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Tablet formulation studies on an oxcarbazepine-β cyclodextrin binary system

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Oxcarbazepine is a poorly water-soluble (0.083 mg/ml) anti-epileptic drug according to the BCS system (class II) and its dissolution is rate-limiting step for its absorption. The objective of this work was to develop tablet formulations of oxcarbazepine-β-cyclodextrin (OX-β-CD) binary systems. Three types of binary systems – physical mixtures, kneaded systems, and coevaporated systems – were studied. Phase solubility studies indicated 1 : 1 M complexation of oxcarbazepine with β-cyclodextrin. Drug-β-CD binary systems were prepared at 1 : 1 molar ratios and used in formulation studies. The dissolution properties of OX-β-CD KS (kneaded system, 100.10% drug release in 15 min) were superior than those of the other binary system and pure oxcarbazepine. The tablet formulations containing drug-β-CD binary systems prepared by wet granulation and direct compression showed superior dissolution properties when compared with the formulations of the corresponding pure drug formulations. Tablet formulations containing drug-β-CD binary systems prepared by the kneading method showed good dissolution properties (100% drug release in 15 min in direct compression method and 99.9% drug release in 20 min in wet granulation method). Overall, the dissolution properties of tablet formulations prepared by the direct compression method were superior to those of tablets prepared by the wet granulation method. Accelerated stability studies on some selected tablet formulations were also conducted by keeping the samples at 40 ± 2 °C and 75% relative humidity. There were no statistical differences in the percentage of drug dissolved at 15 and 20 min between fresh and stored samples at the different time points ($P < 0.05$). Drug content also remained within acceptable limits. Thus, drug-β-CD binary systems are useful in developing tablet formulations of oxcarbazepine with improved dissolution properties.

1. Introduction

Cyclodextrins (CDs) are able to form inclusion complexes with poorly water-soluble drugs. These inclusion complexes have been shown to improve stability, solubility, dissolution rate, and bioavailability (Duchene and Wouessidjewe 1990; Bekers et al. 1991). Improvement in hydrophilicity may be attributed either to the formation of inclusion complexes or to the highly homogeneous assembly between CDs and drugs in the solid state. In most cases, this association increases the solubility of poorly soluble drugs. Drug-CD binary systems are also useful in dosage form development for increasing the solubility, dissolution, and absorption rates of poorly soluble drugs in tablet or capsule form.

Oxcarbazepine is a poorly water-soluble drug (0.083 mg/ml) according to the BCS systems (class II) and its dissolution is the rate-limiting step for its absorption. The poor aqueous solubility and wettability of oxcarbazepine give rise to difficulties in pharmaceutical formulations intended for oral use, which may lead to variation in bioavailability (Piel et al. 1997).

The solubility and dissolution properties of oxcarbazepine were improved by complexation with β-CDs. The drug-β-CD complex was characterized by infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), powder x-ray diffractometry (X-RD) and scanning electron microscopy (SEM). Thus, in the present investigation we have evaluated the feasibility of formulating these drug-β-CD binary systems into tablet dosage forms. These drug-β-CD binary systems were formulated into tablets by both the conventional wet granulation method and the direct compression method. The tablet formulations were evaluated for their physical and dissolution properties. Accelerated stability studies on some selected tablet formulations were also conducted to assess the formulation shelf life and determine any possible degradation.

2. Investigations, results and discussion

2.1. Phase solubility studies

The phase-solubility diagram for the complex formation between oxcarbazepine and β-cyclodextrin is presented in Fig. 1. This plot shows that the aqueous solubility of the drug increases linearly as a function of β-cyclodextrin concentration. It is clearly observed that the solubility diagram of oxcarbazepine in the presence of β-cyclodextrin can be classified as the A_L type. The linear host-guest correlation with slope of less than 1 suggested the formation

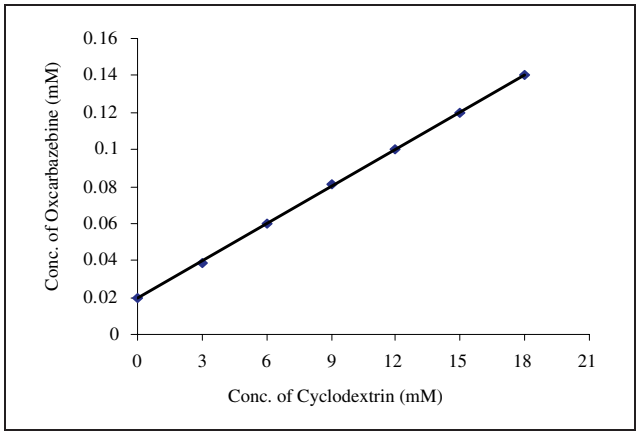

Fig. 1: Phase-solubility pattern of oxcarbazepine-β-cyclodextrin system in water (mean ± SD; n = 3)

of a 1 : 1 (oxcarbazepine β-cyclodextrin) complex with respect to β-cyclodextrin concentrations. The apparent stability constant, Kc, obtained from the slope of the linear phase solubility diagram was found to be 221.9 M^{-1}, which indicates that the oxcarbazepine-β-cyclodextrin complexes at 1 : 1 ratios are adequately stable.

