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Formulation and evaluation of fluconazole and ichthammol ointment

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ABSTRACT

The fluconazole drug is used for treatment of anti-fungal infections like eczema, itching, pruritis. Reason for this study to formulate the ointment with different ointment bases. The ointment bases having good consistency, better diffusion, anti-fungal and antiseptic properties. Combination of fluconazole and ichthammol is used to treat the infection caused by coryne bacteria. Fluconazole and ichthammol having good anti-fungal and antiseptic property respectively. So it is used to cure the skin infection on the epidermis layer. The prepared formulation is evaluated for assay drug release, uniformity, viscosity, diffusibility, stability, permeability and other physical characteristics. Two formulations, formulation F1 and F2 were prepared with same active ingredients except different bases. Formulation F1 contains white soft paraffin, cetostearyl alcohol, light liquid paraffin and microcrystalline wax. Formulation F1 was found better than formulation F2 in all aspects like viscosity, stability, diffusibility etc.

Keywords: Ointment, Fluconazole, Ichthammol, Viscosity, Diffusion.

INTRODUCTION

Ointment

Ointments are semisolid preparations intended for external application to the skin or mucous membranes. Ointment may be medicated or non-medicated.

Ointment bases

Ointment bases may be used for their physical effects or as vehicles in the preparations of

medicated ointments. Ointment bases are classified into 4 types.

1. Hydrocarbon bases
2. Absorption bases
3. Water-removal bases
4. Water-soluble bases

Hydrocarbon bases

Hydrocarbon bases are also termed oleaginous bases. On application to the skin, they have an emollient effect. They are immiscible with water so they cannot be removed easily.

E.g. Petrolatum, white petrolatum, white ointment, yellow ointment.

Absorption bases

These bases may be used as emollients although they do not provide the degree of occlusion by the hydrocarbon bases. Absorption bases are not easily removed from the skin with water washing since the external phase of the emulsion is oleaginous. Absorption bases are of two types.

1. Those that permit the incorporation of aqueous solutions resulting in the formation of water-in-oil emulsion eg: Hydrophilic Petrolatum.
2. Those that are water-in-oil emulsions and permit the incorporation of additional quantities of aqueous solution eg: lanolin

Water removable bases

Water removable bases are oil-in-water emulsions resembling creams in appearance. The external phase of the emulsions is aqueous, they are easily washed from skin and are called “water – washable” bases. eg :Hydrophilic ointment.

Water soluble bases

Water soluble bases do not contain oleaginous components. They are completely water- washable and often referred to as “greaseless “. They are used for the incorporation of solid substances. eg :polyethylene glycol ointment.

Anti-fungal agents

An anti-fungal medication is a pharmaceutical fungicide used to treat mycoses such as athlete’s foot ringworm, candidiasis. Topical treatment of fungal infections has several superiorities including, targeting the site effects, enhancement of the efficacy of treatment and, high patient compliance. Different type of topical effective anti-fungal compounds has been used in the treatment of a variety of dermatological skin infections. The efficiency of the topical anti-fungal treatment

depends on the penetration of drugs through the target tissue.

Fluconazole

Fluconazole is a triazolefungistatic agent used in the treatment of systemic and superficial fungal infections. It is an antifungal medication that is given either by mouth or intravenously. It is used to treat a variety of fungal infections of the vagina (yeast infection), mouth, throat and blood stream. It is also used to prevent infections in people with weak immune systems, including those with neutropenia due to cancer chemotherapy, transplant patients, and premature babies.

Ichthammol

Ichthammol is an anti- inflammatory agent it is used to treat eczema, dry and sore skin. It is mildly astringent, irritant and local anti-bacterial agent with moderate emollient and demulcent properties. Ichthammol belongs to a class of preparations containing as essential constituents salts or compounds of a mixture of acids designated by the group name sulfoichthyolic acid.

MATERIALS

Fluconazole, Ichthammol, boric acid, zinc oxide, menthol, cetostearyl alcohol, hard paraffin, white soft paraffin, microcrystalline wax, light liquid, methyl paraben, propyl paraben, triethanolamine, propylene glycol, demineralized water were provided by Madras pharmaceuticals, bafna pharmaceuticals, and chennai, India.

