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Research Article

Design Development and Characterisation of Mupirocin Loaded Emulsion Based Gel

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ABSTRACT

The objective of the present study was to develop more retentive and effective drug delivery system for mupirocin. The research was going on in achieving effective formulation. Mupirocin is an anti-microbial agent that is used in wounds healing treatment. First Screening of oil, surfactant and co-surfactant for SEDDS carried out. Solubility of drug was investigated in different oils, surfactant and co-surfactants by UV method. A drug was dissolved in available oil in which it exhibited maximum solubility, then surfactant and co-surfactant were added in which drug showed maximum solubility, mixed well on a magnetic stirrer. Transparent SEDDS were formed. Carbopol 940 and Polyacrylate sodium gelling agent was suspended in water and hydrated for overnight separately. For preparation of Emulgel, various ratios of gel and SEDDS were set. Emulgel was evaluated for %drug release, pH, and drug content. The results indicated that Emulgel gave better controlled release. The formulation F11 showed 99.27 percent drug release, pH 6.7 ± 0.1 and drug content 99.4 ± 0.11%. Formulation F11 was selected as an optimized formulation. The formulations of Emulgel delivered very good therapeutic efficacy for topical application.

Introduction

Diabetes mellitus is a metabolic disorder that obstructs normal steps of wound healing process. Many histopathological studies showed prolonged inflammatory phase in diabetic wounds, which causes delay in the formation of mature granulation tissue and a parallel reduction in wound tensile strength. Diabetic foot ulcers frequently become infected and are a major cause of hospital admission. The healing of cutaneous wounds is a dynamic, complex, and well-organized process and requires the balance of many different cell types and cellular processes. The classic model of wound healing is divided into three sequential phases: inflammatory, proliferative, and maturation.[1]

The topical delivery system increases the contact time and mean residence time of the drug at the applied site leading to an increase in local drug concentration. While the pharmacological action of Emulgel formulations may not change as rapidly as the solution form.[2]

An emulgel is a gellified emulsion prepared by mixing an emulsion either water-in-oil (W/O) type or oil-in-water (O/W) type with a gelling agent. Due to solubility problem, most of lipophilic drugs cannot be formulated directly as hydrogel. Hence, the emulgel provides better stability and releases of the lipophilic drug in comparison with simple hydrogel base. When gel and emulsion are used in a combined form, such dosage form is referred as emulgel.[3-6] The aim of the present work was to formulate, develop and evaluate Emulgel formulation of mupirocin using polyacrylate sodium as a gelling agent.

Materials and Methods

Materials

Mupirocin was received as a generous gift sample from Concord Biotech Limited, Ahmedabad, Gujarat, India.

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Castor oil, methanol, dimethyl formaldehyde (DMF) and Whatman paper were purchased from Oxford Laboratory, Mumbai, India. Span 80 and PEG 400 were purchased from Loba Chemie Lab., Mumbai, India. Carbopol 940, and Polyacrylate sodium were purchased from Cadila Pharmaceuticals Ltd, Ahmedabad, India. All other chemicals were used of analytical grade and tried without any further chemical modification.

Methods

Supersaturated Solubility Study

Measured quantity of oil, surfactant (S) or cosurfactant (Co-S) were taken in a test tube and an excess quantity of mupirocin mixed together, kept for 48 hours in Orbital Shaking Incubator (1HB-164, Remi Equipment Ltd., Vasai, India) at 200 rpm. Thereafter, sufficient quantity of supernatant was withdrawn and diluted with respective solvents (phosphate buffer pH 6.8, methanol and DMF). Absorbance at a specific wavelength (methanol 220 nm and DMF 224 nm) was measured in Double Beam UV visible Spectrophotometer (LT-2900, Labtronics (I) Pvt. Ltd., Ambala, India). Solubility was achieved by using equation derived from the calibration plot equation (y = 0.049x + 0.0287 for phosphate buffer pH 6.8, y = 0.0523x + 0.034 for methanol and y = 0.052x + 0.0107 for DMF). Solubility study of oil, S and Co-S were performed using DMF as reference solvent.[7] Preliminary batches (P1–P27) were formulated with a S/Co-S ratio of 1:1, 1:2, and 2:1 w/w (Table 1) and evaluated for pH, cloud point, robustness, thermodynamic stability study, and self-emulsification time (SET).

Table 1: Composition of SEDDS batch P1 to P27

Batch Code	*Castor oil (g)*	*Span-80 (g)*	*PEG-400 (g)*
P1	1	4.5	4.5
P2	2	4	4
P3	3	3.5	3.5
P4	4	3	3
P5	5	2.5	2.5
P6	6	2	2
P7	7	1.5	1.5
P8	8	1	1
P9	9	0.5	0.5
P10	1	3	6
P11	2	2.66	5.32
P12	3	2.33	4.66
P13	4	2	4
P14	5	1.67	3.34
P15	6	1.33	2.66
P16	7	1	2
P17	8	0.67	1.34
P18	9	0.33	0.66
P19	1	6	3
P20	2	5.32	2.66
P21	3	4.66	2.33
P22	4	4	2
P23	5	3.34	1.67
P24	6	2.66	1.33
P25	7	2	1
P26	8	1.34	0.67
P27	9	0.66	0.33

