Pharmaceutical Design and *in vitro* Evaluation of Sustained release Matrix Tablets of Carbamazepine

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ABSTRACT: The objective of this study is to design and evaluate sustained release tablets of Carbamazepine (CZP).The effects of various viscosity grades of Methocel(Methocel K4M, Methocel K100M and combination of both) on the release of Carbamazepine have been evaluated. Tablets were evaluated for physical and chemical parameters such as Hardness, Friability, Thickness, Weight variation, Drug content uniformity and *in vitro* release. All batches are complied physical and chemical parameters within the U.S.P limit. The amount of Carbamazepine at different time intervals were estimated by HPLC method. *In vitro* release profile of Carbamazepine from combination of both Methocel K4M and Methocel K100M polymers (F10) showed that 90% of the drug was released at the end of 12th hr which is considered as optimized formulation. The release profile of formulation F10 has achieved the optimum U.S.P limit when compared to marketed formulation. The tablets showed no significant change either in physical appearance or in dissolution pattern after storing at 4^{0}c, 40^0 c / 75% RH and 60^{0}c / 80% RH for three months. The TG/DTA study revealed that there is a weak intermolecular interaction occurs between drug and excipients. The drug release data fit well to Higuchi, Peppas and Korsemeyer equation. The drug release was found to have swelling, diffusion and little extent by erosion.
Key words: Carbamazepine; sustained release; hydrophilic matrix; Methocel; wet granulation.

INTRODUCTION

Carbamazepine is an anticonvulsant drug widely used in the treatment of simple and complex seizures, trigeminal neuralgia and bipolar affective disorder. Carbamazepine overdose leads to various side effects. Thus for patient compliance, improve bioavailability, minimize total drug quantity minimize accumulation on chronic use and reduce fluctuation in drug level sustained release of Carbamazepine is desirable[1]. Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery system because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance[2]. Drug release from hydrophilic matrices is known to be a complex interaction between dissolution, diffusion and erosion mechanism. Methocel is the first choice for formulation of hydrophilic matrix system, providing robust mechanism, choice of viscosity grades, nonionic nature, consistent reproducible release profiles, cost effectiveness and utilization of existing conventional equipment and methods[3].Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion from dosage form is controlled by the hydration of Methocel, which forms the gel barrier through which the drug diffused [4]. Several mathematical models have been published, to elucidate the water and drug transport processes and to predict the resulting drug release kinetics [5]. The dissolution profile of some of the sustained release products available in their market are in the lower side of the U.S.P limit. So, an effort was made in this work to achieve an optimum USP limit. The aim of the work

was to prepare hydrophilic matrix tablets containing Carbamazepine as a drug and Methocel as hydrophilic matrix to retard drug release. The above discuss suggests that the sustained release product may enhance the bioavailability and control the seizures during sleeping.

MATERIALS AND METHODS
Materials
The following materials were used: Carbamazepine (Sun Pharma, Mumbai),
Poly Vinyl Pyrrolidone (Himedia labs, Mumbai), Methocel [Methocel K4M, Methocel $K_{100}M$] (Dow Chemicals, USA), Talc and magnesium stearate (Merck KgaA, Darmstadt, Germany), Isopropyl alcohol (Ranbaxy Ltd, India) were obtained and used as received. All other chemicals and solvents used were of analytical grade.

Pre formulation studies
The parameters like identification of pure drug Carbamazepine by IR spectra, drug excipients compatibility studies, angle of repose, bulk density, tapped density, Hausner ratio, Carr's index [6] and loss on drying.

Compatibility study
About 200 mg of Carbamazepine alone and mixtures, consisting of Carbamazepine with various excipients in 1: 1 and 1: 10 ratio in glass vial were taken and kept at various accelerated condition [30°C / 65% RH, 40°C / 75% RH, 60°C / 80% RH] in stability chamber. It is

carried out for one month in open and closed glass vials. At the interval of 1, 2, 3, 4, 5, 6, 14, 21 and 30 days, the samples were withdrawn and physical characteristics like colour change were recorded. Finally the mixtures with no colour change were selected for formulations[7].

