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# Formulation and Evaluation of Minoxidil Gels for Topical Application

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## *ABSTRACT*

*The commercial minoxidil formulation for topical application requires repeated application with the scalp as they suffer from less contact time. In the present study minoxidil gels were prepared using carbopol, hydroxyl propyl cellulose, hydroxyl propyl methyl cellulose and combination. The prepared gels were evaluated for drug content, viscosity determination, in vitro and ex vitro permeation studies. The drug content of the gels was found to range from94.48±4.22 % to 98.55±3.54%. The viscosity of the gels ranged between 589.9±6.8 to 156.24±20.3(cPs). The drug permeation across dialysis membrane from all the formulations at the end of 24 h was almost same and ranged between 90% to 40 %. The percentage release of drug was found to be more in carbopol gels and was affected with the percentage of gelling agent. Formulation M1 was found to release around 90% across the mouse skin. The results also indicated that the drug permeation from these minoxidil gels is following the diffusion mechanism. The flux of the optimised gel has 94.26±14.46 (µg/cm²/hr) with permeation coefficient 38.21±5.16 (cm/hr). The formulated gels did not show any dermatological reactions when tested. The gels were found stable on storage and results suggested that minoxidil gels will be more promising for topical delivery of minoxidil in hair loss treatment in comparision to solution based commercial formulations.*

***Key words:*** *Minoxidil, hydrogels, carbopol, hydroxyl propyl methyl cellulose.*

## INTRODUCTION

The success rate of treatment for androgenic alopecia barely exceeds 30% using antihypertensive agents or modulators of androgen metabolism, implying that other pathophysiologic pathways may be involved in this condition. Alopecia is a serious problem in most of the individuals irrespective of gender and age [1-4]. The skin is very effective as a selective penetration barrier. Percutaneous absorption involves the passage of the drug molecule from the skin surface into the stratum corneum under the influence of a concentration gradient and its subsequent diffusion through the stratum corneum and underlying epidermis through the dermis and into the blood circulation. The skin behaves as a passive barrier to the penetrating molecule. The stratum corneum provides the greatest resistance to penetration and it is the rate-limiting step in percutaneous absorption [5-8].

Minoxidil is an antihypertensive agent widely used in topical formulations for the treatment of hair loss in women and men who suffer from androgenic alopecia (AGA) AGA is a hereditary and progressive androgen dependent thinning of the scalp hair which will follow a definite pattern of hair loss. Hair growth can be stimulated by different mechanisms like increasing the linear growth rate of hair, increase the diameter of the hair fibre, alter the hair cycle, shortening telogen or prolonging anagen, or act through a combination of these effects[9]. Though many drugs are used for the treatment of alopecia, minoxidil is one of the drugs available in the market as 2% or 5% topical aqueous or organic solutions suffering from the major drawback of less contact time with the scalp. As the mechanism of hair growth is by local vasodilatation the less contact time of the drug solution with the scalp indicates repeated applications for the therapeutic benefit. Hence there is a need to increase the contact time by which the local drug concentration level increases to cause better vasodilatation. In the present study, an attempt has been made to formulate and evaluate the hydrogels of minoxidil for increasing contact time of the drug with the scalp and to attain control release of a drug for a longer time period, which may help in reducing the frequency of application and thereby increasing the patient compliance.

In recent years, numerous drug penetration enhancement techniques were studied through the transdermal route [10, 11]. Among them, one of the most promising found is the microemulsion formulations and gels for the transdermal delivery [12-19]. Gels are transparent to opaque semisolids containing a high ratio of solvent to gelling agent merge or entangle to form a three-dimensional colloidal network structure. This network limits fluid flow by entrapment and immobilization of the solvent molecules. Gels tend to be smooth, elegant, non greasy and produce cooling effect and utilize better drug release as compared to other semisolid formulation. Gels have better potential as a vehicle to administered drug topically in comparison to ointment, because they are non-sticky requires low energy during the formulation are stable and have aesthetic value.In this study, minoxidil hydrogels were formulated and evaluated for its physical appearance, viscosity, drug release and stability.

## MATERIALS AND METHODS

**Materials:**

Minoxidil was obtained as gift sample from Dr. Reddy's labs Hyderabad. Carbopol 934 HPMC, HPMC K 15, HPC were purchased from SD Fine chemicals Ltd, India. All the solvents and reagents use are of analytical grade

**Methods**:

***Formulation of minoxidil hydrogel:***

Minoxidil hydrogel were prepared by the various polymers like carbopol 934, HPMC, HPC and combination of polymers. Gel of 2.5%, 5% were prepared in distilled water. 150mg of drug was dissolved in mixture of ethanol, propylene glycol, and distilled water in the ratio of 3:2:5. Then the drug solution was added slowly to the gels of respective concentrations and stirred well on a mechanical stirrer at 300 rpm and care was to prevent the entrapment of the air. The pH of the gels was adjusted by adding triethanolamine to obtain a pH of 6.8 to 7. Finally limonene 0.1% was added to the formulations as a permeation enhancer methyl paraben and propyl paraben 0.1% was added as a preservative and stirred well and stored for further evaluation test.

