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Research Article

Stability-enhanced Hot-melt Extruded Amorphous Solid Dispersions *via* Combinations of Soluplus® and HPMCAS-HF

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Abstract. The aim of this study was to evaluate a novel combination of Soluplus® and hypromellose acetate succinate (HPMCAS-HF) polymers for solubility enhancement as well as enhanced physicochemical stability of the produced amorphous solid dispersions. This was accomplished by converting the poorly water-soluble crystalline form of carbamazepine into a more soluble amorphous form within the polymeric blends. Carbamazepine (CBZ), a Biopharmaceutics Classification System class II active pharmaceutical ingredient (API) with multiple polymorphs, was utilized as a model drug. Hot-melt extrusion (HME) processing was used to prepare solid dispersions utilizing blends of polymers. Drug loading showed a significant effect on the dissolution rate of CBZ in all of the tested ratios of Soluplus® and HPMCAS-HF. CBZ was completely miscible in the polymeric blends of Soluplus® and HPMCAS-HF up to 40% drug loading. The extrudates were characterized by differential scanning calorimetry (DSC), X-ray diffraction (XRD), Fourier transform infrared (FTIR) spectroscopy and dissolution studies. DSC and XRD data confirmed the formation of amorphous solid dispersions of CBZ in the polymeric blends of Soluplus® and HPMCAS-HF. Drug loading and release of CBZ was increased with Soluplus® (when used as the primary matrix polymer) when formulations contained Soluplus® with 7–21% (*w*/*w*) HPMCAS-HF. In addition, this blend of polymers was found to be physically and chemically stable at 40°C, 75% RH over 12 months without any dissolution rate changes.

KEY WORDS: carbamazepine; hot-melt extrusion; HPMCAS-HF; Soluplus®; stability.

INTRODUCTION

Hot-melt extrusion (HME) has attracted considerable attention in the pharmaceutical industry in the last couple of decades (1). HME has some advantages over other more traditional processing techniques such as being a solvent-free, continuous process requiring fewer processing steps (2). HME works as any solid dispersion system, that is, by converting the drug from its crystalline form into its amorphous form or by the formation of a molecular dispersion/solid solution (3). The amorphous form has more free energy than the crystalline lattice, which will lead to increasing the dissolution rate (4). However, increasing the free energy of the materials will affect the thermodynamic stability during storage (5). The inherent thermodynamic instability tends to lead to a phenomenon known as recrystallization. Recrystallization will reduce the dissolution rate and solubility of the active pharmaceutical ingredient (API), which leads to decreased pharmacological delivery and efficacy (6). The lack of physical stability is one of the main drawbacks of any amorphous dispersion (7). In the literature, many research papers showed the feasibility of producing a solid dispersion using HME. However in the market, only a limited number of extruded products can be found. The most commonly cited issue with solid dispersions is the lack of physical stability (8). For this reason, the need of producing a stable solid dispersion is as essential as the desired solubility enhancement.

Carbamazepine is an antiepileptic drug with poor water solubility (17.7 mg/L at 25°C, log *P* value of 2.45) (9). It is considered a class II drug according to the Biopharmaceutical Classification System (BCS) which is characterized by low water solubility and high permeability. For oral administration, CBZ absorption is mainly dependent on the dissolution rate (10). A correlation between the oral bioavailability and physical state of CBZ was revealed during an *in vivo* pharmacokinetics study (11). It was suggested that formulation enhancements might result in overall improved bioavailability (12). However, the formulation of CBZ for oral administration faces challenges in addition to solubility enhancement.

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These challenges include a narrow therapeutic window, high dosage requirement (100 mg/200 mg, BID or TID), and a narrow thermally stable window for HME processing. CBZ has a high melting point (193°C) and is thermally stable only up to 220°C. The high melting point makes CBZ a good candidate for HME. However, the narrow thermally stable processing window poses certain challenges for the HME formulation of CBZ. Additionally, CBZ can pose certain stability challenges post processing as many polymorphs have been identified, and any of them could result from recrystallization after HME processing (13).

To overcome the challenges of CBZ, Soluplus®, polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer, was selected as the primary carrier. It is an amphiphilic polymer that can work as solubilizing agent as it forms micelles in solution. It is used to enhance the solubility of poorly water soluble APIs by solid dispersion. The glass transition temperature for Soluplus® is 70°C; this low glass transition temperature makes Soluplus® a good candidate for extrusion of CBZ at relatively low temperatures; in fact, the polymer is very easily extruded. Another advantage of Soluplus® is the low hygroscopicity of the polymer, which will help stabilize the dispersion during storage. Based on the literature, Soluplus® can successfully enhance the solubility of CBZ if less than 10% drug loading is used (14), while recrystallization and poor dissolution were observed in one study when CBZ drug loading increased to be above 10% (15). However, high drug loading is required for CBZ as the therapeutic dose starts from 100 mg. For this reason, another material with stabilizing effect was employed.

Another method to stabilize a solid dispersion is by using a carrier with a high glass transition temperature (16). It was reported that the stabilized formulation can be achieved if the formulation's glass transition temperature is higher than 50°C compared to the storage temperature (17). It was found that polymers with high glass transition temperature can potentially prevent recrystallization by delayed kinetics (18). Thus, hypromellose acetate succinate (HPMCAS-HF) polymer with a high glass transition temperature was selected as a secondary carrier with potential stabilizing effects (19). HPMCAS-HF is not suitable for extrusion alone due to its high glass transition temperature. However, blending HPMCAS-HF with Soluplus® facilitates its extrudability in addition to increasing the formulations' glass transition temperature, which subsequently enhances physical stability.

In this study, the objective was to improve the solubility and physical stability of carbamazepine (CBZ) using hot-melt extrusion technology. This was accomplished by converting the poorly water-soluble crystalline form of carbamazepine to the more water-soluble amorphous form utilizing polymeric blends. Solubility enhancement was accomplished by producing an amorphous solid dispersion utilizing Soluplus® as the solubilizing carrier, while physical stability was enhanced by adding HPMCAS-HF as a stabilizing agent.

MATERIALS

CBZ was purchased from Afine Chemicals Limited, Zhejiang, China, and was of high purity. Polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus®) was received as a generous gift from BASF Chemical Co. (Ludwigshafen, Germany). Hypromellose acetate succinate (HPMCAS-HF) was supplied by Shin-Etsu Chemical Co. (Brand name Shin-Etsu AQOAT). All other chemicals used were of analytical grade and obtained from Fisher Scientific.

METHODS

Thermogravimetric Analysis

A PerkinElmer Pyris 1 thermogravimetric analyzer (TGA) equipped with Pyris manager software (PerkinElmer Life and Analytical Sciences, 719 Bridgeport Ave., CT, USA) was utilized to perform thermogravimetric analysis of samples. Each sample weighed 3 to 5 mg and was heated from 20 to 250°C at a heating rate of 10°C/min.

