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Formulation Design, Optimization and Evaluation of Mupirocin Emulgel

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ABSTRACT

Emulsified gels are stable and better vehicles for hydrophobic or poorly water soluble drugs. Mupirocin is an antibacterial drug. Mupirocin works to kill the bacteria which include strains of Staphylococcus aureus and Streptococcus pyogenes. Conventionally, Mupirocin is available in the form of ointments in most South East Asian countries. However, emulgels have been found to be better suited with an added advantage of sustained release, which is necessary for the treatment of skin infection. Mupirocinemulgels were formulated using PEGs, Carbomer 940 and flax seed oil. The pH of the emulgel formulations were found to be close to that of the human skin. Drug excipient compatibility analysis was carried out by FTIR. Emulgel was evaluated for its physical characterization, in-vitro release and antimicrobial properties. FTIR analysis confirmed drug excipient compatibility. Release studies indicated controlled release of drug carbomer 940 due to its higher gelling capacity. Formulation EG3 showed good results against Staphylococcus aureus. Mupirocin was stable in topical emulgel formulations and showed enhanced retention in the skin indicating better potential of the delivery system for treatment of primary and secondary skin infections, such as impetigo,eczema, and atopic dermatitis.

Key words: *Emulgel; topical; mupirocin; antimicrobial; FTIR; carbomer 940.*

INTRODUCTION

Emulgels

Gels are currently receiving increasing attention, especially hydrogel formulations, for topical application of drugs since they have an attractive appearance and develop pleasant cool feeling. Gels for topical use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, non-staining, compatible with several excipients, and water-soluble or miscible [1]. Gel dosage forms are successfully used as drug delivery systems to control drug release and protect the medicaments from a hostile environment. In spite of many advantages of gels, a major limitation is in the delivery of hydrophobic drugs.

Since gels have a higher aqueous component, it limits the dissolution of hydrophobic drugs, and also retards migration of the drug through a vehicle that is essentially a liquid. To overcome this limitation, emulgels are prepared and used so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels [2].

Eumlgels are emulsions either of oil-in- water or water-in-oil type, which is gelled by mixing with gelling agent. They have been recently used as vehicles to deliver various drugs to the skin and vagina [6]. Emulsified gels are stable and better vehicles for hydrophobic or poorly

water soluble drugs**.** They have the advantages of emulsions and gels. They are used to deliver various drugs to the mucosa due to enhanced drug absorption through the mucosa since the drug substance is in solution.

MATERIALS AND METHOD

The whole project was carried out atM/s Denium Laboratories Pvt. Ltd., Birgunj, Nepal. MupirocinIP wassourced from Concord biotech Ltd., Gujarat., Carbomer 940 from Maruti Chemicals, Gujarat., Triethanolamine from Triveni Chemicals, Gujarat., PEG-400from India Glycols Limited, Uttarakhand., PEG-4000 from India Glycols Limited, Uttarakhand., Di sodium EDTA from New Alliance Dye Chem, Mumbai., Glycerine from SaliusPharma Private Limited, Mumbai.Flax seed oil sourced from local purchase.

Preparation of emulgels comprises of simple and short steps which increase feasibility of the production. There are no specialized instruments needed for the production of emulgels. Moreover, materials used are easily available and cheap. All these; decrease the production cost of emulgels. The rheological properties and the breakdown behavior of gels filled with emulsions droplets can be varied by changing the interactions between oil droplets and gel matrix, the oil content and the oil droplet size [10].

Basically emulgel preparation consists of two steps; emulsification and incorporating the emulsion into a gel base (Fig.1& 2). Important constituents of the emulgel are the aqueous phase, the oil phase and the gelling agents [2]. Commonly used aqueous agents arewater and alcohols.

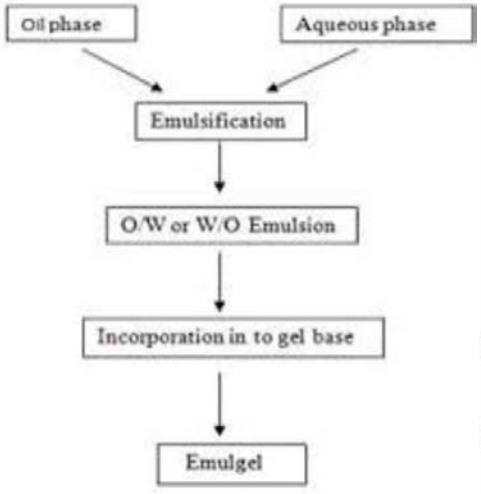


Fig.1. Preparation of Emulgel

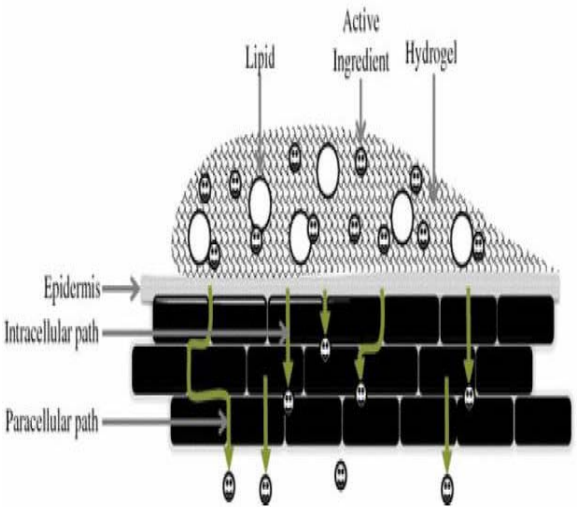


Fig.2. Schematic Representation of Emulgel System

PREFORMULATION STUDIES

Preformulation studies are important for the development of dosage form for achieving the goal of designing optimum drug delivery system.

