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Oral Sustained Delivery of Atenolol from Floating Matrix Tablets—Formulation and In Vitro Evaluation

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ABSTRACT Floating matrix tablets of atenolol were developed to prolong gastric residence time and increase drug bioavailability. Atenolol was chosen as a model drug because it is poorly absorbed from the lower gastrointestinal tract. The tablets were prepared by direct compression technique, using polymers such as hydroxypropyl methylcellulose (HPMC K15M, K4M), guargum (GG), and sodium carboxymethylcellulose (SCMC), alone or in combination, and other standard excipients. Tablets were evaluated for physical characteristics viz. hardness, swelling index, floating capacity, thickness, and weight variation. Further, tablets were evaluated for in vitro release characteristics for 8 hr. The effect of effervescent on buoyancy and drug release pattern was also studied. In vitro release mechanism was evaluated by linear regression analysis. GG- and SCMC-based matrix tablets showed significantly greater swelling indices compared with other batches. The tablets exhibited controlled and prolonged drug release profiles while floating over the dissolution medium.

KEYWORDS Atenolol, Swelling index, Floating matrix, Guargum, HPMC

INTRODUCTION

Floating drug delivery systems (FDDS) or hydrodynamically balanced systems were first described by Davis (1968). It is possible to prolong the gastric residence time (GRT) of drugs using these systems. Other approaches to prolong GRT include swelling, bioadhesive, altered density, and magnetic and extendable or expandable hydrogel systems (Brahma & Kwon, 2000). FDDS float due to their lower bulk density than the gastric contents or due to gaseous phase formed inside the system in the gastric environment (Michaels, 1979; Sheth & Tossounian, 1994). They remain buoyant in the stomach for prolonged period of time without affecting the gastric emptying rate of other contents. A floating dosage form is useful for those drugs that act locally in the proximal gastrointestinal tract (GIT), are unstable in lower parts of GIT, or are

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poorly absorbed in the intestine. An important issue in the development of such a dosage form is to ensure its presence in the upper GIT until the entire drug is released for the desired period of time (Deshpande et al., 1996; Hwang et al., 1998).

Various attempts have been made to develop a floating system. Empty globular shells with lower density than that of gastric fluid have been reported (Watanabe et al., 1976). Alternately, a system comprising a drug and hydrocolloid mixture, which swells to form a soft gelling mass, has been developed and evaluated (Sheth & Tossounian, 1978). Literature also includes a gel-type matrix with light oil incorporated with drug (Desai & Bolton, 1993), or a bilayer capsule with separate drug release and floating layers (Oth et al., 1992).

Atenolol is a cardioselective beta-1 adrenoceptor blocker devoid of intrinsic sympathomimetic and membrane-stabilizing activity. It is poorly absorbed from the lower GIT. The oral bioavailability of atenolol has been reported to be 50% (Melander et al., 1979). The human jejunal permeability and extent of absorption is also low (Amidon et al., 1995). Thus, it seems that an increase in GRT may increase the extent of absorption and bioavailability of the drug.

Based on this, an attempt was made through this investigation to formulate floating matrix tablets of atenolol using different polymers and their combinations. The prepared tablets were evaluated for physical characteristics such as hardness, weight variation, drug content uniformity, thickness, floating capacity, and swelling index. All the tablets were evaluated for in vitro release characteristics. The effect of effervescents on drug release from tablets was also studied.

MATERIALS AND METHODS

Materials

Atenolol was obtained as gift sample (Suchem Laboratories, Ahmedabad, India). Other chemicals and polymers such as hydroxypropyl methylcellulose (HPMC K15M, K4M) (G.S.C., Mumbai, India), polyvinylpyrrolidone (Sisco Research Lab, Mumbai, India), sodium carboxymethyl cellulose (SCMC) (Loba Chemical Pvt. Ltd., Mumbai, India), microcrystalline cellulose (MCC), guargum (GG), and dicalcium phosphate (all from S.D. Fine Chemicals, Mumbai, India) were obtained commercially and used as such.

Methods

Fabrication of Floating Matrix Tablets

Drug (atenolol), HPMC, GG, and SCMC were passed through sieve no. 80 separately. The drug was then mixed with the polymers and other ingredients in the weight proportion mentioned in Table 1. Magnesium stearate and talc were uniformly mixed with the above mixture, and compressed on a Manesty E_2 single-punch tableting machine using flat-faced punches (diameter 12 mm).

