

Floating bioadhesive drug delivery system using novel effervescent agents

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Oral sustained release gastroretentive dosage forms offer many advantages for drugs having absorption from the upper gastrointestinal tract and improve the bioavailability of medications that are characterized by the narrow absorption window. A new gastroretentive sustained release delivery system using the novel effervescent system was developed with floating, swellable, and bioadhesive properties. Various release retarding polymers like psyllium husk, HPMC K15M, and a swelling agent crosspovidone in different combinations were tried and optimized to get the release profile for 12 hours. The formulations were evaluated for physicochemical characteristics, *in vitro* drug release profile, swelling characteristics, floating capacity, and *in vitro* bioadhesive property. *In vitro* drug release followed the Higuchi kinetics and the release mechanism was found to be of a non-Fickian type. The swelling properties were increased with increasing crosspovidone concentration and contributed to the drug release from the tablet matrix. In this study, an attempt has been made to explore novel effervescent agents such as citroglycine and disodium glycine carbonate for achieving the desired floating time.

Key words: Atenolol, bioadhesion, floating matrix, gastroretentive delivery, novel effervescent agents, psyllium husk

INTRODUCTION

The floating drug delivery system (FDDS) or hydrodynamically balanced system was 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.^[1] FDDS float as their bulk density is lower than the gastric contents or due to the gaseous phase formed inside the system in the gastric environment.^[2,3] They remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate of the other contents. A floating dosage form is useful for those drugs that act locally in the proximal gastrointestinal tract (GIT), are unstable in the lower parts of GIT, or are poorly absorbed in the intestine.

Atenolol is a beta-adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic activities and it has been used for the treatment of hypertension, either alone or with other antihypertensives such as thiazide diuretics.^[4]

It is poorly absorbed from the lower GIT. The oral bioavailability of atenolol has been reported to be 50%.^[5] The drug is slightly water soluble and has elimination half life, after an oral dose, of six to seven hours. It is prescribed widely in diverse cardiovascular diseases, for example hypertension, angina pectoris, arrhythmias, and myocardial infarction.^[6] The drug is also frequently indicated in the prophylactic treatment of migraine. Administration of conventional tablets of atenolol has been reported to exhibit fluctuations in the plasma drug levels, resulting either in the manifestation of side effects or reduction in drug concentration at the receptor site.^[7,8]

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 a combination of different polymers. 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.

Various hydrophilic polymers, synthetic in origin, such as methylcellulose, HPMC, as well as those from the natural world, such as, guar gum and xanthan gum have been used to formulate oral sustained release formulations. Psyllium husk has the ability to swell and forms a hydrogel.^[9] It is biocompatible, inexpensive, inert, nonabsorbable, environment friendly, and easily available.^[10] Researchers have developed a novel,

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swellable, and bioadhesive gastroretentive dosage form using psyllium husk as a release retardant.^[11] However, its use as a release retardant has not been fully explored.

MATERIALS AND METHODS

Materials

Atenolol was obtained as a gift sample from Zydus-cadila, Ahmedabad, India. Psyllium husk was a kind gift from Emil Pharmaceuticals, Mumbai. HPMC K15M was a generous gift from Colorcon Asia Pvt. Ltd. Goa, India. Microcrystalline cellulose PH 101, Crosspovidone was supplied by Kopran Pharmaceuticals, Mumbai. Magnesium stearate was procured from S.D. fine chemicals, Mumbai. Effervescent agents, such as, citroglycine and disodium glycine carbonate (DSGC) were gifted by Tessenderlo Chemie, Belgium.

Methods

Fabrication of floating bioadhesive matrix tablets

Atenolol, HPMC K15M, and psyllium husk were passed through sieve no. 80, separately. The drug was then mixed with the polymers and other ingredients as mentioned in Table 1. Magnesium stearate was uniformly mixed with the above mixture in a polybag and then directly compressed on a rotary tablet machine (Rimek Mini Press I, Ahmedabad, India) using 9 mm flat faced punches.

Evaluation of formulation

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 buffer pH 1.2. 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 1700, Shimadzu, Japan) at 224 nm.

Floating capacity

The floating capacity of the tablets ($n = 5$) was determined using the USP (type II) dissolution apparatus containing 900 ml 0.1 N HCl at 75 rpm. The time (minutes) 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 floated on the surface of the medium (duration of floating or TFT) was measured.

