

International Journal of Pharmaceutical Sciences and Drug Research

2018; 10(1): 01-06



Research Article

ISSN: 0975-248X
CODEN (USA): IJPSP



Formulation and Evaluation of Minoxidil Gel Using Acrylamide/Sodium Acryloyldimethyl taurate copolymer for Alopecia areata

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ABSTRACT

Alopecia areata is a common, chronic inflammatory disease, characterized by patchy hair loss on the scalp, affecting about 2.1% of world population. Presently, minoxidil has been used for treatment of alopecia as topical lotion, but associated with many drawbacks like systemic side effects and low contact time with skin. Therefore, in the present work, minoxidil gel was prepared using a novel copolymer, Sepineo P 600 to overcome these drawbacks. The prepared gel was characterized for pH, drug content, viscosity, spreadability, skin adhesivity, occlusivity, *in vitro* drug release, *ex vivo* skin permeation, stability and finally for skin corrosivity. The drug content of the finalized gel was found to be $99.80 \pm 0.82\%$. The formulation showed good spreadability, occlusivity, adhesiveness and viscosity. *In vitro* release studies showed that the drug release from prepared gel followed matrix release pattern as compared to lotion. Mathematical modelling of the drug release data suggested Higuchi release model. The formulated minoxidil gel was found to be non-corrosive and stable when subjected to accelerate as well as real time stability studies. Overall, the minoxidil gel formulation was suitable for skin application and can be an effective dosage form for the treatment of Alopecia areata.

Keywords: Minoxidil, Skin permeation, Sepineo P 600, Gel.

DOI: 10.25004/IJPSPDR.2018.100101

Int. J. Pharm. Sci. Drug Res. 2018; 10(1): 01-06

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 03 October, 2017; **Revised:** 08 November, 2017; **Accepted:** 15 November, 2017; **Published:** 15 January, 2018

INTRODUCTION

Alopecia areata (AA) is a recurrent, genetic, immune mediated disease that affects 2.1% of population including children and adults, characterized as patches of hair loss to total hair loss of scalp (alopecia totalis) or loss of entire scalp and body hair (alopecia universalis).

[1] Although the etiology of AA is poorly understood, but the number of factors such as genetics, stress, hormones, diet, infectious agents, vaccination, etc. determine the physical and biochemical status of the immune system and hair follicles. It is also known that T-lymphocytes play an important role in AA infiltrating against the hair follicles leading to abrupt conversion from anagen to telogen phase. [2] Minoxidil (MXD), an antihypertensive drug, appears to be effective in the treatment of AA by prolonging the anagen phase and increasing the size of smaller hair follicles. [3] Presently, MXD is available as 2% w/v and 5% w/v topical solution in market. But commercial MXD formulations contain high percentage of ethanol and propylene glycol and their repeated application leads to severe adverse effects such as scalp dryness, irritation, burning sensation, redness and allergic contact dermatitis. [4-5] Other drawbacks associated with topical MXD solutions includes less contact time with application area and high systemic absorption of drug resulting in cardiovascular side effects. [6-7] Therefore, to resolve these drawbacks, new formulation was required in the form of gel which can provide sufficient contact time and capable of sustain drug delivery. Gels are transparent or translucent semisolid dosage form produced by entrapment of large amounts of aqueous or hydro-alcoholic liquid in a three dimensional colloidal network commonly employed in topical delivery of drugs. [8] In recent years, there has been great interest in the use of Sepineo P 600, a novel copolymer for the preparation of gels. [9]

Therefore, in the present study, an attempt has been made to formulate and evaluate the gel containing MXD at the therapeutic concentration used in commercial product (2% w/v) using self gelling agent Sepineo P 600. The rheology, spreadability, *in vitro* drug release, bioadhesion strength, *ex vivo* skin permeation, stability and skin corrosivity of the prepared gel were also evaluated.