Instruments

- Brooke field viscometer.
- PH meter
- Water bath
- Microscope
- Uv-visible spectrophotometer
- Stability chamber
- Digital weight box

METHODS

The composition for formulation F1 and F2 are depicted in table 1

TABLE 1: Formula for ointment formulation

Sr.no	Name of Ingredients	Formulation	
		F1 %W/W of Formulation	F2
1	Fluconazole	0.5 gm	0.5 gm
2	Ichthammol	0.20gm	0.20gm
3	Boric acid	1.0gm	1.0gm
4	Zinc oxide	3.0gm	3.0gm
5	Menthol	1.0gm	1.0gm
6	Hard paraffin	-----	1.5gm
7	Microcrystalline wax	-----	2.5gm
8	Light liquid paraffin	-----	26gm
9	White soft paraffin	25gm	-----
10	Cetostearyl alcohol	20gm	15gm
11	Sodium lauryl sulphate	1.0gm	1.0gm
12	methyl paraben	0.1gm	0.1gm
13	Propyl paraben	0.1gm	0.1gm
14	Triethanolamine	0.5gm	0.5gm
15	Propylene glycol	10gm	10gm
16	Purified water	q.s	q.s

FORMULATION F1

Oil phase was prepared by heating soft paraffin and cetostearyl alcohol in a stainless steel vessel till temperature of oil phase attains 75°C to 80°C. water phase was prepared by heating zinc oxide, boric acid, sodium lauryl sulphate, methyl paraben and tri-ethanolamine in a vessel till temperature attains 75° c to 80°c. Both water phase and oil phase were mixed. The mass was stirred and cooled .Active ingredients like propylene glycol, menthol, fluconazole and ichthammol were made into homogenous slurry by stirring it for 30 minutes. Then it was cooled and again stirred till ointment is obtained. Temperature was maintained at 35° c to 37° c .

FORMULATION F2

Oil phase preparation

The required quantities of hard paraffin, microcrystalline wax, cetostearyl alcohol, light liquid paraffin were added. It is considered as oil phase. The oil phase was heated till the temperature attains 75 °c to 80° c.

Water phase preparation

Water phase was prepared by heating zinc oxide, boric acid, sodium lauryl sulphate, methyl paraben and tri-ethanolamine in a vessel till temperature attains 75° c to 80°c. Both water phase and oil phase were mixed. The mass was stirred and cooled .Active ingredients like propylene glycol, menthol, fluconazole and ichthammol were made into homogenous slurry by stirring it for 30 minutes .Then it was cooled and again stirred till ointment is obtained .Temperature was maintained at 35°c to 37°c.

EVALUATION PARAMETERS

Description

1 gm of ointment was taken to a clean and dry petridish and observed visually.

Identification

The ointment was subjected to identification tests for active ingredients 10g of ointment equivalent to 50mg was taken in a separating funnel. Water was added and extracted with

chloroform and anhydrous sodium sulphate. The layer was collected. The residue obtained was used for the identification tests of fluconazole and ichthammol.

Fluconazole

The residue was diluted with methanol and methyl orange solution was added. Yellow colour was developed

Ichthammol

The residue was treated with 2M hydrochloric acid. The gas evolved turns lead acetate paper black. Solution was filtered. Residue was taken in water and 2M hydrochloric acid and barium chloride solution was added. A white precipitate was produced.

Menthol

To weighed quantity of ointment little quantity of sulphuric acid and vanillin was added. Orange yellow colour was produced.

Zinc oxide

The residue obtained shows yellow colour when hot and white colour when cool.

Boric acid

To the weighed quantity of ointment methanol and few drops of sulphuric acid were added. It was warmed, shaken and ignited. The flame shows green border.

EVALUATION OF OINTMENT

Uniformity of weight

Ten tubes were filled randomly and weighed. Ointment was removed from each tube and each empty tube was washed with methanol. The empty tubes were dried and their weight was taken. The difference between two weights was calculated as net weight of the ointment of tube. The average of net weight of ointment of ten tubes was noted.

Globule diameter

The average globule diameter was calculated with help of microscope.

PH

The pH of ointment solution was measured with the help of PH meter.

Loss on drying

Loss on drying was determined by placing ointment in petridish on water bath and dried for 105⁰ C.

Percentage loss on drying = $100 \times (W_t - M_w) / W_t$

Viscosity of ointment

The viscosity was determined by CAP-2000 Brookfield viscometer. Test sample was taken in a clean and dry 250 ml beaker and the viscosity of the test sample was determined by standard operating procedure of viscometer by using spindle nos.1 to 4. Each spindle was used for finding the viscosity of the sample at speeds of 0.3, 0.6, 1.5, 3, 6, 12, 30 and 60 r.p.m. respectively. Their rheological characteristics were also tested at 25⁰ using Brookfield viscometer.

Diffusion study

In modified kiescarychein diffusion cell, 2gm of ointment was kept in donor compartment. The entire surface of cellophane membrane was in contact with the receptor compartment containing 22 ml of phosphate buffer pH 7.4. The receptor compartment was continuously stirred (100 r.p.m) using the magnetic stirrer. The temperature was maintained 37 ± 1⁰ c. The surface area available for diffusion was calculated and found to be 3.14 cm². The study was carried out for 5 hours and the sample was withdrawn at 30 minute time interval and same volume was replaced with free phosphate buffer. The content of fluconazole and ichthammol from withdrawn sample was measured after suitable dilution. The experiment was carried out in triplicate and average values are reported.

