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Research Article

FORMULATION AND EVALUATION OF CARBAMAZEPINE SUSTAINED RELEASE ORAL MATRIX TABLETS

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ABSTRACT

Sustained release drug delivery systems proved to be consistent for delivering doses of drugs to treat acute diseases or chronic illness. The present study relates to the formulation and evaluation of carbamazepine sustained release oral matrix tablets for the treatment of trigeminal neuralgia. Ten formulations (f1-f10) of Carbamazepine were prepared with various types of polymers (HPMC, Eudragit RSPO) in varying ratios to formulate the sustained release matrix tablets. Avicel 102 was used as a diluent in the preparation of the tablets. Magnesium stearate (1% w/w) was added in the formulation as a lubricant. The tablet weight was adjusted so as to contain 200 mg of drug in each tablet. Standard curve of Carbamazepine was prepared at λmax 285.4 nm and the regression value was found to be 0.999. The tablets of various formulations of Carbamazepine were prepared and the tablet hardness was found to be in range of 6.5 to 7.3 Kp.The average weight of the prepared tablets of various formulations was found to be within the USP limit i.e. ± 5%. The average percentage (%) drug content was also found within the USP limit and shows the effectiveness of the mixing procedure.From the in vitro studies, it was observed that with increasing the concentration of Eudragit RSPO, the rate and extent of drug release from the tablet decreases.From in vitro studies, it was also observed that with increasing the concentration of HPMC E50LV the rate and extent of drug release form the tablets not much more effect. B8 the best formulations as the extent of drug release was found to be around 101.10 % at the desired time 24 hrs. This batch *invitro* dissolution profile readings also matched with the USP results. The 'n' value for B8 was found to be 0.735 which is indicates that the release approximates non-fickian diffusion mechanism.

Keywords: Carbamazepine, Trigeminal neuralgia, Eudragit RSPO, HPMC,Matrix tablets.

INTRODUCTION

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, Pharmacokinetics,Pharmacodynamics and Formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.

Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration and the belief that oral administration of the drug is well absorbed[1].

Modified release delivery system may be divided conveniently into four categories.

A) Delayed release.
B) Sustained release.
   i) Controlled release.
   ii) Extended release.
C) Site specific targeting Drug Delivery.
D) Receptor targeting Drug Delivery.

POTENTIAL ADVANTAGES OF SUSTAINED AND CONTROLLED DRUGTHERAPY

All controlled release products share the common goal of improving drug therapy over that achieved with their non-controlled counter parts. This improvement in drug therapy is represented by several potential advantages of the use of controlled release systems are

A) Avoid patient compliance problems.
B) Employ less total drug.
   i. Minimize or eliminates local side effects.
   ii. Minimize of eliminates systemic side effects.
   iii. Obtain less potentiation or reduction in drug activity with chronic use.
   iv. Minimizing drug accumulation with chronic dosing.
C) Improves efficiency in treatment.
   i. Cure on control condition seems to be more promptly.
   ii. Improve control of condition i.e reduce fluctuation in drug level.
   iii. Improve bioavailability of some drugs.
   iv. Make use of special effects e.g. sustained release aspirin for morning relief of arthritis by dosing before bedtime.

Oral Sustained and Controlled Release System[5]

Total 5 types of oral controlled release systems are available.

- Dissolution controlled release system.
- Diffusion controlled system.
- Bioerodible and combination diffusion and dissolution system.
- Osmotically controlled release system.
- Ion exchange systems.

Matrix devices

Matrix devices consist of drug dispersed homogeneously throughout a polymer matrix, in the model, drug in the outside layer exposed to the bathing solution when it is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. For this system rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of the dissolved drug leaving the matrix.

Advantages of matrix diffusion system

i) Easier to produce that reservoir devices.
ii) Can deliver high molecular weight compounds

Disadvantages of matrix diffusion system

i) Cannot obtain zero order release.
ii) Removal of remaining matrix is necessary for implanted system.

MATERIALS AND METHODS

Carbamazepine was gifted from Matrix Laboratories Hyderabad. Eudragit RSPO was obtained as gift sample from Evonik Industries. HPMC E 50 LV was taken from Colorcon Asia Pvt Ltd. Avicel and Magnesium Stearate was procured fromLoba Chemicals Mumbai.

