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Formulation and Evaluation of Topical Hydrogel Containing Luliconazole for the Treatment of Fungal Infections

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ABSTRACT

The Hydrogel are three-dimensional, hydrophilic, polymeric network capable of absorbing large amounts of water or biological fluids due to high water content, porosity and soft consistency stimulate natural living tissue, and has rapid absorption rate. The aim of present study is to formulate topical hydrogel containing Luliconazole to treat fungal infections using synthetic gelling agents such as Carbopol-934, and Sodium Alginate evaluated for various parameter. The drug-excipient compatibility studies shows that there is no interaction between drug and selected polymer(s). For present work 3^2 factorial design was selected, two independent variables were selected i.e., Carbopol-934 (X1) & Sodium Alginate (X2) and nine formulations were formulated as per experimental design. The Nine formulation were evaluated for the various parameters and their result were found to be as for pH (6 to 6.9), the viscosity (3130 to 10318) cp, % drug content (95.18 to 98.26), the cumulative % drug release in 8 hours (79.49 to 53.15). The Batch F1 was selected as optimized formulation containing Carbopol-934 1%w/v, Sodium Alginate 1%w/v, Methyl Paraben 0.1% w/v, Propyl Paraben 0.05% w/v, Glycerin 1ml and water up to 10ml. and follows zero order kinetic. The optimized batch was found to be stable as per ICH study. It was concluded that problem associated with Luliconazole by oral administration like GIT ulceration can be overcome by topical route of administration of hydrogel

Keywords: Hydrogel, Luliconazole, Carbopol-934, Sodium Alginate, Topical.

1. Introduction

The topical route of drug delivery has been utilized to produce local effect for treating skin diseases and produce systemic drug effects. Hydrogels are prepared both in cosmetics and in pharmaceutical preparations. Gels often provide better release of drug substance independent of the water solubility of the drug when compared to creams and ointments. Local application of therapeutic compounds has many advantages over oral and parenteral drug delivery systems. The advantages include ease of application to skin, ability to deliver drugs selectively to a site of local action, elimination of hepatic first-pass metabolism and better patient compliance. Hydrogels are widely used in topical drug delivery systems due to their physical and chemical properties such as controllable and prolonged release of drug. These formulations on contact with the skin forms a semi occlusive film over the skin and release the drug in controlled manner. Lipophilic drug can cross the Stratum corneum, but rate of diffusion decreases as it enters the more aqueous lower regions of the epidermis. Fungal infections have been divided into superficial and systemic infections.10 Antifungal drugs are classified according to their chemical structure as azoles, polyenes, allylamines, echinocandins. Luliconazole is an antifungal medication used in the treatment of superficial skin infections such as tinea corporis, tinea pedis and tinea cruris caused by T. rubrum and E. flocossum. Luliconazole acts by inhibiting enzyme synthesis like lanosterol demethylase and lansosterol demethylase is major ingredient for synthesis of fungal cell. The goal of our research to formulate and evaluate Luliconazole hydrogels for prepared formulations. [1,2]

2.Methodology

2.1 Materials

Luliconazole was obtained from Virupaksha Organics Limited (Hyderabad), Sodium Alginate, Carbopol-934, Glycerine, Triethanolamine, Methyl Paraben and Propyl Paraben provided by the Vidyabharati college of pharmacy, Amravati, Maharashtra

2.2 Methods

a) Determination of Lambda Max

Stock (100µg/ml) of Luliconazole was prepared in Phosphate buffer pH 7.4. The solution was kept in Quartz cuvette having thickness 10mm. the UV spectrum was in the range of 200-400nm Shimadzu UV- visible spectrophotometer (UV- 1800) at 1cm, slit width. It showed lambda max at 296 nm using spectrophotometer. The procedure was repeated for accuracy at least three times.

b) Standard Calibration Curve of Luliconazole in pH 7.4 Phosphate

Buffer100mg of Luliconazole pure drug was liquefied in 10 ml of ethanol and made upto 100ml with phosphate buffer pH 7.4 in a volumetric flask. 20-50 µg/ml dilutions were primed with buffer from the stock solution. The absorbance's of the solutions were analysed at 296 nm.

