Research Article

Formulation of Oral Selective Polysaccharide Based, Synthesized Prodrug (Ibuprofen-B-Cyclodextrin) For Targeting Colon

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A B S T R A C T
A colonic drug delivery system is expected to protect the drug during the transit time in the GIT and to allow its release only in the colon. Colonic drug delivery is also useful for systemic absorption of drugs, especially peptides and proteins, because of less hostile environment prevailing in the colon compared to stomach and small intestine. The purpose of the present study is to investigate the colon specificity of polysaccharides in synthesis of prodrug and to formulate. The polysaccharides as polymer are mainly used to carry the drug moiety to the colon both in prodrug concept and formulation. Prodrug, Ibuprofen - β-cyclodextrin have been synthesized and investigated and was found to be colon specific, though, the yield was found to be very poor. From the in-vivo study it was also found to be very effective. As far as the formulations with polysaccharides are concerned, a novel polymer khaya gum was investigated for its colon specificity and compared with a well-established polysaccharide polymer guar gum. It was found that the polysaccharides are very effective for targeting the drug to colon provided they are further coated with enteric polymer. Further, the present investigation also revealed that the effect of solubility of the drugs on the colon specificity of the polysaccharides. The investigation revealed that the prodrugs of drug molecules with polysaccharides are better colon specific compared to the formulations prepared with the polysaccharides. This is because the hydrophilicity nature of the polysaccharides releases the drug in the stomach to some extent especially weakly basic drugs. However, they are very effective when coated further with enteric polymer. Prodrugs with polysaccharides, though soluble in the aqueous solutions, there is a need of enzyme system to break the covalent bond formed between the drug molecule and the polysaccharide. Hence, irrespective of the nature of the drug, prodrug approach is better to target the drugs to colon compared to the formulations with polysaccharides.

Keywords: Prodrug, polysaccharide, khaya gum, guar gum, colon specificity

A R T I C L E  I N F O

CONTENTS
1. Introduction ........................................................................................................................................34
2. Materials and Method. ..................................................................................................................34
3. Results and Discussion. .................................................................................................................36
4. Conclusion. .......................................................................................................................................37
5. References ........................................................................................................................................37

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1. Introduction

Targeted drug delivery to the colon is highly desirable for local treatment of a variety of bowel diseases such as (ulcerative colitis, crohn’s disease) amebiosis, colonic cancer, and for local treatment of local colonic pathologies, and the systemic delivery of protein and peptide drugs. The colon specific drug delivery system (CDDS) should be capable of protecting the drug on route to colon (i.e. drug release and absorption should not occur in the stomach and the small intestine and bioactive agent should not be degraded) and to allow drug release only in the colon. The colon is a site where both local and systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, for example Ulcerative Colitis or Crohn’s disease. The treatment of disorders of the large intestine, such as irritable bowel syndrome (IBS), colitis, Crohn’s disease and other colon diseases, where it is necessary to attain a high concentration of the active agent, may be efficiently achieved by colon-specific delivery.

Prodrugs should be considered a chemistry-enabled drug delivery tool used to address shortcomings in the bioavailability, efficacy or safety profile of otherwise promising candidates. Ideally, a prodrug is not active and is efficiently converted to the active molecule, via an in vivo chemical or enzymatic transformation, ultimately enabling delivery of the active molecule at efficacious levels without adverse effects. Prodrugs should be evaluated for enhancing compound solubility in addition to salts and co-crystals, as much as formulation-enabled drug delivery technologies (i.e. nanomilling, amorphous solid dispersions, and other solubilizing vehicles) are considered routinely. Similarly, prodrugs that mask charge and increase lipophilicity should be utilized to enhance the permeability of molecules. Active consideration of prodrugs is essential to a medicinal chemist’s armamentarium and can provide molecules with more desirable biopharmaceutical and pharmacokinetic properties.

Prodrugs are designed to enhance the properties of active parent molecules, such as permeability, solubility, dosing frequency, chemical stability and metabolism. In addition, prodrugs can be used to provide specific organ-targeted delivery. There are a number of reviews published recently that provide key examples of improvements in absorption properties provided by prodrugs.