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**Characterization of minoxidil hydrogels:**

***1. Fourier Transforms Infrared Spectroscopy (FT-IR):***

The FT-IR spectra were taken for the dried samples of drug and polymers used by taking spectras of drug, various polymers used and for the physical mixture of drug and excipient. An FT-IR (7000) spectrometer was used for the analysis in the frequency range between 4000 and 400 $cms^{-1}$. 1 mg of the above mentioned samples were triturated with 100 mg of dry, finely powdered potassium bromide IR grade to prepare disc of 13mm in diameter. Grinded the mixture thoroughly, spread it uniformly in a suitable die and compressed under vacuum at a pressure of about 800. Then the resultant disc was mounted in a suitable holder in the spectrophotometer. The IR spectra of the sample were determined from 600-4400 $cm^{-1}$. Several factors, such as inadequate or excessive grinding, moisture or other impurities in the halide carrier, may give rise to unsatisfactory discs. A disc should be rejected, if visual inspection shows lack of uniformity or if the transmittance at about 2000 cm-1 (5µm) in the absence of a specific absorption band is less than 75% without compensation.

**Drug content:**

An amount of hydrogel containing 5 mg of drug was taken and dissolved in 50 ml of phosphate buffer pH 7.4 in 100 volumetric flasks and was kept for 2 h over a mechanical shaker to mix it properly. The solution was filtered and drug content was measured UV spectrophotometrically at 288 nm.

**Measurement of pH:**

The pH of minoxidil hydrogel formulations was determined by using digital pH meter. The measurement of pH of each formulation was done in triplicate and average values were calculated.

**Viscosity:**

The measurement of viscosity of the prepared minoxidil hydrogels was measured using a viscometer (Brookfield digital viscometer (DV II RVTDV-II USA) was used to measure the viscosity (in cPs) of the gels at 25 ±0.3 °C. The measurement of viscosity of each formulation was done in triplicate and average values were calculated.

***2. In Vitro Drug Release Studies:***

In vitro skin permeation study was performed by using Franz diffusion cells with an effective diffusion area of 2.2 $cm^2$. The dialysis membrane was clamped between the donor and the receptor chamber of Franz diffusion cells. Then, gel containing minoxidil was placed onto the donor chamber. The receptor chamber was filled with phosphate buffer pH7.4 (PBS). The receptor medium was maintained at 37±0.5 $^0$C and stirred at 600 rpm throughout the experiment. For each experiment, 10 ml receptor medium was sampled at predetermined time intervals and then the same volume of pure medium was immediately added into the receptor chamber. All samples were analyzed by UV-spectrophotometer at 288nm. The cumulative amount of minoxidil permeated through dialysis membrane was plotted as a function of time.

***Ex vivo* skin permeation studies using rat skin:**

*Ex vitro* skin permeation study was performed by using Franz diffusion cells with an effective diffusion area of 2.2 $cm^2$. Wistar rats of weight 180-200gms were taken and were depilated with trimmer and skin samples were excised and clamped between the donor and the receptor chamber of Franz diffusion cells with the stratum corneum facing the donor chamber. Then, micro emulsion containing minoxidil was placed onto the donor chamber. The receptor chamber was filled with phosphate buffer pH7.4 (PBS). The receptor medium was maintained at 37 ± 0. 5°C and stirred at 600 rpm throughout the experiment. For each experiment, 10 ml receptor medium was sampled at predetermined time intervals and then the same volume of pure medium was immediately added into the receptor chamber. All samples were analyzed by UV-spectrophotometer at 288nm to determine the amount drug released from the gel.

**Calculation of Permeation Parameters:**

The cumulative amount of minoxidil permeated per unit of rat skin surface area, Qt/S was plotted as a function of time. The permeation rate of minoxidil at steady-state (Jss, µg/$cm^2$/hr) was calculated by linear regression analysis by interpolation of the cumulative amount permeated through rat skin per unit area versus time.

$$Jss=\Delta Qt/S.\Delta t \ldots. (1)$$

**Kinetic Analysis of Drug Release:**

To examine the mechanism of drug release from minoxidil hydrogel, the *in vitro* dissolution data were fitted to zero order, first order, Higuchi release model, and Korsemeyer Peppa's model. The model with higher correlation coefficient was decided to be the best fit model for the drug release.