Table1: Formula for Carbamazepine Sustained Release Tablets of Different Bathes

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Carbamazepine	200	200	200	200	200	200	200	200	200	200
EudragitRSPO	176	0	180	98	78	58	38	18	138	158
HPMC E50LV	0	176	58	78	98	118	138	158	38	18
Avicel102	20	20	20	20	20	20	20	20	20	20
Mg Stearate	4	4	4	4	4	4	4	4	4	4
Total	400	400	400	400	400	400	400	400	400	400

All quantities are in 400 mg

IDENTIFICATION OF DRUG (CARBAMAZEPINE) SAMPLE

It was confirmed by

- FT-IR spectral analysis.
- UV absorption maxima.

FTIR Spectra

IR spectra of drug in KBr pellets at moderate scanning speed between 4000-400 cm^{-1} was carried out using FTIR (SHIMADZU). The peak values (wave number) and the possibility of functional group shown in spectra which compare with standard value. The comparison of these results with Carbamazepine chemical structure shows that the sample was pure Carbamazepine.

UV absorption maxima of Carbamazepine

Carbamazepine (100mg)was accurately weighed and transferred into the 100 ml volumetric flask. It was dissolved in 3ml of Methanol and volume was made up to the mark with Distilled water to get a 1000 mcg/ml solution. 10 ml of the above solution was then further diluted to 100 ml with distilled water to get a stock solution of 100 mcg/ml, and again pipette out 10ml of this solution in to a 100ml volumetric flask, and made up the volume with distilled water to get a stock solution of 10 mcg/ml, and the solution were scaned in the wavelength range of 200-400nm. The wavelength was selected at 285.4 nm

PREFORMULATION STUDY[5, 34]

Preformulation studies are usually the first quantitative assessment of chemical stability of a drug as well as stability in presence of other excipients. The primary objectives of this investigation are identification of stable storage conditions for drug in the solid state and identification of compatible excipients for a formulation. Preformulation studies were performed on the drug, which include melting point determination, solubility and compatibility studies.

A)DETERMINATION OF MELTING POINT

Melting point of Carbamazepine was found in the range of 190- 192^{0}c, which complied with the standard, indicating purity of the drug sample.

B)SOLUBILITY

Carbamazepine is found to insoluble in water, soluble in methanol and ethanol.

C) DRUG-EXCIPENTS COMPATIBILITY STUDY

Compatibility of the drug with recipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after combined it with the recipients. The samples were taken for FT-IR study. All these spectrums are shown in Fig. 9 - 13

PREPARATION OF MATRIX TABLETS BY DIRECT COMPRESSION METHOD [36]

Carbamazepine drug was used with various types of polymers (HPMC, Eudragit RSPO) in varying ratios to formulate the sustained release matrix tablets. Avicel 102 was used as a diluent in the preparation of the tablets. Magnesium stearate (1% w/w) was added in the formulation as a lubricant. The tablet weight (404 mg) was adjusted so as to contain 200 mg of Candidate drug in each tablet.

PROCEDURE

The Carbamazepine sustained release matrix tablets were prepared by passing drug, Polymers, Avicel 102 through a #30 mesh sieve.

Finally add Magnesium stearate by passing through the #60 mesh sieve.

The blend was compressed in a Cadmach tablet compressing machine fitted with concave punches (14.5 mm × 4.5 mm).

Finally the tablet weight was adjusted to 400mg.

RESULTS AND DISCUSSION

Table 2:Standard Curve of Carbamazepine in Water at 285.4 nm

S.NO	CONCENTRATION (µg/ml)	ABSORBANCE (285.4 nm)
1	0	0.000
2	5	0.107
3	10	0.212
4	15	0.439
5	20	0.649
6	25	0.860
7	30	1.090

