Preparation and *in vitro* evaluation of bilayer and floating-bioadhesive tablets of rosiglitazone maleate

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Received 7 April 2007; Revised 26 June 2007; Accepted 5 September 2007

Abstract

Purpose: The aim of the present research was to develop a bilayer and floating-bioadhesive drug delivery system exhibiting a unique combination of floatation and bioadhesion to prolong residence in the stomach using rosiglitazone maleate as a model drug. **Methods:** The sustained layer was compressed and granules of the floating layer were added to it then both layers were compressed using a single station rotary press. Granules and tablets were characterized using the official method. Hydroxypropyl methylcellulose (HPMC) and sodium bicarbonate were added to the floating layer and, when immersed in 0.1 mol/l HCl, the tablet expands and rises to the surface where the drug is gradually released without interference from gas bubbles. The *in vitro* drug release, buoyancy lag-time, detachment force and swelling index were evaluated. The *in vitro* drug release from the tablet was controlled by the amount of HPMC in the sustained release layer. The floating ability of the tablets was studied by gamma scintigraphy. **Results:** The release of rosiglitazone maleate from the tablets followed the matrixfirst-order release model. The concentration of HPMC significantly affects the drug release rate, buoyancy lag-time, detachment force and swelling characteristics of the tablets. The tablet was buoyant for up to 8 h in the human stomach.. **Conclusion:** This kind of tablet exhibits independent regulation of buoyancy and drug release.

Keywords: Rosiglitazone maleate; Bilayer and floating-bioadhesive tablet; Detachment force; Gamma scintigraphy

1. Introduction

Rosiglitazone maleate (±)-5-[[4-[2-(methyl-2-pyridinylamino) ethoxy]-phenyl] methyl]-2, 4-thiazolidinedione, (Z)-2-butenedioate is an oral antidiabetic agent, which acts primarily by increasing insulin sensitivity. It is effective only in the presence of insulin. It decreases insulin resistance at peripheral sites and in the liver. This results in insulin-dependent glucose disposal and reduced hepatic glucose output. The half-life of rosiglitazone maleate is 3-4 h and it reaches a peak plasma concentration after 1 h. It is highly soluble in 0.1 mol/l HCl (11.803 mg/ml) and its solubility decreases with increasing pH over the physiological range [1, 2, 3]. Several methods have been reported which can be used to retain the dosage form in the stomach, which then results in the drug slowly spreading over the absorptive surface. A gastroretentive dosage form will release the drug over an extended period in the stomach and upper gastrointestinal tract (GIT) thus enhancing the opportunity for absorption.

Various approaches have been proposed to control the gastric residence of drug delivery systems in the upper part of the GIT including floating drug delivery systems (FDDS) [4, 5] high density DDS [6], mucoadhesive systems [7, 8, 9], swelling and expanding DDS [10], modified shape systems [11] and other delayed gastric devices [12]. FDDS is a gastroretentive dosage form (GRDF), which can prolong the gastric residence time (GRT) to produce an acceptable drug bioavailability [13, 14]. FDDS is suitable for drugs with an absorption window in the stomach or the upper small intestine [15], for drugs which act locally in the stomach [16] and for drugs that are poorly soluble or unstable in the intestinal fluid [17]. FDDS or hydrodynamically balanced systems have a bulk density lower than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time [11]. Based on the mechanism of buoyancy, two distinctly different

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technologies, *i.e.* non-effervescent and effervescent systems, have been used in the development of FDDS. The effervescent system uses matrices prepared with swellable polymers and effervescent components *e.g.* sodium bicarbonate and citric acid or stearic acid. In non-effervescent FDDS, the drug mixes with a gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration to maintain a relatively stable shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy on these dosage forms [11, 18]. In a bioadhesive system, the dosage form adheres to the gastric mucosa ensuring sustained release of the drug from this site [11]. In this study, an effervescent floating system and a bioadhesion system were used in combination. Floating dosage forms are meant to remain floating on the gastric fluid when the stomach is full after a meal. However, as the stomach empties and the tablet reaches the pylorus, the buoyancy of the dosage form may be reduced. It may be that the dosage form will then pass through the pylorus into the small intestine. Thus, the buoyancy of an FDDS in the stomach may be limited to only 3–4 h. Furthermore, floating systems do not always release the drug at the intended site. In a bioadhesive drug delivery system, it is quite likely that the system becomes dislodged from the stomach mucosa wall when the system is full and the semi-liquid contents are churning around due to the effect of peristalsis [19]. A floating-bioadhesive system would overcome these drawbacks of floating and bioadhesive systems and would have a significant effect on improving the therapeutic effect of the drug involved [20].

