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Formulation and Evaluation of Fusidic Acid Emulgel

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ABSTRACT

Emulgel have emerged as one of the most interesting topical delivery system as it has dual control release system i.e gel and emulsion. Topical applications of drug offers many advantages for delivering drug directly to the site of action and deliver the drug for extended period of time at effected site. The major objective behind this formulation is to enhance topical delivery of hydrophobic drug (Fusidic acid) by formulating Fusidic acid emulgel by using carbopol 934 as gelling agent. In addition light liquid paraffin as oil, span 20 as emulsifier and propylene glycol as co-surfactant were selected for the preparation of emulgel. Fusidic acid is steroidal bacteriostatic agent produced from Fusidium coccineum fungus belongs to class of steroids but has no corticosteroids effect and which is useful for the treatment of number of infections. Fusidic acid binds to protein and ribosomes and inhibits bacterial protein synthesis. The prepared emulgel were evaluated for their physical appearance, pH determination, viscosity, spreadability, in-vitro drug release, antimicrobial activity, skin irritation study and stability. All the prepared emulgel showed acceptable physical properties. The best formulation E9 shows better drug release when compared to all formulation.

Keywords: Emulgel, Carbopol 934, Topical formulation, Antimicrobial activity, optimization, Fusidic acid

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INTRODUCTION

Topical drug administration is simplest and best route for restricted drug delivery within a body by route as ophthalmic, rectal, vaginal and skin.[1] Topical drug delivery is defined as localized application of formulation within the body through ophthalmic, rectal, nasal, vaginal and skin with approach to extend its bioavailability and reduction in side effects. Emulgel are the combination of emulsions and gels.[2] Emulsion either of oil in water or water in oil type, which are gelled by mixing with a gelling agents.[3] Emulgel acts as dual control of drug release from the formulation, due to the presence of both aqueous and non-aqueous phase.[4] Emulgel are widely used for delivery of drug through the skin. Its function in dermatology is realized mainly due to the advantages such as easy incorporation of hydrophobic drugs, thixotrophy, greaseless, easily spreadable, easy removable, emollient, non-staining, water soluble, biocompatibility with greater shelf life and pleasant appearance.[5]

Gel formulations typically show higher drug release than ointment and creams. In spite of many advantages of emulsions and gels a major disadvantages is their inability to deliver hydrophobic drug and instability during storage. Such type of problems are overcome by using the emulsion based approach that is emulgel preparation and thereby hydrophobic drug and successfully incorporated and have unique property of gels.[6] Fusidic acid is steroidal bacteriostatic agents produced from Fusidium coccineum fungus belongs to class of steroids but has no corticosteroids effects. It is used to treat atopic dermatitis, cellulitis, contact dermatitis and prurigo. It is BCS class II drug whose bioavailability is rate limited.[7] It binds to protein and ribosomes and inhibit further bacterial protein synthesis. The action of FA is largely bacteriostatic but at high concentration the effect may be bactericidial.[8]

MATERIALS AND METHODS

Materials:

Fusidic acid was received as gift sample from Bharat Parenteral Pvt. Ltd (Vadodara, India). Carbopol 934 was obtained from Chiti-chem Corporation, Light liquid paraffin was obtained from Qualikems fine chem. Pvt. Ltd. Propylene Glycol was obtained from Suvidhinath Laboratories, and Span 20 was obtained from Qualikems fine Chem. Pvt. Ltd. Peppermint oil was obtained from Aaturinstru chem. Triethanolamine was obtained from Chemdyes Corporation and methyl paraben was obtained from Oxford lab.

Preparation and evaluation of all batches (E1-E9) of emulgel

Table 1: Design summary

Factor	Name	Coded level			Actual level		
		Low	Medium	High	Low	Medium	High
A	Carbopol 934	-1	0	+1	1.75	2	2.25
B	Light liquid paraffin	-1	0	+1	5	6	7

Table 2: Formulation table of (E1-E9) batches of emulgel

Ingredients (%w/w)	E1	E2	E3	E4	E5	E6	E7	E8	E9
Fusidic acid	1	1	1	1	1	1	1	1	1
Carbopol 934	**2**	**2.25**	**1.75**	**1.75**	**2.25**	**2**	**1.75**	**2.25**	**2**
Liquid paraffin	**6**	**7**	**5**	**6**	**5**	**5**	**7**	**6**	**7**
Propylene glycol	5	5	5	5	5	5	5	5	5
Span 20	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Peppermint oil	2	2	2	2	2	2	2	2	2
Methyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Triethanolamine	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

