Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 13 [12] November 2024: 14-20

Online ISSN 2277-1808
Journal's URL: http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

Preparation and Characterization of Minoxidil Emulgel

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ABSTRACT
Approximately 70% of males and 30% of females experience hair loss, highlighting the need for effective topical delivery systems to enhance the contact time of minoxidil and increase its local concentration for hair loss treatment and promotes hair growth by improving blood flow to the scalp through vasodilation. Minoxidil, with a half-life of 4.2 hours and a melting point of 248°C, and class of BCS-II with criteria low solubility and high permeability which is suitable for topical drug delivery, To develop a suitable formulation, pre-formulation studies, including FT-IR and preliminary assessments, were conducted. Topical emulgels were prepared using polymer carbopol934 in varying ratios, with ethanol and water serving as solvents. Span 20 and Tween 80 were used as emulsifiers. Prepared emulgels were evaluated for the selected parameters like physical appearance, homogeneity, pH, drug content, viscosity, in-vitro diffusion studies. Among the formulations, the one containing 2500 mg of Carbopol-934 with emugel of formulation F5 exhibited superior drug release and stability compared to the other five formulations. This suggests that this emulgel formulation may be an effective option for delivering minoxidil in the treatment of hair loss.
Keywords: *Minoxidil,Emulgel, hair loss, topical drug delivery, polymers.*

Received 12.08.2024 Revised 18.10.2024 Accepted 19.11.2024

INTRODUCTION

Topical based drug delivery refers to application of medication containing emulsions directly onto the skin for treating cutaneous conditions. This delivery method is commonly used for localized skin infections, such as fungal infections, and is particularly beneficial than routes;such as oral, sublingual, rectal, or parenteral administration are ineffective (1). A key advantage of topical systems is their ability to bypass first-pass metabolism, which can enhance the drug's effectiveness. Additionally, topical delivery minimizes the risks and complications associated with intravenous administration, such as variability in absorption due to factors like pH changes, presence of enzymes , and gastric emptying times (2).

Topical drug administration is one of the simplest methods for localized drug delivery, applicable through various routes including ophthalmic, rectal, vaginal, and dermal applications. This approach is utilized for a wide range of skin care products designed for both healthy and damaged skin, serving cosmetic and dermatological purposes alike. Formulations can be found in various forms-solid, semisolid, and liquid allowing for broader applications (3,4). Medications can be applied topically for either systemic effects or localized action. Absorption through the skin is maximized if the drug is in solution, possesses a favourable lipid/water partition coefficient, and when it is non-electrolytic. The spectrum of preparations caters to both cosmetic and dermatological needs, addressing both healthy and diseased skin. Most medications, whether derived from natural sources or synthesized, typically fall into Class II of the Biopharmaceutical Classification System (BCS).

Topicals for local activity can be administered both orally and externally, and they are categorized into two main types of topical delivery systems. The primary advantages of these systems include the ability to avoid first-pass metabolism, circumvent gastrointestinal incompatibilities, enhance patient compliance, facilitate self-medication, and accommodate medications with less shelf life and narrow therapeutic indices (5,6).

However, penetrating the skin barrier poses significant challenges, as it is a complex process influenced by various physiological and physico-chemical factors (7). Physiological aspects such as skin thickness, hydration levels, inflammation, pH, lipid content, hair follicle and sweat gland density, and blood flow can all impact the effectiveness of topical drug delivery. Additionally, physico-chemical factors, including partition coefficients, molecular related structure, degree of ionization, and the properties of the vehicle

used for delivery, play crucial roles in determining how effectively a drug is absorbed through the skin (8,9).

EMULGEL

Water-in-oil and oil-in-water emulsions are commonly used for topical drug application due to their excellent skin penetration properties. When a gelling agent is incorporated into the water phase, the emulsion transforms into an emulgel. Emulgels offer numerous advantages for dermatological use, including thixotropic behaviour, a greaseless texture, easy removability, rapid solubility, emollient properties, non-staining qualities, prolonged shelf life, biocompatibility, and a transparent appearance (10).

For drug molecules to penetrate the skin, they typically access the skin through three main pathways: sweat ducts, sebaceous follicles, and the intact stratum corneum. Emulgels present an intriguing area of research in topical drug delivery, yet they remain less commercialized compared to other formulations (11).

