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Bioadhesive Ranitidine Hydrochloride for Gastroretention with Controlled Microenvironmental pH

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Ranitidine hydrochloride is a H_2 receptor blocker used in the treatment of gastric ulcers. Pharmacological factors, in addition to the dosage regimen, favor development of a sustained-release system for ranitidine especially in the therapeutic condition of erosive esophagitis. This investigation delves into the development of bioadhesive type of gastroretentive formulation (tablets) of ranitidine. The effect of mucoadhesive polymers such as Carbopol, hydroxypropyl methyl cellulose, and dextrose were studied. Mucoadhesion, in vitro drug release profile, water uptake, and swelling of the tablet were evaluated. Alkalizing agents were incorporated in an attempt to maintain an alkaline microenvironment within the tablet and improve the stability of the drug in acidic medium. The stability was evaluated using dye test and degradation studies. The drug release profiles were fit into various kinetic models.

Keywords ranitidine; gastroretentive; bioadhesive; microenvironmental pH; release kinetics

INTRODUCTION

There are various drugs that modify gastric secretion, among which ranitidine hydrochloride (RAN), a histamine H_2 receptor antagonist, is one of the most widely used. It is a BCS (biopharmaceutics classification system) Class III drug with a good solubility but poor permeability; hence, it shows a low bioavailability (52%) (Kortejarvi et al., 2005). RAN is absorbed from upper part of intestinal mucosa by a combination of saturable facilitated diffusion (anionic carriers, transcellular) and nonsaturable passive diffusion process (paracellular) (Lee & Thakker, 1999). Despite a short biological half-life of 1.7–2.1 h, gastric inhibitory effect lasts for 5–7 h probably because a part of the drug, after absorption, is stored in a depot (bile and parenchyma tissues), which is released after food intake (Kortejarvi et al., 2005; Miller, 1984). The secondary peak in plasma concentration time curves seen in human volunteers supports this phenomenon (Miller, 1984). High inter- and intrasubject variation in pharmacokinetics after oral administration has been observed (Shim & Hong, 1989). Oral dosage of the drug is 150 mg twice a day or 300 mg once daily. The drug has been recently approved for esophagitis, which requires a regimen of 150 mg four times a day (Sweetman, 2002). This leads to poor patient compliance. Therefore, a sustained-release drug delivery system of the drug (for 12 h), which will act in combination with the depot phenomena in the body, will ensure a biological effect of greater than 18–20 h without saturation of the absorption process. Sustained release will also lessen pharmacokinetic inter- and intrasubject variation and reduce the frequency of dosing, especially in conditions such as esophagitis.

The drug is absorbed in initial part of the intestine (Lauritsen, 1990). RAN is metabolized in the colon (Basit & Lacey, 2001); hence, when a conventional sustained-release dosage form reaches the colon, the released drug will get metabolized, resulting in low absorption and poor bioavailability. Furthermore, the drug is basic in nature having good solubility at acidic pH. These factors favor the development of a gastroretentive type of drug delivery system.

Earlier attempts have been made to formulate gastroretentive (floating) dosage forms of RAN (Dave, Amin, & Patel, 2004). However, their work has failed to consider the fact that the drug is unstable at acidic pH and degrades at pH < 5 (Tearaoka et al., 1993). A gastroretentive formulation will expose drug to lower pH (<3 units) for greater than 12 h, increasing the possibility of degradation of the unreleased drug. The objective of this work involves preparation of a swellable, bioadhesive (to the gastric mucosa) matrix delivery system combining mucoadhesive polymers and the incorporation of microenvironmental pH modifiers that will maintain an alkaline pH within the tablet for 12 h.

The effects of different polymer concentrations, channeling agent, and pH modifiers on the drug release rate, bioadhesive properties, and the ability to maintain an alkaline microenvironment were investigated.

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MATERIALS AND METHODS

Materials

RAN was obtained as a gift sample from Neuland Laboratories (Hyderabad, India). Carbopol 71G was obtained commercially from Noveon (Mumbai, India) and hydroxypropylmethyl cellulose (HPMC) 100,000 cps (Methocel K100M) from Colorcon (Mumbai, India). Dextrose, bromophenol blue, potassium dihydrogen phosphate, disodium hydrogen phosphate, sodium dihydrogen phosphate, magnesium oxide (MgO), sodium chloride, sodium hydroxide, calcium carbonate, calcium hydroxide, magnesium hydroxide, and acetonitrile were purchased from S.D. Fine Chemicals (Mumbai, India). Other chemicals such as microcrystalline cellulose (Avicel PH102), dibasic calcium phosphate, meglumine, and magnesium stearate were obtained from Bayer (Mumbai, India).

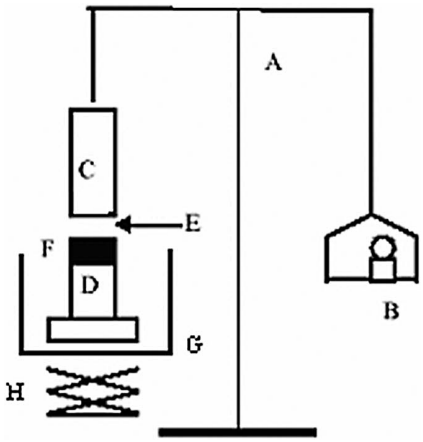

FIGURE 1. Modified balance device to measure bioadhesive (detachment) force. A, modified balance; B, weights; C, upper ceramic cylinder; D, lower ceramic cylinder; E, bioadhesive tablet; F, mucosal tissue; G, vessel with wetting medium; H, height adjustable pan.

