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ORIGINAL ARTICLE

# Preparation and physicochemical characterization of carbamazepine (CBMZ): para-sulfonated calix[n]arene inclusion complexes

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**Abstract** The formation of inclusion complexes with para-sulfonated calix[n]arene (PSC[n]A) was studied for carbamazepine (CBMZ), a poorly water soluble anticonvulsant drug. The effect of PSC[4]A and PSC[6]A on aqueous solubility of carbamazepine was studied extensively. The complete complexation of the drug was achieved after 48 h of shaking with PSC[n]A in water and evaporation of water to get solid complex. The interaction between PSC[n]A and CBMZ in solid state inclusion complexes was accomplished by aqueous phase solubility studies, HPLC, DSC, PXRD, FTIR, UV–Vis, and FT-Raman spectroscopy. The solubility of CBMZ increases as a function of PSC[n]A concentration. The results of the two phase solubility experiments are in good conformity to signify the formation of 1:1 (PSC[6]A:-CBMZ) and 2:1 PSC[4]A:CBMZ complexes. The order of dissolution rate of CBMZ is inclusion complex > physical mixture > drug alone. The purpose of this study was to enhance solubility resulting in high dissolution rate and bioavailability of this essentially water insoluble drug.

**Keywords** Carbamazepine · Para-sulfonated calix[n]arene · Inclusion complexes · Solubility · Dissolution

## Introduction

Carbamazepine (CBMZ) (5H-dibenzazepine-5-carboxamide) is an anticonvulsant drug widely used in the treatment of simple and complex seizures, trigeminal neuralgia and bipolar affective disorders. The drug is practically insoluble in water (<200 μg/mL) and its absorption is dissolution rate limited [1]. The best possible way to increase the aqueous solubility of this drug is to use complexing agents to form host–guest complexes. Among the complexing agents available, cyclodextrins (CD) are most widely used in drug formulations [2]. Alternative complexing agents are calixarenes which are cyclic oligomers synthesized by condensation of *p-tert*-butyl phenol with formaldehyde [3]. Among the water soluble calixarenes, the *p*-sulfonated calix[n]arenes (PSC[n]A) have been widely used as complexing agents for organic molecules, because these molecules possess the highest known aqueous solubility, >0.1 mol/L [4, 5]. These calixarenes provide not only a hydrophobic environment, but also hydrophilic heads ($SO_3^-$) imparting to them properties of both CDs and micelles.

The formation of inclusion CD complexes and the nature of the complexes have been widely investigated by the pharmaceutical industry [6]. Many of the early investigations involved complexation by native/natural cyclodextrins. The use of cyclodextrins in human and animal pharmaceutical products was hindered by their toxicity problems [7]. However toxicity profiles have been improved by bringing modifications in the structure of CDs.

Carbamazepine is reported to form an inclusion complex with β-cyclodextrin (β-CD), which could improve its dissolution rate [8–10]. Co-grinding of carbamazepine with microcrystalline cellulose resulted in its increased dissolution rate, and an improvement in both in vivo and in vitro anticonvulsive effects was observed [11].

There are few publications in the literature that describe the formation of complexes between drug substances and calixarenes. Parini et al. [12] has described the solid state interaction of steroids with water in soluble *tert*-

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butylcalix[n]arene. A preliminary investigation of the solution complexation of *p*-sulfonated calix[n]arene with testosterone has been reported by Jeffery [13]. However, there are no reports of possible uses of calixarenes as pharmaceutical enabling agents. *p*-Sulfonato-calix[n]arenes in acidic aqueous solution are studied by Yang et al. [14–17] with three practically insoluble drugs, nifedipine, furosemide and niclosamide for solubilisation. The complexation of an anti bacterial drug norfloxacin with *p*-sulfonated calix[4]arene also has been reported recently [18].

The present investigation is concerned with improving the solubility and dissolution rate of carbamazepine (CBMZ) in aqueous solution in order to modify its bioavailability. This was achieved through the formation of inclusion complexes (Fig. 1) with *p*-sulfonated calix[n]arene. The formation of the inclusion complexes was confirmed by a variety of techniques such as FTIR, FT-Raman, PXRD, and DSC. The work also included the determination of dissolution profile.

## Materials and methods

### Reagents and standards

Carbamazepine was a gift sample from Claris Lifesciences Ltd. Ahmedabad. PSC[6]A (MW = 1,117.11) and PSC[4]A (MW = 744.74) was synthesized by reported procedure [19]. Purified water was prepared by Millipore (synergy) system and was used throughout the study. All other chemicals and reagents used were of AR grade and supplied by Merck (India). The 0.45 μm nylon filters were obtained from Millipore, Bedford, MA, USA.

