

FORMULATION AND EVALUATION OF CARBAMAZEPINE EXTENDED RELEASE TABLET BY CONTROLLED EROSION TECHNOLOGY

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ABSTRACT

The objective of the present study was to design and develop the carbamazepine extended release tablet fabricated by controlled erosion technology. The core tablets were prepared by wet granulation technique using hydroxypropyl methyl cellulose E5 as hydrophilic matrix. The prepared core matrix tablets were characterized for weight variation, hardness, friability, thickness and drug content. The erosion controlled coating was applied to the core tablets using cellulose acetate as the polymer to retard drug release. *In vitro* dissolution studies for both the core and the coated tablets were carried out in distilled water using USP Type II dissolution apparatus. The optimized formulation showed a release of 85.3% release in 12 hours complying with USP limits. The mathematical models were applied to study the release kinetics of the optimized tablets. The stability study of the optimized formulation was done as per ICH guidelines ($40\pm 2^\circ\text{C}/75\pm 5\%\text{RH}$) for 3 months and all the prepared formulations were found to be stable.

Keywords: Controlled erosion technology, Carbamazepine, Matrix tablet.

INTRODUCTION

Oral drug delivery systems has been the most convenient and commonly employed route of drug delivery owing to its ease of administration, hence patient compliance, minimal aseptic restraint and flexibility in the design and development of the dosage form.

Various ways to design modified release dosage forms for oral administration has been explored such as film coated pellets, tablets or capsules and more sophisticated and complicated delivery systems such as osmotically driven systems, systems controlled by ion exchange mechanism, systems using three dimensional printing technology and systems using electrostatic deposition technology¹.

The main intention of designing modified release drug product is usually to develop a therapeutic regimen by providing slow and continuous delivery of drug over the entire dosing interval whilst also providing greater patient compliance and convenience^{2,3}. The most common controlled delivery system has been the matrix type such as tablets and granules where the drug is uniformly dissolved or dispersed throughout the polymer, because of its effectiveness, low cost, ease of manufacturing and prolonged delivery time period^{4,5}.

Carbamazepine, a drug indicated for the treatment of epilepsy, trigeminal neuralgia, bipolar affective disorder and acute mania, is characterized by a low and an erratic absorption⁶. Thus a sustained release of Carbamazepine is advantageous for patient compliance, improve bioavailability, minimize total drug quantity, minimize accumulation on chronic use and reduce fluctuation in drug level^{7,8}.

Erosion based Drug delivery

Erosion is one of the fundamental mechanisms that control the release of drugs from degradable polymer matrices⁹. The major advantage of pure erosion-controlled release is the predictability of drug release, which is usually harder to achieve if additional mechanisms have to be taken into account¹⁰. Another advantage is that drug release coincides with the completeness of polymer erosion, which is desirable from the point of view of biocompatibility¹¹.

Controlled Erosion technology¹²

In erosion-controlled extended-release systems, the rate of drug release is controlled by the erosion of a matrix in which the drug is dispersed. The matrix is normally a tablet, i.e. the matrix is formed by a tableting operation, and the system can thus be described as a single-unit system. The erosion in its simplest form can be described

as a continuous liberation of matrix material (both drug and excipient) from the surface of the tablet, i.e. surface erosion. The consequences will be a continuous reduction in tablet weight during the course of the release process.

Drug release from an erosion system can thus be described in two steps:

- Matrix material, in which the drug is dissolved or dispersed, is liberated from the surface of the tablet.
- The drug is subsequently exposed to the gastrointestinal fluids and mixed with (if the drug is dissolved in the matrix) or dissolved in (if the drug is suspended in the matrix) the fluid.

MATERIALS AND METHODS

Materials

Carbamazepine was provided by Amoli Organics Ltd, Mumbai, Hydroxy propyl methyl cellulose E5 was procured from Loba chemie Pvt. Ltd, Isopropyl alcohol was procured from RFCL Limited., New Delhi, Polyvinylpyrrolidone (PVP K30) was purchased from Sisco Research Laboratories Pvt. Ltd, Mumbai, India. All the chemicals and reagents used were of analytical grade.

