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Formulation, evaluation and characterization of climbazole gel for the treatment of fungal infection

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Abstract
Anti-dandruff hair gels were prepared and evaluated as part of a study. Hair gels' physiochemical properties have been established. Hair gel *in-vitro* drug release profiles were carried out. It was discovered that prepared hair gels released medication based on the *In-vitro* drug release profile. The Climbazole formulation F5 demonstrated an excellent release profile when compared to other formulations, and it displayed the same zone of inhibition as the pure drug. F5 was therefore thought to be an effective composition for treating dandruff. In conclusion, the contact time in terms of hours in the affected area might be improved for the hair gels by using regularly used gelling agents. To establish stable gel products, however, long-term stability tests are required. To confirm its effectiveness in the treatment of dandruff, more clinical trials are required.

Keywords: Climbazole, anti-dandruff hair gels, clinical trials

Introduction
Fungal infection of the skin is nowadays one of common dermatological problems. The physicians have a wide choice for treatment from solid dosage to semisolid dosage form and liquid dosage formulation. Among topical formulation, clear transparent gels have widely accepted in both cosmetics and pharmaceuticals [1].

Topical treatment of dermatological disease as well as skin care, a wide variety of vehicle ranging from solids to semisolids and liquids preparations is available to clinicians and patients. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparation [2].

For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, cream, gel, ointments, liquids, aerosols and inject able, as drug carriers. Delivery of drugs to the skin is an effective and targeted therapy for local dermatological disorders. This route of drug delivery has gained popularity because it avoids first-pass effects, gastrointestinal irritation, and metabolic degradation associated with oral administration. Due to the first past effect, only 25-45% of the orally administered dose reaches the blood circulation. In order to bypass these disadvantages, the gel formulations have been proposed as a topical application. Gels are defined as “semisolid system in which a liquid phase is constrained within a polymeric matrix in which a high degree of physical and chemical cross-linking introduced.

Fungal Infection Symptoms
Most common mild mycoses often present with a rash. Infections within the skin or under the skin may present with a lump and skin changes. Less common deeper fungal infections may present with pneumonia like symptoms or meningitis [3-4].

A fungal skin infection might cause
- Irritation.
- Scaly skin.
- Redness.
- Itching.
- Swelling.
- Blisters.

Causes

Mycoses are caused by certain fungi; yeasts, melds and some fungi that can exist as both a mold and yeast. They are everywhere and infection occurs after spores are either breathed in, come into contact with skin or enter the body through the skin such as via a cut, wound or injection. *Candida albicans* is the most common cause of fungal infection in people, particularly as oral or vaginal thrush, often following taking antibiotics [5-8].

Risk factors

Fungal infections are more likely in people with weak immune systems. This includes people with illnesses such as HIV/AIDS, and people taking medicines such as steroids or cancer treatments. People with diabetes also tend to develop fungal infections. Very young and very old people, also, are groups at risk.

Individuals being treated with antibiotics are at higher risk of fungal infections.

Children whose immune systems are not functioning properly (such as children with cancer) are at risk of invasive fungal infections [7-10].

Materials and Methods

Table 1: List of Chemicals

S. No.	Chemicals	Brand
1	Drug (Climbazole)	Continental Chemicals, Bawana Delhi
2	Carbopol-940	Bo International Wazirpur Delhi
3	Propyl Paraben	Subala Labchem, Delhi
4	Propylene Glycol	Subharty University Meerut
5	Triethanolamine	TIPER Meerut
5	Methanol	TIPER Meerut

Table 2: List of Equipments Used

S. No.	Equipments	Manufacturer
1	UV-Visible double beam Spectrophotometer	Shimadzu UV 1700
2	Electronic Balance	Sortorius Single Pan
3	Magnetic Stirrer	Remi equipment, Mumbai.
4	pH meter	Elico L 1120
5	Brookfield Viscometer	LVII model
6	FTIR	Perkin Elmer
7	Optical microscope	Nikon U.S
8	AFM	Commercial Nanoscope III Digital Instruments, Veeco,
9	TEM	Topcon, Paramus, NJ
10	Cooling centrifuge	Remi

Pre-formulation Studies

Pre-formulation may be described as a stage of development process during which the researches characterize the physical, chemical and mechanical properties of the drug substance to form effective, stable and safe dosage form. Hence, pre-formulation studies are essential to characterize the drug for proper designing of the drug delivery system. The pre-formulation studies which were performing in this project include [11-12].

Description

Organoleptic characters of drug was observed and recorded by using descriptive terminology.

Melting point

Capillary tube, which is sealed at one end is charged with sufficient amount of dry powder to form a column in the bottom of the tube 2.5 mm to 3.5 mm, and packed down as closely as possible by moderate tapping on a solid surface. The apparatus is operated according to the standard operating procedure. The block is heated until the temperature is about 30 °C below the expected melting point. The capillary tube is inserted into the heating block, and the heating is continued at a rate of temperature increase of about 1 °C to 2 °C per minute until melting is completed [13-14].

Solubility Studies

The spontaneous interaction of two or more substance to form a homogenous molecular dispersion is called as solubility. 10 mg of drug was a suspended separately in 10 ml of different solvents at room temperature in tightly closed tubes and shaken. The solubility profiles of two drugs in various solvents are shown in the table (3) [15-16].

Table 3: Solubility Profile I.P. 1996

Descriptive term	Parts of solvent required for I part of solute
Very soluble	Less than I
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly Soluble	From 30 to 100
Slightly Soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10.000
Practically Insoluble of Insoluble	Greater than or equal to 10.000

Hygroscopic Nature

Procedure

2 gm of the test specimens were weighed accurately in petridish and the weight were noted down. Then the test specimens were exposed to 75% RH at 40 °C in environment stability testing camber and the other was kept at room temperature for 7days period. The specimen was weighed after 7 days and the difference in weight was noted down [17].

