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DEVELOPMENT AND CHARACTERIZATION OF CLOTRIMAZOLE EMULGEL FOR TOPICAL DELIVERY

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Emulgel, Clotrimazole, Topical drugs delivery, Gelling agent, Anti fungal

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ABSTRACT

The topical applications of the drug offers the potential advantages of delivering the drug directly to the site of action and delivering the drug for extended period of time at the effected site that mainly acts at the related regions. The major objective behind this investigation was to enhance the topical delivery of hydrophobic drug (Clotrimazole) by formulating Clotrimazole Emulgel using water soluble polymers; carbopol-940 and carbopol-934, Tween-20 and Span-20 as emulsifiers and propylene glycol as plasticizer. The emulgel was prepared in three phases; first being the hydration of polymers to obtain gel followed by preparation of emulsion containing clotrimazole and then incorporation of gel bases into emulsion to formulate emulgel. The prepared Emulgel were evaluated for their physical appearance, pH determination, viscosity, spreadability, extrudability, *in vitro* drug release and stability. The Emulgel prepared by using carbopol 940 showed desired and better physical properties, homogeneity, consistency, spreadability, viscosity and in-vitro drug release.

1.1 INTRODUCTION

Over last decades, the treatment of illness has been accomplished by conventional routes namely oral, topical, parental etc. Topical drug administration is a localized drug delivery system through ophthalmic, rectal, vaginal and skin as topical routes. The main advantage of topical delivery system is to bypass first pass metabolism[1, 2.] Avoidance of the risks and inconveniences of intravenous therapy and overcoming the varied conditions of absorption like pH changes, presence of enzymes, gastric emptying time are other advantages of topical preparations[3, 4]. Dermatological products are diverse in formulation and range in consistency from liquid to powder but the most popular products are semisolid preparation. Among the various semi-solid dosage forms, Emulgels have emerged as novel drug delivery systems thereby expanding horizons for topical drug delivery of hydrophobic drugs. When gels and emulsions are used in combined form the dosage forms are referred as Emulgels. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. Direct (oil-in-water) system is used to entrap lipophilic drugs whereas hydrophilic drugs are encapsulated in the reverse (water-in-oil) system[5]. Emulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate the skinner shelf life, bio-friendly, transparent & pleasing appearance[6]. Emulgels for dermatological use have several favourable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble and pleasing appearance.

Clotrimazole is an antifungal medication commonly used in the treatment of fungal infections (of both humans and other animals) such as vaginal yeast infections, oral thrush and ringworm. The aim of the present investigation is to design a topical drug delivery system for treatment of fungal infection.

2.1 MATERIALS AND METHODS

Clotrimazole was kindly supplied as a gift sample by Anpher Organics Pvt. Ltd (Jammu, India). Carbopol was purchased from Loba Chemicals Pvt. Ltd. (Mumbai, India) and propylene glycol was purchased from S.D Fine Chemicals Ltd. All other chemicals were of analytical grade and were used as received.

3.1 PREPARATION OF EMULGEL

Emulgel preparation was carried out in three steps:

3.1.1. Preparation of Gel Base

The gel bases were prepared by dispersing required quantity of Carbopol 940 and Carbopol 934 in distilled water separately. The mixture was constantly stirred with the help of mechanical stirrer at moderate speed to form uniform mixture. The pH of the mixture was adjusted between 6 and 6.5 using triethanolamine to prepare a transparent, viscous and glossy gel bases. Formulations F1- F4 were prepared by using Carbapol 940 and F5- F8 by using Carbopol 934 as gelling agent in different concentrations [7, 8].

3.1.2 Preparation of emulsion (oil in water emulsion)

The oil phase of the emulsion was prepared by dissolving measured amount of Span 20 in light liquid paraffin. The aqueous phase was prepared by dissolving Tween 20 in distilled water. Methyl and propyl parabens were dissolved in propylene glycol and mixed with the aqueous phase. Clotrimazole and mentha oil were dissolved in oil phase. Permeation enhancer was also added in oil phase. Both the oily and aqueous phases were separately heated so that all the components get properly mixed. Then the oily phase was added to the aqueous phase slowly with continuous stirring to prepare emulsion.

3.1.3 Preparation of Emulgel using 1:1 Ratio of Gel Base and Emulsion

To prepared emulsion was mixed with the gel bases i.e. Carbapol gel bases respectively in 1:1 ratio to form emulgel [9]. The composition of different formulation has been shown in Table 1.