Differential Scanning Calorimetry

A PerkinElmer hyper differential scanning calorimeter (DSC) (PerkinElmer Life and Analytical Sciences, 710 Bridgeport Ave., CT, USA) was used to analyze the samples. This instrument was equipped with Pyris manager software (Shelton, CT, USA). Each sample in this study weighed approximately 2–5 mg and was hermetically sealed in an aluminum pan. These samples were heated from 20 to 250°C at a linear heating rate of 10°C/min.

Preparation of Solid Dispersions

The polymers were sieved using USP mesh screen (#35) and kept in an oven (40°C) overnight to remove any residual moisture. The polymers were then blended in multiple ratios with the API (Table I) using a twin shell V-blender (GlobePharma, Maxiblend®) at 25 rpm for 10 min. Each sample was subsequently melt extruded using a twin-screw extruder (16 mm Prism EuroLab, ThermoFisher Scientific) under different processing conditions (Table I). After extrusion, the melt extrudates were cooled to ambient temperature, milled using a comminuting mill (Fitzpatrick, model L1A), sieved using USP mesh screen (#35), and stored in the glass vials with a rubber-lined cap for further studies.

High-Performance Liquid Chromatography (HPLC) Chromatographic System and Conditions

The drug content was determined by a Waters high-performance liquid chromatography (HPLC) consisting of a Water 600 binary pump, Waters 2489 UV/detector, and Waters 717 Plus autosampler (Waters Technologies Corporation, 34 Maple St., Milford, MA 0157). A Phenomenex Luna® C18 reverse phase column (5 μm 100 Å, 250×4.6 mm) was used as the stationary phase. Empower 2 software was used to analyze the data. The mobile phase was water, methanol, and acetic acid (34:65:1% *v*/*v*), and the UV detector was set at 285 nm wavelength. The flow rate was maintained at 1.0 mL/min, and 20 μL was injected from each sample. Drug content uniformity was assessed by dissolving accurately weighed CBZ extrudates in 20 mL methanol then transferring 1 mL into a 10-mL flask and adding 9 mL of methanol. These 1.5-mL samples were then centrifuged (Centrifuge Eppendorf 5415

Table I. Formulation Composition on Polymer Ratio Study of HPMCAS-HF and Soluplus®

Formulation	Polymers ratio (HPMCAS-HF:Soluplus®)	HPMCAS-HF %, *w/w*	Soluplus® %, *w/w*	CBZ %, *w/w*	Extrusion condition	
					Temp (°C)	Speed (rpm)
F1	1:9	8	72	20	100–120	95
F2	2:8	16	64	20	110–120	85
F3	3:7	24	56	20	110–120	80
F4	4:6	32	48	20	110–120	80
F5	5:5	40	40	20	110–130	75

R) for 5 min at 10,000 rpm and 25°C and subsequently quantified using the previously outlined HPLC procedure. Six replicates were used for all of the assay studies. Dissolution study samples were centrifuged and injected at a 20-μL injection volume.

X-ray Powder Diffraction (XRD)

XRD was performed using a powder X-ray diffraction apparatus (Bruker AXS, Madison, MI) using CuKα radiation, generator voltage at 40 kV, and current at 40 mA. The diffraction angles were (2θ) of 5–40° at 2°/min scanning rate.

Fourier Transform Infrared (FTIR) Spectroscopy

Fourier transform infrared FTIR studies were conducted on an Agilent Technologies Cary 660 (Santa Clara, CA.). The bench was equipped with an ATR (Pike Technologies MIRacle ATR, Madison, WI) which was fitted with a single bounce diamond coated ZnSe internal reflection element.

In Vitro Dissolution Study

In vitro release studies (n=3) were carried out utilizing a Hanson SR8-Plus™ dissolution test station (Chatsworth, CA) operated at 100 rpm paddle speed with 900 mL of distilled water as the dissolution medium, which was maintained at 37±0.5°C. CBZ extrudate samples were accurately weighed (100 mg each) and added to the dissolution medium. Drug release profiles were compared using the similarity factor (f_2), which can be calculated using the following equation (20):

$$f_2 = 50 \cdot \log \left\{ \left[1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \cdot 100 \right\}$$

where R_t and T_t are the cumulative percentage dissolved at each time point n of the reference and test product, respectively. In accord with the FDA guidance for industry, two dissolution profiles are considered similar or equivalent when the value of similarity factor (f_2) is greater than 50.

Stability Study

Two methods were used to compare the formulations after 12 months of storage. The first utilized XRD to show the morphology changes with time. The second involved comparing the *in vitro* release at different storage time intervals to show the difference between each formulation with respect to time. Extrudate samples were stored in a stability chamber at 40°C and 75% RH. Stability studies were performed after 3, 6, and 12 months, and samples were tested for crystalline content by XRD, chemical stability by HPLC, and *in vitro* release profile comparisons.

RESULTS AND DISCUSSION

TGA

The drug and excipients were evaluated for thermal stability at high temperatures. TGA studies revealed that Soluplus®, HPMCAS-HF, and CBZ were stable under the employed extrusion conditions with no trace of any drug degradation being observed when heated to 190°C (Fig. 1). In this study, the formulations were processed below this temperature, which eliminated the modest thermal instability issue.

Polymer Ratios

Different polymer ratios between HPMCAS-HF and Soluplus® were studied to investigate the effect of HPMCAS-HF on extrudability and dissolution profiles. Formulations with different ratios of HPMCAS-HF to Soluplus®, at a fixed drug loading of 20% (Table I), were processed to determine their HME feasibility and dissolution rate enhancement. All of the extruded formulations demonstrated a higher dissolution rate relative to the pure drug. The dissolution rate of CBZ was enhanced with increasing concentrations of Soluplus®, indicating that Soluplus® played a key role in the dissolution enhancement of the drug. The addition of HPMCAS-HF was associated with limited extrudability and decreased drug release (Fig. 2). It was determined that HPMCAS-HF can be extruded with Soluplus® up to a 1:1 ratio (formulation F5). At higher drug loading, excessively high pressures and torque values were observed. At the same time, it was observed that an increase in HPMCAS-HF content was detrimental to the dissolution rate when it was higher than 30%. Figure 2 indicates that there was no effect from the addition of HPMCAS-HF on drug dissolution when added up to 30% (F3). These results indicated that 3:7 polymers ratio (HPMCAS-HF:Soluplus) was the maximum extrudable ratio with drug release enhancement.