Construction of Ternary Phase Diagram

For ternary phase diagram construction, oil was added to the S and Co-S mixture and prepared SEDDS in 200 mL phosphate buffer pH 6.8. For constructing a phase diagram at a ratio of S/Co-S (i.e., 1:1, 1:2, and 2:1 w/w), 1 mL of bland of the S/ Co-S was added in 200 mL of phosphate buffer pH 6.8 and evaluated for self-emulsification ability. A clear and homogenous mixture of oil and S/Co-S was formed using a magnetic stirrer (2MLH, Remi Equipments Ltd. Mumbai, India) for 5 minutes at 200 rpm. The resultant mixture was observed visually for phase clarity. The chosen value of oils and S/Co-S mixing ratio was used to determine the boundaries of emulsion domain. To determine the effect of mupirocin on emulsion boundary, phase diagrams were also constructed in the presence of mupirocin using drug enriched oil as a hydrophobic component (Fig. 1). Phase diagrams were constructed using Prosim ternary diagram software (ProSim, Inc., USA).[7]

Preparation of SEDDS Formulations

A series of SEDDS formulations were prepared with selected S/Co-S blend and oil by using simplex lattice design. An accurately weighed mupirocin was placed in a test tube, the added amount of oil, S, and Co-S. Then all components were mixed by a magnetic stirrer at 200 rpm until mupirocin was perfectly dissolved. The mixture was kept in a well closed container at room temperature.[8]

Formulation Optimization

The simplex lattice design was used to optimize the formulation of SEDDS containing mupirocin. The concentration of oil (X1), surfactant (X2), and co-surfactant (X3) were chosen as the independent variables. The emulsification time, cloud point, and cumulative % drug release were taken as responses (Y). The equation for the simplex lattice model is described as follows:

$$Y = \beta o + \beta 1X1 + \beta 2X2 + \beta 3X3 + \beta 12X1X2 + \beta 13X1X3 + \beta 23X2X3$$

Where *Y* is the dependent variable and βi is the estimated coefficient for the factor *Xi*. The major effects (X1, X2, and X3) represented average changes one factor from its low to high value. The interactions X1X2, X2X3, X1X3,

and polynomial terms show how the responses change when two or three factors change simultaneously. According to simplex lattice design and the selected concentration ranges of oil, surfactant, and co-surfactant, seven different formulations of SEDDS containing mupirocin were constructed (Table 2). The responses for seven formulations were used to fit the equation for simplex lattice model to predict properties of all possible formulations. With the aid of Design Expert® trial version 7, the model equation was developed to represent the relationship between the self-emulsification time and cumulative % drug release and cloud point.[9]

Preparation of Gel

Accurately weighed quantity of polyacrylate sodium was taken in a dry beaker, and 10 mL of distilled water was added. It was mixed well using a mechanical shaker with constant stirring. More distilled water was added to it to maintain the consistency of the gel. The pH of the formulation was adjusted to 6.0 to 7.0 using Triethanolamine.[10]

Formulation of Emulgel

Optimized SEDDS batch F8 was selected for the preparation of Emulgel formulation. Oily and gel phases were mixed with the (ratio 1:1) continuous stirring at 60°C and allowed to cool to room temperature to obtain the Mupirocin Emulgel formulation. (Table 3).[10]

Table 2: Composition of formulation of Simplex lattice design using 1:2 S: Co-S ratio

Formulation code	*Castor oil (g)*	*Span-80 (g)*	*PEG-400 (g)*
F1	6.1	0.35	3.55
F2	3.9	2.55	3.55
F3	3.9	0.35	5.75
F4	5	1.45	3.55
F5	5	0.35	4.65
F6	3.9	1.45	4.65
F7	4.63	1.08	4.28

* Dose of Mupirocin 2 % w/w

Characterization of SEDDS formulations

Visual Observation

Visual observation of the formulation was done. Parameters such as Clarity, transparency/translucent, and phase separation were included and the formulations which had better clarity with no phase separation were confirmed for selection as clarity of the formulation was the initial priority of the emulsion.[11]

Density Measurement

The density of the SEDDS formulation was determined using specific gravity bottle. Weight of the empty Specific gravity bottle was noted. SEDDS was taken up to the neck of the specific gravity bottle and the weight was determined by using electronic balance. The difference between the total weight and empty specific gravity bottle weight gave weight of SEDDS. The volume of the SEDDS that was filled up to the neck was noted. The density of SEDDS was then calculated.[11]

$$\text{Density [g / mL]} = \frac{\text{Weight[g]}}{\text{Volume[mL]}}$$

Viscosity Measurement

The viscosity of the SEDDS formulation was determined by Brookfield Viscometer using spindle NO. 61 at 50 rpm at room temperature.[11]

Measurement of pH

The pH of SEDDS formulation was determined by using pH meter. The pH was determined by bringing the electrode in contact with the formulation allowing it to equilibrate for a min. pH meter was calibrated with the solution of pH 4.9 and 7.9 with water initially.[11]

Cloud Point Measurement

SEDDS was diluted with distilled water in the ratio of 1:40, placed in a water bath, and gradually increased

