FORMULATION AND EVALUATION OF NIOSOMAL BASED GEL OF MUPIROCIN TRANSDERMAL DRUG DELIVERY

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ABSTRACT

The objective of the present study was to formulate Niosomal gel of Mupirocin to prevent severe gastrointestinal side effects associated with its oral administration as well as to improve the residence time of drug into skin for show antifungal activity. In this research work initially nine formulations were prepared after selecting appropriate ratio of surfactant & co-surfactant by thin film hydration method prepared niosomes formulation were evaluated for Vesicle diameter, Drug content, Drug entrapment efficiency, SEM & in-vitro drug release. Best batch thus selected was further formulated as niosomal preparation using different geling agents that is HPMC, CMC, MC, Sodium alginate. Prepared gels evaluated for various physicochemical parameters Clarity, Homogeneity, Spreadability, Extrudability, pH, Drug content, Viscosity & in-vitro drug release results. (Clarity), (Homogeneity all formulation were found clear and vesicle were uniformly dispersion medium which was confirmed by homogenesity)**, (**Spreadability 7.2±0.25-10.3±0.3**), (**Extrudability 75.67±0.67-97.56±1.56**), (**pH 5.56-6.77**), (**Drug content 96.44±3.1-99.9±1.9**), (**viscosity 5556-8470**)** on the bases of niosomal gel batch F3 was selected as optimized batch thus reveled about 86.980 % release in pH 7.4 phosphate buffer.

Key words: Niosomal gel, TDDS, surfactant, mupirocin, In-vitro.

INTRODUCTION

To overwhelmed these complications there is a need for the development of new drug delivery systems which would improve the therapeutic efficacy and safety of drugs through Transdermal drug delivery system.[1]

Despite unbroken chains of marathon research efforts all across the globe, the oral therapy still occupies the surmounting considerations over all routes of drug administrations. Even though several advantages are there in support, oral therapy has to face many significant drawbacks i.e. poor plasma availability due to pre-systemic metabolism. The probability of blood level fluctuation causes inconvenience as well as lesser economy.

Transdermal Drug Delivery System [2]

Transdermal drug delivery systems deliver the active medicament across the layers of skin. Such traditional systems include topically applied creams and ointments for skin diseases that showed limited action. Moreover, systemic side-effects such formulations have led to the development of TDDS.

Broadly, transdermal delivery system distribute the active ingredient into the general circulation passing through the skin, viz.; controlled and consistent delivery of drugs. Resultantly, various side effects pertaining to metabolic parameters and sensation of pain can be avoided. Recently, the technological minutes have led to TDDS formulations avoiding direct injections.

Advantages of Transdermal Drug Delivery System [3]

Transdermal drug delivery is advantageous over the oral route due to following reasons:

- Pre-systemic metabolism can be avoided.
- Reduction in plasma concentration levels of drugs with decreased side effects.
- Reduced fluctuations in plasma drug levels. Drugs with shorter half-lives and squeezed therapeutic index are preferable candidates.
- Drug delivery can be removed in case of toxicity.
- Reduced dosing frequency and enhanced of patient compliance.
- Easy to administer and immediate withdrawal is possible.
- Convenient to apply.
- Risks and inconveniences of intravenous therapy can be avoided.
- Efficacy can be achieved with lesser daily dose by continuous drug input.
- Termination of medication can be possible when needed.
- In comparison with buccal or nasal cavity.
- Gastro-intestinal incompatibility can be avoided.
- Improved physiological and pharmacological responses.
- Suitable for self-medication.

Criteria for selection of drug suitable for Transdermal drug delivery [4]

- Drug must have optimum physicochemical properties for better penetration through stratum corneum with therapeutic dose less than 10mg.
- The barrier function of the skin varies between & sometimes within subjects too as well as age.
- Suitable penetration enhancers should be selected to avoid skin irritation and contact dermatitis.

Properties that influence Transdermal Delivery [5]

Biological factors

- a. Condition of Skin
- b. Age of Skin
- c. Blood flow
- d. Regional skin sites
- e. Skin metabolism
- f. Species differences

a. Condition of Skin: Although healthy skin is a strong barrier but acid and alkalis injure barrier cells and thereby endorse penetration, as do superficial ulceration and dermatitis. In larger industries, due to frequent contact with irritant chemicals workers may lose their activity.

b. Age of skin: The skin of young and elderly person is more permeable than adult tissue. Children are susceptible to toxic effects of drugs and chemicals due to larger body surface area. Thus, steroids intended for topical applications, borates and hexachlorophene have resulted in deaths owing to severe side effects.

c. Blood flow: Transdermal absorption can also affected by chances in peripheral circulation. An enhanced blood flow reduces the residence time of penetrating entities and raises the concentration difference across the skin.

d. Regional skin sites: Cutaneous permeability depends on the thickness and nature of the stratum corneum including the number of skin outgrowths. Such permeabilites depend on two factors for example, the intrinsic resistance to permeation per unit thickness of stratum corneum and the overall thickness of the tissue.

e. Skin metabolism: The skin metabolizes steroidal hormones, chemical carcinogens and such other drugs. An estimation has responded around 5% of topically applied drugs getting metabolized through skin.

f. Species differences: Mammalian skins are abundant with horny layer, girth, sweat gland and concentrated hair follicles etc. Such factors ultimately affect skin penetration and barrier to permeation.

Physicochemical factors

- a. Temperature and pH
- b. Diffusion coefficient
- c. Drug concentration
- d. Partition coefficient
- e. Molecular size and shape

a. Temperature and pH: A large variation in temperature can change about 10-fold penetration rate of a material through human skin affecting the diffusion inversely. Occlusivity of vehicles reciprocates skin

temperature marginally. Only intact molecules pass readily across lipoidal membrane while their dissociation depend upon pH, pk_a or pk_b values. A pH range (3-9) confers remarkable resistance to the stratum corneum.

b. Diffusion coefficient: There is huge progressive drop in diffusivities and reaches to the lowest within the stratum corneum. The diffusion coefficient of a drug (in a topical formulation) through the skin varies on nature of drug and its interaction with diffusion medium.

c. Drug concentration: Drug permeation usually follows Fick's Law. Usually, a saturated concentration of donor solution is required for maximum flux in a thermodynamically stable saturation. Apart from the consideration of concentration gradient as the driving force, potential/ activity gradient is the fundamental parameter i.e. pH, complex formation/ the presence of surfactants/co solvents.

d. Partition coefficient: It determines the flux of a drug via the stratum corneum.

e. Molecular size and shape: Such parameters also influence the diffusion of drug molecules through the skin and thus their absorption.

Physiology of the skin:[6,7]

The skin has several layers and amongst them epidermis and dermis are main layers. External most layer of the skin is known as epidermis. The dermis is a hard and elastic layer formed from connective tissue.
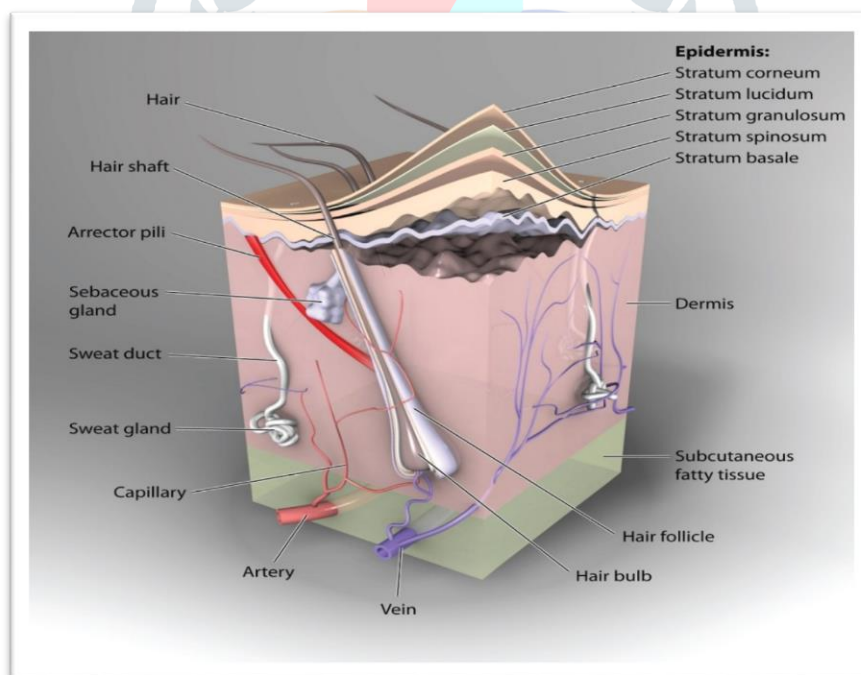

