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Deposition of gold-cellulose hybrid nanofiller on a polyelectrolyte membrane constructed using guar gum and poly(vinyl alcohol) for transdermal drug delivery

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ABSTRACT

Transdermal (TD) route of diltiazem hydrochloride (DH) administration attracts ample attraction, but remains strenuous due to slower penetration of drug across the skin. In the present investigation, we studied the possibility of using gold nanoparticle (GNP) to enhance the skin permeation of DH. A novel TD device was fabricated from polyelectrolyte complex (PEC) reinforced with nanogold-nanocellulose (GNP-NC) composites and characterized using NMR, FTIR, XRD, TEM and SEM. The PEC membrane was designed using the electrostatic interaction between cationic guar gum (CGG) and borate modified poly(vinyl alcohol). The hybrid filler deposited films have been prepared at different loading levels and the influence of loading on drug encapsulation efficiency, tensile properties, thermal stability, water vapor permeability, and skin permeability were evaluated. The effect of storage time and temperature on the drug release behavior was investigated. The devices were also examined for *in vivo* skin adhesion and irritation in human subjects, cell viability and environmental fitness to assess its application in pharmaceutical field. The results of the investigation suggested that the developed film may serve as a potential device for the TD delivery of DH.

1. Introduction

Hypertension (HT) is a long term medical condition, identified as a major health issue ultimately leads to stroke, coronary artery disease, loss of vision, etc [1]. Literature enumerated that HT is a global burden, affecting around 50 million individuals in USA and 1 billion people worldwide [2]. Globally individuals suffering from HT are likely to rise by 60.0% during the first 25 years of the 21st century [3]. DH is a calcium channel blocker, belongs to benzothiazepines class, used in the management of HT [4]. Generally, DH is delivered orally or intravenously with oral route is the most usual technique of administration. However these treatments were associated with severe side effects including dizziness, headache, slow heart beat and nausea [5]. These downsides have led to the progress of TD delivery system for DH. TD route avoids first pass hepatic metabolism, provides painless administration of DH, easy termination of therapy, option of self administration etc [6].

Polysaccharides are biocompatible natural compounds carrying easily modifiable functional groups on molecular chains that make them ideal for biomedical applications [7]. The excellent film forming ability, non-toxicity, biocompatibility and biodegradability of guar gum (GG), triggered significant focus on this polysaccharide especially in TD drug delivery system [8]. GG is a water soluble galactomann composes of β linked (1,4) D-mannopyranose units as backbone with randomly connected α (1,6)-linked galactopyranose units as side chains [9]. Due to its high swelling feature, an undesirable burst release profile is exhibited by GG which limits its application in TD formulations and should be addressed [10]. One approach is to design a double walled composite material with less permeable outer screen. Nevertheless, this may not be the simplest technique to prevent the unpredictable premature leakage [11]. Surface extraction, another technique which involves the concentration of drug in the center and eliminating it from the surface of the delivering device. A serious downside of this approach is the remarkable loss of loaded drug from the device [12]. The development of polyelectrolyte membrane is an alternative strategy which successfully terminates the premature leakage by arresting the particle swelling [13]. The introduction of trimethylammonium group using (3-Chloro-2-hydroxypropyl)trimethylammonium chloride (CHPTAC) generates cationic character to GG. This increases the affinity for negatively charged moieties of the skin constituent which improves its skin residential time [14]. The existence of quaternary ammonium substituents and numerous hydroxyl groups in CGG results in

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the building of various interactions with ionic and non-ionic therapeutic molecules [15].

As the TD films were advocated to wear for long time period, the quality, efficacy and safety of the device is critical. In this scenario, TD device derived from poly(vinyl alcohol) (PVA) gels is explored due to its physiological inertness, significant hydrophilicity and biocompatibility. Moreover PVA can avoid skin occlusion as it is permeable to water vapor and hence not a skin irritant [16,17]. These unique features of PVA inspired our group to use them in combination with CGG for developing a novel TD therapeutic system. Literature reported that crosslinking treatment has appeared as a crucial approach to upgrade the performance of PVA films [18]. Cross-linked hydrogels of PVA can be easily prepared by crosslinking its hydroxyl group with borax to control the moisture effect on PVA as higher swelling produce rapid release of therapeutic cargoes *via* an exchange process. PEC films were then fabricated based on the electrostatic interaction between CGG and PVA.

The utilization of high molecular weight PVA improves the mechanical strength and encapsulation efficiency of the film. Literature stated that the skin adhesion behavior of a TD patch is critical to its quality, safety and efficacy [19]. In general the adhesion performance of polymers enhances with increase in molecular weight. However above a particular level, the adhesion strength decreases as higher molecular weight polymers reduces the wettability ascribed to the entanglement effect. The entangled polymer chain does not flow efficaciously to create sufficient wettability on substrate and reduces the adhesion performance [20]. The patches with poor adhesion strength adversely affect therapeutic efficiency as it produces improper dosing. Moreover, poorly adhered device may fall off and the accidental exposure of these fallen devices to children and others cause severe health issues. In the present investigation, nanocellulose (NC) is incorporated in the device to enhance the tensile properties of the device without reducing the adhesion strength. Nanocellulose was utilized by many research groups as a reinforcing phase because of its high elastic modulus in both axial and transverse direction so as to gain significant reinforcing effect [21].