According to the USP, a gel is defined as a semisolid system formed by dispersing large organic molecules or small inorganic particles within a liquid. This gel structure facilitates controlled drug dissolution by trapping drug particles within a cross-linked network of solid particles, which is suspended in a larger volume of aqueous or hydroalcoholic liquid (12). The formation of a three-dimensional polymeric matrix occurs through chemical or physical cross-linking, resulting in a cohesive structure that exhibits consistent behaviour similar to solids. Both gels and emulsions play crucial roles in the controlled release of medications. Gels can be categorized as hydrophobic (organogels, based on organic solvents) or hydrophilic (water-based hydrogels).

ADVANTAGES (13,14)

- It has an ability to incorporate hydrophobic medications
- Has Greater loading capacity
- It enhances the product stability
- Eliminating intense sonication
- Avoids first pass metabolism
- Avoiding gastrointestinal incompatibility
- Greater site selectivity

Essential Components in the Preparation of Emulgel (15,16)

Aqueous Material: This forms the aqueous phase of the emulsion, which commonly comprising agents such as alcohol and water.

Oils: These substances create the oily phase of the emulsion. Commonly used oils include non-biodegradable mineral and castor oils, known for their laxative properties, as well as fish liver oils and various fixed vegetable oils like arachis, cottonseed, and corn oils, which are often utilized in oral formulations as nutritional supplements.

Emulsifiers: Emulsifiers are crucial for the formation of emulsions. Examples include stearic acid, sodium stearate, polyoxymethylene, sorbitan monooleate (Span 80), and polyethylene glycol (PEG).

Gelling Agents: These thickening agents are used to enhance the stability of the dosage form, contributing to the overall texture and performance of the emulgel.

MATERIAL AND METHODS

The following materials are required for the formulation, along with their respective suppliers: Minoxidil is sourced from Carbanio Products Pvt Ltd in Hyderabad. Carbopol 934, Span 20, liquid paraffin, methyl paraben, ethanol, Tween 80, water, and propylene glycol are all provided by S.D. Fine Chem. Limited in Mumbai.

PREPARATION OF MINOXIDIL LOADED EMULGELS (17,18)

Minoxidil loaded emulgel was prepared by following these steps and their selected composition and ingredients mentioned in table 1.

Gel Phase Preparation: Different ratio of carbopol 934 was dispersed in purified water while stirring at moderate speed by adjusting the pH to 6-6.5 using triethanolamine (TEA).

Oil Phase Preparation: Span 20 was dissolved in light liquid-paraffin.

Aqueous Phase Preparation: Tween 80 was dispersed in purified water. Dissolved methyl paraben in propylene glycol and minoxidil in ethanol, then combined both solutions with the addition of aqueous phase.

Heating Phases: Heated both the oil and aqueous phases to 70-80°C. Gradually the oil phase was added slowly to the aqueous phase while stirring continuously until the mixture lowered to room temperature.

Emulgel Formation: The resulting emulsion was mixed with the gel phase in a 1:1 ratio with gentle stirring.

able 1: Formulation chart of Minoxidil loaded Emulgel

Ingredients	Formulation codes					
	F1	F2	F3	F4	F5	F6
Minoxidil (gm)	1.0	1.0	1.0	1.0	1.0	1.0
Carbopol 934 (%)	0.5	1	1.5	2	2.5	3
Span 20 (ml)	1	1	1	1	1	1
Liquid paraffin (ml)	7	7	7	7	7	7
Tween 80 (ml)	0.5	0.5	0.5	0.5	0.5	0.5
Ethanol (ml)	2.5	2.5	2.5	2.5	2.5	2.5
Methyl paraben (mg)	1.0	1.0	1.0	1.0	1.0	1.0
Propylene glycol (%)	5.0	5.0	5.0	5.0	5.0	5.0
Water	QS	QS	QS	QS	QS	QS

***QS -Quantity Sufficient**

EVALUATION OF MINOXIDIL LOADED EMULGEL

Physical Examination

Physical examination of emulgel formulations can be visually assessed for colour, homogeneity, consistency, and phase separation.

Rheological Studies

The viscosity of the prepared emulgel formulation can be determine at 25^0C using a Brookfield viscometer with spindle 52 and connected to a thermo-statically controlled circulating water-bath.

