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Bio-derived cellulose nanofibril reinforced poly(*N*-isopropylacrylamide)-*g*-guar gum nanocomposite: An avant-garde biomaterial as a transdermal membrane

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ABSTRACT

The delivery of diltiazem hydrochloride in therapeutical doses has attracted an immense research interest. However, its slower penetration through the transdermal route has stipulated to develop a competent transdermal membrane. Therefore, a nanocomposite based patch was formulated by exploring co-polymer and jute derived nano-cellulose. Poly(*N*-isopropylacrylamide) was grafted into guar gum (GG-*g*-PNIPAAm) with different feeding ratios. The co-polymer formation was authenticated by FTIR and 13C NMR spectra. The nanocomposite were prepared by incorporating nanofibre (0.5–2 wt%) into GG-*g*-PNIPAAm. The structural and morphological studies supported good interactions and presence of nano-cellulose on co-polymer. GG-*g*-PNIPAAm has showed higher thermostability than guar gum. Moreover, the addition of CNF has improved the thermo-mechanical and barrier properties of the nanocomposite. The nanocomposite containing 1 wt% CNF was found to be best performing. The patch showed *in-vitro* cyto-compatibility and non-irritant behaviour. The in-vitro release study of best nanocomposite revealed controlled drug release capability with 7.78 and 22.9% after 5 and 20 h, respectively.

1. Introduction

Diltiazem hydrochloride (DH) is a very important drug which is used in the treatment of hypertension (HT). It belongs to benzothiazepines class and function as a calcium channel blocker [1]. The steep increasing risk of HT that leads to stroke, coronary artery disease, loss of vision, is needed to be addressed properly [2]. Another important aspect of drug delivery is to maintain the effective dose of drug (DH) for a prolonged period to manage this disease. Generally, DH is delivered intravenously or orally to those patients suffering from HT. However, DH possessess a short biological life time hence upon oral administration it requires frequent and multiple dosing to maintain its therapeutic index. Additionally on oral administration, DH undergoes hepatic pass metabolism and offers only 40% drug bioavailability. Further, these treatments are co-linked with harsh side effects, to cite dizziness, headache, heart problems and nausea [3]. Therefore to overcome these impediments, the administration of DH through transdermal route has found an ample of research attraction. Foremost, DH through transdermal route could evade the enzymatic degradation and hepatic pass metabolism as imposes by the oral route as drugs are directly released to the blood vessels. Therefore, though DH has a short half life time, but via transdermal route it could be released into the blood stream in therapeutical doses. Thus, in transdermal route the drug bioavailability is more in comparison to the oral route. Further, drugs are released in a controlled and sustained manner from patches for a prolonged period. However, it is likely to mention that the penetration of drug through skin is reported to be too slow in delivery DH. Therefore, the prerequisite is to develop a transdermal patch that could assist in the delivery of optimal dose of drug at an interval of require time period. To address the

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aforementioned issue, a novel cellulose nanofibril (CNF) incorporated guar gum-g-poly(*N*-isopropylacrylamide) (GG-*g*-PNIPAAm) nanocomposite was designed in this study as a biocompatible transdermal path for the delivery of DH.

Guar gum (GG) with excellent biocompatibility and biodegradability has triggered significant research interest, especially in transdermal drug delivery system (TDDS) [4]. However its high swelling feature, burst out effect on drug release accompanied with inadequate physico-mechanical strength to meet biological demands has limited its practical applicability in TDDS [5].

Therefore, poly(*N*-isopropyl acrylamide) (PNIPAAm) was grafted on GG to achieve better performance. PNIPAAm is a biocompatible polymer with thermoresponsive properties. Grafting of PNIPAAm may likely improve the drug-nanocomposite interaction as well as could aid in the slow release of drug molecules while shrinking near body temperature. Further, literature have revealed that the poly(*N*-isopropylacrylamide) grafts on polysaccharides have been already exploited to improve the drug release profile. Therefore, the thrust of this study is the addition of cellulose nanofibre (CNF) on the grafted co-polymer to enhance the performance and to examine the pronounced and remarkable effect of adding small amounts of CNF on drug release rate.

CNF a biopolymer with astonishing properties has attained mammoth interest in drug delivery system. It is a biocompatible, biodegradable, easily available and nontoxic vehicle for the release of active drug molecules [6]. Moreover CNF is also being explored in the realm of polymeric drug delivery system. The most specific feature of CNF is that its glucose unit has three hydroxyl groups, thereby bestowing it a reactive surface embedded with several active hydroxyl groups. The functional groups take vital part in nanocomposite formation, especially when it is utilized in conjugation with polymers and drugs. Polymer's properties show a rapid improvement by the incorporation of a minute amount of CNF. It is due to a high surface area that permits a better polymer-filler interaction [7]. Other desired properties of CNF exclusively that assist TDDS include excellent physico-mechanical, surface reactivity, barrier properties, and biocompatibility for good drug-matrix interaction, metabolic endurance and controlled drug release [7].

