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DESIGN AND EVALUATION OF COLON TARGETED DELIVERY OF TEGASEROD MALEATE FOR IRRITABLE BOWEL SYNDROME

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ABSTRACT

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. To achieve successful colon targeted drug delivery, a drug needs to be protected from degradation, release and /or absorption in upper portion of GI tract and then ensure abrupt or controlled release in proximal colon. The purpose of this research is to develop and evaluate the polysaccharide based compression coated tablets of Tegaserod maleate for the treatment of irritable bowel syndrome. Core tablets of Tegaserod maleate were compression coated with various proportions of Galactosol, xanthan gum and chitosan. This work aimed to prepare compression coated tablets by direct compression method using single polymer and combination of polymers. And to evaluate prepared tablets parameters like hardness, friability, thickness, diameter, weight variation, drug content, swelling index, *in vitro* drug release.

Keywords: Colon, Tegaserod maleate, Galactosol, xanthan gum and chitosan

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INTRODUTION

Tegaserod maleate (TM) is the first selective 5-hydroxytryptamine type-4 (5-HT4) receptor partial agonist used for the treatment of constipation predominant irritable bowel syndrome (IBS), a complex gastrointestinal disorder characterized by a combination of abdominal pain, is comfort, diarrhea, and/or constipation. TM is insoluble in water and has pH dependent solubility. Below pH 3, TM is rapidly degraded through hydrolytic breakdown. TM is readily absorbed following oral administration under fasted condition, and the peak plasma concentration occurs after 1.0-1.3 hr. Absolute bioavailability is about 10 %, and terminal elimination half-life is close to 11 hr. To improve the oral bioavailability and prevent rapid hydrolysis of TM in gastric milieu, a dosage form containing TM is coated with polysaccharides based polymers. Rationale for development of a polysaccharides based delivery system for colon is the presence of large amount of polysaccharidases in human colon as the colon in inhabitated by a large number and variety of bacteria which secrete enzymes viz β-Dglucosidase, β-D-galactosidase, amylase, pectinase, xylanase. Various major approaches utilizing polysaccharides for colon-specific delivery is fermentable coating of the drug core, embedding of the drug in biodegradable matrix and formulation of drug saccharide conjugate (Prodrugs). A large number of polysaccharides have already been studied for their potential as colon-specific drug carrier systems, such as chitosan, pectin, chondroitin sulphate, guar gum, xanthan gum, khaya gum, inulin, amylose and locust bean gum.[1, 2, 3, 4, 5]

This work aimed to prepare compression coated tablets by direct compression method using single polymer and combination of polymers. And to evaluate prepared tablets parameters like hardness, friability, thickness,

diameter, weight variation, drug content, swelling index, *in vitro* drug release.

MATERIALS AND METHODS

Materials

The drug Tegaserod maleate was received as a gift sample from Hetero drugs, Hyderabad. Galactosol was purchased from SD fine chemicals, Mumbai. Chitosan and Xanthan gum were purchased from Himedia laboratories Ltd, Mumbai. Magnesium Stearate and Talc were obtained from SD Fine chemicals Mumbai. All the other chemicals used were of high analytical grade.

Methods

Preparation of tablets:

Preparation of fast disintegrating core tablets:

The core tablets of tegaserod maleate were prepared by direct compression technique using the composition given in Table 1. Tegaserod maleate, sodium starch glycolate, micro crystalline cellulose, magnesium stearate and talc were passed through sieve no #80 (179 µm), weighed and thoroughly mixed in a polybags to ensure complete mixing. The mixture was compressed into tablet on a single station tablet punching machine using 9.5 mm round, flat-faced and plain punches.[6, 7, 8]

Table 1: Composition of core tablet

	Ingredients	Quantity (mg)
1	Tegaserod maleate	8.3
2	Microcrystalline cellulose	55.5
3	Sodium starch glycolate	33.2
4	Magnesium stearate	1.5
5	Talc	1.5
	Total weight	100

