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R E S E A E C H A R T I C L E

Formulation and Evaluation of Colon Targeted Delivery System of tegaserod Maleate based on Osmotic Technology

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A B S T R A C T

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms The stomach is an organ with a capacity for storage and mixing. Under fasting conditions the stomach is a collapsed bag with a residual volume of 50 mL and contains a small amount of gastric fluid (pH 1-3) and air. The stomach has four main areas: cardia, fundus, body, and pylorus. Within 2-4 hrs after eating a meal the stomach has emptied its contents into the duodenum. The present work was aimed at formulating enteric coated tablet of Tegaserod maleate. Direct compression technique and coating solution was used in the manufacturing of controlled release tablet. A microbially activated osmotic pump (MAODS) for colonic delivery of tegaserod was developed. for treatment of crohns disease the main interest in such dosage form was to target the drug to the colon by ensuring minimal amount of drug release in the physiological environment of the upper GIT. and soon after to release most of the tegaserod to the colon between 6th to 14thhr. Hence final selection was conducted from formulation F4, F6, F7 showing 83.85, 91.30, 94.56 but drug release from formulationF1, F2, F3, F6 very slow. There for F7 was selected as an optimized formulation with maximum drug release in colon. The effect of various formulation variables was studied to optimize the release profile.

Keywords: Colon target, Tegaserod maleate, Crohn's Disease

A R T I C L E I N F O

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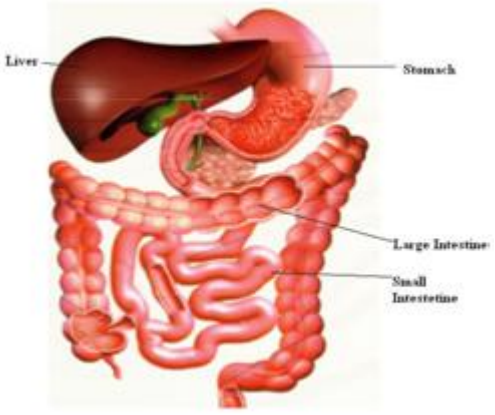
C O N T E N T S

1. Introduction

Oral drug delivery is the most preferred drug administration route due to convenience, cost-effectiveness, and high patient compliance. The challenges in oral drug delivery include aqueous solubility, membrane permeability, and chemical and enzymatic stability of drugs Oral delivery drugs are the simplest and most straightforward, but they can cause several adverse effects. Medicines administered orally must circulate throughout the entire body before taking effect. This poses a potential threat to the patient, as the drug could take action in any part of the body causing adverse effects, as well as creating an opportunity for the drug to be broken down through enzymatic degradation.

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (Immediate, Sustained or Controlled release) and the design of dosage forms (either solid, dispersion, or liquid), must be developed within the intrinsic characteristics of GI physiology. The most sophisticated delivery system, the greater is the complexity of these various disciplines involved in the design and optimization of the system. In any case, the scientific framework required for the successful development of an oral drug delivery system consists of a basic understanding of the following three aspects: The stomach is an organ with a capacity for storage and mixing. Under fasting conditions the stomach is a collapsed bag with a residual volume of 50 mL and contains a small amount of gastric fluid (pH 1-3) and air. The stomach has four main areas: cardia, fundus, body, and pylorus. Within 2-4 hrs after eating a meal the stomach has emptied its contents into the duodenum.



Intestine3

The small intestine is a tubular viscous organ and has enormous number of villi on its mucosal surface that create a huge surface area (4500 m2 compared to only 0.1-0.2 m2 for the stomach). The surface of the mucous membrane of the small intestine possesses about 5 million villi, each about 0.5 to 1 mm long. These villi are minute fingerlike projections of the mucosa and have a length of 0.5-1.5 mm, depending upon the degree of distension the intestinal wall and the state of contraction of smooth muscle fibres in their own interiors. Absorption of material occurs by facilitate diffusion, osmosis, and active transport. The small intestine is the largest section of the digestive tube and it is arbitrarily divided in to three parts. Duodenum (20-30 cm), Jejunum (2-5 m) and the ileum (3-5 m). The duodenum has a pH of 5 to 6 and the lower ileum approaches a pH of 8.

