RESEARCH ARTICLE

Effect of HPMC on solubility and dissolution of carbamazepine form III in simulated gastrointestinal fluids

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The effect of HPMC on solubility and dissolution of carbamazepine form III (CBZ) was investigated in 50% w/w of CBZ form III in HPMC solid dispersion and physical mixture. Powdered samples of CBZ form III, physical mixture, and solid dispersion were characterized for thermal behavior (DSC), crystallinity (PXRD), and compatibility (FT-IR). Solubility and dissolution studies were carried out in different simulated gastrointestinal fluids and de-ionized water. Solubility studies in simulated gastric fluid (SGF) revealed that acidic pH favors formation of CBZ dihydrate. Triton X 100 in blank fast-state simulated gastric fluid (FaSSGF) prevents the formation of CBZ dihydrate in acidic pH. A maximum solubility of 268.77 µg/mL was achieved with fed-state simulated intestinal fluid (FeSSIF). Correlation between solubility and pH could not be established. Both solubility and dissolution studies revealed that HPMC had a profound effect of enhancement of solubility and dissolution of CBZ form III in both physical mixtures and solid dispersions. HPMC prevents the formation of CBZ dihydrate and thereby improves the solubility and dissolution. This was further correlated with results obtained from DSC and XRD. There was no drastic difference in solubility and dissolution of CBZ form III with different media. It was observed that there was no existing relationship between solubility and dissolution of CBZ form III in different media.

Key words: *Bio-relevant media, CBZ form III, dissolution, HPMC, solubility*

INTRODUCTION

Carbamazepine (CBZ), a best-selling antiepileptic drug, is used in the treatment of epilepsy, trigeminal neuralgia, and bipolar disorders. CBZ, being a low-solubility drug with high permeability, is classified as Class II drug in Biopharmaceutical Classification System (BCS) adopted by USFDA.[1] The conventional CBZ tablets yield peak plasma concentration varying from 4 to 32 h. This irregular and delayed absorption of CBZ is attributed to slow dissolution rate.[2] Dissolution enhancement of CBZ can result in an increase in the rate and extent of absorption and hence bioavailability. Several attempts using water-soluble carriers have been made to prepare different formulations of CBZ solid dosage forms with improved dissolution properties.[3-6] Earlier research states that HPMC improves the rate and extent of poorly soluble drugs, particularly CBZ.[7,8] The reason for dissolution enhancement of HPMC-based formulations may be due to the fact that reduction in crystallinity inhibits the formation of CBZ dihydrate[9] and surface-active property.[10] However, the *in vivo* behavior of HPMC-based formulations is very important for the desired clinical response. Moreover, CBZ is not waived from bio-studies for NDA and ANDA submissions in the United States. Optimization of bio-relevant dissolution media not only gives a clue to the formulation scientist to design the formulations but it is also useful for regulatory approval without bio-studies. The present investigation is aimed to explore the effect of HPMC on solubility and dissolution rate of CBZ in different simulated gastrointestinal fluids, so that it will give the clue to design and develop the bio-relevant media. Blank fast-state simulated gastric fluid (FaSSGF), simulated gastric fluid without pepsin (SGF), blank fast-state simulated intestinal fluid (FaSSIF), fed-state simulated intestinal fluid (FeSSIF), and simulated colonic fluid (SCoF) are the different bio-relevant media selected to investigate the effect of HPMC on solubility and dissolution behavior of CBZ.

CBZ has four different polymorphs (I, II, III, and IV) and a dihydrate form. The solubility of dihydrate of CBZ is one third of the solubility of its anhydrous form. CBZ exhibits enantiotropic polymorphism (I and III), i.e., there exists a transition temperature below the melting point of either of the polymorphs at which both these forms have the same free energy.[11] Above the transition temperature, the higher-melting form I has lower free energy and is more stable. Below the transition temperature, however, the lower-melting

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form III is more stable since it has lower free energy. Hence at room temperature, form III is the most stable form and is the one possessed by most commercially available CBZ. CBZ form III is approved by many regulatory agencies and hence it was selected for investigation. To explore the effect of HPMC on solubility and dissolution in both physical mixture and solid dispersion, 50% w/w of CBZ physical mixture and solid dispersion in HPMC was investigated. CBZ, being a high-dose (200 mg) drug with low solubility, more than 50% w/w of HPMC may cause difficulties in formulation development.

