International Journal of Pharmacy and Pharmaceutical Sciences
ISSN- 0975-1491 Vol 2, Suppl 3, 2010

Research Article

DEVELOPMENT AND EVALUATION OF TOPICAL GEL OF MINOXIDIL FROM DIFFERENT POLYMER BASES IN APPLICATION OF ALOPECIA

LOVELEEN PREET KAUR *, RAJEEV GARG, G. D GUPTA

Department of Pharmaceutics, ASBASJSM College of Pharmacy, Bela, Ropar, India. Email: loveleen585@gmail.com, loveleen_pharma85@yahoo.com

Received: 20 Oct 2009, Revised and Accepted: 28 Feb 2010

ABSTRACT

Topical gel formulations of minoxidil were prepared using these polymers such as Carbopol-934, Carbopol-941, Poloxamer 188 in different concentration for the treatment of alopecia. The gels were evaluated for various parameters such as homogeneity, grittiness, skin irritancy, extrudability, *in-vitro* drug release, *in-vitro* permeation study through mouse skin, viscosity(Brooke field viscometer), pH, Spreadability, drug content, stability studies. The *in-vitro* release rate of gel was evaluated using Franz diffusion cell containing cellophane membrane with phosphate buffer pH 7.4 as the receptor medium. The release rate of the gel was found to obey Higuchi model. The percentage of drug release follow following order Poloxamer 188> Carbopol-934 > Carbopol-941.

INTRODUCTION

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 are androgenic alopecia and alopecia areata.[1]

Androgenic alopecia is the most commonly recognized form of nonscaring alopecia in humans and is known by a number of descriptive terms, such as male and female pattern baldness (alopecia), inherited baldness or simply baldness. Androgenic alopecia has been defined as an autosomal dominant disorder with variable penetrance (probably polygenic mode of inheritance) with the strong predominance in males less than 40 years of age. Alopecia areata occur in people who are apparently healthy and have no skin disorder.[2] the most common type of alopecia areata involves hair loss in one or more round spots on scalp. Alopecia areata is characterized by round or oval patches of nonscarring hair loss. 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 are involved with alopecia areata and 1.7 % of population experiences an episode of alopecia areata during their life time.[3] The etiology and pathogenesis of alopecia areata is still uncertain, but many factor have been described in its pathogenesis. Example genetic, family history, atopic state, non specific immune and anagen specific autoimmune reactions, possible emotional stress, infectious agents and neurological factor.[4]

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 loss.[5]

Many substances have been investigated in attempts to cure male pattern baldness e.g. herbal products such as garlic onion gel which are claimed to have hair growth promoting properties but the scientific bases still lacking. Bacteria, fungi, protozoa and viruses have been shown to sensitive to crushed garlic preparation. So one of the well known effective substance is minoxidil which is hypertensive drug but one of its side effects which act in application of alopecia. It was suggested that the hair growth by minoxidil was due to increase of cutaneous blood flow. Topically applied minoxidil was shown to improve blood flow in human balding scalp.[6-8]

A topical gel of minoxidil prepared from binary solvent system of ethanol and propylene glycol. The penetration of minoxidil into and through the skin generally increased as ethanol fraction of binary solvent vehicle was increased due to one or more combination of following

- An effect where in ethanol evaporates quickly and concentrates the drug in the residue of formulation that remains on the skin.
- Penetration enhancement affects wherein ethanol alters the physical integrity of stratum corneum barrier resulting in an increase in the ability of drug to penetrate the skin.

Presently in India minoxidil is marketed as topical solution in aqueous vehicle in treatment of alopecia which offers limited contact time with the scalp. Hence the need for a suitable topical delivery system which would increase the contact time, leading to 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.

Table 1: Different gel formulations

Ingredients	Formulation code											
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
Minoxidil	2	2	2	2	2	2	2	2	2	2	2	2
Carbopol-934	0.5	1	1.5	2.0	-	-	-	-	-	-	-	-
Carbopol-941	-	-	-	-	0.5	1	1.5	2.0	-	-	-	-
Poloxamer 188	-	-	-	-	-	-	-	-	15	20	25	30
Propylene glycol	15	15	15	15	15	15	15	15	15	15	15	15
Triethanolamine	0.4	0.5	0.6	0.7	0.3	0.4	0.5	0.6				
Ethanol	30	30	30	30	30	30	30	30	30	30	30	30
Propyl paraben	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Water	51.6	51.0	50.4	49.8	51.7	51.1	50.5	49.9	37.5	32.5	27.5	22.5

Table 2: Physicochemical characteristics of Minoxidil gels formulations

Formulation	Homogeneity	Grittiness	Extrudibility
F_1	++	-	+
F_2	+++	-	++
F_3	+++	-	++
F_4	+++	-	+++
F_5	++	-	+
F_6	+++	-	++
F_7	+++	-	++
F_8	+++	-	+++
F_9	++	-	+
F_{10}	+++	-	++
F_{11}	+++	-	++
F_{12}	+++	-	+++

Excellent +++, Good ++, Satisfactory +, No grittiness -

MATERIALS AND METHODS

Minoxidil (Cachet pharmaceutical, Baddi), Carbopol-934 and Carbopol-941 (Loba chemicals), Poloxamer 188 (Signet Chemicals), Propylene glycol (S.D Fine chemical, Mumbai) and other ingredients used were of analytical grade.

