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Development and Evaluation of a pH-Dependent Sustained Release Tablet for Irritable Bowel Syndrome

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The overall objective of this study was to develop a pH-dependent sustained release tablet formulation of a model drug, tegaserod maleate (TM), which is a poorly water soluble and acid labile drug in gastric milieu. The formulation's goal was to allow the dosage form to pass through the stomach intact, start disintegrating in the upper small intestine and slowly release the active in a controlled manner. Partition coefficient, contact angle and drug-excipient compatibility were investigated as part of the preformulation studies. A pH-dependent sustained release tablet was prepared using a combination of Eudragit® L100 and Eudragit® S100. The effects of solubilizer, disintegrant, binder, coating polymer concentration, pore former, and plasticizer on the drug release rate were determined. The results demonstrated that approximately 90% of the drug was released in a sustained release manner in the pH 6.8 phosphate buffer within 12 h while no drug was detected when subjected to drug release studies in 0.1 mol/L hydrochloric acid for 2 h. The drug release mechanism involved stress points and/or pore formation in the coated film. The coated tablets were stable at 40°C/75% RH for 3 months. These results highlighted the feasibility of this coated tablet system containing TM, which may contribute to the successful treatment of irritable bowel syndrome.

Keywords tegaserod maleate; pH-dependent; sustained release; Eudragit; preformulation

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INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder characterized by abdominal pain, discomfort, diarrhea, and/or constipation, and classified into constipation-predominant IBS, diarrhea-predominant IBS, and alternating IBS (Rivkin, 2003). The disorder has a broad range of severity, ranging from mild to severe and intractable symptoms. IBS is highly prevalent in the general population and is associated with significant disability and health care costs. IBS affects 14–24% of women and 5–19% of men in North America (Hungin, Whorwell, Tack, & Mearin, 2003). To date, there is no drug that is effective for the treatment of all forms and all symptoms of IBS. Treatment is based on the physician's understanding of the individual patient's symptom pattern and associated psychosocial factors. Current recommendations include anticholinergics for acute episodes of pain, supplemental dietary fiber for constipation, opiates for diarrhea, and in patients with sustained pain or bloating, low doses of antidepressants such as tricyclic agents and selective serotonin reuptake inhibitors (Hadley & Gaarder, 2005).

Tegaserod maleate (TM), 3-(5-methoxy-1H-indol-3-ylmethylene)-*N*-pentyl-carbazimidamide hydrogen maleate (Figure 1), is the first selective 5-hydroxytryptamine type-4 (5-HT_4) receptor partial agonist used for the treatment of constipation-predominant IBS. TM is insoluble in water and has a pH-dependent solubility, and its solubility is about 10-fold lower at pH 7.5 than at pH 1. Below pH 3, TM is rapidly degraded through hydrolytic breakdown. TM is rapidly absorbed following oral administration under fasted conditions, and the peak plasma concentration (C_{max}) occurs after 1.0–1.3 h. The absolute bioavailability is about 10%. The

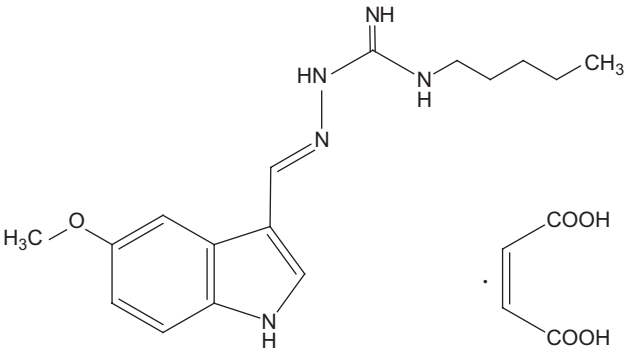

FIGURE 1. Chemical structure of tegaserod maleate.

major elimination route of TM is via the feces and excreted unchanged, and a minor amount of bio-transformed metabolites are eliminated through the urine. The drug is hydrolyzed by the acidic milieu of the stomach, followed by phase 1 and 2 biotransformation in the liver into a major inactive metabolite, 5-methoxy-indole-3-carboxylic acid glucuronide. TM also undergoes direct glucuronidation to inactive 3 isomeric *N*-glucuronides (Rivkin, 2003).