Methods

Calculation of Target Drug Release Profile

The pharmacokinetic parameters of the drug were incorporated into the equations of loading and the maintenance dose and a theoretical release profile for the formulation was computed.

Preparation of Bioadhesive Matrix Tablets

The direct compression method was used to prepare the tablets. The ingredients were sieved through 40# screen, the drug was geometrically mixed with mucoadhesive and retarding polymers, and the rest of the ingredients were blended with the drug mixture. The blend was compressed on a single station (Cadmach, Ahmedabad, India) compression machine using 21 mm × 11 mm, caplet-shaped punches. Magnesium stearate was used as the lubricant at a concentration of 10 mg/tablet and microcrystalline cellulose (Avicel PH102) as the diluent to make up the weight of the tablet. The average weight of the tablets was maintained at 840 mg and the hardness at 10–11 kg/cm^2. Optimization of the quantities of mucoadhesive polymer, retarding polymer, channeling agent, and alkaline pH modifier was carried out.

Evaluation of Formulations

Bioadhesive Strength. Ex vivo mucoadhesion studies were carried out on rat stomach mucosa. Detachment force measurement was performed using the modified balance method (Abd ElHady, Mortada, Awad, Zaki, & Taha, 2003; Parodi, Russo, Caviglioli, Cafaggi, & Bignardi, 1996) (Figure 1) The rat mucosa was dissected into 5 cm × 5 cm pieces and washed of all food debris. The pieces were stored frozen in phosphate buffer saline (pH 7.0) and thawed to room temperature before use. The tissue was secured to the lower cylinder using a rubber band such that the mucosal side was out and the tissue ends were dipped in and constantly in contact with the wetting medium (0.1 N HCl) in the reservoir. The tablet, prewetted with 40 μL of medium on the exposed end, was attached by α-cyanoacrylate glue to the upper cylinder. A volume of 0.1 mL of 0.1 N HCl was slowly added by means of a plastic syringe over the mucus membrane. The platform was slowly raised till the tablet touched the mucosa and left in contact for 2 min, after which the balance was tared and corresponding weights were added on the pan. The addition was stopped upon the detachment of the tablet from mucosa. The equivalent adhesion force was calculated in dynes (Parodi et al., 1996). Each adhesion experiment was repeated six times.

In Vitro Drug Release Study. Drug release studies were conducted on six tablets in 900 mL of 0.1 N hydrochloric acid using United States Pharmacopeia (USP) (29) Apparatus 1 (Electrolab TDT-08L, USP Model, Mumbai, India) at 100 rpm and 37.5 ± 0.5°C. A volume of 5 mL of sample was withdrawn at 1, 2, 4, 6, 8, and 12 h and replaced with fresh medium. The samples were analyzed on a UV spectrophotometer (Double Beam, Jasco Series V-30, Japan) at λ = 313 nm.

Statistical Analysis by F_2 Value. All the in vitro drug release profiles were compared statistically with the target profile using the similarity fit factor (F_2). The factor is a logarithmic transformation of the sum-squared error of the differences between the test and reference products over all time points. F_2 value of above 50 indicates similarity; the closer it is to 100, the more identical the test is to the reference. The fit factor calculation has been adopted by the Center for Drug Evaluation and Research (FDA) and by the Human Medicines Evaluation Unit of The European Agency for the Evaluation of Medicinal Products (EMEA), as a criterion for the assessment of similarity between the two in vitro dissolution profiles (Costa, 2001).

Hydration (Water Uptake) and Swelling Studies. Six dissolution baskets were thoroughly cleaned, accurately weighed on an analytical balance (GR 202, A&D, Japan), and weighed again after insertion of a matrix tablet, so that the accurate weight of each tablet (W_i) could be calculated. The dimensions (length, breadth, and thickness) were noted (D_i) using a vernier caliper (Magumps, Mumbai, India). The baskets and tablets were then rotated in the dissolution medium (900 mL, 0.1 N hydrochloric acid, 50 rpm, USP (29) Apparatus 1) and at regular time intervals (1, 2, 4, 6, 8, and 12 h) a basket was detached, blotted with absorbant tissue to remove any excess medium on the basket surface, and the swollen matrix accurately weighed (W_{wet}). The swollen dimensions were noted (D_t).

$$\text{Hydration index} = (W_{wet} - W_i)/\text{Wi},$$
$$\text{swelling index} = (D_t - D_i)/D_i.$$

Microenvironmental pH. The micro-pH of the prepared tablets was determined (Mohammed & Khedr, 2003) by leaving the tablets ($n = 6$) to swell in 4 mL of distilled water in small beakers. The pH was measured at regular intervals of time by placing the electrode in contact with the microenvironment of the swollen tablets and measuring the pH with a pH meter (Model E610, Equiptronics, Mumbai, India).

Dye Test. A qualitative test was carried out to determine the microenvironmental pH. Bromophenol blue, an indicator which is yellow in color at pH < 4–5 and turns to blue at pH > 5, was used. The indicator was blended into the matrix of the tablet (50 mg/tablet) and compressed on 21 mm × 11 mm caplet-shaped punches. Six separate tablets were immersed in 0.1 N hydrochloric acid for 12 h. One tablet was withdrawn at each of the intervals (1, 2, 4, 6, 8, and 12 h) and cut cross-sectionally to observe the color in the center of the tablet. A blue color indicated microenvironmental pH > 5. The study was carried out for both the optimized batch with alkalizing agent and for the batch without it.

