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Research Article

FORMULATION AND EVALUATION OF CARBAMAZEPINE 200MG IMMEDIATE RELEASE TABLETS USING POLYETHYLENE GLYCOL 6000

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ABSTRACT

Carbamazepine is an anticonvulsant drug used in the treatment of epilepsy. Carbamazepine 200 mg immediate release tablets were prepared by different methods. Effect of processing parameters was explored in order to obtain acceptable product. Various evaluations of the prepared tablets were conducted including differential scanning calorimetry (DSC), Fourier transform infra red spectroscopy (FTIR) and X-ray diffraction (XRD) for the prepared granules, assay, disintegration time, friability and in-vitro dissolution of tablets in distilled water containing 1.0 % SLS. Difference and similarity factors were also calculated.

Keywords: Carbamazepine, PEG 6000 and Immediate release tablets.

INTRODUCTION

Carbamazepine (CBZ) is considered as a first line drug in the treatment of epilepsy [1]. Its solubility is less than 200.0 µg/ml. It has at least four different polymorphs (I, II, III and IV) and the dihydrate form. Polymorph I is less documented in literature compared to the other polymorphs [2].

Polyethylene glycols (PEG) used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds [3]. They have been widely used due to their low toxicity and low cost [4]. PEG 6000 has been widely used to enhance the dissolution rate of many drugs such as griseofulvin, diazepam, tolbutamide, furosemide, norfloxacin, carbamazepine, indomethacin, ibuprofen, piroxicam and naproxen [5].

Immediate release tablets are widely used dosage forms which are designed to disintegrate and release their medicaments with no special rate controlling features such as special coatings and other techniques. Immediate release tablets have the advantages to release the drug immediately within a short period of time, typically less than 30 minutes, dissolution of the drug is fast, immediate action of the drug can be obtained, no dose dumping problems are seen [6].

In this study, the aim was to guide the use of PEG 6000 in very low amounts compared to the amount of carbamazepine used in the preparation of 200 mg immediate release tablets using different formulations and then determining the best produced tablets.

MATERIALS AND METHODS

Materials

Carbamazepine USP 33 (Xiamen, China), microcrystalline cellulose PH102 (FMC, Ireland), polyethylene glycol 6000 (Lyondel, France), magnesium stearate (Alba chemicals, USA), methanol and acetonitrile for HPLC (Merck, Germany), Acetone (El-Nasr Co, Egypt), Sodium lauryl sulphate (SLS) (Surfachem, England), Sodium starch glycolate (SSG)(JRS pharma, Germany) and Tegretol® 200 mg immediate release tablets (Novartis pharma, Switzerland).

Methodology

Assay of carbamazepine in methanol, distilled water and distilled water containing 1.0 % SLS using HPLC methods

These trials have been done according to the methods described in a previous study [2].

Formulation of carbamazepine 200 mg immediate release tablets

Using water as a vehicle for PEG 6000

CBZ: PEG 6000 mixtures were prepared in ratios of 1:0.01, 1:0.03, 1:0.05, 1:0.07 and 1:0.09 w/w by dissolving the required amount of PEG 6000 in least amount of hot distilled water and then incorporating the drug to give a wet mass which was passed through sieve 0.800 mm. The prepared granules were left on stainless steel trays at room temperature. The amount of water used was constant in the prepared mixtures. These granules (which contain the drug, PEG 6000 and water) were subjected to:

a- DSC thermal analysis

Thermal analysis of carbamazepine, PEG 6000, their prepared mixtures 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.

b- Fourier transform infra red spectroscopy (FTIR)

FTIR spectra were obtained on a Thermo Scientific Nicolet iS10 FTIR spectrophotometer (USA) using potassium bromide disk method. The scanning range was 400-4000 cm^{-1} and the resolution was 1 cm^{-1}

c- X- ray powder diffraction

X-ray diffractograms of various samples were measured using XRD (Philips PANalytical X' Pert PRO diffractometer with copper Kα radiation, Netherlands), operating at 45 kV and 40 mA. Difractograms were run at a scanning speed of 4°/minute over a 2θ range of 0-40°.

The last prepared granules were then blended with microcrystalline cellulose, sodium starch glycolate and magnesium stearate. The resultant blends were then incorporated into tablets which now contain water in their formulae in a ratio of 9.33 % w/w per tablet weight. Five formulations were prepared and coded from F1: F5 respectively. The detail of each composition is given in table (1).