Identification: The drug sample obtained was identified by various analytical techniques such as FTIR spectroscopy, UV spectroscopy, Melting point, Partition coefficient and Solubility etc.

Meting point: Melting point of Mupirocin was determined by taking small amountseparately in a capillary tube closed at one end and placed in a Melting Point apparatus (PERFIT) and

the temperature at which Mupirocin molten was recorded. This was performed in triplicate and average value was recorded. The melting point of Mupirocin was found to be 78°C, is similar to reported value indicating that no impurity is present in the sample.

Partition coefficient

Partition coefficient of Mupirocin was determined at 37 ± 0.5 °C by taking 5 ml of octanol which was saturated with 5 ml of water by shaking with externally driven magnetic stirrer. After shaking the system remained undisturbed for half an hour. About 100 mg of drug was added to this solution and was shaken on wrist action mechanical stirrer. Two layers were separate through separating funnel and filtered through Whattman grade filter, and the amount of Mupirocin solubilised, was determined by measuring the absorbance at 220 nm against reagent blank through double beam UV/Vis spectrophotometer (Shimadzu) in both the solution. Partition coefficient was determined as ratio of concentration of drug in octanol to the concentration of drug in water and the value were reported as log P. The Log p values were found to be 2.45 ± 0.12.

Solubility Studies

Solubility studies were carried out with different solvents such as water, ethanol, and methanol in water bath shaker at 25°C and kept it for 24 hours.

Solvents	**Solubility (mg/ml) (mean ±SD)***
Distilled water	0.0265±0.009
Methanol	0.0229±0.007
DMSO	0.436±0.004

PREPARATION OF EMULGELS

Mupirocin was dissolved with flax seed oil and one half of the PEG-400 at 55^0C under continuous stirring. Then the mixture of remaining PEG-400 and PEG-4000 (heated at 65^0C and again cooled to 55^0C) was incorporated with active solution. This emulsion is cooled to room temperature. In a separate SS container, purified water was poured and sequestered with Disodium EDTA. Now the carbomer 940 was wet with continuous stirring for 10 minutes. Then neutralized it to ~7 pH with Triethanolamine. A viscous transparent gel was obtained. Next, incorporation of the mupirocin emulsion to the gel under mild stirring for 20 minutes was done. In the meantime, glycerin added into it. Emulgels were immediately transferred into tubes for observation and stability study.

Table 1: Composition of different formulations

S. No.	**Ingredients**	**EG1**	**EG2**	**EG3**
1.	Mupirocin	2.04	2.04	2.04
2.	PEG-400	18	20	22
3.	PEG-4000	6	4	5
4.	Carbomer 940	4	3.3	3.0
5.	Triethanolamine	2	2	1.5
6.	Di sodium EDTA	0.1	0.1	0.1
7.	Glycerin	5	5	4
8.	Flax seed oil	8	10	12
9.	Purified water	qs to 100g	qs to 100g	qs to 100g
Total		100g	100g	100g

** Quantities in gram.*

EVALUATION OF MUPIROCIN EMULGELS

Percentage (%) Yield

The prepared emulgels were collected and weighed. The measured weight was divided bythe total weight of all the excipients and drug. The % yield was calculated.

Morphological Studies

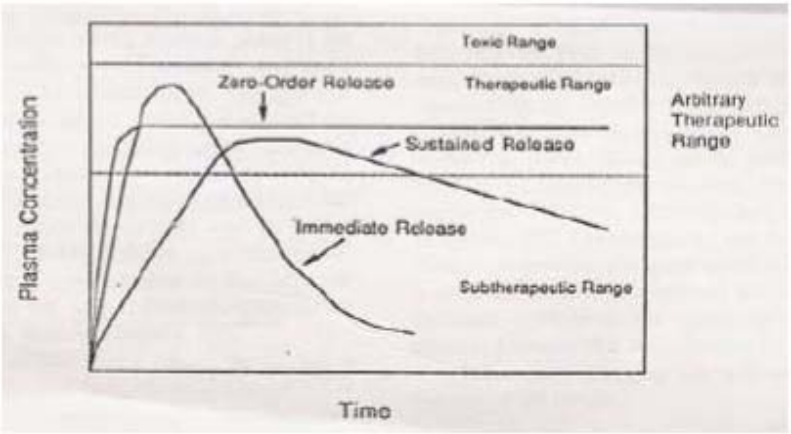
The morphology study of optimized formulation was performed by observing under compound microscope.

