RESEARCH ARTICLE

Development and *in vitro* evaluation of colonic drug delivery systems for tegaserod maleate

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Interest exists in developing site-specific systems of release of drug in the colon via the oral route. Tegaserod maleate was used as a drug for irritable bowel syndrome, whereas Eudragit L 100 and S100 mixture (1:1, 1:2, and 1:3) were used as pH-sensitive polymers. Various approaches, namely microcapsules, compressed microcapsules, and modified tablets were made for this study. The microcapsules were prepared by the emulsion–solvent evaporation method using drug and mixture of polymers. The prepared microcapsules were evaluated for various physicochemical parameters such as particle size, surface morphology, drug loading capacity, and *in vitro* dissolution studies by half-dilution method employing various pH environments (pH 1.2–6.8) for 24 hours. The batch prepared using the 1:2 drug polymer ratio was selected as an ideal batch for compression to get the compressed tablet of the microcapsules. The compressed microcapsules were evaluated for physicochemical parameters such as average weight, hardness, friability, thickness, and *in vitro* dissolution by the half-dilution method. The modified tablets were also prepared using the drug with hydroxylpropylmethylcellulose as the inner material and ethyl cellulose as the outer material employing the double compression technique. The prepared tablets were subjected to various physicochemical parameters, including thickness, weight variation test, drug content, hardness, friability, and *in vitro* dissolution study using the half-dilution method (pH 1:2–6.8) for 24 hours. Comparisons of microcapsules, compressed microcapsules, and modified tablets containing tegaserod maleate indicated that the drug release profiles from the microcapsules were found to be better than the compressed microcapsules and the modified tablets in the colonic environment.

Key words: *Colon specific, eudragit, microcapsules and modified tablets, tegaserod maleate*

INTRODUCTION

The colon is being extensively investigated as a drug delivery site. Colonic drug delivery is a relatively recent approach for the treatment of diseases like ulcerative colitis, Crohn's disease, and irritable bowel syndrome. Such local treatment has the advantage of requiring smaller drug quantities, possibly leading to a reduced incidence of side effects and drug interactions.[1] The colon is an attractive site where poorly absorbed drug molecules may have an improved bioavailability. Additionally, the colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. The simplest method for targeting drugs to the colon is to obtain slower release rates or longer release periods by the application of thicker layers of conventional enteric coating or use of extremely slow releasing matrices,[2] pH-sensitive polymers that dissolve, or above pH 7 may also be used for colonic drug delivery.[3] There are several methods for confirming drug release to the colon. Among them, one of the methods is employing pH-sensitive polymers such as Eudragit (L100/S100), suitable for achieving colonic drug delivery.[4] Most of the commercially available systems for colon-specific drug delivery utilize Eudragit (L100/S100), which is soluble at pH 7. Cellulose acetate phthalate is also an effective enteric coating material[5] as it dissolves at pH 6. The present paper describes the development and *in vitro* evaluation of the colonic delivery system using Eudragit and enteric polymers as carriers.

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MATERIALS AND METHODS

Tegaserod maleate was received as a gift sample from Hetero drugs, Hyderabad, India and Eudragit (L100/S100) was purchased from Rohm Chemicals - Röhm GmbH & Co. KG, Darmstadt, Germany. Hydroxypropylmethylcellulose and ethyl cellulose were procured from S.D. Fine Chemicals, Mumbai, India. Dichloromethane, petroleum ether, methanol, and potassium hydrogen phthalate were procured from Nice Chemicals, Mumbai, India. Sorbitan mono oleate (Span 80) was procured from Sheeji Chemicals, Mumbai, India. Potassium dihydrogen O-phosphate and heavy liquid paraffin were purchased from S.D. Fine Chemicals.

All other reagents used in the study were of analytical grade.

Preparation of microcapsules containing tegaserod maleate

An emulsion–solvent evaporation method[6] was followed to prepare microcapsules with acetone as solvent Eudragit L 100 and S100 (1:1) in which the drug tegaserod maleate (20 mg) was dispersed using a mechanical stirrer at 800 rpm. The suspension was poured slowly into liquid paraffin (60 ml) containing 1 ml of Span 80 as dispersion medium and stirred at 1000 rpm. Acetone was allowed to evaporate at room temperature and further stirring rigidified the microcapsules. They were washed in petroleum ether (40–60^{o} grade) and dried for 12 hours. By adopting the aforesaid method, 16 batches of microcapsules were prepared using different proportions of polymer and different stirring rates, but the concentration of the drug remained constant.

