FORMULATION AND EVALUATION OF MINOXIDIL TRANSDERMAL GEL

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Abstract

Alopecia means hair loss, today 70% males and 30% females are suffering from this disorder. The need for a suitable topical delivery system which would increase the contact time, leading to increase in local drug concentration of Minoxidil for the treatment of alopecia led to the development of topical gel formulation .Minoxidil has a half life of 4.2 hrs and a melting point of 248^0C. It enhances the hair growth by increasing the blood flow to the scalp by vasodilatation. The Preformulation studies like FTIR and solubility were conducted; Trans dermal gels were prepared using HPMC and carbopol in different ratios. Ethanol and transcutol were used as solvents and permeation enhancers; glycofural is used to compare the permeation capacity. The prepared gels were evaluated for the PH, drug content, viscosity, invitro diffusion studies, Ex vivo permeation studies, drug release kinetics and stability studies. The formulation containing 1600mg of HPMC and 10% transcutol showed better drug release and was found to follow non-Fickian release mechanism, it was found to be stable when compared to the marketed formulation-Tugain2%.

Keywords: Minoxidil, alopecia, permeation enhancers.

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1. INTRODUCTION

Alopecia means hair loss, today 70% males and 30% females are suffering from this disorder. Hair loss is seen as normal variant of aging by most individuals, but can have both psychological and pathological consequences and these effects are taken seriously by both patients and physicians. There are many drugs available to increase the hair growth on head. 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. 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 (Loveleen Preet Kaur *et al*,).Hence in the present study an attempt has been made to prepare and evaluate the topical gel formulation of minoxidil.

2. MATERIALS AND METHODS

Minoxidil USP(Dr.Reddy's labs, Hyderabad),HPMC 15cps(Chimi-nnova Remedies, Hyd, India), Carbopol(Chimi-nnova Remedies, Hyderabad, India),Ethanol,Propyleneglycol, Transcutol HP (Gattefosse, Brasil, America),Glycofurol (Gattefosse, Brasil, America), Potassium dihydrogen phosphate, NaOH, Triethylamine, Dialysis membrane(Sigma inc, hyd, India).

Preformulation Studies

FT-IR Studies

The formulated minoxidil gel was subjected to FT-IR studies to find out the possible interaction between the drug and the polymer during the time of preparation. FT IR analysis of the Minoxidil, HPMC, physical mixture and the optimized formulation F9, was carried out using an FT IR spectrophotometer (PERKIN ELMER FT-I Insf. USA). Samples were prepared in KBr disks (1:8 ratio samples: KBr). The spectra were recorded for each sample within the scanning range was 4000 to 400cm^{-1} and the resolution was 2 cm^{-1}. (Fig.1)

Solubility analysis

Preformulation solubility analysis was done to select a suitable solvent system to dissolve the drug as well as various excipients used for formulation and also to test drugs solubility in the dissolution medium, which was to be used.

Preparation of Minoxidil gel

Required amount of Minoxidil was dissolved in solvent mixture (Ethanol, Transcutol, water), 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. (See in Table 1).

Characterization of Gels

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 7.2.The volumetric flasks 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 288 nm against corresponding gel concentration as blanks.

Viscosity study

The spreadability of the topical formulations meant to be applied onto the skin depends on the degree of consistency offered by the preparation which can be measured in terms of viscosity. The rheological behaviour of minoxidil gel formulations was studied by using a controlled stress rheometer with the cone (24 mm) and plate geometry (Brookfield Programmable DVVIII+ Digital Rheometer, MA, USA). Before carrying out the measurement the sample was allowed to equilibrate for 5 min and the torque sweep was in the range of 10-110%. The measurements were performed in triplicate at ambient

temperature. The rheological properties were calculated using Rheocalc 32 software.

In vitro Diffusion studies

In vitrorelease studies through artificial cellophane membrane was performed using fabricated vertical franz diffusion cells with an effective diffusional surface area of 4.153cm^2 and 20 mL of receptor cell volume. Cellophane dialysis membrane is soaked in water for overnight. 25ml of phosphate buffer was used as receptor compartment, and 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}C. The solution on the receptor side were stirred by externally driven teflon coated magnetic bars at predetermined time intervals, pipette out 1ml of solution from the receptor compartment and immediately replaced with the fresh 1ml phosphate buffer. At the end of the study, the samples were suitable diluted and the amount of drug was quantified by UV spectrophotometer at 288 nm.