The oil phase of emulsion was prepared by dissolving span 20 in light liquid paraffin and peppermint oil, also Fusidic acid was mixed in oil phase. While the aqueous phase of emulsion was prepared by dissolving in span 20 in distilled water. Methyl paraben were dissolved in propylene glycol and mixed with aqueous phase. Both the oily and aqueous phases were separately heated at 70°C-80°C, then the oily phase was added to the aqueous phase with continuous stirring until it was cooled to room temperature. The emulsion was obtained, which is stored in well closed air tight container.[9]

Preparation of gel:

The quantity of carbopol 934 were weighed and mixed homogenously with distilled water 65-70°C by using magnetic stirrer, stirring speed is 1000±200 RPM for 10 min to form smooth dispersion. The preparation is allowed to stand, permitting entrapped air to separate. Then the pH was adjusted to 6-6.5 by using triethanolamine.[10]

Preparation of emulgel:

Emulsion was incorporated into gel base in 1:1 ratio under continuous mixing using mechanical stirrer at 5000-6000 RPM for 10-20 minutes to obtained emulgel.

Preformulation study:

Organoleptic characterization of drug:

Melting point: Melting point of the drug was found to be 190°C-195°C by using capillary tube method. The readings were taken in triplicate and average was taken. The reference melting point is in the average 192.5°C.

Solubility: The solubility of Fusidic acid in different solvent was determined by using shake flask method. The result obtained was noted below in table 3.

Table 3: Solubility of Fusidic acid in different solvent

Experiment	Parameter	Observation
Solubility (mg/ml)	Solubility in distilled water (mg/ml)	0.091±0.01
	Solubility in phosphate buffer pH 5.5 (mg/ml)	0.403±0.04
Each observation value are expressed as mean ±S.D. n=3		

FTIR Spectroscopy:

FTIR spectrum (Shown in Figure 1) of drug sample showed all the characteristics IR peaks as reported in indicating the presence of Fusidic acid shown in table 4.

UV spectroscopy:

Maximum absorbance of Fusidic acid in phosphate buffer pH 5.5. The λmax of Fusidic acid in methanol was found to be at 204nm this is characteristics property of Fusidic acid in its pure form, hence it can be confirmed that obtained sample was authentic.

Calibration curve of Fusidic acid in phosphate buffer pH 5.5

The calibration curve of Fusidic acid was prepared in phosphate buffer pH 5.5. table 4 shows the absorbance at λmax 204nm for different concentration of Fusidic acid and figure 1 shows calibration curve.

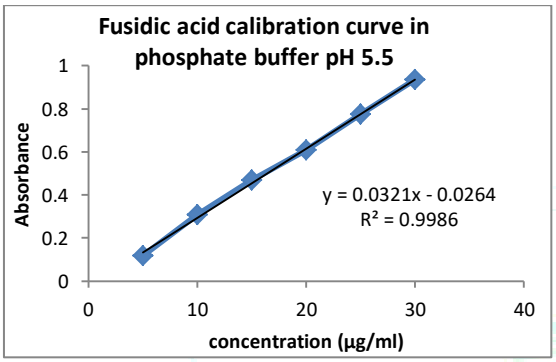

Figure 1: Calibration curve of Fusidic acid in phosphate buffer pH 5.5

Table 4: Calibration curve data of Fusidic acid in phosphate buffer pH 5.5

Concentration (µg/ml)	Absorbance ± SD
5	0.0802±0.06
10	0.1727±0.07
15	0.2908±0.06
20	0.4030±0.06
25	0.5077±0.03
30	0.6094±0.05

Evaluation of emulgel containing emulsion (of optimized batch E9) of Fusidic acid.

1. Physical examination:

The colour of formulation was checked against white and black background. The consistency of emulgel was checked by applying on skin. The odor of emulgel was checked by mixing it in water and by smelling it.[11]

2. pH:

1% solution of emulgel were prepared and subjected to measure pH by digital pH meter.

3. Drug-excipient compatibility study:

FTIR spectra of Fusidic acid and other excipients like carbopol 934 was compared with spectra of prepared emulgel formulation.[12]

4. Viscosity:

The rheological property of emulgel sample was determined by using Brookfield viscometer.