2.2. Detection of inclusion complexation in the solid state

When an assumed drug-CD binary system is dispersed in a dissolution medium, a very rapid dissolution is often observed. Rapid dissolution is the characteristic behavior of inclusion complexes. The most often used dissolution rate tests are the rotating disk method and the dispersed amount method (Chowdary and Buchi 1999). In the present investigation, the dispersed amount method was used to investigate the various dissolution parameters of OXC and OXC-β-CD binary systems. The results in terms of percent of active ingredient dissolved at 30 min (DP_{30}) are

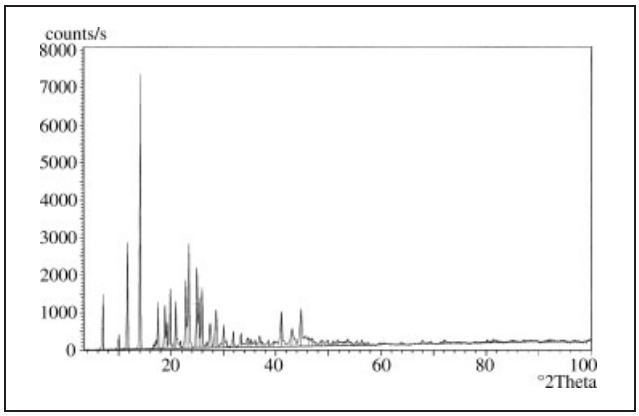

Fig. 2: XRD spectra of oxcarbazepine

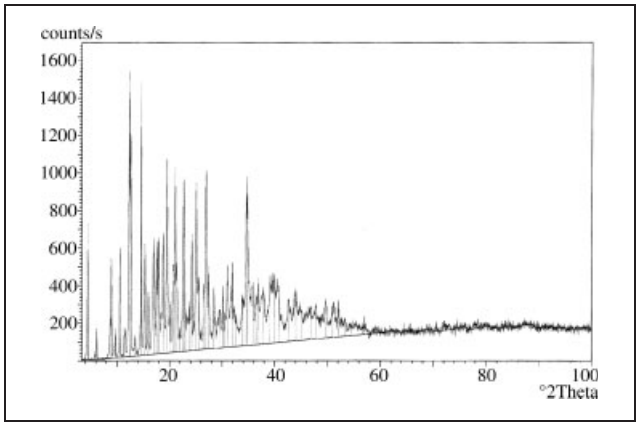

Fig. 3: XRD spectra of β-cyclodextrin

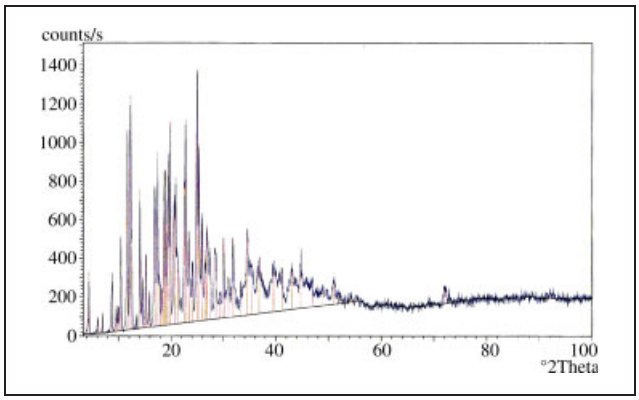

Fig. 4: XRD spectra of oxcarbazepine-β-cyclodextrin kneaded product

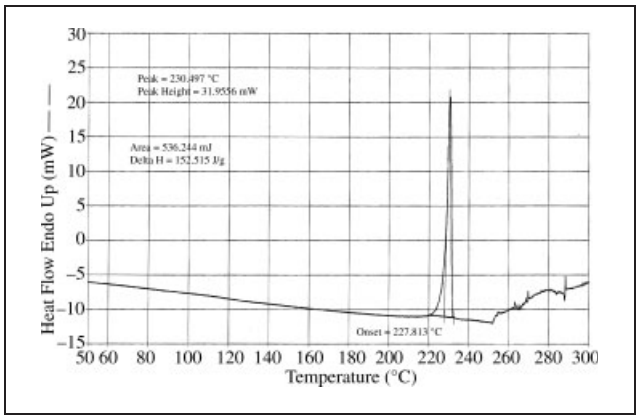

Fig. 5: DSC thermogram of oxcarbazepine

presented in Table 1. The increase in dissolution rate and efficiency values recorded for the binary mixtures may be explained on the basis of the solubility of the drug in aqueous CD solutions. Because the CD dissolve more rapidly in the dissolution medium than the pure drug, it can be

