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Design and Evaluation of Carbamazepine Controlled Release Drug Delivery System

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Abstract: Carbamazepine is a widely used anti-epileptic drug in the therapy of psychomotor seizures and trigeminal neuralgia. The objective of the present study is to prepare oral controlled release matrix tablet of carbamazepine (420 mg) by wet granulation technique using hydrophilic polymers such as HPMC, Sodium CMC of various concentrations. Its solubility was increased by making a complex with β –cyclodextrin thereby increasing its bioavailability. Eudragit incorporated as a release modifier due to its solubility in acidic medium. The tablets were evaluated for preformulation studies like angle of repose, bulk density, compressibility index and physical characteristics like hardness, weight variation, friability and drug content. *In-vitro* release of drug was performed in 0.1 N HCl for 2 hours PBS pH6.8 for 12 hours. All the physical characters of the fabricated tablet were within acceptable limits. *In vitro* release profile of marketed controlled release formulation (tegretol) showed the drug release 84% in 12th hour, where as our selected formulations F13 (HPMCK4m) released at 88% of drug in 12th hour respectively. The relative bioavailability of the selected formulation was 0.435 µg/ml of t_{max} at 12 hr compared with marketed product of 0.369µg/ml. The stability studies showed that it followed zero order kinetics when fitted to kinetic models (Higuchi, Hixson and Peppas).It was clear from the dissolution profile of carbamazepine from matrix tablets prepared using different polymers were indicated an increase in the polymer ratio retarded the drug release to a greater extent. As a concluding remark, F13 carbamazepine matrix tablet showed better oral bioavailability than the marketed tablet, and further animal studies/human studies could be under taken with large number of subjects in order to confirm these results.
Keywords: *Carbamazepine, matrix tablet, HPMC, NaCMC, Eudragit, β –cyclodextrin, Tegretol*

INTRODUCTION

Introduction of matrix tablet as sustained release (SD) have given a new breakthrough for noel drug delivery system (NDDS) in the field of pharmaceutical technology. Hydrophilic polymer matrix is widely used for formulating an SR dosage form [1-4]. Carbamazepine is a drug widely used as anti- epileptic in the therapy of psychomotor seizures and trigeminal neuralgia. The popularity of this drug is related to several beneficial properties, including, poor efficacy in controlling different types of seizures, it is poorly water soluble (170mg/l at 24ºc) with erratic oral absorption and bioavailability less than 70%. The success of therapy depends on selection of appropriate delivery systems as much as it depends on drug itself. HamdyAbdelkadar*et al*[5]**.,** has prepared matrix tablet by using methyl cellulose sodium alginate and sodium CMC by using Baclofen as a model drug .the tablets were prepared by wet granulation method .Methyl cellulose and sodium alginate showed high release retarding efficiency and good reproducibility.

A successful hydrophilic matrix system should possess a polymer that will wet, hydrate and swell to form a gelatinous layer and avoid disintegration of the tablet. To achieve this, different cellulose derivatives or their combinations have been extensively used in the preparation of matrix tablets. Hydroxy propyl methyl cellulose (HPMC) and sodium CMC is the most widely studied hydrophilic swell able matrix forming material for the preparation of modified drug release products. Its popularity can be attributed to the polymer's non-toxic nature, small influence of processing variables on drug release, ease of compression, and its capability to accommodate high levels of drug loading [6-7]

MATERIALS

Carbamazepine was received as a gift sample from Arvind Remedies limited, Chennai. Hydroxypropylmethylcellulose K4M and Sodium carboxymethyl cellulose were obtained as gifts from Paxmy chemicals, Chennai. Eudragit were purchased from Microlabs, Hosur. Magnesium stearates, hydrochloric acid, Acetone, PVP, IPA k-30, Talc, Lactose were purchased from S.D. Fine-Chem Ltd, Ahmedabad, India. Other materials used were of analytical grade, and procured from commercial sources.

METHODS

Formulation of carbamazepine matrix tablets:

Preformulation studies:

Compatibility Studies

A physical mixture (1:1) of drug and polymers was prepared and mixed with suitable quantity of IR grade potassium bromide and prepared transparent pellets. They were scanned from 4000 to 400 cm-1 using AB.Bomemmodel no. MB 104, Canada. DSC thermograph analysis was also performed to test the interactions.

