Turk J Pharm Sci 11(2), 153-162, 2014

Original article

Formulation and *In Vitro* Evaluation of Minoxidil Topical Gel

Rabinarayan PARHI[1]*, Bhaskara Rao TERAPALLI[1], B. B. TEJA[2]

[1] GITAM University, GITAM Institute of Pharmacy, Gandhi Nagar Campus, Rushikunda, Visakhapatnam-530045, Andhra Pradesh, INDIA, [2]TherDose Pharma Pvt Ltd, Pragati Nagar, Kukatpally, Hyderabad-500090, Andhra Pradesh, INDIA

The objective of the present investigation is to develop topical gel of minoxidil using model polymers such as hydroxypropyl methylcellulose K4M (HPMC K4M) and hydroxypropyl cellulose (HPC) at different concentrations (1, 2 and 3%) individually and in combination. The drug and polymers compatibility study was carried out by FTIR technique. The gels were evaluated for drug content, viscosity, pH, homogenity, grittiness and *in vitro* drug release. The FTIR spectra of drug alone and in physical mixture with polymers did not show any shift in major peaks, which indicates no drug-polymer interaction. All the data obtained from above physicochemical parameters were satisfactory. *In vitro* drug release of gels was performed using Franz diffusion cell of 25 mL capacity with cellulose acetate membrane in phosphate buffer pH 6.8 as receptor medium. According to the release study, the drug release was decreasing with the increasing polymer concentration in each formulation. The correlation coefficient (r^2) values demonstrate that the drug release pattern followed Higuchi model and the release exponent (n) values were within 0.45 to 0.85 for all formulations except FG3, FG4 and FG7. The above results showed that swelling and diffusion (Non-Fickian diffusion) were the drug release mechanism. To know the marketing feasibility, the release data of all the formulations were compared with the marketed formulation (Tugain gel) and it was found that formulation FG2 was having highest similarity with similarity factor (f2) of 77.79.

Key words: Minoxidil, Alopecia, Higuchi kinetics, Fickian diffusion, Similarity factor.

Minoksidil Topikal Jel'in Formülasyonu ve *In vitro* Değerlendirmesi

Sunulan bu araştırmanın amacı, hidroksipropil metilselüloz K4M (HPMC K4M) ve hidroksipropil selüloz (HPC)'un model polimer olarak ayrı ayrı ve kombinasyonları halinde farklı konsantrasyonlarda (%1, 2, 3) kullanımıyla minoksidil topical jel geliştirmektir. Etken madde ve polimer geçimliliği çalışması FTIR ile yapıldı. Geller, etken madde içeriği, viskozite, pH, homojenlik, dayanıklılık ve *in vitro* etken madde salımı ile değerlendirildi. Etken maddenin tek başına ve polimerle fiziksel karışımınının FTIR spektrumunun major piklerde kayma olmaması etken madde-polimer etkileşimi olmadığını gösterdi. Yukarıda belirtilen tüm fizikokimyasal parametrelerden elde edilen veriler tatmin ediciydi. Jellerden etken madde salımı 25 mL kapasiteli Franz difüzyon hücrelerinde reseptör ortam olarak pH 6.8 tamponunda selüloz asetat membran ile yapıldı. Salım çalışmalarına göre, tüm formülasyonlarda artan polimer konsantrasyonları ile etken madde salımı azaldı Korelasyon katsayısı (r^2) değerleri etken madde salımının Higuchi modeline uyumunu gösterdi ve salım katsayısı (n) değerleri FG3, FG4 ve FG7 formülleri dışında tüm formüllerde 0.45 ile 0.85 arasındaydı.Yukarıdaki sonuçlar etken madde salım mekanizmasının şişme ve difüzyon şeklinde (Non-Fick) olduğunu gösterdi. Pazarlama fizibilitesini bilmek için, tüm formüllerin salım verileri pazarlanan formülasyon (Tugain Gel) ile karşılaştırıldı ve FG2'nin 77.79'luk f2 benzerlik faktörü ile en fazla benzer olduğu bulundu.

Anahtar kelimeler: Minoksidil, Alopecia, Higuchi kinetiği, Fick difüzyon, Benzerlik faktörü.