Evaluation of Formulations

Assay of Tablets

Six tablets from each batch were weighed and powdered. Powder equivalent to the average weight of the tablet was accurately weighed and transferred into a 100-mL volumetric flask and dissolved in a suitable quantity of distilled water. The solution was made up to the mark and mixed well. A portion of the sample was filtered and analyzed by a UV spectrophotometer (Double-beam Jasco 7800, Hachioji City, Tokyo, Japan) at 224 nm.

Floating Capacity

The floating capacity of the tablets ($n = 5$) was determined using a USP (type II) dissolution apparatus containing 900 mL of 0.1N HCl at 100 rpm. The time (min) taken by the tablet to reach the top from the bottom of the flask (floating lag time or FLT), and the time for which the tablet constantly floats on the surface of the medium (duration of floating), was measured.

Determination of Swelling Index

The swelling index of tablets was determined in 0.1N HCl (pH 1.2) at room temperature. The swollen weight of the tablet was determined at predefined time intervals. The swelling index was calculated by the following equation:

$$\text{Swelling index} = \frac{W_t - W_0}{W_0}$$

where W_0 is the initial weight of tablet, and W_t is the weight of tablet at time t.

TABLE 1 Effect of Formulation Composition on Floating Behavior

	Components (mg)													
Batch code	Atenolol	HPMC K4M	HPMC K15M	Sodium CMC	MCC	GG	NaHCO3	DCP	Citric acid	PVP K-30	Mg. Stearate (%w/w)	Talc (%w/w)	FLT (min)	Floating duration (hr)
HPMC K4M1	50	385	—	—	—	—	—	—	—	50	1	2	10	24
HPMC MCC-1	50	360	—	—	25	—	—	—	—	50	1	2	8.5	24
HPMC MCC-2	50	335	—	—	50	—	—	—	—	50	1	2	8.5	24
HPMC MCC-3	50	310	—	—	75	—	—	—	—	50	1	2	9	24
GG1	50	—	—	—	—	460	54	—	21	—	1	2	0	2.5
GG-HPMC-1	50	360	—	—	—	100	54	—	21	—	1	2	0	24
GG-HPMC-2	50	260	—	—	—	200	54	—	—	—	1	2	0	24
CMC1	50	—	—	385	—	—	—	—	—	50	1	2	0	3
HPMC K15M1	50	—	385	—	—	—	—	—	—	50	1	2	15	24
HPMC K4M-K15M-1	50	285	100	—	—	—	—	—	—	50	1	2	12	24
HPMC K4M-K15M-2	50	310	75	—	—	—	—	—	—	50	1	2	13	24
HPMC K4M-K15M-3	50	335	50	—	—	—	—	—	—	50	1	2	10	24
CMC-HPMC K4M-1	50	335	—	50	—	—	—	—	—	50	1	2	5	24
CMC-HPMC K4M-2	50	310	—	75	—	—	—	—	—	50	1	2	3	24
CMC-HPMC K4M-3	50	285	—	100	—	—	—	—	—	50	1	2	0	24
Effervescent 1	50	370	—	—	—	—	11	—	4	50	1	2	3	24
Effervescent 2	50	360	—	—	—	—	17	—	8	50	1	2	1.5	24
Effervescent 3	50	350	—	—	—	—	24	—	11	50	1	2	0	20
Effervescent 4	50	335	—	—	—	—	34	—	16	50	1	2	0	17
DCP1	50	322.5	—	50	—	—	—	12.5	—	—	1	2	9.5	24
DCP2	50	310	—	50	—	—	—	25	—	—	1	2	10	24
DCP3	50	285	—	50	—	—	—	50	—	—	1	2	8	24

Physical Characterization

The fabricated tablets were characterized for weight variation ($n = 20$), hardness ($n = 10$) (Monsanto hardness tester), and thickness using a screw-gauge micrometer (Campbell Electronics, Mumbai, India).

In Vitro Studies

Dissolution tests were conducted in triplicate for all the batches in a USP XXI dissolution rate test apparatus (type II). The release studies were performed at 100 rpm in 900 mL 0.1N HCl (pH 1.2) at 37±0.2°C. Five-milliliters aliquots were withdrawn at predefined intervals, and the volume of the dissolution medium was maintained by adding the same volume of fresh prewarmed dissolution medium. The absorbance of the withdrawn samples was measured spectrophotometrically at 224 nm.