Preparation of inclusion complexes with β-cyclodextrin by co-precipitation method

The inclusion complex of carbamazepine with β-cyclodextrin (1:1) was prepared. Carbamazepine was dissolved in least volume of ethanol at 40ºc and the required amount of β-cyclodextrin in distilled water was added gradually to the ethanol solution with continuous sonication. The obtained solution was then maintained under stirring for 28 hr at room temperature. The solvent was then evaporated under vacuum at 40ºc using rotator evaporator until constant weight was obtained and the obtained product was pulverized and sieved through a #60 mesh sieve**.**

Preparation of the carbamazepine matrix tablets:

Tablets were prepared by wet granulation technique. All the powders were passed through sieve 16. Required quantities of Carbamazepine complex and other polymers (HPMC and NaCMC) were mixed separately and thoroughly. Lactose is used as diluents so as to adjust the weight of the tablets. Granulation was done with a solution of PVP k-30 in sufficient isopropyl alcohol. The granules (40mesh) were dried in conventional hot air oven at 45^0C. Drying of the granules was stopped when the sample taken from the oven reached a loss on drying (LOD) value of 0.5 to 1.5 %, as measured by a moisture balance at 105°C. The dried granules were sized through 40/60mesh, lubricated with magnesium stearate (1 %w/w) and purified talc (7 %w/w) and then compressed on a single punch tablet machine

(Cadmach Machinery Ltd., Ahmedabad, India). The tablets were off white, round and flat. The hardness of the tablets was kept constant. Ten formulations were prepared and coded them from F1 to F12. The detail of composition of each formulation is given in **Table 1.**

Evaluation of Carbamazepine Granules

The flow properties of granules (before compression) were characterized in terms of angle of repose[8], tapped density, bulk density[9], and Carr's index[10]and Hausner ratio.

Physical evaluation of Carbamazepine matrix tablets[11]

Two tablets from each formulation were randomly selected and organoleptic properties such as colour, odour, taste, and shape were evaluated. Thickness and diameter of ten tablets were measured using vernier calipers. The prepared floating tablets were evaluated for uniformity of weight using 20 tablets[12], hardness (Monsanto tester) [13,] and friability 10 tablets (Roche type friabilator) [13]

Drug Content Estimation[14]

Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 60mg of carbamazepine, transfer to a 100ml volumetric flask, and about 100ml of ethanol (95%), mix and filter. Dilute 5.0ml of the filtrate to 50.0ml with ethanol (95%). Measure the absorbance of the resulting solution at the maximum about 285nm.

***In vitro* dissolution studies[14]**

The release rate of Carbamazepine from matrix tablets was determined using *United States Pharmacopeia* (USP) Dissolution Testing Apparatus 1 (basket method). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at 37 ± 0.5°C and 100 rpm for 2 hours and pH 6.8 Phosphate buffer for 12 hours. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. Absorbance of these solutions was measured at 285 nm using a UV/Visible spectrophotometer. The percentage drug release was plotted against time to determine the release profile.

Comparison with marketed product

The promising formulation was compared with marketed product of carbamazepine (Tegretol 400 mg). The evaluation parameters tested and compared were drug content uniformity and *in-vitro* dissolution profile.

***In vitro* drug release kinetic studies**

Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero order [15], first order[16],Higuchi square root[17], Korsmeyer- Peppas model[18]. The criteria for selecting the most appropriate model were chosen on the basis of goodness of fit test. The data were processed for regression analysis using MS EXCEL statistical function.

Stability studies

The promising formulation was tested for a period of 12 weeks at 40^0C with 75% RH, for their drug content and other parameters.

***In-vivo* release studies of carbamazepine controlled release matrix tablet**

(Protocol Approval No: IAEC/XIII/05/CLBMCP /2008-2009)

The *in-vivo* release characteristics of the selected test formulation FXIII were compared with the marketed formulation (Tegretol CR 200mg). Six male rabbits weighing approximately 1.5 kg and with the age of 12 months were selected for the study. The rabbits were divided in to two groups of three in each. Each group was subjected to a single dose randomized parallel design study. The animals were housed individually under environmental conditions (23 ± 2°C, 55 ± 5% RH, 12 hours light/dark cycle). The rabbits were fasted overnight and allowed free access to tap water only. The test formulation and the marketed formulations were administered to the rabbits by gastric intubation method. 0.5ml of blood samples were withdrawn from the marginal ear vein of rabbit at various time intervals. The plasma samples were separated by centrifugation; drug was extracted and then assayed for carbamazepine by HPLC.