***Correspondence:** E-mail: bhu_rabi@rediffmail.com, Tel: 09052983544

INTRODUCTION

Alopecia or loss of hair affects approximately 70% males and 30% females of the world population (1). Alopecia areata and androgenic alopecia (male pattern baldness) are two common types of alopecia. Alopecia areata is characterized by round or oval patches of non-scarring hair loss. It is believed that it only causes scalp hair loss that may be partial (transient or persistent) or complete (alopecia totalis), but sometimes it may progress to cause total body hair loss (alopecia universalis). Till date there is no clear etiology and pathogenesis, but it is believed that there are many factors such as autoimmune, hereditary and emotional stress, infectious agents and neurological factors behind it (2). On the other hand, androgenic alopecia or inherited baldness is androgen dependent thinning of scalp hair that follows a definitive pattern. For the treatment of androgenic alopecia, US Food and Drug Administration approved finasteride at oral dose of 1mg per day and minoxidil at of 2 and 5% as topical solutions (3, 4).

Minoxidil (6- (1-Piperidinyl) -2, 4-pyrimidinediamine 3- oxide) (Figure 1) has been widely used as only topical drug for the treatment of androgenic alopecia in men and women as well. Hair cycle consisting of four phases namely growth (anagen), regression (catagen), rest (telogen) and shedding (exogen). The mechanism of minoxidil on hair growth is believed to be its direct stimulation on hair follicle, which causes entry of the resting stage of the hair follicles to growing phase (5, 6). Furthermore, enhanced microcirculation around the hair follicles and alteration of androgen effect on genetically programmed hair follicles are also contributed to the effect (7).

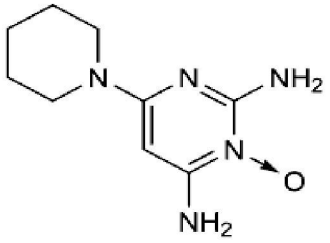

Figure 1. Structure of minoxidil

Conventionally, minoxidil has been formulated as solution containing ethanol-propylene glycol and water due to its lipophilic nature (8). The major problem with this formulation is the reversal of minoxidil in to its insoluble form after the application on the skin due to ethanol evaporation from the solution (4). The next option coming to our mind is to formulate gel as it has several advantages over liquids like ease of fabrication, better occlusion, controlled release of drug for longer period and better stability (9).

The aim of this work is to develop and evaluate gels containing HPMC and HPC individually and combination as well. Subsequently, the best formulation is selected and compared with the Tugain gel in order to find marketing potential.

MATERIALS AND METHODS

The active ingredient, Minoxidil, was obtained from Dr. Reddy Lab Pvt. Ltd, Hyderabad, India. HPMC K4M and HPC were purchased from Colorcon, India. Cellulose acetate membrane (Molecular weight cut off 12,000 Da) was supplied by Sigma Aldrich. All other chemicals used during the course of work were of analytical grades.

Solubility study of the drug in different medium

Drug solubility study was performed to find out best possible combination of water, ethanol and propylene glycol. An excess quantity of minoxidil was taken in each of the medium (10 mL) and was shaken in water bath shaker (Remi, India) for 24 h at 32 °C. The solution was then passed through a filter paper (pore size 0.45 μm, Millipore). After suitable dilution the amount of drug dissolved was determined spectrophotometrically (Model Lambda-35, PerkinElmer, Massachusetts, USA) at 288 nm.

FTIR studies

Before any formulation development, it is necessary to check possible drug-polymer incompatibility. This is performed on

minoxidil, HPMC and HPC individually and in physical mixture by using a FTIR (Bruker-α-T, Germany). The method used was KBr disc method.

Preparation of minoxidil gel

Accurately weighed amount (2 g) of minoxidil was dissolved in solvent mixture (ethanol, propylene glycol and water). Then, the required quantity of polymer (s) (Table 1) was added to the solution with constant stirring on a magnetic stirrer (Remi, India) at 500 rpm for about 2 hours. Later the speed was reduced to avoid air entrapment. Then, the solution was neutralized with triethanolamine.

Viscosity study

The measurement of viscosity of the prepared gel was carried out by using Brookfield Viscometer (Model DV-E). The viscosity was measured at 30 rpm using spindle no. 64 (11, 12).

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 (10).