The purpose of this work was to develop a novel sustained release tablet with a unique combination of bioadhesion and floatation to prolong the gastric residence time of rosiglitazone maleate, which is absorbed from the gastrointestinal tract while its solubility decreases with increasing pH over the physiological range.

2. Materials and methods

2.1. Materials

Rosiglitazone maleate was supplied by Cipla Pharmaceutical Ltd. (Pune, India). Methocel K100M, starch 1500, and maize starch were gifts from Emcure Research Center (Pune, India). Dicalcium phosphate and sodium bicarbonate were purchased from Nulife Pharmaceuticals (Pune, India). All solvents used were of analytical grade.

2.2. Preparation of bilayer and floating-bioadhesive tablets of rosiglitazone maleate

Rosiglitazone maleate bilayer tablets contained two layers *i.e.* a floating layer and a sustained release (SR) layer. All ingredients were passed through a sieve (60#) and mixed well in a mortar. Granules of the floating layer were prepared using a 5% (w/v) PVP ethanolic solution. Weighed quantities of the SR layer equivalent to 150 mg were subjected to mild compression. Weighed granules of the floating layer equivalent to 140 mg were added to the compressed SR layer and both the layers were then compressed in a single station rotary press (Rimek Mini Press II) using a 13 mm diameter die.

2.3. Characterization of granules

The characteristic parameters of the granules were evaluated. The angle of repose and flow rate were determined by the funnel method. The bulk density and tapped density were determined by the cylinder method and Carr's index was calculated using the following equation 1.

$$\text{Carr's index} = \frac{D_f - D_0}{D_f} \times 100 \quad (1)$$

Where, D_f = Poured bulk or bulk density, D_0 = Tapped or consolidated bulk density

2.4. Characterization of tablets

2.4.1. Drug content and physical evaluation

The drug content of the tablets was determined using 0.1 mol/l HCl as a solvent, and the samples were analyzed spectrophotometrically (JASCO, V-530, Japan) at 318.5 nm. Tablets were also examined with regard to their weight variation ($n = 10$), friability ($n = 10$) and hardness ($n = 6$) [21].

2.4.2. Buoyancy lag-time studies

The buoyancy lag-time of the tablets was studied at 37 ± 0.5˚C, in 100 ml 0.1 mol/l HCl (pH 1.2). The time required for the tablet to rise to the surface and float was taken as the buoyancy lag-time.

2.4.3. Dissolution studies

The release rate of rosiglitazone maleate from floating tablets was determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 ml 0.1 mol/l HCl, at 37 ± 0.5˚C and 50 r/min. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly for 24 h, and the samples were replaced with fresh dissolution medium. The samples were passed through Whatman filter paper and the absorbance of these solutions was measured at 318.5 nm. The cumulative percentage drug release was calculated using 'PCP Disso v2.08' Software (Poona College of Pharmacy, Pune, India).

2.4.4. Detachment stress

The mucoadhesive forces of the bilayer tablets were determined by the measuring device shown in Fig. 1.

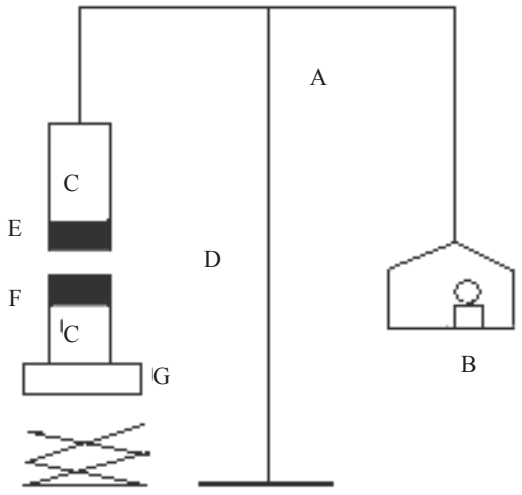

Fig. 1. Detachment stress measuring device.

