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Development and evaluation of a polyvinyl alcohol based topical gel

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ABSTRACT

Topical drug delivery systems provide localized drug action. A hydrophilic polymer such as polyvinyl alcohol is a multi-faceted excipient that can be used as a coating agent, lubricant, stability enhancer and viscosity-increasing agent. The objective of our study was to evaluate the use of polyvinyl alcohol polymer in preparing a topical gel with a diclofenac salt as the pharmaceutical active. The gel was characterized for its rheological and other properties and its effectiveness to deliver drug through dermatomed human skin compared to a similar commercially available topical gel. Topical polyvinyl alcohol based gel was prepared with propylene glycol, isopropyl alcohol, hydroxypropyl cellulose, and Transcutol® P. Formulation was tested for pH, rheology, adhesion, spreadability, skin irritation, *in vitro* drug distribution in skin, and permeation. The formulated topical gel delivered an average cumulative drug amount of 22.85 ± 9.41 μg/cm2 across skin and delivered 10.30 ± 9.09 μg/cm2 in the skin over 24 h. The mean cell viability value of 107.41± 40.81% rendered by *in vitro* skin irritation test confirmed the formulated gel to be non-irritant to human skin. In conclusion, a safe efficacious and rheologically competent polyvinyl alcohol polymer based topical diclofenac gel was developed and characterized successfully.

1. Introduction

The increasing interest in topical drug delivery we see today is a reflection of its advantages and opportunity to create reformulations of established drugs. The rise in demand for convenient self-administrating drug delivery options poses major opportunities for the advancement of topical formulations. Furthermore, advances in modern technologies and polymer sciences are resulting in a larger number of pharmaceuticals being delivered topically for dermal and transdermal delivery. Topical drug delivery systems to treat superficial disorders, systemic ailments and for use as cosmetics are copiously varied, complex, multicomponent, heterogeneous compositions that requires extensive experimentation to attain the final desired formulation. It allows application onto the site of action resulting in numerous advantages: the ability to deliver pharmaceuticals more selectively to the site of interest, improved patient compliance, self-administration, sustained release, reduced fluctuation in drug levels and avoidance of systemic side effects by bypassing gastrointestinal track and first pass metabolism [1]. As a result, several topical semi-solid preparations such as gels, ointments, lotions and creams are currently on the market. Among these, gels are semi-solid preparations that comprise of a dispersion phase of inorganic or organic molecules interspersed by liquid in a three dimensional matrix [2]. Apart from many advantages of topical delivery, gels have a cooling effect upon application, provide quick onset of action and significant long-term efficacy compared to conventional treatments along with good safety profile and high patient satisfaction [3].

The rigidity of a gel structure originates from a network composed by physical or chemical interlinking of particles and the type of force responsible for interlinking determines the structure and properties of gel. While there can be many components in a gel, the fundamental component required to form the structural network of the gel are polymers. Topical gels can be prepared with naturally occurring polymers, natural polymers that are chemically modified or chemically synthesized polymers. Drug release from gel mainly depends upon the physicochemical properties of the drug and its polymer. Polymer blends have been used to control drug release rates and polymers can be blended in different ratios

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to combine the advantages of individual polymers [4,5]. In order to achieve a high degree of swelling, synthetic polymers like polyvinyl alcohol (PVA) that are water-soluble when in non-cross-linked form are commonly used [6,7]. Physical properties of PVA such as solubility, flexibility, tensile strength, adhesiveness, pH, viscosity, loss on drying, melting point, refractive index, heavy metals and residue on ignition vary with their molecular weight (20,000–200,000) and grade used. PVA polymer due to its extensive range of physical properties and good biocompatibility has been used in biomedical applications such as wound dressing, wound management, drug delivery systems, artificial organs and contact lenses [7–13]. Despite its appealing properties, its use is limited to topical patches and jellies, tablets and ophthalmic solutions [14].

In recent years, a combination of polymers have proven to be successful in obtaining polymeric structures of specific properties. For example, research has demonstrated the blending of PVA with natural biopolymers such as hydroxypropyl cellulose (HPC) can change the micro-molecular and macromolecular structure of the gel leading to improved thermal stability and decreased crystalline nature of the polymeric blend. Previous investigations have reported the advantages of using HPC alone or in combination with PVA to formulate gels. HPC belongs to the group of cellulose ethers soluble in water as well as in polar organic solvents, which makes it versatile to combine aqueous and non-aqueous solvents [15,16].

In our current study, we used the combination of PVA and HPC to formulate a diclofenac sodium topical gel to provide local and systemic anti-inflammatory effects. Diclofenac, a member of non-steroidal anti-inflammatory drug (NSAID), is used by more than one billion patients and ranks as the eighth largest selling drug in the world [17]. The aim of the study was further extended to evaluate the physicochemical properties of the formulated gel and compare the *in vitro drug* distribution and permeation to commercially available Voltaren® gel using dermatomed human skin.

