Section A-Research paper
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Formulation and Evaluation of Topical Microemulgel Containing Flucytosine

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Abstract

The current investigation's goal is to create and assess a flucytosine microemulgel. Flucytosine enters the fungal cell by the cytosine permease; as a result, flucytosine is converted inside of fungal cells into 5-fluorouracil and inhibits fungal thymidylate synthase. Its bioavailability is low. In the realm of pharmaceutical sciences, microemulgel has now emerged as one of the most intriguing topical preparations. When used as a delivery mechanism, microemulgel has several advantages over straightforward conventional formulations, including simplicity of administration, increased residence duration at the application site, constant drug release with improved bioavailability, superior thermodynamic stability, and excellent transdermal permeability. Using carbopol 940 and isopropyl myristate as gelling agents, triethanolamine as the oil, methyl parabens and liquid paraben as preservatives and propyl glycol as an emulgent and penetration enhancer, the flucytosine microemulgel is created. Visual examinations were done on the generated microemulgel formulation for things like Spreadability, homogeneity, viscosity, pH, percent drug content, and in vitro diffusion tests. The development of microemulgel containing flucytosine will be more successful, according to the results, but clinical trials are necessary to fully understand their clinical usefulness.

Keywords: Microemulgel, Flucytosine, Fungal thymidylate synthase, Bioavailability and Topical preparations.

Introduction:

Microemulgel is topical drug delivery system that incorporates the properties of both gel and microemulgel shows dual release control system. The microemulgel is prepared by reducing the globule size of the emulsion (less than 200nm) so that the drug particles can easily penetrate through stratum corneum. Topical drug delivery defined as the application of a formulation directly via skin to treat disorder with the advantages of avoiding first-pass metabolism and increasing the therapeutic efficiency of the drug [1].

Topical preparations produce localized effects at the site of their application into the underlying layers of skin or mucous membranes virtue of penetration. It provides flexibility to deliver drugs more effectively to a selective site. It provides utilization of drugs with a short biological half-life, narrow therapeutic window to increase the duration of action. The topical drug can be administered anywhere in the body through ophthalmic, rectal, vaginal,

and on skin as topical routes. The route of administration depends upon the type and severity of the disease. Drug delivery system can provide direct application of a formulation to the skin to get the localized effect of the drug. A topical drug delivery system has many advantages as they deliver drugs more selectively to a specific site. The reason for using topical delivery is to avoid GI incompatibility and metabolic degradation associated with oral administration Moreover, the topical delivery provides an increased bioavailability and consistent delivery of drug at extended release rates from topical dosage form depending on physicochemical properties of the carrier and the drug [2].

The concept of Microemulgel was introduced by Hoar and Schulman during the 1940's. Microemulgel contains water, oil, and amphiphilic which are an optically isotropic and thermodynamically stable liquid micro-dispersion. Microemulgel is the vehicle which improves the delivery, efficacy, and bioavailability of many drugs. "Microemulgel" refers to a thermodynamically stable and clear dispersion of two immiscible liquids; contain oil and water which is stabilized by surfactant molecules by forming interfacial film. A micro-emulsion is considered as a kinetically stable liquid dispersion of a lipid phase and an aqueous phase, with a surfactant. The dispersed particles having a size range of 5-200 nm, and have tiny oil/water interfacial surface tension [3].

Micro-emulsions are transparent because of their globule size (less than 25%). High energy input is not required in the formation of the micro-emulsion. In several cases, a co-surfactant is use additionally to the surfactant, the lipid phase, and therefore the aqueous phase. The micro-emulsion structure is mentioned below fig.1. There are three types of micro-emulsions are formed depending on the composition:

1. Oil in water micro emulsions in which oil phase is dispersed phase and water is continuous aqueous phase.

2. Water in oil micro emulsions in which water phase is dispersed in the continuous oil phase;

3. Bi-continuous micro emulsions in which micro domains of lipid and aqueous phase are inter-dispersed in the system.

When micro-emulsion as well as gels is used in combination to form microemulgel, they exhibit characteristics of both. Microemulgel helps to deliver the hydrophobic drugs by formulating oil in water micro-emulsion and this micro-emulsion can be incorporated into the gel base. They provide a larger area for absorption of drug and lipid portion intensify the bioavailability by better penetrability of drugs. Also, the gel base provides the better stability to micro-emulsion. In comparison to micro-emulsions, microemulgel have a firm degree of elegance and they are easily washable if required [4].

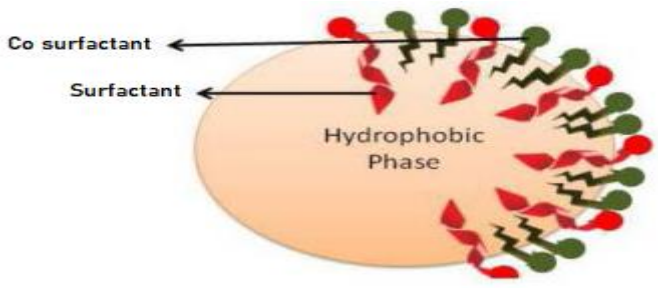

Fig.1: Microemulgel Structure

Advantages of Using Micro-Emulgel as a Topical Drug Delivery System:

- Hydrophobic drugs can be easily incorporated into gels using o/w microemulgel.
- Better loading capacity.
- Production feasibility and low preparation cost.
- No intensive Sonication.
- Controlled release.
- Ability to deliver drug more selectively to a specific site.
- Avoidance of gastro-intestinal incompatibility.

