RESEARCH ARTICLE

Development and investigation of gastro retentive dosage form of weakly basic drug

Samip S Shah[1], Shridhar J Pandya[1], Mahesh K Waghulade[2]

Departments of [1]Pharmaceutical Technology and [2]Pharmacognosy, Pioneer Pharmacy Degree College, Vadodara, Gujarat, India

The release of drug substance from controlled-release dosage forms is often pH-dependent since most drugs are either weak acids or weak bases. A system that permits the drug release to be changed freely while maintaining pH-independent drug release (model drug was Domperidone) was developed. Powder mixture of drug and HPMC K4M, eudragit L100, sodium bicarbonate (as gas-generating agent) and other excipients were mixed and directly compressed using single-punch tablet compression machine. It was found that sodium bicarbonate reacts with HCl and produce carbon dioxide which creates pores in tablet and elevates swelling by wetting the polymer. So it helps in maintaining the buoyancy. The release rate could be modified by varying the polymer ratio. The prepared tablets were evaluated for general appearance, content uniformity, hardness, friability, buoyancy, *in vitro* drug release and *in vivo* studies. The best formulation (D_1) was selected based on *in vitro* characteristics and was used *in vivo* radiographic studies by incorporating $BaSO_4$. These studies revealed that the tablets remained in the stomach for 250±30 min in fasted rabbits and indicated that gastric retention time was increased by the floating principle, which was considered desirable for the absorption window drugs. The linear regression analysis and model fitting showed that all these formulations followed Higuchi model, which had a higher value of correlation coefficient (r). The scanning electron microscopy images of the tablet (D_1 formulation) were taken before and after dissolution and images showed that the drug was released from matrix by diffusion mechanism. Stability studies of all formulations were carried out at elevated temperature and humidity conditions of 40±2°C/75±5% RH and a control sample was placed at an ambient condition for 12 months. It was found that there was no significant change in buoyancy property as well as in drug content from initial drug content of all the formulations at the end of 12 months, indicating that the formulations are stable.

Key words: *Domperidone, sustained release, intragastric floating tablet*

INTRODUCTION

In recent years, oral dosage forms for gastric retention have drawn more and more attention for their theoretical advantage in permitting control over the time and site of drug release.[1] The real challenge in the development of a controlled drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form in the stomach or the upper small intestine until all the drug is completely released in the desired period of time.[2] Gastro retentive drug delivery devices are primarily controlled release drug delivery systems, which gets retained in the stomach for longer period of time, thus helping in absorption of drug for the intended duration of time. This in turn improves bioavailability, reduces drug wastage, improves solubility of drugs that are less soluble at high pH environment (e.g. weakly basic drugs like domperidone, papaverine). It also helps in achieving local delivery of drug to the stomach and proximal small intestine. Gastric retentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs.[3] Many drugs categorized as once a day delivery have demonstrated to have sub optimal absorption due to dependence on transit time of the dosage form. Therefore, a system designed for longer gastric retention will extended the time within which drug absorption can occur in small intestine.[4] Thus it has been suggested that compounding the drugs with narrow absorption window in a unique dosage form prolongs gastric residence time and would enable an extended absorption phase of these drugs. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems or by the simultaneous administration of pharmacological agents that delay gastric emptying.[5]

Domperidone is chosen as a model weakly basic drug. It is a synthetic benzimidazole compound that acts as a dopamine D_2 receptor antagonist. Domperidone is also used as a prokinetic agent for treatment of upper

Address for correspondence:
Mr. Samip S Shah, Department of Pharmaceutical Technology, Pioneer Pharmacy Degree College, Vadodara, Gujarat, India.
E-mail: samipshah2008@yahoo.com

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gastrointestinal motility disorders. It continues to be an attractive alternative to metoclopramide because it has fewer neurological side effects. Patients receiving domperidone or other prokinetic agents for diabetic gastropathy or gastroparesis should be also managing dieting, lifestyle and other medications to optimize gastric motility. After oral administration, domperidone is rapidly absorbed from the stomach and the upper part of the GIT with fewer side effects. It is a weak base with good solubility in acidic pH but significantly reduced solubility in alkaline medium. Such a weak base, formulated as an oral controlled release dosage form is exposed to environments of increasing pH with subsequent precipitation of poorly soluble free base within the formulation that is no longer capable of being released from the formulation.[6,7]

The present study involved the design of gastro retentive floating matrix tablets of weakly basic drug (domperidone as model drug) by using HPMC K4M and eudragit L100 and their combinations. The prepared tablets were investigated for the effect of these polymers on the buoyancy behavior and *in vitro* release pattern of the drug. *In vivo* study was also carried out with the best formulation.