Spreadability

The spreadability of emulgels can be assessed using a specially modified laboratory apparatus. This setup includes a wooden block equipped with a pulley at one end. To measure spreadability based on the 'slip' and 'drag' characteristics of the emulgel, a ground glass slide is affixed to the block. Approximately 2 grams of the emulgel under investigation is placed on this slide, which is then sandwiched between it and another glass slide of the same dimensions that has a hook attached. 1 kg weight wasinitially placed on the upper slide for 5 minutes to eliminate air and ensure a uniform film of emulgel is formed. Excess emulgel is scraped off from the edges. After this, a pull of 80 grams is applied to the top slide, and the time (in seconds) it takes for the upper slide to move a distance of 7.5 cm was recorded.

pH Measurement

The pH value of a freshly formulated emulgel formulation were measured by using a digital pH meter.

Grittiness

All the prepared topical preparation must be free from particulate matter. To ensure it formulations were evaluated microscopically (light microscope) for the presence of particles.

Drug Content Measurement

The drug concentration in the gellified emulsion was determined using a spectrophotometer. A known quantity of the gellified emulsion was dissolved in methanol via sonication. After appropriate dilution, the absorbance was measured using a UV/VIS spectrophotometer. The drug content was calculated using the formula:

Drug Content (%)=(Concentration×Dilution Factor×Volume Taken)×Conversion Factor

FT-IR Spectroscopy

FT-IR spectra of minoxidil, carbopol 934, methyl paraben, and optimized formulation (F5) were recorded. Approximately 1 mg of each sample was thoroughly mixed with 100 mg of potassium bromide (KBr) powder and then compressed under vacuum. The resulting disc was mounted in a suitable holder in a thermo electron IR spectrophotometer, and the IR spectral peaks were recorded and taken over the range of 4000 to 400 cm^{-1}. The obtained spectra were analysed for any spectral changes, and the results were tabulated accordingly.

***In Vitro* Release Studies**

In vitro drug release studies were conducted using a Franz diffusion cell with an effective diffusion area of 3.14 cm^2 and a cell volume of 15.5 ml. A 200 mg sample of gellified emulsion was evenly applied to the surface of an egg membrane, which was then clamped between the donor and receptor chambers of the diffusion cell. The receptor chamber was filled with a freshly prepared PBS solution (pH 5.5) to facilitate drug solubilization, and the chamber was stirred with a magnetic stirrer. At designated time intervals, 1.0 ml aliquots of the receptor solution were collected for analysis. The samples were analysed for drug content using a UV-visible spectrophotometer after appropriate dilutions. Cumulative corrections were made to

determine the total amount of drug released at each time point, allowing for the evaluation of the cumulative drug release across the egg membrane as a function of time.

RESULTS AND DISCUSSION

Physical Examination

Most formulations (F1- F6) are described as "white," indicating a consistent visual characteristic, likely due to the composition of the emulgel. Addition of different ingredients or concentrations does not affected colour of emulgels. Additionally, the homogeneity of all formulations was confirmed to be normal and consistent as mentioned in Table2.

Table 2: Physical appearance and Homogeneity of minoxidil loaded emulgels

FORMULATION	APPEARANCE	HOMOGENICITY
F1	White	Homogenous
F2	White	Homogenous
F3	White	Homogenous
F4	White	Homogenous
F5	White	Homogenous
F6	White	Homogenous

Rheological Studies: Different ratio's of emulgel formulations (F1 to F6) being tested for rheology property**.** Viscosity measurements of each formulation at two different rotational speeds (20 RPM and 30 RPM) during rheological testing. The numerical values indicate the viscosity (likely in centipoise) of each formulation at the respective RPM.The rheological properties of the emulgel were measured, showing values between 17700 and 25,801 at 20 RPM and between 13,960 and 19,260 at 30 RPM, as shown in Table3.**F3** shows the highest viscosity at both speeds, suggesting it may have a thicker or more gel-like consistency. **F6** has the lowest viscosity at 20 RPM, indicating a less viscous formulation that may be easier to spread and F5 has shown an optimum viscosity which suitable range for emulgel and all prepared formulations exhibited a decrease in viscosity when the RPM increases, which is a typical behaviour of shear-thinning materials, indicating viscosity decreases under higher shear rates as shown in table 2.