Table 1: Composition of Clotrimazole Emulgel Formulations (%w/w)

Ingredients % (w/w)	Formulation Batches							
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
Clotrimazole	1	1	1	1	1	1	1	1
Carbopol 940	0.5	1	1.5	2.0				
Carbopol 934					0.5	1	1.5	2.0
Tween 20	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Span 20	1	1	1	1	1	1	1	1
Liquid Paraffin	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Propylene Glycol	5	5	5	5	5	5	5	5
Mentha oil	1	1	1	1	1	1	1	1
Propyl Paraben	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Methyl paraben	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

4.1 EVALUATION OF EMULGEL

4.1.1 Physical Examination

The prepared emulgel formulations were inspected visually for their colour, homogeneity, consistency, grittiness and phase separation [10, 11]. The data is shown in Table 2.

Table 2: Physicochemical characteristics of Clotrimazole Emulgel formulations

S. No.	Formulation code	Colour	Phase separation	Grittiness	Homogeneity	Consistency
1	F1	White	None	-	Excellent	+++
2	F2	White	None	-	Excellent	+++
3	F3	White	None	-	Excellent	+++
4	F4	White	None	-	Excellent	+++
5	F5	White	None	-	Excellent	++
6	F6	White	None	-	Excellent	+
7	F7	White	None	-	Fair	++
8	F8	White	None	-	Fair	++

Excellent+++, Good++, Satisfactory+

4.1.2 Measurement of pH

The pH of emulgel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100 ml of distilled water and kept for two hours. The measurement of pH of each formulation was done in triplicate and average values were calculated. The data is reported in Graph 1.

4.1.3 Rheological Study

The viscosity of the formulated batches was determined using a Brookfield Viscometer (RVDV-I Prime, Brookfield Engineering Laboratories,USA) with spindle 7. The formulations whose viscosity was to be determined were added to a beaker and kept for 30 min to maintain them at the assay temperature (25±1ºC) before the measurement. Spindle was lowered perpendicular in to the centre of emulgel taking care that spindle does not touch bottom of the jar and rotated at a speed of 50 rpm for ten minutes. The spindle was moved up and down giving viscosities at number of points along the path [12]. The average of three readings was taken and the data is reported in Graph 2.

4.1.4 Spreadability

Spreadability was determined by apparatus suggested by Mutimer et al (1956) which was suitably modified in the laboratory and used for the study. About 1 gm emulgel under study was

placed on this ground slide. The emulgel was then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. Weight of one g was placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the emulgel between the slides. Measured quantity of weight was placed in the pan attached to the pulley with the help of hook. The time (in sec) required by the top slide to separate from ground slide was noted. A shorter interval indicates better spreadability [13]. The Spreadability was calculated by the following formula and results have been reported in Graph 3.

It is calculated by using the formula = M.L/T

Where, S = spreadability,

M = Weight tied to upper slide,

L = Length of glass slides

T = Time taken to separate the slides completely from each other

4.1.5 Extrudability study

It is a usual empirical test to measure the force required to extrude the material from tube. The method applied for determination of applied shear in the region of the rheogram corresponding to a shear rate exceeding the yield value and exhibiting consequent plug flow. The method adopted for evaluating emulgel formulation for extrudability was based upon the quantity in extruded from lacquered aluminium collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of emulgel in 10 seconds. More the quantity of emulgel extruded, better is the extrudability [14]. The extrudability was then calculated by using the following formula and results have been reported in Graph 4.

Extrudability = Applied weight to extrude emulgel from tube (in gm) / Area (in cm^2)

