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Towards a Universal Dissolution Medium for Carbamazepine

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ABSTRACT The aim of this study was to develop a dissolution medium for assessment of various carbamazepine (CBZ) formulations with different strengths. The design of a system inhibiting transformation of the anhydrous CBZ (CBZ A) to the dihydrate form (CBZ D), with minimum surface-active properties and suitable sink was investigated. The effect of pH, different concentrations of sodium lauryl sulphate (SLS), polyvinylpyrrolidone (PVP), and methyl cellulose (MC) on dissolution rate, solubility, dissolution solubility, and polymorphic transformation of CBZ was assessed. Solution-mediated transformation of CBZ A into CBZ D was monitored using optical microscopy, Fourier transform infrared spectroscopy and differential scanning calorimetry. Results showed that different strengths (100, 200, 400 mg) of the same CBZ tablet formulation exhibited different dissolution patterns, in 1% SLS (USP system). Such differences were reduced in 0.5% SLS solution which provided sufficient sink for up to 200 mg CBZ. It was also shown that solubility of CBZ A could not be detected in the media under study (water, SGF, SIF, and SLS solutions) due to its rapid transformation into CBZ D. The use of 3% PVP solution protected CBZ A from conversion for 75 min, while 0.01% MC completely inhibited the transformation up to 24 h. Therefore, a medium consisting of 0.5% SLS and 0.01% MC was selected. The medium provided: a) protection against transformation of CBZ A to CBZ D, b) increased solubility of CBZ A (204 mg % compared to 128 mg % of CBZ D in 0.5% SLS), c) suitable sink for up to 400 mg CBZ and d) overlapping dissolution profiles of various strengths of the same CBZ formulation. The suggested system may be a step in the way of solving CBZ dissolution problems that forced the USP to specify two similar dissolution tests with two different limits for conventional 200 mg CBZ tablets.

KEYWORDS Carbamazepine, Dissolution medium, Polymorphic transformation, Dissolution solubility, Sodium lauryl sulphate, Methyl cellulose

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INTRODUCTION

Drug dissolution is a prerequisite for drug absorption and bioavailability for almost all orally administered drugs intended for systemic action. The recently proposed Biopharmaceutics Classification System (BCS), correlating in vitro drug

product dissolution and in vivo bioavailability, categorizes drugs into four classes, according to their aqueous solubility and intestinal permeability (Amidon et al., 1995). These classes are defined as ClassI, high solubility-high permeability; ClassII, Low solubility- high permeability; ClassIII, High solubility-low permeability and ClassIV, Low solubility-low permeability drugs. The BCS can be used as a guide for recognizing when and how dissolution tests can help in the design and evaluation of oral dosage forms (Galia et al., 1998; Rinaki et al., 2003). For ClassII drugs, dissolution is the rate-limiting step to absorption. Further, dissolution of these drugs can depend on various factors such as the volume available for dissolution, the pH, the presence of surfactants, and ionic strength. Therefore, the choice of the dissolution medium is expected to play an important role in the in vitro dissolution tests of class II drugs.

Carbamazepine is a large dose antiepileptic drug belonging to class II. Before 1990 (USP XXII), dissolution testing was not an official requirement for CBZ tablets. USP XXI (1985) specified a disintegration test for CBZ tablets using simulated gastric fluid as an immersion medium. In 1987, FDA proposed a solution containing 10.5% alcohol and 0.1% tween 20 as a dissolution medium. However, the use of dissolution in alcoholic medium as a quality measure is questionable; since the former has no relevance to the physiological milieu. Moreover, the use of relatively high co-solvent concentration may be implicated in dissolution variability as a result of potential interaction with some components of the formulation (Dodge & Gould, 1987). Further, Shah et al. (1989) studied the dissolution of CBZ in different media and SLS (1%) was chosen as the most suitable medium. Following this study, USP XXII (1990) incorporated the dissolution test for CBZ tablets using the paddle method at 75 rpm and 900 mL of 1% SLS. However, discrepancies between in vitro and in vivo data, upon using this medium, were reported by many authors (Meyer et al., 1992; Jung et al., 1997; Meyer et al., 1998; Lake et al., 1999)

In a multinational survey of the quality of CBZ tablets, 86 samples from 19 countries worldwide were evaluated (Davidson, 1995). The results showed that 30% of the tested samples failed to comply with the USP dissolution limit for CBZ tablets. The U.S. pharmacopeial forum proposed a 15 min sampling time with a limit of 40–70% to be included for in vitro dissolution testing to exclude products that have a very rapid or very slow dissolution rate and which might not be bioequivalent to the innovator product. The same study showed that assessment of the tested samples against the proposed limit resulted in a failure of 81% of total samples to comply with this limit. Accordingly, the authors suggested the application of a wider limit between 40% and 80% dissolved at 15 min.

Further, USP 24 introduced four different dissolution tests for CBZ 100 and 200 mg tablets. Two of these tests are specified for conventional 200 mg tablets as shown in the following table:

	Conventional 200 mg tablets		Chewable 100 mg tablets	
Test conditions	Test 2	Test 3	Test 1	Test 4
Medium	Water containing 1% SLS; 900 ml		Water containing 1% SLS; 900 ml	0.1 N HCl containing 1% SLS/ 2 drops simethicone; 225 ml
Apparatus	2: 75 rpm		2: 75 rpm	3: 35 dips per min.
Time & Tolerances	15 min: 45–75%. 60 min: not less than 75%.	15 min: 60–80%. 60 min: not less than 75%.	60 min: not less than 75%.	60 min: not less than 70%.

It could be noticed that these dissolution requirements present an unusual case among USP monographs for two reasons: a) the dissolution requirement is assigned to specific dosage strength of both conventional and chewable tablets; b) two tests with the same medium, apparatus and procedure, but with two different limits are specified for 200-mg conventional tablets. Further, USP 25 and 27 specified a different dissolution test for CBZ extended release tablets, using 900 mL and 1800 mL water, as a dissolution medium, for 200 mg and 400 mg tablets, respectively.

It should be noted that CBZ exhibits polymorphism and the various polymorphs and hydrate show differences in their physicochemical stability and dissolution rate (Matsuda et al., 1994; Kobayashi et al., 2000). It has been reported (Young & Suryanarayanan, 1991;

Murphy et al., 2002) that the anhydrous CBZ polymorph (CBZ A) converts to the less soluble dihydrate form (CBZ D) in aqueous solution via a solution-mediated mechanism. The solution-mediated transformations are sensitive to solution conditions such as additives, pH, supersaturation and temperature. The presence of sodium lauryl sulphate in aqueous solution has been shown to accelerate the crystallization of CBZ D (Luhtala, 1992a; Rodriguez-Hornedo & Murphy, 2004). This emphasizes the important role of SLS in determining the dissolution behaviour of the metastable form of CBZ (CBZ A) and in developing a meaningful dissolution medium for such drug.