Water uptake study (determination of swelling index)

The swelling index of the tablets was determined in distilled water at room temperature. The swelling property of the formulation was determined by various techniques.^[11] The water uptake study of the tablet was done using USP dissolution apparatus II. The medium used was distilled water, 900 ml, rotated at 50 rpm. The medium was maintained at $37 \pm 0.5^\circ\text{C}$ throughout the study. After selected time intervals, the tablets were withdrawn, blotted to remove excess water, and weighed. The swelling characteristics of the tablets were expressed in terms of water uptake (WU) as,

Table 1: Formulation composition of prepared batches of tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
Atenolol	50	50	50	50	50	50	50
HPMC K15M	60	60	60	40	80	60	60
Psyllium husk	10	20	30	10	10	10	10
DSGC	20	20	20	20	20	20	20
Citroglycine	8	8	8	8	8	8	8
Crosspovidone	48	48	48	48	48	0	28
Magnesium stearate	4	4	4	4	4	4	4
MCC	50	40	30	70	30	98	70

HPMC = Hydroxypropyl methylcellulose DSGC = Disodium glycine carbonate

MCC = Microcrystalline cellulose

$$WU = \frac{\text{Weight of the swollen tablet} - \text{Initial weight of the tablet \%}}{\text{Initial weight of the tablet}} \times 100$$

In vitro mucoadhesion study

The mucoadhesive strength of the tablet was measured on a modified physical balance.^[12-14] The apparatus consisted of a modified double beam physical balance in which the right pan was replaced by a lighter pan and the left pan was replaced by a Teflon cylinder suspended by a Teflon ring and copper wire. The left side of the balance was exactly 5 g heavier than the right side. Another Teflon block of 3.8 cm diameter and 2 cm height was fabricated with an upward protrusion of 2 cm height and 1.5 cm diameter on one side. This was kept in a petridish, which was then placed below the left hand set of the balance.

Porcine gastric mucosa was used as the model membrane and 1.2 pH solution was used as the moistening fluid. The Porcine stomach mucosa was obtained from slaughter house and was kept in tyrode solution at $37 \pm 0.5^\circ\text{C}$ for two hours. The underlying mucous membrane was separated and washed thoroughly with 1.2 pH solution. It was then tied over the protrusion in the Teflon block using a thread. The block was then kept in the petridish. Two sides of the balance were made equal before the study, keeping a 5 g weight on the right pan. The petridish with Teflon block was kept below the left hand set up of the balance. The tablet was stuck on the lower side of the hanging Teflon cylinder. The five-gram weight from the right pan was then removed. This lowered the Teflon cylinder along the tablet over the membrane with a weight of 5 g. This was kept undisturbed for three minutes. Then the weights on the right hand side were slowly added in an increment of 0.5 g, till the tablet just separated from the membrane surface. The excess weight on the right pan, that is, the total weight minus 5 g was taken as the measure of the mucoadhesive strength. From the mucoadhesive strength, the following parameter was calculated. Results are summarized in Table 2.

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength}}{100} \square 9.81$$

Physical characterization

The fabricated tablets were characterized for weight variation ($n = 20$), hardness ($n = 10$) (using Monsanto hardness tester, USA), friability ($n = 10$) (using Roche friabilator, India), and thickness (using digital micrometer screw gauge). The results are summarized in Table 2.

Dissolution study

The release of atenolol from the tablets was studied using USP dissolution apparatus (type II). The dissolution medium was simulated with gastric fluid without enzymes of pH 1.2 (900 ml). The rotation speed was 50 rpm. The temperature was maintained at $37 \pm 0.5^\circ\text{C}$. Five milliliters of aliquot was withdrawn at predetermined time intervals and the volume of the dissolution medium was maintained by adding the same volume of fresh prewarmed buffer every time. The absorbance of the withdrawn samples was measured spectrophotometrically at 224 nm.

Kinetic modeling of drug release

The dissolution profile of all the batches was fitted to zero order, first order, Higuchi equation, and Korsmeyer-Peppas equation to ascertain the kinetic modeling of drug release.

RESULTS AND DISCUSSION

Assay of tablets

The drug content in all the batches of atenolol floating bioadhesive tablets was in the range of 95-105%. This ensured the uniformity of the drug content in the tablets [Table 2].

Floating capacity

Floating capacity of the fabricated tablets was determined by placing the formulated tablets in a dissolution vessel containing 900 ml of acid buffer pH 1.2. Floating lag time was observed and was found to be different for various batches of prepared tablets. The total floating time for all the formulated batches was found to be more than 12 hours [Table 3].

Water uptake study

The 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. The percentage of swelling of the tablet was determined by the method previously described. Complete swelling was achieved by the end of seven hours. Thus, the percentage of swelling was determined at the end of seven hours for all the developed formulations. It was observed that as the concentration of the Psyllium husk increased, the percentage of swelling also increased (Batch F1 to F3). It was seen that the swelling had increased with varying concentrations of crosspovidone. Similarly, increasing concentrations of HPMC K4M also showed an increase in swelling, but not to the extent of psyllium husk. In all the formulations the maximum swelling was observed at eight hours, with a sharp increase for up to four hours, in all concentrations of crosspovidone. Thus swelling polymers of psyllium husk and HPMC K15M had definitely contributed to the swelling properties apart from their release retarding property. HPMC K15M swells immediately, while psyllium husk swells completely in three to four hours [Figure 1].

