Evaluation of a Natural Polymer for the Development of Colon Specific Drug Delivery System

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Abstract

Objective: Polysaccharide gums represent one of the most abundant industrial raw materials and have been the subject of intensive research due to their sustainability, biodegradability and safety. The purpose of present study was to evaluate a novel polymer, Anogeissus latifolia, as a carrier in the development of colon targeted drug delivery system.

Method: The matrix tablets of Diclofenac sodium were prepared using a 3^2 randomized full factorial design. The amount of natural polymer (X1) and amount of HPMC K100M (X2) were selected as independent variables. While the percentage cumulative drug release in lag time (Y1) and percentage cumulative drug release at 12 hours (Y2) were selected as dependent variables. The developed formulations were evaluated for Hardness, Friability, Weight variation, Drug content and in vitro drug release behaviour.

Results: The outcomes of physicochemical evaluation of developed formulations showed that all formulations showed optimum hardness, friability within limit and uniform weight and drug content. The formulation containing 40%w/v natural polymer and 10%w/v HPMC K100M was found to be optimized in terms of minimum drug release in lag time (≤ 25%) and % cumulative drug release in 12 h (>95%).

Conclusion: The developed system exhibited a promising targeting behaviour proving Anogeissus latifolia gum to be an excellent carrier for colon targeting and thus it can be exploited commercially.

Keywords: Anogeissus latifolia gum; Colon targeted drug delivery system; Diclofenac sodium; HPMC K100M; In vitro dissolution.

Introduction

Targeted drug delivery into the colon is highly desirable for local treatment of bowel diseases such as ulcerative colitis, Crohn’s disease, amoebiasis, colon cancer and also for systemic delivery of protein and peptide drugs because of less digestive enzymatic activity compared to stomach and small intestine. To deliver the compounds in non degraded form to lower part of the Gastrointestinal Tract (GIT), they must first of all pass through the stomach, the upper part of intestine and must use the characteristics of the colon to specifically release the drugs in this part of digestive tract [1]. Various approaches have been developed for colon targeting including pH dependent systems, Time dependent system and Microbially triggered delivery system. The pH dependent delivery system protects the formulation in the stomach and proximal part of small intestine but it may start to dissolve in the lower part of small intestine and thus it shows poor site specificity [2]. Similarly time dependent delivery systems are not able to sense any variation in upper GIT transit time [3,4]. Colonic bacteria possess ability to degrade a variety of polysaccharides present in the diet that are not degraded either in stomach or small intestine. Hence, the use of biodegradable polymers holds great promise for drug delivery to colon [1].

Gums and mucilages are used as inert pharmaceutical excipients and also as medicinal agent. They are widely used in food and pharmaceutical industry as thickening, stabilizing emulsifying and disintegrating agents [5]. The polysaccharide gums represent one of the most abundant industrial raw materials and have been the subject of intensive research over comparable synthetic materials due to their sustainability, biodegradability and safety [6]. The most of the natural polymers are obtained from trees in the forms of gums as tree exudates. Tree exudates gum are polysaccharides with high molecular weight mainly composed of monosaccharide unit, uronic acid and to some extent proteins and fibers. The purpose of this study was to evaluate novel polymer derived from the tree exudates of Anogeissus latifolia (Combretaceae, Myrtales) as a colon specific drug delivery carrier. It is a large deciduous tree found in dry areas of India. It is also known as Gum ghatti or Indian gum. This plant exudates has been in use for a long time and its name is derived from the word “Ghat” which means a mountain pass because of its ancient mountain transportation routes. It is approved as a food additive in Japan and has Generally Recognized as Safe (GRAS) in United States.