Disadvantages of Microemulgel Based Gel:

- The larger particle size drugs not easy to absorb through the skin.
- Poor permeability of some drugs through the skin.
- Can be used only for drugs which require very small plasma concentration for action.
- Possibility of allergenic reactions.
- An enzyme in the epidermis may denature the drugs.
- Skin irritation of contact dermatitis may occur due to drug or Excipients [5].

Mechanism of Action:

Although the exact mode of action is unknown, it has been proposed that flucytosine acts directly on fungal organisms by competitive inhibition of purine and pyramiding uptake and indirectly by intracellular metabolism to 5-fluorouracil. Flucytosine enters the fungal cell via cytosine permease; thus, flucytosine is metabolized to 5-fluorouracil within fungal organisms. The 5-fluorouracil is extensively incorporated into fungal RNA and inhibits synthesis of both DNA and RNA. The result is unbalanced growth and death of the fungal organism. It also appears to be an inhibitor of fungal thymidylate synthase.

Materials and Methods:

Materials:

Table.1 List of Chemicals

S. No.	Chemicals	Brand
1	Flucytosine	Mamta Enterprises New, Delhi
2	Isopropyl Myristate	Swami Enterprises Shiv Ram Park, *Delhi*
3	Carbopol- 934	IIMT University Meerut
4	Propylene glycol	Loba Chem Pvt. Ltd. Mumbai
5	Borax	IIMT University Meerut
6	Methyl Paraben	IIMT University Meerut
7	Propyl Paraben	IIMT University Meerut
	Liquid Paraben	IIMT University Meerut

	Triethanolamine	IIMT University Meerut
	H2O	IIMT University Meerut

Table.2: List of Equipment

Equipment	**Model/Company**
Electron Analytical Balance	Electron balance, Shimadzu, Japan.
UV-Visible double beam Spectrophotometer	Shimadzu UV 1700
Fourier Transform Infrared Spectroscope	Tensor 27, Bruker optics.
Magnetic Stirrer	2-ML Remi Equipment Pvt. Ltd
pH Meter	EUTECH Instrument
Franz Diffusion Cell	Sci. Work, Peenya 1st stage, Bengaluru.
Ultra Sonicator	Sonics & materials inc, USA
Brookfield Viscometer	PRO-II extra model, Brookfield Viscometer, USA

Preformulation Study:

Preformulation is a stage of the development process when the physical, chemical, and mechanical characteristics of the drug material are studied in order to create a dosage form that is efficient, stable, and secure. In order to properly develop the medication delivery system and characterise the medicine 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:

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

Solubility Studies:
The spontaneous interaction of two or more substance to form a homogenous molecular dispersion is called as solubility. 10mg of drug was a suspended separately in 10ml 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 [6].

Table.3: Solubility Profile I.P. 1996

Descriptive term	**Parts of solvent required for 1 part of solute.**
Very soluble	Less than 1

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

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 2.5mm to 3.5mm, 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℃ below the expected melting point. The capillary tube is inserted into the heating block, and the heating is continued at a rate of temperature increased of about 1℃ to 2℃ per minute until melting is completed [7].

Determination of λmax by UV-Spectrophotometer:

Development of Standard Calibration Curve:

Accurately weighed 50mg of Flucytosine was dissolved in 50ml of methanol and from this 1ml is diluted using phosphate buffer pH 7.4 in 100ml volumetric flask to get the stock solution of 10µg/ml concentration. From the stock solution 2, 4, 6, 8, 10 and 12ml were withdrawn and further diluted to phosphate buffer pH 7.4 in 100ml volumetric flasks to obtain a concentration range of 0.2-1.2µg/ml. The absorbance of the solutions was measured at 288nm by using a UV spectrophotometer [8].

FTIR Analysis:

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 [9-10].

Preparation of Micro-emulgel Formulation:

Different formulations were prepared using varying amount of gelling agent and penetration enhancers. The method only differed in process of making gel in different formulation. The preparation of emulsion was same in all the formulations. The gel phase in the formulations was prepared by dispersing Carbopol 934 in purified water with constant stirring at a moderate speed using mechanical shaker, then the pH was adjusted to 6-6.5 using Propylene glycol. The oil phase of the emulsion was prepared by dissolving Castor oil in liquid paraffin while the aqueous phase was prepared by dissolving Borax in purified water. Methyl and propyl parabens were dissolved in propylene glycol where as Flucytosine was dissolved in

ethanol, and both solutions were mixed with the aqueous phase. Isopropyl Myristate and Triethanolamine were mixed in oil phase. Both the oily and aqueous phases were separately heated to 70–80℃, then the oily phase was added to the aqueous phase with continuous stirring until it got cooled to room temperature. The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the microemulgel (Jain et al., 2011). The composition of different formulations has been discussed in Table.4.

Table.4: Composition of different formulation batches (%w/w).

