Research Article

Formulation and Evaluation of Imiquimod Emulgel for Treatment of Common Warts

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ABSTRACT

The objective of the present work is to develop and optimize emulgel system for epidermal and dermal delivery of drug which delivers the drug in local sites more efficiently than cream and other gel preparations. The drug imiquimod is locally acting antifungal drug with wide spectrum of anti fungal activity. Imiquimod given only topically. Well absorbed through skin. Half life: 20 hrs (topical) 2 hrs (subcutaneous). The gel were prepared by dispersing Carbopol 934 in purified water with constant stirring and Carbopol 940 in purified water with constant stirring then the pH was adjusted to 5.5 using Tri Ethanol Amine (TEA). The preparation of emulgel is based on the use of different types of gelling agent, liquid paraffin concentration and emulsifying agent concentration. It has demonstrated that the formulation possess better drug content and drug release in comparison to marketed product for local treatment of fungal diseases. The spread ability of formulations ranges from 12.10±0.95g.cm/sec to 16.57±1.17 g.cm/sec. The drug content in emulgel is 73.5 ± 1.82 % to 83.31 ± 1.20 %. The higher drug content determination in emulgel F5 and F3 are 83.31 ± 1.20 % and 80.2 ± 2.50 % respectively. The prepared formulation (emulgel) shows better release profile than marketed preparation. Emulgel will act as depot of drug which releases drug in sustained manner. Emulgel formation was confirmed by Transmission electron microscopy. The size of emulgel particle found within the range of 1µm by TEM. It concludes that the Emulgel formulation show sustained release of drug as compared to the marketed product. No irritation was found by the skin irritation test of the emulgel on the rabbit skin. The skin penetration potential of developed emulgel was further confirmed by the fluorescence microscopy for topical drug delivery. The formulations found to be stable for period of 3 months; it can be observed that the emulgel formulation showed no major alteration in relation to the pH, microbiological study, consistency, skin irritation test and in vitro release study.

Keywords: Imiquimod, Emulgel, Transmission electron microscopy, In-vitro drug release, Ex vivo drug release study.

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INTRODUCTION

A wart is a small, rough growth resembling a cauliflower or a solid blister It typically occurs on humans' hands or feet but often in other locations. Warts are caused by a viral infection, specifically by one of the many types of human papillomavirus (HPV). There are as many as 10 varieties of warts, the most common considered to be mostly harmless. It is possible to get warts from others; they are contagious and usually enter the body in an area of broken skin. Warts can be treated by Salicylic acid, Cantharidin, Bleomycin, Dinitrochlorobenzene, Cidofovirs, and most of the Minor surgery/major Surgery[1].

The drug imiquimod is locally acting antifungal drug with wide spectrum of anti fungalactivity. Imiquimod given bu only topically. Well absorbed through skin. Half life: 20 hrs (topical) 2 hrs (subcutaneous). The Emulgel formulation show sustained release of drugs and increase the residence timeof drug in the skin because emulsion acts as a depot in skin and release the drug.

The objective of the present work is to develop and optimize emulgel system for epidermal and dermal delivery of drug which delivers the drug in local sites more efficiently than cream and other gel preparations[1].

Emulgel is stable and better vehicle for hydrophobic or water insoluble drugs. In the emulgel formulation, the drug may be dissolved in the oil core or incorporated into the oil/water interface according to their lipophilicity. The drug release from the emulgel in the skin it acts as a depot and release the drug in a controlled manner for a longer periods of time. The better release of drug from emulgel across skin other than the ointment and cream because it shows the better release forlonger period of time[2].

Imiquimod is antifungal agent, that could be given topically to treat systemic or superficial fungal infection. It has a broad spectrum of activity against dermatophyte, yeast and fungi. Imiquimod drug belongs to a group of drug called immune response modifiers. Drug activate immune system to fight these abnormal skin growth[2].

METHODS

Materials

Imiquimod was received as a gift sample from Glenmark (Pithampur). Carbopol 934, Carbopol 940 from SD fine chemical. Span 20 and Tween 20 from Qualichem. Methyl Paraben, Propyl Paraben From molychem Pvt. Ltd (Mumbai). All other solvent and reagent are used was of analytical grade.

