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Formulation and Evaluation of Novel Styling Posaconazole Hair Gel Topical Dosage Form:

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Abstract:

Posaconazole is an imidazole compound which exerts its antifungal activity through inhibition of lanosterolde methylation.This blocks the synthesis of ergosterol, the major sterol component of the fungal cell membrane. In mammalian cells, Posaconazole also inhibits lanosterol demethylation, with a subsequent decrease in the biosynthesis of cholesterol, the major sterol component of mammalian cell membranes. In addition, Posaconazole interferes with cellular fatty acid and phospholipids biosynthesis. The proceeding amount about physical aspects of the gel, chemical structure of the gel & its utilization as dermatological base has led to the developmental work regarding the use of these gels for topical usage.

Keyword: Hair Gel, Topical Dosage, Posaconazole**,** Preparations, Diffusion.

Topical dosage forms are those which are applied to the skin. These preparation are applied to the skin either for their physical effects, that is for their ability to act as skin protectants, lubricants, emollients, drying agents, etc. or for their specific effect of medicinal agents present. Preparations sold over the country frequently contain mixtures of medicinal substance used in the treatment of such condition as minor skin infection, itching, bruise, acne, psoriasis and eczema. Skin application, which require a prescription generally contain a single medicinal agent intended to counter a specific diagnosed condition[15].

Topical dosage forms have been used since very ancient times. The application of medicinal substance to skin or to various body orifices is a concept as old as humanity. Various ointments, creams, gels, lotions, pastes, powders and plasters have been used for many years[16]. The primary topical drug delivery system (TDDS) is that they could provide controlled constant administration of a medicament by simple application to the skin surface.

Advantages of Topical Systems[17]:

1) They are of least therapeutic interest but of practical relevance is good patient compliance. The systems are easy to apply and remove. It avoids risks and inconveniences associated with intravenous therapy.
2) They eliminate the variables, which influences gastrointestinal absorption such as food intake, stomach emptying, intestinal motility and transit time.

3) Produces sustained and controlled level of drug in plasma thus reduces the chance of over or under-dosing.

4) Reduces frequency of drug dosing.

5) Topical systems are easily retractable thereby termination of drug input, if toxic effects are observed.

6) Offers an alternative route when oral therapy is not possible as in case of nausea and vomiting.

7) Helps in achievement of more constant blood levels with lower dosage of drug by continuous drug input and by by-passing hepatic first-pass metabolism and consequent degradation.
8) In certain circumstances, enzymatic transformation within epidermis may be used to improve permeability of certain hydrophilic drugs when applied to the skin in the form of prodrug.

Limitations of Topical Systems[18]:

1) Drugs with reasonable partition coefficient and possessing solubility both in oil and water are most ideal, as drug must diffuse through lipophilic stratum corneum and hydrophilic viable epidermis to reach the systemic circulation. Only drugs, which are effectively absorbed by the percutaneous routes as such or by using penetration promoters, can be considered.

2) The route is not suitable for drugs that irritate or sensitize the skin.

3) The route is restricted by the surface area of delivery system and the dose that needs to be administered in the chronic state of disease.

4) Topical drug delivery systems are relatively expensive compared to conventional dosage forms. They may contain a large amount of drug, of which only a small percentage may be used during the application period. Apart from these limitations other problems include pharmacokinetics and pharmacodynamic restrictions. Thus clinical need has to be examined carefully before developing a TDDS.

Skin As Route Of Topical And Transdermal Drug Delivery:

The transdermal permeation of a chemical involves partitioning into and transport through

the cutaneous layers, namely the stratum corneum, the viable epidermis (stratum basale) and the upper dermis[17]. A topical product is designed to deliver the drug into the skin to treat dermal disorders and therefore skin is the target organ. Non steady state transport generally characterizes a topical product. The skin isa barrier to topically administered drugs[19]. Topical formulations usually contain several excipients, which also partition into the skin according to their physicochemical properties. Certain excipients change the integrity of stratum corneum. Stratum corneum can exhibit swelling by water. Thus, the permeability of drugs depends on the degree of hydration. Cosolvents may later the barrier properties of the skin. Some substances having considerable polarities also enhance the permeability of the horney layer. It is known that use of oleaginous vehicles enhances the skin permeation. Topical preparation applied to the skin may be designed for surface, local or systemic offers. In order to understand these effects, a brief review of the skin structure is provided[20,21].

1. Determination of Drug Content Uniformity In The Gel:

The drug content of all the formulations was found in range of 85.2 to 100.6 %as shown in Table 11 showing the drug was uniformly distributed in the gels.

