Formulation and Evaluation of Cefotaxime Sodium Loaded Emulgel for Topical Bacterial Infections

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Abstract: The bacterial infections are very common and become a serious issue like in case of infections of one and more reproductive organ, inflammation on protective membrane of brain and spinal cord, inflammation of lungs air sacs, body drainage system infections, problem in body's extreme response and infection caused by sexually transmitted bacteria in male and female. Generally, these bacterial infections are treated by using antibiotics like cefotaxime that is a semisynthetic, β-lactamase resistant, third-generation broad-spectrum cephalosporin. The common side effects of cefotaxime are uneasiness of stomach before vomiting, sneezing, itching.

The topical antibacterial dosage forms like creams, gel, and ointment have some demerits and low duration of drug release. The emulgel is an alternative for topical drug delivery with several merits like enhanced skin penetration and improved bioavailability, reduced dosing, improved patient acceptability with targeted drug delivery, freedom of termination of the therapy at any time, drug delivery in controlled fashion for prolong duration.

The aim of study was to develop a biphasic promising drug delivery system emulgel of cefotaxime. The 2^3 experimental design was used to prepare various emulgel batches to determinant the effect of liquid paraffin, span 20 and tween 20 on the performance of emulgel. The Batch F1 showed the maximum drug release while batch F8 up to 240 minutes. The drug release kinetics study of Batch F8 showed the Higuchi-Matrix as a best fit model and the Fickian Diffusion as a mechanism of drug release with R^2 value 0.9158 and K value 8.4741.

Keywords: Antibiotics, Carbopol, Cefotaxime, Cephalosporin, Emulgel, Topical, Delivery.

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1. Introduction

Infectious complaints have always been cruelling the menace to human and plant life (Fauci. et al., 2005, Porwal et al., 2020, Porwal et al., 2014, Chandrasekar et al., 2012, Porwal et al., 2015, Porwal et al., 2021, Sing et al., 2007 and Anwer et Al., 2021). Therefore, the remedial is compulsory using suitable antimicrobial mediators. Cefotaxime is a semisynthetic, β-lactamase resistant, third-generation broad-spectrum cephalosporin that hinders natural production of protective covering of bacteria that is made of peptidoglycan of numerous bacteria that gives a positive as well negative color to bacteria. It also hinders by holding to drug and binding site protein. It constrains synthesis of peptidoglycan that will be the final transpeptidation step in bacterial cell walls (hence inhibit cell wall biogenesis), resulting in lysis of bacterial cell wall. It is used to treat several bacterial infections in joint, of infections of one and more reproductive organ, inflammation on protective membrane of brain and spinal cord, inflammation of lungs air sacs, body drainage system infections, problem in body's extreme response and infection caused by sexually transmitted bacteria in male and female. The common side effects of cefotaxime are uneasiness of stomach before vomiting, sneezing, itching, blockade of running nose, and redness and swollen condition at the site of action and *Clostridium difficile* diarrhea. It metabolizes in the liver with an exclusion half-life 0.8-1.4 hours and excrete by kidney (50–85%). It has shorter half-life and administers twice a day for efficacy. Cefotaxime is administered as deep into the muscle inoculation and within a vein like infusion. It is involving in the set of life sustaining chemicals reactions in organism to both dynamic and indolent endogenous compounds by the hepatic and chiefly excreted in the discharge. The measure tunings may be apt in individuals with excretory or hepatic diminishing (Zakaria et al., 2016, Yerikala et al., 2017, Kirchner et al., 2013 and Azza et al., 2016).