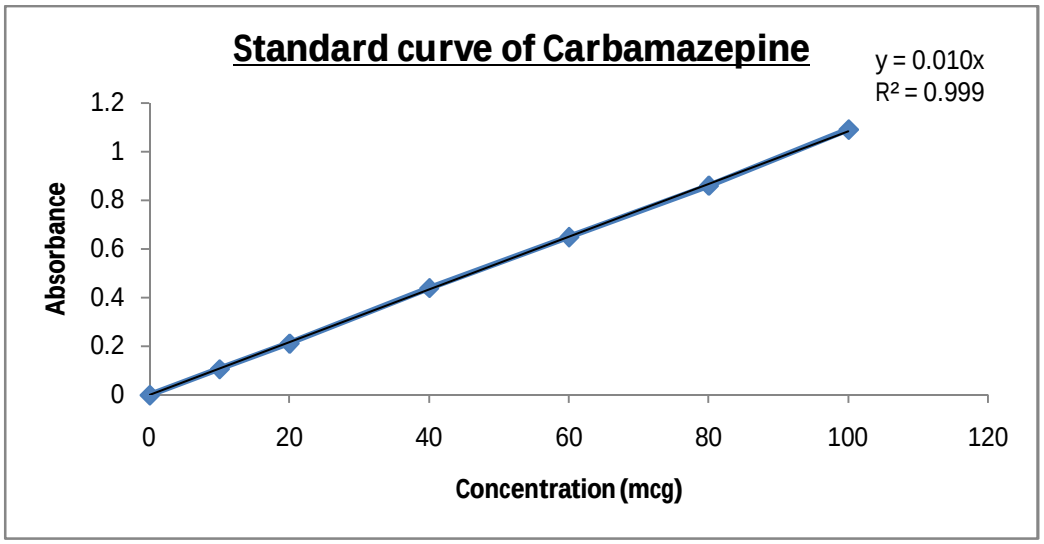

Fig. 1: Standard curve of Carbamazepine

Table 3: Physical Observation of Compatibility Study

Drug & Excipients (Ratio 1:1)	Observation			Results
	Room Temp	40⁰C/75% RH after 30 days	2-8⁰C after 30 days	
Carbamazepine	White to off white powder	White to off white powder	White to off white powder	Compatible
Carbamazepine + Eudragit RSPO	White to off white powder	White to off white powder	White to off white powder	Compatible
Carbamazepine + HPMC E50LV	White to off white powder	White to off white powder	White to off white powder	Compatible
Carbamazepine + Avicel 102	White to off white powder	White to off white powder	White to off white powder	Compatible
Carbamazepine + Mg Stearate	White to off white powder	White to off white powder	White to off white powder	Compatible

Table 4:Characterization of Trial Blends

F.No	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose
F1	0.560	0.608	8	1.08	33⁰
F2	0.608	0.700	13	1.15	32⁰
F3	0.630	0.700	9.09	1.10	29⁰
F4	0.583	0.700	16.66	1.20	28⁰
F5	0.625	0.681	8.33	1.09	27⁰
F6	0.652	0.750	13.04	1.15	32⁰
F7	0.638	0.714	10.63	1.11	25⁰
F8	**0.681**	**0.750**	**9.09**	**1.10**	**34⁰**
F9	0.714	0.789	9.50	1.10	30⁰
F10	0.681	0.750	9.20	1.10	28⁰

Table 5:Physical Parameters of Tablets of Each Batch

B.NO	Weight Variation (mg)	Thickness (mm)	Hardness (kp)	Friability (%)	Assay (%)
F1	400.67 ± 1.53	5.24 ± 0.02	6.67 ± 0.12	0.06	99.49
F2	401.33 ± 0.58	5.20 ± 0.01	6.73 ± 0.31	0.04	101.24
F3	401.33 ± 1.53	5.24 ± 0.01	6.93 ± 0.21	0.03	100.32
F4	402.67 ± 1.53	5.23 ± 0.02	6.50 ± 0.50	0.09	100.87
F5	401.00 ± 2.65	5.20 ± 0.02	7.03 ± 0.35	0.02	98.87
F6	401.00 ± 2.00	5.23 ± 0.01	7.33 ± 0.21	0.04	100.05
F7	400.67 ± 1.53	5.20 ± 0.02	7.10 ± 0.20	0.03	98.99
F8	**403.00 ± 2.00**	**5.17 ± 0.02**	**6.80 ± 0.44**	**0.08**	**100.64**
F9	401.33 ± 2.08	5.14 ± 0.01	6.50 ± 0.17	0.06	99.45
F10	399.00 ± 2.00	5.16 ± 0.01	6.50 ± 0.17	0.05	98.56