Stability of Ranitidine Bioadhesive Tablets in Acidic Medium—Degradation Studies. Six separate tablets of formulation containing alkalizing agent were subjected to in vitro drug release studies in 0.1 N hydrochloric acid. At each of the predetermined sampling points, one tablet was removed and assayed for its drug content using the high-performance liquid chromatography (HPLC) analysis. The study was repeated for the formulation without alkalizing agent.

The initial assay of the tablets was carried out by crushing 20 tablets in a mortar and accurately weighing a quantity of the powder equivalent to 250 mg of drug into a 250-mL volumetric flask. A volume of 200 mL of methanol was added and the slurry sonicated for 15 min to ensure complete extraction of drug into the solvent. The volume was made up with methanol. In the case of the assay of the tablet after removal at the predetermined sampling point, the tablet was crushed in a mortar, sonicated with 50 mL of methanol, and the volume made up to 100 mL with methanol. The slurries were filtered through a 0.45-μm membrane filter. Suitable dilutions were made in mobile phase to give the working concentration of the drug (100 ppm). These solutions were injected into the chromatograph.

HPLC analysis was conducted on Phenomenex Luna, C_{18} column of dimensions 250 mm × 4.6 mm and packing of 10 μm. The system (Jasco PDA-2015 Multiwavelength Detector, Borwin Intelligent V1.12 software) was operated at 1.0 mL/min flow rate, UV detection at 230 nm, using a mobile phase of a mixture of 80 volumes of phosphate buffer (10 mM, pH 7.1), and 20 volumes of acetonitrile. The drug in each tablet was quantified and the percent degradation calculated.

Kinetic Modeling of Drug Release. The drug release profile was fit into the Higuchi and Korsmeyer–Peppas models. Diffusion and erosion mechanisms of drug release were studied. The Peppas–Sahlin model (Sujja-areevath, Munday, Cox, & Khan, 1998) was used to determine the contribution of diffusional and erosional mechanisms in the optimized drug release profile.

RESULTS AND DISCUSSION

Design Rationale

A bioadhesive sustained release system for ranitidine at a dose of 300 mg (336 as hydrochloride) was designed to give a 12-h drug release. A target release profile was calculated using the following parameteric values (Brinton, 1996): C_{ss} = 575 ng/mL, V_d = 1.4 ± 0.04 L/kg, F = 52%, and K_{el} = 0.276 h^{-1} and showed that the formulation should release 33.33% in the first hour followed by 6.22%/h up to 11 h thereafter.

Effect of Carbopol and HPMC on the In Vitro Drug Release Profile, Mucoadhesion, Swelling, and Hydration of Ranitidine Bioadhesive Tablets

Carbopol 71G (directly compressible grade), well known as a good mucoadhesive polymer, was selected as the retarding agent. However Carbopol (CBL) alone was not able to retard the drug till 12 h (Table 1, Figure 2) Hence, it was decided to add HPMC 100,000 cps as the additional retarding agent. Celluloses have also been reported to show bioadhesive properties but much weaker than CBL (Choi et al., 1998).

CBL and HPMC were tried at various ratios such as 1:0, 5:1, 3:1, 2:1, and 1:1 (Table 1); CBL when used alone at high concentrations (RT01) surprisingly showed a lower adhesion. It is possible that at higher polymer concentrations, the polymer fails to be completely hydrated because of incomplete access to moisture (Surapaneni, Das, & Das, 2006). The partial hydration reduces the uncoiling of polymer molecules and fewer adhesive sites will be exposed, manifesting as lower adhesive strength. The slow hydration and conversion of glassy to rubbery state of CBL is one of the reasons why it shows a gradual drug release profile in the first 4–6 h.

TABLE 1
Formulation Details to Study the Effect of Carbopol and HPMC in Bioadhesive Tablets

	mg/tablet				
Ingredient	RT01	RT02	RT03	RT04	RT05
Ranitidine HCl	336	336	336	336	336
Carbopol 71G	300	250	225	200	150
HPMC 100,000 cps (Methocel K100M)	0	50	75	100	150
Mucoadhesion(dyn)	7,676.67	7,905.33	7,676.67	7,513.33	6,370.00
Swelling index(after 12 h)	1.24	1.43	1.52	1.64	2.34
Hydration index (after 12 h)	2.05	2.34	2.61	2.95	3.67
F_2 value	57.05	66.13	69.98	74.41	65.57
Higuchi diffusion constant (k)	31.38	30.37	29.90	27.06	25.58
Korsemeyer release exponent (n)	0.434	0.445	0.475	0.474	0.522

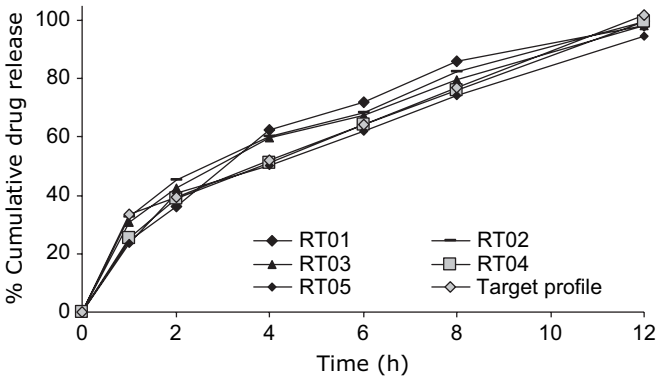

FIGURE 2. In vitro drug release profile of bioadhesive tablets with different quantities of Carbopol and hydroxypropylmethyl cellulose (HPMC).