Determination of the average particle size of the microcapsules

Determination of the average particle size of the tegaserod maleate microcapsules was carried out by the optical microscopy method.[7] A minute quantity of microcapsules was spread on a clean glass slide and the average sizes of 100 microcapsules were determined in each batch.

Morphology and surface appearance

An aqueous dispersion of the microcapsules was finely spread over a stab and dried by keeping in a desiccator. The dried film of microcapsules was given a 25μ-m-thick gold layer and was observed by scanning electron microscopy[8] (Joel JVA 840 A, Japan). The scanning electron micrograph is depicted in Figure 1.

Estimation of the amount of drug incorporated into the microcapsules

Twenty-five milligrams of tegaserod maleate microcapsules were taken in an equal dilution of dimethyl formamide and phosphate buffer at pH 6.8 and stirred for 12 hours. After stirring, the solution was filtered through Whatman filter paper and from the filtrate 1 ml of the sample was taken and appropriate dilutions were made and measured UV spectrometrically at 315 nm (Shimadzu-UV-1601, Kyoto Japan).

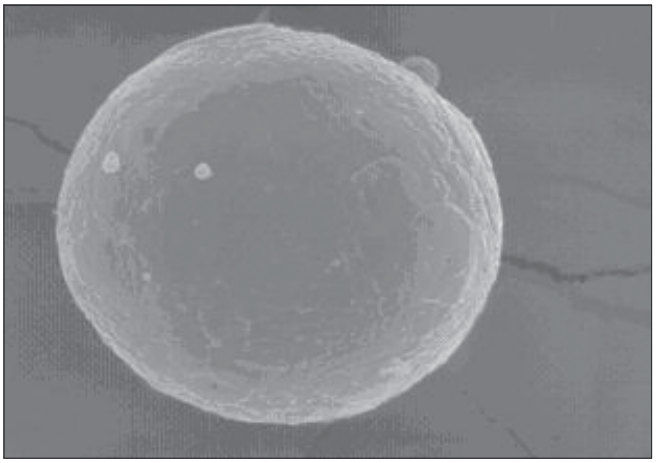

Figure 1: Scanning electron micrograph of tegaserod maleate microcapsules

Formulation of compressed microcapsules

It was accomplished by the direct compression method. Required quantities of microcapsules equivalent to 20 mg of tegaserod maleate were mixed thoroughly with microcrystalline cellulose, talc, and magnesium stearate. The tablets were compressed using a rotary tablet compression machine (8 mm diameter, 10 station; Rimek, Ahmedabad, India) and named as Batch 'A'. Similarly, required quantities of microcapsules equivalent to 20 mg of tegaserod maleate were mixed thoroughly with hydroxyprophylmethylcellulose (HPMC), talc, and magnesium stearate. Composition of the compressed microcapsules is shown in Table 1. The tablets were compressed using the same instrument as explained above and named as Batch 'B'. The prepared tablets were evaluated for average weight, hardness, friability, thickness,[9] and *in vitro* dissolution using half-dilution techniques.

Formulation of modified tablets

It was accomplished by the double compression technique,[10] where all the powders were passed through sieve No. 80. Drug and other excipients were mixed thoroughly. The tablets (inner core) were prepared using a rotary tablet machine (8 mm diameter punches, 10 stations; Rimek). Then, the core tablets obtained were compressed with ethyl cellulose, sodium chloride, and potassium chloride using a rotary tablet compression machine. The compositions of the modified tablets are as shown in Table 2. The modified tablets were then coated with cellulose acetate phthalate solution, the coating formula being shown in Table 3. About 100 tablets were placed in a mini coating pan of 9.4 in. diameter using a 1 mm fluid nozzle spray gun. The rotation of the coating pan, the automizer's air pressure, and the drying temperature were maintained at 30 rpm, 3–3.5 kgf/cm^2, and 55–60°C, respectively. The coated modified tablets were evaluated for thickness, weight variation test, drug content, hardness, friability, and *in vitro* release studies using the half-dilution

Table 1: Composition of the compressed microcapsules

Ingredients	Batch 'A' (mg/tablet)	Batch 'B' (mg/tablet)
Microcapsules ≈ 20 mg of tegaserod maleate	62	62
Microcrystalline cellulose	35	-
Talc	1.5	1.5
Magnesium stearate	1.5	1.5
Hydroxypropylmethylcellulose	-	35

techniques.

