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Development of gellan gum containing formulations for transdermal drug delivery: Component evaluation and controlled drug release using temperature responsive nanogels

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ABSTRACT

Enhancing skin permeation is important for development of new transdermal drug delivery formulations. This is particularly relevant for non-steroidal anti-inflammatory drugs (NSAIDs). To address this, semisolid gel and solid hydrogel film formulations containing gellan gum as a gelling agent were developed and the effects of penetration enhancers (dimethyl sulfoxide, isopropyl alcohol and propylene glycol) on transport of the NSAID diclofenac sodium was quantified. A transwell diffusion system was used to accelerate formulation development. After 4 h, diclofenac flux from a superior formulation of the semisolid gel or the solid hydrogel film was 130 ± 11 μg/cm^2 h and 108 ± 7 μg/cm^2 h, respectively, and significantly greater than that measured for a currently available diclofenac sodium topical gel (30 ± 4 μg/cm^2 h, $p < 0.05$) or solution formulation (44 ± 6 μg/cm^2 h, $p < 0.05$) under identical conditions. Over 24 h diclofenac transport from the solid hydrogel film was greater than that measured for any new or commercial diclofenac formulation. Entrapment of temperature-responsive nanogels within the solid hydrogel film provides temperature-activated prolonged release of diclofenac. Diclofenac transport was minimal at 22 °C, when diclofenac is entrapped within temperature-responsive nanogels incorporated into the solid hydrogel film, but increased 6-fold when the temperature was increased to skin surface temperature of 32 °C. These results demonstrate the feasibility of the semisolid gel and solid hydrogel film formulations that can include thermo-responsive nanogels for development of transdermal drug formulations with adjustable drug transport kinetics.

1. Introduction

Transdermal drug delivery is an alternative to oral or parenteral administration (Prausnitz and Langer, 2008; Rehman and Zulfakar, 2014) for long-term, low-dose systemic delivery of drugs such as nicotine (Prausnitz and Langer, 2008), hormones (Kopper et al., 2008) and analgesics (Prausnitz and Langer, 2008). For localized subdermal delivery of drugs such as analgesics (Singh and Roberts, 1994), transdermal drug delivery provides lower levels of systemic drug exposure that reduces the side effects (Prausnitz and Langer, 2008) and avoids gastrointestinal and hepatic first pass metabolic degradation of the drug (Vaile and Davis, 1998). However, the natural barrier properties of the skin make transdermal drug delivery a challenging task. Development of novel formulations to enhance drug permeation while providing drug release in a controlled manner is needed.

Drug penetration into the skin from a transdermal drug delivery formulation is primarily regulated by penetration enhancers that

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interact with or modify the epidermis, the major skin transport barrier (Parhi et al., 2012). Dimethyl sulfoxide (DMSO), isopropyl alcohol and propylene glycol are commonly used penetration enhancers in transdermal formulations (Liu et al., 2009; Marren, 2011) that alter the skin barrier properties and modify the drug transport profile (Prashant, 2006). Penetration enhancers are incorporated in transdermal drug delivery systems formulated as solutions, semisolid gels, or hydrogel films (BoddÉ et al., 1989; Prashant, 2006; Rehman and Zulfakar, 2014). The rate of drug penetration is dependent on the delivery system (Asbill and Bumgarner, 2007; Mahalingam et al., 2007) and can be modulated by varying the composition and concentration of the gelling polymer and penetration enhancers (Asbill and Bumgarner, 2007). Controlling drug permeation in transdermal delivery formulations requires tailoring the mixture of excipients and penetration enhancers during *in vitro* development.

In addition to formulation strategies to modulate skin permeation of drugs, there is a growing interest in developing temperature-responsive systems (Zhang et al., 2005). One approach to modulate drug release involves incorporating thermo-responsive nano- or microgels (Acciaro et al., 2011; Lynch et al., 2005; Sivakumaran et al., 2011) into hydrogel formulations. In addition to temperature, drug release rate can be regulated by physical or covalent cross-linking nanogels with the gelling agent in the hydrogel formulation (Schexnailder and Schmidt, 2009). Incorporation of stimuli-responsive nanomaterials can provide an additional level of control over the drug release kinetics, promising to achieve controlled stimuli-triggered delivery (Acciaro et al., 2011; Lynch et al., 2005; Sivakumaran et al., 2011). Despite the progress made in designing stimuli-responsive drug delivery systems and the apparent advantage of nanogels and microgels embedded into the bulk hydrogels, transdermal formulations with encapsulated temperature-responsive nanomaterials have rarely been explored.