Preparation of compression coated tablets

The composition of compression coating material is shown in Table 2. All the ingredients of each coat formulation were weighed accurately and mixed in a polybag. 150 mg of coating mixture was placed in the die cavity of single station tablet punching machine, the core tablet was placed on it at centre, remaining 150 mg of coating mixture was carefully transferred to the die cavity and tablets were compressed using 12.6 mm flat punches. The total weight of the compression coated tablet was about 400 mg (100+300 mg). [6-8]

Table 2: Composition of compression coated tablets

Formulation	Galactosol (mg)	Xanthin gum (mg)	Chitosan (mg)	Microcrystalline cellulose (mg)	Magnesium stearate (mg)	Talc (mg)
F1	240			55	1`.5	3.5
F2		240		55	1`.5	3.5
F3			240	55	1`.5	3.5
F4	130		110	55	1`.5	3.5
F5	160		80	55	1`.5	3.5
F6	190		50	55	1`.5	3.5
F7	210		30	55	1`.5	3.5
F8		130	110	55	1`.5	3.5
F9		160	80	55	1`.5	3.5
F10		190	50	55	1`.5	3.5
F11		210	30	55	1`.5	3.5
F12	130	40	70	55	1`.5	3.5
F13	100	70	70	55	1`.5	3.5
F14	70	100	70	55	1`.5	3.5
F15	40	130	70	55	1`.5	3.5

Evaluation of tablets:

A. Physico-chemical evaluation of compression coated tablets:

The prepared tablets were evaluated for diameter, thickness, hardness, friability, weight variation and drug content.

(a) Thickness and Diameter: The thickness and diameter of the tablets was determined by using dial thickness apparatus and vernier calipers respectively. Five tablets from each formulation were used and average values were noted.[8,9]

(b) Hardness: Tablet hardness of all the formulations was determined by using Monsanto hardness tester. Five tablets from each formulation were used and average values were recorded.[9,10]

(c) Friability: Both core and compression coated tablets from all formulations were subjected for friability test using friabilator. Ten tablets were weighed and placed inside the Roche friabilator. The instrument was operated for 4 mins at 25rpm. The resulting tablets after

100 falls from a height of six inches were collected; weighed and percentage loss was calculated using following equations.[10-12]

$$\% \text{ Friability} = \frac{\text{Initial wt of the tab - final wt of tab}}{\text{Initial wt of tab}} \times 100$$

(d) Weight variation test: The weight variation study of the prepared formulations was performed as per the standard procedure following Indian pharmacopoeia. The mean and standard deviation of each batch of tablets were tabulated.[11-12]

(e) Determination of drug content: One tablet from each formulations of compression coated and the core tablets were powdered and transferred in to 100 ml volumetric flask. Initially 50 ml of phosphate buffer (pH 6.8) was added and allowed to rotate in a rotary shaker for 24 h; the final volume was made up with phosphate buffer (pH 6.8). The solution was filtered and amount of secnidazole present in the solution was estimated by using UV- spectrophotometer (UV 1601, Shimadzu, Japan) at 315 nm against a suitable blank.[10-12]

B. Swelling index:

One tablet from each formulation was randomly selected, weighed individually (W_O) and placed separately in a wire basket which was placed in a 100 ml beaker containing 0.1 N HCl for first 2 h and pH 6.8 for remaining 22 h. At the end of 2, 4, 6, 8 and 24 h the tablets were removed from wire basket and excess water was removed using filter paper. The swollen tablets were reweighed (Wt) and swelling index of each tablet was calculated using the below equation.[12-14]

$$\% \text{ Swelling ratio} = \frac{W_t - W_0}{W_0} \times 100$$

C. Preparation of 2% rat caecal content:

Male wistar rats weighing 150-200 gm maintaine to rotate in a rotary shaker for 24 h; the final volume was made up with phosphate buffer (pH 6.8). The solution was filtered and amount of secnidazole present in the solution was estimated by using UV- spectrophotometer (UV 1601, Shimadzu, Japan) at 315 nm against a suitable blank.[13-15] In order to assess the susceptibility of Galactosol and xanthan gum, being ac upon by colonic bacteria, drug release studies were also carried out in presence of caecal content because of the similarity with human intestinal flora. *In vitro* d release studies in the presence of rat caecal contents were same as mentioned abo except that rat caecal content (2% w/v) was added only to phosphate buffer (pH 7 to simulate colonic condition.[11-15]

D. Release kinetics:

In vitro release data were fit to zero order, first order and higuchi equations to analyze the kinetics of drug release from the tablets. Further, *in vitro* release results were fit to the following Koresmeyer-Peppas equation, to analyse drug release mechanism.

