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Research Article

FORMULATION & EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF CARBAMAZEPINE

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ABSTRACT

Monolithic matrix tablets of carbamazepine were formulated as sustained release tablet employing HPMC polymer and the sustained release behavior of the fabricated tablet was investigated. Sustained matrix tablet contain 200 mg of carbamazepine were developed using different grade of HPMC alone or in combination. Tablets were prepared by direct compression. Formulation was optimized on the basis of acceptable tablet properties and in-vitro drug release. The resulting formulation produced robust tablets with optimum hardness, consistence weight uniformity and low friability. The result of dissolution study indicated that formulation C07 the most successful of the study, exhibited drug release pattern very close to USP data for carbamazepine extended release tablet. A decrease in release kinetic of drug was observed on increasing polymer ratio.

Keywords: Carbamazepine , sustained release matrix tablet, epilepsy and HPMC.

INTRODUCTION

Carbamazepine is an anticonvulsant drug used in the treatment of epilepsy. Carbamazepine is related chemically to tricyclic antidepressant. This is derivative of iminostilbin with a carbamil group at 5th position, this moiety is essential for antiseizure activity. It is chemically described as 5H-Dibenz[b,f] azepine-5-carboxamide[1-5].Sustain release formulation of carbamazepine present the formulator with significant chalanges due to its physical propertie s(like polymorphism)[6], due to its increase metabolism (autoinduction by repeated dosing), pronounced daily fluctuation in serum concentration of carbamazepine[7], and limited water solubility.

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Because there is a correlation between peak concentration of carbamazepine and CNS side effects especially in patient receiving polytherapy (elilepsia)[8]. It is of great clinical importance to assure a steady level of carbamazepine during 24 hr carbamazepine delivery.

MATERIALS AND METHODS

Carbamazepine, Colloidal Silicon Dioxide and magnesium stearate, was obtained from Arbro Pharmaceuticals Ltd, New Delhi.Various grades of Hydroxy propyl methyl cellulose were purchased from colorcon, India. All other chemicals used were of analytical grade.

Preparation of matrix tablets:

Different tablet formulations were prepared by direct compression method by mixing required amount of the drug, the polymer, diluents and lubricant by geometric addition procedure .All ingredients were passed through sieve no.60 prior

to weighing based on theoretical weight of each tablet, the filling capacity of the lower punch was adjusted and tablets were compressed at 7-10 kg/cm^2 hardness using a 16 station rotary tablet-punching machine.

Evaluation of Uncoated Sustained Release Matrix Tablets

Weight Variation Test

Twenty tablets were randomly selected and weighed to determine the average weight and were compared with individual tablet weight. The percentage weight variation was calculated. The results are given in table III.

Friability Test

20 dedusted tablets were subjected to rotating drum of friability test apparatus. The drum was rotated at a speed of 25 rpm. The apparatus was operated for 4 minutes and the tablets were weighed. Friability was calculated by the following formula.

$$F = 100\left[\frac{W_0 - W}{W}\right]$$ F = Friability, W = Final weight, Wo = Initial weight

The results are given in table III.

Hardness Test

The hardness of tablet was determined by using Monsanto type hardness tester. The hardness of the tablet kg / cm² was measured. The result are given in table no. III.

Thickness & diameter

The dimensional specifications were measured using digital micrometer calipers. The thickness of the tablet is mostly related to the tablet hardness can be used as initial control parameter. The result is given in Table no. III.

Assay (carried by UV)

Preparation of test solution:

Crushed 20 tablets and weighed equivalent to 100 mg(approx 151 mg of powered drug) of Carbamazepine and dissolved in 100 ml distilled water (Solution – A) 10 ml of the solution – A was further diluted to 100 ml with distilled water. (Solution – B). From solution B, 10 ml of solution was again diluted to 100 ml (Solution – C) and recorded the absorbance at 284 nm with the help of UV spectrophotometer.

Preparation of standard solution

Weighed 100 mg of standard Carbamazepine powder and diluted to 100 ml distilled water. Further 10 ml of this solution diluted to 100 ml. from this solution 10 ml diluted to 100 ml with distilled water and read the absorbance at 284 nm with the help of UV spectrophotomete.

