Research paper

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

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Abstract:

Carbamazepine 200 mg controlled release tablets were prepared by both wet granulation and direct compression methods. Different methocel grades with different ratios were used. Tablets prepared by 30.0, 35.0 and 40.0 % w/w methocel K 100 , 25.0 % methocel K 100 in combination with 5.0 % methocel K 4M and 15.0 % w/w methocel K 4M were conforming to USP limits, while tablets prepared by 15 % K4M are not conforming to these limits. Tablets prepared by 12.5 % methocel 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) wasdone. All the results of the saaling up were conforming to specifications and indicated that scaling up process has been done successfully.

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].

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 methocel grades as a matrixing agent.

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) Methocel K100 LV, K 15M ,K 4M , E5 (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 methocel grades:

Thermal analyses of different methocel 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].

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].

Carbamazepine 200 mg controlled release tablets were prepared by different methocel grades (K100 LV, K4 M, K15 M) using both wet granulation and direct compression techniques. So the following trials were done:

2-1 Using different methocel grades by wet granulation technique.

A proposed formula from colorcon mentioned that it contained carbamazepine 57.14 % w/w , SLS 0.5 %, methocel E3LV 0.16%, methocel 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 methocel E3LV, it was replaced by methocel 2910 and magnesium stearate ratio was increased to 1.0 % w/w. The following table summarizes the proposed formulae for eight preparations done using different methocel grades with different ratios.

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
Methocel K100	105.0	105.0	122.5	140.0	-----	87.5	------	------
Methocel K4M	------	------	------	------	52.50	17.5	------	------
Methocel K15M	------	------	------	------	------	------	26.25	43.75
Methocel 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 methocel 2910 were dissolved in the least amount of distilled water. Half the quantity of the other methocel was mixed geometrically with the drug and then granulated by the prepared aqueous solution of methocel 2910. The coherent granules were then dried in an oven at 60 °C and passed on 0.800 mm sieve. The resulting granules were geometrically mixed with microcrystalline cellulose pH 102, the other half of the quantity of methocel, aerosil 200 and magnesium stearate.

The preparation of formula F8:

SLS was mixed geometrically with methocel K 15M, carbamazepine, aerosil 200, microcrystalline cellulose pH 102, 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 the following table [18]:

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 the following table:

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 also 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 (Levin., 2006). Scaling up of carbamazepine 200 mg controlled release tablets from lab scale (500 tablets) to full production scale (500,000 tablets) was done. 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.

Results and Discussion

1- Estimation of possible interactions between the drug and different methocel 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 methocel grades K 100 LV, E5 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 S.B. and Rajkumar.M.and Dadarwal S.C. et al. [19&20].

Figure (1-e) shows the DSC thermogram of carbamazepine physical mixture with methocel 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 methocel 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 methocel 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 methocel grades. These results are in accordance with the results obtained by Barakat N.S. et al. [6] and Katzhendler I. et al. [21].

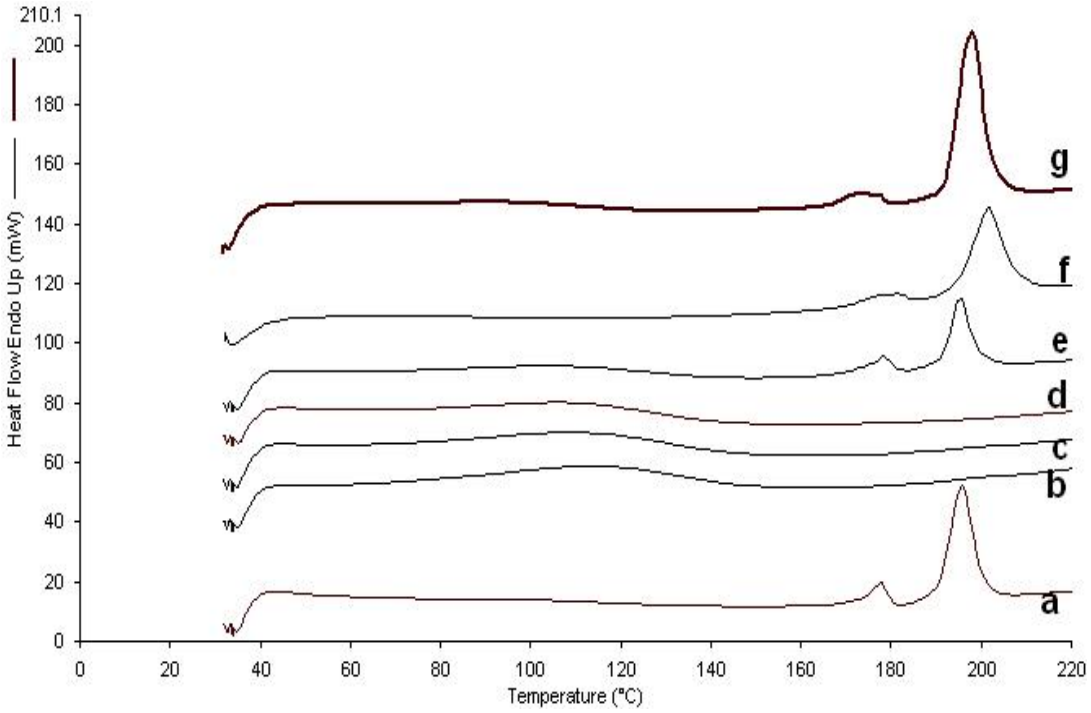

Figure 1: DSC thermal analysis for : a- carbamazepine alone, b- methocel K 100 LV, c- methocel E5, d- methocel K 15M, e- carbamazepine/ methocel K 100 LV 1:1 physical mixture, f- carbamazepine/methocel E5 1:1 physical mixture, g- carbamazepine /methocel K 15M 1:1 physical mixture.