Table 1: Mean ± SD values of DP_{30} for OXC and OXC-β-CD binary systems (n = 3)*

Sample	OXC	OXC-β-CD PM 1 : 1 M	OXC-β-CD CS 1 : 1 M	OXC-β-CD KS 1 : 1 M
DP_{15}	15.02 ± 0.59	45.32 ± 0.60	85.44 ± 0.58	100.10* ± 0.01
DP_{30}	36.44 ± 0.65	65.02 ± 0.27	99.52 ± 0.29	101.15 ± 0.08

* Complete drug dissolution achieved within 15 min. DP indicates percent of active ingredient dissolved at 15 and 30 minutes; OXC, oxcarbazepine; β-CD, β cyclodextrin; PM, physical mixture; KS, kneaded systems; CS, coevaporated systems

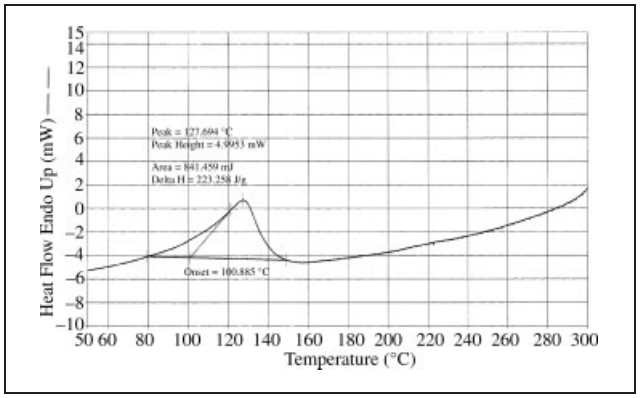

Fig. 6: DSC thermogram of β-cyclodextrin

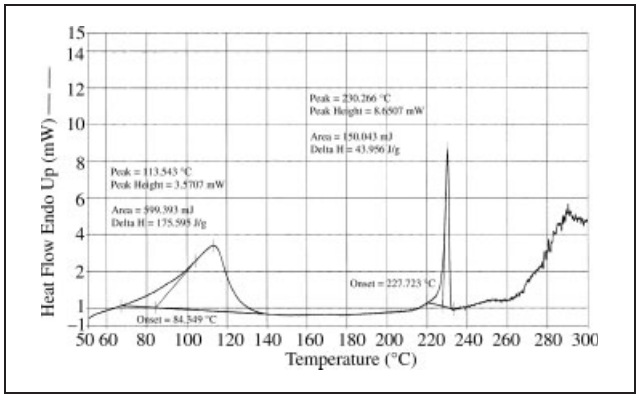

Fig. 7: DSC thermogram of oxcarbazepine-β-cyclodextrin kneaded product

assumed that, in early stages of the dissolution process, the CD molecules will operate locally on the hydrodynamic layer surrounding the particles of the drug. This action results in an in situ inclusion process, which produces a rapid increase of the amount of the dissolved drug. The DP_{30} values of OXC-β-CD kneaded systems were higher than those of coevaporated systems. The superior dissolution properties observed with kneaded systems over coevaporated systems may be due to the better interaction of OXC with β-CD during the kneading process. Various authors suggested that dissolution rates from drug-CD binary systems are also dependent on other factors, such as diffusion and dissociation of the complex in the dissolution medium and decrease in crystallinity and enhanced wettability of the drugs by the inclusion complexation. In the present investigation, mainly crystallinity of the drug along with other factors played an important role in increasing dissolution rate.

The powder x-ray diffractometry patterns for the oxcarbazepine, β-cyclodextrin and oxcarbazepine-β-cyclodextrin kneaded systems are represented in Figs. 2–4. As a consequence of the coincidence of diffraction peaks between