Despite well documented importance of the ability of gut microflora to hydrolyze glycosides; natural polysaccharides have been used only recently to exploit the unique glycosidase activity in the colon. A glycoside / glycosidase based delivery system should derive its site specificity from the colonic location of intestinal microflora, and their unique glycosidases. Among the glycosides which have been used in the research field to deliver the drugs to colon, in the form of drug- conjugation, cyclodextrins and dextran are only exploited to some extent with very few drugs.

Cyclodextrins are cyclic oligosaccharides consisted of 6-8 glucose units through -1, 4-glycosidic bonds and have been utilized for improvement of certain properties of drugs, such as solubility, stability, bioavailability, etc., by formation of inclusion complexes. CyDs are barely known to be hydrolysed and only slightly absorbed in passage through the stomach and small intestine. Most bacteroids isolated from the human colon are capable of degrading CyDs, as evidenced by their ability to grow on CyDs using them as sole carbon source and by the stimulation of cyclodextranase activity by exposure to CyDs. This biodegradable property makes CyDs useful as a colon targeting carrier; thus, CyD prodrugs may serve as a source of site specific delivery of drugs to the colon. A particular challenge in the pharmaceutical field is the development of site specific dosage forms that are able to control time of delivery, for the release of active ingredients in the lower part of the small intestine or colon.

The large intestine, though difficult to reach by peroral delivery, is still deemed to be the ideal site for the delivery of agents to cure the local diseases of the colon. A number of other serious diseases of the colon like colorectal cancer might also be capable of being treated more effectively, if drugs were targeted to the colon. Colonic drug delivery is also useful for systemic absorption of drugs, especially peptides and proteins, because of less hostile environment prevailing in the colon compared to stomach and small intestine. Due to the distal location of the colon in the gastrointestinal tract, a colon specific drug delivery should prevent drug release in the stomach and small intestine, and produce an abrupt onset of drug release upon entry into the colon. Ibuprofen (2-(4-isobutylphenyl)-propionic acid) is almost insoluble in water. Its pKa is 5.3 and its bioavailability is approximately 85%. The elimination half-life of ibuprofen is about 2 h. Ibuprofen is 90-99% bound to plasma proteins. It is rapidly excreted in urine mainly as metabolites and their conjugates. About 1% is excreted in urine as unchanged ibuprofen and about 14% as conjugated ibuprofen.

2. Materials and Methods

Materials:

Ibuprofen was obtained as a gift sample from Astra Zeneca (Banglore), Khaya gum, Eudragit S-100 obtained from Inaba University, Nigeria and Degussa Pvt Ltd, Germany respectively. Other chemicals like acetic acid, Pot. dihydrogen phosphate, Hydrochloric acid are obtained from...
Method of synthesis
It involves four steps
1. Synthesis of Ibuprofen-β-cyclodextrin
2. Preparation of Fast disintegrating core tablets
3. Compression coating of fast disintegrating core tablets
4. Enteric coating of the compression coated tablets

Synthesis of Ibuprofen-β-cyclodextrin
Ibuprofen-β-cyclodextrin was synthesized through a two-steps process involving tosylation of β-cyclodextrin (Step 1) and nucleophilic substitution of tosylated β-cyclodextrin by sodium ibuprofen (Step 2).

Step 1: Tosylation of β-cyclodextrin
Tosylated β-cyclodextrin was synthesized adapting the procedure described\(^{13}\). Briefly, to a solution of 5 g of β-cyclodextrin (4.4 mmol) in water (110 mL) 1.25 g of p-toluenesulfonyl chloride (6.55 mmol) was added and the resultant solution was stirred at room temperature for 2 hours under inert atmosphere. Aqueous sodium hydroxide (NaOH) (2.5 M, 20 mL) was added and the solution stirred for 10 minutes before unreacted p-toluenesulfonyl chloride was filtered off. 5.8 g of ammonium chloride (108 mmol) was added to lower the pH to approximately pH 8. The solution was cooled overnight and the resultant white precipitated collected by filtration. The white powder was washed with acetone and water to remove the non-reacted cyclodextrin and then dried under vacuum. The product obtained was used directly in the next step.

Step 2: Nucleophilic reaction
This step was performed following two different approaches - with and without the use of microwaves.

Non-microwave reaction:
In this method sodium ibuprofen (0.7 mmol) was added to β-cyclodextrin tosylate (5 mmol) in anhydrous DMF (5 mL) and the mixture stirred at 100 °C for 24 hours (Hirayma, Ogata et al., 2000).

