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Research Article

Design formulation and evaluation of chronotherapeutic drug delivery system of carbamazepine treatment for epileptic seizures

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ABSTRACT

The objective of the study was to improve the oral therapeutic efficacy a formulation has been designed which contains one drug carbamazepine but dual releases An object of the present invention is to provide a dosage form comprising of an active ingredient as sustained release and half of an active ingredient as immediate release. Using HPMC K-4M, Povidone K30 and ethyl cellulose sustained dosage form has been formulated by wet granulation method. Tablet compressing was done with core rod tooling in which only one surface of core is expose to outside and other drug is incorporated in cup portion. The % drug release for carbamazepine as immediate release is 99.98 % and sustained release is 99. 53%. The kinetic release carbamazepine chrono tablets show zero order and Higuchi model. This drug will time dependent from sudden releases at 11.00 P.M and after that sustained and peak time shows at 7.00 PM. According to the circadian rhythm the formulation is prepared.

Keywords: Chronotherapeutics; Carbamazepine; Inlay tablet; Kinetic release

INTRODUCTION

Chronotherapeutic drug delivery system is useful in the treatment of disease, in which drug availability is timed to match rhythms of disease, in order to optimize therapeutic effect and minimize side effects. (Michael.H.Smolenky et al., 2007) Carbamazepine is an effective anti-convulsant agent, used for the control of major motor and psychomotor epilepsy and is used in the treatment of simple and complex partial seizures, tonic-clonic seizures as well as partial with secondarily generalized tonic-clonic seizures (Belgamwar et al., 2011) For the ideal pharmacotherapeutic treatment, optimal control of the plasma level should be constant and within the therapeutic window throughout the period of treatment so as to avoid adverse effects due to high toxic peak concentrations as well as to avoid adverse effects due to sub therapeutic plasma concentration. (Manoranjan Sahu et al., 2010) These delivery systems are designed to release a drug at two different rates or in two different periods of time: they are either quick/slow or slow/quick. A quick/slow release system provides an initial burst of drug release followed by a constant rate (ideally) of release over a defined period of time. This type of system is used primarily when maximum relief needs to be achieved quickly, and it is followed by a sustained release phase to avoid repeated administration. (Carla Martins Lopes, et al., 2007) The design, prepare, and characterize a quick/slow delivery dosage form as a chrono tablet in which the coat (immediate released the drug quickly and the core (central tablet) provided a slow and sustained release of carbamazepine. Proper combination of the quick and sustained release phases would allow the optimization of the fast- and slow-dose fractions as a function of the drug pharmacokinetics and metabolism. Inlay tablets is a type of layered tablet. While preparation, only the bottom of the die cavity is filled with coating material and core is placed upon it. When compression force is applied, some coating material is displaced to form the sides and compress the whole tablet. It is a novel platform technology for decreasing the mechanical shear on double compressed products which can lead to decrease in unknown process related impurities. Incompatible drugs can also be designed by this dosage form (S. Brito Raj, et al., 2011) Chronopharmaceutical formulations are synomous with time delayed release dosage forms that have onset of release after a predetermined interval. (Shyam Sunder Agrawal et al., 2011).

Selection and optimization of polymers was done on the basis of release profile in vitro with respect to both lag time interval and constant release in therapeutic concentration up to 10 hrs. The major objectives of this study were (1) to develop and evaluate a compressed core tablet system, to achieve a quick and slow release of the drug; (2) to study the influence of the type of matrix core on the in vitro performance; (3) to obtain a slow drug release period at a constant rate (zero order

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kinetics); and (4) to evaluate the combined effect of a fast release coat together with a sustained release core. Figure 1 Shows Compressed core tablet system as biphasic delivery.

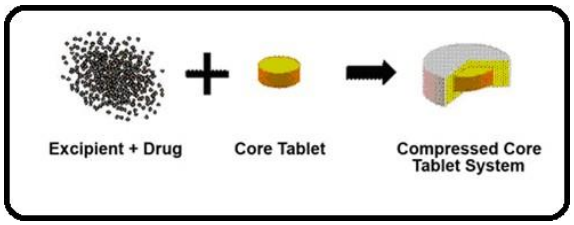

Figure 1: Compression core tablet system as a bilalayer delivery

MATERIALS AND METHODS

Carbamazepine gifted from Gujarat Mitul Petro-Pharma (Pvt.) Ltd, Gujarat, Did calcium phosphate, HPMC K 4M, Povidone K-30 and Avicel 101gifted from Rubicon Research Pvt. Ltd, Mumbai, HPMC K100 M purchased from Amoli organics Pvt.Ltd., Mumbai, Sodium Starch Glycolate and Talc purchased from NR Chem, Mumbai

Preparation of Inlay Tablet

Both Immediate release core tablet and Sustained release cup portion with different polymers proportions are prepared by Wet granulation technique.

