

## FORMULATION AND EVALUATION OF CARBAMAZEPINE 200 MG CHEWABLE TABLETS USING CYCLODEXTRINS

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### ABSTRACT

Carbamazepine/ cyclodextrins solid dispersions were prepared by the kneading method. These prepared solid dispersions were subjected to DSC thermal analysis and in-vitro dissolution studies in distilled water. No chemical incompatibilities existed between the drug and cyclodextrins. The use of cyclodextrin in small ratios compared to carbamazepine ratio enhanced the dissolution rate of the drug in comparison with pure untreated one. Carbamazepine/ $\beta$ CD solid dispersions were then incorporated into tablets which showed acceptable assay, disintegration time, friability and dissolution results. Difference and similarity factors were acceptable. Stability study at different temperatures showed that assay, disintegration time and loss on drying were stable, while dissolution results increased.

**Keywords:** Carbamazepine, Cyclodextrins and Chewable tablets.

### INTRODUCTION

Carbamazepine is 5H -Dibenz [b, f] azepine-5-carboxamide<sup>1</sup>. B.P (2010) describes the drug as a white or almost white, crystalline powder<sup>2</sup>. It melts within a range of 3°C between 187°C to 193°C<sup>3</sup>. Koester L.S. et al (2004) indicated that carbamazepine is practically insoluble in water and its solubility is less than 200.0  $\mu$ g/ml<sup>4</sup>. Yadav A.V. (2009) indicated that the solubility of carbamazepine in distilled water is 0.161 mg/ml and in distilled water containing 1.0 % sodium lauryl sulphate is 0.466 mg/ml<sup>5</sup>.

Carbamazepine has at least four different polymorphs (I, II, III and IV) and the dihydrate form<sup>6,7</sup>. Polymorph I is less documented in the literature compared to the other carbamazepine polymorphs. On the other hand, polymorphs III and IV are fully described in the literature. The melting points of these four polymorphs have been reported to be in the 175-190°C range<sup>8</sup>. In addition, control of the polymorphic properties of the drug is an important issue as USP stipulates the use of polymorph III in pharmaceutical formulations<sup>9</sup>.

Carbamazepine is considered a first line drug in the treatment of epilepsy<sup>10</sup>. Novartis produces it under the trade name of Tegretol® as an anticonvulsant and specific analgesic for trigeminal neuralgia. It is available for oral administration as 100 mg chewable tablets, immediate release tablets of 200 mg, extended release tablets of 200 and 400 mg and as a suspension of 100 mg/5 ml<sup>1</sup>. Literature indicates that Novartis Pharma (Switzerland) and Taro pharmaceutical industries (Israel) produces carbamazepine as 200 mg chewable tablets<sup>11,12</sup>. Shire US Inc (USA) produces carbamazepine as 300 and 400 extended release capsules under the trade name Carbatrol®<sup>13</sup>.

Cyclodextrins (CDs) have been extensively used to increase the solubility, dissolution rate and absorption characteristics of poorly water-soluble drugs<sup>14</sup>. A number of different methods have been applied to enhance the complex efficiency of the CDs: ionization of the drug, salt formation and addition of organic co solvents to the aqueous complexation media and the use of supercritical fluids all promote the enhancement of the intrinsic solubility of the drug-favoring complexation<sup>15</sup>. Preparation of cyclodextrin inclusion complexes is done by: complex preparation in solution: by solvent evaporation method, preparation in suspension, preparation by kneading and complex preparation by melting.

The molecular weight of betadextrin ( $\beta$ CD) is 1135<sup>16</sup>. It has a water solubility of 1.85 gm /100 ml<sup>17</sup>. It is the least expensive cyclodextrin and has the ability to form inclusion complexes with a number of molecules of pharmaceutical interest<sup>18</sup>. Hydroxypropyl-betacyclodextrin (HP $\beta$ CD) has been widely investigated in pharmaceutics and has principally been used as a solubilizer for

hydrophobic molecules in oral liquids, oral solids, parenterals and topical formulations.

The objective of this study is to prepare carbamazepine /cyclodextrins solid dispersions (SD) by the kneading method in a molar ratio of 1 (drug): 0.1 (carrier) and then incorporation into 200 mg chewable tablets.

### MATERIALS

Carbamazepine was supplied from Xiamen (China), Betacyclodextrin ( $\beta$ CD) (Parth overseas, India), 2-Hydroxypropylbetacyclodextrin (HP $\beta$ CD) (Lyg, China), orange flavor powder (Givudan, France), Spray dried Mannitol (Mannogem EZ) (SPI Pharma, France), sodium starch glycolate (explotab) (JRS pharma, Germany), microcrystalline cellulose PH 102 (FMC, Ireland), magnesium stearate (Alba chemicals, USA), methanol and acetonitrile for HPLC (Merck, Germany), acetone was supplied from (El-Nasr pharmaceutical chemicals co, Egypt), sodium lauryl sulfate (SLS) (Surfachem, England), empty hard gelatin capsules (the Arab company for gelatin and pharmaceutical products, Egypt) and Tegretol® 200 mg immediate release tablets (Novartis Pharma, Switzerland).