### Preparation of carbamazepine PSC[n]A complex

Solid complexes of carbamazepine and PSC[n]A were prepared by rotary shaking. A molar ratio mixture of 1:1 CBMZ:-PSC6A (47:223 mg) and 1:2 CBMZ:PSC4A (47:298 mg) were taken into 250 mL stoppered conical flasks containing 100 mL distilled water. These flasks were then shaken on rotary shaker for 48 h at ambient temperature and then solution mixtures were filtered through 0.45 μm filter. The solutions were dried at 45 °C under vacuum (2–5 torr) to obtain solid complexes.

### Phase solubility studies

The intent of the research work is to increase the water solubility and dissolution rate of carbamazepine by preparing the inclusion complex. Phase solubility studies were carried out at 25 °C temperature, in triplicate according to the method reported by Higuchi and Connors [20]. Excess amounts of CBMZ (200 mg) were added into different stoppered conical flasks containing 100 mL aqueous solutions of PSC[n]A at different concentrations (0.56–8.95 × $10^{-4}$ M PSC[6]A and 0.84–13.4 × $10^{-4}$ M PSC[4]). These flasks were then sonicated for 1 h and shaken at a rate of 100 strokes per min in orbital shaker incubator (Newtronic, India) for 48 h. The suspensions were then filtered through 0.45 μm filter and assayed for CBMZ by using HPLC. The solubility of CBMZ was also determined in water at 25 °C by the same method.

The association constant ($K_c$) for the complex formed was calculated from the slope of the phase solubility diagram and the solubility of CBMZ in water at 25 °C in water $S_0$ according to following equation [21]

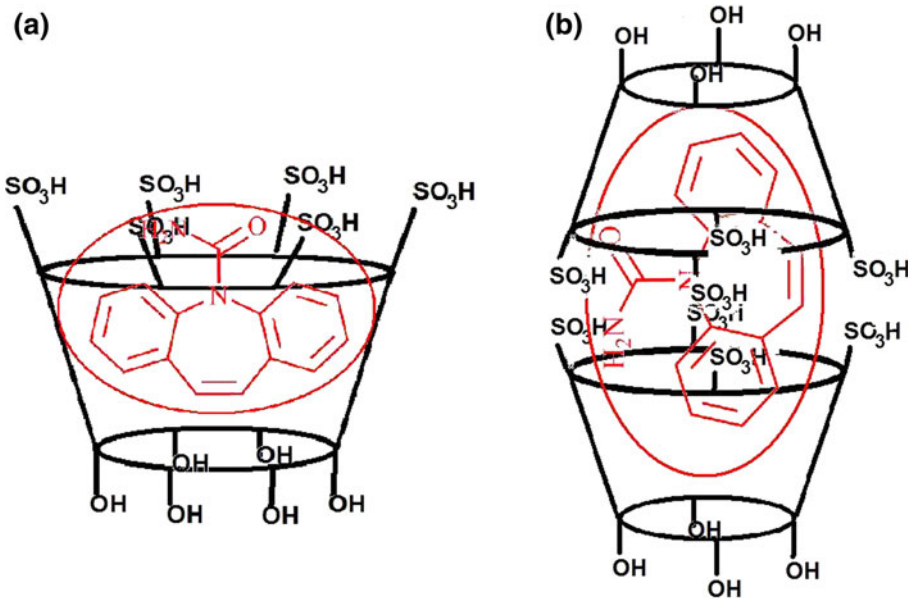


**Fig. 1** Inclusion complexes of **a** CBMZ:PSC[6]A 1:1 and **b** CBMZ:PSC[4]A 1:2

$$K_c = \frac{\text{Slope}}{S_0(1 - \text{slope})}. \quad (1)$$

Dissolution studies

The dissolution studies were performed by the USP XXIV rotating paddle method [22] at 37 °C. The dissolution rate of pure CBMZ, CBMZ:PSC[n]A physical mixture and inclusion complexes were studied by mixing with placebo. Complex sample equivalent to 10 mg CBMZ was placed into 900 mL dissolution medium (phosphate buffer pH 7.4) and was stirred at 50 rpm. Aliquots (5 mL) of the dissolution mixture were withdrawn after appropriate time intervals, followed by immediate filtration (0.45 μm pore size filter), and analyzed by HPLC–UV. The experiment was performed in triplicate and the standard deviation was evaluated.