MATERIALS AND METHODS

Domperidone was obtained as a gift sample (Vaikunth pharmaceutical, Ankleshwar, India). HPMC K4M (Merck, Mumbai, India), Eudragit L100 (FMC Biopolymer, Mumbai, India), Sodium bicarbonate (Reachem Chemicals, Chennai, India), Micro crystalline cellulose (Sd Fine Chemicals, Mumbai, India), Magnesium stearate (Loba Chemical Pvt. Ltd., Mumbai, India), Talc (Swastic Pharmaceutical, Mumbai, India), Lactose (Reachem Chemicals, Chennai, India) used were of analytical grade.

Preparation of domperidone floating matrix tablets

The powder mixture containing drug, polymers and other excipients were weighed as per required quantity as mentioned in Table 1 and thoroughly blended in a mortar and pestle and then passed through sieve No. 100. An appropriate amount of the mixture was weighed and fed manually into the die of an instrumented Cadmach single-punch tablet machine using flat-faced non-beveled punch and die set of 8 mm diameter to get tablets of average weight 200 mg. The punched tablets were subjected to various evaluations.

Evaluation of physical property of floating matrix tablets

The thickness using a screw gauge micrometer, hardness (n = 6, Monsanto hardness tester), weight uniformity (n = 20) and % friability (n = 20, Roche friabilator) were determined in a similar manner as stated for conventional oral tablets in the accredited pharmacopoeia.[7,8]

Uniformity of drug content

Uniformity of drug content experiment was carried out by the procedure stated in the British pharmacopoeia.[9]

Table 1: Formulation composition of gastro retentive tablets of domperidone

Batch code	Dom	HPMC K4M	Eudragit L100	SB	MCC	MS	Talc	Lac	Total weight
D_1	20	40	-	28	26	5	5	76	200
D_2	20	40	24	28	26	5	5	52	200
D_3	20	48	-	28	26	5	5	68	200
D_4	20	48	-	36	26	5	5	60	200
D_5	20	40	32	28	26	5	5	44	200
D_6	20	40	-	20	26	5	5	84	200
D_7	20	40	-	24	26	5	5	80	200
D_8	20	-	24	28	26	5	5	92	200
D_9	20	30	24	28	26	5	5	86	200
D_{10}	20	48	32	28	26	5	5	36	200

*Quantities given for each tablet in mg; Dom = domperidone; SB = sodium bicarbonate as a gas-generating agent; MCC = microcrystalline cellulose as binding agent; MS = magnesium stearate as a lubricant; Lac = lactose as a diluent

Table 2: Result of *in vitro* study

Formulation	Floating lag time (sec)	Total floating time (min)	%CDR* after 8 hours	%CDR* after 14 hours
D_1	30	> 14	59.51	89.27
D_2	35	> 14	54.40	82.77
D_3	37	> 14	57.06	86.29
D_4	28	> 14	56.26	85.47
D_5	40	11	50.75	79.58
D_6	67	< 3	-	-
D_7	51	< 5	-	-
D_8	39	11.5	56.11	-
D_9	32	14	61.51	84.33
D_{10}	39	13	45.11	-

*%CDR, %cumulative drug release

Table 3: R^2 values for all the formulations

Batch code	Zero order	First order	Higuchi model	Korsmeyer model
D_1	0.9831	0.9434	0.9731	0.9615
D_2	0.9843	0.9670	0.9713	0.9528
D_3	0.9869	0.9569	0.9701	0.9634
D_4	0.9881	0.9575	0.9660	0.9561
D_5	0.9902	0.9618	0.9745	0.9495
D_6	-	-	-	-
D_7	-	-	-	-
D_8	0.9875	0.9165	0.9811	0.9235
D_9	0.9924	0.9255	0.9887	0.9387
D_{10}	0.9876	0.9399	0.9891	0.9448