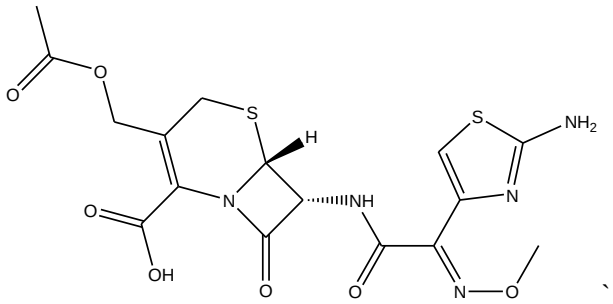


Figure 1: Structure of Cefotaxime

Several antibacterial topical dosage forms like creams, gel, and ointment are available in the market for the treatment of skin and soft tissue infections. Emulgel/ creamed gel/ quassi emulsion/ gelled emulsion is an alternative for topical drug delivery with several advantages like enhanced skin penetration and improved bioavailability, reduced dosing, improved patient acceptability with targeted drug delivery, freedom of termination of the therapy at any time, drug delivery in controlled fashion for prolong duration. Both the hydrophilic/ hydrophobic drugs, have short half-life can be easily incorporated in emulgel. Emulgels even have better mass drug ratio entrapment volume than other any dosage forms like niosome and liposome. Emulgels are the combination of biphasic system of fine dispersion of minute droplets of two liquids and fine particle dispersed in continuous system, gaining the two-fold controlled release effect where the emulsion either oil in water or water in oil is gelled by incorporation in the gel base. Emulgel is water soluble, non-staining, greaseless, thixotropic, bio-friendly formulation that also shows emollient effect. The current study also focuses on the effect of the oil, and the emulsifying agent on performance of cefotaxime sodium emulgel to prolong the drug

release (Yadav et al., 2016, Sharam et a., 2010, Chak et al.,2013, Shrivastav et al., 2013 and Sharad et al., 2018).

2. Materials and Methods

Analytically pure sample of drug, Cefotaxime sodium (CFT) was a generous gift from Glenmark Pharma Ltd., Baddi, along with their analytical reports. The sorbitan laurate, polyosyetehlene sorbitol were acquired from clever scientific, Erbil, Iraq. The gelling agent acrylate polymer 941 was purchased from CDH Laboratories, New Delhi, India. The paraffinum liquidum, propane-1,2-diol, 4-hydroxy benzoate, and propyl ester of p-hydroxybenzoic acid pure were purchased from clever scientific, Erbil, Iraq. Rest different chemicals were used of analytical grade without any chemical alteration.

2.1 Pre-Design Studies of Cefotaxime Sodium

2.1.1 Organoleptic Properties

The color, taste and odor were determined (Sharad et al., 2016 and Sharad et al., 2015).

2.1.2 Loss On Drying

Accurately weighed 5 g drug sample was taken and placed in aluminum pan. The drug loaded pan was placed in electronic moisture balance and two constant readings were observed (Sharad et al., 2016 and Sharad et al., 2015).

2.1.3 Melting Point

The melting point of drug was leisurely using a pre-calibrated digital melting point apparatus (INOVIA LABS, Model-INOMELT P-300) using capillary method. The L-ascorbic acid AR and sodium bicarbonate AR were used as standard for calibration of digital melting point apparatus (Sharad et al., 2016 and Sharad et al., 2015).

2.1.4 UV-Visible Spectrophotometric Analysis and Determination of λmax

Precisely balanced 10 mg of drug was dissolved in 10 mL of 7.4 pH phosphate buffer solutions in 10 ml of volumetric flask to prepare the stock solution with concentration 1 mg/mL or 1000 µg/mL. The 0.1 mL of solution was pipette out from stock solution and transfer into 10 mL volumetric flask. The volume was made up with 7.4 pH phosphate buffer solution to prepare the concentration of dilution 10 µg/mL. Similarly, 20-100 µg/ml dilutions were prepared. The sample concentration 10 µg/mL was scanned from 200-400 nm range to determine the λmax (maximum absorbance) of drug cefotaxime sodium using double beam UV-visible spectrophotometer (Cintra 2020, Model-921) (Sharad et al., 2016 and Sharad et al., 2015).

2.1.5 Fourier Transforms Infrared Spectroscopy and Compatibility Study

FTIR study was performed by scanning the samples between 450 cm-1 to 4000 cm-1 using IR spectrometer (Shimadzu, IR Affinity-1S) to determine the compatibility behavior with cefotaxime. The Infrared spectra of pure drug, excipients and formulation were examined using potassium bromide disc method (Shrivastva et al., 2010 and Sharad et al., 2014).

2.1.6 Differential Scanning Calorimetery

The DSC-60APlus, Shimadzu was used to analysis about any possible collaboration with drug heat relation. The inert nitrogen gas environment used with the rate of 10 mL/ minutes. The sample holding time was 10 minutes (Jagdale et al., 2020).

2.1.7 Development of Various Batches of Cft Loaded Emulgel

2.1.7.1 Preparation of Primary Emulsion

The drug was dissolved in water and span 20 was added followed by addition of liquid paraffin as oil phase in different ratio to prepare the primary w/o emulsion.