### METHODOLOGY

#### Assay of carbamazepine using HPLC methods

#### Assay of carbamazepine in methanol

Literature indicates the use of HPLC method for performing assay and dissolution of carbamazepine<sup>19,20</sup>. A solution of 0.4 mg/ml was prepared. Serial dilutions (0.05, 0.1, 0.2 and 0.3 mg/ml) were prepared using methanol and injected on HPLC (Waters, USA). The area under the curve for each solution was measured and the drug content was calculated. The HPLC conditions for carbamazepine were: mobile phase: Acetonitrile: Potassium dihydrogen phosphate buffer (0.025M) PH 3.5 in a ratio of 35: 65 %, column: Thermo, BDS, C18, UV detector wavelength at 254.0 nm, flow rate: 1.5 ml/ minute, Injection volume: 5  $\mu$ l and Temperature: 25 °C.

#### Assay of carbamazepine in distilled water

A solution of 0.4 mg/ml was prepared. Serial dilutions (0.05, 0.1, 0.2 and 0.3 mg/ml) were prepared using water and injected on HPLC. The area under the curve for each solution was measured.

#### Assay of carbamazepine in distilled water containing 1.0% Sodium lauryl sulphate

A solution of 0.4 mg/ml was prepared. Serial dilutions (0.05, 0.1, 0.2 and 0.3 mg/ml) were prepared using water containing 1.0 % sodium

lauryl sulphate and injected on HPLC. The area under the curve for each solution was measured.

#### Preparation of carbamazepine/cyclodextrins physical mixtures

They were prepared by triturating carbamazepine and the corresponding cyclodextrins, passing through 0.355<sup>21</sup> mm screen (Fritsch, Germany) and stored in closed containers away from light and humidity until use<sup>22</sup>.

#### Preparation of carbamazepine/cyclodextrin solid dispersions

The most common stoichiometry of drug: cyclodextrin complex is 1:1<sup>23</sup>. Ratios of drug: cyclodextrin such as 1: 2, 1:3 and 1:5 were used<sup>17,24</sup>. In the present study, because of the high dose of drug, the molar ratio of drug: cyclodextrin complex was 1:0.1. Carbamazepine inclusion complexes were prepared by the kneading method. The drug was mixed geometrically with  $\beta$ CD or HP $\beta$ CD. Distilled water was added dropwise until a coherent mass is formed, dried in oven at 60°C (Heraeus, Germany), sieved through 0.355 mm screen and stored in closed containers away from light and humidity until use<sup>22</sup>.

#### Study of the possible interaction between the drug and cyclodextrins

Thermal analysis of carbamazepine,  $\beta$ CD, HP $\beta$ CD, their physical mixtures and solid dispersions were performed in a Perkin Elmer Diamond DSC differential scanning calorimeter. Samples were inserted into aluminum pans and thermograms obtained at a heating rate of 10 °C/minute over a temperature range of 30 to 220°C<sup>21</sup>.

#### Dissolution study

The drug was placed either alone, as a physical mixture or SD with cyclodextrins in dissolution vessels (Varian, USA). (900 ml distilled water maintained at 37°C and adjusted at 75 r.p.m for 120 minutes). Samples were taken after 10, 15, 20, 30, 45, 60, 90 and 120 minutes and analyzed for carbamazepine content by HPLC method.

#### Preparation of carbamazepine 200 mg chewable tablets using carbamazepine/ $\beta$ CD solid dispersions

Carbamazepine 200 mg chewable tablets were prepared using carbamazepine (44.44 % w/w),  $\beta$ CD (21.33 %), microcrystalline cellulose PH 102 (11.56 %), sodium starch glycolate (7.11%), aspartame (0.9%), saccharin sodium (0.22%), sodium cyclamate (0.67 %), mannogem EZ (11.56 %), magnesium stearate (0.44 %) and orange flavor powder (1.77 %), compressed using Korsch XL-100 tablet compression machine (Germany) on target weight 450.0 mg. The prepared tablets were evaluated by determination of:

**Uniformity of weight:** According to B.P 2010<sup>2</sup>.

Twenty tablets were individually weighed at random, and the average weight was determined. The requirement of this test is met if not more than two of the individual weights deviate from the average weight by more than the percentage deviation 5.0 % and none deviates by more than twice that percentage.

**Disintegration time:** According to B.P 2010<sup>2</sup>.

Water was used as the medium. This test is provided to determine whether tablets disintegrate within 15 minutes when placed in a liquid medium under experimental conditions.

**Resistance to crushing of tablets:** According to B.P 2010<sup>2</sup>.

This test is intended to determine, under defined conditions, the resistance to crushing of tablets, measured by the force needed to disrupt them by crushing.

**Friability:** According to USP 33(2010)<sup>1</sup>.

A friability tester calibrated at 24 revolutions per minute was used. Ten tablets were carefully dedusted prior to testing, accurately weighed, and placed in the drum. The drum was rotated 100 times. The tablets were removed, dedusted and accurately weighed. A maximum weight loss of not more than 1% of the weight of the tablets being tested is considered acceptable for most products.