Grittiness

All the topical preparations must be free from the particulate matter. To ensure it,

Table 1. Composition of different gel formulations of minoxidil

Ingredients	Formulation Code								
	FG1	FG2	FG3	FG4	FG5	FG6	FG7	FG8	FG9
Minoxidil (g)	2	2	2	2	2	2	2	2	2
HPC (g)	1	2	3	---	---	---	0.5	1	1.5
HPMC (g)	---	---	---	1	2	3	0.5	1	1.5
Ethanol (g)	30	30	30	30	30	30	30	30	30
Propylene glycol (g)	15	15	15	15	15	15	15	15	15
Water (g)	52	51	50	52	51	50	52	51	50

Drug content

Accurately, 500 mg of minoxidil gel was transferred in to a volumetric flask containing 50 mL of phosphate buffer pH 6.8. The volumetric flask was shaken for 2 h in water bath shaker. Then, the solution was filtered and the drug content was measured spectrophotometrically at 288 nm (10).

Measurement of pH

The pH of minoxidil gel formulations was determined by using digital pH meter (Model S40K, Mettler Toledo). One gram of the 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 (11).

formulations were evaluated microscopically (light microscope) for the presence of particles (10).

In vitro drug release studies

The *in vitro* drug release studies of prepared gel were carried out in modified Franz diffusion cell (Murthy lab, Hyderabad, India) through a dialysis membrane (cellulose acetate membrane, Sigma Aldrich). The receptor compartment was filled with 25 mL of phosphate buffer pH 6.8. Amount of gel equivalent to 10 mg of minoxidil was taken and spread uniformly over the dialysis membrane. The donor compartment was kept in contact with a receptor compartment with the clamps and the temperature was maintained at 32±0.5 °C. The medium on the receptor compartment was stirred by

externally driven magnetic bars. At pre-determined time intervals (1, 2, 3, 4, 5, 6, 7, 8 h), aliquots of 5 mL were withdrawn from the receptor compartment with the help of pipette and replaced immediately with the same volume phosphate buffer maintained at same temperature. The drug concentration on the receptor fluid was determined spectrophotometrically at 288 nm against appropriate blank (13, 14).

Drug release kinetics

To understand the mechanism of drug release from different formulations, *in vitro* drug release data were fitting to various kinetic models such as zero order, first order, Higuchi and Korsemeyer-Peppas equation.

Statistical analysis

The release profiles of all formulations were compared with pure drug by using similarity factor (f_2), presented in the following equation

$$f_2 = 50 \log \{[1+ (1/n) \Sigma (R_t - T_t)^2]^{-0.5} \times 100\}$$

where n is the number of time points. Rt and Tt are the percent drug released at each time point for the reference and the test, respectively. The similarity factors of all the formulations were found out in comparison to Tugain gel in order to get highest similarity. In addition, comparisons were also made between the prepared formulations. A similarity factor (f_2) between 50 and 100 suggests that the two release profiles are similar (15, 16).

One way analysis of variance (One-way ANOVA) with student Newman Keuls multiple comparison test was used to measure statistical significant differences between various *in vitro* drug release data at 95% confidential level (5% significance level). It was performed employing 30 days trial version of GraphPad Instat software.

RESULTS AND DISCUSSION

Drug solubility

The drug solubility was conducted in water, ethanol and propylene glycol and data were presented in the Table 2. From the data, it is clear that the drug has highest solubility (22mg/mL) in ethanol and lowest in water which is accordance with the literature (4). The ratio of ethanol to propylene glycol was fixed at 2:1 in all the formulations.

Table 2. Solubility data of minoxidil in different medium.

Solvent	Solubility (mg/mL)
Water	2.2 ± 0.10
Ethanol	22 ± 2.50
Propylene glycol	13 ± 1.43

FTIR studies

FTIR studies were conducted to ascertain the interaction between the drug and selected polymers. FTIR spectra of pure drug, individual polymers and their physical mixture with drug were presented in Figure 2. The spectra of pure drug shown the major peaks at 3423.72 cm^{-1} (N-H stretching, primary amine), 1643.98 cm^{-1} (N-H bending, primary amine), 1450.06 cm^{-1} (C=C aromatic stretching), 1227.04 cm^{-1} and 1210.62 cm^{-1} (C-N stretching), 756.60 cm^{-1} (N-H wag). There was no significant shift in major peaks observed from the spectra of drug and polymer physical mixtures, which indicates there were no major interaction between drug and selected polymers.