2.1.7.2 Preparation of Carbopol 941 Gel

The dispersion method was used to prepare the gel of carbopol 941. Accurately weighed amount of carbopol 941 was mixed with 50 ml purified water in 100 ml beaker and maintained at 50 rpm stirring speed. The pH of final gel was adjusted to 6-6.5 using 0.5 N of sodium hydroxide (Khalil et al., 2011).

2.1.7.3 Formulation of Cefotaxime Sodium Loaded Emulgel

Total eight batches of cefotaxime sodium loaded emulgel were prepared using formula depicted in Table 1. The tween 20 was added to gel phase and the above prepared emulsion was added and stirred at 500 rpm for 15 minutes to prepare emulgel. Further propylene glycol containing, 4-hydroxy benzoate, propyl ester of p-hydroxybenzoic acid were dissolved the emulgel.

Table 1: 2^3 Experiment design to prepare different batches of emulgel

Ingredients	Quantity
Cefotaxime	500 mg
Carbopol acrylate polymer 941	1 g
Paraffinum liquidum	X1
Sorbitan laurate	X2
Polyosyetehlene sorbitol	X3
Propane-1,2-diol	1 ml
4-hydroxy benzoate	0.1 %
Propyl ester of p-hydroxybenzoic acid	0.1 %
Water q.s.	1 g

	Levels	
	Low	High
Volume of liquid paraffin	5	10
Span 20	1	2
Tween 20	1	2

Combination	X1	X2	X3
A1	-	-	-
B	-	-	+
C	-	+	-
D	+	-	-
E	+	+	+
F	+	+	-
G	+	-	+
H	-	+	+

3. Assessment of Emulgel

The ready batches of emulgel were evaluated for physical examination, determination of pH, washability, extrudability, spreadability, skin irritation test, drug content uniformity, viscosity, in-vitro drug release studies, drug release kinetics study and stability studies (Yadav et al., 2016).

3.1 Physical Inspection

The prepared batches of emulgel formulations were inspected visually appearance for color, consistency, homogeneity, grittiness, texture, and phase separation (Khullar et al., 2012, Dantas et al., 2016 and Shen et al., 2015).

3.2 Determination of pH

The pH of all batches of emulgel were determined by pre-calibrated digital pH meter (Model-860031 Benchtop). The 1 g emulgel was dissolved in 25 ml of distilled water and the electrode was dipped into the emulgel to equilibrate. Experiment was performed in triplicate (Madhulatha et al., 2020, Deshmane et al., 2018 and Malavi et al., 2021).

3.3 Washability

Formulations were applied on the skin and then ease and extent of washing with water were manually checked (Chavda et al., 2013, Ranjan et al., 2019 and Singh et al., 2021).

3.4 Extrudability

The emulgel formulations were filled into aluminum collapsible tubes and the tubes were pressed to extrude the material and the extrudability of the formulation was checked (Chodankar et al., 2020, Jaber et al., 2020 and Varma et al., 2014).

3.5 Spreadability

Two glass slides of standard dimensions (6×2) were taken and the emulgel was placed over one of the slides. The second slide was placed over the first slide to make like emulgel sandwiched between slides. The 100 g weight was placed up on the upper slide to removed and the excess amount of the Emulgel. After fixing the lower side on the board and upper side a string a load with 20 G end with the help of simple pully application. After that the time was noted upper side travel up to length of glass slide 6 cm in contrast with lower side that was towards the load. Reading was taken in triplicates

overall average of 6 and calculated spreadability for each biphasic preparation (Rao et al., 2013 and Kusuma et al., 2016).

Spreadability = m.l/t

Where,

S = Spreadability (g.cm/sec)

m = Weight tied to the upper slide (20 g)

l = Length of glass slide (6 cm)

t = Time taken is second

3.6 Skin Irritation Test

Skin irritation test for emulgel formulation was conducted over skin of human volunteers. The study was conducted by taking volunteer's consent. Healthy eight human volunteers were selected for the skin irritation test. The prepared emulgel formulation was applied on area of 2 inch2 skin of hand and observed for any type of undesirable effect (irritation or lesions) (Payyal et al., 2020, Goyani et al., 2018 and Aiyalu et al., 2016).

3.7 Drug Content Uniformity

Accurately weighted 100 mg emulgel was taken in 100 ml volumetric flask containing phosphate buffer solution of pH 6.8 and shake for 2 hrs on an orbital shaker. After mixing the solution was filtered and the absorbance was assessed spectrum analysis. (Cintra 2020, Model-921) at 260 nm using phosphate buffer (pH 6.8) as blank (Shah et al., 2021 and Fong et al. 2015).

