EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 01
254-262
Year: 2018

FORMULATION AND CHARACTERIZATION OF FAROPENEM SODIUM EMULGEL FOR TOPICAL APPLICATION

[1]*Kavita Varma and [2]Dr. Seema Kohli

[1]Research Scholar, Faculty of Pharmacy, Pacific Academy of Higher Education and Research University, Udaipur.
[2]HOD Pharmacy Department, Government Kalaniketan Polytechnic College, Jabalpur, M.P.

***Corresponding Author: Kavita Varma**
Research Scholar, Faculty of Pharmacy, Pacific Academy of Higher Education and Research University, Udaipur.

Article Received on 02/11/2017 **Article Revised on 23/11/2017** **Article Accepted on 13/12/2017**

ABSTRACT
Topical drug delivery systems have been utilized for centuries for the treatment of local skin disorders. One side the topical applications of the drug provides the potential advantages of delivering drug straightly to the site of action and delivering drug for extended period of time at the effected site that mainly acts at the related regions. On the other hand, topical delivery system elevates the contact time and mean resident time of drug. The objective of the study was to prepare emulgel of Faropenem sodium, using Carbopol 940 and 934 as a gelling agent. Propylene glycol was used as penetration enhancer. The emulsion was prepared and it was incorporated in gel base. The formulations were evaluated for rheological studies, spreading coefficient studies, extrusion studies, skin irritation studies, in vitro release, ex vivo release studies. Stability studies showed satisfactory results. It can be concluded that faropenem sodium emulgel showed good consistency, homogeneity, spreadability and stability and has wider prospect for topical preparations.

KEYWORDS: Emulgel, Faropenem Sodium, Topical gel, Carbopol.

1. INTRODUCTION

Faropenem Sodium is 1-4 Monosodium (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[(2R)- tetrahydrofuran-2-yl]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate hemipentahydrate. The antibacterial spectrum of Faropenem includes Gram-positive, Gram-negative and some anaerobic bacteria. Faropenem Sodium is a sodium salt of novel β-lactam antimicrobial with a pane (furanem) structure used to treat bacterial sinusitis, pneumonia, bronchitis and skin infections. Faropenem Sodium occurs as white to light yellow, crystals or crystalline powder. It is freely soluble in water and in methanol, slightly soluble in ethanol.[1-4]

As with other penems, faropenem induces bactericidal effects by binding to PBPs and inhibiting bacterial cell wall synthesis. These bactericidal effects were found to be affected by the nature of the tetrahydrofuran side chain, with an unsaturated derivative showing reduced activity compared with that of the saturated derivative (faropenem).[5]

Many widely used topical agents like ointment, cream, lotion have many disadvantages. They have very sticky causing uneasiness to the patient when applied. Moreover they also have lesser spreading coefficient and need to apply with rubbing . And they exhibit the problem of stability also. Due to all these factors within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. When gels and emulsions are used in combined form the dosage forms are referred as EMULGELS.[6]

Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, long shelf life, bio-friendly, transparent & pleasing appearance.[7,8,9]

The aim of this work was to develop an emulgel formulation of faropenem sodium, a hydrophilic drug, using Carbopol 940 and Carbopol 934 as gelling agent and two types of penetration enhancer, propylene glycol and oleic acid. The influence of gelling agent and penetration enhancers was investigated. The rheological studies, spreading coefficient studies, pH, extrusion studies, stability studies ,skin irritation studies, in vitro release, ex vivo release studies, of emulgels were also evaluated.

2. MATERIALS AND METHOD

2.1 Materials

Faropenem sodium was obtained as a gift sample from Macleods Pharmaceuticals, Vapi (Gujrat), Carbopol 940 was obtained from Loba chemicals Mumbai. Dialysis

membrane was procured from Hi media, Mumbai. All other chemicals used were of analytical grade and were used without any further chemical modification.

Preparation of emulgel formulation

1. Preparation of gel base

Carbopol 934 and Carbopol 940 were dispersed in distilled water separately with constant stirring at a moderate speed using a mechanical shaker.

2. Preparation of emulsion

The oil phase was prepared by dispersing the drug in light liquid paraffin. To this oleic acid and span 80 were added and heated to 70-80°C. the aqueous phase was prepared by dissolving Tween 80 and propylene glycol in purified water. To this methyl paraben and propyl paraben were added and heated to 70-80°C. The emulsion was prepared by adding the oil phase slowly to the aqueous phase with constant stirring. Then, the mixture was stirred using a homogenizer with a speed of 1500 rpm at room temperature and the emulsion was formed.

3. Preparation of emulgel

The emulgel was prepared by incorporating the emulsion into the gel base in the ratio of 1:1.

Table 1: Composition of different formulation batches (%w/w).

