SJIF Impact Factor: 5.464

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 5.
Issue: 6.
Page N. 118-133
Year: 2021

Research Article www.wjahr.com

FORMULATION AND EVALUATION OF TERBINAFINE HYDROCHLORIDE EMULGEL FOR TOPICAL DRUG DELIVERY

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Received date: 10 September 2021 **Revised date:** 30 September 2021 **Accepted date:** 20 October 2021

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ABSTRACT

Terbinafine is a broad spectrum antifungal drug. Terbinafine hydrochloride is an orally and topically active drug belonging to allylamine class of antifungal effective against dermatophytes and candida group of fungi. The aim of research work is the formulation and evaluation of Terbinafine Hydrochloride emulgel for topical drug delivery using different concentration of excipients to avoid hepatic first pass metabolism, improve stability of emulsion, reduce dosage regimen and enhance residence time in the treatment of fungal infecton. The compatibility of drug with excipients was studied by FTIR spectroscopy. Formulations were prepared composed of carbopol 934 as gelling agent, liquid paraffin used as vehicle (oils), surfactants (span 20,tween 20) ,emulsifier or co- surfactant(propylene glycol), preservatives(methyl paraben, propyl paraben),solvent(ethanol),triethanolamine. All the different formulations were prepared by varying concentration of (polymer,emulsifier,surfactants and co surfactants).Polymer can function as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulations of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase. In fact the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. The effect of concentration of the oil phase and emulsifying agent on the drug release was investigated using a 2^2 factorial design. The Terbinafine HCl emulgel formulation with the oil phase concentration 8%w/v and emulsifying agent concentration 3.5% w/w was the formula suggested as an optimized formulation by design expert software. All the prepared emulgels showed satisfactory physicochemical properties like colour, homogeneity,consistency, spreadability and pH value. The pH of prepared emulgel was found in the range of **5.4±0.66 to 6.3±0.9,** drug content of all the prepared emulgel was found in the range of **87.34±1.5% to 94.72 ± 0.3%.** In-vitro release results revealed that **91.51% to 97.31%** of drug released from the formulations in 6 hrs.study. By observing the values of n it was confirmed that the Non Fickian diffusion is dominant in all formulations from F1 to F4.

INTRODUCTION

Topical drug administration is considered as simplest and easiest route of localized drug delivery anywhere in the body by different routes. These are wide spectrum of preparations in case of cosmetic as well as dermatological, to the healthy or diseased skin.[1] Gels and emulsions when used in combined form the dosage forms are referred as emulgels. Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly to treat cutaneous formulation disorder. Dermatological products applied to skin are diverse in formulation & range in consistency from liquid to powder but the most popular products are semisolid preparations includes ointments, creams, pastes, gels. Topical gel formulations provide a suitable delivery system for drugs because they are less greasy and can be easily removed from the skin. Percutaneous absorption of drugs from topical formulation involves the release of the drug from the formulation and permeation through skin to reach the target tissue. The release of the drug from topical preparations depends on the physicochemical properties of the vehicle and the drug employed. The delivery through skin is known as topical drug delivery system.[2] Skin being the most readily accessible part of human body, the molecules on surface application easily penetrate the skin via three routes: through intact stratum corneum (it presents about more than 99% of total skin area for percutaneous drug absorption), through sweat ducts, and through sebaceous follicles.[3] Topical drug delivery system there are two basic types of topical drug delivery products, externally used topicals and internally used topical. The externally

used topicals are spread, sprayed or otherwise dispersed on the tissue to shield diseased area, while the internally used topicals are applied to mucous membrane orally, vaginally or on the rectal tissues for local activity.

1.2 Classification of Topical Drug Delivery System

1. **Solid:** Powders, Plasters Ointments,
2. **Semi solid:** Creams, Poultices, Gels, Pastes
3. **Liquid:** Liniment, Lotions, solution, tinctures, Emulsions, Suspensions, Paints
4. **Miscellaneous:** Transdermal drug delivery systems, Tapes and Gauzes, Rubbing alcohols, Liquid cleanser and Topical aerosol.

1.3 Factors Affecting Topical Absorption of Drugs

1. Physiochemical factors

1. Molecular weight (<400 dalton)
2. Diffusion coefficient
3. Water/lipid partition coefficient
4. Permeability coefficient
5. Ionization- unionized drug are well absorbed
6. Protein binding capacity.

2. Physiological factors

1. Skin thickness
2. Lipid content
3. Density of hair follicles
4. Density of sweat glands
5. Skin pH
6. Blood flow
7. Hydration of skin
8. Inflammation of skin

3. Vehicle

1. Solubility/polarity
2. Volatility
3. Concentration
4. Distribution in a stratum corneum
5. Excipients
6. 12.Penetration enhancer
7. PH

4. Site of application

1. Skin area dose (film thickness, concentration)
2. Total skin area in contact with vehicle
3. Duration of exposure

1.4 Emulgel: Emulgel is evolving field for the topical drug delivery, and up to the date it has less marketed product, so it is thought-provoking and challenging to focus on emulgel formulation. Before starting the concept of emulgel we need to know the concept of emulsion and gel that is being used for the topical drug delivery. Emulsions are well-ordered drug release system containing two immiscible phase in which one is dispersed (internal phase) into other (external phase), with the use of emulsifying agent to make system stable. Emulsions are of oil-in-water or water-in-oil type, in which the drug particle entrapped in internal phase passes through the external phase and then slowly gets absorbed into the skin to deliver controlled effect. USP defines gel is a semisolid system comprises dispersions of either small inorganic particles or large organic molecules enfolding and interpenetrated by liquid. The gel contains the larger amount of aqueous or hydro alcoholic liquid entrapped in a network of colloidal solid particles where it entangled small drug particles and maintain the controlled release of drug. The liquid phase form a three-dimensional polymeric matrix like structure which results a physical or chemical cross-linking network. The continuous structure which behaves like solid that are homogenous and clear. The emulsion and gel both are liable for the controlled drug release from the systems [4-6]. There are two types of gels first the organic solvent based also known as hydrophobic or organogels and second the water based also known as hydrophilic or hydrogels. First one consist of liquid paraffin with polyethylene or fatty oils gelled with colloidal silica, aluminium or zinc soaps along with base and the second one consist of base of water, glycerol, or propylene glycol.[7-8] Gels having many advantages has still restrictions in the delivery of hydrophobic drugs so to overcome this and enjoy the delivery in the form of gel for the hydrophobic drug, the theory for emulgel was introduced where the hydrophobic drugs are merged in emulsion and then to gel[9]. Emulgel is the approach using the aids of both emulsion and gels, gaining the twofold controlled release effect where the emulsion either oil in water or water in oil is gelled by incorporation in the gel base[10], Emulgel are seen better choice for the class II of drug as per the BCS classification systems that show poor solubility and high permeability.[11] Emulgel possess the properties as thixotropic, greaseless, water soluble, easily spreadable, no staining, easily removable, emollient, long shelf life, bio- friendly and attractive appearance that increases the patient acceptability.[12]

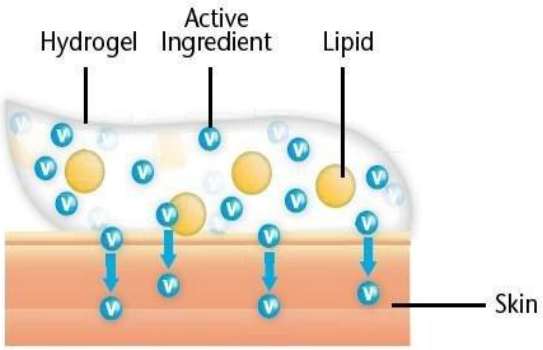


Figure 1.4: Structure of emulgel.