3.8 Viscosity

The Brookfield AMETEK DV2T viscometer (DV2TLVCJ0) was used to measure the viscosity of prepared batches of emulgel. The 500 mg emulgel was placed on platform at 25°C with spindle no. 6 at 10 rpm (Jagdale et al., 2017 and Bansal et al., 2015).

3.9 In-Vitro Drug Release Studies

The Franz diffusion cell was used for in-vitro drug diffusion study. The clear film lining of egg shell was used as semi-permeable sheath and phosphate buffer (pH 6.8) as media. The emulgel sample was placed in donor compartment. The egg membrane was placed on receptor compartment of the Franz diffusion cell. The receptor compartment contained 15 mL phosphate buffer (pH 6.8). The temperature of diffusion medium was thermostatically controlled at 37 ± 1 ºC by surrounding water in a jacket and the medium was stirred by a magnetic stirrer at 50 rpm. The sample were withdrawn at predetermined intervals (15, 30, 45, 60, 120, 240 minutes) and replaced by equal volume of fresh phosphate buffer of pH 6.8 to maintain sink conditions. The absorbance of withdrawn samples was determined at 260 nm by UV-visible spectrophotometer (Cintra 2020, Model-921) using phosphate buffer of pH 6.8 as blank (Hua et al., 2014, Baibhav et al., 2012 and Rafiee et al., 2000).

3.10 Drug Release Kinetics Study

The drug release kinetic study of all formulations were evaluated by plot in kinetic models as below (Akram et al., 2013, Paarakh et al., 2018 and Abouelmagd et al., 2015).

1. In zero order kinetics model we measured period against collective free medicine.
2. In first order kinetics model we measured time versus log cumulative percent drug that was residual to rivetted.
3. While in Higuchi model we measured cumulative amount of drug release versus square root of time.
4. In Korsmeyer-Peppas model log time versus cumulative drug release.

3.11 Constancy Studies

The physical stability studies were performed according to ICH guideline with the main aim to examine stability of the drug in formulation during storage. The selected batch was sealed in 20-ml glass vials and stored at refrigeration temperature (2-8°C), room temperature (25±2°C) storage condition light, dark and moisture 4 for a period of 1, 2 and 3 months. The remaining amount of drug was determined in triplicate (Kapoor et al., 2021 and Ambala et al., 2015).

4. Results and Discussion

The color, odor and taste of cefotaxime sodium was found to be white to slightly yellowish powder with faint odor and bitter taste. The loss on drying of cefotaxime sodium was found to be 0.01±0.2%. The melting point of cefotaxime sodium was found to be 203±1ºC while the reported values were 201-210ºC. The λ max was found to be at 260 nm and the line of equation was created to be $y = 0.0028x + 0.0009$ with R^2 value 0.9997.

Table 2: Calibration curve data of cefotaxime sodium in 7.4 pH phosphate buffer at 260 nm

Concentration (µg/ml)	Absorbance
10	0.027
20	0.061
30	0.083
40	0.111
50	0.139
60	0.166
70	0.194
80	0.222
90	0.25
100	0.278