Figure 1.1 : Structure of Skin

Skin has consist three layer:

1. **Epidermis**
2. **Dermis**
3. **Hypodermis**

1. **Epidermis:** Epidermis is external layer of the skin which is work as water-proof barrier of body. Epidermis layer of skin are composed the keratinized stratified squamous epithelium tissue and contains the four types of cells: Markel cells, Melanocytes, Langerhans cells, and fourth are Keratinocytes. The keratin protein is produced by the keratinocytes of epidermal cell which helps to protect the skin and tissue from the heat, microbes and other chemical.   In the epidermal layer the melanocytes are very effective role play in our body. Melanin enzymes are secreted by the melanocytes of epidermal cells. Approximately 8% of epidermal cells are melanocytes.[10, 11]
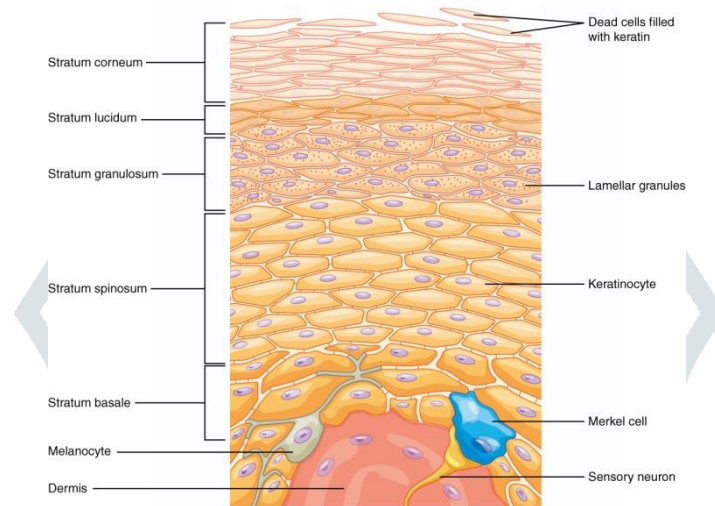
Figure1.2 : epidermis layer

2. **Dermis:** It is the far down or lower layer of the skin and it is the large part of skin. Dermis is composed connective tissue, blood vessels, nerve, hair follicles, and gland. Dermis is categorized in to papillary region and reticular region. The papillary region is made up the one fifth part of total layer. It is also composed of connective tissue. Fibrous elastic and collagen are supply the skin strength, elasticity, and covering or extensively.
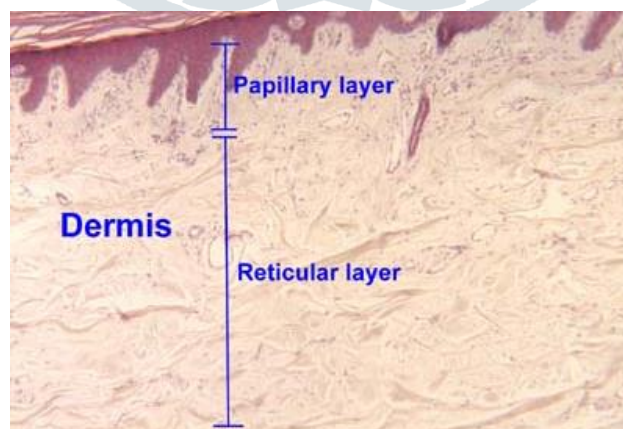
Figure 1.3 : anatomy of dermis

3. **Hypodermis:** It is the deeper part after the dermis of the skin. Hypodermis layer are composed by fat, and connective tissue also consist the some part of hair follicle and sweat gland nerve are also available

here. Actually the hypodermis is not a part of skin but it is counting in the third layer of skin. It is made up of areolar and adipose tissue.

OBJECTIVE OF THE STUDY

The present work is to **Formulation and Evaluation of noisomal gel of Mupirocin.** Mupirocin is generally used in the management of fungal infection. Although conventional gels are available in market but present work is designed to increase the patient compliance:

The drug shows low aqueous solubility, low permeability and low bioavailability. Thus development of dosage forms that increases it solubility and mixing rate will be batter the bioavailability of drug.

In this research work initially nine formulations were prepared after selecting appropriate ratio of surfactant & co –surfactant by thin film hydration method prepared neosomes formulation were evaluated for vesicles diameter, drug content, drug entrapment efficiency & in vitro dispersion study.

The rational of present research work is to develop and characterize gel of Mupirocin. Mupirocin gel it prepared by using Carbopol 934 and PEG 6000 and peg 4000 to increase the solubility, mixing rate and to improve bioavailability and therapeutic efficacy.

In the present research work a step has been made to formulate gel by kneading and solvent evaporation method using Carbopol 934 and peg 4000, in different ratio are prepared and evaluated for various characterization studies.

Preparation of standard stock solutions:
(a) Preparation of Stock solution A & B:
Initially,100 mg drug (MUPIROCIN) was dissolved in 100 ml of pH 7.4 phosphate buffer to prepare (1000µg/ml) stock solution A. From this, 10 ml was pipetted out and diluted to 100 ml with pH 7.4 phosphate buffer to prepare (100µg/ml) stock solution B.
(b) Estimation of λmax:
A sample solution (2.5µg/ml) was scanned between 240-400 nm the λmax value for Mupirocin was reported and which was established by locating the overlain UV spectra of the drug using different concentrations (2.5-7.5 µg/ml).

Preparation of standard calibration curve of Mupirocin in pH 7.4 Phosphate buffer: The standard calibration curve of drug was obtained with same samples as opted in the above process by plotting absorbance vs. concentration graph.

RESULTS AND DISCUSSION

Preformulation studies:

Spectrophotometric scan of Mupirocin:

A sample solution of Mupirocin scanned between 300-400 nm which concluded λ max of 223 nm.
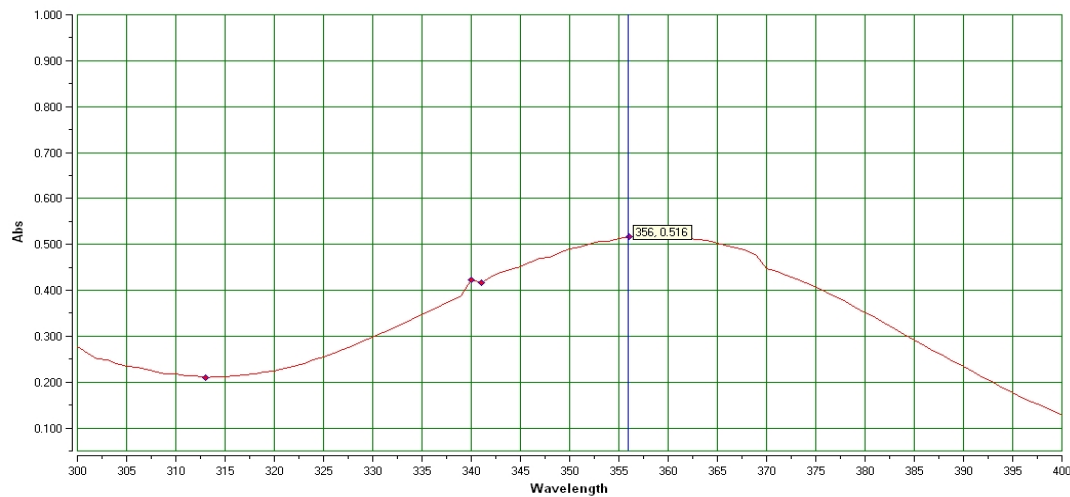
Figure: U.V scan of Mupirocin showing characteristic wavelength

Validation of max:

The samples comprised different concentrations (2-20 µg/ml) of the Mupirocin were run and overlain spectra describing the reproducibility of λ max was obtained, that confirmed and validated the process.
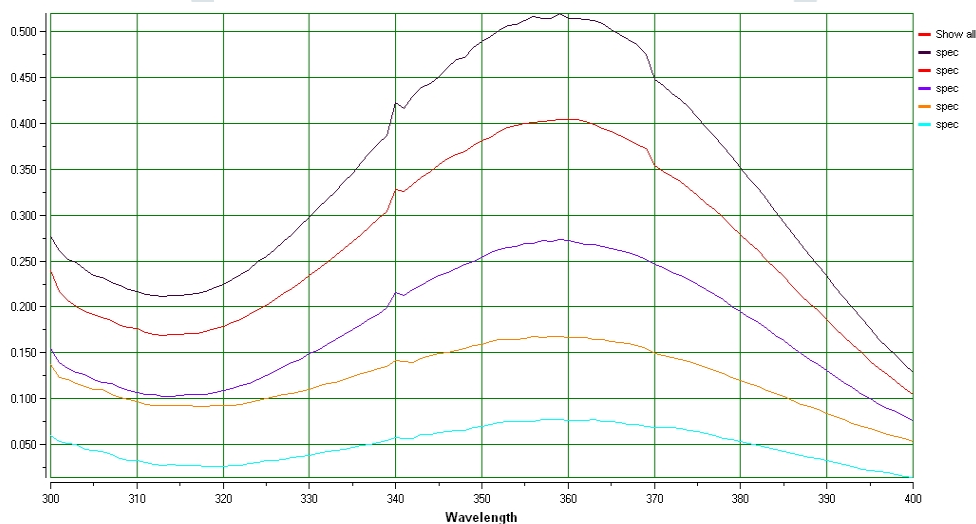
Figure: Overlain spectra of Mupirocin

Preparation of standard curve of Mupirocin in pH 7.4 Phosphate buffer:

A standard curve of Mupirocin was obtained by measuring absorbance of various aliquots at 223 nm and plotting the graph concentration (µg/ml) Vs absorbance].

Table: Concentration Vs absorbance data of Mupirocin in pH 7.4 Phosphate buffer at 223 nm

S. No.	Concentration (µg/ml)	Absorbance
1	2	0.00
2	4	0.205
3	6	0.299

4	8	0.394
5	10	0.482
6	12	0.579
7	14	0.699

y = 0.0881x
R² = 0.9986
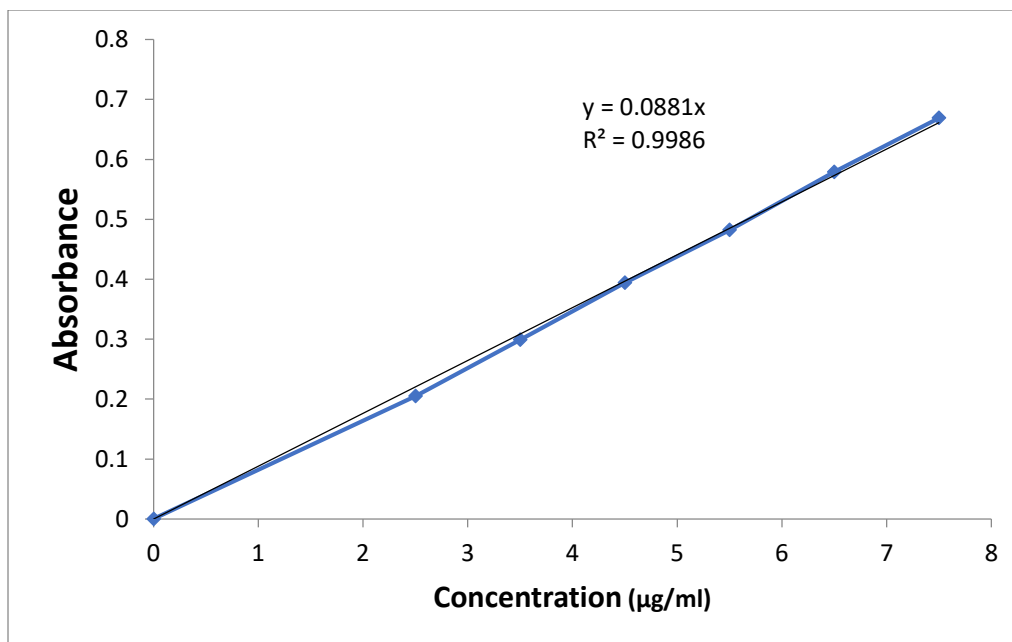
Figure: Standard curve of Mupirocin in pH 7.4 phosphate buffer
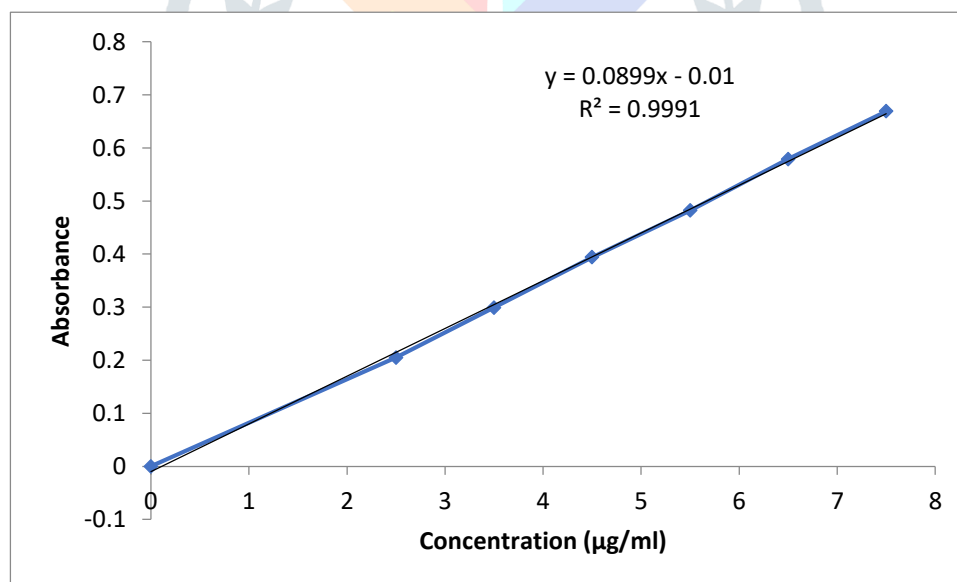

y = 0.0899x - 0.01
R² = 0.9991

Figure: Regression curve of Mupirocin in pH 7.4 phosphate buffer

Compatibility studies:-

FTIR analysis: The FTIR spectral analysis revealed that the characteristic peaks of pure drug were retained in its combination with different excipients (polymers). Conclusively, the drug was found compatible with all other excipients used in the formulations.

Background Scans: 32
Resolution: 8 cm-1
System Status: Good
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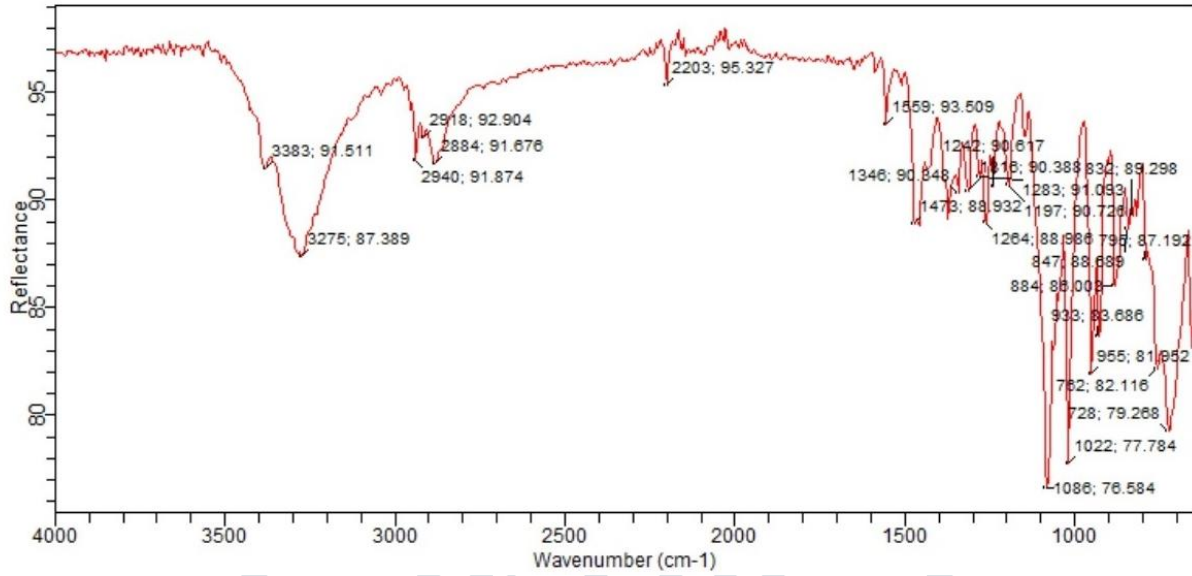Range: 4,000.00 - 650.00
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Figure no. 5.5 FTIR spectra of Mupirocin (pure drug)

