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Short communication

Boswellia gum resin/chitosan polymer composites: Controlled delivery vehicles for aceclofenac

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ABSTRACT

This study was undertaken to evaluate the effect of *Boswellia* gum resin on the properties of glutaraldehyde (GA) crosslinked chitosan polymer composites and their potential as oral delivery vehicles for a non-steroidal anti-inflammatory drug, aceclofenac. The incorporation of resinous material caused a significant improvement in drug entrapment efficiency (~40%) of the polymer composites. Fourier transform infrared (FTIR) spectroscopic analysis confirmed the formation of chitosan-gum resin composites and did not show any evidence of drug–polymer chemical interaction. Field emission scanning electron microscopy (FE-SEM) suggested the formation of particulate polymer composites up to chitosan:gum resin mass ratio of 1:3. Only 8–17% drug was released into HCl solution (pH 1.2) in 2 h. The drug release rate of polymer composites was faster in phosphate buffer solution (pH 6.8). The composites released ~60–68% drug load in 7 h. In same duration, the drug release rate suddenly boosted up to 92% as the concentration of gum resin in the composites was raised to 80%. The drug release mechanism deviated from non-Fickian to case-II type with increasing resin concentration in the composites. Hence, GA-treated *Boswellia* resin-chitosan composites could be considered as alternative vehicles for oral delivery of aceclofenac.

1. Introduction

Composites can be defined as materials that consist of two or more chemically and physically different phases separated by a distinct interface [1]. The different systems are combined judiciously to achieve a composite system with necessary mechanical strength or stiffness non-attainable by any of the constituent alone. Composite materials have bulk properties significantly different from those of any of the constituents [2].

Currently, the research workers are trying to develop a new class of fully biodegradable green composites by combining fibres with biodegradable resins. The application of bio-based composites with their constituents developed from renewable resources has been extended further to drug delivery fields. Polymer matrix composites are very popular due to their low cost and simple fabrication methods [3].

Tree exudates are characterized by low toxicity, abundant availability, biocompatibility, biodegradability, inertness, and low cost compared to that of synthetic polymers [4]. *Boswellia* serrata (family: Burseraceae) is the scientific name for a tree which grows in the dry hilly areas of India. It chiefly contains an acid resin, and polysaccharides (~65% arabinose, galactose, xylose) which are soluble in water [5–7]. The resinous part of *Boswellia* serrata possesses β-boswellic acid, responsible for the inhibition of pro-inflammatory enzymes [8]. The *Boswellia* gum resin (BGR) is used for treating osteoarthritis, juvenile rheumatoid arthritis, soft tissue fibrositis and spondylitis [9]. Moreover, it shows anti-inflammatory and anti-arthritic activities which are mainly attributed to a component in the resin containing β-boswellic acid [10]. BG resin has also been investigated as microencapsulating material [11–13] and binding agent [14,15]. However, there is no report on the use of BGR for the fabrication of polymer matrix composites.

Chitosan (CS) is a biocompatible, biodegradable and cationic polysaccharide obtained by alkaline deacetylation of chitin and composed of α-1,4-linked 2-amino-2-deoxy-α-D-glucose (*N*-acetyl glucosamine) [16]. It is generally recognized as safe material and thus, has been widely studied in various biomedical and pharmaceutical applications including drug delivery, tissue engineering and food technology [17].

Aceclofenac is an orally administered phenyl acetic acid derivative with effects on a variety of inflammatory mediators. Its frequent administration and prolong treatment was associated with various side effects like gastric irritation, ulcer, particularly diarrhoea, nausea, abdominal pain and flatulence, etc. [18].

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Considering the anti-inflammatory constituent, the use of BGR as matrix material in the design of polymer composites could be an interesting delivery vehicles for aceclofenac. The specific objective of this investigation was to evaluate CS-BGR polymer composites as possible controlled release carriers of aceclofenac in vitro.

2. Materials and methods

2.1. Materials

Aceclofenac was a gift sample from Drakt Pharmaceutical Pvt. Ltd., Gujarat, India. Chitosan (Everest Edward, Kochi, India), Glutaraldehyde (25% (v/v), GA) was obtained from Loba Chemie Pvt. Ltd., Mumbai, India. *Boswellia* gum resin (BGR) was purchased from Associated Traders, Kolkata, India. Fehling's reagent (Qualigens Fine Chemicals, Mumbai, India) and glycine were the products of Merck Specialties Pvt. Ltd., Mumbai, India. All other reagents were of analytical grade.

2.2. Aceclofenac-loaded CS-BGR microcomposites

Chitosan (200 mg) was dissolved in 10 ml of 1% (v/v) glacial acetic acid and to this; an aqueous BGR solution (2–8%, w/v) was added. A pre-weighed amount of aceclofenac (100 mg) was added to the polymer solution under continuous magnetic agitation until homogeneous drug dispersion was obtained. The pH of dispersion was adjusted to pH 5.5 using 0.2 M sodium hydroxide solutions. Then, 2 ml GA was added to the dispersion and stirred for 1 h. The cross-linked polymer composites thus formed were centrifuged at 5000 rpm for 20 min and were isolated by filtration process. The composites were washed with glycine/water to remove non-reacted GA. As soon as the orange colour of the washings disappeared, the final washings were heated with a deep-blue alkaline Fehling's solution. A negative test, i.e. the formation of no brick-red precipitate confirmed the absence of GA in the washings [19]. Lastly, the composites were dried at 40 °C for overnight and stored in desiccators for further use.