Table 1: Composition of different matrix tablet formulations of carbamazepine

Ingredients* (mg per tablet)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**
Carbamazepine complex	420	420	420	420	420	420	420	420	420	420	420	420	420	420
HPMC K4M	50	100	150	200	400	-	_	_	_	_	100	100	100	100
Sodium cmc	_	_	_	_	_	50	100	150	200	400	_	_	_	_
Eudragit E100	_	_	_	_	_	_	_	_	_	_	50	100	150	200
Lactose	194	144	94	44	64	194	144	94	44	64	194	144	94	44
PVP-k 30	28	28	28	28	28	28	28	28	28	28	28	28	28	28
Talc	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Total	700	700	700	700	920	700	700	700	700	920	700	700	700	700

- All the quantities are in mg

RESULTS AND DISCUSSION

Carbamazepine is a drug widely used as anti- epileptic in the therapy of psychomotor seizures and trigeminal neuralgia. The popularity of this drug is related to several beneficial properties, including, poor efficacy in controlling different types of seizures, it is poorly water soluble (170mg/l at 24ºc) with erratic oral absorption and bioavailability less than 70% . HPMC is the most widely used polymer for oral controlled delivery due to its pH independent drug release. Its mechanism is well known as a swelling controlled release system and the release of hydrophilic drugs from this polymer is by diffusion process [19]

The aim of the work is to prepare controlled release matrix tablet of carbamazepine and to increase its solubility by making complex with β – cyclodextrin thereby increasing its bioavailability. An attempt was also made to improve the pH - independent drug profile of carbamazepine. In order to extend the release of carbamazepine, Hydroxypropylmethylcellulose (HPMC), Sodium CMC employed in the formulations. Both polymers provide drug release at slower rate at acidic pH than alkaline pH. Eudragit incorporated as a release modifier due to its solubility in acidic medium. PVP K30 in an optimized concentration (28mg/tablet) was employed for such unique disintegration properties. The present study was designed to evaluate the influence of these variables in the formulation. The optimized formulation were subjected to stability study and compared to a commercially available. The present investigation also focused to testing the therapeutic efficacy of the drug by performing *in vivo* experiments. The prepared tablets of all the formulations were evaluated for pre compression parameters like angle of repose, bulk and tapped density and compressibility index and physical characters like tablet hardness, friability, weight variation, assay, *in-vitro* drug release. The main aim was to optimize the formulation for 12 hours *in-vitro* release and to get oral bioavailability more than the compared marketed formulation.

Pre formulation studies

Development of calibration curve for Carbamazepine

The scanning of the drug solution in the UV range showed maximum absorbance at 285 nm and hence, the calibration curve was developed at this wavelength. The straight line were obtained which fit in the linear regression line of R2=0.9956.

Table 2: Results of Precompression Flow Properties of Granules of Carbamazepine

Formulation code	Angle of Repose (θ)	Loss on drying (%)	Bulk density(gm/cm^3)	Tapped density (gm/cm^3)	Hausner ratio(H_R)	Carr's Index (%)
F1	25.64	1.21	0.350	0.420	1.20	16.6
F2	25.568	1.10	0.361	0.430	1.19	16.20
F3	26.42	1.12	0.370	0.440	1.18	15.9
F4	25.43	1.13	0.350	0.410	1.17	14.63
F5	26.42	1.10	0.380	0.450	1.20	15.50
F6	26.03	1.11	0.356	0.421	1.18	15.43
F7	26.32	1.15	0.361	0.432	1.19	16.43
F8	25.98	1.21	0.351	0.412	1.17	14.80
F9	25.43	1.15	0.354	0.425	1.20	16.70
F10	25.64	1.20	0.371	0.442	1.19	16.07
F11	26.45	1.16	0.364	0.434	1.16	16.23
F12	25.86	1.19	0.371	0.420	1.19	16.75
F13	26.78	1.20	0.358	0.441	1.17	15.38
F14	25.89	1.17	0.358	0.410	1.20	15.69

Compatibility studies

The compatibility between the drug and the selected polymers was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the polymer-drug mixture, which confirmed the absence of any chemical interaction between the drug and the polymers. DSC analysis was also performed with polymers in combination with drug 1:1 its seems to be no interaction in the melting point of carbamazepine . Carbamazepine complex with β cyclodextrin will increase the solubility of carbamazepine four times.