To improve the oral bioavailability and prevent rapid hydrolysis of TM in gastric milieu, a dosage form containing TM in a core is coated with pH-dependent materials which dissolve at the pH of the small intestine. The pH values of the stomach and the small intestine in humans are 1–3 and 6.5–7, respectively (Ashford & Fell, 1994). The most commonly used pH-dependent coating polymers are methacrylic acid copolymers — Eudragit® L100 and Eudragit® S100 which dissolve at pH 6.0 and 7.0, respectively. Hence, neither polymer is suitable to be used alone for coating dosage forms that start releasing the drug at pH 6.5. Because Eudragit® S100 dissolves at the higher pH within the range, it would be possible to combine Eudragit® S100 with Eudragit® L100 at various ratios to manipulate the drug release within the pH range of 6.0–7.0. To date, no report is available regarding the use of a combination of pH-dependent polymers to deliver TM for treating IBS. To our knowledge, most of the literature on tegaserod focused on the pharmacology and human pharmacokinetics with no emphasis on formulation development and evaluation (Appel, Kumle, Hubert, & Duvauchelle, 1997; Appel-Dingemanse, Lemarechal, Kumle, Hubert, & Legangneux, 1999; Appel-Dingemanse, Hirschberg, Osborne, Pommier, & McLeod, 2001a, 2001b; Fox, Menne, Stutz, Fried, & Schwizer, 2006; Swan et al., 2003; Talley et al., 2006; Zhou et al., 1999).

The objective of this study was to develop a pH-dependent sustained release tablet formulation of TM that would allow the dosage form to pass through the stomach intact, start disintegrating in the upper small intestine and slowly release the active in a controlled manner. The drug release profiles were optimized by evaluating the influence of formulation and coating parameters.

MATERIALS AND METHODS

Materials

TM was synthesized by the Department of Organic Chemistry, Shenyang Pharmaceutical University (China). Lactose (Shenyang Xinxi Reagent Co., Shenyang, China) as a diluent, poloxamer 188 (Shenyang Pharmaceutical Inc., Shenyang, China) as a solubilizer, sodium carboxymethyl starch (CMS-Na) (Shanghai Yongri Co. Ltd., Shanghai, China) as a disintegrant, povidone K30 (Tianjin Tiantai Fine Chemical Co., Tianjin, China) as a binder, diethyl phthalate (DEP) (Tianjin Reagent Co., China) as a plasticizer, and polyethylene glycol 400 (PEG 400) (Shenyang Chemicals Co., Shenyang, China) as a pore former were obtained from the indicated sources. Methacrylic acid copolymers (Eudragit® L100 and Eudragit® S100) were donated by Degussa-Röhm Co. (Darmstadt, Germany). Acacia, sodium dodecylsulfate (SDS), low-substituted hydroxyproxyl cellulose (L-HPC), and sodium cross-linked carboxymethyl cellulose (CCNa) were provided by Shanghai Yongri Co. Ltd (Shanghai, China). Starch (North China Pharmaceutical Inc., Hebei, China), sucrose (Shenyang Reagent Co., Shenyang, China), hydroxypropyl methyl cellulose (HPMC, Methocel® K4M and Methocel® E5) (Colocron Coating Technology Limited, Shanghai, China), sorbitan monooleate (Span 80) (Bodi Chemical Co., Tianjin, China), and propylene glycol (PG) (Fisher Scientific, NJ, USA) were commercially available.

High-Performance Liquid Chromatograph conditions

TM degraded rapidly to 5-methoxyindole-3-formaldehyde (MIF) below pH 3. Therefore, the amount of TM released from the coated tablets in 0.1 mol/L hydrochloric acid (HCl) was calculated by measuring the MIF amount in the dissolution samples incubated at 80°C for 10 min. The analysis of TM and MIF was performed utilizing a Shimadzu high-performance liquid chromatograph (HPLC) system equipped with a SPD-10A VP detector (Shimadzu Inc., Kyoto, Japan) at 220 nm. A mobile phase consisting of acetonitrile-0.003 mol/L phosphate buffer (40: 60, vol/vol) was pumped through a Kromasil C_8 column (200 mm × 4.6 mm, 5 μm; Turner, Tianjin, China) at a flow rate of 1.0 mL/min. The retention times of MIF and TM were 4.7 and 7.0 min, respectively.

Preformulation Studies

Partition Coefficient

The partition coefficient (P_{ow}) of TM in octanol/water was measured using a slow-stirring method (Organization for Economic Co-operation and Development, 2006). Briefly, mutual saturation of octanol and water was made before the investigation. The octanol/water system containing TM was stirred for 48 h at 25°C, and then the concentrations of drug in both phases were determined using spectrophotometry at 310 nm. The following equation was used to calculate P_{ow}:

$$P_{ow} = \frac{C_o}{C_w}$$

where C_o and C_w are the concentration of the drug in octanol and water, respectively.