1.5 Advantages of Emulgel[13,14]

1. Improved patient acceptability.
2. Offer targeted drug delivery.
3. Termination of the therapy at any time.
4. Enhance bioavailability as well as the low doses can be effective in comparison with other conventional semi solid preparation.

5. Became a stable formulation by decreasing surface interfacial tension which leads to increase the viscosity of aqueous phase, more stable as compare to transdermal preparations which are comparatively less stable.
6. Hydrophobic drug can be easily incorporated in emulgel form by using emulsion as the drug barrier which is finally dispersed in to gel.
7. Provide the controlled effect of that helps to prolong the effect of drug with short half life.
8. Easy to formulate and cost effective preparation.
9. Drug loading capacity is better than other novel dosage forms like niosomes and liposomes
10. Skin penetration is enhanced due to both hydrophilic and hydrophobic nature.

1.6 Disadvantages[15-17]

1. Create problem in absorption of macromolecules.
2. Entrapment of air bubble during formulation.
3. Only hydrophobic drugs are the best choice for such delivery systems.

2. MATERIALS AND METHODS

2.1 Materials

Terbinafine Hydrochloride was the gift sample obtained from Med Manor Pvt.Ltd Bhagwanpur, Roorkee. Tween 20, span 20, Triethanolamine were generously gifted by Central Drug House(P) Ltd, Carbopol 934,Liquid paraffin, propylene glycol generously gifted by Central Drug House(P) Ltd, New Delhi., ethanol was generously gifted by Central Drug House(P) Ltd, New Delhi. Methyl and Propyl paraben were obtained from Central Drug House, New Delhi.

2.2 Method

2.2.1 UV Spectroscopy for the determination of absorbance maxima[18-19]

Wave length maximum (λmax) of terbinafine hydrochloride was determine as follows.

a) Preparation of standard stock solution

For the preparation of standard stock solution, 10mg of Terbinafine hydrochloride was weighed and transferred to 100ml volumetric flask. It was dissolved in small amount of ethanol: water (40:60) and then volume was adjusted to up to the mark to make final concentration of 100µg/ml.

b) Selection of analytical wavelength (λmax)

From stock solution withdrawn 0.5 ml and 4.0 ml solution and volume make up to 10ml with ethanol: water (40: 60). The resulting obtained concentration of solution 5µg/ml and 40µg/ml. Absorbance was determined by UV spectrophotometer, the maximum absorbance showed by UV spectrophotometer at λ max in range of 200-400 nm.

2.2.2 Preparation of calibration curve of Terbinafine Hydrochloride

a. Preparation of phosphate buffer pH 7.4 (PBS)

Dissolve 2.3gm of disodium hydrogen phosphate, 0.19gm of potassium dihydrogen phosphate and 8gm of sodium chloride in sufficient water to produce 1000ml.

b. Calibration curve of Terbinafine in Phosphate buffer pH 7.4 solution

A10mg of drug dissolve in 20ml of methanol and 8ml of phosphate buffer in a 100ml volumetric flask and volume was adjusted up to the mark to obtained 1000µg/ml. The solution was filtered through Whattman filter paper No. 41(solution A).

From this solution an aliquot of 1ml was withdrawn and diluted to 10ml with PBS pH7.4 to get concentration of 100 µg/ml(solution B), filtered out all solution by whattman filter no. 41. From these aliquots of 0.2ml, 0.4ml, 0.6ml, 0.8ml and 1ml were pipette out in to a 10ml volumetric flask and diluted to PBS pH 7.4 upto the mark and get the concentration 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml respectively.

Absorbance of this solution was measured at 283 nm using UV spectroscopy against blank 2:8. (Methanol: PBS pH7.4)

2.2.3 Compatibility studies of drug and selected polymer by using FTIR

For the determination of compatibility of Terbinafine Hydrochloride with respect polymer (Carbopol 934). Fourier transform infrared spectrophotometer was used. For the determination of IR spectra for compatibility study of drug and polymer KBr disc method was used.

In KBr disc method, drug sample and respected polymer (1:1) was taken and finely grounded with the help of mortar and pestle made up of agate. Then the drug sample was mixed with 100 mg of potassium bromide powder to obtain a uniform mixture. The mixture is then converted into a transparent disc or pellets in an evacuable die by applying sufficient high pressure by using the device hydraulic press. For the base line correction dried potassium bromide was used. To obtain the spectrum the pellet made up of mixture (drug, polymer and potassium bromide) was scanned between 4000 to 400cm^{-1}.

2.3 Preparation of Terbinafine Hydrochloride emulgel for topical drug delivery

In the formulation of emulgel the adequate quantity of polymer were mixed with water with vigorous stirring and left for 15 min for dissolving the polymer. Then the mixture of aqueous phase was formed by dissolving tween 20 in purified water while oily phase was formed by dissolving span 20 in liquid paraffin. Required quantity of methyl and propyl paraben was dissolved in propylene glycol whereas drug was in ethanol. Both oily and aqueous phase were separately heated at 70-80♂ C

and then cooled at room temperature and mixed together to form emulsion. The obtained emulsion was the mixed with gel in the ratio 1:1 with gentle stirring.

The gel was prepared by dispersing Carbopol 934 in purified water with the help of magnetic stirrer and continues the stirring till the uniform solution was obtained.

This uniform solution was neutralized at pH 6- 6.5 with tri ethanolamine to form gel.

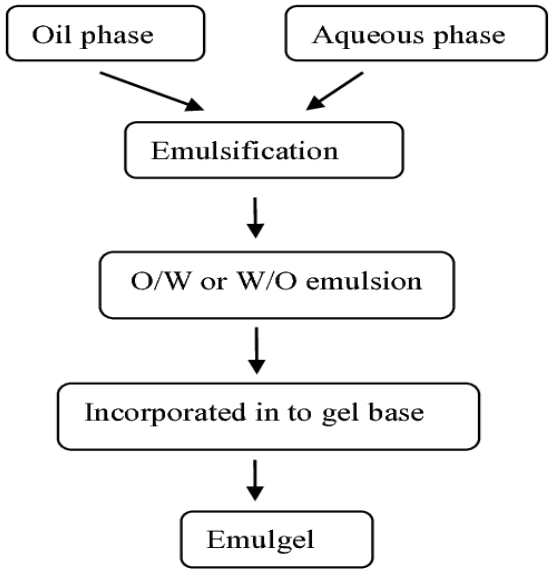
The oil phase of the emulsion was prepared by dissolving Span 20 in liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in purified water.

Methyl and propyl paraben were dissolved in propylene glycol whereas Terbinafine hydrochloride was dissolved in ethanol, and both solutions were mixed with the aqueous phase.

Both the oily and aqueous phases were separately heated to 70 to 80°C then the oily phase was added to the aqueous phase with stirring continue for 15-20 minutes and cooled to room temperature.

The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring at 500rpm until the uniform emulgel was obtained.

2.3.1 Steps involved in the preparation of emulgel



2.3.2 Important Constituents of Emulgel Preparation

1. Aqueous Material[20]

This forms the aqueous phase of the emulsion. Commonly used agents are water, alcohols.