ASSAY (BY HPLC)[9]

Assay was performed as per USP 2004. 20 Tablets were weighed and powdered. High performance liquid chromatography was carried out, using the following solutions

Chromatographic conditions

- Mobile phase: A mixture of water, methanol, methylene chloride in ratio (500:450:45)
- Column used: Lichrosphere C-18
- Wavelength :284nm
- Flow rate: 2.0ml/min
- Injection vol.: 20µL

Preparation of standard solution:

Weighed 50mg of standard Carbamazepine powder and diluted to 50ml with methanol.and sonicated for 10 min. Further 2 ml of this solution diluted to 25 ml with mobile phase

Prepration of test solution

Weighed tablet powder equvivalent to 50 mg carbamazepine drug and dissolved in 50 ml volumetric flask with few ml of methanol .Volume made up to 50 ml with methanol.and sonicated for 10 min. Further 2ml of this solution diluted to 25 ml with mobile phase.

Drug excipient compatibility studies

IR spectra of drug, drug and polymers were obtained using Jasco FTIR-410 to establish the compatibility of ingredients. Physical mixture of the drug and the polymer [1:1] were mixed with 400 mg of Potassium Bromide. About 100 mg of the mixture was taken and compressed to form a trasnsparent pellet in a hydraulic press at 15 tonnes pressure. The samples were scanned from 4000 to 400 cm^{-1} in a FTIR spectrophotometer. Similar, the IR spectra of the individual drug and the polymers were also recorded .Changes if any in the spectra were observed to assess any physical or chemical interaction.

Formulation development

Various factors that may influence the drug release profile such as tablet shape, dissolution medium, apparatus, combination of polymers and their proportions, viscosity of polymers are studied.

The composition and tablet weight (theoretical weight) for the formulations prepared are listed in Table: IA &IB

In-vitro Drug release kinetics

Dissolution data was fitted kinetic model mentioned in introduction and regression analysis was carried out. The criteria for selecting the most appropriate model was based on best goodness of fit and smallest standardize residuals.

Gel layer dynamics

The tablets were clamped between two glass slides and placed in cobalt (II) thiocynate solution and allowed to hydrate for 12 hours. The hydrated matrices were photographed.

Gel Layer Dynamics and Front Visualization

When hydrophilic matrix former matrices were hydrated in cobalt (II) thiocynate solution (6.8 gm cobalt chloride and 4.3 gm ammonium thiocynate in 100 mL water) is permeated into the tablet along with water. Cobalt (II) thiocynate gives a pink colour when diluted and forms a blue complex with compounds containing amino groups. Thus a blue colour was developed in the hydrated region of the tablet containing carbamazepine while drug free hydrated region appeared pink due to cobalt (II) thiocynate. The un-hydrated glassy core of the matrix retained it's off- white colour. The junction of these regions mark the different fronts observed in a hydrating matrix and are marked in figure.

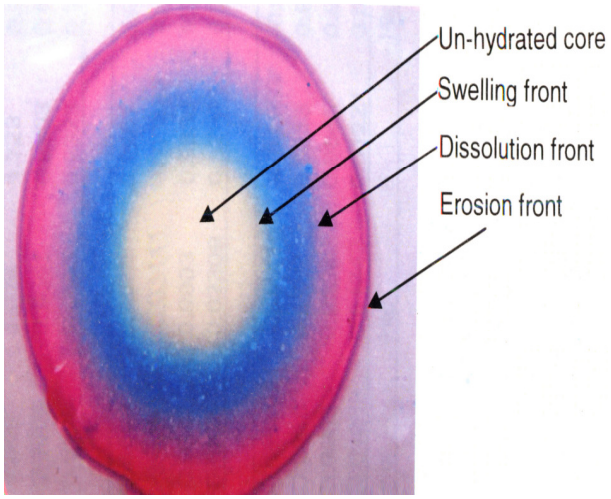

Figure 1: Hydrophilic matrix containing drug after hydration for 8 hours in cobalt (II) thiocynate solution. The white region is the unhydrated core, blue region is the hydrated region-containing drug and pink region is the drug free hydrated polymer

RESULT AND DISCUSSION

Selection of Target Release Profile

The primary aim of the project was to develop a generic equivalent which has release profile in range as specified in USP(2004). Hereby physical properties of the tablets of all batches were found satisfactory but the parent drug release and dissolution profile were not satisfactory in batch C01 to C16 except C07 that having $f_2$value 65.65 that achieved by comparing with USP specified release datas as shown in following figure 24 and table 10. So we concluded that C07 is optimized batch formula.