Methods

Drug excipient compatibility studies

Differential scanning calorimetry (DSC)

DSC was performed using DSC-60, (Shimadzu, Japan) to study the thermal behaviour of drug alone, mixture of drug and polymer. The instrument comprising calorimeter (DSC 60), flow controller (FCL 60), thermal analyser (TA 60) and operating software TA 60 from Shimadzu Corporation, Japan. The samples were heated in sealed aluminium pans, under nitrogen flow (30 ml/min) at a scanning rate ($5^\circ\text{C}/\text{min}$) from 25°C to 250°C . Empty aluminium pan was used as a reference.

Fourier transform infrared spectroscopy (FTIR)

Infrared spectroscopy was conducted using a Shimadzu FTIR 8300 spectrophotometer and the spectrum was recorded in the region of 4000 to 400 cm^{-1} . Samples (drug alone and mixture of drug and polymer) were mixed with Potassium bromide (200 - 400 mg) and compressed into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The compressed disc was placed in the light path and the spectrum was obtained.

Preparation of core matrix tablets of Carbamazepine

Matrix tablets containing 200mg of Carbamazepine along with varying amounts of polymers such as HPMC E5, Polyvinyl pyrrolidone K30 and other excipients (such as, Sodium lauryl sulphate, Sodium chloride, magnesium stearate and talc) were prepared by wet granulation technique (Table1).

In the first step, accurately weighed amounts of Carbamazepine and HPMC E5 were sifted and blended for 30mins. Required materials except lubricant were then blended and passed through 60-mesh sieve 10 times. Granules were prepared with PVP K-30 solution in Isopropyl alcohol which were dried at 40°C for 2hrs, and then sifted through sieve no 22, to get uniform sized granules ready for compression. Sifted Talc and Magnesium stearate were added to the prepared granules and mixed properly to ensure uniform mixing of all the ingredients, which were then

compressed by a 12mm concave round automatic Multi station tablet punching machine. Before compression, the surfaces of the die and punch were lubricated with magnesium stearate. All preparations were stored in airtight containers at room temperature for further study.

Controlled erosion coating

Different coating solutions were prepared as per table 2. The uncoated, de-dusted tablets were loaded into the coating pan and the tablets were warmed up to 40°C. The Coating solution was sprayed over the warmed tablets using 1.2mm air nozzle spray gun for efficient coating. Hot air was passed between each application of coats. Tablets coating procedure was done to obtain 5% coating. Coating parameters were maintained as: Inlet Temperature (45°C), Air flow (120m³/h), Pan Speed (20rpm), Spray rate (15ml/min), Nozzle diameter (1.2mm).

Table1: Composition of carbamazepine core tablets CET 1-CET 7

Ingredients (mg)	Quantity for one tablet						
	CET 1	CET 2	CET 3	CET 4	CET 5	CET 6	CET 7
Carbamazepine	200	200	200	200	200	200	200
HPMC E5	150	200	250	300	250	250	250
PVP K30	5	5	5	5	7.5	9	11.5
Sodium chloride	10	10	10	10	10	10	10
SLS	5	5	5	5	5	5	5
Magnesium stearate	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Talc	1.25	1.25	1.25	1.25	1.25	1.25	1.25

Table 2: Composition of coating materials in solvent mixture*

Ingredients	Coat 1	Coat 2	Coat 3
Cellulose acetate	10%	15%	20%
PEG 400	15%	15%	15%
HPMC E5	75%	70%	65%

* Dichloro methane: methanol (70:30)

Pre-Compression characteristics of the prepared granules¹³

Flow property

The flowability of the drug granules were assessed by determining the angle of repose.

Angle of repose was determined by fixed funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The drug powder was allowed to flow through the funnel freely onto the surface. The height and diameter of the powder cone was measured and angle of repose was calculated using the formula, $\tan \theta = h/r$. Where, θ = angle of repose, h = height in cm, r = radius in cm.

Compression behaviour

It can be described by Carr's compressibility index (I) and Hausner's ratio.

The Carr's index and Hausner's ratio were calculated by determining bulk and tapped density using USP density tester (Electro Lab, Mumbai, India) using following equation.

$$\text{Carr's Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

Tapped Density

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Bulk Density

Core Tablets Evaluation

Weight variation

To study weight variation, 20 tablets of each formulation were weighed using an electric balance, and the test was performed according to the official method.

Friability

Twenty tablets for each formulation were weighed and placed into a Roche friabilator (Remi Electronics, Mumbai, India). The samples underwent 25 rotations per minute, for 4 min, and were then re-weighed. This process was repeated for all formulations and the percentage friability was calculated.

Hardness

For each formulation, the hardness of 5 tablets was determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and average of values was found out.