Batch code	Drug conc	Polymer conc.		Emulsifier concentration		Penetration enhancers		Stirring rate	Temperature range
		Carbopol 934	Carbopol 940	Span 80	Tween 80	Propylene glycol	Oleic acid		
F1	2.5	1	1	1	0.5	5	2	1500	40-50
F2	2.5	1	1	1	0.5	5	2	1500	50-60
F3	2.5	1	1	1	0.5	5	2	1500	60-70
F4	2.5	1	1	1	0.5	5	2	1500	70-80
F5	2.5	0.5	1	1	0.5	5	2	1500	50-60
F6	2.5	1	1	1	0.5	5	2	1500	50-60
F7	2.5	1.5	1	1	0.5	5	2	1500	50-60
F8	2.5	2	1	1	0.5	5	2	1500	50-60
F9	2.5	1	0.5	1	0.5	5	2	1500	50-60
F10	2.5	1	1.5	1	0.5	5	2	1500	50-60
F11	2.5	1	2	1	0.5	5	2	1500	50-60
F12	2.5	1	1	0.5	0.5	5	2	1500	50-60
F13	2.5	1	1	1.0	0.5	5	2	1500	50-60
F14	2.5	1	1	1.5	0.5	5	2	1500	50-60
F15	2.5	1	1	2	0.5	5	2	1500	50-60
F16	2.5	1	1	1.0	0.3	5	2	1500	50-60
F17	2.5	1	1	1.0	0.4	5	2	1500	50-60
F18	2.5	1	1	1.0	0.6	5	2	1500	50-60
F19	2.5	1	1	1.0	0.5	3	2	1500	50-60
F20	2.5	1	1	1.0	0.5	4	2	1500	50-60
F21	2.5	1	1	1.0	0.5	5	2	1500	50-60
F22	2.5	1	1	1.0	0.5	6	2	1500	50-60
F23	2.5	1	1	1.0	0.5	5	1	1500	50-60
F24	2.5	1	1	1.0	0.5	5	1.5	1500	50-60
F25	2.5	1	1	1.0	0.5	5	2.5	1500	50-60
F26	2.5	1	1	1.0	0.5	5	2	1000	50-60
F27	2.5	1	1	1.0	0.5	5	2	1250	50-60
F28	2.5	1	1	1.0	0.5	5	2	1500	50-60
F29	2.5	1	1	1.0	0.5	5	2	1750	50-60

OPTIMIZATION OF FAROPENEM SODIUM EMULGEL

1. Effect of temperature

The temperature was optimized during preparation of the emulgel, at different temperature range viz, 40-50°C, 50-60°C, 60-70°C, 70-80°C keeping other variables constant as described in general procedure of preparing faropenem sodium emulgel.

2. Effect of polymer concentration.

Amount of carbapol 934 and carbapol 940 for the preparation was optimized by preparing the emulgel in different amount and there ratios, keeping other variables constant as described in general procedure of preparing faropenem sodium emulgel.

3. Effect of emulsifier concentration.

Emulsifier concentration was optimized at different concentration of tween 80 and span 80, keeping other

variables constant as described in general procedure of preparing faropenem sodium emulgel.

4. Effect of penetration enhancer concentration.
Concentration of polyethylene glycol and oleic acid as penetration enhancer was optimized at different concentration, keeping other variables constant.

5. Effect of stirring rate.
Stirring rate for the preparation of emulgel was optimized at different stirring rate, viz, 1000, 1250, 1500 and 1750 rpm and keeping other variables contant.

EVALUATION O FAROPENEM SODIUM GEL
Physical examination
The prepared emulgel formulations were inspected visually for their color, appearance and consistency.

Measurement of pH
The pH of the optimized hydrogel was determined using Dynamic pH meter [Electrolab] which was previously calibrated using pH 4 and pH 7 buffer solutions. The pH of the optimized hydrogel formulations was measured in triplicate and average values were calculated.

Drug content
The optimized emulgel (100 mg) was taken in a 100 ml volumetric flask and dissolved in 100 ml of phosphate buffer pH 6.8. It was sonicated for 20 minutes for the hydrogel to get completely solubilized in the phosphate buffer pH 6.8. One ml of this solution was withdrawn and filtered using Whatmann filter paper in a 10 ml volumetric flask, volume was made up using phosphate buffer pH 6.8.The drug was quantitated using a developed and validated UV method of analysis.[10]

Rheological study
The viscosity of the formulated batches was determined using a cone and plate viscometer with spindle 7 (Brookfield Engineering Laboratories). The assembly was connected to a thermostatically controlled circulating water bath maintained at 25°C. The formulation whose viscosity was to be determined was added to a beaker covered with thermostatic jacket. Spindle was allowed to move freely into the emulgel and the reading was noted.[11]

Spreading coefficient
Spreading coefficient was determined by apparatus suggested by Mutimer. It consists of a wooden block, which is attached to a pulley at one end. Spreading coefficient was measured on the basis of 'Slip' and 'Drag' characteristics of emulgels. A ground glass slide was fixed on the wooden block. An excess of emulgel (about 2 g) 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 hook. Weight of 500 mg 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 was placed in the pan attached to the pulley with the help of hook. The time (in s) required by the top slide to cover a distance of 5 cm was noted. A shorter interval indicates better spreading coefficient.[12]

In vitro release studies
The in vitro drug release studies were carried out using a modified Franz diffusion (FD) cell. The formulation was applied on dialysis membrane which was placed between donor and receptor compartment of the FD cell. Phosphate buffer pH 7.4 was used as a dissolution media. The temperature of the cell was maintained at 37 _C by circulating water jacket. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead. A similar blank set was run simultaneously as a control. Sample (5 ml) was withdrawn at suitable time intervals and replaced with equal amounts of fresh dissolution media. Samples were analyzed spectrophotometrically at 285 nm and the cumulative % drug release was calculated. The difference between the readings of drug release and control was used as the actual reading in each case.[13]

Stability studies
The stability of any pharmaceutical product is usually defined as the capacity of the formulation to remain within defined limits over a predetermined period of time (shelf life of the product).

