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Formulation and evaluation of gel containing fluconazole as an antifungal agent

S.Valarmathi*, M.Senthil Kumar*, P.Ashvini, S.Flowerin Sheena, N.Shakila, B.Vinodhini.

Annai Veilankanni's College of Pharmacy Saidapet, Chennai-600015
Corresponding Author: S.Valarmathi
Email: sahanashree2012@gmail.com

ABSTRACT

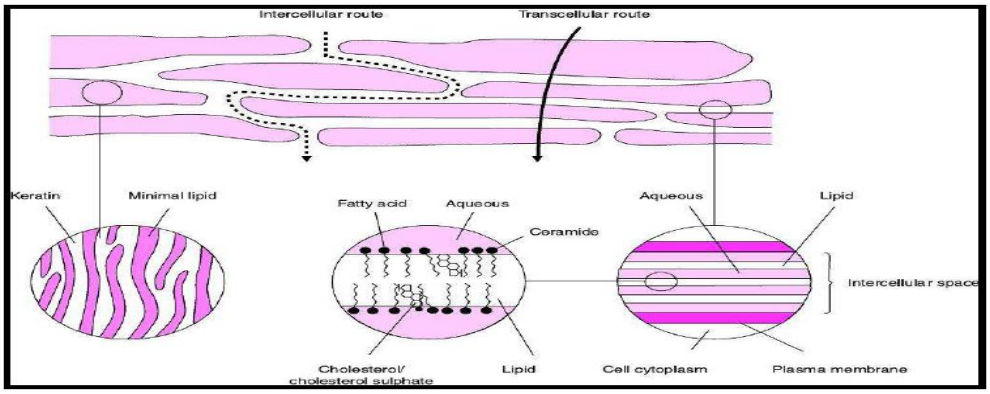
Fluconazole is an imidazole derivative used for the treatment of local and synthetic fungal infection. The oral use of fluconazole is not recommended as it has many side effects. The present study was designed to formulate and evaluate different formulae of topical gel containing fluconazole for treatment of fungal infection of skin. The gel was formulated by using carbapol in different concentration (0.5, 1, and 1.5) as gelling agent. Three different formulae (F1, F2, F3) was prepared and characterized physically in term of colour, spreadability, pH and rheological properties (viscosity). Drug-excipients compatibility studies were confirmed by FT-IR. In-vitro diffusion study using phosphate buffer pH 5.5 as medium and permeation study using Modified Franz diffusion cell was performed. The result of in-vitro drug release permeation studies showed that the higher values was from F1 (85% of drug release) when compared to other formulation F2&F3.

Keywords: Carbopol 940, Propylene glycol, Glycerin, Methyl Paraben, Purified water.

INTRODUCTION

Skin is one of the most accessible organ of human body for topical administration and main route of topical drug delivery system. Fungal infection of skin is one of the common dermatological problems .Among the topical formulation the clear transparent gels have widely accepted in both cosmetics and pharmaceuticals. Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical route. There are various hydrophilic polymers such as carbapol 940 used in topical drug delivery system.

The epidermis is 0.1-1.5mm thickness. It is further divided into five parts: stratum germinativum, stratum spinosum, stratum granulosum, stratum lucidem and stratum corneum, the epidermis form the pigment melanin.



ROUTE OF PENETRATION

At the skin surface, drug molecules come in contact with cellular debris, micro organisms and other materials, with effect permeation. The applied medical substance has three pathways to the viable tissue

1. Through hair follicle
2. Via sweat ducts
3. Across stratum corneum between appendages (hair follicles, sebaceous glands, urine, apocrine glands and nails).

The intact stratum corneum is the main barrier and therefore many enhancing techniques aim to disrupt (or) bypass this layer. Viable layers may metabolize a drug (or) activate a prodrug. Usually a deeper region does not significantly influence absorption. This route of drug delivery has gained popularity because as it avoids first-pass effect, gastro infection irritation and metabolic degradation associated with oral administration. The topical route of administration has been utilized either to produce local effect for treating skin disorder or to produce systemic drug effects.

Gels are defined as "semisolid system in which a liquid phase is constrained within a polymetric matrix in which a high degree of physical and chemical cross-linking introduced".

Gels can be classified based on colloidal phases, nature of solvent used, physical nature and rheological properties.

Based on colloidal phases

They are classified as

- Inorganic (two-phase system)
- Organic (single phase system)

Two phase system (inorganic)

If the particle size of the dispersed phase is relatively large and form the dimensional structure throughout gel such a system consist of floccules of small particles layer molecules of gel structure this system is not always stable .They must be thixotropic forming semi solid on standing and liquid on agitation.

