Research paper

Formulation And Evaluation Of Carbamazepine 200 mg Controlled Release Tablets Using Different HPMC Grades

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Abstract:

Possible interaction between carbamazepine and different HPMC grades was done using DSC thermal analysis. The results indicated that the drug was compatible with these grades. Seven preparations of carbamazepine 200 mg controlled release tablets were prepared by wet granulation method and one preparation was prepared by direct compression method where different HPMC grades with different ratios were used. Concerning uniformity of weight, hardness and assay; all tablets conformed to pharmacopeal limits. Dissolution of the prepared tablets was done using basket method for 24 hours and paddle method for 4 hours.Tablets prepared by 30.0, 35.0 and 40.0 % w/w HPMC K 100, 25.0 % HPMC K 100 in combination with 5.0 % HPMC K 4M and 15.0 % w/w HPMC K 4M were conforming to USP limits, while tablets prepared by 15 % K4M are not conforming to these limits. Tablets prepared by 12.5 % HPMC K 15M by direct compression technique showed similar dissolution values to the innovator in five different media: distilled water, distilled water containing 1.0 % SLS, buffer pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8. The difference and similarity factors were found very acceptable. Scaling up of carbamazepine 200 mg controlled release tablets formulation from lab scale (500 tablets) to full production scale (500,000 tablets) was done. All the results of the scaling up were conforming to specifications and indicated that scaling up process has been done successfully and drug release kinetics indicated that the drug dissolution was zero order.

Key words: Carbamazepine, controlled release tablets and dissolution.

General introduction:

Carbamazepine (CBZ) is considered a first line drug in the treatment of epilepsy and specific analgesic for trigeminal neuralgia [1]. It is practically insoluble in water and has four different polymorphs and the dihydrate form [2]. It is available for oral administration as chewable tablets 100 mg, immediate release tablets of 200 mg, extended release tablets of 200 and 400 mg and as a suspension of 100 mg/5 ml [3]. The major advantages of carbamazepine include proven efficacy and less cost [4].

Sustained release formulations of carbamazepine have been introduced into drug therapy with a twofold purpose: to reduce the number of single doses during the day, and to decrease the fluctuation of serum levels in view to obtain better therapeutic efficacy and diminished toxicity [5].

Controlled–release formulations have been one of the major focuses in pharmaceutics [6]. Matrix systems appear to be a very attractive approach in controlled-release system. Cellulose polymer has received much attention as a hydrophilic matrix for sustained release formulations [7]. The release of drug from this type of matrix is controlled by the rapid formation of the hydrogel layer around the matrix following exposure to aqueous fluid. Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. Drug release from hydrophilic matrices is known to be a complex interaction between dissolution, diffusion and erosion mechanisms [8]. Hydroxypropyl methylcellulose (HPMC) is the first choice for formulation of hydrophilic matrix system, providing robust mechanism, choice of viscosity grades, nonionic nature and cost effectiveness [9].

Many researchers prepared carbamazepine extended release tablets using hydroxypropyl methylcellulose (HPMC). Koester L.S. et al. used 15 or 30 % w/w HPMC K 100 LV and βCD in the preparation of carbamazepine 20 and 80 mg extended release tablets respectively [10]. Patel D.M. et al. used 20, 30, 40 or 45 % w/w HPMC K4 M in the preparation of carbamazepine 200 mg extended release floating tablets [11]. Fasiuddin A.M. et al. prepared carbamazepine 200 mg extended release tablets using HPMC K4 M in different ratios ranging from 10: 30 % w/w [12]. Halith S.M. et al. used 3, 5, 8 and 10 % w/w HPMC 2910, 4 and 5 % w/w HPMC K4 M and a combination of 17.5, 15 % HPMC K4 M with 12.5 % HPMC K100 M in the preparation of carbamazepine 200 mg sustained release matrix tablets [13]. Razzak S.M. et al. used 40

% w/w HPMC K15M in the preparation of carbamazepine 200 mg sustained release matrix tablets [14].

The objective of this study was to formulate and evaluate carbamazepine 200 mg controlled release tablets by both wet granulation and direct compression techniques using different HPMC grades as a matrixing agent and then selecting the best formula for carrying out the scaling up process.

Experimental

Materials:

Carbamazepine USP 33 (Xiamen, China), microcrystalline cellulose PH102 (FMC, Ireland), magnesium stearate (Alba chemicals, USA), methanol and acetonitrile for HPLC (Merck, Germany), Sodium lauryl sulphate (SLS) (Surfachem, England), Colloidal silicon dioxide (Aerosil 200) (Degussa, Germany), Lactose monohydrate DC (DMV, Holland), HPMC K100 LV, K 15M ,K 4M , 2910 (Colorcon, United Kingdom) and Tegretol® 200 mg controlled release tablets (Novartis pharma, Switzerland).

