

Formulation of sustained release drug delivery of carbamazepine to modulate release of drug to achieve specific clinical purpose

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ABSTRACT

Carbamazepine (CBZ) is a water-insoluble anti-epileptic drug of choice for the treatment of partial and tonic clonic seizure disorders. In the present study, an attempt made to develop the bilayer matrix tablets of CBZ using EUDRAGIT RSPO, RLPO and HPMC K100M. The sustained release pattern of CBZ evaluated by in-vitro drug release for 24 h. In the immediate release layer contains crosscarmellose sodium as superdisintegrant and water immiscible polymers such as Eudragits in the sustaining layer. Formulations were evaluated for the release of CBZ over a period of 24 h using USP type-I dissolution apparatus and were compared to the pharmacopoeial standards. The prepared formulations gave an initial burst effect to provide loading dose of the drug followed by sustained release for 24 h from the sustaining layer of matrix embedded tablets. The drug release from the formulation F11 was increased satisfactorily upto 102% (10%HPMC K100M) till 24 h which meet the specifications as specified in the USP. In-vitro dissolution kinetics of the formulation was found to follow first order and the release mechanism was best fitted in Korsmeyer-Peppas model via Fickian diffusion controlled mechanism after the initial burst release.

Keywords: Carbamazepine, extended release tablets, bilayer matrix tablets, Eudragit RLPO, Eudragit RSPO, HPMC K100M.

INTRODUCTION

Sustained release (SR) drug delivery systems are developed to modulate the release of drug in order to accomplish specific clinical purpose that can't be attained with conventional dosage forms. Probable therapeutics benefits of a properly proposed SR dosage form include low cost, simple processing, improved efficacy, reduced adverse events, flexibility in terms of the range of release profiles attainable, increased convenience and patient compliance[1]. Inclusion of drug in the matrix of hydrophilic polymers have been successfully utilized in the development of controlled release delivery systems to present the desired release profile[1]. Controlled drug delivery usually results in substantially steady state blood levels of the active ingredient as compared to the uncontrolled variations observed when multiple dose of quick releasing conventional dosage forms are administered to a patient.

Bilayer tablet is a type of multiple compressed tablet. Tablets are composed of two layer of granulation compressed together. Controlled release tablets of CBZ using Hydroxypropyl methyl cellulose (HPMC) and Ethylcellulose (EC) as release retardants were formulated and were performed for in-vitro and in-vivo studies. They found that EC based formulation was found to be more stable and compared well with the innovators product[2]. Sustained release matrix

tablets of CBZ were formulated and the effects of various viscosity grades of methocel (K4M, K100M and combination of both) on the release profile of CBZ have been evaluated. In-vitro release profile of CBZ from combination of both polymers showed that 90% of the drug was released at the end of 12 h. The release profile of formulation F10 has achieved the optimum United States Pharmacopoeial limits when compared to marketed formulation[3]. Sustained release bilayer tablets of propranolol Hcl were formulated using super disintegrant sodium starch glycolate (SSG) for the fast release layer and water immiscible polymers such as ethylcellulose, eudragit RLPO and RSPO for the sustaining layer. Propranolol Hcl tablets in-vitro dissolution kinetics followed the Higuchi model via a non-fickian diffusion controlled release mechanism after the initial burst release[4]. Extended release matrix tablets of Zidovudine using hydrophilic polymers Eudragit RLPO and RSPO alone and in combination with Hydrophobic Ethylcellulose(EC). The in-vitro drug release study revealed that Eudragit preparation was able to sustain the drug release for 6 h. Combining Eudragit with EC sustained the drug release for 12 h[5]. CBZ is the drug of choice for the treatment of partial and tonic clonic seizure disorders. Consequently, chronic drug therapy in epileptic patients requires steady-state plasma concentration's with minimal variations below the minimum effective concentration or above the maximum toxic concentration, in order to prevent seizure relapse or the occurrence of adverse side effects.

The extended release system of CBZ with controlled and predictable release kinetics, when compared to conventional dosage forms are likely to result in improved drug therapy. The use of extended release dosage form for the delivery of CBZ may therefore, appropriate and desirable to enhance patient compliance with the added advantage of minimal fluctuations in plasma carbamazepine levels.