MATERIALS AND METHODS

Carbamazepine crystal was gifted by Sun Pharmaceutical Advanced Research Centre (SPARC), Baroda. Hydroxypropyl methylcellulose E_5 (low-viscosity grade) and dichloromethane were purchased from Loba Chemie, Mumbai, India. All other chemicals used were of HPLC grade or analytical grade.

Preparation of CBZ form III, solid dispersions and physical mixtures

Most of the commercially available CBZ samples are Form III crystals, but sometimes it may contain forms I and II. In order to obtain pure CBZ form III, carbamazepine crystals were re-crystallized with ethanol. Solid dispersions (SDs) were prepared by gel-entrapment technique. HPMC, 2.5 g, was dissolved in 50 mL of dichloromethane (DCM) to form a clear and transparent gel, and 2.5 g of CBZ form III was dissolved in gel by sonication for a period of 2 min at 10°C in a RB flask sealed with rubber cork. DCM was evaporated under vacuum at 30°C for a period of 12 h. Solid dispersions were reduced in size by glass mortar and sieved through a sieve number 180 and stored in desiccators under silica pouches. Specified quantities of CBZ form III (2 g) and polymer (2 g) were mixed in poly bags for 15 min and sieved in sieve number 180. Prepared physical mixtures were stored in airtight containers in desiccators over the silica pouches.

Preparation of simulated gastrointestinal fluids

Simulated gastrointestinal fluids are widely used as bio-relevant dissolution media to understand the dissolution behavior of drug in an *in vivo* environment. Four different bio-relevant media were prepared and used to understand the dissolution behavior of CBZ form III and HPMC-based formulations. The compositions of different bio-relevant media are listed in Table 1.[12]

Saturation solubility studies

Saturation solubility studies were carried out using simulated gastrointestinal fluids and de-ionized water as solvents. Excessive quantity of CBZ (25 mg) or formulations (50 mg) was taken in screw-capped test tubes with fixed volume (20 mL) of different bio-relevant media as solvents. The resulting suspension was treated at 27°C at a speed of 100 rpm in an incubator shaker. After 24 h, samples were withdrawn and filtered through 0.2-μ filters. The filtrate was diluted with respective solvents and analyzed at 287.5 nm by UV-Vis spectrophotometer (Pharma spec 1700, UV-Vis spectrophotometer, Shimadzu Corporation, Kyoto, Japan).

Differential scanning calorimetric studies

Differential scanning calorimetric (DSC) analyses of the drug, carrier, solid dispersion formulation, and corresponding physical mixtures were carried out using Shimadzu TA-60 differential scanning calorimeter equipped with computer analyzer (Shimadzu Corporation, Kyoto, Japan). Samples weighing 3 to 7 mg were heated in nitrogen atmosphere on an aluminum pan at a heating rate of 10°C/min over the temperature range of 20°C to 210°C.

Powder X-ray diffraction studies

Powder X-ray diffraction (PXRD) patterns were traced employing X-ray diffractometer (Philips PW 1729, Holland) for the samples using Ni-filtered CuK(α) radiation, a voltage of 35 kV, a current of 20 mA, and receiving slit of 0.2 inches. The samples were analyzed over 2θ range of 5° to 80° with scanning step size of 0.020° (2θ) and scan step time of 1 s.

Fourier transform infrared spectroscopy

FT-IR spectra of CBZ, HPMC, and prepared formulation were recorded on Shimadzu FT IR - 8400 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). Potassium bromide-pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 400 to 4000 cm^{-1} at spectral resolution of 2 cm^{-2} and ratioed against background interferogram.