Methodology

1- Study of the possible interactions between the drug and different HPMC grades:

Thermal analyses of different HPMC grades alone and with carbamazepine physical mixtures in a ratio of 1:1 w/w were performed in a Perkin Elmer Diamond DSC differential scanning calorimeter (USA).

2- Preparation of carbamazepine 200 mg CR tablets:

The quantitative composition of the reference formulation Tegretol 200 mg CR tablets is not disclosed, but the following excipients are listed: colloidal silicon dioxide, ethyl cellulose, microcrystalline cellulose, co-polymers of acrylic acid and methacrylic esters, magnesium stearate, sodium croscarmellose, talc, hydroxypropyl methyl cellulose, polyethylene sorbitan monooleate, red iron oxide, yellow iron oxide and titanium dioxide [5].

Carbamazepine 200 mg controlled release tablets were prepared by different HPMC grades (K100 LV, K4 M, K15 M) using both wet granulation and direct compression techniques.

A proposed formula from colorcon mentioned that it contained carbamazepine 57.14 % w/w , SLS 0.5 %, HPMC E3LV 0.16%, HPMC K100 LV in a ratio of 30.0 % w/w, microcrystalline cellulose pH 102 10.95 %, aerosil 200 1.0 % and magnesium stearate 0.25 % [15]. To study the effect of SLS; this formula was prepared using SLS in ratios of 0.5 and 1.0 % w/w respectively. Due to unavailability of HPMC E3LV, it was replaced by HPMC 2910 and magnesium stearate ratio was increased to 1.0 % w/w. Table (1) summarizes the proposed formulae for eight preparations done using different HPMC grades with different ratios.

Table (1): Composition of eight preparations of carbamazepine 200 mg controlled release tablets prepared by different HPMC grades.

Ingredients	**F1 (mg)**	**F2 (mg)**	**F3 (mg)**	**F4 (mg)**	**F5 (mg)**	**F6(mg)**	**F7 (mg)**	**F8 (mg)**
Carbamazepine	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0
HPMC K100	105.0	105.0	122.5	140.0	-----	87.5	------	------
HPMC K4M	------	------	------	------	52.50	17.5	------	------
HPMC K15M	------	------	------	------	------	------	26.25	43.75
HPMC 2910	0.56	0.56	0.56	0.56	0.56	0.56	0.56	7.00
Aerosil 200	3.50	3.50	3.50	2.44	3.50	3.50	3.50	3.50
Magnesium stearate	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.5
Microcrystalline cellulose pH102	35.69	33.94	16.44	------	86.44	33.94	112.69	67.75
SLS	1.75	3.50	3.50	3.50	3.50	3.50	3.50	3.50
Lactose monohydrate DC	------	------	------	------	------	------	------	24.50
Total	350.0	350.0	350.0	350.0	350.0	350.0	350.0	350.0

The preparation of formulae F1: F7:

SLS and HPMC 2910 were dissolved in the least amount of distilled water. Half the quantity of the other HPMC was mixed geometrically with the drug and then granulated by the prepared aqueous solution of HPMC 2910. The coherent granules were then dried in an oven at 60 °C and passed on 0.800 mm sieve. The resulting granules were mixed with microcrystalline cellulose pH 102, the other half of the quantity of HPMC, aerosil 200 and magnesium stearate.

The preparation of formula F8:

SLS was mixed with HPMC K 15M, carbamazepine, aerosil 200, micro-crystalline cellulose, lactose monohydrate DC and magnesium stearate. Compression into tablets was done using 10 mm concave punches. The compressed tablets were evaluated by determination of: uniformity of weight, resistance to crushing, assay and dissolution.

Jung et al. have carried out in vitro and in vivo studies for carbamazepine commercial formulations and found that United States Pharmacopeia (USP) in vitro dissolution method cannot be used to accurately predict the bioavailability of a carbamazepine formulation and suggested for additional work in order to obtain good in vitro and in vivo correlation [16]. Literature have mentioned the usage of many dissolution media (1.0 % SLS, 0.1 N Hydrochloric acid and water) for dissolution studies of carbamazepine controlled release tablets. It was also mentioned that 1% SLS and 0.1 N HCl were preferred on the basis of IVIVC studies [17]. The dissolution was performed according to USP 33 (2010) as illustrated in table (2) [18]:

Table (2): Dissolution parameters for the prepared carbamazepine 200 mg controlled release tablets in distilled water.

Medium	Water, 900 ml
Apparatus	I (basket), 100 rpm.
Time	After 3.0, 6.0, 12.0 and 24.0 hours
Tolerance	Between 10.0 % and 35.0 % is dissolved after 3.0 hours. Between 35.0 % and 65.0 % is dissolved after 6.0 hours.

	Between 65.0 % and 90.0 % is dissolved after 12.0 hours. Not less than 75.0 % is dissolved after 24.0 hours.

