ORIGINAL ARTICLE

Solubility and dissolution enhancement of HPMC - based solid dispersions of carbamazepine by hot-melt extrusion technique

Sharadchandra Dagadu Javeer, Purnima Dhanraj Amin

Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Matunga, Mumbai, Maharashtra, India

The objective of this study was to investigate solid dispersions (SDs) of poorly water soluble drug carbamazepine (CBZ), prepared using low viscosity grade hydroxypropyl methyl cellulose (HPMC) (Methocel® E3 LV and Methocel® E5 LV) by hot-melt extrusion (HME) technology. Saturation solubility and dissolution profile of CBZ was studied. Characterization of hot-melt extruded samples was done by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and X-ray diffraction studies (XRD). The result of the study showed the conversion of crystalline form of drug into amorphous form indicating increase in saturation solubility and dissolution rate of CBZ.

Key words: *Carbamazepine, hot-melt extrusion, hydroxypropyl methyl cellulose*

INTRODUCTION

Carbamazepine (CBZ) is an effective antiepileptic drug that is characterized by a slow and irregular absorption into the systemic circulation.[1] According to the biopharmaceutical classification system (BCS), CBZ belongs to class II having poor solubility and high permeability. This tends to present solubility and dissolution rate-limited absorption. Despite having high permeability, it has low oral bioavailability because of its slow and limited release in the gastrointestinal fluid.[2] Due to poor solubility, low bioavailability, narrow therapeutic index, and relatively high plasma concentration variability, CBZ was selected as a drug candidate for this study.

Solid dispersion (SD) is defined as the dispersion of one or more active ingredients in an inert carrier or matrix at solid state, prepared by the melting, solvent, or melting-solvent method.[3] When SD is exposed to aqueous media and the carrier is dissolved, the drug is released in the form of very fine colloidal particles. Because of the enhanced surface area, the dissolution rate and bioavailability of poorly water soluble drugs is greatly enhanced.[4] Solid solution is different from SD in that the former is a single phase system, whereas SD is a binary or multiphase system. Because of such an advantage in the bioavailability enhancement of poorly water soluble drugs, SD/solution is one of the most prominent areas of research in the pharmaceutical field.

Hot-melt extrusion (HME) is a process applied for preparation of SD or solution. The process of HME is divided in to four sections, feeding of the drug and polymer mixture, conveying and heating of mass, flow through the die, exit from the die, and downstream processing.[5] The drug and polymer mix is processed using single or double screw extruder. The mix is simultaneously melted, homogenized, and then extruded. The extruded material can be further processed into a variety of dosage form such as pellets, capsules, tablets, granules, sheets, sticks, or powder.[6] Compared with other pharmaceutical production processes, HME has the benefit of being a solvent and a dust-free, environment friendly, cost-efficient, and continuous process.[7-9] Such benefits have led to an increased interest of HME technology in recent years.

Solubility enhancement of CBZ by HME using different polymers such as polyethylene glycol-polyvinyl

Address for correspondence:
Mr. Sharadchandra Dagadu Javeer,
Department of Pharmaceutical Sciences and Technology,
Institute of Chemical Technology, N. P. Marg, Matunga (E),
Mumbai - 400 019, Maharashtra, India.
E-mail: Sharad_uict@yahoo.com

Access this article online

Quick Response Code:

Website: www.asiapharmaceutics.info

DOI: 10.4103/0973-8398.134950

caprolactam-polyvinyl acetate-grafted copolymer[10] and polyvinylpyrrolidone/vinyl acetate copolymers[11] is reported in the literature. Solubility enhancement of CBZ using low viscosity grade hydroxypropyl methyl cellulose (HPMC) polymer by HME technique has not been reported. HPMC or hypromellose is an odorless and tasteless, white or creamy-white, and fibrous or granular powder. It is partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in various grades that vary in viscosity and extent of substitution. It is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations. In oral products, HPMC is primarily used as a tablet binder, in film coating, and as a matrix for use in extended release tablet formulations. HPMC is also used as a suspending and thickening agent in topical formulations and as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.[12]

In the present study, CBZ SD was prepared by HME technology using low viscosity grades of HPMC (Methocel® E3 LV and Methocel® E5 LV).