In-vitro Dissolution Studies

The emulgel equivalents to weight containing 100mg of mupirocin were immersed in dissolution medium. To assure the release of drug in solution at appropriate rate, dissolution test has been performed for optimized formulation in triplicate. The in-vitro release of mupirocin from the emulgel was examined using USP Type II dissolution apparatus. 6.8 phosphate buffer (900 ml) was used as the dissolution medium and maintained at 37±0.5°C at a rotation speed of 100 rpm. An aliquot of 5 ml of the solution was withdrawn at predetermined time intervals and replaced by 5 ml of fresh dissolution medium. Samples were assayed with spectrophotometer at 220 nm after filtration througha 0.45 µm membrane filter (Millipore) against 6.8 phosphate buffer as blank.

Drug release Kinetic Studies

In the present study, raw data obtained from in vitro release studies was analyzed, wherein data was fitted to different equations and kinetics model to calculate the percent drug release and release kinetics of mupirocin from emulgel formulations. The kinetic models used were a Zero-order equation, First-order, Higuchi's model and Korsmeyer- Peppas equation. When the data was plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follows first-order kinetics. The constant 'K' can be obtained by multiplying 2.303 with slope values.

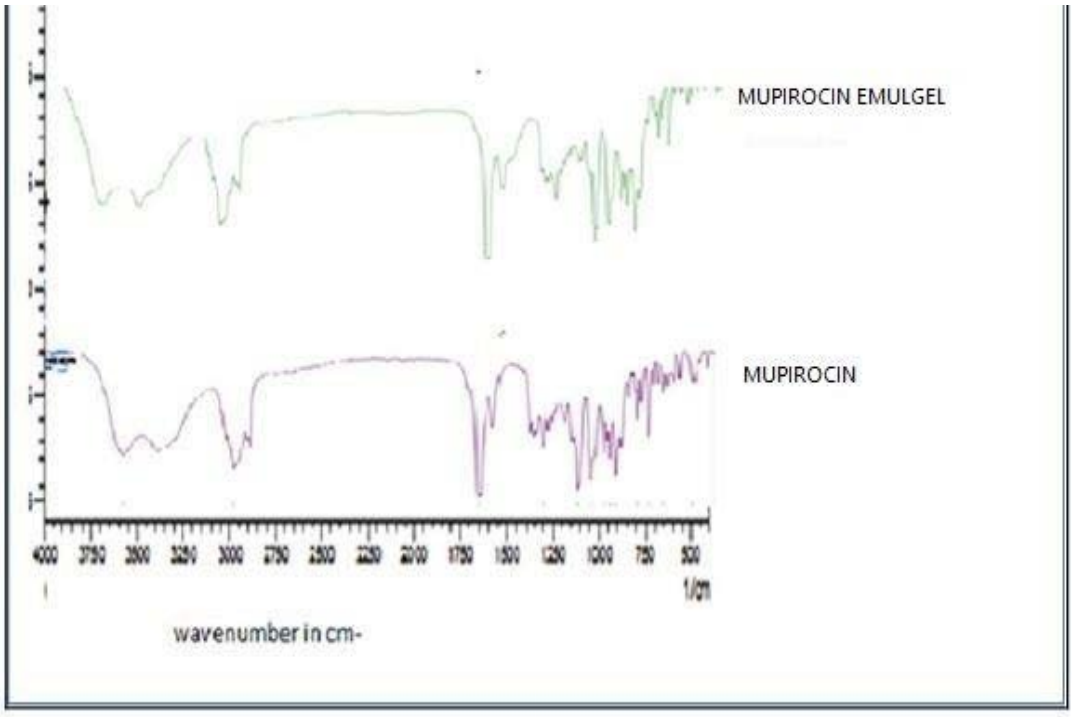


Graph1: Drug level verses time profile showing difference between zero order, controlled releases, slow first order sustained release and release from a conventional tablet

Accelerated Stability Studies

To assess the drug and formulation stability, stability studies were done according to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and World Health Organization recommended Good Manufacturing Practice (WHO-MGP) guidelines. The optimized Mupirocin Emulgel tubes were stored at

40±2°C/75±5% relative humidity for 6 months. Emulgels were analyzed at specified time intervals (0, 1, 2, 3 & 6 months) for the physicochemical properties and in vitro dissolution study.



Graph 2: FT-IR spectrum of Mupirocin Emulgel

RESULTS AND DISCUSSION

Physical Appearance

Emulgel formulations were white viscous creamy preparation with a smooth homogeneous texture and glossy appearance. Results have been discussed in Table5.7.