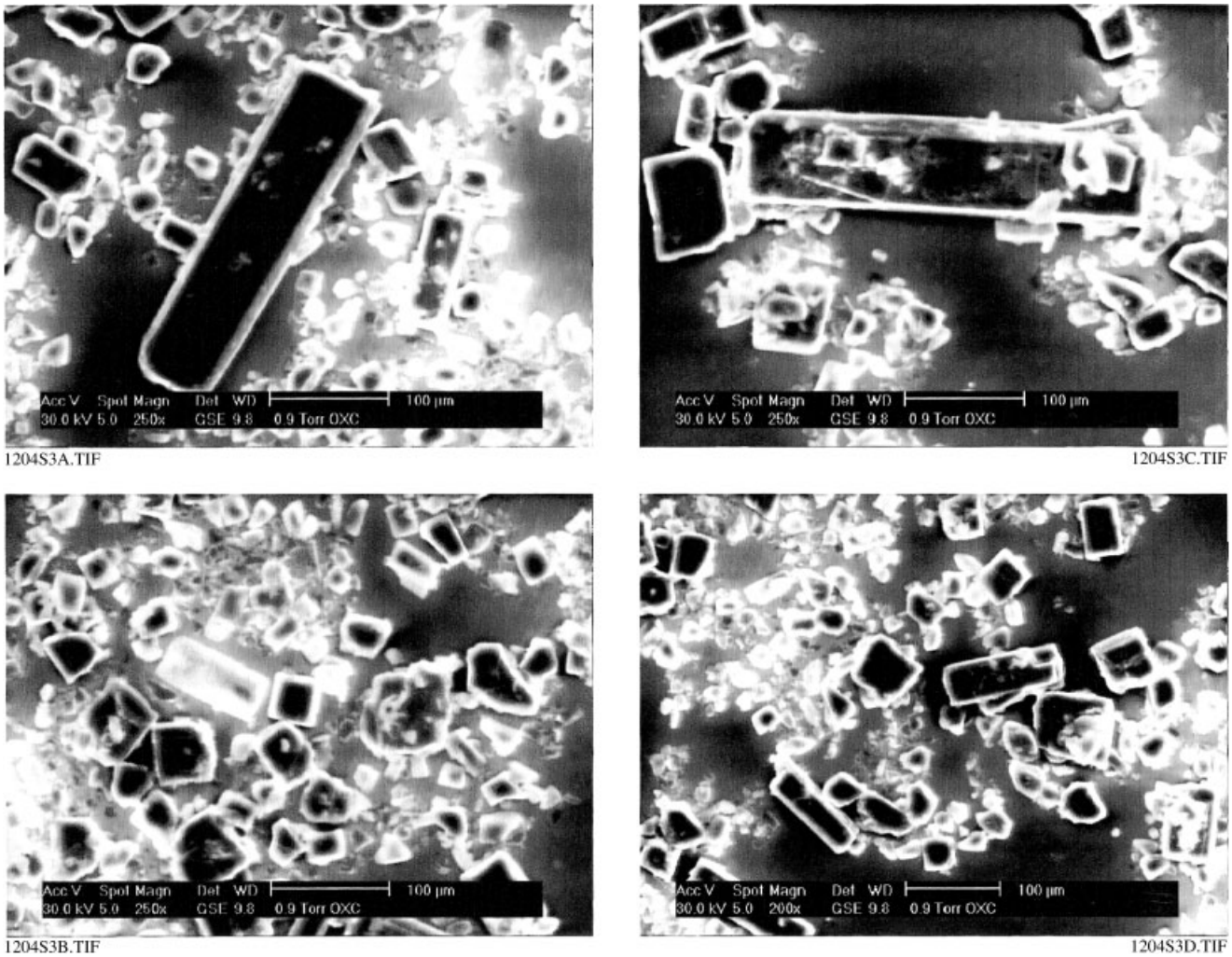

Fig. 8: Scanning electron photomicrographs of oxcarbazepine

oxcarbazepine and β-cyclodextrin, we have selected as characteristic peaks of oxcarbazepine those situated in between 6° and 45° (2φ), for confirmation of the nature of oxcarbazepine for these studies. The presence of several different peaks in the oxcarbazepine diffraction pattern indicates that the drug is in crystalline from. The kneaded system exhibits considerable diminution of the diffraction peaks, suggesting that it is less crystalline than pure drug. The reduction in crystallinity attributed to the kneaded system is clearly evident for pure β-cyclodextrin, while oxcarbazepine does not show this effect. These results suggest that oxcarbazepine and β-cyclodextrin form an inclusion complex in the solid state, demonstrating that a new solid phase is formed in the kneaded product. It may be concluded that as the heights of the diffraction peaks were reduced, the degree of crystallinity was reduced in the case of solid inclusion complexes. The results also suggest a partial inclusion at 1 : 1 M ratio in solid state.

The Differential scanning calorimetry thermograms for the oxcarbazepine, β-cyclodextrin and oxcarbazepine-β-cyclodextrin kneaded systems are shown in Figs. 5–7. Oxcarbazepine exhibits a characteristic endothermic fusion peak at 230.5 °C; hence no polymorphs of oxcarbazepine could be found. Furthermore, β-cyclodextrin shows a broad endothermic effect at 127.7 °C. The DSC thermograms for the oxcarbazepine-β-cyclodextrin systems show the endothermic peak of oxcarbazepine for the kneaded product is very small; this result can be explained on the basis of a major interaction between the drug and cyclodextrin. Furthermore, the characteristic thermal peak of the drug appeared to lower temperatures, but strongly reduced in intensity and somewhat broadened, in the kneaded product of oxcarbazepine-β-CD, indicating that oxcarbazepine has complexed with β-cyclodextrin. In fact, even though not un-ambiguously attributable to inclusion complexation, this phenomenon is indicative of a stronger interaction between oxcarbazepine and β-cyclodextrin in the solid state.