***Each value represents the mean ± standard deviation (n = 3)**

Table 6:dissolution profile of batch no. F1 to F10

F.NO	Time in Hours (Cumulative % Drug Release)				
	1	**3**	**6**	**12**	**24**
F1	2.94	5.88	9.77	27.12	34.2
F2	5.88	19.55	30.16	88.58	100.2
F3	3.89	9.57	14.4	22.9	38.9
F4	3.64	11.27	18.23	27.46	52.64
F5	3.79	10.62	19.45	29.75	79.38
F6	4.85	18.54	33.67	53.72	86.38
F7	6.62	22.08	38.48	61.51	100.0
F8	**9.46**	**31.44**	**48.05**	**73.18**	**101.1**
F9	3.87	8.46	13.65	26.66	37.22
F10	3.34	7.45	11.76	24.43	35.94

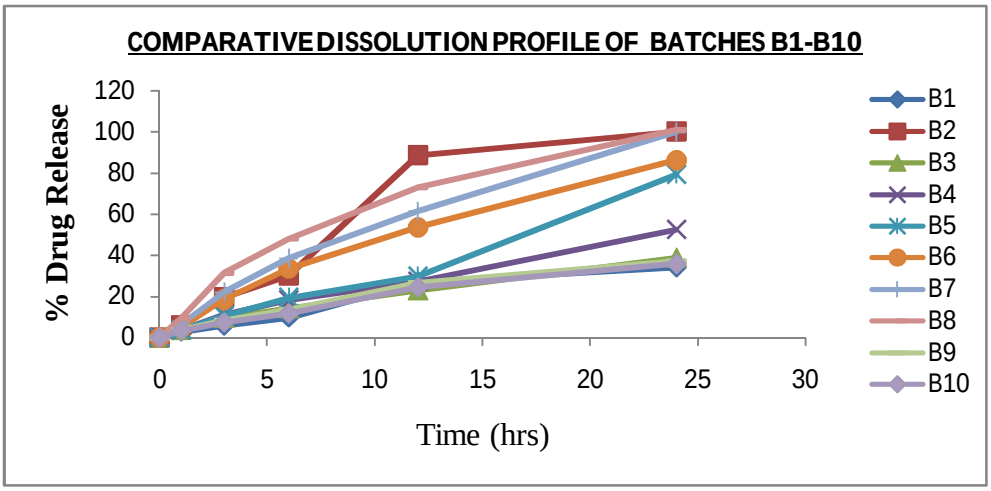

Fig. 2: Comparative Dissolution Profile of Formulations F1-F10

Table 7:Kinetic values obtained from invitro released data of formulation F1-F10

Batch	Zero order release		First order release		Higuchi		Peppas model		Hixson crowell	
	K	**r**	**k**	**R**	**K**	**R**	**n**	**R**	**k**	**r**
F1	1.482	0.927	-0.511	0.923	7.66	0.924	0.824	0.968	-0.494	0.927
F2	4.451	0.884	-0.742	0.801	23.32	0.905	0.933	0.968	-1.483	0.884
F3	1.548	0.979	-0.503	0.532	7.98	0.973	0.710	0.997	-0.516	0.979
F4	2.108	0.987	-0.512	0.561	10.71	0.951	0.812	0.989	-0.702	0.987
F5	3.189	0.981	-0.517	0.573	15.49	0.864	0.917	0.987	-1.063	0.981
F6	3.553	0.971	-0.572	0.736	18.38	0.971	0.895	0.978	-1.184	0.971
F7	4.085	0.974	-0.593	0.795	21.12	0.972	0.844	0.985	-1.361	0.974
F8	**4.061**	**0.919**	**-0.635**	**0.891**	**21.79**	**0.988**	**0.735**	**0.965**	**-1.353**	**0.919**
F9	1.537	0.954	-0.509	0.546	8.02	0.971	0.732	0.994	-0.512	0.954
F10	1.490	0.969	-0.506	0.534	7.68	0.961	0.765	0.993	-0.497	0.969