Single phase system (organic)

These consist of large organic molecules existing on the twisted stands dissolved in a continuous phases. They are either natural (or) synthetic polymer are referred as gel forms.

Based on the nature of solvent used

Hydrogels

[water-based] – Water acts as continuous liquid phases.
Example: Gelatin, cellulose derivative.

Organic gels

[With a non-aqueous solvent]- contains non-solvent as continuous phases
Example: Plastibase

Xerogels

Solid gels with low concentration are known as xerogels. They are produced by solvent or freeze drying, leaving the gel framework behind on contact with fresh fluid.
Example: Tragacanth ribbons, dry cellulose and polystyrenes.

Based on rheological properties

Usually gels exhibit non-Newtonian flow properties. They are classified into

a. Plastic gels
b. Pseudo-plastic gels
c. Thixotropic gel

Plastic gels

E.g. Bingham bodies, flocculated suspensions of Aluminum hydroxide exhibit a plastic flow and the plot of rheogram gives the yield value of the gels about which the elastic gel distorts and begins to flow.

Pseudo-plastic gels

E.g. liquid dispersion of tragacanth, sodium alginate, Na CMC etc exhibits pseudo-plastic flow. The viscosity of these gels decreases with increasing rate of shear, with no yield value. As the shearing stress is increased the disarranged molecules begin to align their long axis in the direction of flow with release of solvent from gel matrix.

Thixotropic gels

The bonds between particles in their gels are very weak and can be broken down by shaking. The resultant solution will revert back to gel due to the particles colliding and linking together again.

Based on physical nature

Elastic gels – Aliginate and Carbapol
Rigid gels – Silica and Silic acid

Molecules are held by Si-O-Si-O bond to give a polymer structure.

Preparation of gels

Gels are normally in the industrial scale under room temperature. However few of the polymers need special treatment before processing.

Gels can be prepared by following methods

1. Thermal changes – E.g. Gelatin, agar sodium oleate.
2. Flocculation – E.g. Solution of ethyl cellulose.
3. Chemical reaction –E.g. Aluminum hydroxide gels.

Introduction of drug

- Fluconazole is an antifungal drug of triazole class.
- It is new existing drug.
- It overcomes all the side effects of the other fungal drugs like ketoconazole, amphotericinB, clotrimazole and miconazole.
- Even though it has some of the side effects in the oral and I.V dosage forms.

Fluconazole remains one of the most frequent prescribed triazoles because of its excellent bioavailability, tolerability and side effect profile. More than 80% of ingested drug is found in the circulation and 60-70% is excreted in the urine. Only 10%of fluconazole is protein bound.

Fluconazole also exhibits excellent tissue penetration. CSF levels are 70% of matched serum levels and levels reported in saliva, sputum and other sites are well within therapeutic ranges. The half-life is 27-34hours in the presence of normal renal function allowing once daily dose.

Available dosage form:

- Tablets
- Capsules

But the gel dosage of this antifungal agent was not formulated. Numerous dosage forms are used in the topical treatment of superficial fungal infections including creams, liquids, gels, ointments, lacquers and others. The treatment of athlete's foot and ringworms can easily be accomplished with creams, liquids, gels and ointments.

Side effects

- Headache
- Diarrhea
- Nausea
- Stomach pain

MATERIALS AND METHODOLOGY

Materials

MATERIALS	SOURCE
Fluconazole	Madras pharmaceuticals.
Carbopol940	Loba Chemie Pvt. Ltd, Mumbai.
Methyl Paraben	Nice Chemicals Pvt. Ltd, Kerala.
Propylene glycol	Chenchems.

EQUIPMENT	MODEL/COMPANY
Electronic analytical balance	Electron balance, Shimadzu, Japan.
UV-visible spectrophotometer	Spectrophotometer UV-1700, Shimadju.
Fourier transform infrared spectroscope	JASCO, MODEL-4100.
Magnetic stirrer	2-ML Remi Equipment Pvt. Ltd.
Ph tutor	EUTECH Instrument.
Franz diffusion cell	Sci.Work, Peenya Ist stage, Bangalore.
Ultra Sonicator	Sonics and material inc, USA.
Brookfield viscometer	PRO-II Extra Model, Brookfield viscometer, USA.

Drug-excipients compactability studies

Drug-excipients compatibility studies were carried out using FT-IR spectrum between 400-4000 $cm^{-}1$by using KBR pellet techniques. The study was carried out on individual pure drug and its physical mixture with the excipients used in the study.