Formulation of tablets
Formulations were prepared as per the composition in table1
For preparing hydrophilic matrix tablets, Carbamazepine (73.52%) and various concentration of Methocel, Methocel K4M, Methocel K100M and combination of Methocel K4M and Methocel K100M were first sieved and blended in a Kenwood mixer (Kenwood, Geesthacht, Germany) for 5 minutes. The powder blend was granulated with Poly vinyl pyrollidone (PVP 4%) and the wet mass was sieved through mesh No.20 and air dried. The dried granules were passed through sieve No.10 and the fractions of the granules retained on the sieve were discarded. Finally magnesium stearate 2% w/w and talc 2.5 % w/w were mixed for lubrication purpose. Then compressed with 12 / 32 mm concave single punch in a 16 station tablet compression machine (Cadmach, Ahemadabad). The compressed tablets were film coated by conventional pan system using protectab with brilliant blue (colorant). Protectab is a readymade available coating material which consists of hydroxy propyl methyl cellulose as a polymer. It is dissolved in sufficient quantity of Isopropyl alcohol which acts as a coating solution.

Table1: Composition of different formulations (mg) of matrix tablets

S. No	Ingredients	Formulation code									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	Carbamazepine	200	200	200	200	200	200	200	200	200	200
2.	Methocel	20	25	40	65	-	-	-	-	-	-
3.	Methocel K4M (HPMC 2208)	-	-	-	-	40	50	50	40	35	30
4.	Methocel K100M (HPMC 2208)	-	-	-	-	-	-	10	20	25	25
5.	PVP K-30	8	8	8	8	8	8	-	-	-	-
6.	PVP K– 90	-	-	-	-	-	-	8	8	8	8

Note: In all formulations Talc (2.5%), Magnesium stearate (2%) and Isopropyl alcohol q.s were included.
HPMC 2208: Various viscosity grades of Methocel K4M (viscosity: 3000 – 5600 cp)
and Methocel K100M (viscosity: 80,000-1, 20,000 cp) were included in above formulations.

Evaluation of tablets
A) Physical test
Tablets were subjected to various physical tests which include weight variation (AX,Shimadzu-corporation,Japan), Thickness (Mitu toyo corps, Japan), Hardness tester (Toyoko, Japan), Friability (Friabilator, H.Jurgens GmbH & Co, Breman, Germany) as per B.P official methods.

B) Dissolution test
In vitro drug release was performed using dissolution apparatus USP type I Rotating
Basket Method (TDT – 08L, Electro lab, India) with a stirring speed of 100 rev / min at 37 ± 0.5^oC in 900ml of distilled water for 12 hours. The samples (5ml) were collected at an interval of 1, 3, 6 and 12 hours with replacement of equal volume of fresh medium and absorbance was measured (λ=285) after filtration and suitable dilution[8] (UV–visiblespectrophoto meter1601, Shimadzu corporation, Japan)
The drug content was analyzed using HPLC (Perkin Elmer Shimadzu – corporation, Kyoto, Japan) at 230 nm a Kromosil LC – 18 column [250 mm x 4.6 mm internal diameter, $5\mu m$ particle size]. The mobile phase consisted of acetonitrile – 0.02M sodium phosphate (pH 7.2) buffer [45: 55 V/V] and was pumped at a flow rate of
1.0 ml/min.The injection volume was $20\mu l$.The retention time of Carbamazepine was found to be 6 min[9].

C) Stability studies
The Stability study was conducted for optimized formulation (F10). The tablets were packed and kept for 30 days at 4^0C, 40^0C / 75% RH & 60^0C / 80% RH in a stability chamber (Osworld, Mumbai). At the interval of 15 days tablets were withdrawn and evaluated for physical properties like Thickness, Hardness, Diameter, Friability, Weight Variation and Content uniformity. *In vitro* drug release and assay were also carried out.

D) TG / DTA Studies
Thermogravimetry / Differential Thermal Analysis (TG/DTA) were performed to characterize drug – excipients compatibility. The TG/DTA thermograms of pure drug and mixture recorded in a TG / DTA analyzer (SDT Q 600, India) at a heating rate of 20^oC/min from 0 to 600^oC in a nitrogen atmosphere[10].