Therefore, the aim of the present study was to develop a universal dissolution medium for assessment of various CBZ product formulations (conventional and extended-release) with different strengths (100, 200, and 400 mg). The design of a system inhibiting transformation of the CBZ A to CBZ D, with minimum surface-active properties and suitable sink conditions was investigated. The effect of variables such as pH, different concentrations of sodium lauryl sulphate, polyvinylpyrrolidone and methyl cellulose on the solubility, dissolution solubility and polymorphic transformation of CBZ was studied. The suitability of the developed dissolution medium for assessment of the dissolution characteristics of CBZ products with different strengths was then evaluated.

MATERIALS AND METHODS

Materials

The following materials were used as received: carbamazepine (Novartis Pharma, Egypt), sodium lauryl sulphate (El-Nasr pharmaceutical Chemical Co., Egypt), methyl cellulose (Courtesy of Pharco pharmaceuticals, Alexandria, Egypt), polyvinylpyrrolidone MW 24000 (K25. BASF Aktiengesellschaft D-6700 Ludwigshafen, Germany). All solvents were of analytical grade. A commercial brand of carbamazepine tablets, Tegretol® (Novartis Pharma Egypt under Licence of Novartis Pharma, Basle, Switzerland BN: 7140) and the Innovator tablets, Tegretol® (Novartis Pharma, Basle, Switzerland, BN: 225900) and an imported commercial brand, Neurotop® (Gerot Pharmazeutika, Vienna, Austria BN: 574) were used. All tablets contained 200 mg carbamazepine.

Solubility Study of CBZ

Excess CBZ powder (particle size 125–200 μ) was added to 20 mL of each of the following media: distilled water containing 0, 0.2, 0.5, 0.75, and 1% w/v SLS, simulated gastric (SGF) and intestinal fluids (SIF) without enzymes. The mixtures were shaken for 24 h in a thermostated water bath at 37°C and left to equilibrate at the same temperature for 48 h. The concentration of CBZ in the filtered samples was determined spectrophotometrically at 286 nm, after suitable dilution. Each experiment was run in duplicate.

Dissolution Solubility Study of CBZ

Excess CBZ powder (particle size 125–200 μ) was added to 70 mL of each of the following media: distilled water, SGF and SIF without enzymes, polyvinylpyrrolidone aqueous solutions (PVP 0.1, 1, 2, 3% w/v), methyl cellulose aqueous solutions (MC 0.001, 0.005, 0.01, 0.05% w/v) and 0.01% w/v MC aqueous solutions containing 0.2, 0.3, 0.4, 0.5, or 1% SLS. The mixtures were shaken in a thermostated water bath at 37°C. Samples were taken at predetermined time intervals (5, 10, 15, 20, 30, 45, 75, 90 min, 2, 4, 6, 8, and 24 h). The concentration of CBZ in each sample was determined spectrophotometrically at 286 nm, after suitable dilution.

Dissolution Rate Studies

All dissolution rate studies were carried out in 900 mL of the dissolution medium. The medium was kept at 37°C and stirred with USP dissolution apparatus 2, at 75 rpm. Filtered samples were analyzed for CBZ content spectrophotometrically at 286 nm after suitable dilution. The dissolution media used were (a) 0.5 and 1% SLS aqueous solutions; (b) SGF and SIF without enzymes; and (c) 0.01% MC solution containing 0.5 % SLS.

Characterization of CBZ Polymorphic Transformation

The transformation of the anhydrous CBZ to the dihydrate form was examined in the media under study at different time intervals, using optical microscopy (optical microscope Olympus connected to a camera, Olympus-35 mm, Japan), Fourier-transform

infrared (FT-IR) spectroscopy (Perkin Elmer IR Spectrophotometer, potassium bromide disk method) and differential scanning calorimetry (Shimadzu DT-40, heat between 25°C and 300°C at 10°C/min, under nitrogen as purging gas).

RESULTS AND DISCUSSION

Several reports have attributed the variability in dissolution results not only to differences in the dosage forms but also to the variable flow-dynamic and poor mixing/ stirring in the USP dissolution device (Qureshi & Shabnam, 2001; Kukura et al., 2004; McCarthy et al., 2004; Qureshi, 2004; Baxter et al., 2005) and/or the use of an improper dissolution medium (Galia et al., 1998; Lobenberg et al., 2000). For CBZ, being a class II drug exhibiting solution-mediated transformation from the anhydrous to the dihydrate form, the design of a proper dissolution medium seems to be a critical parameter that should be investigated for this drug.

The literature survey presented in this study about the choice of dissolution medium for CBZ has questioned the suitability of USP 24 dissolution medium (1% w/v SLS solution) for in vitro assessment of various strengths of CBZ conventional formulations. Therefore, this medium was used to assess the dissolution characteristics of different strengths of three different CBZ products, together with CBZ raw material. To omit the effect of formulation factors, 200 mg CBZ tablets of each product were used to test for the dissolution of 100 mg (1/2 tablet), 200 mg (1 tablet) and 400 mg (2 tablets) mg CBZ. Figure 1 shows that different strengths of the same formulation exhibited different dissolution profiles. In all cases, except for the innovator product; superior dissolution rate of the 100 mg strength was observed even in case of CBZ raw material. These differences may be attributed to the excessive wetting effect of SLS on the 100 mg dose of CBZ as well as to the rapid polymorphic transformation and crystal growth of CBZ dihydrate. This observation may explain the reason for which USP 24 specified CBZ dissolution testing for products labeled as 200 mg tablets.

For better understanding of the possible factors contributing to the differences in dissolution profiles of different strengths of CBZ in 1% SLS, dissolution of 100 and 200 mg doses of the commercial product B was tested in different systems without or with low surfactant concentration. The results are shown in Fig. 2. In 0.5% SLS aqueous solution, differences between dissolution profiles of different strengths were still observed but to a lesser extent. On the other hand, overlapping profiles of 100 mg and 200 mg CBZ were observed in SGF and SIF, confirming the role played by SLS as a wetting agent in the dissolution medium. Therefore, development of a dissolution medium with minimized SLS concentration without affecting sink conditions as well as inhibiting transformation of the CBZ A to CBZ D during dissolution was investigated.

Equilibrium Solubility Study

Table 1 presents the values of equilibrium solubility of CBZ in different media together with the number of folds of saturation volume (FSV) provided by 900 mL of various media for different CBZ tablet strengths. Solubilities in water, SGF and SIF were nearly the same indicating that CBZ solubility is pH independent. CBZ may be considered as a neutral compound with no acidic or basic functions in a wide pH range. Water, SGF, and SIF failed to give enough sink conditions even for the lowest strength (2.1 FSV for 100 mg CBZ). Therefore, the specification of 900 mL and 1800 mL water as a dissolution medium for CBZ extended-release tablets (200 mg and 400 mg, respectively) by USP 27 is questionable.

The addition of surfactant to provide sink within a suitable volume was studied. Table 1 shows that the addition of SLS resulted in a marked increase in drug solubility. As low as 0.25% SLS could provide suitable sink for 100 mg strength with FSV of 3.24. The FSV provided by 0.5% SLS for 100 and 200 mg were 11.58 and 5.79, respectively. Thus, 0.5% SLS offers suitable sink for both strengths and the use of 1% SLS, the medium suggested by USP 27 for 200 mg CBZ conventional tablets, seems to be more than required. Concentrations higher than 0.5% may be needed for higher doses.