Dissolution study

Effect of different concentrations of psyllium husk on the *in vitro* release of atenolol was studied. Initially, in low concentration, psyllium husk could not retain its physical integrity for the desired period of time. As the concentration of the psyllium husk increased, the burst release as well as release in the latter hours decreased [Figure 2]. Psyllium husk formed a thick gel layer at a higher concentration, which could have contributed to the decrease in drug release. The drug associated with the surface of the tablet matrix could have also contributed to the initial burst release.

It was found that as the concentration of HPMC K15M increased there was a low burst release of the drug [Figure 3]. Also reduction in the drug release amount was obtained.

Thus, batch F1 containing 60 mg HPMC K15M was selected for further studies. Psyllium husk and HPMC K15M used

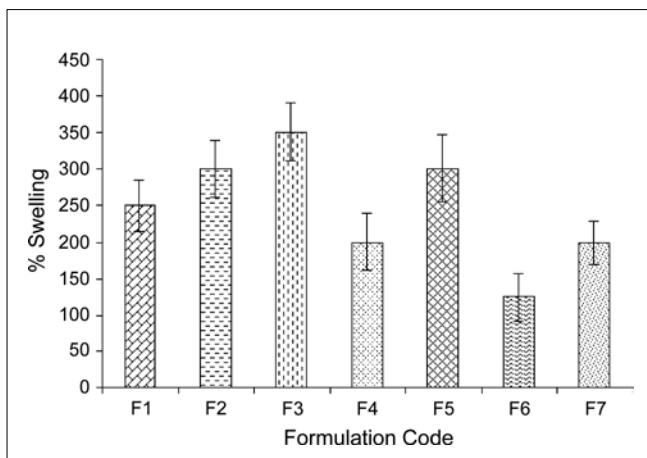
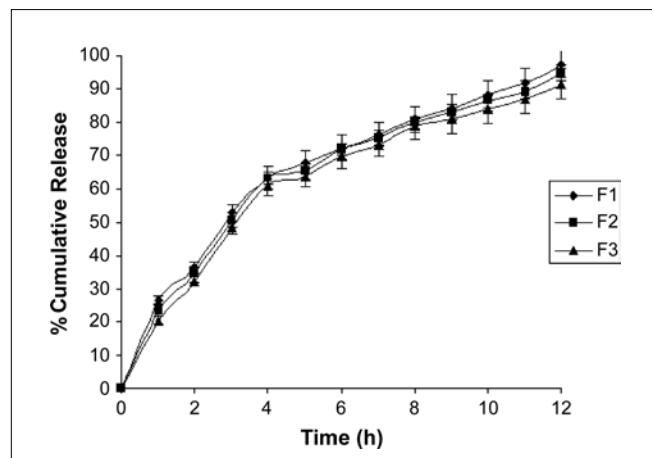
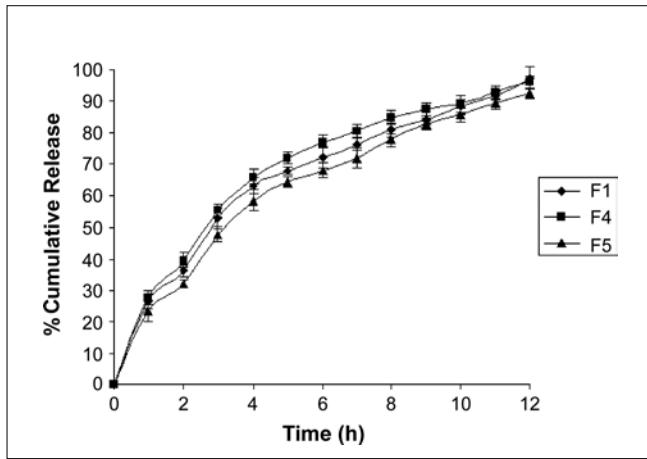
Table 2: Post-compression properties and mucoadhesive strength study of formulated batches

Batch	Thickness (mm)	Hardness (Newton)	Friability (%)	Drug content (%)	Weight variation (mg)	Mucoadhesion force (dyne/cm ²)
F1	3.62.05	40.2 ± 2.94	0.65 ± 0.07	98.45 ± 1.53	249.2 ± 2.04	11281.5
F2	3.59 ± 0.03	44.1 ± 4.9	0.59 ± 0.05	99.12 ± 1.27	248.5 ± 2.45	11772
F3	3.60 ± 0.04	39.2 ± 3.92	0.42 ± 0.09	98.78 ± 2.34	248.65 ± 3.12	12262.5
F4	3.57 ± 0.03	34.3 ± 1.96	0.56 ± 0.02	98.94 ± 1.45	249.45 ± 2.84	10104.3
F5	3.59 ± 0.02	39.2 ± 2.94	0.31 ± 0.05	97.78 ± 2.11	250.11 ± 1.98	12851.1
F6	3.60 ± 0.03	44.1 ± 5.88	0.71 ± 0.06	99.26 ± 2.78	248.65 ± 2.35	8829
F7	3.59 ± 0.01	39.2 ± 4.9	0.63 ± 0.03	98.56 ± 1.33	249.25 ± 1.78	9025.2