E) Mechanism of drug release
Korsemeyer et al., (1983) desired a simple relationship which described drug release from a polymeric system eq 2: To find out the mechanism of drug release, the drug release data was fitted in Korsemeyer- Peppas model.

$$M_t/ M_\alpha = Kt^n$$

$M_t/ M\alpha$ is the fraction of drug released at time't,' K is the rate constant and n is the release exponent. The n value is used to characterize different release mechanism[11].

i) Swelling study
The swelling and erosion studies on tablets containing Carbamazepine were performed using the method described by Tahara et al., 1995. The axial and radial swelling was measured using vernier calipers[12].
The relative swelling was calculated as the ratio of the wet weight to the initial weight

$$\text{Relative swelling} = \frac{W_w}{W_i}$$

The percent absorption was calculated as,[13]

$$A\% = \frac{100(W_w - W_d)}{W_d}$$

The percent erosion was calculated as

$$E\% = 100\ \frac{100(W_i - W_d)}{W_i}$$

ii) Data analysis
To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate eq 1: describes the system where the drug release rate is independent of its concentration[14]
$C=k_0t$
Where $k_{0\ is}$ zero order rate constant expressed in units of concentration /time and t is the time.
The following plots were made; Cumulative % release Vs time (zero order kinetic model); Cumulative % release Vs square root of time **(**Higuchi model); log cumulative % of release Vs log time (Korsemeyer-Peppas model).

RESULTS AND DISCUSSION
I) Pre-formulation studies
Bulk density, tap density, loss on drying, Carr's index, and angle of repose and Hausner ratio were studied for both pure drug and granules. (table2)
The angle of repose for pure drug was very less and hence the poor flow of the pure drug was exhibited. Also the Carr index of the pure drug was found to be high, confirming that the drug has poor flow properties and compressibility. Good flow of powders / granules is essential in tableting because the compressibility and flow properties of the drugs likely to influence the compression process in the preparation of sustained release tablets. Hence improve the flow property the formulations were prepared by wet granulation technique to improve the flow as well as compressibility.

Table 2: Physical and chemical parameters of granules

Formulation code	Angle of Repose (°) ± S.D	Loss on drying ± S.D	Bulk density ± S.D	Tap density ± S.D	Hausner ratio ± S.D	Carr's Index ± S.D
F1	25.64 ± 0.762	1.21 ± 0.987	0.350 ± 0.011	0.420 ± 0.002	1.2 ± 0.004	16.6 ± 0.701
F2	25.568 ± 0.671	1.10 ± 0.851	0.361 ± 0.010	0.430 ± 0.005	1.19 ± 0.002	16.2 ± 0.180
F3	26.42 ± 0.397	1.12 ± 0.891	0.370 ± 0.012	0.440 ± 0.004	1.18 ± 0.001	15.9 ± 0.181
F4	25.43 ± 0.754	1.13 ± 0.956	0.350 ± 0.011	0.410 ± 0.006	1.17 ± 0.003	14.63 ± 0.680
F5	26.42 ± 0.397	1.10 ± 0.9598	0.380 ± 0.012	0.450 ± 0.004	1.20 ± 0.002	15.5 ± 0.7111
F6	26.03 ± 0.590	1.11 ± 0.865	0.356 ± 0.011	0.421 ± 0.005	1.18 ± 0.002	15.43 ± 0.651
F7	26.32 ± 0.31	1.15 ± 0.945	0.361 ± 0.021	0.432 ± 0.002	1.19 ± 0.003	16.43 ± 0.621
F8	25.98 ± 0.42	1.21 ± 0.985	0.351 ± 0.010	0.412 ± 0.003	1.17 ± 0.004	14.80 ± 0.521
F9	25.43 ± 0.754	1.15 ± 0.961	0.354 ± 0.012	0.425 ± 0.06	1.20 ± 0.002	16.70 ± 0.181
F10	25.64 ± 0.9533	1.20 ± 0.980	0.371 ± 0.020	0.442 ± 0.003	1.19 ± 0.003	16.07 0.101