c) FTIR Spectrophotometry

The spectrum was recorded in the wavelength region of 4000 to 400cm-1. A disc sample of the drug and polymer were mixed uniformly and filled into the die cavity and the sample holder and an IR spectrum was recorded using diffuse reflectance FIR spectrophotometer

d) Formulation of Luliconazole Hydrogel: -

For the present work 3^2 factorial was selected. Two independent variables were selected Carbopol-934-K4M (X1) and Sodium Alginate (X2) and nine formulations formulated as per experimental design. Formulation table by factorial design. All the ingredients were collected according to the formula given in table no 1, Required number of gelling agents such as Sodium Alginate & Carbopol-934 were added in water with constant stirring at 500 rpm for about 2hours. Drug was added to the above mixture. Methyl Paraben & Propyl Paraben were added to it. Final weight was made with water. All the samples were collected to equilibrate for 24 hours at room temperature prior to performing evaluation test Triethanolamine used to Maintain pH of sample

Table NO.1 Formulation Table by Factorial Design

Formulation Code	Luliconazole(mg)	Carbopol-934 (%)	Sodium Alginate (%)	Methyl Paraben (%)	Propyl Paraben (%)	Glycerine (ml)	Water up to (ml)
F1	1	1	1	0.1	0.05	1	10
F2	1	1	1.5	0.1	0.05	1	10
F3	1	1	2	0.1	0.05	1	10
F4	1	1.5	1	0.1	0.05	1	10
F5	1	1.5	1.5	0.1	0.05	1	10
F6	1	1.5	2	0.1	0.05	1	10
F7	1	2	1	0.1	0.05	1	10
F8	1	2	1.5	0.1	0.05	1	10
F9	1	2	2	0.1	0.05	1	10

3. Evaluation of Prepared Hydrogel Using Combination of Gelling Agent Under Study [13]

3.1 Appearance

The hydrogel formulated were observed or their visual appearance, colour, and feel upon application such as grittiness, grassiness, smoothness, stuffiness and tackiness.

3.2 Spredability

Spredability is expressed in terms of time in seconds taken by two slides to slip off from gel and placed in between the slides under the direction of certain load, lesser the time taken for separation of two slides, better the Spredability. It is calculated by using the formula

S= M. L/T

Were,

M= weight tied to upper slide

L= length of glass slides

T= time taken to separate the slides

The results are shown in table no.4

3.3 pH

The pH was measured in each gel, using a pH meter, which was calibrated before each use with standard buffer solutions at pH 4, 7, 9. The electrode was inserted in to the sample 10 min priors to taking the reading at room temperature.

3.4 Viscosity

The viscosity of formulated hydrogel was determined using Brook-field viscometer (spindle number 7) Mounted the guard leg. Attached the spindle (left hand thread) to the viscometer lower shift by lifting the coupling screw slightly. It washed firmly with one hand while screwing the spindle on with the other (note left hand thread). Avoid spindle, do the following before attaching the spindle. Begin by immersing the spindle in a diagonal path, slowly drag the spindle across the fluid surface, and bring the spindle to an upright position and thread on to screw. Lower and center spindle in the test material until the "meniscus" of the fluid is at the center of the immersion groove on the spindle shaft. To make a viscosity measurement, turn the motor switch "ON". This energizes the viscometer drive motor. Allow time for the indicated reading to stabilize. The required for stabilization will depends on the speed at which the viscometer was running and the characteristics of the sample fluid. When making a viscosity measurement, the reading should be noted.