Uv spectrum analysis of fluconazole

The solution was scanned in the range of 200-400nm to find the maximum wavelength and Uv spectrum was obtained.

PREPARTION OF STANDARD GRAPH

Standard stock solution of fluconazole

Accurately weighed 100mg of fluconazole was dissolved in 100ml of methanol, from this stock solution was withdrawn and transferred into 100ml volumetric flask. Volume was made with methanol in order to get standard stock solution containing 100µg/ml.

Standard graph of fluconazole

From this standard solution a series of dilution (10, 20, 30, 40, 50 µg /ml) were prepared using methanol. The absorbance of these solutions was measured spectrophotometrically against blank of methanol at 260nm for fluconazole.

Preparation of gel base

Carbopol940p (0.5, 1.0, 1.5%w/w) and purified water were taken in a beaker and allowed to soak for 24hour. To this required amount of drug (1gm) was dispersed in water and then carpobol940p was then neutralized with sufficient quantity of Triethanolamine. Glycerin as moistening agent, Methyl Paraben and Propyl Paraben as preservatives were added slowly with continuous stirring until the homogenous gel was formed.

EVALUATION OF FLUCONAZOLE GEL

Determination of ph

Weighed 20gm of each gel formulation were transferred in 10ml of beaker and measured it by using the digital pH meter.

pH of the topical gel formulation should be between 3 - 9 to treat skin infection.

FORMULATION CODE	PH
F1	6.6
F2	6.3
F3	7.0
F4	6.9
F5	6.6

Spreadability

A sample of 0.5g of each formula was pressed between two slides (divided into squares of 5mm sides) and left for about 5 minutes where no more spreading was expected19.diameters of spreaded circles were measured in cm and were taken as comparative values for spreadability.the results obtained are average of three determinations.

FORMULATION CODE	QUANTITY(mg)	DIAMETER (cm)
F1	3mg	2.3cm
F2	3mg	1.9cm
F3	3mg	1.8cm
F4	3mg	1.5cm
F5	3mg	1.2cm

Viscosity

A viscometer (Brookfield digital viscometer DV II RVTDV II USA) was to measure the viscosities (in CPS) of the gels. The spindle (TF 96) was rotated at 0.5rpm. Sample of the gel were to settle over 30mins at the assay temperature (25±/1° c) before the measurements were taken.

FORMULATION	SPINDLE NO	RPM	VISCOSITY CENTIPOISE
F1	18	10	18.60
F2	18	10	86.70
F3	18	10	1.20

Invitro diffusion study

The release of fluconazole from various gel formulations was studied using a Modified Keshary-chien diffusion cell. A standard cellophane membrane [soaked in pH 6.8 for 2 hours before use] was fixed to one end of the cylinder with the aid of an adhesive to result in the permeation cell. One gram of gel was taken in the cell [donor compartment] and the cell was immersed in beaker (100ml) containing drug free phosphate buffer ph 6.8 (90ml) as receptor compartment.

The cell was immersed to a depth of 1cm below the surface of phosphate buffer in the receptor compartment and was agitated using a magnetic stirrer and a temperature of 32°c ± 1°c was maintained.

Sample (5 ml) of the receptor compartment was taken at various interval of time (30,60,90,120,150,180,210,240,270,300,330,360 minutes) over a period of 6hours and assayed for fluconazole at 260 nm.

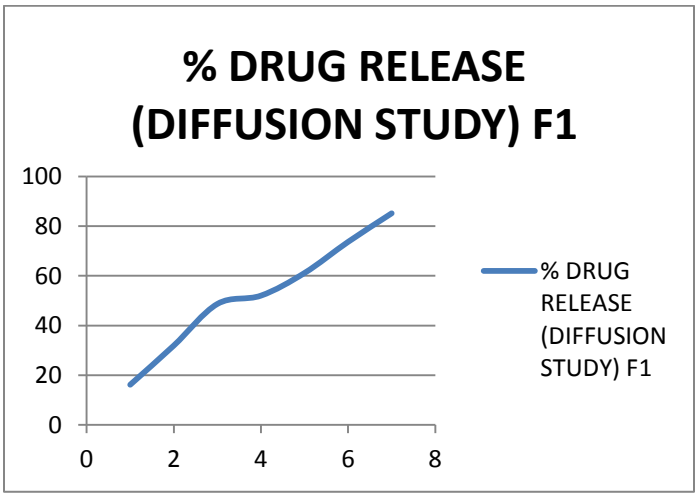
The volume withdrawn at each time was replaced with drug free phosphate buffer. Amount of fluconazole released at various intervals of time was calculated against time.

