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An interfacially plasticized electro-responsive hydrogel for transdermal electro-activated and modulated (TEAM) drug delivery

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ABSTRACT

This paper highlights the use of hydrogels in controlled drug delivery, and their application in stimuli responsive, especially electro-responsive, drug release. electro-conductive hydrogels (ECHs) displaying electro-responsive drug release were synthesized from semi-interpenetrating networks (semi-IPNs) containing a poly(ethyleneimine) (PEI) and 1-vinylimidazole (VI) polymer blend as the novel electro-active species. The semi-IPNs are systems comprised of polyacrylic acid (PAA) and poly(vinyl alcohol) (PVA). This paper attempts to investigate the various attributes of the electro-responsive ECHs, through institution of a statistical experimental design. The construction of a Box–Behnken design model was employed for the systematic optimization of the ECH composition. The design model comprised of three variables, *viz.* poly(ethyleneimine) volume; 1-vinylimidazole volume; and applied voltage, critical to the success of the formulation. Electro-responsive drug release was determined on formulations exposed to varying environments to ascertain the optimal environment for the said desired release. A comparison method of formulation water content and swelling through gravimetric analysis was also conducted. Matrix resilience profiles were obtained as an insight to the ability of the ECH to revert to its original structure following applied stress. Response surface and contour plots were constructed for various response variables, namely electro-responsive drug release, matrix resilience and degree of swelling. The outcomes of the study demonstrated the success of electro-responsive drug release. The findings of the study can be utilized for the development of electro-responsive delivery systems of other drugs for the safer and effective drug delivery. Volumes of poly(ethyleneimine) (>2.6 mL) and 1-vinylimidazole (>0.7 mL), resulted in ideal therapeutic electro-responsive drug release (0.8 mg) for indomethacin. Lower amounts of poly(ethyleneimine) and amounts of 1-vinylimidazole ranging from 0.2 to 0.74 mL are consistent with greater than 1.6 mg release per stimulation. Swelling of <25–45% was seen.

1. Introduction

Controlled-release formulations of opioid analgesics are widely assumed to be less subject to abuse than their immediate-release counter-parts in their ability to provide better quality of pain relief (Fisher, 2004). Drug delivery has been defined by Flynn (1979) as 'the use of whatever means possible, be it chemical, physico-chemical or mechanical, to regulate a drug's access rate to the body's central compartment, or in some cases, directly to the involved tissues". Drug delivery accounts for the carrier, the target and the route. It has advanced into a plethora of devices or processes that are designed to make therapeutic agents more efficacious through modified release, augmented therapeutic index and bioavailability, and enhanced patient acceptance and patient compliance. Advancements in drug delivery technology have thus proven to bring commercial and therapeutic value to drug delivery products.

The unique capabilities of hydrogels allows for an electric current to be used as an environmental signal in the induction of a required hydrogel response (Qiu and Park, 2001). The use of an electric-stimulus offers advantages such as the duration of electric pulses, intervals between pulses, the availability of equipment which allows precise control with regards to the magnitude of current, *etc.* (Murdan, 2003). Currently a large volume of literature exists on the *in vivo* use of electric currents, in the form of electroporation and iontophoresis, in the field of transdermal and

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dermal drug delivery, with the safe limits of electric field strengths been determined (Delgado-Charro and Guy, 2001; Murdan, 2003; Vanbever and Preat, 1999).

Electro-conductive hydrogels (ECHs) are composed of polyelectrolytes or electroactive polymers (EAPs) such as polyaniline and its derivatives (Bajpai et al., 2008; Qiu and Park, 2001). The EAPs have been the key focus in the research for their unique electrochemical, electrical and/or optical properties (Bajpai et al., 2008; Guiseppi-Elie, 2010; Qiu and Park, 2001; Vanbever and Preat, 1999). Various EAPs are in existence which may be used as Electro-Conductive Polymers (ECPs) or conjugated polymers, such as polypyrrole (Geetha et al., 2006; Iseki et al., 1995), polythiophene (Chen et al., 2012), polydimethylsiloxane (Chen et al., 2012) poly(methyl methacrylate) (Posadas and Florit, 2004; Small et al., 1997), poly(3,4-ethylenedioxythiophene) (PEDOT) (Richardson-Burns et al., 2007) and polyvinyl alcohol (PVA) (Chen et al., 2012). The reason of their intrinsic semiconducting nature is the fact that all the macromolecules have unique redox properties, which allow controlled ionic transport through the polymeric membrane (Pernaut and Reynolds, 2000).

As a means to increase the limited number of electro-responsive species, an electro-responsive hydrogel incorporating a novel poly(ethyleneimine)-vinylimidazole blend was developed and is thus discussed herein. The proposed drug release mechanism is that the ECH will allow for drug release only in response to an applied electric field. Once the electric field is removed drug delivery will cease.

