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# Formulation and Evaluation of Extended Release Carbamazepine Matrix Tablets

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The aim of study was to prepare and characterize extended release matrix tablets of carbamazepine using hydrophilic polymers like HPMCK-100M, AVICEL PH-102 with or without HPMC K4M. Release kinetics evaluated by using USP-22 TYPE-I dissolution apparatus. The newly formulated extended release tablets of carbamazepine were compared with conventional marketed tablet. The *in vitro* drug release study revealed that HPMC K-100M formulation was able to sustain the drug release for 15 h (90.93 %). Fitting the *in vitro* drug release data to Koresmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release. Further evaluation by DSC thermogram and FTIR studies conclude that no interaction between polymer and drug. The results suggest that the developed extended release tablets of carbamazepine could perform therapeutically equivalent to conventional dosage forms, leading to better patient compliance.

**Key Words: Formulation, Extended release, Carbamazepine.**

## INTRODUCTION

Hydrophilic polymer 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[1]. Hydroxypropylmethylcellulose (HPMC), hydroxy propylcellulose, sodiumcarboxymethylcellulose and carbopols are a few representative examples of hydrophilic polymers that have been extensively used in formulation of oral controlled release system. Drug release from hydrophilic systems is known to be a complex interaction between dissolution, diffusion and erosion mechanisms. This dissolution can be depending on polymer molecular weight and thickness of different boundary layer[2]. HPMC is first choice for formulation of hydrophilic systems, providing robust mechanism, choice of viscosity grades, nonionic nature, consistent reproducible release profiles and utilization of existing conventional equipment and methods,. The formulation factors influencing drug release from hydrophilic matrices system are polymer viscosity, polymer particle size, drug loading, compression force, tablet shape, formulation excipient, coatings and processing techniques[3-6]. Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion from dosage form is controlled by hydration of HPMC, which forms gel barrier through which drug diffuses[7].

Epilepsy is one of the most common neurologic disorders with a prevalence of *ca*. 6:1000. The periods of highest incidence occur in patients younger than 1 year and in patients older than 75 years. Some of the most difficult to control seizure types and epilepsy syndromes occur during childhood and include complex partial, tonic and atonic seizures, infantile spasms and the Lennox-Gastaut syndrome. Annually worldwide about 50 million people have epilepsy and 10 % of population has seizure with appropriate treatment while 70 % of patient can become seizure free. Immediate release dosage forms of carbamazepine have to administer 3 doses daily. Development of delivery systems that releases drug in a sustained manner at the therapeutic concentration over a period of time can ensure patient compliance and may also minimize risk of emergence of drug and potential toxicity.

Carbamazepine is used for anticonvulsant and antineuralgic effects. The popularity of this drug is related to several beneficial properties, including, proven efficacy in controlling different types of seizures. It is poorly soluble in water with erratic oral absorption and bioavailability less than 70 %. Moreover carbamazepine has a narrow therapeutic range and shows bioavailability differences. In efforts to reduce the frequency of dosing required for chronic carbamazepine therapy and to decrease variability in plasma concentration, various formulations have been developed by many researchers[8-10].

Hence, in the present work, an attempt has been made to formulate the extended release matrix tablets of carbamazepine using hydrophilic matrix material.

## EXPERIMENTAL

Carbamazepine USP was a gift sample from Hindustan Chemicals Ltd, Chennai, India. HPMC K4M and K100M are purchased from Laser chemicals, Ahmedabad, India. All other chemicals used were of analytical grade and used as received.

**Preparation of the extended release (ER) tablets:** Extended release tablets were prepared by wet granulation method[11]. Carbamazepine (200 mg) was dry blended with appropriate quantity of polymers and granulated with 5 % w/v iso-propyl alcohol solution of PVP-K30. The wet mass was milled through multimill by using 10 mm sieve. The wet granules were dried by IR drier for 0.5 h at 40-50 ºC and sieved through (No. 16/22 sieve). The oversize granules (retained on No. 16 sieve) were kept aside. The undersize granules (passed from No. 22 sieve) were mixed with granules (retained on no. 16 sieve) in a ratio of 1:9 as fines[12]. The granules mixture was blended with magnesium sterate and compressed using double punch tablet machine, equipped with beveled, flat-faced punches of 8mm diameter (Cadmach machinery Co, Ahmedabad, India). The formulation ingredients of various batches are summarized in Table-1.