Effect of polymer concentration:

Granular characteristics

The results of evaluation of granules are shown in Table no: 2 Angle of repose, bulk density and compressibility index were found for batches HPMCK4M (F1-F5) respectively, which indicated good flow properties. The granules evaluation indicated good physicochemical properties. This results also applicable to batches of NaCMC (F6-F10) and HPMCK4M with release modifier Eudragit (F11-F14) respectively and results are shown in (**Table2).**

Post compression parameters of carbamazepine tablets

The shape of the tablets of all formulations remained off white, smooth, flat faced circular with no visible cracks. The thickness and diameter of tablets was measured by vernier calipers and was ranged between 4.1±0.04 to 4.6± 0.048 mm to9.14 ± 0.049 to 9.54 ± 0.048 mm respectively. The hardness of the tablets was measured by Monsanto tester (Electrolab Mumbai, India) and was in between 5.8 to 7.7 kg/cm2. The friability was measured by Friabilator (Electrolab, Mumbai) and was found to be 0.26-0.36% which is an indication of satisfactory mechanical resistance of the tablets. The drug content estimations showed values in the range of 100.7 to 103% which reflects good uniformity in drug content among different formulations. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits of ±5% of the weight. The results are shown in table 3. All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality.

Table 3: Results of Post Compression Properties of Carbamazepine matrix Tablets

Formulation Code	Weight variation(mg)	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Diameter (mm)	Drug content (%)
F1	700 ± 2.71	5.8	0.31	4.3 ±0.024	9.54	102.56
F2	700 ±1.96	6.4	0.26	4.14±0.04	9.14	103
F3	700 ± 2.60	6.3	0.36	4.26 ± 0.048	9.46	101.5
F4	700 ± 3.07	7.7	0.36	4.3 ± 0.024	9.42	101.5
F5	700 ± 4.50	6.5	0.33	4.26 ± 0.048	9.23	102.63
F6	700 ± 3.92	6.5.	0.33	5.12 ± 0.09	9.18	100.3
F7	700 ± 4.87	6.3	0.33	4.56 ± 0.024	9.16	101.6
F8	700 ± 4.61	7.2	0.30	4.58 ± 0.004	9.03	100.7
F9	700 ± 3.90	7.0	0.33	4.64 ± 0.048	9.35	100.7
F10	700 ± 3.81	7.2	0.40	4.56 ± 0.048	9.5	100.83
F11	700 ± 4.45	7.3	0.35	4.43 ± 0.018	9.28	102.54
F12	700 ± 2.61	6.7	0.33	4.61 ± 0.038	9.19	101.4
F13	700 ± 3.68	7.1	0.38	4.22 ± 0.009	9.44	100.5
F14	700 ± 3.91	6.8	0.36	4.33 ± 0.028	9.17	102.35

***In vitro* dissolution studies**

In vitro dissolution studies of all the formulations of matrix tablets of carbamazepine were carried out in 0.1N HCl for 2 hours and pH6.8 for 24 hours. The study was performed for 24 h and cumulative drug release was calculated at every one hour time interval. *In vitro* dissolution studies of all the formulations are shown in **figure 1, 2 and 3.** Two different polymers and their combinations with release modifier (Table 1) were used to prepare matrix tablets. It was observed that the type of polymer influences the drug release pattern. A significantly higher rate and extent of drug release was observed from the batches based on HPMC K4M. Varying amount of HPMC K4M affect the drug release when compared to NaCMC.

Formulations containing different ratios of HPMC K4M (F1-F5) shows the release less than 8% in acidic medium and formulations containing NaCMC (F6-F10) releases less than 5.39 ± 0.98 to 8.41 ± 0.57 at 2^{nd} hour. Only the formulation F2 (HPMC K4M 100 mg) releases nearly 15% at pH 1.2. Both polymers provide drug release at a slower rate at acidic pH than alkaline pH. Eudragit incorporated as a release modifier (F11-F14) due to its solubility in acidic medium. As expected, the drug release rate was dependent on the viscosity grade and the concentration of the polymer used. Tablets containing HPMC and Eudragit combination (F13) showed a release of 23% in acidic medium and 88% at 12^{th}hour.

Comparison with the marketed tablet

The promising formulation (F13) as found by evaluation studies was compared with marketed product. The comparative *in-vitro* dissolution study of optimized formulation (F13) and marketed product are presented in **Fig 4.**The result showed that the optimized formulation F13 has better control over release rate in comparison to the commercial product. The marketed product released the drug and 44% in acidic medium and 83% in 12 hours whereas the optimized formulation F13 released the drug 88 % in 12hrs.