As for any formulation, design criteria (material selection and network fabrication) are crucial for drug delivery as well as for the mathematical modelling of drug release. These criteria are essential in governing the mode and rate of drug release from hydrogel matrices. Prior to the fabrication of the hydrogel and drug loading, these criteria have to be evaluated. These criteria include transport properties such as physical properties and molecule diffusion as well as structural properties and stimuli responsiveness and biological properties such as biocompatibility (Lin et al., 2006). For a formulation comprised of an electro-responsive species within a hydrogel matrix, three design criteria are apparent: electro-responsive drug release, degree of swelling and matrix resilience. These criteria will be further elaborated on. The use of such electroactive polymers offers means to combine the desired and useful properties exhibited by the individual native polymer-gel components in the ECH system with a simultaneous enhancement of selected properties. As a result, in this investigation a new strategy for the preparation of an electro-conductive hydrogel, with optimization through a Box–Behnken design experimental design is reported on.

2. Materials and methods

2.1. Materials

Poly(ethyleneimine) solution (M_w750,000; 50%, w/v) 1-vinylimidazole (≥99%), Indomethacin (≥99%), Poly(vinyl alcohol) (M_w89,000–98,000, 99+% hydrolysed), Acrylic acid (anhydrous, 99%), *N*,*N*′-methylenebisacrylamide (≥99.5%) and Potassium Persulfate (≥99.0%) were all purchased from Sigma–Aldrich (St. Louis, USA). All other ingredients were of analytic grade and were used as received.

2.2. Preparation of an electro-responsive poly(ethyleneimine)-1-vinylimidazole-polyacrylic acid hydrogel

Aqueous solutions of the electro-responsive release hydrogel (6%, w/w) were prepared by dissolving the weighed amount of PVA in a 1 M NaOH solution. The poly(ethyleneimine) solution and 1-vinylimidazole were added in the quantities obtained as per a Box–Behnken design (Table 1) as an electro-active species and plasticizer respectively. Subsequently, indomethacin (100 mg) and acrylic acid (0.6 mL) was added. *N*,*N*′-Methylenebisacrylamide (100 mg) was then added as a cross-linking agent to facilitate the formation of a semi-interpenetrating hydrogel network (IPHN), instituting vinyl addition polymerization to increase the interconnectivity of the matrix. The electro-responsive transitions of the PEI- PAA IPHN were ascertained.

2.3. Synthesis validation of the ECHs

Fourier transform infrared spectroscopy (FTIR) utilizing a Spectrum 100 FTIR Spectrometer (Perkin-Elmer, Beaconsfield, BUCKS, UK) was used to detect the vibration characteristics of chemical functional groups in the ECH samples. FTIR was performed on the native polymers involved in the blend as well as the ECH formulation as a means of validating the successful synthesis of the polyelectrolyte ECH. Samples were placed on a diamond crystal and processed by the universal ATR polarization accessory for the FTIR spectrum series at a resolution of 4 cm^{-1}. Each sample was analyzed at wave numbers ranging from 650 to 4000 cm^{-1}.

2.4. Experimental design and constraint optimization of the ECH

A model-independent approach (Minitab® V15, Minitab Inc., PA, USA) was used to optimize the ECH. Statistical optimization using a Box–Behnken design model was employed to ascertain the ideal combination of electro-responsive polymeric species (X_{1+2}), as well as the ideal voltage (X_2) required capable of attaining desirable drug release, swelling and matrix resilience efficiencies. Table 1 summarizes the fifteen experimental runs studied, their factor combinations, and the translation of the coded levels to the experimental units employed during the study.

2.5. Response surface analysis as per Box–Behnken design

Response surface analysis of various response variables was carried out employing Minitab® statistical software (V15, Minitab Inc., PA, USA). The results were demonstrated using response surface and contour plots derived for the measured responses (electro-responsive drug release, degree of swelling and matrix resilience), based on the experimental model.

2.6. In vitro drug release studies

2.6.1. Determination of the effect of an enhanced conductive environment on the drug release profiles of the ECH system

Aluminium foil was used as means of method modulation to determine the effects on drug release. In addition the foil proves that the ECH is not electro-sensitive by providing a constant surface area for an enhanced conductive environment. *In vitro* drug release studies on the ECH were performed as detailed: hydrogel samples were immersed in 20 mL of phosphate buffered saline (PBS) (pH 7.4; 37 °C), and a potential difference as per the Box–Behnken design was applied to each corresponding formulation respectively using a potentiostat/galvanostat (PGSTAT302N, Autolab, Utrecht, Netherlands). An aluminium foil covered the ECH on which two electrodes were directly placed. A 5 mm platinum electrode served as the cathode and the anode, a 5 mm gold electrode. PBS aliquots (2 mL) were sampled at hourly intervals. The aliquots were removed and were replaced with the original removed aliquots both prior to and after the application of the electrical stimulation in order to maintain sink conditions. Filtered samples (0.22 μm) were analyzed for indomethacin content using