Gum ghatti is an extremely complex polysaccharide that occurs in nature as mixed calcium and magnesium salts of uronic acid and/or ghattic acids and has also been reported to contain approximately 3% protein. It consists of L-arabinose, D-galactose, D-mannose, D-xylene and D-glucuronic acid in a 48:29:10:5:10 molar ratio and <1% of rhamnose, which is present as nonproducing end groups. Gum contains alternating 4-O-substituted and 2-O-substituted D-mannopyranose units and chains of 1→6 linked β-D-galactopyranose units with side chains of L-arabinose units. This gum has been reported to be an excellent emulsifier, thickener and binder. The gum is comprised of around 80% soluble dietary fiber, acts as a prebiotic by supplying the matrix required to sustain the bacterial flora of the human colon. This hydrocolloid is resistant to gastrointestinal enzymes and known to be degraded enzymatically only by the specific microflora of the colon such as Bifidobacterium longum [6,7,9-11]. In this investigation, gum ghatti in the form of matrix tablets have been evaluated for its ability to deliver formulation to the colon using Diclofenac Sodium (DS) as a model drug.
Experimental

Materials

Diclofenac Sodium (DS) was received as gift samples from Aarti drugs ltd., Mumbai. Natural polymer was received as gift sample from PJ Enterprises, Mumbai, India. Dicalcium phosphate, HPMC and magnesium Stearate were purchased from Loba Chemicals Pvt ltd., Mumbai, India.

Methods

Characterization of drug: Characterisation of drug was done by determining the solubility, melting point using capillary method and comparing the IR spectra of obtained drug with standard spectrum using FTIR spectroscopy [11].

Characterization of natural polymer: Natural polymer was characterized for swelling index, viscosity, pH of solution, acid insoluble ash, water soluble ash, alcohol soluble extractive [6,7,12-15]. The flow property of polymer was determined by calculating Carr’s index, Hausner’s ratio, Angle of repose.

Drug-excipient compatibility study: The drug-Excipient interaction study was carried out by physical observation and FTIR spectroscopy [8].

Physical observation: The physical interaction between DS and natural polymer, HPMC K 100 M, Dicalcium phosphate, Magnesium Stearate was studied in a stability chamber at temperature 55±2˚C for period of two weeks [8]. Samples like DS: natural polymer (1:1), DS: HPMC K 100 M (1:1), DS: DCP (1:1), Diclofenac Na: Magnesium Stearate (1:1) and between DS: natural polymer: HPMC K 100 M; Dicalcium phosphate: Magnesium Stearate (1:1:1:1) were kept for evaluation of interaction and observed for caking, liquefaction, color change or any other incompatibility.

Fourier transform infrared spectroscopy: IR spectroscopy was also used to determine the molecular interaction between polymer and drug (DS). For FTIR spectroscopy natural polymer (Anogeissus latifolia gum) and DS (in 1:1 ratio) were mixed with dried KBR in ratio 1:100. A small fraction of this mixture was compressed on Automatic IR Press at a pressure 10 ton to form transparent pellet. IR spectrum was obtained using FTIR spectrophotometer. The interaction between Anogeissus latifolia gum and DS was studied by comparing the spectrum of pure drug and the mixture.

Preparation of DS matrix tablet: Tablets weighing 300 mg containing 50 mg DS were prepared by direct compression method. Natural polymer and HPMC K 100 M were used in different proportion as per experimental design. Dicalcium phosphate was used as diluent and magnesium stearate as lubricant. The tablets were prepared by tablet compression machine (Minipress 2D 8 stations) using 8 mm biconcave punch.

Experimental design: In the present investigation, after carrying out preliminary trials a 3² randomized full factorial design was used in development of the matrix tablet. In this design, 2 factors were evaluated each at 3 levels and experimental batches were prepared using all possible 9 combinations. The amount of natural polymer and amount of HPMC K 100 M were selected as independent variables. All the other formulation aspects and processing variables were kept invariant throughout the study period. The Percentage cumulative drug release in lag time and percentage cumulative drug release at 12 hours (Q₁₂) were selected as dependent variables. Formulations F1 to F9 were prepared by varying the levels of the independent variables as required by the experimental design and factors levels were suitably coded in table 1.

Physicochemical evaluation of prepared batches: The prepared batches were evaluated for precompression parameters viz. bulk density tapped density, Carr’s index, Hausner’s ratio and angle of repose. While tablets were evaluated for weight variation, hardness, friability and drug content uniformity. Tablet hardness was evaluated using a Monsanto hardness tester, friability using Roche friabilitator and weight variation using analytical balance [12,15].