2. Oils[21,22]

These agents form the oily phase if the emulsion. For externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffins, are widely used both as the vehicle for the drug and for their occlusive and sensory characteristics. Widely used oils in oral preparations are nonbiodegradable mineral and castor oils that provide a local laxative effect, and fish liver oils or various fixed oils of vegetable origin (e.g., arachis, cottonseed, and maize oils) as nutritional supplements.

3. Emulsifiers[23,24,25,26,27]

Emulsifying agents are used both to promote emulsification at the time of manufacture and to control stability during a shelf life that can vary from days for extemporaneously prepared emulsions to months or years for commercial preparations.eg Polyethylene glycol 40 stearate, Sorbitan monooleate32 (Span 80), Polyoxyethylene sorbitan monooleate (Tween 80), Stearic acid, Sodium stearate.

4. Gelling Agent[28,29]

These are the agents used to increase the consistency of any dosage form can also be used as thickening agent.

5. Permeation Enhancers[30]

These are agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability.

2.3.3 Quantitative composition of Terbinafine hydrochloride emulgel formulations (%w/w) as per 2^2factorial design

Factorial design Various batches (F1-F4) of Terbinafine hydrochloride emulgel were prepared based on the 22 factorial design in which two independent factor i.e. Concentration of Liquid paraffin(X1), Span20: Tween 20(X2) and two level ie. High (+) & Low (-) which were optimized on the basis of preliminary trial. The concentration 6%(-)& 8%(+) w/w of Liquid paraffin whereas the concentration 2.5%(-) & 3.5%(+) w/w of span20: tween20 were taken as low and high level.

Ingredients	Formulation Code			
	F1	F2	F3	F4
Terbinafine hydrochloride B.P	1.0	1.0	1.0	1.0
Carbopol 934	1.0	1.0	1.0	1.0
Liquid paraffin	6.0	6.0	8.0	8.0
Span 20	2.0	1.5	1.5	2.5
Tween 20	1.5	1.0	1.0	1.0
Propylene glycol	5.0	5.0	5.0	5.0
Ethanol	5.0	5.0	5.0	5.0
Methyl paraben	0.03	0.03	0.03	0.03
Propyl paraben	0.01	0.01	0.01	0.01
Triethanolamine	0.9	0.9	0.9	0.9
Purified water	q.s.	q.s.	q.s.	q.s.

2.4 Evaluation parameters of formulated Topical emulgel

2.4.1. Physical Characterization

The prepared emulgel formulations were inspected visually for their colour, appearance, consistency, phase separation and homogeneity.

2.4.2 pH Measurement[31]

One gram of emulgel was dissolved in 10 ml of distilled water and the pH meter was prior standardized with standard buffers of pH 4 and pH 7. The electrode was then dipped in to emulgel formulation and constant reading was noted.

2.4.3 Measurement of Viscosity[32]

The viscosity of emulgel was determined without any dilution using Brookfield viscometer. The sample (30mL) was taken in a beaker and allowed to equilibrate for 5min before measuring the reading using a spindle at 20 and 30rpm. At each speed, the corresponding reading on the viscometer was noted.

Brookfield Viscometer

2.4.4 Centrifugation Test[33]

This technique of centrifugation helps to determine the phase separation of emulgel. 10ml emulgel was placed in centrifugation tube and put in apparatus at 3000rpm for 30mint and examined for any phase separation.

2.5.5 Spreadability[34]

An excess of emulgel (about 1g) under study was placed on this ground slide. The emulgel preparation was then sandwiched between this slide and second glass slide having same dimension as that of the fixed ground slide. The second glass slide is provided with the hook15. Weight of 100 g was placed on the top of the two slides for 5 min to expel air and to provide a uniform film of the emulgel between the two slides. Measured quantity of weight (35g) was placed in the pan attached to the pulley with the help of hook. Time in seconds taken by two slides to slip off from emulgel and placed in between the slides under the direction of certain load. Lesser the time taken for separation of two slides, better the spreadability. It is calculated by using the formula.

$S = m.l / t$

Where S is spreadability,

m is weight placed on upper slide,

l is length of upper slide, and t is the time taken.

2.4.6 Drug content determination[35]

Quantity of Terbinafine in emulgel was determined by UV-Spectrophotometer. 1.0 g of formulation was accurately weighed, dissolved in 100 ml of methanol: phosphate buffer (2:8). It was filtered and diluted if required. Absorbance was determined using UV spectrophotometer at 283nm.

Drug content = (concentration × dilution factor × volume taken × conversion factor)

2.4.7 In-vitro release study[36]

The In-vitro drug release studies were carried out using a modified Franz diffusion cell (With effective diffusion area 2.54 cm2 and 20 ml cell volume). The formulation was applied on dialysis membrane (which was previously soaked in Phosphate buffer pH 7.4 for 24 hours) which was sandwiched between donor and receptor compartment of the Franz diffusion cell. Phosphate buffer pH 7.4 was used as dissolution media. The temperature of the cell was maintained at 37±0.2°C by kept it in water bath. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead at 50rpm. The samples (1ml aliquots) were withdrawn at suitable time interval and analyzed for drug content by UV visible spectrophotometer at 283.7 nm after appropriate dilutions.

Diffusion cell

2.4.8 In-vitro drug release kinetics[37]

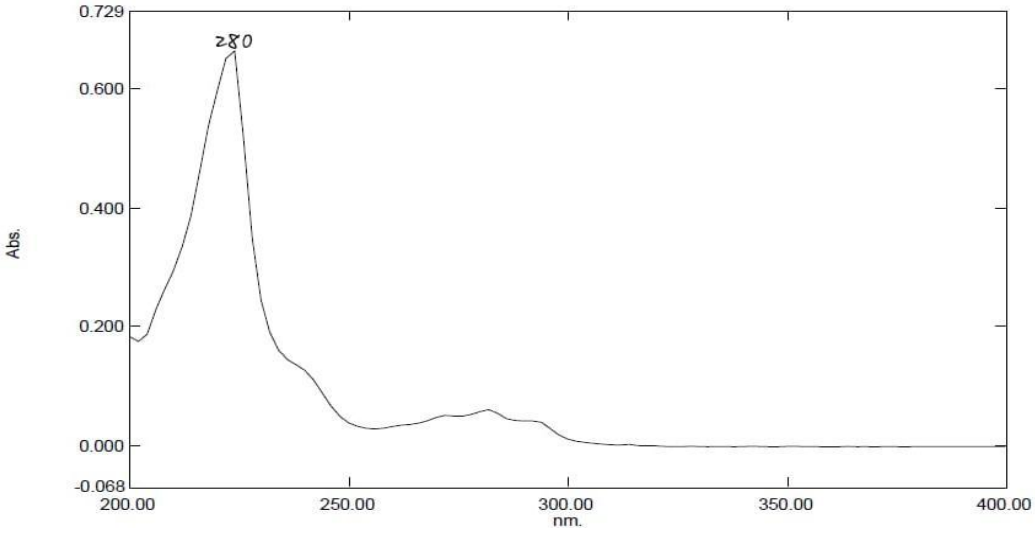
To study the release kinetics of in-vitro drug release, data was applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer-Pappas . In short, the result obtained from in-vitro release studies were plotted in four kinetic models of data treatment as follows:

- Cumulative % drug release Vs. Time (zero order rate kinetics)
- Log cumulative % drug release Vs. Time (First order rate kinetics)
- Cumulative % drug release Vs. Time √T (Higuchi's classical diffusion equation)
- Log cumulative % drug release Vs. log Time (Korsmeyer Peppas equation).