MATERIALS AND METHODS

Materials

CBZ was a kind gift by Bajaj Healthcare Pvt. Ltd., India. Methocel® E3 LV and Methocel® E5 LV were gifted by Dow Chemical Company. All other chemicals and solvents used were of analytical grade and were procured from Merck India Ltd. Purified water was used throughout the study.

Preparation of SD by HME

CBZ and HPMC (Methocel® E3 LV or Methocel® E5 LV) were passed through #60 sieve and mixed in a blender with propylene glycol (PG) as a plasticizer. This mixture was then fed into a single-screw hot-melt extruder (fabricated by S.B. Panchal and Co., India) equipped with a 0.8 mm die. The prepared blend was then processed using hot-melt extruder at a temperature of 78-80°C. The extrudates were collected and powdered. The powdered extrudes were passed through #40 and filled in the capsule. The SDs were prepared by varying drug loading from 10-50% and are listed in Table 1. The SDs were then subjected to solubility and dissolution study.

Phase solubility studies

Phase solubility studies were performed according to the method reported by Higuchi and Connors.[13] An excess amount of CBZ was placed in aqueous solutions containing 10, 20, 30, 40 and 50% w/v concentrations of Methocel E3 and Methocel E5 in glass test tubes. These test tubes were covered with cellophane membrane to avoid solvent loss and then shaken for 48 h at 37°C in orbital shaking incubator (Boekel Scientific, Germany). After 48 h, the samples were removed and kept for centrifugation for 20 min at 10,000 rpm. A total of 5 ml of supernatant was withdrawn and filtered through Whatman filter paper (grade 1). The filtrates were then analyzed using ultraviolet (UV) visible spectrophotometer at 284 nm after suitable dilutions. All solubility determinations were performed in triplicate.

Table 1: SDs containing CBZ prepared by HME[a]

Component	SDs									
	1	2	3	4	5	6	7	8	9	10
CBZ	10	20	30	40	50	10	20	30	40	50
Methocel® E3 LV	83	73	63	53	43	-	-	-	-	-
Methocel® E5 LV	-	-	-	-	-	83	73	63	53	43
PG	7	7	7	7	7	7	7	7	7	7

[a]All quantities are in percentage (w/w). HME: Hot-melt extrusion, SD: Solid dispersion, PG: Propylene glycol, CBZ: Carbamazepine

Saturation solubility studies

Solubility studies were carried out in triplicate. Excess quantities of drug and SDs were added to the 10 ml of distilled water with and without 1% sodium lauryl sulfate (SLS). The samples were sonicated for 20 min at room temperature and capped glass test tubes were shaken at 37 ± 0.5°C for 48 h using thermostable bath (Boekel Scientific, Germany). The solutions in the test tubes were vortexed and kept for centrifugation at 5000 rpm for 20 min. The supernatant layer was then filtered through 0.45 μm millipore membrane filter and the amount of drug dissolved was analyzed using UV-spectrophotometer (UV-1601PC, Shimadzu, Japan) at 287 and 284 nm for samples in distilled water with and without SLS as a dissolution medium, respectively.

In vitro dissolution studies

In vitro dissolution studies were carried out in USP type 2 dissolution apparatus (Electrolab) for 1 h in 900 ml of distilled water with and without 1% SLS at 75 rpm.[14] The temperature was maintained at 37 ± 0.5°C. The aliquots were taken at 15, 30, 45, and 60 min interval. Samples were analyzed using UV-spectrophotometer at 287 and 284 nm for samples in distilled water with and without SLS as a dissolution medium, respectively. SDs equivalent to 200 mg of CBZ were taken. CBZ neat drug (200 mg) was also subjected to the same dissolution study.

Statistical analysis

The statistical analysis was performed for estimation of significant differences among neat CBZ and SDs with respect to their solubility and dissolution profile. The data were treated by *t* test and one-way analysis of variance (ANOVA) test (GraphPad Prism® software version 6.01), and the result with $P < 0.05$ was considered significant.