Experimental results were expressed as mean±SD (standard deviation). Student's *t*-test was applied to determine the level of significance. One-way analysis of variance was also applied to check significant difference in drug release from different formulations. Differences were considered to be statistically significant at $p < .05$.

RESULTS AND DISCUSSION

Assay of Tablets

The drug content in all the batches of atenolol floating tablets was in the range of 95 to 105% (i.e., a variation of ±5%). This ensured the uniformity of the drug content in the tablets.

Floating Capacity

Floating capacity of fabricated tablets was determined in 0.1N HCl, and the results are presented in Table 1. The tablets of batch HPMC K4M1 exhibited FLT of 10 min. Incorporation of MCC reduced the FLT. MCC has a porous structure and may have more

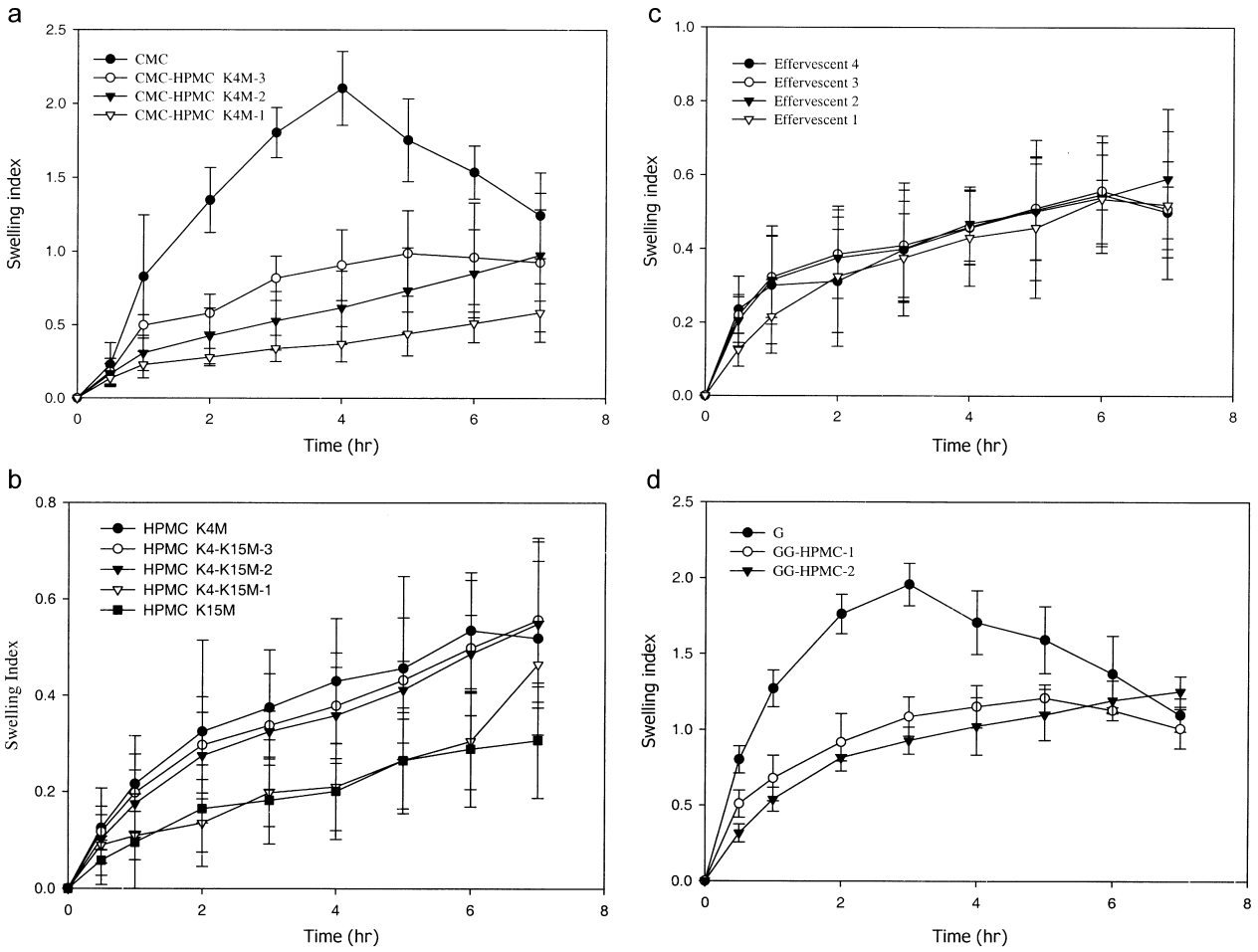

FIGURE 1 **Results of Swelling Index Studies of Atenolol Floating Matrix Tablets in 0.1N HCl (pH 1.2). (Bars Represent SD.)**