Experiementals

Identification of Drug

UV Spectroscopic Characterization

Estimation of Drug by UV – Visible Spectrophotometer Preparation of Buffer solution (pH 5.5):

Dissolve 13.61 gm of potassium dihydrogen phosphate in sufficient water toproduce 1000 ml. Dissolve 35.81 gm of disodium hydrogen phosphate in sufficient water to produce1000 ml. Mix 96.4 ml of solution (a) with 3.6 ml of solution (b) to get PBS of pH 5.5. Maintainthe pH with HCl/ NaOH if necessary. Determination of absorption maximum (Zmax) in PBS (pH 5.5). The Ultraviolet absorption maximum of Imiquimod in PBS (PH 5.5) was determined by scanning 10µg/ml solution the range of 200 to 400nm[2].

Melting point

Melting point of drug sample was determined by using melting point apparatus. The drug sample was taken and placed in a thin walled capillary tube; the tube was approximately 10-12 cm in length with 1mm in diameter and closed at one end[3]. The capillary was placed in melting point apparatus and heated and when drug sample was melted the melting point of sample powder was recorded.

Partition coefficient

The partition coefficient of Imiquimod was determined in n-Octanol: water system/ PBS 5.5. Weighed amount of Imiquimod was added into 10 ml each of n-Octanol and water. The mixture was shaken and put for 24 hours until equilibrium was reached. Phases were separated using separating funnel and the aqueous phase was filtered through 0.2 µ filter, suitably diluted and amount of Imiquimod in aqueous phase was determined at 226 nm using UV spectrophotometer[3].

Preparation of standard Calibration curve of imiquimod

Accurately weighed quantity of Imiquimod (10 mg) was dissolved in 3 ml of methanol and volume was made up to 10 ml with PBS (pH 5.5). From the stock solution, 1 ml sample was taken and volume made up to 10 ml with PBS (pH 5.5). From this stock solution different dilutions were prepared in the concentration range of 5, 10, 15, 20,25 and 30 µg/ml and absorbance were measured at 226 nm[3].

Solubility studies of drug

Solubility of imiquimod was determined in distilled water and various non-aqueous solvents like phosphate buffer 5.5, methanol, ethanol, Hcl, chloroform. The various types of solubility studies include Qualitative solubility study and Quantitative super saturation solubility study[4].

Qualitative solubility study

Qualitative solubility analysis for imiquimod was determined in distilled water and various non-aqueous solvents like phosphate buffer 5.5, methanol, ethanol, Hcl and chloroform. Ten mg of drug was dissolved in 10 ml of solvent taken in conical flask. For the determination of solute dissolved in each solvent. The solvents were shaken at 25°C for 24 hrs. After shaking, the samples were examined for the presence of any dissolved, suspended particles and clarity[4].

Drug-excipient interaction study (Fourier Transform Infrared Spectroscopy)

In this study, FTIR spectra for the pure drug and the drug-excipients mixture were obtained. One part of Potassium Bromide was mixed with 100 parts of the pure drug and the drug-excipients mixture and used for the FTIR spectrum[5]. Pure drug was also mixed with Potassium Bromide and spectrum was obtained. Both spectra were compared for possible deviations.

Formulation of Imiquimod Emulgel

Preparation of Imiquimod Emulgel

The gel was prepared by dispersing Carbopol 934 in purified water with constant stirring and Carbopol 940 in purified water with constant stirring then the pH was adjusted to 5.5 using Tri Ethanol Amine (TEA).

The oil phase of the emulsion was prepared by dissolving Span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in purified water. Methyl and Propyl paraben was dissolved in propylene glycol whereas drug (Imiquimod) was dissolved in ethanol and both solutions was mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70°-80°C; then the oily phase was added to the aqueous phase with continuous stirring until cooled to room temperature. Add Glutaraldehyde during the mixing of gel and emulsion in ratio 1:1 to obtain the Emulgel[5].