Table-IA : Tablet Weight and Composition of Prototype Formulation Prepared (C01-08)

S.NO.	*Ingredients*	*B. No. C01 (%w/w)*	*B. No. C02 (%w/w)*	*B. No. C03 (%w/w)*	*B. No. C04 (%w/w)*	*B. No. C05 (%w/w)*	*B. No. C06 (%w/w)*	*B. No. C07 (%w/w)*	*B. No. C08 (%w/w)*
1.	Cbz	66.66	66.66	66.66	66.66	66.66	66.66	66.66	66.66
2.	$HM1^1$	14.66	-	-	23.33	7.33	7.33	7.33	13.93
3.	$HM1^2$	-	14.66	-	-	-	-	-	-
4.	$HM1^3$	-	-	14.66	-	-	-	7.33	-
5.	HM2	-	-	-	-	7.33	-	-	-
6.	HM3	-	-	-	-	-	7.33	-	-
7.	D_1	16.66	16.66	16.66	8.00	16.66	16.66	16.66	16.66
8.	MS	1	1	1	1	1	1	1	1
9.	CSD	1	1	1	1	1	1	1	1
10.	ISM	-	-	-	-	-	-	-	0.73
11.	D_2	-	-	-	-	-	-	-	-
12.	PVP	-	-	-	-	-	-	-	-
13.	SLS	-	-	-	-	-	-	-	-
14.	$HM1^0$	-	-	-	-	-	-	-	-
15.	Tablet Wt.	300	300	300	300	300	300	300	300

Cbz- Carbamazepine,**MS-** Magnesium stearate,**CSD**-Colloidal silicone dioxide,**HM-**Hydrophilic matrix former **ISM**-Insoluble matrix former **$HM1^0$** – Hydroxyl Propyl Methyl Cellulose K100LV,**$HM1^1$** - Hydroxyl Propyl Methyl Cellulose K4M **$HM1^2$** - Hydroxyl Propyl Methyl Cellulose K15M,**$HM1^3$** - Hydroxyl Propyl Methyl Cellulose K100M, **D_1, D_2-**Different diluents

Table I B: Tablet Weight and Composition of Prototype Formulation Prepared (C09-16)

S.NO.	Ingredients	B. No. C09 (% w/w)	B. No. C10 (% w/w)	B. No. C11 (% w/w)	B. No. C12 (% w/w)	B. No. C13 (% w/w)	B. No. C14 (% w/w)	B. No. C15 (% w/w)	B. No. C16 (% w/w)
1.	Cbz	66.66	66.66	66.66	66.66	66.66	65.35	72.20	72.20
2.	$HM1^1$	13.2	31.33	23.33	14.66	14.66	22.87	-	-
3.	$HM1^2$	-	-	-	-	-	-	-	-
4.	$HM1^3$	-	-	-	-	-	-	-	-
5.	HM2	-	-	-	-	-	-	-	-
6.	HM3	-	-	-	-	-	-	-	-
7.	D_1	16.66	-	-	-	15.66	6.53	-	-
8.	MS	1	1	1	1	1	1	1	1
9.	CSD	1	1	1	1	1	1	1	1
10.	ISM	1.466	-	-	-	-	-	-	-
11.	D_2	-	-	8.00	16.66	-	-	-	-
12.	PVP	-	-	-	-	-	3.26	-	-
13.	SLS	-	-	-	-	-	-	-	1
14.	$HM1^0$	-	-	-	-	-	-	25.79	24.79
15.	Tablet Wt.	300	300	300	300	300	300	270	270