Using acetone as a solubilizing agent

In this preparation; CBZ: PEG 6000 ratio was 1:0.03 w/w. PEG 6000 was dissolved in the least amount acetone while stirring and slight heating at 50 ºC. SSG was geometrically mixed with microcrystalline cellulose and carbamazepine. This powder mixture was granulated using the prepared PEG/acetone solution. The granules were allowed to dry, passed through sieve 0.800 mm and mixed with magnesium stearate. The resultant blends were then compressed into tablets. This formulation was coded F6. The detail of this composition is also given in table (1).

Table 1: Composition of different formulations of carbamazepine 200 mg tablets

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
Carbamazepine	200.0	200.0	200.0	200.0	200.0	200.0
PEG 6000	2.0	6.0	10.0	14.0	18.0	6.0
Microcrystalline cellulose	54.5	50.5	46.5	42.5	38.5	78.5
Sodium starch glycolate	14.0	14.0	14.0	14.0	14.0	14.0
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5
Water	28.0	28.0	28.0	28.0	28.0	------
Acetone	-----	-----	-----	-----	-----	Q.S
Total	300.0	300.0	300.0	300.0	300.0	300.0

Evaluation of the prepared tablets

The prepared tablets were evaluated by determination of:

Uniformity of weight: According to B.P 2010 [7].

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

Disintegration time: According to B.P 2010[7].

Water was used as the medium. This test was 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[7].

This test was intended to determine the resistance to crushing of tablets, measured by the force needed to disrupt them by crushing.

Friability: According to USP 33[8].

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[8].

Twenty tablets were finely powdered and assayed for its drug content by HPLC method. The requirements for 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[8].

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 in an oven at 120 ºC for two hours. A maximum weight loss of not more than 5.0 % is considered acceptable for carbamazepine tablets.

Dissolution in distilled water containing 1.0 % SLS: According to USP 33[8].

It was carried out using apparatus II, 75 rpm, 900 ml water containing 1.0 % SLS 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.

Calculation of difference and similarity factors:

In order to analyze the dissolution data equivalence, FDA guidance documents consider some approaches such as difference (f1) and similarity (f2) factors [9]. The main advantage of the f1 and f2 equations is to provide a simple way to describe comparison of data. The f1 should be computed using the following equation:

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

While the f_2 should be computed using the equation:

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

Where R_t and T_t 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 f1 between zero and 15 and of f 2 between 50 and 100 ensure dissolution profile and the sameness or equivalence of the two curves, and thus the performance of the two products [9]. The dissolution profiles of the last prepared carbamazepine 200 mg tablets and the innovator product Tegretol® 200 mg immediate release tablets were carried out by USP dissolution apparatus II in water containing 1.0 % Sodium lauryl sulphate, 900 ml, paddles, 75 rpm and then the difference and similarity factors were then calculated.

RESULTS AND DISCUSSION

Assay of carbamazepine in methanol, distilled water and distilled water containing 1.0 % SLS using HPLC methods

In a previous study, it was concluded that this method is suitable for assay of carbamazepine, dissolution of carbamazepine tablets in distilled water containing 1.0 % SLS [2].

Evaluation of carbamazepine 200 mg tablets prepared by PEG 6000 and water

DSC thermal analysis of the prepared mixtures:

Figure (1-a) shows an endothermic onset of peak at 173.75ºC and an exothermic one at 178.42 ºC followed by a sharp endothermic peak at 189.23 ºC corresponding to CBZ melting point as indicated by Florey K. [10] and Zerrouk N. et al [11]. Figure (1-b) shows a sharp endothermic peak at 56.98 corresponding to PEG 6000 melting point [8]. Figure (1-c) shows a sharp endothermic peak at 189.12 ºC corresponding to CBZ melting point. The absence of the characteristic peak corresponding to PEG 6000 may be due to the very low amount of PEG 6000 used. Figures (1-d:1-g) show sharp endothermic peaks at 188:190 ºC corresponding to carbamazepine melting point , broad endothermic peaks at 44:45 ºC and broad peaks at 80: 100 ºC which may be due to dehydration and loss of the used water in the preparation of the mixtures [12]. It is observed that the melting point of PEG 6000 is not around its normal range (55-63ºC), but it has decreased to a lower range (44:49 ºC). This behavior may be attributed to the fusion of an eutectic mixture between carbamazepine and PEG 6000 [11]. This may also be in accordance with Xin Wang et al (2004) who attributed that the melting peak of PEG 6000 in the dispersion of 80 % itraconazole was not around 63 ºC; but it was 58 ºC [13].