Table 1: Various Parameters of Gels:

Formulation	Spreadability G cm/s	Viscosity Cps	pH	Drug content (%)
I	16.29	3020	6.4	95.43
II	17.03	2329	7.2	97.60
III	13.33	3890	6.9	95.65
IV	14.07	3510	6.5	100.62
V	11.48	4370	6.6	85.21
VI	11.85	3930	6.9	93.48

2.*In Vitro* Diffusion From The Gel Formulations:

Diffusion studies on all the six formulations of Posaconazole hair gel was carried out using cellophane membrane and pH 5.4 neutralized phthalate buffer as the dissolution medium.
The results obtained in *in-vitro* diffusion studies were plotted in five models ofdata treatment as follows

- Cumulative percent drug diffusion Vs. Time (Zero order rate kinetics).
- Log Cumulative percent drug retained Vs. Time (First order rate kinetics).
- Cumulative percent diffusion Vs. □T [Higuchi's classical diffusion equation (Higuchi)].
- Log of cumulative percent drug diffusion Vs. Log Time (Peppas exponential equation).

The *in vitro* diffusion data obtained for formulation F I to F VI are shown in Table 12 to 17 and Figure 6, 10 and 14.

Cumulative percent drug diffusion after 4 hours was found to be 93.50 % and

94.65 % for the formulation F I & F II respectively while cumulative percent drug diffusion after 6 hours was found to be 94.23 %, 96.52 %, 78.19 %, and 83.23 % for the formulations F III, F IV, F V & F VI respectively.

***In vitro* diffusion of the gel:**

The results showed 22.6 % of drug diffusion in the first 15 min and the drug was slowly diffused upto 93.50 % of 240 min respectively for F I formulation. The *in vitro* diffusion of drug for formulation F I is shown in Table12.

Table 2: *In Vitro* Diffusion of Posaconazole Hair Gel of F I

TIME	%CDD	% CD REMAIN	LOG % CD REMAIN	SQURE ROOT "T"	LOG CDD	LOG "T"
15	22.60	77.40	1.888	3.873	1.354	1.176
30	31.86	68.14	1.833	5.477	1.503	1.477
45	37.86	62.14	1.793	6.708	1.578	1.653
60	55.30	44.70	1.650	7.746	1.742	1.770
90	70.54	29.46	1.469	9.487	1.848	1.954
120	80.04	19.96	1.300	10.95	1.903	2.079
180	88.00	12.00	1.079	13.41	1.944	2.255
240	93.50	6.500	0.812	15.49	1.970	2.380

The results showed 25.21 % of drug Diffusion in the first 15 min and the drug was slowly Diffused upto 95.65 % of 240 min respectively for F II formulation. The *in vitro* diffusion of drug for formulation F II is shown in Table13

TIME	%CDD	% CD REMAIN	LOG % CD REMAIN	SQURE ROOT	LOG CDD	LOG "T"

				"T"		
15	25.21	74.78	1.870	3.873	1.401	1.176
30	34.54	65.45	1.815	5.477	1.538	1.477
45	38.86	61.14	1.798	6.708	1.569	1.653
60	58.93	41.07	1.640	7.746	1.750	1.778
90	73.39	26.61	1.426	9.487	1.865	1.954
120	82.95	17.05	1.234	10.995	1.918	2.079
180	91.84	8.160	0.917	13.416	1.962	2.255
240	95.65	4.350	0.644	15.491	1.980	2.380

Table 3: *In Vitro* Diffusion of Posaconazole Hair Gel of F II

The drug diffused was found to very fast as almost all the drug was diffused 93.50 % & 95.65 % within 4 hour of F I formulation & FII formulation respectively.

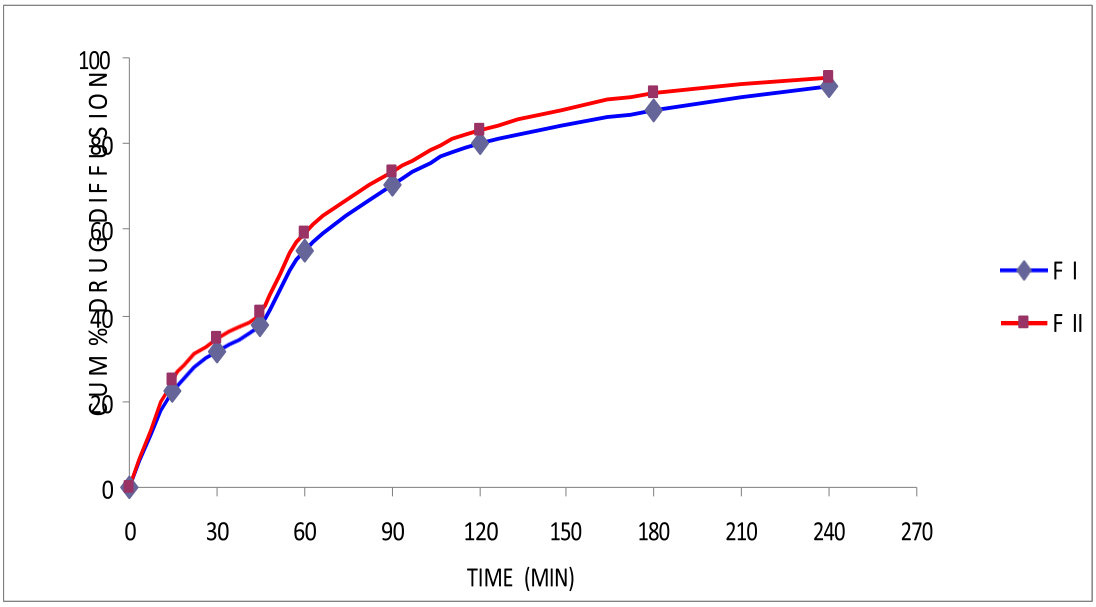

Fig 2: *In Vitro* Cumulative % Drug Diffusion of FI & FII Formulation

In order to ascertain the rate of diffusion of drug from this formulation the data of FI & FII formulation the data was plotted according to first order rate kinetics in which log % drug retained was plotted against time this plot is shown in fig 7. the plot is found to be linear