Evaluation of the complexes

An accurately weighed amount of the complex was dissolved in water and assayed for CBMZ using HPLC with UV detection. The HPLC system consisting of a CROMPACK ISOS isocratic pump and a CROMPACK variable wavelength UV–visible detector (UV var), a manual injector with a 20 μL loop (RHEODYNE 7125, USA) and detector output was processed and recorded by SPINCHROM software (version 2.4.1.93) on a Pentium computer. The analytical column used to achieve chromatographic separation was a stainless steel (250 mm × 4.6 mm I.D., 5 μm particle size) Wakosil C18 (SGE). A JASCO V-570 spectrophotometer was used for scanning and selecting detection wavelength. The compounds were separated isocratically with a mobile phase consisting of water and methanol (50:50% v/v). Before use, the mobile phase was filtered by passing through a 0.22 μm membrane filter (Millipore, Bedford, MA, USA) degassed ultrasonically. The flow rate was 1.0 mL $min^{-1}$. Chromatographic analysis was carried out at ambient temperature (25 ± 1 °C). The effluent was monitored by UV detector at 230 nm.

FT-IR and FT-Raman have previously been shown [23, 24] to be useful techniques for characterizing drug-cyclodextrin inclusion complexes. Accordingly, we chose to employ these techniques to characterize the drug–PSC[n]A interactions. Samples were analyzed using Bruker Tensor-27 FT-IR and Bruker Vertex-3 FT-Raman spectrometers. Complex formation was evaluated by comparing the spectra of the solid complex, physical mixture, PSC[n]A and of the pure drug.

Similarly, based on previous studies of drug–cyclodextrin interactions using differential scanning calorimetry (DSC) [25], we used DSC to study the solid state interaction of the drug with PSC[n]A. Samples of the inclusion complex, pure drug, physical mixture, and PSC[n]A were heated in crimped aluminum pans over a temperature range of 30–450 °C at a constant rate of 30 °C/min with purging of nitrogen (50 mL $min^{-1}$) using alumina as a reference standard in a Shimadzu model DSC-7 Differential Scanning Calorimeter.

Along with DSC, we also employed powder X-ray diffraction (PXRD) to investigate the interaction between the drug and PSC[n]A [26]. The powder X-ray diffraction studies were carried out in a Shifert XRD-7 X-ray diffractometer with Ni monochromated Cu $K_\alpha$ radiation in transmission mode. The PXRD pattern of solid complex, pure drug, and PSC[n]A were recorded between $2\theta$ = 10–45° at tube power of 40 kV and 30 mA.

## Results and discussions

Phase solubility studies

In the present work, complexation of carbamazepine with PSC[n]A was carried out in an attempt to improve its solubility and dissolution rate. The phase solubility studies revealed a linear relationship (correlation coefficient > 0.99) between the aqueous drug solubility with increase in PSC[n]A concentration (Fig. 2) with the formation of soluble complexes. The slopes of the curves observed in the regression analysis would indicate the formation of soluble complex of CBMZ:PSC[6]A (slope 0.80) with 1:1 stoichiometry and CBMZ:PSC[4]A (slope 0.43) with 1:2 stoichiometry. The extent of complexation is calculated based on the solubility diagram. The stability constant Kc (Eq. 1) values were found to be 5,390 $M^{-1}$ for PSC[4]A and 2,047 $M^{-1}$ for PSC[6]A indicating that the complex formed

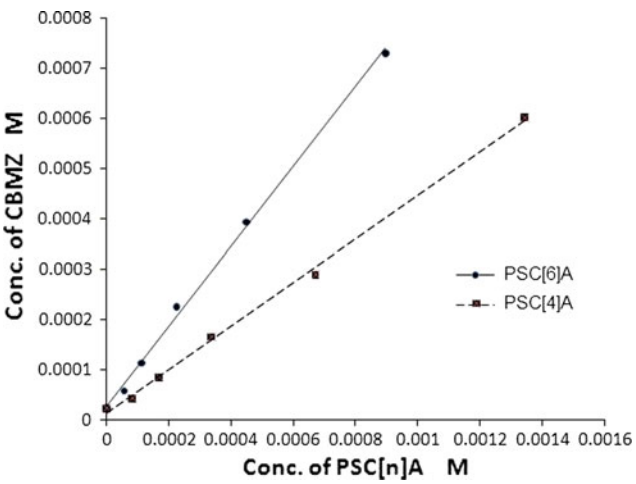


**Fig. 2** Higuchi phase solubility diagram of PSC[n]A and CBMZ system in water at 25 °C. Each data point is the mean of three determinations

was adequately stable. These values of stability constants are much higher than the stability constant of same drug reported in literatures [9, 10] with cyclodextrin.

