

STUDIES ON FORMULATION AND INVITRO EVALUATION OF GASTRORETENTIVE DRUG DELIVERY SYSTEM OF CARBAMAZEPINE

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ABSTRACT: The purpose of this study is to formulate gastroretentive floating tablets of carbamazepine and to optimize drug release profile. Hydroxypropylmethylcellulose (HPMC) of different viscosity grades and ethyl cellulose were used in formulating the gastric floating drug delivery system (GFDDS). Main effect and interaction terms of the formulation variables could be evaluated in terms of drug release. It was found that both HPMC viscosity, the presence of ethyl cellulose and their interaction had significant impact on the release and floating properties of the delivery system. The decrease in the release rate was observed with an increase in the viscosity of the polymeric system. Polymer with lower viscosity (HPMC K4M) was shown to be beneficial than higher viscosity polymer (K15M) in improving the floating properties of GFDDS. Incorporation of ethyl cellulose, however, was found to compromise the floating capacity of GFDDS and release rate of carbamazepine. The observed difference in the drug release and the floating properties of GFDDS could be attributed to the difference in the basic properties of three polymers (HPMC K4M, K15M and ethyl cellulose) due to their water uptake potential and functional group substitution.

Key words: HPMC, Ethyl Cellulose, GRDDS, Carbamazepine.

INTRODUCTION AND EXPERIMENTAL

Carbamazepine (CBZ) is used for anticonvulsant and antineuralgic effects. The popularity of this drug is related to several beneficial properties, including proven efficacy in controlling different types of seizures. CBZ is poorly soluble in water with erratic oral absorption and bioavailability less than 70%. Preparing the drug in a floating dosage form can control the extent of bioavailability for such a poorly water-soluble drug. The drug also presents a decrease in the half-life during chronic dosing due to metabolism autoinduction.¹ Carbamazepine comes under Biopharmaceutical Classification System (BCS) Class II drugs which exhibits low solubility and high permeability characteristics. Their oral absorbance is mostly governed by in vivo dissolution rate are therefore key determinants for the oral bioavailability of these drugs.² In view of this absorption characteristic, the hypothesis of the current investigation is that if the gastric residence time of a

carbamazepine -containing formulation could be prolonged to allow carbamazepine to reach the site of active absorption in a controlled manner, then the oral bioavailability of carbamazepine might thereby be increased. The controlled delivery system for carbamazepine would also be beneficial for patients with epileptic seizures, because carbamazepine will be released in a controlled manner.

Combined usage of hydroxypropyl methylcellulose (HPMC) and Carbopol in a mucoadhesive delivery has been reported³ to improve the mucoadhesiveness of the combined system. Marcos et al⁴ studied the potential of combining Carbopol 974P and HPMC K4M using propranolol hydrochloride as a model drug and found that the amount of water imbibed in Carbopol was lower than that by HPMC alone or 1:1 mixture of two polymers. K. Srivastava et al⁵ was made an attempt through investigation to formulate floating matrix tablets of atenolol using different polymers and their combinations. Drug release from HPMC K15M was

lesser owing to its high viscosity. Formulations containing a combination of two grades of HPMC were evaluated, addition of HPMC K4M increased the drug release, but the increase was not significant. D. M. Patel *et al*⁶, made an attempt to develop gastro-retentive drug delivery system of carbamazepine by melt granulation technique using HPMC, sodium bicarbonate, and ethyl cellulose as matrixing agent, gas generating agent and floating enhancer, respectively using simplex lattice design as an optimization technique.

The objective of this study was to systematically investigate the contribution of several formulation variables on the drug release rate and swelling properties of gastric floating drug delivery system (GFDDS) using carbamazepine as a model drug. To achieve this objective, the contribution of two independent formulation variables of the mixed polymeric GFDDS fabricated from a combination of polymers was examined. Independent variables evaluated included different ratios of HPMC K4M and K15M and the addition of ethyl cellulose. Dependent variables studied included release parameters, i.e. carbamazepine release at 12 h and swelling property.

MATERIAL AND METHODS

Carbamazepine was received from Encore Healthcare Pvt. Ltd., Paithan, HPMC K4M and K15M was received from Accutech Research Laboratories, Mumbai. Ethyl cellulose and PVP K 90 were purchased from the commercial sources Burgoyne Chemicals, New Delhi. Citric acid was purchased from S.D. Fine Chemicals Ltd., Mumbai. Sodium Bicarbonate and magnesium stearate were purchased from Rankem Chemicals Ltd., New Delhi. All other chemicals used were of analytical reagent grade and used as received.