with a regression coefficients value of 0.9887 & 0.9905 respectively indicating that the diffusion data has obeyed the first order rate kinetics.To assess the mechanism involved in the drug diffusion the date was plotted according to Higuchi's equation in which the cumulative percent drug diffusion was plotted against □T is shown in fig 8. The results indicated that the plot is linear with regression coefficient of 0.9454 & 0.9372.

The results further showed the plot has shown linearity up to a time of 240 min and showed some deviation from this formulation almost the entire drug was found to be diffused.To confirm whether the diffusion mechanism is the only operating factor for the diffusion of the drug the data has been plotted according to Peppas equation the plot is shown in fig 9. In this equation log of cumulative percent drug diffusion was plotted against log time it can be seen from the fig that the plot is linear with a regression coefficient value of 0.9614 & 0.9520.

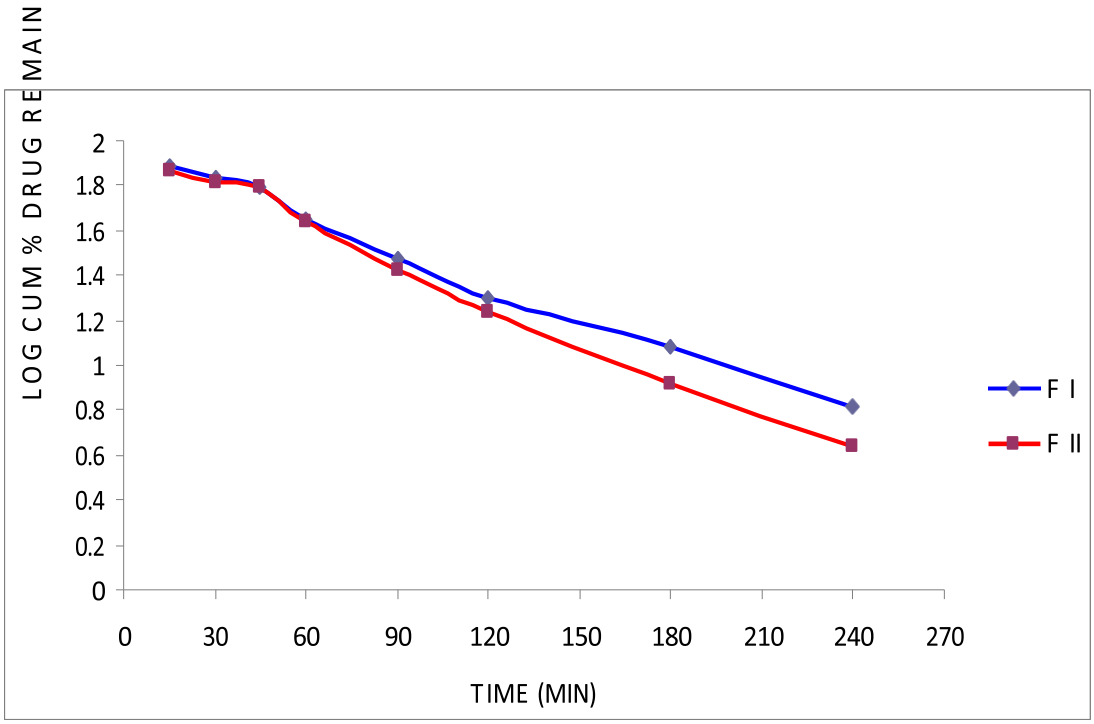

Fig 3: First Order Rate Diffusion of Formulation FI & FII

Fig 4: Higuchi's Sq Root Plot Showing the Diffusion of Formulation FI & FII

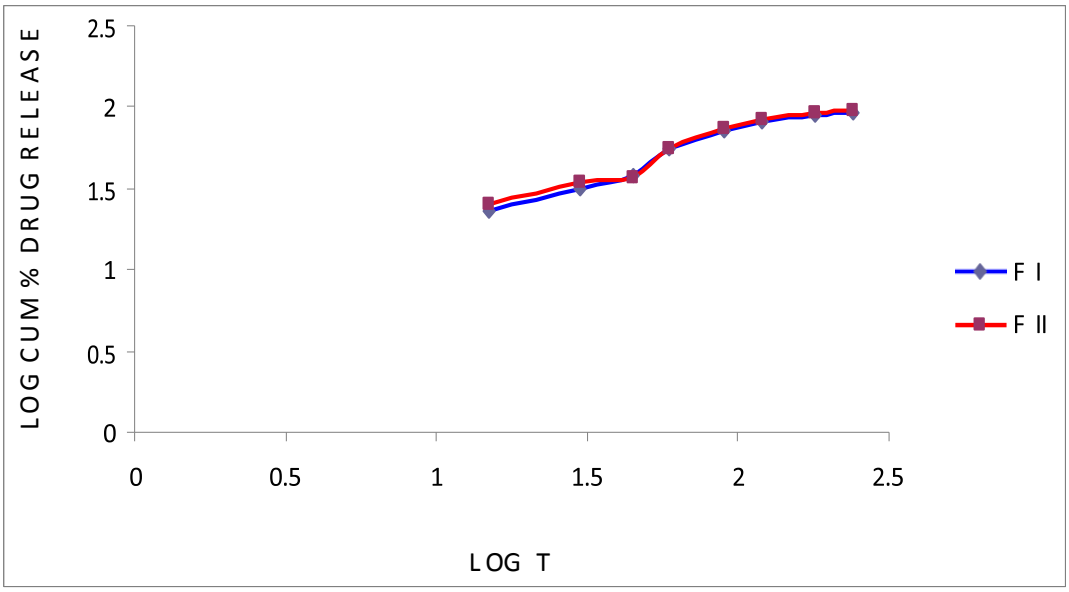

Fig 5: Peppas Equation Plot Showing the Diffusion of Formulation FI & FII

The results showed 18.26 % of drug diffusion in the first 15 min and the drug was slowly diffused upto 94.23 % of 360 min respectively for F III formulation. The *in vitro* diffusion of drug for formulation F III is shown in Table14.

Table 5: *In Vitro* Diffusion of Posaconazole Hair Gel of F III

TIME	%CDD	% CD REMAIN	LOG % CD REMAIN	SQURE ROOT "T"	LOG CDD	LOG "T"
15	18.261	81.739	1.912	3.873	1.261	1.176
30	23.935	76.065	1.881	5.477	1.379	1.477