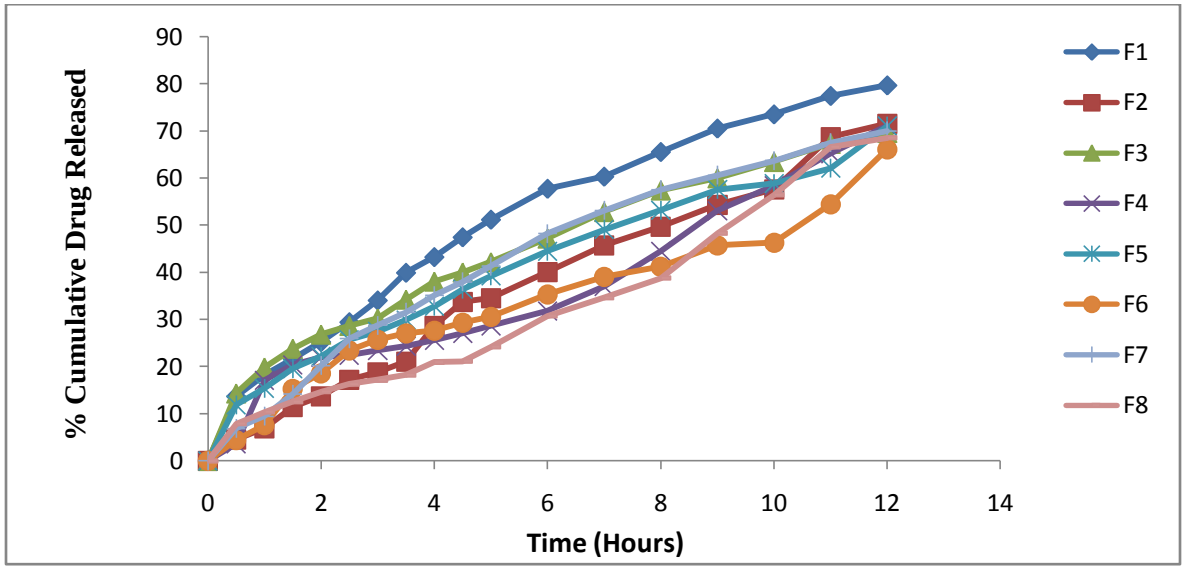
4.1.6 Drug Content Determination

Accurately weighed 1 gm of emulgel was dissolved in 100 ml of methanolic phosphate buffer pH 5.5 in a volumetric flask. It was kept for 2 hours and shaken well to mix it properly. The solution was passed through the filter paper and filtered. The absorbance was measured spectrophotometrically at 261 nm after appropriate dilution against corresponding Buffer concentration as blanks. The drug content was determined using standard plot with the help of following formula. Data is shown in Graph 5.

Drug Content = (Concentration × Dilution Factor × Volume taken) × Conversion Factor

4.1.7 *In Vitro* Release Study:

The *in vitro* drug release studies of the emulgel were carried out in modified Diffusion cell using Dialysis membrane (Himedia laboratories Pvt Ltd: dry, unwashed, open ended; flat width: 28.46mm; inflated diameter: 17.5mm; Length: 1m). The membrane was soaked in Phosphate buffer pH 5.5 for 9-12 h and clamped carefully to one end of the hollow glass tube of dialysis cell (2.3 cm diameter; 4-16 cm^2 area). Then emulgel was spread uniformly on the dialysis membrane. Fifty ml of phosphate buffer was taken in a beaker, which was used as receptor compartment. The donor compartment was kept in contact with receptor compartment. This whole assembly was kept on a magnetic stirrer and the solution on the receptor side was stirred continuously using a magnetic bead and temperature of the cell was maintained at 37^0C. Sample of 5 ml was withdrawn at suitable time interval and replaced with equal amounts of fresh dissolution media. Samples were analyzed spectrophotometrically at 261 nm and the cumulative % drug release was calculated [15]. The difference between the readings of drug release and control was used as the actual reading in each case [16]. The cumulative % drug release profile of all the formulation batches has been shown in Graph 6.