Durability of a product may be defined as the capability of a particular formulation in a specific container to remain within the physical, chemical, microbiological, therapeutic and toxicological specifications. Storage stability of formulation based on drug carriers is of great concern as it is the principal requirement in the development of any formulation. Hence, a well-designed stability testing plan is essential for the development of an emulgel. The prepared formulations were tested for stability on storing them at 4±1ºC and 25±1ºC. The formulations were filled in aluminum collapsible tubes at 4±1°C and 25±1°C. Samples were analyzed for residual drug content after a storage period of 10, 20, 30, & 60 days.

Microbiological assay
The microbiological assay is done to determine the activity of prepared formulation with the strain *Staphylococcus aureus* and the Sabouraud agar medium ditch plate technique was used. It is mainly applied for semisolid formulations using previously prepared Saburaud's agar plates. 1 gm of emulgel was places in a ditch cut in the plate for 24 hrs at 37 °C and the percentage inhibition was measured as follows.

$$percentage\ inhibition = \frac{L2}{L1} X100$$

Where L1= total length of the streaked culture
L2= length of inhibition.

RESULT AND DISCUSSIONS

OPTIMIZATION OF FAROPENEM SODIUM EMULGEL

1. Effect of temperature

The temperature was optimized during preparation of the emulgel, at different temperature range viz, 40-50°C, 50-60°C, 60-70°C, 70-80°C keeping other variables constant as described in general procedure of preparing faropenem sodium emulgel.

The effect of temperature on drug release are given in table 2 and shown in figure 1.

Table 2: Effect of temperature on cumulative % drug release with time intervals

Time(min)	F1	F2	F3	F4
0	0	0	0	0
30	16.11±0.12	19.21±0.81	17.54±1.92	14.44±0.43
60	23.17±1.22	27.05±1.81	21.07±0.31	18.69±1.76
90	29.05±0.98	35.08±1.43	24.44±0.79	21.05±0.31
120	37.4±1.33	40.18±0.21	29.11±1.82	25.66±1.88
150	41.23±0.55	43.34±0.67	36.31±2.21	34.67±1.90
180	45.48±0.99	47.99±0.91	39.89±1.73	36.87±0.62
210	49.37±1.54	56.33±1.82	45.35±0.93	40.48±0.21
240	54.15±1.89	60.78±1.81	49.98±0.69	44.94±1.31
270	61.2±0.67	67.35±1.62	57.78±1.99	49.05±0.53
300	69.43±0.99	75.88±0.72	62.45±1.82	53.41±1.82
330	77.04±1.45	86.57±0.34	67.77±0.41	56.59±1.69
360	81.96±0.23	91.83±1.41	74.08±0.91	61.13±0.44

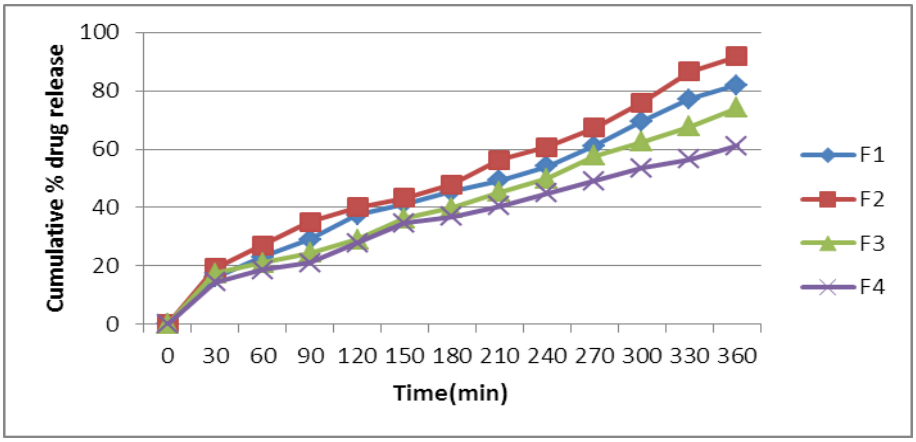

Fig 1: Effect of temperature on cumulative % drug release with time intervals.

2. Effect of polymer concentration.

Amount of carbapol 934 and carbapol 940 for the preparation was optimized by preparing the emulgel in different amount and there ratios, keeping other variables constant as described in general procedure of preparing faropenem sodium emulgel. The effect of polymer concentration on drug release are given in table 3 And shown in figure 2 respectively.

Table 3: Effect of polymer concentration cumulative % drug release with time intervals.