$Mt/M\alpha = Kt$ Where $Mt/M\alpha$ is the fraction of drug released at time t, K is kinetic constant and *'n'* is release exponent that characterize the drug transport.[13-15]

RESULTS AND DISUSSION

In the present work colon targeted compression coated tablets were prepared by direct compression technique using Tegaserod maleate as a model drug for treatment of diseases like ulcerative colitis, Crohn's disease, and irritable bowel syndrome. The compression coated tablets of Tegaserod maleate were prepared using natural polymers
like Galactosol, xanthan gum and chitosan. Further, it was aimed to identify the most suitable polysaccharide either alone or in combinations for colonic delivery of Tegaserod maleate based on microbial degradation. Hence attempts were made to formulate the compression coated tablets using Galactosol, xanthan gum, chitosan, either alone or in combination. The formulations were evaluated for physical parameters like diameter, thickness, hardness, friability and drug content. Evaluations of other parameters like swelling index, *in vitro* drug release, release kinetics and stability were also conducted.

Evaluation of tablets

Physico-chemical characterization of core tablet and compression coated tablets

a) Thickness: The thickness of core tablets were found to be 1.96±0.05 mm and for compression coated tablets of all the batches of formulation prepared ranges in between 2.54±0.05 mm and 2.71±0.09 mm.

b) Diameter: The diameter of core tablets was found 9.67±0.02 mm and for compression coated tablets of each formulation was ranged between 13.13±0.05 mm and 13.15±0.08 mm.

c) Hardness: The hardness for compression coated tablets of each formulation was found in the range of 5.86±0.05 and 6.13±0.06 kg/cm^2, this ensures good handling characteristics of all batches. The hardness of core tablets of Tegaserod maleate was found to be 3.1±0.15 kg/cm^2.

d) Friability: The values of friability test were depicted in table 21. The percentage friability of all formulations was found in the range of 0.91±0.13 to 0.98±0.05%; indicating that the friability is within the acceptable limits and tablets were mechanically stable. In case of core tablets the percentage friability was more and it was found to be 2.96±0.15%, because core tablets are compressed at lower compressional force.

e) Weight variation: The percentage weight variations for all formulations were depicted in table 3. The results of weight variation of tablets for all compression coated tablet formulations was found in the range of 398.19±0.05 to 399.05±0.05 mg and in case of core tablets it was found to be 98.81±0.12 mg; indicating that the weight variation is within the pharmacopoeial limits.

f) Drug content: The percentage drug content both for core tablets and compression coated tablets of all formulations was found in the range of 98.95±0.15 to 99.62±0.25%, which was well within acceptable limits of official standards.

