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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF OZCARBAZEPINE BY USING VARIOUS POLYMERS

Brahmaiah Bonthagarala*, Prasanna Kumar Desu, Sreekanth Nama, Donthiboina Sudarshan

Department of Pharmaceutics, Priyadarshini Institute of Pharmaceutical Education & Research (PIPER), 5th Mile, Pulladigunta, Kornepadu (V), Vatticherukuru (M), Guntur-522017, Andhra Pradesh, India.

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ABSTRACT

The objective of this study is to design and evaluate sustained release matrix tablets of Ozcarbazepine. The effects of various viscosity grades of Eudragit RSPO and HPMC E50LV on the release of Ozcarbazepine have been evaluated. Tablets were evaluated for physical and chemical parameters such as Hardness, Friability, Thickness, Weight variation, Drug content uniformity and *in vitro* release. All batches are complied physical and chemical parameters within the U.S.P limit. The amounts of Ozcarbazepine at different time intervals were estimated by UV Spectrophotometer method. *In vitro* release profile of Ozcarbazepine from combination of Eudragit RSPO and HPMC E50LV polymers (F8) showed that 100% of the drug was released at the end of 24 hr which is considered as optimized formulation. The tablets showed no significant change either in physical appearance or in dissolution pattern after storing at room temperature, 40° c and 75% RH and 2-8°c for three months. The drug release data fit well to Higuchi, Peppas and Korsemeyer equation. The drug release was found to diffusion and little extent by erosion.

INTRODUCTION

Ozcarbazepine is an anticonvulsant drug widely used in the treatment of simple and complex seizures, trigeminal neuralgia and bipolar affective disorder. Ozcarbazepine overdose leads to various side effects. Thus for patient compliance, improve bioavailability, minimize total drug quantity minimize accumulation on chronic use and reduce fluctuation in drug level sustained release of Ozcarbazepine is desirable [1]. Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery system because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance [2]. Drug release from hydrophilic matrices is known to be a complex interaction between dissolution, diffusion and erosion mechanism. HPMC is the first choice for formulation of hydrophilic matrix system, providing robust mechanism, choice of viscosity grades, consistent reproducible release profiles, cost effectiveness and utilization of existing conventional equipment and methods [3].Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion from dosage form is controlled by the hydration of HPMC, which forms the gel barrier through which the drug diffused [4]. Several mathematical models have been published, to elucidate the water and drug transport processes and to predict the resulting drug release kinetics [5]. The dissolution profile of some of the sustained release products available in their market are in the lower side of the U.S.P limit. So, an effort was made in this work to achieve an optimum USP limit. The aim of the work was to prepare hydrophilic matrix tablets containing Ozcarbazepine as a drug and HPMC as hydrophilic matrix to retard drug release. The above discuss suggests that the sustained release product may enhance the bioavailability and control the seizures during sleeping.

Corresponding Author

Brahmaiah Bonthagarala
Email:- brahmaiahmph@gmail.com

There are number of techniques applied in the formulation and manufacturing of sustained release dosage form. However, matrix tablet prepared by direct compression method has attracted much attention due to its technological simplicity in comparison with other controlled release systems. Direct compression method had been applied for preparation of matrix tablet that involved simple blending of all ingredients used in the formulations and then underwent direct compression. It required fewer unit operations, reduced number of personnel and reduced processing time, increased product stability and faster production rate [6]. There are three primary mechanisms by which active agents can be released from a delivery system: diffusion, degradation, and swelling followed by diffusion. The release of drug from the matrix tablet depends on the nature of polymer. HPMC K4M, HPMC K15M CR and HPMC K100LV CR are hydrophilic polymers that become hydrated, swollen and facilitates to diffuse the drug [7]. The effect of hydrophilic polymer PEG 6000 which act as a channeling agent was evaluated on the matrix tablet with combination of HPMC K4M. Here Ph independent swelling of Eudragit RSPO and Eudragit RLPO released the drug from the matrix. In the present study an attempt had been made to formulate Ozcarbazepine as sustained release matrix tablet with the addition of release retarding polymers HPMC E 50 LV, Eudragit RSPO.

MATERIALS & METHODS

Ozcarbazepine, Eudragit RSPO, HPMC E 50LV, Avicel and magnesium stearate, were obtained and used as received. All other chemicals and solvents used were of analytical grade.