## Evaluation of the complexes

The characterization of the complex was carried out by FT-IR, FT-Raman, DSC and PXRD to study the solid state interaction of drug with PSC[n]A.

The FTIR spectra of CBMZ (Fig. 3a) showed a characteristic peak at 3,466 $cm^{-1}$ ($–NH_2$ starching), two bands at 3,341 and 3,283 $cm^{-1}$ (-CONH stretching in solid state), 1,678 $cm^{-1}$ (–CO-R vibration), 1,595 and 1,605 $cm^{-1}$ (primary amide in solid state, $–NH_2$ bending), and 1,384 $cm^{-1}$ (–NH deformation) [25].

PSC[n]A spectra (Fig. 3b, e) presents two large band of –OH bond peaks at 3,455 and 3,244 (3,235 $cm^{-1}$ in PSC [4]A) and, peaks at 1187, 1116 and 1056 $cm^{-1}$ of $\nu SO_3$.

In the IR spectra of the solid complex (Fig. 3d, g), the PSC[n]A main bands were found to overlap with the characteristic drug peaks, which can be attributed to low drug content in the solid complexes (about 19.0% for PSC[6]A and 25% PSC[4]A % w/w). The spectrum of solid inclusion complex did not show any new peaks which indicates that no new chemical bonds are formed in the complex. However, the CBMZ characteristic peak at 3,466 $cm^{-1}$ (–NH valence vibration), 3,341 and 3,283 $cm^{-1}$ (-CONH stretching in solid state) disappeared and hence could not be detected in the IR spectra of the solid complex. CBMZ characteristic peak at 1,678 $cm^{-1}$ appear as broad shoulder in the complex as compared with physical mixture (Fig. 3c) and PSC[n]A spectra, same way 1,605 and 1,595 $cm^{-1}$ peaks of CBMZ were also detected as broad shoulder peak which confirmed the formation of the inclusion complex. The peaks at 1187, 1116 and 1056 $cm^{-1}$ due to $–SO_3$ shifted to lower wavenumber at 1183, 1114 and 1049 $cm^{-1}$.