Also the dissolution was also carried out in distilled water containing 1.0 % SLS according to table (3):

Table (3): Dissolution parameters for the prepared carbamazepine 200 mg controlled release tablets in distilled water containg 1.0 % SLS.

Medium	Water containing 1.0 % SLS, 900 ml
Apparatus	II (paddle), 75 rpm.
Time	After 1.0, 2.0, 3.0 and 4.0 hours

The selection of the two media was to compare the behavior of the prepared tablets in these media.

Dissolution of the directly compressed tablets was done in buffer pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8. The difference and similarity factors in these media were then calculated according to the calculations mentioned in a previous study [2].

3- Scaling up of carbamazepine 200 mg CR tablets prepared by direct compression technique:

Scaling up is generally defined as the process of increasing the batch size. Scaling up of a process can also be viewed as a procedure for applying the same process to different output volumes. In mixing applications, scale-up is concerned with increasing the linear dimensions from the laboratory to the plant size [19]. Scaling up of carbamazepine 200 mg controlled release tablets from lab scale (500 tablets) to full production scale (500,000 tablets) was done.

Samples from the mixed powders (Before compression) and subjected to:

1. DSC thermal analysis: to study the compatibility of carbamazepine with the totally mixed excipients.

2. Flowability measurements:

The flow characteristics were assessed by calculating the angle of repose which is one of the measures of flow properties of powders. It is measured by Erweka Flow meter (Germany). The angle of repose was calculated by a simple geometry where the base (D) and height of the conical heap (h) were measured and utilized in calculation of the angle of repose according to the following equation: Tan $\theta = 2h / D$ [20].

Also samples of the compressed tablets from the scaled up first production batch were taken at start, middle and end of compression process and subjected to the tests mentioned before.

- Drug release kinetics:

In order to describe the kinetics of carbamazepine dissolution process, various equations were used such as [21]:

- 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.
- Hixon-Crowell cube root law where there is a change in surface area and diameter of the particles.

Results and Discussion

1- Estimation of possible interactions between the drug and different HPMC grades by DSC thermal analysis:

Figure (1-a) shows a sharp endothermic onset of peak at 173.75 ºC and an exothermic onset of peak at 178.42 ºC followed by a sharp endothermic one at 189.23 ºC corresponding to carbamazepine melting point. Figures (1-b:1-d) show that HPMC grades K 100 LV, 2910 and K 15 M have no characteristic peaks over the range from 30 ºC to 290 ºC. These results are in accordance with the results obtained by Bhise and Rajkumar and Dadarwal et al. [22&23].

Figure (1-e) shows the DSC thermogram of carbamazepine physical mixture with HPMC K 100 LV in a ratio of 1:1 w/w. It shows an endothermic onset of peak at 174.43 ºC and an exothermic onset of peak at 181.42 ºC followed by a sharp endothermic onset of peak at 191.66 ºC.

Figure (1-f) shows the DSC thermogram of carbamazepine physical mixture with HPMC 2910 in a ratio of 1:1 w/w. It shows a sharp endothermic onset of peak at 172.59 ºC and an exothermic peak at 183.31 ºC followed by a sharp endothermic peak at 194.85 ºC. Figure (1-g) shows the DSC thermograms of carbamazepine physical mixture with HPMC K 15 M in a ratio of 1:1. It shows a sharp endothermic onset of peak at 170.50 ºC and an exothermic peak at 178.06 ºC followed by a sharp endothermic peak at 191.95 ºC.

From these different thermograms, it is indicated that carbamazepine is compatible with different HPMC grades. These results are in accordance with the results obtained by Barakat N.S. et al. [6] and Katzhendler I. et al. [24].