However, in all the solubility media under study, rapid transformation of CBZ A into needle shaped crystals of CBZ D was observed. It is worth noting that the solubility data presented in this study is that of the dihydrate and not of the anhydrous form of CBZ. It has been reported (Kahela et al., 1983; Laine et al., 1984) that it is difficult to determine the solubility of the anhydrous form because of its rapid transition to the dihydrate crystals in water.

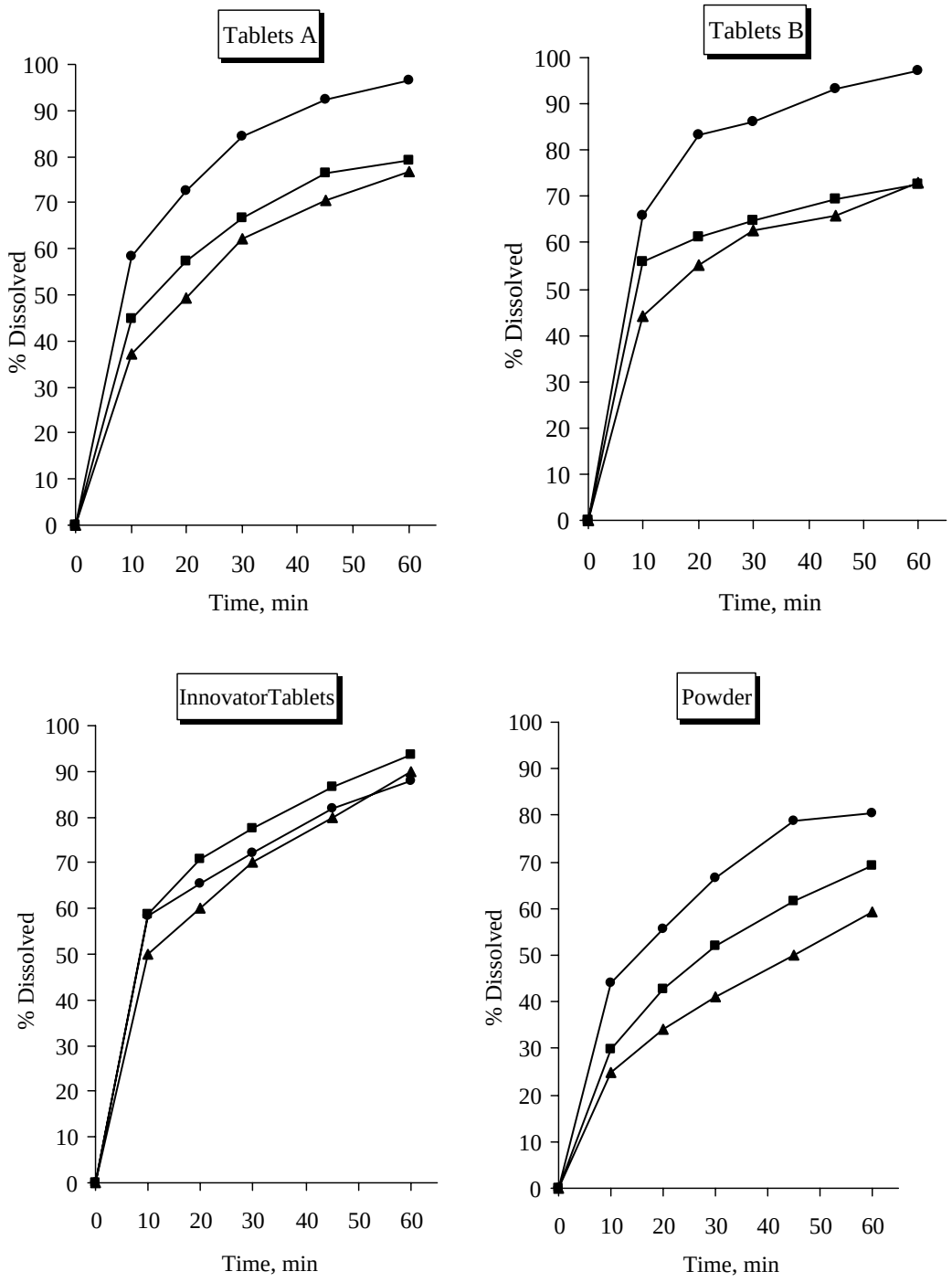


FIGURE 1 **Dissolution Profiles of Different CBZ Tablet Formulations and CBZ Powder (p.s.125–200 μm) with Different Strengths (●) 100 mg (■) 200 mg and (▲) 400mg, Using USP Dissolution Medium (1% SLS).**

Dissolution Solubility Studies

Dissolution solubility studies of CBZ in different vehicles were performed to test for the polymorphic transformation of anhydrous CBZ into dihydrate form and to determine the solubility of this form in different media in absence and presence of polymorphic transformation inhibitors. The results of this study are presented in Table 2 and Figs. 3–8. In general, the anhydrous form has greater aqueous solubility and faster dissolution rate than the hydrated form (Kobayashi et al., 2000; Di Martino et al., 2001; O'Connor & Corrigan, 2001). Dissolution solubility profiles of drugs exhibiting polymorphic transformation from anhydrous to dihydrate form are characterized by initial peak corresponding to the solubility