5. Spreadability:

A lower glass slide was fixed on this block. An excess of prepared emulgel (1gm) was placed on ground slide. Emulgel formulation was then sandwiched between the slide and another glass slide having the dimension of fixed ground slide and provided by hook. Weight of 100gm was placed on top of two slides for 5 min to expel air and to provide uniform film of gel between the slide. Excess of emulgel was scrapped off from the edges. Upper slide was then subjected to pull 20g weight with the help of string attached to hook and the time required by upper slide to cover distance. Shorter interval indicated better spreadability.

Spreadability (S) was calculated as follow:

S=M.L/T

6. Drug content:

Drug content in emulgel was measured by dissolving 1gm of emulgel in 100ml of solvent (a mixture of ethanol). After filter the solution to obtain a clear solution and subjected to spectrophotometric analysis after suitable dilution.

7. In-vitro drug diffusion study:

Release of Fusidic acid from emulgel formulation was measured through dialysis membrane by using franz diffusion cell. Dialysis membrane was soaked in diffusion media for overnight and then placed on support screen of diffusion cell assembly. Phosphate buffer at pH 5.5 was used as the receptor medium and 1g of gel was placed on the donor side. At predetermined time interval, 2ml of sample was withdrawn from the receptor compartment and replaced with same volume of phosphate buffer at pH 5.5. The aliquots were analyzed by UV spectrophotometer at 204nm.

8. Skin irritation study:

All the procedure related with animal experiment were carried out in accordance with committee for purpose of experiments on animal guidelines (CPSCEA). The study was reviewed and approved by Institutional Ethics Committee (protocol No. OGECT/PPDC/IAEC/2019/18/2). Adult New Zealand rabbit was kept in controlled condition, temperature 26-28°C relative humidity 60-70°C and 12/12 hour light-dark cycle and was provided with standard pellet diet and water. Emulgel with drug was applied on one side three test was applied to the animal. First emulgel was removed after three minutes no serious reaction. Second emulgel applied and removed after 1hour no observation a third emulgel was applied and removed after 4hours and response was graded then animal was observed for 14days if corrosive effect observed the test was immediately terminated.[13, 14]

9. Stability study:

Emulgel was packed in aluminium collapsible tubes (5gm) and subjected to stability study at 5°C, 25°C/60% RH, 30°C/65%RH for 1 month. Samples are withdrawn at each 10days as per ICH guidelines and analyzed for their physical appearance, pH, drug content, drug release profile etc.[15]

RESULT AND DISCUSSION

The λmax value of Fusidic acid was found to be 204nm in phosphate buffer pH 5.5 by using UV spectrophotometer.

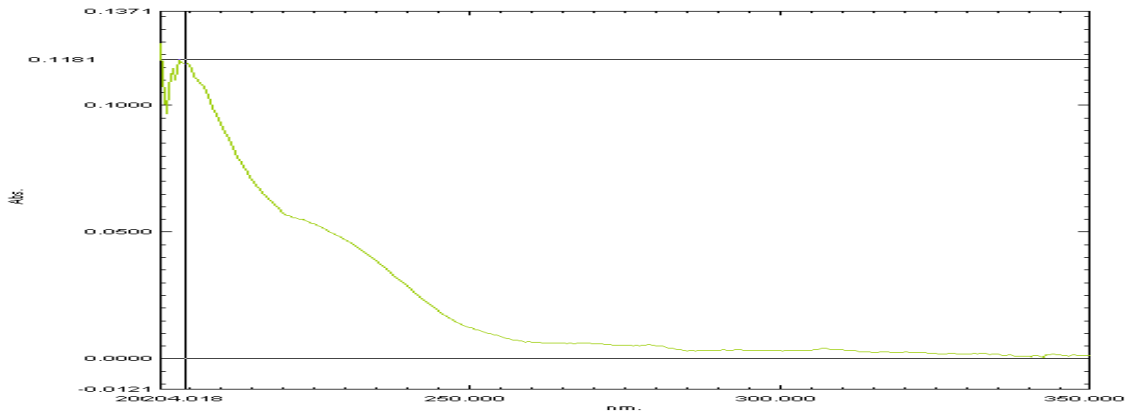

Figure 2: UV spectrum of Fusidic acid in phosphate buffer pH 5.5

The IR of Fusidic acid (figure 3) showed the presence of functional group which are present in Fusidic acid (figure) so it indicate Fusidic acid is in pure form.