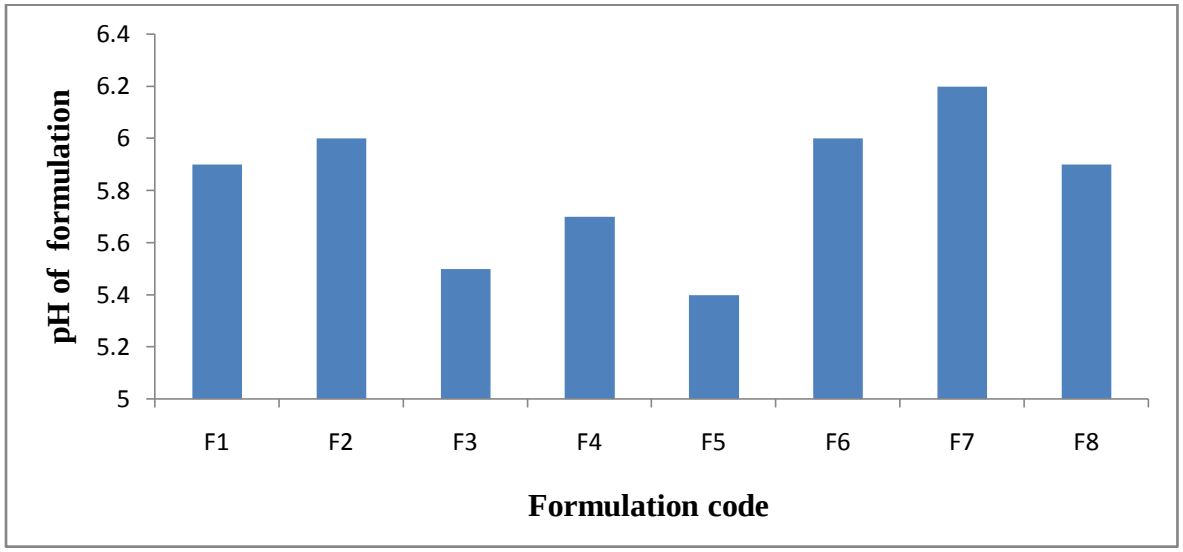


Graph 6: *In Vitro* Cumulative % Drug Release profile of Formulation F1-F8

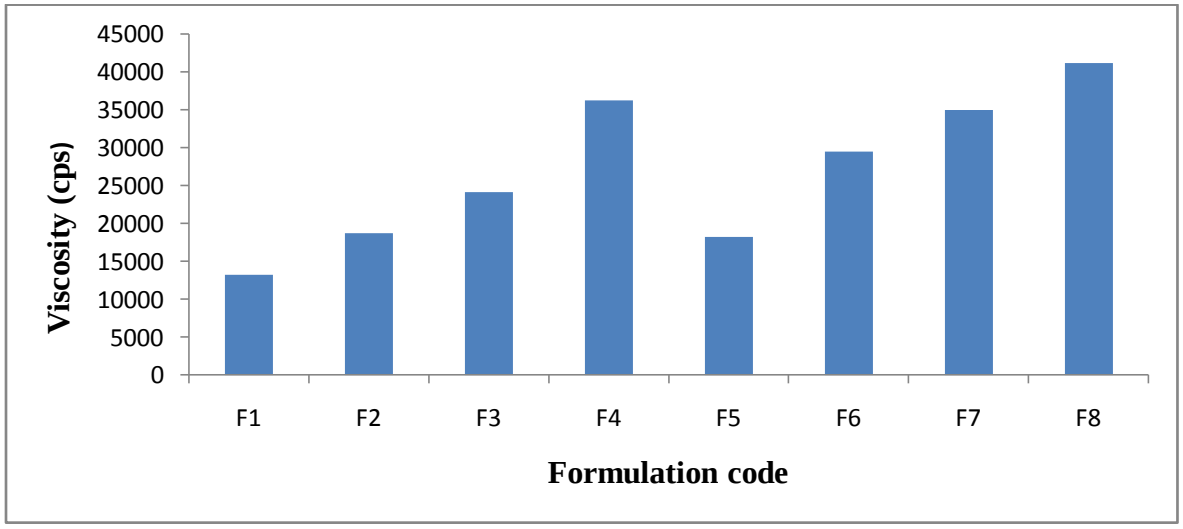
4.1.8 STABILITY STUDY

Stability study was performed on F2 formulations. The preparations were packed in collapsible aluminum tubes (5 g) and subjected to stability study at 25°C and for a period of 2 months.

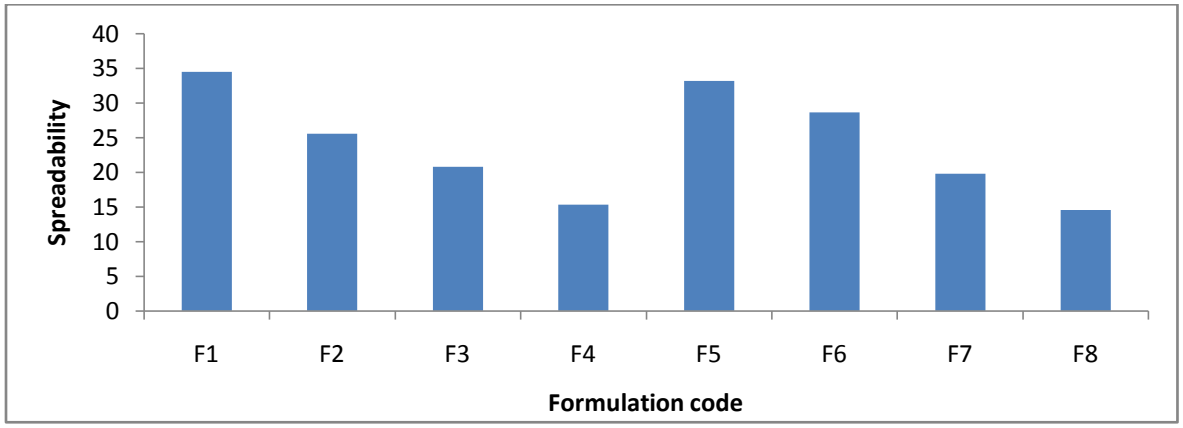
Samples were withdrawn at interval of 15 days and were evaluated for physical appearance, rheological properties and drug content [17]. The drug content is shown in Graph 7.