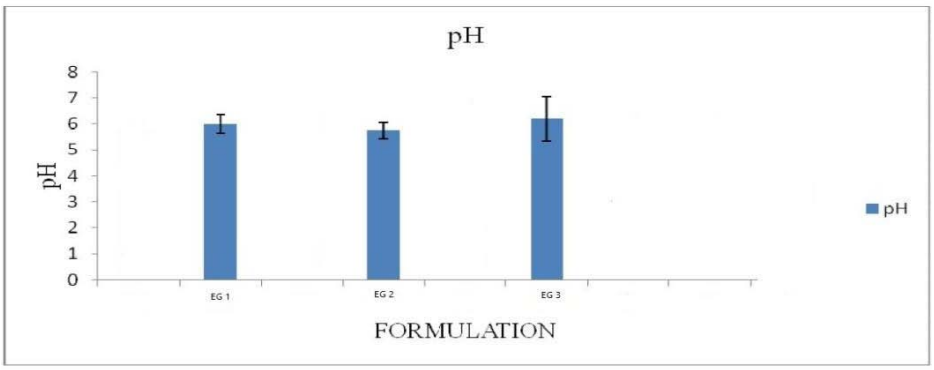
Table 2: Physicochemical characteristics of Mupirocin Emulgel formulations

S.N.	Formulation Code	Color	Phase Separation	Grittiness	Homogeneity	Consistency
1	EG1	White	None	-	Excellent	++
2	EG2	White	None	-	Good	+++
3	EG3	White	None	-	Excellent	+++

pH

The pH of the Emulgel formulations was in the range of 5.5 ± 0.54 to 6.4 ± 0.43, which lies in the normal pH range of the skin and would not produce any skin irritation. There was no significant change in pH values as a function of time for all formulations.

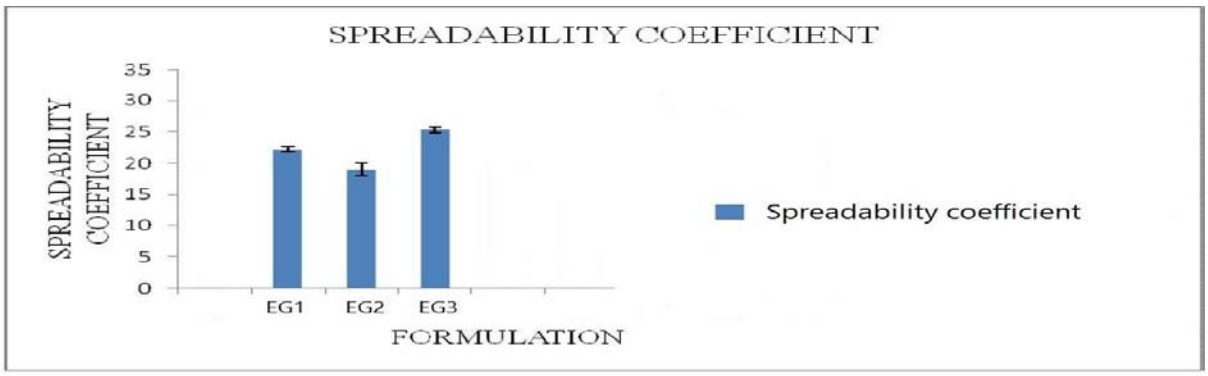
The data is shown below in Graph 3.



Graph 3: pH of Different Formulations EG1 - EG3

Spreadability Test

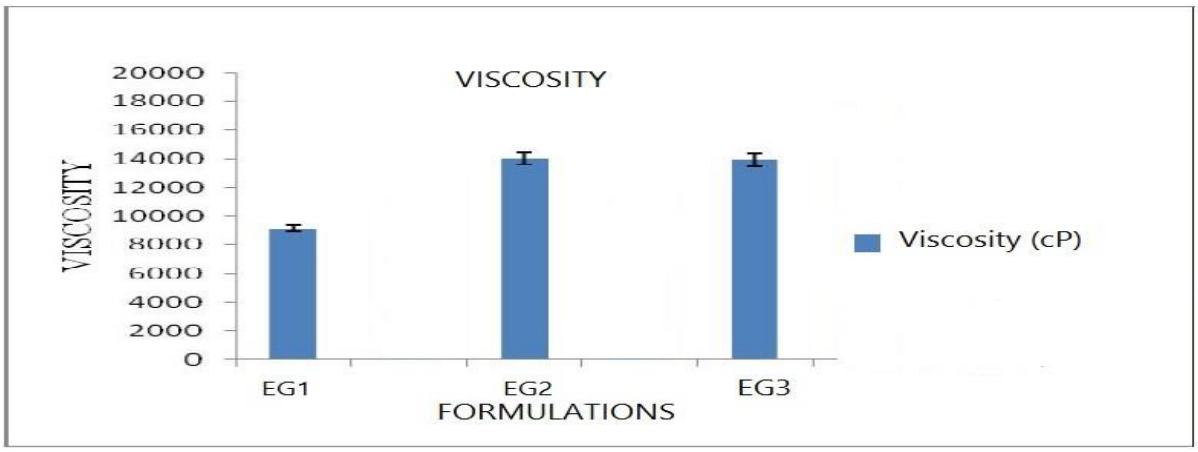
Spreadability tests were carried out for all the formulations. The spreadability indicates that the Emulgel is easily spreadable by small amount of shear. Spreadability of the Emulgel decreases with the increase in the concentration of the polymer. The spreadability is very much important as it shows the behaviour of Emulgel when it comes out from the tube as given in graph 2.