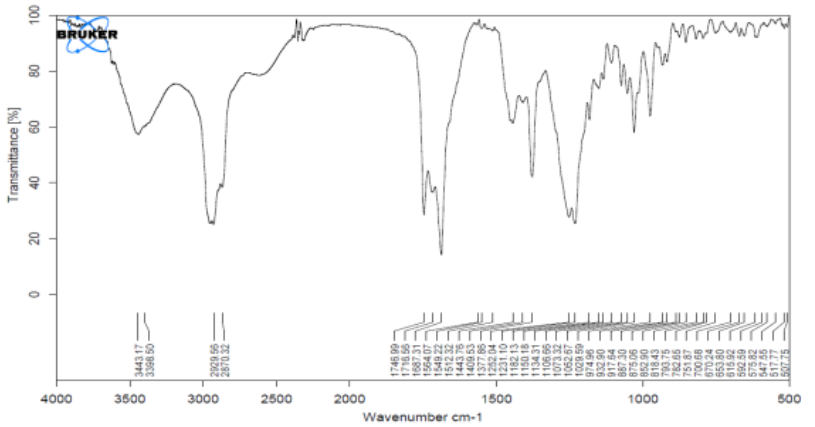

Figure 3: FTIR spectrum of Fusidic acid

Sr.no	Functional group (stretching)	wavenumber(cm^{-1})
		Fusidic acid
1	OH	3443.11
2	C-H(Aliphatic)	2869.26
3	C-H	2949.28
4	C=O(Ester)	1747.38
5	C=C	1563.92
6	C-O	1149.08

Table 5: FTIR spectrum of Fusidic acid

The observed emulsion was found to be oil in water type. The pH of all batches (E1-E9) was found to be in the range of 5.1±0.05 to 5.7±0.15. The viscosity of all batches (E1-E9) was found to be in range of 8791±2.25 cps to 9928 ±1.51 cps. The spreadability of all batches (E1-E9) was found to be range of 10.88±0.12 to 17.25±0.15. The % Drug Content of all batches (E1-E9) was found to be 96.6±0.1 to 99.86±0.03.

Data analysis of formulations:

A 3^2 full factorial design was selected and the 2 factors were evaluated at 3 levels. The amount of carbopol 934 (A) and light liquid paraffin (B) were selected as independent variables and the dependent variables were % Drug release and viscosity. The data obtained was treated using stat-Ease Design Expert software. The data clearly indicates that %drug release and viscosity were strongly dependent on the selected independent variables.

ANOVA for Quadratic model:

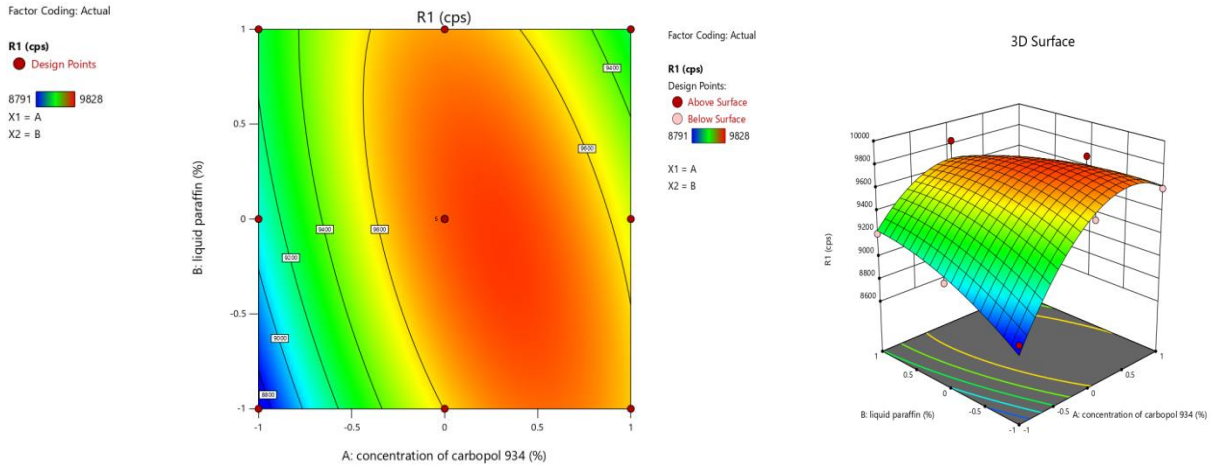

Figure 4: Contour plot and Response 3D surface plot of carbopol 934 and light liquid paraffin for %drug release