Diffusibility gives the amount of ointment diffused with the body surface. When a drug system applied topically; the drug diffuses out of its vehicle on to the surface tissues of the skin. The transient diffusion that occurs shortly after the application of a substance to the surface of the skin is potentially far greater through the appendages than through the matrix of the stratum corneum. After steady state diffusion has been established, the dominant diffusion mode is probably no longer intra appendageal, but occurs through the matrix of stratum corneum. Once a substance passes through the stratum corneum, there is apparently no significant further hindrance to penetration of the remaining epidermal layer and corneum. There is

then a ready entry into the circulation via the capillaries.

The infusibility experiment was carried out by preparing agar nutrient medium of any concentration. It was poured into petri dish. A hole was made at the center and ointment was placed in it. The time taken for the ointment to get diffused was noted.

Stability studies

The international conference on harmonization (ICH) harmonized tripartite guide lines on stability testing of new drug substances and product was issued on 27, 1993. The formulated fluconazole and ichthammol ointment were filled in the collapsible

tubes and stored at different temperature condition viz. $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$, $300^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$, $400^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$ for a period of three months and studied for appearance, pH, extrudability, viscosity, and assay of the drug.

Infrared spectroscopy

Infrared spectroscopy was conducted using FTIR spectrometer and the spectrum was recorded in the region of $500\text{--}4000 \text{ cm}^{-1}$. The procedure consisted of dispersing a sample (drug and KBr preparation) into disc by applying a pressure of 5 times for 5 minutes in a hydraulic press. The powder was placed in the path and spectrum was obtained.

RESULT AND DISCUSSION

TABLE 2: Identification of active ingredients for formulation A and B

Sr.no	Identification test	specification
1	Fluconazole	Yellow colour produced
2	Ichthammol	A white precipitate is produced
3	Menthol	Violet colour is produced
4	Zinc oxide	White colour produced
5	Boric acid	Flame has green border

All the parameters like uniformity of weight, pH, globule diameter, loss on drying, drug content

were found to comply with standard. The results are shown in table 3

TABLE 3: Evaluation of different parameters fluconazole and ichthammol ointment

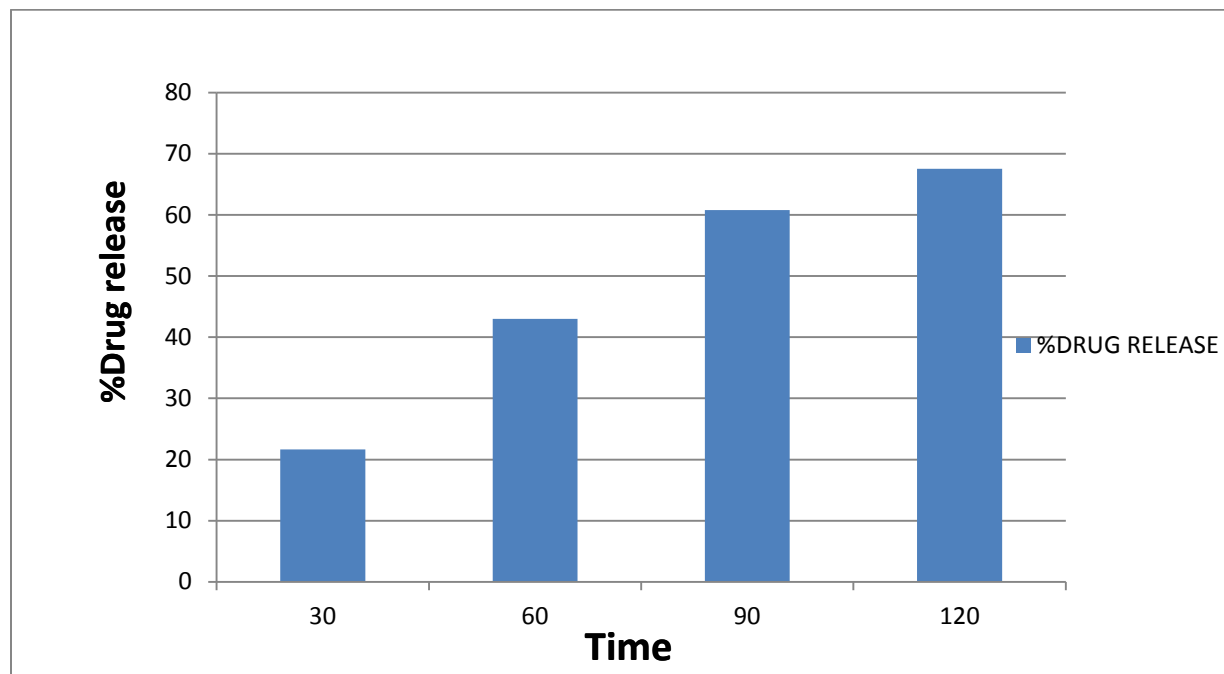
Evaluation parameters	Formulaion F1	Formulation F2
Description	Colour- light brown Odour- metholated	Colour- light brown Odour- metholated, soft semi solid
Uniformity of weight	Comply with standard	Comply with standard
Globule diameter	4.98 mm	4.32 mm
pH(10%W/V solution)	5.9	6.7
Loss on drying	39%W/W	40%W/W
Viscosity	135cps	128cps