In term of biological properties, it could be asserted that CNF and guar gum being biopolymers would invoke an insignificant foreign body reaction within host. However, the synthetic procedure and precursor material play a pivotal role in attaining biocompatibility. The mild is the extraction process, better is the biocompatibility. It is also relevant to mention that CNF can be obtained from variety of sources which has a direct influence on its properties. The impetus of various research strategies is to fabricate promising biomaterials from natural resource.

In this context, jute was entwined as the starting material for the synthesis of CNF for its easy bioavailability and cost effectiveness. Furthermore, the performance of the nanocomposites by incorporating CNF in the synthesized co-polymer was investigated, in terms of mechanical strength, viscosity, thermostability, swelling and barrier property, biocompatibility and drug release profile. To examine the effect of CNF, the performance of the nanocomposites were compared with the co-polymer. Therefore it is speculated that the developed biocompatible formulation has the potency to be used as transdermal patch.

2. Experimental section

2.1. Material

Guar gum was purchased from Sisco Research Laboratories Pvt. Ltd., Maharashtra, India. Potassium persulphate ($K_2S_2O_8$), caustic soda (97% pure), sulphuric acid (98%) and hydrogen peroxide (50%) standard laboratory grade, were purchased from Merck Specialties Pvt. Ltd., Worli, Mumbai, India. Hydroquinone and Sodium chlorite (80% pure) were purchased from Loba chem., Mumbai, India. Diltiazem hydrochloride of molecular weight 450.98 was a gift sample received from Ranbaxy Int., Gurgaon, Haryana, India. Adhesive tape USP type (Medi-Grip) was purchased from Precision Coatings Private Limited, Indore, MP, India. Jute fibres were collected from the Department of Jute and Fibre technology, University of Calcutta. Sodium sulphite was purchased from Qualigens Fine Chemicals, Mumbai, India. *N*-isopropylacrylamide (97%) and N,N,N,N-tetramethyl ethylene diamine (TEMED) were purchased from Sigma-Aldrich, India.

2.2. Preparation of cellulose nanofibril

2.2.1. Pre-treatment

The jute fibres were chopped into 2–4 mm lengths and leached in 17.5–18% NaOH solution to weaken the fibre structure. Then, the mixture was heated at 80–90 °C for 2 h under vigorous stirring. The fibres were collected through filtration and washed repeatedly with water to remove the basic trace and finally air dried for 3 h at 105 °C. The obtained fibres were treated with 0.7% sodium chlorite at moderate acidic pH = 4, at 90 °C to remove the lignin. In this condition, the mixture was stirred for 2 h. After filtration, the fibres were washed followed by the antichlorination with 2% sodium bisulfite for 20 min. Furthermore, the fibres were treated by using 3–6 wt% (with respect to the weight of fibres) 50% H_2O_2 solution at a pH range of 10–11 for 2 h and then again the fibres were washed with water to neutralize the pH. The treated fibres were then subjected to react with 17.5% sodium hydroxide at room temperature for 1 h to remove hemicelluloses from fibres. Finally the product was neutralized by washing with water and dried at 100 °C.

2.2.2. Acid hydrolysis

The dried mass of pre-treated jute fibres was digested with 47–48% (v/v) solution of sulphuric acid (H_2SO_4) at room temperature for 3 h under vigorous stirring. The obtained suspension was neutralized by washing with water followed by the centrifugation and freeze drying. The extraction process of CNF is pictorially depicted in Fig. 1.

2.3. Synthesis of guar gum-g-poly(N-isopropylacrylamide) (GG-g-PNIPAAm) via free radical polymerization

The free radical polymerization process was adopted to synthesize GG-*g*-PNIPAAm copolymer in the presence of potassium persulfate ($K_2S_2O_8$) as initiator. 1.0 g of guar gum was added in a three necked round bottom flask containing 80 mL of distilled water. Then the mass was continuously stirred under constant flow of nitrogen for 30 min at 50 °C to ensure complete dissolution. After that the guar gum solution was cooled to ambient temperature. Required amount of *N*-isopropylacrylamide (NIPAAm) as listed in Table 1 was separately dissolved in 10 mL of distilled water at room temperature. Then the NIPAAm solution was poured into the guar gum solution. For the purpose to make a homogeneous mixture it was stirred for another 30 min at room temperature under nitrogen atmosphere. Further, the aqueous potassium persulfate ($K_2S_2O_8$) solution and N,N,N,N-tetramethylethylene diamine solution were poured into the homogeneous mixture respectively. Finally the total volume of the reaction mixture was adjusted to 100 mL by adding water and the polymerization reaction was carried out at room temperature for about 12 h with continuous purging of nitrogen gas. To terminate the reaction, a sufficient amount of hydroquinone was added to the reaction medium after the reaction period. The reaction mass was then cooled to room temperature