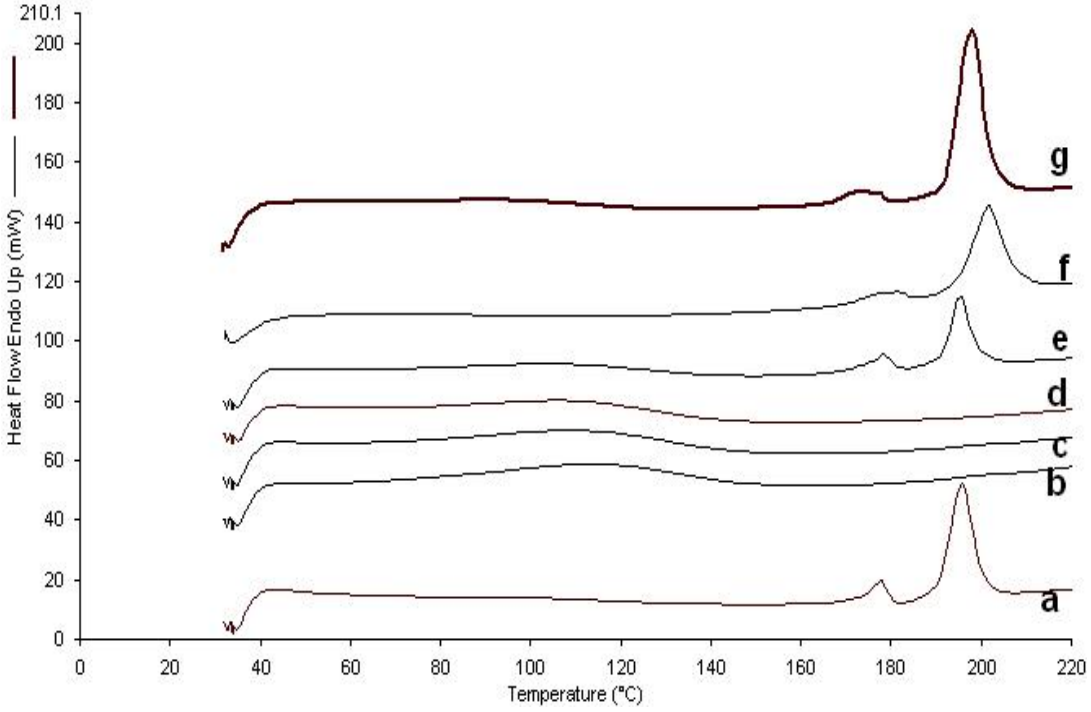

Figure 1: DSC thermal analysis for : a- carbamazepine alone, b- HPMC K 100 LV, c- HPMC , d- HPMC K 15M, e- carbamazepine/ HPMC K 100 LV 1:1 physical mixture, f- carbamazepine/HPMC 1:1 physical mixture, g- carbamazepine /HPMC K 15M 1:1 physical mixture.

2– Evaluation of carbamazepine 200 mg CR tablets prepared by different HPMC grades:

2-1 Uniformity of weight, resistance to crushing of tablets and assay:

Table (4) shows that the average weight values of all formulae are very close to the target weight 350.0 mg. Hardness values are more than 120.0 N. Assay values are within the accepted range.

Table (4): Average weight, average hardness value and assay for carbamazepine 200 mg CR tablets prepared by different HPMC grades.

Formula No:	Average weight (mg) ± SD, n = 20	Average hardness value (N) ± SD, n = 10)	Assay (%) (mean ± SD, n = 10)
F1	351.2 ± 2.94	185.0 ± 5.10	103.53 ± 2.38
F2	351.1 ± 2.44	198.0 ± 6.02	99.45 ± 0.51
F3	352.6 ± 4.26	201.0 ± 4.15	99.34 ± 0.71
F4	351.0 ± 2.34	192.0 ± 2.76	98.68 ± 1.36
F5	349.7 ± 1.89	203.0 ± 3.93	99.89 ± 0.88
F6	353.0 ± 3.07	180.0 ± 2.56	99.23 ± 1.21
F7	352.14 ± 2. 91	165.0 ± 6.20	100.22 % ± 0.21
F8	350.2 ± 2.98	125.0 ± 4.16	100.42 ± 0.89.

2-2 Dissolution in distilled water:

Table (5) shows that the percents of drug dissolved from Tegretol 200 mg CR tablets in distilled water are 34.85 , 52.89 , 67.42 and 82.92 % after 3.0, 6.0, 12.0 and 24.0 hours. The percentages of drug dissolved from tablets in distilled water are 20.0 : 39.0 , 47.0 : 59.0 , 81.0 : 91.0 and more than 100.0 % after 3.0, 6.0, 12.0 and 24.0 hours. According to USP limits: tablets of formula F1and F2 are conforming to USP limits after 3, 6 and 24 hours and not conform after 12 hours, Tablets of formula F5 are conforming after 3 and 24 hours and not conform after 6 and 12 hours and tablets of formula F3, F4, F6, F7 and F8 are conforming to USP limits at all time intervals.

Table (5): Dissolution of carbamazepine 200 mg CR tablets prepared bydifferent HPMC grades in distilled water.