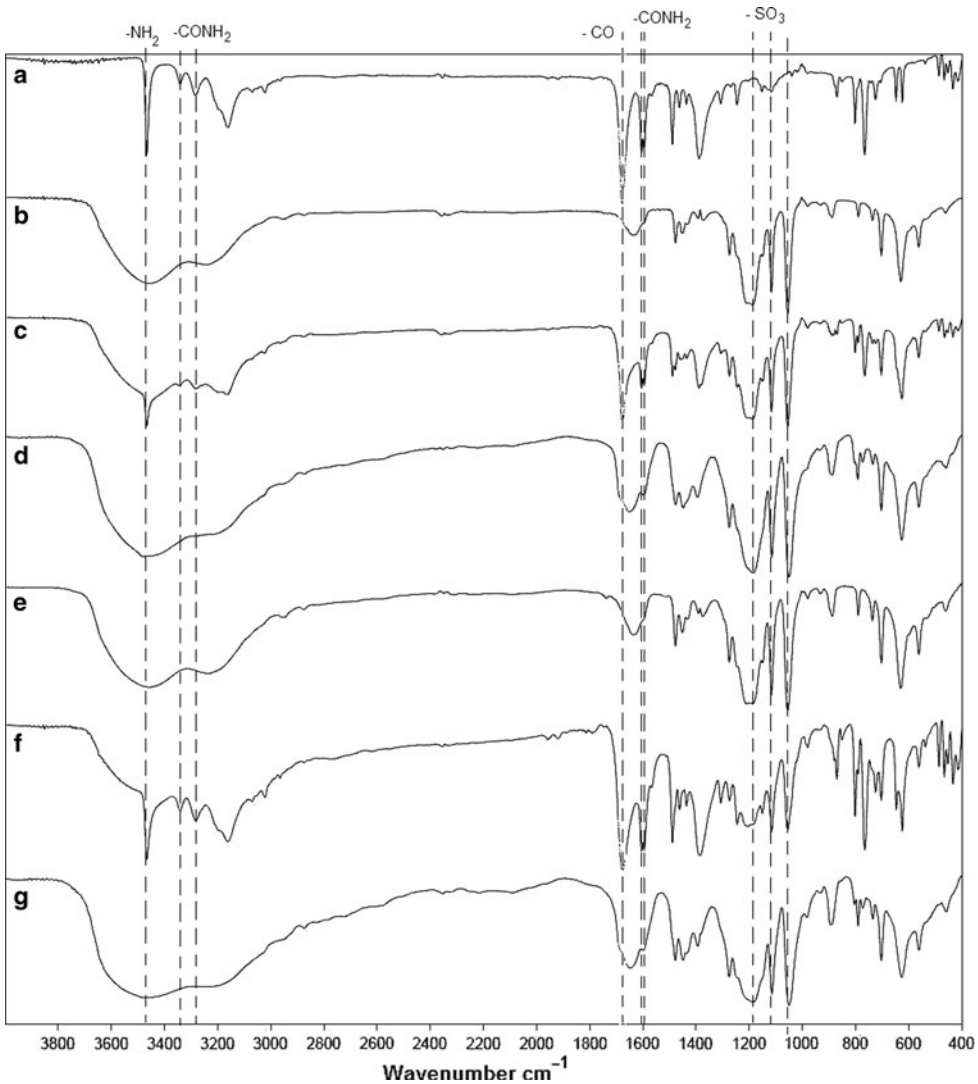


**Fig. 3** FT-IR spectra of: (*a*) CBMZ, (*b*) PSC[4]A, (*c*) CBMZ:PSC[4]A physical mixture, (*d*) PSC[4]A inclusion complex, (*e*) PSC[6]A, (*f*) CBMZ:PSC[6]A physical mixture, (*g*) PSC[6]A inclusion complex