Cbz- Carbamazepine,**MS-** Magnessium stearate,**CSD**-Colloidal silicone dioxide,**HM-**Hydrophilic matrix former **ISM**-Insoluble matrix former, **$HM1^0$** – Hydroxyl Propyl Methyl Cellulose K100LV, **$HM1^1$** - Hydroxyl Propyl Methyl Cellulose K4M **$HM1^2$**- HydroxylPropyl Methyl Cellulose K15M,**$HM1^3$**-HydroxylPropyl Methyl Cellulose K100M,**D_1,D_2-**Differentdiluent

Table II: showing limit and observed value for the % drug release

Sr. No.	Time (hours)	Limit (% drug release)	Observed value	F_2 value
1	3	10-35	32.2	65.65
2	6	35-65	58.43	
3	12	65-90	85.5	
4	24	NLT 75	95.6	

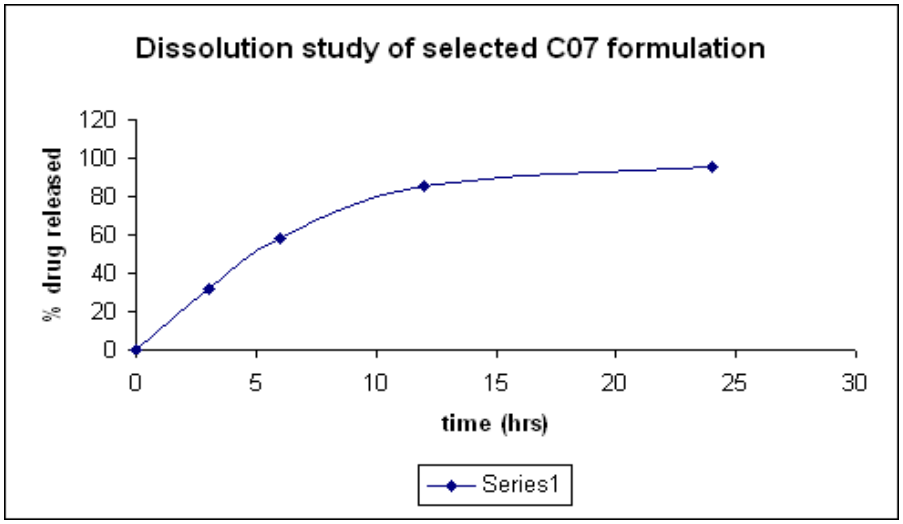

Figure 2: Dissolution study of selected formulation

Formulation development

Evaluation of tablet formulation (Physical characteristics of fabricated tablets)

The tablet is evaluated for the following parameters as given below in table.

1. Weight variation test was conducted as per specifications.
2. Thickness and length using a vernier caliper.
3. Hardness test was performed using a Monsanto hardness tester.
4. Friability test was performed using a Roche friability testing machine.
5. Drug content (Assay) by HPLC and UV spectroscopic method.

Table III: Weight variation test of uncoated sustained release Carbamazepine matrix tablets

Sr. no	Theoretical weight(mg)	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness(kp)
1	300	305	4.70	9.38	8.7
2	300	302	4.60	9.38	7.1
3	300	305	**4.45**	9.42	7.7
4	300	310	4.60	9.38	7.2
5	300	302	4.72	9.39	7.3
6	300	301	4.72	9.38	7.8
7	300	302	**4.60**	9.38	9.1
8	300	304	4.62	9.39	8.6
9	300	**302**	4.67	9.39	8.2
10	300	301	4.60	9.38	**9.1**
11	300	304	4.67	**9.38**	8.2
12	300	303	4.76	9.39	9.5
13	300	299	4.63	9.39	8.8
14	300	**302**	4.65	9.39	7.5
15	277	285	4.67	8.12	8.3
16	277	279	4.73	8.08.	8.2

Drug –Excipient compatibility studies

The interaction was verified and found carbamazepine did not interact with excipient used. From the FTIR spectra shown in figures below.It was found that carbamazepine was compatible with excipients used.