**Assay:** According to USP 33(2010)<sup>1</sup>.

Twenty tablets were finely powdered and assayed for its drug content by HPLC method. The requirements for dosage uniformity are met if the amount of the active ingredient lies within the range of 92.0 % to 108.0% of the target.

**Loss on drying:** According to USP 33(2010)<sup>1</sup>.

Twenty tablets were finely powdered in a mortar. Accurately weighed 1.5 gm of this fine powder was put in a dry evaporating dish and dried at 120 °C for two hours. A maximum weight loss of not more than 5.0 % is considered acceptable for carbamazepine tablets.

**Dissolution in distilled water:** it was carried out using apparatus II, 75 rpm, water 900 ml was used as medium and samples were withdrawn after 10,15,20,30, 45, 60, 90 and 120 minutes.

#### Dissolution in distilled water containing 1.0 % sodium lauryl sulphate (SLS)

It was carried out using apparatus II, 75 rpm, water containing 1.0 % SLS 900 ml was used as medium and samples were withdrawn after 10,15,20,30, 45, 60, 90 and 120 minutes. To comply with dissolution test 2: between 45.0 % and 75.0 % is dissolved in 15 minutes and not less than 75.0 % is dissolved in 60 minutes. To comply with dissolution test 3: between 60.0 and 75.0 % is dissolved in 15 minutes and not less than 75.0 % is dissolved in 60 minutes.

#### Drug dissolution kinetics and mechanism of drug dissolution

In order to describe the kinetics of dissolution process, various equations were used such as: zero-order rate equation, which describes the systems where the dissolution rate is independent of the concentration of the dissolved species, first-order equation, which describes the systems where the dissolution rate is dependent on the concentration of the dissolved species and Hixon-Crowell cube root law where there is a change in surface area and diameter of the particles by time<sup>25</sup>.

Data for the first 60.0 % drug dissolution were plotted in Korsmeyer and Peppas equation as log cumulative percentage of drug released versus log time, and the exponent n is calculated through the slope of the straight line<sup>26</sup>. If exponent n= 0.5, then the drug dissolution is Fickian diffusion (Higuchi matrix), and if 0.5< n <1, this indicates that it is non-Fickian or anomalous transport, 1 indicates case-II transport or typical zero order dissolution process. For the values of n higher than 1, the mechanism is as super case-II transport<sup>27</sup>.

#### Calculation of difference and similarity factors

The dissolution profiles of the prepared carbamazepine 200 mg chewable tablets and Tegretol® 200 mg immediate release tablets (Novartis Pharma, Switzerland) were carried out by USP dissolution apparatus II in water containing 1.0 % Sodium lauryl sulphate, 900 ml, paddles and 75 rpm.

In order to analyze the dissolution data equivalence, FDA guidance documents consider some approaches such as difference (f<sub>1</sub>) and similarity (f<sub>2</sub>) factors<sup>4</sup>. The main advantage of the f<sub>1</sub> and f<sub>2</sub> equations is to provide a simple way to describe comparison of data. The f<sub>1</sub> should be computed using the following equation:

$$f_1 = \left\{ \left[ \sum_{t=1}^n |R_t - T_t| \right] / \left[ \sum_{t=1}^n R_t \right] \right\} \times 100$$

While the f<sub>2</sub> should be computed using the equation:

$$f_2 = 50 \cdot \log \left\{ \left[ 1 + \left( \frac{1}{n} \right) \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \right\} \cdot 100$$

Where, R<sub>t</sub> and T<sub>t</sub> are the cumulative percentage of the drug dissolved at each of the selected n time points of the reference and test product, respectively.

Values of f<sub>1</sub> between zero and 15 and those of f<sub>2</sub> between 50 and 100 ensure dissolution profile and the sameness or equivalence of the two curves, and thus the performance of the two products.

**Stability of the prepared chewable tablets**

In order to determine the influence of the storage conditions on the dissolution rate; carbamazepine 200 mg chewable tablets were placed into amber colored stoppard glass vials<sup>28</sup> and stored in incubators under the following conditions:

- Three months at 50 ± 2°C 29 where samples were withdrawn at 0.5, 1.0, 2.0 and 3.0 months.
- Three months at 40 ± 2°C and 75 ± 5 % RH30 where samples were withdrawn at the same time intervals.

The withdrawn tablets were analyzed for assay, disintegration time, resistance to crushing, dissolution in distilled water containing 1.0 % SLS and loss on drying.