Physicochemical evaluation

The physicochemical parameters were determined and presented in Table 3. From the data, it is clear that formulation FG1, FG2, FG7 and Tugain gel shown excellent homogeneity and no formulation indicated grittiness. The drug content of all the prepared formulations was found to be between 93.84 and 103.84 %, which is in limit of 100±10 % (17, 18). The pH values were either slightly acidic or alkaline. All the formulations can be taken for further studies as data of above parameters were within the limits.

The viscosity of any semisolid should provide two important properties such as smooth flow of content out from the container and spread on the affected area easily (11). The viscosity results were depicted in bar graphs (Figure 3). The first three formulations containing HPC (at three different

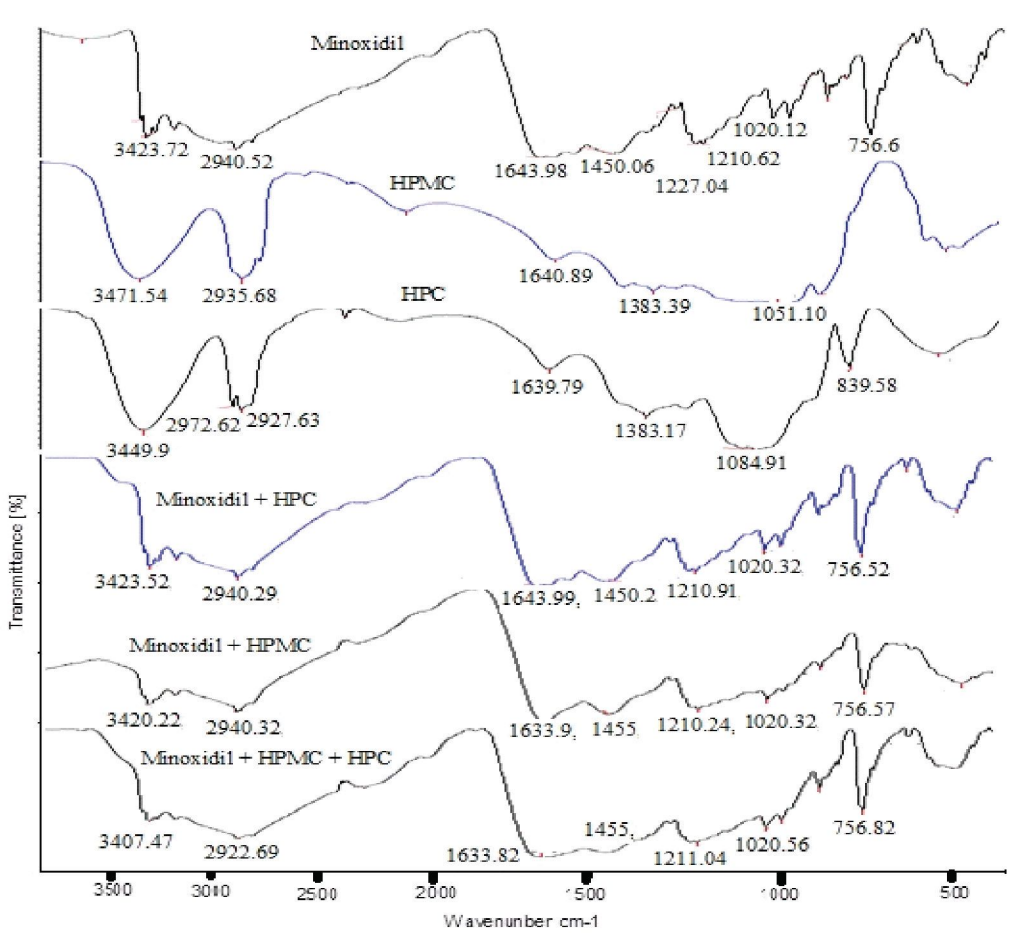

Figure 2. FTIR spectra of minoxidil, HPMC, HPC and physical mixture of minoxidil with HPMC, HPC and with both HPMC and HPC.