Time (hours)	Percent of dissolved carbamazepine from its CR tablets made with:								
	Tegretol 200 mg CR tab	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.0	20.04 ± 1.91	9.43 ± 7.67	11.37 ± 8.23	6.06 ± 0.75	5.63 ± 0.70	3.50 ± 0.57	4.01 ± 0.51	15.35 ± 3.24	20.35 ± 1.12
2.0	29.33 ± 0.48	20.36 ± 6.06	21.49 ± 7.05	17.19 ± 1.40	16.51 ± 1.64	7.77 ± 1.45	11.28 ± 1.69	25.54 ± 4.22	28.61 ± 1.49
3.0	34.85 ± 1.46	28.96 ± 3.87	32.97 ± 4.71	28.39 ± 1.68	26.10 ± 2.55	12.79 ± 2.39	20.16 ± 2.76	33.16 ± 3.51	33.96 ± 1.94
4.5	46.72 ± 1.64	41.52 ± 4.79	49.03 ± 6.64	43.67 ± 1.25	43.38 ± 2.31	22.67 ± 4.16	33.93 ± 3.60	45.38 ± 2.16	49.36 ± 2.01
6.0	52.89 ± 1.51	59.49 ± 6.80	64.17 ± 8.17	58.30 ± 1.64	57.48 ± 2.90	31.59 ± 5.56	47.04 ± 4.22	50.61 ± 2.83	55.75 ± 3.22
9.0	61.72 ± 1.55	77.03 ± 5.82	83.04 ± 4.65	77.28 ± 2.28	75.99 ± 3.11	47.39 ± 4.67	67.84 ± 5.01	65.33 ± 4.33	64.68 ± 4.53
12.0	67.42 ± 1.85	91.12 ± 6.17	98.63 ± 3.79	89.97 ± 2.33	87.87 ± 2.88	62.34 ± 1.32	81.61 ± 4.78	76.54 ± 1.14	71.26 ± 5.03
18.0	76.48 ± 2.52	95.54 ± 3.24	100.12 ± 4.01	100.50 ± 2.97	98.86 ± 1.31	83.17 ± 1.25	96.95 ± 4.50	94.15 ± 3.19	79.79 ± 4.68
24.0	82.92 ± 1.61	101.13 ± 2.20	102.50 ± 0.27	102.84 ± 2.76	101.24 ± 1.40	95.70 ± 1.23	102.5 ± 2.72	100.39 ± 0.55	85.54 ± 5.92

All values are expressed as mean ± SD (n = 12).

It is observed that the dissolution values of tablets prepared by 15.0 % HPMC K4 M (F5) at different time intervals are less than that of other tablets prepared by different concentrations of HPMC K100. This may be due to the fact that HPMC K4M acts as a matrixing agent and has an excellent gelling activity in sustained release formulations [25]. The dissolution results of F5 tablets are very close to the results obtained by Fasiudin A.M. et al. who prepared carbamazepine 200 mg extended release tablets and

concluded that the amount of drug dissolved is 15.1, 33.9, 63.9 and 95.6 % after 3.0,6.0,12.0 and 24.0 hours respectively [12].

From all the previous results, it is concluded that the release of drug depends not only on the nature of matrix but also upon the drug polymer concentration [12]. Also Giunchedi P. et al mentioned that the amount of hydroxpropyl methylcellulose is the determining factor in the controlling release of carbamazepine from its tablets [26].

2-3 Dissolution in distilled water containing 1.0 % SLS:

Table (6) shows that the percents of drug dissolved from Tegretol 200 mg CR tablets in distilled water containing 1.0 % SLS are 51.74 , 75.96 , 88.53 and 95.71 % after 1.0, 2.0, 3.0 and 4.0 hours. The percentages of dissolution from the prepared tablets are: 7.0: 45.0, 17.0: 76.0, 26.0: 85.0 and 35.0: 93.0 after 1.0, 2.0, 3.0 and 4.0 hours. It is evident now that the presence of SLS greatly enhanced carbamazepine dissolution from the prepared tablets.

Table (6): Dissolution of carbamazepine 200 mg CR tablets prepared by different HPMC grades in distilled water containing 1.0 % SLS.

Time (hours)	**Percent of dissolved carbamazepine from its CR tablets made with:**								
	Tegretol 200 mg CR tab	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.0	51.74 ± 5.85	9.43 ± 0.65	10.49 ± 0.85	7.53 ± 0.42	7.42 ± 0.60	7.33 ± 1.02	7.35 ± 1.07	59.83 ± 2.53	44.31 ± 6.25
2.0	75.96 ± 2.76	20.38 ± 1.73	22.40 ± 1.19	17.26 ± 0.76	16.86 ± 4.04	17.85 ± 1.01	17.43 ± 2.35	75.55 ± 1.72	66.18 ± 3.32
3.0	88.53 ± 2.31	28.67 ± 2.12	33.99 ± 1.68	26.33 ± 2.44	28.30 ± 3.13	27.19 ± 2.41	26.86 ± 4.12	85.38 ± 1.44	78.27 ± 3.91
4.0	95.71 ± 1.77	39.54 ± 2.36	44.99 ± 1.48	35.66 ± 2.95	37.39 ± 3.84	38.79 ± 2.41	35.86 ± 3.76	92.25 ± 0.99	85.35 ± 3.98

All values are expressed as mean ± SD (n = 12).

2-4 Calculation of difference and similarity factors:

By calculating the difference and similarity factors, it is found that all the prepared carbamazepine 200 mg controlled release tablets have difference factor more than 15.0 and similarity factor less than 50.0 while the prepared carbamazepine 200 mg controlled release tablets prepared by 7.5 % metocel K 15M have difference factor 7.0 and similarity factor 60.0 which are considered acceptable.

2-5 Dissolution of directly compressed tablets in different buffers:

Table (7) shows that the percentages of drug dissolved in different buffers are similar to the innovator results.