Fourier transform infrared spectroscopy

FTIR analysis was carried out to investigate possible interaction between drug and excipients in the formulation. FTIR spectra were recorded for neat CBZ, excipients, and SDs using a Perkin Elmer FTIR spectrophotometer (Spectrum RX1, USA). Samples were mixed with potassium bromide KBr using mortar and pestle. KBr disk was prepared by means of a hydrostatic press Model HP-15. The samples were scanned

in the range from 500 to 4000 cm^{-1} and the resolution was 4 cm^{-1}.

Differential scanning calorimetry

DSC analysis was performed to check the physical state of SD with respect to neat drug using Perkin Elmer DSC Pyris-6 (USA) on 4-8 mg sample. Samples were heated in the aluminium pan at the rate of 10°C/min in 50-240°C temperature range under nitrogen flow of 20 ml/min using an empty sealed pan as a reference. The obtained spectra were then studied for the interaction between drug and the excipients in the SD.

Powder X-ray diffraction analysis

SDs were further characterized by PXRD to study the amorphous or crystalline nature of CBZ and SDs. PXRD patterns were recorded on a Bruker AXS D8 advance powder diffractometer (Germany) using Ni filter, a voltage of 40 kV and a 40-mA current using Cu Kα radiation (λ = 1.5406 Å) and a step size of 0.0388. The scanning rate used was 1° min^{-1} over the 5-60° diffraction angle (2θ) range. Structure of CBZ is shown in Figure 1.

RESULTS AND DISCUSSION

Phase solubility studies

Phase solubility studies of CBZ in aqueous solutions containing 5, 10, 15, 20, and 25% of Methocel® E3 and Methocel® E5 showed enhanced solubility of drug with increased polymer concentration. The difference in solubility enhancement of drug due to Methocel® E3 and Methocel® E5 was not found significant. Figure 2 shows phase solubility studies of CBZ in aqueous media.

Saturation solubility studies

Saturation solubility of neat CBZ was found to be 25.08 µg/ml in distilled water and 1437.58 µg/ml in distilled water with 1% SLS. Saturation solubility studies of SDs prepared by HME showed increase in the drug solubility with increase in the carrier polymer. The solubility of CBZ was found to be higher in SDs with higher concentration of HPMC polymer. The solubility of drug was more in SDs containing 10 and 20% drug loading. As the drug concentration is increased, with decrease in polymer concentration, the solubility of drug was also found to be decreased. This clearly emphasizes the role of polymer for solubility enhancement of drug.

The solubility of SDs was less in distilled water alone as compared with in presence of 1% SLS. The difference in the solubility enhancement of drug by using Methocel® E3 and Methocel® E5 was not significant. The increase in solubility of drug was due to the formation of SD that converted drug from crystalline state to amorphous state. The hydrophilic polymer improved the wettability of the drug by decreasing surface tension. The 10 and 20% drug loading was found to be optimum for solubility enhancement of drug.

The solubility of neat drug and SDs was higher in distilled water with 1% SLS as dissolution medium as compared with only distilled water. This was due to the solubilizing effect of SLS, which act as a surfactant. A surfactant or surface-active agent is a substance that, when present at low concentration in a system, has the property of adsorbing onto the surfaces or interfaces of the system and of altering to a marked degree the surface or interfacial free energies of those surfaces.[15] This leads to the enhanced solubility of the solute in the medium. The saturation solubility of drug alone and drug in different SDs in distilled water with and without SLS is given in Table 2.

In vitro dissolution studies

Dissolution study of SDs prepared by HME was carried out by using distilled water with and without SLS as a dissolution medium. All the readings were taken in triplicate. *In vitro* drug release study of neat drug showed only 32.14% drug release in distilled water after 60 min. Whereas SDs prepared using