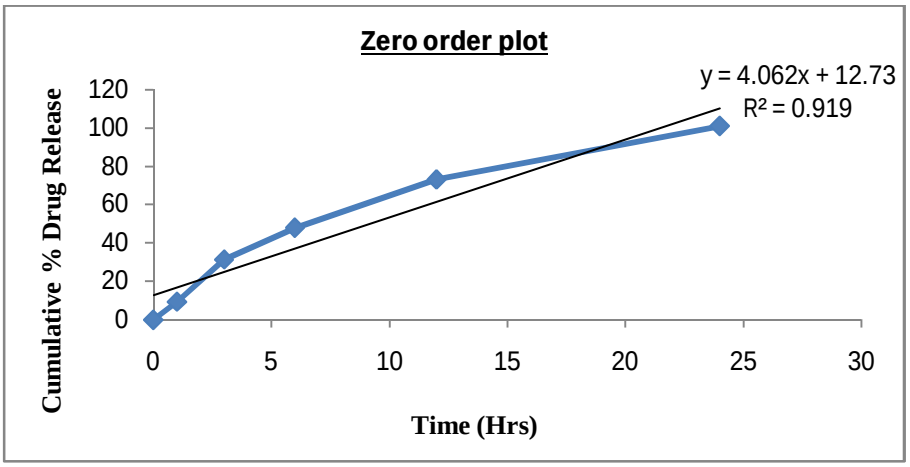

Fig.3:Cumulative % Drug Release V/S Time for Formulation (B8) Of Carbamazepine (Zero Order Release)

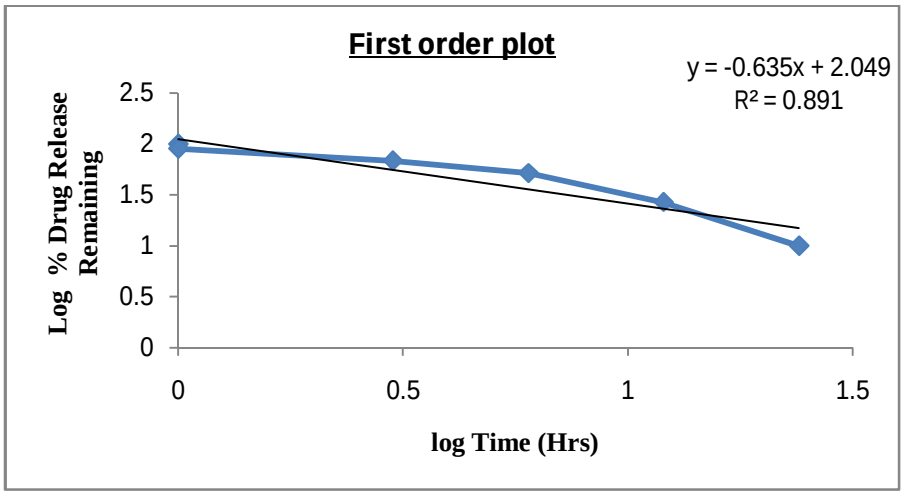

Fig. 4:Log % Drug Release Remaining V/S Log Time for Formulation (B8) of Carbamazepine (First Order Plot)

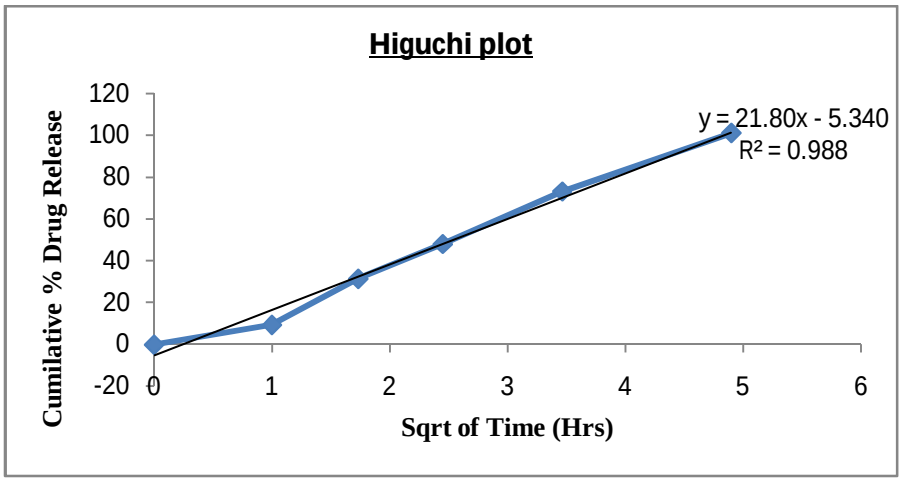

Fig. 5:Cumulative % Drug Release V/S Sqrt of Time for Formulation (B8) of Carbamazepine (Higuchi plot)