Among the different polymers used in pharmaceutical formulations, gellan gum has gained attention for use in controlled drug release systems (Alhaique et al., 1996; Kesavan et al., 2010; Lee et al., 2010). Gellan gum is an anionic polysaccharide with excellent biocompatibility and adjustable mechanical properties that degrades into non-toxic byproducts (Matricardi et al., 2009). Gellan gum can be prepared in semisolid gels, hydrogel films and has been used to entrap nanomaterials (Laurence et al., 1993; Lopez-Cebral et al., 2013; Osmalek et al., 2014; Posadowska et al., 2015; Salim et al., 2012). In addition, gellan gum has been used for the formulation of nanogels for delivery of prednisolone and in the stabilization of gold nanoparticles (D'Arrigo et al., 2012; Dhar et al., 2008). The film forming ability of gellan gum makes it an ideal material for hydrogel transdermal patches. The high water content of hydrogels facilitates drug permeation due to skin hydration with less irritation than other polymeric patches (BoddÉ et al., 1989; Mazzitelli et al., 2013).

Improvement of transdermal drug delivery systems requires quantifying the effect of penetration enhancers on drug release *in vitro*. This is often carried out using human skin (OECD, 2004), animal skin (Puglia et al., 2006), epidermis preparations (Vitorino et al., 2013), or synthetic skin equivalent membranes (Uchida et al., 2015). Franz diffusion chambers (Ng et al., 2010) are widely used to quantify drug transport across skin or a synthetic skin membrane. Although frequently used, Franz diffusion chambers are expensive, cumbersome to operate, require constant monitoring and manipulation to measure drug flux (Scheindlin, 2004; Sinko et al., 2012) and do not readily incorporate into available analytical equipment. Thus, there is a need for a simple and reliable method to quantify drug transport *in vitro* to accelerate development of transdermal drug formulations.

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID) for osteoarthritis pain management mostly prescribed as an oral medication (Todd and Sorkin, 1988). However, oral diclofenac administration causes serious side effects such as gastrointestinal tract and hepatic damage (Akarca, 2005), particularly in older patients (Stanos and Galluzzi, 2013). To avoid these complications, transdermal delivery of diclofenac to the painful joint has proven effective for many patients (Kienzler et al., 2010). In the present work, semisolid gel and solid hydrogel film formulations incorporating gellan gum as a hydrogel and diclofenac sodium were developed. Diclofenac transport was quantified using a transwell diffusion system and a synthetic membrane designed for transdermal transport (Strat-M, 2016; Joshi et al., 2012; Uchida et al., 2015) and compared to transport with currently used topical diclofenac formulations. To further improve control of the drug release, diclofenac-loaded temperature-responsive nanogels were incorporated into the solid hydrogel film. We believe that our work provides a new prospective for developing "intelligent" transdermal delivery systems with enhanced drug permeation and tunable drug delivery properties.

2. Materials and methods

Isopropyl alcohol, propylene glycol, DMSO, pharmaceutical grade heavy mineral oil (Mineral oil), Tween 20, phosphate buffered saline (PBS, pH 7.4), methanol (HPLC grade), acetonitrile (HPLC grade), water (HPLC grade), potassium persulphate (KPS), sodium dodecyl sulfate (SDS), acrylic acid (CH_2 = CHCOOH), sodium bicarbonate ($NaHCO_3$) paraffin wax, 22 millimeter round glass coverslips, cell scrapers, large orifice pipettes, parafilm and 96 well deep well plates were purchased from Fisher Scientific (Waltham, MA). Diclofenac sodium, N-vinylcaprolactam, and gellan gum were purchased from Sigma (St. Louis, MO). Diclofenac-$^{13}C_6$ sodium salt was purchased from Toronto Research Chemicals (Toronto, ON, Canada). Six well-plates and 24 mm transwell inserts were purchased from Corning Life Sciences (Tewksbury, MA). Strat-M membranes (25 mm diameter) were purchased from EMD Millipore (Billerica, MA). Commercial diclofenac sodium semisolid gel and solution formulations, Voltaren Emulgel® (1 wt% diclofenac sodium) (Novartis) and Pennsaid solution® (1.5%wt diclofenac sodium) (Nuvo Research) were obtained from a local pharmacy.

2.1. Preparation of semisolid gel and solid hydrogel film formulations

The base semisolid gel composition was prepared in the weight ratios listed in Table 1 as follows: water, propylene glycol, DMSO, diclofenac sodium and Tween 20 were mixed in a 20 ml scintillation vial. Propylene glycol, Isopropyl alcohol and DMSO were selected due to their wide use as penetration enhancers (Williams and Barry, 2004). Mineral oil and Tween 20 were selected for the oil phase and the surfactant, respectively for the semisolid gel (Nikumbh et al., 2015; Williams and Barry, 2004). Gellan gum was slowly incorporated into the liquid mixture under constant stirring and dissolved by heating at 75 °C. When the gellan gum dissolved, mineral oil was added and the mixture was slowly cooled under high speed stirring (1200 rpm) for 30 min until an emulsion formed. Calcium chloride solution (150 μl at 0.5 mM) was added as a cross linking agent. Isopropyl alcohol was added to the mixture under high speed stirring. To improve the homogenization of the base semisolid gel, the mixture was prepared as described above, but after the addition of isopropyl alcohol and calcium chloride the mixture was homogenized using a high-speed homogenizer (Omega, Stamford CT) at 32,000 rpm for 20 min on an ice bath.