Table 1: Various composition of Imiquimod Emulgel formulations

Ingredients (%w/w)	F1	F2	F3	F4	F5	F6	F7	F8
Imiquimod	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Carbopol 934	0.5	0.5	0.5	0.5	-	-	-	-
Carbopol 940	-	-	-	-	0.25	0.25	0.25	0.25
Light liquid paraffin	2.5	3.75	2.5	3.75	2.5	3.75	2.5	3.75
Tween 20	0.3	0.3	0.5	0.5	0.3	0.3	0.5	0.5
Span 20	0.45	0.45	0.75	0.75	0.45	0.45	0.75	0.75
Propylene glycol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Ethanol	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Methyl paraben	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Propyl paraben	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005
Glutaraldehyde	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Distilled water (q.s.)	50	50	50	50	50	50	50	50

Evaluation of Optimized Formulations

Physical Examination

The prepared emulgel formulations were inspected visually for their color, odor, Appearance.

Determination of pH of ointment formulation

About 2.5 g of all formulations were taken in dry beaker and 50 ml of water was added. Beaker containing ointments was heated on water bath at 60–70°C. The pH of emulgel was determined using a pH meter[6]. The determinations were carried out in triplicate and average of three readings were note.

Spreadability

Spreadability of the formulation was determined by an apparatus, which was suitably modified in the laboratory and used for the study. It consists of a wooden block, which was provided by a pully at one end. A rectangular ground glass plate (20cm x 20cm) was fixed on the block.

Two grams of the formulation was sandwiched between the ground fixed plates and another glass plate having the same dimensions of the fixed ground plate. The movable glass plate is provided with the hook. A 300gm weight was placed on the tip of two plates for five minutes to expel air and to provide a uniform film of the formulation between the plates. Excess of the formulation was scrapped off from the edges. The top plate was then subject to a pull of a 30 gms, initially with the help of a string attached to the hook and moves over the pulley. The time required by the top plate to move at a distance of 10 cms was noted. A shorter time interval indicates better spreadability.

The spreadability was calculated by using the formula

$s = m \times l / t$

s = spreadability

m = weight tied to the upper side

l = length of the glass slides

t = time taken in seconds

In case the slide did not move with 30 gms, weight was increased gradually. In case the slide was moving fastly, the weight was decreased gradually[6].

Extrudability study

For this study, a closed collapsible tube containing20 grams of emulgel was pressed firmly at the crimped end and a clamp was applied to prevent any rollback. The cap was removed and the emulgel extrudes until the pressure was dissipated[6].

Rheological Properties

Viscosity

The viscosity was determined by using Brookfield viscometer. The viscometer is placed on the "Standby Mode". Samples were allowed to reach room temperature and the samples were shaken vigorously. Then the samples were filled in a 600-mL, low-form Griffin beaker at least 3/4 full of slurry from the sample bottle. The spindle number 64 was selected. The spindle was inserted in to the appropriate beaker containing sample. Care was to be taken to avoid air bubbles since it may be trapped beneath the spindle. The beaker was moved in to the position beneath the viscometer and the spindle was attached so that the spindle remains submerged into the sample. The sample viscosity is measured at 30°c. The reading was recorded in centipoises[7].

Drug content

The ointment formulation equivalent to unit dose of drug was weighed accurately and dissolved in 100 ml of phosphate buffer 5.5 and filtered through whatman filter paper. The solutions were analyzed by UV spectrophotometer at 226 nm and drug content calculated accordingly[7].

Particle Size determination

Mean particle size and size distribution analysis was carried out by using Malvern zeta sizer Nano- S90.Which follows principle of LAZER light differaction or also called photon correlation spectroscopy(pcs). It is based on measurement of Brownian motion of particles. The prepared nanosuspension of 100 µl was diluted to 5 mlwith double distilled water and diluted dispersion was measured by using Malvern Zetasizer[8].

Transmission electron microscopy (TEM)

The emulgel formulation after hydration was confirmed by Transmission electron microscopy (TEM). Samples were prepared by adding phosphate buffer (pH 5.5) to emulgel and shaking the mixture manually for 1 minute.A drop of the sample was placed on a carbon-coated copper grid after 15 minutes and negatively stained with 1% aqueous solution of phosphotungstic acid. The grid was allowed to air dry thoroughly and samples were viewed on a TEM (Philips, TEM, NewBrunswick, Canada)[8].