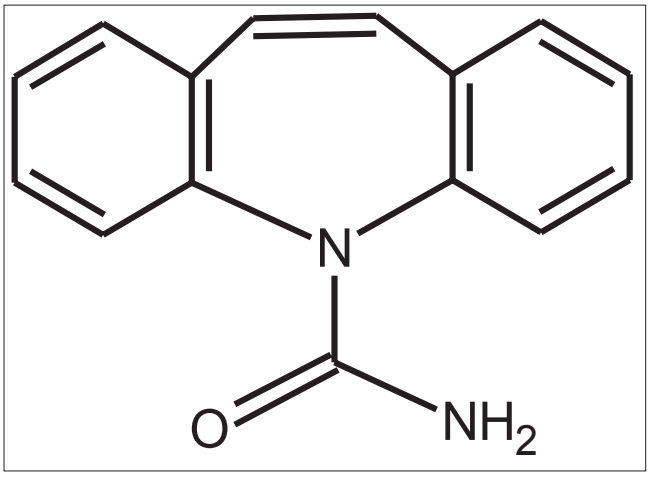

Figure 1: IUPAC name: 5H - dibenzo [b,f] azepine -5- carboxamide. Structure of CBZ. IUPAC = International Union of Pure and Applied Chemistry, CBZ = Carbamazepine

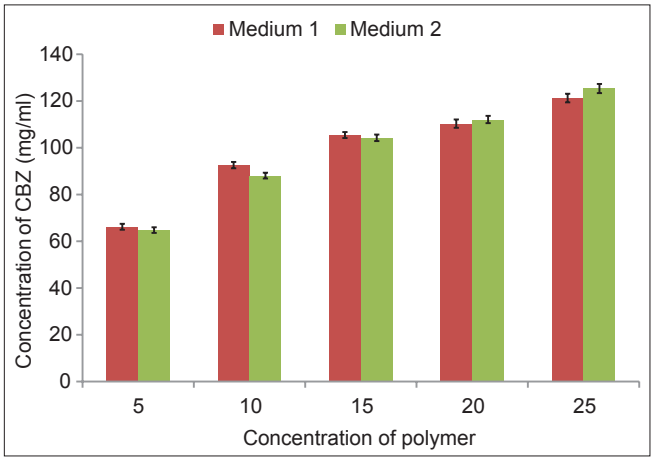

Figure 2: Medium 1: Distilled water containing Methocel® E3. Medium 2: Distilled water containing Methocel® E5. Phase solubility studies of CBZ in aqueous media. CBZ = Carbamazepine

Methocel® E3 showed improved dissolution profile by HME technology. SD1 showed maximum dissolution of drug up to 66.68%. The dissolution of drug was slightly decreased with decrease in the polymer concentration. SDs prepared using Methocel® E5 also showed increased dissolution profile up to 64.53%, with slightly decreased dissolution thereafter. This improved dissolution is attributed toward the formation of SD by the process of HME. HPMC, used as a polymer in the formulation of SDs, contains a number of methoxyl and hydroxy propyl groups. These groups are responsible for hydrogen bond formation between drug and polymer. This resulted in the enhanced solubility and dissolution of the drug. The release of neat drug in a dissolution medium containing distilled water with 1% SLS was found to be more as compared with release of neat drug in distilled water alone. This was due to the solubilizing effect of SLS. The release of neat drug was found to be 61.37% and that of SD1 was found to be 100.24%. Release of drug from SD6, which contains Methocel E5, was also found to be more than neat drug, i.e., up to 98.07%. Here, dissolution of drug is not only improved by the formation of SD but also by the action of SLS. The dissolution behavior of SDs prepared using HME was found to exhibit superior dissolution profile as compared with neat drug, as the ANOVA test showed $P < 0.05$. The dissolution of neat drug and various formulations is given in Table 3.

Table 2: Saturation solubility of drug in different SDs

SDs	HME (µg/ml)	
	Medium 1	Medium 2
Neat drug	25.08±1.2	1437.58±1.7
SD1	591.87±1.0	2497.21±1.8
SD2	587.39±1.1	2527.22±2.1
SD3	573.74±1.5	2666.66±1.9
SD4	500.32±1.4	2480.74±2.0
SD5	473.03±1.6	1966.13±1.8
SD6	556.20±1.3	2231.70±1.5
SD7	587.39±1.3	2379.15±1.8
SD8	521.11±1.0	2458.16±1.6
SD9	559.45±1.2	2279.54±2.0
SD10	474.98±1.6	2160.15±1.9

Medium 1: Distilled water. Medium 2: Distilled water with 1% SLS. SD: Solid dispersion, HME: Hot-melt extrusion, SLS: Sodium lauryl sulphate