Identification of Drug Sample

Finding the Absorption Maxima (λ max)

The absorption maxima were found for drug identification. Ultraviolet visible spectrophotometry has been used to obtain specific information on the chromophoric part of the molecules. Organic molecules in solutions when exposed to light in the visible/ultraviolet region of the spectrum absorb light of particular wavelength on the type of electronic transition associated with the absorption [18-20].

Preparation of Phosphate Buffer Solution [pH 7.4] I.P 1996

- 27.218 g of potassium dihydrogen ortho phosphate was dissolved in 1000 ml of distilled water to give a 0.2N solution.
- 8g of sodium hydroxide was dissolved in 1000 ml of distilled water to give 0.2N solution.
- 1250 ml of 0.2N potassium dihydrogen ortho phosphate and 977.5 ml of 0.2N sodium hydroxide were mixed together and made upto 5000 ml with distilled water.
- The drug solution (10, 20, 30, 40, 50, 60 µg/ml) in Phosphate buffer pH 7.4 was taken in standard cuvette, and scanned in the range of 200-300nm in a UV spectrophotometer.
- It exhibits maxima at 262 nm. UV spectrum of drug taken in phosphate buffer pH 7.4 also exhibits maxima at 262 nm. Therefore, further all measurements were taken at 262 nm.

Standard Curve

Preparation of Standard plot for Climbazole in phosphate Buffer pH 7.4

Accurately weighed amount of Climbazole (2 mg) was dissolved in small quantity of 0.1N NaOH & then diluted to 100 ml with phosphate buffer pH 7.4. Each ml of the stock solution contains 100 µg of Climbazole. From this stock solution different standard of working standard solutions i.e., 10, 20, 30, 40, 50, 60 µg/ml were made up with phosphate buffer pH 7.4 and the absorbance was measured at 262nm using phosphate buffer pH 7.4 as blank by UV spectrophotometry method. A graph is plotted by using concentration at X-axis and absorbance at Y-axis [21-22].

Fourier Transforms Infrared (FTIR) Spectral Analysis

FTIR is used to identify the functional groups in the molecule. The drug is mixed with KBr disk was scanned at 4 mm/s at a resolution of 2 cm over a wave number region of 400 to 4000 cm^{-1}. The characteristic peaks were recorded. Drug-Excipients Compatibility Studies by FT-IR Analysis Infrared spectrum of any compound or drug gives information about the groups present in that particular compound. The IR absorption spectra of the pure drug and physical admixtures of drug with various Excipients were taken in the range of 4000-400 cm^{-1} using KBr disc method (Schimadzu IR- Prestige-21) and observed for characteristic peaks of drug. Drug-Excipients compatibility was carried out by FT-IR analysis. Initially the IR spectrums of pure drug, Climbazole, Carbopol-940, Propylparaben, propylene glycol were obtained. After that admixtures of drug with other Excipients were prepared and IR Spectra was obtained. The obtained spectra of physical admixtures was observed for major peaks and recorded. The results of this observation were concluded that there is no interaction between the drug (Climbazole) & other Excipients (Carbopol-940, Propylparaben, propylene glycol & Triethanolamine) [23-26].

Method of Preparation of Topical Gel Containing Climbazole

Climbazole (2% w/w) was dissolved in oily phase (Carbolpol-940) consisting of equal amount of menthol. The Climbazole solution was then mixed with mixture of surfactant- Propylparaben & co-surfactant (Propylene Glycol). Finally, an appropriate amount of water was added to the Climbazole solution mixture drop by drop to get micro-emulsion (Yang *et al*., 2004). The composition of the different formulated micro-emulsion [27-30].

Table 4: Preparation of Topical Gel

S. No.	Ingredients	F1	F2	F3	F4	F5	F6
1	Climbazole	2	2	2	2	2	2
2	Carbolpol-940	1	1.5	2	2.5	3	2
3	Propylparaben	3	3	3	4	3	3
4	Propylene Glycol	2	2	2	2	2	2
5	Triethanolamine	2	4	6	8	10	12
6	Methanol	5	4	6	4	3	3
6	Final Volume H2O	50	50	50	50	50	50

Evaluation of Physicochemical Parameters of Prepared Climbazole Gel

Drug-Excipients Compatibility Studies

FTIR

The drug, polymer, and Excipients interactions are studied using the FTIR method. In general, drug and Excipients must be coinciding with each other which produce a stable, safe, and efficacious product. IR spectral analysis of pure drug and polymers was transported out. Pure drug that gives peak and patterns were compared with the peaks and patterns with the combination of polymer and drug [31].

Zeta Potential

Zeta potential is the measurement of attraction or repulsion in between particles. Its measurement brings details about the dispersion mechanism which is used to measure electrostatic dispersion. The zeta potential calculation is a important limitation across a various range of industries incorporates pharmaceuticals, brewing, medicine, ceramics, and water treatment. For colloidal stability, the repulsive forces between two particles should be ascendant. Zeta potential is a useful index of magnitude for interaction between colloidal particles. In general, the colloidal systems stability is determined using measurements based on zeta potential [32-35].

Determination of pH

The digital pH meter is used to find out the pH value of a formulated topical gel. The values of prepared formulations are between the ranges of 4–8 that ignores the chance of skin irritation [36].

Spread Ability

The assessment of spread capacity, two glass slides were taken, and the prepared gel was compressed in between the two glass slides to steady stability by applying weight and leaves it for 6min. The value of spreadibility is gathered by determining the time taken for the two glass slides to get separated [37].

Percentage Yield

The practical yield of each sample is determined by weighing the empty container and the container along with the gel formulation and subtraction of empty container with the container along with the gel [38].