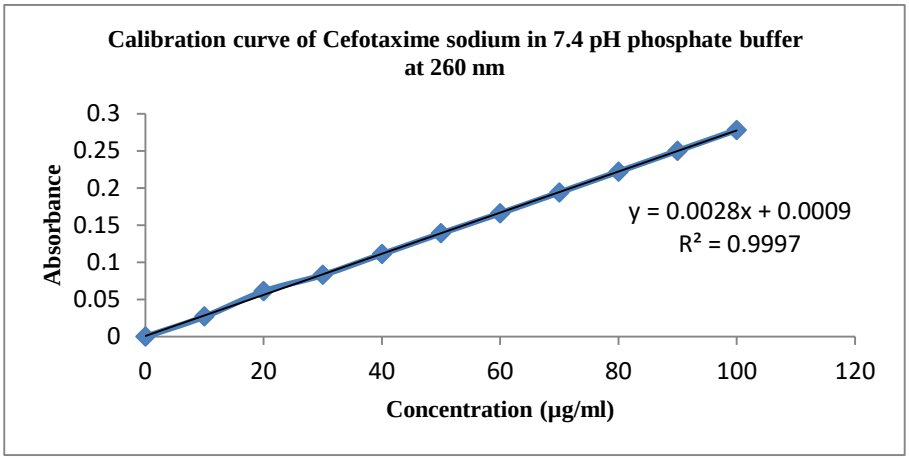
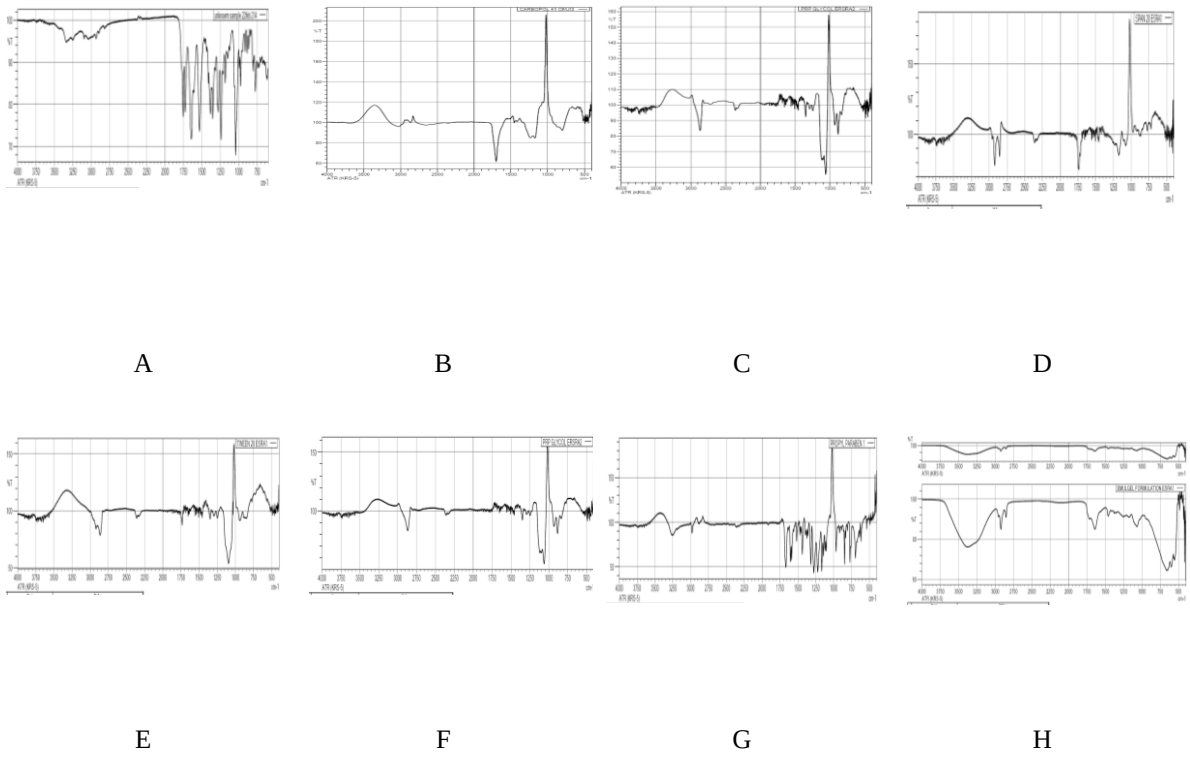


Figure 2: Calibration curve of cefotaxime sodium in 7.4 pH phosphate buffer at 260 nm

FTIR study showed no drug-excipient interaction. The FTIR of cefotaxime sodium showed the presence of N-H bond at 3280, C-H bond at 2850, C=O bond at 1710, C=C bond at 1575, C-N bond at 1050, 1240, O-H bond at 3334, C-O bond at 1150, C-C bond at 1065, C=O bond at 1050, 1240. The FTIR of sorbitan laurate, polyosyetehlene sorbitol, gelling agent acrylate polymer 941, paraffinum liquidum, propane-1,2-diol, 4-hydroxy benzoate, and propyl ester of p-hydroxybenzoic acid and best emulgel batch was showed in Figure-3. The formulation showed no interaction with drug and excipients.

The DSC of cefotaxime sodium and best batch of emulgel showed no drug-excipient interaction as showed in Figure-4. The exothermic peaks of drug and formulation at 208ºC & 207°C for drug and formulation.