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

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

Table (1) 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 1: Average weight, average hardness value and assay for carbamazepine 200 mg CR tablets prepared by different methocel grades

Tablets prepared by:	Average weight (mg)	Average hardness value (N)	Assay (%)
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.

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

2-2 Dissolution in distilled water:

Table (2) shows that the percentages of drug dissolved from tablets in distilled water are 20.0 : 39 , 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 prepared by 0.5 % and 1.0 % SLS are conforming to USP limits after 3, 6 and 24 hours and not conform after 12 hours.

Table 2: Dissolution of carbamazepine 200 mg CR tablets prepared by different methocel grades in distilled water.

Time	Percent of carbamazepine dissoluted from its CR tablets made with:							
(hours)	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
1.0	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	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	30.61 ± 1.49
3.0	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	38.96 ± 1.94
4.5	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	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	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	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	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	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 = 6).

It is observed that the dissolution values of tablets prepared by 15.0 % methocel K4 M at different time intervals are less than that of other tablets prepared by different concentrations of methocel K100. This may be due to the fact that methocel K4 M acts as a matrixing agent and has an excellent gelling activity in sustained release formulations [22]. The dissolution results of tablets prepared by methocel K4 M 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 3,6,12 and 24 hours respectively [12].

According to USP limits; tablets prepared by30.0, 35.0, 40 % w/w methocel K 100, 25.0 % methocel K 100 in a combination with 5.0 % methocel K4M are conforming to these limits, while tablets prepared by methocel 15 % methocel K4 M are not conforming to these limits after 12 hours. Upon decreasing the amount of methocel K4 M from 15 to 5 % and incorporation of 25 % methocel K100 LV, the release of drug was extended. These results are in agreement with Fasiuddin A.M. et al. who 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 [23].

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

Table (3) shows that the percentages of dissolution of 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.

Table 3: Dissolution of carbamazepine 200 mg CR tablets prepared by different methocel grades in distilled water containing 1.0 % SLS.

Time (hours)	Percent of carbamazepine dissoluted from its CR tablets made with:							
	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
1.0	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	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	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	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 = 6).

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

Table 4: 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 dissoluted 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 (5), 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 5: 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 2.0	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:

Table (6) 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 6: Average weight, hardness, loss on drying and assay of carbamazepine 200 mg CR tablets prepared from the scaled up production batch.

Items	Start	Middle	End
Average weight (mg)	351.70 ± 5.54	349.90 ± 3.71	347.80 ± 2.80
Hardness (N)	103.6 ± 5.72	103.1 ± 8.02	103.5 ± 3.72
Loss on drying (%)	1.92 ± 0.03	1.71± 0.04	1.67 ± 0.04
Assay	101.41 ± 1.89	99.65 ± 3.93	101.53 ± 0.88
Friability (%)	0.24 ± 0.04	0.27 ± 0.03	0.26 ± 0.03

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

Table (7) 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 after these time intervals.

Table 7: Dissolution of carbamazepine 200 mg controlled release tablets prepared from the first production batch in distilled water.

Time (hours)	Percent of carbamazepine dissoluted from its tablets made with:		
	Start	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 = 6).

Conclusion

Carbamazepine 200 mg controlled release tablets were prepared by both wet granulation and direct compression methods. Different methocel grades with different ratios were used. Upon the application of the modified colorcon formula and performing dissolution testing according to USP standard limits, conforming dissolution values were obtained after 3.0, 6.0 and 24.0 hours while non-conforming dissolution results were obtained after 12 hours. Tablets prepared by 30.0, 35.0 and 40.0 % w/w methocel K 100 , 25.0 % methocel K 100 in combination with 5.0 % methocel K 4M and 15.0 % w/w methocel K 4M were conforming to USP limits, while tablets prepared by 15 % K4M are not conforming to these limits. Controlled release tablets 200 mg prepared by 7.5 % methocel K15M showed similarity to the innovator dissolution results in distilled water containing 1.0 % SLS with a difference factor 7.0 and a similarity factor 60.0. Controlled release 200 mg tablets prepared by 12.5 % methocel 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). Different samples were withdrawn at start, middle and end of compression process and were subjected to the following tests: Uniformity of weight, assay, resistance to crushing of tablets, friability and in-vitro dissolution. All the results of these tests were conforming to specifications and indicated that scaling up process has been done successfully.

Acknowledgement:

The authors gratefully acknowledge the contribution to this paper for the Egyptian international pharmaceutical industries Co, Egypt and the members of pharmaceutics and industrial pharmacy, faculty of pharmacy, Zagazig University, Egypt.

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