MATERIALS AND METHODS

Materials

Minoxidil was received as a gift sample from Zee laboratories Ltd., Baddi, India. Sepineo P 600 (concentrated dispersion of acrylamide/sodium acryloyldimethyl taurate copolymer in isohexadecane) was received as a kind gift sample from Seppic (India). Propylene glycol was purchased from Sigma-Aldrich, Mumbai, India. Dialysis membrane (Molecular weight cut off 14000 Da) was purchased from Hi-Media, Mumbai, India. All other chemicals were of the analytical grade.

Preparation of drug loaded gel

For the formulation of gel (MXD-Gel), the drug was dissolved in sufficient amount of propylene glycol and then gelled by adding a self-gelling and thickening agent Sepineo P 600 (1%, 2% and 3% w/v) with continuous stirring for 5 min. Similarly, blank gel (B-Gel) was formulated without the addition of drug. Three different concentration of gelling agent was used to formulate the optimum viscosity gel. The formed gel was left equilibrating for 24 h at room temperature ($25 \pm 1^\circ\text{C}$) to remove entrapped air. For the preparation of MXD-Lotion, drug was dissolved in a solvent mixture (ethanol: propylene glycol: water in the ratio of 50:30:20).

Drug content and pH

To quantify the amount of drug in the formulation, 500 mg MXD-Gel was dissolved in 50 ml of phosphate buffer (pH 7.4) in a 100 ml volumetric flask with continuous shaking. Finally, it was analyzed after appropriate dilution on UV-visible spectrophotometer (Varian Cary-5000, Netherlands) at λ_{max} 231 nm. The digital pH meter (pH Tutor Bench Meter, EUTECH Instruments, Singapore) was used to measure the pH of the gel. [10]

Occlusion factor

For the determination of occlusive properties of MXD-Lotion, B-Gel and MXD-Gel, Vringer et al. method was used. [11] 50 ml water was added into a beaker (capacity 100 ml) and covered with a filter paper (Whatman number 6). 200 mg of test formulations were applied on the surface (area 12.56 cm²) of filter paper (test) and compared with the similar beaker having filter paper without formulation (control) by storing at $32 \pm 0.5^\circ\text{C}$ for 24 h. Weight of water remaining in the beakers was measured at 24 h to calculate the occlusion factor (F) using the equation-

$$F = (A - B/A) \times 100$$

Where A = Water loss with blank (control) and B = Water loss with sample; F = 0, means no occlusive effect; F = 100, means maximum occlusive effect

Rheological measurements

The viscosity of the B-Gel and MXD-Gel samples was measured by Brookfield viscometer (RVT, Brookfield Engineering Laboratories, Inc., USA) using spindle #2 at rotational speed of 0.5, 1.0, 2.0, 5, 10, 25, 50 and 100 rpm. The flow property of the gels was measured by recording the variation in shear stress (τ) by increasing and then decreasing the shear rate (rpm) from 0 to 100 rpm at temperature of $25 \pm 1^\circ\text{C}$. [12]

Spreadability study

The spreadability of the gel was used to measure the extent of area to which formulation readily spreads on topical application to skin. To assess spreading ability, weighed cellulose acetate filter paper (W1) was placed in the center of the aluminum foil sheet. 20 drops of test formulation was added over the defined area of the cellulose acetate filter paper using 5 ml syringe (Becton Dickinson & Co., USA). After 10 min, saturated portion of the filter paper was cut away from the unsaturated portion. Unsaturated portion of the filter paper (W2)

was weighed and spreadability was calculated using the following equation [12].

$$\text{Spread by Weight} = (W1 - W2 / W1) \times 100$$

Skin adhesion test

The modified Patel *et al* (2007) [13] method was used to measure the bioadhesive strength of prepared gel with excised pig ear skin. Two arm balance was used in which left arm was tied with one glass slide having the skin and other glass slide with skin was fixed on the wooden block. The right and left pans were balanced by adding extra weight to the right pan. 1 g of the prepared gel was sandwiched between these two slides by the application of small pressure to remove air bubbles and kept for 5 minutes. Weight was added to the right pan slowly at 50 mg/ min till the patch detached from the skin surface. Bioadhesive strength was measured as the weight (gram force) required detaching the gel from the skin surface [14] and calculated using the formula.