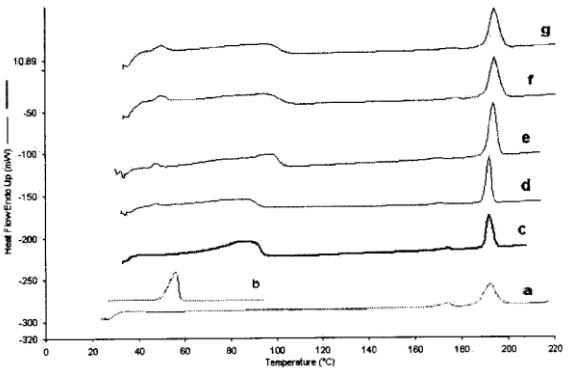

Fig. 1: DSC thermal analysis for a- carbamazepine, b- PEG 6000, c- carbamazepine/ PEG 6000 mixture 1:0.01, d- 1:0.03, e- 1:0.05, f- 1:0.07.

Fourier Transform Infrared spectroscopy (FTIR) of the prepared mixtures

Figure (2-a) shows the FTIR spectrum of carbamazepine which shows a sharp peak at 3465 and another peak at 3159 cm^{-1} (–NH valence vibration), peak at 1677 cm^{-1} (–CO–R vibration), and another one at 1605 cm^{-1} (–C=C– vibration). These results are similar to the results obtained by Prajapati S.T. et al (2007) [14]. Figure (2-b) shows the FTIR spectra of PEG 6000 which shows a C-H stretching at 2889 cm^{-1} and C-O (ether) stretching at 1110 cm^{-1}. These results are similar to the results obtained by Kalia A. et al (2009) [15].

Figure (2-c) shows the FTIR spectra of carbamazepine physical mixture with PEG 6000 in a ratio of 1:0.03 w/w which shows a sharp peak at 3465, another peak shifted from 3159 to 3163 cm^{-1} which indicates lesser interaction between the drug and polymer when physically mixed together.

Figure (2-d) shows the FTIR spectra of carbamazepine mixture with PEG 6000 and water which shows a sharp peak at 3464, another peak shifted from 3159 to 3162 cm^{-1} which indicates lesser interaction between the drug and polymer.