Controlled Release Drug Delivery Systems[4, 5]

The goal of any delivery system is to provide a therapeutic amount of drug to the proper site in the body to promptly achieve and then maintain the desired drug concentration. There are mainly two most important aspects for the delivery of a drug namely, spatial placement and temporal delivery. Spatial placement relates to targeting of a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to target tissue. An appropriately designed sustained-release drug delivery system or controlled drug delivery system can be a major advance towards solving these two problems. Sustained release and controlled release drug delivery systems are primarily used to ensure the patients compliance like frequent dosing and improved efficacy of the drug. The sustained release and controlled release drug delivery systems are gaining popularity due to these reasons nowadays. Over the years, there has been available a variety of drug modification and dosage form with which formulation scientist have attempted to control the time course and specificity of drug in the body. To maximize drug utilization, it is necessary to deliver drug to its target tissue in the correct amount at the proper time to elicit the desired response.

The majority of the controlled release dosage forms are designed for oral administration; however, recently such systems have also been introduced for parenteral administration, ocular insertion and for transdermal application. Targeted drug delivery, sometimes called smart drug delivery[1] is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. This means of delivery is largely founded on nanomedicine, which plans to employ nanoparticle-mediated drug delivery in order to combat the downfalls of conventional drug delivery. These nanoparticles would be loaded with drugs and targeted to specific parts of the body where there is solely diseased tissue, thereby avoiding interaction with healthy tissue. The goal of a targeted drug delivery system is to prolong, localize, target and have a protected drug interaction with the diseased tissue.

The conventional drug delivery system is the absorption of the drug across a biological membrane, whereas the targeted release system releases the drug in a dosage form. The advantages to the targeted release system is the reduction in the frequency of the dosages taken by the patient, having a more uniform effect of the drug, reduction of drug side-effects, and reduced fluctuation in circulating drug levels. The disadvantage of the system is high cost,

which makes productivity more difficult and the reduced ability to adjust the dosages.Targeted drug delivery systems have been developed to optimize regenerative techniques. The system is based on a method that delivers a certain amount of a therapeutic agent for a prolonged period of time to a targeted diseased area within the body. This helps maintain the required plasma and tissue drug levels in the body, thereby preventing any damage to the healthy tissue via the drug. The drug delivery system is highly integrated and requires various disciplines, such as chemists, biologists, and engineers, to join forces to optimize this system. Contraction of smooth muscle fibres in their own interiors. Absorption of material occurs by facilitate diffusion, osmosis, and active transport. The small intestine is the largest section of the digestive tube and it is arbitrarily divided in to three parts. Duodenum (20-30 cm), Jejunum (2-5 m) and the ileum (3-5 m). The duodenum has a pH of 5 to 6 and the lower ileum approaches a pH of 8.

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Colon Targeted Drug Delivery Systems:[7, 8, 9]

- Over the past two decades the major challenge for scientist is to target the drugs specifically to the colonic region of g.i.t. previously colon was considered as a innocuous organ solely responsible for absorption of water, electrolytes & temporary storage of stools. colon is used to treat –
- Seriousness from constipation & diarrhoea to the debilitating inflammatory bowl diseases (ulcerative colitis & Crohn's disease) through to colon carcinoma which is two third cause of cancer in both man & women.
- Colon can be utilized as portal for the entry of drugs into the blood stream for the systemic therapy.
- Colon having the lower level of luminal & mucosal digestive enzymes as compared with the small intestine reduces the chances of drug degradation. Colon delivery also a mean of achieving chronotherapy of disease those are sensitive to circadian rhythm such as asthma & arthritis.