Water plays a primodial role in mucoadhesion as it results in relaxation of stretched entangled molecules, thereby liberating their adhesive sites for creating bonds with mucus (Duchêne, Touchard, & Peppas, 1988). However, there exists optimum water content for maximum bioadhesion beyond which overhydration results in the formation of wet slippery mucilage without adhesion (Lee, Park, & Robinson, 2000).

The high uptake of water (hydration index) with an increase of HPMC may be because of a faster hydration rate of HPMC (Agarwal & Mishra, 1999). The swelling index also increased with HPMC content.

The addition of HPMC to CBL (RT02) improved mucoadhesion as it enhanced the uncoiling of polymer chains by increasing hydration. However, the mucoadhesive strength decreased with increase in HPMC quantity as it is a weaker bioadhesive and resulted in overhydration of the matrix (Table 1) This is probably why the 5:1 ratio of CBL/HPMC (RT02) gave the maximum adhesion because it contained just the right balance of CBL and HPMC resulting in optimum hydration and complete uncoiling of polymer chains, whereas the 1:1 ratio (RT05) showed poor mucoadhesion because of overhydration.

As the fraction of HPMC increased, the release rate retarded, although the initial drug release was fast because of rapid hydration of HPMC. The batch with 200 and 100 mg/tablet of CBL and HMPC, respectively (RT04), gave an in vitro release profile that agreed well with the target profile (Figure 2), which is also reflected in the high value of the F_2 factor (Table 1).

The hydrophilicity and water swellability of CBL and HPMC caused the drug-containing matrices to swell in size in the gastric cavity because of ingress of water. They achieved a size that would be retained in the stomach when introduced during the fed mode. In 1 h the tablet attained a dimension of 24 mm × 13 mm × 12 mm, thereby obstructing its passage through the pyloric sphincter (12.9 ± 7 mm) and aiding in gastroretention. These qualities also cause the matrices to become slippery, which provides resistance to peristalsis and further promotes their retention in the stomach (Klausner, Lavy, Friedman, & Hoffman, 2003).

Effect of Dextrose as the Channeling Agent on the In Vitro Drug Release

As our selected formulation (RT04) did not give the required burst release, dextrose was added as the channeling agent. Dextrose is a highly water-soluble excipient, which gets solubilized and released from the matrix when it gets hydrated, thereby creating the necessary pores and channels for the initial release of the drug. The channeling agent was tried at 15 (RT06) and 30 mg/tablet (RT07). Figure 3 shows the drug release of batches with dextrose as the channeling agent in the first 4 h. A 30 mg/tablet (RT07) gave the necessary burst release without bringing about any significant change in the latter part of the drug release.

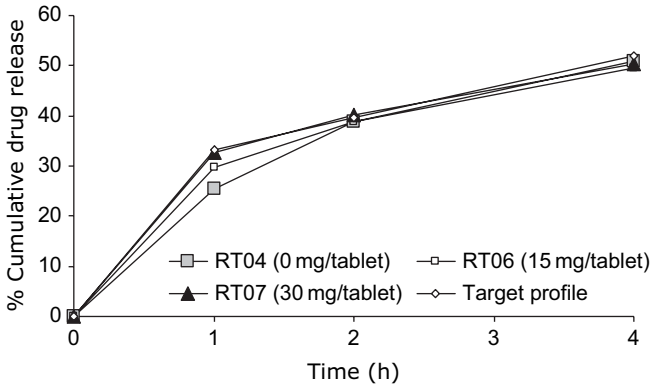

FIGURE 3. In vitro drug release profile of bioadhesive tablets with different quantities of dextrose as the channeling agent.

Effect of Alkali Materials on the Formulation Characteristics

Various alkalizing agents such as meglumine, calcium carbonate, calcium phosphate, calcium hydroxide, magnesium hydroxide, buffering agents, and MgO were incorporated into the tablet matrix in an attempt to stabilize the drug (Table 2) RAN is unstable at lower pH and the rate of degradation is greatest when the pH < 5 (Teraoka, Otuska, & Matsuda, 1993). The microenvironmental pH, when measured at regular intervals of time (Table 2), revealed that MgO (RT09) was successful in maintaining a micro-pH > 6.5 till 12 h. MgO is a hydrophobic and practically insoluble alkali material. When entrapped in the swollen matrix, it protects the tablet matrix from penetration by gastric fluid, due to its strong waterproofing effect (Yong, Jung, Rhee, Kim, & Choi, 2001). The small amount of MgO that manages to react with water generates magnesium hydroxide, a highly alkaline material that maintains the micro-pH above 6.5.

TABLE 2
Microenvironmental pH with Different Alkalizing Agents

Batch No.	Alkalizing Agent	Micro-pH 2 h	4 h	8 h	12 h
RT07	With no alkalizing agent	3.78	3.53	3.11	2.91
RT08	Meglumine[a]	4.56	4.07	3.27	3.00
RT09	Magnesium oxide[a] (MgO)	6.45	6.55	6.42	6.48
RT10	Calcium carbonate[b] (CC)	4.08	4.26	4.38	4.08
RT11	Calcium phosphate[b] (CP)	4.27	4.38	4.61	5.06
RT12	Calcium hydroxide[a] (CH)	3.27	4.20	4.15	4.19
RT13	Buffering system[c] (BS)	6.51	5.24	5.00	4.61
RT14	Magnesium hydroxide[a]	4.16	4.00	4.10	3.99
RT15	MgO[a] + CP[b]	6.54	6.46	6.52	6.49
RT16	MgO[a] + BS[c]	7.12	6.81	6.69	6.35

[a]Used in concentration of 30 mg/tablet.
[b]Used as diluent in concentration of 100 mg/tablet.
[c]Disodium hydrogen phosphate 80 mg, sodium dihydrogen phosphate 5 mg, sodium chloride 8 mg (buffer pH 7.0).