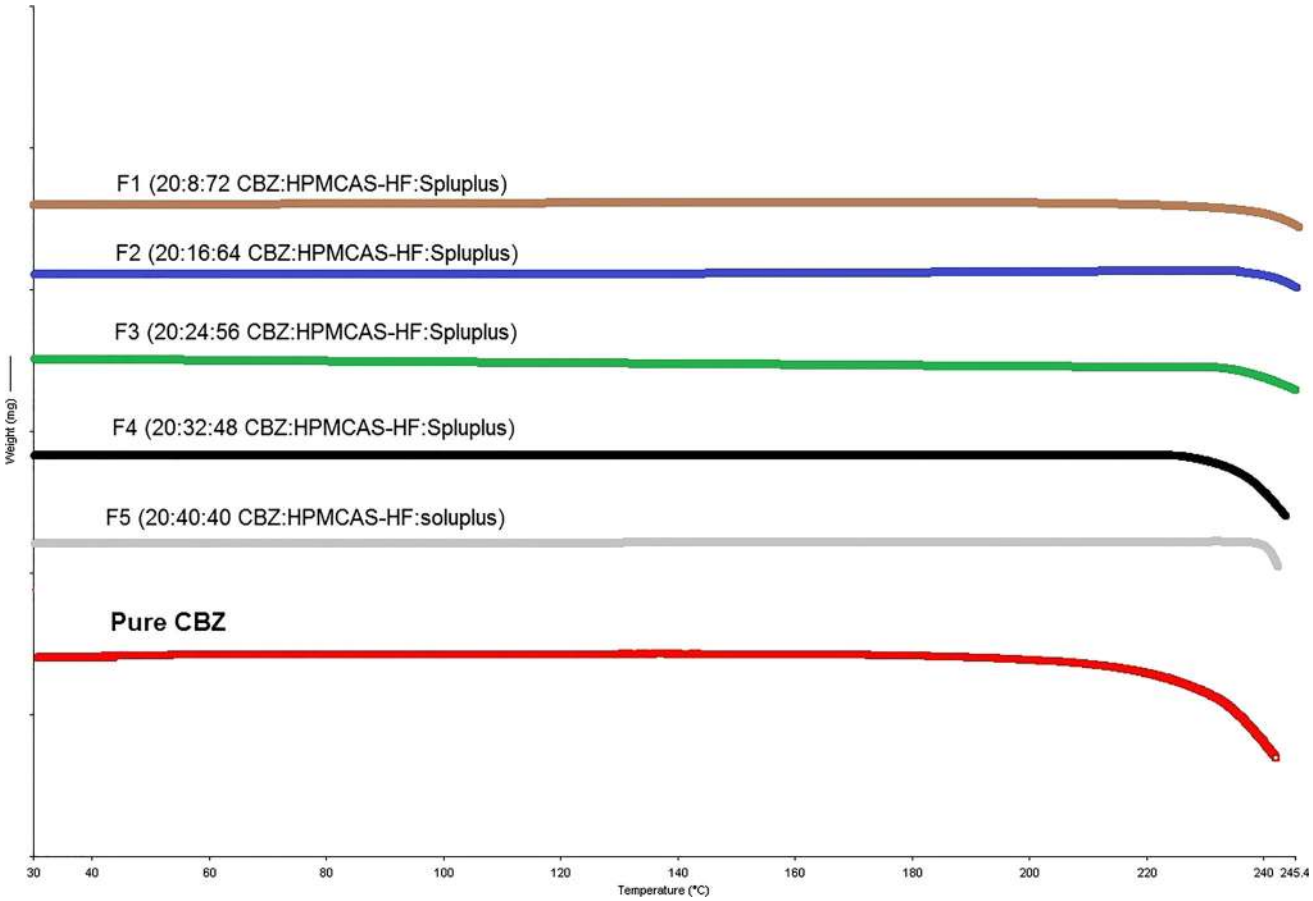

Fig. 1. TGA data for pre-extrusion for different polymers ratios and pure CBZ

Drug Loadings

The influence of drug loading was evaluated in order to reach an optimized loading in terms of both extrudability and dissolution rate. A polymer ratio of 3:7 (F3 in Table I) was selected to change the drug loading to 10, 20, 30, 35, and 40% as the polymer ratio studies indicated that HPMCAS-HF presented no effect on drug release if used up to that ratio. The extrusion parameters were kept constant for all of the formulations to eliminate any other interference or changes. It was determined that the drug loading demonstrated a significant effect on the dissolution rate of CBZ with Soluplus® and HPMCAS-HF. The DSC studies show that the CBZ melting peak disappeared in the extrudates, indicating that CBZ was completely miscible in the polymeric blends of Soluplus® and HPMCAS-HF up to 40% drug loading (Fig. 3a). The DSC thermograms indicate that molten formulations were able to depress the melting point of CBZ and produce an amorphous solid dispersion at the employed extrusion conditions. Additionally, this confirms that dissolution rate enhancement for drug loading was below 40%. This enhancement is due primarily to the presence of the amorphous form of CBZ after extrusion. Moreover, at up to 35% drug loading, the extrusion process was still producing transparent extrudates and