The formulation F1 was found to be more viscous (135cps) than formulation F2 (128cps). The amount of ointment diffused with body surface and percentage drug release was determined. From the results it was found that formulation F1 has diffusion power in particular interval of time

diffusing 0.5 cm length after 60 minutes than formulation F2 which diffuse only 0.4 cm length after 60 minutes and drug release for formulation.

F1 after 5th hour was found to be 58% and drug release for formulation F2 after 5th hour was found to be 50%. The results are depicted in graph 2.

Graph 1 diffusion study of formulation F1



Diffusion study of formulation F2

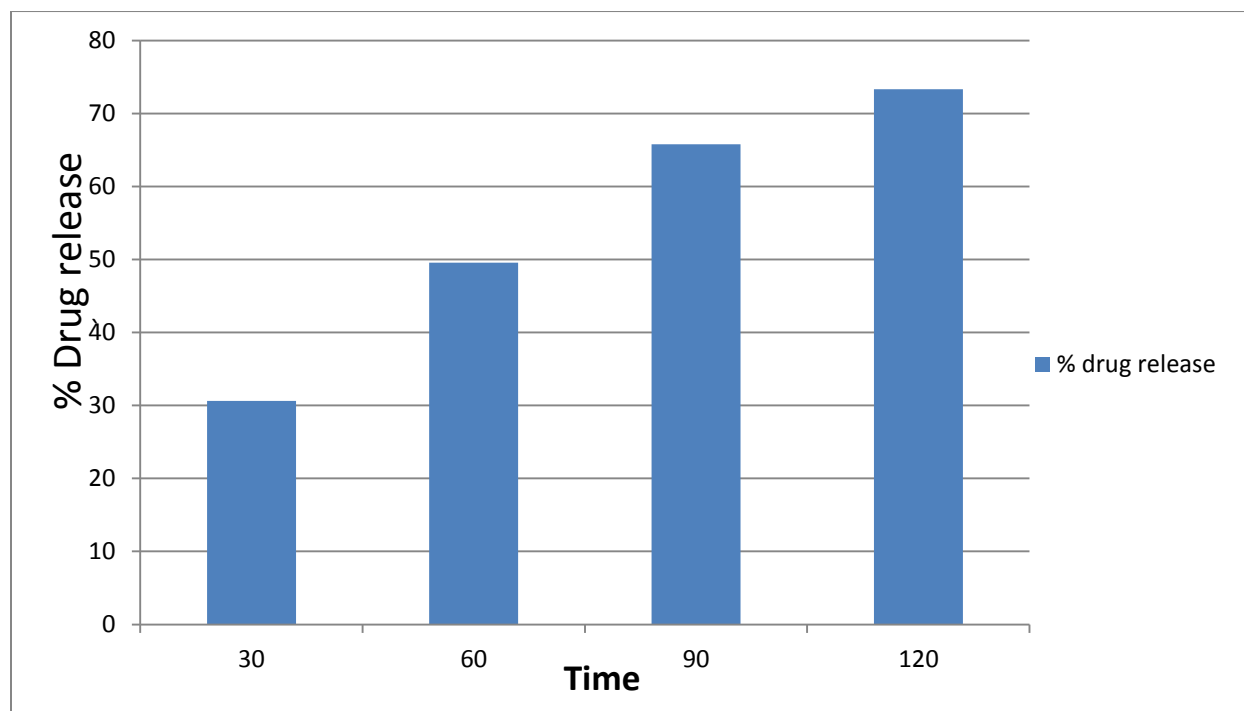


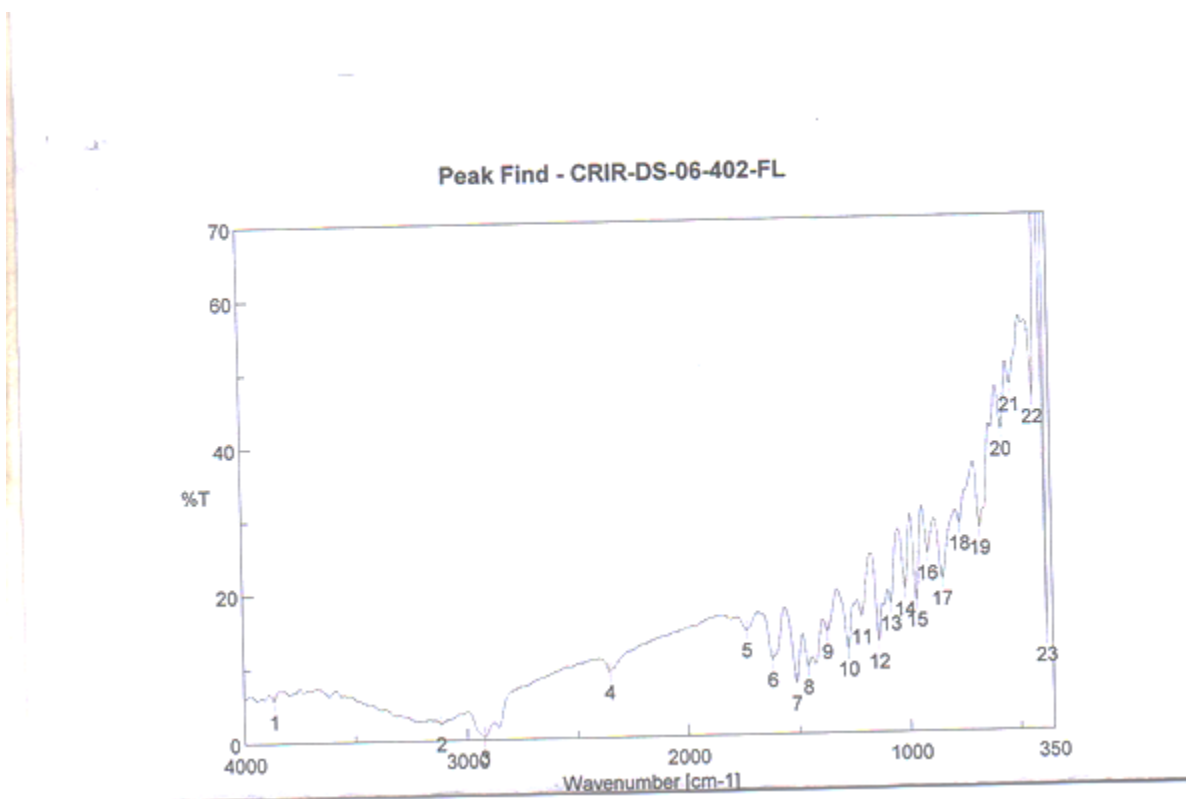
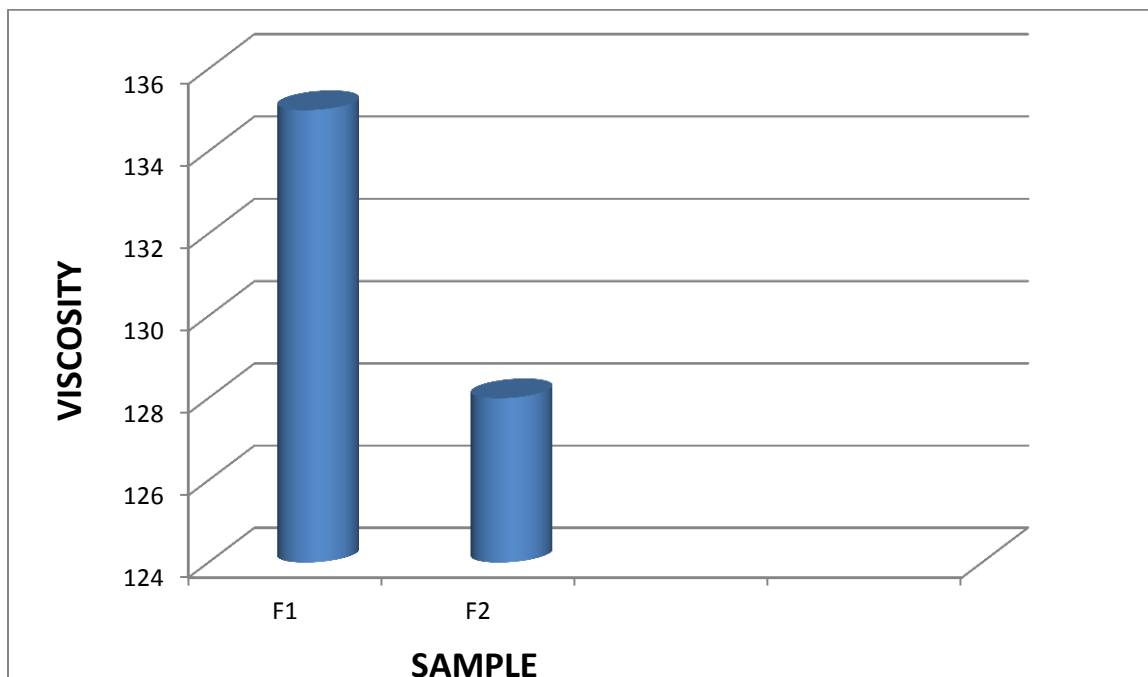
Table 4 stability parameters