Drug Targeting Importance[6]

Drug Targeting can be defined as the ability to direct a therapeutic agent specifically to the desired site of action with little or no interaction with non-target tissues. The rationale for drug targeting includes:

- The ability to reach specific cells or diseased site in the body with concomitant reduction in the dose and side effects.
- To reach previously inaccessible sites or areas.
- To protect the drug and the body from one another until the desired site of action is reached.
- To control the rate and frequency of drug dosing to pharmaceutical receptor.

The present work was aimed at formulating enteric coated tablet of Tegaserod maleate. Direct compression technique and coating solution was used in the manufacturing of controlled release tablet. A microbially activated osmotic pump (MAODS) for colonic delivery of tegaserod was developed for treatment of crohns disease the main interest in such dosage form was to target the drug to the colon by ensuring minimal amount of drug release in the physiological environment of the upper GIT.

Mechanism: Zelnorm® (tegaserod maleate) tablets contain tegaserod as the hydrogen maleate salt. Tegaserod, a selective and partial agonist at the 5-hydroxytryptamine (5-HT [serotonin]) receptor subtype 4 (5-HT4), is the only United States Food and Drug Administration-approved drug for the treatment of constipation-predominant irritable bowel syndrome (IBS) in women. Zelnorm® (tegaserod maleate) is indicated for the short-term treatment of women with irritable bowel syndrome (IBS) whose primary bowel symptom is constipation. The safety and effectiveness of Zelnorm in men with IBS with constipation have not been established. The drug's pharmacokinetic, pharmacodynamic parameters do not differ significantly with age or sex. Tegaserod safely and effectively relieves overall gastrointestinal symptoms and abdominal discomfort and normalizes bowel habits in patients with constipation-predominant IBS.

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Drug profile

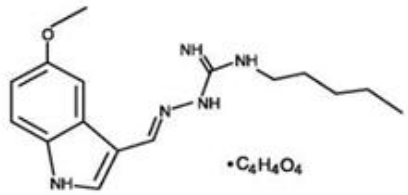


Figure 1: Structural formula of Tegaserod maleate

Table 1: Pharmacokinetic property of Tegaserod maleate

Name	3-(5-methoxy-1H-indol-3-ylmethylene)-N-pentylcarbazimidamide hydrogen maleate.
Formula	C16H23N5O•C4H4O4
Molecular weight	417.47
Solubility	Slightly soluble in ethanol and very slightly soluble in water.
Stability	stable in water
Bio availability	bioavailability of an oral dose is 10%
Protein binding	approximately 98% bound to plasma proteins
Release	In intestine
Absorption	In colon
Cmax	20%-40%
t ½	11 ±5 hour

2. Materials and Methods

Preformulation Study

Preformulation stability studies are usually the first quantitative assessment of chemical stability of a drug as well as stability in presence of other excipients for a formulation. Preformulation testing is the first step in the rational development of dosage form of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be man produced. Pre-formulation is a branch of pharmaceutical sciences that utilizes biopharmaceutical principles in the determination of physicochemical properties of a drug substance.

The goal of pre-formulation studies is to choose the correct form of the drug pre-requisite for formulation. Therefore, in pre-formulation substance, evaluate its physical properties and generate a thorough understanding of the materials stability under various conditions, leading to the optimal drug delivery system. The preformulation study focuses on the physicochemical parameters that could effect the development of efficacious dosage form. A thorough understanding of these properties may ultimately provide a rationale for formulation design. Also it will help in minimizing problems in later stages of drug development, reducing drug development costs and decreasing product's time to market. The compatibility of the drug and formulation is an important study; compatibility evaluation was carried out using infra-red spectra. Infrared spectrum of formulated granules and drug alone were recorded and observed between 400 nm and 4000 nm. Infra -red spectrum of pure drug was also run individually.

Objective:

The overall objective of pre-formulation testing is to generate information useful to the formulation in developing stable and bio-available dosage forms.

Scope: The use of pre-formulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product.

