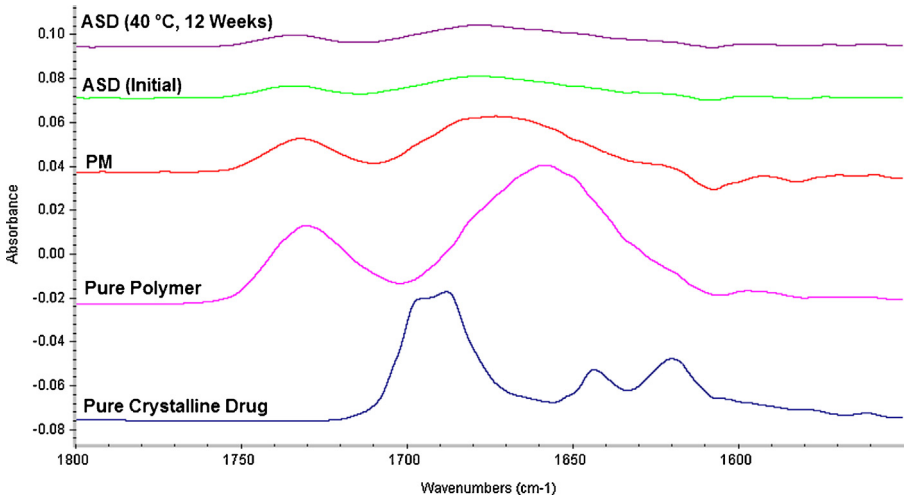


**Fig. 5.** FTIR plots of FLD:PVP-VA system, where peak broadening of C=O stretching vibrations of PVP-VA in the ASDs suggests hydrogen bonding.

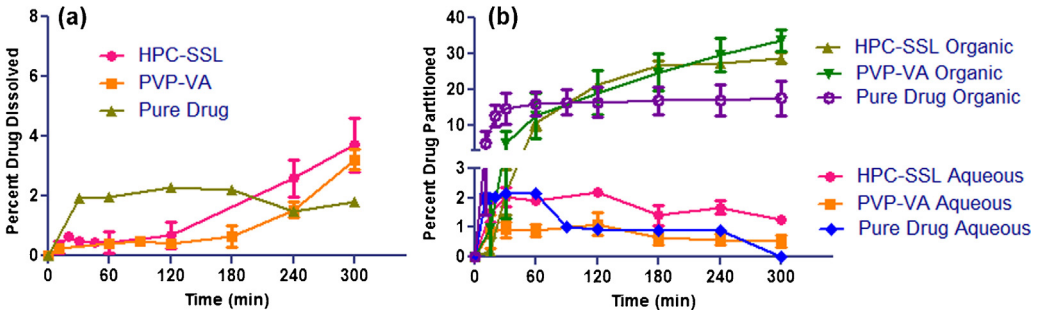


**Fig. 6.** Dissolution (a) and partitioning (b) profiles of initial ASDs of FLD during single and biphasic dissolution, respectively, where the dissolution and partitioning was improved using both the polymers as compared to the pure crystalline drug.