The expression “uniformity of dosage unit” is explained as the substances degree of uniformity among dosage units. The content uniformity test depends on the assay of the active medicament. 2 mg of the formulated gel is taken and dissolved in 100 ml of phosphate buffer of pH 6.8. The

above solution is allowed to stand for 30 min followed by gentle stirring to enhance the solubility of the drug. Then, it is treated, and the absorbance of the solution was identified spectrophotometrically at 262 nm using phosphate buffer pH 6.8 as blank [39-40].

Viscosity Estimation

Alteration in viscosity of the product displays adjustment instability and efficacy of the product. Uniformity of formulation lies on the ratio of the solid fraction to liquid fraction which constructs gel structure. The viscosity of topical gels was acquired using Brook- Field viscometer DE-V model using spindle no 61 and spindle speed of 50 rpm at 37 °C [41].

***In vitro* drug Release Study:**

Franz-diffusion cells equipment is used to study the *in vitro* drug release using various formulations. The specific quantity of formulation was applied on the membrane positioned between the donor and receptor chambers with an available diffusion area. Fill the receptor chamber with phosphate buffer pH 6.8 and is blended repeatedly with a tiny magnetic bead, the speed of 50 rpm is continued at the temperature at 37 °C±2 °C. At different meantime, the samples were taken and then it is exchanged with the same volume of phosphate buffer pH 6.8 to maintain the volume of dissolution medium. In all cases, sink conditions are seen. The obtained samples were analyzed spectrophotometrically at 262 nm [42-43].

Antidandruff Activity

Antidandruff activity was evaluated by using agar well method against Candida albicans, Aspergillus Niger and Mucor. Microbial inoculums of tested organisms (0.5% v/v) were spread over the nutrient-agar media in the separate petri dishes for each fungal strain. After solidifying the agar plate, well of 10 mm in diameter were made. The gel formulations were added to the wells by means of sterile syringe. Then the zone of inhibition of each well was visualized after the incubation period of 24 hrs. The radius of zone of inhibition was calculated and compared to the zone of inhibition of control formulation (Akhtar *et al*. 2012).

Stability Study

The concentration of an active ingredient of all formulation may fall with upraise in the temperature and time. This assists in drop in the potency of the product. Stability study in various temperatures ought to be dispensed to anticipate the formulation stability. Stability studies are strenuous at regulating the outcome of aging and storage under divers circumstance on the formulated gel. Stability studies take place to detect whether any chemical breakdown of Climbazole formulations take place or not. The chief formulation was kept at 30±2°C and 40±2°C at RH 65±5 and 75±5 RH for 2 months in a glass vial. After 1 or 2 months, the samples were repeatedly tested for the drug content and *in vitro* release studies [44-46].

Result and Discussion

Preformulation Studies

Description

Nature: It is a topical antifungal agent commonly used in the treatment of human fungal skin infections such as dandruff and eczema

Taste: Bitter

Melting point

Table 5: Melting Point Determination

Drug	Melting Point	Normal Range
Climbazole	198±0.134	95-97 °C

Solubility

Table 6: Solubility Profile of Itraconazole

S. No	Solvents System	Solubility (mg/ml) at 37±2 °C
1	Distilled H_2O	0.06
2	Ethanol	90
3	Chloroform	85
5	CCL_4	82
6	Diethyl Ether	18

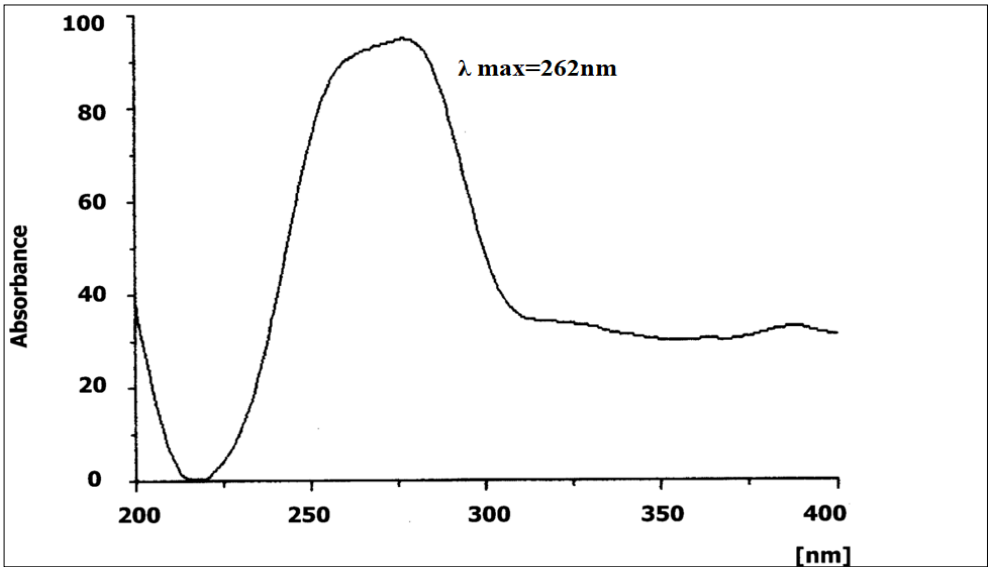

Fig.1: UV spectrum of Climbazole in phosphate buffer pH 7.4

Table 7: Absorption maxima of Climbazole in phosphate buffer pH 7.4

Solvent	Conc. (µg)/ml	λ max (nm)	Abs.
Phosphate buffer Ph7.4	50	262	0.5108

Standard plot of Climbazole in phosphate buffer pH 7.4:

Table 8: UV Absorbance of phosphate buffer pH 7.4

S. No.	Conc. (µg)/ml	Abs. at 262nm
1	10	0.1120
2	20	0.2030
3	30	0.3810
4	40	0.4414
5	50	0.5410
6	60	0.6199

Standard Plot of Climbazole in Phosphate Buffer pH 7.4:

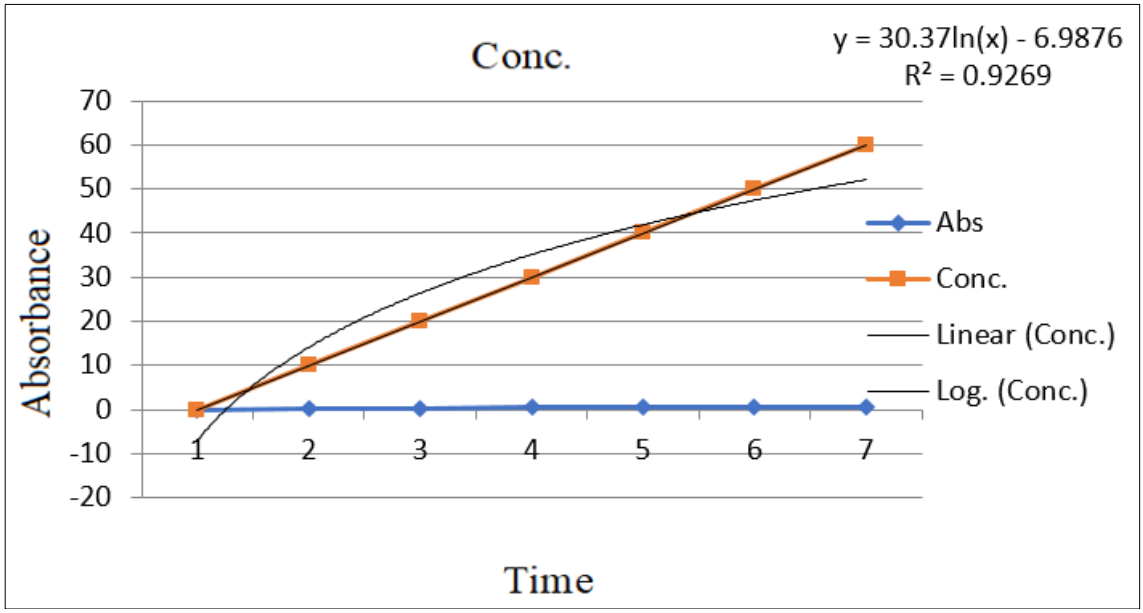

Fig 2: Standard plot of Climbazole in Phosphate Buffer pH 7.4

FTIR Study

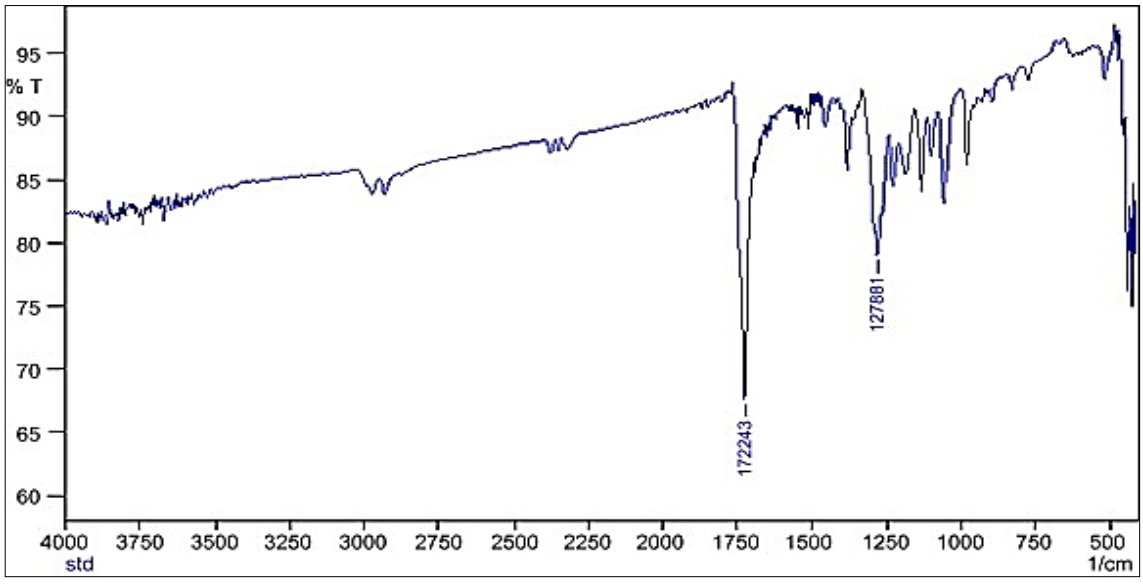

Fig 3: Fourier-Transform Infrared Spectrum of Climbazole