II) Physico-chemical parameters of tablets

Weight variation was within the limit of B.P (±5%) and Hardness of the formulations ranged from 4-7 kg/cm^2. All   formulations exhibited less than 1% friability. Actual values are given in table: 3 length and breadth was found fixed as per punch size and thickness was controlled as well to an average of 6.442 mm and S.D was found as little as 0.048. By holding the tablet weight and thickness constant, the surface area and volume were essentially fixed. All tablets contained 200mg ± 5% (73.52%) of Carbamazepine as confirmed by assay procedure. Mean drug content value obtained was 99.40 S.D of 0.115 which was found satisfactorily within limits.

Table 3: Physical and Chemical parameters of formulated Carbamazepine tablets (F10).

Weight variation (%) n = 20	Thickness (mm) n =20	Friability (%) n= 10	Hardness (kg) n=20	Drug content (%) n = 10
Mean= 259.9mg +2.81%, -3.71% S.D = 0.3815	Mean= 6.442mm +4.12mm, - 3.14mm S.D = 0.048	0.40% S.D = 0.009	Mean= 5.69kg +6.7kg, -4.8kg S.D = 0.244	Mean= 99.40% S.D = 0.115

S.D = Standard Deviation, + = Maximum, - = Minimum

III) *In vitro* dissolution studies

In formulations, **F1, F2, F3** and **F4** the concentration of Methocel was used as 10%, 8%, 5% and 3%.In all these formulations release at the end of 12th hour were found to be 50.68%, 6102%, 63.02% and 67.03% respectively. In all the above F1 to F4 formulations, the release increased marginally but it is less than the USP limit. . It may due to less viscous polymer.

Other viscous grade of Methocel which retards the release is Methocel K4M. The apparent viscosity (2% solution) of Methocel K4M was 3000 – 5600 cp. In **F5** formulation, Methocel K4M was added in the concentration of 5% and the release at the end of 12th hour was found to be 70.73%. Though the release was within the USP limit, the release was in lower side of the limit. In **F6** formulation, Methocel K4M was added in the concentration of 4% but the first 3 hours release was found to be 37.82% which was more than the USP limit.

Other viscous grade Methocel like Methocel K100M was selected which is used to control the drug release within the USP limit. Since it has higher viscosity.

In formulation **F7** both Methocel K4M and Methocel K100M were used. The first 3 hours release was 31.25% which was within the USP limit but the 6th hour release was more than the USP limit.

In formulation **F8** the amount of HPMC K4M was reduced and slightly increased the amount of Methocel K100M. Formulation F8 controlled the 6th hour release but 12th hour release was only 70.86%.

In formulation **F9** Methocel K4M 17.5% and Methocel K100M 12.5% were included in which the release at the end of 12th hour was found to be 86.26%.

In formulation **F10** Methocel K4M 15% and Methocel

K100M 12.5% were included. The other additives and compositions were same as that of **F9**.

Based on investigation, which is a matrix-tablet comprising a drug, and hydrophilic polymer, the release should follow three steps. First step is the penetration of the dissolution medium in the tablet matrix (hydration). Second step is the swelling with concomitant or subsequent dissolution or erosion of the matrix and third step is the transport of the dissolved drug either through the hydrated matrix or from the part of the eroded tablet, to the surrounding dissolution medium (Harris Shoaib et al., 2006).

The stability studies of optimized formulation F10 at 4°C, 40°C / 75% RH, 60°C, for 30 days did not show any variation in the tested parameters and release also.

CONCLUSION

Carbamazepine sustained release matrix tablets were prepared successfully using combination of Methocel K4M & Methocel K100M polymers and achieve required dissolution profile. The release pattern of optimized formulation F10 was achieved the optimum USP limit when compared to marketed formulation. Drug release kinetics of this formulation correspond best to Higuchi, Peppas and Korsemeyer model. The optimized formulation is controlled by a complex mechanism of swelling mediated diffusion and lesser extent by erosion.

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