A. Formulation of Immediate Release (IR) outer cup portion

Sift Carbamazepine through #80 mesh, rest of all material Sift by 40 # mesh. The model formulations consisted of Carbamazepine, Avicel -101, Sodium starch glycolate. Load the materials of into v-blender in and mix for 20 mins. Dissolve PovidoneK-30 in boiled water. After complete addition of binder solution, mix until to get granules. Then the wet granules passed through 20# sieve, after load the wet granules of into Tray drier, dry until the moisture content of granules is not more than 1.0%.Mill the dried granules through Multimill with 1.5 mm screen and sift through # 20mesh sieve. Retained granules mill through Multimill and sift through # 20 mesh. Sift Talc, magnesium stearate # 40 mesh, into v-blender. Mix for 3 minutes at slow speed. Immediate release granules were prepared by wet granulation technique using different concentration of disintegration agent. The (Table 1) showing formulation of immediate release granules

B. Formulation of Sustained release (SR): Core Tablet

All ingredients except magnesium stearate and aerosil were weighed properly and mixed separately in mortar in geometric order. Sift Carbamazepine through #80 mesh, rest of all material Sift by 40 # mesh. The model formulations consisted of Carbamazepine, Ethyl cellulose, HPMC K 4 M, HPMC K 100 M, Di Calcium phosphate. Load the materials of into v-blender in and mix for 20 mins. Dissolve Povidone (K-30) in boiled water and mix with ferric oxide. After complete addition of binder solution, mix until to get granules. Then the wet granules passed through 20# sieve, after load the wet granules of into Tray drier, dry until the moisture content of granules is not more than 1.0%.Mill the dried granules through Multimill with 1.5 mm screen and sift

Table 1: Formulation of Carbamazepine immediate release granules

Sl.No	Ingredients	F1 mg	F2 mg	F3 mg	F4 mg	F5 mg	F6 mg	F7 mg	F8 mg	F9 mg	F10 mg
1	Carbamazepine	200	200	200	200	200	200	200	200	200	200
2	Avicel 101	15	14.5	14	13.5	13	12.5	12	11.5	11	10.5
4	Povidone-K30	8	8	8	8	8	8	8	8	8	8
5	Sodium starch Glycolate	6	6.5	7	7.5	8	8.5	9	9.5	10	10.5
6	Magnesium Stearate	2	2	2	2	2	2	2	2	2	2
7	Talc	4	4	4	4	4	4	4	4	4	4
	Total	**235**	**235**	**235**	**235**	**235**	**235**	**235**	**235**	**235**	**235**

Table 2: Formulation of Carbamazepine sustained release Tablets

SL.No	Ingredients	F1 mg	F2 mg	F3 mg	F4 mg	F5 mg	F6 mg	F7 mg	F8 mg	F9 mg	F10 mg
1.	Carbamazepine	200	200	200	200	200	200	200	200	200	200
2.	Di Calcium phosphate	20	20	20	20	20	20	20	20	20	20
3.	HPMC K4M	70	80	90	100	20	20	20	80	90	100
4.	HPMCK100M	65	55	45	35	60	70	80	--	--	--
5.	Ethyl Cellulose	--	--	--	--	55	45	35	55	45	35
6.	Povidone K-30	9	9	10	9	9	9	9	9	9	9
7.	Ferric oxide	1	1	1	1	1	1	1	1	1	1
8.	Aerosil	4	4	4	4	4	4	4	4	4	4
9.	Magnesium stearte	6	6	6	6	6	6	6	6	6	6
	Total	**375**	**375**	**375**	**375**	**375**	**375**	**375**	**375**	**375**	**375**

through # 20mesh sieve. Retained granules mill through Multimill and sift through # 20 mesh. Sift Colloidal silicon dioxide, magnesium stearate # 40 mesh, and lubricants into v-blender. Mix for 3 minutes at slow speed. After granules formed compress the sustained release tablet by Cadmech presscoata machine. (Table-2)

C. Formulation of Inlay Tablet

The final formulation of Inlay tablet includes both SR and IR granules. The granules of Carbamazepine sustained release granules were punched Carbamazepine were being placed centrally over the Immediate release granules and it was compressed by using 16×32''round flat plain upper and lower punches. Feed frame was adjusted until optimized weight and hardness of the tablet results and Inlay tablets were formulated

Preformulation studies

DSC thermogram studies

Differential Scanning Calorimetry was performed in order to characterize the physical state of drug and polymer. Thermogram was obtained using DSC. About 2-5mg of sample was weighed, crimped into an aluminum pan and analyzed at a scanning temperature range from 50°C – 300°C at the heating rate of 2ºC/min under nitrogen flow of 25ml/min. The DSC thermogram obtained shows that the melting point obtained in pure drug and drug mixture was similar in range which infers that, no drug polymer interaction was there in the formulation and the drug was compatible with excipients (Figure 2, 3).

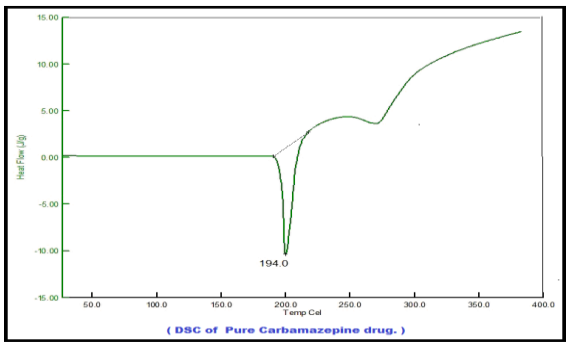

Figure 2: DSC of pure carbamazepine drug

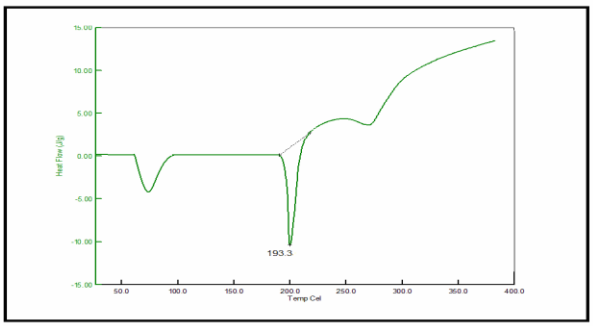

Figure 3: DSC for physical mixtures of drug with excipients

Fourier transforms infrared spectroscopy (FTIR)