**Characterization of granules:** Prior to compression, granules were evaluated for their characteristic parameters. Moisture content was determined using moisture balance equipped with an IR unit (IEC, Mumbai). Angle of repose, bulk density, tapped density and Carr's index were also determined[13]. The drug content in the

TABLE-1
FORMULATION OF EXTENDED RELEASE MATRIX
TABLETS OF CARBAMAZEPINE

| Formulation ingredients | B-1 | B-2 | B-3 | B-4 | B-5 | B-6 |
|---|---|---|---|---|---|---|
| CBZ | 200 | 200 | 200 | 200 | 200 | 200 |
| Avicel PH 102 | 20 | 20 | 20 | 20 | 15 | 15 |
| SLS | 5 | 5 | 5 | 5 | 5 | 5 |
| HPMC K4M | 40 | 35 | 20 | 5 | - | - |
| HPMC K100M | 45 | 50 | 65 | 80 | 95 | 100 |
| P.V.P K30 | 20 | 20 | 20 | 20 | 20 | 15 |
| I.P.A | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Aerosil 200 | 4 | 4 | 4 | 4 | 4 | 4 |
| Talc | 10 | 10 | 10 | 10 | 5 | 5 |
| Mg. Sterate | 5.25 | 5.25 | 5.25 | 5.25 | 5.25 | 5.25 |
| Colour | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 |

CBZ = Carbamazepine; SLS = Sodium lauryl sulphate; HPMC = Hydroxy propyl methyl cellulose; PVP- = Poly vinyl pyrrolidine; IPA = Iso propyl alcohol.

granules was determined by extracting an accurately weighed amount of powdered granules with methanol. The solution was filtered through 0.45 µm membrane and absorbance was measured at 285 nm after suitable dilution.

**Characterization of tablets:** The properties of compressed ER tablets, such as hardness, friability, weight variation and content uniformity were determined using reported procedure. Briefly, hardness and friability were determined by using Monsanto hardness tester, Roche Friability apparatus, respectively. Weight variation and uniformity of drug content were performed according to the IP procedure[14]. Content uniformity was determined by weighing 10 tablets individually and the drug was extracted in methanol. The drug content was determined as described for granules.

***In vitro* drug release studies:** The *in vitro* dissolution studies were performed using the USP-22 type I dissolution apparatus at 50 rpm. The dissolution medium consisted of 0.1 N hydrochloric acid for first 2 h and the phosphate buffer saline pH 7.4 from 3 to 15 h (900 mL), maintained at 37 ± 0.5 ºC. An aliquot (5 mL) was with drawn at specific time intervals and drug content was determined by UV-visible spectrometer (DU640B, Backman, Fullerton, CA) at 285 nm.

**Kinetic analysis of dissolution data:** To study the mechanism of drug release from the matrix tablets, the release data were fitted into zero order, first order and higuchi equation[15]. These models fail to explain drug release mechanism due to swelling (Upon Hydration) along with gradual erosion of matrix. Therefore, the dissolution data was also fitted to well known exponential equation (Korsmeyer equation), which is often used to describe drug release behaviour from polymeric systems[16].

$$\log (M_t/M_f) = \log k + n \log t \quad (1)$$

To clarify the release exponent for different batches of matrix tablet, the log value of percentage drug dissolved was plotted against log time for each batch according to eqn. 1. The value of n equal to 0.45 indicates fickian case I release; > 0.45 but < 0.89 for non-fickian (anomalous) release; and > 0.89 for super case II type of release. Case II generally refers to erosion of the polymeric chain and anomalous transport (Non-fickian) refers to combination of both diffusion and erosion controlled drug release[17].

Mean dissolution time (MDT) calculated from dissolution data using following equation.

$$MDT = (n/n + 1)^{k-1/n} \quad (2)$$

## RESULTS AND DISCUSSION

Tablets were compressed without any problem and do not require any change in ratio of excipient in formulation. Tablets prepared were smooth, shiny and do not require coating as per experimental purpose (for patient compliance and palatability aqueous polymer coating can be performed). The granules for matrix tablet were prepared according to the formula given in Table-1 and characterized with respect to angle of repose, moisture content, bulk density and total drug content (Table-2). Angle of repose was less than 30º for all batches of granules indicating satisfactory flow behaviour. Moisture content of less than 2 % indicates optimum drying of granules. Other parameters for granules were also determined and found to be in acceptable range.