Graph 4: Spreading Coefficient of Different Formulations EG1 – EG3

Rheological Study

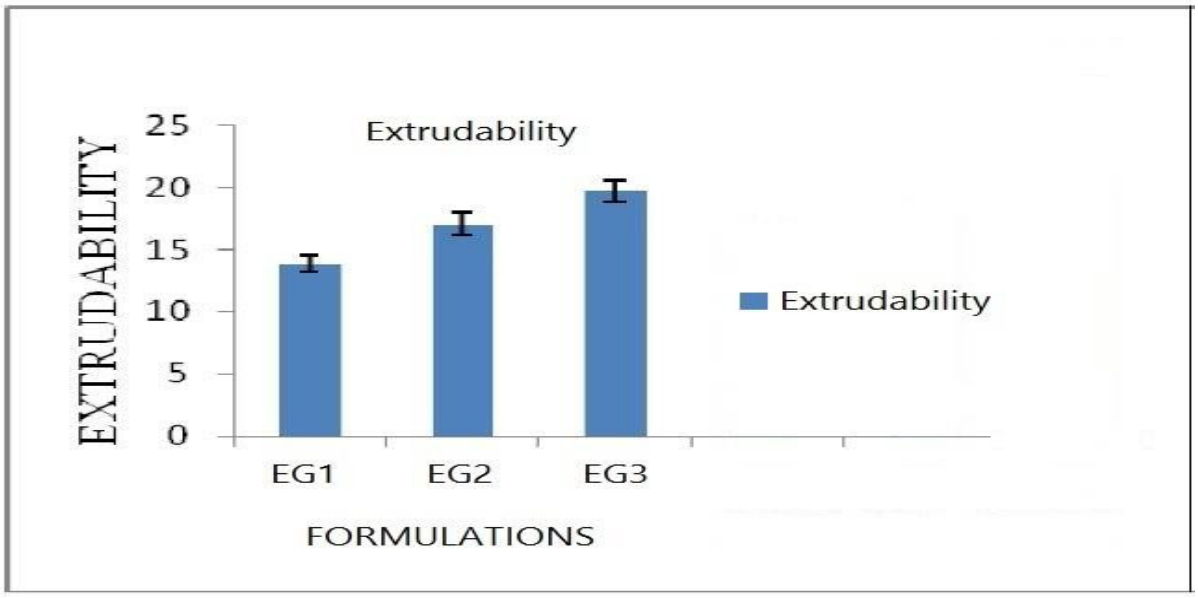
The Emulgel was rotated at 50 rpm for 10 min with spindle C25-1. The corresponding reading was noted. The viscosity of the Emulgel was obtained (Graph 3). The viscosity ofthe formulations increases as concentration of polymer increases.



Graph 5: Viscosities of Different Formulations EG1 - EG3

Extrudability

The gels were filled into collapsible tubes after formulating them. The extrudability of the formulation has been checked as shown below in graph 4.



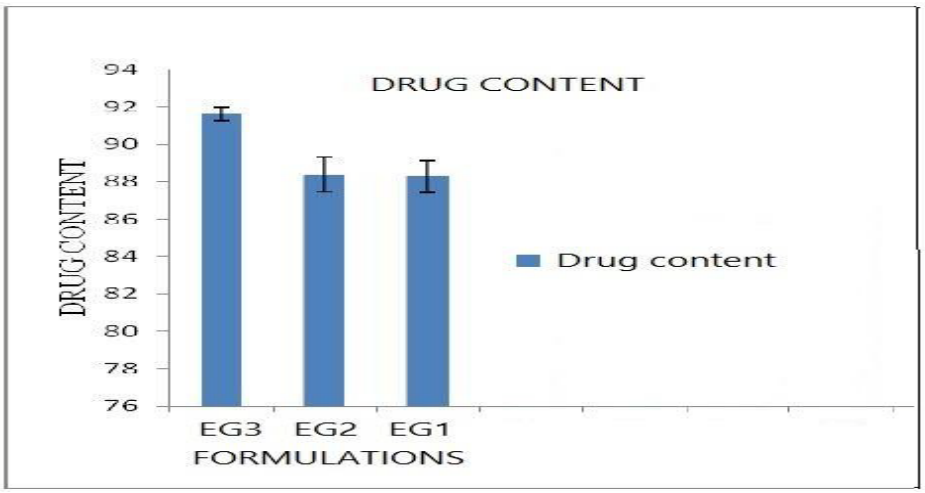
Graph 6: Extrudability of Formulations EG1 – EG3

Drug Content

The drug content of the formulated Emulgel was estimated spectrophotometrically at λmax 220. The results were in the limits as shown in Table 4 and Graph 5.

Table 3: Drug content of all formulations

S.N.	Formulations	Drug Contents (% Assay)
1	EG 1	88.38 ± 0.92
2	EG2	88.26 ± 0.87
3	EG3	91.60 ± 0.37



Graph 7: Drug Content of Formulations EG1 - EG3

In Vitro Drug Release

The release of Mupirocin from the Emulgel was varied according to concentration of polymer. The release of the drugs from its emulsified gel formulation can be ranked inthe following descending order: EG1 > EG2 > EG3.