MgO with calcium phosphate (RT15) showed a micro-pH similar to that of MgO when used alone. MgO in combination with buffering system (RT16) did not show any additional improvement in the micro-pH, although in the first 2 h it showed a pH > 7. This was probably because of the fact that the buffering system, containing salts that are highly water soluble, liberated from the matrix in 1–2 h no longer showed their effect. When the buffering system was used alone (RT13), a similar phenomenon was seen, where in the initial 2–4 h, a pH of around 6.5 was maintained, but as the buffering system got solubilized and released from the tablet, the pH dropped to around 4 in 12 h.

It has been reported that divalent ions may act as cross-linking agents by interacting with the carboxyl groups of polyacrylic acids, forming bridges between the polymer chains, thereby reducing adhesion. However, in the present case, the opposite result was observed because sparingly water-soluble alkalizing agents were used where few divalent cations were generated. Contrary to literature reports, adhesion improved because of the generation of alkaline micro-pH (Figure 4) CBL has a high percentage of carboxylic acid groups that dissociate highly in alkaline environment. The dissociation results in electrostatic repulsions between these negatively charged functional groups causing uncoiling and expansion of the molecule, making it more susceptible to mechanical chain entanglement, resulting in the formation of strengthened gel network and allowing the mucoadhesive to remain adhesive for prolonged periods of time (Singla, Chawla, & Singh, 2000).

An increase in alkaline micro-pH also brought about an increase in swelling index (Figure 4) as the dissociation of polymer chains increased.

The optimal quantity of MgO giving a good micro-pH and in vitro drug release profile was determined (Table 3). A 100 mg/tablet of MgO (RT18) proved to give a good micro-pH with the highest F_2 value (Figure 5) The release rate of a drug from the matrix is primarily dependent on the rate of water imbibition and the rate at which the drug dissolves and diffuses from the swollen polymer. At 50 and 100 mg/tablet, there was no significant difference in the in vitro drug release profile in comparison with the batch without MgO. However, as the quantity of MgO increased to 120 and 150 mg/tablet, the release profile became progressively slower, showing the increase in waterproofing effect and reduction in hydration (Table 3, Figure 5) This may also be due to the fact that the alkaline pH being maintained in the microenvironment reduced the solubility of drug, a base, thereby slowing down its dissolution and hence diffusion from the matrix. However, at quantities of greater than 150 mg/tablet of MgO, the blend showed poor compression characteristics because MgO, a highly

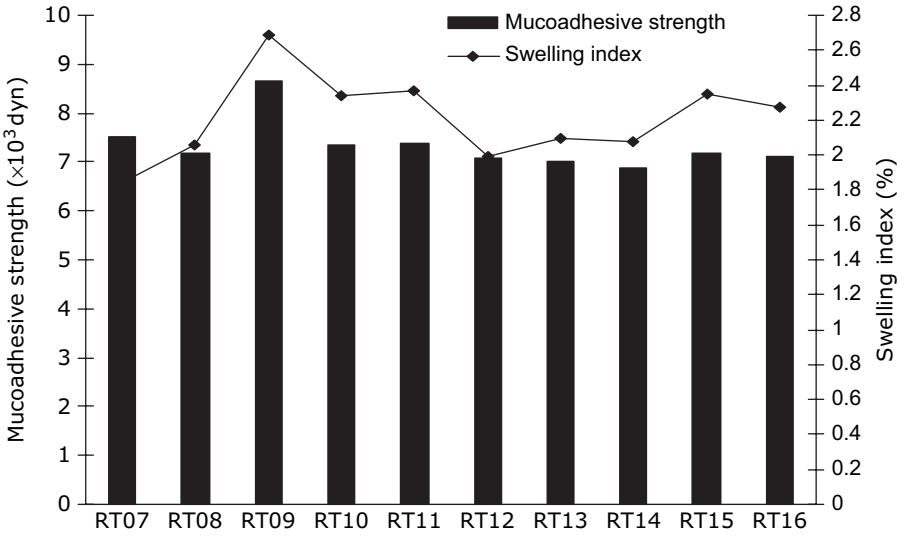

FIGURE 4. Mucoadhesive strength and swelling index of batches with different alkalizing agents.

TABLE 3
Optimization of Quantity of Magnesium Oxide

	mg/tablet				
Quantity of MgO	0	50	100	120	150
Formulation properties	RT07	RT17	RT18	RT19	RT20
Micro-pH (after 12 h)	2.91	6.54	6.46	6.89	7.15
Adhesion force (dyn)	7,513.33	7,970.67	8,068.67	7,676.67	6,533.33
F_2 value	88.01	82.28	86.87	66.74	61.03
Hydration index	2.84	2.77	2.66	2.49	2.20

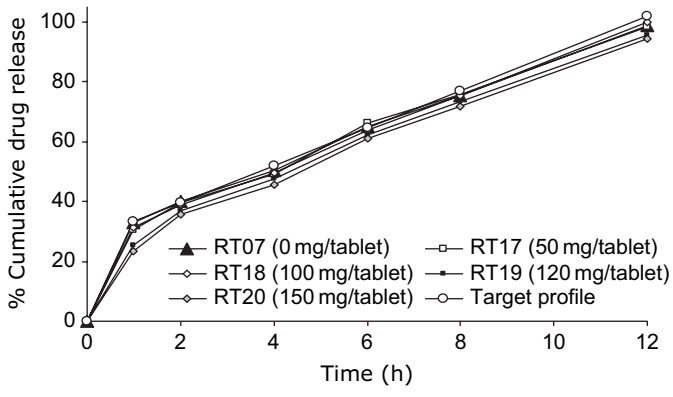

FIGURE 5. In vitro drug release profile of bioadhesive tablets with different quantities of magnesium oxide as the alkalizing agent.

fluffy, water-repellent powder, reduced the binding capacity of the polymers.

