

Enhanced Topical Formulation of Minoxidil Gel for Alopecia Condition

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Abstract

Minoxidil as topical solution in aqueous vehicle in treatment of alopecia offers limited contact time with the scalp. Hence, there is a need for a suitable topical delivery system which would increase the contact time leading to an increase in local drug concentration & therapeutic effect. The objective of the study was to formulate, characterize and evaluate Minoxidil gel for enhanced topical drug delivery. Formulations were prepared by using Natrosol, Carbopol 974 and HPMC K100 (hydroxyl propyl methyl cellulose) as viscosity enhancing agents. The kinetics of drug release mechanism was evaluated by PCP Disso version 2.08 software revealed anomalous transport. The formulations were evaluated for appearance, gelation ability, sterility, pH, drug content and viscosity. The developed formulations were stable, non-irritant to guinea pig and *in vitro* drug release was found to be 95.19% over the period of 12 h through cellophane membrane. The similarity factor (f_2) was found to be 83.12, 65.41, and 59.13 for the optimized formulations F3, F7 and F11 respectively indicating the release was similar to that of the marketed formulation (Tugain5%). A stable Minoxidil gel formulation is prepared by using Natrosol, Carbopol 974 and HPMC K100 and is a promising approach in the treatment of alopecia.

Keywords: Minoxidil gel, Natrosol, Carbopol 974, HPMC K100, Similarity factor (f_2).

1. Introduction

Topical administration is employed to deliver drug at, or immediately beneath, the point of application. In man, percutaneous absorption probably occurs mainly from the surface. Absorption through the hair follicles occurs, but the follicles in man occupy too small a portion of the total integument to be of primary importance. Absorption through sweat and sebaceous glands generally appears to be minor. When the medicament rubbed on vigorously, the amount of the preparation that is forced into the hair follicles and glands is increased. Rubbing also forces some material through the stratum corneum without molecular dispersion and diffusion, through the barrier.¹ the purpose of topical dosage forms is to conveniently deliver drugs across a localized area of skin. To develop an ideal dosage form one must take into account the flux of drug across skin, retention of dosage form on the skin surface, the reservoir capacity of the dosage form, and patient acceptability of the formulation.² A gel is a soft, solid or solid-

like material consisting of two or more components, one of which is a liquid, present in substantial quantity. Gels can be used to administer drugs topically or into body cavities.³ Alopecia mean hair loss, today 70% males and 30% females are suffering from this disorder loss of hair is the most common problem of modern societies, which create much economical and psychological effect. Recently, a great effort has been made to treat hair loss or alopecia. One of the most common types of alopecia is androgenic alopecia and alopecia aerata⁴. Alopecia aerata occur in people who are apparently healthy and have no skin disorder⁵. The most common type of alopecia aerata involves hair loss in one or more round spots on scalp. Men and women are equally affected and prevalence is almost the same for all ethnic groups. It is common disease at any given time, about 0.2% of people is involved with alopecia aerata and 1.7% of population experiences an episode of alopecia aerata during their life time⁶. Alopecia affects approximately 50% of men over 40 years of age and may also affect just as many

women. The majority of men and women want to reverse or halt their hair loss, feel frustrated or helpless about the condition are self-conscious about their hair loss⁷. Minoxidil (Rogaine) was first developed as an antihypertensive agent and was noted to be associated with hypertrichosis in some patients. A topical formulation of Minoxidil then was developed to exploit this side effect. Topical Minoxidil is available as a 2% solution (Rogaine) and a 5% solution (Rogaine extra strength for men)⁸. Presently in India Minoxidil is mostly marketed as topical solution in aqueous vehicle in treatment of alopecia which offers limited contact time with the scalp. Hence, there is a need for a suitable topical delivery system which would increase the contact time leading to an increase in local drug concentration. The topical gel formulation overcomes the above disadvantage. Hence, in the present study an attempt has been made to prepare and evaluate the topical gel formulation of Minoxidil.

2. Materials and methods

2.1 Materials

The Minoxidil, Natrosol and Carbopol 974, HPMC K100 were gifted by Naxpar Lab Mumbai, Ashland Pune, Lubrizol Mumbai and Colorcon Goa respectively, Goa. All chemicals used were of analytical grade.

2.2 Method

The preliminary formulations of Minoxidil 5% were formulated using Natrosol, Carbopol 974, HPMC K100, methyl paraben, propyl paraben and triethanolamine. The formulations were evaluated for *in vitro* diffusion in phosphate buffer of pH 7.4 and viscosity to optimize the concentration of Natrosol, Carbopol 974 and HPMC K100 for final formulation. The formulations were formulated as shown in Table.1.