Thickness

The thickness of the tablets was determined using Vernier Caliper. Five tablets from each batch were used and average values were calculated.

Drug content estimation

20 tablets were weighed accurately and finely powdered. 100 mg of this powder was accurately weighed and transferred to the 100ml volumetric flask. About 10ml of methanol was added and subjected to sonication for 15 minutes. Sufficient quantity of distilled water was added to produce 100 ml mixed well and filtered. To 1 ml of the filtrate distilled water was added to produce 100 ml and mixed well. The absorbance of the resulting solution was measured at the 285 nm using blank in the reference cell. The total content of Carbamazepine in the solution was analyzed accordingly. The above test was done in triplicate.

In-vitro dissolution studies¹⁴

In-vitro drug release studies of the prepared matrix tablets as well as coated tablets were conducted for a period of 12 hrs using USP type 2 apparatus at 37±1°C and 100 rpm speed. The dissolution studies were carried out for 12 hrs under sink conditions. At every specified

time interval samples of 5 ml was withdrawn from the dissolution medium and replaced with fresh medium to maintain the sink conditions. After filtration and appropriate dilution, the samples were analyzed by a UV spectrophotometer at 285nm using dissolution medium in reference cell. Dissolution data of matrix tablet and coated tablets are reported in Fig 3, 4, 5 and 6.

Effect of Sodium Chloride on the drug release

In order to investigate the effect of sodium chloride on the release of drug from the tablets fabricated by controlled erosion technology, the drug release from the optimized formulation was compared with that of the tablet which was prepared devoid of sodium chloride.

Study of release rate kinetics¹⁴

Different kinetic models (zero-order, first-order, Higuchi's equation and Korsmeyer's equation) were applied to interpret the drug release kinetics from matrix system with the help of Equations 1-4.

1. $M_t = M_0 K_0 t$
2. $\ln M_t = \ln M_0 - K_1 t$
3. $M_t = K_H \sqrt{t}$
4. $M_t/M_\infty = k_k t^n$

In these equations, M_t is the cumulative amount of drug released at any specified time point and M_0 is the dose of the drug incorporated

in the delivery system. k_0 , k_1 , k_H and k_k are rate constants for zero order, first order, Higuchi and Korsmeyer's model respectively. For the same number of parameters, the coefficient of correlation (R^2) can be used to determine the best of the model equations.

Stability Studies

The stability study of the optimized formulation was done as per ICH guidelines (40 ± 2 °C/ $75 \pm 5\%$ RH) for 3 months. The samples were withdrawn at predetermined time intervals and evaluated for physical characteristics drug content and *in vitro* release.

RESULTS AND DISCUSSION

Drug excipients compatibility

The possible interactions between drug and the excipients were investigated by FTIR spectroscopy and DSC analysis. The DSC thermograms are given in Fig 1. Pure carbamazepine showed a sharp endotherm at 175.6°C corresponding to its melting point. This indicated the absence of interaction between drug and excipients used in the Controlled erosion based tablets. This observation was further supported by FTIR analysis. The results revealed no considerable changes in the IR peaks of carbamazepine in the physical mixture when compared with pure drug thereby indicating the absence of any interaction (Fig 2).