Preparation of carbopol gel

Required amount of Minoxidil was dissolved in solvent mixture, then the required quantity of polymer was added to the solution with constant stirring at 500 rpm for about 2 hours. Later the speed was reduced to avoid air entrapment. Then the solution was neutralized with triethanolamine.

Preparation of poloxamer gel

The pluronic gels were prepared by modification of the "Cold dispersion" method described by Schmolka. The weighed amount of drug and poloxamer were placed in beaker and left in an oven at 110^0C for 15 minutes to obtain a homogeneous liquefied mixture. After the solution was cooled to room temperature, the other ingredient was added with continuous agitation. The beaker was left in a refrigerator until a clear solution was obtained. The gel was formed when the solution was brought back to room temperature and stored at ambient temperature prior use.

Evaluation

Following parameters were used for the evaluation of gels:

Homogeneity

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates.

Grittiness

All the formulations were evaluated microscopically for the presence of particles if any no appreciable particulate matter was seen under light microscope. Hence obviously the gel preparation fulfils the requirement of freedom from particular matter and from grittiness as desired for any topical preparation.

Extrudability study

A good gel extrude optimally from the gel with slight pressure applied. The extrudability of formulations from aluminium collapsible tubes, was determined using universal tube filling machine. Aluminium collapsible tubes filled with 10g gels were held between two clamps. A tube was compressed and extrudibility of the formulation was determined in terms of weight in grams required to extrude a 0.5 cm. ribbon of gel in 10 seconds.

Measurement of pH

The pH of minoxidil gel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100 ml of distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values were calculated.

Drug content

A 500 mg of Minoxidil gel was taken and dissolved in 50 ml of phosphate buffer pH 7.4.The volumetric flask were kept for 2 hours and shaken well in a shaker to mix it properly. The solution was passed through the filter paper and filtered. The drug content was measured spectrophotometrically at 290 nm against corresponding gel concentration as blanks.

Viscosity study[9]

The measurement of viscosity of the prepared gel was done with a Brookfield Viscometer. The gels were rotated at 20 and 30 rpm using spindle no. 64. At each speed, the corresponding dial reading was noted.

Spreadability[10]

One of the criteria for a gel to meet the ideal quantities is that it should possess good Spreadability. It is the term expressed to denote the extent of area to which gel readily spreads on application to skin or affected part. The therapeutic efficacy of a formulation also depends upon its spreading value.

Spreadability is expressed in terms of time in seconds taken by two slides to slip off from gel and placed in between the slides under the direction of certain load, lesser the time taken for separation of two slides, better the spreadability.

It is calculated by using the formula: $S = M. L / T$

Where M = weight tied to upper slide

L = length of glass slides

T = time taken to separate the slides

In-vitro diffusion studies[11-13]

The in vitro diffusion studies of prepared gel were carried out in Keshary–Chien diffusion cell using through a cellophane membrane.100 ml of phosphate buffer was used as receptor compartment, then 500 mg of gel containing 10 mg of minoxidil was spread uniformly on the membrane. The donor compartment was kept in contact with a receptor compartment and the temperature was maintained at 37 ± 0.5^0. The solution on the receptor side were stirred by externally driven Teflon coated magnetic bars at predetermined time intervals, pipette out 5ml of solution from the receptor compartment and immediately replaced with the fresh 5ml phosphate buffer. The drug concentration on the receptor fluid was determined spectrophotometrically against appropriate blank. The experiment was carried out in triplicate.

Table 3: Physicochemical evaluation data of Minoxidil gels

Formulation	pH	Drug content	Viscosity	Spreadability
F_1	7.29±0.18	96.54±0.14	16426.67±17.55	32.87±1.60
F_2	6.78±0.08	95.42±0.24	17628.33±7.63	25.49±1.83
F_3	6.56±0.15	97.21±0.25	18648.33±10.40	21.68±1.11
F_4	6.34±0.06	93.70±0.60	18938.33±15.27	17.61±1.48
F_5	7.12±0.24	96.52±0.48	17341.67±20.20	24.68±2.04
F_6	6.67±0.17	97.37±0.31	18521.67±12.58	18.67±1.53
F_7	6.61±0.13	96.08±0.40	19761.67±7.63	14.65±1.51
F_8	6.56±0.12	98.26±0.21	19963.33±10.40	11.22±1.02
F_9	6.68±0.08	96.34±0.70	7866.67±7.64	34.81±0.84
F_{10}	6.41±0.19	93.60±0.40	8931.66±10.40	31.19±1.24
F_{11}	6.46±0.13	96.47±0.40	9943.33±11.54	26.29±2.70
F_{12}	6.70±0.12	95.77±0.67	11226.67±11.54	24.43±1.64