*A, modified balance; B, weights; C, glass vial; D, Bioadhesive bilayer tablet; E, Intestine tissue; F, supportive adhesive tape; G, height adjustable pan [21].

Pieces of sheep fundus tissue were stored frozen in saline solution and thawed to room temperature immediately before use. At the time of testing a section of tissue (E) was transferred, keeping the mucosal side out, to the upper glass vial (C) using a rubber band and an aluminum cap. The diameter of each exposed mucosal membrane was 1.1 cm. The vials with the fundus tissue were stored at 37˚C for 10 min. Next, one vial with a section of tissue (E) was connected to the balance (A) and the other vial was fixed on a height-adjustable pan (F). A bilayer tablet (D) was applied to the lower vial with the help of two pieces of adhesive tape. The height of the vial was adjusted so that the tablet could adhere to the mucosal tissues in the vial. A constant weight (10 g) was placed on the upper vial and applied for 2 min, after which it was removed and the upper vial was then connected to the balance. Weights (B) were added at a constant rate to the pan on the other side of the modified balance of the device until the two vials were separated. The bioadhesive force, expressed as the detachment stress in dyne/cm^2, was determined from the minimum weight required to detached the two vials using the following equation 2 [22].

$$\text{Detachment stress (dyne/cm}^2) = m \cdot g/A \qquad (2)$$

2.4.5. Swelling characteristics

The swelling properties of HPMC matrices containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml 0.1 mol/l HCl at 37 ± 0.5˚C. The tablets were removed periodically from the dissolution medium and, after remooving free water, the weight gain was measured. The swelling characteristics were expressed in terms of the percentage water uptake (WU%) according to the equation 3 [23].

2.4.6. In vivo scintigraphic study

Gamma scintigraphy was used for monitoring the *in vivo* behavior of the oral dosage forms. Of the methods available, gamma scintigraphy is the most widely used noninvasive technique for studying the *in vivo* behavior

$$WU\% = \frac{\text{Weight of the swollen tablet} - \text{Initial weightof the tablet}}{\text{Initial weight of the tablet}} \times 100 \qquad (3)$$

of oral dosage forms under normal physiological conditions. The *in vivo* floating ability was studied by gamma scintigraphy in 3 healthy volunteers aged 23–26 years and a body weight of 60–70 kg. They were nonalcoholic, nonsmokers, and were not taking any other medication. The most common radionuclides used to correlate the gastro-intestinal behavior of dosage forms with their pharmacokinetic parameters, *i.e.* correlation of the location of the dosage forms in a certain region of the GIT to maximum plasma concentration, are Technetium-99 m (Tc-99) and Indium 111 (In-111) [24]. Tc-99 m is the most widely used radionuclide in nuclear medicine. It has a very short half-life of 6 h and emits photons but not particulate radiation (β rays harmful to tissues). A dose of 6 MBq Tc-99m was incorporated into the tablet blend during manufacture to facilitate scintigraphic imaging. The volunteers were asked to swallow a tablet of B5 (without drug) along with 100 ml water after taking a light breakfast in the morning. The dosage form was visualized using a gamma camera (low energy high resolution colorimeter integrated with an ENTEGRA work station) by moving the table under the camera. Images were recorded at intervals of 1, 2, 4 and 8 h.

2.5. Dose calculation

For sustained drug release up to 24 h, the total dose of drug required was calculated based on the fact that the conventional dose was 2 mg. The total dose was calculated using the following equation 4 [25],

$$D_t = \text{Dose}\ (1 + 0.693 \times t/t_{1/2}) \quad (4)$$

Where, D_t = Total dose, Dose = Immediate release dose, t = Total time period for which sustained release is required, $t_{1/2}$ = Half-life of drug. For rosiglitazone maleate: $D_t = 2\ [1+ (0.693 \times 24)/3.5)]$, D_t = 11.50 mg rosiglitazone and 15.2348 mg rosiglitazone maleate is equivalent to 11.50 mg rosiglitazone.

2.6. Stability studies

The stability studies were carried out according to ICH and WHO guidelines [17] to assess the drug and formulation stability. Optimized B5 formulations were sealed in aluminum packaging having a polyethylene coating on the inside. Samples were kept in a humidity chamber maintained at 45˚C and 75% RH for 3 months (Yorco Scientific Industries, India). At the end of the study period, samples were analyzed for drug content, buoyancy lag-time, buoyancy time and detachment stress.