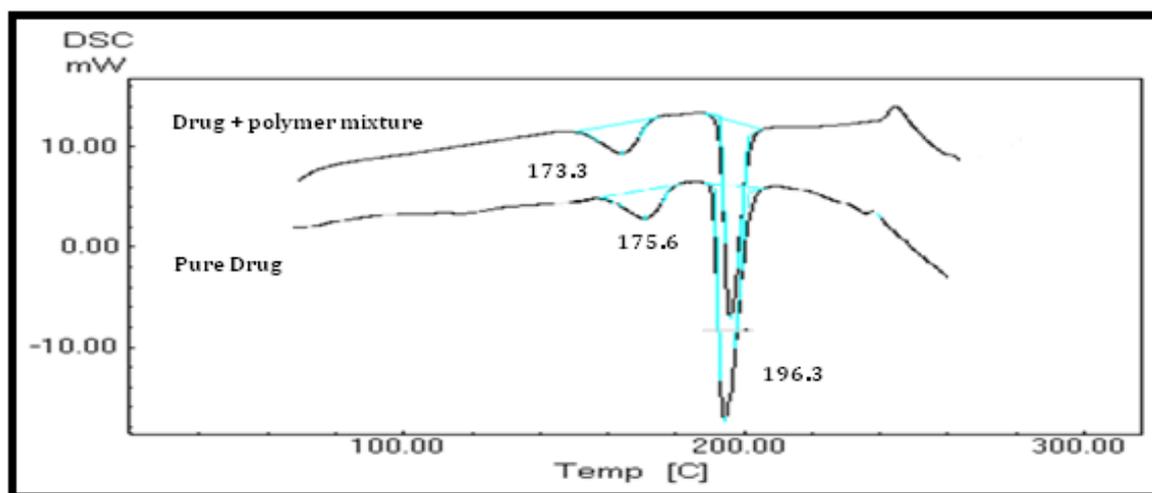


Fig. 1: DSC endotherms of the pure drug and physical mixture

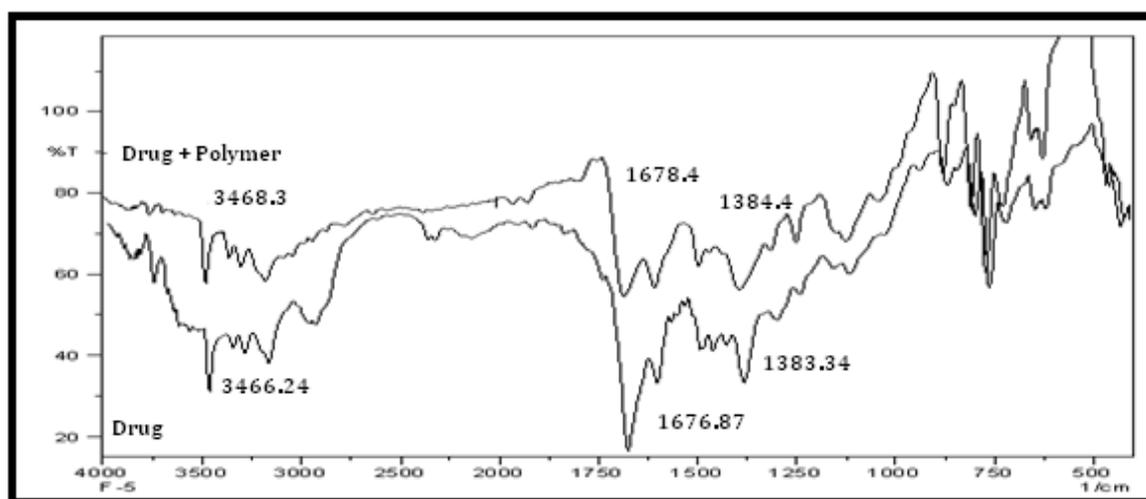


Fig. 2: FTIR thermograms of the pure drug and physical mixture

Pre-Compression characteristics of the prepared granules

Flow property

The results of angle of repose (<30) indicate excellent flow properties and the values for prepared formulations ranges from 25.8 to 29.1 (Table 3).

Compression behaviour

The bulk density, tapped density, compressibility index and Hausner's ratio were calculated.

The results of angle of repose were below 30 and Carr's Index (<10) indicate good compressibility and the Carr's index values for the prepared granules were in the range of 7.64 to 8.68. The results of Hausner's ratio indicate good compressibility and the values for the prepared granules were in the range of 1.01 to 1.10. It reveals that all the formulation blend having good flow and compressibility characteristics. Degree of compression is characteristic of compression capability of the granules and the results obtained exhibited good compression capability of the granules.

Core Tablets Evaluation (Table 4)

Weight variation

The weight variation test was carried out as per official method and the average percentage deviation of all the formulation was found to be within the limit (as per pharmacopoeia standard the deviation should be $\pm 5\%$ for tablet having weight >350 mg) i.e. $\pm 5\%$.

Friability

Compressed tablets that lose less than 1% of their weight are generally considered acceptable. For all formulation tried here, the weight loss was less than 1%, hence acceptable.

Hardness

The tablet hardness of all the formulations was determined and it was found in the range 5.27 to 5.92 kg/cm².

Thickness

The thickness of all the formulations varied with drug: polymer ratio, it ranges from 3.60 to 3.8 mm. All the formulation showed uniform thickness.

Drug content estimation

The content uniformity test was also carried out as per official method and it was found that different batches shows good content uniformity. All prepared batches showed drug content in the range of 95-105%.