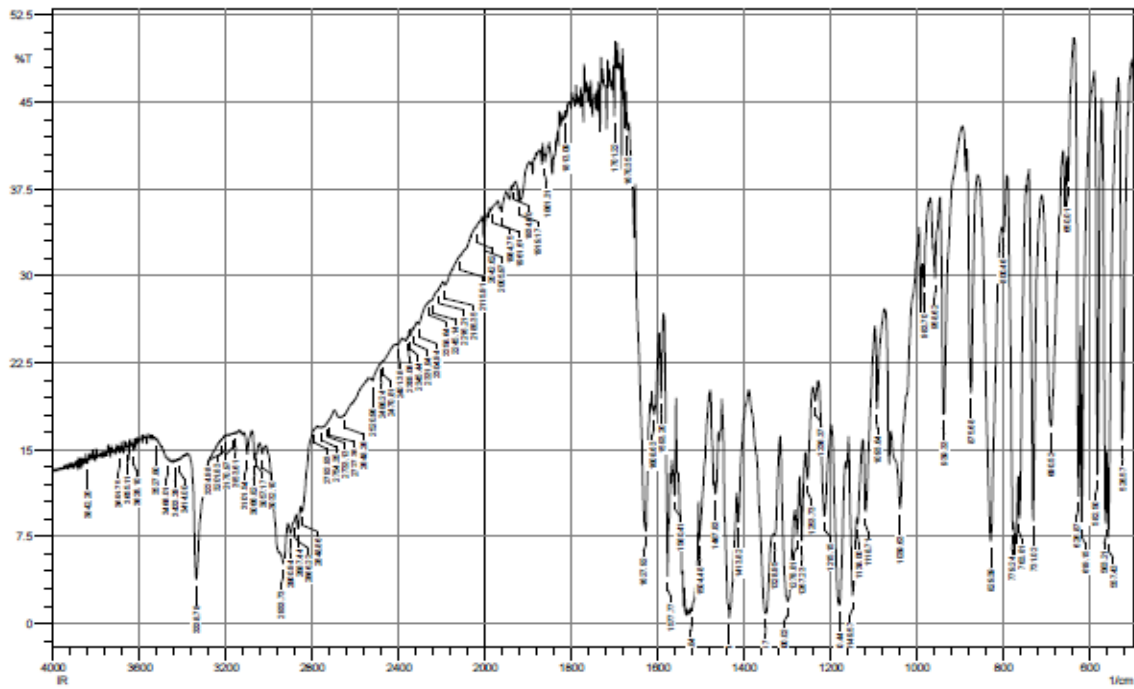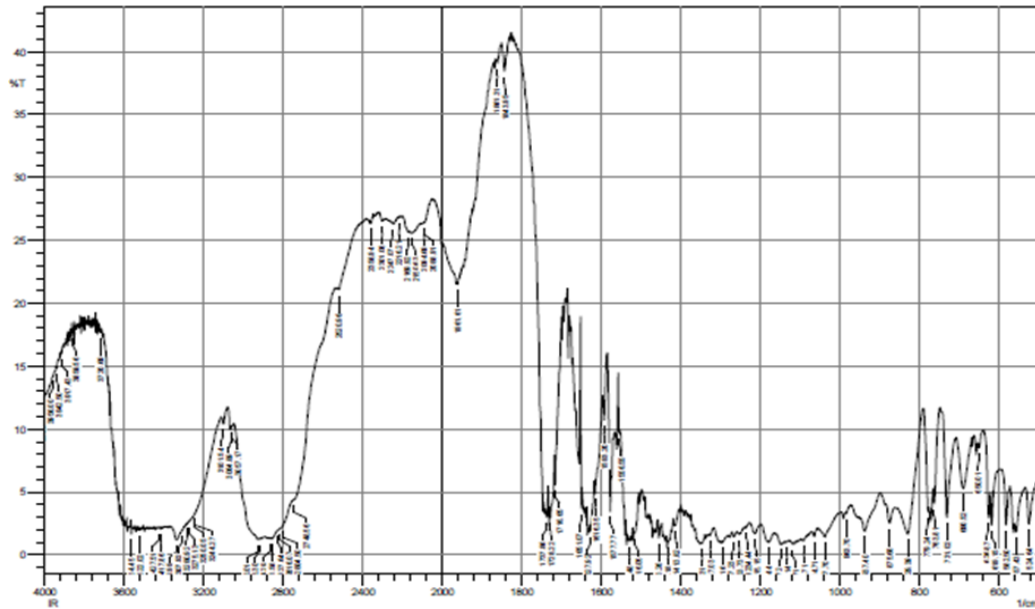**Figure: FTIR spectra of Mupirocin with cholesterol**

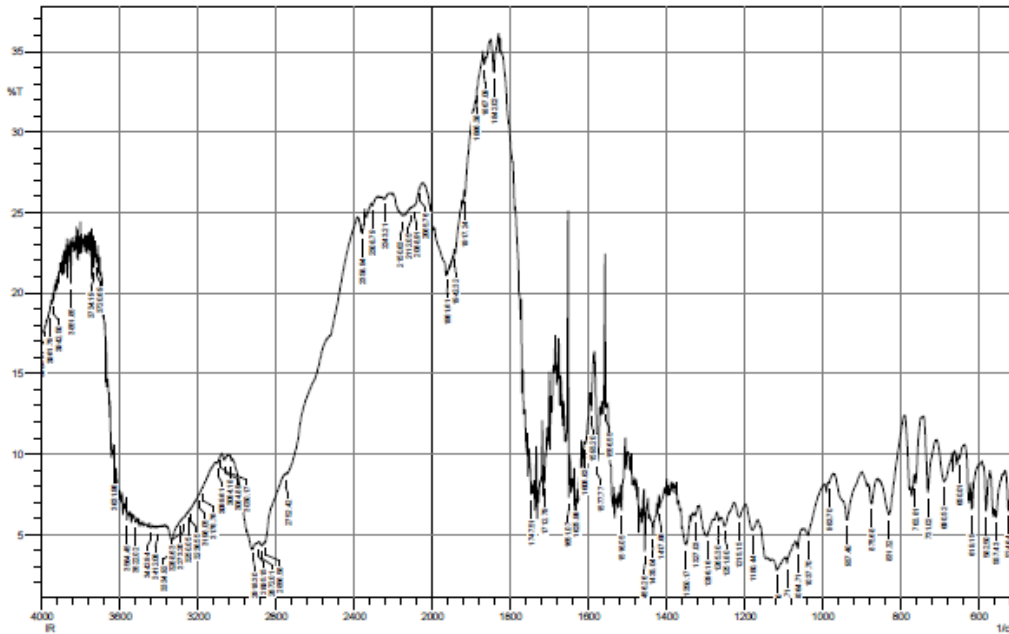**Figure : FTIR spectra of Mupirocin with span 20**