**RESULTS AND DISCUSSION**

**Assay of carbamazepine using HPLC method**

**Assay of carbamazepine in methanol**

Table (1) and figure (1) represent a linear relationship between carbamazepine concentration and the area under the curve. The

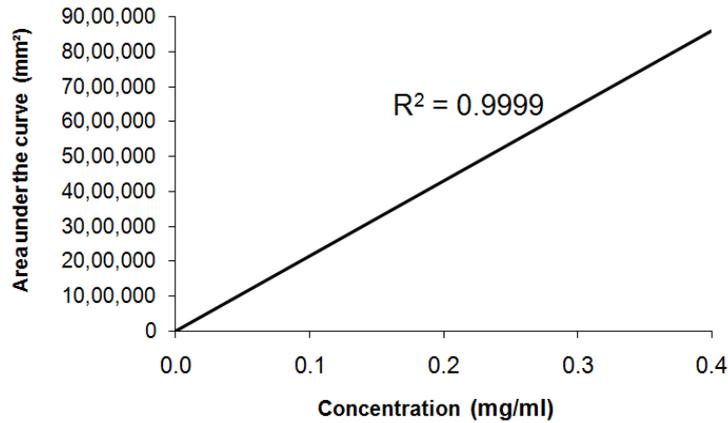
linearity is established as  $R^2 = 0.9999$ . So carbamazepine obeys Beer's Lambert law in the range from 0.1 to 0.4 mg/ml. So this method is considered suitable for assay of carbamazepine.

**Table 1: Assay of carbamazepine in methanol**

Concentration (mg / ml)	Area under the curve (mm <sup>2</sup> )
0.05	1054890.000
0.1	2109779.000
0.2	4301575.000
0.3	6434193.000
0.4	8635846.000

**Assay of carbamazepine in distilled water**

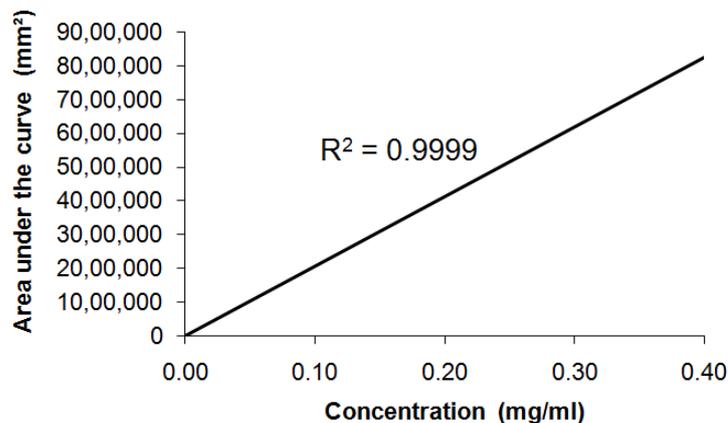
Table (2) and figure (2) represent a linear relationship between carbamazepine concentration and the area under the curve. The linearity is established as  $R^2 = 0.9999$ . So carbamazepine obeys Beer's Lambert law in the range from 0.05 to 4.0 mg/ml. This method is considered suitable for testing dissolution of carbamazepine tablets in distilled water.



**Fig. 1: Assay of carbamazepine in methanol.**

**Table 2: Assay of carbamazepine in distilled water**

Concentration (mg / ml)	Area under the curve (mm <sup>2</sup> )
0.05	1011636.500
0.10	2047913.000
0.20	4106706.000
0.30	6222343.500
0.40	8254115.000



**Fig. 2: Assay of carbamazepine in distilled water.**

### Assay of carbamazepine in distilled water containing 1.0 % Sodium lauryl sulphate

Table (3) and figure (3) represent a linear relationship between carbamazepine concentration and the area under the curve. The

linearity is established as  $R^2 = 0.9999$ . So carbamazepine obeys Beer's Lambert law in the range from 0.05 to 4.0 mg/ml. This method is considered suitable for testing the dissolution of carbamazepine tablets in distilled water containing 1.0 % sodium lauryl sulphate.

Table 3: Assay of carbamazepine in distilled water containing 1.0 % sodium lauryl sulphate

Concentration (mg /ml)	Area under the curve (mm <sup>2</sup> )
0.050	1038511.333
0.100	2052209.333
0.200	4075383.000
0.300	6092686.000
0.400	8072613.330

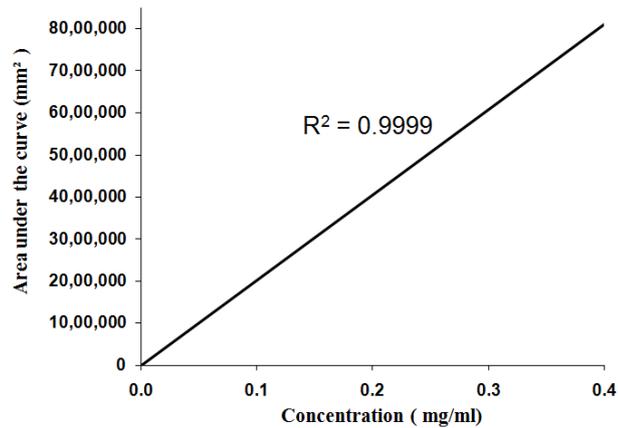


Fig. 3: Assay of carbamazepine in distilled water containing 1.0 % sodium lauryl sulphate.

### Estimation of possible interactions between the drug and cyclodextrins By DSC thermal analysis

Figure (4-a) shows a sharp endothermic onset of peak at 173.75 °C and an exothermic onset of peak at 178.42 °C followed by a sharp

endothermic onset of peak at 189.23 °C corresponding to carbamazepine melting point as indicated by Florey K. (1980)<sup>3</sup>. This behavior is typical for carbamazepine form III and it is in accordance with Zerrouk N. et al<sup>31</sup>.