In-vitro dissolution studies

All prepared core tablets were subjected to in vitro dissolution studies. The effect of polymer concentration on the drug release was studied. The effect of Sodium chloride on drug release was also studied.

Table 3: Results of pre compression properties of prepared granules of formulations CET1-CET7

Formulations	Angle of repose	Carr's Index	Hausner's ratio
CET 1	25.8	8.23	1.02
CET 2	26.3	8.66	1.08
CET 3	26.8	7.91	1.10
CET 4	28.1	8.38	1.01
CET 5	26.5	7.64	1.09
CET 6	29.1	8.21	1.10
CET 7	28.4	8.68	1.06

Table 4: Results of post compression properties of the core tablets CET1-CET7

Formulations	Weight variation %	Friability %	Hardness kg/cm ²	Thickness Mm	Drug content %
CET 1	2.02 \pm 0.25	0.79 \pm 0.3	5.61 \pm 0.56	3.8 \pm 0.45	99.5 \pm 0.71
CET 2	2.36 \pm 0.60	0.77 \pm 0.3	5.40 \pm 0.53	3.6 \pm 0.21	100.8 \pm 2.6
CET 3	2.50 \pm 0.50	0.76 \pm 0.2	5.92 \pm 0.98	3.8 \pm 0.32	99.7 \pm 2.2
CET 4	2.51 \pm 0.60	0.80 \pm 0.2	5.56 \pm 0.52	3.7 \pm 0.54	99.8 \pm 0.91
CET 5	2.30 \pm 0.22	0.76 \pm 0.4	5.83 \pm 0.57	3.7 \pm 0.61	101.9 \pm 2.43
CET 6	2.22 \pm 0.32	0.78 \pm 0.2	5.27 \pm 0.39	3.5 \pm 0.26	99.6 \pm 2.36
CET 7	2.50 \pm 0.66	0.77 \pm 0.3	5.92 \pm 0.56	3.8 \pm 0.42	98.3 \pm 1.72

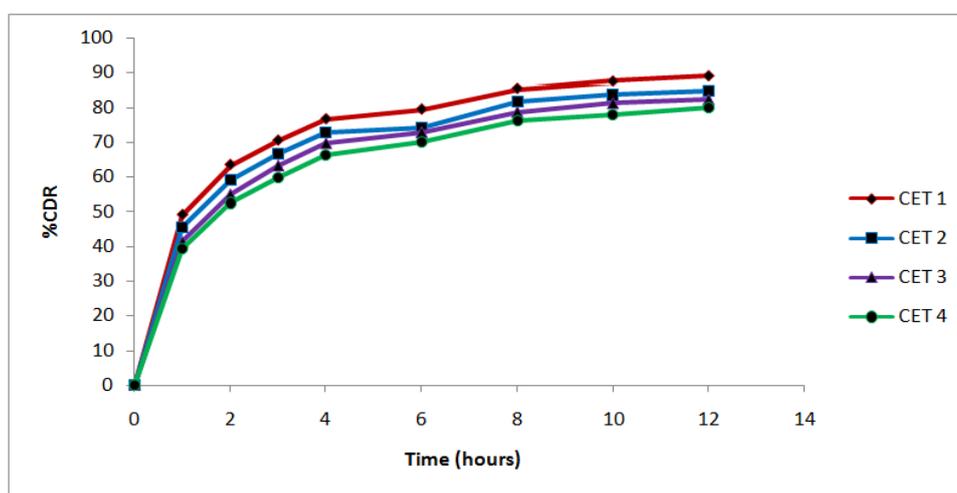


Fig. 3: In-vitro dissolution profile of carbamazepine from core tablets CET1 to CET 4