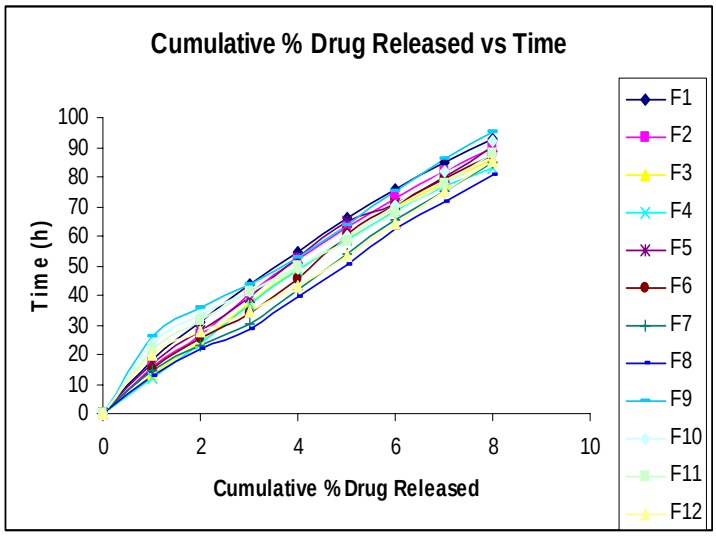

Fig. 1: *In-vitro* release of Minoxidil from different gel formulations through Cellophane Membrane

Skin irritation studies

The albino mice of either sex weighing 20-22gms were used for this test. The intact skin was used. The hair was removed from the mice 3 days before the experiment. The animals were divided into two batches and each batch was again divided into two groups. The gel containing drug were used on test animal. A piece of cotton wool soaked in saturated drug solution was placed on the back of albino mice taken as control. The animal were treated daily upto seven days and finally the treated skin was examined visually for erythema and edema.

***Ex vivo* evaluation**

The abdominal hair of albino mice, weighing 22-25 g, was shaved using an electric razor after sacrificing with excess chloroform inhalation. The abdominal skin was surgically removed and adhering subcutaneous fat was carefully cleaned. The epidermis was then separated from dermis by soaking the full thickness skin in 2 M sodium bromide solution in water for 6-8 h. The epidermis was thoroughly washed with water, dried at 25% RH, wrapped in aluminium foil and stored in freeze until further use. For *ex vivo* 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 was applied on the skin and then fixed in between donor and receptor compartment of Keshary-Chien diffusion cell.

The receptor compartment containing phosphate buffer of pH 7.4. The temperature of the medium was thermostatically controlled at 37±1^{0}C by surrounding water jacket and the medium was stirred with bar magnet using magnetic stirrer. Aliquots, withdrawn at predetermined intervals of time, were spectrophotometrically estimated at 290 nm against their respective blank formulation treated in the same manner.

RESULTS AND DISCUSSION

Topical gels of minoxidil were prepared with an intention of increasing the contact time of drug with the scalp as compared to topical solution. The carbopol-941, carbopol-934 and poloxamer 188 in different concentrations were employed for the preparation of topical gel of minoxidil shown in table 1.

The results of skin irritancy studies are shown in table.4 which indicated that the prepared gels donot produce any dermatological reaction and are well tolrated by mice. The results of *ex vivo* studies of gel formulations and topical minoxidil solution were shown in figure 2. The release pattern of drug from marketed topical solution showed a maximum drug releases this could be due to formation of saturated solution due to evaporation of alcohol and water which leads to increased mass transfer to receptor compartment. As reported earlier propylene glycol in addition to being absorbed, also evaporates resulting in supersaturated solution followed by precipitation of minoxidil leading to abrupt absorption pattern.

Table 4: Skin irritation scores following gel application

Skin reaction	Score	Experimental score formulations		
		F2	F6	F10
Erythema and eschar formation				
Very slight erythema	1	0	0	0
Well defined erythema	2	0	0	0
Moderate to severe erythema	3	0	0	0
Severe erythema	4	0	0	0
Total possible erythema score	4	0	0	0
Edema formation				
Very slight edema	1	0	0	0
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

