



DEVELOPMENT AND IN-VITRO CHARACTERIZATION OF CATIONIC POLYSACCHARIDE GEL OF MINOXIDIL

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Abstract:

The major concern of topical fabrications is to facilitatively administer API into the area wherever it is required, consistently on external and manifest dermis membranes and exterior mucosa. Minoxidil (Rogaine) was initially considered a blood pressure-lowering agent, but over time, it was also considered hypertrichosis for patients suffering from scarcer trichome problems. To make the genesis of an ideal fabrication, we must always look for permeation of a formulation where it is needed and whereby holding of API is vital. Three Formulations were developed as a part of this study F2, F4 and F6. Amongst the 3 formulations formulation, F2 was found to be most suitable as per the initial assessment, and also subsequent release studies indicate that formulation F2 can be a suitable candidate for the management of male pattern baldness.

.Keywords: Alopecia Cationic Polysaccharide, Gel, Minoxidil, Spreadability Study,

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1.1. INTRODUCTION

A doctor or specialist usually addresses hair disorders that change colour, density, thickness, or structure. Androgenic alopecia is caused by an increase in dihydrotestosterone production via 5-alpha reductase. ¹Ethnicity and family history is linked to hair loss. Age, genetics, and androgenic hormones are other contributors. US Food and Drug Administration has authorised oral finasteride and topical minoxidil (MXD) to treat alopecia. Historically, it was administered as an oral antihypertensive. However, hypertrichosis is the drug's main "adverse" effect and manifests after long-term use. Patients with androgenic alopecia have benefited from this

side effect. MXD increases hair growth topically as it dilates skin capillaries and increases blood flow. MXD boosts cell proliferation, inhibits collagen formation, and promotes VEGF and prostaglandin production. MXD prevents early and advanced hormonal hair loss. Long-term therapy (months to a year) grew terminal hair in 50 to 80% of patients.^{2,3}

More than 40% of recently synthesised chemical entities (potential medicines) are hydrophobic, making these substances less bioavailable. Particle size reduction, pH change, the addition of surfactant or cosurfactant, and other methods are effective in increasing medication dispersibility.



Microemulsions (MEs) and self-emulsifying systems are two innovative strategies.⁴⁻⁶

Topical drug delivery systems are only required when the intended outcome is quick or when other medication delivery methods fail, most typically for pain alleviation or any lasting absence. As explained, topical drug administration refers to any medicine or dose type delivered to the body's exterior to treat any localised or occasionally systemic activity. [2] Due to their primary focus on effects and actions localised to a single target, topical medicines frequently serve as an effective tool for focused intervention. It is common to employ these procedures to deliver medications to various organs, cavities, or mucous membranes. Some advantages of topical preparations include avoiding first-pass metabolism and G.I.-related concerns, adsorption, pH fluctuations, and other key problems.^{1,7} The present study aims to develop and evaluate herbal hair gel formulations containing minoxidil and guar gum concentrations.⁸

MATERIALS&METHOD

1. MATERIAL AND METHODS

Materials:

Minoxidil was requisitioned from Neptune Life Sciences Private Limited, Baddi, while Guar Gum was purchased from Sigma Aldrich, St. Louis. Sodium Hydroxide, Isopropyl alcohol, Methanol, Ethanol, Acetone and Chloroform were procured from Fisher Scientific India Pvt. Ltd., Mumbai; all other chemicals and reagents were of analytical quality.

2. METHODOLOGY

2.1. Preformulation Investigation

Preformulation investigations are required to create optimal dosage forms for drug delivery. Preformulation studies help formulators configure long-lasting, bioavailable dosage forms.

2.1.1 Pre-formulation studies

Preformulation investigations comprised assessment of melting point, UV spectroscopic evaluation for λ_{max} of API.

Preparation of minoxidil calibration curve, solubility studies and partition coefficient were determined per protocol.⁹⁻¹¹

2.2 FTIR of drugs and Excipients¹²

FT-IR (Fourier Transform Infrared) spectrum of any API or additives gives an idea about the groups in that particular moiety within the IR range of 4000–400 cm^{-1} . The spectra of the pure drug (Minoxidil) and the drug with excipients were compared to check for any incompatibility and physical abnormalities.