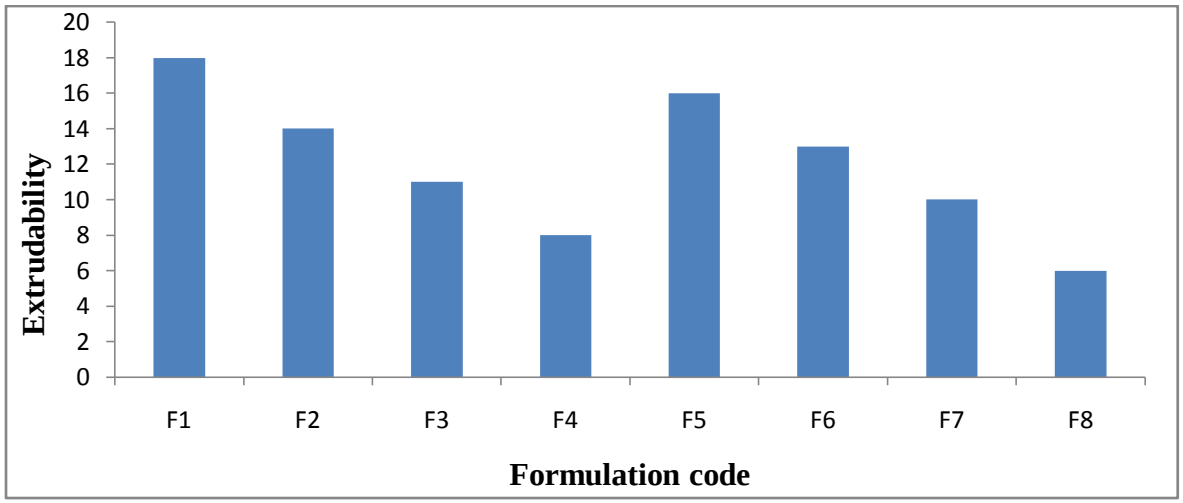
Graph 1: pH of Different Emulgel Formulations F1- F8



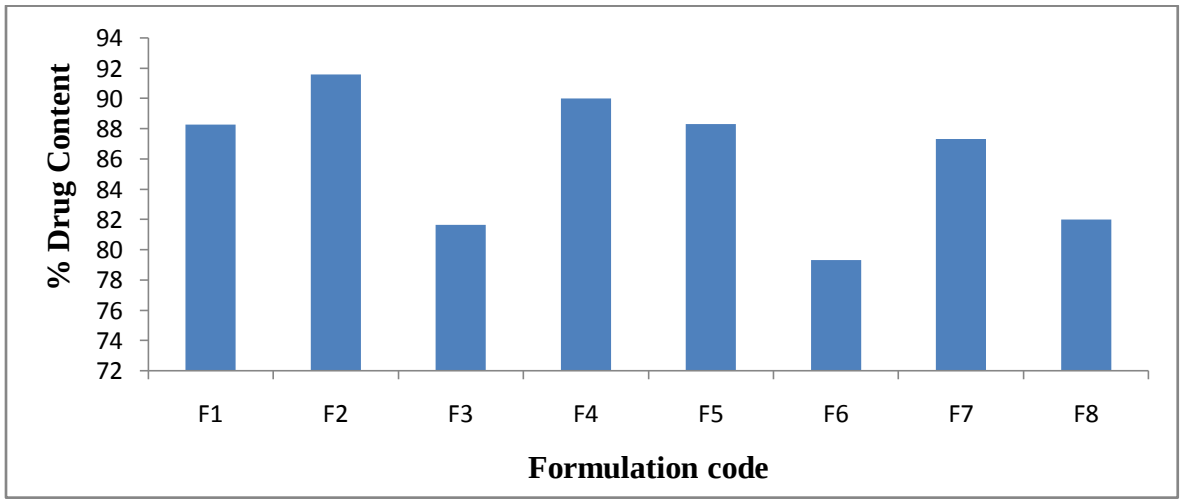
Graph 2: Viscosity of Different Emulgel Formulations F1 – F8



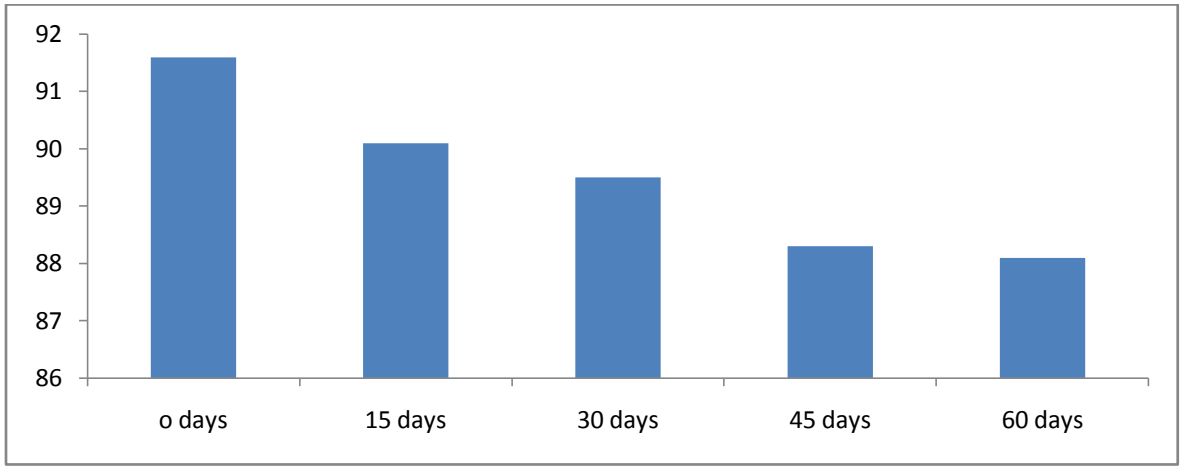
Graph 3: Spreadability of Different Formulations F1-F8