Table 3: Rheology of Minoxidil loaded emulgels

FORMULATION	20RPM	30RPM
F1	20100	18620
F2	19320	13960
F3	25801	18602
F4	20160	19260
F5	17700	18220
F6	10560	14680

Table 4: Evaluation of Minoxidil loaded emulgels

FORMULATION	DRUG CONTENT (%)	SPREADABILITY (g.cm/s)	pH	GRITTINESS
F1	56.85	31.82	6.5	No Powder Particles
F2	68.41	16.61	5.8	No Powder Particles
F3	58.05	32.18	5.7	No Powder Particles
F4	74.55	33.33	7.1	No Powder Particles
F5	82.35	35.53	6.1	No Powder Particles
F6	64.65	25.92	5.4	No Powder Particles

The drug content of the minoxidil loaded emulgel formulations (F1-F6) varied according to the number of polymers used, ranging from 56.85% to 82.35%, and the spreadability of the emulgel formulations ranged from 16.61 to 35.53, and the pH values of the formulations was found to be between 5.4to 7.1, as indicated in Table4. All emulgel formulations exhibited normal grittiness, with no presence of powder particles detected.

In-vitro drug diffusion

In-vitro drug diffusion profiles of the prepared emulgel formulations revealed differences based on composition, with rapid diffusion observed in all preparations. Notably, 87.54% of minoxidil diffused

during the test as shown in table5, with formulation F5 showed the highest drug release when compared to remaining formulations due to following reasons;
Based on their Composition: Emulgent agents or polymers used in emugesl formulations may enhance solubility and stability of the drug, allowing for a more efficient release.
Viscosity: The specific viscosity of emugels can facilitate better diffusion of the drug molecules, leading to faster release.
Hydrophilicity: If the emugels contains hydrophilic components, it can enhance water absorption, promoting drug solubilization and release.
Matrix Structure: The gel matrix may provide a more favourable environment for drug dissolution compared to other formulations, allowing for sustained or immediate release.
pH and Ionic Strength: The formulation's pH and ionic strength may optimize drug solubility and stability, contributing to higher release rates.
Surface Area: Larger surface area available for interaction with the release medium can also enhance the rate of drug release is also one of the reasons for enhancing drug release.

Table 5: *In-vitro* drug release data profile of minoxidil loaded emulgels (F1-F6)

Time (hr)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	34.15±0.35	36.25±0.24	45.62±0.35	37.67±0.15	36.47±0.35	36.81±0.22
2	42.62±0.12	48.11±0.12	46.08±0.22	48.86±0.22	42.15±0.22	44.54±0.22
3	53.14±0.38	53.29±0.19	55.11±0.15	50.96±0.21	52.16±0.21	51.62±0.21
4	57.21±0.20	59.48±0.20	55.39±0.35	52.61±0.27	61.29±0.29	57.04±0.13
5	62.95±0.25	61.42±0.35	64.94±0.35	57.84±0.26	69.29±0.32	63.39±0.19
6	67.51±0.25	67.55±0.28	70.11±0.15	60.56±0.17	71.17±0.21	68.63±0.17
7	71.35±0.30	73.52±0.18	71.99±0.22	63.35±0.25	79.39±0.24	72.51±0.21
8	79.82±0.25	75.45±0.22	78.52±0.22	70.51±0.35	87.54±0.23	77.63±0.24

All values are expressed as mean± SD

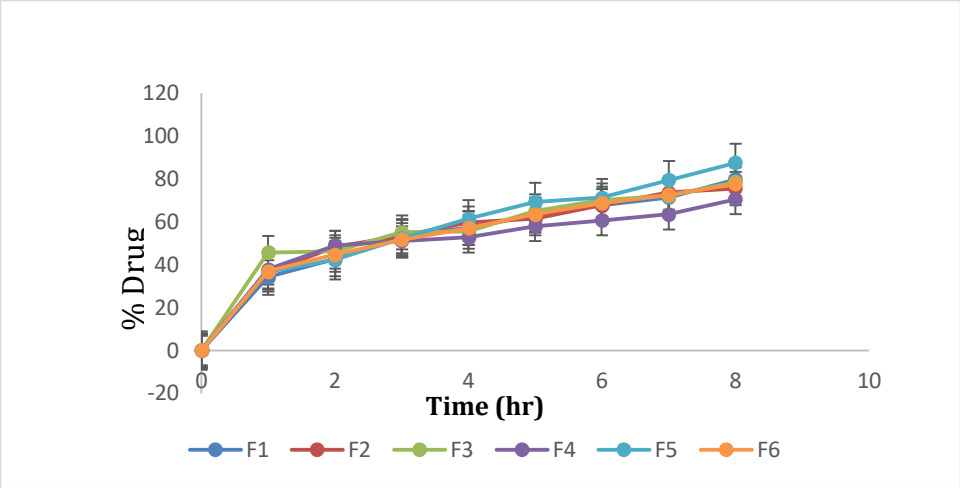

Figure 1. % Drug release of emulgel formulations (F1-F6)

FT-IR Spectroscopy studies:
From the obtained spectra of emulgel it was observed that all characteristics peak of minoxidil were also present in the optimized physical mixture formulation of emulgel (F5) indicating that there is no notable interaction between the excipients and the drug.