Parameters (after 3 rd week)	Formulation F1			Formulation F2		
	25 ⁰ C	30 ⁰ C	40 ⁰ C	25 ⁰ C	30 ⁰ C	40 ⁰ C
Ph	5.7	5.7	5.5	6.6	6.5	6.4
Globule diameter(mm)	4.24	4.22	4.15	4.39	4.36	4.26

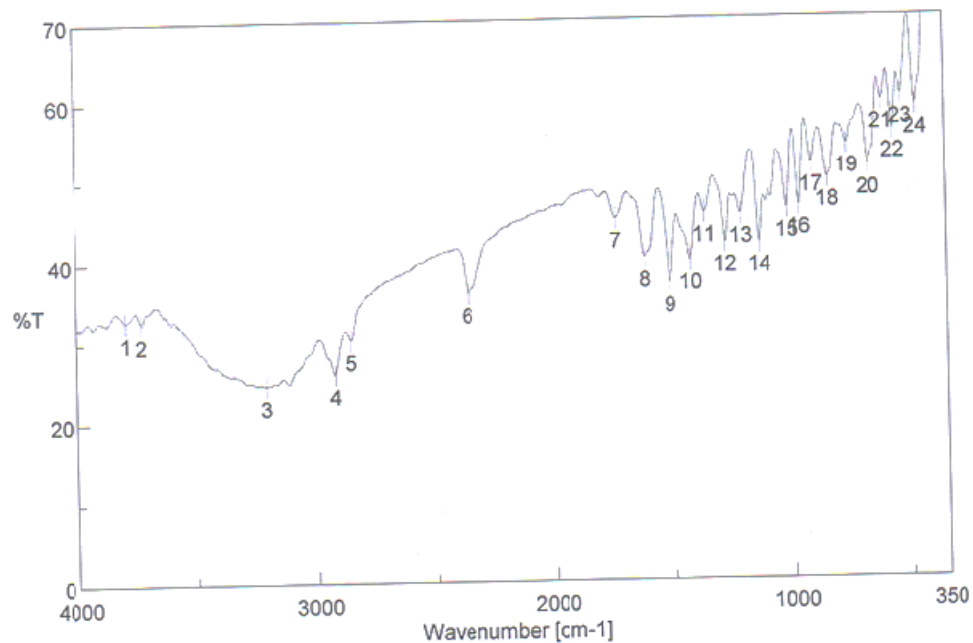
From the data it is clearly evident all the physico chemical characteristics of both the formulation were found satisfactory and there were no significance changes in evaluation parameters. The formulation F1 containing hard paraffin, micro

crystalline wax, cetostearyl alcohol, light liquid paraffin was found to be more satisfactory than formulation F1. From all above results It is concluded that the formulation F1 exhibited stable and good physical properties like viscosity.