The infrared spectra of the pure CBZ and CBZ, HPMC, and Ethyl cellulose the physical mixture, and the prepared granules were obtained on a Fourier transform infrared spectrometer (Perkin-Elmer, Norwalk, CT) in order to detect the existence of interactions between CBZ and hydrophobic or hydrophilic excipients in the granulation. The samples were first ground gently in a mortar and mixed with Kerr before being compressed into tablets. Scans were obtained at a resolution of 2 cm−1, over a frequency range of 4000 to 400 cm−1. (Figure 4-7).

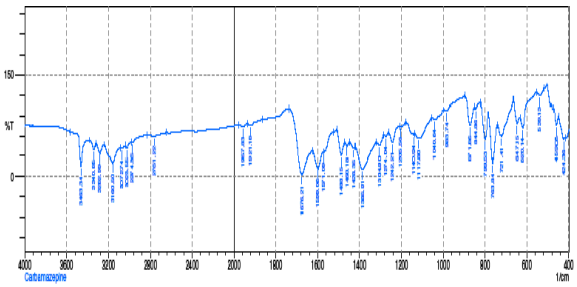

Figure 4: FTIR of pure Carbamazepine drug

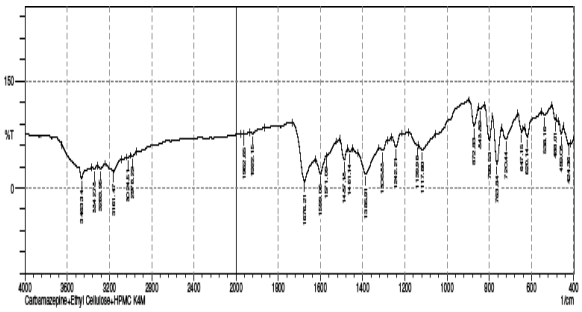

Figure 5: FTIR of pure Carbamazepine drug with ethyl cellulose and HPMC K4M

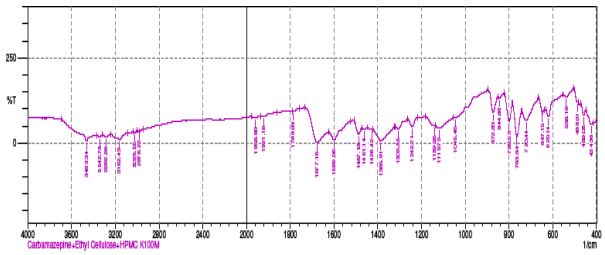

Figure 6: FTIR of pure Carbamazepine drug with ethyl cellulose and HPMC K100M

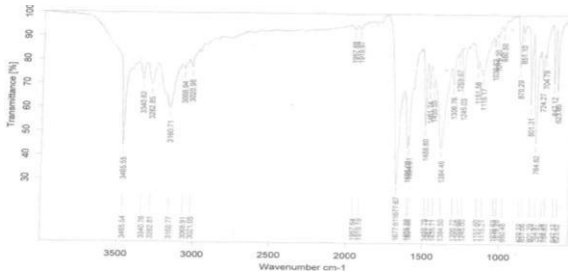

Figure 7: FTIR of pure Carbamazepine drug with blend of granules

Table 3: Evaluation of Carbamazepine Immediate Release granules

Formulation	Angle of re-pose	Tapped Density	Bulk Density	Compressibility Index (%)	Hausner's Ratio	Bulkiness	% of LOD	Dispersibility (%)
F1	28.34 ±0.45	0.452± 0.04	0.382± 0.01	15.48± 0.44	1.183± 0.031	2.61± 0.01	1.24 ±0.01	82.04±0.02
F2	24.56 ±0.18	0.456± 0.06	0.367± 0.03	19.51± 0.21	1.242± 0.01	2.72± 0.02	1.21± 0.01	76.89±0.52
F3	27.42± 0.26	0.468± 0.05	0.374± 0.04	20.08± 0.13	1.251± 0.23	2.67± 0.02	1.36± 0.01	79.45±0.21
F4	26.13 ±0.25	0.457± 0.02	0.366± 0.02	19.91± 0.24	1.248± 0.05	2.73± 0.01	1.29± 0.01	76.23±0.11
F5	26.03± 0.06	0.489± 0.04	0.387± 0.02	20.85± 0.27	1.263± 0.01	2.58± 0.021	1.15± 0.01	78.66±0.21
F6	28.64± 0.15	0.453± 0.02	0.358± 0.08	20.97± 0.11	1.265± 0.03	2.79± 0.08	1.27± 0.01	79.01±0.03
F7	24.32± 0.11	0.483± 0.01	0.389± 0.01	16.34± 0.17	1.301± 0.01	2.69± 0.06	1.78± 0.01	80.22±0.05
F8	25.67± 0.14	0.475± 0.03	0.391± 0.02	17.68± 0.18	1.214± 0.02	2.55± 0.01	1.26± 0.01	80±0.04
F9	26.53± 0.09	0.476± 0.02	0.384± 0.01	19.32± 0.12	1.239± 0.01	2.60± 0.05	1.38± 0.01	81.66±0.12
F10	26.78± 0.04	0.433± 0.05	0.371±	14.31± 0.16	1.167± 0.01	2.69± 0.01	1.32± 0.01	81.58±0.02