Preparation of Matrix Tablets by Direct Compression Method

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

Pre formulation studies

The parameters like identification of pure drug Ozcarbazepine by IR spectra, drug excipients compatibility studies, angle of repose, bulk density, tapped density, Hausner‘s ratio, Carr’s index.

Physical evaluation of powders

The powders were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index, total porosity etc.

Bulk density

LBD (Loose Bulk Density) and TBD (Tapped Bulk Density) were determined by 2g of powder from each formula. The powder was previously lightly shaken to break any agglomerate formed and then it was placed into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to tap under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The reading of tapping was continued until no further change in volume was noted. Using the following equation LBD and TBD was calculated LBD = Weight of the powder / bulk volume of the packing. TBD = Weight of the powder / Tapped volume of the packing. The results were shown in Table 2.

Compressibility index

The compressibility index of the granules was determined by Carr’s Compressibility index [8]. The results were shown in Table 2.

Carr’s index (%) = {(TBD – LBD) X 100}/TBD

Angle of repose

The angle of repose of granules was determined by the funnel method [9]. The results were shown in Table 2.

Hausner’s Ratio

It is the frictional resistance of the drug .The ideal range should be 1.2-1.5. It is determined by the ratio of tapped density and the bulk density [10]. The results were shown in Table 2.

Formula:

Hausner’s ratio= V_i/V_t

Where, V_t is the tapped volume

V_i is the untapped volume

EVALUATION OF TABLETS

Weight Variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviates from the average weight by more than the percentage shown in Table 3 and none deviate by more than twice the percentage shown [11].

Thickness

Three tablets were randomly selected from each batch and there thickness was measured by using vernier calipers. Thickness of three tablets from each batch was measured and mean was calculated. The results were shown in Table 3.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^{2}Three tablets were randomly picked and hardness of the tablets was determined. The results were shown in Table 3.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Five tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not lose more than 1% of their weight. The results were shown in Table 3

The percentage friability was measured using the formula

$$\% F = \{1-(W_0/W)\} \times 100$$

Where,

% F = friability in percentage

W_0 = Initial weight of tablet

W = weight of tablets after revolution

Assay

Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg Ozcarbazepine. Dissolve the weighed quantity of powder into 100ml of 1 % SLS in water solution by stirring it for 1hr. Immediately analyze the drug by taking absorbance at 285.4 nm. The Assay of all Batches are shown in Table No.3

***In- Vitro* Drug Release Study**

In Vitro dissolution study was carried out using USP I (Basket) apparatus in 900mL of 1% SLS in water for 24 hours. The temperature of the dissolution medium was kept at 37± 0.5^{o}C and the basket was set at 100 rpm. 10 ml of sample solution was withdrawn at specified interval of time and filtered through 0.45 µm Whatman filters. The absorbance of the withdrawn samples was measured at λmax 285.4 nm using UV visible spectrophotometer. The concentration was determined from the standard curve of Ozcarbazepine drug prepared in water at λ max 285.4 nm. The results were shown in the Table .4

***IN-VITRO* DISSOLUTION STUDY AND KINETIC MODELLING OF DRUG**

Mechanism of drug release

Korsmeyer *et al* (1983) derived a simple relationship which described drug release from a polymeric system Equation (1). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas Model:

$$M_t / M_\infty = Kt^n \quad \ldots\ldots (1)$$

Where, M_t / M_∞ is the fraction of drug release data time t, k is the rate constant and n is the release exponent. The results were shown in the Table 5.

Stability Studies

The stability study of the formulations was carried out according to ICH guidelines at room temperature, 40°C ± 2° C and 75 % RH, 2-8°C for one month by storing the samples in stability chamber (Lab-care, Mumbai). The results were shown in the Table 6-8.

RESULTS & DISCUSSIONS

Oral dose of Ozcarbazepine is 200-1200 mg, hence it is required to be taken 200 mg three times a day. U.V. Scanning of Ozcarbazepine 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 Ozcarbazepine was prepared at λmax 285.4 nm and the regression value was found to be 0.999. The tablets of various formulations of Ozcarbazepine were prepared and the tablet hardness was found to be in range of 6.5 to7.3 Kg/cm^2. 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.