Time(min)	F5	F6	F7	F8	F9	F10	F11
0	0	0	0	0	0	0	0
30	14.46±1.02	18.86±0.21	16.62±1.82	11.89±1.88	13.37±1.99	15.97±1.33	11.09±0.88
60	19.37±0.44	26.9±1.90	22.66±1.98	17±0.31	18.42±1.82	21.87±1.83	16.22±1.31
90	27.63±0.92	35.4±1.82	29.04±0.77	24±0.83	28±1.93	28.36±0.21	29.68±1.32
120	34.5±1.77	39.9±0.99	36.72±1.38	29±0.34	35±1.33	35.77±0.61	35.57±1.87
150	39.6±1.54	44.07±1.38	42.11±2.91	37±1.89	41±0.81	42.55±0.29	41.69±0.45
180	44.4±1.93	48.5±0.82	46.17±0.62	41±1.78	46±1.93	47.48±0.82	45.02±0.71
210	49.7±0.81	55.8±1.72	53.47±1.88	47±0.71	51±0.82	52.34±0.31	48.57±0.31
240	54.9±0.82	61.07±0.86	57.09±1.93	51±0.77	56±0.21	56.99±0.62	56.17±1.91
270	59.37±1.77	68.01±1.92	64.11±1.11	59±0.92	62±0.83	62.91±1.67	63.38±0.63
300	69.67±1.92	76.7±0.91	72.30±1.45	63±1.76	70±0.63	71.42±1.81	69.02±0.55
330	77.73±0.81	87.04±0.89	81.09±0.82	70.07±0.67	78±2.81	79.89±1.91	75.97±1.33
360	83.71±1.93	92.61±2.77	88.3±1.83	78.26±0.82	87.3±0.91	86.7±0.55	81.32±1.72

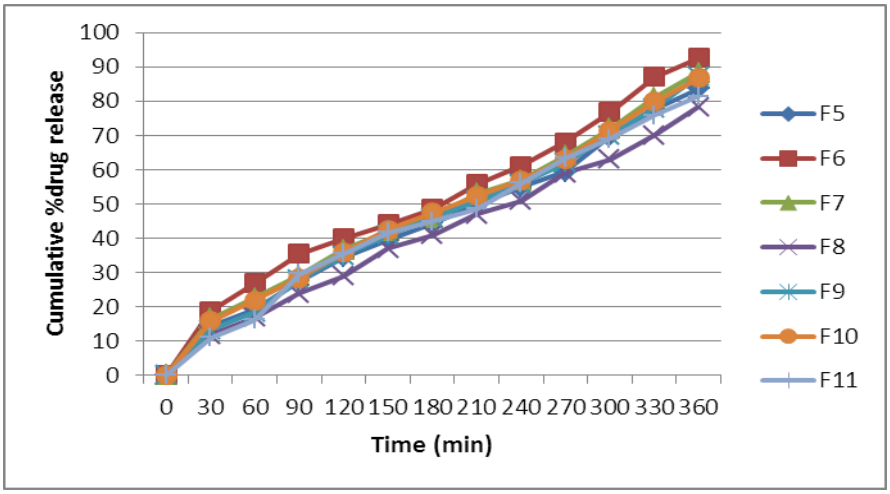

Fig 2: Effect of polymer concentration cumulative % drug release with time intervals.

3. Effect of emulsifier concentration.

Emulsifier concentration was optimized at different concentration of tween 80 and span 80, keeping other variables constant as described in general procedure of preparing faropenem sodium emulgel. The effect of emulsifier concentration on drug release are given in table 4 And shown in figure 3 respectively.

Table 4: Effect of emulsifier concentration cumulative % drug release with time intervals.

Time(min)	F12	F13	F14	F15	F16	F17	F18
0	0	0	0	0	0	0	0
30	14.22±1.23	19.45±0.64	17.53±0.54	16.52±0.83	11.13±0.72	11.89.±0.94	13.32±2.01
60	19.32±0.22	27.83±1.05	26.23±1.13	21.82±0.18	15.53±0.93	16.04±0.83	23.17±1.77
90	29.57±1.03	37.85±0.83	38.56±1.75	31.94±1.51	19.49±0.37	24.71±1.12	31.49±0.92
120	38.88±0.73	43.66±0.74	42.82±0.34	41.73±1.44	27.93±0.83	32.73±0.88	35.25±1.11
150	42.47±1.74	47.43±1.66	44.62±0.83	45.53±1.13	34.39±0.44	39.79±1.84	41.07±1.42
180	46.58±1.27	51.94±1.09	49.26±0.73	49.34±1.66	39.02±0.73	42.66±0.48	45.32±0.93
210	51.39±0.37	59.84±0.71	58.87±1.67	57.93±0.83	45.69±0.29	48.93±1.74	52.92±1.77
240	58.35±0.73	66.69±1.23	64.73±1.37	64.59±0.34	49.59±0.86	54.22±0.45	57.83±0.30
270	64.32±0.28	72.82±0.83	70.83±0.94	71.25±0.92	55.77±0.93	60.40±1.23	64.45±0.92
300	69.28±0.92	79.74±0.96	77.75±0.48	77.53±0.83	58.80±1.38	63.19±1.76	71.05±1.48
330	74.91±1.58	85.02±1.12	84.66±0.39	83.90±0.77	62.39±1.06	69.11±0.72	79.77±1.12
360	82.83±0.84	93.04±1.84	89.49±0.97	90.38±0.93	71.93±0.89	75.25±0.55	87.66±1.73