Table 3: Composition of Mupirocin emulgel formulations

Ingredient (%w/w)	*Formulation code*									
	F9	*F10*	*F11*	*F12*	*F13*	*F14*	*F15*	*F16*	*F17*	*F18*
					SEDDS					
Castor oil	6.05	6.05	6.05	6.05	6.05	6.05	6.05	6.05	6.05	6.05
Span 80	0.38	0.38	0.38	0.38	0.38	0.38	0.38	0.38	0.38	0.38
PEG 400	3.57	3.57	3.57	3.57	3.57	3.57	3.57	3.57	3.57	3.57
Mupirocin	2	2	2	2	2	2	2	2	2	2
Gel										
Polyacrylate sodium	0.5	0.75	1	1.25	1.5	-	-	-	-	-
Carbopol 940	-	-	-	-	-	0.5	0.75	1	1.25	1.5

Triethanolamine was added to adjust the pH of all formulations from 5.5 to 6.5

its temperature. Cloud point was measured as the temperature at which there was a sudden appearance of cloudiness visually.[11]

Robustness to Dilution for SEDDS

Robustness to dilution was studied by diluting SEDDS to 20, 50, and 100 times with distilled water. The diluted SEDDS were stored for 12 hours and observed for phase separation or drug precipitation signs.[11]

Drug Content

Mupirocin from preweighed SEDDS was extracted by dissolving in 10 mL DMF. Mupirocin content in the DMF extract was filtered and analyzed spectrophotometrically at 224 nm, against the standard placebo DMF solution of SEDDS.[12]

In-vitro Diffusion Study of SEDDS Formulations

Mupirocin diffusion study was performed using a modified dialysis technique. One end of pretreated cellulose dialysis tubing (7 cm in length; Nipro Medical India Pvt. Ltd) was tied to IP type I dissolution test apparatus (Electro lab, Mumbai, India) using thread and then 0.1 mL of SEDDS (equivalent to 2% w/w mupirocin) was placed with 2 mL of dialyzing medium (phosphate buffer pH 6.8). The opposite end of the tube was also shared with thread and was rotated freely in the dissolution vessel containing 200 mL dialyzing medium, maintained at 37 ± 0.5°C, and stirred at 50 rpm. The samples were withdrawn at time intervals of 5, 10, 15, 30, 45, 60, 75, and 90 minutes, each and analyzed for the drug.[12]

Thermodynamic Stability

Heating-cooling Cycle: Three cycles of storage refrigerator temperature at 8°C of 48 hours was studied. Those formulations, which were stable at this temperature, were subjected to centrifugation test.

- *Centrifugation:* Formulation was centrifuged at 3500 rpm for 30 minutes. Those formulations that did not show any phase separation were taken for the freeze-thaw stress test.
- *Freeze-thaw cycle:* Three freeze-thaw cycles stored at -15°C temperature for not less than 48 hours was done for the formulations. Those formulations, which passed these thermodynamic stress tests, were further taken for the dispersibility test for assessing the efficiency of self-emulsification.[13]

Dispersibility Test

The efficiency of self-emulsification of SEDDS was assessed using standard IP type - I dissolution apparatus. 1 mL of the formulation was added to 200 mL of distilled water at 37 ± 0.5°C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. In-vitro performance of the formulations was visually assessed using the following grading system:

- Grade A: Rapidly forming (within 1 min) emulsion, having a clear or bluish appearance.
- Grade B: Rapidly forming, slightly less clear emulsion, having a blue-white appearance.
- Grade C: Fine milky emulsion that formed within 2 minutes.[13]

Self-emulsification Time

0.5 g of the SEDDS formulation was introduced into 20 mL of distilled water in beaker under the magnetic stirrer rotating at a constant speed. Emulsification time was determined at room temperature.[14]

Characterization of Emulgel and BACTROBAN® CREAM

Physical Examination

Emulgel formulation was inspected visually for their color, homogeneity, consistency, and phase separation.[15] pH and viscosity were also determined.

Spreadability

Formulation whose spreadability was determined was placed over one slide, and the other slide was placed over its top such that the gel is sandwiched between the two slides. The slides were pressed upon each other to displace any air present, and the adhering gel was wiped off. The two slides were placed onto a stand such that only the lower slide is held firmly by the clamp's opposite fangs, allowing the upper slide to slip off freely by the force of weight tied to it. 20 g weight was tied to the upper slide carefully. The time taken by the upper slide to completely detach from the lower slide was noted.[16] The spreadability was calculated by using the following formula.

$$S = \frac{M.L}{T}$$

Here,
M = weight tied to upper slide
L = length of glass slides
T = time taken to separate the slides

Extrudability

Emulgel formulation was filled within a clean, lacquered aluminum collapsible tube with a 5 mm opening nasal tip. Extrudability was then determined by measuring the gel extruded through the tip when a constant load of 1 kg was placed over the pan.[17] The extrudability of emulgel formulation was calculated by using the following formula.