Kinetic analysis of diffusion data

In order to understand the kinetics and mechanism of drug release, the result of the *in-vitro* diffusion study of all formulations was fitted with various kinetic equations like zeroorder as cumulative percentage released Vs Time, First order as log percentage of drugremaining to be released Vs. Time, and Higuchi's model, cumulative percentage drug releasedVs Square root of time. The R^2 values were calculated for the linear curves obtained by regression analysis of the above plots.Themathematical modeling of the *in-vitro* drug release data for all theformulations were complied in Fig.16, Fig.17, Fig.18, Fig.19, and R^2 values of all formulations was shown in Table.13. It is evident from the R^2 values that the drug release from formulations was found to follow first order kinetics. The mechanism of drug release from the formulations was by non-fickian diffusion as the value of n is less than 0.89 and greater than 0.45.

Stability Studies

The stability studies were carried out for all the gel formulations at different temperature conditions (4^o, 25^o and 37^{o}C) at a relative humidity of 75±5% for 3 months. Known amounts of gels were taken out at different time intervals like 0, 1, 2 and 3 months and analysed for drug content and physical appearance.

3. RESULTS AND DISCUSSIONS

Minoxidil gels is formulated by using HPMC polymer increased its permeation capacity across the stratum corneum by using transcutol as a permeation enhancer. Preformulation studies were performed on the drug and excipients. FTIR studies revealed that the drug and excipients showed good compatibility without any interaction. Solubility studies showed its solubility ranges in different solvents all the result directed for the further course of formulation.

The drug content of the gel preparations was found to be uniform among various batches prepared and was found to range from 90.21±1.25 to 97.82±1.24%.The viscosity of the gels was found between 5491±16.54 to 13447±11.65 cps (table 2). In F1-F3, formulations minoxidil+HPMC were used in the gel formulations at different ratios and maximum drug release was found to very less.

In F4-F7, minoxidil+HPMC were used in the gel formulation at different ratios and F6 showed a better sustained release of the drug from the formulation. In F8-F10, to the F6 formulation different concentrations of transcutol (5%, 10%, 20%) is added and F9 showed a better sustained release of the drug from the formulation. To compare the permeation capacity of permeation enhancers glycofurol (5%, 10%, 20%) is used in F11-F13. To the F6 formulation different concentration of glycofurol is added and F12 showed better release but it was less than the release of transcutol. The *in-vitro* and *ex-vivo* release of drug from the F9, F12 and innovator was compared F9 showed a better drug release when compared to the innovator product.

The obtained dissolution data indicated that the drug release through the gel formulation follows non-fickian diffusion. Stability Studies of Optimized formulation shows better results when compare to the marketed formulation. F9

was the optimized formulation showing higher drug release than the Innovator (Tugain2%).

4. CONCLUSION

When compared the release rate was good and consistent in case of formulations with transcutol than glycofurol.Hence we here by conclude transcutol (10%) can be used as the best permeation enhancer in allowing the drug to release from the formulation in consistent pattern. The release of drug varies with the concentration of permeation enhancer proportionally in case of both the enhancers from the gel formulation. Gels are better than solution form because increase contact time with the scalp and decrease the severe adverse effects (e.g., scalp dryness, irritation, burning, redness, and allergic contact dermatitis).