RESULTS AND DISCUSSION

2.2.1 UV Spectroscopy for the determination of absorbance maxima

As per the observed data the absorption maxima test was found to be 280nm in ethanol:water which comply with standard value.(figure no.1).



2.2.2 Preparation of calibration curve of Terbinafine Hydrochloride

Table 1: Standard curve of Terbinafine Hydrochloride in Phosphate Buffer 7.4 (Methanol:PBS).

Sr. No	Concentration(µg/ml)	Absorbance(nm) Phosphate Buffer 7.4(Methanol:PBS,2:8)
1	2	0.203
2	4	0.431
3	6	0.621
4	8	0.824
5	10	0.962

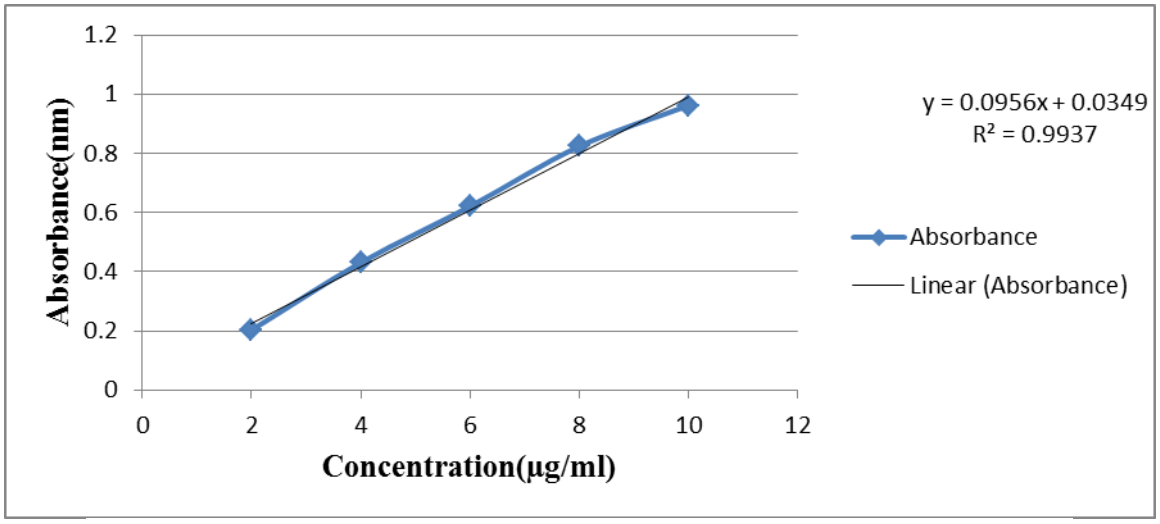


Figure 2: Standard curve of Terbinafine hydrochloride in methanol: phosphate buffer.

Discussion:- Standard curve of Terbinafine Hydrochloride was prepared in different solvents. Graph between absorbance and corresponding concentration were plotted. The obtained r^2 valuewere 0.9995, 0.9937 in corresponding solvent ethanol: water, phosphate buffer pH 7.4.The r^2 value of sample suggest linearity in equation. Thus this equation can be used for further calculation purpose.

2.2.3 Compatibility studies of drug and selected polymer by using FTIR

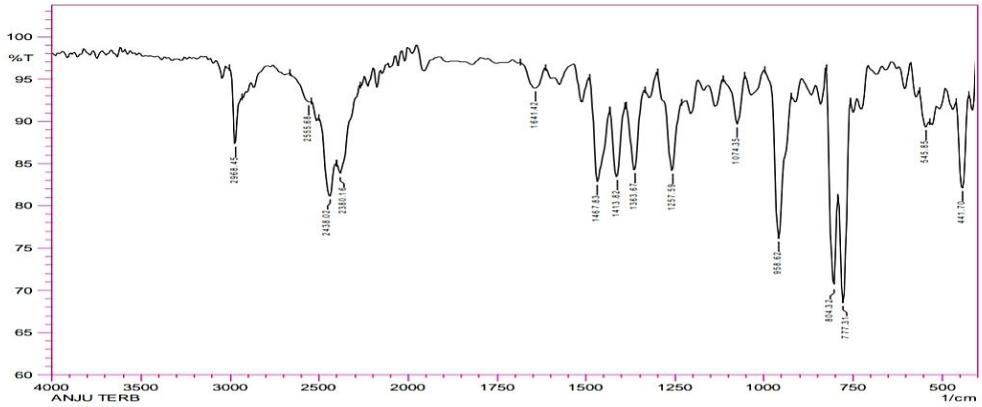


Fig. 3: FT-IR Spectrum of Terbinafine hydrochloride.

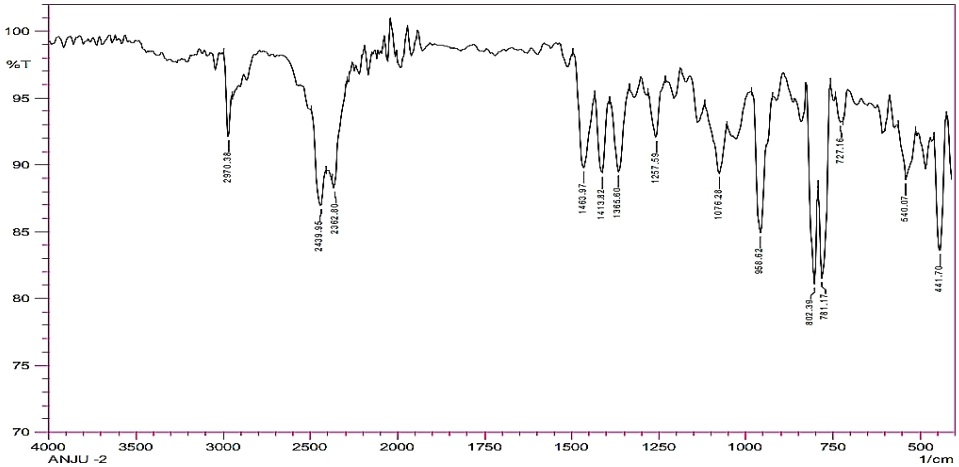


Figure 4: FTIR Spectrum of Terbinafine hydrochloride + carbopol934 + span 20.

Table 2: Different peaks of Terbinafine Hydrochloride.

Functional groups	Range of functional groups(cm^{-1})	Terbinafine hydrochloride observed(wave number cm^{-1})	Terbinafine hydrochloride excipient mixture(wave number)
C-N	1350-1000	1257.59	1076.28
C-H	3000-2800	2968.45	2970.38
Enes	900-650	804.32	802.39
C-F	1400-1000	1363.67	1365.60

Discussion: From the obtained FTIR of terbinafine with excipient functional group detected in table 7.5 was C-N(stretching) at 1076.28 cm^{-1}, C-H (stretching) at 2970.38 cm^{-1}, enes at 802.39 cm^{-1} and C-F (stretching) at 1365.60cm^{-1} whereas the test drug fuctional group observed as C-N at 1257.59 cm^{-1}, C-H at 2968.45 cm^{-1}, enes at 804.32cm^{-1}, C-F at1363.67cm^{-1}.