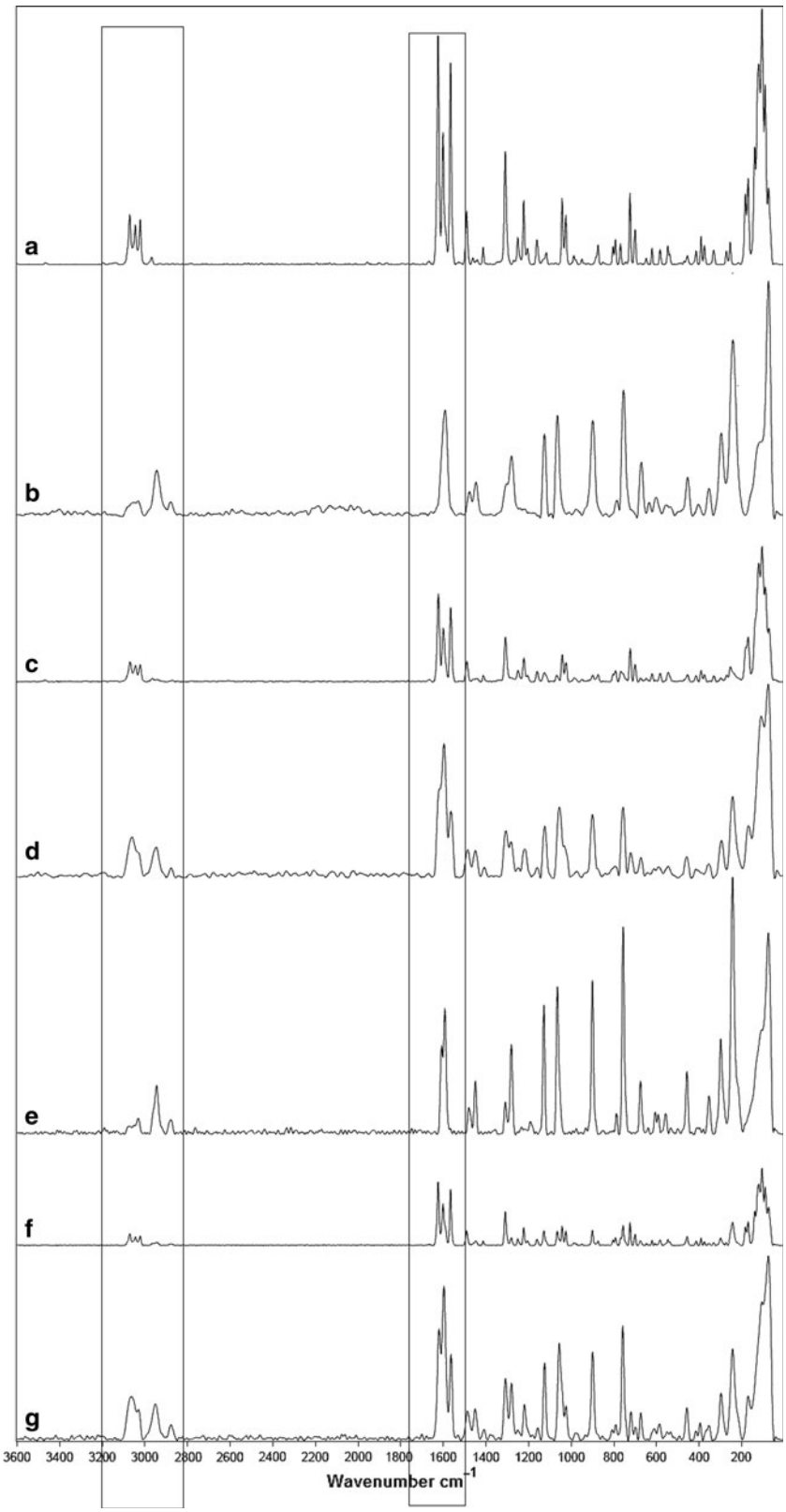


**Fig. 4** FT-Raman spectra of: (*a*) CBMZ, (*b*) PSC[4]A, (*c*) CBMZ:PSC[4]A physical mixture, (*d*) PSC[4]A inclusion complex, (*e*) PSC[6]A, (*f*) CBMZ:PSC[6]A physical mixture, (*g*) PSC[6]A inclusion complex

Solid state complex formation was evidenced from the results of Raman spectroscopy. The support of this study was the existence of some spectral ranges, where the Raman bands associated to atom group vibrations directly involved in interaction are not overlapped (Fig. 4). Changes in the peak positions and the widths of the Raman bands of the

complex, compared with their corresponding bands of the pure CBMZ and physical mixture, were observed. Raman data revealed the existence of interactions between both CBMZ and the PSC[n]A molecule for the increased solubility of the solid complex when compared to that of the pure drug.

In the solid state FT-Raman spectra of pure CBMZ and CBMZ:PSC[n]A physical mixture, CBMZ characteristics triple peaks of n mono substituted amide at 1624, 1600, and 1565 $cm^{-1}$ were observed at the same wavenumber. However, these frequencies were shifted to lower wavenumber in solid complexes of drug. The solid complex also gives triplet peaks in region 3,000–3,100 $cm^{-1}$. All of them were observed in CBMZ and CBMZ PSC[n]A physical mix but in CBMZ PSC[n]A solid state complex it turns into two broad bands in the above region but shifted to lower wavenumber. The peak at 1,066 $cm^{-1}$ due to $-SO_3$ in PSC[n]A and peaks at 1,042 $cm^{-1}$ of CBMZ were observed in the spectra of physical mix as different peaks but in solid state complex the peak of PSC[n]A at 1,066 $cm^{-1}$ and CBMZ of 1,042 $cm^{-1}$ shifted to 1,056 with shoulder at 1,043 $cm^{-1}$.

DSC thermograms of CBMZ, PSC[n]A, and the solid complex are plotted in Fig. 5. The thermogram of the pure drug presents two sharp endothermic peaks: one at 175.38 °C, corresponding to transition from polymorph III to I, and the second at 194.5 °C, corresponding to melting transition temperature of polymorph I [27]. The relaxation endotherm (72.26–212.26 °C) observed with PSC[n] A

