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Transdermal film-loaded finasteride microplates to enhance drug skin permeation: Two-step optimization study

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ABSTRACT

The goal was to develop an optimized transdermal finasteride (FNS) film loaded with drug microplates (MIC), utilizing two-step optimization, to decrease the dosing schedule and inconsistency in gastrointestinal absorption. First; 3-level factorial design was implemented to prepare optimized FNS-MIC of minimum particle size. Second; Box–Behnken design matrix was used to develop optimized transdermal FNS-MIC film. Interaction among MIC components was studied using physicochemical characterization tools. Film components namely; hydroxypropyl methyl cellulose (X_1), dimethyl sulfoxide (X_2) and propylene glycol (X_3) were optimized for their effects on the film thickness (Y_1) and elongation percent (Y_2), and for FNS steady state flux (Y_3), permeability coefficient (Y_4), and diffusion coefficient (Y_5) following *ex-vivo* permeation through the rat skin. Morphological study of the optimized MIC and transdermal film was also investigated. Results revealed that stabilizer concentration and anti-solvent percent were significantly affecting MIC formulation. Optimized FNS-MIC of particle size 0.93 μm was successfully prepared in which there was no interaction observed among their components. An enhancement in the aqueous solubility of FNS-MIC by more than 23% was achieved. All the studied variables, most of their interaction and quadratic effects were significantly affecting the studied variables (Y_1–Y_5). Morphological observation illustrated non-spherical, short rods, flakes like small plates that were homogeneously distributed in the optimized transdermal film. *Ex-vivo* study showed enhanced FNS permeation from film loaded MIC when compared to that contains pure drug. So, MIC is a successful technique to enhance aqueous solubility and skin permeation of poor water soluble drug especially when loaded into transdermal films.

1. Introduction

Benign prostatic hyperplasia (BPH) is considered as the most common proliferative disorders affecting older men (Welén and Damber, 2011). BPH can cause troublesome urinary symptoms such as intermittency, decreased urinary flow, straining, urgency, frequency, getting up during the night to urinate, and incomplete emptying (Tacklind et al., 2010). Finasteride (FNS) is considered the first specific competitive inhibitor of steroid type-II 5α-reductase. This enzyme is an intracellular bioactive component that converts testosterone to dihydrotestosterone (DHT). FNS was approved by U.S. Food and Drug Administration (USFDA) for the treatment of BPH and male pattern baldness (MPB) (Wilde and Goa, 1999). FNS decreases the prostatic DHT level by 70–90% and reduces the prostate size (Aggarwal et al., 2010). FNS belong to Class II in the Biopharmaceutical Classification System (BCS) which characterized by their high permeability and low solubility that represent the major factors affecting the development of successful therapeutic dosage form (Maria et al., 2013). FNS low solubility influences both the process of drug dissolution and the rate and the extent of drug bioavailability. Enhancing the dissolution rate of these categories can be achieved by improving their aqueous solubility which will be of high impact in their pharmacological effect (Kumar and Krishna, 2011). One of the most common mechanisms that could be employed to increase the aqueous solubility is drug micronization technique. In this process, the drug powder is reduced to a size between 1 and 10 μm which will result in increasing the surface area, solubility, dissolution rate and bioavailability for those drugs of limited aqueous solubility (Junghanns, 2008). When the technique of drug particle size reduction results in the formation of solid flat particles in the micron size range, the term microplates (MIC) could be assigned. Particle size reduction could be achieved by mechanical or engineered particle size control techniques. The former includes jet milling, ball milling and the high pressure homogenization approaches, while the later involves cryogenic spray process and crystal engineering method (Khadka et al., 2014). In addition to the above mentioned methods, micronization could also be attained using spray drying, freeze-drying, crystallization, supercritical fluid technologies and anti-solvent precipitation process (Krishnaiah, 2010; Kurakula et al., 2015). The process of anti-solvent precipitation is based on the interfacial deposition of a polymer

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following displacement of a semi-polar solvent miscible with water. The technique is easy, less complex, less energy consuming as well as widely applicable without any additives for the manufacturing of defined nanospheres (Mandal et al., 2010).

Transdermal drug delivery systems (TDDS) are pharmaceutical dosage forms intended to deliver a therapeutic effective dose of medication across the patient's skin and into the blood stream. The main advantage of these systems is the release of the incorporated drug through the patient skin into the blood in a controlled release manner that attain a steady state flux of drug in the blood circulation for long period of time (Ahmed and El-Say, 2014; El-Say et al., 2015a). Delivery of the therapeutic agent *via* the transdermal route reduces inconsistency in gastrointestinal absorption due to the effect of pH and intestinal motility; avoids the first-pass metabolism; and decreases the dosing schedule (Ahmed et al., 2014a). This route offers a large and varied surface as well as ease of application through self-administration. The gradual release of the incorporated drug from the transdermal system allows the achievement of more stable drug plasma levels over time with considerably less associated variability compared to other routes of drug administration. Transdermal delivery from patches also avoids the "peaks and valleys" in blood levels observed with discrete dosage forms such as tablets, capsules and even injections (Ramachandran and Fleisher, 2000). Limitation of these systems comes from the effective skin barrier function that prevents penetration except for those of low molecular weight molecules.