Table 3. Physicochemical parameter data of prepared and innovator gels of minoxidil (n=3)

Formulation code	Homogenity	Grittiness	Drug content (%)	pH
FG1	+++	-	97.82±2.34	6.32±0.12
FG2	+++	-	94.40±3.9	6.91±0.1
FG3	++	-	93.54±1.42	7.12±0.2
FG4	++	-	95.43±0.68	6.56±0.23
FG5	++	-	93.84±0.23	6.31±0.4
FG6	+	-	96.23±5.1	7.27±0.03
FG7	+++	-	103.84±3.58	5.95±0.21
FG8	++	-	93.84±2.35	6.47±0.01
FG9	+	-	101.28±1.08	7.25±0.05
Tugain Gel	+++	-	98.57±0.27	6.93±0.24

concentration of 1, 2 and 3%), shown the increase in viscosity with the increase in concentration. The same trend was also seen in case of formulation containing only HPMC and the combination of HPC and HPMC in equal ratio. For the formulations containing equal concentration of HPC and HPMC, the formulation containing HPMC indicated higher viscosity. This is due to higher viscosity grade of HPMC as compared to HPC.

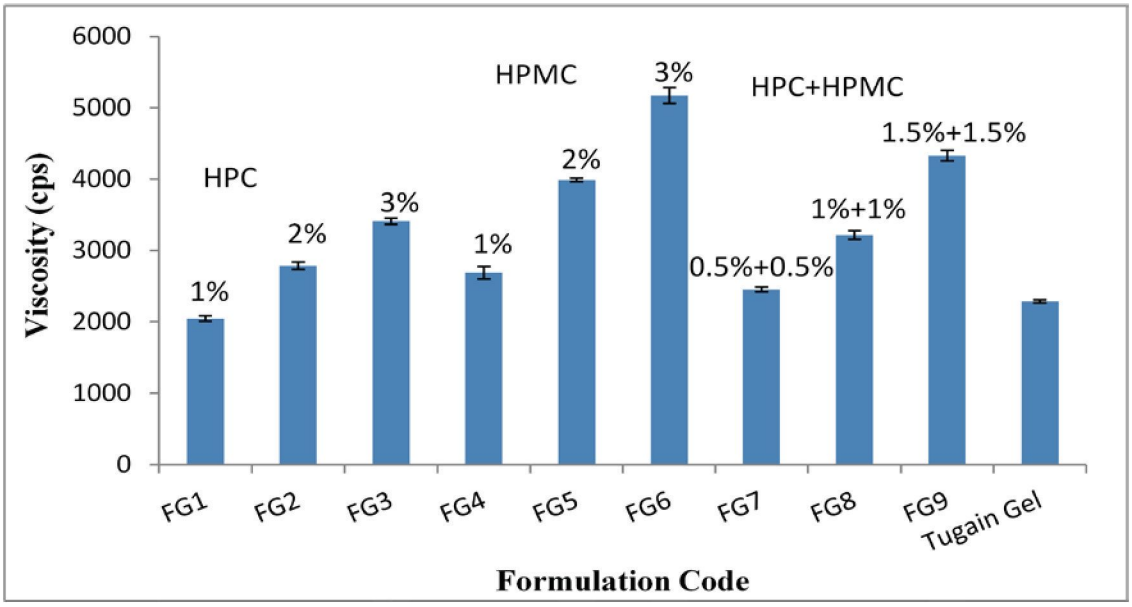

Figure 3. Comparison of viscosity of different formulations (n=5)

In vitro drug release studies

The *in vitro* drug release of all the prepared formulations were performed using Franz-diffusion cell for 8 h and data were used to plot a graph (Figure 4). The graph is demonstrating that the increase in individual polymer (either HPC or HPMC) concentration led to decrease in drug release. Increase in viscosity of gels upon increase in polymer concentration would have been contributed to the above cause. When the release of drug from the formulations containing two different polymers (HPC and HPMC) taken into consideration, the formulations having HPMC shown lower release than HPC at the same concentration. These differences in drug release are mainly due to difference in viscosity of the gel matrix (18). The viscosity of gel matrix may play a crucial factor in modifying the release of drug through the membrane when the drug diffusion through the gel is rate limiting step (19). In this case, HPMC is higher viscosity grade than that of HPC (20). The semi-synthetic polymer, HPMC, is used as carrier in most of the topical/transdermal formulation because of its non-toxic and high bioadhesion properties (21-23). From our studies, it was clear that HPC has demonstrated higher drug release. So, to prepare binary gel of above polymers was to provide optimum properties of bioadhesion, more drug release and patient compliance. The formulation FG7 showed highest drug release of 83% among the equal combination polymer gel.