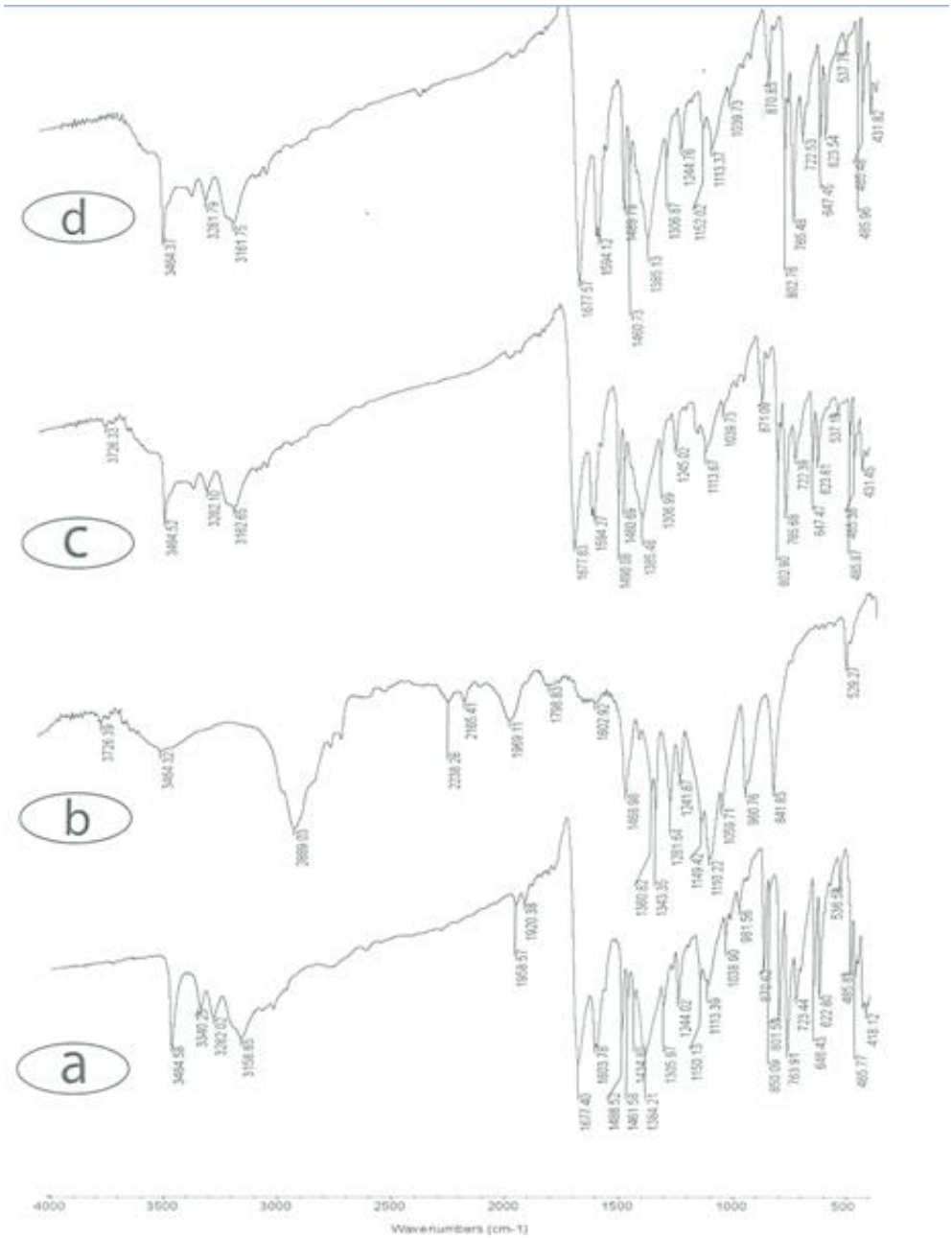

Fig. 2: FTIR for a- carbamazepine, b-PEG 6000, c-carbamazepine /PEG 6000 physical mixture 1:0.03, d- Carbamazepine bound with PEG 6000 and water.

XRD

Figure (3-a) shows that pure CBZ has characteristic peaks at 2θ 14.12, 15.237, 15.839, 27.218 and 31.975º which are specific for polymorph III [16]. This is in accordance with the results obtained by Rustichelli C. et al. (2000) and Biswal S. et al. (2009) [17 & 18]. Figure (3-b) shows that PEG 6000 reveals two distinct peaks at 19.8 and 23.326 2θ which are characteristic for its crystalline nature. Figure (3-c) shows peaks of CBZ polymorph III at 2θ 13.067 and 15.276 in the physical mixture. Thus; simply mixing of the drug and PEG 6000 doesn't change the physical state of either the components. This is also observed in figure (3-d) which indicates that mixing of CBZ and PEG 6000 and water don't change the physical state of the drug.

