EMPRO

Current Research in Pharmaceutical Sciences

Available online at www.crpsonline.com

crps online CRPS

ISSN: 2250 – 2688

Received: 29/10/2020
Revised: 15/11/2020
Accepted: 25/11/2020
Published: 31/12/2020

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DOI: 10.24092/CRPS.2020.100401

Website: www.crpsonline.com

Quick Response Code:

Formulation and Evaluation of Emulgel of Cephalexin to Enhance Topical Delivery

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ABSTRACT

Emulgel dosage formulation of cephalexin which has enhanced solubility release and bioavailability properties with less inter and intra - subject variability would be desirable. Thus, it was aimed to formulate and evaluate emulgels ofthe cephalexin. By the preformulation studies it is observed that cephalexin is a white to off white amorphous powder having no odor and characterstic taste. Five different type formulations (E-1 to E-5) formed using oil phase having fixed amount of Capric/caprylic Triglyceride (CT) and different ration of Cetyl Palmitate (CP) and fixed quantity of oil soluble emulsifiers Cetyl dimethicone copolyol (CDC) and Sorbitan stearate (Span 60) with Aqueous Phase contain Purified water at pH 6.8. Then observed visually that all formulations were clear, there was no phase separation and Stable during Thermo dynamic changes, heating cooling cycle and centrifugation stressed test. Characterization of all cephalexin emulsion formulations were evaluated for Droplet size, Zeta potential and Poly Dispersity Index (PDI) and % drug content, all emulgels showed excellent results droplet size was found between 1.12 to1.97 µm. All five cephalexin emulgel formulations were odorless, washable, homogeneous, stable and free from grittiness and was evaluated under the various parameters, pH of all formulations were observed at 6.8 and viscosity between 40.23 to 76.38 centi Poise and spreaability between 4.326 to 5.341 gm.cm/sec. *In-vitro* Drug Release of Cephalexin emulgel formulations were studied and found EG-1 (64.75), EG-2 (68.37), EG-3 (51.32), EG-4 (90.32) and EG-5(94.89). Emulgel formulations **EG-4** and **EG-5** were found excellent on the basis of cumulative percentage of drug release profile. Release data of both selected formulations was fitted into kinetic models. Drug release data were fitted into the zero order, first order, Higuchi and Peppas-Korsemeyer model of drug release kinetics. Emulgel EG-4 and EG-5 both were followed Zero Order Kinetics explained as continuous and steady release of Cephalexin from the formulation. All five formulations were also tested for stability and found formulation EG-3, EG-4 and EG-5 were stable after 30 days against color change, creaming, creaking and phase separation.

Key words: Emulgel, Cephalexin, Topical delivery, Cetyl dimethicone copolyol, Cetyl Palmitate

1. INTRODUCTION

Emulgel are emulsions, either of the water-in-oil or oil-in-water type, which are gelled by mixing with a gelling agent.[1] The emulsion also acts as controlled release drug delivery system in which drug particles entrapped in internal phase go through the external phase to the skin and slowly get absorbed. The drug reaches the external phase of the skin in a controlled manner through the internal phases which act as a reservoir of the drug.[2] Gel captures small drug particles and provides its release in a controlled manner because of a crosslinked network. It prolongs the contact period of medication over the skin because of its mucoadhesive property.[3]

Since Emulgel possesses the property of both gel and emulsions it acts as dual control release system. Water-in-oil emulsions are employed more extensively for emollient actions and for the treatment of dry skin and emollient applications while oil-in-water emulsions are most useful in general cosmetic acts as a water washable drug bases[4].

For dermatological use, the emulgels possess several advantages such as being greaseless, easily spreadable, transparent, easily removable, thixotropic, emollient, non-staining, bio-friendly, long shelf life and a pleasing appearance. Molecules can penetrate the skin mainly by three routes which include the intact stratum corneum, through the sweat ducts or through sebaceous follicles.[5] For percutaneous drug absorption, the stratum corneum's surface presents more than 99% of the total skin surface for this purpose.[6]

Cephalexin belongs to cephalosporin class of antibiotic. It works by fighting bacteria in body. Cephalexin is a beta-lactam, first-generation cephalosporin antibiotic with bactericidal activity. Cephalexin binds to and inactivates penicillin-binding proteins (PBP) located on the inner membrane of the bacterial cell wall. Inactivation of PBPs interferes with the cross-linking of Peptidoglycan chains necessary for bacterial cell wall strength and rigidity. This results in the weakening of the bacterial cell wall and causes cell- lysis[7].