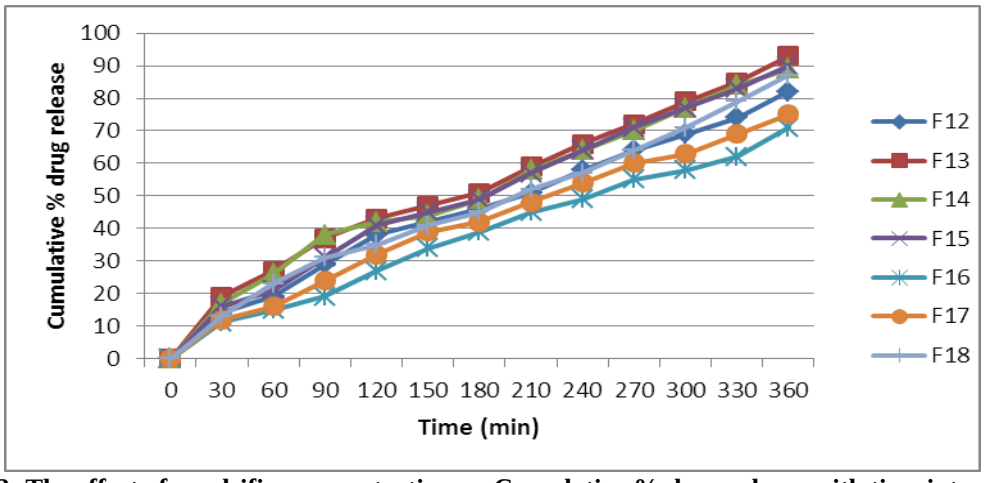

Fig 3: The effect of emulsifier concentration on Cumulative % drug release with time intervals.

4. Effect of penetration enhancer concentration.

Concentration of polyethylene glycol and oleic acid as penetration enhancer was optimized at different concentration, keeping other variables constant. The effect of penetration enhancer on drug release are given in table 5 And shown in figure 4 respectively.

Table 5: The effect of penetration enhancer on Cumulative % drug release with time intervals.

Time (min)	F19	F20	F21	F22	F23	F24	F25
0	0	0	0	0	0	0	0
30	12.21±0.44	16.45±1.98	19.54±1.38	17.75±1.36	11.67±0.56	14.47±0.47	18.04±1.06
60	18.43±1.07	22.56±2.11	27.09±0.55	26.87±1.58	19.31±1.45	22.43±0.67	25.65±1.44
90	23.34±0.76	28.47±1.84	35.88±1.74	33.48±1.11	26.54±1.39	29.56±1.23	34.55±1.28
120	28.05±0.37	35.66±1.58	41.31±1.36	39.93±0.83	31.67±1.49	36.84±0.59	39.04±0.72
150	34.34±1.21	39.73±0.49	45.65±1.88	44.08±0.75	37.24±0.88	41.38±1.66	44.03±0.851.29
180	39.05±0.32	45.82±0.77	48.75±0.69	47.31±0.84	42.85±0.49	45.03±1.37	46.37±1.45
210	46.37±1.45	50.43±0.28	56.67±0.47	53.52±1.73	45.38±0.92	47.94±1.62	49.87±1.73
240	53.27±0.93	54.78±1.07	61.93±1.83	59.26±0.62	49.56±1.38	51.69±1.03	57.92±0.23
270	59.71±2.01	59.05±0.96	68.83±2.03	65.38±0.99	54.29±1.48	58.66±1.56	64.59±0.93
300	63.28±1.71	63.57±1.78	78.02±1.23	74.63±0.89	59.64±1.52	65.73±1.27	72.38±1.18
330	67.73±0.52	69.44±0.93	87.69±0.98	84.19±0.76	65.05±1.83	71.82±0.77	78.66±1.53
360	71.42±1.49	76.27±1.74	93.06±0.42	89.28±1.06	72.55±1.03	79.04±1.12	84.59±1.44

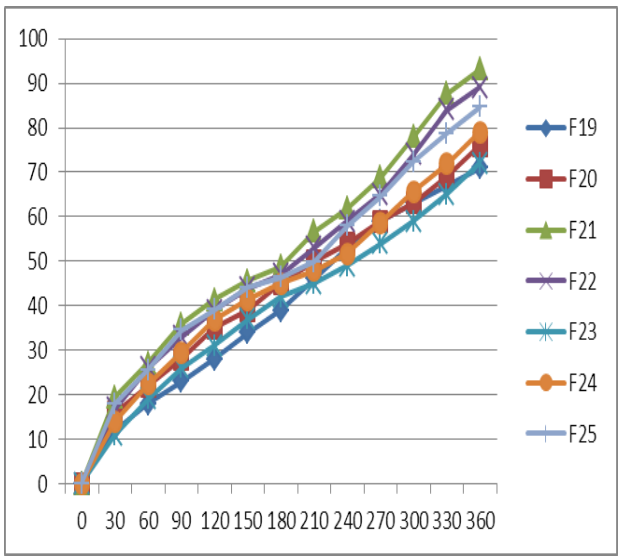

Fig 4: The effect of penetration enhancer on cumulative % drug release with time intervals.