Powder dissolution studies

In vitro dissolution was evaluated using the method adopted by Agarwal S. and coworkers.[13] Powder dissolution studies were carried out first on pure drug and then on solid dispersion with the corresponding physical mixture. Each test

Table 1: Composition of bio-relevant media

Ingredients	FaSSGF	SGF	FaSSIF	FeSSIF	SCoF
Sodium chloride (gm)	2	2	6.186	11.874	170*
Hydrochloric acid (gm)	3	7	-	-	-
Triton X 100 (gm)	1	-	-	-	-
Sodium dihydrogen phosphate (gm)	-	-	3.438	-	-
Sodium hydroxide (gm)	-	-	0.348	4.04	157*
Glacial acetic acid (gm)	-	-	-	8.65	-
Deionized water (L) *qs ad*	1	1	1	1	1

*1 M solution in mL

was carried out in 750 mL dissolution medium at 37°C ($n = 6$) with a six-flask USP type II dissolution apparatus (Lab India, Disso 2000, digital dissolution testing apparatus, Mumbai, India). An accurately weighed quantity of each sample equivalent to 200 mg of CBZ was subjected to the test. To avoid the aggregation of powder in contact with dissolution media, 200 mg of sample was treated with 10 g of silica beads. Samples were taken at appropriate time intervals. The volume of dissolution medium was kept constant throughout the run by replacing the removed samples with an equivalent volume of fresh dissolution medium. Samples were filtered through 0.44-μ filter, suitably diluted with respective media, and analyzed at 287.5 nm for each media using validated analytical methods by UV-Vis spectrophotometer (Pharma spec 1700, UV-Vis spectrophotometer, Shimadzu Corporation, Kyoto, Japan).

RESULT AND DISCUSSIONS

Authentication of carbamazepine form III

CBZ form III was authenticated by various sophisticated techniques such as melting point determination, UV spectra, IR analysis, and differential scanning calorimetry. The mean flash point of 169°C and melting point of 171°C confirmed that the drug was CBZ form III. The absorption maximum at 287.5 nm in UV spectra and nature of the peak were comparable with standard UV spectra of CBZ. The IR spectrum of CBZ showed typical peaks of CBZ. The peaks at 3465.84 cm^{-1} and 3340.48 cm^{-1} correspond to symmetric and asymmetric N-H stretching in primary amide group respectively. The C = O stretching from amide group of drug appeared at 1690 cm^{-1}.[14] The peak at 1604.66 cm^{-1} was due to C = C stretching in aromatic ring. Thermal analysis by DSC revealed the crystalline behavior of CBZ form III.

Saturation solubility studies

Saturation solubility studies were carried out with five different simulated gastrointestinal fluids and distilled water. The result of solubility studies is displayed in Table 2. The maximum solubility of CBZ form III (268.71 μg/mL) was observed with FeSSIF, and minimum solubility (190.90 μg/mL) was observed with SGF. Significant enhancement in solubility of CBZ was achieved with both physical mixtures and solid dispersions in all dissolution media. However, solubility of drug in solid dispersion was more than that in the physical mixture. This result was supported by reduction in crystallinity of CBZ form III in solid dispersion by DSC and PXRD studies. Being a weakly basic drug, CBZ has good solubility in acidic pH, but the correlation between pH of the solution and solubility was not possible to establish. Moreover, interestingly, solubility of drug in SGF was lower than the solubility of drug in other media. It was observed that SGF favors crystallization of CBZ dehydrate and thereby brings about reduction in solubility; whereas in case of solid dispersion, polymer prevents the formation of dihydrate and hence enhancement of solubility was achieved with SGF. CBZ form III had solubility of 218.25 μg/mL in FaSSGF. Triton X was used to mimic the surface tension of GI fluids.[15] CBZ dihydrate formation was not observed with FaSSGF, even though it has acidic pH. This may be probably due to the fact that surface-active property of Triton X 100 reduces the formation of CBZ dehydrate. The various compositions of the different bio-relevant media and their ionic nature may be the reason for disordered solubility behavior of CBZ III and its formulation with respect to pH.