Table 4: Evaluation of Carbamazepine Sustained release granules

Formulation	Angle of repose	Tapped density	Bulk density	Compressibility Index (%)	Hausner ratio	Bulkiness	% of LOD	Dispersibility (%)
F1	27.38± 0.25	0.467± 0.03	0.377± 0.14	19.27±0.07	1.238± 0.09	2.65±0.01	1.19± 0.01	78.44±0.11
F2	28.12± 0.33	0.531± 0.05	0.334± 0.11	37.09±0.27	1.589 ±0.47	2.99±0.03	1.37± 0.01	75.23±0.01
F3	29.88± 0.11	0.488± 0.02	0.348± 0.02	28.68±0.34	1.402 ±0.11	2.87±0.05	1.48± 0.02	77.56±0.03
F4	28.23± 0.24	0.466± 0.22	0.345± 0.03	25.96±0.09	1.350 ±0.16	2.89±0.04	1.25± 0.01	79.76±0.09
F5	27.07± 0.32	0.453± 0.27	0.324± 0.05	28.47±0.13	1.398± 0.24	3.08±0.11	1.35± 0.02	78.2±0.17
F6	29.44± 0.61	0.467± 0.19	0.361± 0.22	22.69±0.09	1.293± 0.36	2.77±0.09	1.22± 0.01	74.19±0.11
F7	28.36± 0.22	0.444± 0.26	0.389± 0.26	12.38±0.13	1.141± 0.08	2.57±0.18	1.67± 0.01	80.33±0.13
F8	27.53± 0.15	0.439± 0.52	0.358± 0.06	18.45±0.14	1.226± 0.15	2.79±0.18	1.25± 0.01	82.65±0.17
F9	26.53± 0.29	0.469± 0.45	0.367± 0.19	21.74±0.13	1.277± 0.04	2.72±0.12	1.46± 0.01	82.11±0.14
F10	25.67± 0.27	0.423± 0.38	0.364± 0.47	13.94±0.11	1.162± 0.03	2.74±0.17	1.17± 0.01	81.24±0.14

Flow Measurements

Angle of Repose

The angle of repose is the angle formed by the horizontal base of the bench surface and the edge of a cone-like pile of granules. Funnel used was a stainless steel funnel and the size of the orifice was 10 mm and the height from the beginning of funnel to end of orifice was 111 mm. The funnel was fixed in place, 4 cm above the bench surface. After the cone from 5 g of sample was built, height of the granules forming the cone (h) and the radius (r) of the base were measured. The angle of repose (θ) was calculated as follows:

$$\theta = \tan^{-1}(h/r)$$

Results were only considered valid when a symmetrical cone of powder was formed. (Rakhi B et al, 2008)

Bulk Density

It is the ratio of total mass of powder to the bulk volume of powder

$$Db = M / VO$$

Where, M: Mass of the blend

Vo: Untapped Volume

A weighed amount is introduced into 100 ml graduated cylinder. The cylinder is fixed on bulk density apparatus. The timer knob is set for 100 tapping. The volume occupied by powder by powder noted. Further, another 50 taps may be continued and final volume achieved. For reproducible results, the process of tapping may be continued until concurrent volume achived. The final volume is bulk volume. During transfer the volume occupied by granules was measured. Bulk density was measured by using formula, (Brabander CD, et al., 2002)

Tapped Density

Tapped density is the ratio of mass of powder to the tapped volume. Tapped volume is the volume occupied by the same mass of the powder after a standard tapping of a measure.

$$Dt= M / Vt$$

Where, M: Mass of the blend

Vt : Tapped Volume

Weighed quantity of Carbamazepine granules was taken into a graduated cylinder, volume occupied by granules was noted down. Then cylinder was subjected to 500/ 750 and 1250 taps in tapped density tester (Electro Lab USP II) According to USP, the blend was subjected for 500 taps the % Volume variation was calculated. (Basak SC et al., 2004)

Compressibility index and Hausner ratio

This was measured for the property of a powder to be compressed; as such they are measured for relative importance of interparticulate interactions. It helps in measuring the force required to break the friction between the particles and the hopper. It is indirectly related to relative flow rate, cohesiveness and particle size. (Syed Nemaha Ulla et al., 2011). Compressibility index was calculated by following equation

$$\text{Compressibility index} = (D_t - D_b) / D_t \times 100$$

Where, D_t = tapped density;

D_b = bulk density

Hausner ratio is the ratio between tapped density to bulk density

$$\text{Hausner ratio} = D_t / D_b$$

Where, D_t = tapped density;

D_b= bulk density

Dispersibility

It is the ability of a material to flow or pour easily over a plane. Dispersibility, dustiness and flood ability are interrelated term.