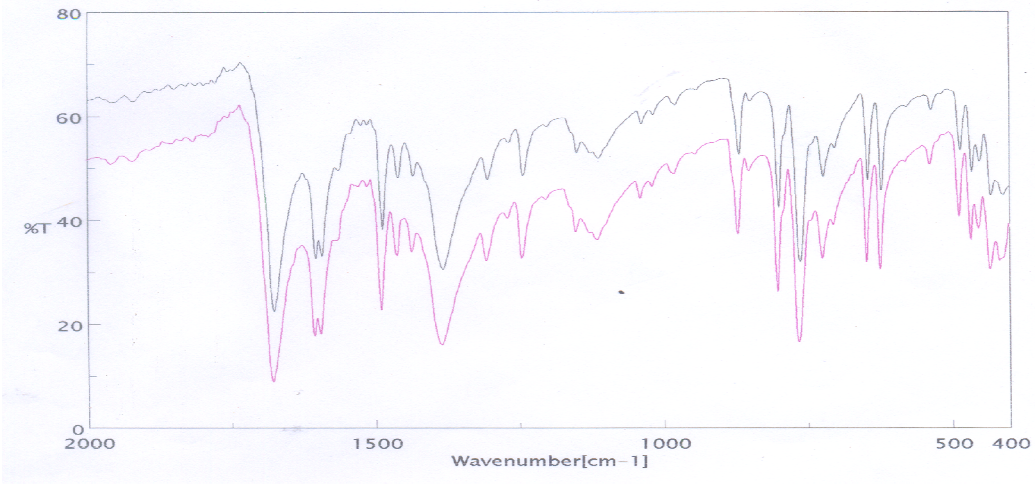

Figure 3: IR Spectrum of Carbamazepine drug and Standard Carbamazepine drug

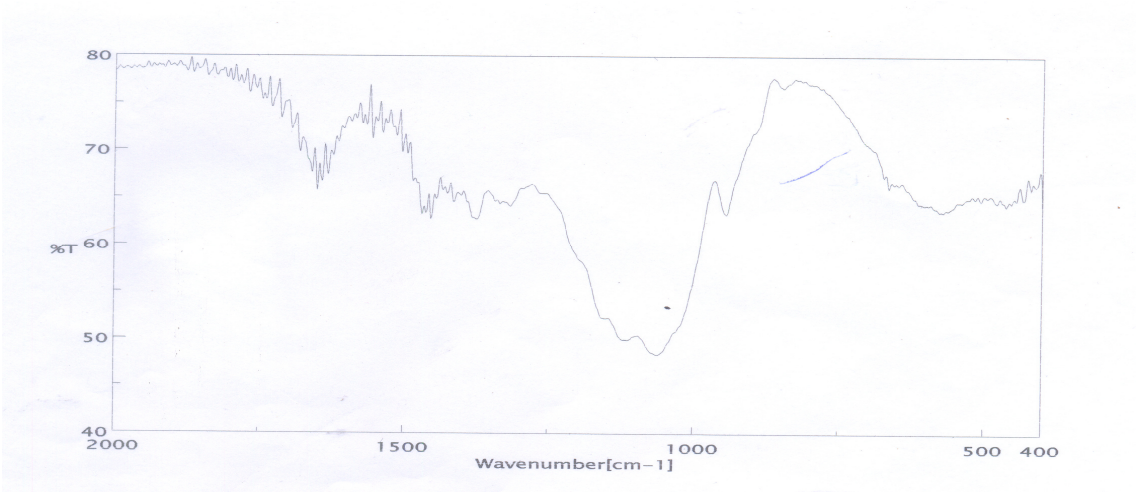

Figure 4: IR Spectrum of HPMC (Hydroxy Propyl methyl Cellulose)

Figure 5: IR Spectrum of Carbamazepine, HPMC, Carbamazepine + HPMC

Release kinetics

Dissolution data of each formulation was fitted to various models using the equations mentioned in section. By regression analysis of curves, slopes, intercepts, correlation coefficient ® and standardized residuals were calculated. The data are summarized in table IV. In cases where the correlation coefficients were high for more than one model best fit model was selected based on minimum value for standardized residuals.