3. Results and discussion

All formulations were prepared as two-layered tablets. The first layer contains a mixture of sodium bicarbonate, starch 1500 and HPMC K100M, with the HPMC K100M being used as a matrix material to retain the air bubbles. The first layer allowed the tablets to float. Sodium bicarbonate was added as a gas-generating agent. The ideal amount of both, effervescent mixture and polymer, for the floating layer was estimated by determining the onset time of floating. In an attempt to shorten the onset time by increasing the concentration of effervescent mixture, it was found that tablets were dispersed; on the other hand, a lower concentration prolongs this. The SR layer provided controlled release of active material and contains the drug, with HPMC K100M as a hydrophilic matrix material (Table 1). Hence, the unique combination of floating and bioadhesion is highly likely to prolong the gastric retention time of rosiglitazone maleate, resulting in high aqueous solubility and restricting GI absorption to the upper part of the small intestine.

The prepared granules of the floating layer were characterized with respect to the angle of repose, flow rate, bulk density, tap density and Carr's index (Table 2). The angle of repose was less than 25º for all the batches of granules indicating satisfactory flow behavior. Other granule parameters were also determined and found to be within acceptable limits. Table 2 shows that, as the concentration of HPMC increases, the angle of repose and Carr's index increase while the flow rate decreases.

3.1. Physical evaluation

The weight variation, friability, hardness and content uniformity were found to be within acceptable limits (Table 2). Thus, all the physical properties of these tablets were satisfactory as specified in the Indian Pharmacopoeia [19].

3.2. Buoyancy lag-time studies

All tablet formulations exhibited satisfactory floatation ability and remained buoyant for more than 24 h in dissolution medium subjected to rotation. The buoyancy lag-time of tablets depends on the amount of sodium bicarbonate involved in CO_2 formation. For a floating system, the ideal matrix or coating material should be highly permeable to dissolution media in order to initiate rapid generation of CO_2 and allow release of CO_2 to promote floating. Both the layers contain HPMC K100M, which leads to a reduced buoyancy lag-time. Formulations B1 to B5 showed buoyancy lag-times ranging from 6.56 ± 1 to 12.71 ± 1.56 min (Table 3). These results indicate that the buoyancy lag-time was satisfactory when using 40 mg sodium bicarbonate.

3.3. Detachment force

The values given in Table 3 indicate that the bioadhesive force increased significantly as the concentration of mucoadhesive polymer increased. All bilayer formulations showed mucoadhesive force in the range of 79.772 to 123.361 dynes/cm^2. Bioadhesion is a surface phenomenon in which a material of natural or synthetic origin adheres or sticks to a biological surface, usually mucus membrane. Many hydrophilic polymers adhere to mucosal surfaces as they attract water from the mucus gel layer adhereing to the epithelial surface. This is the simplest mechanism of adhesion and it has been defined as "adhesion by hydration". There are various kinds of adhesive force, *e.g.* hydrogen bonding between the adherent polymer and the substrate, *i.e.* mucus, which are involved in mucoadhesion at the molecular level [26]. So, as the concentration of polymer increases, the detachment force also increases.

3.4. Swelling characteristics

The percentage water uptake of the formulations (B1–B5) ranged from 144.084 to 272.907%. The percentage water uptake was found to be increased on increasing the concentration of HPMC K100M in the formulations and, hence, the water uptake capacity increases. Drug diffusion depends significantly on the water content of the tablet. This may be because the mobility of the polymer chains is very dependent on the water content of the system. In the case of a high water content, polymer chain relaxation takes place with volume expansion resulting in marked swelling of the system. Also, a higher water content could lead to greater penetration of the gastric fluid into the tablet leading to faster carbon dioxide gas generation, thereby reducing the floating lag-time. Consequently, faster and greater swelling of the tablet would lead to an increase in the dimensions of the tablet leading to an increasing in the diffusion pathways and, thus, a reduction in diffusion rate. So, the drug release was found to be high initially and then gradually decreased [27].