Weight approximately 10 g of the carbamazepine, the material is dropped en mass from a total height (610 mm) on to a tarred watch glass (diameter 102 mm) through a hollow cylinder (330 × 102 mm) placed vertically 102 mm above the watch glass. The cylinder is secured to a supported –stand by 102 mm diameter support rings placed above and below the cylinder. The drop point is approximately 178 mm vertically above the cylinder. The material landing within the watch glass is weighed. Any loss of powder during the fall is the result of dispersion. The % of dispersibility is calculated using the relationship. (C.V.S.Subrahmanyam et al., 2010)

Dispersibility (%) = Weight of powder in watch glass / initial weight of sample * 100

Loss on drying

The Loss on drying test is designed to measure the amount of water and volatile matters in a sample when the sample is dried under specified conditions. The loss on drying of the blend (2g) was determined by using electronic LOD apparatus at 105°C

Flow properties and angle of repose, Compressibility and Hausnerratio is shown in (Table-3, 4)

Physical evaluation of tablets

Determination of Thickness

Thicknesses of five randomly selected tablets from each batch were measured with a Vernier caliper. Then the average Thickness and standard deviation were calculated. Tablet thickness should be controlled within ±5% variation of a standard value.

Weight variation

Tablet designed to contain a specific amount of drug. The weight of the tablet being made is routinely measured to ensure the tablet contains the proper amount of drug. 20 tablets were selected randomly from each batch and average weight was calculated. Then the deviation (as per IP limit ±5% for 500 mg tablet) of individual weights from the average weight and then standard deviation was calculated (Remya P.Net al., 2010)

Hardness

The Monsanto hardness tester consists of a barrel containing a compressible spring held between two plungers. Then lower plunger is placed in contact with the tablet and a zero reading is taken. The upper plunger is then forced against or spring by turning a threaded

Table 5: Shows physical evaluation of carbamazepine compress coated tablet

Formulation Code	Weight variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)
F1	618±0.11	6.7±0.24	0.23±0.04	98.53±0.30
F2	618±0.01	7.0±0.22	0.16±0.01	97.39±0.16
F3	617±0.01	8.6±0.08	0.32±0.01	97.45±0.11
F4	621±0.02	7.6±0.09	0.19±0.03	99.04±0.12
F5	623±0.01	6.5±0.07	0.31±0.11	98.01±0.18
F6	622±0.02	7.5±0.55	0.28±0.06	101.4±0.35
F7	622±0.25	7.8±0.26	0.12±0.05	**99.37**±0.27
F8	622±0.15	6.8±0.18	0.11±0.03	101.4±0.16
F9	621±0.16	6.5±0.37	0.14±0.04	**99.78**±0.25
*F10	618±0.17	6.5±0.03	0.17±0.03	**99.96**±0.12

Table 6: *In vitro* Dissolution Data

Time (Hours)	F1±SD (%)	F2±SD (%)	F3±SD (%)	F4±SD (%)	F5±SD (%)	F6±SD (%)	F7±SD (%)	F8±SD (%)	F9±SD (%)	*F10±SD (%)
0.08	30.56± 0.52	32.46± 0.11	33.12± 0.42	33.28± 0.22	40.11 ± 0.74	45.24± 0.10	48.91± 0.36	50.58± 0.93	52.11± 0.64	52.12± 0.48
0.16	42.51± 0.34	44.18± 0.26	45.62± 0.18	46.21± 0.56	48.2± 0.17	50.78± 0.65	60.54± 0.42	70.86± 0.28	78.99± 0.85	80.34± 0.37
0.33	58.13± 0.12	60.89± 0.55	61.58± 0.64	65.53± 0.37	69.34± 0.33	70.98± 0.24	73.55± 0.41	77.37± 0.55	90.95± 0.66	91.25± 0.29
0.5	65.45± 0.77	67.24± 0.97	69.82± 0.37	70.45± 0.74	71.83± 0.12	75.14± 0.29	77.28± 0.13	84.37± 0.92	96.05± 0.46	96.18± 0.16
0.75	72.89± 0.23	75.29± 0.72	76.99± 0.11	78.92± 0.77	79.27± 0.15	81.87± 0.11	83.92± 0.37	89.95± 0.17	99.12± 0.59	99.86± 0.64
1	76.11± 0.66	80.15± 0.59	82.31± 0.05	84.67± 0.97	86.33± 0.06	87.48± 0.14	91.63± 0.63	94.83± 0.84	99.87± 0.49	99.98± 0.75
1.5	12.23± 0.45	11.56± 0.44	10.56± 0.68	9.88± 0.07	13.65± 0.47	10.12± 0.39	15.45± 0.23	10.75± 0.92	9.58± 0.13	8.37± 0.28
2	23.79± 0.28	21.44± 0.19	19.08± 0.37	17.34± 0.66	25.43± 0.48	24.23± 0.17	27.43± 0.11	19.74± 0.86	18.35± 0.33	16.23± 0.57
3	42.73± 0.25	35.59± 0.48	28.98± 0.27	27.79± 0.31	50.24± 0.29	30.45± 0.63	39.75± 0.38	32.64± 0.44	30.49± 0.16	28.88± 0.39
4	68.44± 0.45	59.14± 0.73	46.37± 0.45	47.65± 0.89	65.55± 0.36	59.37± 0.94	52.07± 0.26	44.58± 0.18	42.48± 0.41	43.13± 0.58
5	88.31± 0.01	84.01± 0.24	74.82± 0.28	72.21± 0.48	80.43± 0.37	75.28± 0.28	78.45± 0.86	56.85± 0.29	55.96± 0.19	54.58± 0.39
6	99.34± 0.49	93.67± 0.16	91.89± 0.24	84.13± 0.25	85.12± 0.59	85.34± 0.68	85.32± 0.06	65.59± 0.58	63.68± 0.55	65.13± 0.35
7	--	100.5± 0.15	99.26± 0.20	95.58± 0.34	90.58± 0.61	91.45± 0.17	93.39± 0.51	80.52± 0.07	79.57± 0.72	78.52± 0.52
8	--	--	--	100.74± 0.69	99.49± 0.76	94.78± 0.54	96.57± 0.05	86.45± 0.91	85.32± 0.47	88.71± 0.96
9	--	--	--	--	--	98.05± 0.33	101.9± 0.84	97.54± 0.74	98.44± 0.05	**99.53**± 0.44

bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force and the force of fracture is recorded (Rajesh SJ et al., 2009).

Friability

The laboratory friability tester is known as the Roche friabilator. Ten tablets are weighed and placed in the plastic chamber which revolves at 25 rpm dropping the tablets a distance of six-inches with each revolution which is operated for 100 revolutions. The tablets are then dusted and reweighed to find out the % of loss in weight (as per IP limit it should be <1%). The friability ofthe tablet is determined by the formula given below. Then average hardness and standard deviation was calculated. (V. Felix Joe.et al. 2011)

$$\text{Friability} = \frac{\text{Final weight} - \text{initial weight}}{\text{Initial weight}} \times 100$$

Assay of the tablets

Twenty tablets from each brand product were weighed and powdered. A quantity of the powder containing 60 mg of carbamazepine was boiled with 25 ml of 96% ethanol for a few minutes. The hot mixture was stirred in a closed flask for 10 minutes and filtered through sintered glass. The flask and the filter were washed with 96% ethanol and sufficient 96% ethanol was added to the cooled filtrate to produce 100 ml. 5 ml of this solution was diluted to 250 ml with 96% ethanol and the absorbance of the resulting solution was measured using an ultraviolet spectrophotometer at the wave length maximum, λmax, of 285 nm. Then the content of carbamazepine $C_{15}H_{12}N_{2O}$ was calculated taking 490 as the value of A (1%, 1cm) at the λmax of 285 nm.

In vitro dissolution study

In vitro dissolution studies are valuable tools to judge quality and stability of dosage forms and are often used to predict in vivo performance. Dissolution of the tablet of each batch was carried out using USP dissolution type II apparatus (Electrolab, TDT-08 L; Dissolution Tester USP) using paddle at 75 rpm. 900 ml of 0.1 N HCl (pH 1.2) for 2 hours and phosphate buffer the pH is adjusted to 6.8 for the rest of the period. Dissolution medium was filled in a dissolution vessel and the temperature of the medium was set at 37 ± 0.5 0C. 5ml of the sample was withdrawn at regular intervals up to 10 hours and replaced with the same volume pre-warmed with fresh dissolution medium. After filtration, the amount of drug release was determined from the standard calibration curve of pure drug. The absorbance was measured (λ=285) after filtration and suitable dilution by UV–visible spectrophoto meter (Table-6). The percentage drug release was plotted against time to determine the release profile (Figure 8, 9).

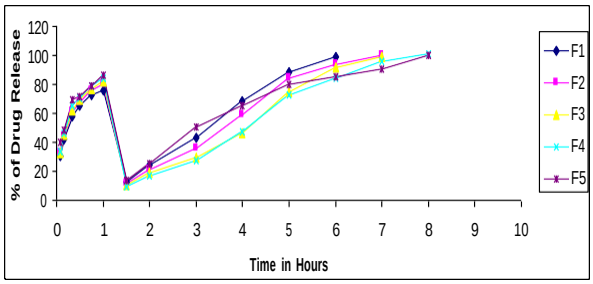

Figure 8: Dissolution studies of Carbamazepine chronotablets (F1-F5)

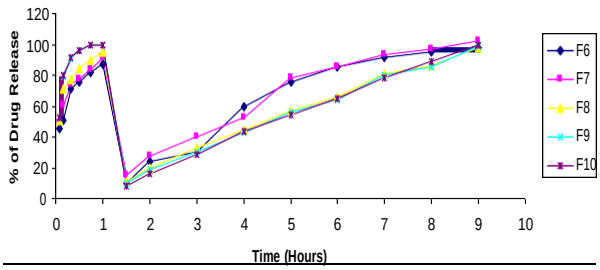

Figure 9: Dissolution studies of Carbamazepine chronotablets (F6-F10)

Kinetics modeling of drug dissolution profile

The dissolution profile of most satisfactory formulation was fitted to zero order, first order and Higuchi model, korymer –peppas model to ascertain the kinetic modeling of the drug release. The methods were adopted for deciding the most appropriate model. (Table-7)