45	28.87	71.13	1.852	6.708	1.460	1.653
60	35.652	64.348	1.808	7.746	1.552	1.770
90	45.196	54.804	1.738	9.487	1.655	1.954
120	51.478	48.522	1.685	10.95	1.711	2.079
180	63.978	36.022	1.556	13.41	1.806	2.255
240	71.543	28.457	1.454	15.49	1.854	2.380
300	85.348	14.652	1.165	17.32	1.931	2.477
360	94.239	5.761	0.760	18.97	1.974	2.556

The results showed 20 % of drug Diffusion in the first 15 min and the drug was slowly diffused upto 96.52 % of 360 min respectively for F III formulation. The *in vitro* diffusion of drug for formulation F III is shown in Table15.

Table 6: *In Vitro* Diffusion of Posaconazole Hair Gel of F IV

TIME	%CDD	% CD REMAIN	LOG % CD REMAIN	SQURE ROOT "T"	LOG CD D	LOG "T"
15	20.00	80.00	1.903	3.873	1.301	1.176
30	25.71	74.28	1.870	5.477	1.4102	1.477
45	31.56	68.43	1.835	6.708	1.4992	1.653
60	39.28	60.71	1.783	7.746	1.5942	1.770
90	47.17	52.82	1.722	9.487	1.6737	1.954
120	55.23	44.76	1.650	10.95	1.7422	2.079
180	66.08	33.91	1.530	13.41	1.8201	2.255
240	75.43	24.56	1.3903	15.49	1.8775	2.380
300	87.58	12.41	1.0938	17.32	1.9424	2.477
360	96.52	3.478	0.541	18.97	1.9846	2.556

The drug Diffused was found to very fast as almost all the drug was diffused 94.23 % & 96.52 % within 6 hour.

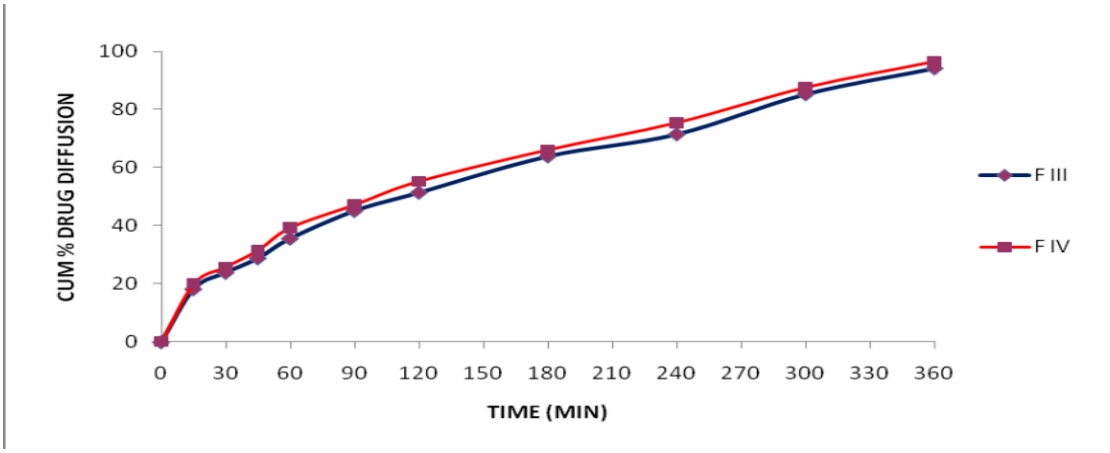

Fig 6: *In Vitro* Cumulative % Drug Diffusion of FIII & FIV Formulation

In order to ascertain the rate of diffusion of drug from this formulation the data of FIII & F IV formulation the data was plotted according to first order rate kinetics which is shown in fig 11. The plot is found to be linear with a regression coefficients value of 0.9407 & 0.9191 respectively indicating that the diffusion data has obeyed the first order rate kinetics.