Drug release kinetics

The mechanism of drug release from different formulation were determined by fitting *in vitro* drug release data to kinetic models such as zero order, first order, Higuchi and Korsemeyer-Peppas equation. The correlation coefficient (r^2) and release exponent (n) values were presented in the table 4. When the data were fitted to Higuchi equation, r^2 values for all the formulations except FG6 were above 0.95 indicating diffusion is the drug release. The n values for

formulations FG3, FG4 and FG9 were above 0.85 indicating superclass-II transport and for all other formulations it was between 0.45 and 0.85 demonstrating swelling and diffusion (non-Fickian diffusion) were the drug release mechanisms.

Analysis of in vitro drug release studies

The similarity factor (f2) was calculated for all the formulations in comparison to Tugain gel and also between the prepared formulations. All the f2 values are presented in the Table 5. Formulations FG1, FG2, FG4

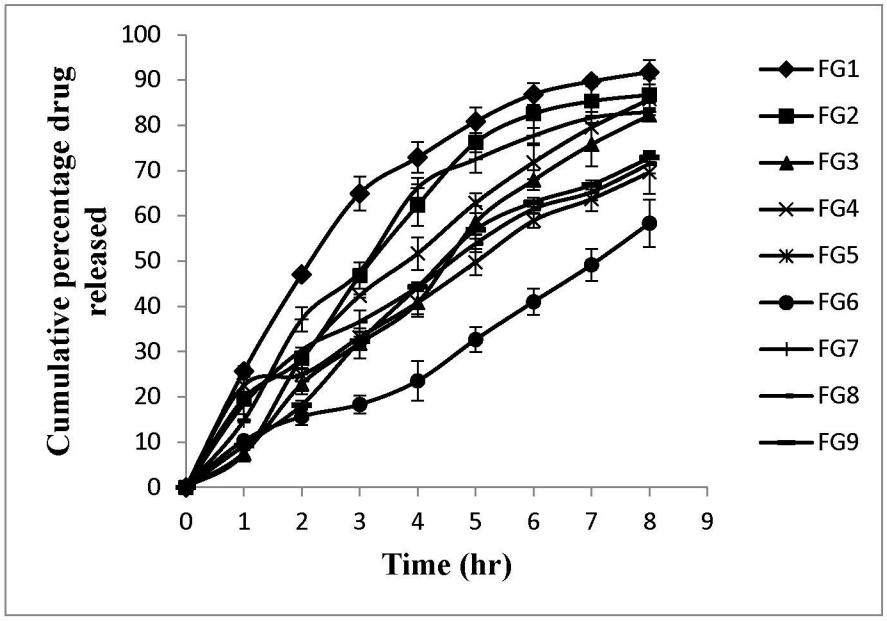

Figure 4. *In vitro* minoxidil release from different gel formulations through artificial membrane (n=3).

Table 4. Values of correlation coefficient and kinetic exponent of different minoxidil gels

Formulation Code	Zero Order	First Order	Higuchi	Korsmeyer-Peppas		
	Correlation coefficient (r^2)				n	Drug release Mechanism
FG1	0.877	0.767	0.955	0.953	0.606	Non-Fickian Diffusion
FG2	0.94	0.969	0.964	0.971	0.787	Non-Fickian Diffusion
FG3	0.99	0.893	0.986	0.983	1.128	Super case-II transport
FG4	0.976	0.887	0.997	0.942	1.113	Super case-II transport
FG5	0.969	0.979	0.962	0.944	0.593	Non-Fickian Diffusion
FG6	0.982	0.948	0.917	0.951	0.837	Non-Fickian Diffusion
FG7	0.914	0.945	0.959	0.943	0.817	Non-Fickian Diffusion
FG8	0.965	0.961	0.993	0.996	0.653	Non-Fickian Diffusion
FG9	0.976	0.935	0.986	0.984	1.034	Super case-II transport

and FG7 were having f2 values more than 50, indicating similar dissolution profile withTugain gel. Among above four formulations, f2 value for FG2 and Tugain gel was found to be highest (77.79). The f2 value of 71.63, highest among formulation pairs, was found between formulation FG5 and FG8.

One-way ANOVA data showed that there were no significant difference of *in vitro* drug release ($P < 0.05$ level) between the batches except between FG1 and FG6. The latter case indicates the types of polymer in association with concentrations (HPC at 1% in FG1, whereas HPMC at 3% in FG6) influencing the *in vitro* drug release from the above batches.

Table 5. Dissolution profiles comparison of prepared gels and innovator by similarity factor (f2).