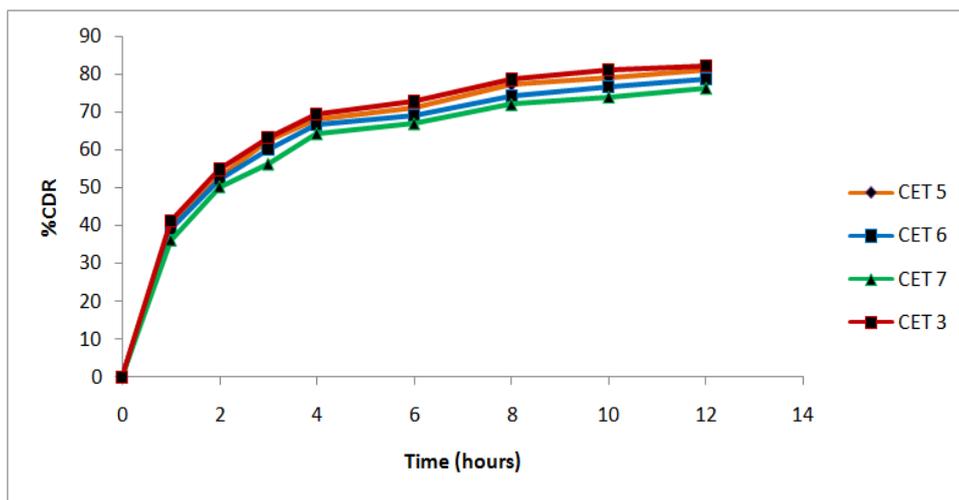


Fig. 4: *In-vitro* dissolution profile of carbamazepine from core tablets CET 3, CET 5, CET 6 and CET 7

Formulations CET 1 to CET 4 contain varying concentrations of HPMC. CET1 and CET2 showed a drug release of more than 80 % within 8hours, which was not optimum for erosion controlled coating and hence were rejected from the further studies. The effective sustained release (82.25% in 12 hours) was found to be from CET 3.

CET 4 to CET 7 also showed effective rate of dissolution, however keeping in mind the cost effectiveness associated with minimum

amount of ingredients to produce a product, CET 3 with minimum amount of excipients with satisfactory release profile was considered as the optimized core formulation.

***In vitro* release profiles for CET 3 after Erosion controlled coating**

The release profiles for CET 3 core tablets with 5% coating are as shown in fig 5.

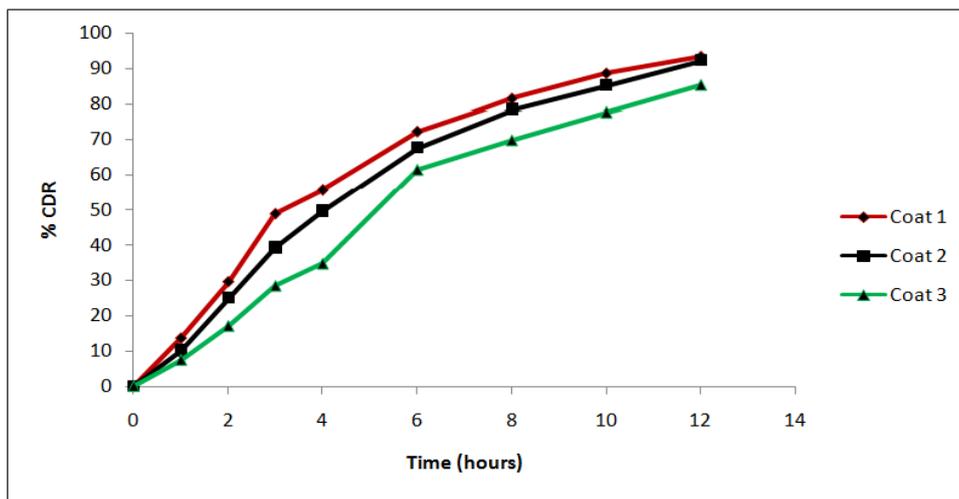


Fig. 5: *In-vitro* dissolution profile of core tablets from CET 3 after Erosion controlled coating

The drug release from the core tablets is sufficiently and effectively controlled by the controlled erosion coating employed. The erosion controlled coating effectively prolongs the drug release for a period of 12 hours and the optimized formulation CET 3 with Coat 1 showed a drug release of 85.338% at the end of 12 hours, complying with the USP release limits. This controlled erosion can be attributed to the cellulose acetate-HPMC coating, which effectively prolongs the drug release with controlled erosion of the coating membrane.

Effect of Sodium Chloride on the drug release

The release profile of the optimized core tablet CET3 and tablet without sodium chloride CET 0 is shown in fig 6.

The CET 3 (with sodium chloride) showed relatively faster release in comparison to its counterpart, CET 0 (without Sodium chloride). This may be attributed to the osmotic behaviour of the sodium chloride which potentially imbibes water in to the core there by releasing drug faster.