In vitro buoyancy study

The *in vitro* buoyancy was determined by floating lag time as per the method described by Rosa *et al*. The tablets were placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as buoyancy lag time. Total floating times were measured during *in vitro* dissolution studies.[10]

***In vitro* drug release study**

The release rate of domperidone from floating matrix tablets (n = 6) was determined as per British Pharmacopoeia (BP) using dissolution testing apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl at 37±0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 16 hours and the samples were replaced with fresh dissolution medium. The samples were filtered through 0.45 μ membrane filter and diluted to a suitable concentration with 0.1 N HCl. Absorbance of these solutions was measured at 283 nm using a Jasco V-350 UV-visible spectrophotometer. Duration of time the tablet constantly floats on dissolution medium was noted as total floating time.[11]

Scanning electron microscopy

Scanning Electron Microscopy of intact tablet containing formulation D_1 was done before and after dissolution of 24 hours. The morphological characters of these 2 scans were compared to hypothesize the mechanism of drug release and floating.

The surface of the tablets was studied by SEM. The preparation of the samples was accomplished by placing the intact tablets before and after 24 hours of dissolution by drying them to remove water content and placing these tablets on a specimen holder. The samples were coated with a goldpalladium target using a Novatec (Palazzuolo Sul Senio, Italy) vacuum evaporator for 15 minutes. SEM images were obtained at an acceleration voltage of 8 to10 kV. Study of the morphology of the particles using SEM was done, which provided information about the 3-D structure of the particles, with the resolution power up to 5-A. Imaging was done at a magnification of 200 μm and pressure of 0.98 torr.

Curve fitting analysis

Mathematical models, zero-order, first-order, Higuchi and Peppas were applied to analyze the release mechanism and pattern.[12]

Tablets for *in vivo* radiographic studies

Tablets of 5.879 mm thickness and of 200 mg mass were prepared. To make the tablet X-ray opaque, incorporation of $BaSO_4$ was necessary. The tablets were characterized for hardness, buoyancy lag time and buoyancy duration.

***In vivo* radiographic studies**

The protocol of radiographic studies on healthy rabbits was approved by the Animal Ethical Committee, K.S. Hegde Medical Academy (KSHEMA/AEC/068/2007). The study was conducted on four healthy rabbits, weighing between 1.8-2.5 kg. The tablets prepared for radiography (D_1) were administered orally with a glass of water. During the study, the subjects were not allowed to eat but water was available *ad libitum*. After ingestion of D_1 floating tablets containing barium sulphate, the rabbits were exposed to X-ray photography in the abdominal region, at the Veterinary Faculty, which has the authorization to perform this kind of imaging under the law on animal health. The X-ray photographs were taken at 1, 3 and 5 hours after administration of the tablets. The mean gastric residence time was calculated.[13,14]

Short-term stability study

The tablets were stored in an aluminum foil and subjected to elevated temperature and humidity conditions of 40±2°C/75±5% RH and a control sample was placed at an ambient condition. Both test and control samples were withdrawn at the end of every 2 weeks and evaluated for active drug content, *in vitro* buoyancy and drug release profile.

RESULTS AND DISCUSSION

The weight variation (n = 20) and thickness (n = 6) of all the floating matrix tablets were determined and found to comply with the standards of Indian pharmacopoeia. The hardness of all the formulations was in the range of 5.0±0.01 to 6.3±0.004 kg/cm^2. The percentage friability of all the formulations was ranged between 0.42±0.03% to 0.89±0.02% (n = 20). There was no significant difference in drug content among different batches, though the experimental parameters were changed i.e. changing the polymer concentrations. So, it was evident from the results that these parameters had least effect on drug content. The duration of *in vitro* buoyancy was carried out [Figure 1]. The amount of sodium bicarbonate concentration was optimized by preparing the tablets with 10% (D_6), 12% (D_7) and 14% (D_1) sodium bicarbonate. It was found that the floating time of tablets containing 10% of sodium bicarbonate was less than 3±0.07 hours and tablets containing 12% of sodium bicarbonate was around 5±0.04 hours whereas the tablets with 14% sodium bicarbonate exhibited the *in vitro* buoyancy for more than 8±0.02 hours. Hence we used 14% of sodium bicarbonate in all formulations.