Formulation	FG1	FG2	FG3	FG4	FG5	FG6	FG7	FG8	FG9
Tugain gel	51.91	77.79	41.6	51.76	35.29	23.76	64.82	38.45	38.08
FG1	--	48.57	32.02	38.35	29.15	19.71	49.19	31.66	30.07
FG2	--	--	43.11	52.77	36.8	24.58	65.87	39.95	39.8
FG3	--	--	--	59.74	51.45	34.88	43.31	55.04	63.15
FG4	--	--	--	--	44.75	29.94	54.75	49.87	51.31
FG5	--	--	--	--	--	41.74	37.88	71.63	59.59
FG6	--	--	--	--	--	--	25.32	38.26	38.84
FG7	--	--	--	--	--	--	--	41.97	40.65
FG8	--	--	--	--	--	--	--	--	61.65

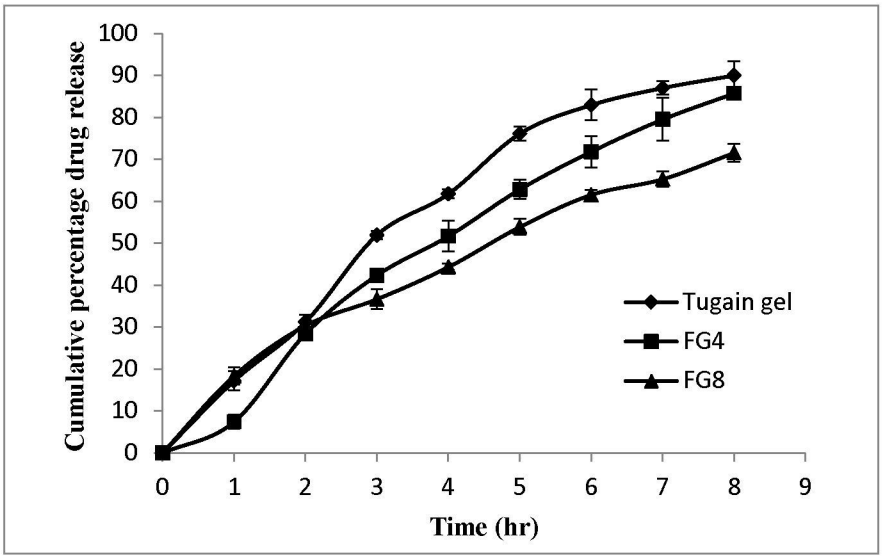

Figure 5. Comparison of *in vitro* drug release profiles of FG4, FG8 and Tugain gel (n=3)

Comparison of in vitro drug release profile of formulation FG4, FG8 and Tugain gel

The formulations FG4 and FG8 were selected as best formulations among all the prepared formulations as the r^2 values were above 0.99 for Higuchi model. So, the *in–vitro* drug release profiles of above formulations were compared with Tugain gel and presented in Figure 5. It is observed from the graph that the highest cumulative percentage of drug release (90.01%) is from the Tugain gel in 8 h as compared to 85.74 and 71.53% from the formulation FG4 and FG8, respectively.

CONCLUSIONS

In the present investigation, HPMC and HPC based gel formulations of minoxidil were developed and their *in vitro* drug release along with physicochemical parameters were evaluated. In order to find out marketing potential, all the formulations were compared with Tugain gel for similarity. The findings from above activities revealed that gel formulation to deliver minoxidil efficiently is feasible with above polymers. Further studies will be undertaken on *in vitro* skin permeation to realize clinically effective topical gel formulation for the treatment of androgenic alopecia.

ACKNOWLEDGEMENT

The authors are grateful to TherDose Pharma Pvt Ltd, Hyderabad, India, for providing necessary facilities to carry out the research work.