Figure: FTIR spectra of Mupirocin with span 60
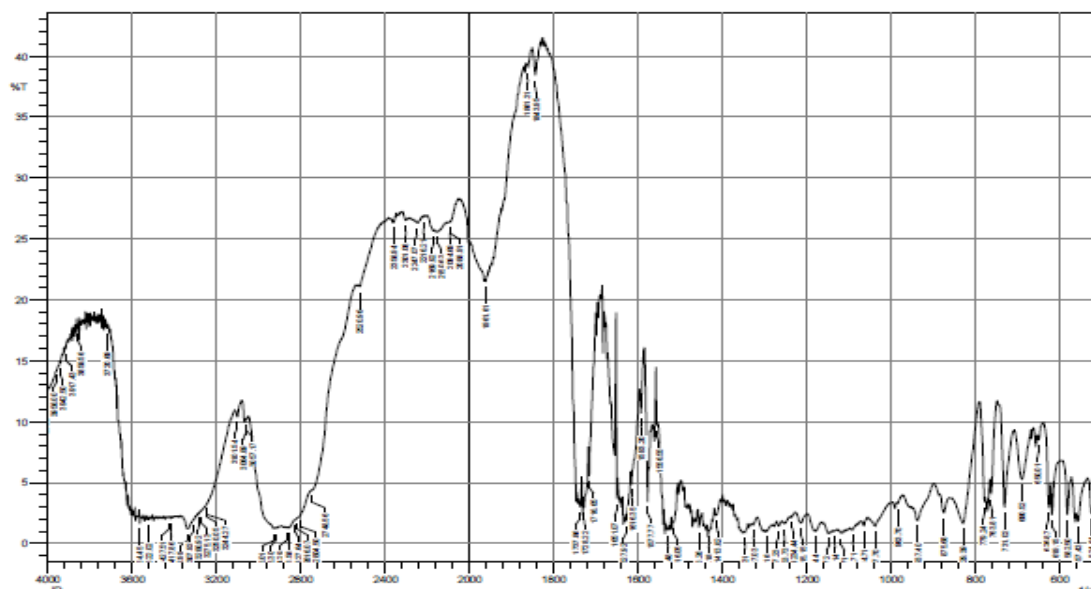
Figure: FTIR spectra of Mupirocin with span 80

Thin layer chromatography method:

The Rf values of niosomes of Mupirocin (0.725-0.829) with various excipients were found nearly similar with that of the pure drug and thus showed compatibility between drug & different excipients used.

Table: Rf values of different combination of drug and excipients

Spot No.	Ingredients	Rf value
A	Mupirocin	0.829
B	Mupirocin: Cholesterol	0.725
C	Mupirocin: Span 60	0.739
D	Mupirocin: Chloroform	0.757
E	Mupirocin: HPMC	0.785
F	Mupirocin: CMC	0.745

Figure: Photographic representation of TLC with different drug polymer combination

Evaluation parameter for Mupirocin Niosomes:

Vesicle diameter: Prepared niosomes were spherical in shape and their size ranged between 51.4-131.7µm.

Table: Particle size analysis of prepared niosomes of Mupirocin (batch A1 to C3):

S. No.	Formulation code	Particle size (µm)
1	A1	51.4
2	A2	62.4
3	A3	90.5
4	B1	126.2
5	B2	129.4
6	B3	131.7
7	C1	65.7
8	C2	95.1
9	C3	98.3

Drug content:-The Maximum drug content was found to be 99.9±1.5 with batch B2 and minimum of 88.08±1.2 with batch A1.

Table: Drug content of prepared Niosomes of Mupirocin (batch A1 to C3):

S. No.	Formulation code	Drug content
1	A1	88.08±1.2
2	A2	92.90±3.4
3	A3	96.33±2.7
4	B1	89.84±3.2
5	B2	99.9±1.5
6	B3	97.14±3.1
7	C1	89.22±1.09
8	C2	94.56±3.21
9	C3	93.57±0.27

Drug entrapment efficiency: The maximum drug entrapment was found to be 99.68% for batch C3 and minimum entrapment of 80.371% obtained with batch A1.

Table: Drug entrapment efficiency of Niosomes of Mupirocin (batch A1 to C3):

S. No.	Formula code	%Entrapment Efficiency
1	A1	90.042
2	A2	92.975
3	A3	89.025
4	B1	98.708
5	B2	99.680
6	B3	95.541
7	C1	80.371
8	C2	86.739
9	C3	84.603

Table: In-vitro diffusion profile of Mupirocin Niosomes (batch A1-C3) in pH 7.4 Phosphate buffer:

Time (min.)	A1	A2	A3	B1	B2	B3	C1	C2	C3
0	0	0	0	0	0	0	0	0	0

60	7.44	8.667	6.66	9.444	10.66	9.22	5.44	8.24	6.11
120	12.18	13.2	11.23	14.189	15.2	12.95	9.18	12.95	10.17
180	15.09	16.316	14.3	17.093	18.31	16.85	13.09	16.12	15.09
240	18.27	19.51	17.51	19.277	22.56	19.04	18.27	21.26	19.26
300	23.20	24.437	22.4	24.203	26.43	23.96	22.20	26.20	24.21
360	27.95	28.188	26.18	28.955	30.18	27.62	26.95	29.94	28.92
420	32.64	33.882	31.88	33.648	34.88	32.40	31.64	33.64	32.64
480	36.83	37.072	35.07	38.838	40.07	37.70	35.83	39.82	36.81
540	41.61	42.848	40.84	43.614	44.84	42.33	40.61	44.61	42.61
600	46.3	48.554	45.55	47.32	49.55	46.08	44.32	48.31	46.31
660	52.4	53.699	51.69	53.46	55.69	53.92	51.46	54.44	53.43
720	57.70	58.607	55.60	58.706	60.60	57.36	56.70	59.71	58.66
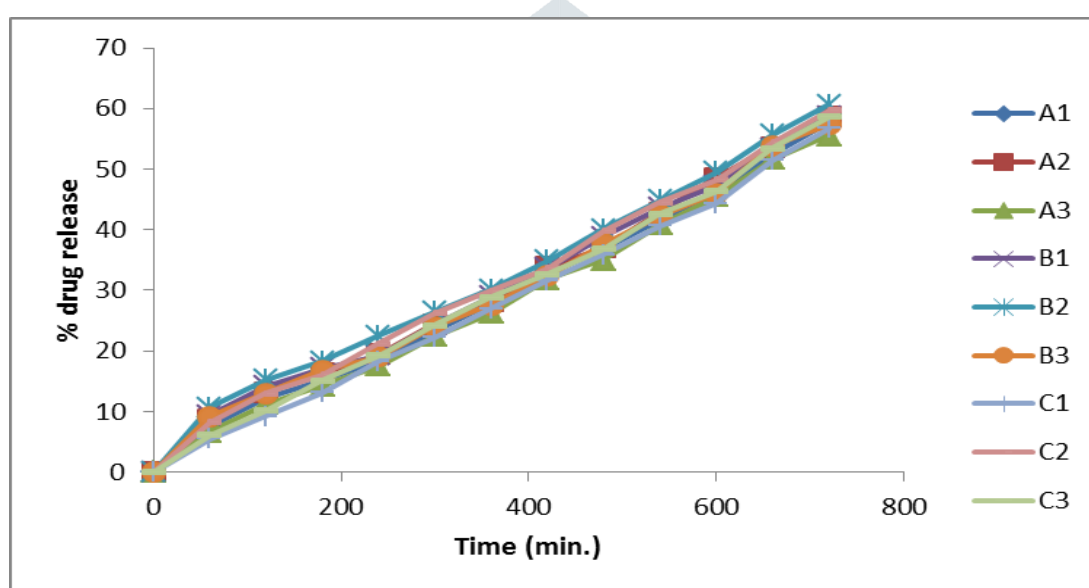
Figure: Percentage (%) drug release profile of Niosomes of Mupirocin (batch A1-C3) in pH 7.4 phosphate buffer

Based on the results, obtained from evaluation parameters of Mupirocin niosomes revealed that batch B2 was considered as optimized formulation as it showed maximum drug content, entrapment efficiency and drug release. Optimized batch thus selected was subjected to release kinetic study and then formulated as niosomal gel using different gelling agents i.e. sodium alginate, methyl cellulose, HPMC and CMC.