2.3 Blend of guar gum solution

Cationic guar gum was made by dissolving two grams of guar gum in 100 ml of a pure aqua solution of 2% concentration, then admixing 10 ml of 50% NaOH, spinning for 2 hours at room temperature.¹¹⁻¹³

2.4 Etherification of Guar gum solution

Guar gum dispersion was transferred to a 50-mL three-necked flask and pre-cooled with an ice bath to 0°C. The cooled dispersion was then admixed with 20 ml of 50% (3-chloro-2-hydroxypropyl-trimethylammonium chloride) CHPTAC aqua solution using a constant pressure drop funnel. The dispersion was then neutralised with 10% hydrochloric acid for 12 hours at 50°C with frequent agitation. The dispersion medium was warmed to room temperature before combining with isopropanol sol. Water was evacuated for 6 hours in a 40°C vacuum hot air oven.¹⁴⁻¹⁶

2.5 Preparation of Cationic gel

The topical fabrication of Minoxidil (5%) was fabricated by adding different constituents of Cationic guar gum polymer. An accurately measured quantity of distinct constituents of Cationic guar gum (0.5 to 2%) was fabricated in aqua. The gum uninspired was made to hydrate in full night and swell completely, also called as jellification process. Minoxidil was admixed to polymer dispersion with regular disturbance until the entire dispersion medium got admixed with aqua. The pH was made to 7.4 by incorporating NaOH solution (about 0.5 ml 0.1 M) and distributed gradually till a gel was obtained (**Table No 1**).¹⁸⁻²⁰



Table No. 1: Composition of Minoxidil Loaded Cationic guar gum-based gels

Sr. No	Ingredients	FORMULATIONS		
		F2	F4	F6
1	Minoxidil (%w/v)	5	5	5
2	Cationic Guar gum (%w/v)	0.5	1	1.5
3	NaOH	q.s	q.s	q.s
4	Distilled water (mL)	q.s	q.s	q.s

2.6. Evaluation of most optimised formulation

2.6.1 Physical Appearance: An eye look-up methodology detected the external morphology of fabrication. The noticed appearances of the fabricated systems were tested on colour and clarity.²¹

2.6.2 pH determination

The pH of gel formulae was determined by taking the samples under the digital apparatus pH meter. Accurate ratios of API constituted hydrogel were taken in dispersed media in 100ml of an aqua sol, the pH amount of gel was dispersed in 100 ml of pure aqua, and the pH was noted by implying instrument. Readings were analysed in triplicate to avoid errors.²³

2.6.3 Viscosity: Viscometer was implicated for rheological parameters. The API-loaded hydrogel (30 g) was taken in suitable glassware and was allowed to come to equilibrium before and later taken and noted at the rotation of 10 & 50 pm. At the quickest pace, the noteworthy and reading were jotted down. Readings were analysed in triplicate to avoid errors.²⁴

2.6.4 Spreadability Study²⁵

Spreadability of the formulae was checked using the following methodology: 0.5 g of gel was spread onto a circle of 1 cm in diameter premarket on a glass plate over which a

second glass plate was kept. A 500 g was allowed to rest on the upper glass plate. The increment in the circular figure's size due to the gels' spreading was seen.

2.6.5 Drug content

The drug content of distinct fabrications gel was recorded separately; about 500 mg of the gel was accurately measured in a 100 mL volumetric flask and dispersed in 50 mL of phosphate buffer of pH 7.4. The volumetric flask was kept for 2 h and agitated well in a shaker to mix it evenly. The ready dispersions were excavated with a 0.45 mL filter to procure crystal clear dispersions. The drug content was implied spectrophotometrically at a wavelength of λ_{max} 288 nm.^{22,23-25}

2.6.6 In vitro drug release study

Franz diffusion cell was implied to conclude the study of the release pattern of API from Minoxidil coated guar gum gels positively and market entered product. The cells comprised donor and receptor sections which collaborated to form a cellophane diffusion layer. The holding capacity of the receptor chamber was 18 ml. A magnetic bead was placed in the receptor chamber. The dispersion medium contained phosphate buffer (P.B.) pH 7.4. The entire assembly was put on a magnetic stirrer at 100rpm stirring speed, and the temperature was adjusted to 37.0 ± 0.5 °C. The samples were made to rest



over the layers and agitated. 1ml samples were taken off the receptor section at prefixed time durations, and the volume was remarked with the same volume of dispersion media. Add-on fresh dispersion media was done with utmost care to prevent entrapping of air beneath the present dispersion medium. The samples were checked spectrophotometrically at 288nm after predetermined dilutions. The % drug release was evaluated, and a graph of % drug release vs time was plotted. For each fabrication, the release studies were performed and studied to avoid any errors in code in triplicate.^{23,26-28}

2.7 FTIR Study of F-31 formulation

The optimised gel formulation was studied using FTIR spectroscopy.

2.8 Drug release kinetic studies²⁹⁻³⁴

To study the release pattern of any specific fabrications newly developed, it is better to go with the pre-existing mathematical models. The data extracted from ex vivo permeation studies were plotted in different models of data analysis as follows;

- Zero Order model
- First Order model
- Higuchi's Model
- Korsmeyer-Peppas model

RESULTS & DISCUSSIONS

3.1 Pre-formulation

Pre-formulation studies aim to scrutinise the physical and chemical properties of API substances. Minoxidil was evaluated by exploring physical characterisation parameters such as organoleptic properties, Melting point UV-visible spectra, and Solubility Partition coefficient.

3.1.1 Organoleptic properties

Minoxidil is a white to off-white crystalline, odourless powder as per organoleptic studies.