$$\text{Bioadhesive Strength} = \text{Weight required (in g)} / \text{Area (cm}^2\text{)}$$

In vitro drug release

The *in vitro* release of drug from MXD-gel was evaluated by Franz Diffusion Cell using dialysis membrane. The membrane was mounted between the donor and receptor compartments of a locally fabricated Franz diffusion cells (diffusion area of 0.785 cm²; receptor volume of 5.5 ml). Mixture of phosphate buffer solution pH 7.4 and ethanol (60:40 v/v) was used as receptor medium maintained at 37 ± 0.5°C. Defined amount of formulation was then placed on the surface of the membrane in the donor compartment. The aliquots from the receptor compartment were withdrawn at predetermined time interval (0.5, 1, 2, 3, 6, 12 and 24 h) and replaced with an equal volume of fresh medium. The samples were analyzed for drug content by UV-visible spectrophotometer (Varian Cary-5000, Netherlands) at λ_{max} 231 nm. To study the mechanism of MXD release from gel formulation, the data obtained from *in vitro* release studies was fitted to different kinetic models (Zero order, First order, Higuchi and Korsmeyer Peppas). The criterion for selecting the most appropriate model was based on a goodness of fit test. [15]

Ex vivo skin permeation study

Franz diffusion cell (diffusion area 0.785 cm²) was used for permeation study. Fresh hairless full thickness pig ear skin from dorsal region was obtained from local slaughterhouse. The skin was washed under tap water followed by drying with tissue paper. Skin specimen was mounted on Franz diffusion cells in such a way that *stratum corneum* and dermal side faced donor and receiver compartments, respectively. The receptor compartment was filled with 6.0 ml phosphate buffer pH 7.4 maintained at 37 ± 1°C throughout the experiment under continuous stirring. After equilibrium, specified amount of MXD-Gel was added to donor compartment. Aliquots (1.0 ml) were withdrawn from the receptor compartment at an

interval 0.5, 1, 2, 3, 6, 12 and 24 h and analyzed for drug content by UV-Visible spectrophotometer at 231 nm. [16] The receptor phase was immediately replenished with equal volume of fresh buffer after each sample withdrawal.

Stability Studies

MXD-Gel was subjected to two different conditions 30 ± 2°C, 65 ± 5 relative humidity (RH) and 40 ± 2°C, 75 ± 5 RH for 3 months as per ICH guidelines (Q1AR2) of stability testing using stability chamber (Newtronic Lifecare Equipment Pvt. Ltd, Mumbai, India). The sampling was done at the end 1st, 2nd and 3rd month to measure the pH, drug content and viscosity. [17-18]

Ex vivo skin corrosion studies

Corrositex® test was performed to determine the corrosive potential of gel containing MXD. The corrosive product act by irreversibly damaging epidermal proteins and show color shift in an underlying chemical detection liquid. Pig ears skin was used for this study obtained from a local slaughter house. The skin was washed under tap water and the full thickness skin was carefully removed from the dorsal/external region of the pig ears. The prepared pig ear skin was clamped on Franz- diffusion cells. 37% nitric acid solution (positive control) and 0.9% NaCl solution (negative control) was used for the experiment. 200µl of test formulation and both positive and negative control was applied on pig ear skin. After 15 min, these formulations were removed followed by washing with 2×1 ml of distilled water to remove the residual sample from the epidermis. Then, 1ml of sulforhodamine B was applied on the epidermis of above used skin to detect the protein destruction. The applied dye was removed after another 15 min and washed the epidermis with 1 ml of distilled water. Analyze this washed water using UV-visible spectrophotometer (Varian Cary-5000, Netherlands) at λ_{max} 265.5 nm. [19] The study was performed six times and the value of corrosive factor F was measure by given equation, when, F > 0 (non corrosive) and F < 0 (corrosive sample).

$$F = \frac{\text{Absorbance of sample} - \text{Absorbance of 0.9\%NaCl}}{\text{Absorbance of 0.9\%NaCl}}$$

Statistical analysis

All the results were statistically evaluated using one way analysis of variance with post-hoc Turkey's test; (*p*<0.05) was considered as statistically significant.