TABLE-2
CHARACTERIZATION OF GRANULES AND MATRIX TABLETS OF CARBAMAZEPINE

| Parameters | B-1 | B-2 | B-3 | B-4 | B-5 | B-6 |
|---|---|---|---|---|---|---|
| **Granules** | | | | | | |
| Angle of Repose | 28 | 25 | 27 | 22 | 28 | 26 |
| Bulk Density | 0.63 | 0.53 | 0.39 | 0.48 | 0.36 | 0.35 |
| Tap. Density | 0.78 | 0.65 | 0.53 | 0.61 | 0.50 | 0.62 |
| Carr's index | 19.20 | 18.50 | 26.40 | 21.30 | 28.20 | 24.10 |
| Moisture content | 2.10 | 2.40 | 1.90 | 2.80 | 2.30 | 2.50 |
| Drug Content | 98.60 | 99.30 | 98.50 | 99.20 | 98.30 | 99.40 |
| **Tablets** | | | | | | |
| Wt. Variation | 3 | 2 | 4 | 3 | 2 | 2 |
| Friability | 0.24 | 0.32 | 0.11 | 0.22 | 0.19 | 0.15 |
| Hardness | 6.50 | 7.20 | 8.10 | 8.20 | 10.10 | 6.20 |
| Content uniformity | 98.30 | 99.20 | 98.50 | 99.40 | 98.70 | 99.60 |

The tablets of different formulations were subjected to various evaluation tests such as weight variation, friability, hardness and content uniformity according to procedure specified in Indian Pharmacopoeia. The weight variation and friability was less than 4 and 0.4 %, respectively. Good uniformity in drug content was found among different batches of tablets and drug content was more than 95 %.

***In vitro* dissolution studies and duration of release:** For the controlled release under investigation, which is the matrix tablet comprising 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 parts of the eroded tablet, to the surrounding dissolution medium[18]. The drug release pattern of different formulations of carbamazepine from B-1 to B-6 is shown in Fig. 1. From these formulations B-6 was found to be the best formulation because the release pattern of this batch was within the USP limit. The comparison of the best formulation with conventional marketed tablet is shown in Fig. 2. This reveals that release pattern was better than conventional tablet.

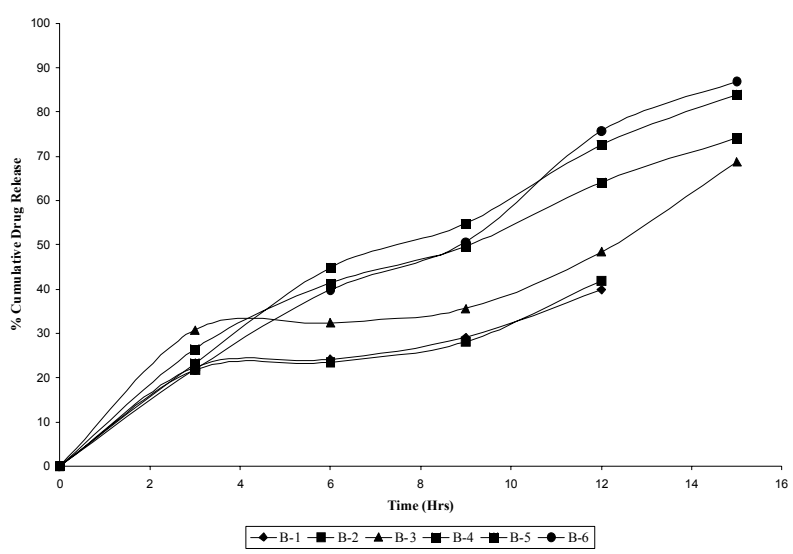


Fig. 1. *In vitro* dissolution studies of carbamazepine ER tablets

**Drug release kinetics:** The rate release kinetic data for all models is shown in Table-3. B-6 gives $r^2$ value 0.9672 in zero order plots and first order gave 0.9933 describing the drug release rate relationship with concentration of drug. The best linearity was found in Higuchi equation plot where $r^2$ is 0.9994, indicating the release of drug from matrix as a square root of time dependent process based on Fickian diffusion.