3.1.2 Melting Point²⁴

Melting point phenomena influence API effectiveness and purity. Minoxidil's melting point was determined with capillary tubes and was close to the benchmark. Minoxidil melting point was detected to be $246.333 \pm 0.577^\circ\text{C}$, and the standard drug melting point is 248°C . Therefore, API used for the study were free from any unwanted impurities, and any likelihood of undesirable effects was lessened.

3.1.3 UV Spectroscopy

3.1.3.1 Determination of absorption maxima of Minoxidil in Methanol³²

A dispersion of Minoxidil ($15 \mu\text{g/mL}$) was checked over the U.V. range from 400 nm to 200 nm, and the λ_{max} of Minoxidil was depicted as 285nm, respectively. The absorption maxima of Minoxidil are shown in Figure 1.

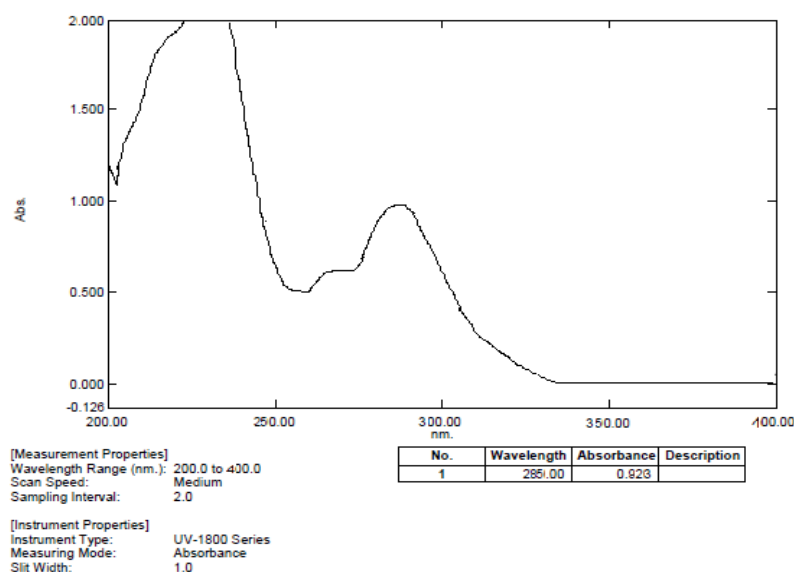


Figure 1: U.V. Spectrum of Minoxidil in Methanol



3.1.2 Preparation of standard curve of Minoxidil in Methanol

A minoxidil calibration curve was obtained using the 3 to 15 µg/ml solution of Minoxidil in Methanol. The absorbance was scaled at 285nm. The calibration curve of Minoxidil, as shown in the graph, depicted the regression equation $Y = 0.066x - 0.078$ and R^2 value 0.999, which shows good linearity at 285nm, as shown in **Table No 2**, and **Figure 2**.

Table No 2: Calibration curve of Minoxidil in Methanol

Sr. no.	Concentration µg/ml	Absorbance
1	3	0.124±0.002
2	5	0.257±0.001
3	7	0.375±0.001
4	9	0.524±0.002
5	11	0.644±0.001
6	13	0.775±0.001
7	15	0.924±0.002

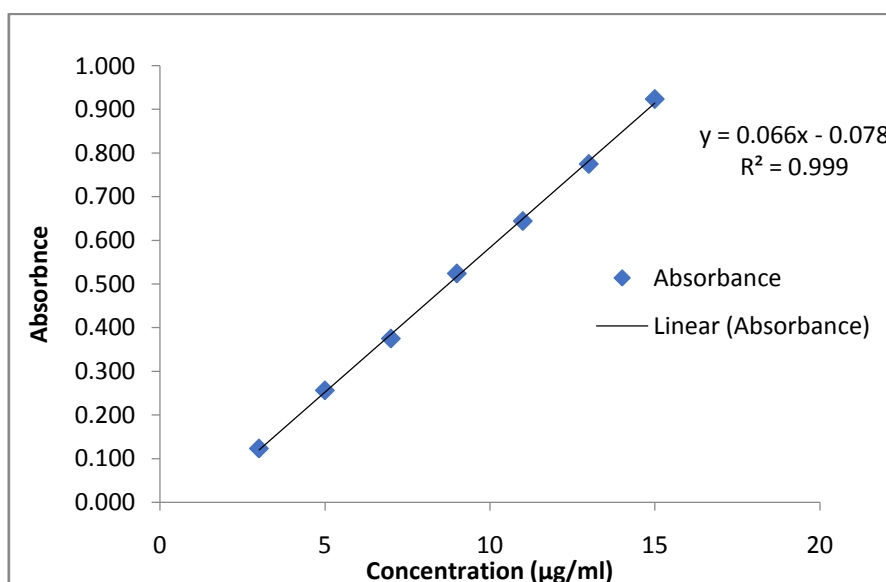


Figure 2: Graph of standard calibration curve of Minoxidil in Methanol

3.1.2.2 Determination of absorption maxima of Minoxidil in Phosphate buffer(pH7.4)³⁶A solution (20 µg/mL) of Minoxidil in phosphate buffer (pH7.4) was inspected over the U.V. range from 400 nm to 200 nm and the λ_{max} of Minoxidil was declared 288nm, respectively. The absorption maxima of the buffer solution of the drug are depicted in **Figure 3**, along with the standard curve and graph in **Table No 3** and **Figure 4**, respectively.