Table IV: Kinetical study of dissolution datas of various formulations

Zero Order Table

Zero Order	C01	C02	C03	C04	C05	C06	C07	C08
Slope	0.374	0.031	0.309	0.032	0.508	0.055	0.159	0.045
y-intercept	0.108	0.073	0.057	0.070	0.522	0.036	0.001	0.080
r^2	0.769	0.822	0.850	0.834	0.889	0.964	0.973	0.843
Sy.x	0.11	0.695	0.587	0.067	0.074	0.037	0.029	0.090
Zero Order	**C09**	**C10**	**C11**	**C12**	**C13**	**C14**	**C15**	**C16**
Slope	0.049	0.019	0.023	0.044	0.036	0.077	0.049	0.046
y-intercept	0.072	0.046	0.047	0.085	0.099	0.055	0.050	0.074
r^2	0.870	0.828	0.858	0.791	0.782	0.785	0.934	0.882
Sy.x	0.082	0.041	0.043	0.106	0.100	0.048	0.049	0.071

First Order Table

Zero Order	C01	C02	C03	C04	C05	C06	C07	C08
Slope	0.027	0.034	0.038	0.036	0.042	0.069	0.035	0.034
y-intercept	1.772	1.627	1.527	1.596	1.533	1.469	1.588	1.653
r^2	0.560	0.930	0.919	0.916	0.869	0.987	0.879	0.851
Sy.x	0.049	0.035	0.044	0.042	0.074	0.024	0.055	0.065
Zero Order	**C09**	**C10**	**C11**	**C12**	**C13**	**C14**	**C15**	**C16**
Slope	0.038	0.045	0.045	0.028	0.026	0.035	0.057	0.043
y-intercept	1.624	1.647	1.481	1.679	1.730	1.523	1.543	1.639
r^2	0.866	0.996	0.994	0.799	0.834	0.989	0.979	0.937
Sy.x	0.065	0.007	0.010	0.073	0.055	0.011	0.027	0.041

Higuchi Table

Zero Order	C01	C02	C03	C04	C05	C06	C07	C08
Slope	0.184	0.137	0.130	0.145	0.207	0.166	0.036	0.206
y-intercept	0.458	0.005	-0.002	0.009	-0.028	-0.083	0.069	0.003
r^2	0.946	0.956	0.968	0.972	0.986	0.960	0.843	0.981
Sy.x	0.053	0.034	0.027	0.027	0.039	0.039	0.071	0.031
Zero Order	**C09**	**C10**	**C11**	**C12**	**C13**	**C14**	**C15**	**C16**
Slope	0.215	0.079	0.094	0.194	0.176	0.081	0.168	0.190
y-intercept	0.001	0.008	-0.005	-0.004	0.014	0.008	-0.047	-0.001
r^2	0.992	0.939	0.951	0.985	0.951	0.930	0.969	0.983
Sy.x	0.022	0.024	0.025	0.047	0.047	0.027	0.034	0.026

Hixson Table

Zero Order	C01	C02	C03	C04	C05	C06	C07	C08
Slope	0.017	-0.046	-0.045	-0.047	-0.058	-0.056	-0.049	-0.058
y-intercept	0.300	0.315	0.321	0.319	0.320	0.332	0.317	0.312
r^2	0.037	0.090	0.100	0.085	0.034	0.049	0.075	0.030
Sy.x	0.262	0.274	0.280	0.277	0.279	0.289	0.276	0.272
Zero Order	**C09**	**C10**	**C11**	**C12**	**C13**	**C14**	**C15**	**C16**
Slope	-0.058	-0.038	-0.040	-0.055	-0.057	-0.037	-0.054	-0.054
y-intercept	0.314	0.327	0.326	0.304	0.303	0.323	0.326	0.316
r^2	0.030	0.146	0.130	0.035	0.050	0.15	0.054	0.069
Sy.x	0.272	0.284	0.284	0.266	0.264	0.281	0.284	0.274

Stability studies

Drug release studies of final formulation C07 were conducted as per the planned scheduled as above.