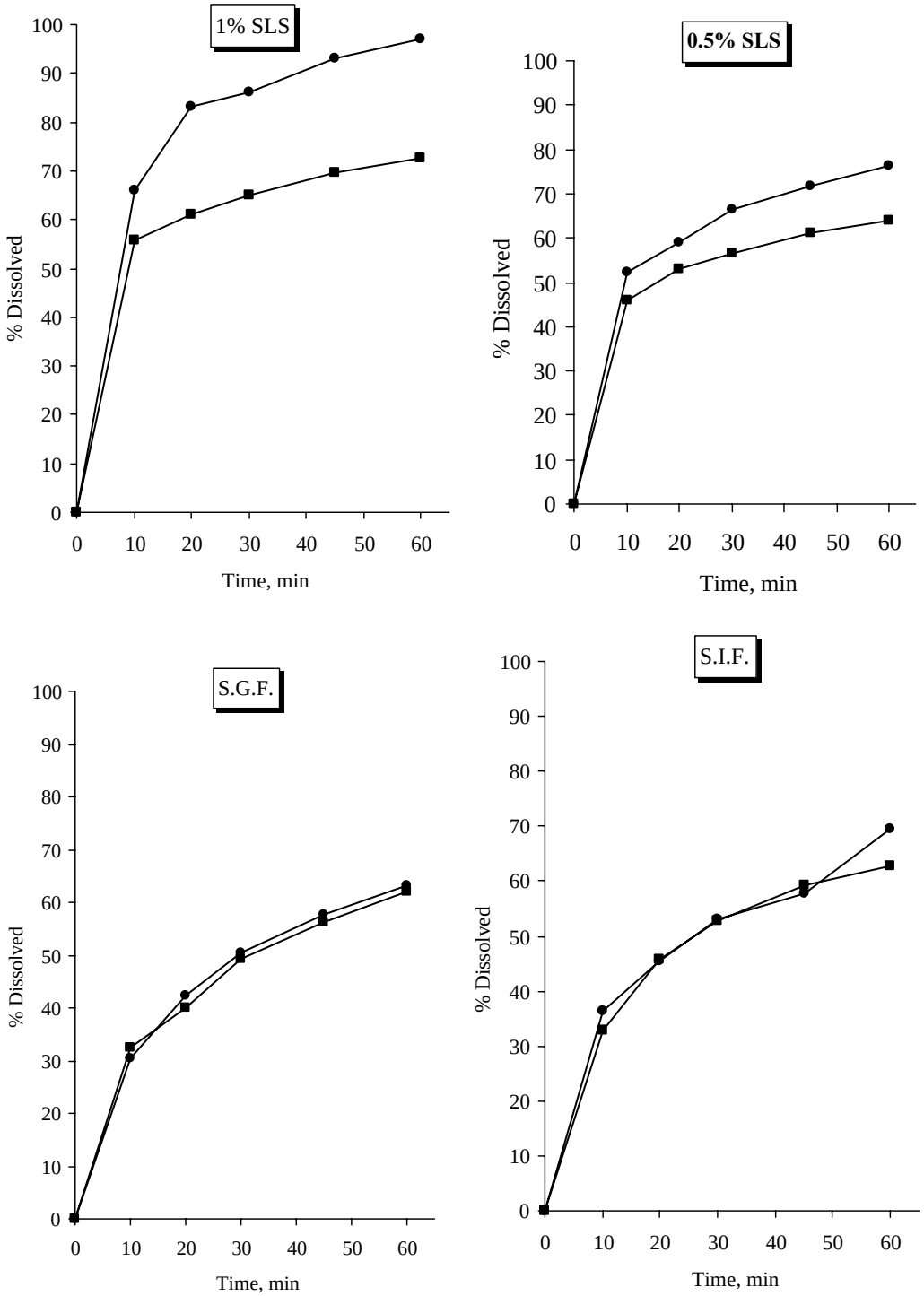


FIGURE 2 **Dissolution Profiles of Tablet Formulation B with Different Strengths: (●) 100 mg and (■) 200 mg, Using Different Dissolution Media.**

value of the anhydrous form and a possible short-term steady state, in which the rates of dissolution of the anhydrous form and crystallization of the hydrate are equal. Following this peak, a decline phase is observed, which is attributed to nucleation followed by crystallization of the more stable hydrate. The onset of decline phase is dependent on the rate of interconversion. In many cases where the transformation is very rapid, peak solubility could not be detected (Shefter & Higuchi, 1963). This dissolution behaviour, characteristic for

TABLE 1 Equilibrium Solubility of CBZ in Different Media (37°C)

Medium	Solubility (mg%)	Number of folds of saturation volume of CBZ in 900 mL		
		100 mg	200 mg	400 mg
0.1N HCl	25.682	2.31	1.15	0.57
S.G.F.	23.613	2.12	1.06	0.53
S.I.F.	23.982	2.15	1.07	0.53
Water	24.783	1.23	1.11	0.55
0.25% SLS	36.018	3.24	1.62	0.81
0.5 % SLS	128.728	11.58	5.79	2.89
0.75% SLS	218.550	19.66	9.83	4.91
1% SLS	296.458	26.68	13.3	6.65

TABLE 2 Peak and Equilibrium Solubility Data of CBZ in Different Media (37°C)

Medium	Peak solubility (mg%)	Equilibrium solubility (mg%)
Water	N.D.*	24.8
SGF (without enzymes)	N.D.	23.6
SIF (without enzymes)	N.D.	24.1
0.1% PVP	40.145	25.210
1% PVP	49.455	30.330
2% PVP	62.923	40.683
3% PVP	78.016	53.418
0.001% MC	42.406	40.533
0.005% MC	43.346	39.487
0.01% MC	42.014	41.02
0.05% MC	42.526	41.711
0.2% SLS/ 0.01% MC	93.328	88.502
0.3% SLS/ 0.01% MC	123.668	119.72
0.4% SLS/ 0.01% MC	167.637	159.67
0.5% SLS/ 0.01% MC	204.456	192.340
1.0% SLS/ 0.01% MC	375.486	367.52

*N.D.: Not detected.

polymorphs, was previously demonstrated by anhydrous CBZ in solutions of SLS (Luhtala, 1992a; Rodriguez-Hornedo & Murphy, 2004).

In the present study, peak solubility i.e. solubility of anhydrous CBZ could not be detected in media containing no transformation inhibitors, including SLS solutions of different concentrations, due to the very rapid polymorphic transformation. The 5 min samples gave nearly the same solubility data as equilibrium solubility. A photomicrograph of the crystals separated from 1% SLS solution, after 5 min, shows the abundance of the needle-shaped crystals of CBZ dihydrate (Fig. 3). Rodriguez-Hornedo and Murphy (2004) reported that as SLS concentration increased the threshold concentration for CBZ nucleation decreased and the crystallization rate of CBZ D occurred at a faster rate than the dissolution of CBZ A. The facilitated solution-mediated nucleation of CBZ D on the dissolved CBZ A was demonstrated to be due to adsorption of SLS at the CBZ A crystal-solution interface and solubilization of CBZ in these adsorbed SLS assemblies. This lead to high interfacial concentration of CBZ on the dissolving anhydrous surface and provide the driving force for crystallization of CBZ D on the surface of CBZ A.

Polymorphic transformation during dissolution run leads to dynamic changes of saturation solubility in the diffusion layer as well as changes in the particle size due to crystal growth. These two effects result in continuous change in the rate of drug dissolution through the dissolution run which might affect the validity of the dissolution system. Therefore, the use of transformation inhibitors in CBZ dissolution medium seems to be essential. Moreover, the presence of inhibitors leads to better sink conditions, as the equilibrium solubility will be that of the anhydrous form. The use of various additives to stabilize drug polymorphs has been reported (Ziller & Rupprecht, 1988; Luhtala, 1992b; Otsuka et al., 2003; Schmidt et al., 2003). These may include structurally related compounds, viscosity imparting materials (hydrocolloids) and surfactants. In the present study the effect of PVP and MC as polymorphic transformation inhibitors was studied. PVP was selected as an effective inhibitor of crystal transformation and growth and as a solubilizer (Motawi et al., 1982, Crowley & Zography, 2003, Miyazaki et al., 2004). MC is a protective colloid that has been also successfully used to inhibit crystal transformation and growth in pharmaceutical suspensions (Ebian et al., 1975; Raghavan et al., 2001).