To assess the mechanism involved in the drug diffusion the date was plotted according to Higuchi's equation which is shown in fig 12. The results indicated that the plot is linear with regression coefficient of 0.9962 & 0.9977. The results further showed the plot has shown linearity up to a time of 360 min and showed some deviation from this formulation almost the entire drug was found to be diffused.

To confirm whether the diffusion mechanism is the only operating factor for the diffusion of the drug the data has been plotted according to Peppas equation which is shown in fig 13. It can be seen from the fig that the plot is linear with a regression coefficient value of 0.9958 & 0.9962.

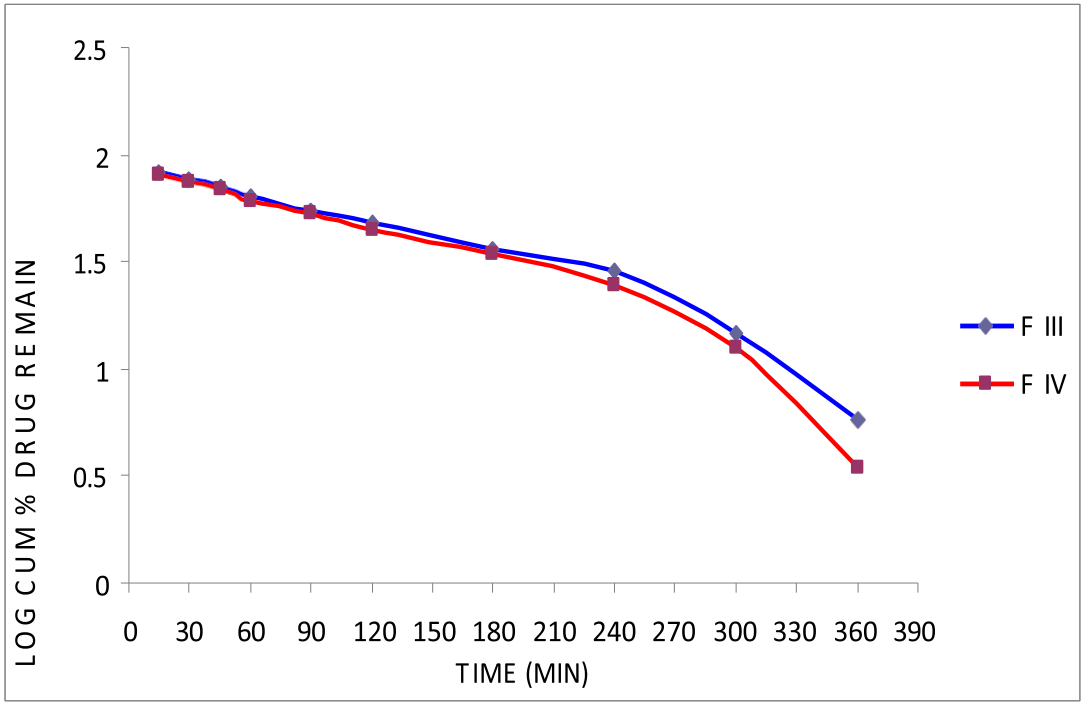

Fig 7: First Order Rate Diffusion of Formulation FIII & FIV

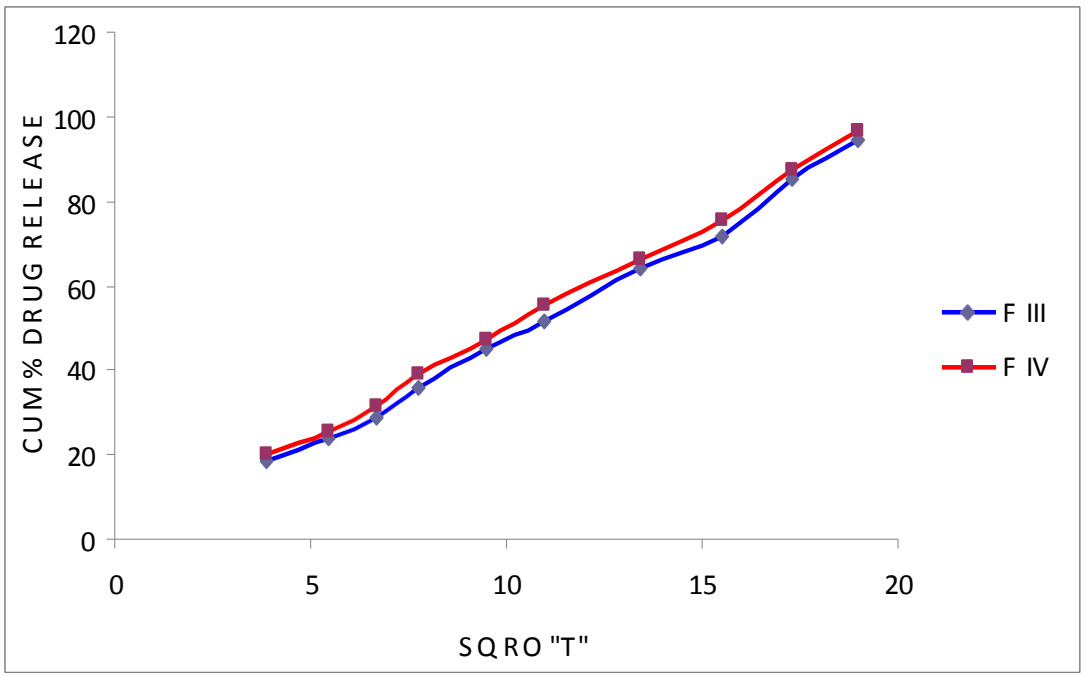

Fig 8: Higuchi's Sq Root Plot Showing Diffusion of Formulation FIII & F IV

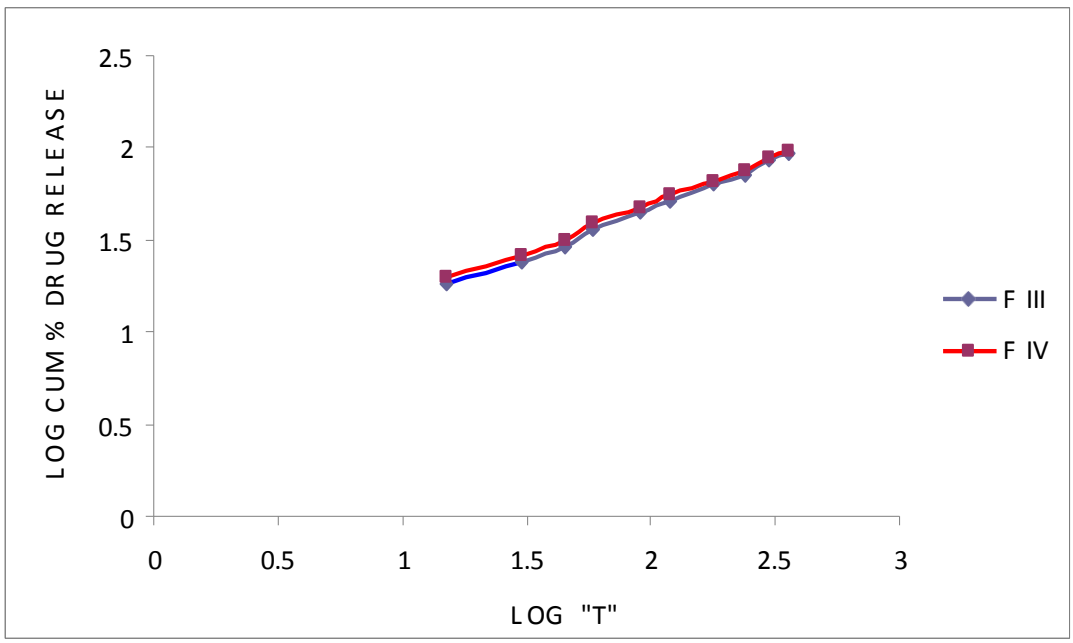

Fig 9: Peppas Equation Plot Showing Diffusion of Formulation FIII & FIV