Determination of uniformity of drug content: 20 tablets were weighed and powdered by using pestle mortar. An amount equivalent to 50 mg DS was shaken with 100 ml methanol and sonicated for 10 minute. The solution was filtered through Whatman filter paper and the content of DS was determined by measuring absorbance at 275 nm on double beam UV spectrophotometer (Jasco V-630) after suitable dilution [12].

In vitro drug release study: All batches F1–F9 were further evaluated for in vitro drug release study. In vitro drug release study was carried out using USP apparatus II (Paddle) and the medium was 0.1N HCl (pH 1.2) and phosphate buffer pH 6.8. The quantity of dissolution medium was 900 ml. The speed of paddle was 50 rpm and temperature of dissolution medium was 37±0.5˚C. Dissolution study was carried out in 0.1 N HCl for 2 hrs and then placed in phosphate buffer (pH 6.8) until complete release of the drug. Five ml aliquots were withdrawn at fix intervals and replacement was made each time with five ml of fresh dissolution medium to maintain sink condition. Every time withdrawn sample was filtered through Whatman filter paper and analyzed drug content at 275 nm using UV-visible spectrophotometer, (Jasco V-630, Japan). In vitro drug release study for each sample was done in triplicate.

Optimization data analysis: Response Surface Methodology (RSM) is a widely practiced approach in the development and optimization of drug delivery devices. Based on the principle of design of experiments, the methodology encompasses the use of various types of experimental designs, generation of polynomial equations and mapping of the response over the experimental domain to determine the optimum formulation. The technique requires minimum experimentation and time thus proving to be far more effective and cost-effective than the conventional methods of formulating dosage forms. Various computations for the current optimization study were performed using Design Expert® software (trial version 8.0.4; State-Ease Inc., Minneapolis, MN, USA). The values of % CDR in lag time and % CDR in 12 hours of all 9 batches (F1–F9) were put in Design Expert software and analysed [16].

Kinetic analysis of dissolution data: To study the mechanism of drug release from the matrix tablets, the drug release data of optimized batch were fitted to zero-order, first-order, Higuchi equations and Korsemeyer equation [17].

Stability study: The stability studies were carried out for the optimized formulation. The samples were stored at 40±2˚C and 75±5% RH for period of two weeks [8]. The samples were withdrawn at every 7 day, filtered through 0.45 μm pore size membrane and analyzed for drug content as per their procedure.

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| Coded levels | Actual value in percent |
|-------------|------------------------|
| X₁          | X₂                     |
| -1          | 20                     | 10                   |
| 0           | 30                     | 20                   |
| 1           | 40                     | 30                   |

Table 1: Translation of the coded levels in actual units.
75±5 %RH for three month to access their stability. The protocol of stability studies was in compliance with ICH guidelines for stability testing intended for the global market. After every 30 days the samples were withdrawn and characterized for hardness, friability, drug content and in-vitro drug release study [18].

Results and Discussion

Characterization of drug

Melting point: The melting point of the drug was found to be in the range of 282-284°C which matches with the reported value.

Solubility: DS is a slightly soluble drug in distilled water and 0.1 N HCl. The solubility of drug was found to be 0.0010 mg/ml and 0.64 mg/ml in 0.1N HCl and phosphate buffer pH- 6.8 respectively.

FTIR spectrum of diclofenac sodium: The IR spectra of DS (Figure 1a) exhibited principal peaks at wavenumbers 1573, 756, 1509, 1089, 51 cm⁻¹ (-C-O stretching region as complex bands resulting from C-O and C-O-C stretching vibrations) and 643.71 cm⁻¹ (pyranose ring).

Drugs-excipients compatibility study: IR spectra of physical mixture of drug and polymer (Figure 1c) reveals that the principal peaks of DS for NH₃ at 3387 cm⁻¹, aromatic at 1573 cm⁻¹ and at 746 cm⁻¹ (ortho-disubstituted phenol) are present in both, the spectra of pure drug and physical mixture with the natural polymer.