Scanning electron microscopy pictures of oxcarbazepine and the oxcarbazepine-β-cyclodextrin kneaded system are shown in Figs. 8 and 9. Oxcarbazepine appeared as irregular-shaped crystals and oxcarbazepine-β-cyclodextrin kneaded product was constituted by relative bulky particles (β-cyclodextrin), with other small ones (oxcarbazepine) adhered on its surface. The comparable morphology of these systems with pure components could reveal that apparently no oxcarbazepine-β-cyclodextrin interaction has taken place in the solid state, although the number of oxcarbazepine particles that adhered on β-cyclodextrin surface was greater in the kneading system. The drastic change of the particles' shape and aspect in the kneaded samples suggested the presence of a new solid phase, leading us to estimate the existence of a single phase, thus corroborating the PXRD observations.

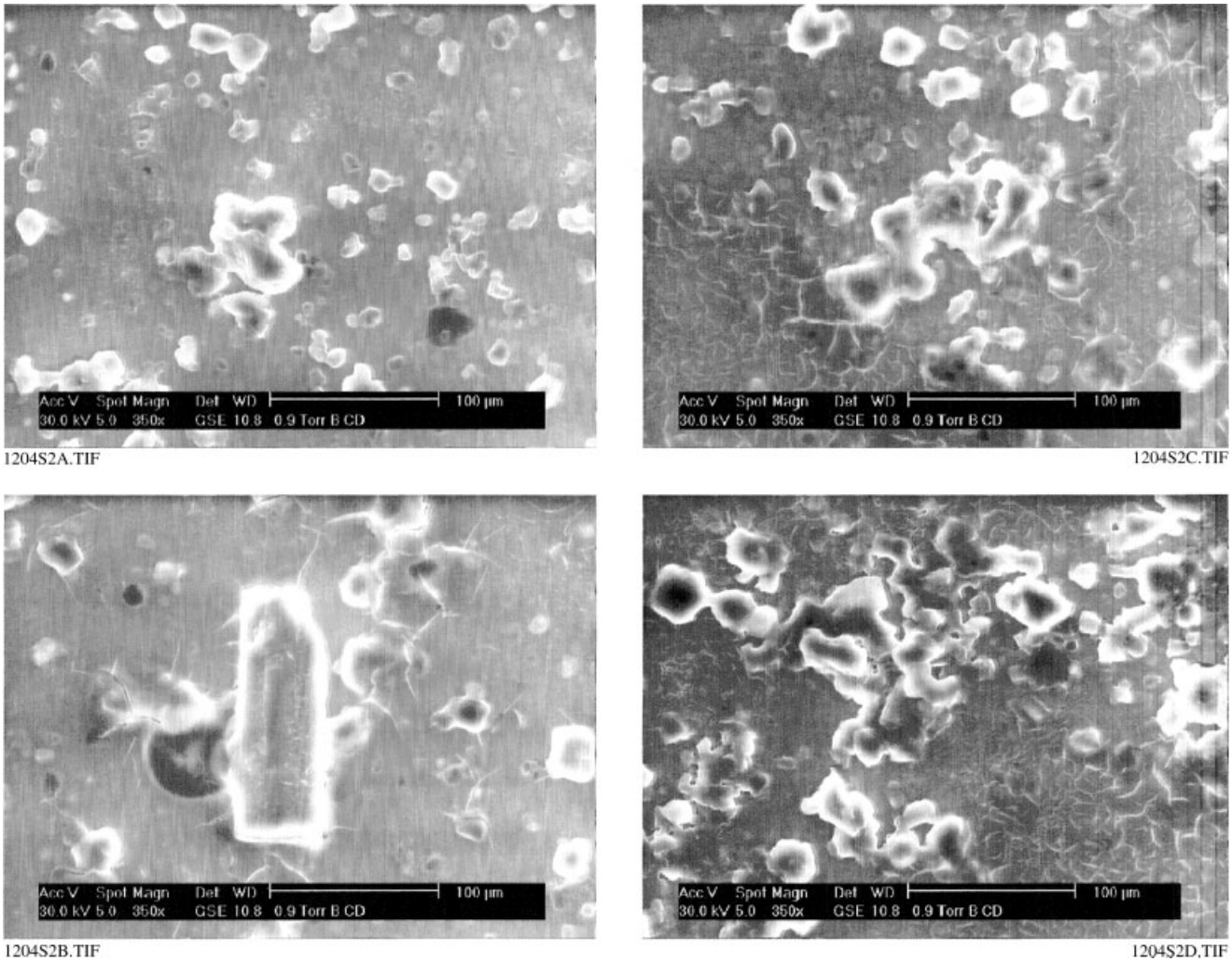

Fig. 9: Scanning electron photomicrographs of oxcarbazepine-β-cyclodextrin kneaded product