The results showed 12.17 % of drug Diffusion in the first 15 min and the drug was slowly diffused upto 78.19 % of 360 min respectively for F V formulation. The *in vitro* diffusion of drug for formulation F V is shown in Table16.

Table 7: *In Vitro* Diffusion of Posaconazole Hair Gel of F V

TIME	%CDD	% CD REMAIN	LOG % CD REMAIN	SQURE ROOT "T"	LOG CDD	LOG "T"
15	12.17	87.82	1.943	3.873	1.085	1.176
30	19.43	80.56	1.906	5.477	1.288	1.477
45	24.26	75.73	1.879	6.708	1.384	1.653
60	30.93	69.06	1.839	7.746	1.490	1.770
90	39.50	60.50	1.781	9.487	1.596	1.954
120	45.65	54.34	1.735	10.95	1.659	2.079
180	57.15	42.84	1.631	13.41	1.757	2.255
240	66.30	33.69	1.527	15.49	1.821	2.380
300	73.91	26.08	1.416	17.32	1.868	2.477
360	78.19	21.80	1.338	18.97	1.893	2.556

The results showed 14.78 % of drug Diffusion in the first 15 min and the drug was slowly diffused upto 83.23 % of 360 min respectively for F V formulation. The *in vitro* diffusion of drug for formulation F VI is shown in Table 8.

