Design, Development and In Vitro-In Vivo Study of Colon Specific Fast Disintegrating Tablet Based on Time Dependent Approach

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SUMMARY. Targeted delivery systems for treatment of Inflammatory bowel disease (IBD) are designed to increase local tissue concentrations of anti-inflammatory drugs from lower doses compared with systemic administration. The objective of this study was to formulate and evaluate an oral system designed to achieve site specific and instant drug release in colon for effective treatment of IBD based on time dependent approach. The system consists of core tablet containing model drug diclofenac sodium, superdisintegrant sodium starch glycolate, and coated with pH independent polymer Eudragit RSPO to achieve different total percentage weight gain. Drug release studies were carried out using changing pH method. Placebo formulation containing barium sulphate in the tablet was administered to human volunteers for in vivo X-ray studies. In vitro studies revealed that tablet with 5% coating level release the drug after 5 h lag time corresponding to the colonic region. Tablets with 5% coating level could maintain their integrity in human volunteers for 5 h, approximating colon arrival time and release the drug instantaneously. Colon targeting and instant drug release for 5% coating level was due to swellable hydrophilic polymer, which is responsible for a lag phase preceding the onset of release and the immediate release effect of superdisintegrant. It was observed that as coating level increases, lag time also increases. This is because of increased diffusion path length and tortuosity at higher coating levels. In vivo - in vitro study reveals thickness of coating of Eudragit RSPO play an important role in colon delivery and tablet with superdisintegrant and 5% coating level achieved the desired performance of the colon targeting.

INTRODUCTION

Oral Colon Specific Drug Delivery Systems (CSDDS) have emerged as important site specific drug delivery systems. Colon drug delivery has gained increased importance not just for the delivery of drugs for the treatment of local diseases of the colon but also for its potential for the delivery of proteins and peptides.1,2 In a number of colonic diseases such as colorectal cancer, Crohn’s disease, and spastic colon it has been shown that local delivery of drug is more effective than the systemic delivery.3 For a formulation to act as an effective drug delivery system in colon, the primary condition is that a minimum amount of drug should release in the environment of the upper gastrointestinal tract, i.e. in stomach and small intestine. The targeting of orally administered drugs to the colon is accomplished in several ways, prodrugs, pH controlled drug release, time controlled drug release, enzyme controlled drug release, and pressure controlled drug release.4,5 Time dependent delivery system release their drug load after a preprogrammed time delay. The system consists in a drug-loaded core coated with a swellable hydrophilic polymer, which is responsible for a lag phase preceding the onset of release. To attain colonic release the lag time should equate to the time taken for the system to reach the colon. The lag time of 5 h is usually considered sufficient, given that small intestine transit time

KEY WORDS: Colon targeting, Diclofenac sodium, Eudragit RSPO, Inflammatory bowel disease, Superdisintegrant.

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is reported to be relatively constant at 3-4 h. The normal transit time in the stomach is 2 h (though it may vary), while in the small intestine it is relatively constant and is around 3 h. The usual transit time varies from 20-30 h. Time dependent drug delivery system release their drug load after a preprogrammed time delay. The first formulation introduced based on this approach was Pulsicap. Sinha & Kumaria demonstrated use of shellac, Eudragit L100 and ethylcellulose at various thicknesses for colon specific drug delivery of indomethacin tablet and out of this shellac showed promising result. Time dependent approach was also been used for chronopharmacotherapy using nifedipine and coating with polyethylene oxide- polyethylene glycol mixtures which release the drug in colon. Hydroxy propyl ethyl cellulose, Hydroxy propyl methyl cellulose acetate succinate were also been used for the time dependent colon specific drug delivery. The basic fact such systems are unable to sense and adapt to an individual’s transit time and merely release their drug load after a preset lag time, irrespective of whether the formulation is in the colon or not clearly limits their utility. Accelerated transit through different regions of the colon has been observed in patients with irritable bowel syndrome, carcinoid syndrome. Time and pH sensitive approach has been combined together to improve the specificity of colonic drug delivery.

The purpose of this research was to establish a new time triggered colonic drug delivery system based on Eudragit RSPO coating and use of a superdisintegrant in tablet core which will release drug specifically and instantly in the colon. Diclofenac sodium was selected as a model drug which is very well absorbed throughout the GI tract has good anti-inflammatory effect in irritable bowel syndrome and also has cancer protective activity in the colon. The influence of formulation variables such as coating thickness on drug release was studied and the passage of optimized formulation through GIT was investigated by in vivo X ray roentgenography using human volunteers. In vivo studies showed that tablet with 5 % w/w coating level has lag time of 4.30 h which corresponds to ileocecal region and it release the drug instantly after lag time, so drug is available in disperse or dissolved form. In vivo studies shows similar result as that of in vitro with lag time of 4-5 h before disintegration of tablet.