3.5 Drug Content Studies

To ensure uniform formulation of the gel, it was sampled from the different locations in the mixer and assayed for the drug content. Drug content of the gels was determined by dissolving an accurately weighed quantity of gel (about 1 gm) in about 100 ml of pH 7.4-phosphate buffer. These solutions were quantitatively transferred to volumetric flasks and appropriate dilutions were made with the same buffer solution. The resulting solutions were then filtered 0.45 mm membrane filters before subjecting the solution to Spectrophotometric analysis for Luliconazole at 296nm. Drug content was determined from the standard curve of Luliconazole

3.6 In-Vitro Release

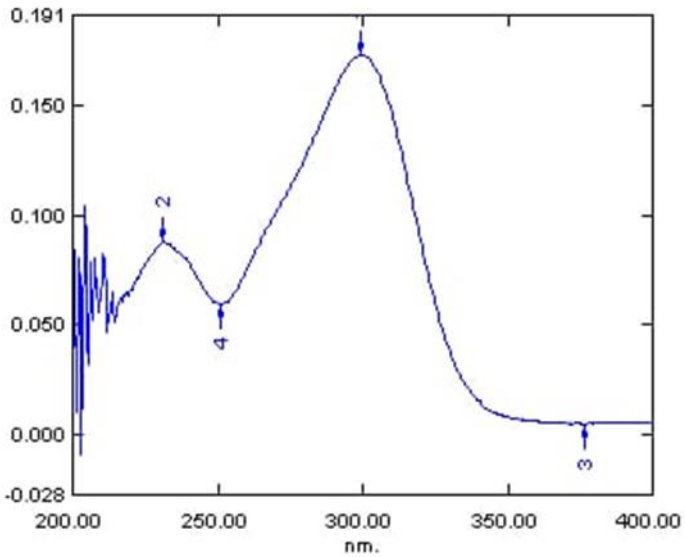
The in vitro release experiments were carried out by using Franz-diffusion cells apparatus from different formulations. An exact number of formulations (1.0 g) was spread out on membrane positioned between the donor and receptor chambers with an available diffusion area. The receptor compartment was filled with phosphate buffer 7.4 and continuously stirred with a small magnetic bar at a speed of 50 rpm during the experiments to ensure homogeneity and maintained at 37.2+0.5 0C. The samples were withdrawn at various time intervals and replaced with the same volume of PBS. Sink conditions were met in all cases. The samples were analysed Spectrophotometrically at 296nm

3.7 Kinetics of Drug Release

In vitro dissolution has been recognized as an important element in drug development. To analysis the mechanism for the release and release rate kinetics of the formulated dosage form, the data obtained from conducted studies was fitted into Zero order, First order, Higuchi matrix, Korsmeyer-Peppas and Hixson Crowell model. In this by comparing the R-values obtained, the best-fit model was selected.

4. Result and Discussion

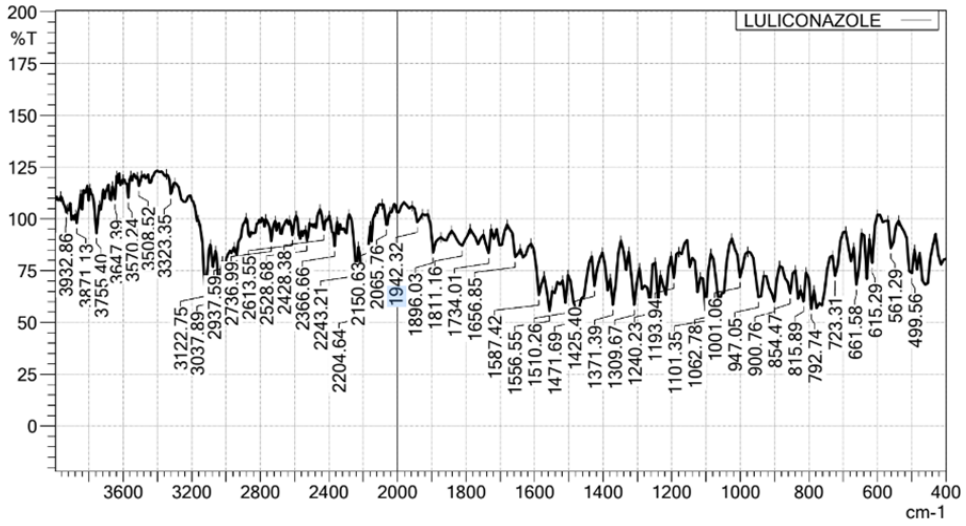
4.1.a Determination of Lambda Max:



Graph No 1. UV Spectrum of Luliconazole

Discussion: - The lambda max was found to be 296 nm in Phosphate buffer 7.4

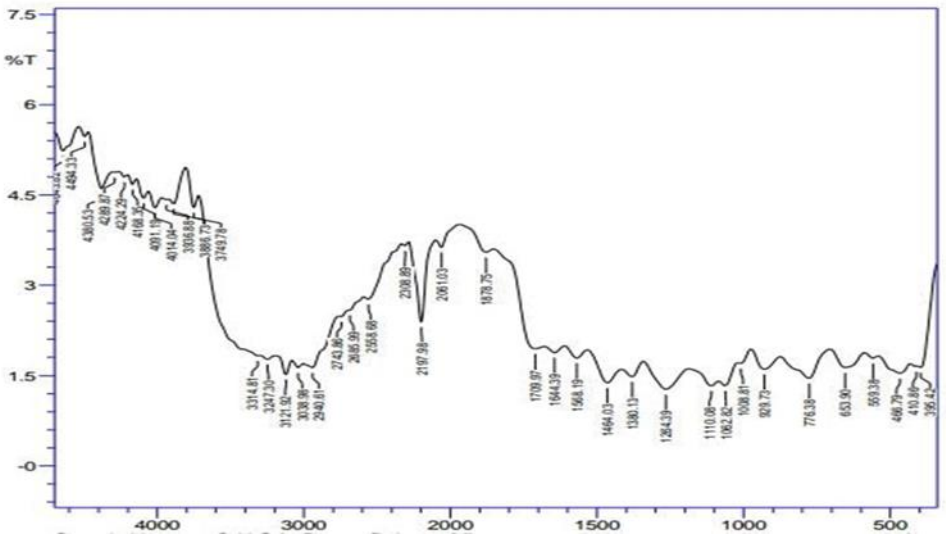
FTIR Spectroscopy Drug characterization study by FTIR was carried out as per standard procedure. FTIR spectra of Luliconazole are shown in graph No. 2. It was observed that principal peak of Drug was found in FTIR spectra of a drug. It was suggested that there was no interaction.



Graph NO 2: FTIR SPECTRA OF PURE DRUG

Table No. 2 Functional groups and their frequencies with pure drug

Characteristics Peaks	Reported (cm^{-1})	Observation (cm^{-1})
C - H stretch	2850-3000	2937.59
C Ξ N stretch	2100-2400	2204.64
C Ξ C aromatic stretch	1450-1650	1556.55
C=C-C Aromatic Ring Stretch	1510-1450	1510.26
Para C-H distribution	860-800	854.47



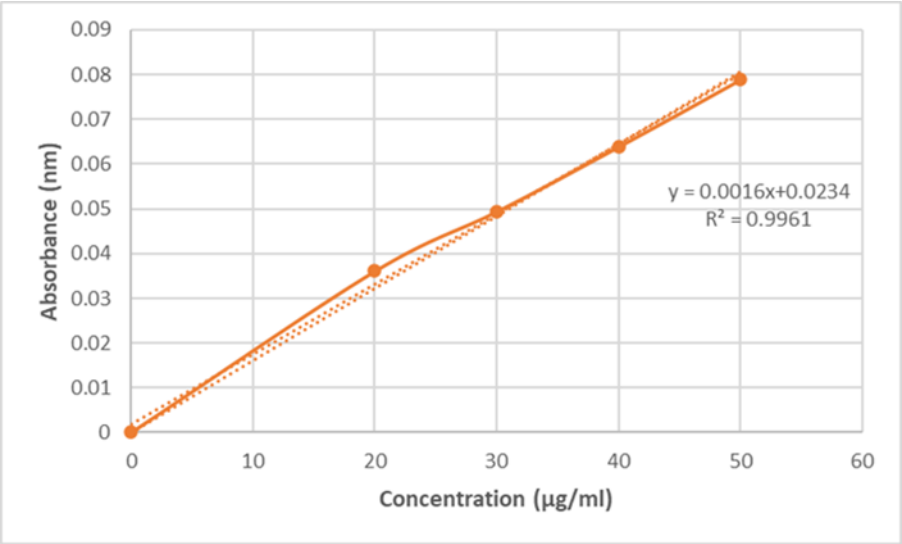
Graph No: - 3 FTIR Spectrum of Luliconazole and Polymers