Table 2: Tablet properties of OXC and OXC-β-CD formulations*

Formulation	Drug Content (mg/tab)	Mean Weight (% deviation)	Hardness (kg/cm^2)	Friability (% wt loss)	Disintegration time (min)
F1	99.20	960.90 (−0.01 to 0.41)	5	0.53	6.15
F2	100.12	961.85 (−0.01 to 0.43)	4.5	0.38	6.10
F3	100.07	961.35 (−0.06 to 0.59)	5.5	0.42	5.50
F4	99.82	961.85 (−0.01 to 0.64)	5	0.46	4.25
F5	99.92	962.00 (−0.04 to 0.63)	4.5	0.50	4.10
F6	100.17	960.20 (−0.02 to 0.82)	5	0.37	4.00

* OXC indicates oxcarbazepine; OXC-β-CD, oxcarbazepine-β-cyclodextrin. F_1 to F_3, tablet formulations prepared by the wet granulation method; F_4 to F_6, tablet formulations prepared by the direct compression method

2.3. Tablet properties

The drug content of tablets was within the $100 \pm 5\%$ of label claim, and the results were satisfactory (Table 2). A good degree of uniformity of weight was achieved for all the batches of tablet formulations prepared. The percent deviation did not exceed 5%, indicating excellent uniformity of weight in all the batches of tablet formulations prepared. All the tablet batches exhibited good mechanical properties with regard to both hardness and friability (Table 2). No significant difference in hardness values within the batches of tablet formulations was observed. In the friability studies, weight loss values of all the tablet batches were less than 1%. All the tablet formulations prepared by wet granulation and direct compression methods, respectively, fulfilled the compendial requirement for disintegration time for compressed tablets: less than 15 min (Table 2). Tablet formulations containing drug-β-CD binary systems prepared by the direct compression method showed significantly lower disintegration time values than did the formulations prepared by the wet granulation method.

All tablet formulations were subjected to *in vitro* dissolution rate studies using 0.1 N HCl containing 0.25% sodium lauryl sulfate (SLS) as the dissolution medium to assess various dissolution properties. The dissolution properties of tablets prepared by direct compression were superior when compared with those of tablets prepared by wet granulation (Fig. 10). However, tablet formulations containing PM prepared by the wet granulation method (F_2) showed superior dissolution properties when compared with the tablets prepared by the direct compression method (F_5). This may be attributed to the greater interparticle interaction of oxcarbazepine with β-CD that may occur during the granulation process, where a doughlike mass is used for the preparation of granules. The tablet formulations containing OXC-β-CD KS (kneaded system) showed superior dissolution (100% drug release in 15 min in direct compression method and 99.9% drug release in 20 min in the wet granulation method) compared with formulations containing PM, irrespective of the method of tablet preparation. These results indicate that the fast release characteristics of these binary systems were not changed, even though they were formulated into tablets. Thus, OXC-β-CD binary systems can be used in developing tablet formulations of oxcarbazepine with good tabletting and dissolution properties. Overall, tablet formulations prepared by the direct compression method showed dissolution properties superior to those of the formulations prepared by the wet granulation method. This can be better explained by the fact that for tablets prepared by direct compression, the drug is readily available to the dissolution medium and thus does not require a granule "splitting time," as is the case for tablets prepared by wet granulation.

Table 3: In vitro drug release data (mean ± SD) on OXC-β-CD tablet formulations obtained from stability studies

Sample	Time (min)	Drug percent dissolved	
		F_3	F_6
Fresh	15	81.35 ± 1.12	99.86 ± 1.26
	20	100.12 ± 0.15	100.01 ± 1.09
	25	100.01 ± 1.06	99.98 ± 1.12
6 months	15	78.19 ± 1.05	96.25 ± 2.88
	20	98.29 ± 0.19	96.98 ± 1.12
	25	98.36 ± 1.12	98.59 ± 1.12

Selected oxcarbazepine tablet formulations (F3 and F6) were subjected to accelerated stability studies by keeping the samples at 40 ± 2 °C and 75% relative humidity (maintained using a saturated solution of NaCl) in an oven. The *in vitro* drug release results of stability studies on both drug formulations are given in Table 3. None of the tablet formulations showed any discoloration during storage. There were no statistical differences in the percentage of drug dissolved at 15, 20, and 25 min between fresh and stored samples at the different time points ($P < 0.05$). Also, no changes in hardness and disintegration times of the tested formulations were observed. Drug content also remained within acceptable limits. Assuming that a shelf life of 6 months at 40 °C corresponds to a shelf life of 3 years at 25 °C, based on the present results

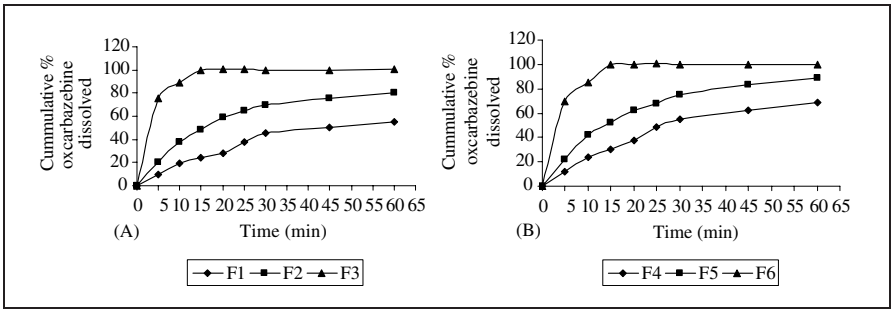

Fig. 10:
Dissolution profiles of oxcarbazepine and oxcarbazepine-β-cyclodextrin tablet formulations prepared by the wet granulation method (A) and the direct compression method (B)