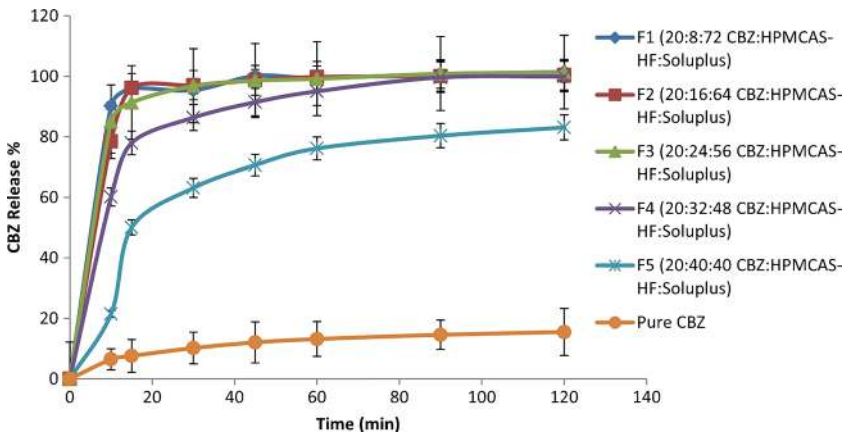

Fig. 2. *In vitro* release studies for different polymer ratios and pure CBZ

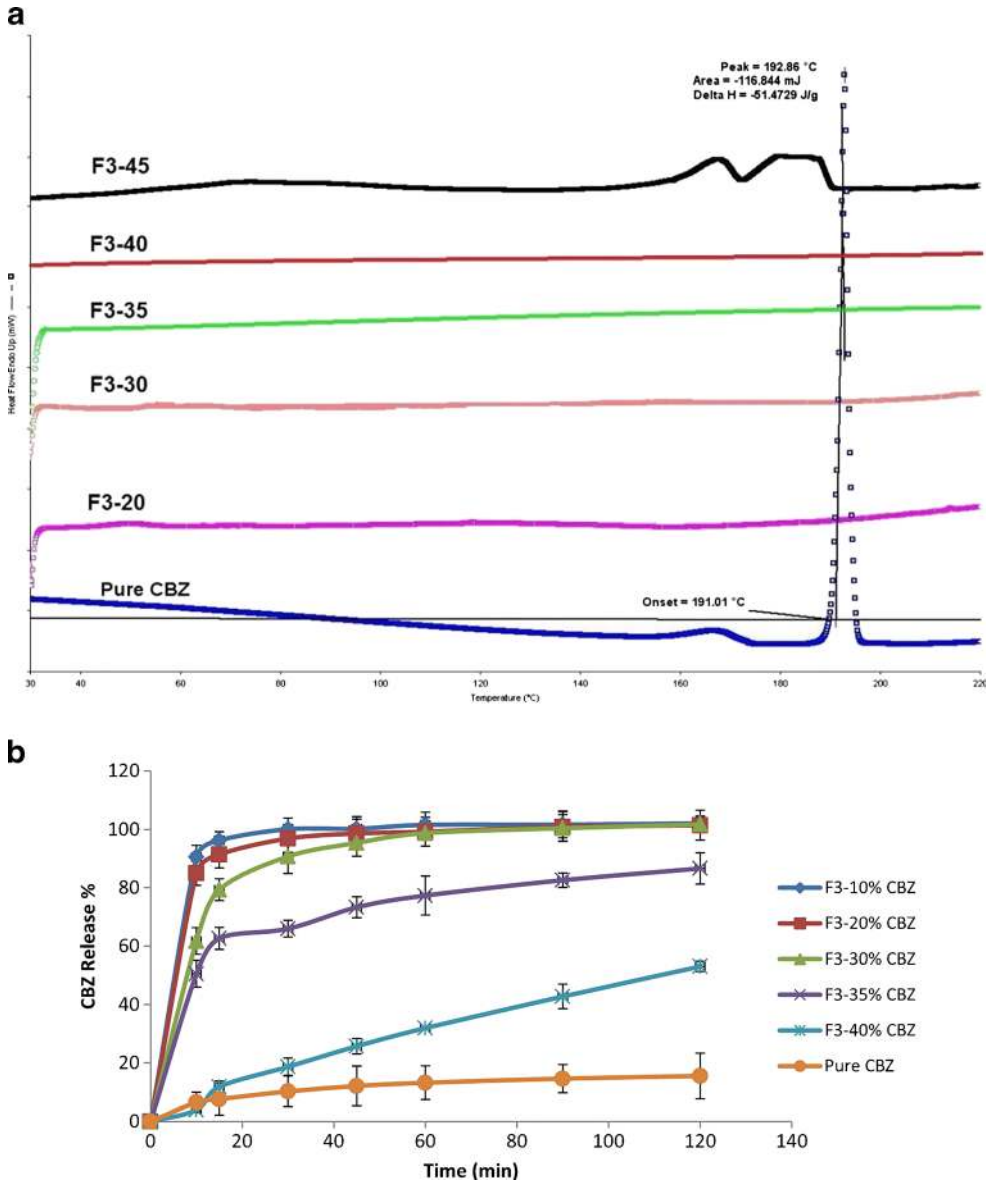

Fig. 3. Drug loading study on formulation F3 at polymer ratio of 3:7 (HPMCAS-HF:Soluplus®). **a** DSC data on miscibility study for drug loading of 20, 30, 35, 40, and 45% (CBZ *w*/*w*); **b** *in vitro* drug release profiles for F3 at different drug loadings

amorphous CBZ, compared to the opaque crystalline CBZ which was observed at higher levels, which suggests a phase separation at higher drug loading. Furthermore, *in vitro* release studies showed that each drug loading produced a different release profile (Fig. 3b). It was observed that above 35% drug loading, a significant dissolution rate change was observed. At the same time, 35% drug loading demonstrated a delay in drug released when compared to lower drug loadings. This delay may due to residual crystalline CBZ present with the amorphous form that cannot be detected by the DSC. This drug loading limitation was because of hydrophilic and hydrophobic balance as well as the dispersibility limitation in the molten polymers, which is in agreement with previous literature reports (21). Moreover, for any solid dispersion, drug loading significantly affects the interplay between the characteristics of API (melting temperature, anti-plasticizing, or plasticizing effect), processing conditions employed, and the relative melt viscosities of the polymeric carrier. In this study, a 16-mm twin-screw extruder with three mixing zones was used. The number of mixing zones and configuration was selected based on preliminary studies. This screw configuration imparted a high degree of shearing force and intense mixing below 150°C. This reduced the chance that CBZ would exhibit polymorphic changes from form III to polymorph I, which has a lower pharmacological effect and can be produced by heating polymorph III above 150°C (22). Moreover, solid dispersion produced by HME can be predicted by the Flory–Huggins lattice theory for miscibility between the polymer and API. This theory indicates that the thermodynamics (entropy of mixing) is dependent on the ratio between the carrier and the polymer. The CBZ-polymer miscibility will depend on its ratio and extrusion processing parameters. This is consistent with a reported miscibility study between CBZ and Soluplus® (23). It was found that Soluplus® has limited dispersibility and

Table II. Final Formulation Composition and Processing Conditions for Stability Study (A with no HPMCAS-HF, B Has Low HPMCAS-HF Ratio, and C Has High HPMCAS-HF ratio)

Formulation	CBZ %, *w/w*	HPMCAS-HF %, *w/w*	Soluplus® %, *w/w*	Extrusion conditions	
				Temp (°C)	Speed (rpm)
A	30	0	70	110–120	80
B	30	7	63	110–120	80
C	30	21	49	110–120	80

miscibility with CBZ according to CBZ content percentage and the temperature used. For this reason, 30% drug loading was used as the optimized drug loading, however, which is higher than the drug loadings employed in previous publications by 3-fold ((14),(23)). Therefore, the stability study was conducted by using minimum and maximum HPMCAS-HF ratios to investigate the recrystallization inhibitory effect of HPMCAS-HF (Table II). A control formulation consisting of Soluplus® (70%) and CBZ (30%) without HPMCAS-HF was used to show the influence of HPMCAS-HF on stability. The drug loading was kept as high as 30% to prove the stability issues associated with the higher drug loading. All extrusion parameters were held constant to eliminate other factors except the formulation composition.

Drug Content

After extrusion, each formulation was analyzed for drug content and content uniformity using HPLC. All formulations were in the acceptable range according to FDA guidelines and the US Pharmacopeia for carbamazepine tablet. Moreover, drug content was compared between fresh extrudates and after storage (Fig. 4). It was found that before and after storage, the content of CBZ in all extrudates ranged between 99.01 and 103.04% (Fig. 4). That indicated that CBZ was chemically stable with no trace of degradation or weight loss after storage for 12 months (at 40°C and 75% RH). Additionally, each formulation demonstrated uniform drug content with relative standard deviation ranging between 1.05 and 2.86% for fresh extrudates and after storage for 12 months, respectively. This indicated that the HME processing conditions imparted excellent content uniformity with high chemical stability.