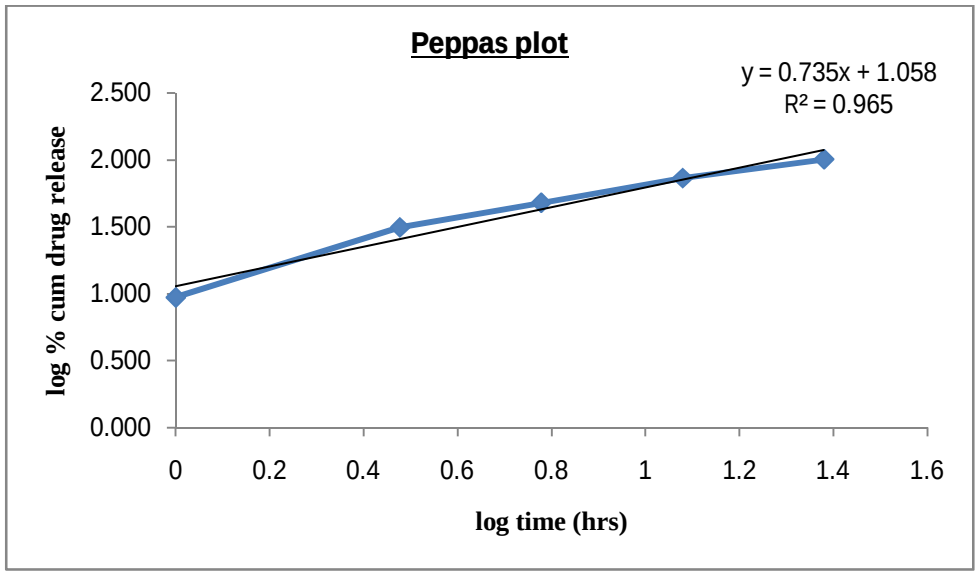

Fig.6:Log cum % Drug Release V/S Log Time for Formulation (B8) of Carbamazepine (Peppas Plot)

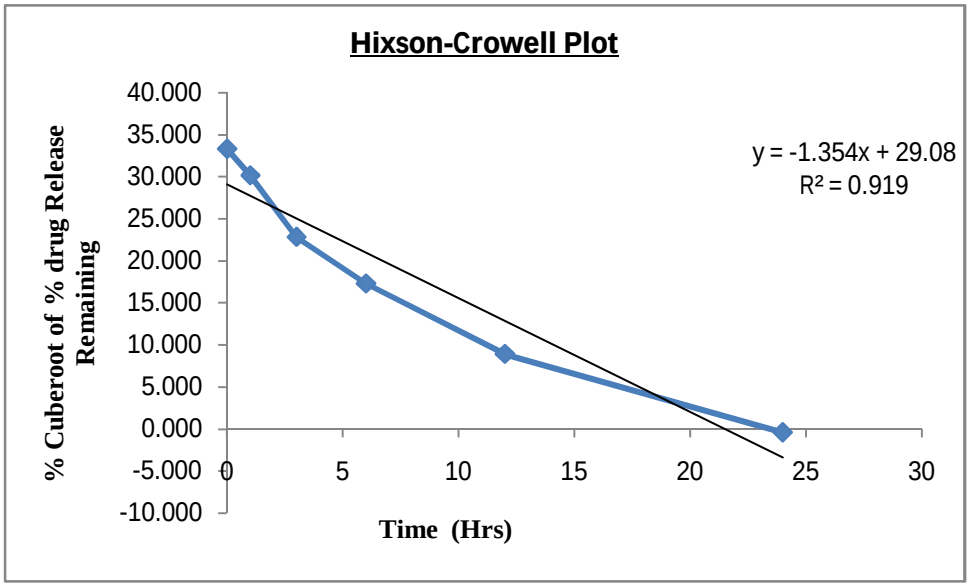

Fig. 7:% Cube Root of % Drug Release Remaining V/S Time for Formulation (B8) of Carbamazepine (Hixson-Crowell Plot)