Extrudability=(Amount of gel extruaded from the tube × 100)/(Total amount of gel filled in the tube)

Drug Content

1 g of the formulation was taken into 10 mL volumetric flask, and 1 mL methanol was added to it, and it was shaken well and made up the volume with phosphate buffer pH 6.8. The volumetric flask was kept for 2 hours and shaken well

in a shaker to mix it properly. The solution was passed through the filter paper, filtered the mixer, then measured absorbance using a spectrophotometer at 224 nm.[18]

Drug Content = (Conc.× Dilution Factor × Vol.taken) × Conversion Factor

In-vitro Drug Release Study

The *in-vitro* drug release of the Emulgel was carried out on a Diffusion cell using an egg membrane. This was clamped carefully to one end of the hollow glass tube of the dialysis cell. Emulgel (1 g) was applied onto the surface of the egg membrane dialysis membrane. The receptor chamber was filled with freshly prepared phosphate buffer solution pH 6.8 to solubilize the drug. A magnetic stirrer stirred the receptor chamber. The samples were collected at suitable time intervals sample and analyzed for drug content by a UV visible spectrophotometer at 224 nm after appropriate dilution. The cumulative amount of drug release across the egg membrane was determined as a function of time.[19,20]

Results and Discussion

Fourier Transform Infrared Spectroscopy (FTIR) Study

IR spectrum of mupirocin was recorded, and it was found following the reported peaks (Fig. 2). The IR spectra of mupirocin comply with its chemical structure and show peaks for principal groups.[21]

Drug Solubility Study

The solubility study of the drug in various oils, surfactants and co-surfactants was carried out, and the results were summarized in Table 4. The solubility of the mupirocin in castor oil was found to be 4848.65 µg/mL, in Span 80 is 3645.44 µg/mL and in PEG 400 is 4098.00 µg/mL. Among the various oils studied, the highest solubility was found in Castor oil, Span 80 exhibited the highest solubility among surfactants, and PEG 400 was among the co-surfactant. So based on the solubility, castor oil, Span 80, and PEG 400 were selected for further study of emulsion. The results of the emulsification study showed that Castor oil, PEG 400, and Span 80 had the highest solubility capacity of mupirocin. Therefore, Span-80 and PEG-400 were selected as surfactants and co-surfactant, respectively.[22]

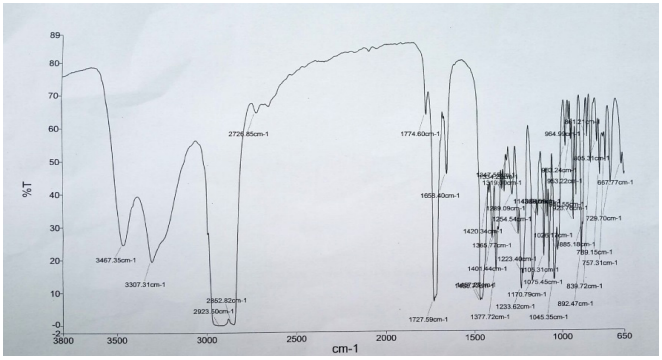

Fig. 1: FT-IR study of Mupirocin
Characterization peak: O-H group 3467.35 and 3307.31 cm^{-1}, C=O group 1774.60 and 1727.59 cm^{-1}, C-O group 1233.62 and 1223.40 cm^{-1}.

Pre-formulation Parameter for Batch P1–P27

Formulation P1-P27 showed pH in the range of 6.1 to 6.6, which was desirable pH for SEDDS formulation (neither

Table 4: Solubility of Mupirocin in Oil, Surfactant, Co-surfactant

Oil	*Solubility (µg/mL)**
Almond Oil	425.57 ± 78.91
Arachis Oil	740.95 ± 93.40
Castor Oil	4848.65 ± 200.96
Cinnamon Oil	2683.90 ± 127.36
Cod liver Oil	259.54 ± 21.27
Coconut Oil	356.98 ± 34.95
Corn Oil	797.36 ± 82.90
Glyceryl monooleate Oil	3055.05 ± 246.94
Isopropyl myristate Oil	584.54 ± 42.54
Isopropyl palmitate Oil	2453.14 ± 151.74
Labrafac Oil	226.85 ± 38.85
Neem Oil	495.44 ± 35.68
Olive Oil	193.52 ± 35.78
Oleic acid Oil	525.57 ± 100
Palm Oil	4075.05 ± 205
Pippermint Oil	1356.31 ± 55.67
Rose Oil	515.95 ± 52.06
Soyabean oil	2181.98 ± 108
Sunflower Oil	4267.24 ± 83.96
Triacetin Oil	3326.85 ± 165
Acrysol K140	844.80 ± 43.55
Acrysol K150	426.21 ± 67.45
Acrysol K160	487.75 ± 40.53
Cremophor	227.49 ± 20.26
Gelucire 44/14	444.80 ± 56.75
Labrafil 1944	246.08 ± 52.50
Span 20	2380.7 ± 273
Span 80	3645.44 ± 310
Tween 20	2323.65 ± 162
Tween 60	956.07 ± 159
Tween 80	2413.39 ± 247
PEG 200	2944.85 ± 430
PEG 400	4098.00 ± 150
PEG 600	806.98 ± 88.46
Propylene glycol	1730.7 ± 112
Transcutol-P	323.01 ± 56.86

* The values represent mean ± S.D, n=3

Table 5: Results of formulation P1-P9 of SEDDS

Batch Code	*S.E.T (S)*	*C.P (°C)*	*pH*	*Batch Code*	*S.E.T (S)*	*C.P (°C)*	*pH*	*Batch Code*	*S.E.T (S)*	*C.P (°C)*	*pH*
P1	3.21	58	6.2	P10	3.22	62	6.3	P19	3.22	64	6.3
P2	3.38	66	6.4	P11	3.31	68	6.4	P20	3.31	60	6.1
P3	3.41	64	6.1	P12	3.43	60	6.4	P21	3.43	62	6.2
P4	3.57	70	6.2	P13	3.57	64	6.1	P22	3.57	64	6.2
P5	3.48	74	6.5	P14	3.38	70	6.2	P23	3.38	60	6.5
P6	3.51	72	6.2	P15	3.41	64	6.2	P24	3.41	62	6.6
P7	3.44	62	6.1	P16	3.45	62	6.2	P25	3.45	62	6.3
P8	3.31	60	6.3	P17	3.37	60	6.4	P26	3.37	60	6.4
P9	3.58	64	6.4	P18	3.54	60	6.1	P27	3.54	64	6.1