Table 4: Formulas of the tablets of OXC and OXC-β-CD binary systems*

Ingredients (mg/tablet)	Wet granulation			Direct compression		
	F1	F2	F3	F4	F5	F6
OXC	150	–	–	150	–	–
OXC-β-CD PM 1 : 1M	–	824	–	–	824	–
OXC-β-CD KS 1 : 1M	–	–	824	–	–	824
Croscarmellose sodium	38	38	38	38	38	38
PVP	19	19	19	–	–	–
Talc	19	19	19	19	19	19
Magnesium stearate	10	10	10	10	10	10
Lactose monohydrate	724	50	50	–	–	–
Avicel PH 101	–	–	–	743	69	69
Total wt. of the tablet (mg)	960	960	960	960	960	960

* OXC indicates oxcarbazepine; OXC-β-CD, oxcarbazepine-β-cyclodextrin; KS, kneaded systems; PVP, polyvinylpyrrolidone

it can be predicted that the tablet formulations examined in Table 7 should have a shelf life of ~3 years.

3. Experimental

3.1. Materials

Oxcarbazepine was obtained as gift sample from Zydus cadila, Ahmedabad and β-cyclodextrin from S.A. Chemicals, Bombay. All other reagents and solvents were of analytical grade.

3.2. Methods

3.2.1. Phase solubility studies

The solubility measurements of oxcarbazepine with cyclodextrins were performed according to Higuchi and Connors (1965). Excess amounts of oxcarbazepine (150 mg) were added to 15 ml. of cyclodextrin aqueous solutions (3–15 mM concentration range) taken in a series of 25 ml stoppered conical flasks and the mixtures were shaken for 48 h at room temperature (28 ± 2 °C) on a rotary flask shaker. The solutions were kept aside for 12 h to achieve equilibrium; 2 ml aliquots were withdrawn and filtered immediately using a Whatman filter no 41. The filtered samples were diluted suitably and assayed for oxcarbazepine by measuring absorbance at 256.5 nm. The solubility experiments were conducted in triplicate (conformed on the same concentrations of CDs in water so as to cancel any absorbance that may be exhibited by the cyclodextrin molecules). The apparent 1 : 1 binding constants of the oxcarbazepine-CD complexes were calculated from the slope and intercept of the straight lines of the phase-solubility diagrams, according to the following equation:

$$Kc = \text{slope}/So(1 - \text{slope}) \quad (1)$$

where Kc is the apparent binding/stability constant, and So (intercept) is the intrinsic solubility of the compound in absence of complexing agent.

3.2.2. Preparation of solid binary systems

Three different drug-β-CD binary systems in 1 : 1 M ratio were prepared from the previously sieved (75–150 μm) individual components (Erden and Celebi 1988): (1) by mixing for 20 min in a mortar with a spatula (PM); (2) by triturating PM in a mortar with a small volume of water-methanol (1 : 1 v/v) solution, then kneading the thick slurry for 45 min and drying it at 45 °C (KS); and (3) by adding the aqueous solution of CD to an alcoholic solution of oxcarbazepine, stirring the resulting mixture for 1 h, and evaporating at 45 °C until dryness (CS). Each solid product was sieved, and the 75 to 150 μm sieve fraction was collected.

3.2.3. Characterization of inclusion complexation in the solid state

3.2.3.1. *In vitro* dissolution studies

In vitro dissolution studies of pure drug and its binary systems prepared were carried out in 900 mL of 0.1 N HCL containing 0.25% sodium lauryl sulfate (SLS, pH 1.2) using an USP XXI type II dissolution rate test apparatus by powder dispersed amount method. Samples equivalent to 150 mg of oxcarbazepine, a speed of 50 rpm, and a temperature of 37 ± 1 °C were used in each test. A 5-mL aliquot was withdrawn at different time intervals, filtered using a 0.45-μm whatman filter, and replaced with 5 mL of fresh dissolution medium. The filtered samples were suitably diluted if necessary and assayed for oxcarbazepine by measuring absorbance at 256.5 nm. The dissolution experiments were conducted in triplicate (Corrigan and Stanley 1982).

3.2.3.2. Powder X-ray diffractometry

The powder X-ray diffraction patterns were determined for oxcarbazepine, β-CD and oxcarbazepine-β-cyclodextrin kneaded product. X-ray diffractograms were obtained using X-ray diffractometer (X'pert Philips, Holland) with Xe-filled counteract, Cu target, voltage 2 kw, current 15 ma and 2θ over a 0 to 107 °C (Gandhi and Karara 1988).