DSC

Differential scanning calorimetry (DSC) was performed to confirm drug–polymer miscibility and the amorphous nature of extrudates. The DSC thermograms showed that pure CBZ was characterized by a single, sharp melting endotherm peak at 192.9°C (Fig. 5). Miscibility was determined by scanning multiple samples with different drug loadings. The DSC thermograms (Fig. 3a) showed that the maximum CBZ miscibility with Soluplus® and HPMCAS-HF was found at 40% drug loading. Samples with drug loading higher than 40% had CBZ crystalline melting peaks reappearing (formulation F3–45%). The physical mixtures showed a thermal peak for CBZ between 188 and 190°C, while the extrudates showed no thermal peak for CBZ (Fig. 5). This indicates that CBZ was solubilized and converted into the amorphous form in the polymer melt after extrusion.

XRD

XRD was used to study the morphology and physical stability of CBZ in the extrudates. Carbamazepine has characteristic

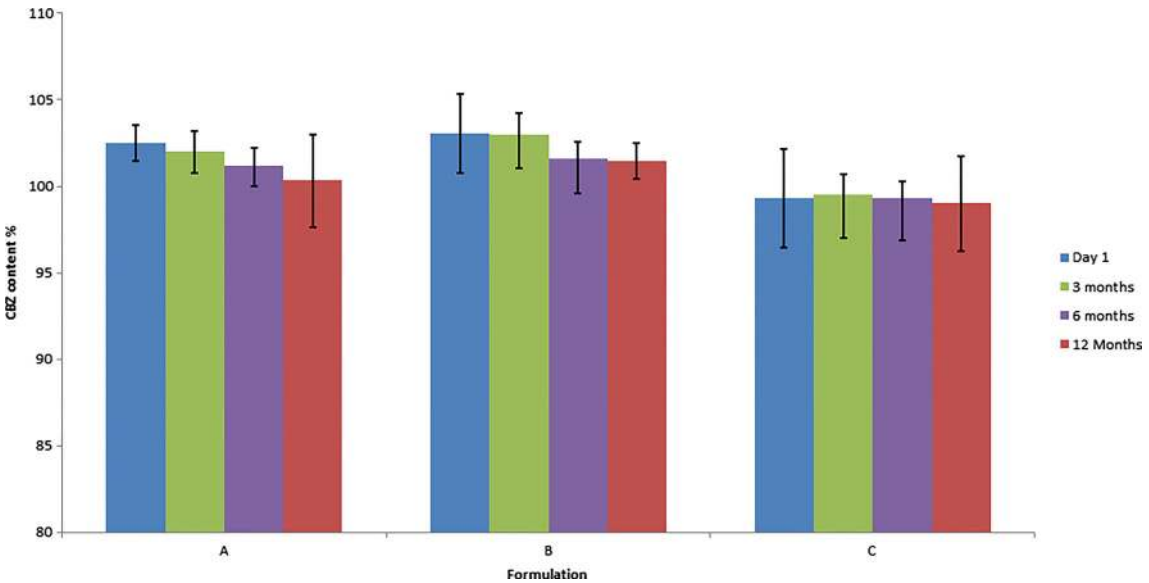

Fig. 4. Drug contents of formulations **a** 30:70 CBZ:Soluplus®, **b** 30:7:63 CBZ:HPMCAS-HF:Soluplus®, and **c** 30:21:49 CBZ:HPMCAS-HF:Soluplus® extrudates at day 1, 3, 6, and 12 months after storage at 40°C/75% RH

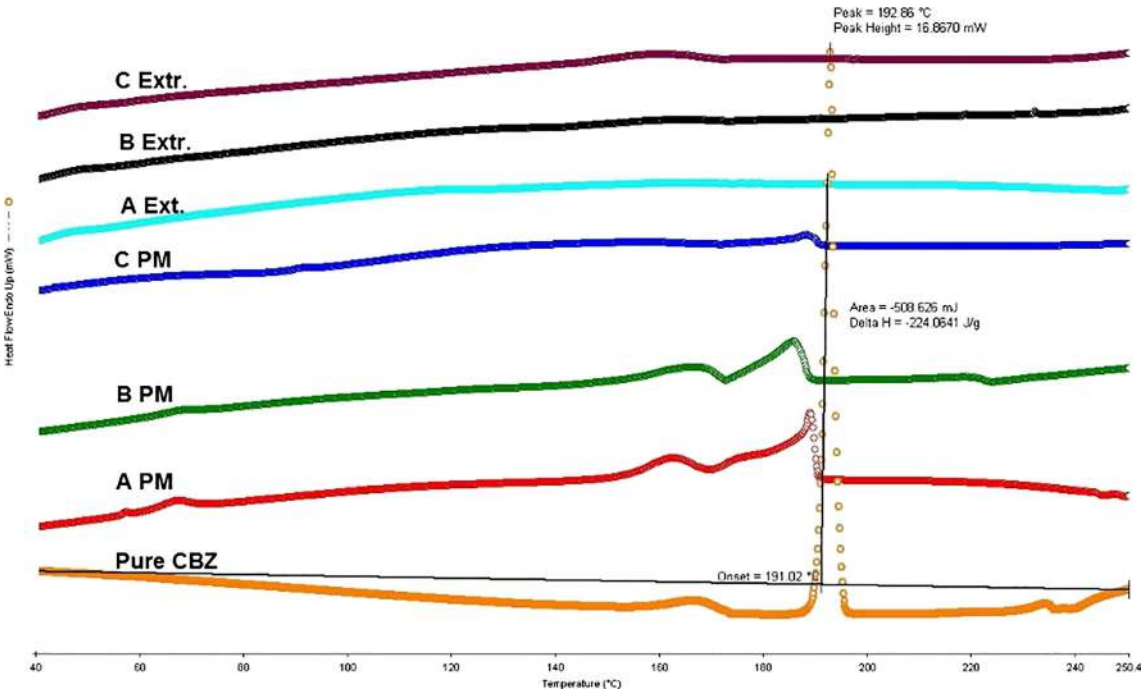

Fig. 5. DSC data for pure CBZ, formulations **a** 30:70 CBZ: Soluplus®, **b** 30:7:63 CBZ:HPMCAS-HF:Soluplus®, and **c** 30:21:49 CBZ:HPMCAS-HF:Soluplus® with their corresponding physical mixtures

peaks at 2θ=16, 18, and 27° (Fig. 6). The examined extrudates showed no traces of crystallinity as the characteristic peaks disappeared completely from the obtained diffractograms apparent when analyzing the pure drug (Fig. 6), while the corresponding physical mixtures did show the characteristic crystalline peaks from CBZ. XRD and DSC data confirmed that HME produces a solid dispersion system wherein the crystalline form of CBZ was converted to its amorphous form.