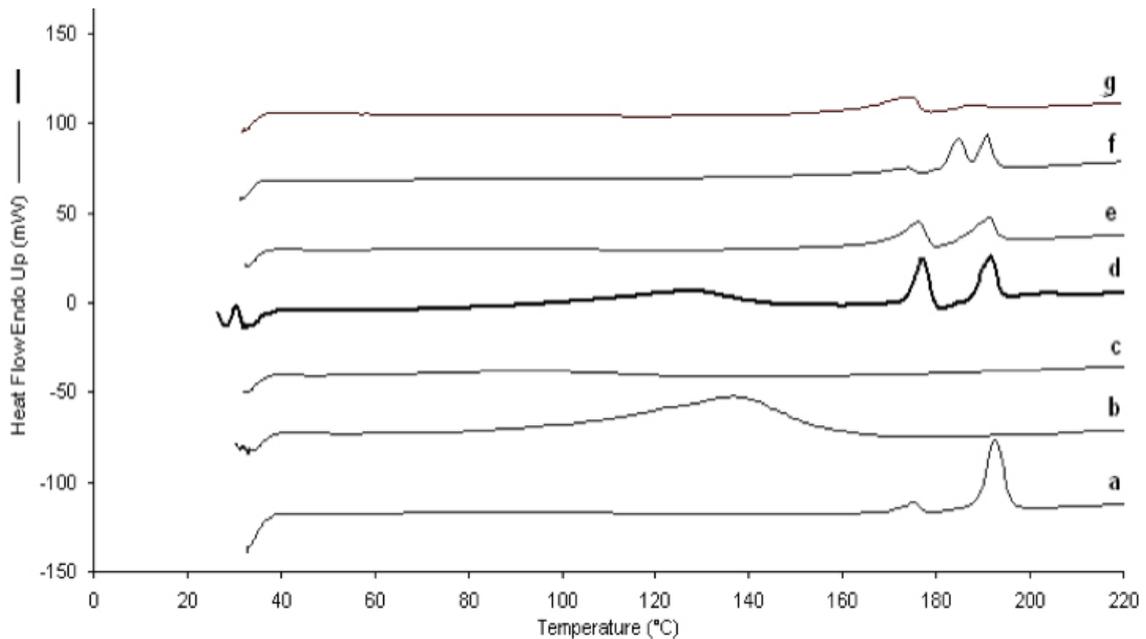


Fig. 4: DSC thermal analysis for a-carbamazepine alone, b-  $\beta$ CD alone, c-HP $\beta$ CD alone, d- carbamazepine/ $\beta$ CD physical mixture, e- carbamazepine /HP $\beta$ CD physical mixture, f- carbamazepine/ $\beta$ CD Kn, g- carbamazepine/HP $\beta$ CD Kn.

Figure (4-b) shows that  $\beta$ -cyclodextrin has a broad band ranging from 100 °C to 160°C corresponding to the loss of water. This is in accordance with Koester L.S et al.<sup>32</sup> who showed a broad peak ranging from 130 °C to 170 °C corresponding to loss of water, and in accordance with Ning li and Liang Xu<sup>33</sup> who showed that  $\beta$ CD displayed a wide endothermic peak in the 100-130 °C range which could be ascribed to dehydration.

Figure (4-c) shows that hydroxypropyl  $\beta$ -cyclodextrin (HP $\beta$ CD) has no characteristic endothermic peak over the range from 100 °C to 220°C. This is in accordance with Bettinetti G.P. et al.<sup>34</sup>, Fernandes C.M., et al.<sup>35</sup> and El-Zein H.<sup>36</sup>.

Figure (4-d) shows the DSC thermograms of carbamazepine physical mixture with  $\beta$ CD in a molar ratio of 1:0.1. It shows a broad band ranging from 100 to 150 °C which is characteristic for  $\beta$ CD, a sharp endothermic onset of peak at 173.62 °C and an exothermic onset of peak at 178.42 °C followed by a sharp endothermic onset of peak at 187.7 °C corresponding to carbamazepine melting point.

Figure (4-e) shows the DSC thermograms of carbamazepine physical mixture with HPBCD in a molar ratio of 1:0.1. It has a sharp endothermic onset of peak at 170.22 °C, an exothermic onset of peak at 178.42 °C followed by a sharp endothermic onset of peak at 184.04 °C which is corresponding to carbamazepine melting point.

Figure (4-f) shows an endothermic onset of peak at 170.64 °C followed by an exothermic peak at 182.35 °C and then another endothermic onset of peak at 188.99 °C which corresponds to carbamazepine melting point.

Figure (4-g) shows an endothermic onset of peak at 164.48 °C followed by an exothermic peak at 182.35 °C and another endothermic onset of peak at 183.72 °C which is corresponding to carbamazepine melting point. From the same DSC thermograms; the prepared carbamazepine solid dispersions show one endothermic peak and then an exothermic peak followed by another endothermic one that indicates that the drug which is commercially available as form III was remained unchanged.