Stability Analysis

- Stability (heat / light / acid / base / oxidizer)
- Solution stability
- Solid-state stability – Bulk stability
- Excipient compatibility (depending on dosage route).

Considerations of CR/ER/SR Formulations:

There are several factors which influence the releases of drug from a sustained release tablets mass.

- Particle size
- Dose
- Solubility
- Partition coefficient
- Polymer concentration
- Dissociation constant

The particle size is critical as the small particle size produces faster release. Moreover, particles that are too small can give rise to flow property problems. The dose of the drug often limits the technique that can be employed. High dose drugs mostly require the wet granulation method because of the relatively small quantities of excipients needed for powder flow. Highly soluble drugs require larger quantities of retarding polymer.

Experimental Work

Physical Description:

Tegaserod Maleate: White to off white crystalline powder

Solubility:

Freely soluble in water, methanol, and ethanol. Sparingly soluble in isopropanol. Slightly soluble in chloroform, methylene chloride. Practically insoluble in hydrocarbons.

Identification Test (Tegaserod Maleate)

Identification by FTIR & UV Spectroscopy.

Drug-Excipient Compatibility Study

Characterization of drug, polymer and their physical mixture –IR has been the method of choice to prove the nature and extent of interaction in polymer blends. The premise of using an IR to study polymer blend is that the mixing of the two compounds at molecular level will cause changes in oscillating dipole of the molecule. This will manifest itself as changes in frequency and band width of interaction group, in the spectrum. If the drug and polymer interact than functional groups in FTIR spectra will show band shift and broadening compared to the spectra of pure drug.

Determination of λ_{max}The absorption maxima of Tegaserod Maleate were determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer.

Procedure:

Accurately weighed 100 mg of drug was dissolved in 100 ml of water in 100 ml volumetric flask and prepare suitable dilution to make it to a concentration range of 10-100 µg/ml. The spectrum of this solution was run in 200-400 nm range in U.V spectrophotometer (SCHIMADHZU). The Tegaserod Maleate shows the absorbance maxima at 315 nm in distilled water.

Preparation of standard curve of Tegaserod Maleate

Standard solution of Tegaserod maleate (1 mg/ml) was prepared in methanol and further dilutions were made with the same solvent to get the working standard solution of 100 mg/ml. Suitable aliquots of standard solution (0.1 to 3.0 ml) were transferred into a series of 100 ml separating funnels and to each were added 5.0 ml of acid phthalate buffer (pH 2.5) and 1 ml of bromo cresol green (0.01% w/v) and mixed. The yellow colored complex was extracted with two portions (5,3 ml) of chloroform. The extract was dried over anhydrous sodium sulphate and collected in 10 ml volumetric flasks; volume was made up to mark with chloroform and the absorbance was measured at 310 nm against a reagent blank.

The calibration curve was prepared by plotting absorbance v/s concentration of Tegaserod maleate in mg/ml. The concentration of the unknown was read from the calibration graph or decided from the regression equation derived using the Beer's law data. The robustness of the method was studied by varying different experimental condition and the results were found to be depended upon change in pH. The stability of the colored solution was assessed by measuring the absorbance of same solution after every 10 min and the solution found to be stable for 15 min.

Melting Point:

It is one of the parameters to judge the purity of crude drugs. In case of pure chemicals or phytochemicals, melting points are Sharpe and constant. Since the crude drugs contain the mixed chemicals, they are described with certain range of melting point.

Procedure

A small quantity of powder was placed into a fusion tube. That tube is placed in the melting point determining apparatus containing castor oil. The temperature of castor oil was gradually increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted.