Where the amounts of the drug released after 8 hours were 54.21%, 58.43%, 67.02%, respectively.

The progressive increase in the amount of drug diffusion through membrane from formulation attributed to gradual decrease in the concentration of polymer. It has been concluded that, if we increase the concentration of polymer, the diffusion of drug throughthe membrane also decreases. The cumulative % drug release profile of all the formulation batches has been shown in Table 4 and graph is plotted between cumulative
% drug releases versus time as shown in graph 8.

Table 4: *In-vitro* drug release study of Mupirocinemulgel formulations

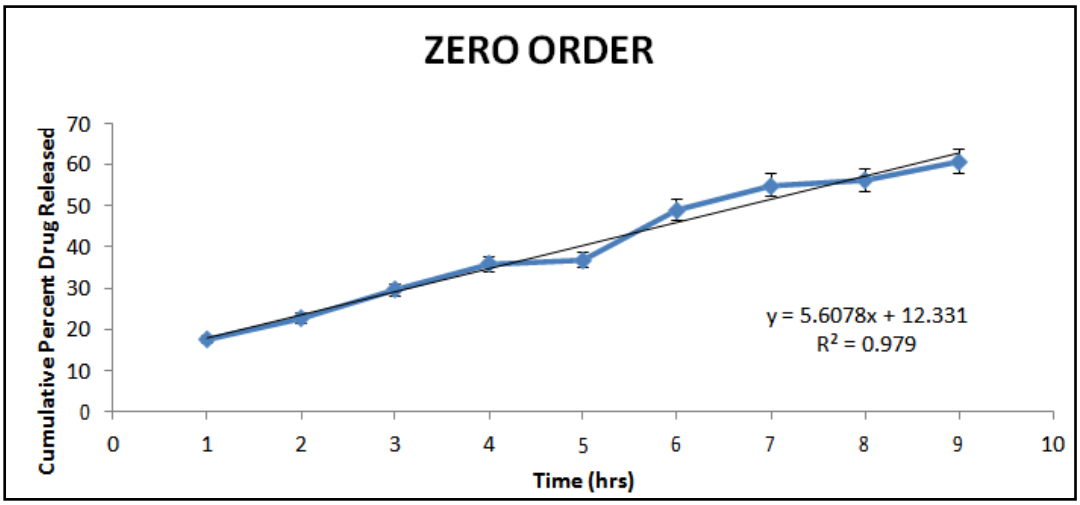
Time (hours)	EG1	EG2	EG3
0	0.00±0.00	0.00±0.00	0.00±0.00
0.5	11.98±1.77	15.44±1.25	14.68±0.015
1.0	16.36±1.51	20.85±0.31	19.19±0.005
1.5	20.61±1.96	24.83±0.05	22.53±0.02
2.0	23.22±0.55	27.81±1.46	27.39±0.003
2.5	26.68±0.56	31.25±2.24	32.11±0.36
3.0	28.46±2.43	35.23±0.57	36.04±0.23
3.5	30.88±2.02	37.66±1.98	38.93±0.47
4.0	34.77±2.67	40.08±1.11	44.27±0.15
4.5	37.42±1.90	42.17±2.87	47.45±0.89
5.0	40.27±0.32	43.39±0.91	52.19±0.20
5.5	43.76±1.86	46.19±1.32	57.21±0.115
6.0	45.48±1.61	47.56±0.65	58.64±0.65
6.5	47.14±0.34	50.85±1.81	59.74±0.11
7.0	50.12±0.56	53.65±1.90	62.09±1.18
7.5	52.20±1.43	56.39±2.49	64.32±0.32
8.0	54.21±0.33	58.43±1.09	67.02±1.04
8.5	54.92±0.79	60.41±0.26	69.32±2.09
9.0	58.56±0.53	61.9±2.65	72.56±0.42
9.5	59.88±0.7	63.06±0.32	74.48±0.01
10.0	61.84±0.83	64.48±0.51	76.18±2.46
10.5	63.2±2.22	66.55±2.54	77.54±2.06
11.0	69.6±1.48	70.33±1.86	78.7±0.69
11.5	69.8±1.27	71.04±0.74	79.14±2.13
12.0	69.91±1.16	71.65±0.65	80.47±1.27