In Vitro Release

CBZ release profiles from the extrudates were compared with pure CBZ and corresponding CBZ/polymers physical mixtures. The results are shown as percent drug dissolved. Due to poor solubility and wettability, the dissolution of pure CBZ was very low, exhibiting less than 20% dissolution after 120 min. The physical mixtures showed slight release improvement when compared to the pure drug (Fig. 7). All of the extruded formulations demonstrated rapid and extensive CBZ release compared with their corresponding physical mixture with more than 80% drug release within 20 min. More than 97% drug released within 15 min for formulation A, while its physical mixture showed less than 8% release in 15 min. By comparing the extrudate release profiles with their corresponding physical mixture, it is evident that HME processing was successfully able to produce a formulation with an enhanced dissolution rate. This was attributed to the production of amorphous CBZ in addition to the hydrophilic properties of the polymer.

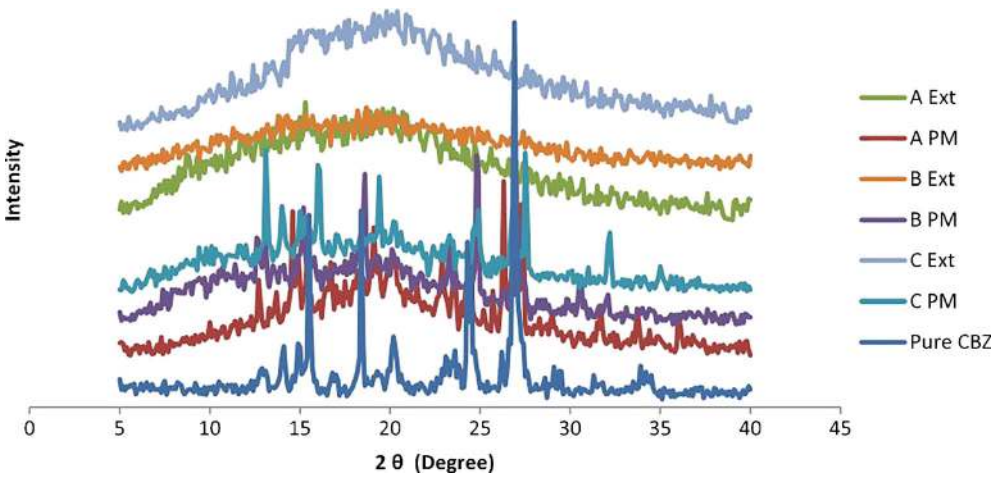

Fig. 6. XRD data for pure CBZ, formulations **a** 30:70 CBZ:Soluplus®, **b** 30:7:63 CBZ:HPMCAS-HF:Soluplus®, and **c** 30:21:49 CBZ:HPMCAS-HF:Soluplus® with their corresponding physical mixtures

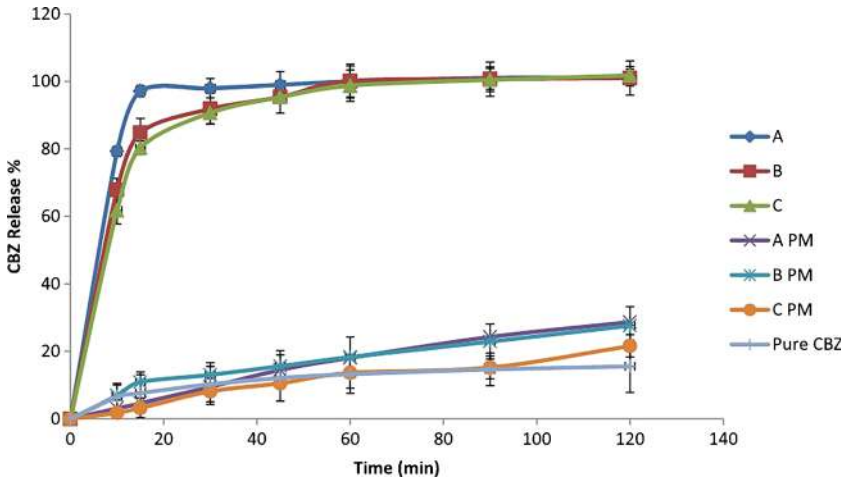

Fig. 7. *In vitro* release profiles of pure CBZ, formulations **a** 30:70 CBZ:Soluplus®, **b** 30:7:63 CBZ:HPMCAS-HF:Soluplus®, and **c** 30:21:49 CBZ:HPMCAS-HF:Soluplus® with their corresponding physical mixtures

FTIR

FTIR spectra (Fig. 8) for pure CBZ demonstrated the characteristic peaks of crystal CBZ form III at wavenumbers 3461 (15). This peak was also shown in the physical mixtures of formulation A, B, and C and suggests that there was no intermolecular interaction between CBZ and the polymers when physically mixed together. Furthermore, the hydrogen bond formation that was suggested in the literature (25) between CBZ and Soluplus® was observed at 1033 cm^{-1}. However, this peak broadening became more pronounced with increasing concentrations of HPMCAS-HF in formulation B and further in formulation C. The absorbance area at wavenumber 1033 cm^{-1} was increased 0.521, 0.668, and 1.20 for formulation A, B, and C, respectively. This increase indicated that the intensity of the hydrogen bond is increased by adding HPMCAS-HF. Moreover, the characteristic peak for N–H stretching vibrations of a primary amide group of CBZ at 3154 cm^{-1} was shifted and replaced with a broader peak at 3158 cm^{-1} in the C extrudates. This potentially indicated the formation of hydrogen bonding with the hydroxyl group of HPMCAS-HF. This shifting became more pronounced by increasing the concentration of HPMCAS-HF. The CBZ carbonyl peak at 1673 cm^{-1} exhibited the same broadening and shifting to 1676 cm^{-1} with increasing HPMCAS-HF ratios (26, 27). The hydrogen bond formation should work synergistically with Soluplus® to enhance the solubility and stability of the formulations.