Table 8: I*n Vitro* Diffusion of Posaconazole Hair Gel of F VI

TIME	%CDD	% CD REMAIN	LOG % CD REMAIN	SQURE ROOT "T"	LOG CDD	LOG "T"
15	14.78	85.22	1.930542	3.873	1.169674	1.176
30	22.97	77.03	1.88666	5.477	1.361161	1.477
45	27.89	72.11	1.857995	6.708	1.445449	1.653
60	33.78	66.22	1.820989	7.746	1.52866	1.77
90	43.28	56.72	1.753736	9.487	1.636287	1.954
120	49.52	50.48	1.703119	10.954	1.694781	2.079

180	61.1	38.9	1.58995	13.417	1.786041	2.255
240	69.47	30.53	1.484727	15.491	1.841797	2.38
300	77.15	22.85	1.358886	17.32	1.887336	2.477
360	83.23	16.77	1.224533	18.973	1.92028	2.556

The drug diffused was found to very fast as almost all the drug was diffused

78.19 % & 83.23 % within 6 hour.

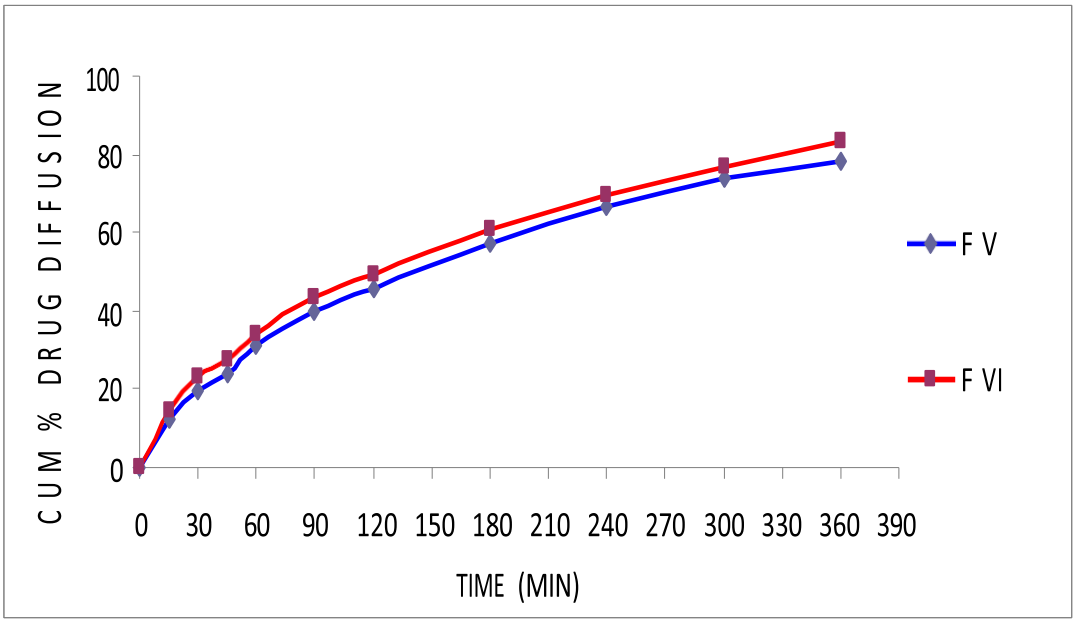

Fig 10: *In Vitro* Cumulative % Drug Diffusion of FV & FVI

In order to ascertain the rate of diffusion of drug from this formulation the data of F V & F VI formulation the data was plotted according to first order rate kinetics which is shown in fig 10. The plot is found to be linear with a regression coefficients value of 0.9973 & 0.9985 respectively indicating that the diffusion data has obeyed the first order rate kinetics.

To assess the mechanism involved in the drug diffusion the date was plotted according to Higuchi's equation which is shown in fig 10. The results indicated that the plot is linear with regression coefficient of 0.9967 & 0.9976. The results further showed the plot has shown linearity up to a time of 360 min and showed some deviation from this formulation almost the entire drug was found to be diffused.

To confirm whether the diffusion mechanism is the only operating factor for the Diffusion of the drug the data has been plotted according to Peppas equation which is shown in fig 11. It can be seen from the fig that the plot is linear with a regression coefficient value of 0.9943 & 0.9963.

The results obtained shows that *In vitro* diffusion profile of Posaconazole Hair Gel, the total amount of drug Diffusion was observed at different time intervals for a period 6 h was found to decreases with increase carbopol and PEG 400 concentration. Even though a good drug Diffusion was observed with 0.3 % of carbopol and 10 % PEG 400 concentration, as it was too soft and less viscous in nature, and an optimum polymer concentration of 0.35 % of carbopol and 15 % of PEG 400, which exhibited good consistency drug Diffusion. The 0.35 % carbopol and 10 % of PEG 400 concentration containing gel diffused maximum of 96.52 % of Posaconazole over period of 6 h.