In vitro Drug Release Studies

Preparation of biological membrane (egg membrane)

The outer shell membrane of the egg that is located inside the shell exactly under the hard calcified layer was obtained by immersing the egg in 1N HCl solution for 30 min,to dissolve the calcified layer and the membrane was cut cautiously to expel the content of the egg and washed it with distilled water for 10 min to remove all adhered content to egg membrane[9].

In vitro drug release studies

Franz diffusion cell (with effective diffusion area 3.14 cm^2 and 15.5 ml cell volume) was used for the drug release studies. Emulgel (200 mg) was applied onto the surface of egg membrane evenly. The egg membrane was clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber was filled with freshly prepared PBS (pH 5.5) solution to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1.0 ml aliquots) were collected at suitable time interval. Samples were analyzed for drug content using UV visible spectrophotometer at 226 nm after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval. The % cumulative amount of drug released across the egg membrane was determined as a function of time[9]. The in vitro release of various formulations are shown in the fig. (7.2.15, 7.2.17).

Ex Vivo Study

For ex vivo release studies, skins were allowed to hydrate for 1 h before being mounted on the Franz diffusion cell with the stratum corneum (SC) facing the donor compartment. The receptor compartment was filled with PBS (pH 5.5) and receptor phase was maintained at 37 ± 0.5OC. 200 mg of the emulgel was placed on the SCside in the donor compartment and covered with aluminum foil to prevent drying out. The amount of drug release was determined spectrophotometrically at 226 nm by removing 1 mL aliquot through a hypodermic syringe fitted with a 0.22 mm membranefilter, at designated time intervals of 1 h. The volume was replenished with the same volume of PBS (pH 5.5) to maintain sink conditions[10].

Fluorescence microscopy

Fluorescence microscopy was performed to confirm the skin penetration ability of emulgel formulations. The emulgel formulation containing fluorescence dye was prepared. The fluorescence dye is used in place of drug. The fluorescence marker loaded formulation was applied topically to rat skin. After 6 hours of application, the rats were humanely killed and skin was removed, cut into small piece, fixation of the tissue on the glass slide for progestational activity, and examined under fluorescence microscopy[11].

Stability Study

Stability is defined as -the capacity of the drug product to remain within specifications established to ensure its identity, strength, quality and purity. The prepared Imiquimod emulgel formulations were stored in dark collapsible tubes at 4±2°C , 25±2°C and 40±2°C for 3 months. Periodically sample were collected and tested for their physical appearance, pH, rheological behavior, drug release, skin irritation test and microbiological assay[12].

RESULTS AND DISCUSSION

Identification of drug

The λmax of Imiquimod was obtained at 226 nm. This found to be similar as given in the reference. Which shows that drug is pure. The UV spectrum of Imiquimod drug is shown in the fig. 2.

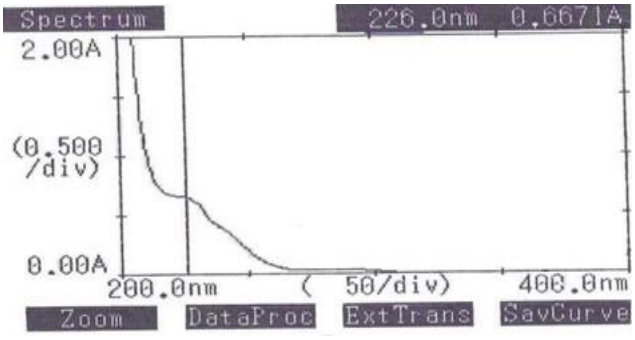


Figure 2: Spectrum of Imiquimod by UV Spectroscopy

Melting point

The melting point of drug sample was determined by using melting point apparatus. The melting point was found to be in the range of 149-151^{0}C, which is found to be similar as given in the reference[13].