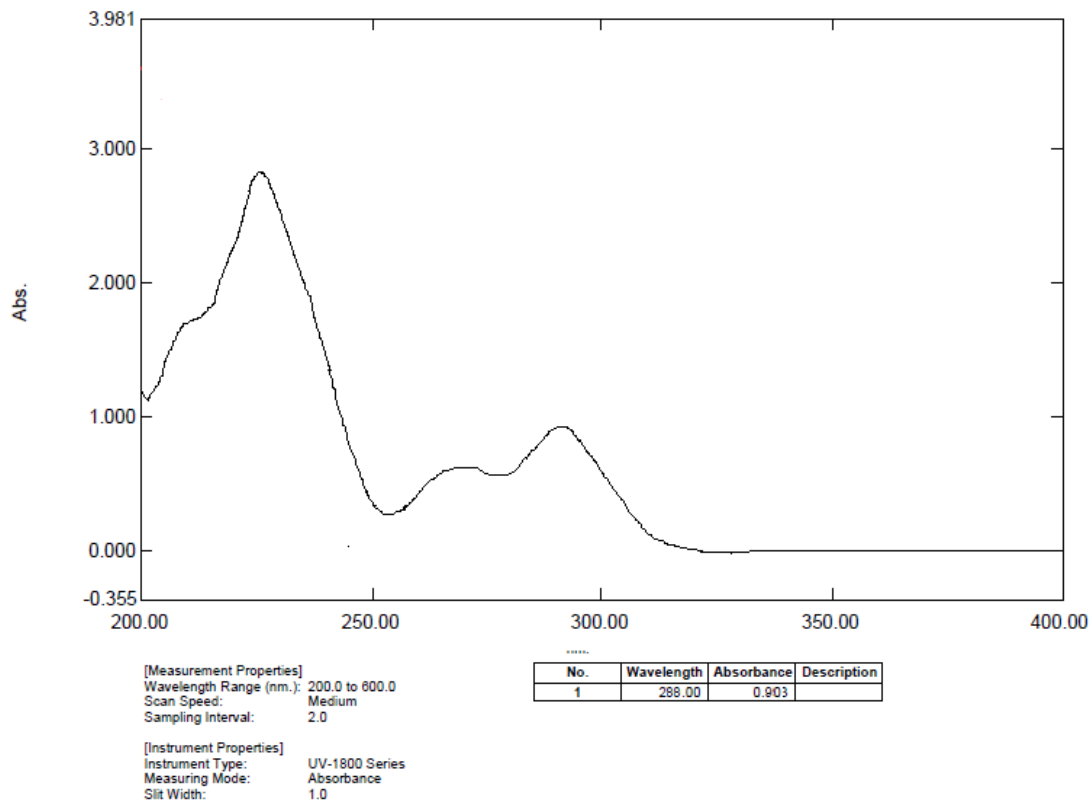


Figure 3:UV Spectrum of Minoxidil

The calibration curve for Minoxidil was procured by utilizing the 2 to 20 µg/ml solution of Minoxidil in application with phosphate buffer maintained at pH 7.4. The absorbance was estimated to be in the value of 288nm. As shown in the graph, the calibration curve of Minoxidil indicated the regression value $Y = 0.046x - 0.017$ and R^2 value 0.999, which shows good linearity at 288nm, as shown in **Figure 4**.

Table 3:Preparation of standard calibration curve of Minoxidilin Phosphate buffer(pH7.4)

Sr.no.	Concentration µg/ml	Absorbance
1	2	0.082±0.002
2	4	0.167±0.001
3	6	0.250±0.002
4	8	0.353±0.002
5	10	0.444±0.001
6	12	0.533±0.002
7	14	0.630±0.001
8	16	0.721±0.001
9	18	0.819±0.003
10	20	0.902±0.001