3.2.3.3. Differential scanning calorimetry

Thermal characteristics of the oxcarbazepine, β-CD and oxcarbazepine-β-cyclodextrin kneaded product were determined by a differential scanning calorimeter (DSC) (Perkin Elmer, pyris-1 DSC). Samples equivalent to approximately 3.5 mg oxcarbazepine were placed in to aluminum pans and DSC analysis were carried out at a nitrogen flow of 20 ml/min and a heating rate of 10 °C/min from 30 to 300 °C.

3.2.3.4. Scanning electron microscopy

The surface morphology of pure materials and oxcarbazepine-β-cyclodextrin kneaded product were examined by scanning electron microscope (Phillips (FEI) ESEM-XL-30 TMP). The samples were fixed on a brass stub using double-sided tape and then gold coated in vacuum by a sputter coater; the pictures were then taken at an excitation voltage of 20 KV.

3.2.4. Formulation of tablets

The tablet formulations containing oxcarbazepine and oxcarbazepine-β-CD (OXC-β-CD) binary systems (equivalent to 150 mg of oxcarbazepine) were prepared by wet granulation and direct compression methods according to the formulas given in Table 4. In each case a batch of 500 tablets was prepared (Bodmeier and Paerataku 1991).

3.2.4.1. Wet granulation method

Required quantities of pure drugs and drug-β-CD binary systems, and half the quantities of disintegrant, croscarmellose sodium, and diluent (lactose monohydrate), were mixed thoroughly in a mortar to obtain a uniform blend. Sufficient binding agent, that is, 2% polyvinylpyrrolidone (PVP) solution in methanol, was added and mixed to obtain a dough mass. The resulting wet mass was passed through a No 10 sieve American Society of Testing and Materials (ASTM) and dried at 50 ^{0}C in a hot-air oven until dryness. The dried granules were resieved through a No 20 sieve ASTM. The granules were then mixed with the remaining half of the disintegrant, talc, and magnesium stearate. The tablets (950 mg) were compressed on a single-punch tablet press (Cadmach, Ahmadabad, India).

3.2.4.2. Direct compression method

In the direct compression method, the appropriate pure drugs and drug-β-CD binary systems were mixed with filler – Avicel PH 101 – in a mortar for 10 min. Croscarmellose sodium (4%), talc (2%), and magnesium stearate (1%) were then added in the same respective order and thoroughly mixed for 3 min. The resulting blend was then compressed into tablets, as described above.

3.2.5. Tablet properties

The following tablet properties were measured:
Uniformity of weight: Sample sizes of 20 were used for determination of weight. Hardness: Sample sizes 6 tablets were used for determination of hardness using Monsanto hardness tester.
Friability: Friability was determined by using a Roche friabilator using 20 tablets for 4 minutes (100 revolutions).

Disintegration time: The disintegration time was determined using 6 tablets in a US Pharmacopeia (USP) disintegration apparatus (Electrolab, Mumbai) without discs at 37 °C, in water.
Drug Content Estimation: The powder content of 20 tablets was mixed well, and a powder sample equivalent to 150 mg of oxcarbazepine was placed in individual 100-mL volumetric flasks. Drug was dissolved in 25 mL of methanol. The resulting mixture was vortexed for 5 min, and the volume was raised to 100 mL with methanol. The solution was filtered through a 0.45-μm nylon disc filter and was analyzed for drug content by measuring UV absorbance at 256.5 nm for oxcarbazepine.

3.2.6. Dissolution studies

In vitro dissolution studies of tablet formulations were performed in 900 ml of 0.1 N HCl Containing 0.25% SLS using an USP type II Dissolution Test Apparatus (Model DR-3, Campbell Electronics, Mumbai). Tablets contained 150 mg of oxcarbazepine and a speed of 50 rpm and a temperature of 37 ± 1 °C were used in each test. A 5-mL aliquot was withdrawn at different time intervals and filtered using a 0.45-μm whatman filter; each sample was replaced with 5 mL of fresh dissolution medium. The filtered samples were suitably diluted, if necessary, and assayed by measuring the absorbance at 256.5 nm for oxcarbazepine. The dissolution experiments were conducted in triplicate.

3.2.7. Stability studies

To determine whether there occurs during storage any change in the hardness, friability, or disintegration time that might affect the in vitro release profile of the drugs, stability studies were performed on formulations F3 and F6. The tablets were stored at 40 ± 2 °C and 75% relative humidity (maintained using a saturated solution of NaCl) in a desiccator. Samples were withdrawn at 0-, 1-, 2-, 3-, and 6-month time periods and evaluated for drug content, change in *in vitro* drug release pattern, hardness, friability, and disintegration time.

3.3. Statistical analysis

The statistical analysis of the data was computed using a 1-way analysis of variance using Microsoft excel software at a significance level of $P < 0.05$.

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