In this study, FNS which is a BCS class II drug was used as a model for water insoluble drugs to develop drug MIC that was subsequently loaded into TDDS utilizing two-step optimization. In the first step, anti-solvent precipitation technique was employed to prepare an optimized drug MIC that was characterized for particle size and morphology. While the second step, the solvent casting technique was used to prepare an optimized transdermal film loaded with FNS-MIC which was evaluated for their quality attributes and *ex-vivo* permeation using male Wistar rat skin.

2. Materials and methods

2.1. Materials

Finasteride was a kind gift from SAJA Pharmaceuticals (Jeddah, Saudi Arabia). Poly vinyl alcohol (PVA) was procured from Spectrum Chemicals & Laboratory Products (Gardena, CA, USA). Sodium lauryl sulfate was purchased from Scharlau, Scharlab S.L. (Barcelona, Spain). Hydroxypropyl methylcellulose (HPMC) viscosity 4000-cp (2% solution) was procured from Acros Organics (Morris Plains, New Jersey). Dimethyl sulfoxide (DMSO) was purchased from Techno Pharmchem (Bahadurgarh, India). Propylene glycol and methanol were obtained from Sigma-Aldrich (Spruce St., St. Louis, USA).

2.2. Methods

2.2.1. Three-level factorial design (1st step) for the preparation of finasteride microplates

A fully randomized three-level factorial design with two center points was employed to study the effect of two factors namely, the stabilizer concentration as X_1 and the anti-solvent percentage as X_2 in 10 formulations. The optimization was carried out to develop FNS-MIC with minimum particle size. Statgraphics® Centurion XV, Software, Version 15.2.05 (StatPoint, Inc., Warrenton, VA) was used to generate and evaluate the statistical experimental design. The response variable was the particle size (Y) of the MIC. The investigated range of stabilizer concentration was from 0.2 to 1% and the solvent ratio from 10 to 30%. A total of 10 formulations with the coded and actual values of the factors as long as the observed and the predicted values of particle size were illustrated in Table 1.

Table 1
A 3-level factorial design matrix including independent variables with their coded and actual values and the corresponding observed and predicted response.

Formula code	Coded values		Actual values		Response Y (μm)	
	X_1	X_2	X_1	X_2	Observed	Predicted
FM1	−1	0	10	0.6	2.33 ± 0.12	2.23
FM2	1	1	30	1.0	4.66 ± 0.24	5.07
FM3	−1	−1	10	0.2	0.99 ± 0.03	0.93
FM4	0	−1	20	0.2	3.61 ± 0.17	3.46
FM5	0	0	20	0.6	3.73 ± 0.18	4.52
FM6	−1	1	10	1.0	2.73 ± 0.13	2.89
FM7	1	0	30	0.6	5.51 ± 0.26	4.89
FM8	1	−1	30	0.2	3.86 ± 0.18	4.06
FM9	0	1	20	1.0	5.51 ± 0.27	4.94
FM10	0	0	20	0.6	4.61 ± 0.23	4.52

Independent variables
Stabilizer concentration; %, w/v (X_1)
Anti-solvent percentage; %, v/v (X_2)

Dependent variable
Particle size (μm)

2.2.2. Preparation of finasteride microplates

FNS-MIC formulations depicted in Table 1 were prepared by "Bottom up technology" namely the solvent displacement method also known as anti-solvent precipitation method given previously by several researchers (Mandal et al., 2010; Yadav et al., 2012; Fessi et al., 1989; Grau et al., 2000). Briefly, known weight of the drug was dissolved in methanol, selected as water miscible solvent, to obtain a drug concentration of 100 mg/ml. The drug solution was then injected into 50 ml distilled water containing known concentration of polyvinyl alcohol (PVA), as stabilizer. The mixture was kept stirring overnight at 1000 rpm on a magnetic stirrer until complete evaporation of the organic solvent leaving FNS precipitated as MIC. The obtained suspension was ultrasonicated under ice for 10 min using Sonics VCX 750, Sonics & Materials INC. (CT, USA). The aqueous FNS suspensions containing MIC were lyophilized using alpha 1–2 LD plus, Christ lyophilizer (Osterode am Harz, Germany) in which the aqueous solvent was sublimed under a pressure of 0.01 mbar at −90 °C for 48 h.

2.2.3. Measurement of the particle size and surface charge of the prepared microplates

After reconstitution of the lyophilized MIC, the particle size, polydispersity index and zeta potential of the obtained MIC were measured by dynamic light scattering technique using Zetatrac of Microtrac Inc., (PA, USA). Each experiment was carried out in triplicate.

2.2.4. Statistical analysis and preparation of the optimized formulation

Following the statistical analysis of the obtained data and identifying the optimum level for each factor that achieve the minimum particle size of the MIC, an optimized formulation was suggested. This optimized MIC formulation was prepared, freeze dried and characterized as previously described.

2.2.5. Determination of the saturated solubility of finasteride microplates

Solubility of the freeze dried optimized MIC was compared to that of the pure drug by placing excess amount of each sample in a screw cap vials containing 3 ml of distilled water, the vials were kept shaking for 72 h at 25 °C in a thermostatically controlled shaking water bath, Model 1031; GFL Corporation (Burgwedel, Germany). Aliquots of each vial were taken every day, filtered using acrodisc® syringe filter of 0.45 μm and analyzed spectrophotometrically until reaching equilibrium solubility. UV spectroscopic scanning was carried out and the maximum wave length was found to be 222 nm. Linearity of the method was studied following the determination of the absorption at different concentrations (5–30 μg/ml) and construction of a calibration plot that was linear with a correlation co-efficient of 0.999. Intra- and