There was no significant change in adhesion force with increase in MgO till 100 mg/tablet (RT18), as there was no significant change in micro-pH and hydration (Table 3) At 120 and 150 mg/tablet, the adhesion force dropped because the micro-pH reached nearly 7, whereas maximum adhesion for polyacrylic acids is reported to occur from pH 5 to 6 (Duchêne et al., 1988). It may also be due to the fact that the hydration capacity decreased with increase in water-proofing effect.

RT18 with 100 mg/tablet of MgO was considered to be the optimized batch.

Dye Test and Degradation Studies

Batches with and without MgO as the pH modifier were both subjected to dye and degradation studies. The dye test (Figure 6) indicated that till 4 h, both the tablets with and

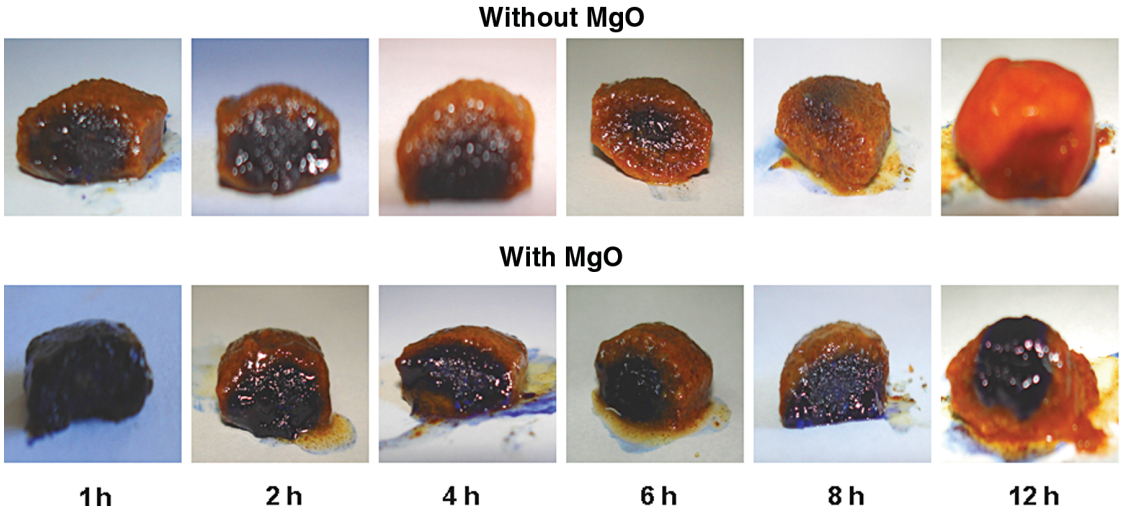

FIGURE 6. Dye test of ranitidine bioadhesive tablets with and without pH modifier.

without MgO showed a blue-colored tablet interior. However at 6 and 8 h, the formulation without the alkalizing agent showed a progressively increasing yellow color in the tablet interior. At 12 h, the entire tablet had turned yellow. The presence of the pH modifier within the tablet, however, maintained a blue interior till 12 h, indicating a micro-pH of greater than 5 pH units within the hydrated matrix till the time period. This can be attributed to a combination effect of waterproofing and alkaline product generation on reaction with the water molecules of MgO.

The degradation profile of formulations with and without the alkalizing agent corroborated the results from micro-pH and dye test. The drug in the tablet formulation without the pH modifier started degrading in 2 h and showed a 11% degradation in 12 h (Figure 7) This showed that the acidic medium penetrated into the ranitidine tablets and degraded the drug within them. Although the tablet formulation with MgO remained stable till 8 h, a 1.6% degradation was observed in the next 4 h (Figure 7) Thus MgO was successful in reducing the degradation of the drug in acidic medium by virtue of its ability to maintain an alkaline microenvironment.

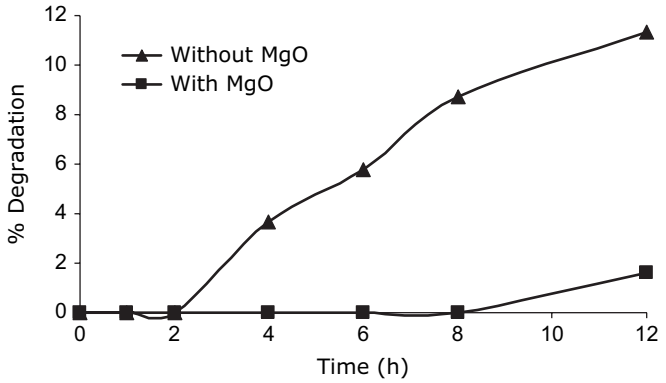

FIGURE 7. Degradation profiles of ranitidine bioadhesive tablets with and without pH modifier.

Mucoadhesive Strength

Figure 8 shows that there is no significant difference in the mucoadhesive strength of optimized formulation (RT19) and it placebo (RT22), indicating that the presence of drug did not interfere with the mucoadhesive properties of the polymers.