The use of transparent gels has increasingly expanded in the pharmaceutical and cosmetic preparations because there are lots of limitations within the major group of semisolid preparations.[8] But in spite of many advantages of gels, their biggest limitation is the delivery of hydrophobic drugs. That is why to overcome this sole limitation an emulsion based approach is being developed and used so that even the hydrophobic drugs could be successfully incorporated and delivered through gels.

2. MATERIALS AND METHODS

Cephalexin was obtained from Cipla pvt. Ltd., Indore (M P) as gift. Capric/caprylic Triglyceride (CT), Cetyl Palmitate (CP), and Carbapol 940 were purchased from HiMedia Laboratories Pvt Ltd., Mumbai. Cetyl dimethicone copolyol (CDC) and Sorbitan stearate (Span 60) from Finar Chemical (India) Pvt Ltd. All other solvents used belong to laboratory grade.

2.1 Methods

2.1.1. Preformulation Studies

Organoleptic properties, melting point, partition coefficient were evaluated.

2.1.2. Determination of Wavelength of Maximum Absorbance (λ_{max})

10 mg of drug was weighed accurately and transferred to 10ml of volumetric flask. Then phosphate buffer pH 6.8 was added to dissolve drug completely. The volume was made up to 10 ml with solvent. The prepared sample was 1000µg/ml. 01 ml of above solution was then transferred to another 10ml volumetric flask and diluted it upto the mark with solvent. This sample was 100µg/ml. 01 ml of above solution was then transferred to another 10ml volumetric flask and diluted it upto the mark with solvent. This sample was 10µg/ml. Cephalexin solution (10µg/ml) was scanned in the U.V. range of 200-400 nm using Systronic Double beam UV Visible spectrophotometer.

2.1.3 Preparation of Calibration Curve of Cephalexin

The calibration curve was plotted between the concentration and absorbance. The different concentrations between 5-30µg/ml were scanned at 261 nm and absorbances were recorded.

2.1.4 Fourier-Transform Infra Red spectroscopy (FT-IR)

The IR spectrum of drug substance was authenticated using IR spectroscopy. The presence of characteristic peaks associated with specific structural characteristics of the drug molecule was noted.

2.2 Method of Preparation of Emulsions

Emulsions (O/W) were prepare d by emulsification process. Firstly W/O emulsion was prepared by slow addition of the aqueous phase to the oil phase containing Cephalexin (1%, *w*/*w*) at 80 ± 2°C under continuous stirring at 250 rpm until approximately 25 °C. The oily phase was prepared dissolving Cephalexin in different ratio of solvent and cosolvent (CT and CP) aided with the lipophilic emulsifying agents (CDC and sorbitan stearate) at 80 ± 2 °C.

2.3 Evaluation of Preparation of Emulsions

2.3.1 Globule Size Analysis

The Globule sizes of loaded formulations were measured by an optical microscope fitted with an ocular and stage micrometer and Globule size distribution was calculated. The Optical microscope having resolution of 100X was used for this purpose. The instrument was calibrated at 1unit of eyepiece. In all measurements at least 100 particles in five different fields were examined. Each experiment was carried out in triplicate. Prepared emulsions were diluted 10 times with distilled water. The droplet size distributions and poly dispersibility index of the resultant dry emulsions were determined using particle size analyzer.

2.3.2 Determination of % Drug content

Percentage of Drug Content was determined by taking freshly prepared W/O multiple emulsions and immediately centrifuged at 4000 rpm for 10min. Then 1ml of the aqueous phase (the lower layer) was precisely withdrawn through 2ml hypodermic syringe and diluted properly with phosphate buffer pH 6.8. The solution was filtered with a Millipore filter (0.45mm in pore size) and drug content was analyzed on UV spectrophotometer at 261 nm. The Drug Content was determined by following equation:

$$\% \text{ Drug Content} = \frac{\text{Amount of drug present in formulation}}{\text{Calculated (added) Amount in formulation}} \text{X } 100$$

2.3.3 Physical Stability of Emulsion Formulations

Organoleptic characters were monitored to detect any visible signs of instability such as creaming, cracking phase separation or color changes.

2.3.4 Thermodynamic stability

Emulsions were thermodynamically stable systems and formed at particular composition (concentration) of oil, surfactant, co-surfactant and water. In addition, no creaming or cracking and phase separation as compared to regular emulsion have kinetic stability results ultimately phase separates, thus selected regions of emulsions also characterized to prove thermodynamic stability. The emulsion formulations subjected to stress tests like heating cooling cycle, centrifugation, and those formulations passed these stress tests were subjected to further test.