The release of Ozcarbazepine from sustained release tablet of the various formulations varied according to the ratio and degree of the different polymer. In case of tablets of F1, containing drug and Eudragit RSPO, HPMC E50LV in the ratio 1:0 the release profile, it was showing 34.20% release in 24 hours. The dissolution study was shown that Eudragit RSPO, HPMC E50 LV in 1:0 ratios more controlled the release of drug from formulation. In case of tablets of F2, containing drug and Eudragit RSPO, HPMC E50LV in the ratio 0:1 the release profile was showing 88.58% release in 12 hours. The dissolution study was shown that Eudragit RSPO, HPMC E50 LV in 0:1 ratio can also not able to control the release up to 24 hours. In case of tablets of F3, containing drug and, Eudragit RSPO, HPMC E50 LV in the ratio 2:1 the release profile was

showing only 38.9% of drug release in 24 hours with very slower release. In case of tablets of F4, containing drug and Eudragit RSPO, HPMC E50 LV in the ratio 1.25:1 the release profile was showing only 52.64% of drug release in 24 hours with very slower release. In case of tablets F5, containing drug and Eudragit RSPO, HPMC E50 LV in the ratio 1:1.25 the release profile was showing only 79.38% of drug release in 24 hours with slower release. In case of tablets F6, containing drug and Eudragit RSPO, HPMC E50LV in the ratio 1:2 the release profile was showing only 86.38% of drug release in 24hours with slower release. But it was observed that release rate was increased when the concentration of Eudragit RSPO polymer concentration was decreased. In case of tablets of F7, containing drug and Eudragit RSPO & HPMC E50 LV in the ratio 1:3.5 the release profile was showing 100 % of drug release in 24 hours. But it was observed that release rate was not matched with the USP results. In case of tablets F9, containing drug and Eudragit RSPO, HPMC E50 LV in the ratio 3.5:1 the release profile was showing only 37.22% drug release in 24 hours, The dissolution study was shown that Eudragit RSPO, HPMC E50 LV in 3.5:1 ratios more controlled the release of drug from formulation. In case of tablets of F10, containing drug and Eudragit RSPO & HPMC E50 LV in the ratio 8:1 the release profile was showing 35.94 % drug release in 24 hours. The dissolution study was shown that Eudragit RSPO, HPMC E50 LV in 8:1 ratios more controlled the release of drug from formulation. In case of tablets of F8, containing drug, Eudragit RSPO & HPMC E50LV in the ratio 1:8 the release profile was showing 100 % of drug release in 24 hours, and also observed that release rate was matched with the USP results. It concludes F8 has better controlled release than the other formulations. The regression coefficients values for formulation F8 of zero order and first order Higuchi matrix, Peppas and Hixson-Crowell plots were found to be 0.919, 0.891, 0.988, 0.965, and 0.919 respectively. The 'n' value for F8 was found to be 0.735 which is indicates that the release approximates non-fickian diffusion mechanism. The regression coefficient of formulation F8 was found to be 0.919. These results indicated that the release rate was limited by the drug particles dissolution rate and erosion of the polymer matrix. The *In-vitro* drug release profile of tablet from each batch (F1 to F10) was carried out and results are shown in Table No 5. Thus, it may be concluded that the drug release from sustained release matrix tablet of Ozcarbazepine is best explained by Higuchi Kinetic model. The values of slope and intercept for Higuchi Kinetic model are 0.988 and 21.80 respectively

The optimized formulation of Sustained release matrix tablets of Ozcarbazepine tablets were subjected to accelerated stability studies. Stability studies of the optimized formulation 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 6-8.The results revealed that no significant changes in appearance, drug content, hardness, friability, and in vitro release for F8 formulation.

Ozcarbazepine sustained release matrix tablets were prepared successfully using combination of HPMC E 50LV & EUDRAGIT RSPO polymers and achieve required dissolution profile. The release pattern of optimized formulation F8 was achieved the optimum USP limit when compared to marketed formulation. Drug release kinetics of this formulation corresponds best to Higuchi, Peppas and Korsemeyer model. The optimized formulation is controlled by a complex mechanism of diffusion and extent by erosion.