2. Material and methods

2.1. Materials

PVA polymer [1.41350 PVA 4 - 88 EMPROVE ® exp Ph Eur, USP, JPE - Viscosity (4%, water) - 3.4–4.6 mPa s; MW: ~31,000 Da, 1.41352 PVA 26 - 88 - EMPROVE ® exp Ph Eur, USP, JPE - Viscosity (4%, water) - 22.1–29.9 mPa s; MW: ~160,000 Da and 1.41353 PVA 40 - 88 EMPROVE ® exp Ph Eur, USP, JPE - Viscosity (4%, water) - 34–46 mPa s; MW: ~205,000 Da] was kindly gifted by MilliporeSigma, a business of Merck KGaA (Darmstadt, Germany). Diclofenac epolamine was obtained from BOC Sciences (Shirley, NY, USA). Diclofenac sodium and diethylamine were obtained from Sigma-Aldrich (St. Louis, MO, USA). Isopropyl alcohol and Transcutol® P were obtained from PHARMCO-AAPER (Brookfield, CT, USA) and Gattefossé (Saint-Priest Cedex, France) respectively. Propylene glycol and pH 7.4 phosphate buffer saline were obtained from EKI Industries (Joliet, IL, USA) and Fisher Scientific (Fairlawn, NJ, USA) respectively. Hydroxypropyl cellulose was kindly gifted by BASF - The Chemical Company (Tarrytown, NY, USA). All other reagents of analytical grade were used.

2.2. Formulation preparation

Gels were formulated using three different grades of PVA [1.41350 PVA 26-88 - 1.41352 PVA 26 - 88 and 1.41353 PVA 40 - 88]. PVA (12% w/v) polymer solution using each of the three grades were prepared by heating deionized water to 95 °C followed by gradual addition of polymer and mixed for 4 h until a homogenous solution was formed. The drug was solubilized in a solvent mix of propylene glycol, isopropyl alcohol and Transcutol® P. HPC was then gradually added to the drug-solvent mixture and homogenized using a Tissue Homogenizer (THq, Omni International, Kennesaw, GA, USA). Previously prepared PVA solution was then added to this homogenized mixture and further blended with low shear mixing overnight using a rotating mixer (Gilson, Lewis Center, OH, USA) to form a clear gel.

2.3. Rheological evaluation

Viscoelastic parameters such as elastic property or storage (G′) modulus, viscous or loss (G″) modulus and overall change in the viscoelastic property or complex viscosity (η^*) of PVA based gel and innovator gels were measured using a rheometer (Anton Paar USA, Ashland, VA, USA) at skin temperature (32 °C). Amplitude sweep test followed by frequency sweep test were conducted with an angular frequency (ω) ranging from 100 to 0.1 radians/second using a rheometer spindle PP25/S of 24.987 mm surface diameter and a gap setting of 0.1 mm to assess the viscoelasticity of the formulations.

2.4. Tack and spreading efficiency

The adhesion and spreading efficiency of PVA and innovator gel was evaluated using a texture analyzer (Texture Technologies Corp, Marietta, GA, USA) with a 2.5 cm diameter probe. The instrument was calibrated for force and height and the parameters such as contact force and hold time were optimized with a return speed of 5 mm/s before testing. The probe was allowed to adhere to the substrate at an approaching speed of 0.5 mm/s with a contact force and hold time of 20 g and 10 s respectively. Subsequent pulling of the probe from the gel resulted in debonding between the surfaces, at which point the adhesion value was recorded. The spreading efficiency was evaluated and recorded based upon the distance spread by the gel because of the force and hold time applied by the probe on the substrate.

2.5. Skin resistance and thickness

Dermatomed human skin (New York Fire Fighters, NY, USA) was tested for thickness using material thickness gauge (0-1in/0-25 mm, Electromatic Equipment Co., Inc. Cedarhurst, NY, USA) and skin barrier property was measured to ensure the integrity using electrical resistance. Skin resistance was measured using silver/silver chloride electrodes, Agilent 33220 A, 20 MHz Function/arbitrary waveform generator and 34410 A 6 ½ digital multimeter (Agilent Technologies, CA, USA). Skin was mounted between the receptor compartment of vertical Franz diffusion cells containing 10 mM phosphate buffer solution (PBS) at pH 7.4 and a donor compartment containing 0.3 mL of the same. The tip of the silver chloride electrode was placed in the donor compartment without touching the skin and the silver wire was placed in the receptor compartment. A frequency of 10 Hz, amplitude of 100 mV and a load resistor of 100 kΩ (R_L) were connected in series. The drop in voltage across the circuit (V_O) and skin (V_S) was recorded as displayed on the multimeter. Skin resistance (R_S) was calculated and recorded in kΩ/cm^2.

2.6. In vitro permeation study

The *in vitro* permeation study was conducted using vertical Franz diffusion cells for 24 h. The thickness and integrity tested and approved skin samples were placed on the receptor compartment of Franz diffusion cells that contained 5 mL of 10 mM pH 7.4 PBS