CHEMICAL ENGINEERING RESEARCH AND DESIGN XXX (2014) XXX–XXX

Contents lists available at ScienceDirect

Chemical Engineering Research and Design

journal homepage: www.elsevier.com/locate/cherd

Development of topical gel containing aceclofenac-crospovidone solid dispersion by "Quality by Design (QbD)" approach

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A B S T R A C T

This article describes the development, optimization, and evaluation of Carbopol 940 topical gel containing aceclofenac-crospovidone (1:4) solid dispersion using "Quality by Design (QbD)" approach based on 2^3 factorial design. The effect of crospovidone, tri-ethanolamine, and ethyl alcohol amount on the drug permeation profile of the topical gel containing aceclofenac-crospovidone solid dispersion was optimized by 2^3 factorial design. The optimized gel showed improved permeation profile with cumulative drug permeation of $26.262 \pm 2.157\%$, and permeation flux of $0.059 \pm 0.011\ \mu g/cm^2/h$. These gels were characterized by pH, viscosity, gel strength and FTIR study. The *in vivo* anti-inflammatory activity of the optimized gel was evaluated in rats using carrageenan-induced rat-paw oedema model and found excellent anti-inflammatory comparable with a marketed gel without producing any skin irritation.

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Keywords: Topical gel; Carbopol 940; Aceclofenac; Factorial design; QbD; Optimization

1. Introduction

In general, gels are formed from a liquid phase that has been thickened with other components. Among them, Carbopol gels offer good alternatives to oil based topical formulations. Carbopols are polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol. They are readily hydrated to swell. Because of the hydrophilic nature, the cross-linked structures of Carbopols make them potential candidates for use as gel type formulation for topical use (Carnali and Naser, 1992; Garcia-Gonzalez et al., 1994). Topical use of these gels is advantageous, as they possess good rheological properties resulting in long residue times at the site of administration. Due to their extremely high molecular weight, they cannot penetrate the skin and offer good alternatives to oil based ointment formulations.

Aceclofenac, chemically [2-(2′,6′-dichlorophenyl)amino] phenylacetoxyacetic acid, is used as a non-steroidal anti-inflammatory drug (NSAID) indicated for the symptomatic treatment of pain and inflammation (Chakraborty et al., 2010). It is also used in the treatment of arthritis, osteoarthritis, rheumatoid arthritis and ankylosing spondylitis (Yadav et al., 2010). However, like other NSAIDs, oral administration of aceclofenac is also associated with gastrointestinal side effects like gastric ulceration, gastrointestinal bleeding and liver and kidney trouble (Insel, 1992). In view of adverse drug reaction associated with oral formulations, aceclofenac is increasingly administered by topical route (Heyneman et al., 2000). Furthermore, the topical route of administration eliminates side effects, increases patient compliance, avoids first-pass metabolism, and maintains the plasma drug level for a longer period. Aceclofenac has a poor aqueous solubility (Nagariya

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http://dx.doi.org/10.1016/j.cherd.2014.01.025

Please cite this article in press as: Jana, S., et al., Development of topical gel containing aceclofenac-crospovidone solid dispersion by "Quality by Design (QbD)" approach. Chem. Eng. Res. Des. (2014), http://dx.doi.org/10.1016/j.cherd.2014.01.025

et al., 2010) that may cause a problem of migrating through hydrophilic base.

Crospovidone is a synthetic polymer derived from the monomer of vinyl pyrrolidone by popcorn polymerization (Haaf et al., 1985). It is mainly used as disintegrant in tablets and capsules. Crospovidone has been used as a carrier of solid dispersion for various drugs to improve their aqueous solubility (Loganathan et al., 2000; Makiko et al., 2005). In the present study, an attempt was made to develop Carbopol 940 gel for topical application containing solid dispersion of aceclofenac using crospovidone as carrier to improve the skin permeation profile of aceclofenac using "Quality by Design (QbD)" approach.

QbD approach encompasses designing and developing formulations, in which manufacturing processes ensure predefined product specifications (Nayak et al., 2011). The important part of this approach is to understand how process and formulation parameters affect the product quality and subsequent optimization parameters with respect to final specifications (Maltesen et al., 2008). QbD refers to the achievement of certain predictable quality with desired and predetermined specifications. Therefore, a very useful component of the QbD is the understanding of various factors (variables) and their interactions by a desired set of experiments using a statistical tool (Menini et al., 2012). In the present investigation, the planned aceclofenac-loaded Carbopol 940 topical gel containing aceclofenac-crospovidone solid dispersion was optimized in terms of cumulative drug permeation through the excised mouse skin after 10 h (%) and permeation flux ($\mu g/cm^2/h$) by three-factor and two-level (2^3) factorial design. The considered factors were amount of crospovidone (mg), amount of tri-ethanolamine (ml) and amount of ethanol (ml). The selected QbD strategy allowed an efficient selection of the best formulation composition and of the most suitable experimental conditions in the shortest time and with the minimum number of experiments. The best formulation was studied for *in-vivo* pharmacodynamic performance in carrageen-induced rat paw oedema model and was compared with marketed gel formulation.