Table 3: Physico-chemical parameters of prepared tablets

Formulation	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Weight of Tablet (mg)	Friability (%)	Drug content (%)
Core Tablet	1.96±0.05	9.67±0.02	3.1±0.15	98.81±0.12	2.96±0.15	99.51±0.09
F1	2.71±0.09	13.14±0.05	5.86±0.05	398.71±0.05	0.95±0.17	99.15±0.16
F2	2.63±0.03	13.15±0.03	6.12±0.09	399.11±0.09	0.91±0.13	99.23±0.21
F3	2.66±0.06	13.15±0.04	5.95±0.06	398.22±0.10	0.93±0.09	99.61±0.27
F4	2.67±0.05	13.14±0.04	6.02±0.13	398.19±0.05	0.94±0.08	98.95±0.15
F5	2.56±0.03	13.15±0.03	5.85±0.15	398.72±0.07	0.89±0.04	99.62±0.25
F6	2.61±0.08	13.13±0.05	5.94±0.05	398.55±0.08	0.90±0.14	99.12±0.31
F7	2.68±0.05	13.14±0.05	6.05±0.05	398.56±0.04	0.95±0.14	99.19±0.34
F8	2.54±0.05	13.15±0.08	6.12±0.08	398.34±0.15	0.94±0.13	99.25±0.15
F9	2.60±0.02	13.13±0.06	6.11±0.08	398.41±0.17	0.95±0.17	99.45±0.19
F10	2.69±0.06	13.13±0.08	6.08±0.05	398.43±0.05	0.98±0.05	99.58±0.27
F11	2.55±0.05	13.14±0.09	6.03±0.11	398.58±0.05	0.88±0.10	99.32±0.25
F12	2.59±0.09	13.14±0.04	5.79±0.03	398.49±0.11	0.91±0.05	99.35±0.05
F13	2.61±0.01	13.15±0.03	6.10±0.04	399.05±0.05	0.94±0.05	99.41±0.33
F14	2.65±0.05	13.14±0.05	6.11±0.03	398.88±0.05	0.91±0.05	99.27±0.51
F15	2.63±0.03	13.14±0.03	6.13±0.06	398.83±0.18	0.93±0.05	99.52±0.24

All values are expressed as mean ±SD, n=3

g) Disintegration test for core tablets: The disintegration time was measured for core tablet and it was found to disintegrate within 60 sec.

h) Swelling index: Swelling index elaborated the amount of water that is contained within hydrogel at equilibrium and is a function of the network structure, hydrophilicity and ionization of the functional groups. Swelling studies was done for first 2 h in 0.1N HCl (pH 1.2) and later in phosphate buffer (pH 7.4) up to 24 h, simulating transition of tablets in GIT. The swelling behavior was dependent upon the polymer or combination of the polymers used for coating the core tablet. The the plot of swelling index against time (h) is depicted in figure 1.

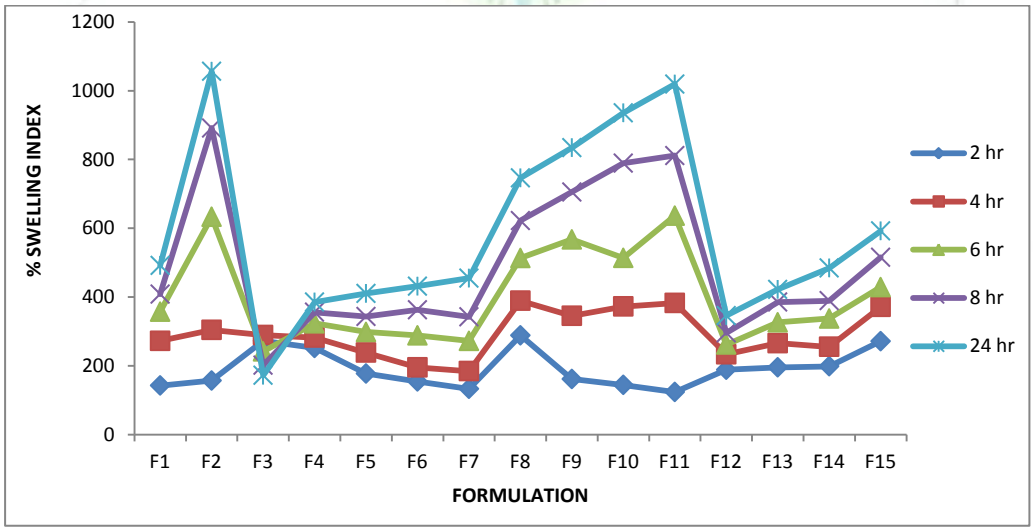

Figure 1: Swelling index of compression coated tablet

***In vitro* release studies:**

Drug release studies were conducted in 0.1N HCl for the initial 2 h, followed by phosphate buffer (pH 7.4) up to 24 h.

Mono polymer based coating formulation:

Among F1, F2 and F3 formulation, F1 and F2 were found to have better *in vitro* release profile required for colon targeting. But formulation F2 showed more sustaining ability in colonic pH after 8 h than formulation F1.