1. Cumulative percent drug released versus time (Zero order kinetic model) (Figure 10)

2. Log cumulative percent drug remaining versus time (First order kinetic model) (Figure 11)

3. Cumulative percent drug released versus square root of time (Higuchi's model). (Figure 12)

4. Log cumulative percentage drug released verses Time (Korymer –peppas model) (Figure 13)

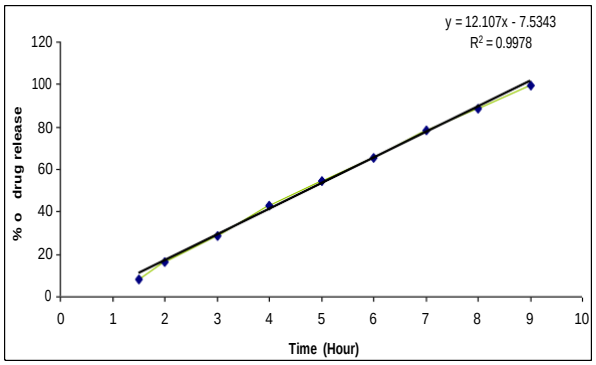

Figure 10: Kinetic release of Carbamazepine for Zero order model

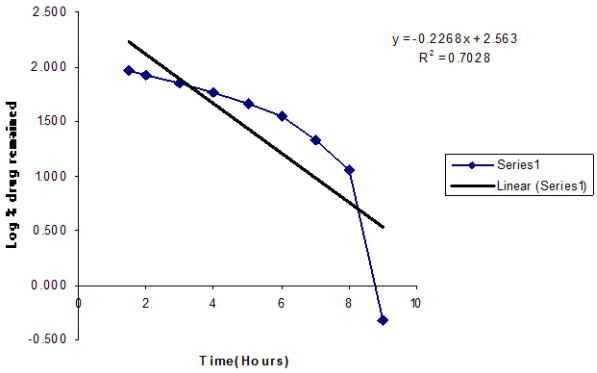

Figure 11: Kinetic release of Carbamazepine for First order model

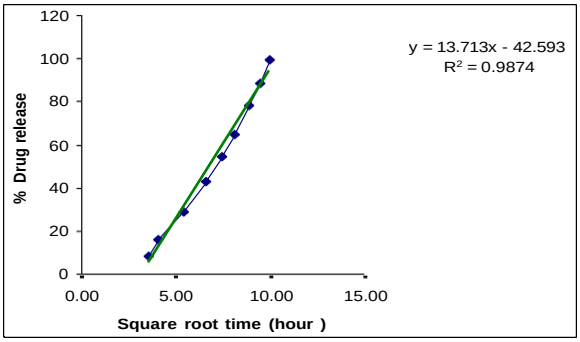

Figure 12: Kinetic release of Carbamazepine for Higuchi order model

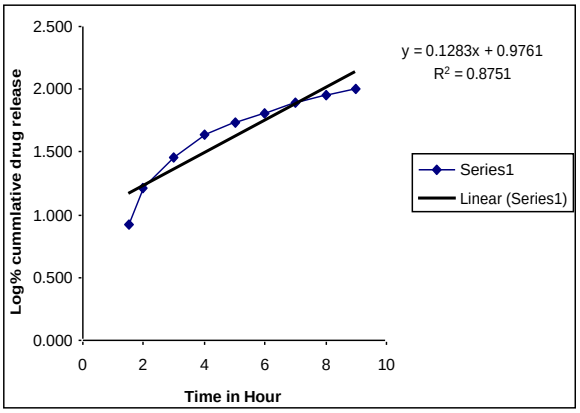

Figure 13: Kinetic release of Carbamazepine for Korsmeyer Pappas model

F.Code	Zero order	First order	Higuchi	Korsmeyer Peppas
F1	0.9882	0.8183	0.9847	0.8751
F2	0.9747	0.8939	0.9875	0.8799
F3	0.9805	0.8114	0.9891	0.8783
F4	0.9773	0.8843	0.990	0.8435
F5	0.9288	0.8100	0.9826	0.7883
F6	0.9197	0.9712	0.9913	0.7864
F7	0.9438	0.9456	0.978	0.8961
F8	0.9938	0.8372	0.9855	0.9363
F9	0.9951	0.7759	0.9869	0.8936
F10	0.9978	0.7028	0.9874	0.9036

RESULT AND DISCUSSION

An attempt was made to develop a chronotherapeutic drug delivery system of carbamazepine using HPMC K4M and Ethyl Cellulose and excellent activity in sustained release formulations along with immediate release effect due to sodium starch glycolate. The granules prepared for different batches were studied for flow property and micromeritic properties sand was found to be good flow property. The drug was standardized using UV Spectrophotometer that will give the idea about chronotherapeutics. Weight variation data of the prepared tablets indicated no significant difference in the weight of individual tablet from average value. Hardness of prepared tablets was observed within the range of 6.5 ± 0.07 to 8.6± 0.08 kg/cm^2. Friability of all tablets was found below 1%. The in-vitro drug release studies of the prepared tablets were performed both in simulated gastric fluids (0.1N HCl) for 2 hrs and continued in changing pH of 6.8 phosphate buffer up to 12 hrs The release pattern of carbamazepine. For all preparation of sustained releases tablet showing that drug and polymer ratio is 1:0.675 .In F1to F4 formulation HPMC K4M : HPMC 100 M ratios are 1: 0.086, 1:0.68,1:0.5,1:0.35 having dissolution are 99.34±0.49% , 100.5±0.15, 99.26 ±0.26,100.74±0.69. In case of F5,F6,F7 formulation three polymers having , ratio of HPMC K4 M : HPMC100 M: ethyl cellulose 1:3:2.75 , 1:3.5:0.22,1:4:1.75 having the % of drug dissolutions are 99.49±0.33 , 98.49±0.33, 101.9±0.84 .In case of F8,F9,F10,formulation are mixing of two polymer ratio like HPMC K4Mand ethyl cellulose are 1:0.68,1:0.5,1:0.35 having dissolution time up to 8 hr sustained like 97.54±0.74, 98.44±0.05, and 99.53±0.44. In case of F4 & F10 formulation polymer ratio is 1:0.35 but different polymer, so F10 was showing better result than other formulation as well showing (TableNo-7) the zero order as well as Higuchi model values are 0.9978, 0.9874 (>1). In case of carbamazepine immediate release outer part having F1 to F10 having disintegration concentration 3.00 to 5.25 %.so F10 showing immediate effect having dissolution 99.98±0.0.75 (Table No-1).