2. Materials and methods

2.1. Materials

Aceclofenac was obtained as the gift sample from Suyash Lab, India. Carbopol 940 and crospovidone were obtained as gift sample from C.I. Laboratories, India. Tri-ethanolamine and ethanol were commercially purchased from Merck, India and Bengal Chemical & Pharmaceuticals Ltd., India. All other reagents were of analytical grade and commercially available.

2.2. Preparation of aceclofenac-crospovidone solid dispersion

Aceclofenac-crospovidone (1:4) solid dispersion was prepared by solvent evaporation technique. Aceclofenac was dissolved in ethanol to get clear solution. Then, crospovidone was dispersed as fine particles and the solvent was removed by evaporation on a water bath at 60 °C. The dried mass was stored in desiccator until constant mass was obtained, pulverized and passed through sieve no. 22.

2.3. Characterization of aceclofenac-crospovidone solid dispersion

2.3.1. Saturation solubility measurement

The known excess samples (solid dispersions, physical mixture and aceclofenac) of 10 mg equivalent weight of aceclofenac was added to 10 ml of phosphate buffer saline, pH 7.4 and these samples were rotated at 20 rpm in a water bath (37 ± 0.5 °C) for 48 h. The samples were then filtered, suitably diluted, and analyzed by UV–vis spectrophotometer (Thermo Spectronic UV-1, USA) at 274 nm wavelength using appropriate blank solution.

2.3.2. Differential scanning calorimetric (DSC) analysis

DSC analyses of the pure aceclofenac, and aceclofenac-crospovidone (1:4) solid dispersion were performed. The samples were heated to remove the moisture. Then the samples (7 mg) were placed into a platinum crucible 40-μl aluminium pan in hermetically sealed condition, where α-alumina powder was used as a reference. Thermograms were recorded from 30 °C to 415 °C at the heating rate of 10 °C/min under a constant flow of an inert nitrogen gas atmosphere with the flow rate of 20 ml/min. These analyses were done using a differential scanning calorimeter (Perkin Elmer® Instrument, Pyris diamond, Osaka, Japan).

2.4. Preparation of Carbopol 940 gel containing aceclofenac-crospovidone solid dispersion

Carbopol 940 gels containing aceclofenac-crospovidone solid dispersion were prepared according to the literature with little modification (Dua et al., 2010). In brief for each formulation, required amount of aceclofenac-crospovidone solid dispersion equivalent to 150 mg aceclofenac was dissolved in ethanol and deionised water, respectively. Both the solutions are mixed together thoroughly. Then 100 mg of Carbopol 940, previously soaked in 6.50 ml of deionised water overnight, was added to the above mixture with stirring at 500 rpm by magnetic stirrer (Remi Motors, India) for 1 h. Finally, weighed quantity of tri-ethanolamine was added to obtain a clear gel.

2.5. Experimental design

For the optimization of Carbopol 940 gels containing aceclofenac-crospovidone solid dispersion, a 2^3 factorial design was employed. Amount of crospovidone (X_1, mg), amount of tri-ethanolamine (X_2, ml) and amount of ethanol (X_3, ml) were selected as independent variables (factors), which were varied at two levels (low and high). The cumulative drug permeation through the excised mouse skin after 10 h (CDP_{10}, %) and permeation flux (PF, $\mu g/cm^2/h$) were used as dependent variables (responses). Design-Expert 8.0.6.1 software (Stat-Ease Inc., USA) was used for generation and evaluation of the statistical experimental design. The matrix of the design including investigated factors and responses are shown in Table 2. For optimization, effects of various independent variables upon measured responses were modelled using following mathematical model equation involving independent variables and their interactions for various measured responses generated by 2^3 factorial design is as follows:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_1X_2 + b_5X_1X_3 + b_6X_2X_3$$

where Y is the dependent variable, while b_0 is the intercept, b_1, b_2, b_3, b_4, b_5, and b_6 are regression coefficients; X_1, X_2 and X_3

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