The major objective of the present investigation is to develop a bilayered matrix tablet of CBZ using Eudragit RLPO, RSPO and HPMC K100M and to evaluate in-vitro drug release for 24 h, the sustained pattern of CBZ. The drug release data plotted using various kinetic equations to assess the order of kinetics and release mechanisms.

MATERIALS AND METHODS

Carbamazepine received as a gift sample from Sun Pharmaceutical Ltd., Vadodara, Eudragit RSPO and RLPO were received as gift samples from Evonik, Mumbai. Hydroxypropyl methylcellulose (HPMC K100M), Avicel PH-102 (MCC), Sodium Lauryl sulphate(SLS) Qualikems, New Delhi. Cross Carmellose Sodium was a gift sample from Signet Chemical Ltd., Mumbai. Talc, Methanol (S.D fine chemicals Mumbai). All other chemicals used were of analytical grade.

Preparation of Bilayer tablet of Carbamazepine

All the tablets were prepared using the direct compression method. The preparation process involved two steps, first, loading dose of the drug (50mg) was mixed with required quantity of crosscarmellose sodium (Superdisintegrant), sodium lauryl sulphate and microcrystalline cellulose by mixing in a polythene bag for 15min, the powder blend was then lubricated with talc (5%). Second, maintenance dose of CBZ (150mg) was mixed along with the polymer, microcrystalline cellulose and Sodium lauryl sulphate by mixing in laboratory polythene bag for 15min. Then the powder blend was lubricated with talc (5%). Twelve formulations were prepared with equal composition of immediate release layer but the composition of sustaining layer differs with varying concentrations of polymers. Quantitative formula for each bilayer tablet is shown in Table 1 and 2.

The quantity of the powder for the sustained release layer was compressed lightly using a pankaz tableting machine (Ahmedabad, India) equipped with 11mm round concave and plain punches. Over this compressed layer the required quantity of the fast release layer blend was placed and compressed. Prior to compression powders were evaluated for their characteristic parameters, such as bulk density, tapped density, carr's index and angle of repose [6]. Carr's compressibility index (CI) was calculated from the bulk and tapped densities [7] using a tap density apparatus. (Electrolab, ETD-1020, India). After compression of bilayer tablets, friability was measured using Roche friabilator (Electrolab, Mumbai, India) and hardness was measured using Pfizer type hardness tester. The diameter of tablet was measured using digital vernier calipers.

Drug content uniformity

The powdered sample equivalent to 200mg drug was weighed, transferred into a 100ml volumetric flask containing 50ml methanol and allowed to stand for 5 h with intermittent sonication in a bath sonicator to ensure complete solubility of drug. Then the solution was adjusted with methanol upto the volume required. The obtained solution

was suitably diluted and analysed for drug content using UV spectrophotometer at 284nm. The drug content was calculated from the absorbance obtained with the help of the calibration curve.

In-vitro drug release study

The in-vitro drug release study was performed using Lab India USP type-I basket apparatus using 900ml of distilled water at 100rpm at $37\pm 0.5^\circ\text{C}$. 5ml of aliquot were withdrawn at pre-determined time intervals for a period of 24 h and replaced with the fresh medium. The samples were filtered through 0.45 μm millipore membrane filter, suitably diluted and analysed at 284nm using double beam UV/VIS spectrophotometer. The content of drug was calculated using the equation generated from a standard calibration curve. The test was performed in triplicate. High reproducibility of data was obtained (SD $\pm 3\%$), hence only average values were considered.

Analysis of Carbamazepine Release:

The drug release data were evaluated by the model-dependent (curve fitting method). In the present study, Korsmeyer Peppas model describing drug release from polymeric system was used. This model takes into account that the drug release mechanism follows anomalous behavior described by the following equation[8] $M_t/M_\infty = Kt^n$ where M_t is drug released at time t , M_∞ is the quantity of drug released at infinite time, K the kinetic constant and n is the release exponent. The value of n is related to the geometrical shape of the delivery systems and determines the release mechanism. A release exponent of $n=0.4$ indicates a diffusion controlled drug release (Fickian diffusion). The CBZ release rates of the tablets analyzed using both first order and Korsmeyer-Peppas models[9].