RESULTS

Preparation of MXD-Gel

MXD-Gel containing 1.0% w/v of Sepineo P 600 form a very thin gel that liquefies within 6 h of preparation, while at 3.0% w/v gel formulation was very thick and sticky that could not be properly spread out. Gel containing 2.0% w/v of Sepineo P 600 formed uniform and smooth gel that does not liquefy upon keeping. Thus, 2.0% w/v concentration of gelling agent was selected as the optimized concentration.

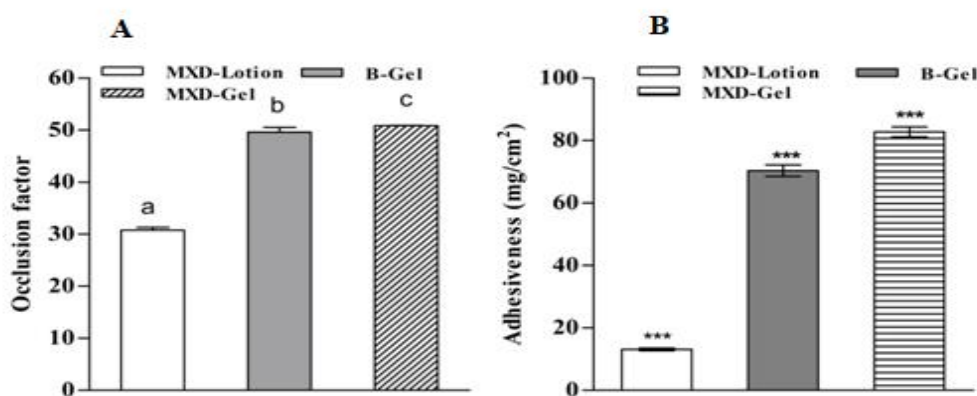


Fig. 1: Occlusion factor (A) and adhesiveness (B) of MXD-Lotion, blank gel (B-Gel), minoxidil loaded gel (MXD-Gel) (***,^{ab,ac} $p < 0.05$, ^{bc} $p > 0.05$)

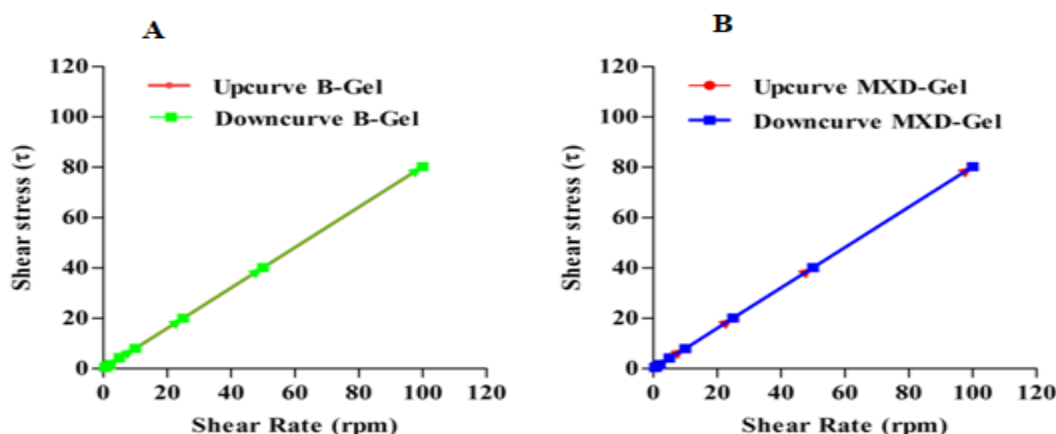


Fig. 2: Flow curves of blank gel (A) and minoxidil loaded gel (B)