However formulation F3 containing chitosan released almost complete drug in gastric buffer pH 1.2.

Bipolymer based coating formulation:

As the chitosan proportion is increased in the coating formulation the percentage of drug released increased slightly in gastric pH. As the Galactosol proportion is increased in the coating formulation the percentage of drug released was slightly decreased in colonic pH. As the xanthan gum proportion is increased in the coating formulation the percentage of drug released was slightly decreased in

colonic pH. The formulation F9 containing xanthan gum is better controlled in colonic condition compared to F5 containing guar gum.

Tripolymer based coating formulation:

Among the formulation prepared by three polymers, the formulation F14 composed of Galactosol, xanthan gum and chitosan showed better *in vitro* release profile. The *in vitro* drug release in presence of rat caecal content when compared with in the absence of rat caecal content, a significant difference ($P < 0.05$) was observed. Hence in the presence of rat caecal matter, drug was released faster from formulations compared to dissolution medium without rat caecal content. This indicates that the drug release from formulations is mainly due to the presence of enzymes released by micro-organisms of rat caecal contents.

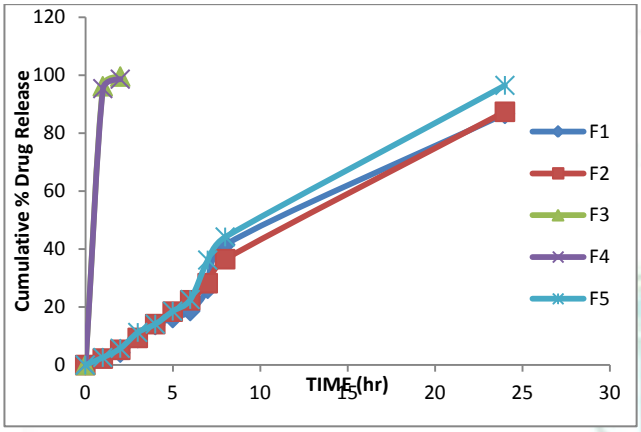

Figure 2: *In vitro* release data of Tegaserod maleate compression coated tablets

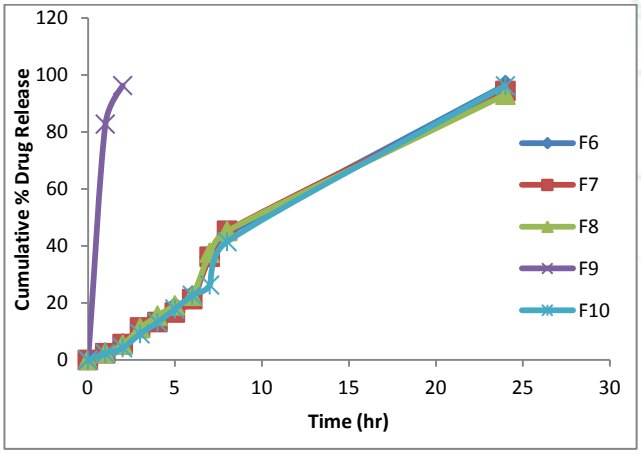

Figure 3: *In vitro* release data of Tegaserod maleate compression coated tablets