Fourier transforms infrared spectroscopy studies for minoxidil
FT-IR spectrum of Minoxidil was shown in figure 2. The characteristic peaks ofthe minoxidil (pure drug) spectrum are 3445.21 it may be due toO–H (Stretching), at 2366.23 C=C (Stretching), 2019.1 C–N (Stretching), 1718.26 C–O (Stretching), 1515.88=C–H (bending), 1451.17 due to C=H (vinyl) and 1173.47 due to C=H (Aromatic).

Fourier transforms infrared spectroscopy studies for minoxidilwith the methyl paraben
FT-IR spectrum of minoxidil with the methyl paraben was shown in Figure 3. Minoxidil with the methyl paraben spectrum shows characteristic absorption peaks 2131.92atO–H (Stretching), 2020.07 atC=C (Stretching), 1918.82 due to C–N (Stretching), 977.73 forC–O (Stretching), 874.56 due to =C–H (bending), 829.24 due to C=H (vinyl) and 804.17 due to C=H (Aromatic).

Fourier transforms infrared spectroscopy studies for minoxidilwith the methyl paraben and carbopol - 934

FT-IR spectrum of minoxidil with the methyl parabin and carbapol 934 was shown in Figure 4.Minoxidil with the methyl paraben and Carbapol 934 spectrum shows characteristic absorption peaks 3854.04 due to O–H (Stretching), 2167.20C=C (Stretching), 1838.79,C–N (Stretching), 884.202 due to C–O (Stretching), 725.104 due to =C–H (bending), 624.823C=H (vinyl) and 444.512 due to C=H (Aromatic).The FTIR spectra of Minoxidil, excipients and Emulgel are compared. From the obtained spectra of emulgel it was observed that all characteristics peak of minoxidil were also present in the emulgel indicating that there was no interaction between the selected excipients and the drug.