Differential scanning calorimetric studies

Thermograms of drug, polymer, and formulations are represented in Figure 1. Carbamazepine form III showed two thermal events - first melting endothermic event, 171.68°C with the fusion enthalpy of 12.2 J/g, followed by a second endothermic peak at 192.10°C with the fusion enthalpy of 109.61 J/g. These two endothermic peaks correspond to form III and transition of form III to form I of CBZ respectively.

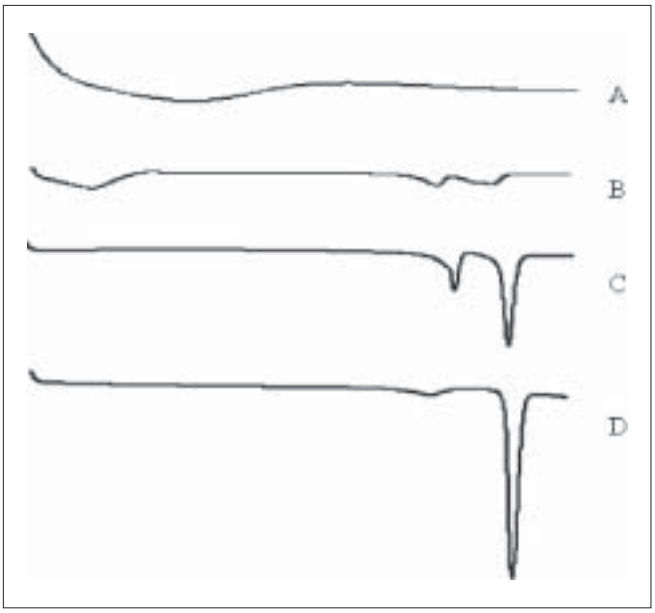

Figure 1: DSC thermogram of A) HPMC, B) solid dispersion, C) physical mixture, and D) CBZ form III

Table 2: Solubility of CBZ form III in different bio-relevant media

Bio-relevant media	Solubility in µg/ml ± S. D.*					
	Water	FaSSGF	SGF	FeSSIF	FaSSIF	SCoF
CBZ form III	159.30 ± 6.15	218.25 ± 5.46	190.90 ± 3.81	268.71 ± 1.07	257.97 ± 10.15	191.61 ± 5.08
Physical mixture	293.97 ± 4.57	290.36 ± 6.80	297.54 ± 6.29	287.18 ± 7.63	280.73 ± 6.54	252.35 ± 1.76
Solid dispersion	362.28 ± 8.46	348.42 ± 2.11	367.89 ± 11.40	354.70 ± 2.37	338.35 ± 7.82	317.79 ± 6.33

*n = 3, S. D. - standard deviation

[16] HPMC being an amorphous carrier did not show any endothermic events. The net reduction in enthalpy was observed with both physical mixture and solid dispersion. However, greater reduction in enthalpy was observed with solid dispersions than with physical mixture.

Powder X-ray diffraction studies

The solid states of CBZ, HPMC, physical mixture, and solid dispersion were studied by PXRD [Figure 2]. HPMC being amorphous did not show any peaks. The powder diffraction patterns of pure CBZ showed characteristic high-intensity diffraction peaks at 2θ values of 13.548°, 13.971°, 14.780°, and 27.295°, which match with the known powder diffraction patterns of CBZ form III.[17] PXRD pattern revealed that the CBZ sample used in this study was form III, further confirmed by DSC pattern of CBZ form III. The reduction in crystallinity of form III in both physical mixture and solid dispersion was observed. The peak intensity of 2149 at 2θ values of 27.152 was observed with CBZ form III, whereas the corresponding values were 383 and 71 with physical mixture and solid dispersion respectively.