DSC studies

The DSC studies were carried out to evaluate the drug-polymer interaction. Accurately weighed sample was placed in an aluminium pan with an empty pan as reference. The experiment was carried out in nitrogen atmosphere with a flow rate of 25ml/min, at a scanning rate of $5^\circ\text{C}/\text{min}$.

RESULTS AND DISCUSSION

The bilayer matrix tablets containing carbamazepine successfully prepared using the direct compression method. Prior to compression, various physical parameters of the pre-compression blend were evaluated. The bulk densities and tapped densities for the powders of all the formulations were ranged in between 0.575-0.641 and 0.672-0.776g/ml. The Carr's index for all the formulations was found to be below 21 indicating good to fair flow and compressibility. The flow properties of the powder were further analysed for determining the angle of repose which ranged between 18.19 ± 0.06 to 24.18 ± 0.042 and the values indicated good flow properties of powder. Then the powder blend were evaluated for various evaluation tests. All the tablets of various formulations complied with the official requirements of uniformity of weights as their weights varied between 442mg and 457mg. The hardness of the tablets ranged from 5.08 to 6.16kg/cm² and the friability values were $< 0.6\%$ indicating that the matrix tablets were compact and hard. Thickness of the tablets ranged between 2.9-3.2mm. All the formulations showed satisfactory results in the drug content as they contained 95-103% of carbamazepine indicating good uniformity in drug content.

Bilayer matrix tablets of carbamazepine were formulated using various synthetic polymers like Eudragit RSPO, RLPO and HPMC K100M. These tablets contain Immediate Release and Sustained Release layers. Immediate Release layer of Carbamazepine containing 50mg of Carbamazepine showed burst effect which is due to the presence of 2% superdisintegrant (Crosscarmellose sodium). This is because of high water uptake by capillary action and strong swelling power causing sufficient hydrodynamic pressure to induce complete disintegration[10].

In order to sustain the action Eudragit RSPO was used as a polymer in the concentration of 5% to 0.75% for the first four formulations (F1-F4). The drug release not only depends on the nature of matrix but also depends on drug: polymer ratio. F1 formulation composed of 5% Eudragit RSPO which failed to release the drug satisfactorily till 24 h. Further decreasing the polymer to 2.5% (F2), 1.5% (F3), 0.75% (F4), drug release was increased upto 77%. As per USP 65% to 90% drug release within 12 h is specified and not less than 75% of the drug should be released within 24 h of dissolution. All the formulations F1-F4 have shown 54-67% drug release after 12 h and maximum drug release of 77% after 24h which is not as per specifications. This may be because of poor solubility of drug in dissolution medium and water insoluble low permeability nature of Eudragit RSPO. The drug release profile using Eudragit RSPO is shown in fig. 1.

Next four formulations were prepared with polymer Eudragit RLPO in the concentrations of 5%-0.75%. Formulation F7 was satisfactory where 89% of the drug was released after 24 h of dissolution. Burst release of Carbamazepine occurred in all the formulations. This is due to hydrophilic and high permeability nature of Eudragit RLPO. Once the tablet gets exposed to the dissolution medium, the solvent penetrates into the free spaces between macromolecular chains of Eudragit RLPO. After solvation of the polymer chains, the dimensions of the polymer molecule increases due to polymer relaxation by the stress of the penetrated solvent. The higher drug release rate of Eudragit RLPO formulations compared to the before formulations may be attributed to the higher hydrophilic groups in Eudragit RLPO creating pores and channels thus facilitating solvent penetration and elevations of drug release[11]. These formulations meets the USP requirements for carbamazepine, as it requires 65% and 90% of the drug to be dissolved within 12 h and not less than 75% of the drug to be release within 24 h. The drug release profile using Eudragit RLPO is shown in fig. 2.

The other four formulations were prepared using high molecular weight HPMC to retard the release of drugs. HPMC K100M was used in concentration of 20%(F9), 15%(F10), 10%(F11), 5%(F12). These formulations have shown initial burst release and extended the release for 12-24 h. Formulation F9 containing 20% of HPMC K 100M failed to release the drug satisfactorily till 24 h. Hence, the polymer percentage was decreased in the further formulations. The drug release from formulation F11 was increased satisfactorily upto 102% till 24 h, which meets the specifications in the USP. Further decrease in polymer concentration to 5% got predominant increase in drug release of 104.2% at 12 h which is not desired. The drug release profile using HPMC K100M is shown in fig.3.