Contact Angle

The contact angle of TM was determined according to the published method (Fell & Efentakis, 1979). Briefly, an appropriate TM-saturated solution was slowly dropped onto the surface of a compact cake of TM powder punched under a pressure of 19,600 kPa at 22°C, and the height and width of the liquid drop were measured. The contact angle was calculated from the following equation:

$$\tan\theta = \frac{2h}{a},$$

where θ is the contact angle, and h and a are the height and width of the liquid drop, respectively.

Drug-Excipient Compatibility

Multi-excipient mixtures and the drug were mixed at a ratio of 1:5, placed in a Petri dish with a thickness of less than 5 mm, and stored at 60°C, 92.5% RH and an illuminance of 4,500 ± 500 Lux for 10 days, respectively. At the end of 10 days, the content of drug remaining and impurity levels were determined using the HPLC method described previously. The physical appearance of drug-excipient blends was observed as well.

Preparation of Core Tablets

TM (8.3%, wt/wt), lactose (50%, wt/wt), CMS-Na (20%, wt/wt), and poloxamer 188 (20%, wt/wt) were tumble-mixed, and 10% wt/vol of povidone K30 in ethanol was added to this powder blend. The wet mass was passed through an 18-mesh standard sieve. The wet granules were dried in the air dryer at 44°C for 1 h, screened through the 16-mesh sieve, and then compressed into tablets with a hardness of 38 N using a single-punch tableting machine (Model TDP, Shanghai First Pharmaceutical Machinery Factory, Shanghai, China) fitted with a 6-mm diameter shallow biconcave punch and die set. The resulting tablets, weighing 100 mg each, contained approximately 8.3 mg of TM each (equivalent to 6.0 mg of tegaserod).

Coating of Core Tablets

A Eudragit® L100 and Eudragit® S100 combination ratio of 1:4 solution in ethanol (5%, wt/wt) was prepared, and DEP (1%, wt/wt) as well as PEG 400 (1%, wt/wt) were slowly stirred into the polymer solution. The coating of TM tablets was performed in a mini-film-coating unit (Model BY300A, Taixing Second Pharmaceutical Machinery Factory, Taixing, China). After the core tablets were warmed at 30°C for 10 min, the coating solution was sprayed through a 0.75-mm spray nozzle at a flow rate of 5 mL/min, the pneumatic spraying pressure being 0.6 MPa. The inlet and outlet temperatures of the drying air were 35 and 30°C, respectively. The pan rotation speed was set at 25 rpm. After being coated to a 5.0% coating level (weight gain), the tablets were dried at 40°C for 6 h to remove the residual solvent and stored in a desiccator until further analysis.

Optimization of Formulation Parameters

To optimize the release rate of TM from the coated tablets, the influence of the following factors was investigated.

- Solubilizer: Acacia, SDS, and poloxamer 188 were studied at a level of 20% (wt/wt).
- Disintegrant: L-HPC, CCNa, and CMS-Na were studied at a level of 20% (wt/wt).
- Binder: Starch paste (20%, wt/vol), HPMC (Methocel® K4M) paste (2%, wt/vol), and povidone K30 solution in ethanol (10%, wt/vol) were investigated.
- Coating polymer concentration: The polymers utilized were investigated at 2, 5, and 7% (wt/vol) concentrations.
- Pore former: Sucrose, HPMC (Methocel® E5), and PEG 400 were investigated at a concentration of 1% (wt/wt).
- Plasticizer: PG, Span 80, and DEP were studied at a concentration of 1% (wt/wt).

Drug Release Study

Release studies were conducted using USP 31 apparatus 2, paddle method (Tianjin University Radio Inc., Tianjin, China) at a rotation speed of 50 rpm at 37 ± 0.5°C. The dissolution media used were 900 mL of 0.1 mol/L HCl for 2 h, followed by 900 mL of the pH 6.8 phosphate buffer solution for 12 h. Samples (5 mL) were withdrawn at predetermined time intervals, passed through 0.45-μm membrane filters, and the amounts of the drug released in 0.1 mol/L HCl and the pH 6.8 phosphate buffer solution were measured by HPLC using the procedure specified in section 2.2 and by spectrophotometry at a wavelength of 310 nm, respectively.