Dissolution solubility profiles of anhydrous CBZ in water containing different PVP concentrations (0.1–3%) are shown in Fig. 4a. In presence of PVP, solubility of anhydrous CBZ could be determined due to delayed transformation to the dihydrate form. However, inhibition of polymorphic transformation by various PVP concentrations was only short term, as shown from the start of the decline phases of solubility profiles (45 and 75 min in case of 0.1% and 3% w/v PVP, respectively). Increasing PVP concentration delayed the crystallization of CBZ dihydrate. Dihydrate crystals were first observed after 30 min in 0.1%

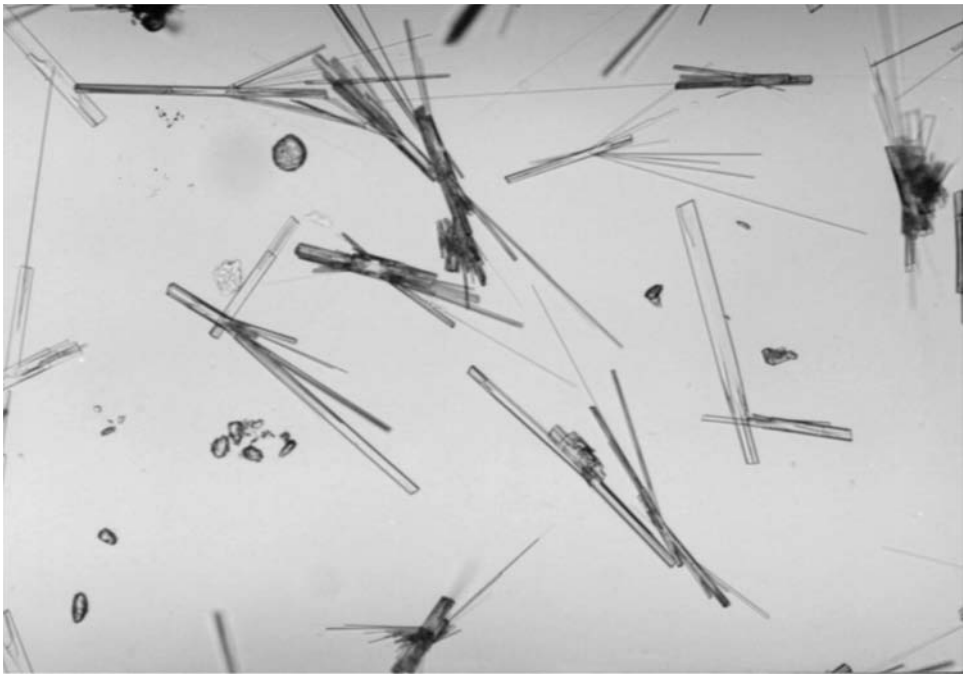


FIGURE 3 **Photomicrograph of CBZ (D) Crystals Separated from 1% SLS Solution After 5 Min of the Dissolution Solubility Study.**

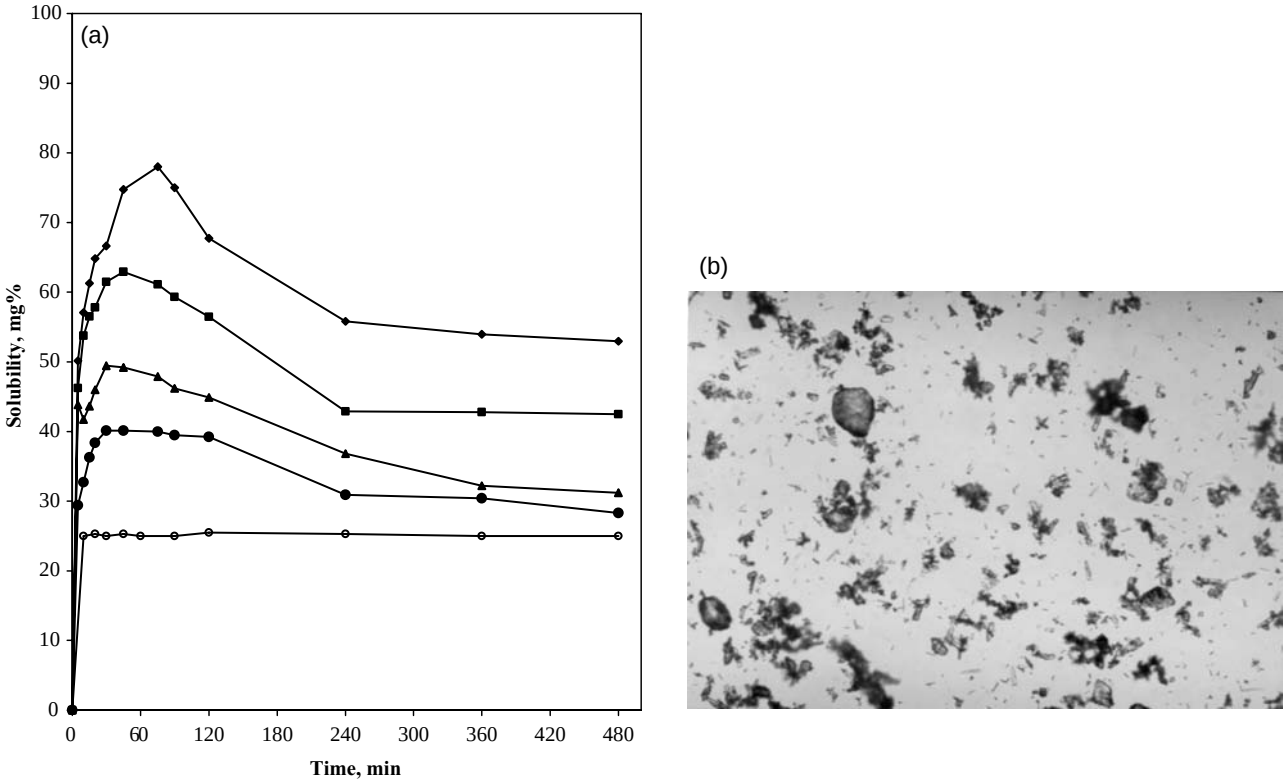
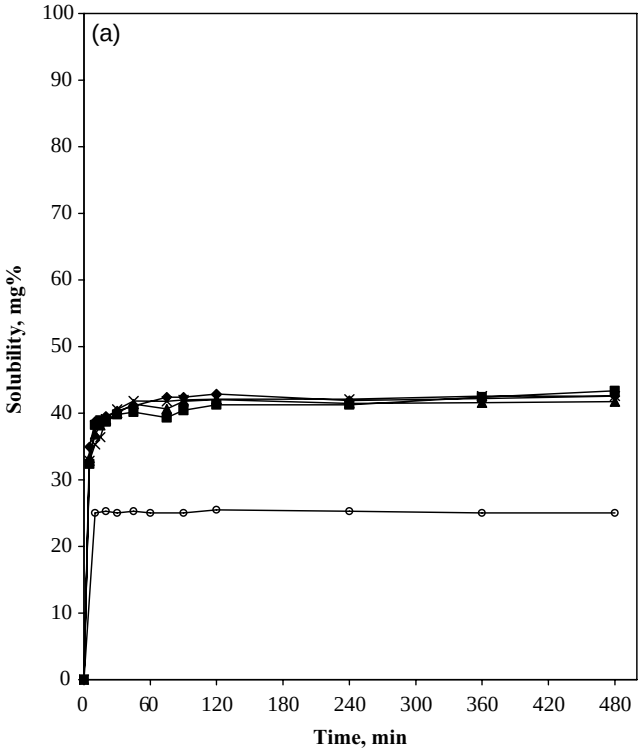