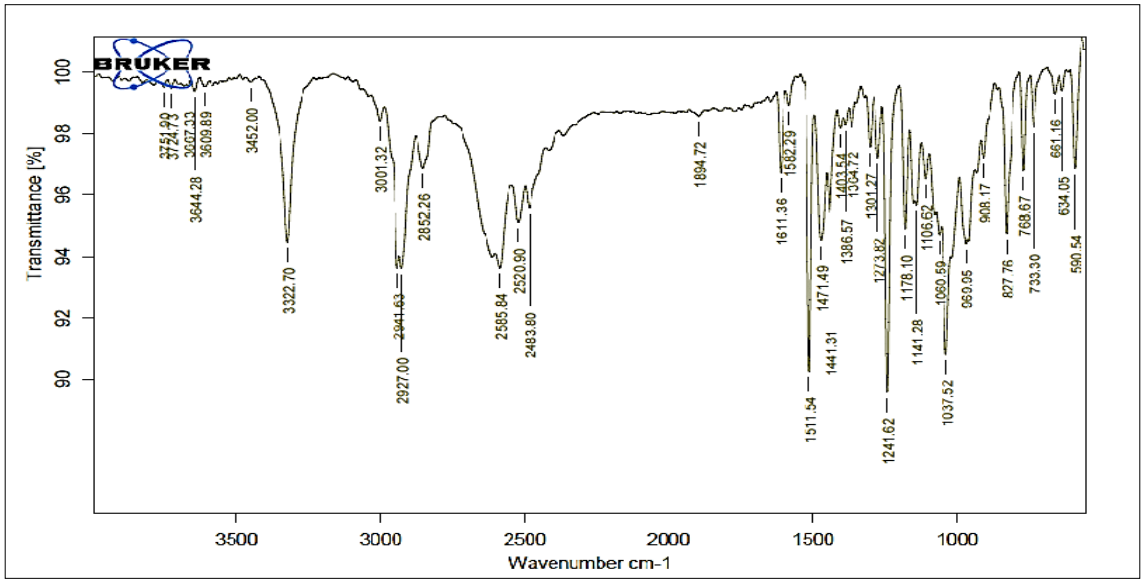

Fig 4: FTIR of Carbolpo-940

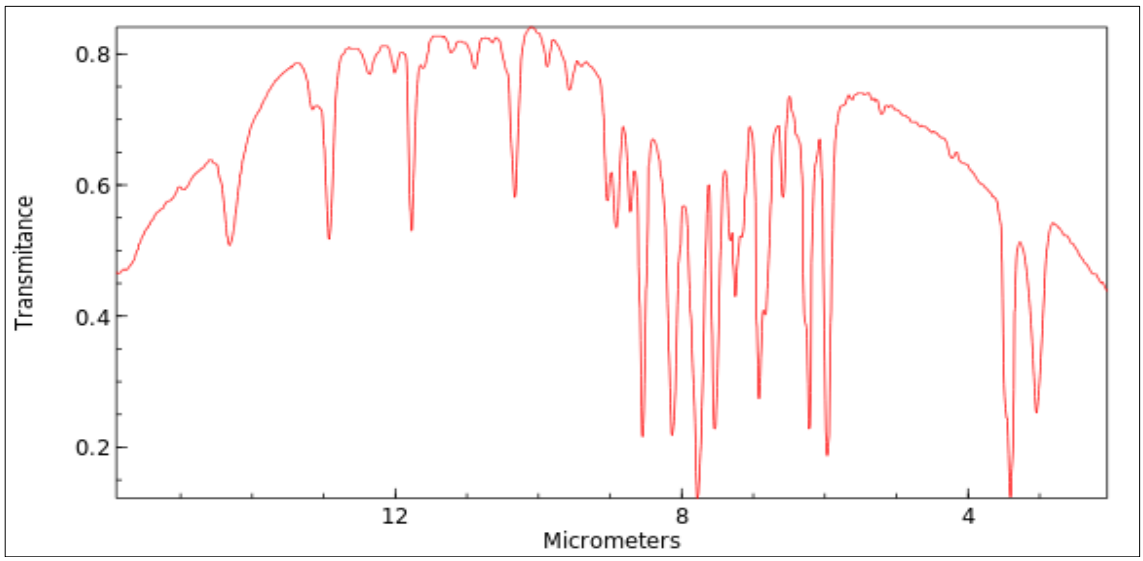

Fig 5: FTIR of Propylparaben

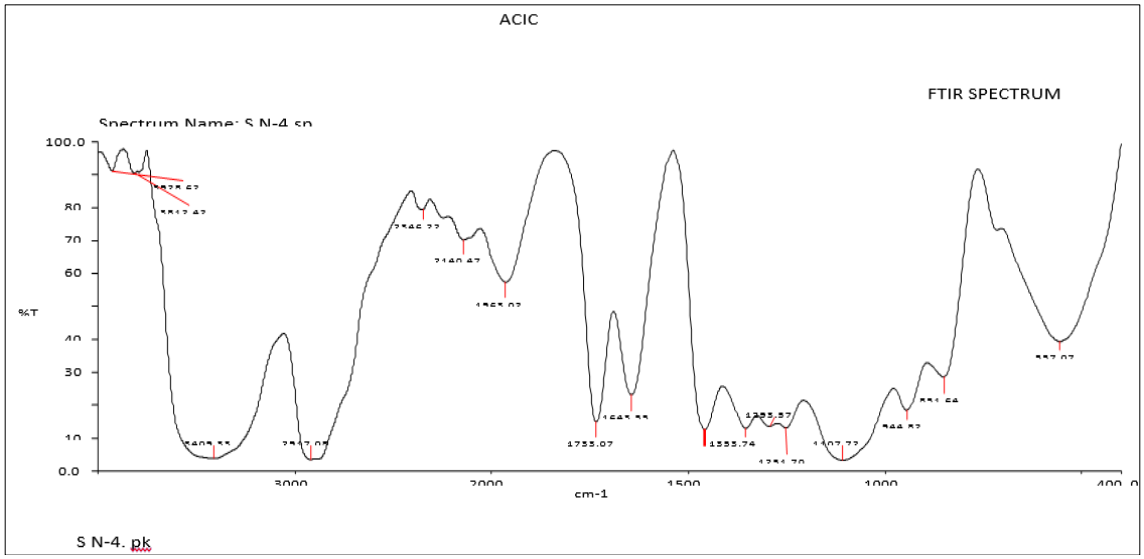

Fig 6: FTIR of Propylene Glycol