Figure: 1 Comparison of *in vitro* dissolution profiles of F1 to F5

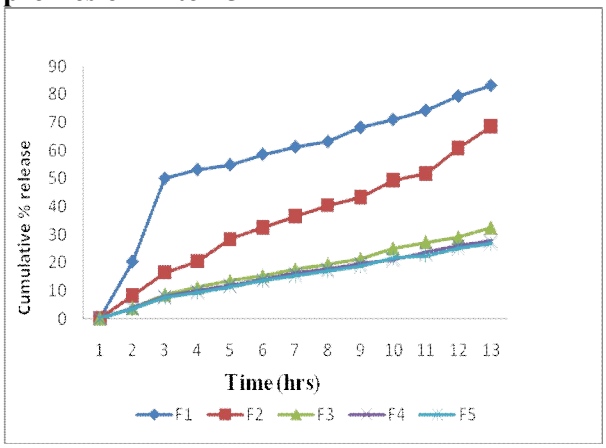


Figure: 2 Comparison of *in vitro* dissolution of F6 to F10

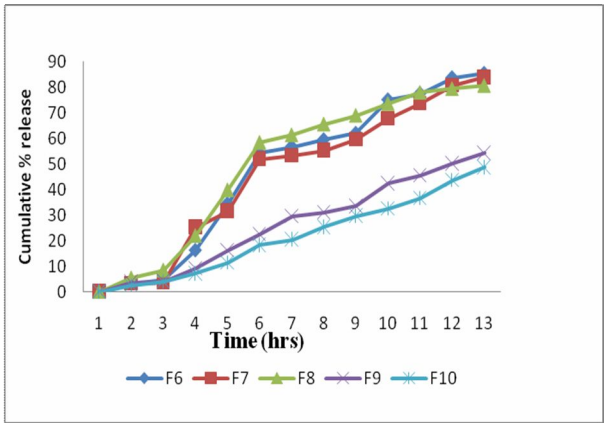


Figure: 3 Comparison of in *vitro* dissolution of F11 to F14

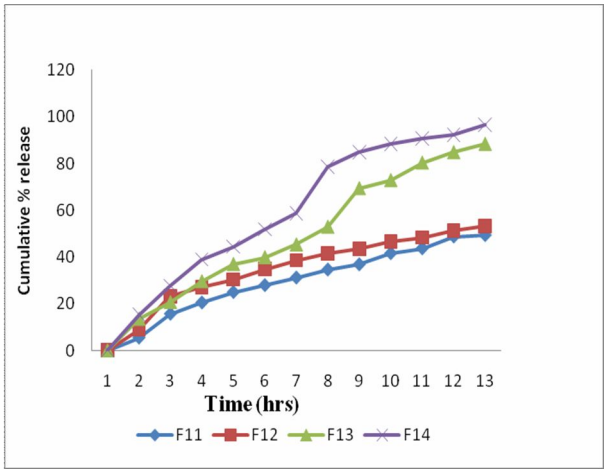


Figure: 4 Comparison of *in vitro* dissolution of F13 and Marketed Product

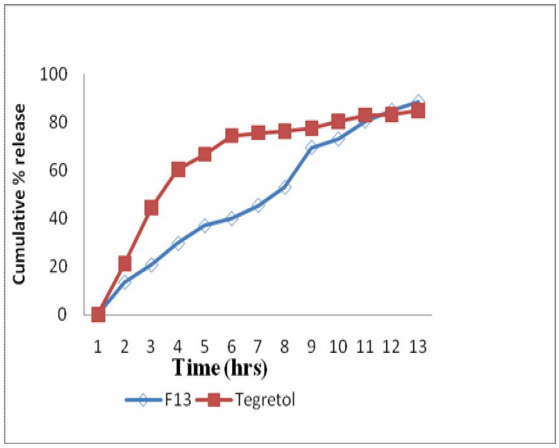
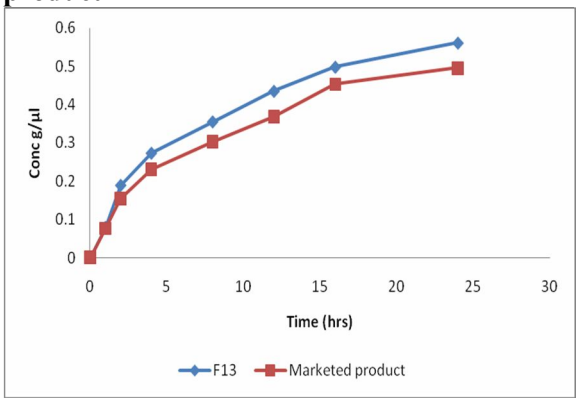