Microwave reaction:
Reactions were carried out in an appropriate 10 mL thick walled glass vials under closed vessel conditions using CEM Discover S-class single mode microwave reactor with temperature, pressure and microwave power monitoring. Ibuprofen (0.333 mmol) was dissolved in 3 mL of anhydrous DMF containing β-cyclodextrin tosylate (0.327 mmol) in an appropriate thick-walled glass vial. The reaction vessel was then sealed with a Teflon cap and the reaction mixture magnetically stirred and heated at 140 °C for 40 minutes under focused microwave irradiation with an initial power setting of 75 W.

The product obtained was precipitated in acetone, filtered, washed several times with acetone and ethyl ether and dried. In order to obtain a purified sample, 300 mg of the crude product was passed through DIAION HP-20 ion-exchange chromatography column eluting with water/methanol, and steadily increasing the methanol content\(^{14}\). The conjugate was eluted with 80% methanol. Methanol in the eluate was removed under reduced pressure, the solution lyophilized in a freeze-dryer (Lyph-International Journal of Chemistry and Pharmaceutical Sciences lock 6 apparatus, Labconco) for 72 hours and the ibuprofen-β-cyclodextrin was obtained with a yield of 20%.

Preparation of Fast disintegrating core tablets
The composition of core tablets of ibuprofen is given in Table 1. The fast disintegrating core tablets of ibuprofen (average weight 250 mg) for compression coating were prepared by direct compression technique. Sodium starch glycolate and spray dried lactose were included in the formulation to obtain ibuprofen tablets with fast disintegrating characteristics (disintegration time < 30 seconds). Ibuprofen, sodium starch glycolate, spray dried lactose, magnesium stearate and talc were weighed and thoroughly mixed. The mixture was compressed into tablet at an applied force of 4000 Kg using 8 mm round, flat-faced, plain punches in single station tablet punching machine (M/s Cadmach, Ahmedabad).

Compression coating of fast disintegrating core tablets
The composition of compression coat formulations is given in Table 5.03. The compression coated formulations were prepared using khaya gum. Granules of the above material were prepared by wet granulation technique using 10% starch paste as binder. The prepared granules were dried at 50°C for one hour and passed through sieve number 16, placed over sieve number 44 to separate granules and fines\(^{15}\). About 15% of fines were added to the granules. The above granules were lubricated using talc and magnesium stearate in the ratio 2:1. Compression coating was carried out using 13 mm round, flat, plain punches. About one third of the granules were placed in 13 mm die cavity, the fast disintegrating core tablets of ibuprofen (8 mm) was carefully positioned in the centre of the die cavity and filled with remainder of granules.

Enteric coating of the compression coated tablets
The compression coated tablets of formulation were further coated using an enteric coating polymer such as eudragit S-100, following dip coating technique. Coating was applied to the tablet core by dipping into the coating liquid (eudragit S100 dissolved in acetone). The wet tablets were dried in a conventional manner in coating pan\(^{16}\). Alternative dipping and drying steps were repeated four times to obtain the desired coating.

Characterization
Study of in process quality control parameters of tablets
Tablets were evaluated during compression for different IPQC parameters like Weight, Hardness, Thickness, Diameter, and Friability. Thickness and diameter of the tablet were measured using caliper scale. Hardness was evaluated manually by using Monsanto hardness tester. Friability test was performed at speed of 25 rpm with tablets dropping from height of six inches with each revolution. After the test, the tablets were dedusted and reweighed.

Drug content uniformity test for tablets
Ibuprofen tablets were analysed by Indian Pharmacopoeia method and results are as shown in table 3. Twenty tablets were weighed and powdered. Crushed powder of tablets equivalent to 0.15gm was taken. 50 ml of 0.1M sodium hydroxide was added to the powder and diluted with 100 ml of water. Resultant solution was exposed to shaking for 15 min. sufficient water was added to same to produce 200 ml
of solution. The solution was mixed and filtered. 10 ml of filtrate was diluted with water up to 100 ml. 10 ml of 0.1M sodium hydroxide was added to 10 ml of resulting solution. This solution was diluted with water up to 100 ml and mixed. Finally absorbance of the resulting solution was measured at the maximum at about 257 nm. Content of ibuprofen was calculated taking 715 as the value of A (1%, 1 cm) at the maximum at about at about 257 nm. (Indian Pharmacopoeia, 1996).