By comparing the values of *in vitro* dissolution studies [Figure 2], the highest drug release was shown by D_1 (89.27%). After carrying out *in vitro* studies of all the ten formulations, it was concluded that the formulations having less polymer exhibits better release of drug [Table 2]. As the concentration of HPMC K4M increases from 20% to 24%, the release rate was decreased. Theoretically speaking, this behavior is expected one since a more amount of polymer always delays the release. However when the release of D_1 is compared with D_2 [Figure 3], it was found that eudragit L100 decreased the release marginally (82.77% against 89.27%). Formulation containing both HPMC K4M and eudragit L100 showed less release in comparison of formulation containing only HPMC K4M. This is due to the presence of eudragit L100. Formulation containing only HPMC K4M (D_1) released the drug at better rate than any other formulations. This is due to the hydrophobic nature of the polymer. Further when the

quantity of polymer increased the release rate decreased (D_1 Vs D_3). When eudragit L100 was added in the formulation, the release was marginally reduced initially (D_2).

In comparison to the HPMC K4M polymer, theoretically speaking, eudragit L100 polymer being insoluble in acidic pH must release the drug in acidic pH very slowly. However, in the present study, the drug incorporated is basic in nature and the presence of sodium bicarbonate, which predominates the basic pH nature in the formulation, makes the polymer soluble to some extent. But, the dissolved polymer also imparts pH changes as it is acidic in nature. Hence the complex nature of these developments might have lead to the initial slow release of the drug. When D_2 formulation compared with D_5, the higher amount of eudragit L100 polymer released the drug further marginally less in the beginning. Comparison of D_1 vs D_2 and D_4 vs D_5 [Figure 4], where part of filler lactose was replaced by eudragit L100, reduces the release of drug marginally. The quantity of sodium bicarbonate did not reflect on the release rate (D_3 Vs D_4). Hence no significant change in the release rate was observed. For a basic drug, even though the dissolution media is acidic, the pH at the solid surface in the diffusion layer ($p^H_b = 0$) is basic depending on the strength of the base. In the current study, the pH regulation within the matrix is achieved using an excipient (HPMC K4M), which then affects the release rate of the drug, another factor that was thought to be responsible for the retardation of release, when using eudragit L100 is the fact that the polymer is less soluble (< 1.5 g/100 ml) than the filler lactose (21.6 mg/100 ml). Hence, if the polymer does not modulate the matrix pH, an increase in matrix porosity due to the dissolution of the polymer is the predominating factor due to which we may see enhancement using insoluble fillers and retardation using soluble fillers. Hence, by replacing a portion of the highly soluble filler with less soluble polymer, a lowering in matrix porosity will be seen and the converse is true for insoluble fillers.

The scanning electron microscopy images of the tablet were taken before and after dissolution. Figure 5a showed intact surface without any perforations, channels or troughs. After dissolution, the solvent front enters the matrix and moves slowly toward the center of the tablet. The drug diffuses out of the matrix after it comes in contact with dissolution medium. The images of the tablet showed a network in the swollen polymer through which the drug diffused to the surrounding medium, as shown in Figure 5b. Thus, it was concluded that the drug was released from matrix by diffusion mechanism. The linear regression analysis and model fitting showed that all these formulations followed Higuchi model, which had a higher value of correlation coefficient (r). The release mechanism of all the formulations followed zero-order kinetics [Table 3].

In vivo studies were conducted on healthy rabbits to find the gastric residence time of the tablet. The studies were based on X-ray radiography. Images were taken at different time points to find the location of the tablet 250±30 min (n = 4) [Figure 6]. The gastric retention time was increased by the floating principle, which was considered desirable for the absorption window drugs.