**Skin irritation test:**

The test was performed on a healthy albino rat weighing around 180-200g g. Aqueous solution of formalin 0.8% was used as the standard irritant. The hair was removed on the hind limbs. The animals were divided into 2 groups [Ethical Committee Reg. No: 1548/PO/a/11/CPCSEA]. The optimized hydrogel formulations was applied to dorsal right limb and the left dorsal limb was used as control, after 24 h the gel was removed with the help of an alcohol swab. The skin of the animals was examined for erythematic reaction or edema.

**Stability Studies:**

The stability study of the gels was performed an ambient condition over a period of two months for knowing the change in physical appearance, pH value, drug content, rheological properties.

## RESULTS AND DISCUSSION

Minoxidil hydrogel were prepared by the various polymers like carbopol 934, HPMC and HPC gel of 2.5%, 5% alone and in combination in distilled water and incorporated 150 mg of drug was dissolved in mixture of ethanol, propylene glycol, and distilled water in the ratio of 3:2:5. The pH of the gels was adjusted to pH of 6.8 to 7. Limonene 0.1%, methyl paraben and propyl paraben 0.1% were added as permeation enhancer and as preservative. [20-21].

The drug content formulations were ranging from 94.48 ± 4.22 to 98.85 ± 3.54 respectively. Viscosity of the gels was ranging from 589±6.8 ± to 156.24 ± 20.3 cps. Compatibility studies were performed using IR spectrophotometer The IR spectral analysis of minoxidil was showing its principal peaks at wave numbers 3449.95, 2936.63, 1643.57, 1612.90, 1557.2 and 1449.90 $cm^{-1}$. The peaks of IR spectra were in accordance with previous report and confirming the purity of the drug (**Fig. 2**). The IR spectra of the physical mixture of drug and polymer were in accordance with the drug and the results suggest that there was no interaction between drug and polymer used in the present study. This indicates that the drug is compatible with the formulation components. The spectra's for all formulations are shown in **Fig. 1**.

The various minoxidil gels were evaluated for *in vitro* permeation studies by using dialysis membrane with a cut off of molecular weight of 12,000. The *in vitro* permeation studies were performed for all the prepared formulations including the marketed topical solution. At the end of the 24 h the drug release of all the formulations is ranging between 37 ± 3.26 to 80.4 ± 3.78 percentage of drug release. As the viscosity of the gels increased the release from the gels decreased as the release of active substance is related to the penetration through the diffusion barriers [22, 23]. The viscosity has a negative effect on the release of drug. The results of *in vitro* drug release studies of gels are depicted in **Fig. 3 & 4**. Immediate release with highest drug permeation was observed for the marketed formulation when compared to the hydrogel formulation. The *in vitro* release data obtained were treated for different kinetics models like zero-order, first-order, Higuchi's, and Korsmeyer-Peppa's model to assess the mechanism of drug release. The results of the curve fitting into these above mentioned models indicated that the release of drug is by diffusion ($R^2$=0.921to 0.998) over 24 h as a best fit amongst all other models investigated. The results also indicated that the drug permeation from these minoxidil gels is following the diffusion mechanism (**Table 2**). The results of skin irritation test of optimized hydrogel were compared with formalin solution as a standard irritant. The formulations showed negligible erythema and edema when compared to formalin and prepared formulations did not produce any dermatological reaction and was well tolerated by the rat.

**Table No. 1: Formulae of minoxidil gels with various percentages of polymers used**

| Formulation code | Polymer and its concentration | Minoxidil taken (mg) |
|---|---|---|
| **M1** | HPC (2.5%) | 150 |
| **M2** | HPC (5%) | 150 |
| **M3** | Carbopol 934 (2.5%) + HPC (2.5%) | 150 |
| **M4** | Carbopol934 (2.5%)+ HPMC(2.5% ) | 150 |
| **M5** | HPMC (2.5%) | 150 |
| **M6** | HPMC (5%) | 150 |
| **M7** | Carbopol 934 (2.5%) | 150 |
| **M8** | Carbopol 934 (5%) | 150 |

**Table No. 2: kinetic data treatment of cumulative drug release from different formulations**

| Formulation code | Zero order | | First order | | Higuchi | | Peppa's | |
|---|---|---|---|---|---|---|---|---|
| | $r^2$ | K | $r^2$ | K | $r^2$ | K | $r^2$ | K |
| **M1** | 0.448 | 0.002 | 0.368 | 0.003 | 0.747 | 0.026 | 0.921 | 0.360 |
| **M2** | 0.694 | 0.003 | 0.531 | 0.0004 | 0.929 | 0.024 | 0.987 | 0.345 |
| **M3** | 0.734 | 0.003 | 0.524 | 0.0005 | 0.949 | 0.027 | 0.988 | 0.446 |
| **M4** | 0.745 | 0.006 | 0.484 | 0.000 | 0.946 | 0.028 | 0.971 | 0.568 |
| **M5** | 0.524 | 0.002 | 0.420 | 0.0004 | 0.812 | 0.026 | 0.946 | 0.374 |
| **M6** | 0.479 | 0.004 | 0.389 | 0.0004 | 0.774 | 0.029 | 0.931 | 0.416 |
| **M7** | 0.782 | 0.002 | 0. 439 | 0.000 | 0.957 | 0.031 | 0.957 | 0.809 |
| **M8** | 0.951 | 0.001 | 0.614 | 0.000 | 0.984 | 0.028 | 0.986 | 0.721 |