Stability Study

To assess long-term stability of the optimum formulation, the coated tablets were stored in a sealed plastic container at 40°C/75% RH for 3 months. At predetermined time intervals (0, 1, 2, and 3 months), the formulation was observed for physical appearance, drug content, drug release, and impurity level.

Statistical Analysis

As recommended by the FDA, the similarity factor f_2 was used as a determination for assessing the similarity of dissolution

profiles (Shah, Tsong, Sathe, & Liu, 1998; U.S. Food and Drug Administration, 1997). The compared dissolution profiles were obtained under the same test conditions and their dissolution time points were the same. Two profiles were thought to be statistically similar if the f_2 value was greater than 50.

RESULTS AND DISCUSSION

Preformulation Studies

The experimental difficulties associated with the formation of microdroplets during the shake-flask experiment could be reduced in the slow-stirring experiment utilized in the present study. The shake-flask method is prone to artifacts due to transfer of octanol microdroplets into the aqueous phase. With increasing values of P_{OW}, the presence of these droplets in the aqueous phase leads to an overestimation of the concentration of the test substance in the water. Utilizing the slow-stirring method, water, octanol, and drug were equilibrated in a thermostated stirred reactor. Saturation between the phases was accelerated by stirring. The stirring introduced limited turbulence which enhanced the saturation between octanol and water without microdroplet formation. The partition coefficient of TM was 23.65 ± 2.67, indicating that TM is a hydrophobic drug and preferentially becomes distributed to hydrophobic compartments such as lipid bilayers in the intestinal epithelium. For a drug to be orally absorbed, the drug must be adequately hydrophobic to partition into the lipid bilayers; however, once that it is in the bilayers, it will also partition into the systemic circulation.

Measurement of contact angle provides useful indications of wettability of solid dosage forms, which is an important initial step in drug release. Determination of the contact angle of tablet surfaces to optimize film-coating techniques and to study drug release from matrices has been reported (Lerk, Schoonen, & Fell, 1976). Hydrophilicity of a substance decreases with an increase in contact angle. On most highly hydrophilic surfaces, water droplets exhibit contact angles of 0°–30°. Conversely, highly hydrophobic surfaces have contact angles as high as 150° to nearly 180°. In the present study, TM exhibited a contact angle of 63.52 ± 5.08°, demonstrating a relatively low affinity for water. Therefore, it was necessary to incorporate highly hydrophilic excipients/surfactants in the tablet formulation to increase the release rate of the drug after granulation with a binder.

No interaction between drug and multicomponent mixtures was found on all of the formulations tested. Compatibility results of the optimum formulation based on the dissolution test, that is drug–multicomponent mixtures (lactose: poloxamer 188: CMS-Na = 2:1:1, wt/wt) at a ratio of 1:5, are presented in Table 1. Chromatograms of the mixtures were compared with that of the pure drug for assessing the compatibility. Physical mixtures of TM with the combination of lactose, poloxamer 188, and CMS-Na exhibited no changes in drug content and physical appearance at the tested conditions for 10 days. Also, the retention time and peak shape of the drug were unaltered. These results demonstrated good compatibility between the drug and the excipients employed.

TABLE 1
Compatibility Results of Drug–Multicomponent Excipients (Lactose: Poloxamer 188: CMS-Na = 2:1:1, wt/wt) Mixture at a Ratio of 1:5 at Various Conditions for 10 Days. Data are Expressed as Mean ± *SD* (n = 3)

Condition	Drug Content (%)	Impurities (%)
Initial	100.0 ± 1.45	0.13 ± 0.04
60°C	99.9 ± 2.15	0.34 ± 0.04
92.5% RH	99.9 ± 1.87	0.31 ± 0.05
4,500 ± 500 Lux	99.9 ± 1.34	0.29 ± 0.11