Table (7): Dissolution of carbamazepine 200 mg CR tablets prepared by direct compression method in different buffer in comparison with the innovator.

Time (hours)	Percent of carbamazepine dissolved from its tablets in					
	Buffer pH 1.2		Acetate buffer pH 4.5		Phosphate buffer pH 6.8	
	Brand	D.C tablets	Brand	D.C tablets	Brand	D.C tablets
0.0	0.00	0.00	0.00	0.00	0.00	0.00
1.0	21.90 ± 2.66	22.23 ± 1.73	21.12 ± 2.67	22.08 ± 3.33	18.6 ± 1.07	23.55 ± 3.79
2.0	33.24 ± 3.96	35.67 ± 6.48	32.52 ± 3.67	37.28 ± 3.77	31.26 ± 1.52	36.98 ± 2.45
3.0	41.82 ± 4.42	44.70 ± 6.08	41.35 ± 4.19	48.06 ± 5.23	42.97 ± 1.63	47.55 ± 2.72
4.0	51.80 ± 5.08	56.02 ± 6.73	51.96 ± 4.93	57.11 ± 5.60	50.98 ± 2.00	55.93 ± 2.93
5.0	58.40 ± 5.27	62.60 ± 5.61	58.95 ± 5.00	64.24 ± 4.69	57.17 ± 3.43	62.67 ± 3.10
6.0	63.71 ± 5.24	68.25 ± 5.08	64.42 ± 4.20	69.97 ± 4.03	62.87 ± 2.57	68.43 ± 3.09
8.0	71.43 ± 5.07	76.52 ± 4.64	71.43 ± 4.01	78.70 ± 4.32	71.16 ± 2.35	74.85 ± 2.61
10.0	80.02 ± 3.21	86.17 ± 3.09	80.02 ± 2.91	85.84 ± 3.54	78.85 ± 2.65	80.19 ± 2.44
12.0	83.64 ± 2.95	90.86 ± 2.54	83.64 ± 2.39	89.42 ± 3.15	84.96 ± 0.84	87.07 ± 3.01

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

2-6 Calculation of difference and similarity factors:

By calculating the difference and similarity factors in different media according to table (8), it is found that the prepared carbamazepine 200 mg controlled release tablets

prepared by direct compression technique have difference factors less than 10.0 and similarity factor greater than 50.0.

Table (8): Difference and similarity factors of carbamazepine 200 mg CR tablets prepared by direct compression method.

Dissolution media:	Difference factor	Similarity factor
Water	4.0	74.0
Water containing 1.0 % SLS	4.0	73.0
Buffer pH 1.2	7.0	62.0
Acetate buffer pH 4.5	9.0	58.0
Phosphate buffer pH 6.8	8.0	67.0

3- Evaluation of the scaled up carbamazepine 200 mg CR tablets prepared by direct compression technique:

3-1: DSC thermal analysis for the total mixture:

Figure (2) shows a sharp endothermic onset of peak at 175.22 ºC and an exothermic onset of peak at 180.66 ºC followed by a sharp endothermic one at 190.12 ºC corresponding to carbamazepine melting point. This indicates that carbamazepine has not changed from single state to the combination state in the tablets preparation.

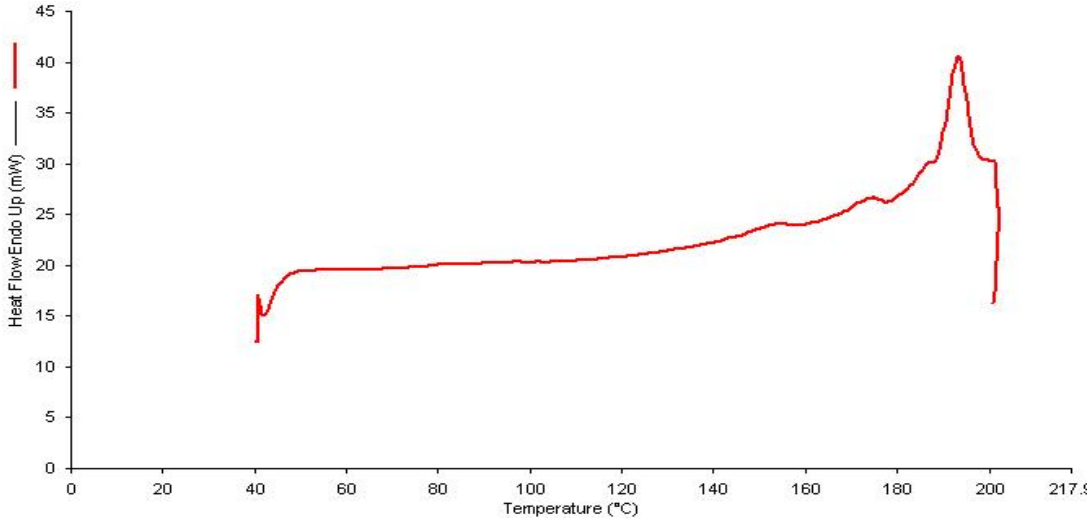

Figure 2: DSC thermal analysis for carbamazepine total mixture.

