Figure (4-b) shows that β-cyclodextrin has a broad band ranging from 100 ºC to 160ºC corresponding to the loss of water. This is in accordance with Koester L.S et al[32] who showed a broad peak ranging from 130 ºC to 170 ºC corresponding to loss of water, and in accordance with Ning li and Liang Xu[33] who showed that βCD displayed a wide endothermic peak in the 100-130 ºC range which could be ascribed to dehydration.

Figure (4-c) shows that hydroxypropyl β-cyclodextrin (HPβCD) has no characteristic endothermic peak over the range from 100 ºC to 220ºC. This is in accordance with Bettinetti G.P. et al.[34], Fernandes C.M., et al.[35] and El-Zein H.[36].

Figure (4-d) shows the DSC thermograms of carbamazepine physical mixture with βCD in a molar ratio of 1:0.1. It shows a broad band ranging from 100 to 150 ºC which is characteristic for βCD, a sharp endothermic onset of peak at 173.62 º C and an exothermic onset of peak at 178.42 ºC followed by a sharp endothermic onset of peak at 187.7 ºC 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 ºC, an exothermic onset of peak at 178.42 ºC followed by a sharp endothermic onset of peak at 184.04 ºC which is corresponding to carbamazepine melting point.

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

Figure (4-g) shows an endothermic onset of peak at 164.48 ºC followed by an exothermic peak at 182.35 ºC and another endothermic onset of peak at 183.72 ºC 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 βCD gives a dissolution rate nearly equals to dissolution of the physical mixture with HPβCD after 15 minutes. The percent of carbamazepine dissoluted from its physical mixture with βCD is 43.92, 63.85, 74.16 and 84.51 % after 15, 30, 60 and 120 minutes. The respected values for physical mixture with HPβCD 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[17].

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

Time (min)	% of carbamazepine dissoluted from				
	Drug alone	Physical mixture of the drug with		Solid dispersion of the drug with	
		βCD	HPβCD	βCD	HPβCD
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).

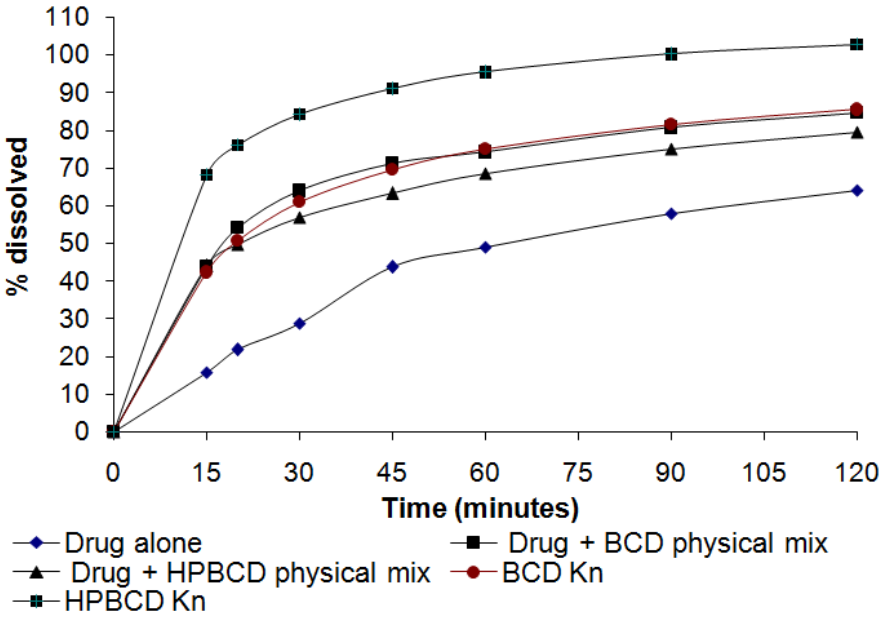

Fig. 5: Dissolution of carbamazepine from its physical mixtures and solid dispersions containing cyclodextrins in distilled water.

The percent of carbamazepine dissoluted from the solid dispersion of the drug with βCD is 42.23, 60.95, 75.02 and 85.44% after 15, 30, 60 and 120 minutes. The solid dispersions of βCD show approximately the same behavior of the physical mixtures with slightly more enhancement in carbamazepine dissolution.