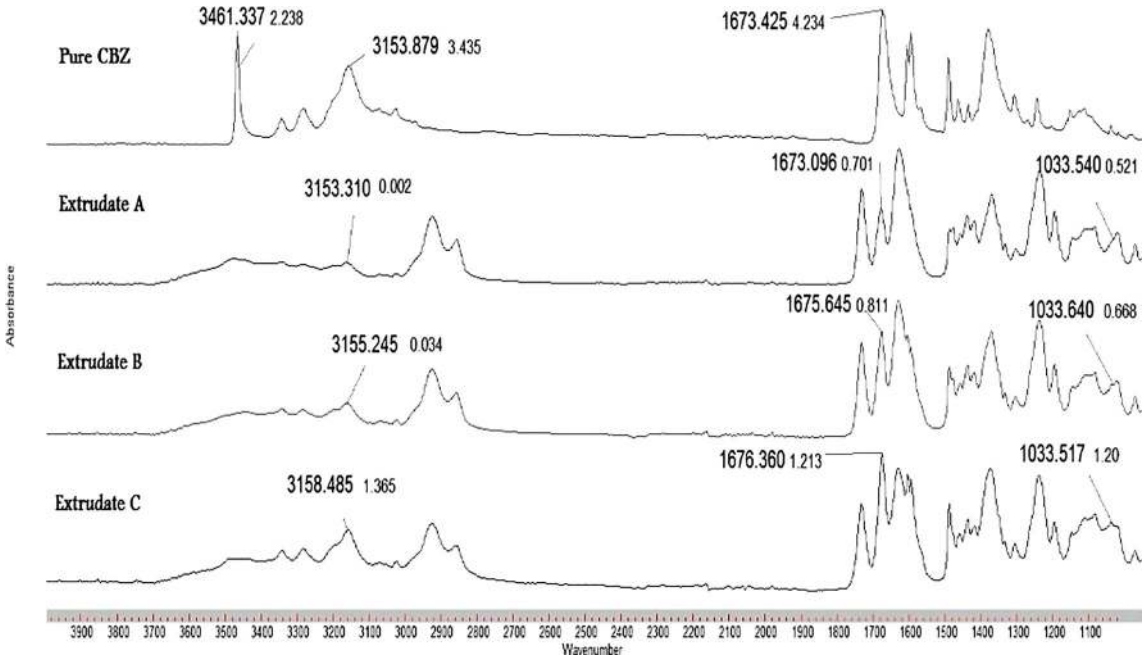

Fig. 8. FTIR spectra of pure CBZ, fresh extrudates for formulations **a** 30:70 CBZ:Soluplus®, **b** 30:7:63 CBZ:HPMCAS-HF:Soluplus®, and **c** 30:21:49 CBZ:HPMCAS-HF:Soluplus®

Stability Study

The chemical and thermal stability of CBZ post extrusion were investigated. According to preliminary screening studies, it was found that HPMCAS-HF can be extruded with Soluplus® up to 30% without any dissolution rate hindrance. Therefore, lead formulations were chosen based on the extrudability and the *in vitro* dissolution results (Table II).

Formulation A (no HPMCAS-HF added) demonstrated retarded drug release profiles with an increase in storage time from day 1 to months 3, 6, and 12 (Fig. 9a). This decrease was due to recrystallization of CBZ during storage, which was confirmed by XRD and FTIR analysis. As shown by the XRD results (Fig. 10a), the characteristic peaks of crystal CBZ had begun to reappear at months 3, 6, and 12. After storage for 12 months (at 40°C/75% RH), formulation A showed the same crystal peaks of CBZ at 3461 cm^{-1} as shown in FTIR results. These results are in agreement with previous literature reports (23). It indicates that only Soluplus® cannot keep amorphous CBZ physically stable in higher drug loading for the duration of the stability studies.

However, for both formulations B and C, as shown in Fig. 9b, c, comparable release profiles were observed over storage times of 0, 3, 6, and 12 months. This clearly indicates that these blends were able to enhance CBZ release without remarkable changes even after the long-term storage of 12 months. The similarity factor values (f_2) for release profiles between fresh and 12 months extrudates were 78.8 and 75.3 for formulations B

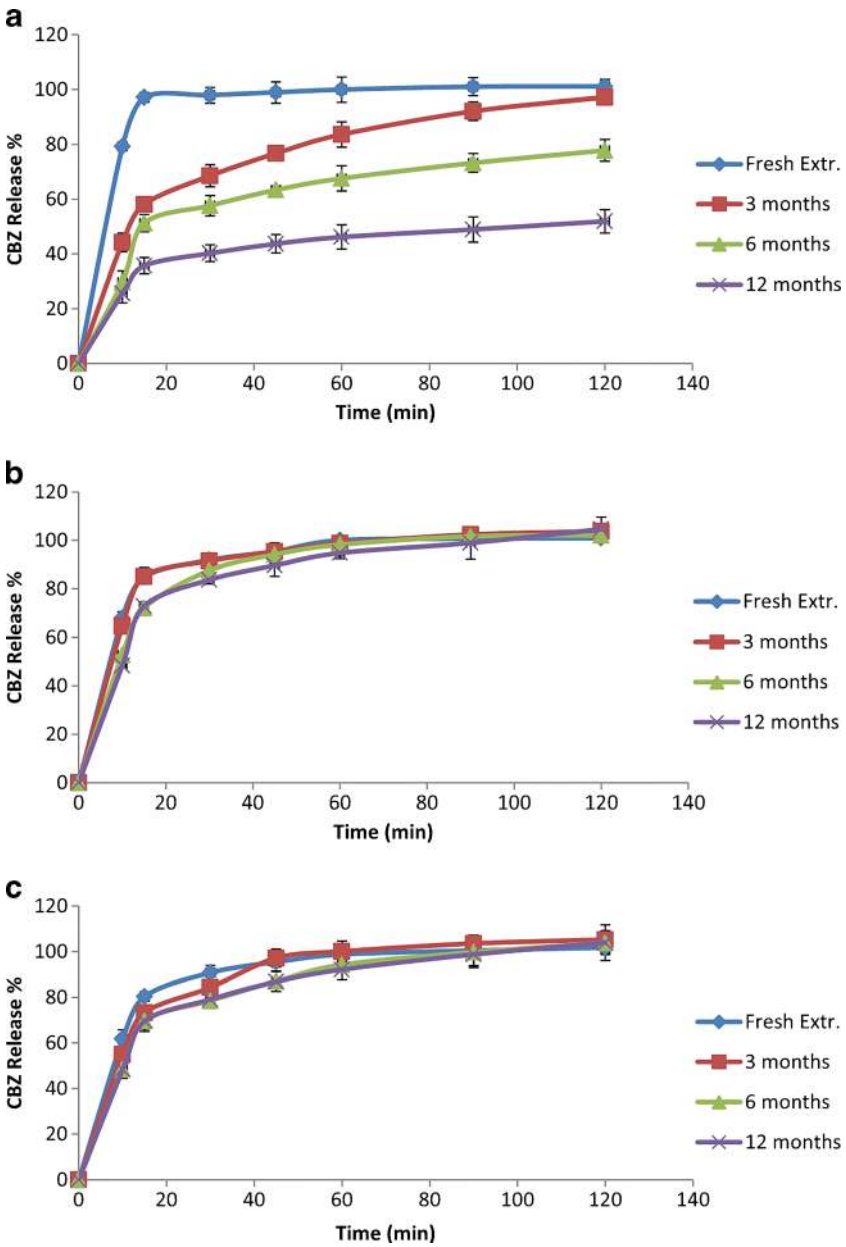

Fig. 9. *In vitro* release profiles of extrudates stored at 40°C/75% RH. **a** Formulation A (30:70 CBZ:Soluplus®). **b** Formulation B (30:7:63 CBZ:HPMCAS-HF:Soluplus®). and **c** Formulation C (30:21:49 CBZ:HPMCAS-HF:Soluplus®) extrudates stored at 40°C/75% RH

and C, respectively, which are considered very similar release profiles according to the FDA guidelines. XRD data confirmed that both formulations B and C did not show any sign of recrystallization or morphology change after a storage time of 12 months (Fig. 10b, c). Likewise, FTIR data indicated the presence of the amorphous form of CBZ after storage for formulations B and C.