Stable*: No phase separation after specific cycle

Table 6: Results of Characterisation of Formulation F1-F8

Formulation code	*S.E.T (S)*	*Viscosity(cP)*	*pH*	*Density (g/mL)*	*C.P (°C)**	*Drug content (%)**
F1	3.11 ± 0.02	144 ± 1	6.2 ± 0.2	0.95 ± 0.01	72 ± 2	99.06 ± 1.02
F2	3.28 ± 0.06	263.9 ± 0.9	6.1 ± 0.3	1.01 ± 0.03	70 ± 3	100.86 ± 0.94
F3	3.41 ± 0.11	251.9 ± 0.7	6.2 ± 0.2	0.99 ± 0.25	74 ± 1	100.21 ± 0.32
F4	3.57 ± 0.03	216 ± 1	6.4 ± 0.1	0.96 ± 0.17	70 ± 3	103.08 ± 0.27
F5	3.38 ± 0.07	168 ± 2	6.3 ± 0.2	0.99 ± 0.02	70 ± 2	98.20 ± 0.43
F6	3.21 ± 0.03	263.9 ± 1.2	6.4 ± 0.2	0.99 ± 0.03	74 ± 2	100.55 ± 57
F7	3.44 ± 0.02	192 ± 1	6.1 ± 0.1	0.99 ± 0.02	72 ± 2	96.93 ± 1.07
F8	3.14 ± 08	145 ± 1	6.2 ± 0.3	1 ± 0.25	72 ± 2	99.66 ± 0.23

Stable*: No phase separation after specific cycle,

1. * The values represent mean ± S.D, n=3

too acidic nor too basic). Cloud point of formulation P1-P27 was n between 60-74°C. It was concluded that higher cloud points indicated good stability. In thermodynamic stability study, Formulation P1-P27 was stable for the heating-cooling cycle, centrifugation test, and freeze-thaw cycle. The appearance of batch P9 & P17 was turbid, and the remaining formulations were translucent. Visual Observation of P1-P27 formulations showed good stability, dispersibility of Grade A, and good robustness. All 27 batches showed a self-emulsification time of less than 4 seconds (Table 5).[11]

Construction of Ternary Phase Diagram

The area of SEDDS increased as the surfactant concentration increased because of Span 80, a non-ionic solvent that forms a clear solution in water (Fig. 1). The largest SEDDS region was obtained for the 1:2 surfactant: co-surfactant ratio, and the smallest SEDDS area was obtained at the ratio 2:1.[9]

Characterization of SEDDS Formulation

Cloud point of SEDDS formulation F1–F7 was found to be higher at 70°C, which indicated that the emulsion was stable at physiological temperature without the risk of phase separation. Robustness to dilution was studied by diluting SEDDS to 20, 50, and 100 times with distilled water. The diluted SEDDS were stored for 12 hours and observed for phase separation or drug precipitation signs. The pH of F1–F7 formulation ranged from 6.1 to 6.4, which was acceptable to avoid any skin irritation. In the thermodynamic stability study, the formulations F1–F7 were stable for the heating-cooling cycle, centrifugation test, and freeze-thaw cycle. The appearance of formulation F1–F3 was translucent and of F4-F7 was transparent. Visual observation was stable, dispersibility of Grade A and good robustness was found for the formulations. The percentage drug content of SEDDS was found in the range of 96.93 to 103.08%. The highest drug content, i.e., 103.08%, was obtained for the formulation F4 (Table 6).[11]

In-vitro Diffusion Study

The percentage cumulative drug release of F1-F8 emulgel formulations at the end of 90 min was represented in Table 7. Maximum drug release was observed for the formulation F8, i.e., 100.12 ± 0.49%, and the minimum was obtained for batch F3, i.e., of 99.54 ± 2.30 %. The higher release was due to the ratio of surfactant and co-surfactant (1:2), as the release of drug from SEDDS might be more because of the more concentration of co-surfactant. The release was dependent on the polymer concentration and the viscosity of the polymer.[8,10]

Table 7: Results of Diffusion profile of Batch F1–F8

Time (min)	*F1* (%)*	*F2* (%)*	*F3* (%)*	*F4* (%)*	*F5* (%)*	*F6* (%)*	*F7* (%)*	*F8* (%)*
5	82.98 ± 0.55	62.21 ± 0.57	70.21 ± 0.21	43.63 ± 0.56	47.88 ± 0.93	61.08 ± 0.55	32.69 ± 0.62	77.08 ± 0.27
10	91.25 ± 0.61	71.25 ± 0.41	81.73 ± 0.42	61.24 ± 0.44	57.50 ± 0.55	72.22 ± 0.47	45.68 ± 0.76	90.58 ± 0.33
15	92.27 ± 0.59	80.83 ± 0.72	90.21 ± 0.52	63.24 ± 0.67	64.27 ± 0.70	87.08 ± 0.54	53.11 ± 0.69	94.68 ± 0.78
30	95.30 ± 0.61	90.31 ± 0.56	94.11 ± 0.33	72.15 ± 0.51	73.19 ± 0.61	92.98 ± 0.72	63.07 ± 0.22	100.12 ± 0.49
45	98.12 ± 0.51	95.20 ± 0.34	97.16 ± 1.40	90.33 ± 0.92	82.98 ± 0.90	95.30 ± 0.54	90.20 ± 0.47	–
60	100.07 ± 0.58	100.11 ± 0.13	99.54 ± 2.30	99.78 ± 2.70	91.38 ± 0.66	99.12 ± 0.56	96.10 ± 0.46	–
75	–	–	–	–	96.99 ± 0.66	–	98 ± 0.08	–
90	–	–	–	–	99.96 ± 0+.84	–	100.1 ± 0.37	–