entrapment of air, which helps the tablets to float (Baumgartner et al., 2000).

Tablets containing effervescents showed much less FLT. Tablets of batch effervescent 3 and effervescent 4 started floating immediately (FLT = 0). The CO_2 generated by effervescent gets entrapped in the gel layer and helps the tablets become buoyant in less time. However, incorporation of larger amounts of effervescent may cause quicker depletion of tablet matrices (Deshpande et al., 1996; Hwang et al., 1998) with an expected decrease in floating duration. This was evident from the floating duration observed in batches effervescent 3 (20 hr) and effervescent 4 (17 hr).

Tablets of batches CMC1 and GG1 showed less FLT and less floating duration. Both are readily swellable polymers, and as a result, the tablets become buoyant in less time. Quicker loss of integrity may be the reason for decreased floating duration. Incorporation of HPMC K4M to formulations containing SCMC and GG increased the floating duration. HPMC takes more time in swelling and is also able to maintain the integrity of the tablets.

Physical Characterization

Weight variation data of the prepared tablets indicated no significant difference in the weight of individual tablet from the average value. Hardness of the prepared tablets was observed within the range of 2.5 ± 0.98 to 3.1 ± 0.72 kg/cm^2. Thickness of all the tablets was found in the range of 3.50 ± 0.46 to 3.92 ± 0.42 mm.

Swelling Index

Tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release. Kinetics of swelling is important because the gel barrier is formed with water penetration. Swelling is also a vital factor to ensure floating. To obtain floating, the balance between swelling and water acceptance must be restored (Baumgartner et al., 1998; Timmermans & Moes, 1990).

GG and SCMC showed significantly higher swelling indices and a faster rate of swelling compared with other polymers and their combinations. However, when HPMC K4M was incorporated in batches containing SCMC and GG, it resulted in decreased swelling index and swelling rate (Fig. 1a and 1d). Combination of HPMC K15M and K4M resulted in a higher swelling index compared with HPMC K15M alone (Fig. 1b). The HPMC grade also affects the swelling and hydration with considerably higher swelling index for HPMC K4M than HPMC K15M. Further, no significant effect of effervescents on swelling indices (Fig. 1c) was observed. Swelling index values start decreasing when polymer erosion starts in the medium. HPMC K15M exhibited low swelling index, but there was no decrease in swelling rate. The reason for this appeared to be its high viscosity and high water retention property.

In Vitro Drug Release

The performance of floating formulations has been reported to be greatly affected by physiological conditions such as food transport, gastrointestinal motility, and so on. A study (Rouge et al., 1998) on floating minitablets of atenolol has indicated lower bioavailability of drug. The reason for this lower bioavailability is attributed to small size of the dosage form, causing too short of a residence time and a premature exit from the stomach (Rouge et al., 1998). The tablets in this investigation are much larger in size and are expected to be retained for longer duration in upper GIT.

Four different polymers and their combinations (Table 1) were used to prepare floating matrix tablets. It was observed that the type of polymer influences the drug release pattern. A significantly higher rate and extent of drug release was observed from the batches based on GG and SCMC than those based on HPMC.

Although combination of SCMC and HPMC K4M sustains the drug release for a longer time, varying the amount of HPMC K4M did not affect the drug release (Fig. 2a). Drug release from HPMC K15M1 was lesser owing to its high viscosity. Formulations containing a combination of two grades of HPMC were evaluated (Fig. 2b). Addition of HPMC K4M increased the drug release, but the increase was not significant.

Formulations containing varying amounts of effervescents were prepared to observe the effect of its presence on drug release and also to find out the optimum amount of effervescent (Fig. 2c). Although the rate of release increased with increasing amounts of effervescent, statistical analysis indicated that the increase was not significant.