Coating Studies

The Effects of Solubilizer, Disintegrant, and Binder

Drug release profiles of various coated formulations utilizing various solubilizers, disintegrants, and binders are presented in Figure 2A, B and C, respectively. The formulations employing acacia and SDS as solubilizers exhibited a significantly longer lag time (5 h) as compared with the formulation containing poloxamer 188 (2 h), and the similarity factor f_2 was 21.0 and 26.7 for formulations with acacia and SDS, respectively. This may be attributed to formation of a complex between these anionic surfactants (acacia and SDS) and the cationic drug, which hinders further dissolution of the drug. In addition, the cations in the pH 6.8 phosphate buffer solution may coagulate with acacia and SDS, reducing their solubilization effects (Levine, 1995). Disintegrants used in the tablets accelerate drug release on contact with the dissolution media. The formulations employing L-HPC and CCNa as disintegrants exhibited significantly lower drug release than the formulation containing CMS-Na with f_2 value of 40.8 and 31.6, respectively. Povidone K30, a hydrophilic tablet binder, enhanced the release of the poorly soluble TM from the coated tablets as compared with starch and HPMC, with which approximately 54% and 67% drug release were observed in 14 h, respectively. Based on the above data, poloxamer, CMS-Na, and povidone K30 were selected as the solubilizer, the disintegrant, and the binder, respectively, in the core tablets for the development of optimum formulation.

The Effects of Concentration of Polymers, Pore Former, and Plasticizer

As shown in Figure 3A, drug release decreased with an increase in concentration of the coating polymers. The higher the concentration of the coating polymers, the larger were the droplets formed on atomization, which led to a