Preparation of Gastroretentive Floating Tablets:

All ingredients except magnesium stearate were weighed properly and mixed separately in mortar in geometric order. Granules were prepared by adding 40% solution of PVP K90 in isopropyl alcohol as a binder by passing the wet mass through sieve no 14. The granules were dried in a hot air oven at 60 °C for 30 min. The dried granules were passed through a 22 mesh standard sieve and lubricated with magnesium stearate (1% w/w). Tablet was made by multi tooling lab scale punching machine (Karnavati, MiniPress II, Multi Tooling, Tablet Punching Machine.) at slow speed and high compression pressure to avoid capping. The total die content was compressed using 12 mm diameter flat faced punch tooling. Tablet of batches F1-F3 contains only HPMC K4M, tablets of batches F4-F6 contains polymeric mixture of HPMC K4M and HPMC K15M in 1:1 ratio, tablets of batches F6-F9 contains only HPMC K15M. Ethyl cellulose (5-10%) was added to the formulation which is outline in table 1.

EVALUATION OF FORMULATIONS

Different batches of formulation were prepared by varying concentration of ethyl cellulose using HPMC K4M, HPMC K15M and combination of HPMC K4M, HPMC K15M. All the formulations of tablets were evaluated for their flow properties, in-vitro buoyancy, swelling characteristic and drug release profile.

Physical characterization

The fabricated tablets were characterized for thickness (vernier caliper), hardness⁷ (n=10) (monsento hardness tester), friability (n=20)⁸, weight variation (n=20).

Drug content uniformity⁹

Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 60 mg of carbamazepine and boil in a flask with 25 ml of ethanol (95%) for a few minutes, stir the hot mixture in the closed flask for 10 minutes and filter through a sintered-glass funnel, washing the flask and funnel with ethanol (95%) and adding sufficient ethanol (95%) to the cooled filtrate to produce 100.0 ml. Dilute 5.0 ml to 250.0 ml with ethanol (95%) and measure the absorbance of the resulting solution at the maximum at about 285 nm. The content was calculated by using 1cm 1% equal to 490 at 285nm.

In vitro buoyancy study

The time required for dosage form to emerge on surface of medium called buoyancy lag time (BLT) or floating lag time (FLT). Duration of time by which the dosage form constantly emerges on surface of medium called Total floating time (TFT).^{10,11}

The in vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al*.¹² The tablets were placed in a 100-mL glass beaker containing 0.1 N HCl (pH 1.2) as per USP. The time required for the tablet to rise to the surface and float was determined as floating lag time and the time for which a tablet constantly floats on the surface of the medium was measured.

Determination Swelling Index

The swelling index of tablet was determined by placing one tablet in a beaker containing 100 ml of 0.1 N HCl (pH 1.2) at room temperature. After each hour the tablet was removed from beaker and weighed again up to 5 hours.¹³ The swelling index of the tablet was calculated by the formula,

$$S.I. = \left\{ \frac{W_t - W_o}{W_o} \right\} \times 100$$

Where, S.I. = swelling index.

Wt = weight of tablet at time t.

Wo = weight of tablet before immersion.

In vitro dissolution studies⁶

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) dissolution medium was filled in a dissolution vessel and the temperature of the medium was set at 37 ± 0.5 °C. 1 ml

of sample was withdrawn at predetermined time interval of 0 min., 30 min., 1 h and thereafter every hour for 12 h and same volume of fresh medium was replaced. The withdrawn samples were diluted up to 10 ml and filtered through 0.45 μ membrane filter. The resulting solution was analyzed by using Elico SL 164, Double Beam Spectrophotometer at 285 nm. Cumulative percentage drug release was calculated using an equation obtained from a calibration curve. The drug release profile is shown in Figure 1.

RESULT AND DISCUSSION

An attempt was made to develop a gastroretentive drug delivery system of carbamazepine using HPMC, sodium bicarbonate, and Ethyl Cellulose as matrixing agent, gas-generating agent, and floating enhancer, respectively. HPMC was selected as a matrixing agent, considering its widespread applicability and excellent gelling activity in sustained release formulations along with its safety, effectiveness, cost and availability. Sodium bicarbonate generates CO₂ gas in the presence of hydrochloric acid present in dissolution medium. The gas generated is trapped and protected within the gel (formed by hydration of HPMC), thus decreasing the density of the tablet. As the density of the tablet falls below 1 (density of water), the tablet becomes buoyant. Ethyl Cellulose was used as floating enhancer. It also works as a dissolution retardant, being insoluble in gastric pH.

The granules prepared for different batches were studied for flow property and micromeritic properties and was found to be excellent flow property. The drug was standardised using UV spectrophotometer (Elico SL 164, Double Beam Spectrophotometer) which shows good linearity in the range of 10-50 μ g/ml ($y=0.01895x$; $R^2=0.9996$).