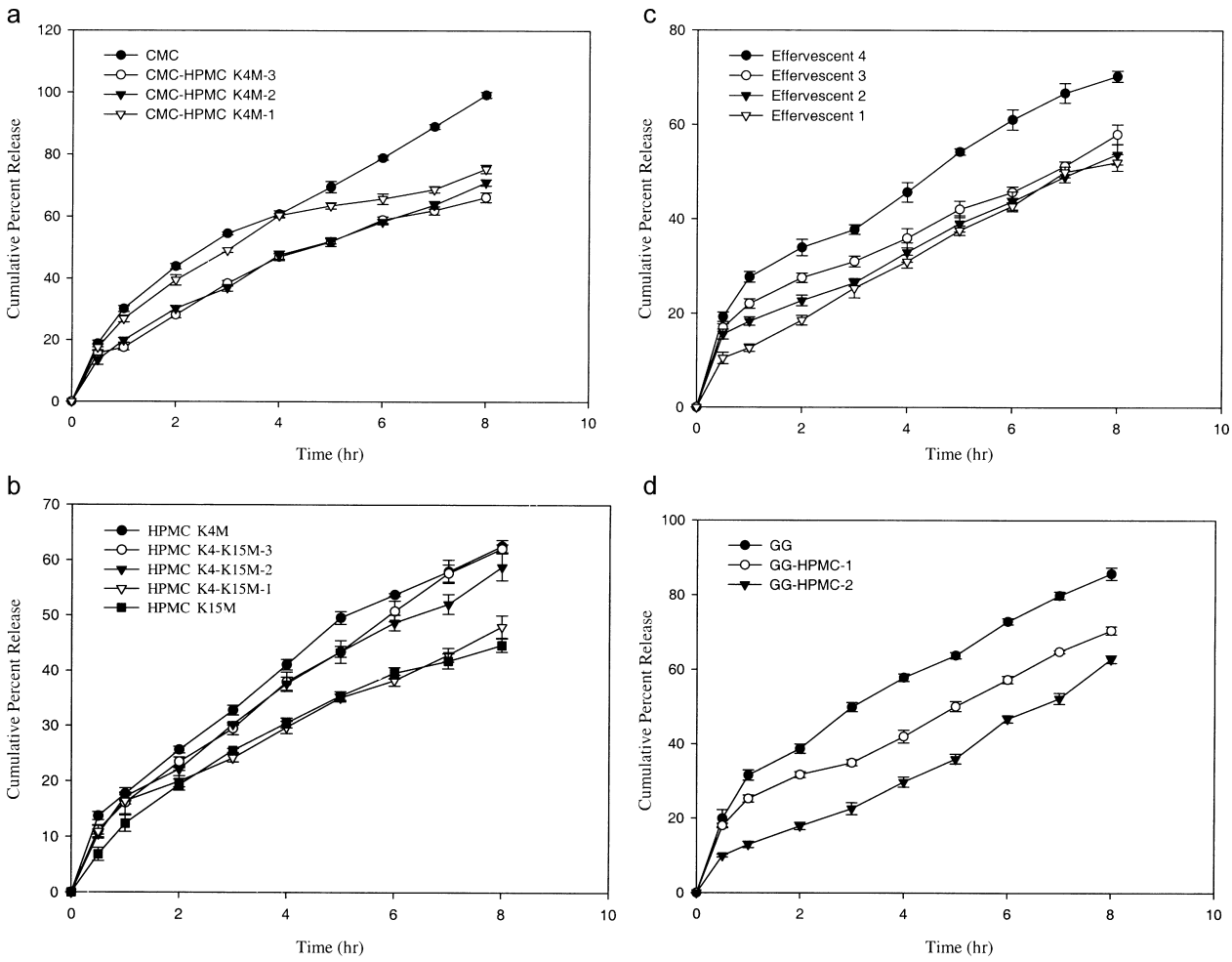

FIGURE 2 **In Vitro Release Profiles of Atenolol from Floating Matrix Tablets in 0.1N HCl (pH 1.2) Dissolution Medium. (Bars Represent SD.)**