3-2 Flowability measurement for the total mixture:

It is found that the prepared mixture has an angle of repose 29.162° in which indicate excellent flowability.

3-3 Post compression parameters of carbamazepine 200 mg CR tablets:

Table (9) shows that weight variation between the three location samples is minimal indicating uniform granular packing in the die. The standard deviation of assay results is less than 4.5. Resistance to crushing values are very close.

Table (9): Post compression parameters of carbamazepine 200 mg CR tablets prepared from the scaled up production batch.

Post compression parameters	Sample points		
	Starting	Middle	End
Average weight (mg) ± SD (n = 20).	351.70 ± 5.54	349.90 ± 3.71	347.80 ± 2.80
Hardness (N) ± SD (n = 10).	103.6 ± 5.72	103.1 ± 8.02	103.5 ± 3.72
Loss on drying (%) ± SD (n = 3).	1.92 ± 0.03	1.71± 0.04	1.67 ± 0.04
Assay ± SD (n = 10).	101.41 ± 1.89	99.65 ± 3.93	101.53 ± 0.88
Friability (%) ± SD (n = 3).	0.24 ± 0.04	0.27 ± 0.03	0.26 ± 0.03

3-4 Dissolution of carbamazepine 200 mg CR tablets:

Table (10) shows that the percentages of drug dissolved from tablets in distilled water after 3, 6, 12 and 24 hours are conforming to the USP dissolution limits these time after intervals.

Table (10): Dissolution of carbamazepine 200 mg controlled release tablets prepared from the first production batch in distilled water.

Time (hours)	Percent of dissolved carbamazepine from its tablets from different location of scaled up production batch at:		
	Starting	Middle	End
0.0	0.00	0.00	0.00
1.0	17.39 ± 3.39	12.13 ± 2.98	11.46 ± 3.05
2.0	26.54 ± 4.52	21.11 ± 4.33	20.89 ± 3.94
3.0	37.75 ± 4.02	28.62 ± 5.61	25.50 ± 2.92
4.5	47.38 ± 2.16	37.52 ± 6.20	36.25 ± 3.56
6.0	53.66 ± 2.83	43.74 ± 5.86	43.62 ± 4.70
9.0	61.61 ± 4.33	56.23 ± 4.03	56.44 ± 4.81
12.0	67.54 ± 5.33	65.39 ± 2.54	66.078 ± 6.15
24.0	78.00 ± 4.79	77.31 ± 5.52	87.41 ± 6.42

All values are expressed as mean ± SD (n = 12).

3-5 Drug dissolution kinetics of the prepared chewable tablets in distilled water:

The dissolution data for the prepared tablets are plotted in accordance with the zero order equation, the first order equation and with Hixon-Crowell cube root law. Figures 3: 5 show that the linearities are established as R^2 values are close to unity. It is indicated that the amount of carbamazepine dissoluted is zero-order.

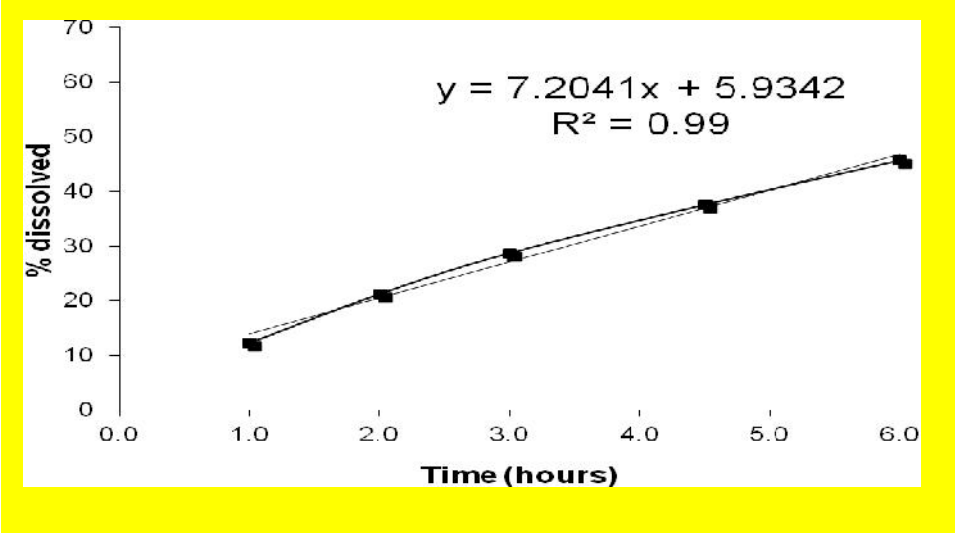

Figure 3: Zero order plots of carbamazepine CR tablets dissolution in distilled water.