5. Effect of stirring rate.

Stirring rate for the preparation of emulgel was optimized at different stirring rate, viz, 1000, 1250, 1500 and 1750 rpm and keeping other variables contant. The effect of stirring rate on drug release are given in table 6 And shown in figure 5 respectively.

Table 6: The effect of stirring rate on Cumulative % drug release with time intervals.

Time(min)	F26	F27	F28	F29
0	0	0	0	0
30	11	14	19	17
60	18	20	26	30
90	26	28	36	44
120	32	36	41	48
150	39	41	45	51
180	42	47	49	57
210	47	53	55	59
240	51	58	60	62
270	57	64	67	65
300	63	70	76	69
330	68	78	86	74
360	74	83	93	77

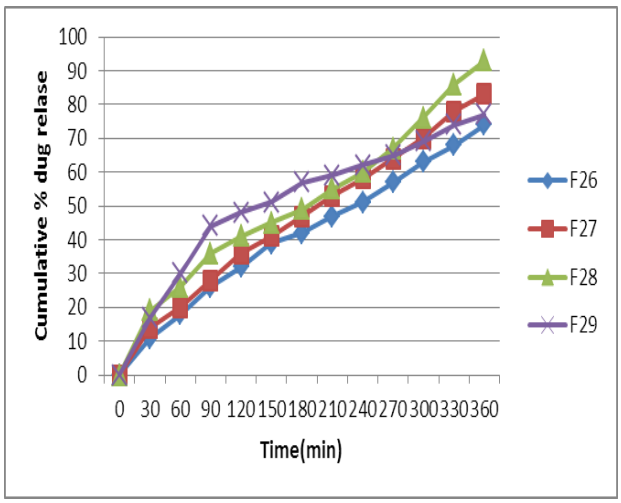

Fig 5: The effect of stirring rate on Cumulative % drug release with time intervals.

EVALUATION PARAMETERS

Physical Appearance

Emulgel formulations were white viscous creamy preparation with a smooth homogeneous texture and glossy appearance.

pH

The pH of emulgel formulation was in the range of 5.9 to 6.8, which lies in the normal pH range of the skin & would not produce any skin irritation. There was no significant change in pH values as a function of time for all formulation.

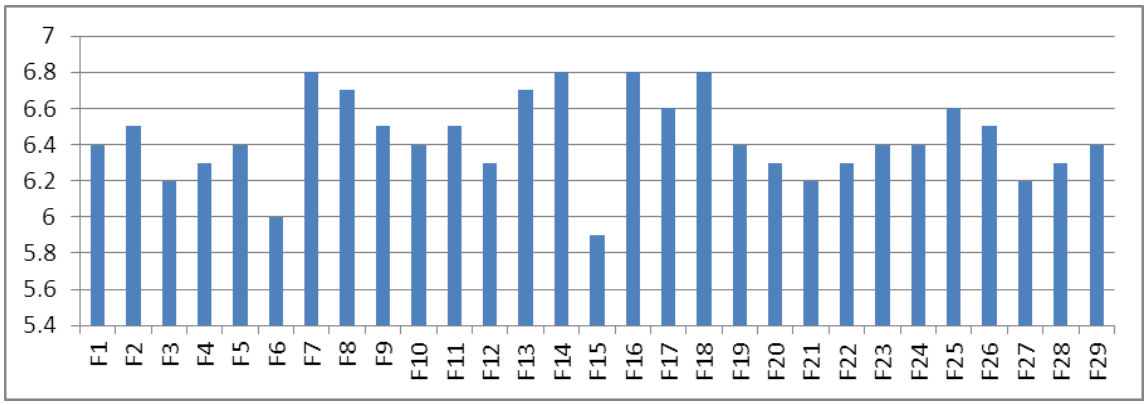

Fig 6: pH of emulgel formulation.

Drug content

The drug content of the formulated emulgel was estimated spectrophotometrically. All emulgel formulation showed the value of % drug content above 90%.

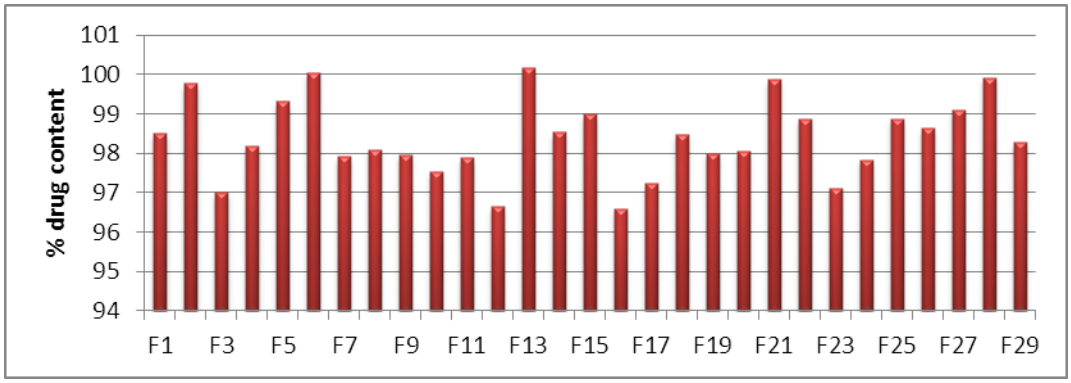

Fig 7: The drug content of the formulated emulgel.