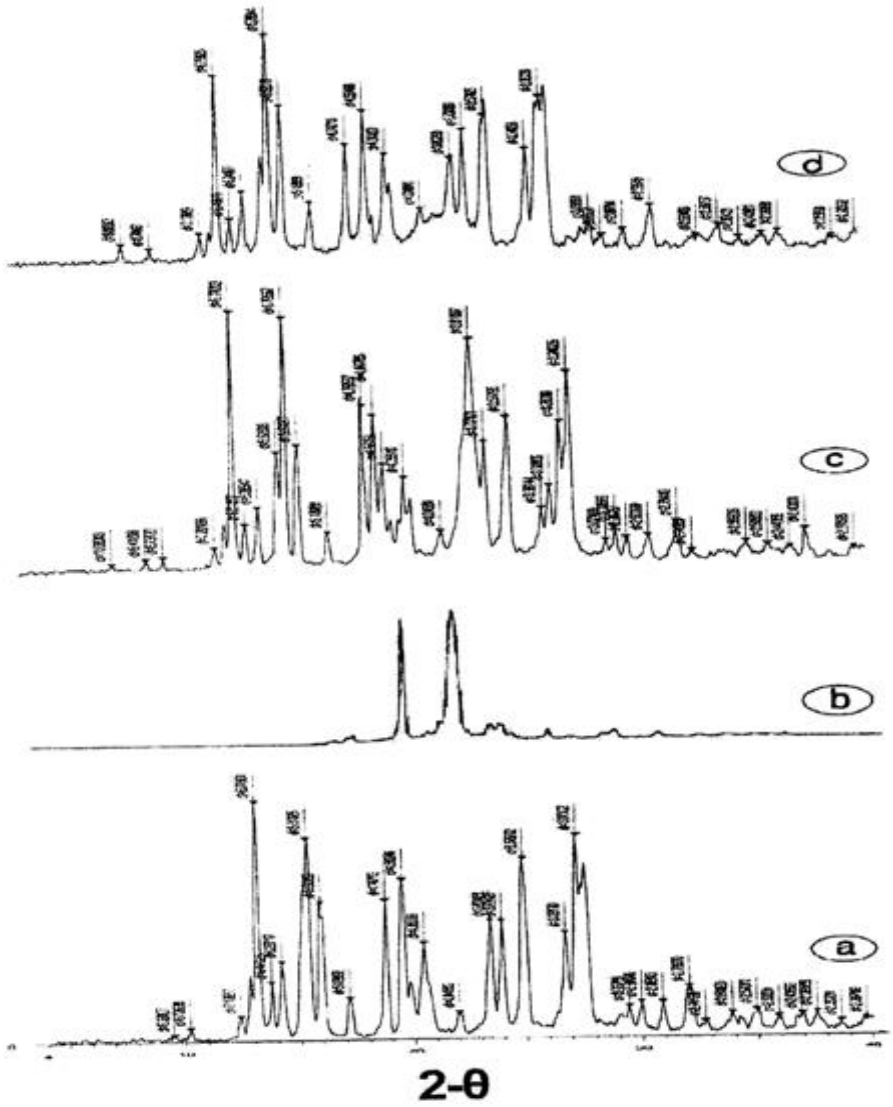

Fig. 3: XRD for a-carbamazepine, b-PEG 6000, c- carbamazepine/PEG 6000 physical mixture and d- carbamazepine bound with PEG 6000 and water.

Evaluation of the prepared tablets

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

Tables (2 and 3) show that the average weights of tablets from each preparation is from 300.0 to 305.0 mg. The disintegration time varies from 0.43 minutes to 25.0 minutes. It is observed that increasing the PEG 6000 ratio incorporated into the tablets lead to elongation of the disintegration time. This may be attributed to the binding action of PEG 6000. All friability results are less than 0.350 %. All hardness values vary from 79.0 to 133.0 N. All assay values are varying from 101.0 to 104.0%. Loss on drying values are less than 0.30 %.

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

The first range in the dissolution process of tablets in distilled water containing 1.0 % SLS is the critical one as it is necessary for CBZ to dissolve from 45.0-75.0 % in the first 15 minutes [8]. Table (4) shows that the dissolution values of the prepared tablets prepared in ratios of formula F1, F2 and F6 lie in the required USP range after 15 minutes.

Therefore, they are conforming to USP official limits after 15 minutes. While dissolution values of tablets of formula F3, F4 and F5 lie outside this range. Thus, they are not conforming to USP specification.

Table 2: **Average weight, disintegration time and friability for CBZ 200 mg tablets.**

Formula	Average weight (mg)	Disintegration time (min)	Friability (%)
F1	303.3 ± 3.76	0.90 ± 2.08	0.212 ± 2.63
F2	302.5 ± 4.55	1.25 ± 0.04	0.342 ± 2.62
F3	303.7 ± 2.83	8.0 ± 1.15	0.216 ± 2.50
F4	305.3 ± 1.16	11.8 ± 1.57	0.329 ± 2.11
F5	305.0± 2.63	25.0 ± 1.92	0.344 ± 1.49
F6	301.0 ± 2.45	0.43 ± 0.03	0.344 ± 2.13

All values are expressed as mean ± SD (n=3).