3.5. In vitro dissolution studies

The release data were evaluated by the model-dependent (Curve fitting) method using 'PCP Disso v2.08' software. The release rate kinetic data for all formulations are shown in Table 4. In present study, the matrix first-order model describing drug release from polymeric systems was used. The matrix first-order models takes into account the fact that the drug release mechanism often deviates from Fick's law and exhibits anomalous behavior described by the following equation 4,

$$M_t/M_\infty = k \times t^n \quad (4)$$

Where M_t is the drug released at time t, M_∞ is the quantity of drug released at infinite time, k is the kinetic constant and n is the release exponent. There are various release behaviors according to the geometric shapes of the drug delivery device. A tablet exhibits slab geometry and, if n takes the value 0.5, this means diffusion-controlled drug release and the value 1.0 indicates swelling-controlled drug release. A value of n between 0.5 and 1.0 can be regarded as an indicator of both phenomena (anomalous transport) [28]. The value of n for all the formulations is shown in Table 4. The value of n was found to range from 0.340 to 0.761 which increases as the concentration of polymer increases, showing that the release mechanism shifted in the direction of anomalous transport. The value of k ranged from 2.593 to 3.4533

Table 1
Formulations of bilayer and floating- bioadhesive tablets[a].

Ingredients	Floating layer	Sustained release layer				
		B1	B2	B3	B4	B5
Rosiglitazone maleate	–	15	15	15	15	15
HPMC K100M	50	15	22.5	30	37.5	45
Starch 1500	50	35	40	45	50	30
Maize starch	–	60	55	50	45	40
Sodium bicarbonate	40	–	–	–	–	–
Dicalcium phosphate	–	25	17.5	10	25	20

[a]HPMC indicates hydroxylpropyl methylcellulose. The floating layer contains ferric oxide as a colouring agent.

Table 2
Characterization of granules and tablets of rosiglitazone maleate[b].

Preparations	Parameters	B1	B2	B3	B4	B5
I. Granules	Angle of repose (º)	15 ± 1.3	17 ± 0.7	18 ± 2.8	21 ± 3.1	23 ± 1.8
	Flow rate (g/min)	1.16 ± 0.3	1.10 ± 0.9	0.98 ± 0.5	0.97 ± 0.5	0.90 ± 0.9
	Bulk density (g/ml)	0.588	0.594	0.602	0.625	0.638
	Tap density (g/ml)	0.714	0.769	0.782	0.833	0.909
	Carr's index	17.65 ± 2.0	23.53 ± 3.9	24.22 ± 1.2	25.0 ± 2.3	31.25 ± 1.6
II. Tablets	Weight variation (%)	± 2.0	± 4.0	± 3.0	± 2.0	± 1.0
	Friability (%)	0.32	0.25	0.11	0.18	0.16
	Hardness (kg/cm^2)	7.2 ± 0.2	8.1 ± 0.3	7.8 ± 0.2	7.3 ± 0.3	8.0 ± 0.2
	Content uniformity (%)	98.5 ± 1.6	98.6 ± 2.5	97.4 ± 2.7	97.3 ± 1.2	98.9 ± 1.4

[b]Each sample was analyzed in triplicate (n=3).

Table 3
Evaluation of bilayer and floating-bioadhesive tablets of rosiglitazone maleate[b].

Formulations	Buoyancy lag time (min)	Detachment force (dynes/cm^2)	Swelling characteristics
B1	12.71 ± 1.56	79.78	144.08
B2	10.7 ± 1.34	84.95	165.88
B3	7.93 ± 2.74	90.86	221.56
B4	6.98 ± 1.89	111.54	256.02
B5	6.56 ± 1.13	123.36	272.91

[b]Each sample was analyzed in triplicate (n=3).

which decreases as the concentration of polymer increases (Table 4).

The results of the *in vitro* release studies are shown in Fig. 2. Formulation B1, B2, B3, B4 and B5 exhibited a release of 92.183, 86.085, 77.983, 64.067 and 49.205%, respectively, in 9 h. The concentration of HPMC K100M in the release layer was the key factor governing drug release. In the bilayer tablet, the drug release layer included the gelling agent forming a gelatinous barrier which controls the drug release without interference from gas bubbles generated in the floating layer. It has been found that bilayer tablets exhibit reproducible release. The time taken to release 50% (t_{50}) and 70% (t_{70}) of the drug from different tablets was determined (Table 4). As the concentration of HPMC K100M increases in the formulation the release rate was found to decrease.