Powder dissolution studies

The results of powder dissolution studies are graphically represented in Figure 3. CBZ form III showed maximum dissolution of 75.09% in FaSSGF. The enhanced drug release of CBZ form III in FaSSGF was due to the presence of Triton X 100. $T_{85\%}$ was achieved within 30 min in FaSSGF, but all other media failed to release 85% of drug even after 60 min. In SGF, the drug release of 60.72% was comparably higher than in other bio-relevant media except FaSSGF; this may be due to acidic pH of dissolution media. However, the results obtained from solubility studies were contradicted by dissolution data. Dissolution studies were carried out in sink conditions, whereas solubility studies in saturated conditions. In sink conditions, formation of CBZ dihydrate was minimal, because of large quantity of dissolution

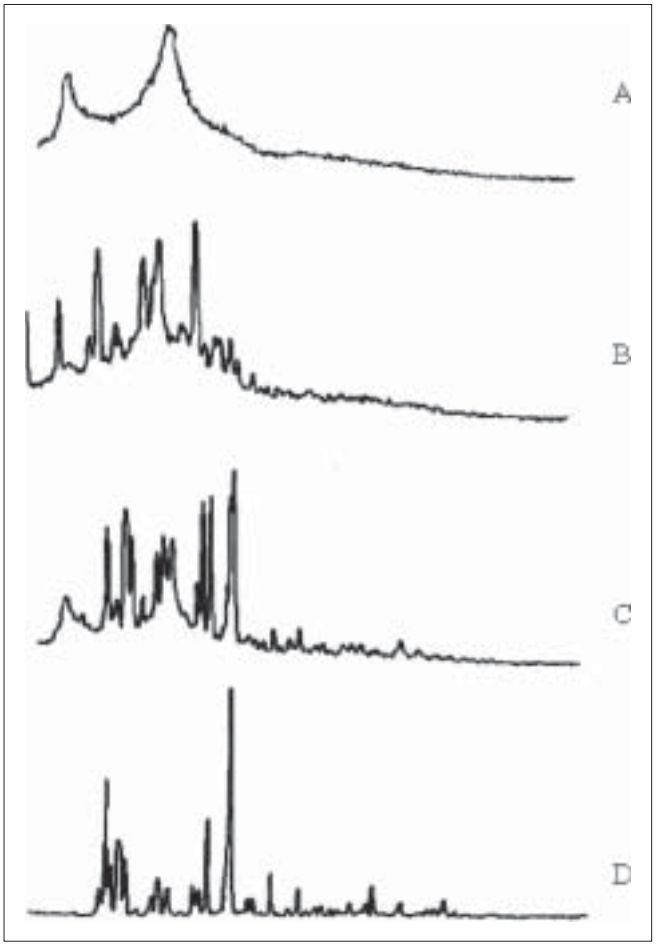

Figure 2: Powder x-ray diffractogram of (A) HPMC, (B) solid dispersion, (C) physical mixture, and (D) CBZ form III