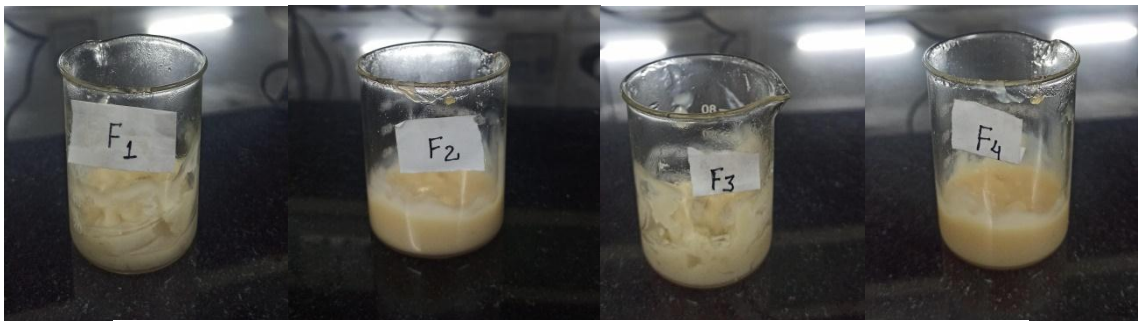
2.4.1. Physical Characterization

Physical evaluation of formulated emulgel was done by physical and visual method. Observed results are shown in Table No. 3.

Table 3: Physical characterization of formulated emulgel of Terbinafine hydrochloride for topical drug delivery.

Formulation Code	Colour	Phase separation	Homogeneity	Consistency
F1	Pale Yellow	None	Good	++
F2	Pale Yellow	None	Average	++
F3	Pale Yellow	None	Good	+++
F4	Pale Yellow	None	Good	++

++ = Good, +++ = Excellent



Formulation 1 **Formulation 2** **Formulation 3** **Formulation 4**

Discussion: As per the visual and physical inspection it was observed that the formulation F1 to F4 were pale yellow in colour with good homogeneity and consistency. There was no phase separation in any formulation.

2.4.2. pH Measurement

The pH value of the formulated emulgel was determined by using digital pH meter. Obtained value were shown in Table No.4

Table 4: pH measurement of prepared formulations.

Sr. No.	Formulation Code	pH
1	F1	6.3±0.9
2	F2	5.6±0.66
3	F3	5.5±0.33
4	F4	5.4±0.66

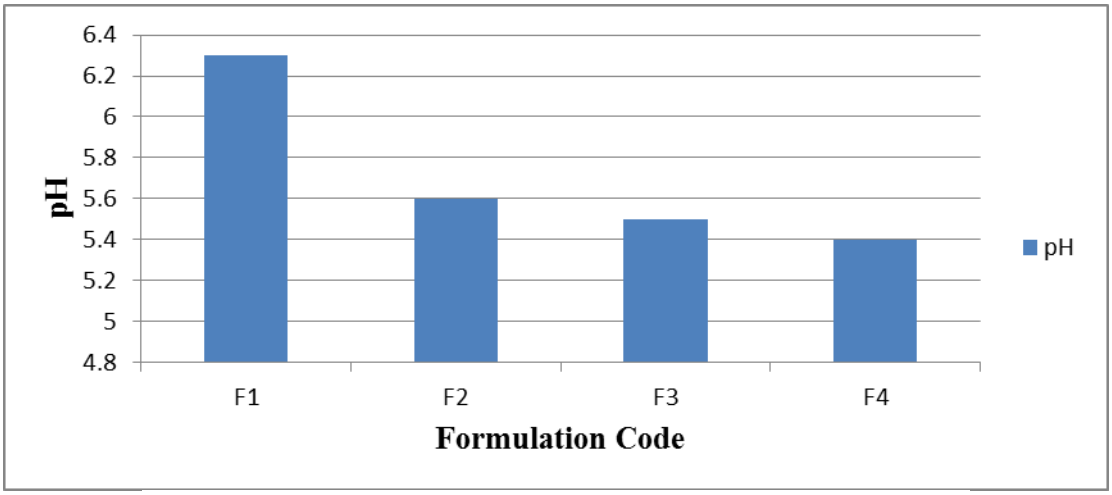


Figure 5: Bar diagram showing pH of prepared formulation from F1-F4.

DISCUSSION

The value of pH of all prepared formulations was observed in between 5.4±0.66 to 6.3±0.9 (Table no.4). As per the obtained value was observed that the pH of all formulations are near to skin pH(5.5) which indicate that there will be not any kind of irritation or side effects on the skin after application of formulated emulgel.

2.4.3. Measurement of Viscosity

Viscosity of the prepared formulations were determined by Brookfield Viscometer. The spindle was rotated at different rpm. Obtained values were shown in table no.5.

Table 5: Measurement of Average viscosity of formulation F1-F4.

Spindle	Formulation Code	Average Viscosity(cps)
64	F1	2082±0.32
	F2	7053±0.33
	F3	2340±0.84
	F4	1860±0.32

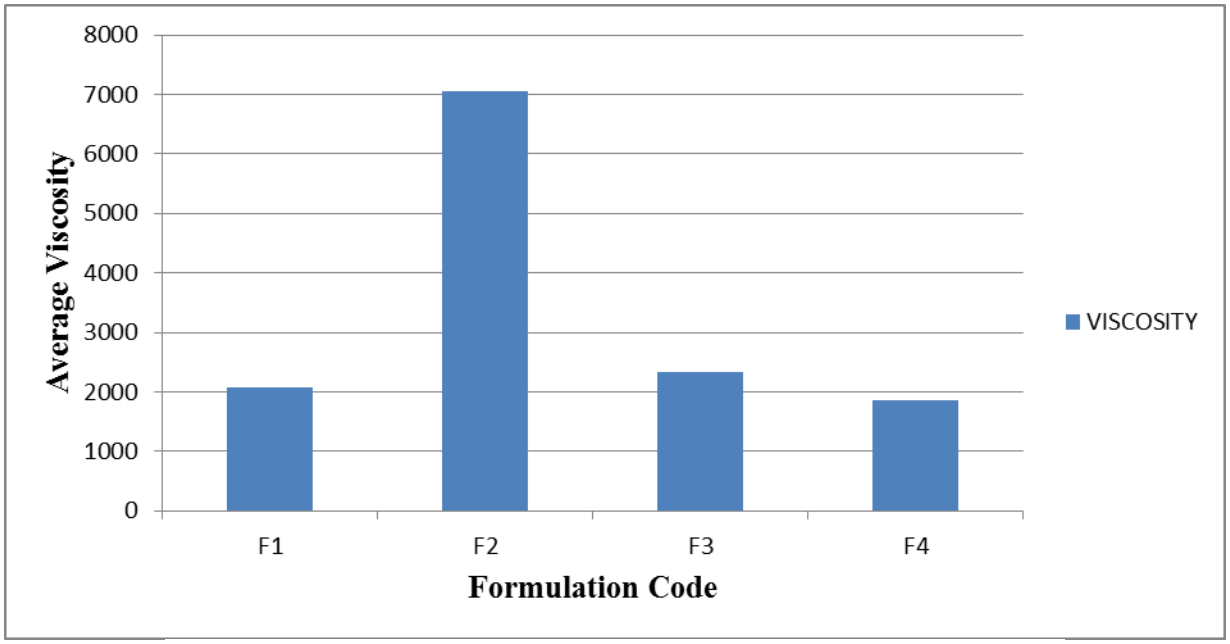


Figure 6: Bar diagram showing viscosity of prepared formulations from F1-F4.

Discussion: From the above results it was concluded that all the formulations follows non Newtonian flow a shear thinning behaviour.

2.4.4. Centrifugation test

Discussion: None of the prepared formulations of emulgel showed phase separation which justified its stability during centrifugation.

2.4.5. Spreadability

Spreadability of the emulgel was calculated and the values which were obtained are as following in table no.7.12.