**Table: Evaluation parameters for optimized batch (B2):**

S. No.	Parameter	Results
1	Vesicle diameter	129.4 μm
2	Drug content	99.9±1.5
3	Drug Entrapment efficiency	99.680
4	In-vitro diffusion study	% drug release- 61.018% in 720 min.

| 5 | Release kinetic model | Korsemeyer- peppas |
| 6 | Surface morphology | Almost spherical in shape |

In- vitro diffusion profile of optimized batch (B2) of Mupirocin Niosomes:

Table: Percentage (%) drug release profile of optimized batch (B2):

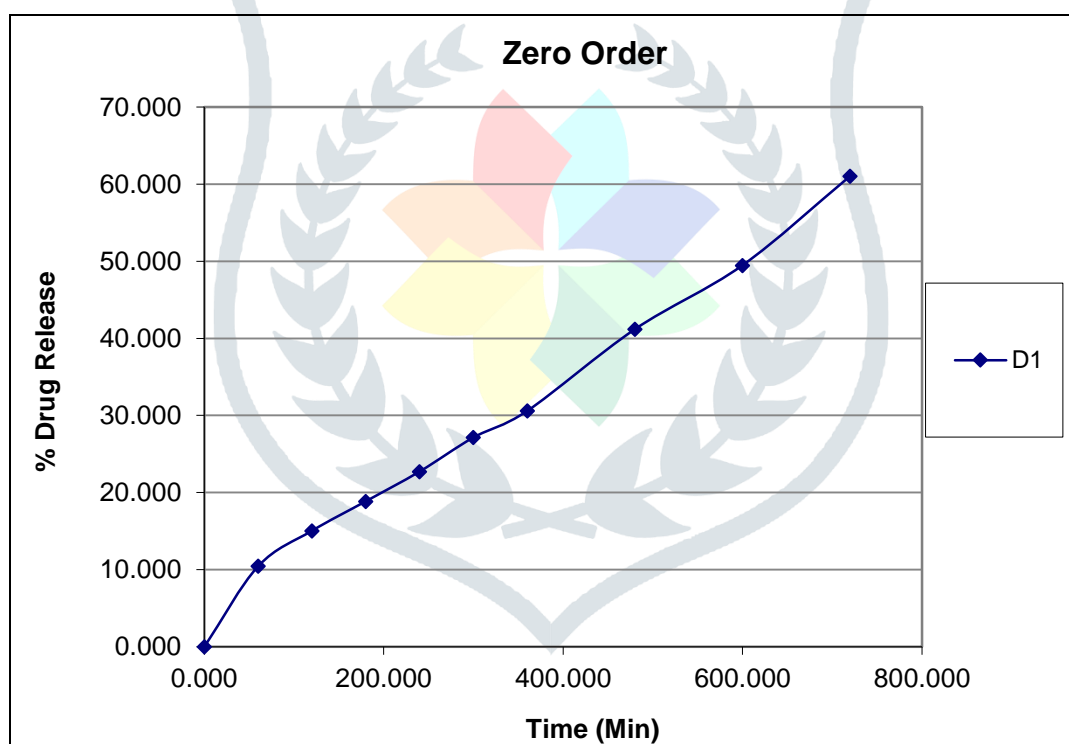| Time (min.)	pH 7.4 phosphate buffer
0	0.000
60	10.444
120	15.041
180	18.863
240	22.721
300	27.136
360	30.579
420	34.418
480	40.165
540	44.725
600	49.458
660	55.177
720	61.018
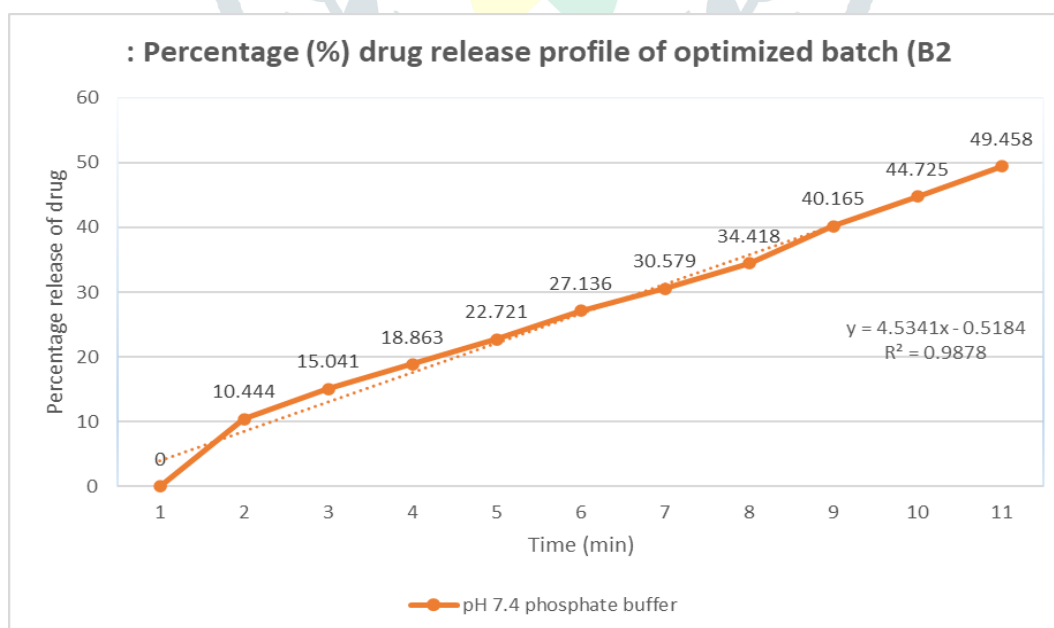
Figure: Percentage (%) drug release profile of optimized batch in pH 7.4 buffer

5.5 Release kinetic studies: In-vitro release data of optimized batch was fitted into various kinetics models like zero & first order, Higuchi, Korsemeyer- peppas and Hixon Crowell models in order to find out the mechanism of drug release from Niosomes.

Table: Estimated value of R^2 after fitting of dissolution data of Optimized batch of (B2) into various release kinetic models in pH 7.4 phosphate buffer.

Formulation Code	Zero Order		First Order		Higuchi		Korsemeyer-peppas	
	pH 7.4 phosphate buffer							
A1	Y	R^2	Y	R^2	Y	R^2	Y	R^2
	0.078	0.995	0.0017	0.683	2.2629	0.938	0.5863	0.997

Figure: Zero order drug release of optimized batch (B2) in pH 7.4 phosphate buffer
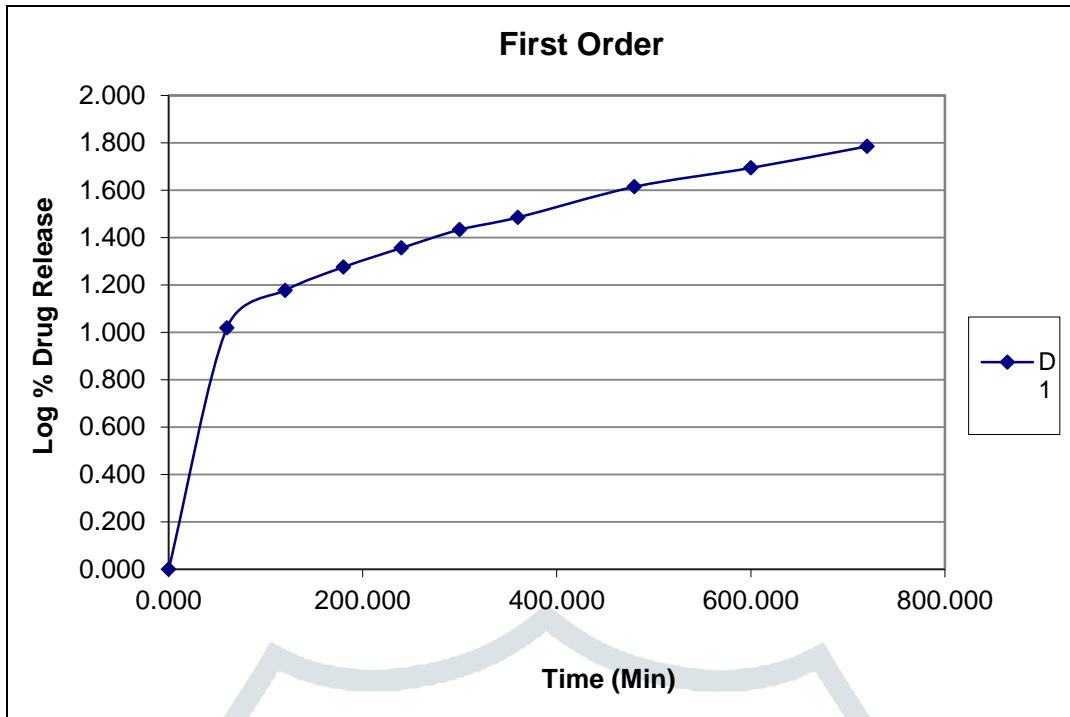
First Order