Discussion: -

Drug characterization study by FTIR was carried out as per standard procedure. FTIR spectra of Luliconazole and polymer mixture are shown in graph No. 3. It was observed that principal peak of Drug was found in FTIR spectra of a drug. It was suggested that there was no physical and chemical interaction is observed. The results are shown in Graph No.3

Table No. 3 Standard Calibration Curve of Luliconazole in Phosphate Buffer pH 7.4 at 296nm

Sr no	Concentration (ug/ml)	Absorbance
1	0	0
2	20	0.0361
3	30	0.0494
4	40	0.0639
5	50	0.0789



Graph No: - 4 Standard Calibration Curve of Luliconazole

Discussion:

From the standard curve, it was observed that the drug obeys beers law in concentration range of 2.0-1.5. µg/ml in phosphate buffer Ph 7.4. drug shown good linearity with regression of coefficient (r^2=0.9961) and equation for this line obtained was found to be y=0.0016x+0.0234 which is used for the calculation of amount of drug and dissolution study.

4.2 Evaluation of Prepared Hydrogel

4.2.A Physical Appearance:

A prepared Evaluation of Prepared Luliconazole hydrogel was inspected visually for color. Homogeneity, consistency. All formulations showed white, white buff color, appearance therefore showed suitable homogeneity and consistency. And the observations are mentioned in Table No. 4

Table No 4. Physical Evaluation of Formulation

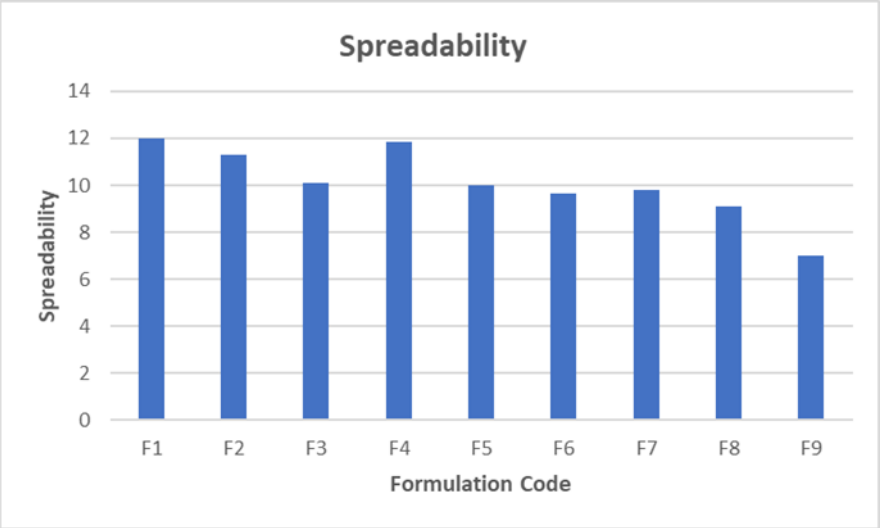
Formulation Code	colour	Feel of application	Spredability gm.cm/sec
F1	White	Smooth	12
F2	White	Smooth	11.30
F3	White	smooth	10.12
F4	White	Smooth	11.83
F5	White	smooth	10
F6	White	Smooth	9.65
F7	White	Smooth	9.81
F8	White	Smooth	9.11