8.6 Evaluation of Powder:

Angle of repose:

The angle of internal friction is a measure of internal stress distribution and is the angle at which an applied stress diverges as it passes through the bed. It is the least slope at which a powder will slide down an inclined plane surface. The typical method is to pour the powder in a conical heap on a level, flat surface and measure the included angle with the horizontal. It is denoted by Ɵ.

$$\tan\Theta = h/r$$

Where,

Ɵ = Angle of repose,

h = Height of pile in cm,

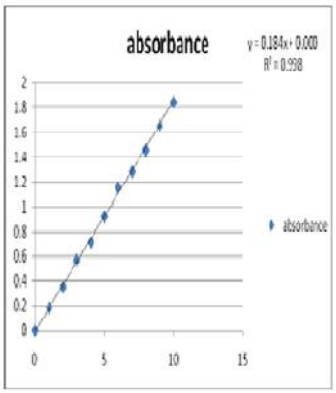
r = radius in cm.

3. Results and Discussion

Pre-formulation studies

The present work was aimed at formulating enteric coated tablet of Tegaserod maleate. Direct compression technique and coating solution was used in the manufacturing of controlled release tablet.

S.No	Concentration (µg/ml)	Absorbance (µg/ml)
1	0	0
2	1	0.185
3	2	0.354
4	3	0.573
5	4	0.711
6	5	0.923
7	6	1.157
8	7	1.285
9	8	1.457
10	9	1.656
11	10	1.845
S.No	Concentration (µg/ml)	Absorbance (µg/ml)



4. Conclusion

A microbially activated osmotic pump (MAODS) for colonic delivery of tegaserod was developed for treatment of crohns disease the main interest in such dosage form was to target the drug to the colon by ensuring minimal amount of drug release in the physiological environment of the upper GIT. and soon after to release most of the tegaserod to the colon between 6th to 14thhr. Hence final selection was conducted from formulation F4, F6, F7 showing 83.85, 91.30, 94.56 but drug release from formulationF1, F2, F3, F6 very slow. There for F7 was selected as an optimized formulation with maximum drug release in colon. The effect of various formulation variables was studied to optimize the release profile. The result showed drug release. is directly proportional to the osmotic agent and wicking agent. increase in level of Osmotic agent and wicking agent(SLS) increase in drug release level of osmotic agent and wicking agent, has direct effect on rate and extent of drug release. Drug release is directly related to the level of pore former, It is clear that level of pore former has direct effect on the drug release. As the level of guar gum increases the membrane becomes more porous due to degradation of larger amount of guar gum by microflora of SCF resulting in higher drug release. The release from the developed formulations was independent of pH, and agitation intensity. The thickness of enteric coating could prevent formation of delivery pores before contact with SCF, but had no effect on the drug release. Results of SEM studies showed the formation of pores in the membrane after coming in contact with simulated colonic fluid with the number of pores dependent on initial level of pore former in the membrane. The manufacturing procedure was standardized and found to be reproducible. The developed formulations were found to be stable during 3 months of storage at accelerated stability conditions. The optimized formulation was performed which showed slight change in the physicochemical parameters and in vitro drug release study

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Table 8: Characterization of Drug tegaserod maleate

S No	Physical characteristics	Result
1	Description	White to off white crystalline powder.
2	Particle size	5um
3	Melting point	Between 152 ºC to 155ºC
4	Bulk density	0.213gm/cm3
5	Tapped density	0.273gm/cm3
6	Angle of repose	25.144
7	**Carr's index (Compreessibslity index)**	21.97%
8	Houser ratio	1.28
9	pKa(partition coefficient)	lower then pH-7.5
10	Solubility	Dissolves in 1.0 N, hydrochloride and practically insoluble in water.

Table 10: Evaluation of powder Blend of F1-F7 formulations

formulation	Bulk density g/cm3	Tap density g/cm3	compressibility	Angle of repose(Θ)
F1	0.486	0.614	21.49	340.15'
F2	0.483	0.606	20.44	300.96'
F3	0.488	0.614	20.52	350.13'
F4	0.468	0.578	19.03	300.37'
F5	0.466	0.574	19.02	280.73'
F6	0.453	0.547	17.19	290.93'
F7	0.475	0.594	20.03	320.82'

The compressibility index percentages of formulations were found to be in the range of 17.19 to 21.49, which is within the acceptable limit.

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