Figure:- First order drug release of optimized batch (B2) in pH 7.4 phosphate buffer
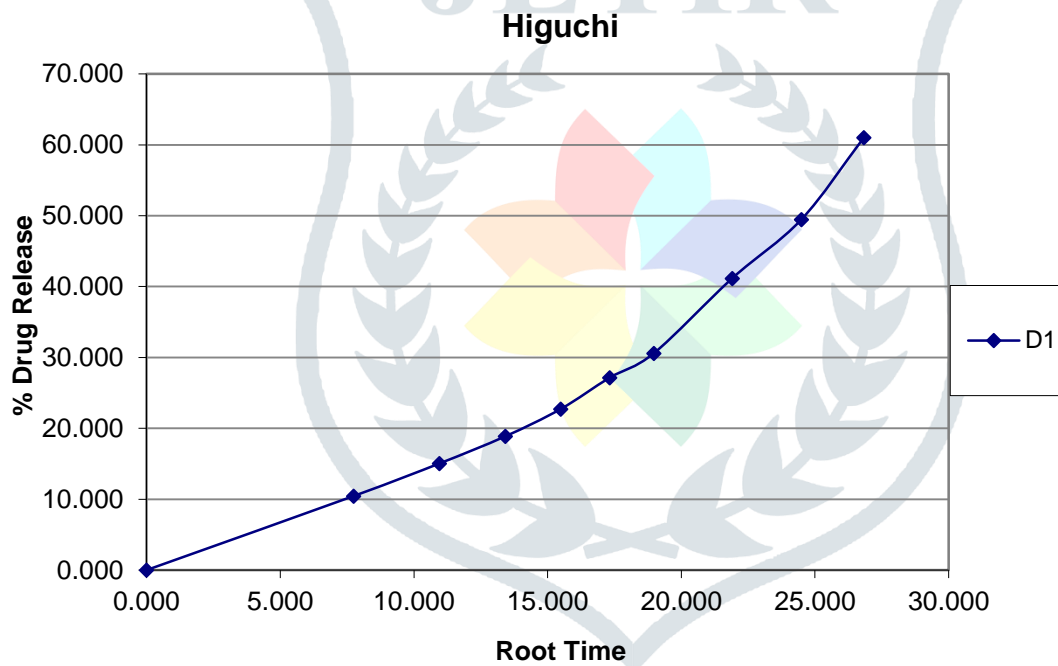
Higuchi

Figure:- Higuchi drug release of optimized batch (B2) in pH 7.4 phosphate buffer
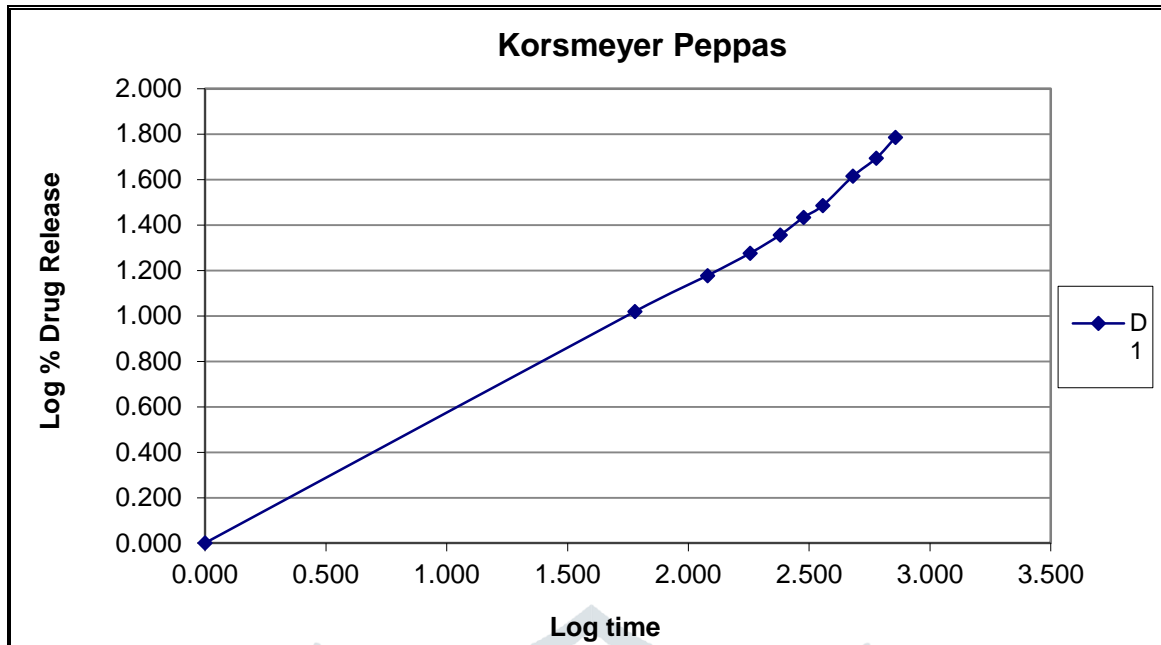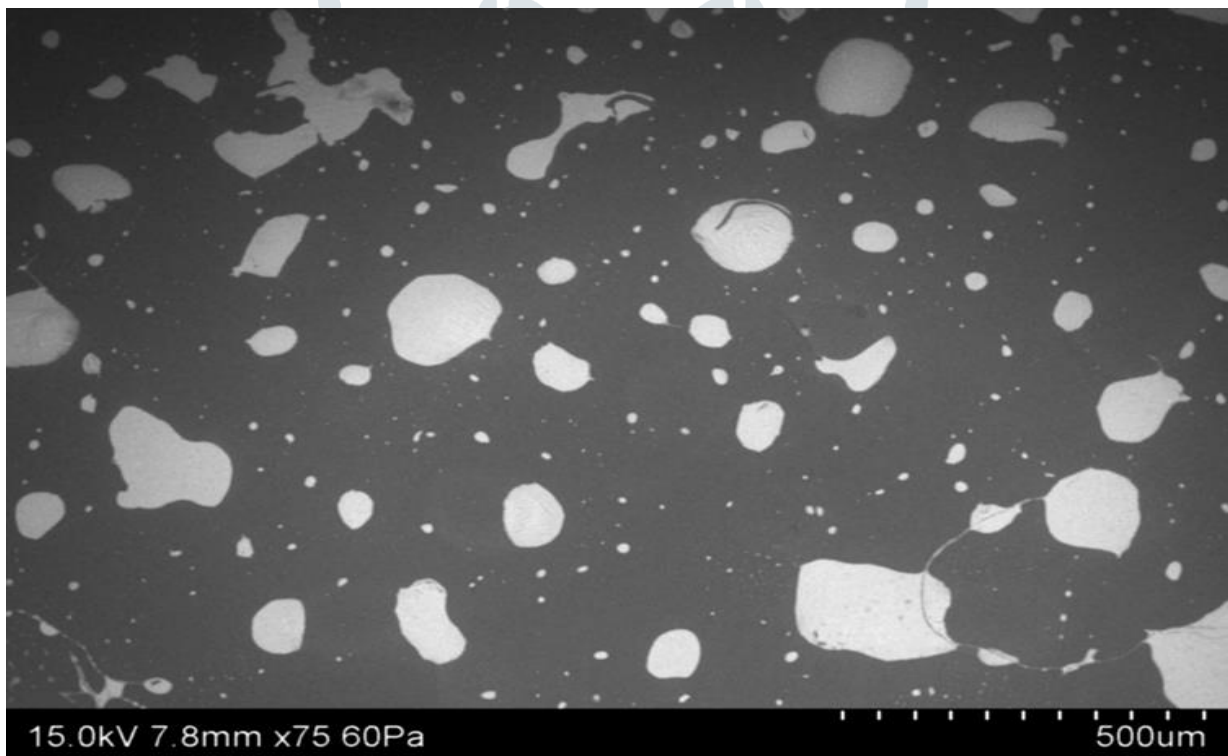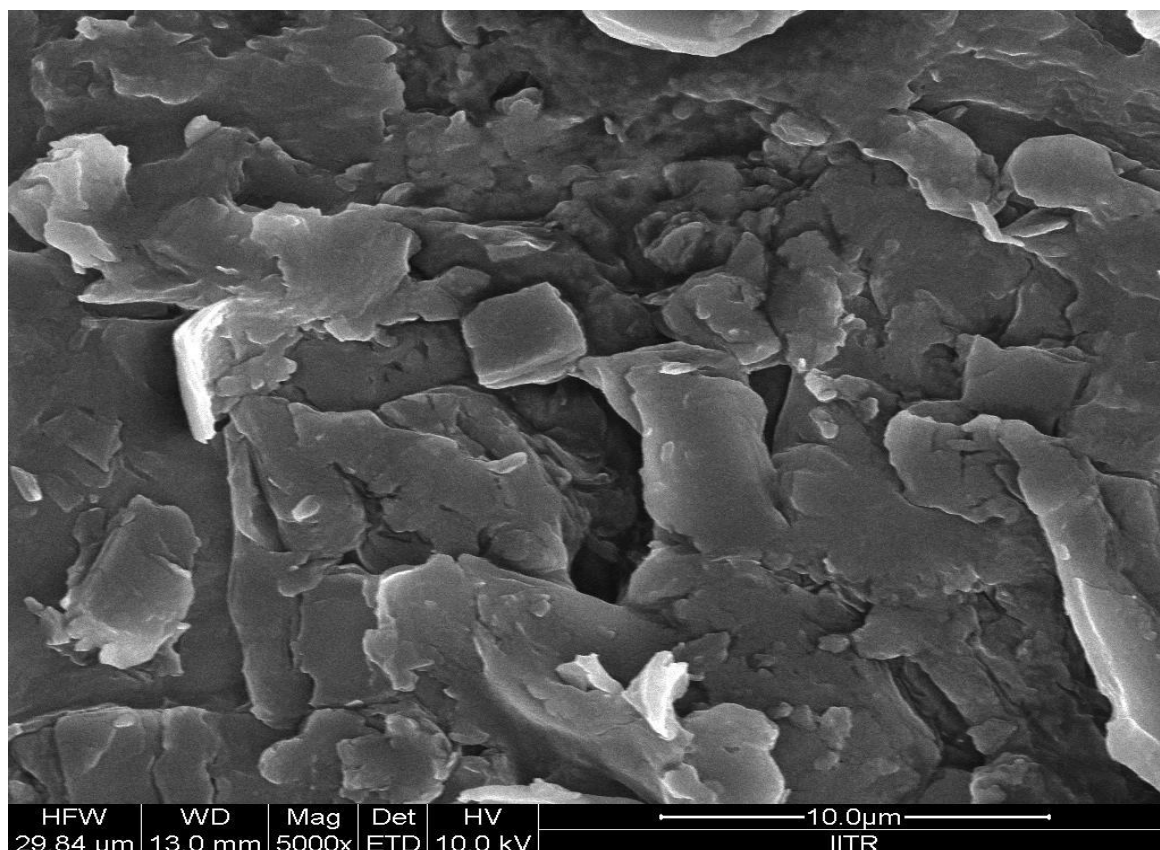
Figure: Korsemeyer peppas drug release of optimized batch (B2) in pH 7.4 phosphate buffer