### MATERIALS AND METHODS

**Chemicals**

Diclofenac sodium was obtained as a gift sample from Arti Pharmaceuticals Ltd., Mumbai and Eudragit RSPO from Degussa India Pvt. Ltd. Mumbai. Hydroxy Propyl Methyl Cellulose (HPMC) 15 cps was provided by Colorcon India Pvt. Ltd. Other excipients used to prepare tablets and for coating were of standard grade.

**Preparation and evaluation of diclofenac sodium core tablet**

Tablet formulations of diclofenac sodium were prepared by wet granulation technique using Sodium starch glycolate as a superdisintegrant. Tablets were compressed on 8 mm standard concave punch on single rotary tablet compression machine (Rimek, Mumbai). Tablets were tested for various official and unofficial evaluation test, similarly tablet without superdisintegrant was prepared and evaluated (Table 1).

**Coating of tablets with HPMC**

Tablets were coated with HPMC 15cps with different coating level of 10 %, 15 % and 20 % coating level. The spray rate and the bed temperature during the coating process were 2 gm/min (till the end of process) and 30-35 °C respectively. Tablet bed was preheated to 40 °C prior to coating.

**Preparation of Eudragit Coating Solution and coating of tablets with Eudragit RSPO**

As indicated in Table 2, required quantity of RSPO was dissolved in sufficient quantity of organic solvent IPA and acetone mixture (1:1) proportion. Then dispersion of talcum, magnesium stearate, glycerin and PEG 400 in IPA and acetone mixture was prepared and added to the

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### Table 1. Composition of core tablet of Diclofenac sodium for coating with Eudragit RSPO.

<table>
<thead>
<tr>
<th>Ingredient (mg/tablet)</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tablet with SD</td>
</tr>
<tr>
<td>Diclofenac Sodium I.P.</td>
<td>50</td>
</tr>
<tr>
<td>Sodium Starch Glycolate</td>
<td>10</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>10</td>
</tr>
<tr>
<td>Talc</td>
<td>5</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>4</td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>131</td>
</tr>
<tr>
<td>Dried starch</td>
<td>--</td>
</tr>
</tbody>
</table>

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**In vivo** studies showed that tablet with 5 % w/w coating level has lag time of 4.30 h which corresponds to ileocecal region and it release the drug instantly after lag time, so drug is available in disperse or dissolved form. In vivo studies shows similar result as that of in vitro with lag time of 4-5 h before disintegration of tablet.
polymeric solution. Diethyl phthalate plasticizer was added to the resultant polymeric dispersion under stirring and passed through 80 no mesh. The tablets were coated in Insta coat R&D coater (Mumbai) with coating parameter as mentioned in Table 3. Coating was continued till desired level of 3 to 7 % w/w weight gain was achieved.

**Drug release studies**

The continuous dissolution method (USP XXIII dissolution apparatus II, Electrolab) was used for simulating pH conditions of the GI tract. Initially tablets were added in 700 ml of 0.1 N HCl (pH 1.2) for 2 h. At the end of 2 h, 200 ml of 0.2 M tribasic sodium phosphate solution was added to all the dissolution vessels and the pH was adjusted to 6.5, 6.8 and 7.2 by using 2M NaOH or 2M HCl for 1, 2 and till the end, respectively.

**In vitro release study**

Simulation of pH environment in GI tract was divided in four parts; stomach with pH 1-2 (residence time 2 h) proximal part of small intestine with pH 6.5 (residence time 1 h), lower part of small intestine with pH 6.8 (residence time 2 h) and finally terminal ileum with pH 7.2 till end of test. Tablet coated with HPMC shown complete drug release in less than 2 h at coating level from 10-20 %, hence it is found to be not suitable for colon targeting. At pH 1.2 (simulated stomach) and pH 6.5 (proximal part of small intestine) formulation does not released drug. After 3 h (pH 6.5) tablets was intact, after 4 h (pH 6.8) it released less than 5 % drug and complete drug release occurred after 5 h lag time within 60 min this is due to core coated with Eudragit RSPO, a swellable hydrophilic polymer, which is responsible for a lag phase preceding the onset of release. When in contact with the aqueous fluids, the hydrophilic polymer undergoes a glassy-rubbery transition and, in the rubbery state, it becomes more permeable, dissolves and/or erodes and hence release start after 5 h and superdisintegrant play an important role in controlling the release of drug.

**In vivo studies**

X-ray imaging was used to monitor the tablet behavior throughout the gastrointestinal system. The in vivo studies were approved by the Medical Ethics Committee, central for clinical ethics, Nagpur vide project No. 55721052009 and performed on six healthy male volunteers, with a mean age of 29 years (range 22-40) and 50-80 kg body weight, they were non-alcoholics, non-smokers and had not taken any medications. Informed consent was obtained from all volunteers and an expert radiologist and physician supervised the studies. Placebo tablets containing superdisintegrant with coating level of 5 % w/w of Eudragit RSPO was administered to two volunteers, also core tablet without superdisintegrant was coated with 5 % w/w of Eudragit RSPO was administered to two volunteers, the tablets were visualized using digital X-ray imaging (Wipro GE 300 MA) to observe their disintegration in the GI tract. In the present study, the position of the tablets in the GI tract was monitored at different time interval.