The percent of carbamazepine dissoluted from the solid dispersion of the drug with HPβCD 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.[37] who concluded that HPβCD, 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[17].

Evaluation of carbamazepine 200 mg chewable tablets prepared by carbamazepine/βCD 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 dissoluted is zero-order dissolution.

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

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

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

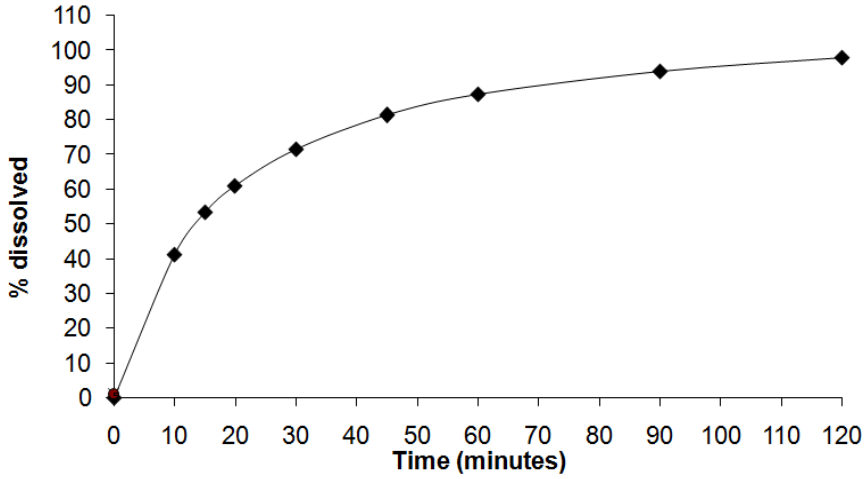

Fig. 6: Dissolution of carbamazepine 200 mg chewable tablets in distilled water.

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^{-1})	First-order rate constant (min^{-1})	Hixon-Crowell rate constant (mg⅓ min^{-1})	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[12].

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 βCD 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 dissoluted from its chewable tablets in distilled water containing 1.0 % SLS
10.0	43.49 ± 1.93
15.0	59.31 ± 1.75
20.0	66.43 ± 1.67
30.0	74.37 ± 1.22
45.0	80.47 ± 1.07
60.0	84.73 ± 0.92
90.0	91.68 ± 0.84
120.0	95.45 ± 0.68

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

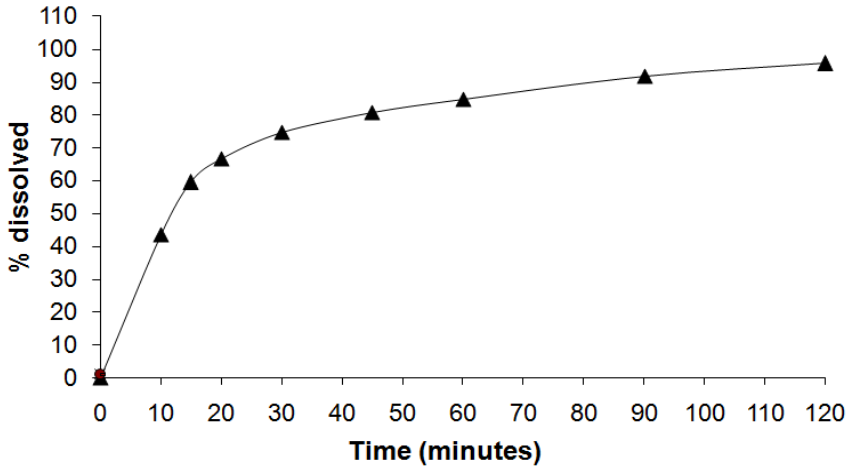

Fig. 7: Dissolution of carbamazepine 200 mg chewable tablets in distilled water containing 1.0 % sodium lauryl sulphate.

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 dissolute 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[38] who concluded that Tegral® 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/ βCD fast dissolving tablets, stored at 40 °C and 75 % relative humidity for four weeks, showed no appreciable change in drug content values[39]. 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[40].

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[38] who concluded that Tegral® 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/βCD and carbamazepine/HPβCD 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 βCD or HPβCD by kneading method to the drug, the results demonstrated that the dissolution of carbamazepine gave very acceptable results. Carbamazepine/βCD 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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