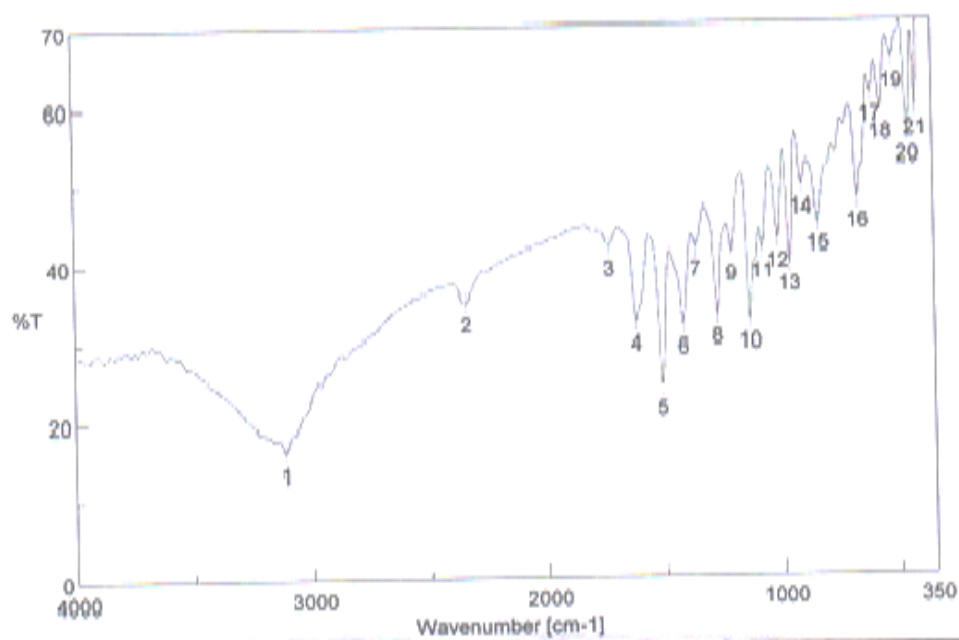
Viscosity of F1 and F2

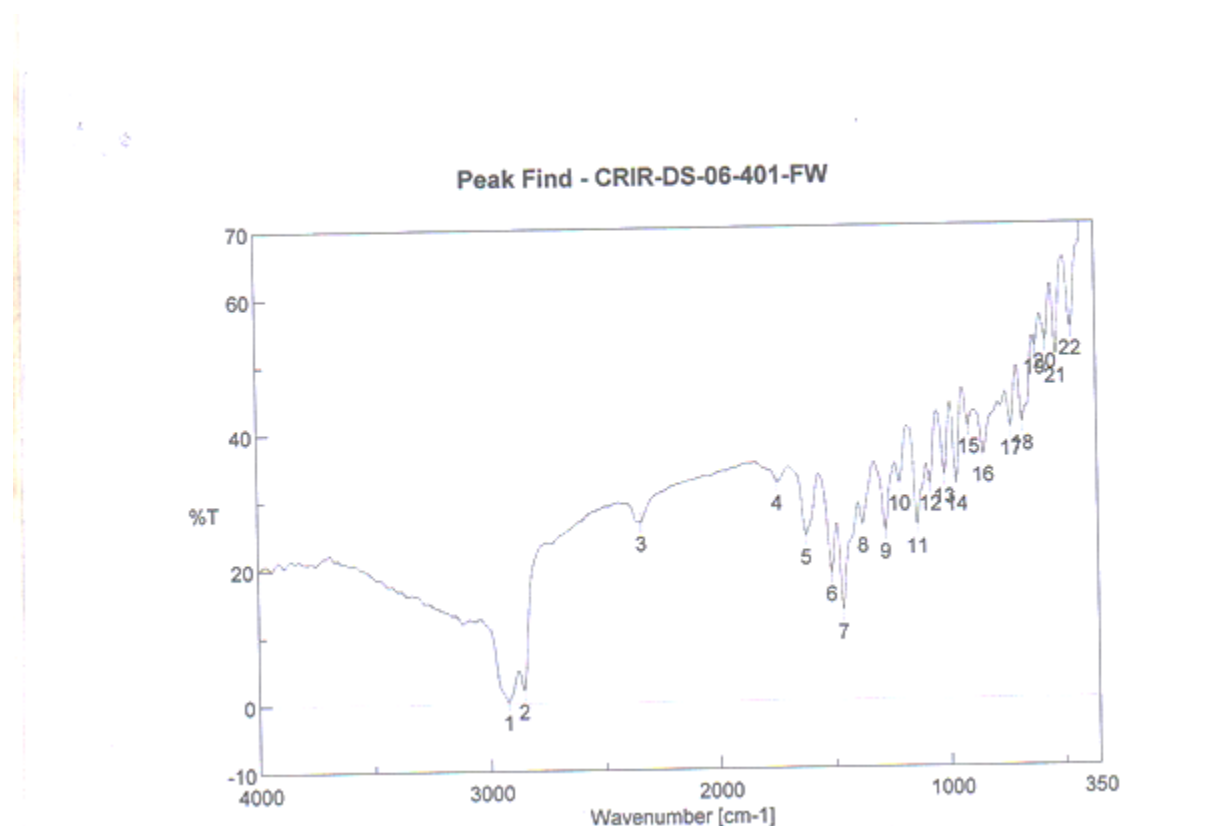
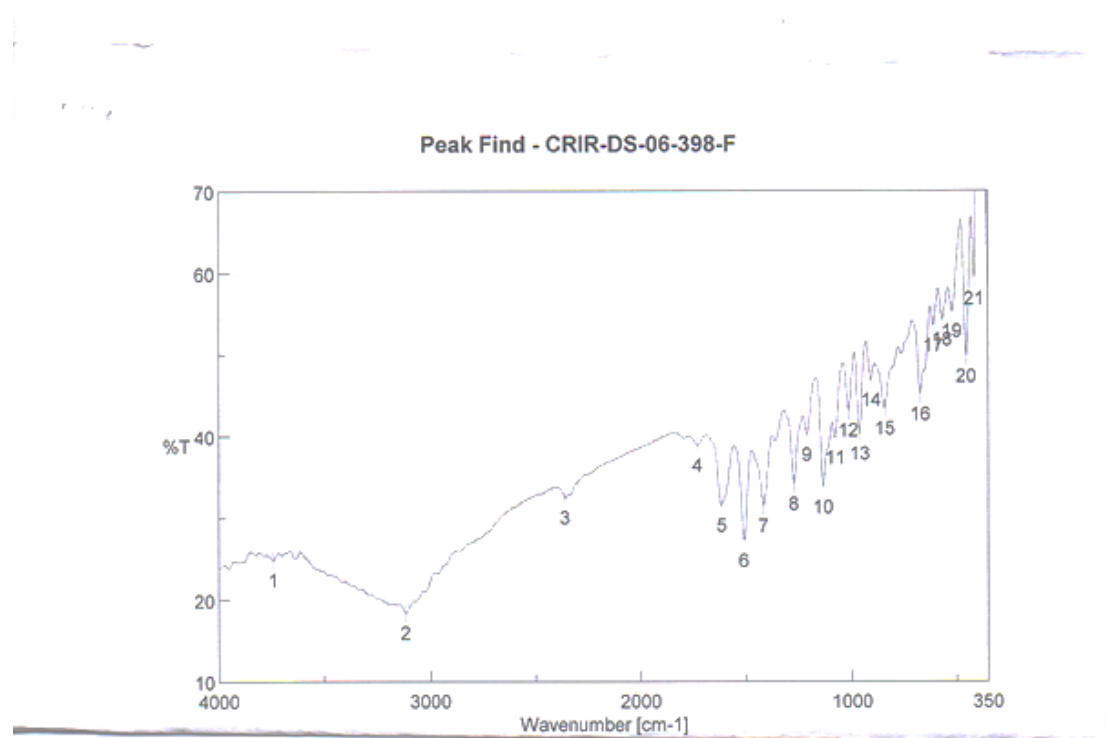