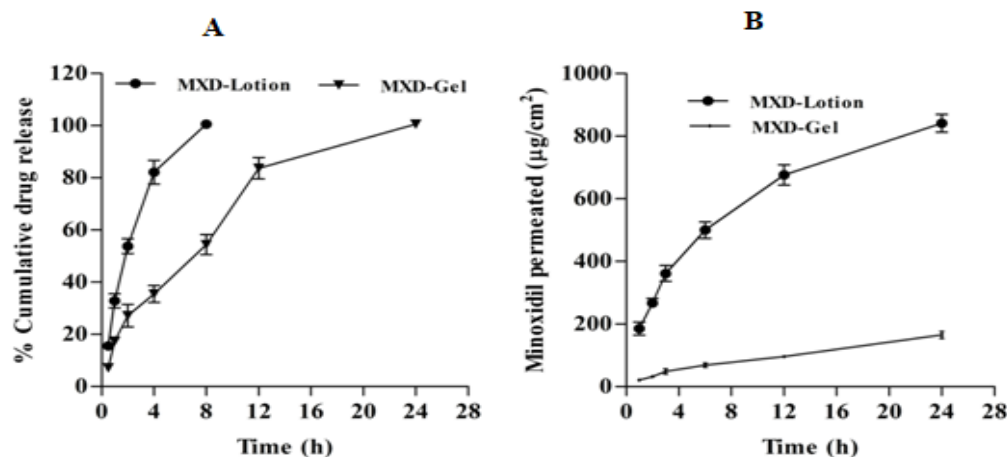


Fig. 3: *In vitro* drug release study (A) and *ex vivo* permeation study (B) after 24 h. Data presented as mean \pm SEM

Table 1: Regression coefficient (R^2) obtained from various kinetics models

Formulation	Zero order Kinetics	Higuchi Kinetics	Korsmeyer Peppas Kinetics	First order Kinetics
MXD-Gel	0.896	0.994	0.953	0.786

Drug content and pH

The amount of drug present in MXD-Gel was found to be $99.80 \pm 0.82\%$ and pH was found to be 6.29 ± 0.18 .

Occlusion studies

The value of occlusion factor [Fig. 1(A)] of MXD-Lotion, B-Gel and MXD-Gel after 24 h was found to be 31.40,

49.88 and 50.92, respectively. MXD-Gel and B-Gel cannot exhibits any significant difference in occlusivity ($p > 0.05$).

Rheological behaviour

The viscosity of gel formulations reflects the spreadability and adherence of transdermal formulations to the skin surface. [20] The viscosity of blank gel and MXD-Gel Fig. 2 (A and B) increased with increasing rate of shear with superimposed ascending and descending flow curves of the rheogram showed Newtonian flow behavior. The flow curves were unaffected ($p > 0.5$) by the presence of drug.

Spreadability

The finalized formulation has approximately equal spread by weight $61.11 \pm 1.18\%$ compared to blank gel $61.47 \pm 1.12\%$. The presence of drug in gel had not affected the spreadability of the formulation ($p > 0.5$).

Skin adhesion test

The value of adhesiveness for MXD-Lotion is 12.73, B-Gel is 70.06 and MXD-Gel was 82.80. The adhesiveness of MXD-Gel was found to be greater than MXD-Lotion as shown in Fig. 1 (B).

In vitro drug release

In the present study, the gel formulation released MXD over a prolonged period of 24 h across dialysis membrane compared to topical lotion as reference Fig. 3 (A) and Table 1. The regression coefficient (R^2) of MXD-Gel for different release kinetics equations are shown in Table 1.

Ex vivo skin permeation study

Fig. 3 (B) shows permeation of MXD from MXD-Lotion and MXD-Gel across the pig skin barrier. Significant difference was found between cumulative MXD flux of lotion (34.50 ± 2.22 mcg/cm²/h) and gel (7.60 ± 1.55 mcg/cm²/h).