2.3.5 Heating Cooling Cycle

The prepared emulsion formulations are tested against heating-cooling cycle. In this test, sample stored at refrigerator temperature 4°C for 48 hrs then at 45°C for 48 hrs, studied in six cycles. Those formulations, which were stable at these temperatures, were subjected to centrifugation test.

2.3.6 Centrifugation

The passed formulations from heating cooling cycles were centrifuged using centrifuge at 3500 rpm for 30 min. Those formulations which did not show any phase separation were taken for the further study.

2.4 Preparation of Gel and incorporation of emulsion

Blank gels of different polymers were prepared using distilled water. Finally, the carbopol gel was prepared by swelling 0.5% carbopol940 w/v in 100 ml of water with stirring on mechanical stir. Additionally preservation of formulations was carried out by 0.01% methyl paraben.

Table No. 1: Formulation of carbopol gel

S. No.	Ingredients	Quantity in (w/v)
01.	Carbopol 940	0.5 %
02.	Water	100ml
03.	Methyl paraben	0.8 %

Optimized formulations of emulsions were incorporated in prepared gel in the ratio of 1:1with stirring on magnetic stir until homogenization.

2.5 Evaluation of Emulgel

2.5.1 Viscosity

The viscosities of the samples were determined at 25°C spindle speeds ranging from 100 to 200 rpm while using a spindle CP 41 in a Brookfield visometer. Rheocalc V 2.6 (Microsoft Corporation) software was used as a support program to produce the results of rheological behavior.

2.5.2 Determination of pH

The pH of fresh sample and samples kept in different storage conditions was determined by a digital pH meter. The pH measurements were also taken for the samples during stability at 24 h, 7th, 15th and 30th days.

2.5.3 Spreadability

Spreadability was determined by apparatus which 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 pro-vided 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.

2.5.4 In vitro drug release study

The *in-vitro* drug release study was carried out on a simple dissolution cell using cellophane membrane (thickness-200mm, breaking strength- 2.7 kg/cm). Prior to release studies, the cellophane membrane was soaked in distilled water for 6 hours, washed frequently 4 times by changing distilled water, then immersed in 5% v/v glycerol solution for at least 60 min and washed finally with 5 portions of distilled water. 15 ml freshly prepared multiple emulsion was added to donor chamber, made up of a hollow glass tube (2.5 cm in diameter and 10 cm in length) and membrane was tied on bottom end of the tube with a nylon string. This tube was dipped into 250 ml vessel containing 100 ml of PBS pH 6.8 and was stirred at 100 rpm on a magnetic stirrer and maintained at 37 °C which acted as receiving chamber. Aliquots of 1ml were collected from receiving chamber at predetermined time intervals and the drug content was determined on UV spectrophotometer at 261 nm after suitable dilution.

2.5.5 Kinetics models of drug release

There are several models to represent the drug dissolution profiles where f (t) is a function of time related to the amount of drug dissolved from the pharmaceutical dosage form.

a) Zero order kinetics
b) First order kinetics
c) Higuchi Model
d) Peppas-Korsmeyer Model

2.5.6 Stability of optimized multiple emulsion formulation

Optimized multiple emulsion formulation was stored in cool and dry place for 30 day. After 30 days stored formulation was observed visually for creaming, creaking, phase separation and color change reaction.

3. RESULTS AND DISCUSSION

3.1 Pre-formulation Studies

In the pre-formulation studies, it is observed that cephalexin is a white to off white amorphous powder having no odor and characteristic taste. Solubility was determined in various solvents found that insoluble in ethanol and methanol, slightly soluble in Distilled Water, soluble in Phosphate Buffer 6.8pH and 0.1N HCl and poorly soluble in 0.1N NaOH. Melting point was observed in range of 333-335 ^{0}C. λ_{max} was determined at 261 nm by scanning sample from 200-400nm and also calibration curve was obtained by absorbance of aliquots from 5-30 µg/ml with following linear equation y = 0.024x-0.01 R^2 = 0.999. Partition coefficient was 1.8077 obtained. Drug: Excipient Compatibility Studies at room temperature, 2^{0}C - 8^{0}C and 45^{0}C - 50^{0}C says it is stable. Stability also confirmed by FT-IR studies.