3.6. In vivo scintigraphic study

Gastric retention studies of the formulation B3 (without drug) was carried out in three healthy volunteers. Fasting conditions were maintained for 12 h before the start of the study. When tested for 8 h, the gamma scintigraphy images showedthat the tablets maintained their matrix integrity, indicating that the gastric conditions had no effect on the gelling properties of the tablets. This effect

Table 4
Drug release kinetics and dissolution parameters of rosiglitazone maleate[b].

Formulations	Best fit model	*R*	*n*	*k*	$t_{50\%}$ (h)	$t_{70\%}$ (h)
B1	Matrix	0.972	0.340	40.777	2.37	5.48
B2	First Order	0.992	0.408	28.553	3.298	5.895
B3	Matrix	0.987	0.495	29.268	4.186	7.184
B4	Matrix	0.986	0.544	19.019	5.392	> 9
B5	First order	0.987	0.761	8.891	> 9	> 9

[b]Each sample was analyzed in triplicate ($n = 3$).

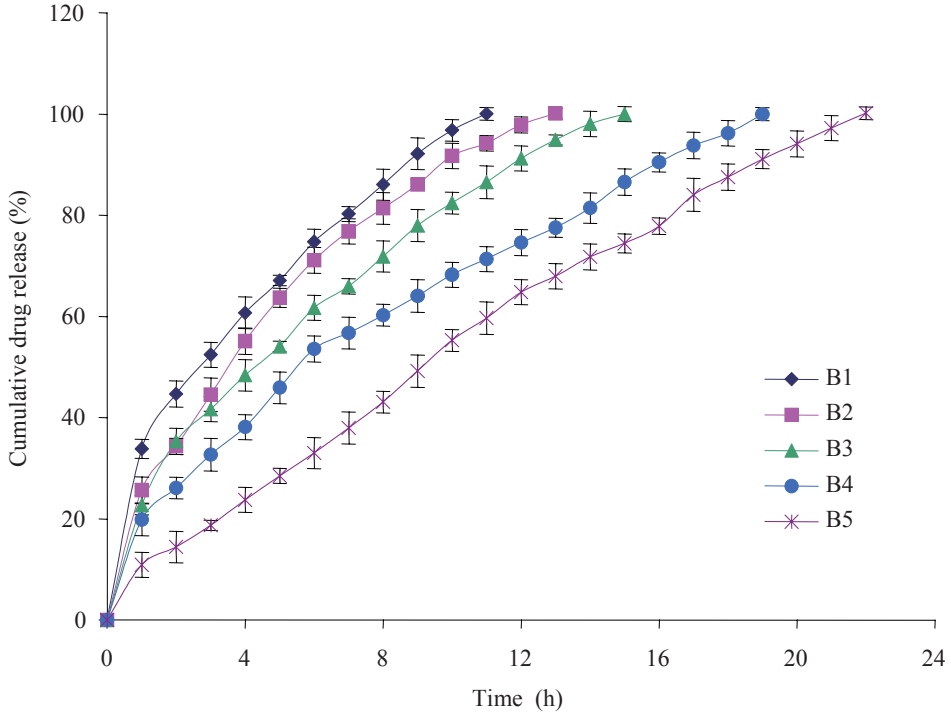

Fig. 2. Drug release profiles from bilayer floating units.

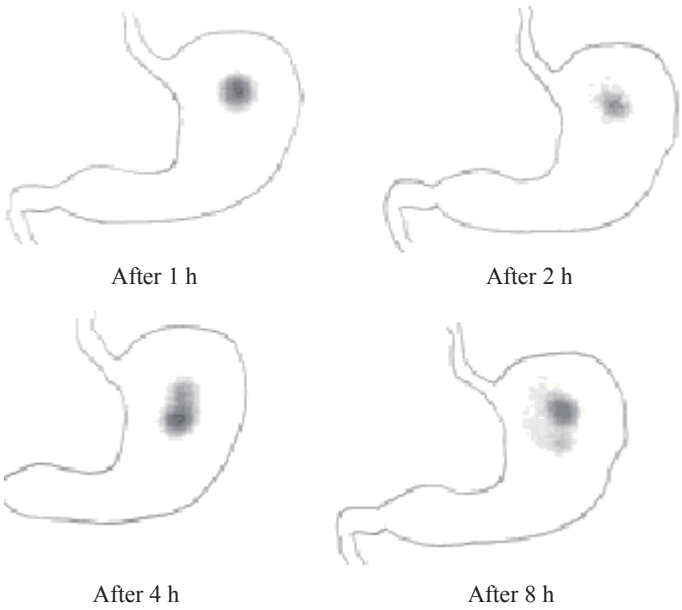

Fig. 3. Gamma scintigraphic images of the optimized formulation (B5) in the stomach of the first volunteer.