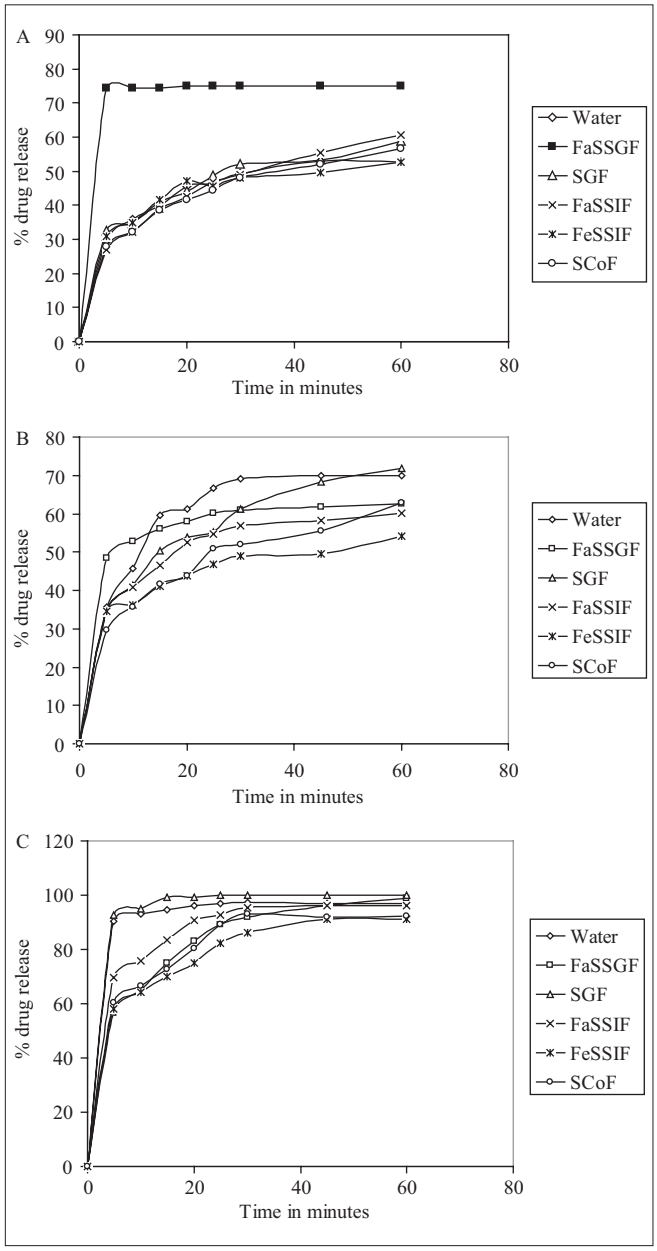

Figure 3: *In vitro* drug dissolution profile of (A) carbamazepine form III, (B) physical mixture, and (C) solid dispersion in different dissolution media in minutes

medium available for solubilization. But in solubility studies, saturation of CBZ form III in SGF leads to the nucleation of CBZ dihydrate crystals and hence reduces the solubility of form III. Dissolution studies of physical mixture revealed that there was no statistically significant increase in dissolution compared to CBZ form III. But in case of saturation solubility studies, profound enhancement of solubility was achieved with physical mixture compared to CBZ form III. There was no correlation established between solubility studies and dissolution studies. The suggested reason may be reduction in concentration of HPMC, with large volume of dissolution media reducing the dissolution rate of CBZ form III. None of the dissolution media used showed $T_{85\%}$ even after 60 min in physical mixture formulation. Solid dispersion formulation showed maximum release profile irrespective of dissolution media. The drug release of 85% was achieved within 30 min with all formulations. The minimum drug release of 75.14% was achieved with FaSSGF at 15 min. This may be due to the physical interaction between Triton X 100 and HPMC.

CONCLUSION

The result of the present investigation leads to the conclusion that bio-relevant dissolution media have no discriminatory status towards CBZ. HPMC in solid dispersion dosage form has profound influence on drug solubility and dissolution. There were no significant differences in drug dissolution rates with different bio-relevant media, whereas different solubilities of CBZ were observed with different media. Moreover, pH was found to play very little role in dissolution of CBZ. There was no correlation between drug solubility and dissolution. The reason suggested for poor bioavailability of CBZ is slow and irregular dissolution of the drug in GIT. Formation of CBZ dihydrate in *in vivo* environment determines the bioavailability of dosage forms. Acidic pH facilitates the formation of CBZ dihydrate in saturated conditions. In fasted state, combination of acidic pH, large dose (200 mg), and low volume of gastric fluids allow the formation of CBZ dihydrate and hence it reduces the availability of CBZ in plasma. The presence of common ion in dissolution medium is the key factor in drug dissolution. However, the present study has not attempted to explore the effect of common ion in dissolution medium on dissolution of CBZ form III. It is therefore concluded that neither solubility studies nor dissolution studies are useful tools in predicting the *in vivo* availability of CBZ in dosage forms. Moreover, bio-studies are essential for NDA and ANDA submission of CBZ.

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