The drug release was faster from matrices containing HPMC K100M compared to Eudragit matrices. This may be due to structural reorganization of HPMC. Increase in concentration and viscosity of HPMC may result in increase in the tortuosity or gel strength of the polymer. When tablet containing HPMC is exposed to dissolution medium, it undergoes rapid hydration and undergoes chain relaxation to form viscous gelatinous layer. Failure to generate a uniform and coherent gel may cause rapid drug release[12].

To analyze the carbamazepine release mechanism the in-vitro release data were fitted into various release equations and kinetic models. The optimized formulation F11 was found to follow first order with the highest value of regression coefficient $R^2=0.935$. To explain the release pattern, results of the in-vitro dissolution data were fitted to the Korsmeyer-Peppas equation which characterizes the transport mechanism. The regression coefficient R^2 was found to be 0.984 with release exponent (n) value of 0.396 which indicates the release governed by Fickian diffusion.

Differential scanning calorimeter was used to measure enthalpy and melting point of pure compounds and different formulations. The pure drug showed a characteristic, sharp endotherm at 194.1°C with enthalpy of fusion 102 .1J/g which corresponds to its melting point and indicates the crystalline nature of drug.

The polymer HPMC K100M depicted endotherm at 73.3°C with enthalpy of 125.5J/g, which corresponds to its melting point. The DSC was carried out to both sustained release layer and immediate release layer of carbamazepine bilayer tablet. The thermogram of sustained release layer showed drug endotherm at 192.0°C with enthalpy 28.5J/g, while the polymer HPMCK 100M exhibits an endothermic hump at 75°C. In the immediate release layer, thermogram of drug only showed endothermic peak at 189.6°C with enthalpy of 55.84J/g and lack of polymer endothermic peak is due to absence of HPMCK100M in immediate release layer. From the above observation it is clear that there is no change in the thermal properties of the drug in pure form and in formulation excipients which indicates no interaction of drug with other ingredients.

The bilayer matrix tablets of carbamazepine were formulated and these formulations complied with the pharmaceutical quality control standards for weight variation, drug content, hardness and friability. Results of the present study demonstrated that hydrophobic polymers polymethacrylate copolymers (Eudragit RSPO and Eudragit RLPO) could not be used for formulating sustained-release matrix tablets and hydrophilic polymer (HPMC K100M) can be successfully employed for formulating sustained-release matrix tablets of Carbamazepine. Among the hydrophobic and hydrophilic matrix formers used, the rate of drug release was in the following order HPMC K100M > Eudragit RLPO > Eudragit RSPO. Among all the formulations F11 formulation showed the maximum release up to 24 hr and it is selected as the best formulation. Majority of the formulations followed the Fickian diffusion mechanism.

Once a day tablets taken orally can be formulated using HPMC K100M. All the prepared tablets tested for powder characterization and physical evaluation parameters were within the limits. The drug release from all the matrix tablets shows polymer concentration dependent sustaining effect. As the amount of polymer in the tablet formulation increases, the drug release rate decreases. The release pattern of the optimized formulation was best fitted to Korsmeyer-Peppas model and first order. Mechanism of drug release followed was Fickian diffusion mechanism. DSC studies showed that there was no interaction between the drug and excipients. It is concluded that the release lag time and release rate could be tailored by adjusting the formulation variables to achieve satisfactory carbamazepine release through bilayer matrix tablets.