SERIAL NUMBER	% DRUG RELEASE (DIFFUSION STUDY)			
	TIME(in hrs)	F1	F2	F3
1	1	16.14	13.29	11.11
2	2	31.91	22.66	20.15
3	3	48.66	32.8	34.11
4	4	52.01	41.02	43.01
5	5	61.13	50.36	52.47
6	6	73.66	61.01	60.17
7	7	85.15	75.25	75.09

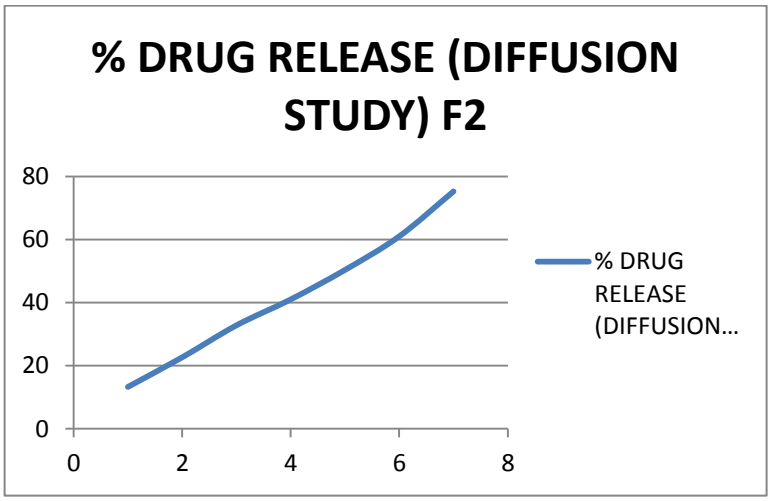
RESULT

% DRUG RELEASE (DIFFUSION STUDY)	
TIME (In hrs)	F1
1	16.14
2	31.91
3	48.66
4	52.01

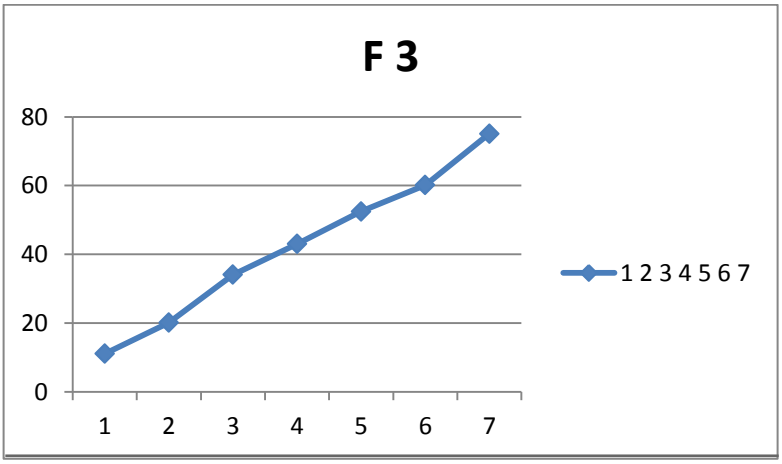