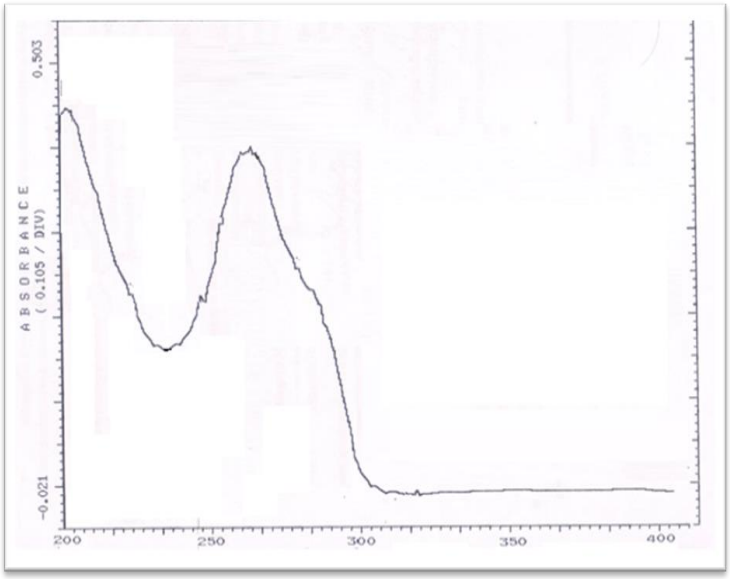

Figure no.1: Scanning of Wavelength of Cephalexin

3.2 Preparation of the Calibration Curves of Cephalexin

Table no.2: Linearity of Cephalexin phosphate buffer pH 6.8

Conc. (µg/ml)	0	5	10	15	20	25	30
Absorbance	0	0.109	0.228	0.352	0.472	0.605	0.727

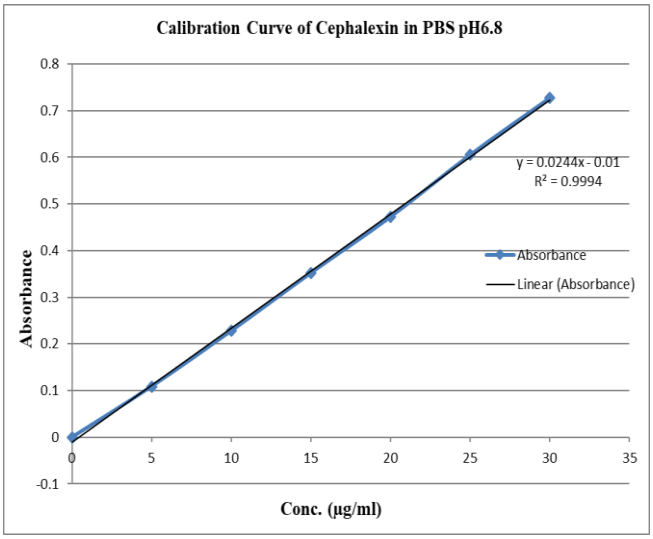

Fig. no.2: Calibration Curve of Cephalexin in phosphate buffer pH 6.8

3.3 Physical Compatibility Study

Table no. 3: Physical Compatibility Study of Cephalexin with polymer

S. No.	Material	Storage at room temperature	Storage at 45^0C - 50^0C	Storage at 2^0C - 8^0C
1	Pure Drug (10mg)	Stable	Stable	Stable
2	Optimized formulation	Stable	Stable	Stable

3.4 Chemical Compatibility Study by FT-IR

Table no.4: FT-IR Peaks of Cephalexin

Standarded Peaks(Cm^{-1})	Observed Peaks(Cm^{-1})	Peak Assigned
3000-3500	3441	N-H str
3200-3000	3184	O-H str
3000-2840	2858	CH_3 str
1650-1600	1634	C=O str

3.5 Formulation of Emulsion

Table no.5: Formulation of Multiple Emulsions

Components	Percentage Composition (w/w)				
	E-1	E-2	E-3	E-4	E-5
Oil phase (O)					
Cephalexin	01.00	1.00	1.00	1.00	1.00
Capric/caprylic Triglyceride (CT)	10.00	10.00	10.00	10.00	10.00
Cetyl Palmitate (CP)	01.00	02.00	3.00	4.00	5.00
Cetyl dimethicone copolyol (CDC)	01.50	1.50	1.50	1.50	1.50
Sorbitan stearate (Span 60)	05.00	5.00	5.00	5.00	5.00
Internal Aqueous Phase (W)					
Purified water at pH 6.8	31.50	30.50	29.50	28.50	27.50