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 49, 1013-1019, 2003.
2. Subramanya RD, Coda AB, Sinha AA, Transcriptional profiling in alopecia areata defines immune and cell cycle control related genes within disease-specific signatures, Genomics 96, 146-153, 2010.
3. Price VH, Treatment of hair loss, N Engl J Med 341, 964-973, 1999.
4. Balakrishnan P, Shanmugam S, Lee WS, Lee WM, Kim JO, Oh DH, Kim DD, Kim JS, Yoo BK, Choi HG, Woo JS, Yong CS, Formulation and *in vitro* assessment of minoxidil niosomes for enhanced skin delivery, Int J Pharm 377, 1-8, 2009.
5. Silva C, Santos D, Ferreira DC, Souto EB, Minoxidil-loaded nanostructured lipid carriers (NLC): characterization and rheological behaviour of topical formulations, Pharmazie 64, 177-182, 2009.
6. Messenger AG, Rundegren J, Minoxidil: mechanisms of action on hair growth, Br J Dermatol 150, 186–194, 2004.
7. Tripathi KD, Antihypertensive drugs. In: Essentials of Medical Pharmacology, 6thed. pp. 539-554, JaypeeBrotheres Medical Publishers (P) Ltd, New Delhi, 2008.
8. Tata S, Flynn GL, Weiner ND, Penetration of minoxidil from ethanol/propylene glycol solutions: effect of application volume and occlusion, J Pharm Sci 84, 688–691, 1995.
9. Nair V, Panchagnula R, Poloxamer gel as vehicle for transdermal iontophoretic delivery of arginine vasopressin: evaluation of *in vivo* performance in rats, Pharmacol Res 47, 555–562, 2003.
10. Kaur LP, Garg R, Gupta GD, Development and evaluation of topical gel of minoxidil from different polymer bases in application of alopecia, Int J Pharmacy Pharm Sci 2, 43-47, 2010.
11. Amasya G, Karavana SY, Sen T, Baloglu E, Tarimci N, Bioadhesive and mechanical properties of Triamcinalone acetate buccal gels, Turk J Pharm Sci 9, 1-12, 2012.
12. Martinez MAR, Gallardo JLV, Benavides M MD, Duran JDGL, Lara VG, Rheological behavior of gels and meloxicam release, Int J Pharm 333, 17-23, 2007.
13. Yamaguchi Y, Sato H, Sugibayashi K, Morim oto Y, Drug release test to asses quality of topical formulations in Japanese market, Drug Dev Ind Pharm 22, 569-577, 1996.
14. Ruckmani K, Jayakar B, Durgamani S, Easwari TS, Hurmathunisea S, *In Vitro* release studies on topical preparations of Ketorolac Tromethamine, Indian Drugs 35, 303-305, 1998.
15. Sirisuth N, Eddington ND, The influence of first pass metabolism on the development and validation of an IVIVC for metoprolol extended release tablets, Eur J Pharm Biopharm 53, 301–309, 2002.
16. Albertini B, Passerini N, Sabatinoa MD, Vitali B, Brigidi P, Rodriguez L, Polymer–lipid

based mucoadhesive microspheres prepared by spray-congealing for the vaginal delivery of econazole nitrate, Eur J Pharm Sci 36, 591–601, 2009.
17. Varshosaz J, Tavakoli N, Saidan S, Development and characterization of a periodontal bioadhesive gel of metronidazole, Drug Delivery 9,127-133, 2002.
18. Csoka I, Csanya E, Zapantis G, Nagy E, Feher-Kish A, Horvath G, Blazso G, Eros I, In vitro and *in vivo* percutaneous absorption of topical dosage forms: case studies, Int J Pharm 291, 11-19, 2005.
19. Hascicek C, Bediz-Olcer A, Gonul N, Preparation and evaluation of different gel formulations for transdermal delivery of meloxicam, Turk J Pharm 6, 177-186, 2009.
20. Singh S, Parhi R, Garg A, Formulation of Topical Bioadhesive Gel of Aceclofenac Using 3-Level Factorial Design, Iranian J Pharm Res 10, 435-445, 2011.
21. Fang J-Y, Huang Y-B, Lin H-H, Tsai Y-H, Transdermal iontophoresis of sodium nonivamide acetate. IV. Effect of polymer formulations, Int J Pharm 173,127–140, 1998.
22. Shin S-C, Lee J-W, Yang K-H, Lee CH, Preparation and evaluation of bioadhesive benzocaine gels for enhanced local anesthetic effects, Int J Pharm 260, 77–81, 2003.
23. Shin S-C, Cho C-W, Enhanced Transdermal Delivery of Pranoprofen from the Bioadhesive Gels, Arch Pharm Res 29, 928-933, 2006.
24. Shina S-C, Chob C-W, Yang K-H, Development of lidocaine gels for enhanced local anesthetic action, Int J Pharm 287, 73–78, 2004.

Received: 25.04.2013
Accepted: 04.07.2013