For all the 10 formulations stability studies were carried out at elevated temperature and humidity conditions of 40±2°C/75±5% RH and a control sample was placed at an ambient condition for a period of 12 months. It was found that there was no change in buoyancy property of all the

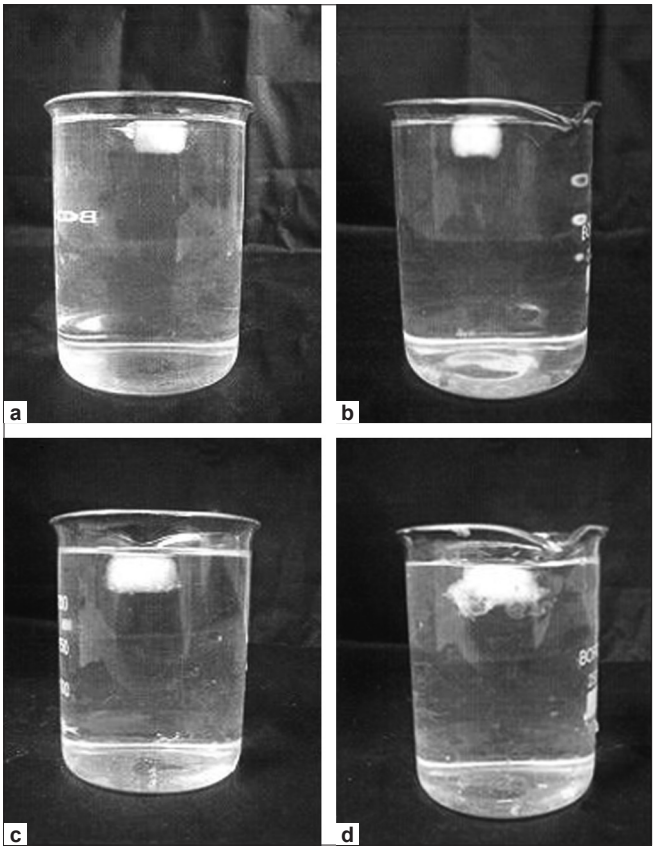

Figure 1: Floating properties (a) after 1 h, (b) after 3 h, (c) after 5 h and (d) after 8 h

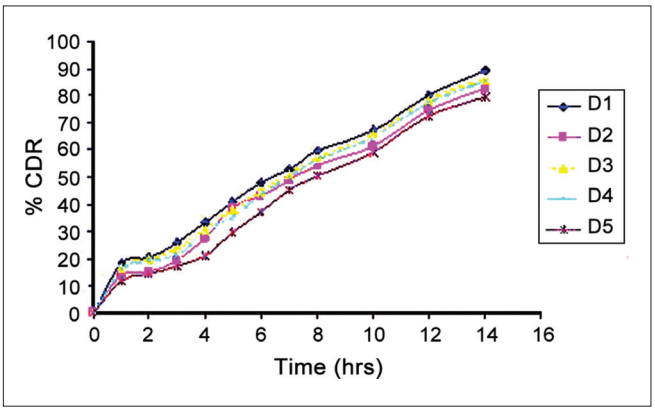

Figure 2: Drug release profiles of domperidone floating tablets (mean±SD, n = 4)

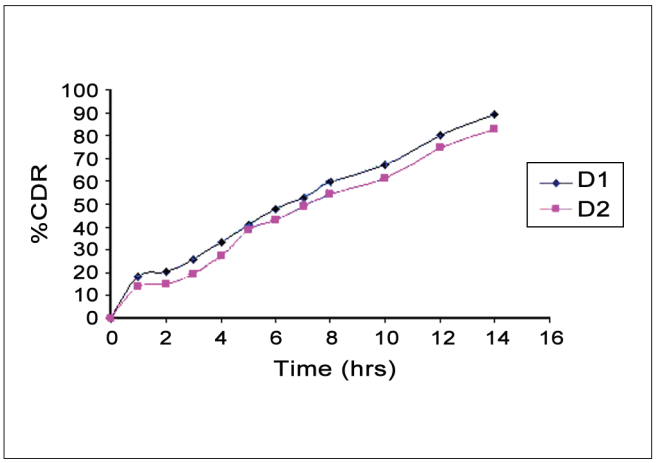

Figure 3: Comparison of drug release profiles of D1 and D2 (mean±SD, n = 4)