2.2.1 Prototype formulations

The polymers which were known to undergo to form soft gel were selected for the formulation of topical gel of Minoxidil. The topical gels of Minoxidil (5%) were prepared using different concentrations of different polymer (Table.2 & 3).

Table.1. Preliminary formulations and Evaluation

Formulation code	Natrosol (%)	Carbopol 974 (%)	HPMC K100 (%)	Gelling capacity	Viscosity (cps)
F1	0.5			Viscous liquid	4526
F2	1			Viscous liquid	9816
F3	1.5			Soft gel	12100
F4	2			Hard gel	29877
F5		0.5		Soft gel	11225
F6		1		Soft gel	18545
F7		1.5		Hard gel	29578
F8		2		Hard gel	40156
F9			0.5	Viscous liquid	620
F10			1	Viscous liquid	2689
F11			1.5	Soft gel	7780
F12			2	Hard gel	15689

Table.2 Formulations of Minoxidil (5%) from F1 to F6

Ingredients (gm)	Formulation Code					
	F1	F2	F3	F4	F5	F6
Minoxidil	5	5	5	5	5	5
Natrosol	1.25	1.37	1.62	1.75		
Carbopol 974					1.25	1.37
HPMC K100						
Propylene glycol	60	60	60	60	60	60
Ethanol	10	10	10	10	10	10
Propyl paraben	0.01	0.01	0.01	0.01	0.01	0.01
Methyl paraben	0.1	0.1	0.1	0.1	0.1	0.1
Water	23.64	23.515	23.26	23.14	24.64	24.51

Table.3 Formulations of Minoxidil (5%) from F7 to F12

Ingredients (gm)	Formulation Code					
	F7	F8	F9	F10	F11	F12
Minoxidil	5	5	5	5	5	5
Natrosol						
Carbopol 974	1.62	1.75				
HPMC K100			1.25	1.37	1.62	1.75
Propylene glycol	60	60	60	60	60	60
Ethanol	10	10	10	10		10
Propyl paraben	0.01	0.01	0.01	0.01	0.01	0.01
Methyl paraben	0.1	0.1	0.1	0.1	0.1	0.1
Water	24.26	24.14	23.64	23.51	23.26	23.14

2.3 Evaluation of topical gel formulations

The formulations were evaluated for various physical and performance characteristics i.e. for appearance/ clarity, pH, viscosity (Brookfield LVDV-II +), homogeneity, grittiness, Extrudability. The drug content was determined spectrophotometrically at 288.4 nm (Shimadzu-1700).

2.3.1 In-vitro drug release study:

The in vitro diffusion studies of prepared gel were carried out in Keshary–Chien diffusion cell (Figure.1) using through a dialysis membrane-150 (pore size- 0.45 μ m) the receptor media was pH 7.4 phosphate buffers (12 ml) maintained at 37 \pm 0.5 $^{\circ}$ C. The samples (1 ml) were withdrawn at regular interval of 1 hr for 7 h and were replaced immediately with the same volume of pH 7.4 phosphate buffer. The samples withdrawn

were observed spectrophotometrically at 288.4 nm^{9,10}.

**Figure.1 In vitro diffusion assembly**

2.3.2 In-vitro diffusion study through abdominal skin of guinea pig:

The abdominal hair of guinea pig is shaved by depilatory. After sacrificing the guinea pig abdominal skin sections is excised with surgical scissors and adhering subcutaneous fat was carefully cleaned. For In-vitro permeation studies, skins were allowed to hydrate for 1 h before being mounted on the Keshary-Chien diffusion cell with the stratum corneum (SC) facing the donor compartment. The gel sample will be applied on the skin and then fixed in between donor and receptor compartment of Keshary-Chien diffusion cell.

All the test conditions followed were same as those mentioned for the *in vitro* diffusion test through dialysis membrane-150 except the membrane was replaced with the biological membrane i.e. freshly excised abdominal skin of guinea pig. The samples withdrawn were observed spectrophotometrically at 288.4 nm. The diffusion of the Minoxidil through the abdominal skin of guinea pig was studied for selected formulations (F3, F7 and F11).

2.3.3 Kinetics Analysis of Drug Release:

To analyze the mechanism of drug release from Minoxidil gel, the *in vitro* dissolution data were fitted to zero order, first order, Higuchi release model, Hixson and Crowell powder dissolution method and Korsmeyer and Peppas model by using PCP Disso Version 2.08 software, and the model with the higher correlation coefficient was considered to be the best model.

2.3.4 Comparison of release profile with marketed product:

The in-vitro release studies were carried out for the optimized formulations and marketed product (Tugain 5%, Cipla). In order to compare its release profile with optimized formulation the in-vitro release studies were carried out on the abdominal skin of guinea pig.

The prominence was placed on comparison of dissolution profile of optimized formulations F3, F7 and F11 (Test) and marketed product Tugain 5% (Reference) by determination of similarity factor (f_2) with the help of PCP Disso Version 2.08 software.