Stability studies

There were no significant changes in the viscosity, drug content and pH of the final gel formulation after storing at $30 \pm 2^\circ\text{C}$ and $40 \pm 2^\circ\text{C}$ at 65 ± 5 and 75 ± 5 RH for 3 months, respectively.

Ex vivo skin corrosion studies

The MXD-Gel was found to be non-corrosive ($F = 0.546$) while the MXD-Lotion ($F = -0.345$) exhibited a corrosive potential.

DISCUSSION

The aim of the present work was to develop a suitable MXD formulation for the treatment of hair loss. Gel of anti alopecia drug was selected from formulation point of view in order to achieve longer contact time with scalp region for adequate penetration of the drug at the site of application. Sepineo P 600, a novel self-gelling agent, in three different concentrations was used to get desired rheological behaviour of the formed gel. Low concentration of polymer (1% w/v) led to thin gel, while high concentration was resulted thick viscous gel causing problems like handling and spreading. [21] Finally, 2% w/v gelling agent concentration was found to be suitable for desirable viscosity. Film formation properties of MXD-Gel on applied area results in reduce evaporation of water claiming higher occlusivity as compared to MXD-Lotion. [22] Moreover, the efficacy of the topical semisolid formulation depends on even spreading of the formulation on the skin. The prepared drug loaded and blank gel had approximately similar spreadability indicating presence of the drug does not affect its spreading ability. The adhesiveness of the MXD-Lotion was less than the MXD-Gel due to the absence of gelling agent responsible for adhesiveness. Higher adhesiveness of the prepared gel offer prolongs drug residence time

with the epithelial barrier of scalp. [23] From *in vitro* release study, it can be concluded that MXD-Gel exhibits slower release in comparison to the MXD-Lotion which is attributed to the presence of gelling agent. The polymeric content of the formulation influence the drug diffusion rate in inverse relationship i.e. by increasing polymer content results in decreasing the drug release rate. The release kinetics study for the prepared gel suggests that Higuchi model ($R^2 = 0.994$) is best fit in comparison to other models. Higuchi model describes the drug release from the matrix system based on Fick's law of diffusion. [24] The cumulative percent of drug permeated through pig ear skin showed significant difference for MXD-Lotion and MXD-Gel. The presence of ethanol and propylene glycol in MXD-Lotion leads to higher permeation as they are established permeation enhancers; high alcohol content may also disrupt SC lipid barrier facilitating drug permeation responsible for systemic side effects. [25] Viscosity of the prepared gel was found to be unaffected by the presence of the drug as indicated by almost similar value of shear stress (τ) for both B-Gel and MXD-Gel. During stability study, no significant changes were observed in the pH, drug content and viscosity of the MXD-Gel when subjected to accelerate and real time conditions justifying a stable formulation. The ideal topical formulation should not produce dermal corrosion which is the production of irreversible skin damage. Products having pH extremes like less than 2 and more than 11.5 may produce dermal effects. [26] Repeated application of such types of formulation results in typical adverse effects. Therefore, it is important to investigate the corrosive factor of formulations available for topical application. The MXD-Gel was found to be non-corrosive as compared to the MXD-Lotion representing an ideal formulation for topical application. Hence, MXD was successfully formulated as gel using Sepineo P 600 as a novel gelling agent. MXD-Gel showed acceptable pH, drug content, viscosity, spreadability and stability along with non corrosivity to skin. Therefore, the present gel formulation could be very promising alternative for lotions available commercially.

ACKNOWLEDGMENTS

The authors would like to thank Zee laboratories Ltd., Baddi (India) for providing the gift sample of Minoxidil and Seppic (India) for the gift sample of Sepineo P 600.

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HOW TO CITE THIS ARTICLE: Kumar P, Singh SK, Jindal DK, Handa V, Bilonia J. Formulation and Evaluation of Minoxidil Gel Using Acrylamide/Sodium Acryloyldimethyl taurate copolymer for Alopecia areata. Int. J. Pharm. Sci. Drug Res. 2018; 10(1): 01-06. DOI: 10.25004/IJPSDR.2018.100101