Figure:5 Comparison of *In vivo* bioavailability study for F13 and marketed product



Analysis of release mechanism

The drug release data of carbamazepine were fitted to models representing Higuchi's, zero order, first order and Korsmeyer equation kinetics to know the release mechanisms. The results are shown in Table 4. The kinetic data (Table-5) showed that the release of drug followed diffusion controlled mechanism for the formulations. Diffusion is related to transport of drug from the dosage form in to the in vitro fluid depending up on the concentration. As the gradient varies the drug is released and the distance for diffusion increases. In the present study, in vitro release profiles could be best expressed by zero order kinetics as optimized formulation (F13) showed good linearity (R^2: 0.9932) indicates that the release pattern is independent of the concentration.

Stability study of optimized formulation (F13)

The optimized matrix tablets (F13) were selected for stability study on the basis of *in vitro* drug dissolution studies. The tablets were investigated at 40°C/75%RH for 3 months. From the data, the formulation was found to be stable under the conditions mentioned before since there was no significant change in the percentage amount of drug content (Table 5). Thus, it was found that the floating tablets of carbamazepine (F13) were stable under these storage conditions for at least 3 months.

***In-vivo* release studies**

The *in-vivo* release characteristics of the selected test formulation F13 were compared with the marketed formulation (Tegretol CR 200mg) using six male rabbits and it was subjected to a single dose randomized parallel design study. The test formulation and the marketed formulations were administered to the rabbits by gastric intubation method. 0.5ml of blood samples were withdrawn from the marginal ear vein of rabbit at various time intervals. The plasma samples were separated by centrifugation; drug was extracted and then assayed for carbamazepine by HPLC. The results showed that the selected formulation has better bioavailability of 0.435µg/ml as compared with Tegretol 0.369 µg/ml at 12 hours.The results are shown in Figure 5.

Table 4: Kinetic Release Data for Optimized Formulation (F13)

Kinetics model	R^2	Slope
First order	0.65614	5.1408
Zero Order	0.9932	7.098
Higuchi	0.98226	24.4136
Peppas	0.99338	0.7839

Table 5: Stability study (40 °C/75%RH) of Optimized Formulation (F13)

Parameters	Optimized formulation (F13)	1st month	2nd month	3rd month
Appearance	No color change	No color change	No color change	No color change
Hardness(kg/cm$^{2)}$	6.8 ± 0.224	6.8 ± 0.221	6.8 ± 0.112	6.7 ± 0.110
Friability (%)	0.40±0.009	0.045±0.005	0.40±0.007	0.43±0.004
Content uniformity	100.83±0.115	100.0±0.110	100.72±0.112	100.20±0.118
Weight variation(mg)	700±3.815	700±3.612	700±3.416	700±4.110
Assay	101.56±0.115	100.0±0.115	100.50±0.21	100.20±0.210
In vitro drug release (%) 12 hr	88.33 ± 0.41	85.66±0.14	85.126±0.33	81.29±0.91

CONCLUSION

The controlled release formulation of carbamazepine have introduced into the drug therapy with a purpose to reduce the number of single doses during the day, and to decrease the fluctuations of serum in view to obtain better therapeutic efficacy and diminished toxicity. This study deals with the investigations carried out with the objective of developing oral sustained release formulations through matrix tablets for the widely used anti-psychotic drug Carbamazepine using hydrophilic polymer Hydroxy propyl methyl cellulose, Sodium Carboxyl methyl cellulose and evaluation of their sustained release potential. In order to achieve pH independent drug release pH modifying agents was studied using Eudragit and HPMC. The addition of Sodium CMC failed in order to achieve pH independent drug release. In contrast, the combination of HPMC with Eudragit was successful to release pH independent release of carbamazepine. From the kinetic model it shows to fit into zero-order kinetics[20]

The relative bioavailability of carbamazepine done using animals was found to be slightly higher than the reference product. The results suggest that further animal studies/human studies could be under taken with large number of subjects in order to confirm these results. They are thus capable of reducing the dose intake, minimize the blood level oscillations, dose-related adverse effects and cost thus ultimately improve the patientcompliance in the therapeutic management.

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