Table 1. Formulation design

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ozcarbazepine	200	200	200	200	200	200	200	200	200	200
Eudragit RSPO	176	0	180	98	78	58	38	18	138	158
HPMC E50LV	0	176	58	78	98	118	138	158	38	18
Avicel 102	20	20	20	20	20	20	20	20	20	20
Mg state	4	4	4	4	4	4	4	4	4	4
Total	400	400	400	400	400	400	400	400	400	400

Table 2. Characterization of Trial Blends of all formulations

Formulation	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibilty Index (%)	Hausner's ratio(HR)	Angle Of Repose(ɵ)
F1	0.560	0.608	8	1.08	33
F2	0.608	0.700	13	1.15	32
F3	0.630	0.700	9.09	1.10	29
F4	0.583	0.700	16.66	1.20	28
F5	0.625	0.681	8.33	1.09	27
F6	0.652	0.750	13.04	1.15	32
F7	0.638	0.714	10.63	1.11	25

F8	0.681	0.750	9.09	1.10	34
F9	0.714	0.789	9.50	1.10	30
F10	0.681	0.750	9.20	1.10	28

Table 3. Physical Parameters of Tablets of all formulations

Formulation	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Assay (%)
F1	400.67±1.53	5024±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±0.035	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	5014±0.01	6.50±0.17	0.06	99.45
F10	399.00±2.00	5016±0.01	6.50±0.17	0.05	98.56

Table 4. Cumulative % Drug release of all formulations

Formulations	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	9059	14.4	22.9	39.9
F4	3.64	11.27	18.23	27.46	52.46
F5	3.79	10.62	19.45	29.75	79.38
F6	4.85	18.54	33.57	53.72	86.39
F7	6.623	22.08	38.348	61.51	100.0
F8	9.46	31.44	48.05	73.18	101.1
F9	3.87	3.46	13.55	26.66	37.22
F10	3.34	7.45	11.76	24.43	35.94

Release Kinetics

Table 5. Kinetic values obtained from *In vitro* released data of formulation F1-F10

Formulation	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	0.0969	-0.506	0.534	7.68	0.961	0.765	0.993	0.497	0.969

Stability studies

Table 6. Formulation F8 Stored at room temperature (25°c ± 2°c & 60% RH)

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

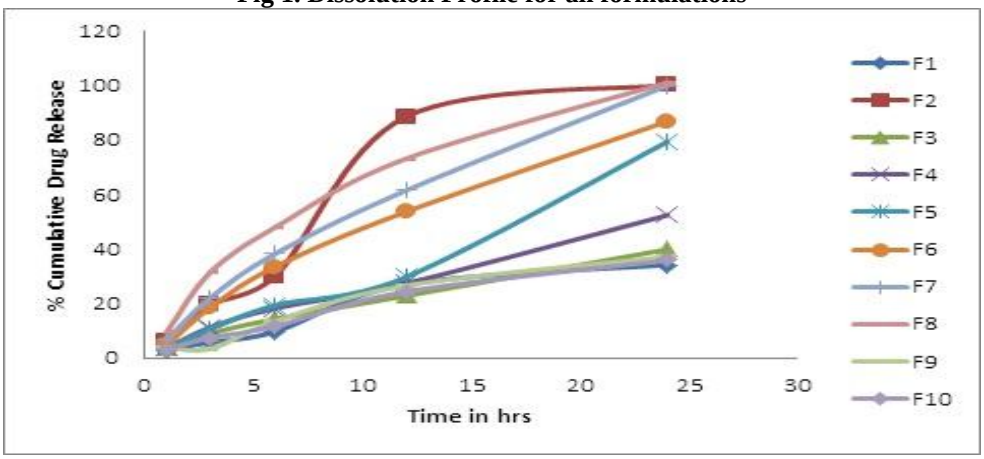
Table 7. Formulation F8 stored at temperature (40°c ± 2°c & 75% RH)

Formulation	Tested after 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 8. Formulation F8 stored at temperature (2-8°c)

Formulation	Tested after 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

Fig 1. Dissolution Profile for all formulations



CONCLUSION

Ozcarbazepine sustained release matrix tablets were successfully formulated by using HPMC E 50LV & EUDRAGIT RSPO polymers U.V. Scanning of Ozcarbazepine 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 Ozcarbazepine was prepared at λmax 285.4 nm and the regression value was found to be 0.999. The tablets of various formulations of Ozcarbazepine were prepared and the tablet hardness was found to be in range of 6.5 to7.3 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. 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.

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