Table 6: Spreadability of the prepared formulations from F1-F4.

Sr. No.	Formulation Code	Spreadability(g.cm/sec)
1	F1	250±0.12
2	F2	222±0.22
3	F3	285±0.71
4	F4	333±0.34

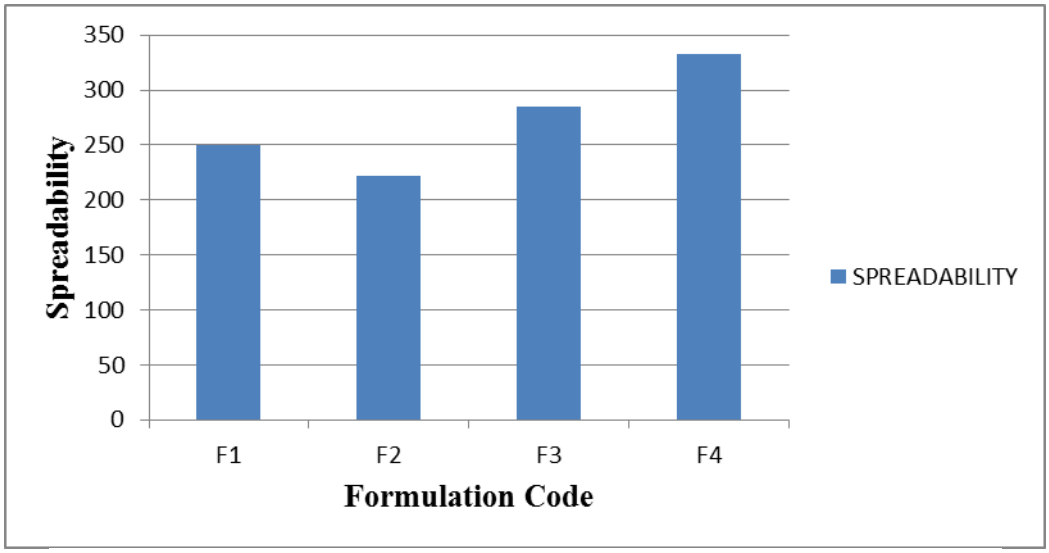


Figure 7: Bar diagram showing spreadability of prepared formulations from F1-F4.

DISCUSSION

The value of spreadability of all prepared formulations was observed in between 222±0.22 to 333±0.34 (Table no.6.) As per the obtained value it was observed that all prepared formulations indicate good spreadability of the formulation and is easily spreaded over the skin and ease the application.

2.4.6 Drug content determination

The drug content value was determined by using UV-spectrophotometer. Obtained value was shown in Table no.7.

Sr. No	Formulation code	Percentage Drug content Mean ±SD (n=3) (%)
1	F1	94.72 ± 0.3
2	F2	91.7±0.9
3	F3	89.65 ± 0.12
4	F4	87.34±1.5

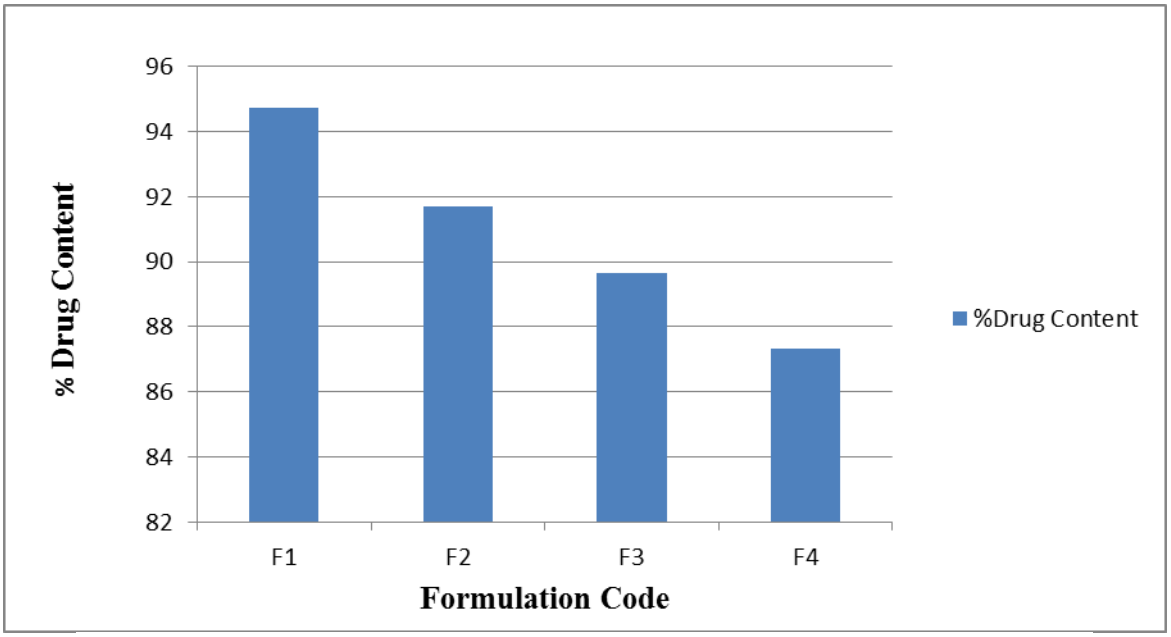


Figure 8: Bar diagram showing % drug content of all prepared formulations from F1-F4.

Discussion: The drug content determination test was performed to ensure uniform distribution of the drug. The content uniformity was performed for all the formulations. The results indicated that in all the formulations that there was good uniformity in drug content which ranged between 87.34±1.5% to 94.72 ± 0.3% (Table No.7.).

2.4.7 In vitro release study

Table 8: Cumulative % Drug Release data of all prepared formulations.

S. No.	Time(min)	% Cumulative Release			
		F1	F2	F3	F4
1	0	0	0	0	0
2	1	23.8	18.58	15.2	17.60
3	2	51.94	45.9	40.78	38.22
4	3	68.45	60.25	60.20	60.1
5	4	81.9	77.55	76.30	75.10
6	5	90.6	87.88	85.1	82.8
7	6	97.31	96.56	93.7	91.51

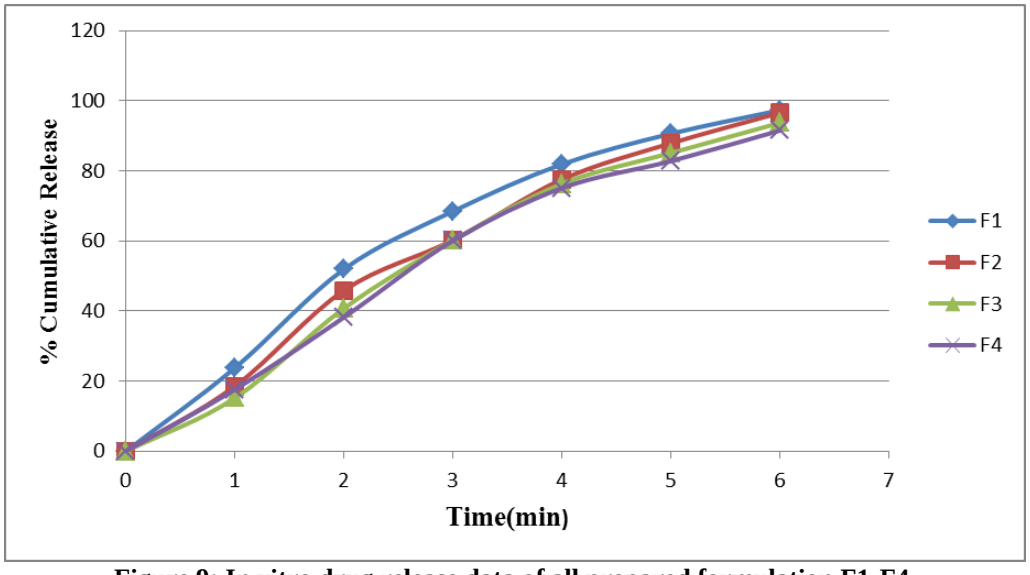


Figure 9: In vitro drug release data of all prepared formulation F1-F4.