STABILITY STUDIES

Sustained release matrix tablets of Carbamazepine formulated in the present study were subjected to accelerated stability studies. Stability studies of the prepared formulations were performed at ambient humidity conditions, at room temperature, at 40^{o}c ± 2^{o}C 75% RH and 2-8^{o}c for a period up to 30 days. The samples were withdrawn after periods of 15 days, and 30 days and were analyzed for its appearance, hardness, friability, drug content and in vitro drug release. The results obtained were shown in Table No 8 to 10 The results revealed that no significant changes in appearance, drug content, hardness, friability, and in vitro release for B8 formulation.

Table8:Formulation B8 Stored at Temperature (40^{0}C ± 2^{0}C & 75% RH)

Formulation	Tested after time (days)	Hardness Kp	Friability (%)	Drug content (%)	Cum % Drug Released
F8	15	6.8	0.08	99.92	100.65
F8	30	6.6	0.06	99.22	99.84

Table9:Formulation B8 Stored at Temperature (2-8^{0}C)

Formulation	Tested after time (days)	Hardness Kp	Friability (%)	Drug content (%)	Cum % Drug Released
F8	15	6.6	0.07	100.42	101.77
F8	30	6.6	0.09	99.62	99.84

Table 10:Formulation B8 Stored at Temperature (26^{0}C ± 2^{0}C & 75% RH)

Formulation	Tested after time (days)	Hardness Kp	Friability (%)	Drug content (%)	Cum % Drug Released
F8	15	6.8	0.06	98.92	97.65
F8	30	7.0	0.07	97.22	98.57

SUMMARY AND CONCLUSION

Oral dose of Carbamazepine is 200-1200 mg, hence it is required to be taken 200 mg three times a day. U.V. Scanning of Carbamazepine was performed and the λmax at 285.4 was found to be the most appropriate for the determination of concentration of unknown samples. Standard curve of Carbamazepine was prepared at λmax 285.4 nm and the regression value was found to be 0.999. The tablets of various formulations of Carbamazepine were prepared and the tablet hardness was found to be in range of 6.5 to 7.3 Kp.The average weight of the prepared tablets of various formulations was found to be within the USP limit i.e. ± 5% (for tablet weight approx. 404 mg). The average percentage (%) drug content was also found within the USP limit and shows the effectiveness of the mixing procedure.

From the in vitro studies, it was observed that with increasing the concentration of Eudragit RSPO, the rate and extent of drug release from the tablet decreases. This was due to the fact that Eudragit RSPO is an insoluble polymer and showed low permeability and pH independent swelling.From in vitro studies, it was also observed that with increasing the concentration of HPMC E50LV the rate and extent of drug release form the tablets not much more effect. This is because HPMC E50LV is a low viscosity polymer.

Swelling study was not performed because drug release was due to erosion and it mainly depends on the Eudragit RSPO but not on HPMC E50LV.IR studies of the prepared matrix tablets and the drug - excipients compatibility showed that no polymorphic changes occurred during manufacturing of tablets as all the peaks were present in the IR graph of tablet sample. Stability studies at room temperature, 40^{0}C, and 2-8^{0}C for one month, indicate that even at extreme conditions, no change in the physical appearance of the mixtures and the tablets was found. The decrease in percentage drug contents of the different formulation was found to be < 1.0%.

From the results obtained, it was concluded that the formulation B8 is the best formulations as the extent of drug release was found to be around 101.10 % at the desired time 24 hrs. This batch invitro dissolution profile readings also matched with the USP results. The 'n' value for B8 was found to be 0.735 which is indicates that the release approximates non-fickian diffusion mechanism.From the above results and discussion it is concluded that formulation of. Sustained tablet of Carbamazepine containing Eudragit RSPO & HPMC E50LVM 1:8 ratio batch B8 can be taken as an ideal or optimized formulation of .Sustained release tablets for 24 hour release as it fulfills all the requirements as that of USP standards.

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