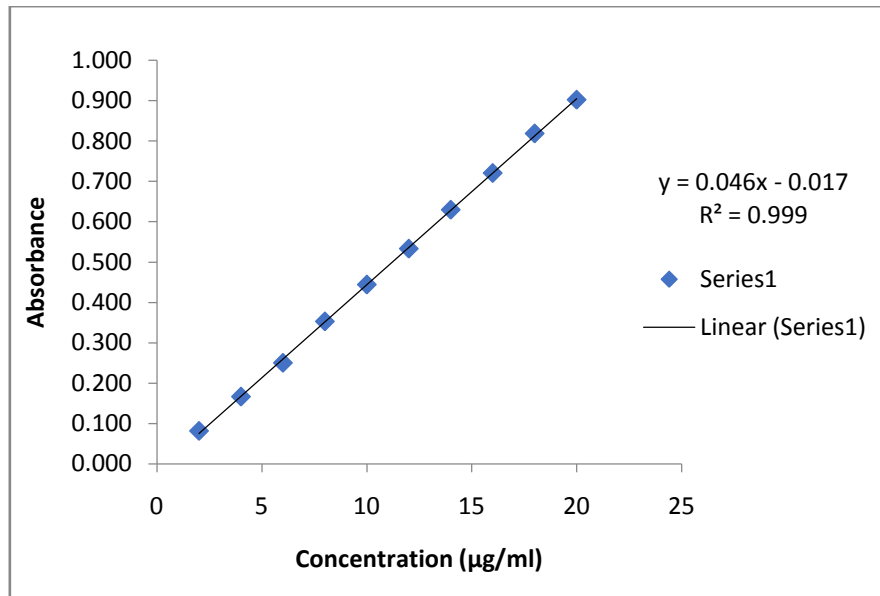


Figure 4: Graph of standard calibration curve of Minoxidil in Phosphate buffer (pH 7.4)

3.1.4 Solubility studies: From the above data, it was studied that Minoxidil is extremely dispersible in Methanol & Ethanol. (Table No 4)³⁶⁻³⁸

Table No 4: Solubility studies of Minoxidil in different solvents

Sr.no	Solvent	Solubility in (mg/ml) (mean±SD) *
1	Methanol	25.986±0.280
2	Ethanol	28.913±0.996
3	Water	2.179±0.007
4	Phosphate buffer 7.4	2.048± 0.004
5	Chloroform	0.029±0.000

Value is expressed as mean ± S.D.; n = 3

3.1.5 Partition coefficient determination

The partition coefficient of Minoxidil in n- Octanol: aqua was 1.205± 0.001 and indicates that Minoxidil is lipophilic.³⁹

3.1.6 FTIR studies of Minoxidil

The FTIR spectra of Minoxidil are shown in Figure 5; and Table 5. The principal IR absorption peaks of Minoxidil at 3279.63 cm⁻¹ (O-H or -N.H. stretching vibrations), 1600.55 cm⁻¹ (C=N stretching vibrations), 1549.15 cm⁻¹ (C-O stretching), and 1180.78 cm⁻¹ (S=O stretching vibration), restricting to the group were all observed in the spectra of Minoxidil. These principal peaks. This vigilance manifested the accuracy and efficacious nature of API Minoxidil.⁴⁰



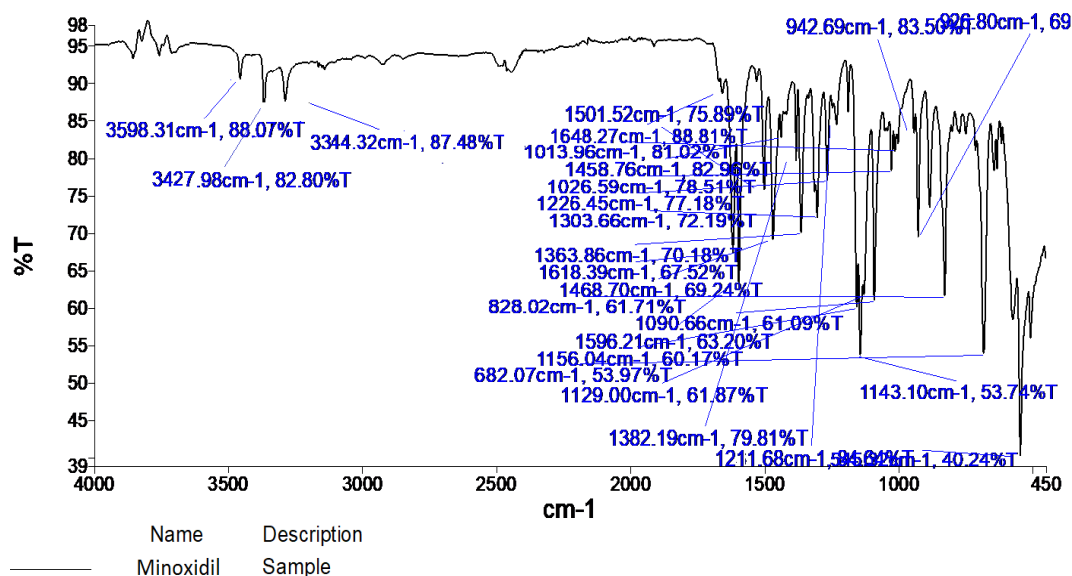


Figure 5: FTIR Spectra of Minoxidil

Table 5: FTIR Spectra peaks of Minoxidil

Reference peak (cm ⁻¹)	Observed peak (cm ⁻¹)	Characteristic peaks
3423.72	3427.98	N-H stretching, primary amine
1643.98	1648.27	N-H bending, primary amine
1450.06	1458.76	C=C aromatic stretching
1227.04 and 1210.62	1226.45 and 1211.68	C-N stretching
756.60	749.08	(N-H wag)