Preparation of standard Calibration curve of imiquimod in Phosphate buffer 5.5 (λmax 226nm)

Calibration curve of imiquimod was prepared in PBS 5.5 at 226 nm. The absorbance values (mean of three

determinations) with their standard deviation at different concentration in the range of 5-50 µg/ml for PBS 5.5 are tabulated. The drug obeys Beer'sLambert law in the concentration range. Linear regression analysis for all calibration curves of imiquimod is given in Table. So, this equation was used for the calculation of the solubility of the drug in different solvent, drug content and drug release. The calibration curve of imiquimod is shown in Table 2.

Table 3: Standard Curve of Imiquimod in PBS (pH 5.5)

S. No.	Concentration(µg/ml)	Absorbance	Statistical parameters
1	0	0.000	R2 = 0.9927 Y=0.043x- 0.0386
2	5	0.189	
3	10	0.361	
4	15	0.581	
5	20	0.790	
6	25	1.008	
7	30	1.319	

Solubility Studies

Solubility of Imiquimod was determined in various aqueous and non aqueous solvents. The drug was found to be freely soluble in methylene chloride, soluble in methanol, sparingly soluble in ethanol. The solubility was observed only by the visual inspection.

Drug-excipient interaction study (Fourier Transform Infrared Spectroscopy)

FT-IR Spectrum: Identification of drug was done by its IR spectrum. The infrared spectrum of Imiquimod was obtained by FT-IR (ABB, FTLA 2000 IR), the drug was directly placed on the cavity and was determined by FT-IR which shows the characteristic peaks of various functional groups of drug 813 cm-1 (C-Cl bending), 1275 cm-1 (C-N Stretching) and 1509cm-1 (C=C Stretching)

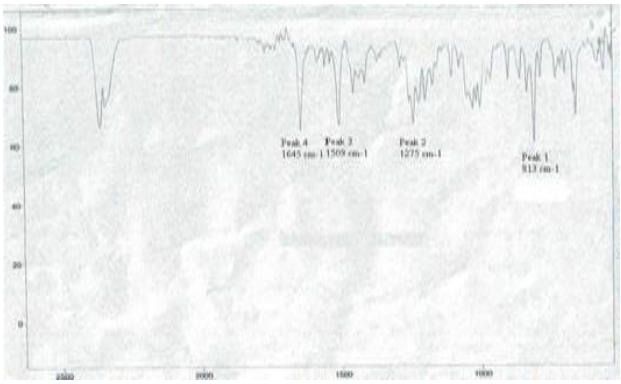


Figure 4 : FT-IR Spectrum of Imiquimod

Evaluation of Emulgel

Physical Examination

Table 5: Physical Properties of the Various Emulgel Formulations

Formulationcode	Color	Consistency	pH	Spreadability (g.cm/sec.)	Extrudability (%)
F1	White	Fine	5.6±0.15	15.33±1.12	91.33±0.95
F2	White	good	5.4±0.21	16.35±0.90	86.43±0.89
F3	White	fine	5.6±0.20	14.69±1.05	90.33±1.87
F4	Off White	good	5.6±0.15	16.13±0.95	84.6±1.26
F5	White	good	5.6±0.15	14.18±0.65	89.33±0.94
F6	Off White	fine	5.8±0.12	12.10±0.95	87.3±0.39
F7	White	good	5.3±0.25	16.57±1.17	87.36±1.19
F8	Creamy	fine	5.6±0.32	16.24±1.10	85.23±0.87

Values are expressed in Mean ± S.D. n=3

Rheological Properties

Viscosity: The measurement of viscosity of the prepared emulgel was done with Brookfield viscometer (Brookfield DV-E viscometer). The highest viscosity was found in Emulgel F4 it may be due to high level of the liquid paraffin concentration and emulsifying agent concentration. The lowest viscosity was found in formulation F2 and F6 due to the low level of emulsifying agent concentration.

The viscosity of different emulgel formulation was determined at 250C using a brook field viscometer (Brookfield DV-E viscometer). The emulgels were rotated at 10 (min.) and 100 (max.) rotation per minute with

spindle 6. At each speed, the corresponding dial reading was noted. The viscosities are reported in Table 16

C. Drug content: The drug content in emulgel was found in range of 73.5 ± 1.82 % to 83.31 ± 1.20 %. The higher drug content found in F5 i.e. 83.31 ± 1.20 % due to the low concentrationof liquid paraffin and emulsifying agent and the lower drug content found in F8 i.e.73.5 ± 1.82 % due to the high concentration of liquid paraffin and emulsifying agent. The drug content of all emulgel formulation given below (Table 6).