**In-vitro drug release study**
Test was carried out using USP apparatus II (paddle) and the medium was Simulated gastric fluid, Simulated intestinal fluid and simulated colonic fluid. Quantity of dissolution medium was 900 mL. The speed of paddle was 50 rpm and temperature of dissolution medium was 37.5°C. One tablet was placed in the dissolution medium and apparatus was run. At intervals of 2, 5, 8, 12, 16, 20 and 24 hours, 5 mL aliquots were withdrawn and replacement was made each time with 5 mL of fresh dissolution medium. Each 5 mL sample was filtered through Whatman filter paper no. 41 and diluted up to 50ml with respective dissolution medium. Then absorbance was measured at 249 nm (USP 27)\(^1\).

**Stability study:** Best formulation was (F9) exposed to three months stability study at 40°C/75% RH. These samples then again evaluated for drug release study\(^1\).\(^8\).

### Results and discussion
Granules were prepared successfully by using wet granulation method and Tablets were prepared by compressing the lubricated granules on rotary tablet compression machine. Tablets were evaluated as per I.P.96 guidelines. The hardness, percent friability and average thickness were found to be in the range of 4.0 to 5.5 kg/cm\(^2\), 0.24 % to 0.33 %, 3.0 to 3.2 mm respectively. Tablets showed 95.68 to 104.63 % of the labelled amount of ibuprofen, indicating uniformity in drug content as per I.P. specification (95%-105%). All formulations were complying with the I.P. specifications.

Resulted tablets were evaluated for drug release by using USP dissolution apparatus II. Assay of tablet shows that tablets are of required purity and matches the I.P. specification. Drug release studies shows that F9 shows good release behaviour in colon and restricts release in stomach and intestine as compare to F1–F8. This study confirms that dextrin can act as good carrier in the form of matrix tablet for ibuprofen to deliver it in colon specifically by using ethyl cellulose as binder. Stability study of formulation No.F9 confirms that tablets are stable and there was no significant change in Hardness, Friability, Drug content and Dissolution profile of F9.

| Table 1: I.P.Q.C. Parameters of different dextrin matrix tablets of ibuprofen |
|-------------------------------|------------------|------------------|------------------|------------------|------------------|
| **Formulation Codes** | **Average Weight of Tablets (mg)** | **Average Diameter of Tablets(cm)** | **Average Hardness of Tablets (kg/cm\(^2\))** | **Friability of Tablets (%)** | **Average Thickness of Tablet (mm)** |
| F1 | 502 | 01 | 5.0 | 0.33 | 3.1 |
| F2 | 501 | 01 | 4.5 | 0.31 | 3.0 |
| F3 | 497 | 01 | 5.5 | 0.31 | 3.1 |
| F4 | 498 | 01 | 5.0 | 0.29 | 3.1 |
| F5 | 501 | 01 | 5.5 | 0.28 | 3.2 |
| F6 | 498 | 01 | 4.5 | 0.24 | 3.1 |
| F7 | 499 | 01 | 5.5 | 0.30 | 3.0 |
| F8 | 502 | 01 | 4.0 | 0.28 | 3.2 |
| F9 | 492 | 01 | 6.5 | 0.29 | 3.0 |

**Table 2: Results of drug content**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Formulation Codes</th>
<th>Assay (% Drug Content)</th>
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<tbody>
<tr>
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</tr>
<tr>
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<td>F2</td>
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### Table 3 Dissolution behavior of different dextrin matrix tablets of ibuprofen

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<tr>
<th>Dissolution Media</th>
<th>Time (Hrs.)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>Stability sample of F9</th>
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<td>25.17</td>
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<td>13.41</td>
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<tr>
<td>Simulated Colonic Fluid</td>
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<td>94.92</td>
<td>62.34</td>
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### 4. Conclusions

The present study was aimed at developing colon targeted drug delivery system of ibuprofen. As far as the in-process parameters are concerned, no significant differences have been observed between the khaya gum and guar gum based formulations. Though not significantly, the formulations containing guar gum released the drug faster than the khaya gum based formulations.

### 5. References