Table 13: Model Fitting Diffusion Profile of Formulations F1- F6

Formulation	Mathematical models (kinetics)					Best fit model
	Zero order	First order	Higuchi	Peppas plot		
	r	R	R	r	N	
F1	0.8382	0.9887	0.9454	0.9614	O.5525	1st order
F2	0.8243	0.9905	0.9372	0.9520	0.5304	1st order
F3	0.9439	0.9407	0.9962	0.9958	0.5272	Higuchi
F4	0.9331	0.9191	0.9977	0.9962	0.5250	Higuchi
F5	0.9280	0.9973	0.9967	0.9943	0.5885	1st order
F6	0.9192	0.9985	0.9976	0.9963	0.5410	1st order

7. Antimicrobial Evaluation

Microbiological evaluation of any antifungal or any antibacterial agents is useful against the sensitive organism. The inhibition of microbial growth under standardized condition may be utilized for demonstrating the therapeutic efficacy of antifungal drugs.

The microbiological evaluation of the gels was done using an agar cup-plate method using *Candida albicans* as test organism. This method depends upon diffusion of the gel from the cup through a solidified agar layer in the petridish to an extent such that growth of the added microorganisms is prevented entirely in a zone around the cup containing the antifungal drug. Wider zone of inhibition is an indicative of better diffusion of the drug from the base. Since the selected compound, Posaconazole were particularly active against fungi.

Candida albicans is used here as the test organism since this is the most prevalent organism causing fungal infection in human beings.

Table 13: Results of Antimicrobial Study

Sr. no.	Formulation	Zone of inhibition
1	III	16.1 mm
2	IV	14 mm
3	Std	18 mm

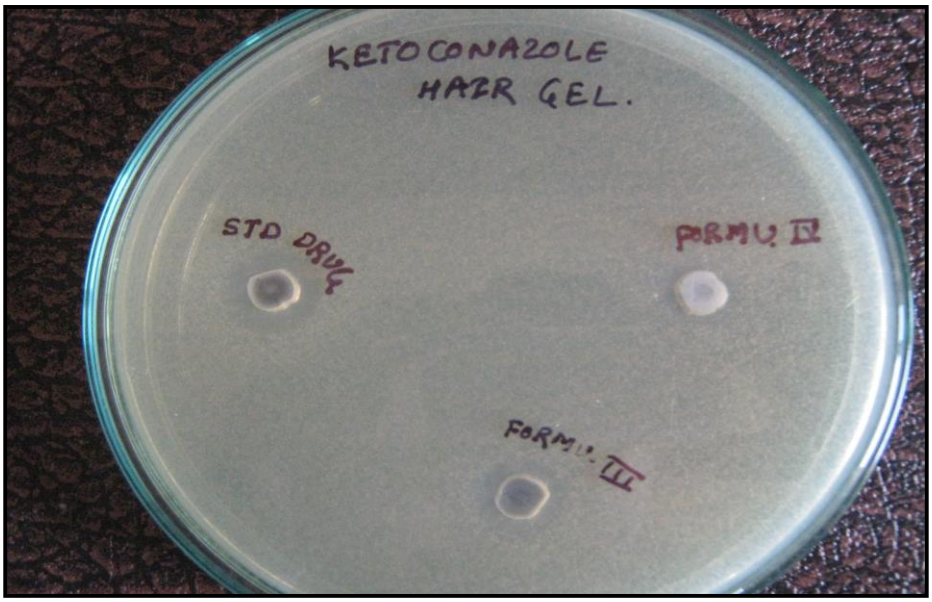

Fig 14: Anti Microbial Activity of Posaconazole Hair Gel Of Formulation III & IV.

Antimicrobial activities for selected gels are shown in Table 19.formulation F III and F IV showed 16.1 mm and 14.6 mm inhibition in comparison with pure drug with 18.2 mm inhibition respectively.

8. Stability Study:

The selective gel is taken for stability study. Optimized formulation FIII was tested for stability at 0-8^{0}c (refrigerator), ambient temperature (R.T) and 45±2^{0}c at 75% 5% RH for 30days. The results show the following Table 21. No significance change in the viscosity, pH, spreadability drug content and drug Diffusion.

SUMMARY AND CONCLUSION

Hair is a part of one's personal identity. It is an expression of beauty and individuality but also creates senses of belonging to a particular culture or group.
Dandruff is the excessive flaking of dead skin that forms on scalp. It is exaggerated in some persons leading to visual nuisance, redness and irritation.

Antidandruff formulation exhibiting some direct or indirect anti-inflammatory activity can improve both dandruff and its subsequent hair cycle disturbance.

Posaconazole is an imidazole compound which exerts its antifungal activity through inhibition of lanosterol demethylation. This blocks the synthesis of ergosterol, the major sterol component of the fungal cell membrane. In mammalian cells, Posaconazole also inhibits lanosterol demethylation, with a subsequent decrease in the biosynthesis of cholesterol, the major sterol component of mammalian cell membranes. In addition, Posaconazole interferes with cellular fatty acid and phospholipids biosynthesis. The proceeding amount about physical aspects of the gel, chemical structure of the gel & its utilization as dermatological base has led to the developmental work regarding the use of these gels for topical usage. Among the gel forming carbopol (carbomer) is widely used. Carbomers are mainly used in liquid or semisolid pharmaceutical formulations as suspending or viscosity-increasing agents.

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