*The values represent mean ± S.D, n=3

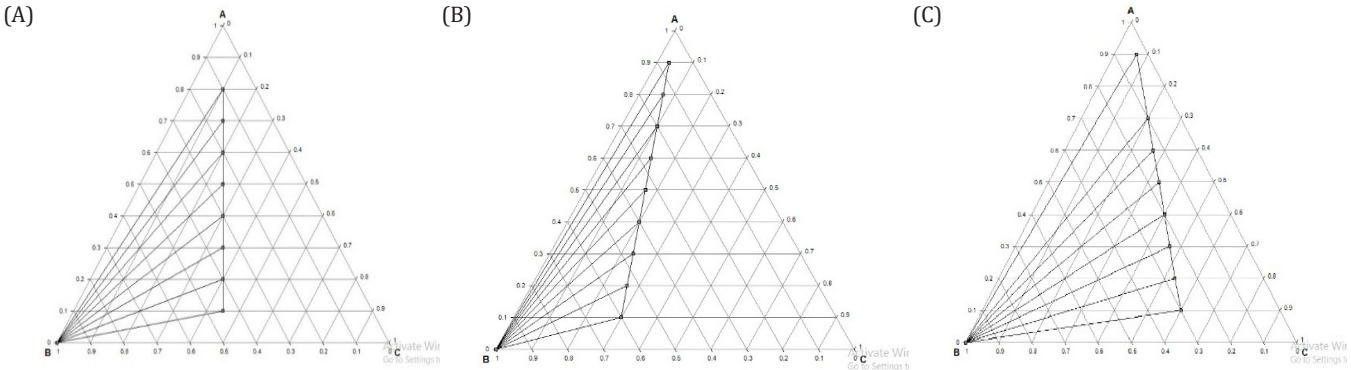

Fig. 2: (A) S/Cos ratio 1:1; (B) S/Cos ratio 1:2; (C): S/Cos ratio 2:1

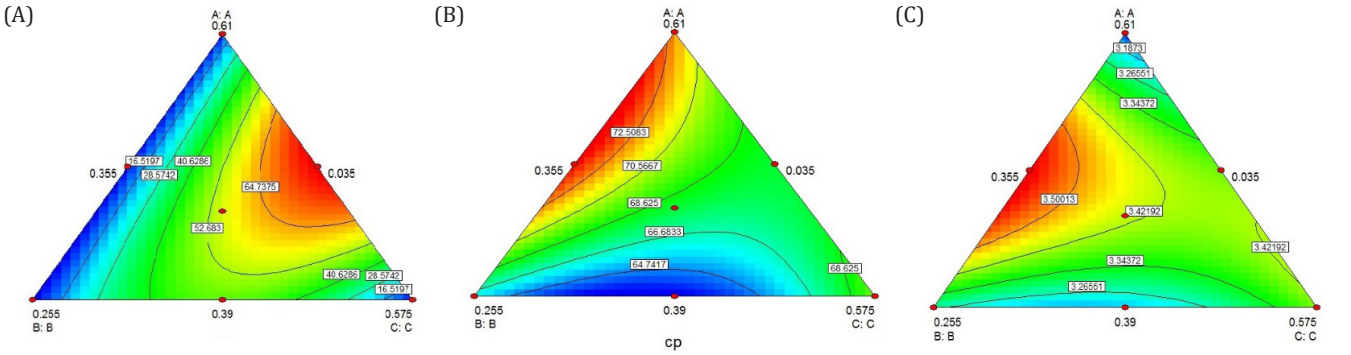

Fig. 3: (A) Contour plot for t90; (B): Contour plot for cloud point; (C): Contour plot for self-emulsification time

Contour Plots

Contour plots showed an inverse relationship between emulsification time, t90, and cloud point (Fig 3 and Table 8). The proportion of oil, surfactant, and co-surfactant in checkpoint batch F8 were 0.6052, 0.0378, and 0.3569, respectively (Fig.4).[9]

Optimization of Formulation

Polynomial Equations from Design Expert

1. Y1 (t90)=-1187.28127*A-403.19036*B-1533.77365 *C+5767.20967*A*C +3494.48240*B*C

Significance value for AC = 0.0036, Significance value for BC = 0.0098, R- Squared = 0.9950, Significance value of mathematical model = 0.0101

2. Y2 (C.P) = +115.91529*A+0.62603*B+144.42769*C+41 3.22314*A*B-247.93388*A*C -413.22314*B*C

Significance value for AB = 0.0001, Significance value for AC = 0.0001, Significance value for BC = 0.0001, R- Squared = 1.0000, Significance value of mathematical model = 0.0001