Table 5
Characteristics of optimized B5 formulation before (0 d) and after storage.

Time (d)	Drug content (%)	BLT (min)	Buoyancy time (h)	Detachment stress (dynes/cm^2)
0	100.3 ± 1.3	6 ± 2.4	>12 h	125.235
7	99.56 ± 1.9	9 ± 3.1	>12 h	117.159
15	99.17 ± 2.0	13 ± 2.7	>12 h	108.427
30	99.65 ± 1.5	15 ± 2.0	>12 h	100.598
60	98.87 ± 1.2	18 ± 3.4	>12 h	95.542
90	98.54 ± 1.7	20 ± 4.1	>12 h	89.348

*Storage at 40˚C and 75% RH for three month (n = 6).

was identical to that found in *in vitro* studies. The gamma scintigraphy study of the bilayer floating-bioadhesive tablet in the first volunteer showed that the formulation remains in the stomach for ~ 8 h (Fig. 3).

3.7. Stability study

The stability studies were carried out on the optimized formulation *i.e.* F3. The formulations were stored at 40 ± 2˚C/75 ± 5% RH for 3 months to assess their long-term stability. The protocol of the stability studies conformed to WHO guidelines for stability testing of protocols intended for the global market. After an interval of 7, 15, 30, 60 and 90 days, samples were withdrawn and retested for drug content, buoyancy lag-time, buoyancy time and detachment stress (Table 5). The results indicated that, irrespective of the concentration of polymer, these formulations remained stable for three months.

4. Conclusion

In this study, we successfully developed optimized bilayer and floating-bioadhesive dosage forms which exhibit a unique combination of floatation and adhesion for prolonged residence in the stomach. The optimized B5 tablet formulation showed a satisfactory dissolution profile, detachment stress and floating characteristics. The tablets remained floating in the stomach for up to 8 h.

Acknowledgements

The authors are very grateful to Dr. Shrikant Solav, Director, Spect Radiology Lab, Pune and the nuclear medicine staff at his laboratory for their co-operation and for providing all the necessary facilities to conduct the gamma scintigraphy study. The authors are also grateful to Cipla Pharmaceuticals for providing rosiglitazone maleate.

References

[1] J. E. F. Reynolds. Martindale-the extra Pharmacopoeia. Director of the Council of Royal Pharmaceutical Society of Great Britain, 2005, 34: 345.

[2] G. K. McEvoy. AHFS Drug Information. Authority of the board of the American Society of the Health-System Pharmacists, 2004, 3055-3058.

[3] M. C. Chapel Sky, K. Thompson-culkin, A. K. Miller, *et al*. Pharmacokinetics of rosiglitazone in patients with varying degrees of renal insufficiency. J. Clin. Pharmacol., 2003, 43: 252-259.

[4] X. Q. Xu, M. J. Sun, F. Zhi, *et al*. Floating matrix dosage form for phenoporlamine hydrochloride based on gas forming agent: *in vivo* and *in vitro* evaluation in health volunteers. Int. J. Pharm., 2006, 310: 139-145.

[5] Y. Sato, Y. Kawasaki, H. Takeuchi, *et al*. *In vitro* evaluation of floating and drug releasing behaviors of hollow microspheres (microballons) prepared by the emulsion solvent diffusion method. Eur. J. Pharm. Biopharm., 2004, 57: 235-343.

[6] A. J. Möes. Gastroretentive dosage forms. Crit. Rev. Ther. Drug Carrier Syst., 1993, 10: 143-159.

[7] T. Dürig, R. Fassihi. Evaluation of floating and sticking extended release delivery systems: an unconventional dissolution test. J. Control. Rel., 2000, 67: 37-44.

[8] M. Chavanpatil, P. Jain, S. Chaudhari, *et al*. Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. Int. J. pharm., 2006, 316: 86-92.