Drug release Kinetic Study

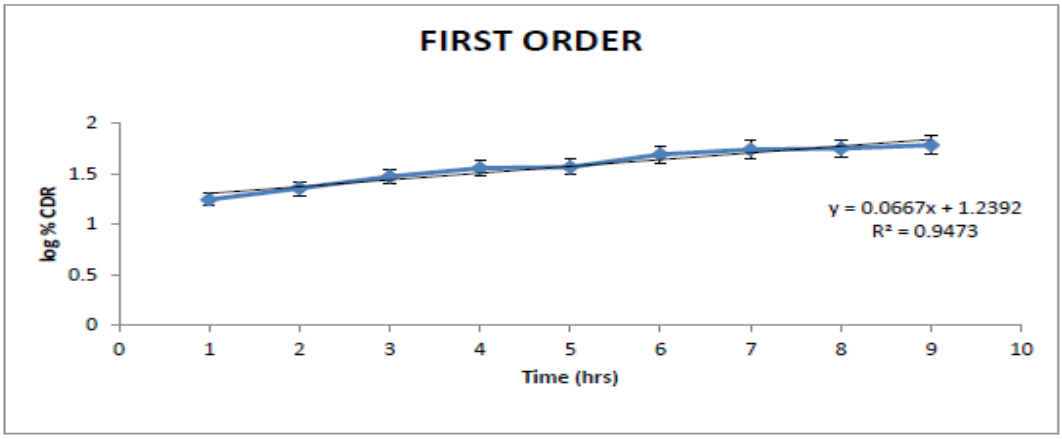
Raw data obtained from *in–vitro* release studies were analyzed, wherein data were fitted to different equations and kinetics model to calculate the percent drug release and release kinetics of Mupirocin from Emulgel.

Table 5: Drug Release Kinetic Data of Formulation EG3

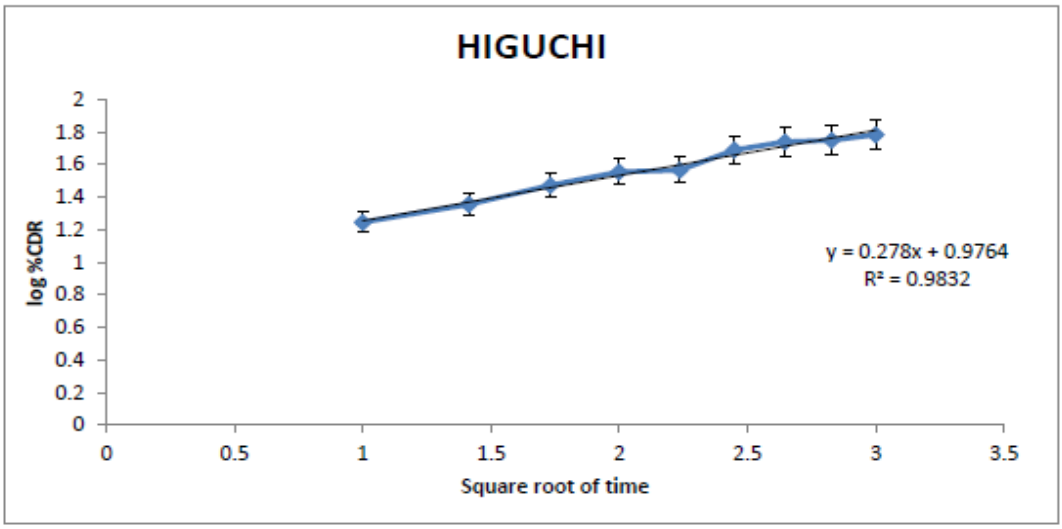
S.N.	Time (hrs)	Square root of time	Log time	Cumulative Percent Drug Release±SD	Log Cumulative PercentDrug Release	Cumulative Percent Drug Remaining	Log Cumulative Percent Drug Remaining
1	0	0	-	0	-	100	2.000
2	1	1	0	17.59±0.500	1.245399	82.41	1.915
3	2	1.414	0.301	22.66±0.438	1.355	77.34	1.888
4	3	1.732	0.477	29.64±0.681	1.471	70.36	1.847
5	4	2.0	0.602	35.87±1.022	1.554	64.13	1.807
6	5	2.236	0.698	36.82±0.520	1.566	63.18	1.800
7	6	2.449	0.778	48.99±0.521	1.690	51.01	1.707
8	7	2.645	0.845	54.87±0.563	1.739	45.13	1.654
9	8	2.828	0.903	56.15±0.691	1.749	43.85	1.641
10	9	3	0.954	60.70±0.522	1.783	39.30	1.594



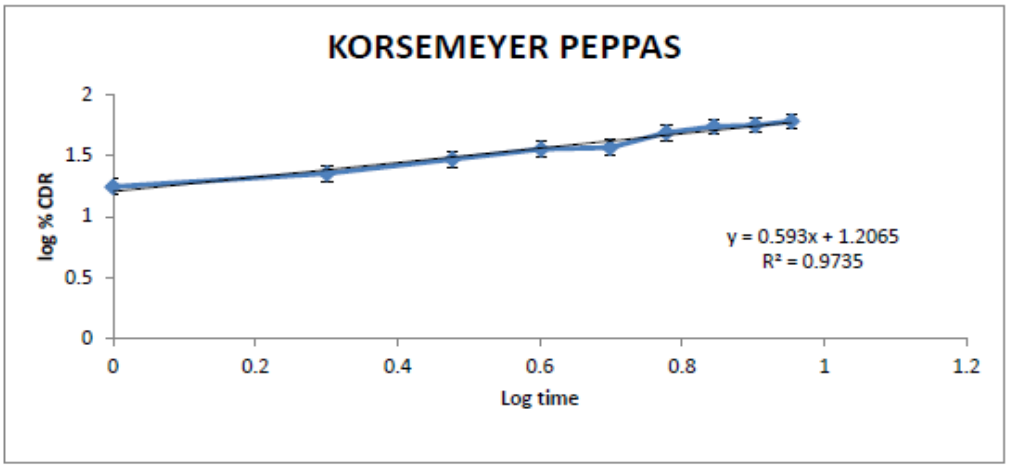
Graph 8: Cumulative Percent Drug Released Vs Time Plot (Zero Order)