#### Dissolution study

Table (4) and figure (5) show that the physical mixture of drug with  $\beta$ CD gives a dissolution rate nearly equals to dissolution of the physical mixture with HP $\beta$ CD after 15 minutes. The percent of carbamazepine dissolved from its physical mixture with  $\beta$ CD is 43.92, 63.85, 74.16 and 84.51 % after 15, 30, 60 and 120 minutes. The respected values for physical mixture with HP $\beta$ CD is 43.94, 56.92, 68.41 and 79.40 %. This indicates that carbamazepine dissolution is enhanced when physically mixed with cyclodextrins due to local solubilization action of the carrier operating in the microenvironment of the drug<sup>17</sup>.

Table 4: Dissolution of carbamazepine from its physical mixtures and solid dispersions

Time (min)	% of carbamazepine dissolved from				
	Drug alone	Physical mixture of the drug with		Solid dispersion of the drug with	
		$\beta$ CD	HP $\beta$ CD	$\beta$ CD	HP $\beta$ CD
10.0	9.14 ± 8.97	29.73 ± 5.91	33.86 ± 1.32	30.94 ± 1.79	51.25 ± 3.31
15.0	15.84 ± 6.42	43.92 ± 4.23	43.94 ± 0.70	42.23 ± 0.89	68.12 ± 1.36
20.0	21.68 ± 5.91	54.02 ± 2.98	49.58 ± 0.61	50.74 ± 1.47	75.91 ± 1.83
30.0	28.64 ± 9.08	63.85 ± 3.45	56.92 ± 0.41	60.95 ± 2.94	84.09 ± 1.97
45.0	43.65 ± 8.46	71.01 ± 2.83	63.16 ± 0.39	69.60 ± 3.67	90.91 ± 1.40
60.0	48.92 ± 7.22	74.16 ± 3.88	68.41 ± 0.44	75.02 ± 3.80	95.34 ± 0.99
90.0	57.78 ± 6.44	80.59 ± 3.58	74.92 ± 0.82	81.44 ± 3.71	100.09 ± 1.35
120.0	63.95 ± 5.65	84.51 ± 3.47	79.40 ± 0.64	85.44 ± 3.95	102.68 ± 1.41

All values are expressed as mean ± SD (n=6).

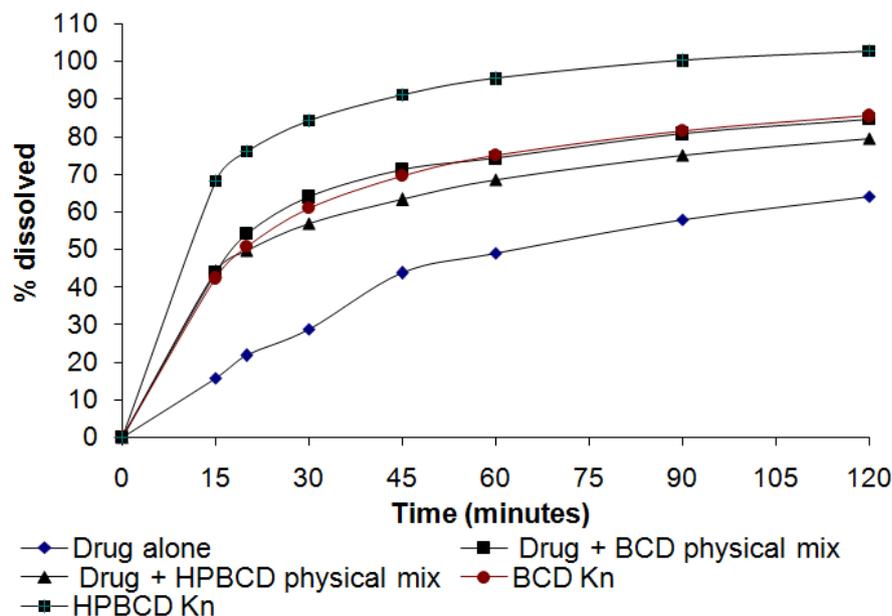


Fig. 5: Dissolution of carbamazepine from its physical mixtures and solid dispersions containing cyclodextrins in distilled water.

The percent of carbamazepine dissolved from the solid dispersion of the drug with  $\beta$ CD is 42.23, 60.95, 75.02 and 85.44% after 15, 30, 60 and 120 minutes. The solid dispersions

of  $\beta$ CD show approximately the same behavior of the physical mixtures with slightly more enhancement in carbamazepine dissolution.

The percent of carbamazepine dissolved from the solid dispersion of the drug with HP $\beta$ CD is 68.12, 84.09, 95.34 and 102.68 % after the same time intervals. This is in accordance with Londhe V. and Nagar-senker M.<sup>37</sup> who concluded that HP $\beta$ CD, as a carrier, reduced the crystalline nature of carbamazepine in the prepared solid dispersions and resulted in better and predictable dissolution profiles. The increase in the drug dissolution rate could be due to the surfactant like properties of cyclodextrins, which reduce the interfacial tension between the water insoluble drug particles and the dissolution medium<sup>17</sup>.