5	61.13
6	73.66
7	85.15

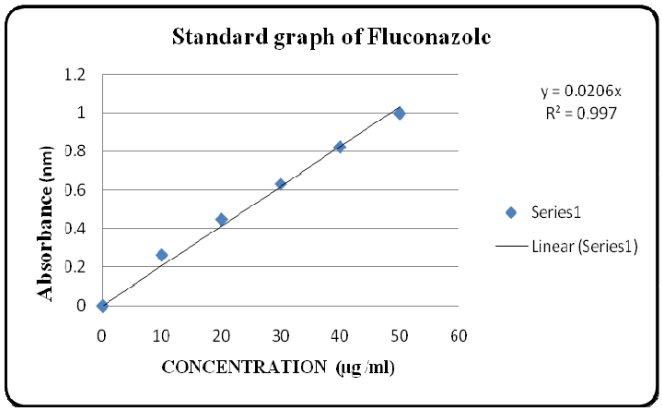


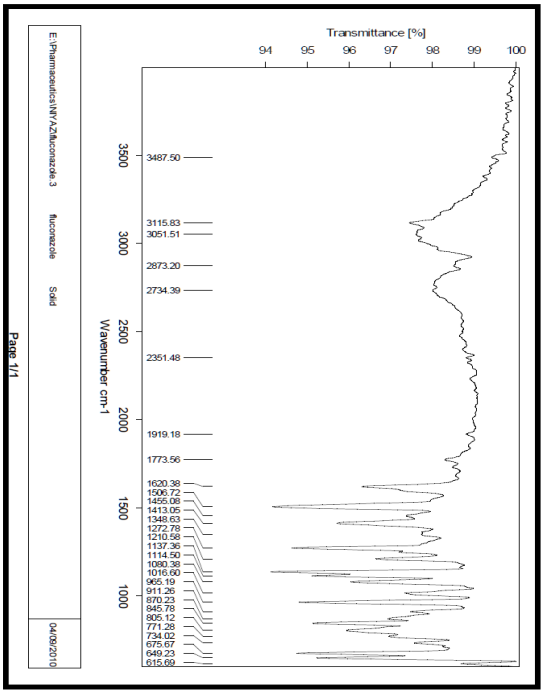
% DRUG RELEASE (DIFFUSION STUDY) TIME (In hrs)	F2
1	13.29
2	22.66
3	32.8
4	41.02
5	50.36
6	61.01
7	75.25



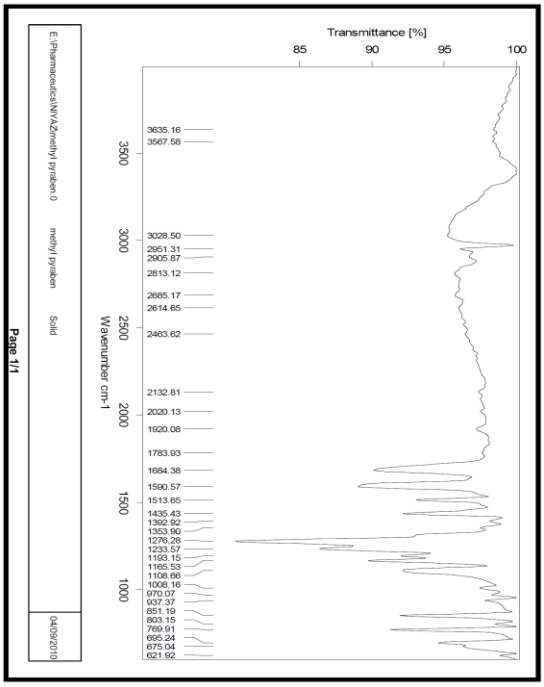
S.NO	% DRUG RELEASE (DIFFUSION STUDY) TIME (In hrs)	F3
1	1	11.11
2	2	20.15
3	3	34.11
4	4	43.01
5	5	52.47
6	6	60.17
7	7	75.09