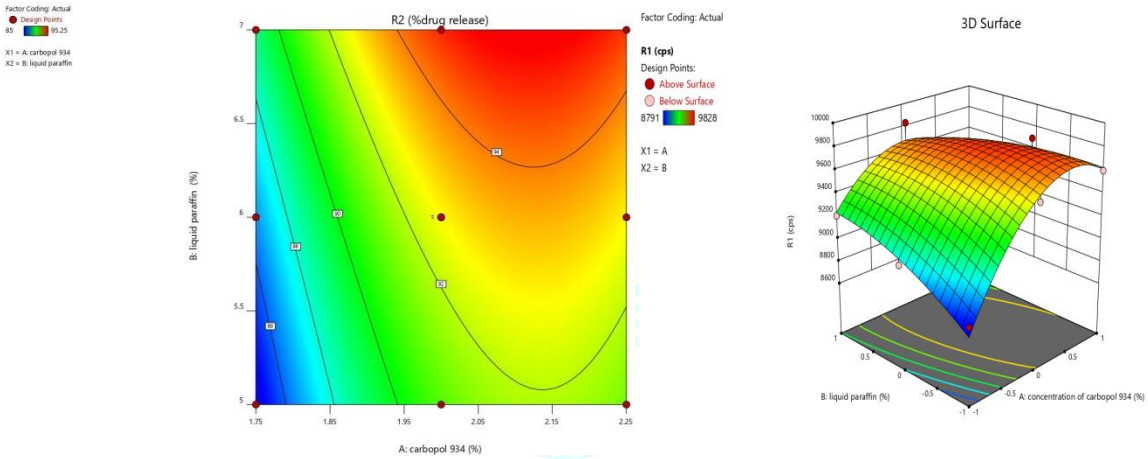

Figure 5: Contour plot and Response 3D surface plot of carbopol 934 and light liquid paraffin for viscosity (cps)

The amount of %drug release from (E1-E2) batches of emulgel varied from 85% to 95.05%. from the p-value 0.0500 it can be concluded that carbopol 934 and light liquid paraffin have prominent effect ($p<0.05$) on %drug release. The amount of viscosity from the (E1-E9) batches of emulsion varied from 8791 to 9925 cps. From the p-value 0.0500 it can be concluded that carbopol 934 and light liquid paraffin have prominent effect ($P<0.05$) on viscosity.

Evaluation of emulgel containing optimized (batch E9) of Fusidic acid:

1. Physical examination:

The prepared emulgel containing (optimized batch E9) of Fusidic acid was inspected visually for their colour white, consistency good and odour aromatic.

2. Determination of pH:

pH of prepared emulgel was found to be 5.1±0.05 to 5.7±0.17 which compliance with skin pH range 4.5 to 6.5.

3. Drug excipients compatibility study:

An FTIR spectrum of formulation shows significant peaks of fusidic acid indicating no interaction between fusidic acid and excipients (figure 6)