#### Evaluation of carbamazepine 200 mg chewable tablets prepared by carbamazepine/ $\beta$ CD solid dispersion

#### Uniformity of weight, disintegration time, friability, resistance to crushing of tablets, assay and loss on drying

The results show that the average weight of 20 tablets is 452.6 mg, average disintegration time is 150.0 seconds, the friability is less

than 0.375 %, assay value is 100.04 % and loss on drying is 0.126%. It also shows that the average hardness value is 52.0 N.

#### Dissolution of carbamazepine 200 mg chewable tablets in distilled water

Table (5) and figure (6) show that the percent of carbamazepine dissolved in distilled water is 41.25, 53.39, 71.58, 87.28 and 97.94 % after 10, 15, 30, 60 and 120 minutes.

#### Drug dissolution kinetics and mechanism of drug dissolution of the prepared tablets in distilled water

Table (6) shows that  $R^2$  values of the zero-order, first-order, Hixon-Crowell cubic root law and Korsmeyer and Peppas equations are very close to unity. In addition, the  $n$  values obtained from Korsmeyer and Peppas equation are more than unity, which indicate that the amount of drug released is considered as super case-II transport. It is indicated that the amount of carbamazepine dissolved is zero-order dissolution.

Table 5: Dissolution of carbamazepine 200 mg chewable tablets in distilled water

Time (minutes)	% of carbamazepine dissolved from its prepared chewable tablets in distilled water
10.0	41.25 $\pm$ 1.76
15.0	53.39 $\pm$ 1.62
20.0	61.00 $\pm$ 1.25
30.0	71.58 $\pm$ 1.51
45.0	81.21 $\pm$ 1.83
60.0	87.28 $\pm$ 1.70
90.0	94.01 $\pm$ 1.45
120.0	97.94 $\pm$ 1.42

All values are expressed as mean  $\pm$  SD (n=6).

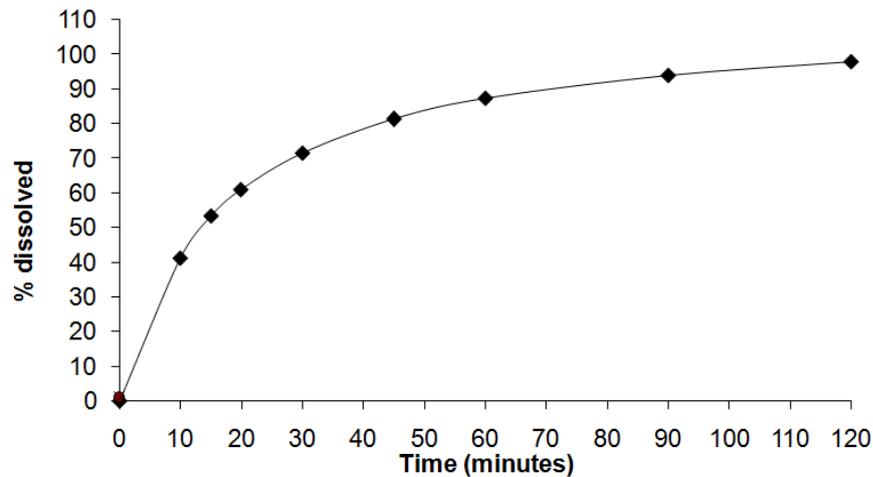


Fig. 6: Dissolution of carbamazepine 200 mg chewable tablets in distilled water.

Table 6: Dissolution rate constants and  $R^2$  values for carbamazepine 200 mg chewable tablets in distilled water after the applications of zero-order, first order, Hixon-Crowell cube root and Korsmeyer and Peppas equations.

Zero-order rate constant (%min <sup>-1</sup> )	First-order rate constant (min <sup>-1</sup> )	Hixon-Crowell rate constant (mg <sup>1/3</sup> min <sup>-1</sup> )	Korsmeyer and Peppas exponent (n)
3.842	0.050	0.069	1.485
$R^2 = 0.993$	$R^2 = 0.960$	$R^2 = 0.984$	$R^2 = 0.983$

#### Dissolution of carbamazepine 200 mg chewable tablets in distilled water containing 1.0 % SLS

Although carbamazepine 200 mg chewable tablets dissolution is not listed in USP 33 pharmacopeia; the dissolution of the prepared chewable tablets was carried out according to USP 33(2010) monograph listed for carbamazepine 200 mg tablets under dissolution test 2. Taro Pharmaceutical industries

pamphlet (Haifa Bay., Israel) mentions that its prepared carbamazepine 200 mg chewable tablets meet USP dissolution test 2<sup>12</sup>.