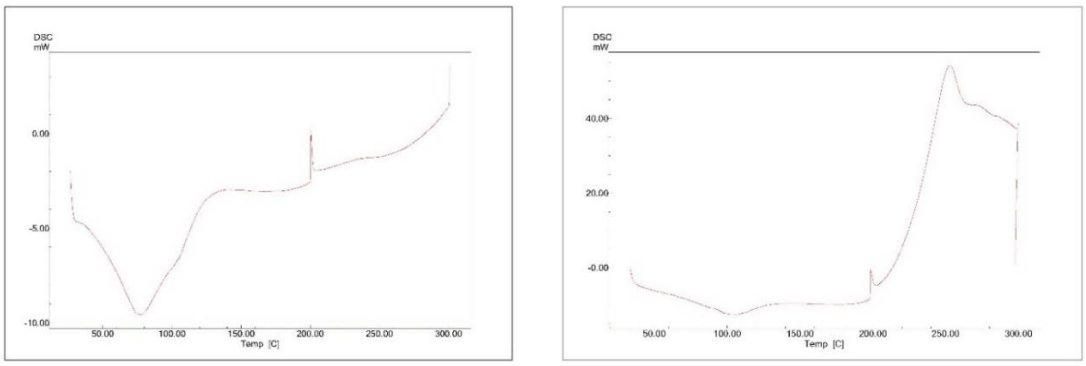
The pH of various batches of emulgel was found to be varied between for 6.02-6.85 as tabulated in Table 3. The emulgels were easily washable and easily extrudable as showed in Table 3. The spreadability varied from 11.15±0.31 to 17.23±0.52 as showed in Table 3. No irritation, lesion, redness at site of application was reported by volunteers. The drug content uniformity varied between 99.97±0.11 - 99.98±0.21% and the viscosity of the emulgel varied between 4625±0.12- 4955±0.31 cP as shown in Table 3. The in-vitro drug release was showed by emulgel batch F1 and minimum drug release was showed by batch F8 i.e. 72.58±0.23 and 98.98±0.10 as showed in Table 4. The emulgel batch F8 was selected best on the basis of prolonged drug release and achievement of sustained release of drug. The drug release kinetics study of emulgel batch F8 showed the Higuchi-matrix as a best fit model and the mechanism of drug release was Fickian Diffusion with R2 value 0.9158 and K value 8.4741 as shown in Table 5.



A B C D

E F G H

Figure 3: FTIR of cefotaxime sodium (A), Carbopol 941 (B), Liquid Paraffin (C), Span 20 (D), Tween 20 (E), Propylene gycol (F), Propyl paraben (G), Formulation (H)



A B

Figure 4: DSC of Cefotoxim (A) Emulg

Table 3: Visually appearance of emulgel formulations

Formulation	F1	F2	F3	F4	F5	F6	F7	F8
Color	White	White	White	White	White	White	White	White
Consistency	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent
Homogeneity	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent
Grittiness	Non-gritty	Non-gritty	Non-gritty	Non-gritty	Non-gritty	Non-gritty	Non-gritty	Non-gritty
Texture	Glossy	Glossy	Glossy	Glossy	Glossy	Glossy	Glossy	Glossy
Phase separation	None	None	None	None	None	None	None	None
pH	6.39	6.49	6.52	6.85	6.77	6.02	6.56	6.35
Washability	+++	+++	+++	++	++	++	++	+++
Extrudability	+++	+++	+++	++	++	++	++	+++
Spreadability (gcm/sec)	11.15±0.31	13.85±0.11	13.51±0.20	15.64±0.57	17.23±0.52	15.85±0.45	16.23±0.23	14.34±0.32
Drug content uniformity (%)	99.97±0.11	99.98±0.12	99.99±0.1	99.98±0.21	99.96±0.09	99.98±0.13	99.97±0.12	99.96±0.15
Viscosity(cP)	4625±0.12	4722±0.24	4665±0.22	4841±0.14	4955±0.31	4878±0.13	4950±0.11	4810±0.32