3.6 Evaluation of Prepared Emulsion Formulations

Table no. 6: Physical evaluation of all prepared formulation

S. No.	Code of formulation	Visual Observation	Phase Separation	Thermo dynamic Stability	Heating cooling cycle	Centrifugation
1	E-1	Clear	Not Observed	Stable	Stable	Stable
2	E-2	Clear	Not Observed	Stable	Stable	Stable
3	E-3	Clear	Not Observed	Stable	Stable	Stable
4	E-4	Clear	Not Observed	Stable	Stable	Stable
5	E-5	Clear	Not Observed	Stable	Stable	Stable

Table no. 7: Globule size analysis of formulations

Formulation Code	Droplet size (µm)	Zeta potential (mV)	Poly Dispersity Index (PDI)	Drug content (%)
E-1	1.12 ± 1.24	12.2 ± 1.02	0.422 ± 0.03	90.21 ± 1.65
E-2	1.34 ± 1.53	11.2 ± 1.10	0.331 ± 0.04	96.23 ± 1.01
E-3	1.13 ± 2.39	11.4 ± 1.07	0.403 ± 0.01	91.32 ± 1.23
E-4	1.97 ± 0.02	12.1 ± 1.07	0.353 ± 0.05	93.52 ± 1.41
E-5	1.38 ± 2.07	11.5 ± 1.16	0.435 ± 0.03	92.31 ± 1.13

Note: All the values are mean of triple reading ± standard deviation

3.7 Incorporation of prepared batches of emulsions into the Gel

Prepared all batches of emulsion were incorporated in prepared gel with stirring on magnetic stir in the ratio of 1:1 now the formulations were called **Emulgels**. The codes added G for gel, now the changed codes are **EG-1, EG-2, EG-3, EG-4 and EG-5**.

3.8 Evaluation of Emulgels

3.8.1. Physical Examination of Emulgels

Table no.8: Physical Examination, pH, Viscosity and spreadability of Emulgels

Emulgel Code	Physical Examination	pH	Viscosity (cP)	Spreadability gm.cm/sec
EG-1	Clear	6.5	40.23	5.334
EG-2	Clear	6.8	55.43	4.334
EG-3	Clear	6.7	54.55	5.341
EG-4	Clear	6.9	68.32	4.326
EG-5	Clear	6.3	76.38	5.265

3.8.2. Drug Release Profile of Emulgels

Table no.9: Cumulative % of cephalexin release from Emulgels

Time (hr.)	EG-1	EG-2	EG-3	EG-4	EG-5
0	0	0	0	0	0
1	7.42	8.44	6.62	12.32	15.41
2	13.88	15.32	13.54	23.47	27.28
3	21.23	24.43	19.32	34.75	39.63
4	29.47	32.49	25.64	45.64	51.77
5	35.76	41.41	31.52	56.86	63.46
6	45.54	50.19	38.54	67.85	73.56
7	54.37	57.38	45.67	78.95	86.97
8	62.33	67.94	50.93	89.64	94.65
9	64.75	68.37	51.32	90.32	94.89

Table no.10: *In-vitro* Drug Release Profile of EG-4

Time (hr.)	S.R.T	Log T.	% C.R	Log % C.R	% Drug remaining	Log% drug remaining
0	0	-	0	-	100	2
1	1	0	12.32	1.091	87.68	1.943
2	1.141	0.301	23.47	1.371	76.53	1.884
3	1.732	0.477	34.75	1.541	65.25	1.814
4	2	0.602	45.64	1.659	54.36	1.735
5	2.236	0.699	56.86	1.755	43.14	1.635
6	2.449	0.778	67.85	1.832	32.15	1.507
7	2.646	0.845	78.95	1.897	21.05	1.323
8	2.828	0.903	89.64	1.953	10.36	1.015
9	3	0.954	90.32	1.956	09.68	0.986

Table no.11: *In-vitro* Drug Release Profile of EG-4

Time (hr.)	S.R.T	Log T.	% C.R	Log % C.R	% Drug remaining	Log% drug remaining
0	0	-	0	-	100	2
1	1	0	15.41	1.188	84.59	1.927
2	1.141	0.301	27.28	1.436	72.72	1.862
3	1.732	0.477	39.63	1.598	60.37	1.781
4	2	0.602	51.77	1.714	48.23	1.683
5	2.236	0.699	63.46	1.803	36.54	1.563
6	2.449	0.778	73.56	1.867	26.44	1.422
7	2.646	0.845	86.97	1.939	13.03	1.115
8	2.828	0.903	94.65	1.976	05.35	0.728
9	3	0.954	94.89	1.977	05.11	0.708