Table (7) and figure (7) show that the dissolution values of the prepared tablets lie in the required USP range for dissolution test 2 after 15 minutes. It is also found that dissolution values of the prepared tablets are more than 75.0 % after 60 minutes. Thus, they

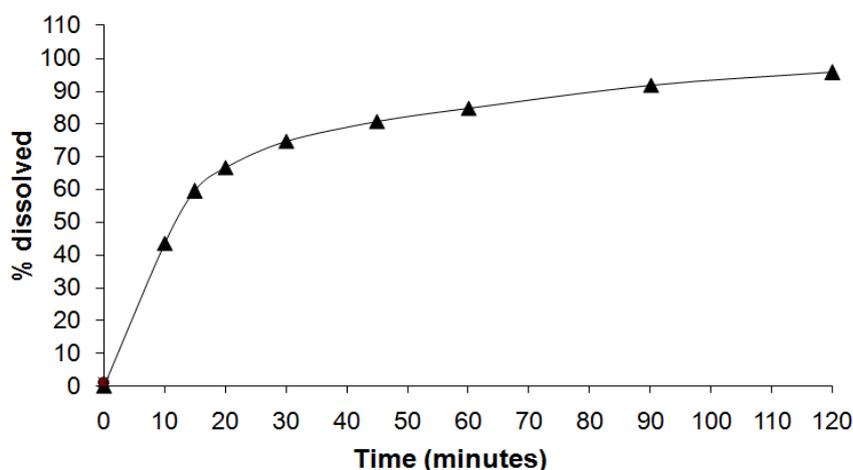
are conforming to the second range of dissolution process listed in the USP 33 (2010). It is concluded that the drug dissolution from

tablets prepared by using  $\beta$ CD inclusion complexes with the drug are conforming to USP official limits after 15 and 60 minutes.

**Table 7: Dissolution of carbamazepine 200 mg chewable tablets in distilled water containing 1.0 % sodium lauryl sulphate**

Time (minutes)	% of carbamazepine dissolved from its chewable tablets in distilled water containing 1.0 % SLS
10.0	43.49 $\pm$ 1.93
15.0	59.31 $\pm$ 1.75
20.0	66.43 $\pm$ 1.67
30.0	74.37 $\pm$ 1.22
45.0	80.47 $\pm$ 1.07
60.0	84.73 $\pm$ 0.92
90.0	91.68 $\pm$ 0.84
120.0	95.45 $\pm$ 0.68

All values are expressed as mean  $\pm$  SD (n=6).



**Fig. 7: Dissolution of carbamazepine 200 mg chewable tablets in distilled water containing 1.0 % sodium lauryl sulphate.**

#### Drug dissolution kinetics and mechanism of drug dissolution from the prepared tablets in distilled water containing 1.0 % SLS

It's indicated that  $R^2$  of the zero-order is very close to unity. In addition, the  $n$  value obtained from Korsmeyer and Peppas equation is more than unity which indicates that the amount of drug dissolved is zero-order dissolution.

#### Calculation of difference and similarity factors

It is found that the prepared carbamazepine 200 mg chewable tablets have a difference factor equals to 7.0 and a similarity factor equals to 63.0 in comparison with Tegretol® 200 mg immediate release tablets (Novartis Pharma, Switzerland).

#### Stability study

Accelerated stability conditions at 50°C for three months showed that all values of assay, disintegration time, resistance to crushing and loss on drying are conforming until the end of the study. Dissolution values of the stored tablets after 15 and 60 minutes have increased. This is in accordance with the results obtained by El-Zein H. et al<sup>38</sup> who concluded that Tegretol® tablets, stored in their strips at 50 or 60 °C and 75 % relative humidity for three months and one month respectively, showed increased dissolution values.

Accelerated stability conditions at 40°C/ 75 % RH for three months showed that all values of assay, disintegration time and loss on drying are conforming to specification until the end of the study. Unchanged assay results were in accordance with the results obtained by Raghavendra Rao N.G. et al (2009) who concluded that carbamazepine/  $\beta$ CD fast dissolving tablets, stored at 40 °C and 75

% relative humidity for four weeks, showed no appreciable change in drug content values<sup>39</sup>. Also no change in physical characteristics, disintegration time and drug content was in accordance with Raghavendra Rao N.G. et al (2010) who concluded that fast dissolving tablets of carbamazepine prepared by natural superdisintegrant plantago ovata seed powder and mucilage showed no appreciable change in physical characteristics, disintegration time and drug content even after the evaluation for 3 months at 40°C/ 75 % RH<sup>40</sup>.

In addition, dissolution values of the stored tablets after 15 and 60 minutes have increased. Resistance to crushing of tablets has increased. This is in accordance with the results obtained by El-Zein H. et al<sup>38</sup> who concluded that Tegretol® tablets, stored at 40 °C and 75 % relative humidity or 40 °C and 97 % relative humidity for six months and one month respectively, showed increased the tablet hardness values.

#### CONCLUSION

Carbamazepine/ $\beta$ CD and carbamazepine/HP $\beta$ CD solid dispersions were prepared by the kneading method. No chemical incompatibilities existed between the drug and cyclodextrins. The use of cyclodextrin in small ratio compared to carbamazepine ratio enhanced the dissolution rate of the drug in comparison with pure untreated one. Upon the incorporation of  $\beta$ CD or HP $\beta$ CD by kneading method to the drug, the results demonstrated that the dissolution of carbamazepine gave very acceptable results. Carbamazepine/ $\beta$ CD solid dispersion was incorporated in chewable tablets which were then subjected to tablet assay, all results were acceptable. Stability studies results at different storage condition were considered acceptable.

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