Graph 4 Extrudability of different formulations F1-F8



Graph 5: Drug Content of Formulations F1 – F8



Graph 6: Stability Study data for formulation F2

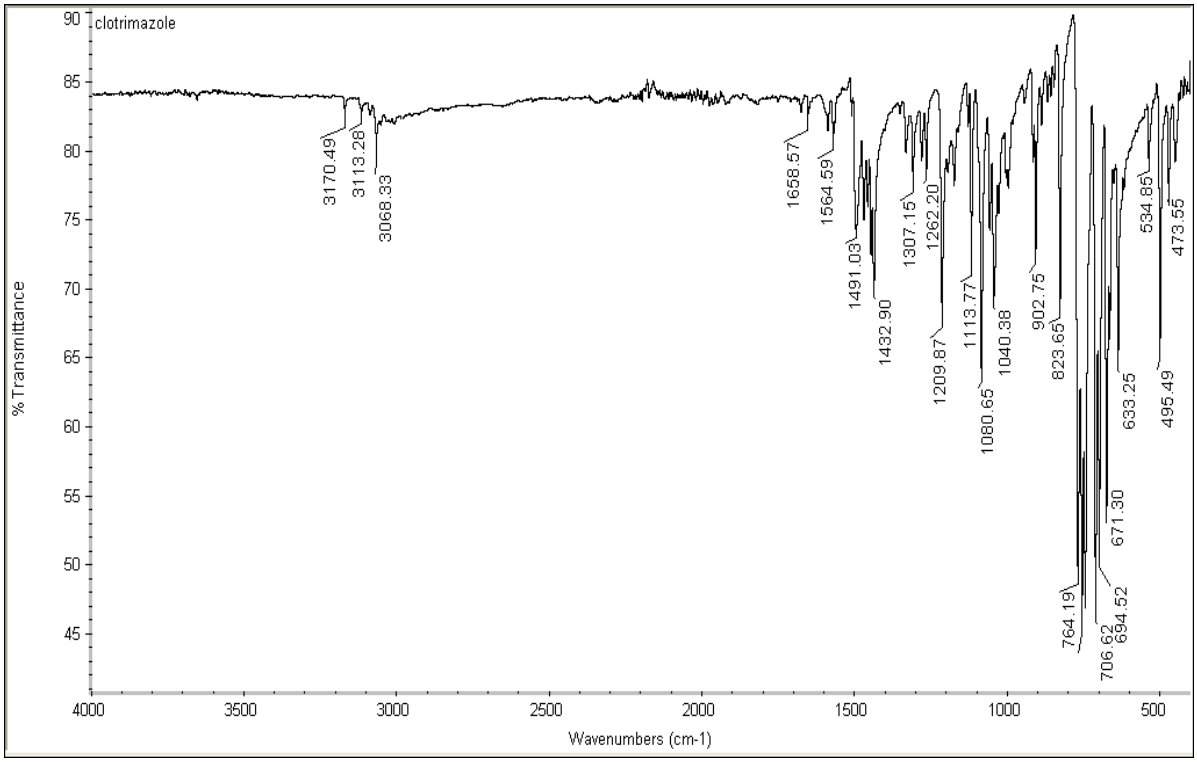


Fig 1: FTIR spectra of Clotrimazole

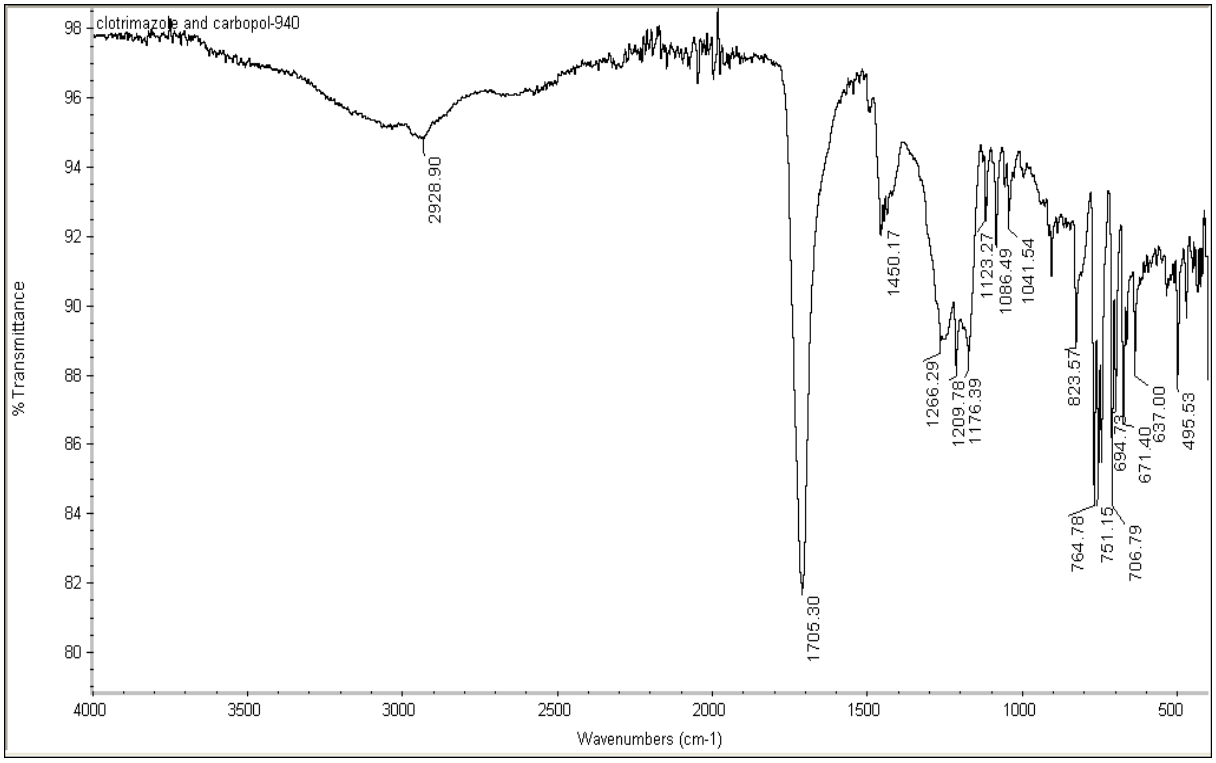


Fig 2: FTIR spectra of mixture of clotrimazole and carbopol-940

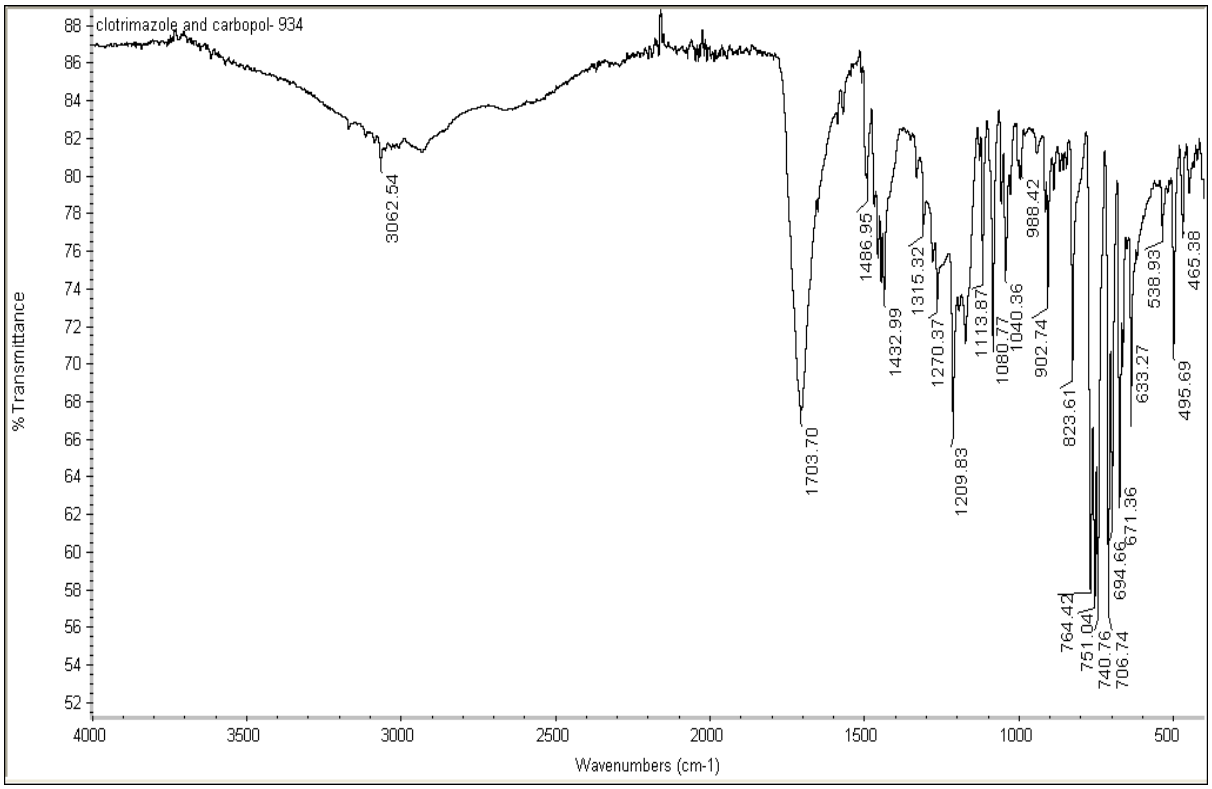


Fig 3: FTIR spectra of mixture of clotrimazole and carbopol-934

5.1 RESULTS AND DISCUSSION

5.1.1 Preformulation

Before preparing formulation the drug and excipient compatibility study was to perform for check out the standard properties of drug by using FT-IR spectrophotometer (Perkin-Elmer, USA). Accurately weighed 10 mg each of Clotrimazole, carbapol-934 and carbopol-940. The mixtures of equal quantities Clotrimazole and carbapol 934, clotrimazole and carbopol 940 were placed separately on the sampling plate of FT-IR spectrophotometer. Then scanning of the samples was performed and IR spectra were obtained as shown in figure 1, 2 and 3 respectively.

5.1.2 Physical Examination

The prepared Clotrimazole emulgel formulations were inspected visually for colour, homogeneity, phase separation, consistency and pH. All formulations showed white colour; formulations prepared using carbopol 940 as gelling agent showed glossy appearance. No phase separation was noticed, formulations showed suitable homogeneity and consistency.

5.1.3 Measurement of pH

The pH of the formulation was in the range of 5.4 - 6.2 which was similar to pH of the skin. Results are shown in Graph 1.

5.1.4 Rheological Study

The viscosity of emulgel was found to increase with increase in the concentration of the polymer used. According to the results viscosity differs in accordance to the concentration of the gelling agent used in preparations. From formulation, F2 with 1% Carbopol-940 showed desired viscosity than those with Carbopol-934 as shown in Graph 2.