Table 1: Preparation of Different Formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Minoxidil (mg)	200	200	200	200	200	200	200	200	200	200	200	200	200
Carbopol 934 (mg)	100	200	250	–	–	–	–	–	–	–	–	–	–
HPMC 15cps (mg)	–	–	–	800	1200	1600	2000	1600	1600	1600	1600	1600	1600
Transcutol (ml)	–	–	–	–	–	–	–	5%	10%	20%	–	–	–
Glycofurol (ml)	–	–	–	–	–	–	–	–	–	–	5%	10%	20%
Propylene glycol(ml)	2	2	2	2	2	2	2	2	2	2	2	2	2
Ethanol (ml)	2	2	2	2	2	2	2	2	2	2	2	2	2
Water (ml)	6	6	6	6	6	6	6	5.5	5	3	5.5	5	3

Table 2: Measurement of pH, Drug content and Viscosity

Formulation code	pH	Drug Content (%)	Viscosity ŋ(cps)
F1	7.11±0.21	90.21±1.25	13021±20.52
F2	6.98±0.14	91.45±1.07	13242±17.45
F3	7.20±0.85	90.47±2.40	13447±11.65
F4	6.78±0.93	96.23±1.78	5754±14.56
F5	6.80±0.02	94.40±1.50	5814±15.89
F6	7.12±0.17	93.54±2.12	5445±14.75
F7	6.69±0.15	90.43±1.54	5897±15.24
F8	6.79±0.51	93.84±1.78	5465±13.48
F9	7.01±0.24	97.82±1.04	5474±14.31

F10	6.98±0.58	95.20±1.98	5489±18.64
F11	6.76±0.12	94.57±1.30	5421±14.65
F12	6.81±0.11	97.12±1.24	5448±12.41
F13	7.02±0.03	92.47±1.14	5491±16.54

Table 3: Mathematical Models for Minoxidil transdermal gel formulations

Formulation Code	Correlation coefficient (R^2)				Release Exponent (n)
	Zero Order	First Order	Higuchi	Korsemeyer Peppas	
F1	0.46	0.412	0.672	0.606	0.193
F2	0.644	0.607	0.856	0.845	0.391
F3	0.504	0.514	0.752	0.710	0.306
F4	0.698	0.753	0.890	0.892	0.406
F5	0.759	0.831	0.926	0.927	0.441
F6	0.884	0.970	0.982	0.979	0.552
F7	0.796	0.850	0.937	0.937	0.531
F8	0.89	0.975	0.984	0.982	0.548
F9	0.948	0.907	0.983	0.991	0.613
F10	0.876	0.931	0.967	0.971	0.575
F11	0.890	0.972	0.983	0.981	0.559
F12	0.943	0.951	0.985	0.991	0.605
F13	0.878	0.937	0.967	0.971	0.588
Innovator	0.963	0.934	0.971	0.988	0.710