3.1.7 FTIR studies of Cationic guar gum

The FTIR spectra of Cationic guar gum are shown in **Figure 6**; and **Table 6**. The principal IR absorption peaks of Cationic guar gum at 2981.17cm⁻¹ (C-H stretching of the -CH₂ groups), 1380.44cm⁻¹ (Symmetrical deformations of CH₂ and COH groups), 1013.38cm⁻¹ (O-H bending vibrations), and 867.38cm⁻¹ (C1-H deformation), representing to the group respectively were all observed in the spectra of Cationic guar gum. These observed principal peaks. This observation confirmed the purity and authenticity of the Cationic guar gum.⁴¹



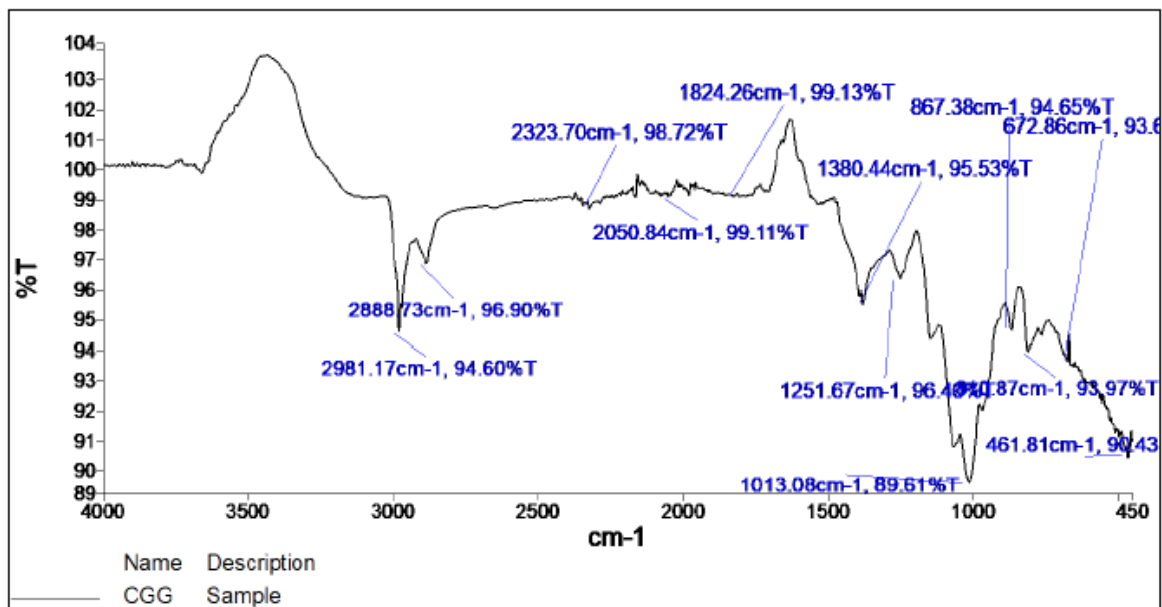


Figure 6: FTIR of biopolymer Cationic guar gum

Table 6: FTIR interpretation of Cationic guar gum

Reference peak (cm ⁻¹)	Observed peak (cm ⁻¹)	Characteristic peaks
2924	2981.17	C-H stretching of the -CH ₂ groups
1350- 1450	1380.44	Symmetrical deformations of CH ₂ and COH groups
1025	1013.38	O-H bending vibrations
890	867.38	C1-H deformation

3.1.7 FTIR studies of Cationic guar gum and minoxidil mixture

FTIR studies of pure drug and physical mixture are shown in **Figure 7**; and **Table 7**. Studies were carried out to eliminate the possibility of interaction between drugs and excipients. All the spectrum peaks revealed that the corresponding peaks of the drug are present in the above spectra along with the peak of polymer used. Hence no interaction was observed in this mixture.

Figure 7: FTIR Spectra of the physical mixture (Minoxidil & Cationic guar gum)