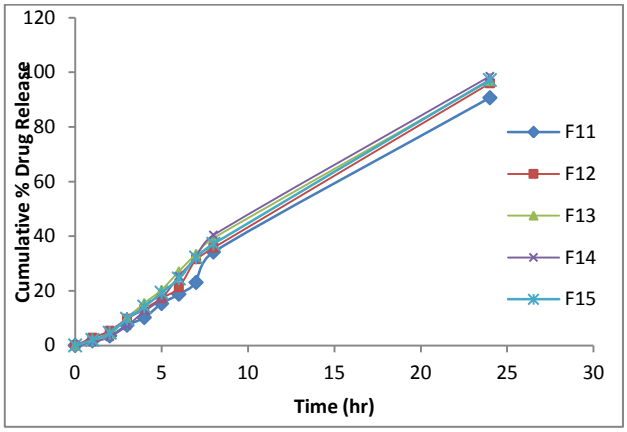

Figure 4: In vitro release data of Tegaserod maleate compression coated tablets

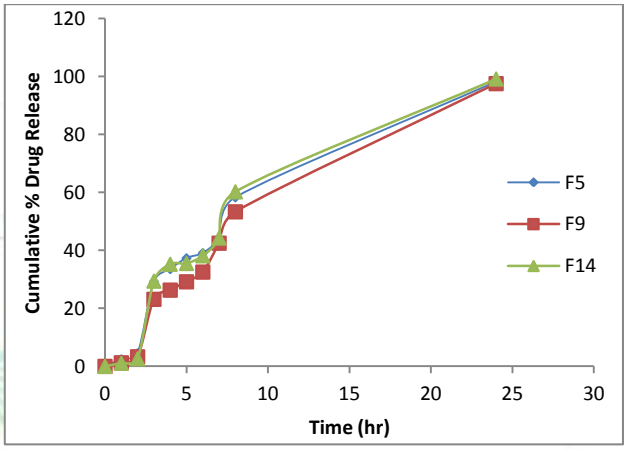

Figure 5: *In vitro* drug release from compression coated tablets of formulation F5, F9 and F14 in 0.1N HCl (2 h) and in pH 6.8 with rat caecal contents

Drug release kinetics studies

All formulations except F3, F4 and F8 showed the linearity with respect to zero order as compared to first order.

Formulation F3, F4 and F8 did not showed linearity with respect to first order equation. In presence of 2% w/v rat caecal content as a dissolution medium, the formulation F5, F9 and F14 showed linearity with respect to first order equation. Higuchi equation regression values for all formulations with and without rat caecal contents ranges shows in the table 4. To confirm precisely the domination mechanism; the data was plotted according to Koresmeyer-Peppas equation.

Table 4: Release kinetic data of prepared compression coated tablet of Tegaserod maleate

Formulations	Zero- order (R^2)	First- order (R^2)	First- order (R^2)	Koresmeyer peppas model (n)
F1	0.9773	0.9648	0.8799	1.290
F2	0.9889	0.9696	0.8990	1.236
F3	0.6525	0.9655	0.8906	0.492
F4	0.6448	0.9467	0.8854	0.481
F5	0.9742	0.9434	0.8928	1.193
F6	0.9654	0.9536	0.8838	1.227
F7	0.9632	0.9646	0.8986	1.269
F8	0.6746	0.9533	0.9004	0.483
F9	0.9874	0.9336	0.8749	1.202
F10	0.9829	0.9510	0.8699	1.213
F11	0.9913	0.9452	0.8563	1.310
F12	0.9925	0.9390	0.8794	1.149
F13	0.9853	0.9471	0.9014	1.319
F14	0.9829	0.9223	0.8793	1.407
F15	0.9903	0.9399	0.8910	1.272

Table 5: Release kinetic data of formulation F5, F9 and F14 Tegaserod maleate compression coated tablets in presence of rat caecal content

Formulations	Zero- order (R^2)	First- order (R^2)	First- order (R^2)	Koresmeyer peppas model (n)
F5	0.8724	0.9703	0.9535	1.412
F9	0.9214	0.9594	0.9290	1.450
F14	0.8702	0.9602	0.9243	1.578

CONLUSION

This work aimed to prepare compression coated tablets by direct compression method using single polymer and combination of polymers. Core tablet of Tegaserod maleate was prepared using sodium starch glycolate and microcrystalline cellulose Core tablets of Tegaserod maleate were compression coated using natural polysaccharides like guar gum, xanthan gum and chitosan for colon targeting. The prepared tablets were evaluated for parameters like hardness, friability, thickness, diameter, weight variation, drug content, swelling index, *in vitro* drug release. The results showed that in the presence of rat caecal matter, drug was released faster from formulations compared to dissolution medium without rat caecal content. This indicates that the drug release from formulations is mainly due to the presence of enzymes released by micro-organisms of rat caecal contents.

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