Excellent: +++, Good: ++, Average: +, Poor: -

Table 4: Percentage cumulative drug release of emulgels

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
15	23.56±0.11	20.25±0.62	20.45±0.23	28.89±0.24	14.89±0.34	13.25±0.33	25.56±0.34	21.45±0.65
30	35.47±0.35	30.45±0.26	32.57±0.26	36.69±0.35	23.56±0.52	25.65±0.53	31.45±0.63	33.56±0.45
45	49.78±0.26	44.58±0.45	46.89±0.63	45.58±0.15	37.98±0.65	36.98±0.36	48.78±0.24	45.89±0.53
60	55.78±0.12	51.56±0.26	55.78±0.25	60.56±0.26	48.78±0.26	45.58±0.18	53.56±0.64	53.56±0.45
120	73.78±0.46	68.78±0.33	65.89±0.46	75.58±0.46	62.58±0.67	60.47±0.38	71.48±0.53	68.89±0.23
240	98.98±0.10	95.58±0.53	94.56±0.6	92.25±0.37	89.78±0.33	88.89±0.32	88.45±0.65	72.58±0.23

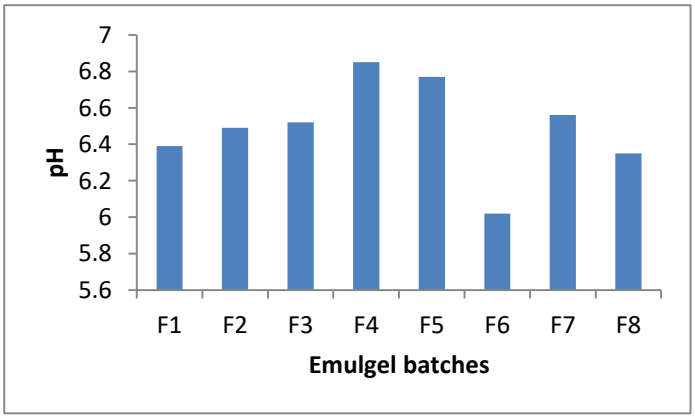


Figure 5: pH of emulgel batches

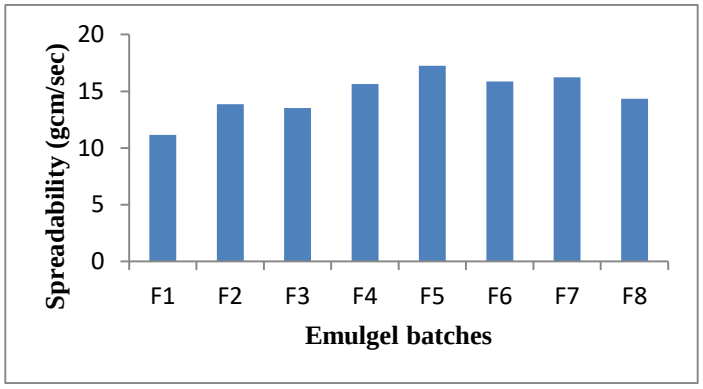


Figure 6: Spreadibility of emulgel batches

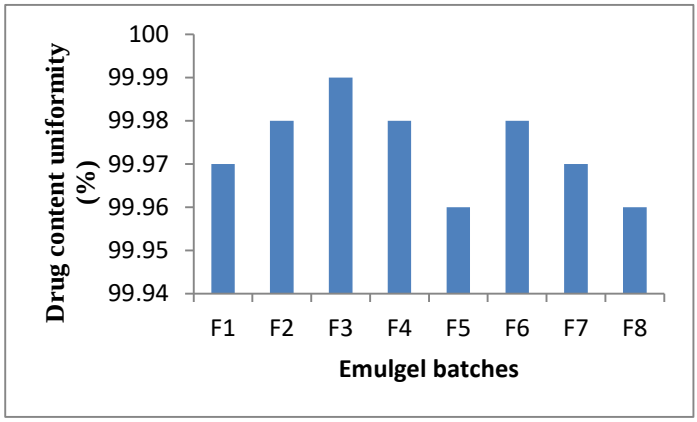


Figure 7: Drug content uniformity of emulgel batches

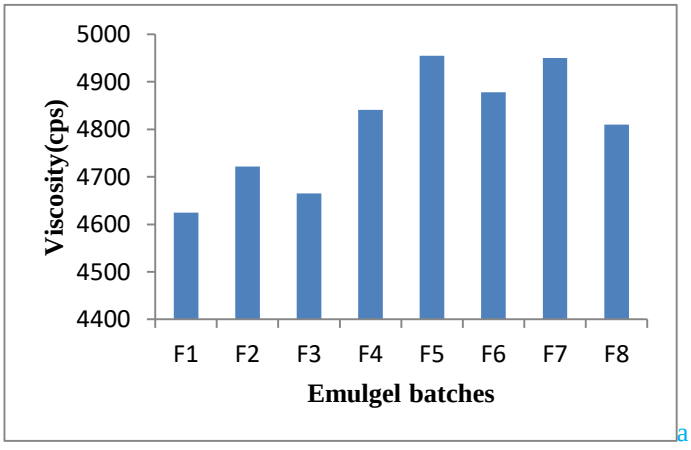


Figure 8: Viscosity of emulgel batches

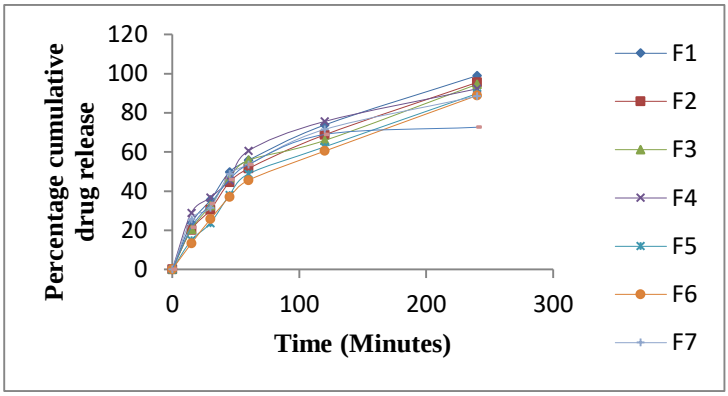


Figure 9: Graph of percentage cumulative drug release of emulgel formulations (F1-F8)

Table 5: Drug release kinetics of Batch F8

Model Fitting	R^2	K
Zero order	0.6815	0.2580
First Order	0.8101	-0.0051
Higuchi Matrix	0.9158	8.4741
Peppas	0.9120	2.3861
Hix. Crow.	0.7708	0.0013
Parameter for Korsmeyer-Peppas Equation		