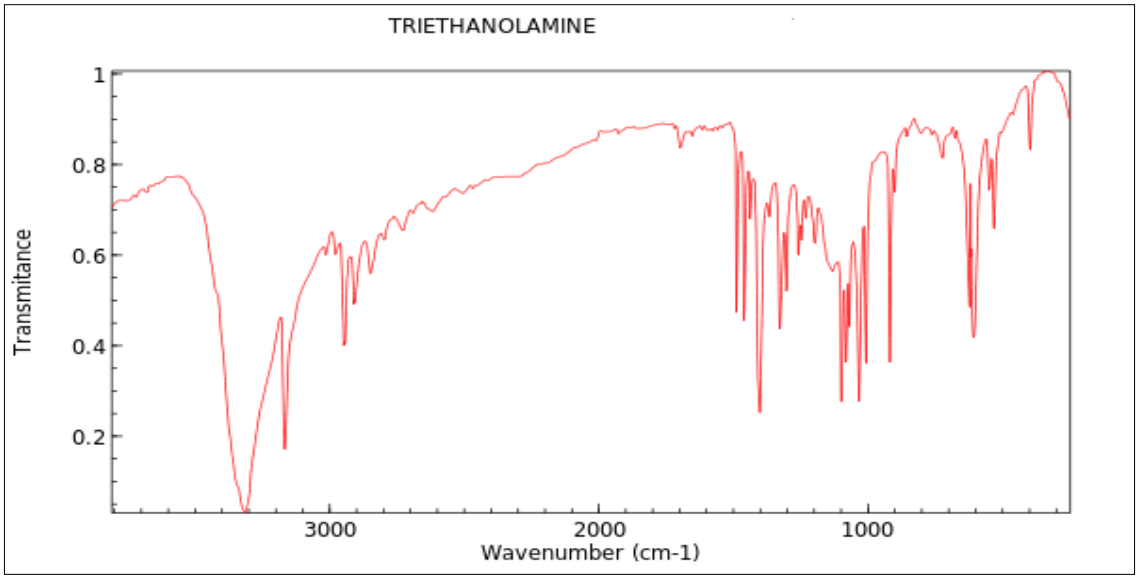

Fig 7: FT-IR of Triethanolamine

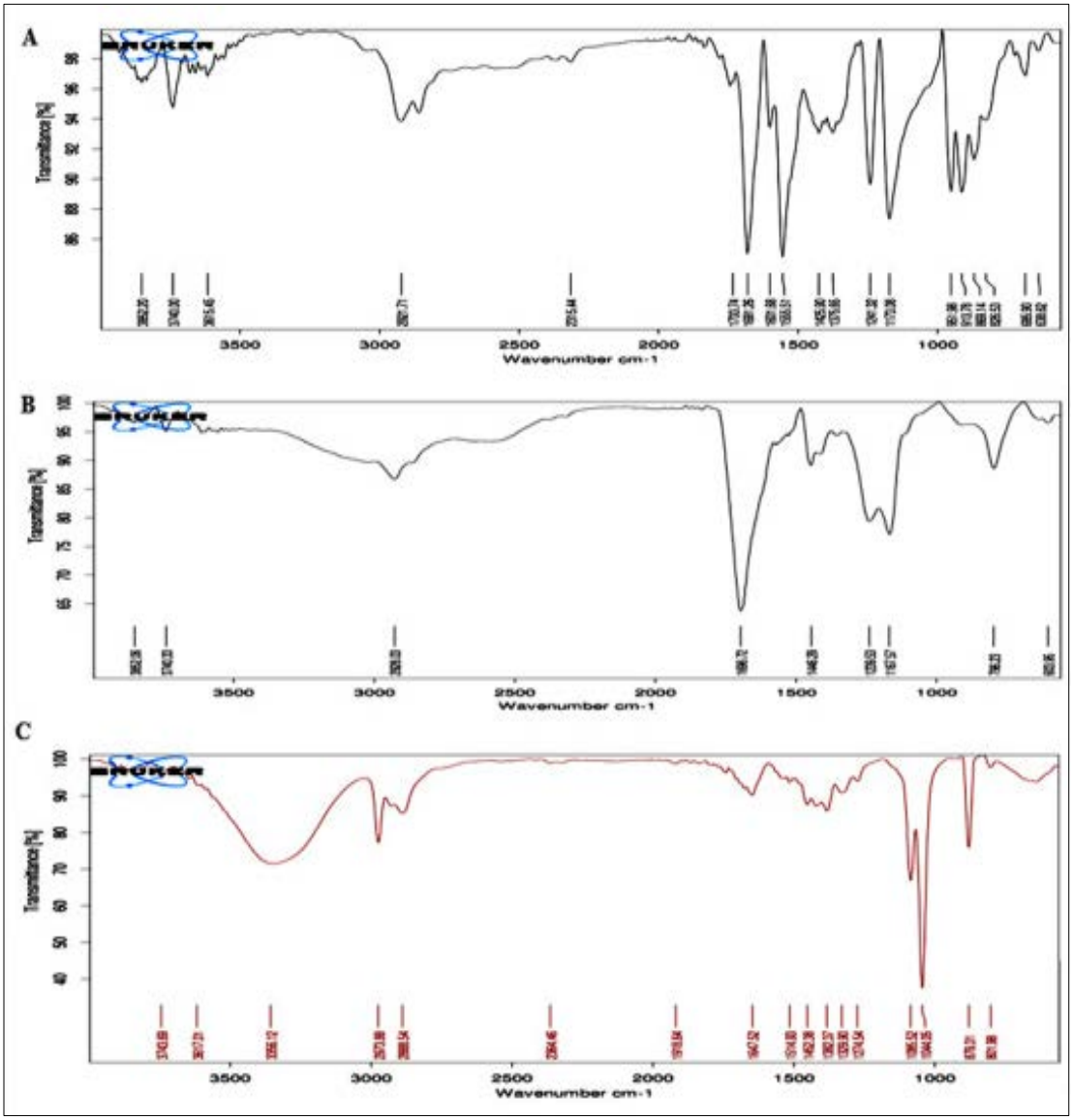

Fig 8: FT-IR of Physical Admixture (Climbazole+Carbolpol-940+Propylparaben+Propylene glycol)