F9	White	smooth	7

n=3

Table No: - 5 pH, Viscosity, and Drug Content

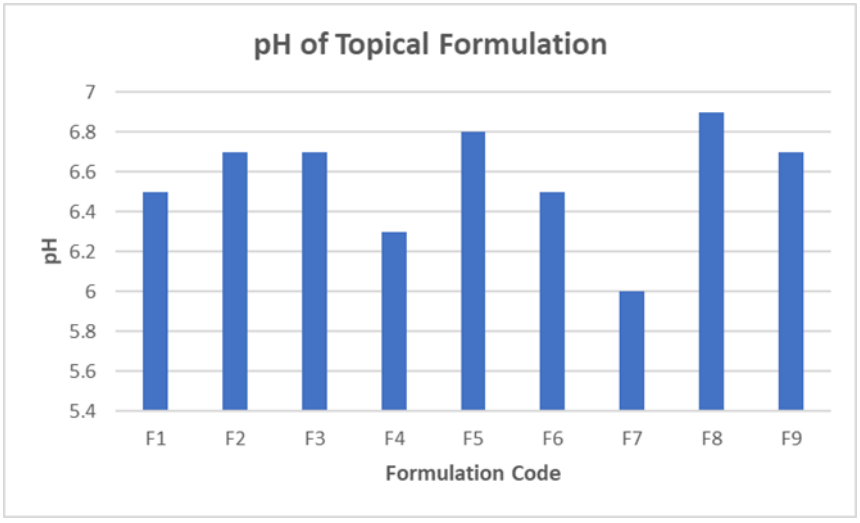
Formulation Code	pH	Viscosity(cp)	Drug content (%)
F1	6.5	3130	96.25
F2	6.7	3544	95.62
F3	6.7	4103	96.87
F4	6.3	3803	98.12
F5	6.8	4215	97.13
F6	6.5	5418	96.45
F7	6	7322	98.26
F8	6.9	8974	95.18
F9	6.7	10318	97.56



Graph No 5: - Comparison of Spredability of Factorial Batches

Discussion:

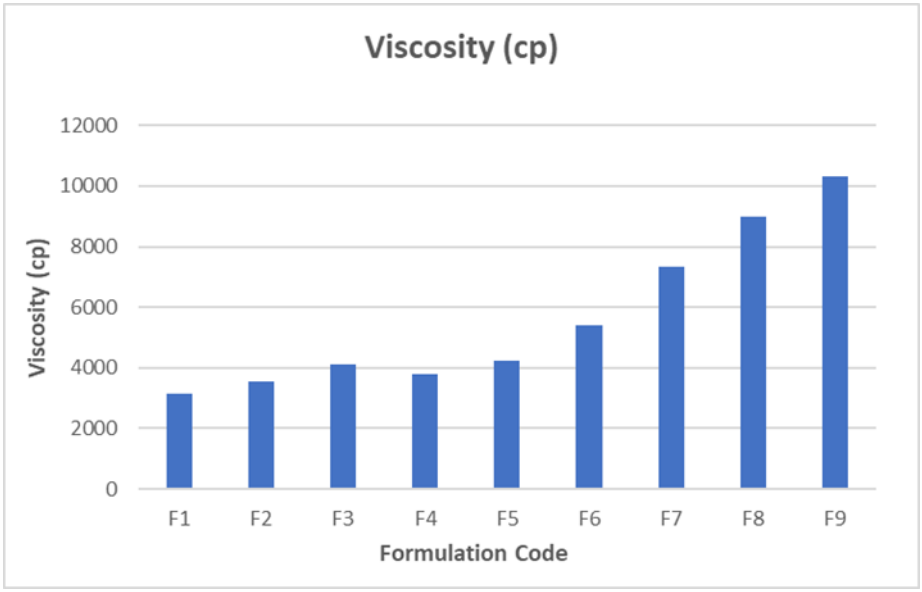
The Spredability of Topical Hydrogel formulation (F1 to F9) was found to be range 7-12. It was observed that Spredability of the Hydrogel depends on the concentration of gelling agent Here, as concentration of gelling agent increases Spredability decreases.