Discussion: The cumulative percent drug release from all prepared formulations was ranging between 91.51% to 97.31% (Table No.8.) during the study period. In vitro drug release study of emulgel was performed by using Franz diffusion cells and the release data of the drug was shown in Table No.8.From the observed that the release rate and the % cumulative release are inversely proportional to surfactant ratio.

2.4.8 In Vitro drug release kinetics

Table 9: In-Vitro Drug Release Data of F1.

S. No.	Time(min)	√T	Log t	%CR	Log% CR	%ARA	Log% ARA
1	0	0	0	0	0	0	0
2	1	1	0	23.8	1.376	76.2	1.881
3	2	1.414	0.301	51.94	1.715	47.05	1.672
4	3	1.732	0.477	68.45	1.835	29.53	1.470
5	4	2	0.602	81.9	1.913	16.1	1.206
6	5	2.236	0.698	90.6	1.951	7.41	0.869
7	6	2.449	0.778	97.31	1.988	1.64	0.214

Table 10: In-Vitro Drug Release Data of F2.

S. No.	Time(min)	√T	Log t	%CR	Log% CR	%ARA	Log%ARA
1	0	0	0	0	0	0	0
2	1	1	0	18.58	1.269	79.41	1.899
3	2	1.414	0.301	45.9	1.661	52.10	1.716
4	3	1.732	0.477	60.25	1.779	39.70	1.598
5	4	2	0.602	77.55	1.889	22.44	1.351
6	5	2.236	0.698	87.88	1.943	14.12	1.149
7	6	2.449	0.778	96.56	1.984	1.42	0.152

Table 11: In -Vitro Drug Release Data of F3.

S. No.	Time(min)	√T	Log t	%CR	Log% CR	%ARA	Log% ARA
1	0	0	0	0	0	0	0
2	1	1	0	15.2	1.181	82.7	1.917
3	2	1.414	0.301	40.78	1.610	59.11	1.771
4	3	1.732	0.477	60.20	1.779	39.70	1.598
5	4	2	0.602	76.30	1.882	21.6	1.334
6	5	2.236	0.698	85.1	1.929	16.1	1.206
7	6	2.449	0.778	93.7	1.971	4.1	0.612

Table 12: In-Vitro Drug Release Data of F4.

S. No.	Time(min)	√T	Log t	%CR	Log% CR	%ARA	Log% ARA
1	0	0	0	0	0	0	0
2	1	1	0	17.60	1.245	81.31	4.146
3	2	1.414	0.301	38.22	1.582	59.71	3.997
4	3	1.732	0.477	60.1	1.778	39.8	3.793
5	4	2	0.602	75.10	1.875	22.71	3.493
6	5	2.236	0.698	82.8	1.918	15.2	3.260
7	6	2.449	0.778	91.51	1.961	6.20	2.669

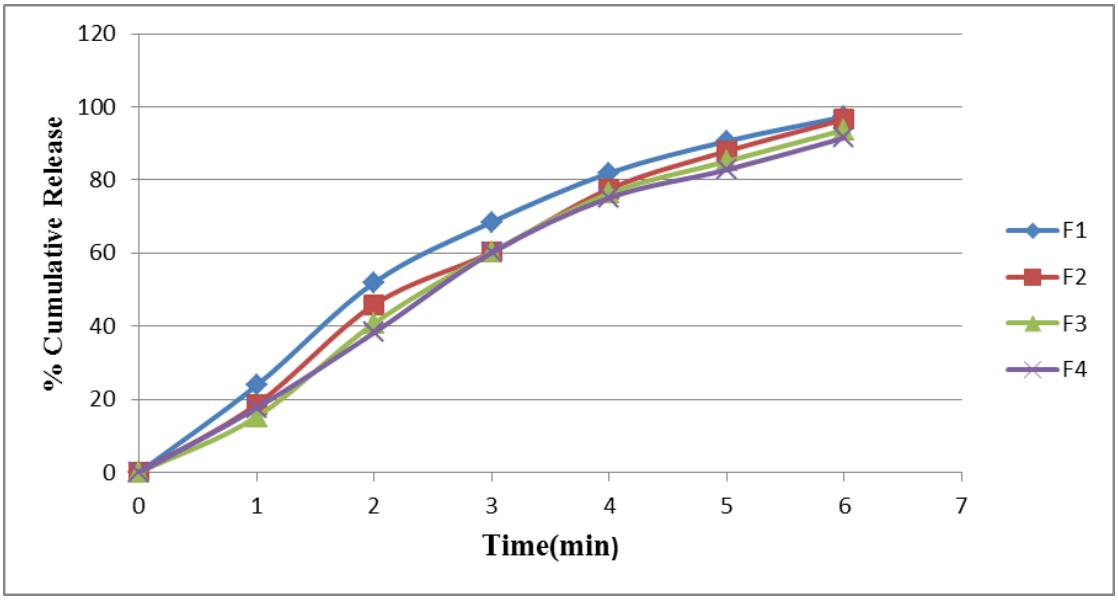


Figure 10: Zero order release kinetics profile of formulation F1 to F4.

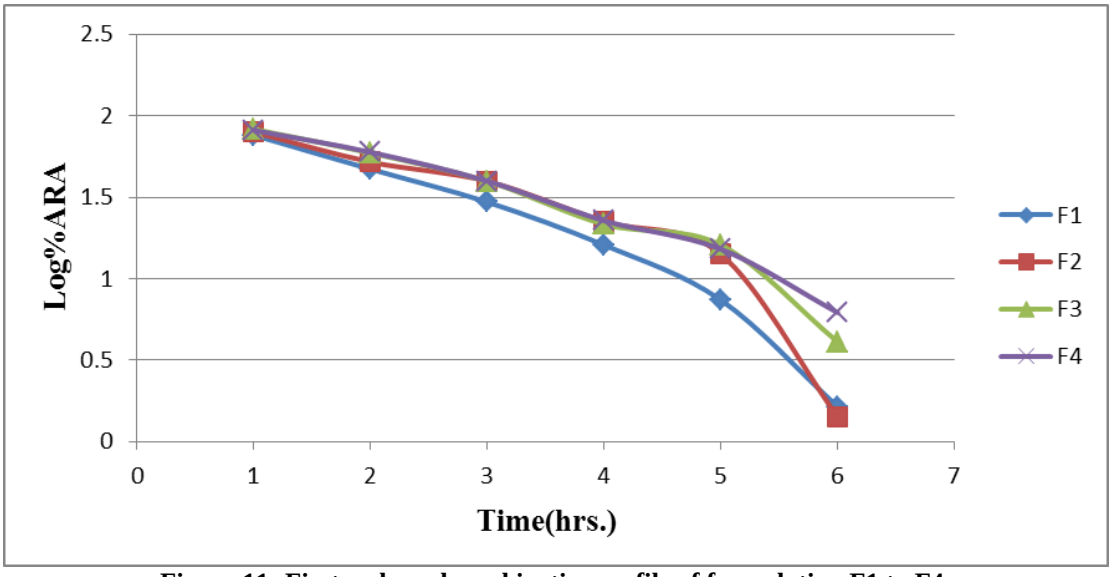


Figure 11: First order release kinetics profile of formulation F1 to F4.