Ingredients (mg/ml)	**Quantity for tablet**					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Flucytosine	2	2	2	2	2	2
Isopropyl Myristate	2	4	6	2	4	6
Carbopol- 934	0.5	1	1.5	2	2.5	`3
Castor Oil	3	3.5	4	4.5	5	5.5
Propylene glycol	5	5	5	5	5	5
Borax	0.5	1	1.5	2	2.5	3
Methyl Paraben	0.2	0.4	0.6	0.2	0.4	0.6
Propyl Paraben	2	2	2	2	2	2
Liquid Paraben	0.2	0.4	0.6	0.2	0.4	0.6
Triethanolamine	0.2	0.2	0.3	0.4	0.4	0.4
H2O	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s

Evaluation of Microemulgel Formulation:

Determination of Particle Size (nm):

The mean particle size was obtained by Differential Light Scattering (DLS) technique (Anton Paar, Particle Analyzer-Litesizer TM 500, Graz, Austria). 2% w/w of each Microemulgel was prepared by diluting with water. The 2% w/w solution was further diluted 100 times. The diluted preparation was then placed in the glass cuvettes and run in triplicates [11].

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 [12].

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 [13].

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 [14].

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 Microemulgel was acquired using Brook- Field viscometer DE-V model using spindle no 61 and spindle speed of 50rpm at 37°C [15].

Drug Content:

The drug content was determined by dissolving 1gm of the formulation equivalent to 20mg of active drug in 100ml of phosphate buffer. It was further subjected to 100 times dilution. After suitable dilution with phosphate buffer, the absorbance was measured at 288nm [16].

Antifungal Activity Studies:

Anti-fungal studies: (42) Weighed 16.25gm of sabouraud dextrose agar was transfered in a 500ml of conical flask and 250 ml of purified water and some amount of heat is applied to dissolve it completely. Sterilized for 15min at 121°C at 15 lb pressure in autoclave for about 20min. Then cooled it at room temperature and the fungal strain (Cryptococcus) was dispersed in the medium and then the medium was poured it in to the three petri-dish and allowed it cool it for sometime at room temperature until it forms solidifies at room temperature and then the three cups are bored in each Petridish with the help of sterile steel bore of 6mm and calculated concentration of the standard drug (Itraconazole) & gel formulation (F5) were placed in the bores and incubated the petri plates for 72 h at 37°C in incubators. Then the zone of inhibition was observed and calculated the radius of the zone of inhibition [17].

Determination of In-vitro Drug Release Study of Microemulgel:

Release study profile of gel was studied using USP apparatus I. Cellophane membrane was used and weighed quantity of microemulgel containing 10mg of drug was introduced in the membrane and clipped on the both sides. This was then dipped in basket containing 5.8 pH buffer as dissolution medium. The speed of the rotation was 50rpm and temperature was maintained at 37±0.5°C. Sample aliquots were withdrawn from dissolution medium at predetermined time intervals and were analyzed by UV-Spectrophotometer at 288nm. The concentration was calculated using the equation of calibration curve [18-20].

Skin Irritation Studies for Optimized Formulation:

A set of 12 rats was used in the study. The microemulgel was applied on the properly shaven skin of rat. Undesirable skin changes, i.e., change in colour, change in skin morphology were checked for a period of 24hrs (Murty and Hiremath, 2001).

Stability Studies:

The prepared Microemulgel were packed in aluminum collapsible tubes (5g) and subjected to stability studies at 5℃, 25℃/ 60% RH, 30℃/65% RH, and 40℃/75% RH for a period of 1months. Samples were withdrawn at 15-day time intervals and evaluated for pH, viscosity and drug content (Harmonized Tripartite Guidelines 2003).

Results and Discussion

Preformulation Study:

Description:

Nature: *It* is a topical antifungal agent commonly used in the treatment of human fungal skin infections such as severe Candida and Cryptococcus infections.

3.1.3 Taste: Bitter**.**

Melting point:

Table.5: Melting Point Determination

Drug	**Melting Point**	**Normal Range**
Flucytosine	198 ± 0.134	295–297°C

Solubility:

Table.6: Solubility Profile of Flucytosine

S. No	**Solvents System**	**Solubility (mg/ml) at 37±2˚C**
1	Distilled H2O	0.06
2	Ethanol	90
3	Chloroform	85
5	CCL4	82
6	Diethyl Ether	18

Determination of λmax by UV-Spectrophotometer:

Development of Standard Calibration Curve:

Table.7: UV Absorbance of phosphate buffer pH 7.4

S. No	**Concentration (µg/ml)**	**Absorbance at 288nm**
1	10	0.1012
2	20	0.1938
3	30	0.3209
4	40	0.4365
5	50	0.5424
6	60	0.6501

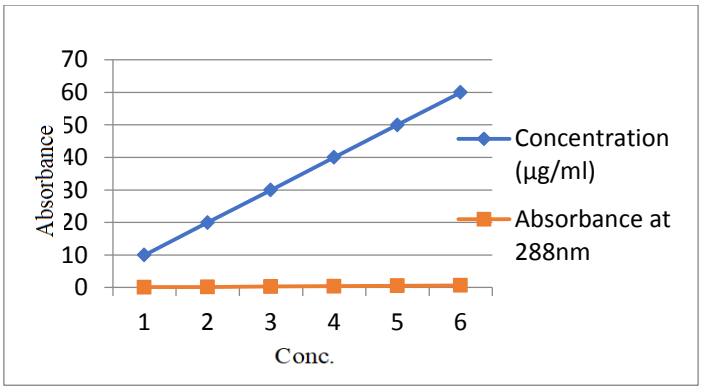

Fig.2: Standard plot of Flucytosine in Phosphate Buffer pH 7.4

FTIR Study:

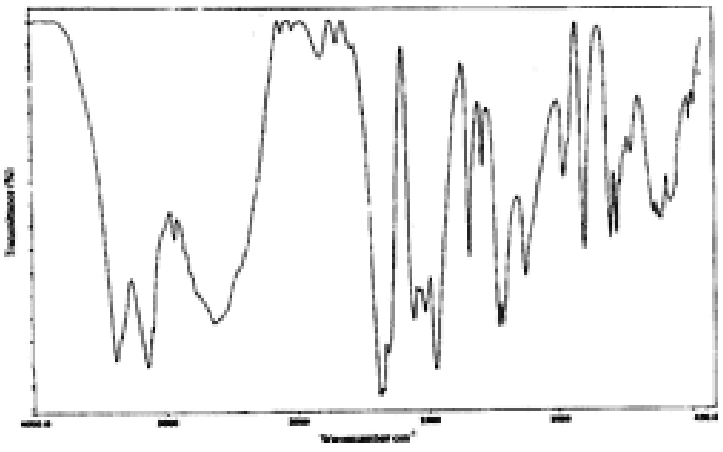

Fig.3: Fourier-Transform Infrared Spectrum of Flucytosine

Table.8: FT-IR Spectral assignment of Flucytosine

S. No.	**Functional Group**	**Range (cm-1)**	**Observed Frequency (cm-1)**
2	N-H Stretching	3000-3500	3039

1	C-N Stretching	1060-1250	1226
3	C=O Stretching	1500-1750	1684
4	C=C stretching	1400-1750	1490.97
5	C=N Bending	1500-1650	1551
6	C-N-H Bending	1000-1400	1356
7	C-N-C Bending	410-550	430
8	C-C=N Bending	450-500	482
9	N-C=O Symmetric Bending	510-710	610

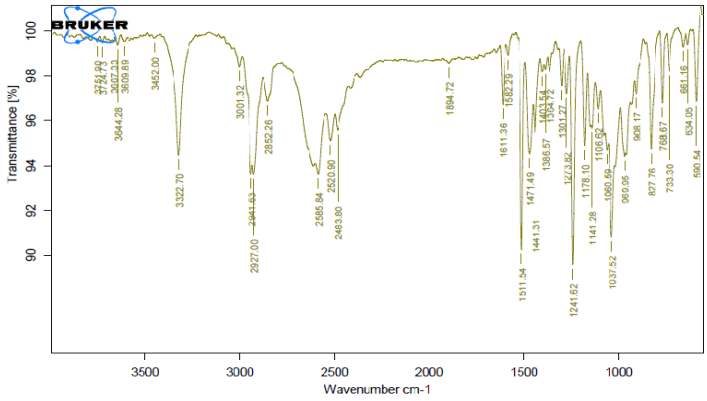

Fig.4: FTIR of drug+Carbolpo-934

Table.9: FT-IR Spectral assignment of drug+Carbolpo-934

S. No.	Functional Group	Range (cm-1)	Observed Frequency (cm-1)
2	N-H Stretching	3000-3500	3200.78
1	C-N Stretching	1260-1250	1200.12
3	C=O Stretching	1500-3050	2970.86
4	C=C stretching	1400-1750	1696.18
5	C=N Bending	1500-1650	1528.62
6	C-N-H Bending	1000-1400	1050.62
7	C-N-C Bending	410-550	489.49
8	C-C=N Bending	450-500	458.52
9	N-C=O Symmetric Bending	510-710	600.78

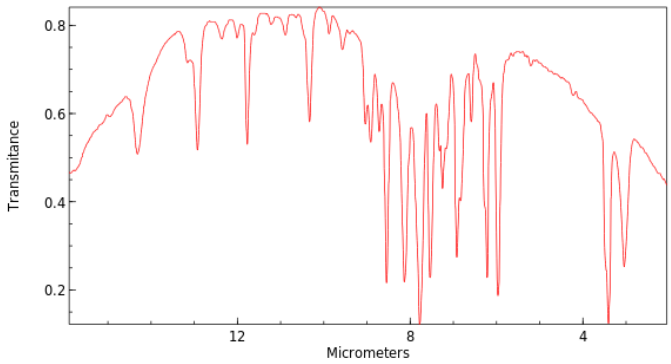

Fig.5: FTIR of Drug+Propylparaben

Table.10: FT-IR Spectral assignment of Drug+Propylparaben

S. No.	Functional Group	Range (cm-1)	Observed Frequency (cm-1)
2	N-H Stretching	3000-3500	3200.78
1	C-N Stretching	1260-1250	1200.12
3	O-H Stretching	1500-3050	2970.86
4	C-H Stretching	1400-1750	1696.18
5	C-O Bending	1500-1650	1528.62
6	O-H Bending	1000-1400	1050.62
7	C=O Stretching	410-550	489.49
8	C-N Bending	450-500	458.52
9	O-H Stretching	510-710	600.78