5.1.5 Spreadability

As per results of spreadability studies, the spreading area was found to decrease with increase in viscosity, since spreadability and viscosity are inversely proportional. The emulgels were found to show excellent spreadabilty, From results it was concluded that formulation F2 with 1 % Carbopol-940 showed desired spreadability and was selected as best formulation among all. The results are shown in the Graph 3.

5.1.6 Extrudability

As per results of Extrudability study, Extrudability decreased with increase in the concentration of polymer i.e. carbopol-940 and carbopol-934. The formulation F2 with 1% Carbopol-940

showed desired extrudability as compared to Carbopol-934 and was selected as the best formulation. The results are shown in the Graph 4.

5.1.7 Drug Content

The drug content was determined for all the formulations by UV spectrophotometer method. The result of the drug content varied between 84.6 % and 91.6 % as shown in Graph 5. The results indicated that the drug dispensed uniformly throughout the Emulgel. Formulation F2 containing 1% Carbopol-940 showed maximum drug content of 91.6 %.

5.1.8 *In-vitro* Drug Release Studies

The results of in-vitro drug release from the different formulation are shown in Table 1.3. The cumulative amount of drug release range varied between 76.69 % to 66.13 % in 12 hours respectively and this study clearly indicated that as the concentration of polymer increases the amount of drug released decreases. The result proved that formulation F2 with 1% carbopol-940 showed 71.53 drug releases were found to be best formulations among all. Drug release is shown in Graph 6.

5.1.9 Stability Study