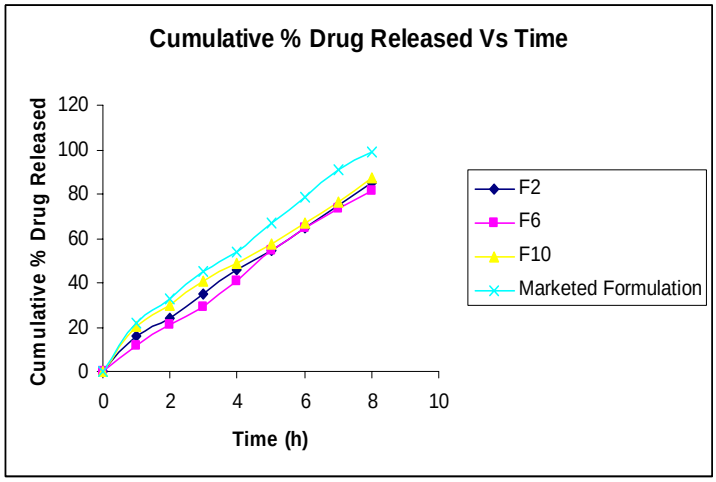

Fig. 2: *Ex Vivo* Plot of Minoxidil From Different Gel Formulation And Marketed Topical Solution

Table 5: Stability data

Temperature	Gels	Time (month)	Drug content (%)	Appearance
4^{0}C	F_2	0	100±0.00	++
		3	96.46±1.16	++
	F_6	0	100±0.00	++
		3	95.48±1.14	++
	F_{10}	0	100±0.00	++
		3	96.54±1.01	++
25^{0}C	F_2	0	100±0.00	++
		3	96.13±1.17	++
	F_6	0	100±0.00	++
		3	95.34±1.15	++
	F_{10}	0	100±0.00	++
		3	96.27±0.95	++
37^{0}C	F_2	0	100±0.00	++
		3	96.02±1.07	++
	F_6	0	100±0.00	++
		3	95.20±1.06	++
	F_{10}	0	100±0.00	++
		3	95.94±1.01	++

It mean drug is absorbed from site of application as long as it remain in site of application as long as it reman in solution form. So with an intention to keep the minoxdil in solution form, and thus prolongng the time of absorption, gel formulations were prepared. The result of stablity studies are shown in table 5 There were no signficant changes in the viscosity, drug content and physical appearance of the gel. After storing at different temperature conditions for three months.

REFERENCES

1. Tang L, Lui H, Sundberg JP, Bissonnette R, Mclean DI, Shapiro J: Restoration of hair growth with topical diphencyprone in mouse and rat models of alopecia areata. J Am Acad Dermatol 2003;49(6):1013-1019.
2. Semalty M, Semalty A, Joshi GP, Rawat MSM : Herbal hair growth promotion strategies for alopecia.Indian Drugs 2008;45(9): 689-700.
3. Shirai A, Ikeda J, Kawashima S, Tamoki T, Kamiya T. KF19418 : a new comound for hair growth promotion *in-vitro* and *in-vitro* mouse models. J Dermatological Science 2001;25: 213-218.
4. Ranganathan S and Shobana S : Evaluation of herbal hair oil in reducing hair fall in human volunteers. Indian Drugs 2007; 45(6): 451-455.
5. John PS, Beamer WG, Uno H, Neste DM, King LE. Androgenetic alopecia : *In Vivo* models. Experimental and Molecular Pathology 1999; 67: 118-129.
6. Adhirajan N, Kumar DV, Gowri C : Developement and Evaluation of herbal formulations for hair growth. Indian Drugs 2001; 38(11): 559-563.
7. Hajheydari Z, Jamshidi M, Akbari J, Mohammad pour: Comparing the therapeutic effects of fenasteride gel and tablet in treatment of androgenetic alopecia. Indian J Venereol Leprol 2009;75(1) : 47-51.
8. Lognathan V, Manimaran S, Jaswanth A, Sulaiman A, Reddy MVS, Kumar BS, Rajaseskaran A. The effects of polymers and permeation enhancers on the releases of flurbiprofen from gel formulations. Indian J Pharm Sci 2001; 63(3): 200-204.
9. Martinez MAR, Gallardo JLV, Benavides MMD, Duran JDGL, Lara V
   G : Rheological behavior of gels and meloxicam release. Int J Pharm 2007; 333: 17-23.
10. Garg A, Aggarwal D, Garg S, Singla AK : Spreading of semisolid formulations: An update. Pharm Tech 2002;84-104.
11. Yamaguchi Y, Sato H, Sugibayashi K, Morimoto Y: Drug release test to assess quality of topical formulations in japenese market. Drug Dev Ind Pharm 1996;22(7): 569-577.
12. Ruckmani K, Jayakar B, Durgamani S, Easwari TS, Hurmathunisea S: In-vitro release studies on topical preparations of Ketorolac Tromethamine. Indian Drugs 1998; 35(5): 303-305.
13. Kattige MAS, Hadkar UB : Diffusion studies on polymorphic forms of drugs. Indian Drugs 1995; 33(3): 112-119.