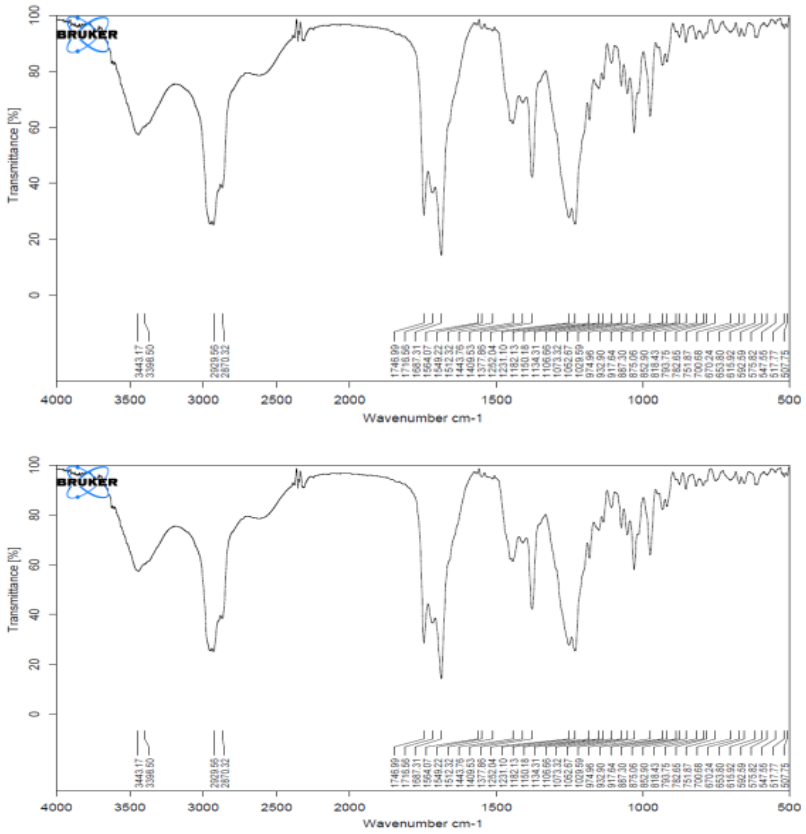

Figure 6: FTIR of Fusidic acid and Fusidic acid and carbopol 934

Table 6: FTIR of Fusidic acid and carbopol 934

Sr.no	Functional group (stretching)	Wavenumber (cm^{-1})	
		Fusidic acid	API+ carbopol
1	OH	3443.11	3443.17
2	C-H(Aliphatic)	2869.26	2870.32
3	C-H	2949.28	2948.25
4	C=O(Ester)	1747.38	1746.99
5	C=C	1563.92	1564.07
6	C-O	1149.08	1150.08

4. Viscosity:

Viscosity was found to 9925 cps. Viscosity was increased with increase in emulsifier concentration.

5. Spreadability:

The spreadability of emulgel was found to 17.25±0.17 gm.cm/sec. Spreadability of emulgel was increased due to presence of propylene glycol as humectants.

6. Drug Content:

%Drug content of emulgel formulation was found to be 99.86±0.03% which is within the pharmacopieal limits.

7. In-vitro drug diffusion study:

At the end of 8 hours the total amount of drug release from the formulation was found to 95.25 so it showed better %CADD from emulgel formulation (Table and Figure)

Table 7: % CADD of emulgel

Time (hrs)	%CADD Average ± SD
0.5	4.7
1	10.1
2	22.1
3	31.4
4	42.3
5	48.5
6	60.4
7	74.3
8	95.25

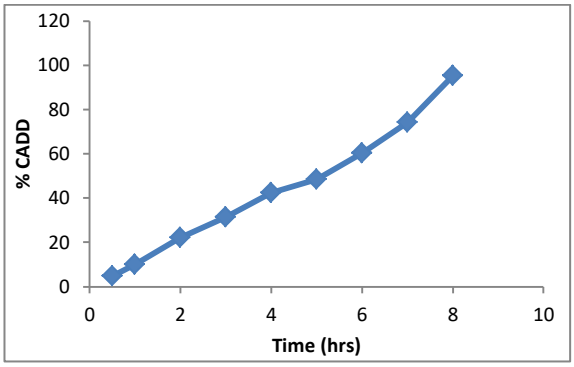

Figure 7: In-vitro drug diffusion study of emulgel

8. Skin Irritation study:

No allergic symptoms like inflammation, redness, irritation appeared on rats upto 24 hours and for 14 days.

Table 8: Stability test of emulgel

PARAMETERS	Optimized Fusidic acid loaded emulgel			
	Room temperature			
	0 Day	10 Day	20 Day	30 Day
Colour	White	White	White	White
Odour	Odourless	Odourless	Odourless	Odourless
pH	5.28	5.22	5.12	5
Spreadability	12.64	12.52	12.42	12.22
Viscosity (CPS)	9928	9919	9912	9905
% Drug content	99.86	99.23	98.56	97.55

Stability study of prepared emulgel formulation was performed as per ICH guidelines. It can observe that the emulgel formulation showed no major alteration in relation to the appearance, pH, drug content and in-vitro drug release study. From (table) it can be concluded that the prepared emulgel formulation was found to be stable upon storage for 1 month.

CONCLUSION

In the coming years topical drug delivery will be used extensively to impart better patient compliance. Since emulgel is helpful in enhancing spreadability, viscosity, this novel drug delivery become popular. Furthermore, they will become a solution for loading hydrophobic drugs in water soluble gel bases for long term stability. Similar in the study, topical emulgel of Fusidic acid was formulated and subjected to physiochemical studies i.e appearance, rheological studies, spreadability and in vitro drug release. In vitro drug release of the tests formulation was performed to determine drug release from emulgel rate and duration of drug release. From in vitro study formulation shows maximum release 95.25% in 8 hours. Prepared emulgel containing Fusidic acid showed significant result of anti-inflammatory activity. So emulgel containing Fusidic acid can be used as an steroidal bacteriostatic agents for topical drug delivery.

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