Table 7: Dissolution profile of optimized formulation in compliance with USP limits

Formulations	% release in 3 h	% release in 6 h	% release in 12 h
USP	10-35	35-65	65-90
CET 3 with Coat 1	28.40	61.49	85.338

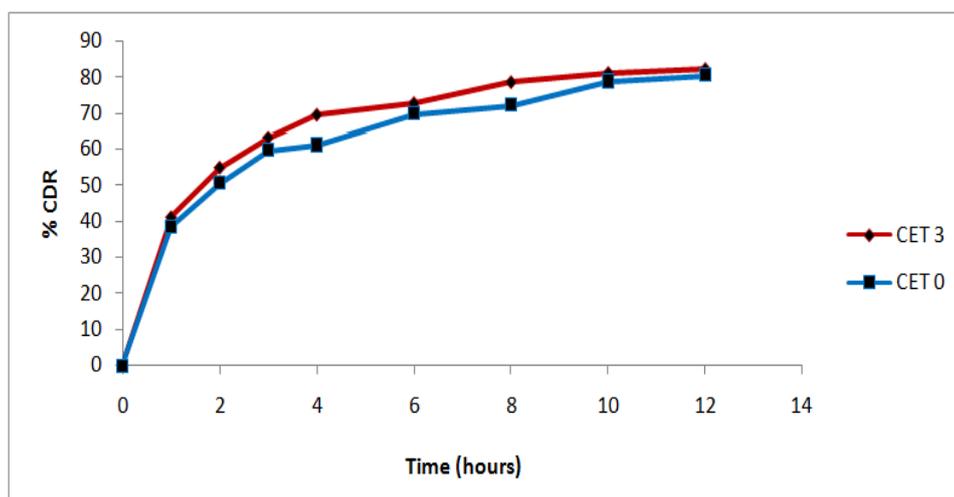


Fig. 6: *In vitro* dissolution profile of carbamazepine from core tablets CET 3 and CET 0

Table 8: Compilation of the results from all the mathematical models applied to the optimized formulation

Formulation	Zero order	First Order	Higuchi Square Root Law	Korsmeyer Peppas's plot, (n)
CET 3 with Coat 1	0.9605	0.892	0.921	0.996 (0.846)

Study of release rate kinetics

From the above results it is apparent that the regression coefficient value closer to unity in the case of the zero order plots indicates that the drug release follows a zero order mechanism. The data indicates a lesser amount of linearity when plotted by the first order equation. Hence it can be concluded that the major mechanism of drug release follows zero order kinetics.

To ascertain the mechanism of release, the dissolution data was fitted into the Peppas's equation. Here the value of the exponent "n" which is obtained from the slope of the graph of log Q (amount of drug dissolved) Vs log t (time) yielded the value of 0.846. From the reference values, above, for a cylinder, the value of exponent n in the range of $0.45 < n < 0.89$ is indicative of anomalous transport or non-Fickian diffusion. It therefore indicates a combination of diffusion and erosion. Since this value lies at the near end of the range give, it tends to show majorly erosion behavior than Fickian release mechanism. When this observation is coupled with that from above, a final conclusion can be drawn that the predominant mechanism of release is erosion and the zero order release rate is the best fit equation for the drug release in this case.

Stability Studies

Accelerated stability studies carried out as per ICH guidelines. Tablets did not show any physical changes during the study period except there was a slight increase in the hardness which was well within the acceptable range. Drug content was found to be more than 95% at the end of 3 months in accelerated conditions. The *in vitro* release profile of the drug from the tablets was well within the USP limits. This indicates that the optimized formulation was stable at accelerated storage conditions.

CONCLUSION

Sustained released matrix tablets of Carbamazepine were successfully prepared using controlled erosion technology. The study was undertaken with the aim to formulate and evaluate Carbamazepine extended release tablet fabricated by Controlled erosion technology using HPMC E5 as the polymer matrix and combination of cellulose acetate and HPMC as the controlled erosion membrane. DSC and FTIR studies demonstrated that there was no interaction between the drug and the excipients. For all the prepared formulations evaluation parameters like thickness, hardness, friability, weight variation and drug content were found to be satisfactory.

Carbamazepine extended release tablets by controlled erosion technology was prepared successfully using HPMC E5 and by using Cellulose acetate as controlled erosion membrane to achieve required dissolution profile for the period of 12 hours. The release pattern of optimized formulation was well within the USP limit.

The effect of Sodium chloride on the drug release was thoroughly studied and from the results it can be concluded that the addition of Sodium chloride, owing to its osmotic behavior exhibits better drug release from the tablets. The optimized formulation was found to be stable throughout the accelerated stability study.

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