3. Y3 (S.E.T) = -0.43465*A -3.31594*B+2.04394*C+31.367 39*A*B+10.29301*A*C-10.78137*B*C Significance value for AB = 0.0200

Significance value for AC = 0.0609, Significance value for BC = 0.0582, R- Squared = 0.9992, Significance value of mathematical model = 0.0469

All three polynomial equations having R square value near to one indicated that mathematical models have better accuracy.[9]

Table 8: Results of Responses of formulation of Simplex lattice design

Formulation code	*T90 (min)*	*Cloud Point (°C)*	*Self-emulsification time (S)*
F1	10	72	3.11
F2	30	70	3.28
F3	15	74	3.41
F4	45	70	3.57
F5	60	70	3.38
F6	30	74	3.21
F7	45	72	3.44

Table 9: Evaluation Parameter of Check Point batch F8

Evaluation Test	Observation
Heating cooling cycle	Stable
Centrifugation	Stable
Freeze thaw cycle	Stable
Appearance	Translucent
Visual observation	Stable
Self-emulsification time (S)*	3.14 ± 08
Viscosity (cP)*	145 ± 1
pH*	6.2 ± 0.3
Density (g/mL)*	1 ± 0.25
Cloud point (°C)*	72 ± 2
Robustness	Yes
Drug content (%)*	99.66 ± 0.23
Dispersibility (Grade)	A

Stable*: No phase separation after specific cycle
1. * The values represent mean ± S.D, n=3

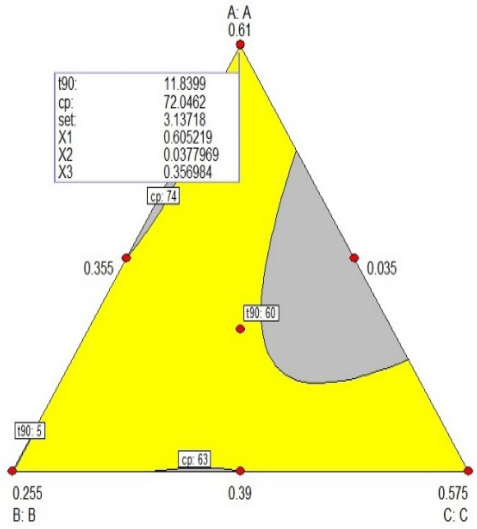

Fig. 4: Overlay plot for t90, cloud point and Emulsification time

Cloud point of SEDDS formulation F8 was higher at 72°C, which indicated that the emulsion was stable at physiological temperature without the risk of phase separation. Heating cooling cycle, centrifugation, and Freeze-thaw cycle indicated that the formulation was stable. Robustness to dilution was studied by diluting SEDDS to 20, 50, and 100 times with distilled water. The diluted SEDDS were stored for 12 hours and observed for any phase separation or drug precipitation signs. The pH value of F8 formulation was 6.2 (Table 9), which was acceptable to avoid any skin irritation.[12] Mupirocin dissolved in SEDDS showed a faster drug release rate into the aqueous phase (Table 7), enhancing bioavailability.[12]

Characterization of Emulgel and BACTROBAN® CREAM

Physical Appearance

The appearance of F9-F18 Emulgel formulations was white viscous, creamy smooth preparation with excellent consistency. The homogeneity of formulations F10-F13, and F15-F16 was excellent with a glossy appearance and excellent extrudability without any phase separation. That indicated the physical stability of the formulations with acceptable features. The results of all formulations were found acceptable in comparison to the BACTROBAN® CREAM.[23]

Determination of pH

The pH of F9–F18 formulation ranged from 6.1 to 6.8, which matches the normal pH range of skin and thus does not produce any skin irritation (Table 10). The pH of all formulations was acceptable in comparison to the BACTROBAN® CREAM.[24]

Measurement of Viscosity

The viscosity of the formulation increases with increasing of polymer concentration. The viscosity of formulation F9-F18 was from 3154 cP to 15234 cP (Table 10). The highest viscosity was observed for Emulgel formulation F13 having 15234 Cp. The viscosity results were acceptable in comparison to the BACTROBAN® CREAM.[25]

Spreadability

The spreadability value of batch F9-F18 was depicted in Table 10. The formulation F11 having viscosity 15234 cP exhibited high spreading coefficient of 35.4 ± 0.1 g.cm/s (Table 10). The spreadability is dependent on the concentration of polymer and viscosity of the formulation. The spreadability of a formulation containing 2% concentration was lower than the one containing 1.5% polymer concentration. The spreadability of the formulation containing Polyacrylate sodium was less than one containing Carbopol 940. All formulation spreadability results were acceptable in comparison to the BACTROBAN® CREAM.[26]

Extrudability

The formulation F11 has excellent extrudability as its viscosity was 15234 cP (Table 10). The extrudability is dependent on the viscosity of the polymer, so as