Formulations without both the bioadhesive polymers (RT23) exhibited a poor strength of adherence. The adhesion force of HPMC was found to be less than that of CBL as seen in Figure 8 The adhesion strength of formulation with HPMC alone (RT25, 5,226 dyn) was around 2,000 dyn less than the batch with CBL alone (RT24, 7,186 dyn). HPMC has more neutral cellulose groups, showing lesser hydrogen bonding and hence weaker adhesive force (Choi et al., 1998). It forms a thick and viscous-swollen gel of HPMC. As this gel is not continuous it forms localized pockets of polymer (Wan, Heng, & Wong, 1991) with poor adhesion. CBL, polyanionic in nature, contains primarily a large number of carboxylic groups that have a good tendency to H-bond with the mucosa and therefore is a better bioadhesive.

When CBL was used alone (without HPMC), there was significant difference in adhesion in presence (RT24) and absence (RT26) of MgO. RT26 gave a adhesion strength 1,000 dyn less than RT24. This showed that the presence of an alkaline microenvironment enhanced the bioadhesion of the formulation.

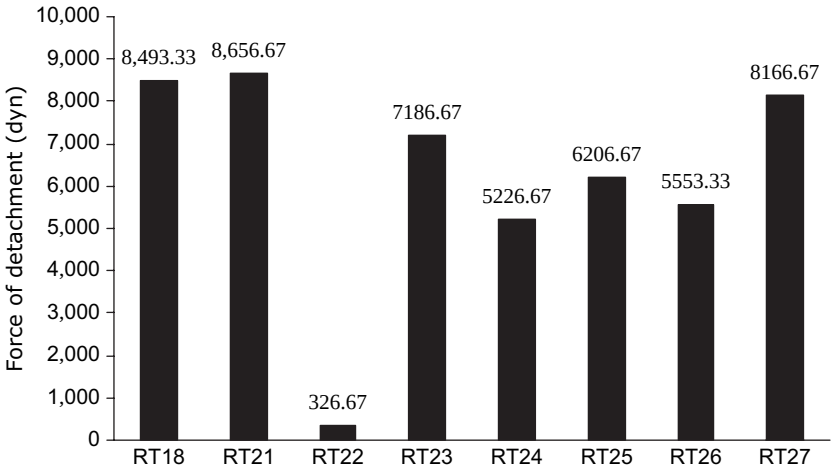

FIGURE 8. Comparative mucoadhesive strengths of various batches of optimized formulation. RT18, optimized batch; RT21, RT18 without drug; RT22, RT18 without Carbopol (CBL) and hydroxypropylmethyl cellulose (HPMC); RT23, RT18 without HPMC; RT24, RT18 without CBL; RT25, RT18 without HPMC and MgO; RT26, RT18 without CBL and MgO; RT27, RT18 without MgO. Note: In batches without the drug or polymer the tablet weight was made up with microcrystalline cellulose.

For cross-linked polymers such as CBL, the interpenetration of large chains occurs with greater difficulty. However, CBL has a high percentage of carboxylic acid groups that strongly dissociate in highly alkaline environment. The dissociation results in electrostatic repulsions between these negatively charged functional groups causing uncoiling and expansion of the molecule, swelling of the polymer, and gel formation. The polymer, in its expanded, uncoiled state makes it more susceptible to mechanical chain entanglement and secondary interactions such as hydrogen bonding with the oligosaccharide chains of mucous glycoprotein, resulting in the formation of strengthened gel network and allowing the mucoadhesive to remain adhesive for prolonged periods of time (Singla et al., 2000). In the absence of MgO, smaller chains and chain ends still contribute to interdiffusion with mucopolysacccharide chains with formation of hydrogen bonds (Duchêne et al., 1988); however adhesion is reduced.

The result is in agreement with the optimized batch with and without MgO, that is RT19 and RT28, respectively, where again RT28 shows a mucoadhesion strength 1,000 dyn less than RT19.

When HPMC is used alone (without CBL), there was no significant difference in adhesion in presence (RT25) and absence (RT27) of MgO, showing that the mucoadhesive characteristic of HPMC is independent of pH. This is because HPMC is nonionic in nature.

However, the formulation with CBL alone without MgO (RT26), where CBL exists in the nonionized form, had a greater adhesion than HPMC alone (RT25), showing that CBL was a much better mucoadhesive than HPMC at all pH.

CBL, when used without MgO, remains unionized in the gastric contents and the numerous proton-donating carboxylic groups form hydrogen bonds with the negatively charged mucus gel following the formation of physical entanglements (Gu, Robinson, & Leung, 1988). There is formation of intermolecular complexes between the glycoprotein and CBL molecules (Mortazavi & Smart, 1994). It has been reported that even the ionized part of CBL has bioadhesion force. Ionization of CBL may result in diminishing the intramolecular hydrogen bonds but generates a stretched cylindrical shape, which is then able to penetrate the mucin network more than the coiled form of unionized CBL (Hassan & Gallo, 1990). Thus CBL has dual mechanisms for mucoadhesion—hydrogen bonding with the mucosa chains after hydration and interpenetration of the CBL chains after uncoiling—the former predominating when the pH is acidic where CBL is nonionized, and the latter in alkaline pH when CBL is ionized. As the interpenetration phenomena results in stronger adhesion, alkaline pH augments bioadhesion. Thus, the ionization of functional groups in alkaline pH was one of the essential features for good mucoadhesion. Although our formulation was meant to be retained in the acidic gastric contents, MgO, the alkaline ingredient, aided in the ionization and uncoiling of the chains thereby augmenting mucoadhesion to the gastric mucosa.