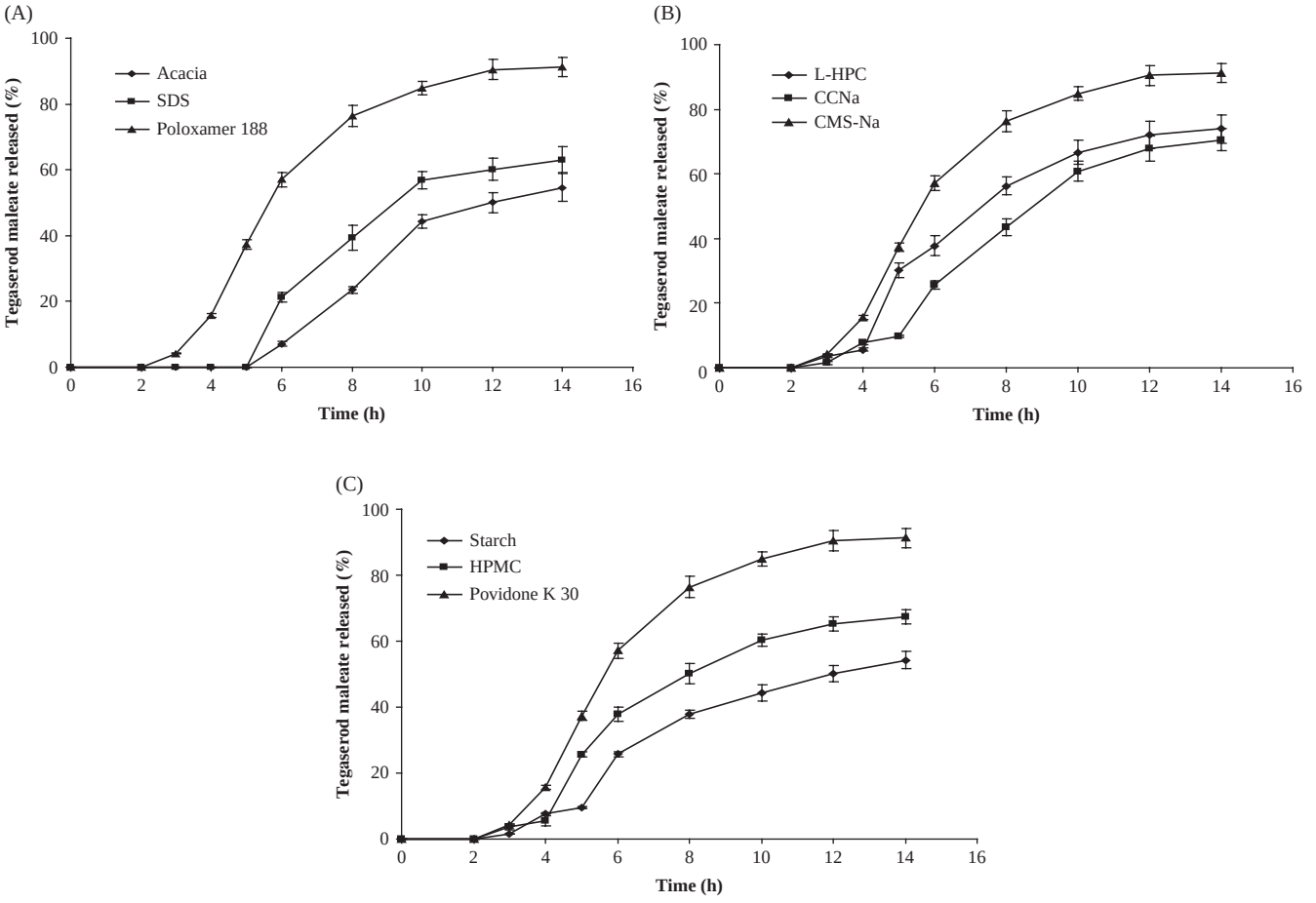

FIGURE 2. The effects of different solubilizers (A), disintegrants (B), and binders (C) on the release of tegaserod maleate tablets in 0.1 Mol/L HCl for 2 h followed by the pH 6.8 phosphate buffer media for 12 h at 37°C. Data are expressed as mean ± *SD* (n = 6).

slower evaporation rate of polymer solvent. Consequently, a tight film with fewer and smaller pores was formed, which decreased the permeability of the film to the dissolution media, leading to a slower drug release. The following equation (Aulton & Twitchell, 1995) could describe the droplet size produced by pneumatic atomization:

$$D_S = \left[\frac{585\times10^3}{\nu}\right]\times\left[\frac{\gamma}{\rho}\right]^{0.5} + 1683^{\ 0.45}[\gamma\times\rho]^{-0.225}\left[\frac{1000}{J}\right]^{1.5},$$

where D_s is the surface mean diameter of the droplet, ν is the velocity of the air relative to liquid at the atomizer nozzle exit, γ is the liquid surface tension, ρ is the liquid density, μ is the liquid viscosity, and J is the air/liquid volume ratio at the air and liquid orifices. In this case, the increase of ρ and γ produced larger droplet size.

Because Eudragit® L100 and Eudragit® S100 films were tight and compact even at thicknesses of 10–20 µm, a pore former was necessary to obtain a desired drug release. Figure 3B demonstrated the effects of sucrose, HPMC (Methocel® E5) and PEG 400 employed as pore formers on the drug release. Sucrose exhibited the fastest drug release of all pore formers studied with an f_2 of 33.3 as compared with PEG 400, which may be attributed to higher porosity and hence higher permeability of these films. No significant difference was observed in the drug release profiles of tablets containing PEG 400 or HPMC (Methocel® E5). However, HPMC (Methocel® E5) increased the risk of obstructing the atomizer nozzle due to its higher viscosity as compared with PEG 400. The presence of a hydroxyl group on each of the carbon atoms of PEG 400 renders the films very hydrophilic, favoring higher water absorption by the polymer with an increased permeability of the film. Hence, PEG 400 was selected as the pore former due to coating method performance.

Sustained drug release was achieved by the incorporation of plasticizers at 1% (wt/wt) in coating polymers, as shown in Figure 3C. Because of their different water solubility, plasticizers significantly affected the drug release from the coated tablets (Frohoff-Hulsmann, Schmitz, & Lippold, 1999; Gutiérrez-Rocca & McGinity, 1994). The release of