FIGURE 4 **(a) Dissolution Solubility Profiles of CBZ Powder (p.s.125–200 μm) in Aqueous Solutions Containing Different Concentrations of Polyvinylpyrrolidone (PVP): (○) 0% (●) 0.1% (▲) 1.0% (■) 2% and (♦) 3% w/v. (b) Photomicrograph of CBZ Crystals Separated at Peak Solubility from 3%w/v PVP Aqueous Solution.**



(b)

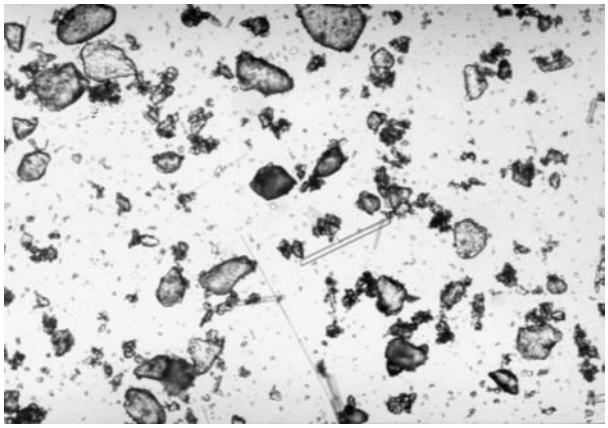
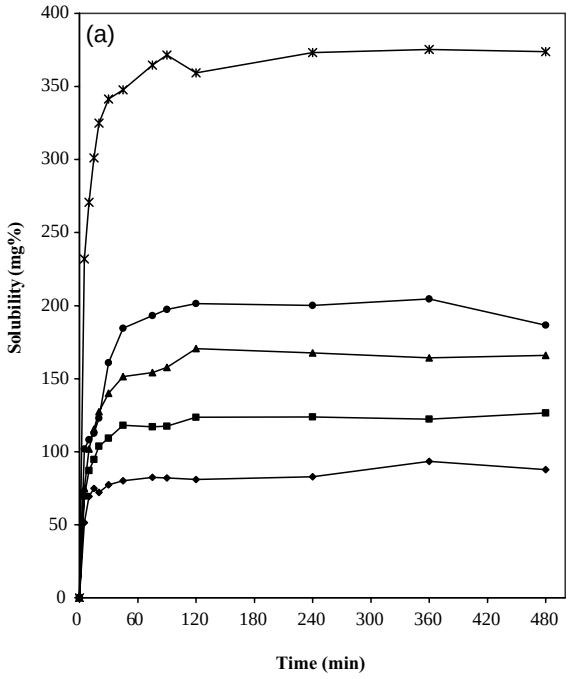


FIGURE 5 (a) Dissolution Solubility Profiles of CBZ Powder (p.s.125–200 μm) in Aqueous Solutions Containing Different Concentrations of Methylcellulose: (○) 0% (♦) 0.001% (■) 0.005% (▲) 0.01% and (x) 0.05%. (b) Photomicrograph of CBZ Crystals Separated from 0.01% Methylcellulose Aqueous Solution after 24 h of the Dissolution Solubility Study.



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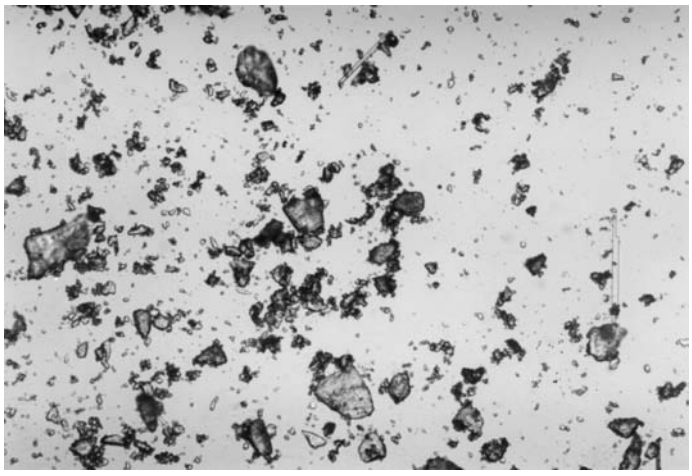

FIGURE 6 (a) Dissolution Solubility Profiles of CBZ Powder (p.s.125–200 μm) in 0.01% Methylcellulose Solutions Containing Different Concentrations of SLS: (♦) 0.2% (■) 0.3% (▲) 0.4% (●) 0.5% and (★) 1% w/v. (b) Photomicrograph of CBZ Crystals Separated from Aqueous Solution Containing 0.5% SLS and 0.01% Methylcellulose, after 24 h of the Dissolution Solubility Study.

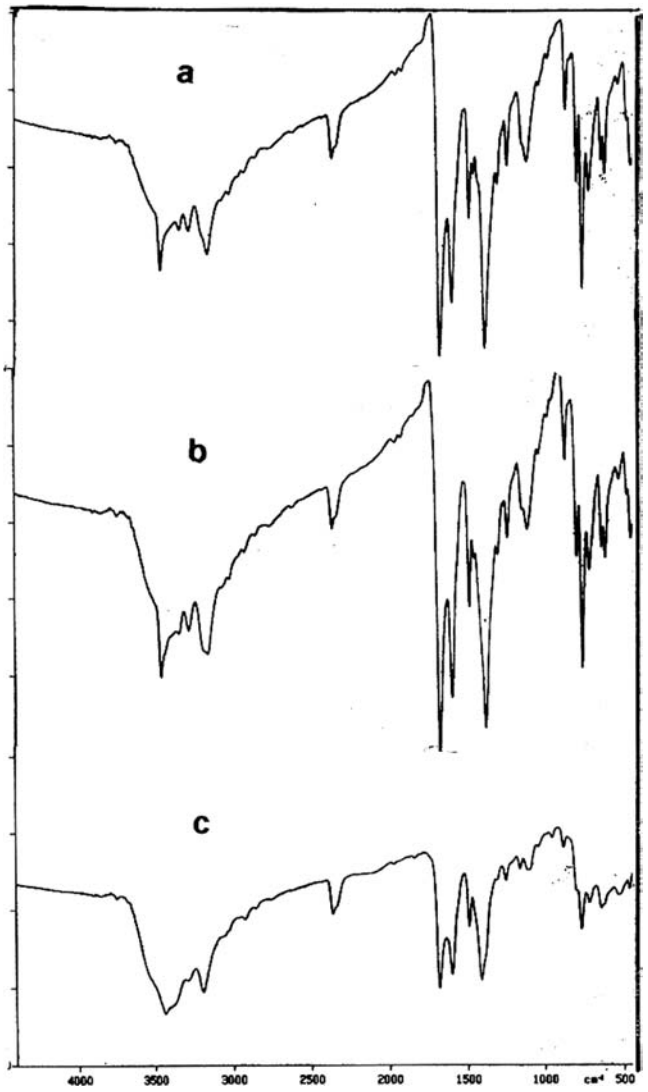

FIGURE 7 **FTIR Spectra of a) CBZ Raw Material, and CBZ Solids Separated after 2 and 24 h of the Dissolution Solubility Study from Aqueous Solutions Containing b) 0.5% SLS and 0.01% Methylcellulose or c) 1% SLS.**