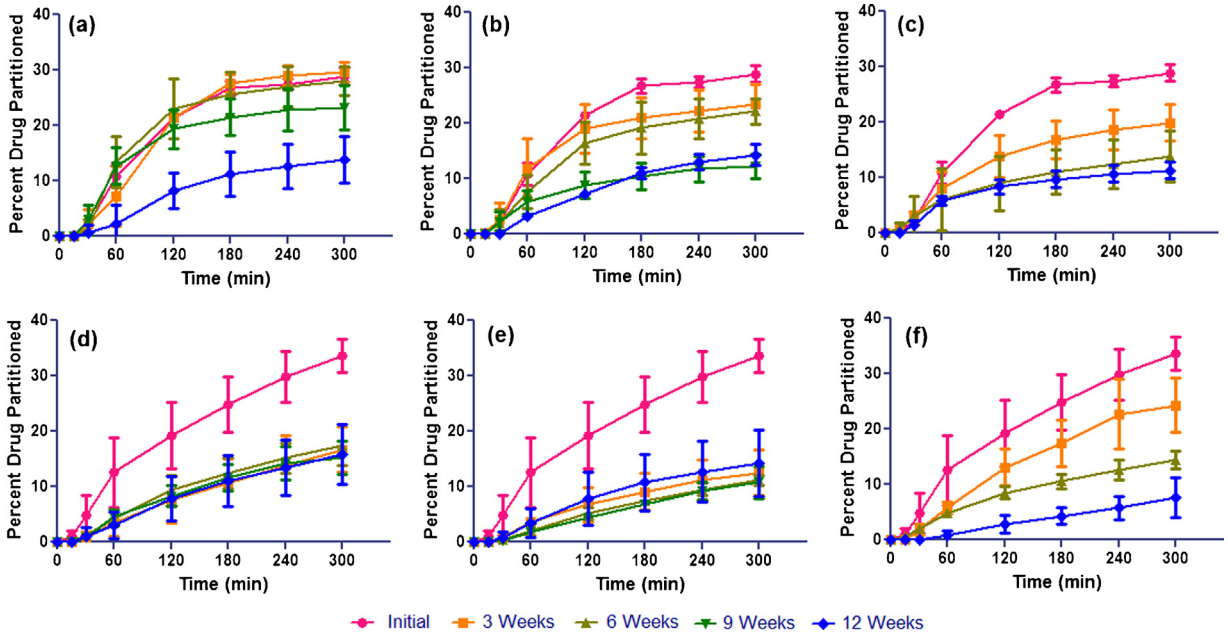


**Fig. 7.** Partitioning profiles of FLD: HPC-SSL ASDs stored at (a) 5 °C, (b) 25 °C, and (c) 40 °C and those of FLD:PVP-VA ASDs stored at (d) 5 °C, (e) 25 °C, and (f) 40 °C. The relative humidity was maintained at 75% for all the samples. The reduction in partitioning was better prevented by HPC-SSL as compared to PVP-VA over the stability period.

partitioning rate was reduced gradually as a function of storage time for the ASDs stored at a particular temperature and it was lower for the samples stored at higher temperature for any particular time point (Fig. 7a–c). On the other hand, in the case of FLD:PVP-VA system, the reduction in partitioning was more dependent on temperature than time. The partitioning rate was reduced with the increase in storage temperature from 5 to 25 °C (Fig. 7d and e), but was nearly same at all the time points for both of these storage temperatures. The sample stored at 40 °C for 3 weeks (Fig. 7f) exhibited higher partitioning as compared to the other stability samples of FLD:PVP-VA (Fig. 7d–f). It has been reported previously that higher storage temperature conditioning of ASDs for a shorter duration can lead to an improvement in dissolution and supersaturation (Jijun et al., 2011; Sarode et al., 2013). Hence, this higher partitioning for the sample store at 40 °C for 3 weeks could be attributed to the formation of a rigid amorphous phase instead of phase separation due to higher temperature conditioning for a relatively short period. It can be seen from the data that the reduction in partitioning due to temperature and/or humidity induced phase separation and/or re-crystallization was better prevented by HPC-SSL as compared to PVP-VA when stored at lower (5 °C) and room (25 °C) temperatures. For example, the partitioning rate of the stability samples of HPC-SSL ASDs (Fig. 7a and b) was higher than those of PVP-VA ASDs (Fig. 7d and e). Such a better performance of HPC-SSL than PVP-VA at lower and room temperature and moderately higher humidity storage conditions could be correlated to later phase separation for FLD:HPC-SSL ASDs as compared to early phase separation of FLD:PVP-VA ASDs, as determined by DSC analysis. Although it could not be demonstrated due to the limitations of FT-IR analysis, including significant carbonyl group peak overlaps, it is possible that the hydrogen bonding interactions occurring between FLD and HPC-SSL could be stronger as compared to those between FLD and PVP-VA. These stronger interactions may have prevented early phase separation for HPC-SSL based ASDs as compared to PVP-VA at lower and room temperature storage conditions. However, at higher storage temperature, the performance of HPC-SSL (Fig. 7c) was similar to that of PVP-VA (Fig. 7f), perhaps due to re-crystallization of the drug in HPC-SSL based ASDs, which could have occurred due to higher temperature and humidity induced enhanced molecular mobility.

## 4. Conclusions

Molecularly dispersed and chemically stable ASDs of poorly water soluble drugs can be manufactured using the low viscosity grade cellulosic polymer HPC-SSL by HMM processing.

Enhancements in aqueous dissolution and biphasic partitioning are seen, and perhaps the oral bioavailability of such drugs will increase as well, since the ASDs exhibited superior dissolution and partitioning as compared to the pure crystalline drug. Higher temperature and humidity induced phase separation and/or re-crystallization of the drug may not be prevented during storage. However, ASDs formulated using HPC-SSL could be relatively more stable as compared to PVP-VA based ASDs when stored at lower and room temperature and elevated humidity.

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