Graph No 6: - Comparison of pH of factorial batches

Discussion:

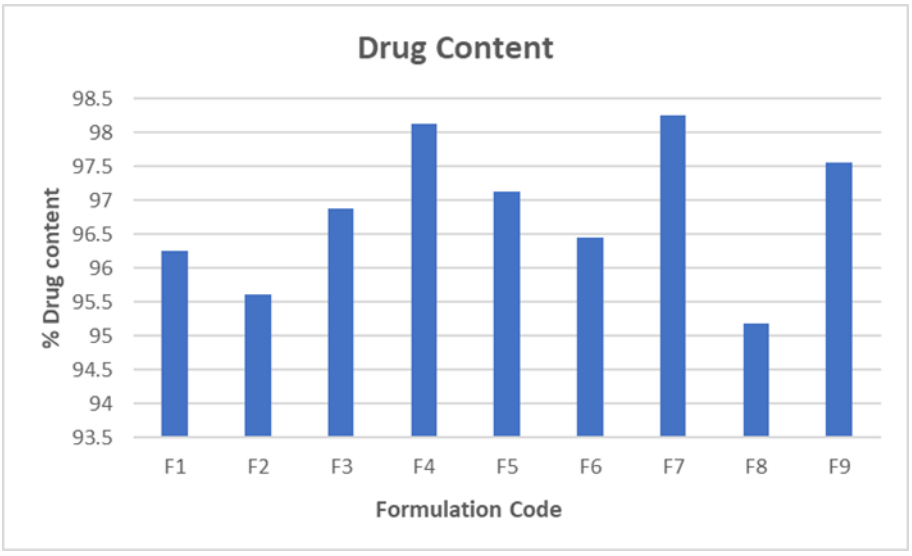
The pH of Topical Hydrogel formulations (F1 to F9) was found to be range 6 to 6.9. it was observed that pH of hydrogel depends upon concentration of preservatives.



Graph No 7: - Comparison of Viscosity of factorial batches

Discussion:

The Viscosity of Topical Hydrogel Factorial formulations (F1 to F9) was found to be range 3130 to 10318 cp. It was observed that viscosity of Hydrogel depends on concentration of polymer used for preparation of Hydrogel. Here, as concentration of polymers increases viscosity of formulation also increases.



Graph No 8: - Comparison of Drug Content of Factorial Batches

Discussion:

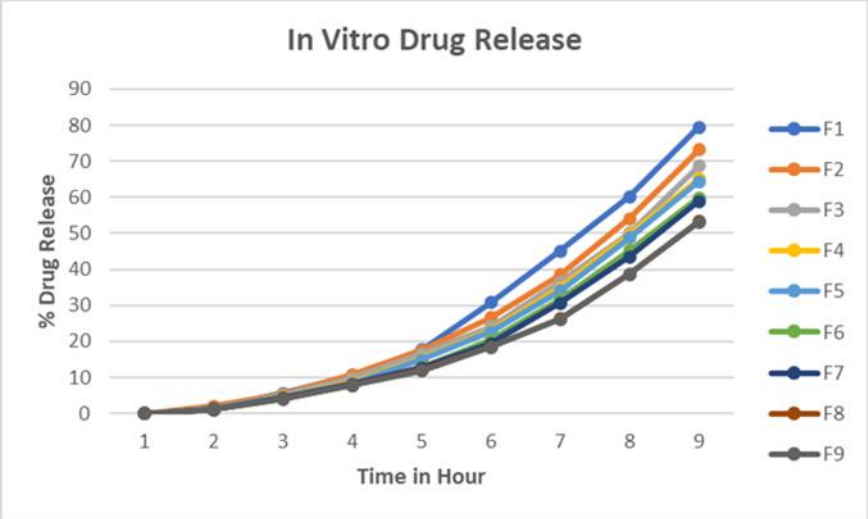
The % Drug content of Topical Hydrogel Factorial formulations (F1 to F9) was found to be range 95.18 to 98.26 it was observed that % drug content of Hydrogel depends on practical skill. Here, as the optimum % drug content be achieved by result reproducibility. can be achieved by result reproducibility.