TABLE-3
RELEASE PARAMETERS OF CARBAMAZEPINE ER TABLETS

| Zero order | | First order | | Higuchi | | Korsmeyer-Peppas | | | Hixon-Crowell | |
|---|---|---|---|---|---|---|---|---|---|---|
| $r^2$ | $K_0$ ($h^{-1}$) | $r^2$ | $K_1$ ($h^{-1}$) | $r^2$ | $K_{11}$ ($h^{-1/2}$) | $r^2$ | n value | $K_{kp}$ ($h^{-n}$) | $r^2$ | $K_{hc}$ ($h^{-1/3}$) |
| 0.967 | 4.004 | 0.993 | 0.141 | 0.999 | 17.56 | 0.994 | 0.246 | 0.426 | 0.996 | 0.141 |

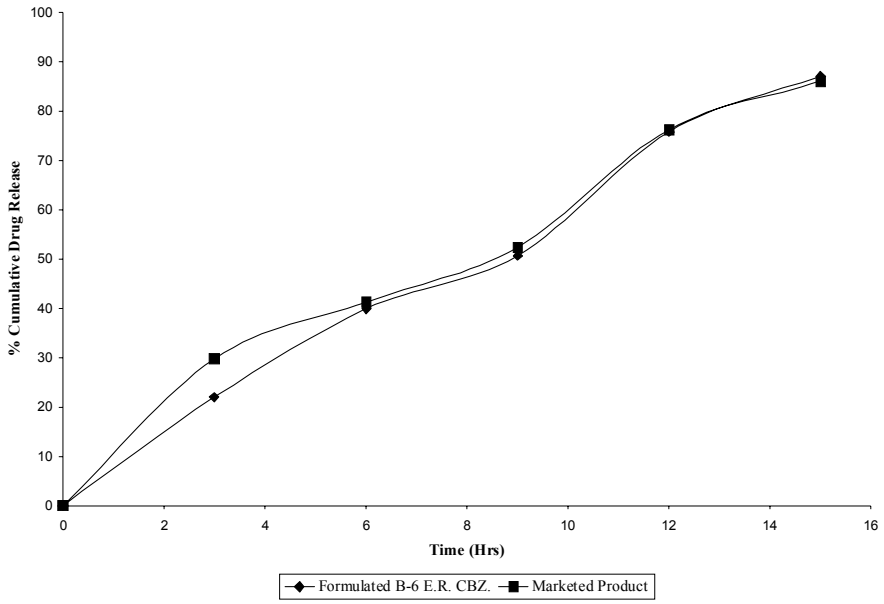


Fig. 2. Comparison of best formulation with marketed product

The dissolution data was also plotted in accordance with Hixson Crowell Cube root law. Applicability of data ($r^2$ = 0.9967) indicates a change in surface area and diameter of tablets with a progressive dissolution of a matrix as a function of time.

**Mechanism of drug release:** By incorporating the first 60 % of release data the mechanism of release can be indicating according to Korsmeyer where n is the release exponent, indicative of mechanism of drug release. Fickian diffusional release and a case II relaxational release are the limits of the phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of drug due to a chemical potential gradient. Case II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion[19]. The value of release exponent in carbamazepine ER obtained as 0.2465 which as per Table-3 is beyond the limits of Koresmeyer model so-called power law. The power law can only give limited insight into the exact release mechanism of the drug. Even if the values of the exponent n are found that would indicate a diffusion controlled drug release mechanism, this is not an automatically valid for HPMC.

Mean dissolution time (MDT) value is used to characterize drug release rate from dosage form and indicates the drug release retarding efficiency of polymer. Tablets prepared with HPMC K100M alone (B-6) shows higher MDT value (3.3 ± 0.3 h) in comparison to tablets prepared with combination of HPMC K100M and HPMC K4M. These findings can be attributed to retarding efficiency of polymer in B-6.

## Conclusion

Carbamazepine ER matrix tablet was prepared successfully using HPMC as a polymer to retard release and achieve required dissolution profile. Drug release kinetics of this formulation correspond best to Higuchi model and drug release mechanism as per 'n' value of the Koresmeyer and Pappas model (Power law) can not be predicted clearly as it appears to be complex mechanism of swelling diffusion and erosion. The investigated ER matrix tablets capable of maintaining constant plasma carbamazepine concentration through 15 h. A DSC and FTIR study shows no interaction between drug and polymer. This all can be expected to reduce frequency of administration and decreasing the dose dependent side effects associated with repeated administration of conventional carbamazepine tablets.

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