CONCLUSION

Both immediate release and sustained release formulation are prepared and contain in a single dosage form. The study describes the formulation of a core in cup design which incorporates both immediate and sustained release drug for increased therapeutic efficacy and patient convenience. In both cases F10 is optimized chronomodulated formulation i.e made by compression coating technology. The sustained core tablets were prepared by wet granulation techniques using HPMC K4 M and ethyl cellulose for the good drug release i.e 99.5 3 as well as shows zero order and Huguchi model. The outer coat immediate release showing with 99.98 % of drug release due to disintegration agent more concentration of sodium starch glycol late. During preformulation it has been observed that there is no drug-drug and drug excipient interaction, so the excipient which has been selected for the formulation is compatible with the drugs. The intention is that the formulation should be administered in the evening at 11.00 P.M in the treatment of symptoms are experienced in early morning hours 7.00 PM. The system was found to be satisfactory in terms of release of drug after sustained time when the greatest need of drug in early morning to treat epilepsy. One promising formulation demanded formulation demanded for dual drug delivery system, hence the existing drug molecule, the chronotherapeutic management with of epilepsy has opening a “new lease of life.

REFERENCES

Basak SC, Shrinivasa R, Manavalan, Controlled release HPMC matrix tablet of propranolol HCl. Indian J. Pharm. Sci. 2004; 66(6): 827-833,

Belgamwar A.V, Gupta A.M, Belgamwar V.V, Kawtikwar P.S Mundhada D.M, Antiepileptic sustained release carbamazepine microcapsules for kids, Volume 7, Issue 2, 2011; Pg.154-158

Brabander CD, Vervacet C and Remon JP. Development and evaluation of sustained release matrix tablet. J. Controlled Release. 2002, 77(1): 245-258

C.V.S.Subrahmanyam, Micromertics, Text book of physical pharmaceutics, 2010, 2nd editon.224-22

Carla Martins Lopes, José M. Sousa Lobo, João F. Pinto, Compressed Matrix Core Tablet as a Quick/Slow Dual-Component Delivery System Containing Ibuprofen, AAPS PharmSciTech 2007; 8 (3), E 1-8

Manoranjan Sahu, S.C.Dinda, Formulation and development of modified release Inlayered tablet, Journal of Pharmacy Research 2010, 3(4), 794-798

Michael.H.Smolenky and Nicholas A.Peppas, Chronobilogy.drug-delivery and Chronotherapeutic, Advanced drug delivery reviews, 2007, 59, 823-824

Raghuram R, Mutalik S, Srinivas R. Once daily sustained release matrix tablets of Nicorandil: formulation and in vitro evaluation, AAPS Pharm Sci Tech 2003; 4(4):61.

Rajesh SJ, Swadesh N, Sabita A, Vikas DV, Prashant K, Sandip S, Nayak S. Taste maskingof Lornoxicam by polymer carrier system and formulation of oral disintegrating tablets. Int J Drug Delivery 2009; 1:27-37.

Rakhi B. Shah, Mobin A., Comparative Evaluation of Flow for Pharmaceutical Powders and Granules, AAPS PharmSciTech, 2008, 9(1), 250-258

Remya P.N, Damodharan N, Formulation and Evaluation of Bilayered Tablets of Ibuprofen and Methocarbamol, International Journal of PharmTech Research, Vol.2, No.2, pp 1250-1255, 2010

S.Brito Raj, E.Mohanambal, Inlay tablet of Atorvastatin calcium with sustained release Metoprolol tartarate, Journal of Pharmacy Research 2011, 4(10), 3585-3589

Shyam Sunder Agrawal, Subhash Chand Dadawal, Sarika Madan, Formulation of inviter characterization of Chronopharmaceutical drug delivery system of metropolis titrate using hydroxyl propyl cellulose, Journal of chronotherapy and drug delivery, 2011, 2(2), 95-101

Syed Namath Ulla, Anup Kumar Roy, Martand Kulkarni, Vinod Kumar SM, . Formulation and Evaluation of Sustained Release Matrix Tablets of Lornoxicam. Int. J. Drug Dev. & Res., Jan-March 2011, 3 (1):31-44

V. Felix Joe, Prasanth V. Formulation and evaluation of Pseudoephedrine hydrochloride and Loratadine extended release tablet, Journal of Pharmacy Research 2011, 4(2), 507-508.