Table 6: Viscosities and drug content of Imiquimod Emulgel Formulations

Formulation code	y max. (Cp)	y min.(Cp)	% Drugcontent
F1	512 ± 30.11	2960 ± 43.75	77.4 ± 2.06
F2	452 ± 31.09	2363 ± 33.53	79.5 ± 1.41
F3	560 ± 30.56	3173 ± 25.50	80.2 ± 2.50
F4	643 ± 37.64	5254 ± 40.15	73.8 ± 1.92
F5	440 ± 40.09	4283 ± 35.76	83.31 ±1.20
F6	534 ± 56.51	3114 ± 36.59	77.5 ± 0.59
F7	442 ± 33.85	4063 ± 32.50	76.4 ± 1.35
F8	504 ± 45.01	3248 ± 46.51	73.5 ± 1.82

Values are expressed in Mean ± S.D. n=3.

Particle Size determination: Mean globule size in emulgel was found to be 666.0 d.nm. The poly dispersity index (PDI) of emulgel was found to be 0.962 which prove the homogeneity of emulgel.

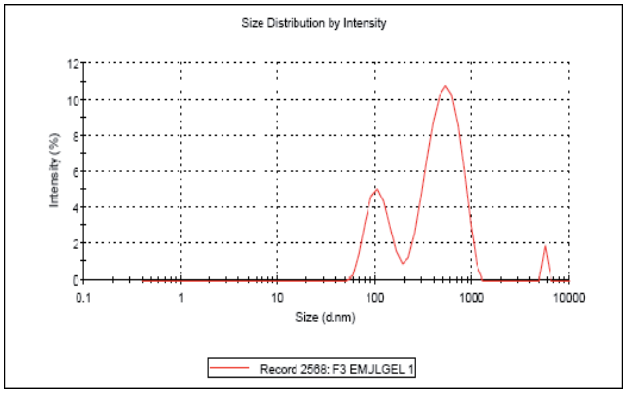


Figure 7: Size distribution curve of optimized emulgel formulation

Transmission electron microscopy (TEM)

The globule of Emulgel formation was confirmed by Transmission electron microscopy. TEM image of the emulgel was observed which confirm that emulgel with approximate diameter within the range of 1 µm was formed from the emulgel, following contact with PBS (pH 5.5).

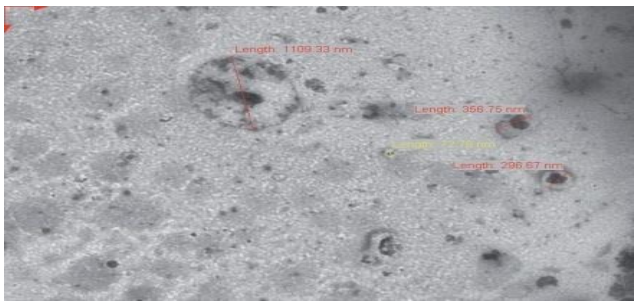


Figure 8: TEM Photomicrograph of emulgel

In vitro Drug Release Studies

The in vitro release profiles of Imiquimod from its various emulgel formulations are represented in (Figure 4.6). It was observed that all the formulation had become liquefied and diluted at the end of the experiments, indicating water diffusion through the membrane figure 4.6, the better release of the drug from all emulgel formulation can be observed and the emulgel formulation can be ranked in the following descending order: F1 > F3 > F5 > F6 > F8 > F4 > F7 > F2, Where the amounts of the drug released after 24 hours were 93.8±0.34%, 76.2±0.65%, 67.94±0.43%, 61.14±0.46%, 60.7±0.41%, 50.06±0.35%, 41.06±0.36% and 34.19±0.41%, respectively. The higher drug release was observed with formulations F1 and F3. This finding may be due to presence of liquid paraffin in its low level and the emulsifying agent in its low level / high level respectively, which lead to an increase in the hydrophilicity of the emulgel which in turn facilitates penetration of the release medium into the emulgel and diffusion of the drug from the emulgel. 0.1% of gluteraldehyde is added to retard the release rate of drug from emulgel formulation. The presence of liquid paraffin leads to retardation of Imiquimod release from its emulgel formulation. The lower drug release from F5, which is Carbopol 940-based, than the drug release from F1 and F3, which is Carbopol 934-based, this may be due tothe higher viscosity of Carbopol 934 emulgel formulations as observed in table 4, this may also be due to the network structure of Carbopol 934.