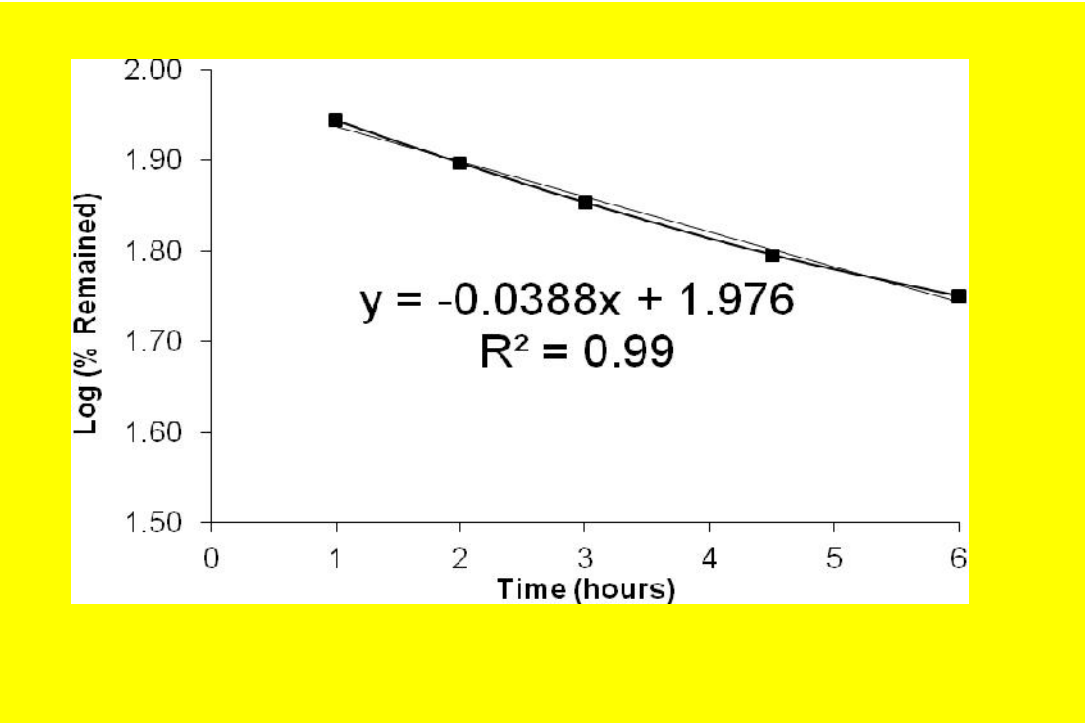

Figure 4: First order plots of carbamazepine CR tablets dissolution in distilled water.

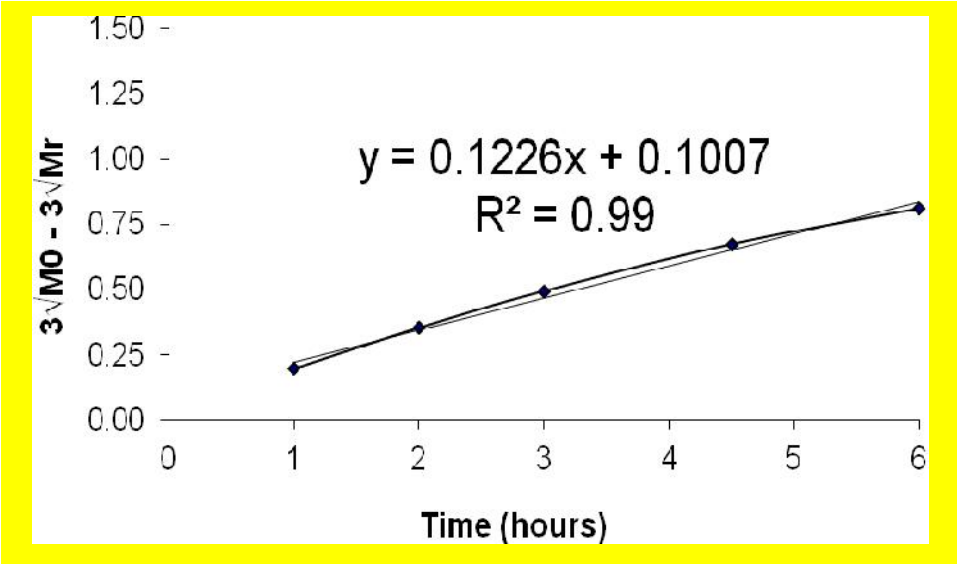

Figure 5: Hixon crowell plots of carbamazepine CR tablets dissolution in distilled water.

Conclusion

This research paper provides a comparison between the wet granulation and direct compression techniques of tablets preparation usindg different HPMC grades. The formula of the direct compression technique was then selected for scaling up process which has been done successfully.

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