According to these studies, it was determined that adding HPMCAS-HF in Soluplus®-based solid dispersions were able to physically stabilize the amorphous form of high-loading CBZ in the extrudates. This stabilization was due to the high Tg and low hygroscopic nature of HPMCAS-HF. Low hygroscopicity will prevent moisture uptake, which is a significant factor for recrystallization. Specific grades of HPMCAS are determined by the ratio between acetyl and succinoyl groups (24). In this study, we used HPMCAS-HF that has the lowest level of succinoyl groups and the highest acetyl substituent level compared with other HPMCAS grades. It was reported that succinoyl substituent level in HPMCAS polymers induce strong affinity with the hydrophobic drug surface, leading to crystal growth inhibition of the API (25). This low level of succinoyl groups in HPMCAS-HF decreased the recrystallization of CBZ by increasing the hydrophobic interaction with CBZ, which will reduce the moisture uptake and subsequently inhibit the recrystallization (26). Moreover, the high glass transition temperature of HPMCAS-HF as well as the hydrophobic nature will suppress the crystallization growth of CBZ by inhibiting the molecular mobility within the solid dispersion. Furthermore, FTIR data suggested that adding HPMCAS-HF increased the intensity of hydrogen bonding formation with CBZ. This H-bond formation may physically stabilize CBZ by inhibiting the mobilization of CBZ within the solid dispersion. On the contrary, Soluplus® alone (formulation A) was not able to maintain the dissolution enhancement or the amorphous morphology of high-loaded CBZ. HPMCAS-HF did not alter the solubility enhancement if used

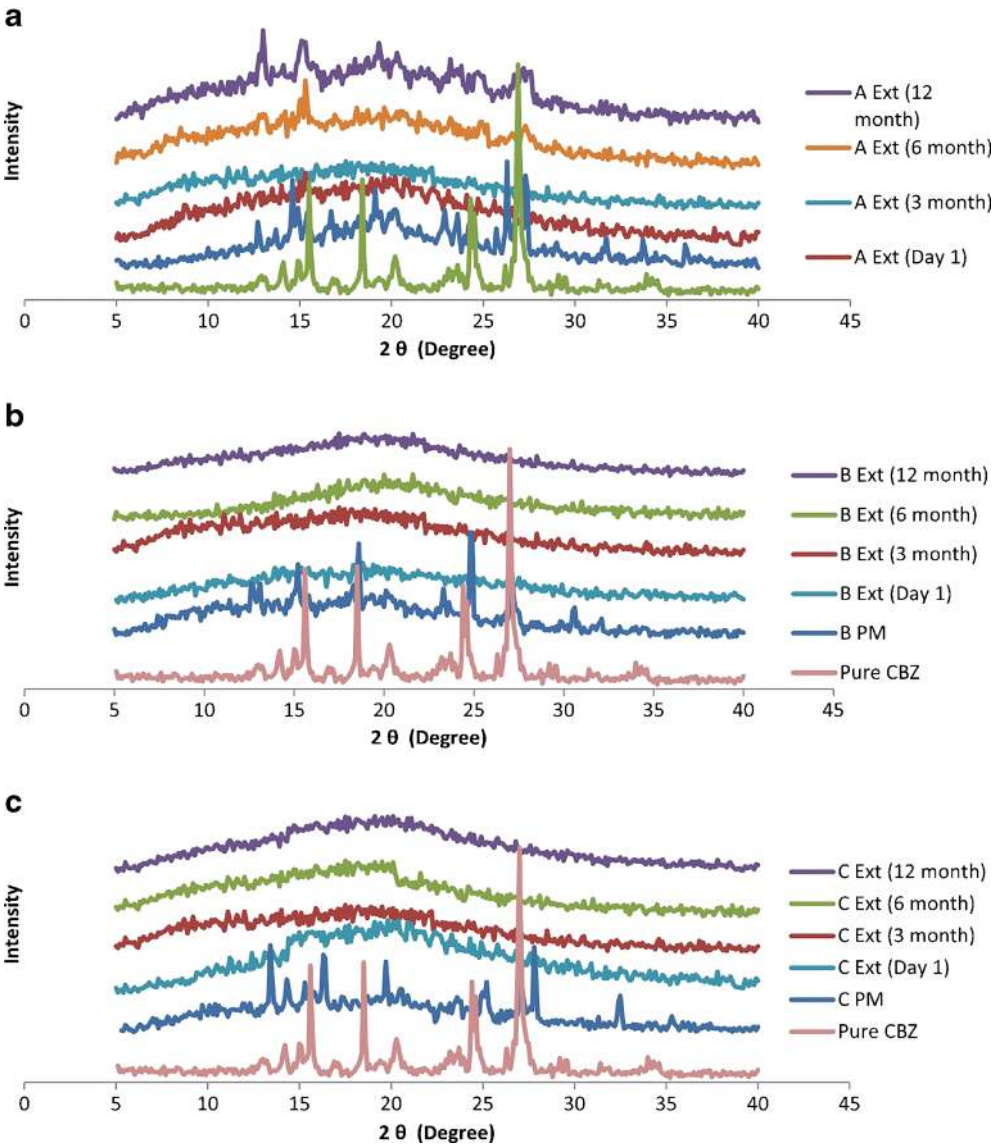

Fig. 10. XRD data for physical mixtures, fresh extrudates, and extrudates after 3, 6, and 12 months storage at 40°C/75%. **a** Formulation A (30:70 CBZ:Soluplus®). **b** Formulation B (30:7:63 CBZ:HPMCAS-HF:Soluplus®). **c** Formulation C (30:21:49 CBZ:HPMCAS-HF:Soluplus®)

in low percentages between 7 and 21%. This ratio demonstrated a promising blend to be used with HME to enhance the solubility and stability of CBZ.

CONCLUSIONS

This work investigated a new combination of polymers that can be used as a simple and effective carrier for hot-melt extrusion processes to enhance solubility and inhibit recrystallization for up to 12 months at accelerated storage. Soluplus® was able to enhance the dissolution rate of CBZ and, adding HPMCAS-HF, increased the stability due to its high Tg and low hygroscopic nature. Soluplus® extrudability enhanced the processing ability of this system and potentially other blended matrices as well. This work showed the effect of multiple factors such as polymer selection, different polymers ratios, and drug loading on drug solubility and stability. These findings emphasize the importance of selecting an appropriate blend of carriers in order to obtain a desired stable formulation with an enhanced release profile. Soluplus® as the primary matrix polymer with HPMCAS-HF, processed by HME, demonstrates a potentially promising carrier to produce physically stable formulations with solubility enhancement and no changes in physical and chemical status after 12-month storage at 40°C/75% RH.

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