FTIR studies suggested absence of any significant interaction between the polymer and the drug in the formulation.

Physicochemical evaluation: The physicochemical evaluation of developmental batches F1-F9 showed good flow property, uniformity of weight & drug content in powder blend as well as optimum hardness and friability limit specified for tablet formulations. The results are depicted in table 3 and table 4.

The precompression parameters of all batches were found to be in acceptable range indicating good flow behaviour.

FTIR spectrum of natural polymer: IR spectrum of natural polymer (Figure 1b) showed broad peaks at 3408.4 cm⁻¹ (O-H stretching of carbohydrates), 2928, 1406, 1234 cm⁻¹ (-CH₂ asymmetric stretching, scissoring and twisting and rocking vibration of methylene groups), 1445.35 cm⁻¹ (-CH and -CH₂ in plane bending in carbohydrates), 1089.51 cm⁻¹ (-C-O stretching region as complex bands resulting from C-O and C-O-C stretching vibrations) and 643.71 cm⁻¹ (pyranose ring).

Characterisation of natural polymer: The results of physicochemical properties of Anogeissus latifolia gum are shown in table 2.

Table 2: Characterisation of natural polymer.

| Parameter            | Results                                      |
|----------------------|----------------------------------------------|
| Solubility           | Soluble in hot water, forming a viscous solution; practically insoluble in chloroform, acetone, methanol. Also polymer swells in 0.1 N HCl and phosphate buffer and shows good gelling properties. |
| Moisture content (%) | 2%                                           |
| Ash Value            | 4%                                           |
| Acid Insoluble ash   | 1.60%                                        |
| Water soluble ash    | 1.40%                                        |
| Viscosity 10% solution (Cps) | 400                                 |
| Swelling Index (%)   | 150                                          |
| Density (g/ml)       | Bulk: 0.9 ± 0.010                             |
|                      | Tapped: 0.984 ± 0.011                        |
| Carr’s index (%)     | 8.54 ± 0.78                                  |
| Hausner’s ratio      | 1.09 ± 0.055                                 |
| Angle of repose (θ)  | 29.34° ± 0.53                                |

The gum powder exhibited insolubility in common solvents except distilled water. The moisture content, ash value and all other parameters were within the limits as specified in official compendium. The values of angle of repose, Carr’s index, Hausner’s ratio indicated that the polymer has good flow property and compressibility.

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The result of drug release study revealed that formulations F1 to F9 containing respectively 20, 30 and 40% of natural polymer (Anogeissus latifolia gum) were able to sustain the drug release for 12 hrs. However, the purpose of colon targeted drug delivery system was not only to sustain the drug release up to 12 hrs but also to minimize drug release in the small intestine. The formulations F3 and F6 were able to minimize the drug release up to 25% in the lag time of 5 hrs. All the developed batches showed cumulative drug release more than 90% after 12 hrs.

**Table 4:** Evaluation of developmental batches F1-F9 (tablets).

| Test | Tablet weight (mg) | Hardness (Kg/cm²) | Friability (%) | Drug Content (%) |
|------|--------------------|-------------------|---------------|-----------------|
| Batch |                    |                   |               |                 |
| F1   | 300.75±3.38        | 4.33±0.28         | 0.32±0.16     | 102.9±1.98      |
| F2   | 298.25±4.6         | 5.13±0.32         | 0.44±0.19     | 100.5±0.57      |
| F3   | 300.7±3.04         | 6.01±0.5          | 0.58±0.13     | 99.26±2.50      |
| F4   | 302.9±4.16         | 6.50±0.5          | 0.24±0.15     | 96.60±2.75      |
| F5   | 300.5±4.17         | 6.50±0.5          | 0.26±0.15     | 96.30±1.13      |
| F6   | 299.9±4.16         | 6.00±0.45         | 0.66±0.10     | 98.96±1.15      |
| F7   | 299.64±4.07        | 6.33±0.5          | 0.20±0.10     | 102.0±1.26      |
| F8   | 301.0±3.62         | 5.83±0.28         | 0.21±0.16     | 96.63±2.56      |
| F9   | 301.1±4.63         | 6.00±0.5          | 0.56±0.20     | 97.03±1.91      |