Table 9: FT-IR Spectral assignment of Climbazole and Other Excipients

Wave number in (cm^{-1})	Functional groups
3600.78	O-H stretching
3260.12	N-H stretching
2970.86	C-H(Aromatic) stretching
1696.18	Carbonyl –C=O stretching
1828.62	NH(Amide) stretching
1550.62	S=O stretching
1489.49	C-S Stretching
1458.52	C-O Stretching
3024.90	C-H Stretching
1895.84	C-O Stretching
1347.65	C-O Stretching
818.78	C-H Out of plane bending
3489.50	N-H Stretching in Primary amine
2822.42	C-H Stretching
857.79	C-O Stretching
754.34	C-H Out of plane bending
3809.60	O-H Stretching
3617.06	C-H Stretching
1554.72	C-O Stretching
3280.60	O-H Stretching
1810.15	C=O Stretching
1797.90	C-N Stretching

There are no extra peaks seen other than the normal peak in the spectra of the mixture of the drug & Excipients so there is no interaction with the drug & Excipients and they are compatible with each other. The IR spectra of the drug & polymer combination were compared with the spectra of the pure drug & individual Excipients, in which no shifting of peaks was significantly found, indicating the stability of the drug during micro emulsion formulation development.

Evaluation Parameter of Climbazole Gel:

Table.10: Evaluation Parameter of Climbazole Gel:

Formulation	P^H	Zeta Potential	Spread ability	% Yield	Drug Content Uniformity	Viscosity Estimation
F1	6.0	13.4mV	1.01	97.40	98.43	89,00,115
F2	6.1	11.3mV	1.09	95.92	97.56	89,00,002
F3	6.4	13.5mV	1.1	98.16	96.22	89,00,133
F4	7.0	14.3mV	1.6	98.45	98.99	90,00,058
F5	7.5		0.99	99.10	99.56	91,01,111
F6	7.8	12.2mV	0.98	97.77	97.67	92,87,457

In-vitro Skin Permeation Study

Table 11: *In-vitro* Skin Permeation Study

S. No	Time (min)	% Drug release					
		F1	F2	F3	F4	F5	F6
1	30	14.90	16.40	15.60	16.54	20.34	10.88
2	60	26.50	26.40	25.63	36.77	35.68	25.90
3	90	36.70	38.79	36.69	45.66	49.99	40.22
4	120	43.76	48.81	47.80	60.71	60.56	56.99
5	150	59.21	54.91	62.13	69.23	71.43	68.90
6	180	74.11	70.43	73.32	78.94	85.32	75.02
7	210	80.17	87.35	84.59	87.88	92.54	88.92
8	240	94.20	96.22	95.11	97.80	99.23	92.34

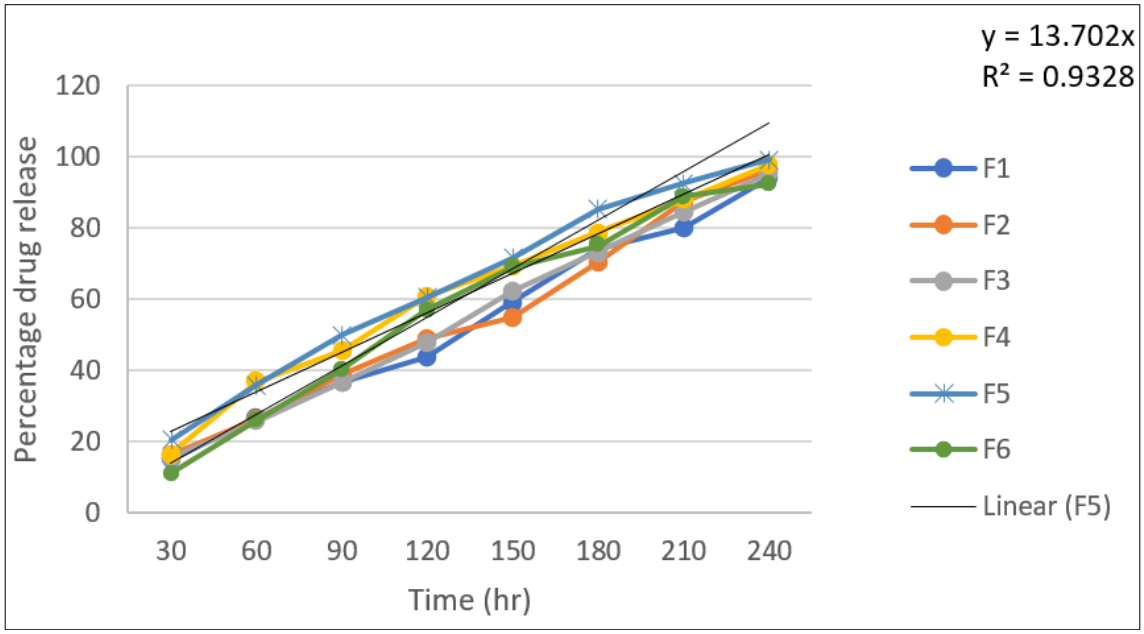

Fig 9: % Drug Release Study

The drug release profile of Climbazole topical gel formulations was accomplished by diffusion cell. As an outcome of the *in vitro* release studies of all formulations are given in Table 6, and the statistically represented is shown in Fig. 6. The percentage drug release of all formulations after 4h using Carbolpol-940+Propylparaben+Propylene glycol was identified to be 94.20% (F1), 96.22% (F2), 95.11% (F3), 97.11% (F4), 99.23% (F5) and 92.34% (F6) respectively. The most essential factors in the drug release are the type of polymer by the concentration of polymer.