3.8.3 Kinetic Modeling for Emulgel EG-4 and EG-5

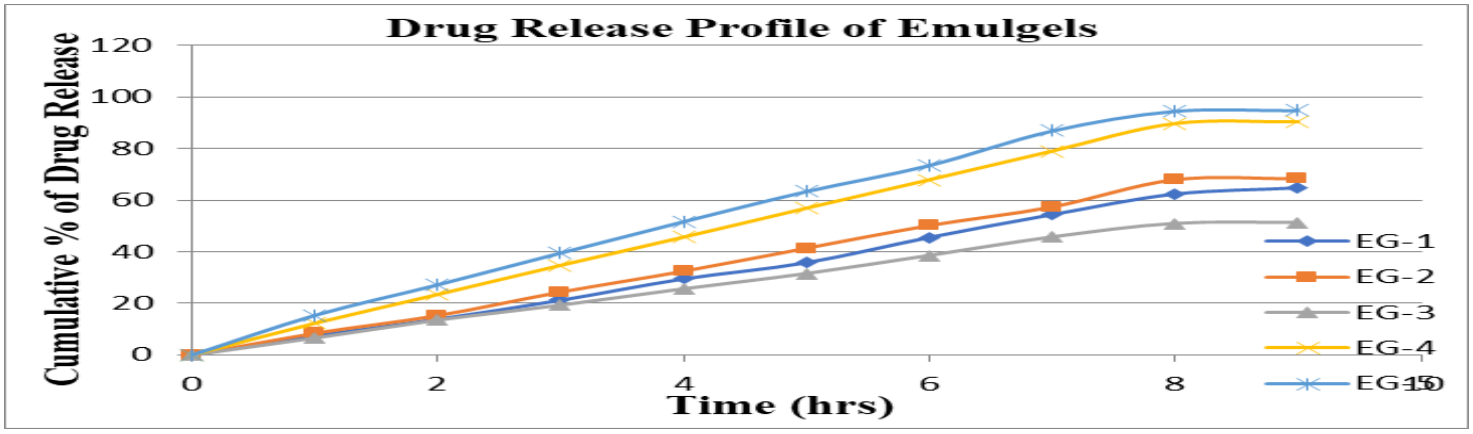

Figure no.3: *in-vitro* cumulative % drug release from Emulgels

Zero Order Kinetics

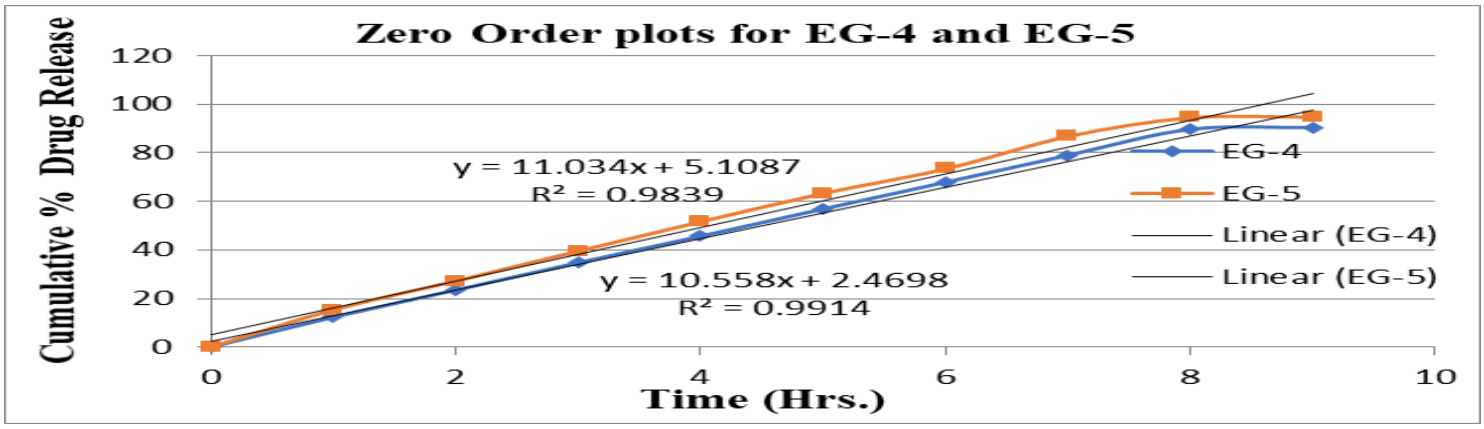

Fig. no.4: Zero Order plots for EG-4 and EG-5

First Order Kinetics

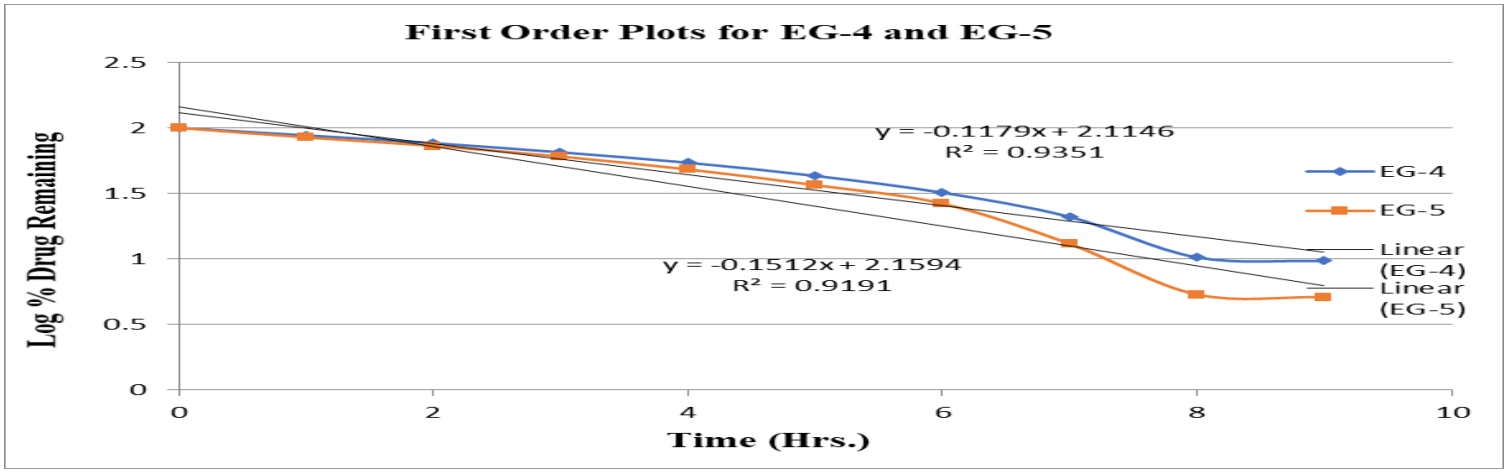

Fig. no.5: First Order plots for EG-4 and EG-5

Higuchi Model of Drug Release Kinetics

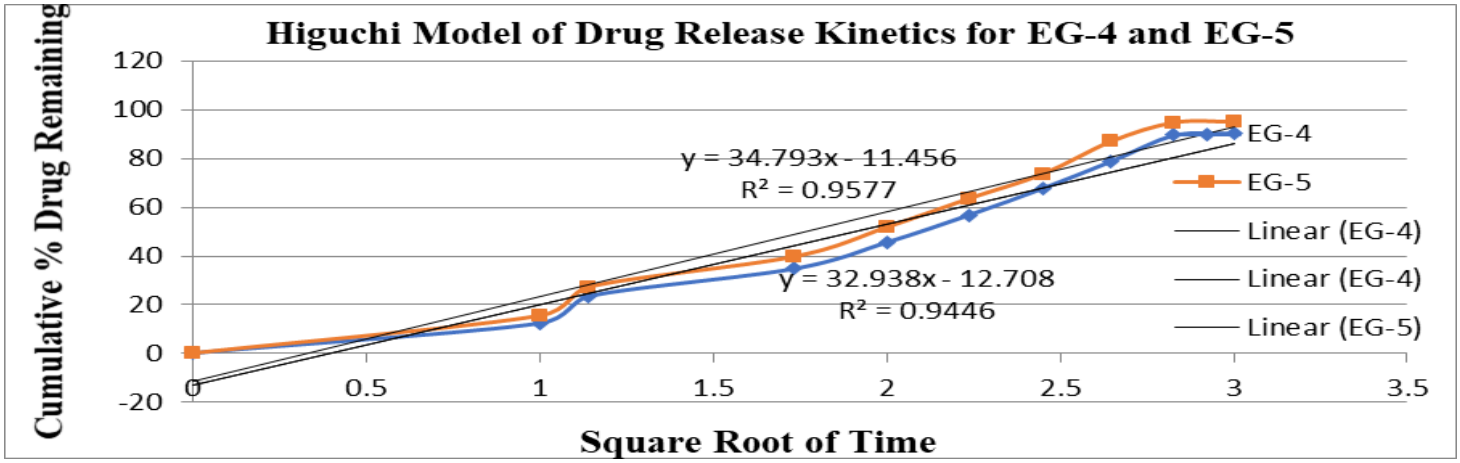

Fig. no. 6: Higuchi Model of Drug Release Kinetics for EG-4 and EG-5

Peppas - Korsemeyer model of drug release kinetics

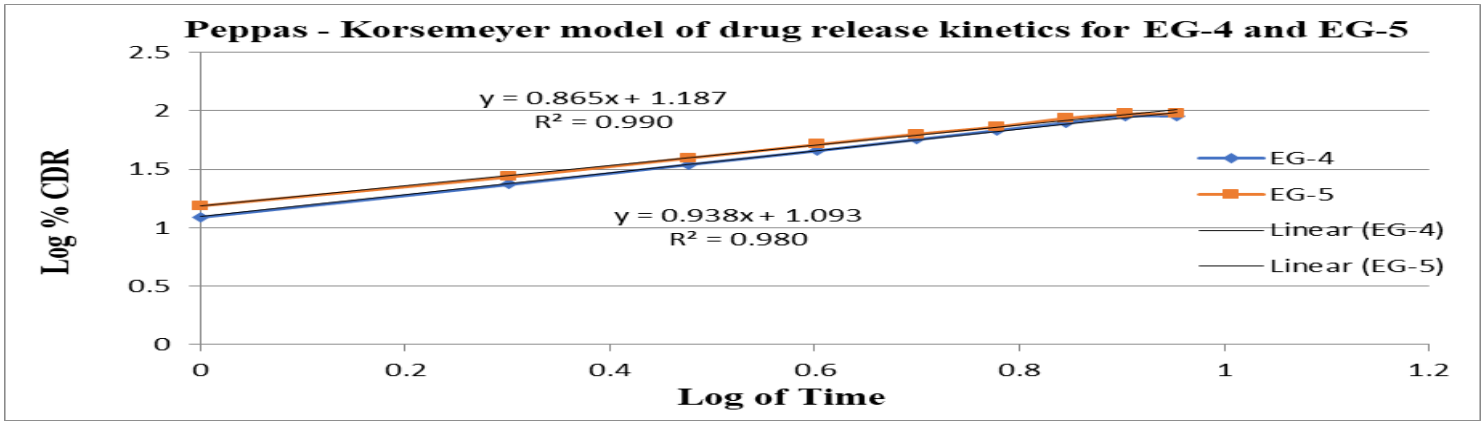

Fig. no.7: Peppas - Korsemeyer model of drug release kinetics for EG-4 and EG-5

Table no.12: Comparative study of kinetic models for EG-4 and EG-5

Name of Model	EG-4	EG-5
	R^2 value	**R^2 value**