[9] J. Wang, Y. Tabata, D. Bi, *et al*. Evaluation of gastric mucoadhesive properties of animated gelatine microspheres. J. Control. Rel., 2001, 73: 223-231.

[10] M. Chavanpatil, P. Jain, S. Chaudhari, *et al*. Development of Sustained release gastroretentive drug delivery system of ofloxacin: *in vitro* and *in vivo* evaluation. Int. J. Pharm., 2005, 304: 178-184.

[11] B. N. Singh, K. H. Kim. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J. Control. Rel., 2000, 63: 235-259.

[12] S. J. Hwang, H. Park, K. Park. Gastric retentive drug-delivery systems. Crit. Rev. Ther. Drug Carrier Syst., 1998, 15: 243-284.

[13] L. Whitehead, J. T. Fell, H. L. Sharma, *et al*. Floating dosage forms: an *in vivo* study demonstrating prolonged gastric retention. J. Control. Rel., 1998, 55: 3-12.

[14] P. L. Bardonnet, V. Faivre, W. J. Pugh, *et al*. Gastroretentive dosage forms: overview and special case of Helicobactor pylori. J. Control. Rel., 2006, 111: 1-18.

[15] N. Rouge, P. Buri, E. Doelkar. Drug absorption sites in the gastrointestinal tract and dosage for site-specific delivery. Int. J. Pharm., 1996, 136: 117-139.

[16] R. B. Umamaheshwari, S. Jain, D. Bhadra, *et al*. Floating microspheres bearing acetohyxamic acid for the treatment of Helicobactor pylori. J. Pharm. Pharmacol., 2003, 55: 1607-1613.

[17] S. K. Jain, A. M. Awasthi, N. K. Jain, *et al*. Calcium silicate based microsheres of rapiglinide for gastroretentive floating drug delivery: Preparation and *in vitro* characterization. J. Control. Rel., 2005, 107: 300-309.

[18] S. Garg, S. Sharma. Gastroretentive drug delivery systems. Business Brief Pharmatech. 2003 Available at: http://www.touchbriefings.com/cdps/cditem.cfm?NID-17&CID-5. Accessed: August 4, 2006.

[19] H. M. Ingani, J. Timmermans, A. J. Moes. Conception and *in vivo* investigation of peroral sustained release floating dosage forms with enhanced gastrointestinal transit. Int. J. Pharm., 1987, 35: 157-164.

[20] A. A. Deshpande, N. H. Shah, C. T. Rhodes, *et al*. Development of a novel controlled-release system for gastric retention. Pharm. Res., 1997, 14: 815-819.

[21] Government of India ministry of health and family welfare. The Pharmacopoeia of India. Controller of publication, 1996.

[22] S. A. E. Seham, D. M. Nahed, A. S. A. Gehanne, *et al*. Development of *in situ* gelling and mucoadhesive Mebeverine Hydrochloride solution for rectal administration. Saudi Pharm. J., 2003, 11: 159-177.

[23] M. K. Senapati, A. Srinatha, J. K. Pandit. *In vitro* release characteristics of matrix tablets: study of karaya gum and guar gum as release modulators. Int. J. Pharm. Sci., 2006, 68: 824-826.

[24] S. Shimpi, B. Chauhan, K. R. Mahadik, *et al*. Preparation and Evaluation of Diltiazem Hydrochloride-Gelucire 43/01 Floating Granules prepared by Melt granulation. AAPS Pharm. Sci. Tech., 2004, 5: Article 43.

[25] K. R. Reddy, S. Mutalik, S. Reddy. Once daily sustained release matrix tablets of nicorandil: formulation and *in vitro* evaluation. AAPS Pharm. Sci. Tech., 2003, 4: article 61.

[26] K. R. Kamath, K. Park. Mucosal adhesive preparation. In. J. Swarbrick, J. C. Boylan, editors. Encyclopedia of Pharmaceutical Technology. Marcel Dekker. 1994, 133-163.

[27] K. P. R. Chowdary, L. Srinivas. Mucoadhesive drug delivery systems: A review of current status. Indian Drugs, 2000, 37: 400-403.

[28] P. L. Ritger, N. A.Peppas. A simple equation for description of solute release II. Fickian and anamolus release from swellable devices. J. Control. Rel. 1987, 5: 37- 42.