2.3. Fourier transform-infrared (FTIR) spectroscopy

The IR spectral data for chitosan, aceclofenac, and drug-loaded microcomposites were collected by making KBr discs with powder samples using Perkin Elmer FTIR spectrophotometer (Spectrum RX1, USA) in the region 4000–600 cm^{-1} at a resolution of 4 cm^{-1} with scan speed of 2 mm s^{-1}.

2.4. Drug entrapment efficiency of CS-BGR microcomposites

CS-BGR microcomposites (100 mg) were powdered and the drug was extracted into 500 ml of phosphate buffer solution (pH 6.8) overnight followed by sonication for 15 min (Frontline Sonicator, FS-600, Frontline Electronics and Machinery Pvt. Ltd., India). The insoluble polymeric debris was removed by filtration through Whatman® filter paper (No. 40) and the filtrate was analyzed by UV-Vis spectrophotometer (Thermo Scientific, UK) at 274 nm. The drug entrapment efficiency of microcomposites was calculated by the following formula:

$$\text{DEE}\,(\%) = \frac{\text{actual drug content in microcoposites}}{\text{experimental drug content in microcoposites}} \times 100$$

2.5. Field emission-scanning electron microscopy (FE-SEM)

The lyophilized microcomposites were spread onto metallic stubs and platinum coating applied by using an ion-sputtering device. The coated particles were then examined under FE-SEM (ZEISS, Japan).

2.6. In vitro drug release study

In vitro release of aceclofenac from CS-BGR microcomposites was studied as follows. The microcomposites equivalent to 100 mg aceclofenac were placed in dialysis bag (MWCO 12–14 kDa, HiMedia Laboratories Pvt. Ltd., Mumbai, India) containing 5 ml of phosphate buffer (pH 6.8) solution. Other end of the dialysis bag was tied off and immersed in the vessel of USP type II dissolution apparatus (Veego VDA-6D, Veego Instruments Co-operation, India) containing 900 ml of phosphate buffer (pH 6.8) solution. The system was maintained at 37 ± 1 °C with a paddle speed of 50 rpm. The dialysis bag acted as a donor and that of dissolution vessel as the receptor compartments. An aliquot (5 ml) was collected at regular time intervals, and the same volume of fresh medium was added into dissolution vessel to maintain the sink condition throughout the experiment. The aliquots were then filtered, suitably diluted and analyzed using a UV-Vis spectrophotometer (Thermo Scientific, UK) at 274 nm. The drug release also continued in pH 1.2 HCl solution for 2 h under similar experimental conditions.

2.7. Prediction of drug release mechanism

Korsmeyer–Peppas modelling of in vitro drug release data (<60%) was done to reveal the hidden mechanisms behind the drug release process. The model was described as follows:

$$Q = kt^n$$

'*Q*' represents the fraction of drug released in time *t*, and '*k*' is the kinetic rate constant. The exponent (*n*) was indicative of Fickian diffusion ($n \leq 0.43$), non-Fickian diffusion ($0.43 < n < 0.85$) and case-II transport ($n > 0.85$) mechanism [20,21].

2.8. Analysis of variance

The drug entrapment efficiency and release data was subjected to one way ANOVA analysis in GrahPad Prism software (Trial verison 5.00). The data was analyzed at 95% confidence level and significant variation was dictated by *p*-value.

3. Results and discussion

Chitosan is an amine group containing polymer which bears highly positive charge at pH 5.5 [22]. On contrary, BGR is enriched with beta-boswellic acid having pK_a value lower than pH 5.5. Therefore, carboxyl groups of gum resin persisted in protonated form and might have interacted with oppositely charged amine groups of chitosan polymer and contributed to the formation of polymer composites. Further, the amine groups of chitosan reacted with GA and formed covalent imine linkages and thus created a more compact polymer composite structure. This was illustrated by FTIR spectra analyses (Fig. 1).

The peaks at 3417.99 cm^{-1} (N–H and O–H stretching vibration), 1656.18 cm^{-1} (N-H deformation), and 1093.11 cm^{-1} (C–O stretching vibration of the pyranose ring a) were noticed in the spectrum of chitosan (Fig. 1a). FTIR spectrum of BGR was given in Fig. 1b. A broad, weak stretch around 3400 cm^{-1} indicated the prevalence of less number of OH groups in the gum. C–H bending vibration of –CH and $-CH_2$ groups (2918.20 cm^{-1}), C=O stretching of carboxyl groups (1702.20 cm^{-1}), C–O stretching of polysaccharide alcohols (1095.91 cm^{-1}), C–H deformation of $-CH_3$ groups (1442.33 cm^{-1}) were the other important bands in the spectrum. Similar spectrum of *Boswellia* gum was reported by Mohanty and Krishna [4].