TABLE 1: Formula for Immediate release layer formulation F1 –F12

S. No	Ingredients	Quantity(mg)
1.	CBZ	50
2.	Cross carmellose sodium	2
3.	SLS (0.5%)	0.5
4.	Talc (5%)	5
5.	MCC (upto 100%)	42.5
	Total	100

Table 2: Formulae for Sustained release layer formulation F1 –F12

Formulations	CBZ (mg)	Eudragit RSPO (mg)	Eudragit RLPO (mg)	HPMC K100M (mg)	SLS (0.5%) (mg)	Talc (5%) (mg)	MCC (mg)	Total (mg)
F1	150	17.5	-	-	1.75	17.5	163.25	350
F2	150	8.75	-	-	1.75	17.5	172.00	350
F3	150	5.25	-	-	1.75	17.5	175.50	350
F4	150	2.62	-	-	1.75	17.5	178.12	350
F5	150	-	17.5	-	1.75	17.5	163.25	350
F6	150	-	8.75	-	1.75	17.5	172.00	350
F7	150	-	5.25	-	1.75	17.5	175.5	350
F8	150	-	2.625	-	1.75	17.5	178.12	350
F9	150	-	-	70	1.75	17.5	110.75	350
F10	150	-	-	52.5	1.75	17.5	128.25	350
F11	150	-	-	35	1.75	17.5	145.75	350
F12	150	-	-	17.5	1.75	17.5	163.25	350

CBZ= carbamazepine, HPMC K100M= Hydroxy propyl methyl cellulose, SLS= Sodium Lauryl Sulphate, MCC=Microcrystalline cellulose.

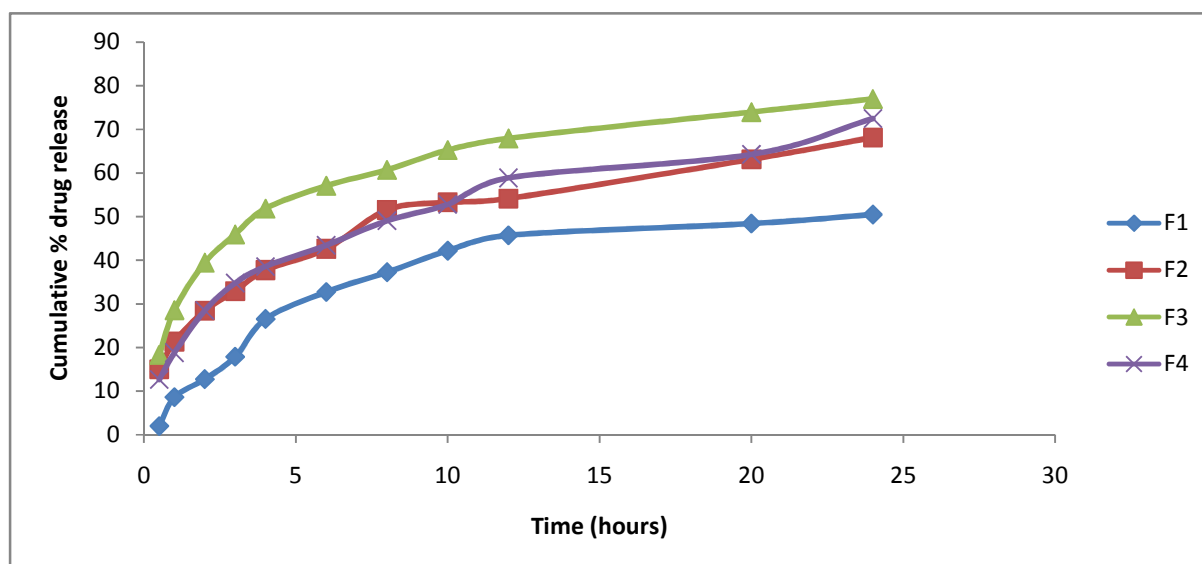


Fig. 1: Release Profiles of carbamazepine from Eudragit RSPO bilayer matrix tablets (F1-F4)