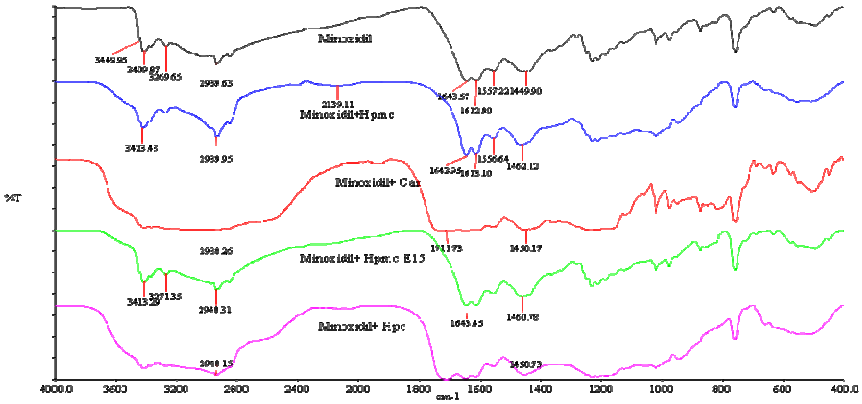


**Fig. 1: FTIR spetctra of pure drug, and in combination with different polymers such as HPMC, Carbopol, HPMC E15, HPC**

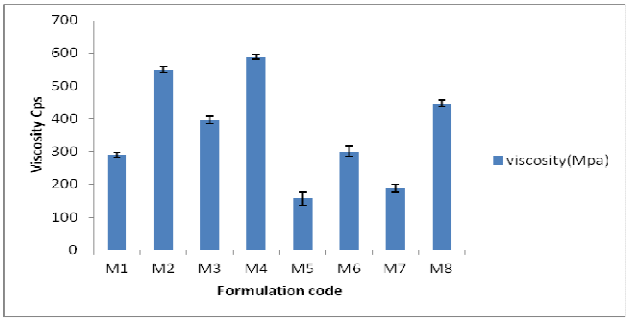


**Fig. 2: Viscosity of the formulated minoxidil gels**

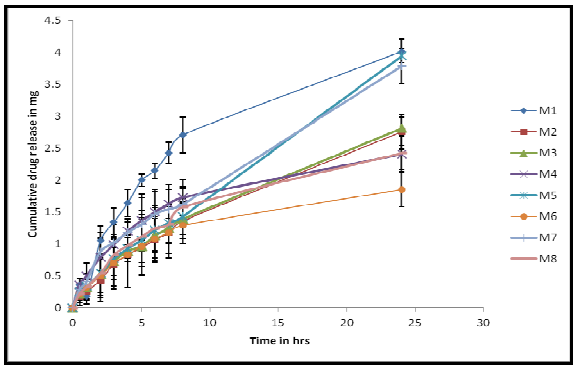


**Fig. 3: *In-vitro* drug release plots of minoxidil hydrogels Formulations**

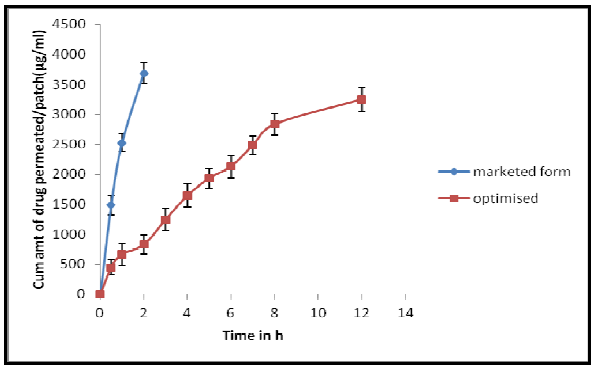


**Fig. 4: *Ex vivo* release plot of optimized and marketed formulation**

**CONCLUSION**

The minoxidil gels were prepared by using HPC, carbopol, HPMC K15 and in combination of the polymers. All prepared gels have shown acceptable consistency and pH value and stable for a period of 2 months without any change in its properties. Among all the gelling agents carbopol gels shown superior release when compared to other gelling agents. The drug release was found to decrease with increase in the concentration of the gelling agent. The *in vitro* permeation from these gels was found to follow korsmeyers –peppas model over a period of 24 hours with non-fickian "anomalous" mechanism. The minoxidil gels can be alternative to the marketed solution form of the drug which improves the patient compliance.

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