Rheological study

Viscosity of formulation lie in the range of 88480-88679 cp at 10rpm. Viscosity has profound significance with respect to the performance of topical products. Product characteristics, such as spreadability, ease of application, drug release and stability are closely linked to the viscosity of the formulation.

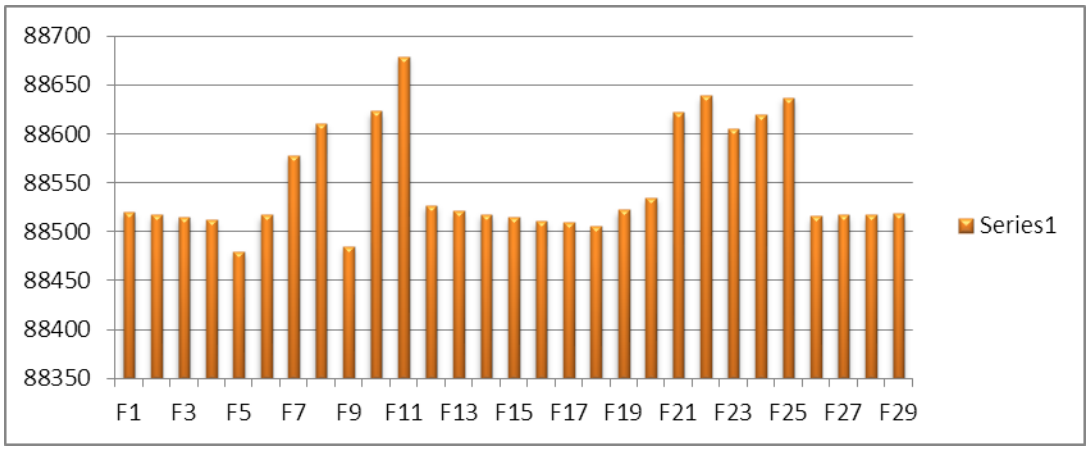

Fig 8: The Viscosity of the formulated emulgel.

Spreading coefficient

Spreading test was carried out for all the formulations. The spreadibilty indicates that the emulgel is easily spreadable by small amount of shear. The spreadibility is very much important as it shows the behavior of emulgel when it comes out from the tube. The spreading coefficient of various emulgel formulations are given below.

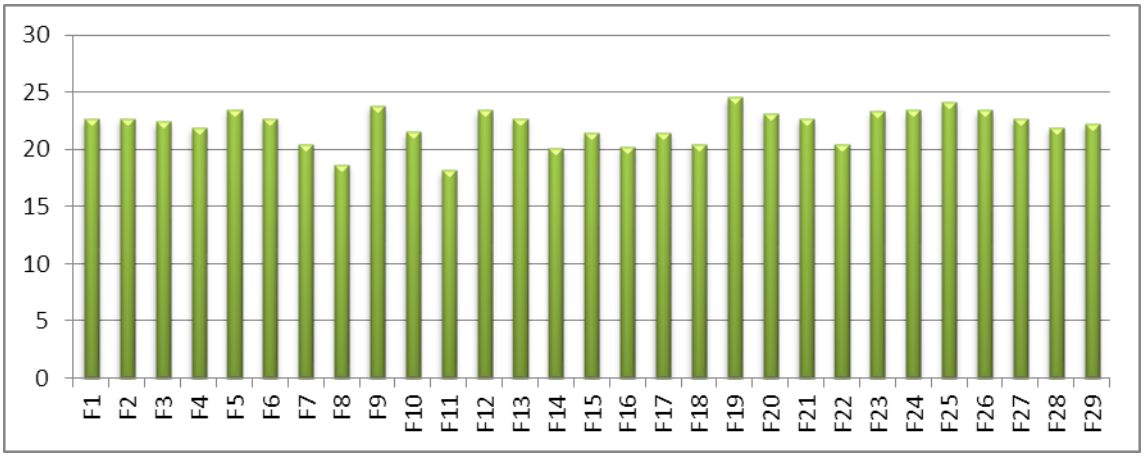

Fig 9: The spreading coefficient of various emulgel formulations.

Effect of storage temperature on the residual drug content

The method of stability testing of any pharmaceutical product is based on principal of chemical kinetics. Drug content of emulgel formulations was determined after storage at 4±1°C, 25±1°C and 40±1°C for 10, 20, 30, and 60 days. The percent residual drug content was calculated to assure the optimum storage conditions for the formulation. The optimized formulation gel were filled in aluminum collapsible tubes and stored at 4±1°C,25±1°C and 40±1°C for the time period of 60 days. Initial drug content was taken nearly as 100% for each formulation. The observations are recorded in Table 7 and shown in fig 10.