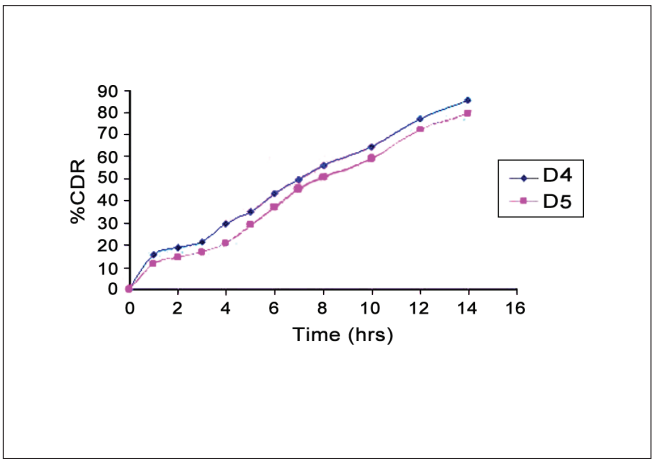

Figure 4: Comparison of drug release profiles of D4 and D5 (mean±SD, n = 4)

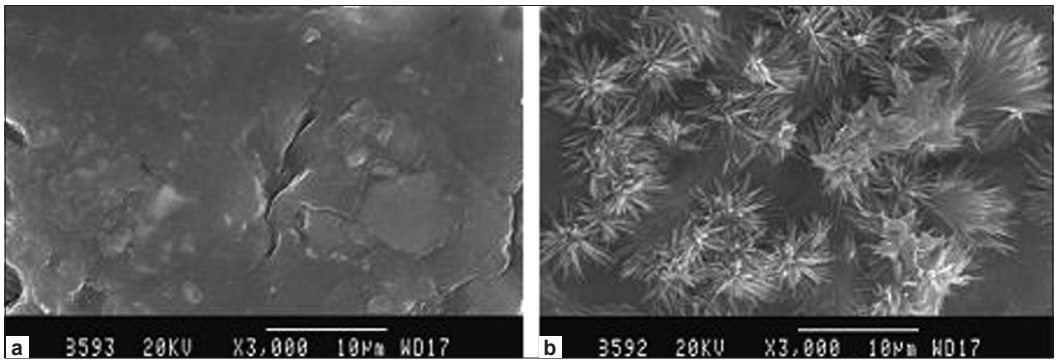

Figure 5: Scanning electro microscopy of the D1 formulation (a) before dissolution and (b) after 14 h

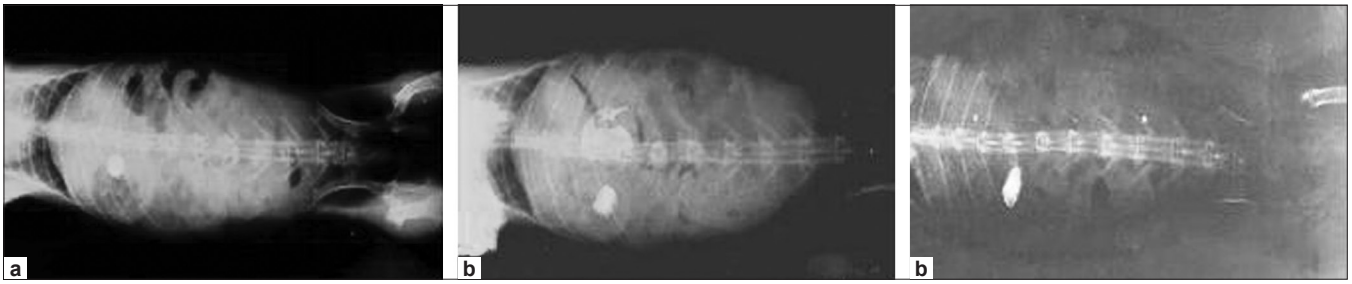

Figure 6: Radiographic images showing the presence of A $BaSO_4$

10 formulations at the end of 12 months. The drug content was obtained every 2 weeks up to 12 months showed that the drug content did not differ from initial drug content by more than 5%, indicating that the formulations are stable.

CONCLUSION

Formulation D_1 gave better controlled drug release and floating properties in comparison to the other formulations. This formula took 30 second to become buoyant. The gastro retentive floating drug delivery is a promising approach to achieve *in vitro* buoyancy and thereby longer gastric residence time for weakly basic drug by using gel-forming polymer HPMC K4M and gas-generating agent sodium bicarbonate. *In vivo* experiments supported the expectations in prolonging the gastric residence time in the fasted state in rabbits. The radiographic studies revealed that D_1 tablets remained in the stomach for 250±30 min (n = 4). This result is encouraging because a longer gastric residence time is an important condition for higher bioavailability of the drugs included in the prolonged/controlled release dosage forms.

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