Table 3: Dissolution of neat drug and various formulations after 60 min in different dissolution media

SDs	Percent cumulative drug release HME	
	Medium 1	Medium 2
Neat drug	32.14±1.1	61.37±1.5
SD1	66.68±1.2	100.24±1.1
SD2	65.10±1.0	98.40±1.7
SD3	63.99±2.1	97.92±1.6
SD4	65.13±1.4	97.56±1.5
SD5	64.15±2.0	98.23±2.0
SD6	64.53±1.6	98.07±1.3
SD7	63.11±1.1	97.86±1.7
SD8	62.37±1.4	88.80±1.4
SD9	60.85±1.7	90.48±2.2
SD10	62.27±2.1	89.65±1.6

Medium 1: Distilled water. Medium 2: Distilled water with 1% SLS. SD: Solid dispersion, HME: Hot-melt extrusion, SLS: Sodium lauryl sulfate

Solid state characterization

The extrudates of Methocel® E3 and Methocel® E5 looked whitish, translucent, and regular. The extrudates obtained from 50% drug loading were whitish, translucent, and rigid. They can be easily milled. As the polymer content was increased, the extrudates become more flexible and difficult to mill. With increasing extrusion temperature, the color turned yellowish and brownish.

Fourier transform infrared spectroscopy

Infrared spectroscopy has been widely used to study the interaction between drug and polymer. In order to evaluate any possible chemical interactions between the drug and carriers, FTIR spectra of CBZ, HPMC, PG, and SDs were examined as shown in Figure 3 and Figure 4. FTIR spectra were recorded in 400 - 4000 cm^{-1} range. The characteristic absorption peaks of CBZ were found at 3467 and 3152 cm^{-1} for (-N-H stretch), 1675 cm^{-1} (C = O stretch), and 760 cm^{-1} polymorph-specific features.[16] Absorption peaks of CBZ indicated characteristics of form III polymorph (*P* - monoclinic) of CBZ.[5] This form of CBZ is suitable for drug formulation because of its thermodynamic stability at ambient temperature and highest bioavailability among all polymorphs. HPMC presented characteristic peak at 3428.57 cm^{-1} (O-H stretching vibration) and peak at 2935.57 cm^{-1} was due to the C-H stretching vibration.

The stretching vibration of all the mentioned functional groups were found to be within range in all the SDs indicating absence of any significant chemical interaction in solid state.

DSC analysis

The DSC thermogram of CBZ showed a single sharp melting endothermic peak at 193.43°C indicating crystalline nature of the drug. The hot-melt extrudates showed no distinct melting endotherm for the drug. The formation of amorphous SD is attributed to the molecular interaction between drug and polymer. This indicated that the drug exists in the amorphous state in the hot-melt extruded powder. The disappearance of the sharp melting endotherm in the DSC scan of hot-melt extruded powder suggested that the drug has been converted to the amorphous form during the extrusion process [Figure 5].

XRD analysis

The X-ray diffractograms of CBZ showed sharp multiple peaks, indicating the crystalline nature of the drug. Neat CBZ showed characteristic XRD pattern with sharp peak at diffraction angle (2θ) value of 10.22°, 13.15°, 15.375°, 19.58°, 25.05°, 27.63°, 29.91°, 23.97°, and 15.94°, indicating crystalline nature of CBZ as shown in

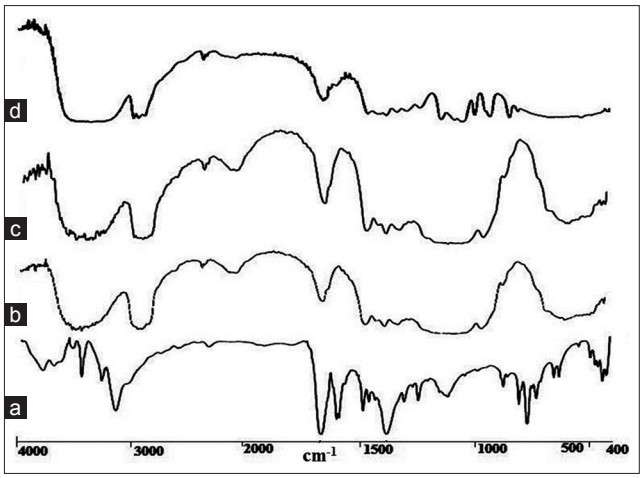

Figure 3: FTIR spectra of (a) neat CBZ, (b) Methocel® E3, (c) Methocel® E5, and (d) PG. FTIR = Fourier transform infrared spectroscopy, CBZ = Carbamazepine, PG = Propylene glycol