Table 10: Results of Evaluation Parameter of Emulgel Formulation

Batch Code	*pH*	*Viscosity (cP)*	*Spreadability (g.cm/s)*	*% Drug content*
F9	6.4 ± 0.1	7920	18.7 ± 0.6	97.3 ± 0.57
F10	6.2 ± 0.3	9540	29.1 ± 0.3	97.7 ± 0.36
F11	6.7 ± 0.1	15234	35.4 ± 0.1	99.4 ± 0.11
F12	6.1 ± 0.2	13370	32.2 ± 0.7	98.4 ± 0.73
F13	6.5 ± 0.2	10246	25.1 ± 0.5	97.2 ± 0.48
F14	6.3 ± 0.3	3154	21.5 ± 0.4	97.9 ± 0.62
F15	6.7 ± 0.1	3878	33.2 ± 0.8	99.1 ± 0.24
F16	6.8 ± 0.1	5242	30.5 ± 0.6	99.2 ± 0.19
F17	6.6 ± 0.2	5982	25.8 ± 0.2	98.6 ± 0.47
F18	6.1 ± 0.3	6870	16.8 ± 0.7	97.2 ± 0.73
BACTROBAN® CREAM	6.7 ± 0.04	9070	29.3 ± 0.4	98.2 ± 0.39

* The values represent mean ± S.D, n=3

Table 11: Results of Drug Release of Emulgel Formulation F9-F18

Time (Min)	*F9* (%)*	*F10* (%)*	*F11* (%)*	*F12* (%)*	*F13* (%)*	*F14* (%)*	*F15* (%)*	*F16* (%)*	*F17* (%)*	*F18* (%)*
10	45.68 ± 0.76	62.21 ± 0.57	33.11 ± 0.69	46.88 ± 0.93	42.63 ± 0.56	32.69 ± 0.62	61.08 ± 0.55	47.78 ± 0.83	37.68 ± 0.73	42.13 ± 0.29
20	64.27 ± 0.70	71.25 ± 0.41	46.08 ± 0.55	58.50 ± 0.55	63.24 ± 0.44	45.68 ± 0.76	72.22 ± 0.47	57.40 ± 0.35	48.50 ± 0.45	51.08 ± 0.45
30	73.19 ± 0.61	80.83 ± 0.72	57.15 ± 0.51	64.27 ± 0.70	66.24 ± 0.67	53.11 ± 0.69	87.08 ± 0.54	64.37 ± 0.50	58.27 ± 0.30	62.15 ± 0.11
40	90.20 ± 0.47	90.31 ± 0.56	68.08 ± 0.54	70.19 ± 0.61	71.15 ± 0.51	63.07 ± 0.22	92.98 ± 0.72	73.29 ± 0.41	73.19 ± 0.21	78.08 ± 0.64
50	93.12 ± 0.51	94.20 ± 0.34	86.10 ± 0.46	81.98 ± 0.90	91.33 ± 0.92	90.20 ± 0.47	95.30 ± 0.54	82.78 ± 0.60	82.98 ± 0.80	89.10 ± 0.36
60	97.00 ± 0.58	96.20 ± 0.17	99.27 ± 0.11	98.38 ± 0.66	97.18 ± 0.70	96.11 ± 0.46	99.02 ± 0.56	98.28 ± 0.36	95.38 ± 0.41	97.07 ± 0.18

* The values represent mean ± S.D, n=3

the viscosity increases, extrudability decreases. As the viscosity depends on the type of polymer and its concentration and even on the surfactant concentration, the extrudability value of the formulation containing F11 was higher than other formulations, and the extrudability was found to be less for the formulation F14 containing Carbopol 940.[27] Extrudability results of the formulation were acceptable in comparison to the BACTROBAN® CREAM.

Drug Content

The percentage of drug content for F9-F18 was in the range of 97.2 ± 0.48% to 99.4 ± 0.11% (Table 10). The highest drug content was found in F11 formulation 99.4 ± 0.11%, due to greater drug solubilization than other formulations. All formulations having drug content within the limits. Therefore it can be concluded that emulgel will deliver an accurate dose of medicament. All formulation drug content results were acceptable in comparison to the BACTROBAN® CREAM.[28]

In-vitro Drug Release Study

The percentage cumulative drug release of F9-F18 emulgel formulations at the end of 60 min is represented in Table 11. Maximum drug release was observed for the formulation F11, i.e., 99.27%, and a minimum of 95.38% was obtained for F17. The reason attributed to a higher release from the formulation depends on polymer concentration. If the polymer amount increased, the diffusion of the drug through the membrane was found to decrease. The release of the drugs from formulation can rank in the following descending order: F11 > F15 > F12> F16 > F13 >F18 > F9> F10>F14>F17. Thus formulation F11 showed good drug release properties than other formulations.[21]

Conclusion

The healing of cutaneous wounds is a dynamic, complex, well-organized process that requires the balance of many different cell types and cellular processes. Mupirocin is an anti-microbial agent that is used in wounds healing treatment. Emulgel formulation is a better option than the conventional topical semi-solid dosage form for better efficacy. The objective of the present study was to develop a more retentive and effective drug delivery system for mupirocin. Oil, surfactant, and co-surfactant were selected based on solubility results of preformulation study. Two gelling agents, carbopol 940 and Polyacrylate sodium were

tried for emulgel preparation. The emulgel formulation prepared using polyacrylate sodium showed excellent results in comparison to carbopol 940. Formulated emulgel showed acceptable physical appearance, pH, spreadability, extrudability, viscosity, drug content, *In-vitro* release. Formulation F11 showed the maximum drug release of 99.27% in 60 minutes with good physical properties compared to the BACTROBAN® CREAM. The emulgel formulation could be the best approach for topical delivery of mupirocin.

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