***In vitro* dissolution studies of microcapsules, compressed microcapsules, and modified tablets**

It was accomplished by half-dilution techniques,[11] where different pH conditions were maintained for the dissolution study. The study was carried out by USP XXIII Type 2 (Paddle) method, where the prepared formulations were taken in 500 ml of 0.1 N HCl with dimethyl formamide buffer (pH 1.2) maintained at 37±0.5°C for first 2 hours and followed by phosphate buffer (pH 6.8) for the remaining period. The dissolution media was rotated at a rate of 50 rpm. At the specified intervals, 5 ml of the sample was withdrawn from the dissolution media and the drug content was analyzed at 315 nm in a UV spectrophotometer (Shimadzu).

RESULTS AND DISCUSSION

The objective of the present work is to develop different colon-specific formulations containing tegaserod maleate and to study its *in vitro* dissolution profiles. Microcapsules were prepared by the solvent evaporation technique employing Eudragit L100 and S100 as polymers. Sixteen batches of microcapsules were prepared using different combinations of polymer ratios and different stirring rates, like 800, 1000, 1200, and 1400 rpm, showing particles with discrete size and shape. The average particle sizes of the microcapsules were found to be 67.13±1.3 microns. The batch prepared with the 1:2 drug: polymer ratio with a stirring rate of 1400 rpm showed good drug entrapment efficiency and the drug content was found to be 89.06±1.5% compared with other batches and this batch was selected for the *in vitro* dissolution study using the half-dilution technique. Also, this batch was selected for the formulation of the compressed microcapsules. The compressed microcapsules were prepared using microcrystalline cellulose (Batch 'A') and hydroxylpropylmethylcellulose (Batch 'B') and were evaluated for various physicochemical parameters. It was revealed that the batch prepared with microcrystalline cellulose (MCC) had a drug content of 98.26±1.25%, hardness of 3.5±0.3 kg/cm^2, friability 0.92%, and average weight of 151.7±0.8 mg. All the above parameters were within the range of official procedures and the batch prepared using HPMC was subjected to *in vitro* dissolution study employing the half-dilution technique. Modified tablets were prepared using HPMC (MT1) and MCC (MT2) as inner core materials at different concentrations and were given an enteric coating using cellulose acetate phthalate. The formulated modified tablets were subjected to various physicochemical parameters. The batch prepared using HPMC (MT1) at a higher concentration showed a drug content of 99.89±1.6%, hardness of 6.5±1.2 kg/cm^2, friability of 0.25%, and average weight of 315.2±2.5 mg with respect to the batch prepared using a higher concentration of MCC (MT2), which showed a drug content of 101.36±2.3%, hardness of 6.5±1.3 kg/cm^2, friability of 0.19%, and average weight of 315.2±2.5 mg [Table 4]. Hence, batch MT2 showed better drug content and therefore this batch was subjected to *in vitro* dissolution study by the half-dilution technique. The selected microcapsules, batch-compressed microcapsules, and modified tablets were subjected to the *in vitro* dissolution technique using the half-dilution method for 24 hours using different pH conditions ranging from 1.2 to 6.8. The release profiles of the prepared formulations are shown in Figure 2. The tegaserod maleate release from the microcapsules was found to be slow and extended over a longer period of time as compared with the compressed microcapsules and the modified tablets. Microcapsules

Table 2: Composition of the modified tablets

Inner core	Modified tablet 1 (mg)	Modified tablet 2 (mg)
Ingredients		
Tegaserod maleate	20	20
Hydroxypropylmethylcellulose	80	60
Microcrystalline cellulose	50	70
Outer core		
Ethyl cellulose	135	135
Potassium chloride	5	5
Sodium chloride	5	5
Talc	2.5	2.5
Magnesium stearate	2.5	2.5

Table 3: Composition of the coating solution

Ingredients	Qty/100 g
Cellulose acetate phthalate	6.0
Titanium dioxide	2.0
Diethyl phthalate	0.8
Ethanol	45.6
Methylene chloride	45.6