Table.12: Anti-dandruff Activity

F Code	Anti-dandruff activity Zone of inhibition (mm)		
	Mucor	A. niger	C. albican
F1	20	17	7
F2	18	16	6
F3	18	18	8
F4	19	20	10
F5	17	15	9
F6	15	21	12

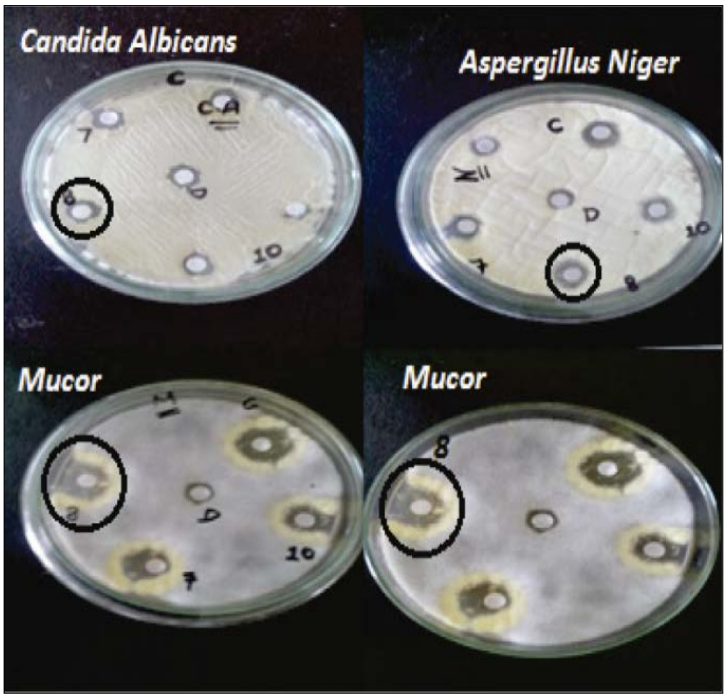

Fig 9: Anti-dandruff activity

Stability Study of F5 Optimized Formulation:

Table 13: Stability Study of Formulation 5

S. No.	Time (min)	1 Days	Percentage % drug release			
			30 days		60 days	
			30±2 °C	40±2 °C	30±2 °C	40±2 °C
1	30	20.34	20.33±0.10	20.32±0.04	20.31±0.12	20.28±0.24
2	60	35.68	35.67±0.11	35.65±0.25	35.50±0.16	35.58±0.13
3	90	49.99	49.45±0.10	49.40±0.46	41.00±0.16	49.94±0.08
4	120	60.56	60.55±1.15	60.50±1.023	60.16±0.89	80.00±0.31
5	150	71.43	71.42±1.10	71.30±1.20	70.90±1.08	70.56±1.01
6	180	85.32	85.22±1.22	85.00±1.17	84.32±1.62	80.06±0.43
7	210	92.54	92.20±0.09	92.00±0.10	91.50±0.08	91.90±0.15
8	240	99.23	99.20±0.09	99.10±0.10	98.80±0.13	98.65±0.06

Table 14: Drug Content Estimation after Storing at Different Temperatures (F5)

S. No.	Formulation	Drug Content			
		30±2 °C		40±2 °C	
		30 days	60 days	30 days	60 days
1	F5	99.23±0.08	98.38±0.10	98.00±0.16	97.53±0.12

There was no noticeable difference in the *in vitro* drug release study F5 (from 99.20% to 98.65%) at 30±2 °C at 65±5 RH. After storing at 40±2°C at 75±5 RH the *in vitro* drug release study of F5 formulation is decreased. The statistics are stated in Table 7. This was discovered that the developed Climbazole gel formulae and its storage were identified to be firm for 2 months at room temperature; there were no changes in the specification that is inflated such as physical aspect as color, drug content, and drug release during the inspection. Stability studies were carried for the most effective formulation-F5, at 30±2 °C and 40±2 °C at 65±5 and 75±5 RH for 2 months. At the end of 2 months, samples were evaluated. Drug content study showed that there was no major change in the content drug of F5 (from 99.23% to 98.38%) at 30±2 °C at 65±5 RH and decrease at 40±2°C at 75±5 RH (from 98.00% to 97.53%). The data were presented in Table.14.

Discussion

Climbazole gels were prepared by using different concentrations of polymers and fixed concentration of active ingredient. Advanced formulations of Climbazole were analyzed for physiochemical parameters such as viscosity, Spreadability, drug content, *in vitro* drug release studies and anti-fungal activity. From all the build out formulation, F4 manifest drug liberates for a phase of 4h. The most efficient formulation of F4 shows a significant change in drug contents. The formulated drug stability was monitored for 2 months at 30±2 °C and 65± 5 RH. It was found that the drug showed good stability at the opted appropriate condition. As carbopol-940 below 0.5% has no semi solid property and above 1% it has jelly nature so formulations were done using these concentrations only. The prepared gels pH was in the range of 6.0-7.8. The drug content in the formulated gels was in the range of acceptable limits. This shows that our prepared gel formulations are according to the limits. Viscosity of the formulated gel preparations was determined and the results were found to be 8900, 115cps, 92, 87, 457cps, for gels F1 to F6 respectively. *In vitro* diffusion studies were carried out and the release profiles of the gels are tabulated in table-2 and fig-7 the release of drug from the formulations. Anti-dandruff activity was also carried out and the diameter of zones of inhibition were recorded and tabulated in table-6. Among the three different concentrations of Carbolpol-940+Propylparaben+Propylene glycol gel formulated using 3% Carbolpol-940 i.e., gel F5 has shown best release properties when compared to the other two formulations.

Conclusion

A study involving preparation and evaluation of anti-dandruff hair gels was made. Physiochemical parameters of hair gels were established. *In-vitro* drug release profiles of hair gel were performed. Based on *In-vitro* drug release profile it was found that release of medicament from prepared hair gels. The formulations F5 of Climbazole exhibited good release profile as compared with other formulations, it exhibited same zone of inhibition as that of the pure drug. Hence, F5 was considered to be suitable formulation in treatment of dandruff. In conclusion, the hair gels could be formulated using commonly used gelling agents with improved contact time in number of hours in effected area. However, long term stability studies are needed to establish stable gel products. Further clinical trials are needed to establish its efficiency in the treatment of dandruff.

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