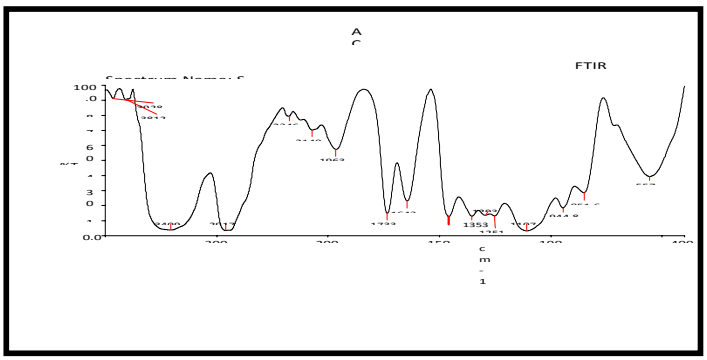

Fig.6: FTIR of Drug+ Propylene Glycol

Table.11: FT-IR Spectral assignment of Drug+ Propylene Glycol

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

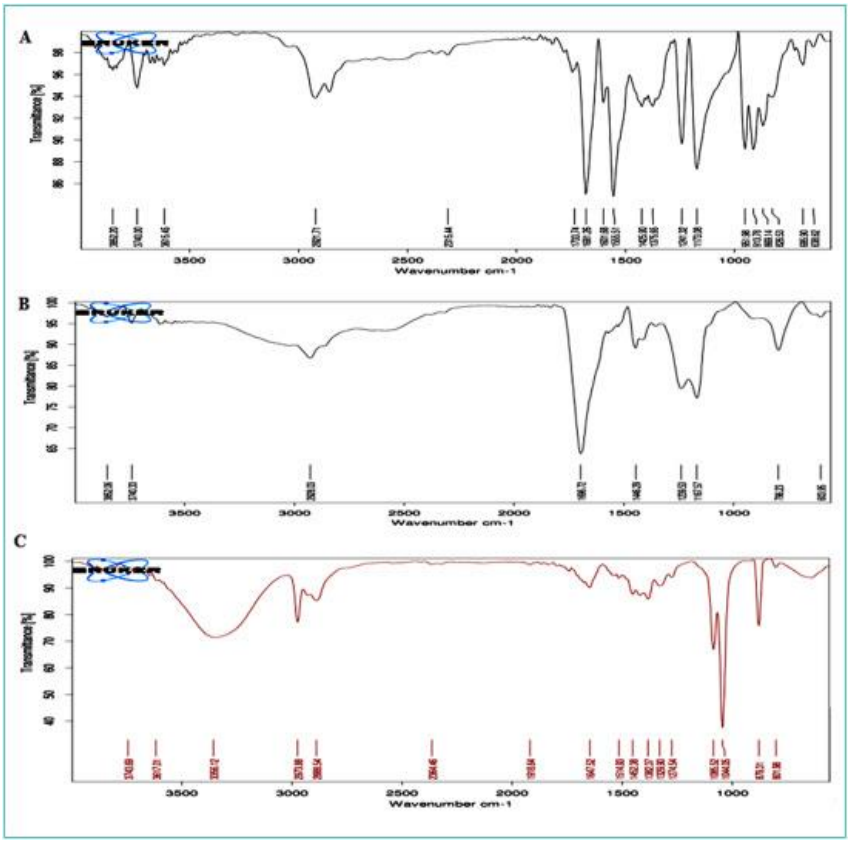

Fig.7: FT-IR of Physical Admixture (Flucytosine+Carbolpol-940+Propylparaben+Propylene glycol+ Triethanolamine)

Table.12: FT-IR Spectral assignment of Flucytosine+Carbolpol-940+Propylparaben+Propylene glycol+ Triethanolamine)

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 Microemulgel formulation development.

Evaluation Parameters:

Particle Size Analysis:

The particle size was found in the range of 58.18-224.6nm for formulation F1 to F6. The zeta potential was found b/w -19.3-25.1. The high value of zeta potential confirms the stability of Microemulgel. The % drug content found to be b/w 84.10 to 98.49. All the results are given table.13.

Table.13: Particle Size Analysis

Formulation	Particle Size (nm)	Zeta Potential	% Drug Content
F1	224.6±1.02	-19.3	86.19±0.51
F2	185.4±0.78	-20.6	84.10±0.68
F3	160±0.62	-22.4	94.70±2.61
F4	58.18±1.08	-24.8	96.35±2.56
F5	87.14±.050	-21.3	98.49±2.13
F6	98.10±.064	-25.1	94.32±2.08