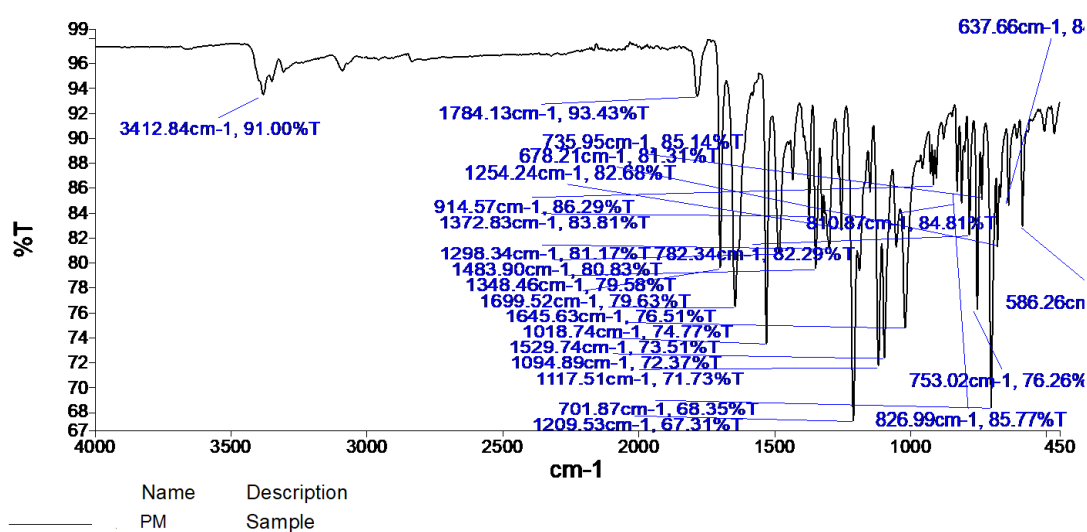


Table 7: FTIR interpretation of physical mixture (Minoxidil & Cationic guar gum)

Reference peak (cm ⁻¹)	Observed peak (cm ⁻¹)	Characteristic peaks
3427.98	3412.84	N-H stretching, primary amine
1648.27	1645.63	N-H bending, primary amine
1458.76	1483.90	C=C aromatic stretching
1226.45 and 1211.68	1209.53	C-N stretching
749.08	753.02	(N-H wag)
1380.44	1372.83	Symmetrical deformations of CH ₂ and COH groups
1013.38	1018.74	O-H bending vibrations
867.38	826.99	C1-H deformation

3.2 Evaluation of cationic guar gels containing Minoxidil

The prepared Minoxidil loaded cationic guar gels were examined visually for their color consistency and found to appear viscous smooth appearance. Out of three developed gel formulations F2 to F6 batches of optimized formulation were found to be free from the presence of particles and showed good after feel test. So F2 to F6 gel formulation were used in further study. All formulations were found to be in a range of 7.13±0.02 to 7.33±0.03. The viscosity of all the formulations was found to be in the range of 12090±15.04 to 32555±32.58 at 10rpm & 10827±11.50 to 31359±13.00 at 50rpm. (Table 8 and Figure 8). Spreadability is considered a vital characteristic from a patient perspective as it enhances patient compliance. The diameter was found in ranges of 7.873±0.04 and 5.887±0.04cm, which indicates good spreadability.



Figure 9: Visual Appearance of Minoxidil cationic guar gel

Table 9: Visual Appearance, pH of Minoxidil cationic guar gel

Sr. no.	Formulation code	Visual Appearance	pH (Mean ± S.D.)	Viscosity (cps) at 10rpm	Viscosity (cps) at 50rpm	Spreadability (cm)
1	F2	Uniform gel formed	7.13±0.02	12090±15.04	10827±11.50	7.873±0.04
2	F4	Uniform gel formed	7.28±0.04	21041±24.19	20258±8.50	6.927±0.06
3	F6	Very viscous gel formed	7.22±0.03	32555±32.58	31359±13.00	5.887±0.04



7.2.1 Drug content

The drug content gels were found to be 96.812 ± 0.905 to $99.275 \pm 0.251\%$, respectively. The actual API ratios were contented to be fully satisfied. As a result, this methodology was supposed to be the most suitable in every form. (Table 10)

Table 10: Drug content of formulations (F2-F6)

Sr. no.	Formulation code	% Drug Content
1	F2	97.696 ± 0.435
2	F4	99.275 ± 0.251
3	F6	96.812 ± 0.905

7.2.2 In vitro drug release studies⁴¹

The in-vitro drug release of Minoxidil-loaded cationic guar gel formulations & Marketed formulations was given in Table 11 and Figure 10. The fabrications predominantly extended the API release compared to drug release from marketed formulae. In the case of marketing, the formulae released was 53.048 ± 0.183 within 3hr. On the other hand, the release of gel fabrications (F2 to F6) was 26 to 37% within 3hrs. In formulae, F2 was majorly intensified with $84.146 \pm 0.207\%$ within 24 hr. It can be concluded that the release rate of formulation F2 gives a protracted API release. Hence, the F2 formulation is most efficacious in sustaining the release of Minoxidil (over 24h).