Stability studies of all the formulation were performed at 25^0C for a period of two month formulations were evaluated for drug content. The test result of the study is presented in graph 7. The physical stability of the emulgel proved to be unchanged after storage up to 2 month at specified condition.

6. SUMMARY AND CONCLUSION

Emulgel have emerged as a promising drug delivery system for the delivery of hydrophobic drugs. They have several favourable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non staining, long shelf life bio-friendly, transparent and pleasing appearance. The objective of the study was to prepare emulgel of Clotrimazole, using Carbopol-940 and Carbopol-934 as a gelling agent. Clotrimazole, being highly hydrophobic in nature was found to be suitable candidate for its incorporation into emulgel. Preformulation study of Clotrimazole was carried out by all the parameters for Organoleptic characteristics, Melting point determination, Ultraviolet absorption maxima, partition coefficient, solubility study. The drug excipient interaction analysis revealed that there are no chemical interaction between the drug and the polymer. The emulsion was prepared and it was incorporated into gel base. Formulations were prepared using different gelling agents in varied concentration. The

formulations were evaluated for pH determination, rheological studies, spreading coefficient studies, extrudability studies, in vitro release and stability studies. The stability study of formulation (F2) at 25^0C showed no significant change in drug content and rheological properties. On the basis of all the characteristics evaluation parameter of emulgel, formulation F2 containing 1% carbopol-940 was selected as best formulation. Thus, designing of emulgel as topical drug delivery would enhance the incorporation of hydrophobic drugs into gel.

7. ACKNOWLEDGMENT

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