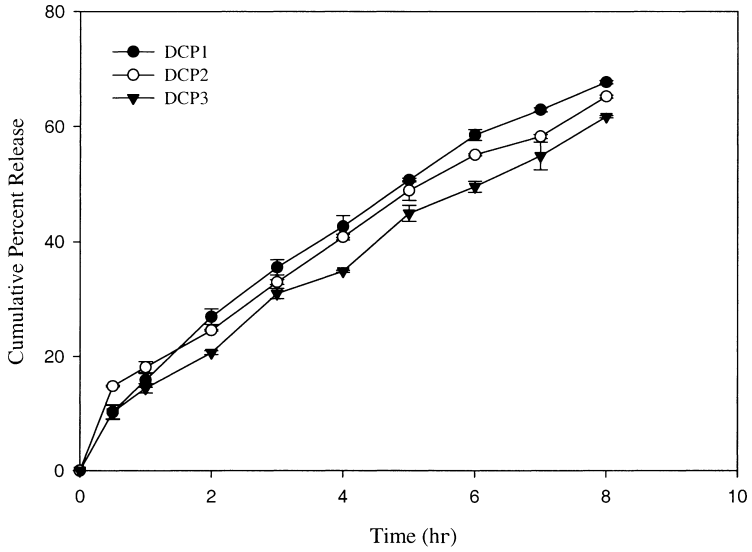

FIGURE 3 **Effect of Dicalcium Phosphate on In Vitro Release Profiles of Atenolol in 0.1N HCl (pH 1.2) Dissolution Medium. (Bars Represent SD.)**

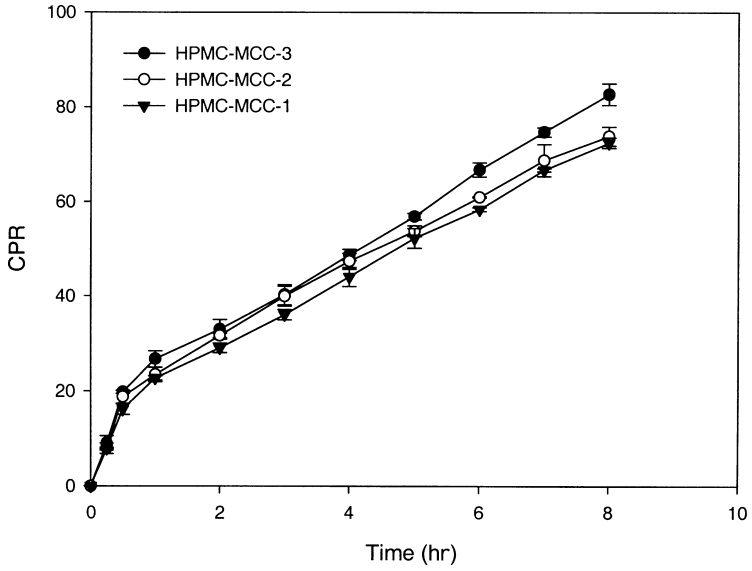

FIGURE 4 **Effect of Microcrystalline Cellulose on In Vitro Release Profile of Atenolol in 0.1N HCl (pH 1.2) Dissolution Medium. (Bars Represent SD.)**

It has been reported that incorporation of an insoluble excipient such as DCP decreases the drug release rate (Sheth & Tossounian, 1979). In this investigation, the release rate was not significantly affected by incorporation of DCP into HPMC K4M matrices (Fig. 3).

Varying the amount of MCC also exhibited a nonsignificant effect on drug release. The cumulative percent release (CPR) at the end of 8 hr was found to be 82.75% from batch HPMC-MCC-3 (Fig. 4) compared with 62.52% from batch HPMC K4M1.

Swelling index and in vitro drug release tend to increase together according to observed positive Pearson correlation coefficient of 0.862 and a *P* value less than .05, indicating a direct relationship among the two variables. It may, thus, be concluded that polymer swelling plays an important role in pattern and amount of drug release from the formulation.

CONCLUSION

Fabricated tablets showed acceptable weight variation, hardness, and uniformity of drug content. A lesser FLT and a prolonged floating duration could be achieved by varying the amount of effervescent and using different polymer combinations. CMC and GG exhibited higher swelling indices compared with other polymers. The in vitro drug release profiles obtained for tablets made with different polymers and their combinations allow efficient control of drug release. The type of polymer affects the drug release rate and the mechanism. Polymer swelling is crucial in determining the drug release rate and is also important for flotation.

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