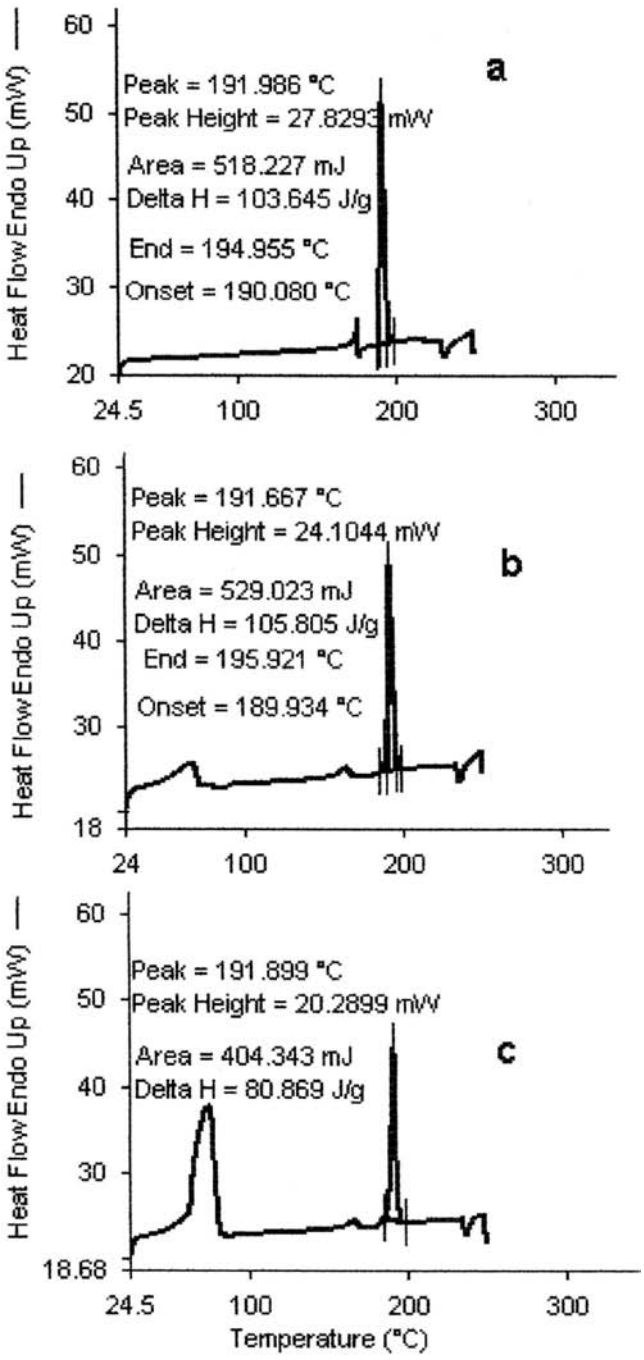

FIGURE 8 **DSC Curves of a) CBZ Raw Material, and CBZ Solids Separated after 2 and 24 h of the Dissolution Solubility Study from Aqueous Solutions Containing: b) 0.5% SLS and 0.01% Methylcellulose or c) 1% SLS.**

PVP compared to 60 min in 3% PVP (Fig. 4b). It could be noticed that the interconversion protection period offered even by 3% PVP is too short to be useful in protection of CBZ during dissolution rate studies. Higher concentrations of PVP were not tested due to increased viscosity, cost and interference with spectrophotometric assay. It is worth noting that addition of relatively high concentration of PVP slightly increased the solubility of CBZ (Table 2). Peak solubility at 3% PVP was 78 mg%, which is not enough to provide sink condition, except for 100 mg CBZ strength.

Dissolution solubility profiles of CBZ in water containing different concentrations of MC are illustrated in Fig. 5a. The profiles overlapped and showed a plateau extending for up to 24 h at a solubility value 1.6 folds that in water. This indicates a solubility curve of the anhydrous form and absence of solubilization effect of MC. A limited number of small dihydrate crystals were microscopically detected in 0.001% and 0.005% MC after 2 and 6 h respectively. Further, addition of 0.01% or 0.05% MC proved to be enough for complete transformation inhibition up to 24 h (Fig. 5b).

The polymorphic transformation inhibitory effect of PVP may be due to formation of adsorption protective layers on the crystal surfaces preventing the diffusion of drug molecules to these surfaces (Ziller & Rupprecht, 1988). The protective effect depends upon the irreversibility of polymer adsorption onto active sites which requires strong adsorption forces and surface properties of the crystal face allowing establishment of adsorption layer (Ziller & Rupprecht, 1990). Short-term protective effect of PVP may be due to reversible adsorption on CBZ crystals. Whereas prolonged inhibition offered by a much lower concentration of MC may be attributed to the formation of stable adsorbates. Lower aqueous solubility of MC, relative to PVP, may contribute to its higher affinity towards adsorption onto CBZ crystal surface.

Based on the results of solubility study of CBZ in SLS solutions and its dissolution solubility study in MC solutions, it seemed interesting to assess the dissolution solubility of CBZ in different concentrations of SLS aqueous solutions in presence of 0.01% MC. The results are presented in Table 2 and Fig. 6a and Absence of peaking and extended plateau was observed in all dissolution profiles obtained (Fig. 6a). In addition, microscopical examination of samples taken at different time intervals showed the absence of dihydrate crystals and confirmed complete protection for 24 h at different SLS concentrations (Fig. 6b). The inhibited conversion of CBZ A into CBZ D in 0.5% SLS/0.01% MC medium, in comparison to that in 1% SLS (USP medium) was further confirmed, using FTIR and DSC.

FTIR spectrum of CBZ raw material (Fig. 7a) showed absorption peaks at 3463, 1677 and 1385 cm^{-1} characteristic of anhydrous CBZ Form III (Grzesiak et al., 2003). CBZ solid particles separated from 0.5% SLS/0.01% MC aqueous solution after 2 and 24 hrs (CBZ/SLS/MC) showed similar spectrum (Fig. 7b) to anhydrous CBZ, indicating the absence of polymorphic transformation. Whereas, solids withdrawn from 1% SLS aqueous medium, after 2 and 24 h (CBZ/SLS 1%) exhibited different spectrum (Fig. 7c). A broad band appeared in the region of 3500–3200 cm^{-1}, representing OH group of the water of crystallization and hydrogen bonding and pointing to the presence of CBZ D.