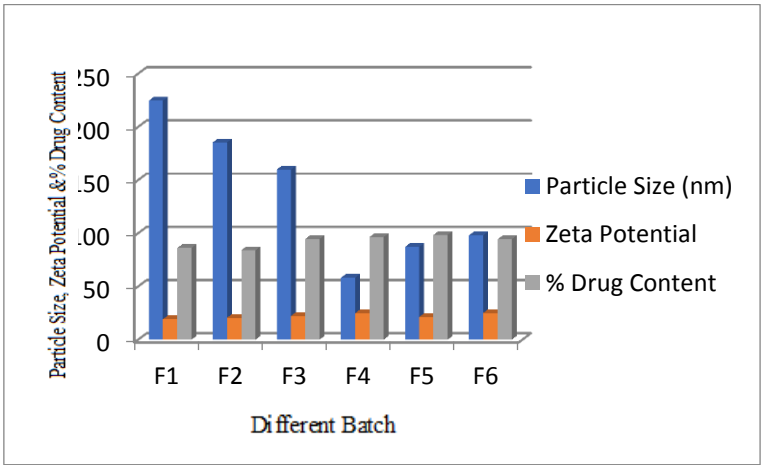

Fig.8: A Graph of Particle Size, Zeta Potential & % drug content

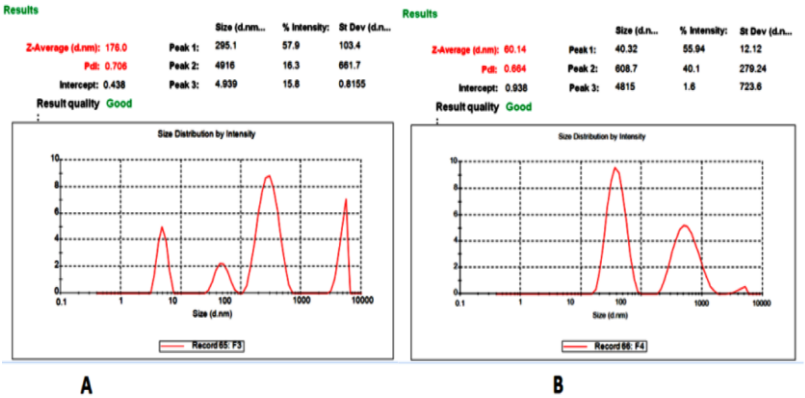

Fig.9: Particle's size A) formulation F3 and B) formulation F6

Viscosity Measurements:

Table.14: Comparative Viscosity, pH & Spread ability values of Formulations

Formulation	Viscosity (cps)*	pH*	Spreadability (g.cm/sec)
F1	67.4±0.5	6.00±0.02	15.64
F2	78.2±0.7	5.14±0.04	24.96
F3	98.6±0.6	6.24±0.06	28.42
F4	112.2±0.2	5.90±0.03	26.78
F5	124.4±0.4	5.35±0.05	32.46
F6	134±0.3	6.12±0.02	34.12

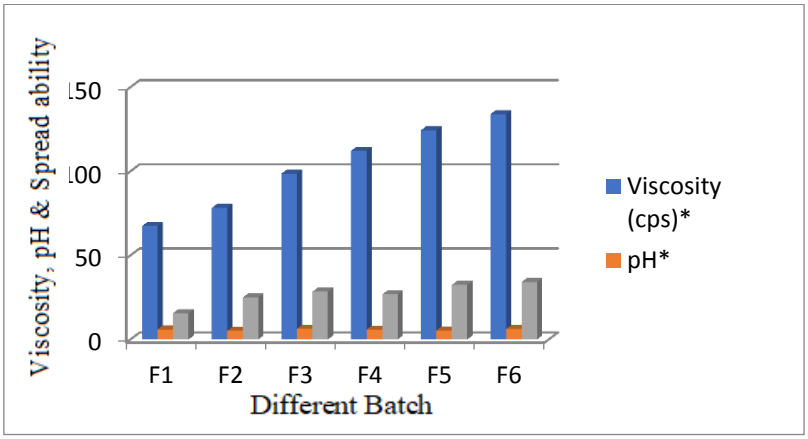

Fig.10: A graph of Viscosity, pH & Spreadability

Homogeneity:

It was evaluated by visual observation and the results were given in Table. All formulated Microemulgel showed good homogeneity without lumps. The physical appearances of microemulgel are opaque in nature were found to be white in colour.

Table.15: Comparative Homogeneity of Formulations

Formulations	Homogeneity
FI	+++
F2	++
F3	++
F4	++
F5	+++
F6	++

Antifungal Activity Study:

Tablet.16: Antifungal Activity Study

Formulation	Zone of Inhibition ($mm^{2)}$
Standard drug	8.4
F5	7.6

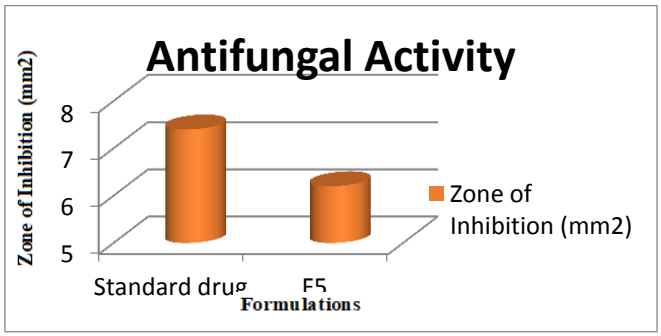

Fig.11: A graph of Anti-fungal Activity

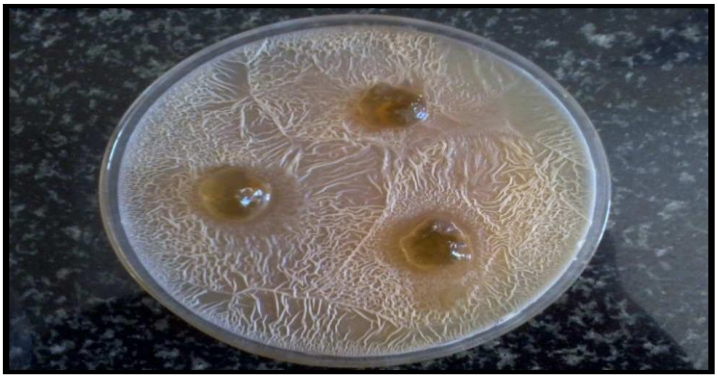

Fig.12: Zone of Inhibition of F5 gel formulation

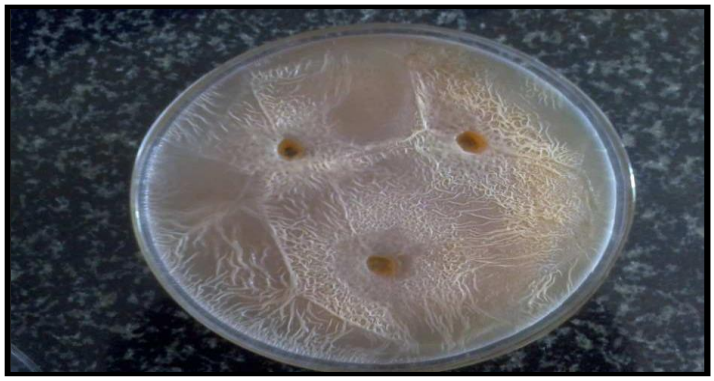

Fig.13: Zone of inhibition of standard Microemulgel formulation

Determination of In-vitro Drug Release of Microemulgel:

Table.17: In-vitro Drug Release of Microemulgel

Time (min)	%CDR					
Code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
30	15.62±0.01	17.42±0.76	13.68±0.74	16.29±0.61	17.33±1.41	14.23±0.75
60	36.90±1.22	33.073±0.44	30.69± 0.86	32.71±0.42	34.83±0.26	31.68±0.97
90	47.89±2.31	42.54±2.31	44.58±1.21	45.35±0.41	46.75±0.26	42.13±0.34
120	56.60±1.43	52.24±1.02	51.437±1.25	52.042±0.71	58.137±1.13	52.042±0.75
150	65.72±0.14	62.01±1.15	62.107±0.32	59.42±0.25	66.68±0.86	59.42±0.24
180	74.53±1.26	71.89±0.56	75.94±0.37	69.91±0.19	76.12±0.64	68.21±0.15
210	80.610±0.84	78.23±1.31	82.15±0.44	79.89±0.22	86.52±0.05	76.99±0.11
240	90.41±0.75	88.26±0.13	94.12±0.07	90.79±0.75	97.14±1.22	94.29±0.34

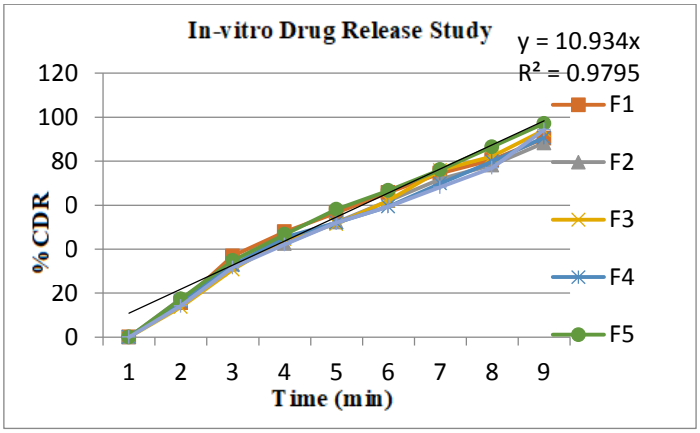

Fig.14: In-Vitro Drug Release Study F1-F6

Skin Irritation Studies for Optimized Formulation:

Wistar rats (12) of either six was used to carry out skin irritation test. Control group was treated with gel base without drug whereas test group was treated with optimized formulation F5. It was observed that both the groups showed no signs of irritation after 24 hr and they were assigned with a score of [Fig.14-15]. This indicates that the prepared formulation is safe for use.