1. Storage condition at $40^0C \pm 2^0C$ / 75% ± 5%RH:

Table V(1): comparison of color of stability samples at accelerated condition

Test	Observation	Inference
Description (color change)	No changed of color	Complies with the stability condition

Result : Best fit Model

C01	Higuchi
C02	Higuchi
C03	Higuchi
C04	Higuchi
C05	Higuchi
C06	First
C07	Zero
C08	Higuchi
C09	Higuchi
C10	First
C11	First
C12	Higuchi
C13	Higuchi
C14	First
C15	First
C16	Higuchi

Table V (2): comparison of dissolution data of stability samples at accelerated condition.

Time (Hr)	Initial (0 days)	15 days (UV)	30 days (UV)	90 days (UV
0.5	10.28	10.26	10.24	10.25
1	15.26	14.28	14.23	14.18
2	24.55	25.55	25.5	26.5
3	32.2	31.3	31.2	31.45
4	41.2	40.2	41.2	40.5
5	48.95	48.65	48.85	48.23
6	58.43	58.45	59.65	59.62
8	70.8	70.5	70.32	69.95
12	85.5	88.5	88.4	88.23
24	95.6	97.8	96.9	97.4

2) Room Temperature (25^{0}C ± 2^{0}C / 60% RH ± 5%):

TableVI (1): comparison of color of stability samples at accelerated condition

Test	Observation	Inference
Description (color change)	No changed of color	Complies with the stability condition

Table VI (2): comparison of dissolution data of stability samples at Room temperature

Time (Hr)	Initial (0 days)	15 days (UV)	30 days (UV)	90 days (UV)
0.5	10.25	10.23	10.25	10.26
1	15.23	14.25	14.22	14.15
2	24.52	25.52	25.51	26.54
3	32.21	31.35	31.23	31.44
4	41.22	40.24	41.21	40.51
5	48.93	48.62	48.83	48.25
6	58.45	58.42	59.62	57.45
8	70.82	70.53	70.33	70.12
12	85.53	88.51	88.42	85.10
24	96.7	97.47	96.23	96.15

SUMMARY & CONCLUSION

In present work attempts have been made to formulate sustained release matrix tablet of Carbamazepine by using hydrophilic polymer, which is preferably used as an anticonvulsant agent in various types of seizures. Matrix tablets were prepared using different polymers, by direct compression technique. Carbamazepine meets all the ideal characteristics to formulate in the form of sustained release drug delivery system. Under Preformulation study, the organoleptic properties were complied with the USP specification. The compatibility evaluations were performed by FTIR spectroscopy. Both studies imply that the drug and polymers are compatible with each other. There ware no interaction found between polymers and drugs.The final formulations were evaluated on the basis of pharmacopoeial specification. Shapes of the tablets were rounding biconcave. The physical parameters like diameter and thickness, hardness, friability and weight variation is carried out.

Assay were carried out for finally selected formulation and the result were found to be 100.91% (by HPLC) and 98.6% (by UV)

Stability studies were carried out by keeping the tablets at room temperature (25^0 C ± 2^0C / 60% ± 5% RH) and at accelerated temperature (40^0 C ± 2^0C / 75% ± 5% RH) in Stability chamber for 90 days. The result of stability studies conducted on C07 reveled no change in physical appearance and in-vitro dissolution profiles, hence C07 formulation was found to be stable at tested temperature. The mechanism of drug release from hydrophilic matrix tablet is governed by

anomalous release and erosion of the swollen matrix due to less solubility of the drug. In all formulation C01 to C16 except C07 that % drug release is out of the specified range in USP. In the present study attempts were made to formulate 200mg sustained release once daily formulation which can provide effective drug release for 24 hours.

SR matrix tablets of Carbamazepine were prepared by direct compression. In vitro study showed formulation C07 were well suited to be extended release formulation.

Final selected formulation gives release profile in range as specified in USP and drug release governed by anomalous release and erosion of the swollen matrix.

From the results obtained, it can be concluded that formulation C07 has achieved the objective of sustained drug release, patient convenience and cost effectiveness as a single daily dose of the drug and appears to be assessed further by conducting bioavailability studies in human volunteers and long term stability testing.

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