Table 11: In vitro drug release of Minoxidil loaded cationic guar gel formulations & Marketed formulation

Time (hr)	% Drug release of formulation (F2)	% Drug release of formulation (F4)	% Drug release of formulation (F6)	% Drug release of Marketed formulation
0	0	0	0	0
0.25	2.959 ± 0.019	2.777 ± 0.026	1.29 ± 0.029	8.902 ± 0.037
0.5	9.083 ± 0.022	8.730 ± 0.112	4.854 ± 0.035	18.626 ± 0.000
1	19.475 ± 0.32	14.943 ± 0.294	11.87 ± 0.316	34.696 ± 0.000
2	30.103 ± 0.134	22.811 ± 0.115	19.326 ± 0.469	45.984 ± 0.226
3	37.867 ± 0.093	32.109 ± 0.19	26.968 ± 0.108	53.048 ± 0.183
4	45.95 ± 0.347	40.548 ± 0.405	35.639 ± 1.487	
5	52.896 ± 0.139	45.743 ± 0.274	41.939 ± 0.139	
6	56.667 ± 0.142	52.470 ± 0.139	47.016 ± 0.082	
8	64.111 ± 0.212	59.591 ± 0.294	54.046 ± 0.265	
10	67.462 ± 0.069	65.678 ± 0.139	57.461 ± 0.139	
24	80.567 ± 0.198	79.709 ± 0.329	69.364 ± 0.134	

Figure 10: In vitro drug release of Minoxidil loaded cationic guar gel formulations & Marketed formulation



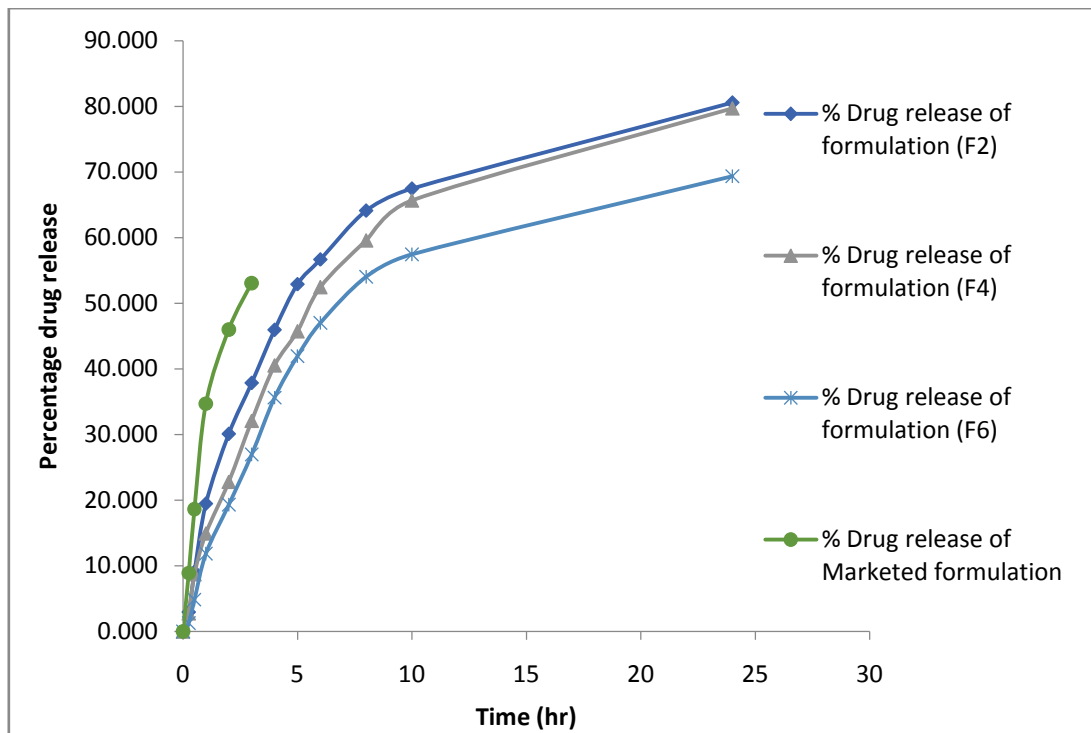


Figure 18: Percentage of drug release of Minoxidil loaded cationic guar gel formulations & Marketed formulation

7.2.7 Drug release kinetic studies

8 Mathematical models are used to obtain the release mechanism and compare the release profile. For the most appropriate formulation F2, the % API evacuation vs time (zero-order), log per cent API vs time (first-order), log % API evacuation vs square root of time (Higuchi plot), and log of log % API release vs log time (Korsmeyer and Peppas Exponential

Equation) were extrapolated. In each case, the R^2 value was defined from the data reported in **Table 12**. Considering the determination coefficients, the Higuchi model was found to be the most dominant ($R^2=0.927$) to fit the release mechanism, culminating the best data. It could culminate from the results that the API was released from cationic guar gum gel by a sustained mechanism.

Table 12: Kinetic equation parameter of formulation F2

Formulation	Zero-order		First-order		Higuchi		Korsmeyer-Peppas	
	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0
F2	0.73	3.636	0.905	-0.034	0.927	20.75	0.916	0.859



CONCLUSION

A cationic gel formulation of minoxidil was successfully formulated and evaluated. Of the various formulations prepared during the study, the F2 formulation was found to be the best and most optimal for various parameters. Further, the release studies indicate that formulation F2 could be a good candidate for the therapeutic management of male pattern baldness.

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