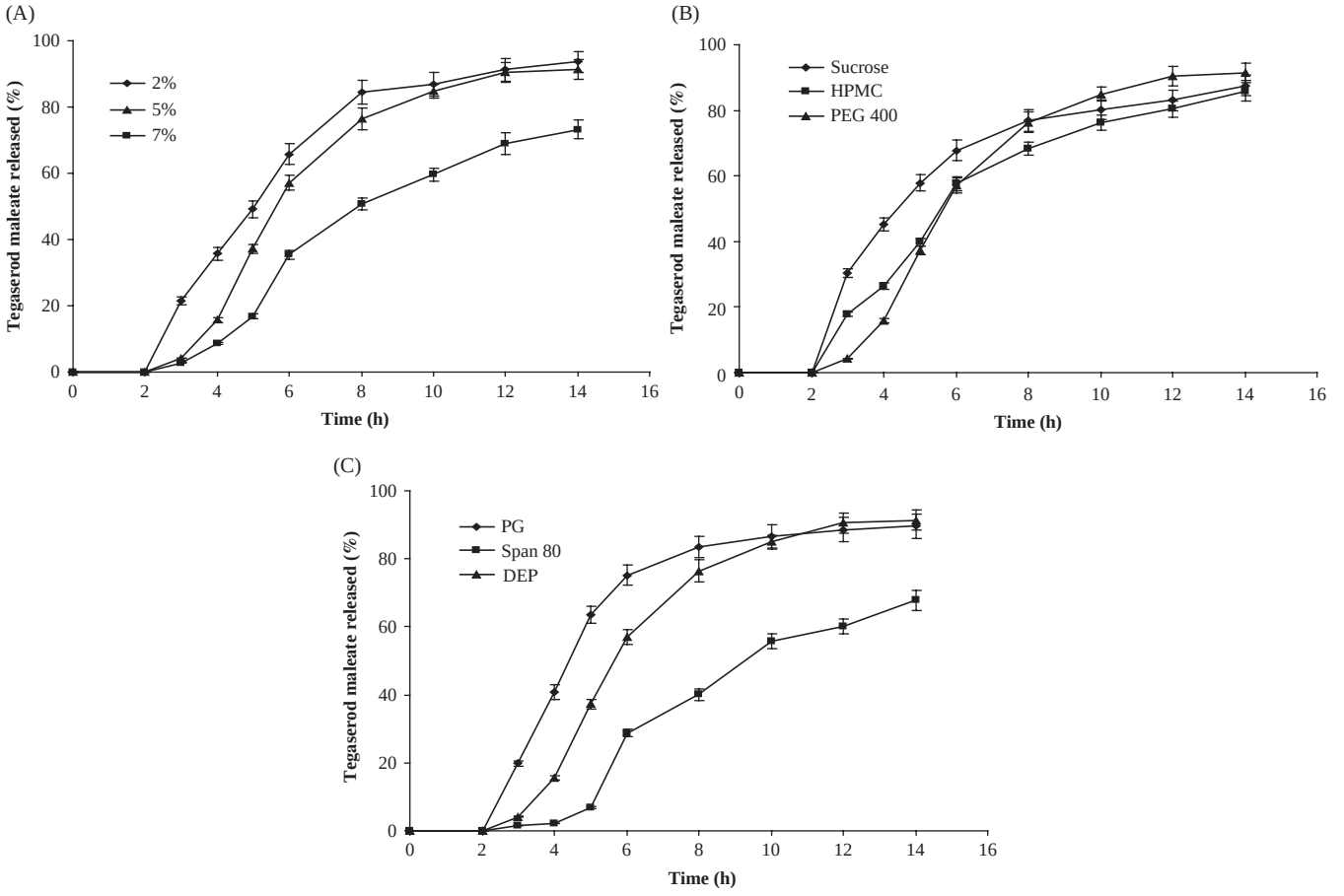

FIGURE 3. The effects of different concentrations of coating polymers (A), pore formers (B), and plasticizers (C) on the release of tegaserod maleate tablets in 0.1 Mol/L HCl for 2 h before the pH 6.8 phosphate buffer media for 12 h at 37°C. Data are expressed as mean ± *SD* (n = 6).

TM from the coated tablets containing the plasticizers was in the order of PG > DEP > Span 80. Due to its highest water-solubility, PG leached from the coating and created pores, thus resulting in a faster release as compared with DEP and Span 80. Span 80 showed a significantly longer lag time (4 h) as compared with DEP (2 h), and therefore DEP was chosen as a plasticizer. Another explanation for an increased drug release rate is that the addition of a plasticizer increases the mobility of the polymeric chains and the free volume between the chains, causing the polymer network to relax and become less dense (Hogan, 1995).

Release Mechanism

The release data of the optimum formulation were fitted to various release models to explain the kinetics of TM release from the coated tablet. The kinetic models used were zero-order, first-order, Higuchi, Ritger-Peppas, Baker-Lonsdale, Weibull and Hixson-Crowell (Costa & Sousa Lobo, 2001). The results of model simulation are presented in Table 2. An examination of the r^2 values demonstrates that drug release most likely follows the Hixson–Crowell mechanism from the coated tablets, indicating that the surface and dimension of the tablets diminished during the dissolution. This is consistent with the observation that some of the coated film dissolved and released from the core during dissolution, and subsequently the core tablet was broken into variable sections or pieces. The coated films were soluble within the pH range of 6.0–7.0, at which pH Eudragit® L100 and Eudragit® S100 start dissolving, respectively. Therefore, the release mechanism may be due to stress points or pore formation within the film. Hence, channels for the release media to penetrate into the tablets were formed, resulting in disintegration of the tablets and/or loss of integrity of the film. These results would lead to a gradual increase in TM release as the polymers dissolve. The dissolution of the two polymers is therefore rate-limiting.