**RESULT AND DISCUSSION**

**Evaluation of diclofenac sodium core tablets**

Tablet formulations prepared were evaluated for physical properties. Tablets from all the formulations exhibited similar breaking force. Optimized Formulation containing 5 % of superdisintegrant, showed disintegration time less than 1 min (0.50 ± 0.03) was considered useful for further studies. Mean drug content of formulation was found to be in the range of 99-102 %, thus tablets passes for content uniformity test.

**Table 2. Composition of coating solution of Eudragit RSPO.**

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Items</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Eudragit RLPO</td>
<td>5 g</td>
</tr>
<tr>
<td>2</td>
<td>Talc</td>
<td>5 g</td>
</tr>
<tr>
<td>3</td>
<td>Glycerin I.P</td>
<td>2 ml</td>
</tr>
<tr>
<td>4</td>
<td>Diethyl Phthalate</td>
<td>0.10 ml</td>
</tr>
<tr>
<td>5</td>
<td>PEG 4000</td>
<td>0.15 ml</td>
</tr>
<tr>
<td>6</td>
<td>Magnesium Stearate</td>
<td>2.0 g</td>
</tr>
<tr>
<td>7</td>
<td>IPA / Acetone A.R (q.s)</td>
<td>100 ml</td>
</tr>
</tbody>
</table>

**Table 3. Coating parameters for tablet coating with Eudragit RSPO.**

<table>
<thead>
<tr>
<th>Coating parameter</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spray rate</td>
<td>0.8 ml/min</td>
</tr>
<tr>
<td>Atomizing air pressure</td>
<td>2 lbs/inch2</td>
</tr>
<tr>
<td>Tablet bed temperature</td>
<td>30-70 °C</td>
</tr>
<tr>
<td>Pan speed</td>
<td>25 rpm</td>
</tr>
<tr>
<td>Preheating of pan</td>
<td>15 min (10 rpm-80 °C)</td>
</tr>
</tbody>
</table>
role in fast release due to it swelling as soon as penetration of water through the pores generated by erosion of polymer, it may provide higher concentration at the site of inflammation to produce local as well as systemic effect at the initial segment of colon. It was also observed that lag time increased with increase in coating level as well as time required to release drug also get increased, i.e. for 5 % coating weight gain lag time is 4.5 h, whereas for 7 % coating level it increased up to 5.5 h and time required to release 90 of drug is 6.5 h as compare to 5 % coating level which is 5.5 h, this is attributed to increase diffusion path length with increased thickness and subsequent erosion of polymer followed by drug release (Fig. 1).

Tablet without superdisintegrant coated with Eudragit RSPO shown 20 % drug after 5 hr for 5 % and 7 % coating level but less than 30 % drug release after 6 h (Fig. 2), which indicates that it may bypass the colonic region without releasing the significant amount of drug for local and systemic effect and they were found to be intact, this shows efficiency of superdisintegrant to allow drug release after 5h lag time corresponding to colonic arrival which may effective for better treatment of colonic disease since drug may get release at the beginning of the ascending colon and spread the drug dose to a larger surface area.

**In vivo X-ray results**

The placebo tablets containing barium sulphate, coated with 5 % w/w coating level of Eudragit RSPO were administered to six subjects each, Abdominal radiographs of these volunteers taken at different time intervals are shown in Figure 3 and values are summarized in Table 4. From the abdominal radiographs, it was observed that tablet with superdisintegrant coated with Eudragit RSPO 5 % coating level disintegrate in ascending colon after 5h, whereas tablet without supedisintegrant, coated with same coating level does not disintegrate in colon in both subjects (Fig. 3). Results of in vivo studies are in agreement with the results of in vitro dissolution study that is optimized formulation having superdisintegrant and 5 % w/w coating level showed similar lag time until tablet reaches to colonic region and instant drug release both in vitro and in vivo. This shows the effectiveness of polymer Eudragit RSPO to solubilize after 5 h corresponding to the colonic region and inclusion of superdisintegrant helps to achieve release in initial segment of colon since tablet without superdisintegrant does not disintegrate in colon up to ascending colon.

**CONCLUSION**

The delivery of drugs directly to the colon via the oral route has several useful therapeutic advantages. The results from this study clearly show the potential of Eudragit RSPO films for colonic drug delivery. These coatings are capable of retarding the release of tablet core materials until they reach the colon, due to swelling of polymer which create a diffusion layer which erode slowly and after 5 h lag time drug get released and superdisintegrant play an important role in drug release to allow disintegration after suitable lag time.
Table 3. X-ray studies of tablet coated with Eudragit RSPO 5% coating level after different time interval. Subject 1 and 2 received tablet with superdisintegrant and Subject 3 and 4 received tablet without superdisintegrant.
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REFERENCES