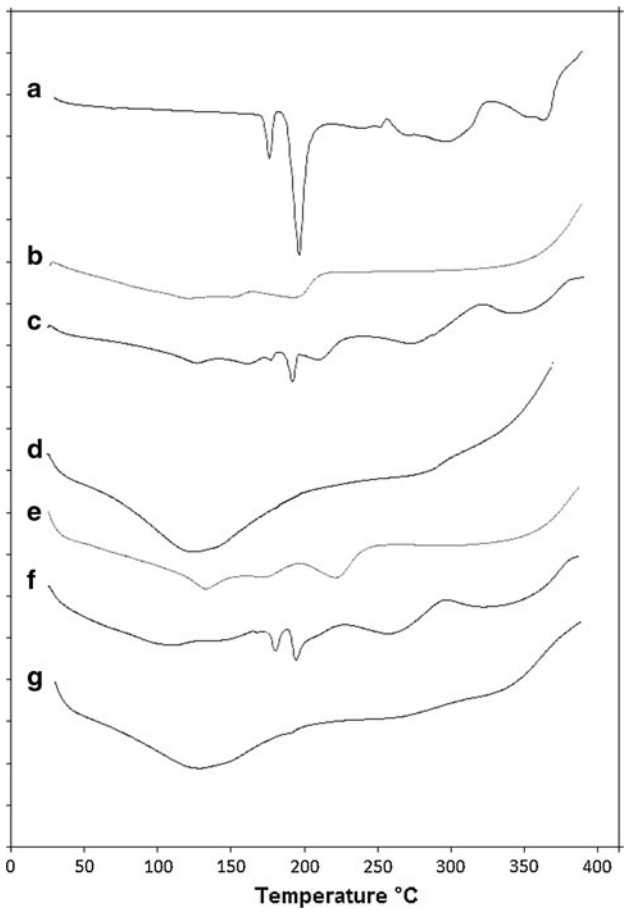


**Fig. 5** DSC curves of: (*a*) CBMZ, (*b*) PSC[4]A, (*c*) CBMZ:PSC[4]A physical mixture, (*d*) PSC[4]A inclusion complex, (*e*) PSC[6]A, (*f*) CBMZ:PSC[6]A physical mixture, (*g*) PSC[6]A inclusion complex

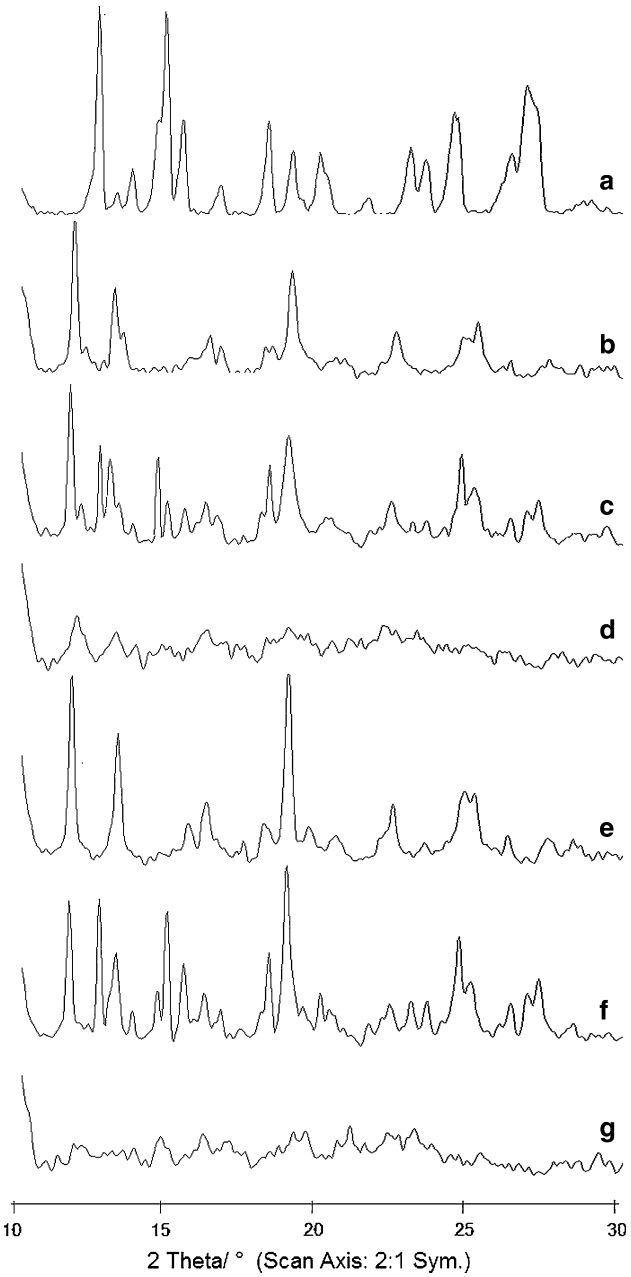


**Fig. 6** X-ray diffraction patterns of: (*a*) CBMZ, (*b*) PSC[4]A, (*c*) CBMZ:PSC[4]A physical mixture, (*d*) PSC[4]A inclusion complex, (*e*) PSC[6]A, (*f*) CBMZ:PSC[6]A physical mixture, (*g*) PSC[6]A inclusion complex