Table 4: Physicochemical parameters of the microcapsules, compressed microcapsules, and modified tablets

Parameter	Microcapsules*	Compressed microcapsules		Modified tablets*	
		Batch 'A'	Batch 'B'	MT1	MT2
Average particle size (μ)	67.13±1.3	-	-	-	-
Drug content (%)	89.06±1.5	98.26±1.25	99.64±0.29	99.89±1.6	101.36±2.3
Hardness (kg/cm^2)	-	3.5±0.3	3.0±0.4	6.5±1.2	6.5±1.3
Friability (%)	-	0.92	0.88	0.25	0.19
Average weight (mg)	-	152.26±0.9	151.7±0.8	315.2±2.5	310.05±3.5

*n = 6. Values in the parenthesis indicate standard deviation.

Table 5: Release mechanism for the formulations

Formulations	Slope (n)	Correlation (r)	Mechanism
Microcapsules	1.067	0.9766	Super case II transport
Compressed microcapsules	1.0538	0.9734	Super case II transport
Modified tablets	0.9944	0.9671	Anamalous diffusion

showed a slow and sustained release (89.06%) as compared with compressed microcapsules (76.71%) and modified tablets (70.94%) over a period of 24 hours. To calculate the release constant 'k', the logarithms of the remaining tegaserod in the microcapsules, compressed microcapsules, and modified tablets was plotted against time. The release of tegaserod maleate from the microcapsules, compressed microcapsules, and modified tablets followed a first order release. On the other hand, to predict and correlate the release behavior of the microcapsules, compressed microcapsules, and modified tablets, it was fitted into a well-known exponential equation,[12] used to describe the drug release behavior from the polymeric system.

Experimental results were fitted according to the following exponential equation:

$$M_t/M_\alpha = kt^n \text{----------1.}$$

where M_t/M_α is the fraction solvent absorbed (or) drug release at time 't'. 'k' denotes a constant incorporating properties of the macromolecular polymeric system and 'n' is the kinetic constant, which depends on time and is used to characterize the transport mechanism. The 'n' value is used for the analysis of the drug release mechanism from the microcapsules, compressed microcapsules, and modified tablets, where log (M_t/M_α) vs log 't' plots. The 'n' values for the microcapsules and the compressed microcapsules were found to be 1.067 and 1.0538, showing the mechanism of super case II transport and the 'n' value for modified tablets was found to be 0.9944, showing diffusion [Table 5]. All the formulations were found to follow a first order release. The microcapsules prepared using Eudragit L100 and S100 (1:2 drug polymer ratio) showed a slow and controlled release system for 24 hours. Formulations of microcapsules and modified tablets exhibited very slow and incomplete release in 24 hours by the half-dilution method. Tegaserod maleate release from all the formulations followed a first order kinetics. Hence, the microcapsules were found to be ideal for colon targeting of tegaserod in conditions like irritable bowel syndrome. However, *in vivo* studies should be carried out to establish its potential effects.

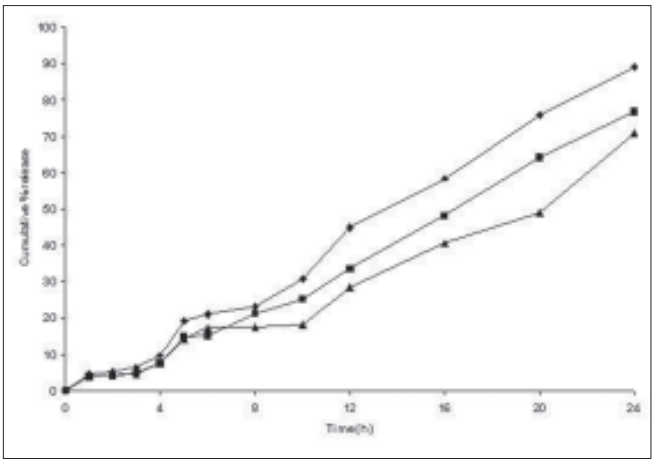

Figure 2: Dissolution profiles of tegaserod maleate from microcapsules (-and#9830;-), compressed microcapsules (-and#9632;-), and modified tablet (-and#9650;-) by the half-dilution technique

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