Table 3: Determination of floating capacity of formulated tablets

Formula	F1	F2	F3	F4	F5	F6	F7
FLT (sec)	145 ± 1.65	159 ± 2.40	167 ± 1.15	154 ± 1.70	172 ± 2.36	289 ± 3.06	254 ± 1.53
TFT	> 12 h for all the formulations						

FLT = Floating lag time; TFT = Total floating time

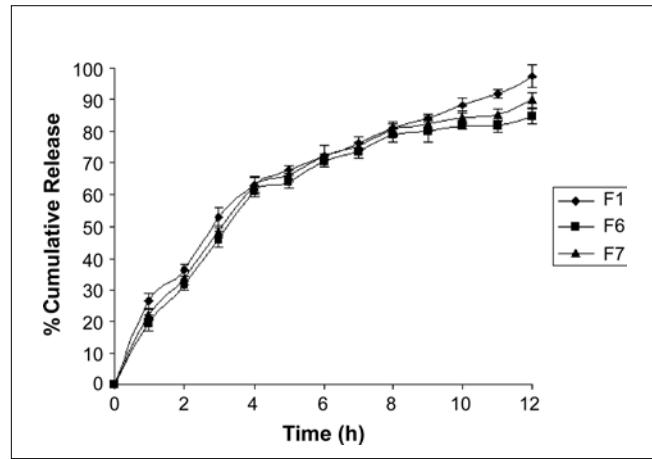
**Figure 1:** Effect of various concentrations of excipients on swelling index**Figure 2:** Effect of psyllium husk concentration on *in vitro* drug release of atenolol**Figure 3:** Effect of HPMC K15M concentration on *in vitro* drug release of atenolol

simultaneously formed a gel network, due to which the swollen mass of crosspovidone was restrained in the tablet and the tablet did not disintegrate. In order to improve the release profile, crosspovidone was used as a swelling agent. Different concentrations 0 mg (F6), 28 mg (F7), and 48 mg (F1) of crosspovidone were tried. As the concentration of crosspovidone increased, the drug release also increased [Figure 4].

Crosspovidone, when it comes into contact with an aqueous medium, swells immediately to at least twice its original volume.

Kinetic modeling of drug release

In vitro release data were fitted in various release kinetic models. The first order plots were found to be fairly linear as indicated by their high regression values ($r^2 = 0.963$ to 0.990). To confirm the exact mechanism of drug release from these tablets the data were fitted according to the Korsmeyer-Peppas equation. Slope values suggested that the release of atenolol from the floating bioadhesive tablets

**Figure 4:** Effect of crosspovidone concentration on *in vitro* drug release of atenolol

followed the non-Fickian transport mechanism. This means that water diffusion and also the polymer rearrangement or relaxation had an essential role in drug release [Table 4].

When n takes the value of 0.5, it indicates diffusion controlled drug release and for the value 1.0 it indicates swelling controlled drug release. Values of n between 0.5 and 1.0 can be regarded as an indicator for both phenomena (Anomalous transport). The value of n in case of optimized formulation is close to 0.5 indicating a diffusion-controlled drug release mechanism.

CONCLUSION

In conclusion, a developed gastroretentive sustained release delivery system, using novel effervescent agents with floating, swellable, and bioadhesive properties, gives sustained release of the drug, for over a period of 12 hours. Release retarding polymers like psyllium husk, HPMC K15M, and a swelling agent crosspovidone, can be used in combination, for getting sustained release of the model drug. In this study, an attempt

Table 4: Drug release kinetics of formulated tablets

Batch	Zero order (r ²)	First order (r ²)	Higuchi Korsmeyer-Peppas kinetics	release exponent (n)
F1	0.885	0.921	0.989	0.5163
F2	0.881	0.970	0.985	0.5482
F3	0.882	0.987	0.981	0.5849
F4	0.852	0.983	0.980	0.5781
F5	0.904	0.990	0.990	0.5637
F6	0.843	0.960	0.963	0.5863
F7	0.858	0.984	0.974	0.5577

has been made to explore novel effervescent agents such as citroglycine and disodium glycine carbonate, for achieving the required floating time. These novel effervescent agents may have a potential for use in the floating drug delivery system and may be suitable as an alternative to commonly used effervescent agents like sodium bicarbonate and citric acid.

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