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 6.367 ± 0.25 to 6.567 ± 0.15 kg/cm². Thickness of all the tablets was found in the range of 0.464 ± 0.005 to 0.480 ± 0.006 mm. Friability of all tablet was found below 1%. The drug content in all the batches of carbamazepine floating tablet was found within the range of 95-105% (i.e. a variation of $\pm 5\%$). This ensured the uniformity of drug content in table no.2

In vitro buoyancy study was studied, floating lag time and floating duration of tablet was determined simply by placing tablet in 500 ml beaker containing 0.1 N HCl. Observed floating lag time of nine formulations was found to be in the range of 26 to 76 second and floating duration was found to be in the range of 19 – 24 h.

Swelling index of formulation F7-F9 (HPMC K15M) was found to be more than formulation F1-F3 (HPMC

K4M) and formulation F4-F6 (combination of HPMC K4M and HPMC K15M 1:1). Hence the swelling property is solely controlled by viscosity of polymer. From the results of swelling study it was concluded that swelling increase as the time passes because the polymer gradually absorbed water due to hydrophilic in nature and swell. The finding also supported by Parakh¹⁴ et al, who studied water absorption rate of swellable matrices. They reported that water absorption rate increases as the viscosity of the polymer increases and at the end of experiment, polymer of the higher viscosity showed the maximum absorption. Thus, the viscosity of polymer had major influence on swelling process, matrix integrity as well as floating capability, hence from above result it can be concluded that the linear relationship may be there in between swelling process and viscosity of polymer. In vitro dissolution test was carried out in 0.1 N HCl for 720 min. Figure 1 shows the percent cumulative drug release of formulation F1-F9. From these results formulation F3, F8 and F9 showed sustained release behaviour was found to be but among these only formulation F9 releases more than 65% of drug in 12 hours which complies with the pharmacopoeial specification for carbamazepine extended release tablet.¹⁵

The formulations F1- F3 containing the HPMC K4M, the formulations F7- F9 containing HPMC K15M in same concentration but due to addition of ethyl cellulose in increasing proportion (5%, 7.5% and 10% respectively), the in-vitro drug release profile was found at optimum concentration of 10%. This shows that ethyl cellulose shows synergistic effect with HPMC as it increases release retardant effect of HPMC. In case of combination formulation F4, F5 and F6 containing polymeric mixture (HPMC K4M and HPMC K15M in 1:1 ratio) the same results were obtained with ethyl cellulose.

Hence as the viscosity of polymer increases in the formulation the release decreases which may be due to increased strength of the gel matrix of the HPMC. Similarly, presence of ethyl cellulose in the formulation also decreases the drug release, which may be attributed due to increased imbibitions of water into polymer.

CONCLUSION

Overall, this study concludes that viscosity is a major factor affecting the release and floating properties of the GFDDS. The higher viscosity seems to inhibit the initial burst effect of carbamazepine release from the GFDDS; however, it does not seem to affect the carbamazepine release rate thereafter. Ethyl cellulose, however, is found to compromise the release properties of drug candidate from GFDDS.

Table no.1: Composition of gastroretentive carbamazepine tablet.

	F1	F2	F3	F4	F5	F6	F7	F8	F9
CARBAMAZEPINE	200	200	200	200	200	200	200	200	200
HPMC K4 M	150	150	150	75	75	75	0	0	0
HPMC K15	0	0	0	75	75	75	150	150	150
ETHYL CELLULOSE	25	37.5	50	25	37.5	50	25	37.5	50
NaHCO₃	75	75	75	75	75	75	75	75	75
CITRIC ACID	25	25	25	25	25	25	25	25	25
PVP K90	15	15	15	15	15	15	15	15	15
Mg Stearate	5	5	5	5	5	5	5	5	5
MCC	25	12.5	0	25	12.5	0	25	12.5	0
TOTAL weight	520	520	520	520	520	520	520	520	520

*all weights are in milligram. NaHCO₃- Sodium bicarbonate, MCC- Microcrystalline Cellulose.

Table no. 2: Physicochemical characterization of gastroretentive tablets of carbamazepine.