Table 7: Effect of storage temperature on residual drug content at 4±1°C, 25±1°C and 40±1°C Storage temperature.

	10 days	20 days	30 days	60 days
4±1°C	99.97±1.84	99.44±2.48	98.93±3.76	97.89±4.65
25±1°C	99.95±2.11	99.29±3.32	98.79±4.21	96.94±5.63
40±1°C	**99.83±1.97**	**98.72±2.66**	**97.35±3.79**	**94.66±4.41**

% Residual drug content after storage for

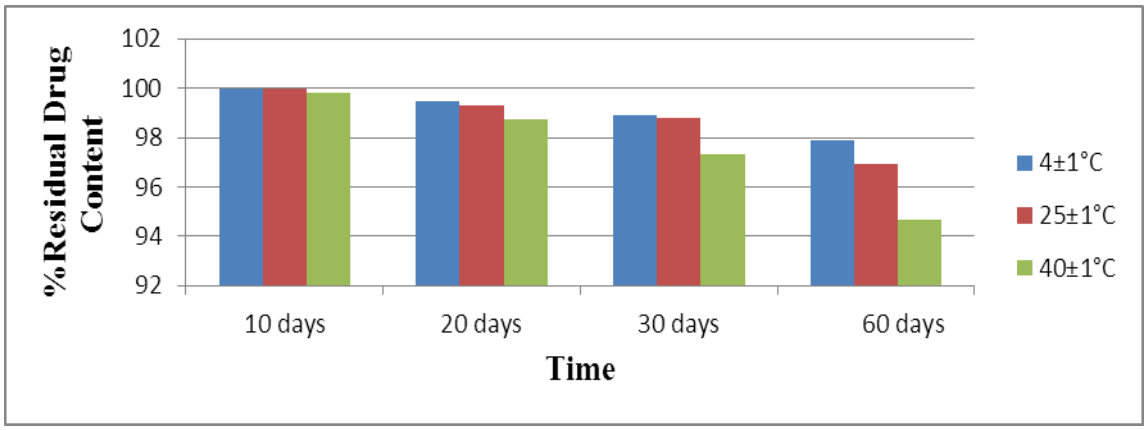

Fig 10: Effect of storage temperature on residual drug content at 4±1°C, 25±1°C and 40±1°C Storage temperature for 10, 20, 30 and 60 days respectively.

Microbiological activity

The use of control plates allowed that the plain emulgel bases were microbiologically inert toward the bacterial strain. The antimicrobial activity of faropenem sodium in its best emulgel formulation was compared with commercially available gel of Azithromycin. Percentage inhibition was taken as a measure of the drug antimicrobial activity. Faropenem sodium was found to inhibit 68.3±1.23% whereas Azithromycin gel was found to inhit 53.5±0.87%.

REFERENCES

1. Schurek K N, Wiebe R, Karlowsky J A, Rubinstein E, Hoban D J and Zhanel G G, Expert Rev Anti Infect Ther, 2007; 5(2): 185-198.
2. Fuchs P C, Barry A L and Sewell D L, Antimicrob Agents Chemother, 1995; 39(7): 1472–1479.
3. Inoue E and Mitsuhashi S, Antimicrob Agents Chemother, 1994; 38(9): 1974- 1979
4. Japanese pharmacopoeia.14th edition, 2006; 472-473.
5. Ishiguro M, Iwata H, Nakatsuka T, et al. Synthesis and in vitro activity of novel 2-chiral substituted penems. J Antibiot, 1988; 41: 1685-93.
6. Mohamed, M.I., 2004. Optimization of chlorphenesin emulgel formulation. AAPS J, 6(3).
7. Kshirsagar N A. Drug Delivery Systems. Ind. J. Pharmacol, 2000; 32: S54- S61.
8. Suneel kumar yadav , Manoj kumar Mishra, Anupama T\tiwari, Ashutosh Shukla. Emulgel: A new approach for enhanced topical drug delivery. Int J Curr Pharm Res, 2017; 9(1): 15-19.
9. Ranga PM, Sellakumar V, Natrajan R, Mohan KK. Formulation and invitro evaluation of ciprofloxacin loaded topical emulgel. Int J Pharm Chem Sci, 2012; 1: 237-42.
10. K. Jamili Reddy, J. V. Shanmukha Kumar and S.V.M. Vardhan., Spectrophotometric Methods for the Determination of New Oral Penem (Faropenem) in Pure and in Formulations. Chem Sci Trans, 2013; 2(3): 936-940.
11. Bonacucina, G., Cespi, M., Palmieri, G.F., Characterization and stability of emulsion gels based on acrylamide/sodium acryloyldimethyltaurate copolymer. AAPS Pharm Sci., 2009; Tech, 2: 10.
12. Gupta, G.D., Gaud, R.S., 2005. Release rate of tenoxicam from acrypol gels. Ind. Pharm, 69–76.
13. Kakkar, A.P., Gupta, A., Gelatin based transdermal therapeutic system. Ind. Drugs, 1992; 29: 308–312.