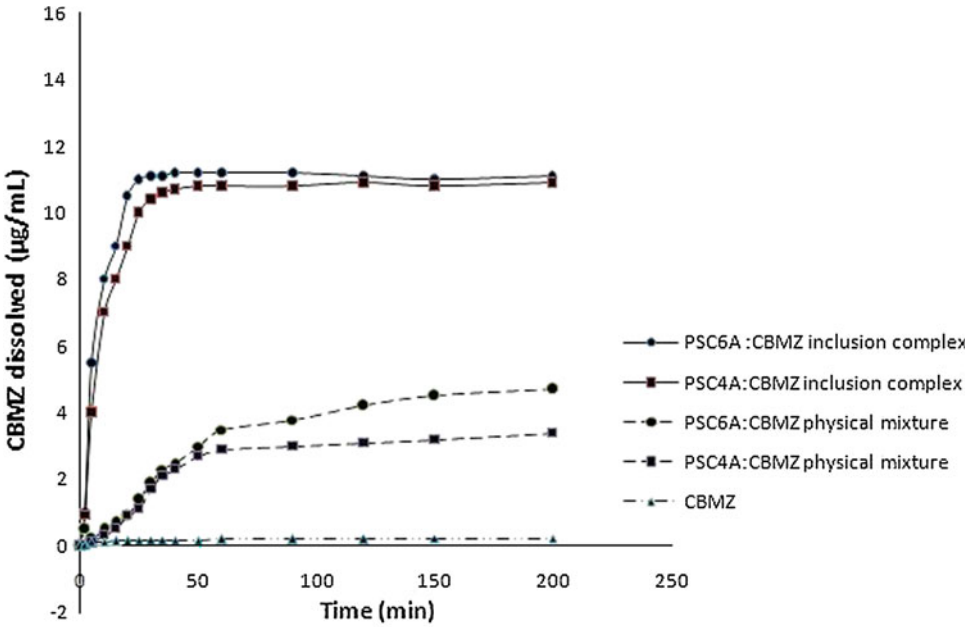


**Fig. 7** Dissolution studies PSC[n]A inclusion complexes, physical mixtures and CBMZ system in (phosphate buffer pH 7.4) at 37 °C

thermogram corresponds to its degradation. DSC curves of solid complex of PSC[n]A and CBMZ showed the disappearance of characteristic peak corresponding to CBMZ melting at 194.5 °C, which is predictable to the formation of CBMZ–PSC[n]A inclusion complex. This also indicates that the drugs are in the amorphous form.

PXRD patterns for CBMZ, PSC[n] A and the solid complexes are shown in Fig. 6. The crystalline nature of carbamazepine was clearly demonstrated by its characteristic PXRD pattern containing well-defined peaks. The drug characteristic peaks were observed at $2\theta$ values 12.94, 15.15, 15.71, 24.72, and 27.11. The PXRD pattern of both PSC[4]A and PSC[6]A showed peaks at 12.03, 13.55 and 19.19 $2\theta$.

The PXRD diffractogram of the physical mixture constituted, appears to represent the superposition of both component although peaks attributable to CBMZ are remarkably reduced, indicating lower crystallinity/concentration of drug compared to pure drug. In contrast, inclusion complex showed no diffraction peaks except halo-pattern in X-ray diffractogram, suggesting an amorphous state of the drug in the inclusion complex. This decrease in the drug crystallinity was responsible for the increase in solubility as cited in literature [28].

Dissolution studies

Figure 7 shows the dissolution profile of CBMZ, CBMZ–PSC[n]A physical mixture, and CBMZ–PSC[n]A inclusion complex at 37 °C in phosphate buffer (pH = 7.4). The dissolution rates of inclusion complexes (both) are manifestly superior to pure drug.

The enhancement in the dissolution rate of the inclusion complex could be explained from an increase in solubility, a marked reduction in crystallinity as confirmed by X-ray diffraction study and an improved wettability of the drug by the inclusion complexation [26, 28]. The dissolution of PSC[4]A inclusion complex is slightly slower compared to PSC[6]A inclusion complex, which is evaluated by the stability constant of complexes. The physical mixtures also shows higher dissolution rate but it is medium to inclusion complex. It is assumed that in the physical mixture of PSC[n]A the dissolution is attributable to the in situ formation of readily soluble inclusion complex.

## Conclusion

Both studied inclusion complex systems PSC[n]A:CBMZ showed more reduced crystallinity. This was evident from smaller characteristic peaks in the X-ray diffractogram and absence of corresponding endotherm in DSC thermogram as compared to those of the corresponding physical mixture of each pure substrates. But no significant difference was observed in FT-IR spectra indicating absence of chemical interaction (new bond formation) between the drug and the PSC[n]A. The FT-IR, FT-Raman, DSC and PXRD studies cooperatively propose a stronger interaction between the drug and PSC[n]A in the solid complex due to formation of inclusion complex. The effect of increased ring size of PSC[n] extensively control the increase in the solubility of the drugs, from which results probably the incorporation of the aromatic groups of the drugs into the cavities of the PSC[n]A. As most of synthetic drugs are not soluble in water, these results are fascinating for their increased solubilisation in aqueous media.

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