n	0.4485	
k	2.3861	
Best fit model	Higuchi-Matrix	
Mechanism of release	Fickian Diffusion (Higuchi Matrix)	

Model Fitting	R^2	k
Zero order	0.6815	0.2580
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Parameters for Korsmeyer-Peppas Equation	
n =	0.4485
k =	2.3861

Best fit model=	Higuchi-Matrix

Mechanism of release ▼
Fickian Diffusion (Higuchi Matrix)

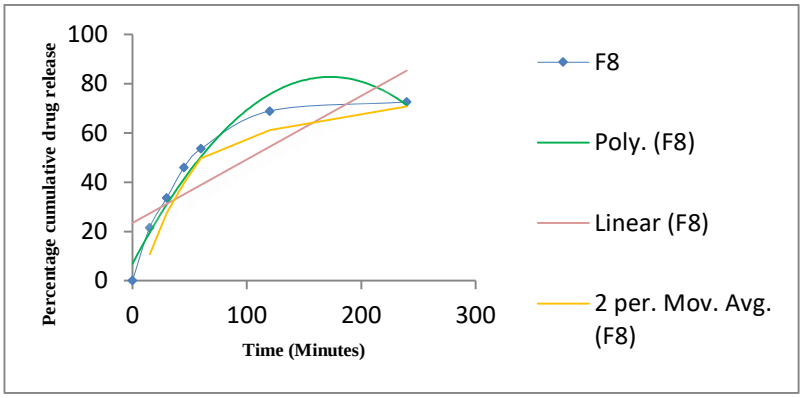

Figure 10: Percentage cumulative drug release graph using linear, polynominal and moving average

The stability studies of emulgel batch F8 was successfully carried out and results were tabulated in table.

Table 6: Drug content data from stability study emulgel batch F8

Storage conditions	Duration in month		
	One	Two	Three
2-8˚C	99±0.99%	99±0.65%	99±0.17%
Dark	99±0.90%	99±0.30%	99±0.05%
Moisture	99±0.45%	99±0.34%	89±0.24%
Light	98±0.56%	98±0.41%	98±0.52%

5. Conclusion

The F5 batch showed the maximum viscosity as the high amount of liquid paraffin, span 20 and tween 20. The Batch F1 showed the maximum drug release and Batch F8 showed the least drug release up to 240 minutes (4 hours). The drug release kinetics study of Batch F8 showed the Higuchi-Matrix as a best fit model and the Fickian Diffusion as a mechanism of drug release with R2 value 0.9158 and K value 8.4741. The constancy studies showed the maximum stability at 2-8˚C up to 3 months.

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