Table No 5: In Vitro Drug Release of Factorial Batches F1-F9

Time (Hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9

0	0	0	0	0	0	0	0	0	0
1	1.64	2	1.13	1.44	1.33	1.14	1.12	1.24	1.23
2	5.63	5.25	5	4.81	4.64	4.35	4.32	4.07	4.05
3	10.5	10.67	9.83	8.4	8.17	7.78	8.14	7.83	7.8
4	17.64	17.53	16.44	15.21	14.97	12.88	12.57	11.96	11.9
5	30.78	26.57	24.09	22.96	22.64	20.34	19.44	18.5	18.42
6	45.14	38.57	36.35	34.75	34.07	31.66	30.64	26.25	26.15
7	60.14	54.07	50.04	49.54	48.81	45.32	43.46	38.72	38.58
8	79.49	73.26	68.76	65.14	64.32	59.79	58.82	53.32	53.15

n=3



Graph No 9 Comparison of % Drug Release of Factorial Batches F1 to F9

Discussion:

The Cumulative % Drug Release of Topical Hydrogel of Factorial Batches (F1to F9) Was found to be range 53.15 (8 hours) to 79.49 (8 hours). It was observed that Cumulative % Drug Release of Hydrogels depends on concentration of Sodium Alginate and Carbopol-934. Here, as concentration of Sodium Alginate and Carbopol-934 increases Drug release time of formulation also decreases. Maximum Drug Release i.e., 79.49 (8 hours) was found to be for F1, and prolong Cumulative % Drug Release 53.15 (8 hours) Found to be F1. Here, Sodium Alginate, and Carbopol-934 shows concentration dependence release behavior for these formulations.

Table No 6 Kinetic Model Studies of Factorial Batches

Kinetic Models	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
	R	**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**
Zero order	0.9961	0.9982	0.8235	0.9991	0.9841	0.9985	0.9740	0.9979	0.8964
1st order	0.9869	0.9954	0.9988	0.9125	0.9147	0.9974	0.9549	0.9912	0.9984
Matrix	0.9950	0.8987	0.9941	0.7928	0.9912	0.8245	0.9534	0.9869	0.9967
Peppas	0.9929	0.9964	0.8354	0.9963	0.9487	0.9874	0.9398	0.8459	0.9986
Hix.Crow	0.9919	0.9923	0.9945	0.8548	0.8945	0.9925	0.9722	0.9958	0.8794
Best fitted to	**Zero order**	**Zero order**	**1st order**	**Zero order**	**Matrix**	**Zero order**	**Zero order**	**Zero order**	**Peppas**

n=3

It was observed that the Topical Hydrogels (F1-F2, F4, F6-F8) have best fitted to the Zero order model. Also, it was Observed that Topical Hydrogels (F3) formulations have best fitted to First order model. Batch (F5) Best suited for matrix model, Batch (F9) Best suited for peppas model, from above it was Concluded that Topical Hydrogel formulation F1 with R Value 0.9919, which follows Zero order kinetic, contains Sodium Alginate and Carbopol-934 1% each and methyl paraben 0.1% and propyl paraben 0.05% which could be most Promising Topical Hydrogel formulation for Luliconazole.

No 7: Stability study for Factorial Batch F1 at 2-8^{0}C at Humidity 60 ± 05%

Duration Time	Drug Content (%)	% Drug Release	pH of Formulation
0	97.26	79.82	6.4
15	97.26	79.82	6.4
30	97.26	79.81	6.4
45	97.21	19.81	6.3

n=3

Discussion: The stability study of optimum batch (F1) revealed that there is slightly reduction in drug content was observed over period of 45 days. No significant change was Observed in % drug content. The release condition depends upon the temp and duration of period. Drug release (after 8 Hrs) at various storing condition 2-8^{0}C, hence formulation was found to be stable for 45 days.

Conclusion: -

The topical hydrogel of Luliconazole was prepared using different concentration of gelling agent such as Carbopol-934, and Sodium Alginate and prepared hydrogel were evaluated for various parameters such as Appearance, spredability, PH, Viscosity, Drug Content, and Drug Release All the results are within limit, further, optimized formulation was studied for stability and formulation was found to be stable. due to its high retention, and rapid absorption from the skin it can be used successfully for the treatment of fungal infections.

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