Graph 9: Log Cumulative Percent Drug Remaining Vs Time Plot (First Order)



Graph 10: Log of cumulative Drug Release Vs Square Root of Time (Higuchi's Plot)



Graph 11: Log Cumulative Percent Drug Released Vs Log Time (Peppas Plot)

Linear regression analysis and model fitting shows that formulation EG3 follows Higuchi kinetics, which has higher value of correlation coefficient (R^2). The final results are reproduced in Table 5.11

Table 6: Regression Coefficient (R^2) Values of Drug Release Data obtained from various Kinetic Models

Formulation Code	Zero Order (R^2)	Higuchi Model (R^2)	First Order (R^2)	Peppas Model (R^2)
EG3	0.979	0.983	0.947	0.9735

Microbiological Assay

The use of control plates allowed that the plain emulgel bases were microbiologically inert toward the *staphylococcus aureus* strain. Percentage inhibition was taken as a measure of the drug's antimicrobial activity.

The highest activity was observed with EG3 where the percentage inhibition found to be 64.3 ± 1.52% while the lowest activity foundwith EG1 where the percentage of inhibition is 41.6

± 0.57% and the percentageinhibition of marketed mupirocin ointment was found to be 51.03 ± 1.23 which is less than the best (EG3) formulation.

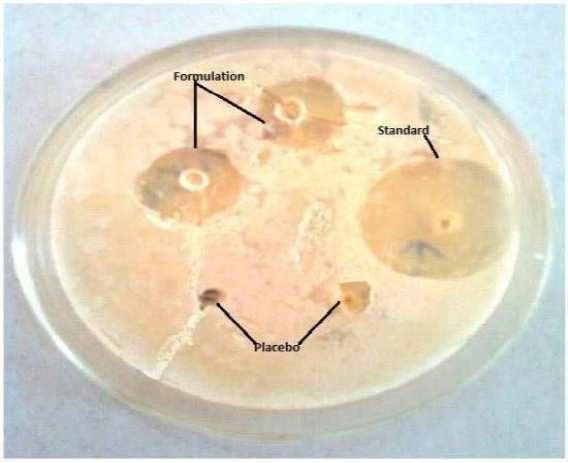


Fig.3: Zone of inhibition obtained with Formulation EG3

Fig.4: Showing % inhibition bymarketed Mupirocin ointment

Accelerated Stability Studies

The optimised formulation was stored at 40±2C/75±5%RH in lamitubes for 6 months. Emulgels were analysed at specified time intervals (1,2,3,4th weeks) for various parameters.

Table 7: Effect on Various Parameters during Accelerated Stability Studies of EG3

S. N0.	Time intervals(months)	pH	Consistency& Appearance	*In vitro* Drug Release (8thhr)	% CDR
1	0	6.4	+++	67.02	66.70
2	1	6.3	+++	66.95	67.45
3	2	6.4	+++	67.79	68.23
4	3	6.5	+++	68.14	68.41
5	6	6.4	+++	68.52	69.63

There are no significant changes in the parameters during accelerated stability condition. Hence, Mupirocin Emulgel is stable at accelerated conditions.

CONCLUSION

After thorough literature survey and these extensive works, we reached into a conclusion that emulgels have proven as most convenient, better, and effective delivery system. Due to its non-greasy, gel-like property and better release of drugs as compared to other topical drug delivery system, it is proved to be one of the better delivery system. Incorporation of emulsion into gel makes it a dual control release system further problem such as phase separation, creaming associated with emulsion gets resolved, and its stability improves. Emulgel loaded with specific drugs has been found effective in some topical disorders, and it is emerging as potential drug delivery system in the area of dermatology. In future, emulgel will provide a solution for topical delivery of hydrophobic drugs. From the above results we can conclude that Mupirocin Emulgel formulations prepared with Carbomer 940, Flax seed oil, PEGs, Glycerin, *etc.* showed acceptable physical properties, drug release, and antimicrobial activity, which remained unchanged upon storage for 6 months. However, the Carbomer 940 based Emulgel in its low concentration with the formulation code EG3 proved to be the formula of choice, since it showed the highest drug release and very good antimicrobial activity when compared to the marketed Azithromycin gel. So, Mupirocin Emulgel can be used as an anti-microbial broad spectrum medication for topical drug delivery. Many of drugs that have utility in the treatment of skin disorders are hydrophobic in nature. Such drugs can be delivered in the form of emulgel where they can be incorporated in the oil phase of the emulsion and combined with gel. Drugs which are still unexplored in this area are Retinoic acid, Adapalene, Tolnaftate, Betamethasone, Dexamethasone, *etc*.

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