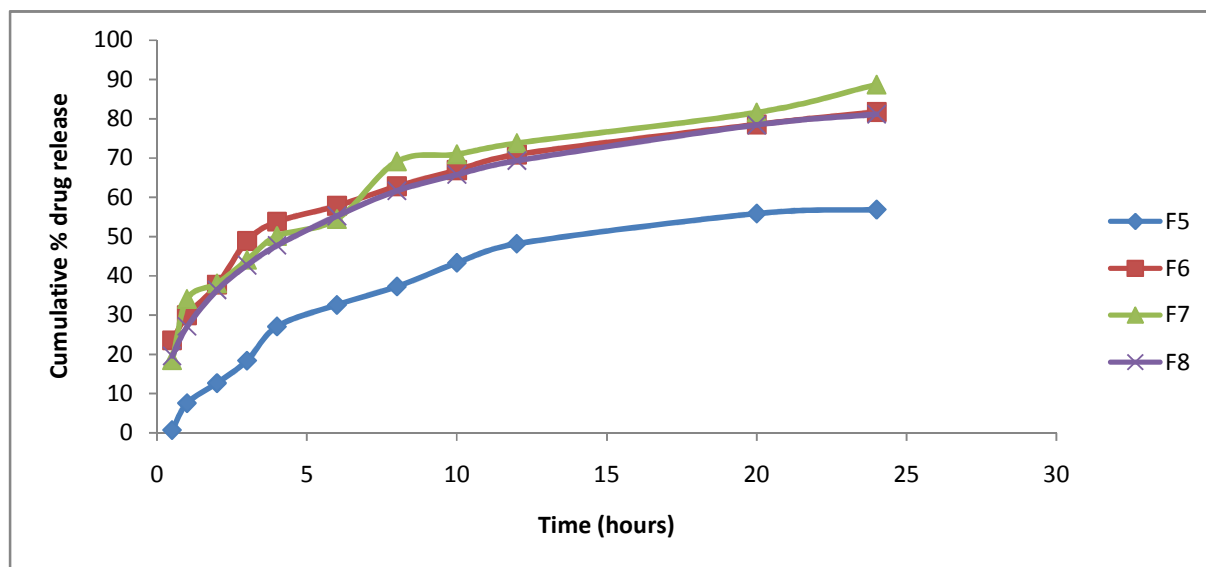


Fig. 2: Release Profiles of carbamazepine from Eudragit RLPO bilayer matrix tablets(F5-F8)

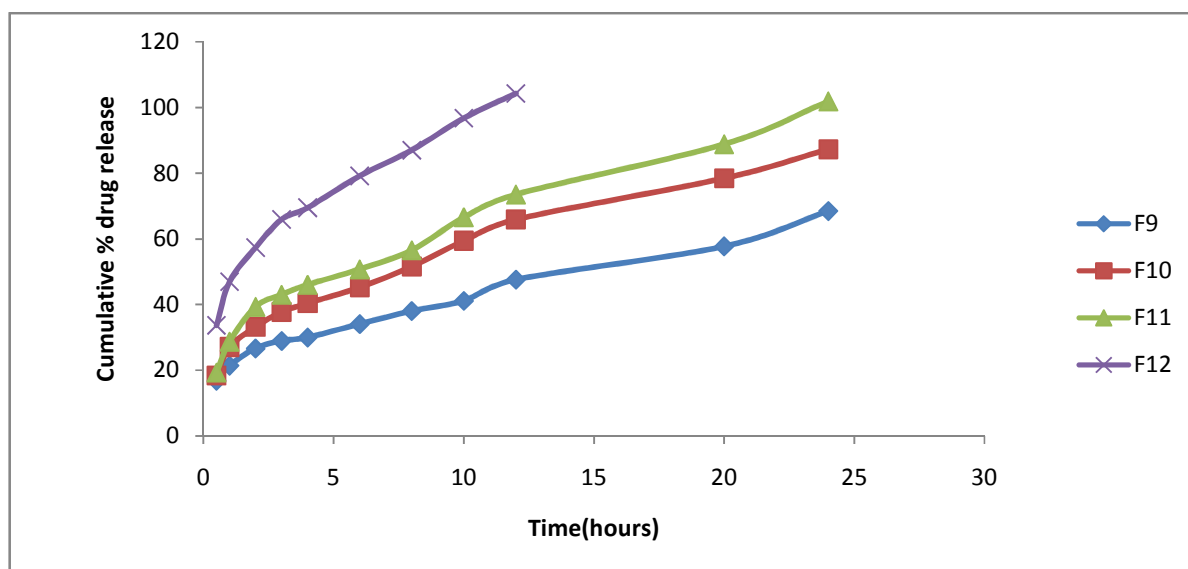


Fig. 3: Release Profiles of carbamazepine from HPMC K100M bilayer matrix tablets(F9-F12)

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