Zero Order Kinetics	$R^2 = 0.991$	$R^2 = 0.983$
First Order Kinetics	$R^2 = 0.935$	$R^2 = 0.919$
Higuchi Model	$R^2 = 0.944$	$R^2 = 0.957$
Peppas Korsemeyer model	$R^2 = 0.990$	$R^2 = 0.980$

3.9 Stability Testing

Table no.13: Stability testing under following parameters

Formulation Code	Stability testing after 30 days			
	Color Change	**Creaming**	**Creaking**	**Phase Separation**
EG-1	Observed	Observed	Not Observed	Not Observed
EG-2	Not Observed	Not Observed	Observed	Not Observed
EG-3	Not Observed	Not Observed	Not Observed	Not Observed
EG-4	Not Observed	Not Observed	Not Observed	Not Observed
EG-5	Not Observed	Not Observed	Not Observed	Not Observed

4. RESULTS AND DISCUSSION

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5. CONCLUSION

The prepared Emulgels of Cephalexin had shown excellent promising results for all the evaluated parameters. On the basis of *in-vitro* drug release and drug content results, **EG-4** and **EG-5** formulation possessed excellent drug release as compared to rest Emulgels which shows higher percentage of drug release.

In vitro release profile was applied on various kinetic models like Zero order, First order, Higuchi equation and Peppas-Korsemeyer model. The best fit with highest regression coefficient was found with Zero order. The rate constants are calculated from the slop of the respective plots the release mechanism of Multiple Emulsion.

Emulgels **EG-4** and **EG-5** formulation can be further study for preclinical and clinical evaluations.

6. CONFLICTS OF INTERESTS

There are no Conflicts of interests

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