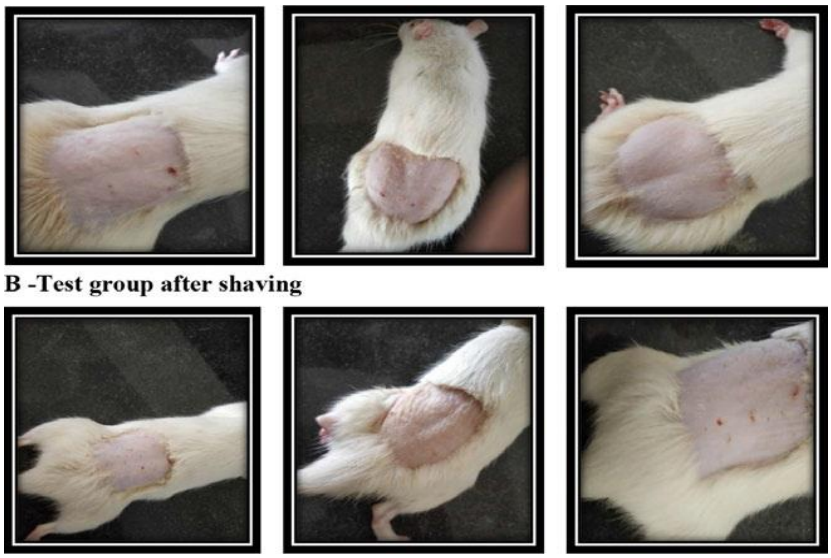

Fig.15: Skin Irritation test of Control & Test group after shaving.

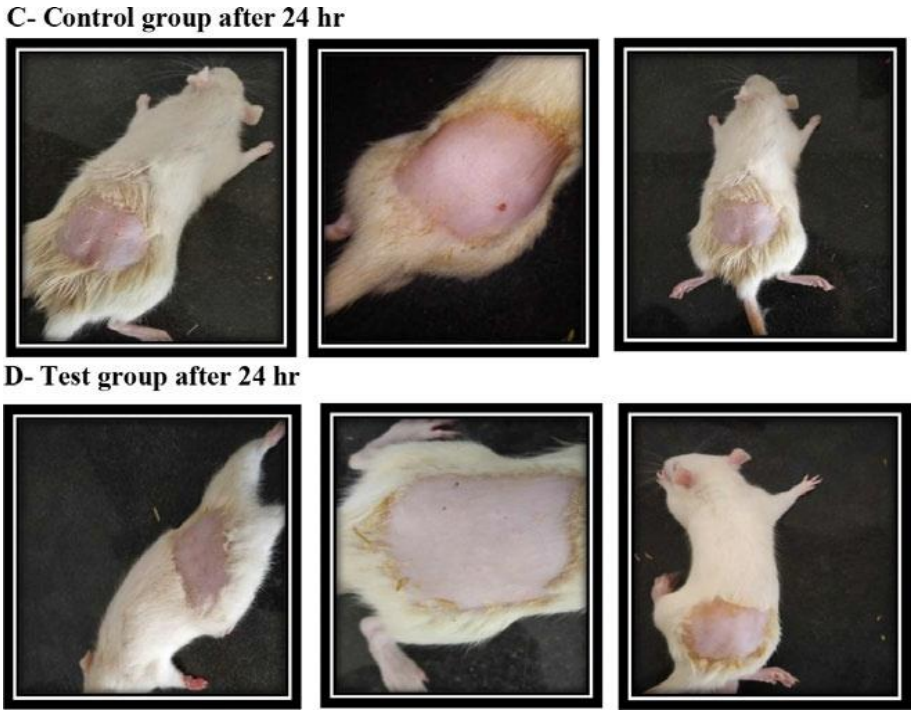

Fig.16: Skin Irritation test of Control and Test group after 24 hr.

Stability Study:

Optimized formulation was examined after 30 days for any changes in pH, rheological properties and drug release profiles. pH was found to be increased slightly. Viscosity was found to be increased at room temperature and then decreased at accelerated temperature. Drug release was found to be slightly decreased with temperature. Not much deviation was observed from optimized formulation F5, So it can be concluded that it showed acceptable stability on a given temperature and humidity.

Table.18: Stability Study best formulation F5

Evaluation Parameters	Initial day	Room Temp. (25°C/ 60% RH)	Accelerated Temp. (40°C/ 65% RH)
pH	5.35±0.05	5.40±0.06	6.10±0.07
Viscosity (cps)	124.4±0.4	124.8±0.5	125.8±0.6
% drug release	97.14±1.242	96.86±1.220	96.26±1.212

Conclusion:

The current investigation's goal is to create and assess a flucytosine microemulgel. Flucytosine enters the fungal cell by the cytosine permease; as a result, flucytosine is converted inside of fungal cells into 5-fluorouracil and inhibits fungal thymidylate synthase. Its bioavailability is low. In the realm of pharmaceutical sciences, microemulgel has now emerged as one of the most intriguing topical preparations. When used as a delivery mechanism, micro-emulgel has several advantages over straightforward conventional formulations, including simplicity of administration, increased residence duration at the application site, constant drug release with improved bioavailability, superior thermodynamic stability, and excellent trans-dermal permeability. Using carbopol 940 and isopropyl myristate as gelling agents, triethanolamine as the oil, methyl parabens and liquid paraben as preservatives and propyl glycol as an emulgent and penetration enhancer, the flu cytosine micro-emulgel is created. Visual examinations were done on the generated micro-emulgel formulation for things like Spreadability, homogeneity, viscosity, pH, percent drug content, and in vitro diffusion tests. The development of micro-emulgels containing flucytosine will be more successful, according to the results, but clinical trials are necessary to fully understand their clinical usefulness. Viscosity studies of various formulations revealed that formulation F5 was better compare to others. Skin irritation study indicated that no irritation have been produced by gel formulation F5. Anti fungal studies also showed the good results of formulation F5 and increased for the treatment of candida and Cryptococcus infections.

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