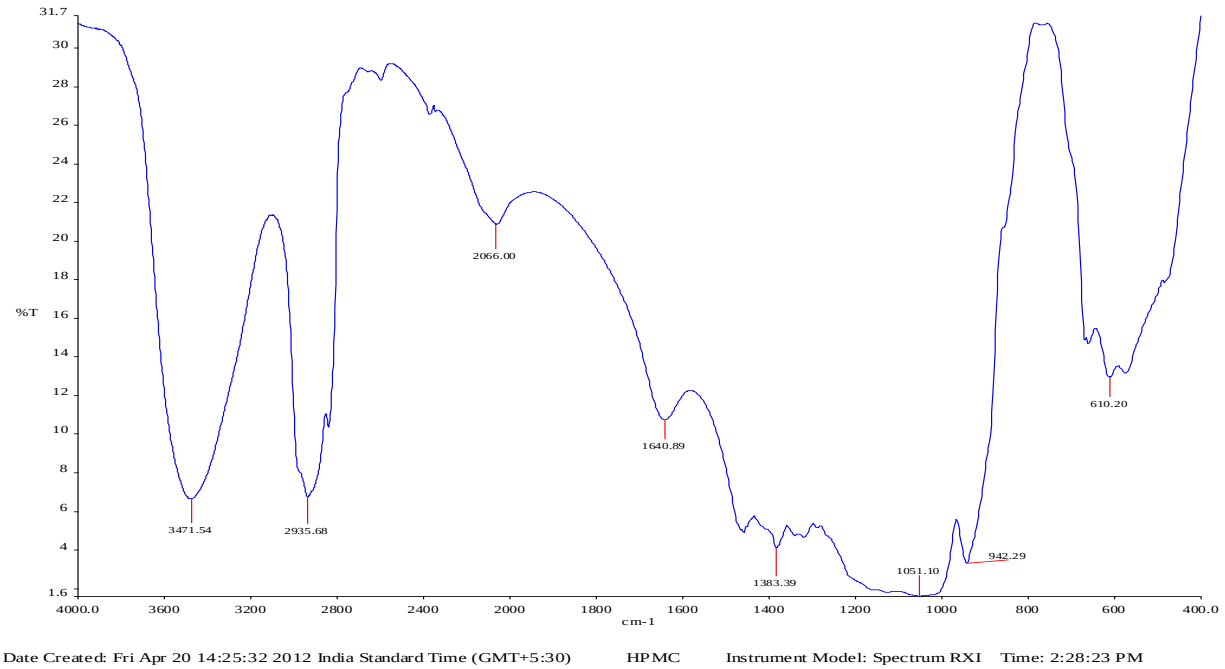

Fig.1: FTIR graph of Minoxidil+HPMC (1:8)