Kinetic Modeling of Drug Release

The drug release profile was fit into the Higuchi and Korsmeyer–Peppas kinetic model. The Higuchi or Fickian diffusion model is described by $M_t = K_h t^{1/2}$, where M_t is the amount of drug dissolved at time t and K_h is the Higuchi diffusion rate constant (Sujja-areevath et al., 1998).

A simple relationship has been described by Korsmeyer–Peppas, which is used to describe drug release from polymeric

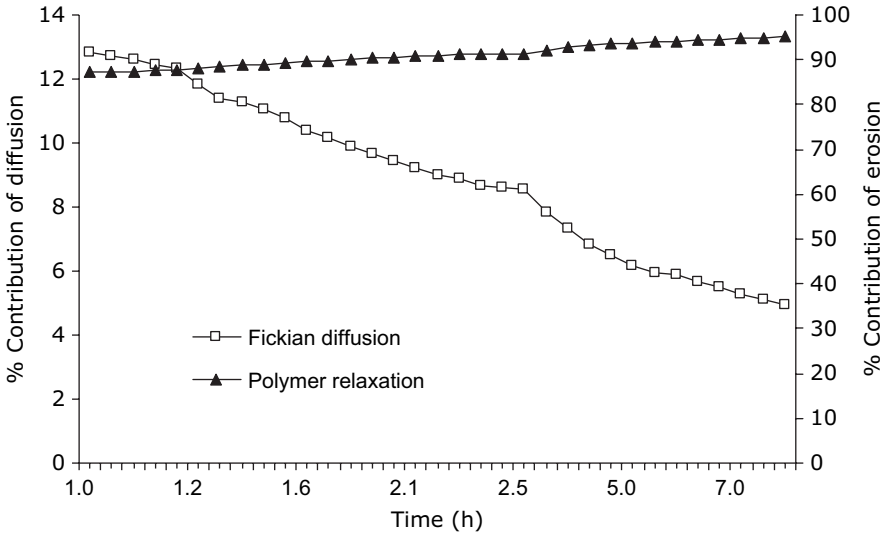

FIGURE 9. Percentage contributions of Fickian diffusion and erosion mechanisms in drug release from bioadhesive tablets.

systems: $M_t/M_\infty = Kt^n$, where M_t/M_∞ is the fractional release of the drug, t is the release time, K is a constant that incorporates structural and geometric characteristics of the release device, and n is the release exponent. For cylindrical swellable matrices, $n = 0.45$ indicates Case I or Fickian diffusion, whereas $n = 0.45$–0.89 indicates anomalous release (a combination of diffusion and erosion) and $n = 0.89$ indicates Case II release due to polymer relaxation (erosion) (Vigoreaux & Ghaly, 1994).

During optimization of CBL and HPMC (Table 1), when CBL was used alone (RT01), the release exponents indicated a Fickian type of release with $n < 0.45$. When combinations of CBL and HPMC were used, the kinetic model implied an anomalous release (R^2 values >.99).

It is generally recognized that drug release from HPMC matrices follows two mechanisms, drug diffusion through the swelling gel layer and polymer relaxation and erosion (Reynolds, Gehrke, Hussain, & Shenouda, 1998). An increase in the quantity of the HPMC resulted in greater swelling and greater water uptake, andmore polymer relaxation. Therefore, the drug release became less diffusion governed as seen by the increasing values of the Korsmeyer release exponent and decreasing values of Higuchi constant, and its approach toward zero-order erosional-type release (Table 1).

The contribution of Case I Fickian (diffusional) release and the Case II erosional release over the first 80% of release (burst release not considered) of the optimized batch (RT19) was quantified according to the heuristic model developed by Peppas and Sahlin (1989): $M_t/M_\infty = k_1 t^{1/2} + k_2 (t^{1/2})^2$, where the first term is the Fickian contribution and the second term the erosional contribution (Sujja-areevath et al., 1998). The nonlinear regression equation was solved (Graphpad Prism 4.0 software) by fitting the drug release data into it, and the Fickian and erosional contributions over different time points was calculated. Figure 9 shows that with time, the contribution of diffusion progressively starts reducing while that of erosion increases with time. This is because in the first 1 h of burst release, maximum swelling of the tablet is seen. Thereafter, the polymer chains increasingly relax, disentangle, and erode. The erosion mechanisms start playing an increasing role in drug release. However, throughout the release process, the relaxation mechanism predominates over diffusion mechanism probably because CBL and HPMC are water-soluble polymers capable of high hydration capacities.

CONCLUSION

The study has demonstrated that a gastroretentive drug delivery system of the bioadhesive type can be rationally designed for RAN with an initial burst release followed by sustained release for 12 h using a combination of mucoadhesive agents and retarding polymers. A combination of polymers CBL and HPMC in the ratio 5:1 proved to give the highest mucoadhesion. The bioadhesion was further enhanced by the presence of the alkaline pH modifiers, the effect being greatest with MgO. The micro-pH, dye test, and degradation studies proved that incorporation of MgO could maintain an alkaline microenvironment in the tablet and prevent degradation of the drug when exposed to acidic gastric contents for prolonged periods of time. The drug release followed a predominantly erosion-governed release kinetics. Thus the bioadhesive feature could prolong the gastric residence of the system, thereby showing potential to increase efficacy of RAN for therapy of erosive esophagitis.

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