2.3.5 Stability study:

The selected topical gel formulations F3, F7 and F11 were subjected to stability studies as per the ICH guidelines in stability chamber (Thermo lab) at test conditions given in Table.5.

Table.4 Test conditions for stability study

Test Conditions of stability studies	
Duration of study	3 months
Temperature conditions	40± 2°C
Relative humidity conditions	75± 5%
Frequency of testing the samples	Initial, 30 days, 60 days, 90 days.

The formulations were evaluated for physical characteristics at the predetermined intervals of 30day, 60day and after 90 days like appearance/clarity, gelling ability, pH, viscosity and drug content.

2.3.6 Skin irritation study in guinea pigs

The guinea pig of either sex weighing 2.0-2.5 kg will be used for this test. The hair is removed from the guinea pig. The animals will be divided into two batches. The gel containing drug was used on test animal. A piece of cotton wool soaked in saturated drug solution was placed on the back of guinea pig taken as control. The animals were treated daily upto seven days and finally the treated skin was examined visually for erythema and edema. For the present study the severity of toxicity symptoms was measured on a scale of 0-4 (Table.8). The frequency of observation was 1, 24, and 48 h, upto 7 days.

3. Results and discussion

The formulation of preliminary formulations revealed Natrosol alone does not possess any gelling properties i.e. F1 to F4. Natrosol, Carbopol 974, and HPMC K100 above 1.5% conc. produce formulation of high viscosity that is not suitable for applying on the scalp i.e. F4, F7, F8 and F12. So level of polymer concentration was decided based on gelling capacity.

The formulations were evaluated for various physical and performance characteristics i.e. for appearance/ clarity, pH, viscosity, homogeneity, grittiness, extrudability and drug content (Table.6)^{11, 12}.

Invitro drug release study & Conclusion:

In-vitro drug release study revealed as concentration of polymer (Natrosol, Carbopol 974, HPMC K100) increased, the release decreased due to formation of gel structure and retarding the release (Figure.2, 3 and 4). Probable mechanism for such retardation of release may be the reduction in number and

dimensions of the channels in the gel structure due to enhanced viscosity of gel.

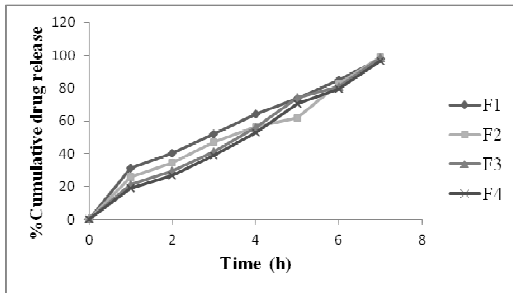


Figure.2 Diffusion of Minoxidil from Natrosol based formulations F1 to F4

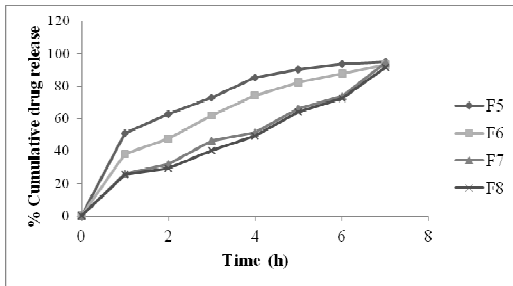


Figure.3 Diffusion of Minoxidil from Carbopol 974 based formulations F5 to F8

The drug release was analyzed by PCP Disso Version 2.08 software to study the kinetics of drug release mechanism. The results showed that the formulations followed matrix model kinetics. The r^2 value of matrix model was found close to one. As a result, a reduction in drug release rate is observed. The drug release from the Natrosol, Carbopol 974 and HPMC K100 formulations were controlled by polymer swelling and diffusion and followed matrix kinetic model. The *in vitro* release profile of formulation F3, F7 and F11 were compared with marketed formulation of Minoxidil (Tugain5%, Cipla). The diffusion of Minoxidil through abdominal skin of guinea pig was slower as compared to the

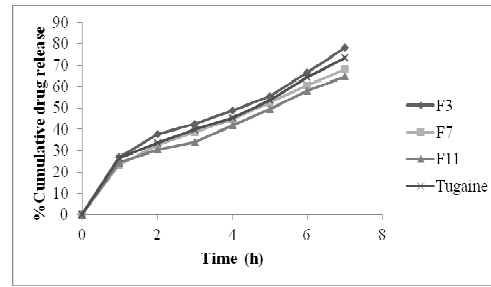


Figure.4 Diffusion of Minoxidil from HPMC K100 based formulations F9 to F12

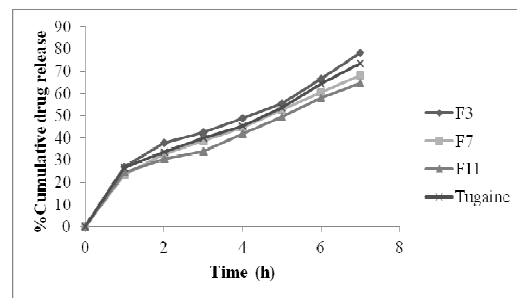


Figure.5 Comparison of release profile of F3, F7 and F11 with marketed product (Tugain 5%, Cipla)

diffusion through dialysis membrane. Hence, the formulation containing Natrosol is most effective in sustaining the release of Minoxidil (over the period 7 h).