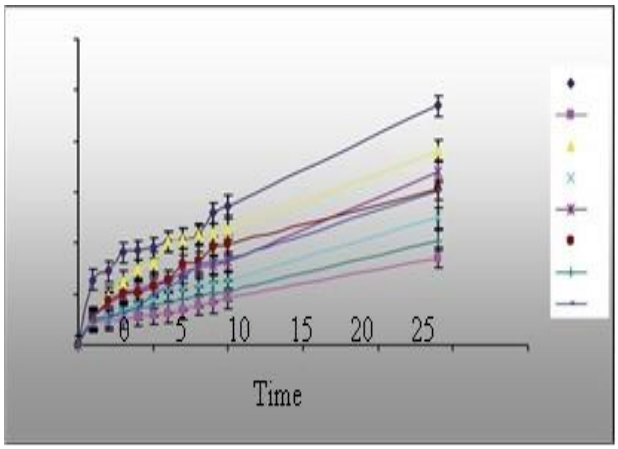
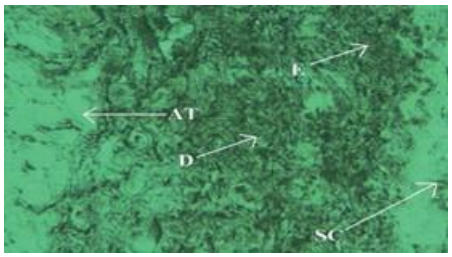


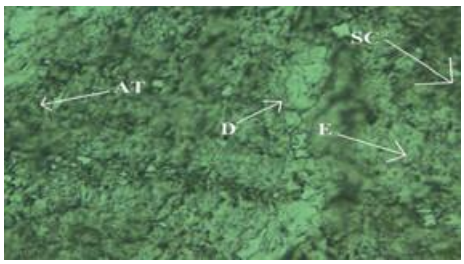
Figure 9: Release profiles of Imiquimod from its emulgel formulations in 24 hours

Fluorescence microscopy

The skin penetration potential of developed emulgel was further confirmed by the fluorescence microscopy for topical drug delivery.



(A)



(B)

Figure 10: Penetration of Flourescein dye after 6-hour application of emulgel formulation on rat skin (SC indicates stratum corneum; E, epidermis; D, dermis; AD, adipose tissue).

CONCLUSION

The preparation of emulgel is based on the use of different types of gelling agent, liquid paraffin concentration and emulsifying agent concentration. It has demonstrated that the formulation possess better drug content and drug release in comparison to marketed product for local treatment of fungal diseases.

The prepared formulation (emulgel) show better release profile than marketed preparation. Emulgel will act as depot of drug which releases drug in sustained manner. Emulgel formation was confirmed by Transmission electron microscopy. The size of emulgel particle found within the range of 1µm by TEM.

The percentage inhibition was taken as a measure of antifungal activity of the drug.The emulgel formulations were found to have the same rank order in their antifungal activities as in the in vitro release studies. Thus, the highest activity was observed with formula F3 and F1, where the percentage inhibition reached up to 46.6±1.15 % and 37.9± 1.34 % respectively. It concludes that the Emulgel formulation show sustained release of drug as compared to the marketed product. No irritation was found by the skin irritation test of the emulgel on the rabbit skin. The skin penetration potential of developed emulgel was further confirmed by the fluorescence microscopy for topical drug delivery.

The formulations found to be stable for period of 3 months; it can be observed that the emulgel formulation showed no major alteration in relation to the pH, microbiological study, consistency, skin irritation test and in vitro release study.

Hence the developed optimized formulation can be used to treat the topical fungal diseases showing superiority over the present marketed formulation.

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