Formulation code	Evaluation Parameters						
	Thickness \pm S.D. (cm) (n = 5)	Hardness \pm S.D. (kg/cm ²) (n = 3)	Friability (%)	Average weight variation \pm S.D. (n=10)	Drug content (%)	FLT \pm SD (SEC) (n=2)	Total Floating Time (h)
F1	0.464 \pm 0.005	6.467 \pm 0.21	0.542	0.5247 \pm 0.00663	97.72	26.545 \pm 5.52	19.30
F2	0.484 \pm 0.005	6.567 \pm 0.15	0.653	0.5275 \pm 0.00753	98.74	42.445 \pm 4.21	23.05
F3	0.474 \pm 0.005	6.500 \pm 0.20	0.575	0.5286 \pm 0.00628	98.16	34.990 \pm 5.01	20.15
F4	0.478 \pm 0.004	6.367 \pm 0.15	0.646	0.5245 \pm 0.00617	101.1	39.865 \pm 3.40	21.45
F5	0.476 \pm 0.005	6.467 \pm 0.21	0.428	0.5280 \pm 0.00757	97.17	76.140 \pm 12.40	23.30
F6	0.472 \pm 0.004	6.500 \pm 0.20	0.68	0.5273 \pm 0.00693	97.24	59.270 \pm 2.91	22.20
F7	0.480 \pm 0.006	6.433 \pm 0.23	0.621	0.5249 \pm 0.00593	97.92	64.985 \pm 5.00	22.45
F8	0.476 \pm 0.005	6.400 \pm 0.20	0.597	0.5265 \pm 0.00685	101.7	63.970 \pm 2.15	23.19
F9	0.474 \pm 0.005	6.367 \pm 0.25	0.567	0.5266 \pm 0.00734	99.08	61.820 \pm 3.49	23.40

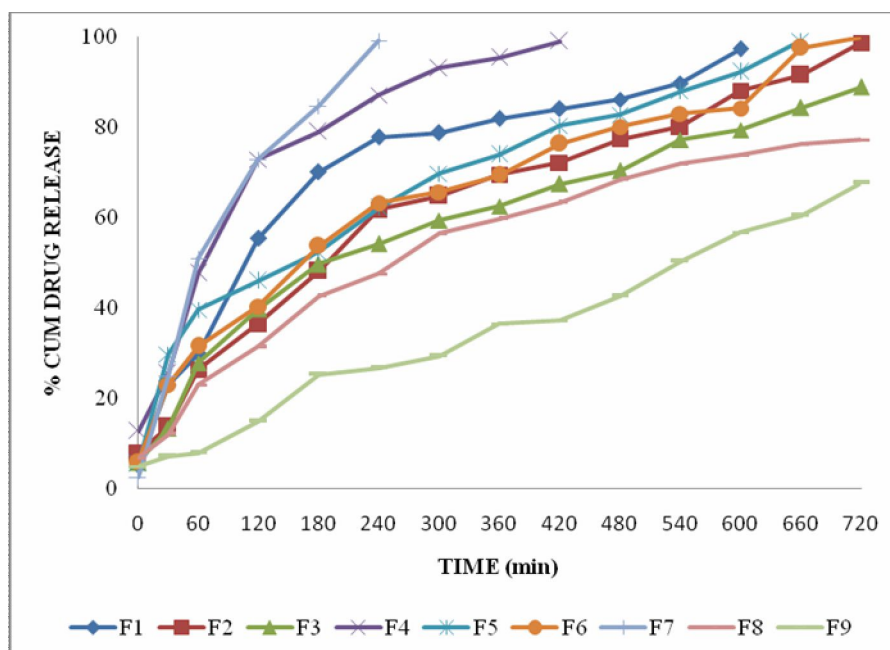


Figure 1: Percent cumulative release of formulation F1-F9.

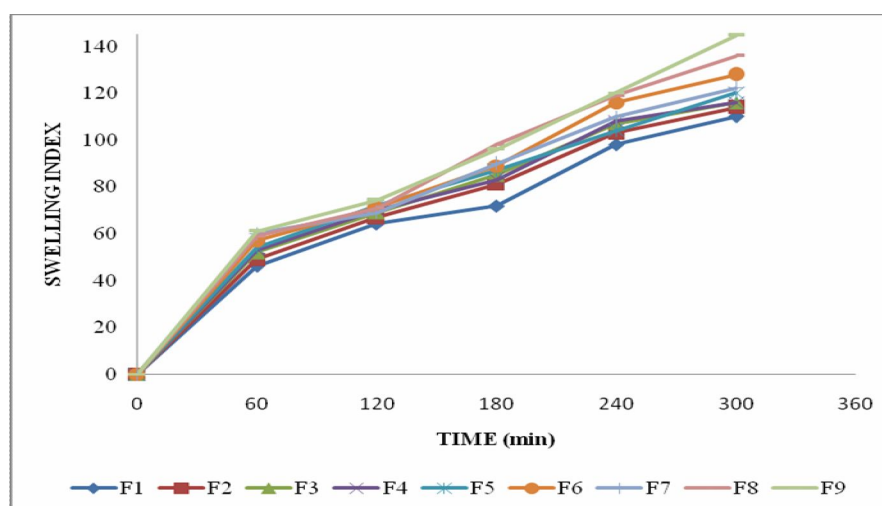


Figure 2: Swelling index V/S Time for formulation F1-F9

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