Table 3: **Assay, average hardness and loss on drying values of CBZ 200 mg tablets prepared by PEG 6000 and water.**

Formula	Assay (%)	Average hardness value (N)	LOD (%)
F1	101.23 ± 1.57	79.0 ± 1.15	1.229 ± 0.06
F2	101.88 ± 3.67	93.0 ± 3.06	1.241 ± 0.07
F3	101.93 ± 1.53	108.0 ± 2.42	1.271 ± 0.09
F4	103.49 ± 0.93	110.0 ± 1.36	1.221 ± 0.02
F5	104.00 ± 1.13	133.0 ± 1.49	1.193 ± 0.05
F6	100.33 ± 0.45	133.0 ± 4.0	0.193 ± 0.03

All values are expressed as mean ± SD (n=3).

Table 4: **Dissolution of CBZ 200 mg tablets in distilled water containing 1.0 % SLS.**

Time	Percent of CBZ dissolute from					
(min)	F1	F2	F3	F4	F5	F6
10.0	37.27 ± 1.80	35.56 ± 3.91	21.01 ± 3.10	19.95 ± 0.90	11.62 ± 1.39	56.01 ± 2.24
15.0	50.21 ± 2.26	49.01 ± 3.81	40.76 ± 2.95	37.12 ± 0.32	19.49 ± 2.28	68.76 ± 2.04
20.0	60.24 ± 2.36	58.76 ± 3.54	55.94 ± 2.66	53.42 ± 1.87	29.44 ± 3.48	74.54 ± 1.89
30.0	73.01 ± 4.04	72.84 ± 3.33	74.23 ± 1.29	66.49 ± 3.24	50.15 ± 6.80	84.05 ± 1.45
45.0	86.34 ± 3.25	86.32 ± 3.38	89.17 ± 1.71	81.72 ± 0.93	73.60 ± 5.02	94.16 ± 1.43
60.0	94.60 ± 1.57	93.76 ± 3.28	96.54 ± 1.36	94.23 ± 1.40	88.49 ± 2.49	96.30 ± 1.22
90.0	101.03 ± 0.76	99.44 ± 2.87	101.8 ± 2.45	100.87 ±2.13	98.21 ± 1.15	100.14± 0.98
120.0	103.35 ±0.85	102.98±1.35	103.57 ±0.66	102.45 ±1.05	103.10 ±0.90	100.63 ± 0.85

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

The second stage in dissolution process is that the total amount of carbamazepine dissolved is not less than 75.0 % after 60 minutes. It is found that dissolution values of the prepared tablets are more than 85.0 % after 60 minutes. Thus, they are conforming to the second range of dissolution process listed in the pharmacopeia. It is also found that the drug dissolution from the prepared tablets are almost 100.0 % after two hours of the dissolution process which mean the complete dissolution of carbamazepine.The increased dissolution values of tablets of F6 is due to the solubilizing effect of acetone used in the preparation.

Calculation of difference and similarity factors:

By calculating the difference and similarity factors, it is found that carbamazepine 200 mg tablets prepared by PEG 6000 dissolved in water of F1 and F2 have acceptable difference and similarity factors. Tablets prepared by PEG 6000 dissolved in acetone (F6) have difference factor 7.0 and similarity factor 62.0 which are very acceptable. Tablets of F3:F5 have unacceptable difference and similarity factors. Thus, the technique used in formulation of F6 can be used for the preparation of carbamazepne 200 mg immediate release tablets on the production large scale.

Table 5: Difference and similarity factors of the prepared carbamazepine 200 mg tablets.

Formula	Difference factor	Similarity factor
F1	12.0	52.0
F2	12.0	50.0
F3	20.0	39.0
F4	20.0	38.0
F5	36.0	27.0
F6	7.0	63.0

CONCLUSION

Carbamazepine 200 mg immediate release tablets were prepared by two different techniques using water and acetone:

The dissolution of the drug from the tablets prepared from carbamazepine /PEG 6000 mixtures is conforming to USP specification when ratios of 1: 0.01 and 1: 0.03 were used while tablets prepared from ratios 1:0.05 , 1: 0.07 and 1: 0.09 are not conforming to specification. The tablets prepared by acetone as a solubilizing agent showed higher dissolution rate and acceptable difference and similarity factors .

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