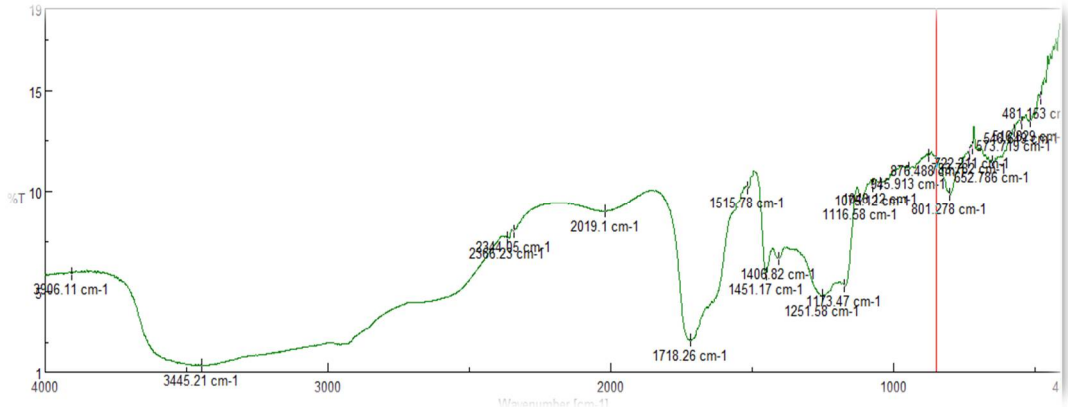

Figure 2.FT-IR Spectrum of Minoxidil

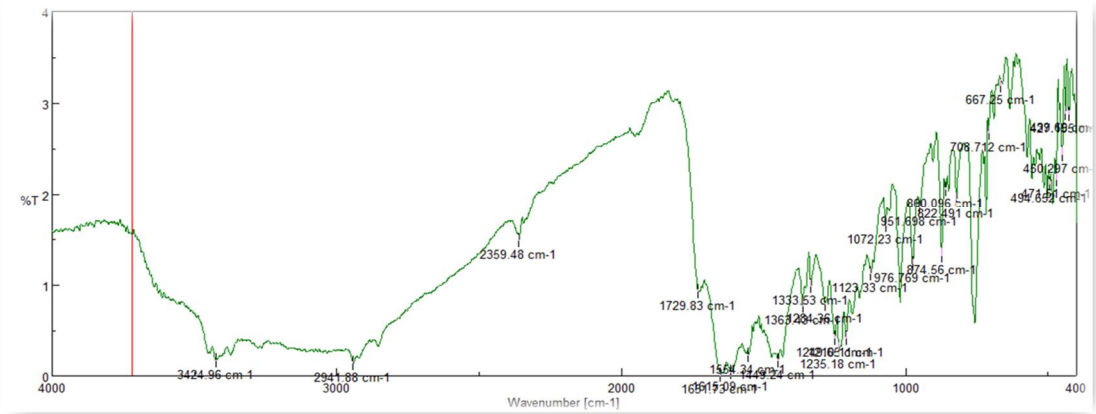

Figure 3. FT-IR spectrum of minoxidil+Carbopol 934

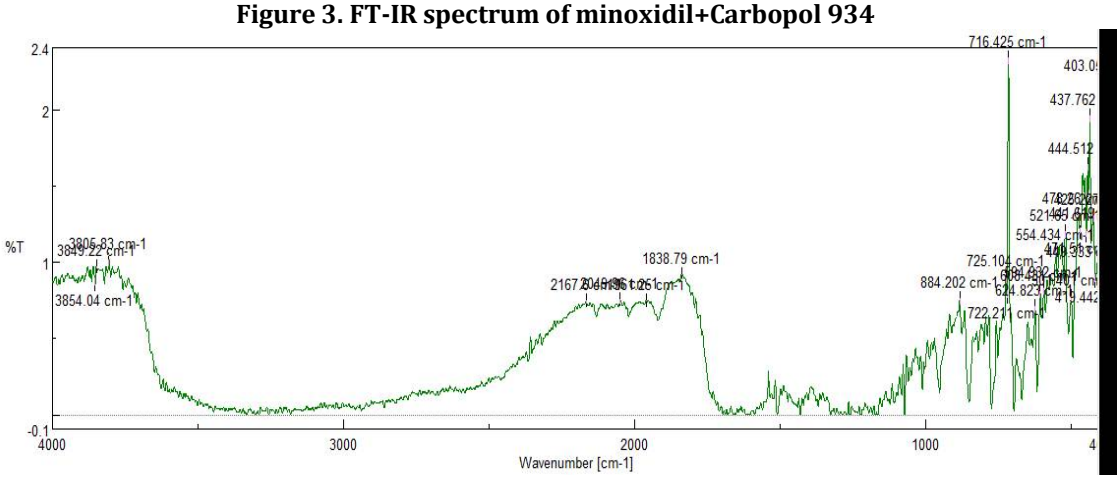

Figure 4.FT-IR spectrum of optimized emulgel formulation (F5)

CONCLUSION

This research aimed to develop a minoxidil loaded emulgel that facilitates systemic drug delivery through the skin, avoiding first-pass metabolism, improving stability, and enhancing residence time. Emulsified gels

offer a stable vehicle for hydrophobic or water-insoluble drugs, combining with the properties of both emulsions and gels. Minoxidil, an antihypertensive and as anti-hair loss agent, is poorly soluble in water. To enhance its delivery, minoxidil emulgels were developed using Carbopol-934, Span 20, liquid paraffin, methyl paraben, ethanol, Tween 80, and propylene glycol as composition. The study investigated the effect of varying concentrations of the gelling agent on the *in-vitro* release of minoxidil. The prepared emulgels were assessed for physical appearance, rheological behaviour, and drug release characteristics. All formulations exhibited acceptable physical properties, including colour, homogeneity, consistency, spreadability, and pH. The *in vitro* drug release results showed varying efficacy across the formulations: F1 (0.5% w/w Carbopol-934) achieved 79.82% drug release, while F2 (1% w/w) released 75.45%. F3 (1.5% w/w) showed 78.52%, F4 (2% w/w) reached 70.51%, F5 (2.5% w/w) exhibited the highest release at 87.54%, and F6 (3% w/w) resulted in 77.63% release. Drug release from the emulgel demonstrated a diffusion-controlled mechanism, following fickian diffusion. Among these, F5 demonstrated superior drug release and other selected parameters compared to the other formulations.

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CITATION OF THIS ARTICLE

Yelamanda J, D Swarna Manjula, L Divya, B Manasa, G Sreevani, B.Reena, R.Radha, M.Niranjan Babu. Preparation and Characterization of Minoxidil Emulgel. Bull. Env. Pharmacol. Life Sci., Vol 13 [12] November 2024: 14-20