**Figure 2:** In vitro drug release profile of developmental batches (F1-F9).

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**Model assessment for the dependent variable: %CDR in lag time**

Final equation in terms of actual factors:

%Drug release in lag time = +57.38222-0.93533(X1)-1.11092(X2)+0.036625(X1)X2

X1=Proportion of natural polymer (Gum Ghatti); X2=Proportion of HPMC K100

| Source | Sum of squares | DF | Mean Square | F-value | P-value | F-value | P-value | Significance |
|--------|---------------|----|-------------|---------|---------|---------|---------|-------------|
| Model  | 50.07         | 2  | 25.03       | 18.23   | 0.0028  | -       |         | Significant  |
| Conc. Of Natural polymer | 0.13 | 1 | 0.13 | 0.094 | 0.7895 | - |         |             |
| Conc. Of HPMC K100 M | 49.94 | 1 | 49.94 | 36.36 | 0.0009 | Significant |         |
| Residual | 8.24 | 6 | 1.37 |  |  |  |  |  |
| Core total | 58.31 | 8 |  |  |  |  |  |  |

**Table 5:** Analysis of variance for Y1.
The Model F-value of 6.34 (Table 5) implies the model is significant. There is only a 3.72% chance that a “Model F-Value” this large could occur due to noise. Values of “Prob > F” less than 0.0500 indicate model terms are significant. In this case AB is significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. The 3D response and contour plot is depicted in figures 3a and 3b.

Model assessment for the dependent variable: % CDR in 12h

The optimized batch was then developed and evaluated for various physicochemical properties and the results of physicochemical evaluation and in vitro drug release study for optimized formulation have been depicted in table 8 and figure 5 respectively.

Solutions for optimized batch: After analysis of both independent variables (i.e., factor) and dependant variables (i.e., response) Design Expert® software gives solutions. One batch from the solutions provided by software was selected as an optimized batch based on desirability value depicted in table 7.
Kinetic analysis of dissolution data: Drug release data of optimized formulation showed good fit to the zero order equation ($r^2=0.9848$), partially fitted in Higuchi equation ($r^2=0.92$) and also showed high linearity with Korsmeyer equation ($r^2=0.94$). The Korsmeyer-Peppas equation for drug release is given below:

$$\frac{M_t}{M_\infty} = K t^n$$

Where, $M_t$= the amount of drug released in time $t$; $M_\infty$=amount of drug release at infinite time $K$ is constant, and $n$ represents the release exponent indicative of mechanism of drug release.

When $n=0.5$ means Fickian diffusion, $0.5>n<1.0$ non-Fickian diffusion, and $n=1.0$ Case II diffusion. The release exponents ($n$) of the formulations suggest that depending on the formulation variables the drug release followed either Fickian or non-Fickian mechanism. The drug diffusion through most types of polymeric systems is often best described by Fickian diffusion.

**Stability study:** The stability studies were carried out for the optimized formulation. The optimized formulation did not show any significant change in hardness, friability and drug content when kept at accelerated conditions of temperature and humidity. Also no significant difference in values of in vitro drug release profile observed during the stability studies (Figure 6).

The formulation was found to be stable under accelerated conditions of temperature and humidity showing proper hardness, optimum friability, uniform drug content and uniform in vitro drug release behaviour during 3 months accelerated stability studies.

**Conclusion**

This study exhibited that it is possible to control the release rate of Diclofenac sodium over a wide time scale using Anogeissus latifolia as a sustained release polymer. The combination of both natural and synthetic polymers can be a better choice in comparison to costly synthetic sustained release polymers to achieve desired sustained release effect of formulation. The present study provides a new alternative which is cheaper, having lesser side effects & biocompatible formulation of Diclofenac sodium in the treatment of IBD. Thus this polymer proved to be an excellent carrier for colon targeting and can be exploited commercially.

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**Author(s)’ Statement(s)**
The author(s) declare(s) no conflict of interest.

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