Apart from several advantages associated with TD delivery system, the transportation of hydrophilic drugs across the skin still remains onerous due to the extremely ordered architecture of stratum corneum (SC) [22]. Literature stated that GNP seem to be an ideal material to disrupt SC barrier due to their nano metric size and non-deformable shape compared to chemical penetration enhancers. GNP could instigate transient and reversible openings on SC as a result of their interactions with intercellular lipids [23]. As a result GNP could vanquish the difficulty of overcoming the SC barrier and provide easy transportation of therapeutic molecules. Moreover doping of GNP on PEC film improves the resistance of the membrane to damages caused by storage time and hence demonstrates better shelf life for the TD device [24]. The GNP-NC nanocomposite was reinforced in the PEC membrane with GNP and NC to disrupt the SC barrier and improve the mechanical properties, respectively.

This project focused to develop DH loaded PEC based TD film and to assess their physicochemical characteristics and stability over time. Finally the *in vitro* DH permeation was investigated in rat skin using modified Franz diffusion cell to evaluate its therapeutic applicability.

2. Experimental section

2.1. Materials

Gold (111) chloride trihydrate ($HAuCl_4{\cdot}3H_2O$), and sodium citrate dihydrate (Na_3Cit) were purchased from Sigma-Aldrich (USA). (3-Chloro-2-hydroxypropyl)trimethyl ammonium chloride (CHPTAC) and diltiazem hydrochloride (DH) were supplied by Tokyo Chemical Industry (Japan). Guar gum (GG) and Polyvinyl alcohol (PVA) 98–99% hydrolyzed (MW − 31,000–50,000) were purchased from Sigma-Aldrich (USA). Cellulose was obtained from HiMedia laboratories (Mumbai). Di-sodium tetraborate, NaOH and all other solvents were purchased from Merck specialities Pvt Ltd. (Mumbai). All aqueous solutions were prepared with deionized water.

2.2. Methods

2.2.1. Synthesis of nanocellulose

Nanocellulose was prepared by the acid hydrolysis of cellulose as described elsewhere [25].

2.2.2. Synthesis of GNP-NC nanofiller

GNP-NC nanofiller was prepared by the reduction of $HAuCl_4{\cdot}3H_2O$ with sodium citrate dihydrate (Na_3Cit) in an aqueous suspension of NC [26]. Briefly 1.0 mL 30 mM Na_3Cit was added to 8.0 mL aqueous suspension of NC (23 mg/mL). The resulting mixture was stirred for 2 h. Next, 0.50 mL 20 mM $HAuCl_4$ was added. The solution was maintained at 60 °C for 1 h, resulting in the development of GNP-NC composite. The product was centrifuged and washed with deionized water until the supernatant became colorless.

2.2.3. Synthesis of CGG

Quaternized GG was synthesized by reacting GG with CHPTAC in the presence of NaOH. First a 2.0 wt% solution of GG was prepared by dissolving 1.0 g GG in 50.0 mL deionized water. About 5.0 mL 10.0 wt % NaOH solution was mixed with the prepared GG solution, while stirring at room temperature. After vigorous mixing for 2 h, 10.0 mL 5.0 wt% CHPTAC solution was slowly introduced into the mixture using a dropping funnel. The reaction was continued for 12 h maintained at 50 °C and then neutralized with 10.0 wt% HCl. The product was precipitated with ethanol and poured into a dialysis bag. The dialysis was continued until the complete removal of chloride ions and the dialyzed CGG was freeze dried to obtain CGG as white powder [15].

2.2.4. Preparation of GNP-NC reinforced PEC film containing DH

The nanofiller loaded PEC film was prepared as follows. First borax powder was dissolved in an aqueous solution containing designed concentration of CGG and nanofillers to acquire a solution with 0.40 wt % of borax. A weighed amount of PVA was dissolved in 25.0 mL water and added to the mixture. The solution was stirred vigorously to obtain a uniform dispersion of nanofillers. The obtained formulations were solution cast into films onto petri plates. The obtained films were placed in a desiccator. The films with 0, 1.0, 4.0, 7.0, and 10.0 wt% of nanofillers were prepared and abbreviated as CGG-PB, CGG-PB-1, CGG-PB-4, CGG-PB-7 and CGG-PB-10, respectively. To prepare DH loaded TD device, DH was added in equal proportion (1 mg) in all formulations and ultrasonicated for 30 min for adequate drug-matrix interaction. The thickness of the films was measured using thickness gauge (S. C. Dey & CO, India). To determine the drug encapsulation efficiency (DEE), accurately weighed DH loaded films were dispersed in deionized water and ultra sonicated for 1 h. The fully dispersed samples were then centrifuged and the supernatant was used for investigating the DEE using Eq. (1).

$$\mathrm{DEE}(\%) = \frac{\text{Total amount of DH} - \text{Free DH}}{\text{Total amount of DH}} * 100 \quad (1)$$

2.2.5. Characterization and analysis

^1H and ^{13}C NMR spectrum of CGG was recorded in D_2O at room temperature on a Bruker Avance 500 MHz NMR spectrometer. Infrared measurements of the prepared materials were made with a fully computerized Agilent Cary ATR spectrometer in the range 4000–650 cm^{-1}. High-resolution TEM image of GNP-NC was obtained using FEI, TECNAIS Twin microscopy operating at 100 kV. After ultrasonication, the test solution was drop casted on a formvar coated copper TEM grid and dried at room temperature. The surface morphology of the materials