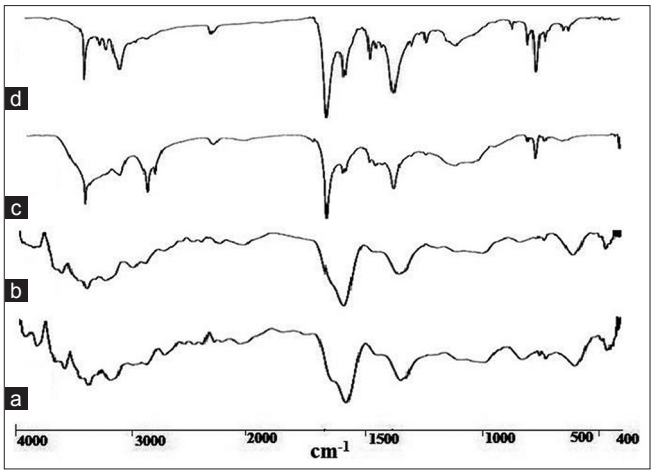

Figure 4: FTIR spectra of (a) SD 1, (b) SD 5, (c) SD 6, and (d) SD 10. FTIR = Fourier transform infrared spectroscopy, SD = Solid dispersion

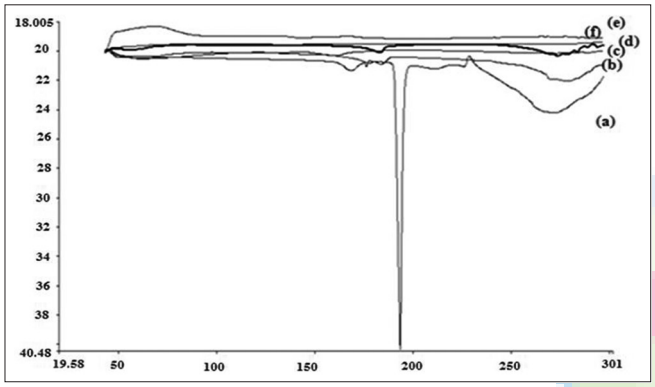

Figure 5: DSC thermogram of (a) neat drug, (b) SD 1, (c) SD 5, (d) SD 6, (e) SD 9 and (f) SD 10. DSC = Differential scanning calorimetry, SD = Solid dispersion

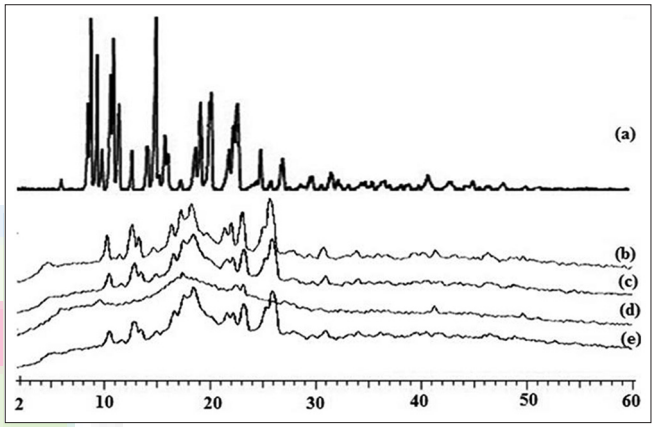

Figure 6: X-ray diffractograms of (a) neat CBZ, (b) SD1, (c) SD5, (d) SD 6, and (e) SD 10. SD = Solid dispersion, CBZ = Carbamazepine

Figure 6. These characteristic peaks are indicative for form III (*P* - monoclinic) of CBZ.[17] In the case of melt-extruded dispersion, the characteristic peaks of CBZ were diminished in large, leading to amorphization of the crystalline drug. The amorphous system contains more free energy that serves as a driving potential for solubility enhancement; therefore the solubility of these systems is more as compared with their crystalline counterpart.[18]

CONCLUSION

From the above study, it was found that solubility and dissolution rate of CBZ can be enhanced by SDs containing Methocel® E3 and Methocel® E5 prepared by using HME. The crystalline drug was converted into the amorphous form through formation of SD by HME technique. HPMC increased wettability and dispersibility of the drug leading to alteration of its surface properties. ANOVA test showed $P < 0.05$, indicating that dissolution behavior of SDs prepared using HME was showing superior dissolution profile as compared with neat drug.