CBZ raw material exhibited a DSC thermogram (Fig. 8a) similar to that of anhydrous CBZ Form III reported by Grzesiak et al. (2003). One endothermic peak occurred at 175°C, followed immediately by an exotherm indicating melting of Form III and crystallization of Form I, respectively. A second endotherm corresponding to the melting of Form I appeared at 191.98°C. While CBZ/SLS/MC solids showed a DSC curve (Fig. 8b) similar to that of the anhydrous form, CBZ/SLS 1% exhibited a thermogram (Fig. 8c) characteristic of CBZ dihydrate III (McMahon et al., 1996). Water removal occurred at 60–80°C, followed by a small endotherm at 165°C and a melting endotherm at 191.89°C. In addition, the enthalpy of this later endotherm was lower than that seen for the CBZ raw material and CBZ/SLS/MC solids (Delta H values were 80.87, 103.65, and 105.81 j/g, respectively). This was previously attributed to the lower crystallinity of the anhydrous form obtained by heating the dihydrate form (McMahon et al., 1996).

A system containing 0.5% SLS and 0.01% MC seems to be a suitable dissolution medium, for CBZ tablets, inhibiting conversion of CBZ A to CBZ D. As a result of the prolonged protective effect of MC, solubility of CBZ was increased to 204 mg % representing that of the anhydrous form, compared to 128 mg % representing that of the dihydrate form in 0.5% SLS alone (Table 2). Thus, it was possible to reduce the amount of SLS to half the amount used in official CBZ dissolution medium and achieve suitable sink conditions for up to 400 mg CBZ with 4.6 FSV.

Evaluation of the Developed Dissolution Medium

Dissolution profiles of CBZ commercial tablets (100 mg and 200 mg) and CBZ powder (100, 200, and 400 mg) in the selected medium are shown in Fig. 9. The nearly overlapping profiles of various strengths of each formulation may be attributed to the reduced wetting effect of SLS due to reduction of SLS concentration to 0.5% and the effect of the polymer protective layer formed by MC. In addition, a discrimination between the dissolution profiles of the different CBZ tablet formulations and of CBZ powder could be observed. Further, in an earlier report (Galal et al., 2004), the developed dissolution medium showed a good discrimination between the release profiles of different CBZ extended-release semisolid matrix filled capsule formulations prepared in our laboratory.

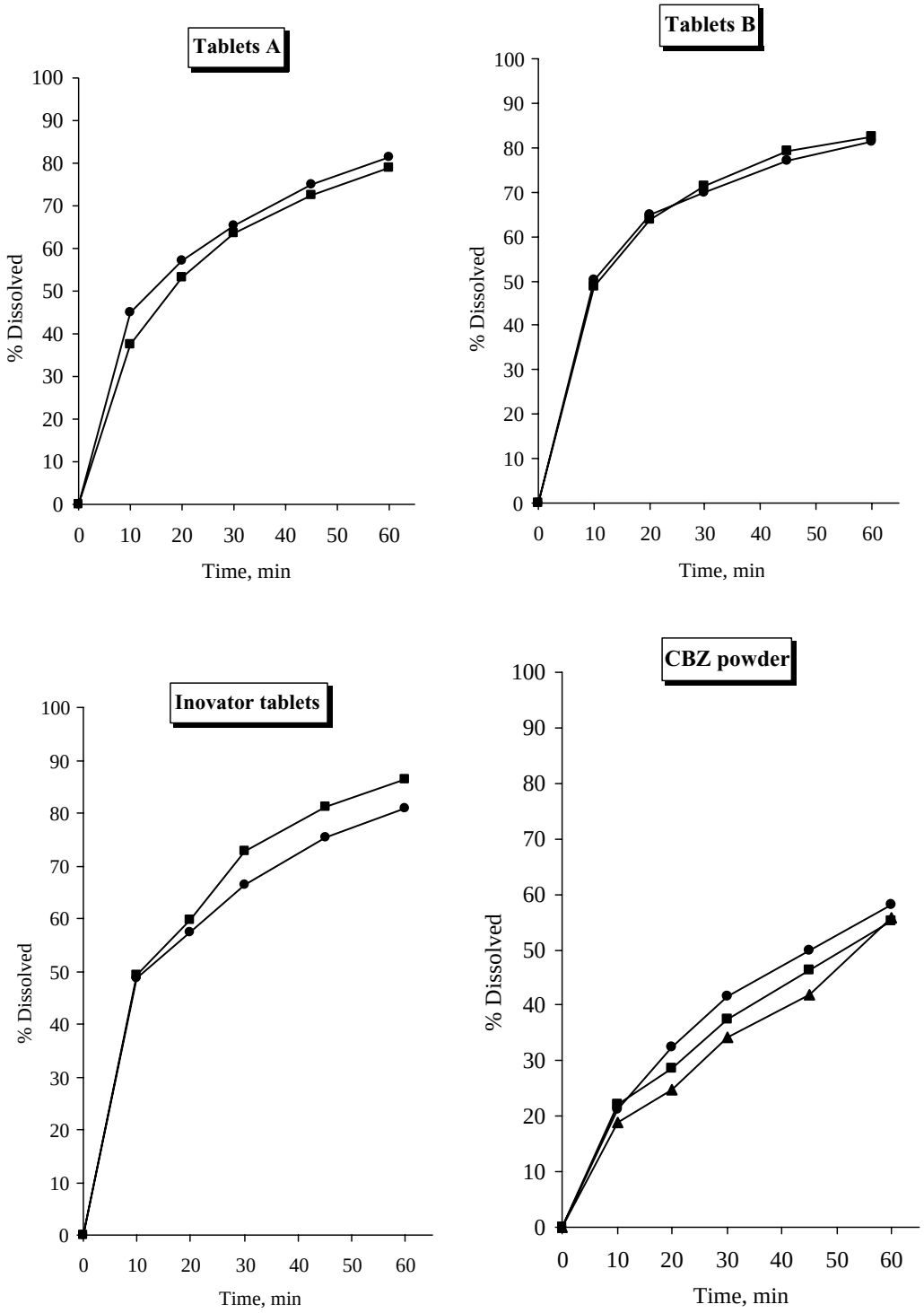

FIGURE 9 **Dissolution Profiles of Different CBZ Tablet Formulations and CBZ Powder (p.s.125–200 μm) with Different Strengths: (•) 100 mg (■) 200 mg and (▲) 400 mg (for powder) Using the Developed Dissolution Medium (0.5% SLS/0.01%MC)**

CONCLUSIONS

Results of the present study show that a system containing 0.5% SLS and 0.01% MC seems to be a suitable dissolution medium for assessment of different CBZ product formulations (conventional and extended-release) of different strengths (100, 200, and 400 mg) since it offers a) protection against transformation of the CBZ A to CBZ D, b) minimization of wetting effect due to reduction of sodium lauryl sulphate concentration to 0.5%, and c) Suitable sink conditions for up to 400 mg CBZ with 4.6 folds of saturation volume.

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