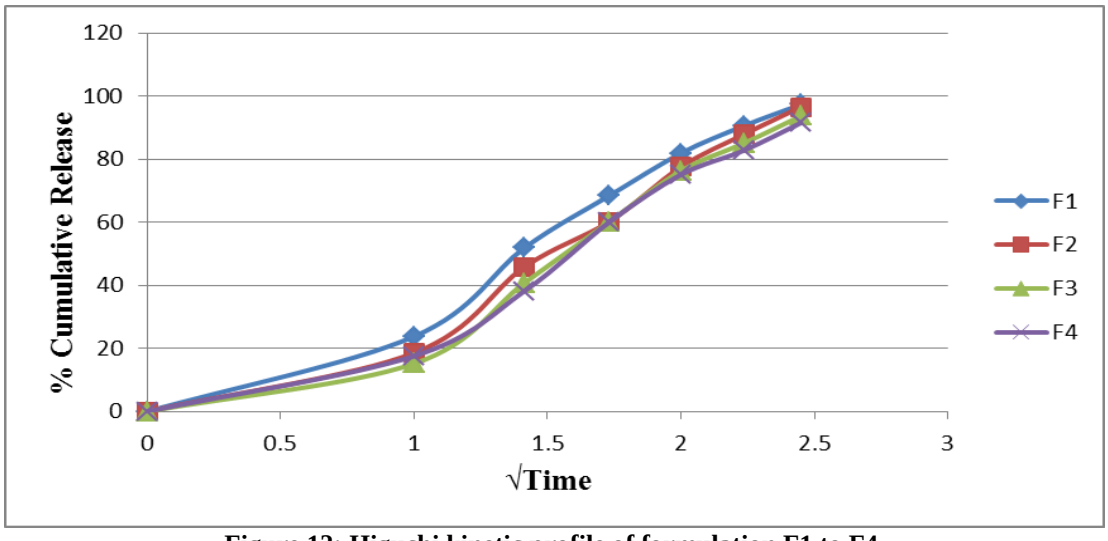


Figure 12: Higuchi kinetic profile of formulation F1 to F4.

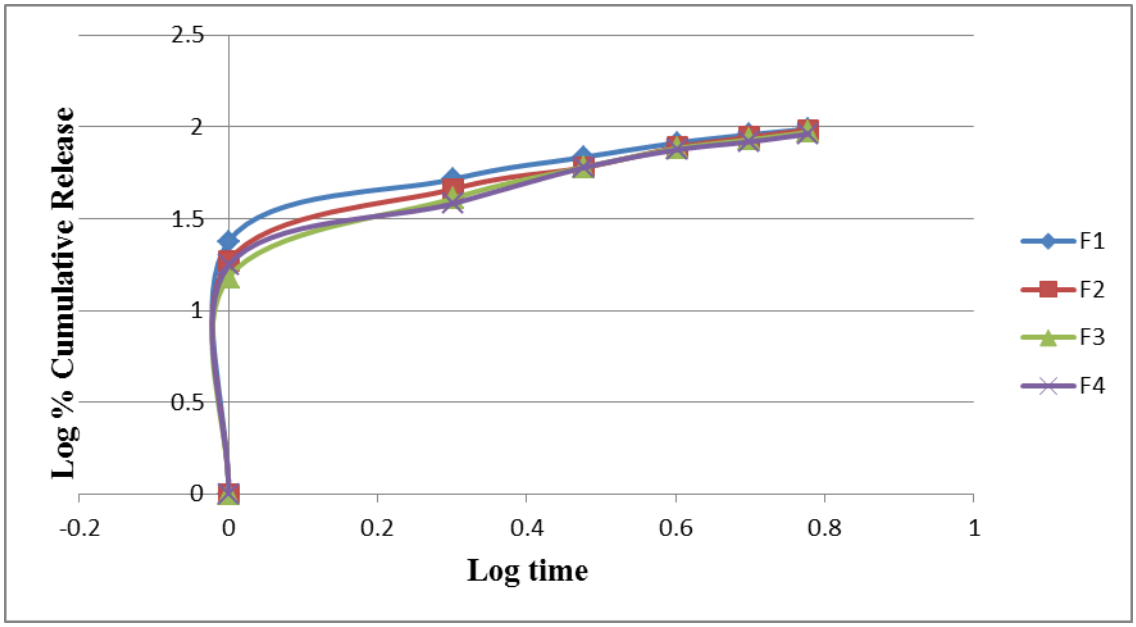


Figure 13: Korsmeyer-peppas release kinetics of formulations F1 to F4

Table 13: Result of correlation coefficients data of prepared formulation F1-F4 Model Fitting Analysis.

Formulation	(r^2)			Korsmeyer-peppas		Best fit model	Mechanism of release
	Zero order	First order	Higuchi matrix	(r^2)	n		
F1	0.9439	0.9412	0.9731	0.9644	0.7815	Higuchi matrix	Non-Fickian
F2	0.9713	0.8304	0.9563	0.9708	0.8804	Zero order	Non-Fickian
F3	0.9702	0.929	0.9424	0.9649	0.9631	Zero order	Non-Fickian
F4	0.9701	0.9719	0.9481	0.979	0.9720	Korsmeyer-peppas	Non-Fickian

DISCUSSION

The main aim behind the kinetic analysis of in vitro release data is to determine the release mechanism of the formulation. Different kinetic graph was plotted like zero order, first order, Higuchi, Korsmeyer-Peppas model to calculate the value of coefficient of regression (r^2). The kinetic model having highest value of coefficient of regression was declared to be best fitted model for the particular formulation. Further the release was also kinetically analysed for the korsmeyer-peppas model to obtain the value of release component (n). For the calculation of n value regression analysis was done by using the following equation:

$$M_t / M_\square = Kt^n$$

The value of release exponent (n) describe the mechanism of drug release of all prepared formulation from the dosage form.

Release exponent	Mechanism of drug release
0.5	Fickian diffusion
0.5 to 1	Non-fickian difffusion
1 or more than 1	Super Case II transport

Kinetic study of formulation F1-F4 was reported in **table no.13.** By comparing the value of r^2 of all kinetic models of different formulations, it was observed that the individual formulations have different r^2 value for different model. Except formulation F1 and F4 other formulation follows zero order models. When the release data were analysed using the zero order, the n values indicated that the mechanism of drug release was strictly followed non fickian for the formulations F1 to F4.

CONCLUSION

In the present study Terbinafine hydrochloride emulgel were prepared. Various variables such as the oil phase and the emulsifying agent were optimized by the factorial design. A 22 experimental design was employed to identify optimal formulation parameters for an emulgel preparation.The optimized batch of emulgel with the liquid paraffin in its high level and the emulsifying agent in its high level proved to be the formula of choice, since it showed the highest release, appropriate spreadability, good consistency and higher percentage inhibition. Also the prepared emulgel stable throughout during shelf life. Hence, the results of the present study clearly indicated promising potentials of emulgel as sustained release for delivering Terbinafine hydrochloride topically in the treatment of fungal infection and could be viewed as a potential alternative to conventional dosage forms.

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