ACKNOWLEDGEMENTS

Authors gratefully acknowledge the financial support provided by the University Grant Commission (UGC, Government of India).

REFERENCES

1. Naima Z, Siro T, Juan-Manuel GD, Chantal C, René C, Jerome D. Interactions between carbamazepine and polyethylene glycol (PEG) 6000: Characteristics of physical, solid dispersed and eutectic mixtures. Eur J Pharm Sci 2001;12:395-404.
2. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today 2007;12:1068-75.
3. Craig DQ. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int J Pharm 2002;231:131-44.
4. Serajuddin AT. Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent break-throughs. J Pharm Sci 1999;88:1058-66.
5. Breitenbach J. Melt extrusion: From process to drug delivery technology. Eur J Pharm Biopharm 2000;54:107-17.
6. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 2000;50:47-60.
7. Klein CE, Chiu YL, Awni W, Zhu T, Heuser RS, Doan T, *et al*. The tablet formulation of lopinavir/ritonavir provides similar bioavailability to the

soft-gelatin capsule formulation with less pharmacokinetic variability and diminished food effect. J Acquir Immune Defic Syndr 2007;44:401-10.
8. Miller DA, McConville JT, Yang W, Williams RO 3rd, McGinity JW. Hot-melt extrusion for enhanced delivery of drug particles. J Pharm Sci 2007;96:361-76.
9. Radl S, Tritthart T, Khinast JG. A novel design for hot-melt extrusion pelletizers. Chem Eng Sci 2010;65:1976-88.
10. Hardung H, Djuric D, Ali S. Combining HME and solubilization: Soluplus - the solid solution. Drug Deliv Technol 2010;10:20-7.
11. Patterson JE, James MB, Forster AH, Rades T. Melt extrusion and spray drying of carbamazepine and dipyridamole with polyvinylpyrrolidone/vinyl acetate copolymers. Drug Dev Ind Pharm 2008;34:95-106.
12. Rowe RC, Sheskey PJ, Quinn ME. Handbook of pharmaceutical excipients, 6th ed. London: Pharmaceutical Press; 2009. p. 326-9.
13. Higuchi T, Connors KA. Phase-solubility techniques. Adv Anal Chem Instrum 1965;4:117-212.
14. United States Pharmacopeia National Formulary, USP30/NF 25. Dissolution Carbamazepine tablets. Rockville MD: United States Pharmacopeial Convention, Inc.; 2007. p. 1616.
15. Rosen MJ. Surfactants and interfacial phenomena. 3rd ed. New Jersy: Wiley Interscience Publication; 2004. p. 1-2.
16. Kipouros K, Kachrimanis K, Nikolakakis I, Tserki V, Malamataris S. Simultaneous quantification of carbamazepine crystal forms in ternary mixtures (I, III and IV) by diffuse reflectance spectroscopy (DRIFTS) and multivariate calibration. J Pharm Sci 2006;95:2419-31.
17. Grzesiak AL, Lang M, Kim K, Matzges AJ. Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I. J Pharm Sci 2003;92:2260-71.
18. Corrigan OI, Holohan EM. Amorphous spray-dried hydroflumethiazide-polyvinylpyrrolidone systems: Physicochemical properties. J Pharm Pharmacol 1984;36:217-21.

How to cite this article: Javeer SD, Amin PD. Solubility and dissolution enhancement of HPMC – based solid dispersions of carbamazepine by hot-melt extrusion technique. Asian J Pharm 2014;8:119-24.

Source of Support: Financial support provided by the University Grant Commission (UGC, Government of India). **Conflict of Interest:** None declared.