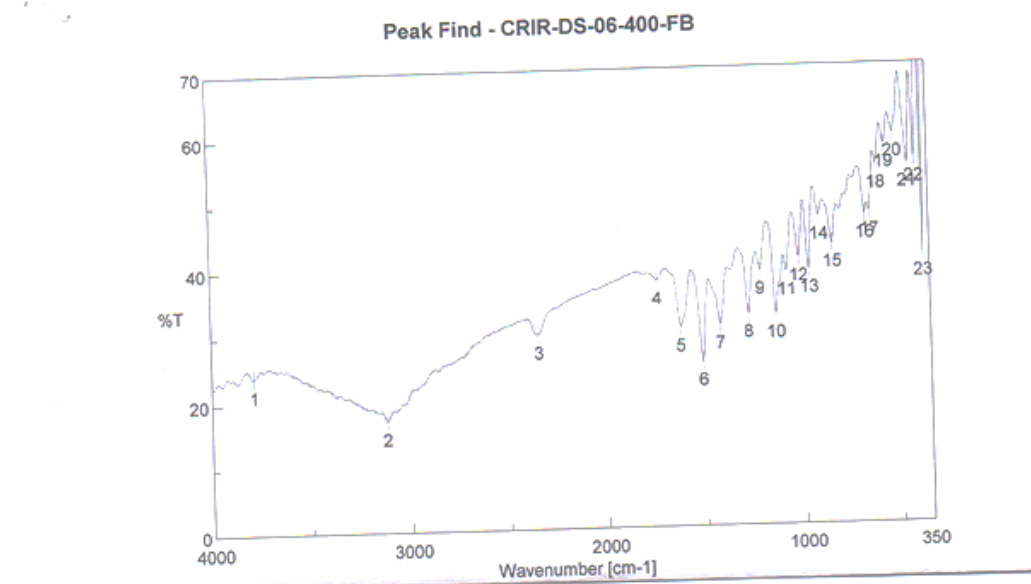
Peak Find - CRIR-DS-06-403-FI



Peak Find - CRIR-DS-06-399-FH







Infrared spectroscopy

From the graph it is shown that there is no more shift in peak when the drug and bases are combined. So the bases are compatible with drug.

CONCLUSION

A combination therapy is the need of hour to treat eczema and pruritis. This can be achieved by fluconazole and ichthammol (an-anti fungal and anti-septic). In this study, ointment was formulated with different bases like white soft paraffin,

cetosearyl alcohol, hard paraffin, light liquid paraffin and micro crystalline wax. From the study, it can be concluded that formulation containing white soft paraffin and cetostearyl alcohol was better than formulation with hard paraffin, cetostearyl alcohol, light liquid paraffin and micro crystalline wax alone. By combining these drugs with appropriate ointment bases (as formulation F1) a better therapy and patient compliance can be attained.

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