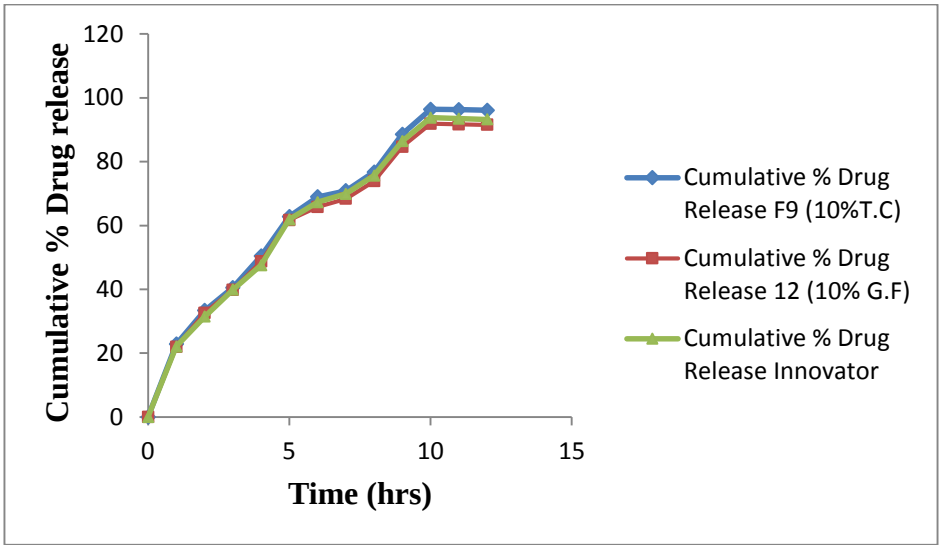

Fig.2: Zero Order Plot for Formulations F9, F12 and Innovator

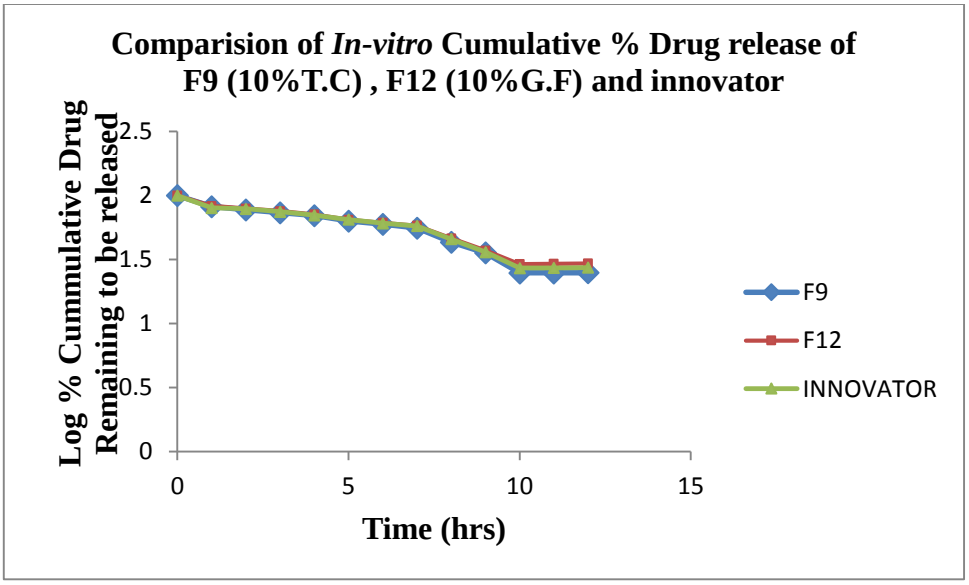

Fig.3: First Order Plot for Formulations F9, F12 and Innovator

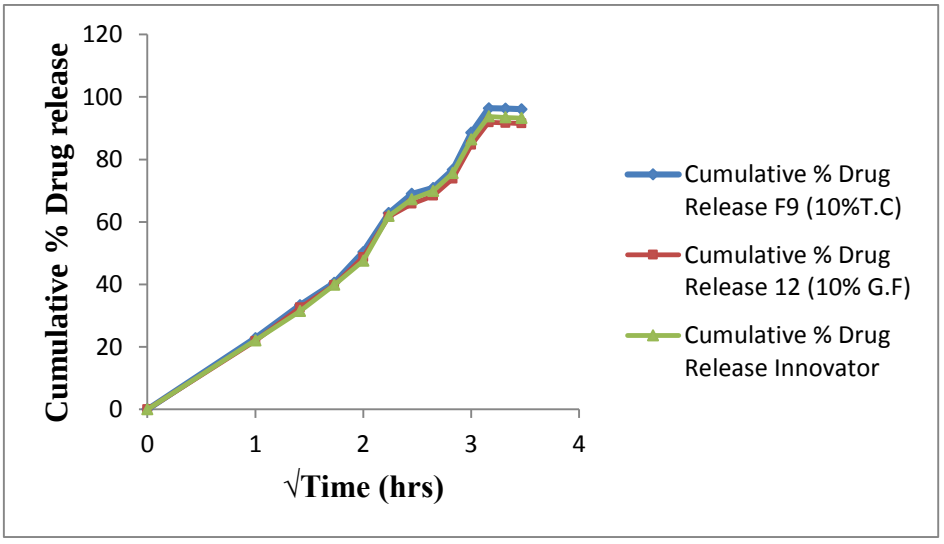

Fig. 4: Higuchi's Plot for Formulations F9, F12 and Innovator

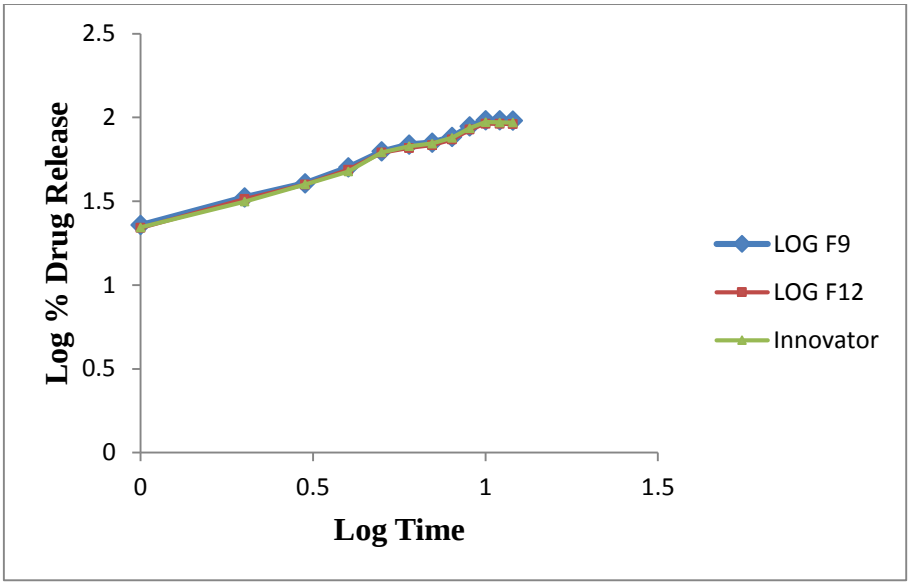

Fig.5: Korsemeyer Peppas Plot for Formulations F9, F12 and Innovator

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