Stability Study

No change in physical appearance of the optimum formulation was observed after 3-month storage at 40°C/75% RH. The entire formulation (coated film and core tablet) was white, and the coated film was intact. No significant difference was observed in the release profiles after storage at accelerated

TABLE 2
The Release Kinetics Models of Tegaserod Maleate Coated Tablets

Model	Equation	k	C	r^2
Zero-Order	$\frac{M_t}{M_\infty} = kt + C$	8.1428	6.3742	0.9013
First-Order	$\ln(100 - \frac{M_t}{M_\infty} = kt + C)$	–0.2132	5.0037	0.9520
Higuchi	$\frac{M_t}{M_\infty} = kt^{1/2} + C$	0.1517	0.7086	0.9326
Ritger-Peppas	$\ln \frac{M_t}{M_\infty} = k \ln t + C$	1.8132	0.2178	0.8125
Baker-Lonsdale	$\frac{3}{2}\left[1-(1-\frac{M_t}{M_\infty})^{2/3}\right] - \frac{M_t}{M_\infty} = kt + C$	0.0260	–0.0593	0.9282
Weibull	$\lg\left[-\ln(1-\frac{M_t}{M_\infty})\right] = k \lg t + C$	2.5130	–2.2677	0.9047
Hixson-Crowell	$\frac{M_t}{M_\infty} = k_1 t^3 + k_2 t^2 + k_3 t + C$	$\frac{M_t}{M_\infty} = -0.1218t^3 + 2.1909t^2 - 0.2966t - 4.2899$		0.9737

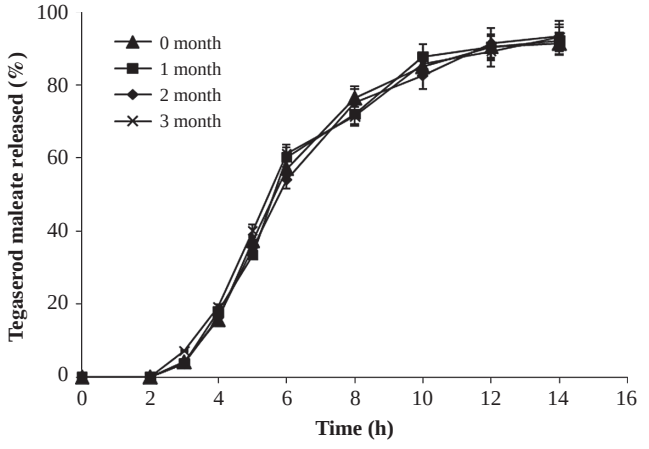

FIGURE 4. The release profiles of tegaserod maleate coated tablets stored at 40°C/75% RH. Data are expressed as $M \pm SD$ (n = 6).

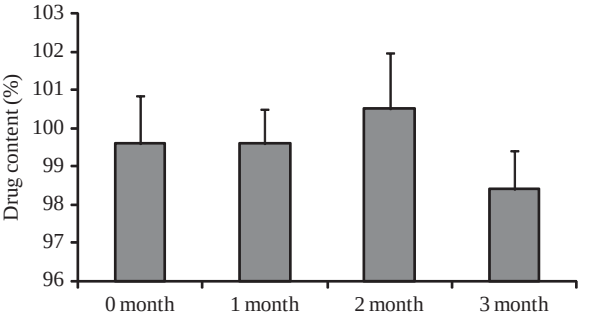

FIGURE 5. The content of tegaserod maleate in the coated tablets stored at 40°C/75% RH. Data are expressed as $M \pm SD$ (n = 3).

conditions for 1, 2, and 3 months as indicated in Figure 4 (f_2 values were 77.4, 82.4 and 73.1 at 1, 2, and 3 months, respectively). In addition, drug content was determined to be 98.4% of the labeled amount after 3-month storage (Figure 5). The total impurity content was found to be less than 0.5% after 3 months.

CONCLUSION

Preformulation studies indicated that TM is a relatively hydrophobic active, and the selected excipients exhibited good compatibility with the drug. Coating studies demonstrated that solubilizers, disintegrants, binders, concentration of coating polymers, pore formers, and plasticizers affect the rate and extent of drug release. The release studies showed that no drug was released in the acidic pH of the stomach in the first 2 h; however, approximately 90% of the drug was released at the

pH of the lower part of the gastrointestinal tract within 12 h in a sustained manner. The drug release mechanism involved stress points and/or pore formation within the coated film. The TM-coated tablets were stable at 40°C/75% RH for 3 months. These findings demonstrate that the pH-dependent sustained release tablet system is a promising dosage form for TM and other selected actives, which may positively impact the treatment of IBS.

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