The similarity factor (f_2) for optimized formulations F3, F7 and F11 were found to be 83.12, 65.41, and 59.13 respectively for Tugain5% which indicated similarity with the marketed product.

Results revealed that formulation F3 (Natrosol) significantly prolonged the drug release when compared to drug release from marketed formulation. (Figure.5)

Table.5 Determination of Gelling Capacity, Viscosity, Homogeneity, Grittiness, Extrudability, Ph and Drug Content

Formulation code	Gelling Capacity	Viscosity (cps)	Homogeneity	Grittiness	Extrudability	pH	% Drug Content
F1	Soft gel	9854	+	-	+	6.4	99.39 ± 1.96
F2	Soft gel	11245	+	-	+	6.3	98.79 ± 3.39
F3	Soft gel	13596	+++	-	++	6.2	99.39 ± 1.09

F4	Hard gel	16852	+++	-	+++	6.4	100.01 ± 0.73
F5	Viscous liquid	4085	++	-	+	6.2	96.61 ± 2.62
F6	Viscous liquid	11226	++	-	+	6.1	98.43 ± 1.42
F7	Soft gel	13549	+++	-	+++	6.3	99.54 ± 1.12
F8	Soft gel	17545	+++	-	+++	6.2	98.79 ± 1.07
F9	Viscous liquid	5265	++	-	+	6.3	99.50 ± 1.43
F10	Viscous liquid	6389	++	-	+	6.3	98.56 ± 1.26
F11	Soft gel	10685	++	-	+++	6.5	99.23 ± 0.89
F12	Hard gel	14596	++	-	+++	6.2	99.15 ± 1.32

Indication: + Poor, ++ Good, +++ Excellent, - Absent

Table.7 Stability study parameters of Minoxidil gel formulations F3, F7 and F11

Parameter for assessment	Formulation Code											
	Initial	F3			F7				F11			
		30 Days	60 Days	90 Days	Initial	30 Days	60 Days	90 Days	Initial	30 Days	60 Days	90 Days
Appearance (Clearance/ Transparency)	√	√	√	√	√	√	√	√	√	√	√	√
pH	6.4	6.3	6.3	6.2	6.4	6.3	6.2	6.1	6.3	6.2	6.2	6.1
Drug content	99.45	99.15	98.89	96.45	99.53	99.25	98.84	98.23	96.02	95.56	95.2	95.94
Viscosity (cps)	16850	16215	16164	16012	17540	17326	17256	17025	7780	7775	7456	7254

Table.8 Scores of skin irritation study

Skin reaction	Score	Experimental score Formulation		
		F3	F7	F11
Erythema and eschar formation	1	0	0	0
Very slight erythema	2	0	0	0
Well defined erythema	3	0	0	0
Severe erythema	4	0	0	0
Total possible erythema score	4	0	0	0
Edema formation	1	0	0	0
Very slight edema	2	0	0	0
Moderate edema	3	0	0	0
Severe edema	4	0	0	0
Total possible edema score	4	0	0	0
Total possible score for skin irritation	8	0	0	0

The experimental findings suggest that formulations F3, F7 and F11 were showed good stability and there is virtually no impact of change on the physical parameters of the selected Minoxidil gel formulations (Table.7).

The numerical score for all the probable toxicity symptoms read zero for the formulations F3, F7 and F11. Hence, they were non irritant and safe for administration (Table.8).

4. Conclusion

The effect of various concentrations of Natrosol, Carbopol 974 and HPMC K100 evaluated in the present study exhibited significant effect on the response release of the formulation. The drug release decreased significantly when the amount of Natrosol, Carbopol 974 and HPMC K100 in the gel formulation is increased from formulation. The drug release is inversely proportional to the viscosity of the gel formulations. The formulation F3 (Natrosol) significantly prolonged the drug release when compared to drug release from marketed formulation. The similarity factor (f_2) for present work is studied which revealed similarity of optimized formulation with marketed product. A stable Minoxidil gel formulation is prepared by using Natrosol, Carbopol 974 and HPMC K100 and is a promising approach in the treatment of alopecia.

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