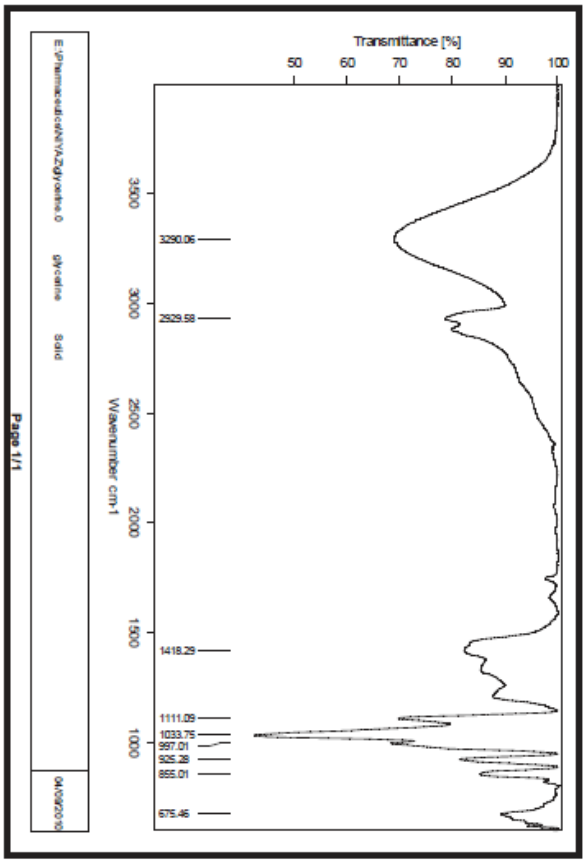




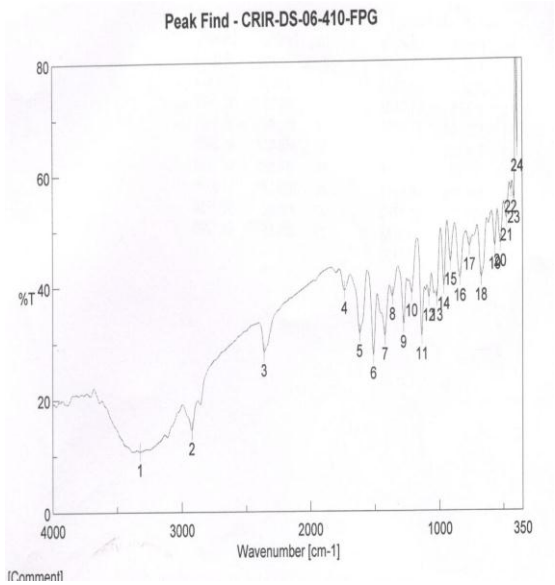
FT-IR SPECTRA OF FLUCONAZOLE



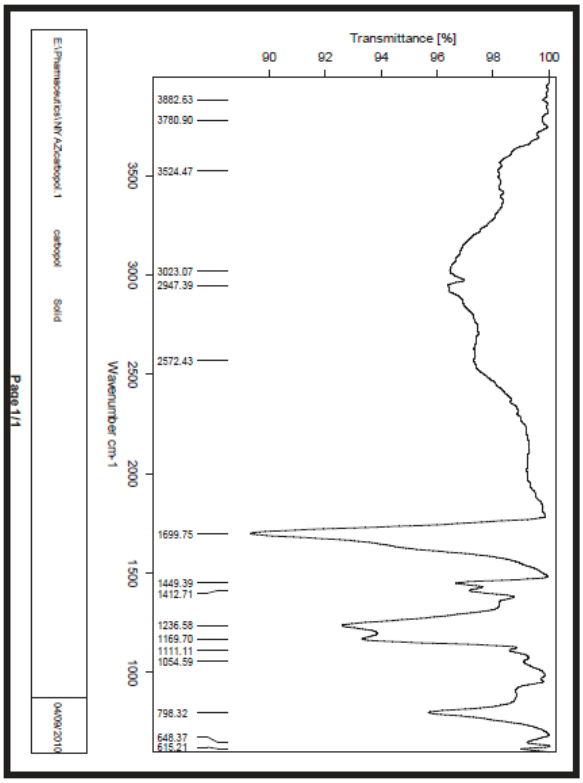
FT-IR SPECTRA OF METHYL PARABEN



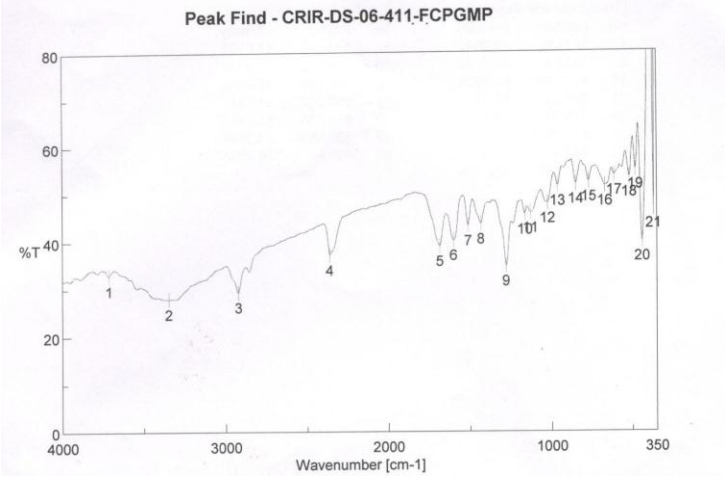
FT-IR SPECTRA OF GLYCERIN



FT-IR SPECTRA OF FLUCONAZOLE PROPYLENE GLYCOL



FT-IR SPECTRA OF CARBOPAL940



FT-IR SPECTRA OF FLUCONAZOLE+CARBOPOL940+PROPYLENE GLYCOL+ METHYL PARABEN.

I.r spectral studies

From the I.R spectrums it was concluded that when comparing drug spectrum & drug with excipients spectrum there is no shift in the peaks.

MAXIMUM λ MAX

When scanning the drug solution at 200-400nm wavelength, the spectrum was obtained at 260nm.

CONCLUSION

From this research study, it was concluded that **F1** formulation having 0.5%carbopol was found to have good release when compared to other formulation F2 & F3.

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