Surface morphology: The surface morphology of Mupirocin belonging to the significant batch (B2) was examined by the Scanning Electron Microscopy.

Figure: SEM image of Optimized formulation (B2)

Evaluation of Niosomal Gels of Mupirocin:

Niosomal gels of Mupirocin thus prepared were subjected to various evaluation parameters viz.; clarity, homogeneity, Spreadability, Extrudability, pH, drug content, viscosity and in-vitro diffusion study which revealed that gel prepared with HPMC exhibited good results and considered as best niosomal gel. Percentage (%) drug release from optimized formulation was found to be 58.645% in 720 min.

Table no. 5.9 Evaluation parameters for Niosomal gel of Mupirocin

Formula	Clarity	Homogeneity	Spreadability	Extrudability	pH	Viscosity (cPs)
F1	good	Very Good	8.9±0.21	92.37±1.31	6.77±0.16	6667
F2	good	Very Good	9.5±0.28	93.77±0.59	5.70±0.12	7239
F3	Very clear	Excellent	10.3±0.3	97.56±1.56	5.56±0.14	8470
F4	turbid	Good	8.2±0.31	87.18±0.22	5.90±0.17	5556

In- vitro diffusion study of the Mupirocin niosomal gel:

Table: Percentage (%) drug release profile of Niosomal gels of Mupirocin (batches F1-F4) in pH 7.4 phosphate buffer:

| S. No.	Time (min.)	% Drug release			
		F1	F2	F3	F4
1	0	0	0	0	0
2	60	8.458	7.458	9.542	6.551
3	120	12.375	11.312	13.311	10.327
4	180	14.771	15.772	16.66	13.663
5	240	19.798	18.795	20.795	17.699
6	300	24.946	23.921	25.899	22.495
7	360	27.132	26.132	29.133	25.135
8	420	32.976	31.133	34.145	30.147
9	480	38.727	36.611	39.522	34.542
10	540	41.628	40.611	43.613	38.613
11	600	46.976	45.973	47.963	43.964
12	660	52.455	51.897	53.651	50.352
13	720	56.98	55.641	58.645	54.655
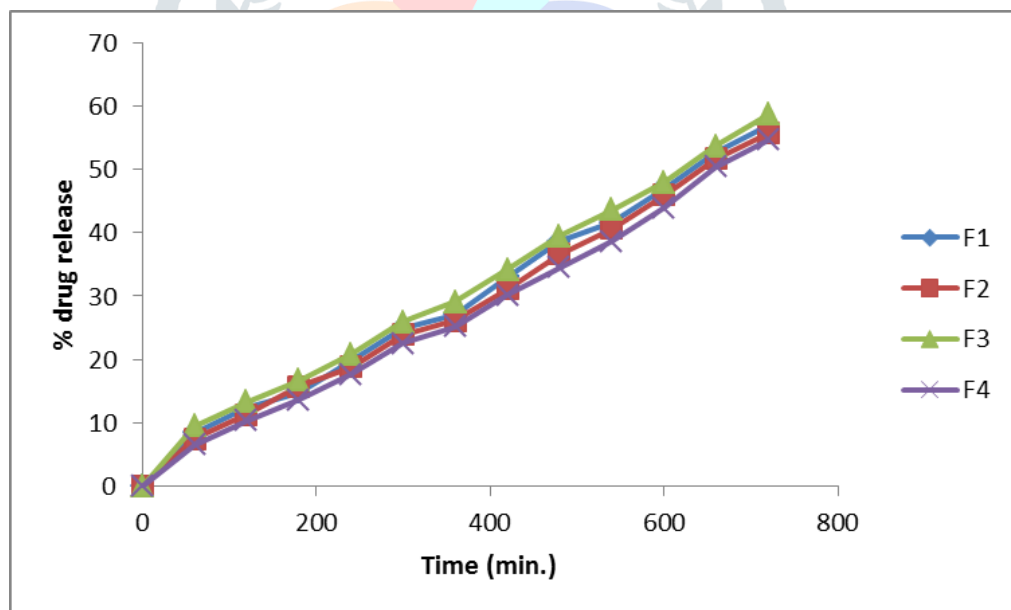
Figure: In-vitro dissolution of Niosomal gels (batch F1-F4) in pH 7.4 phosphate buffer

Stability Studies: -The stability studies were performed on optimized formulation (F3) as per as ICH guidelines at accelerated conditions ($40^0\pm2^0$C/75%$\pm$5%RH).

Table: Observation of parameters for stability studies at accelerated conditions ($40^0 \pm 2^0 C/75\% \pm 5\% RH$):

Time (min.)	0 Day	30 Days	60 Days	90 Days
0	0	0	0	0
60	9.542	9.458	8.996	7.551
120	13.311	13.312	12.985	12.322
180	16.66	16.772	16.262	16.163
240	20.795	20.795	20.438	20.399
300	25.899	25.921	25.519	25.395
360	29.133	29.132	28.942	28.135
420	34.145	34.133	33.839	33.647
480	39.522	39.664	39.175	39.089
540	43.613	43.528	43.455	43.367
600	47.963	47.884	47.733	47.264
660	53.651	53.515	53.459	53.117
720	58.645	58.541	58.333	58.219
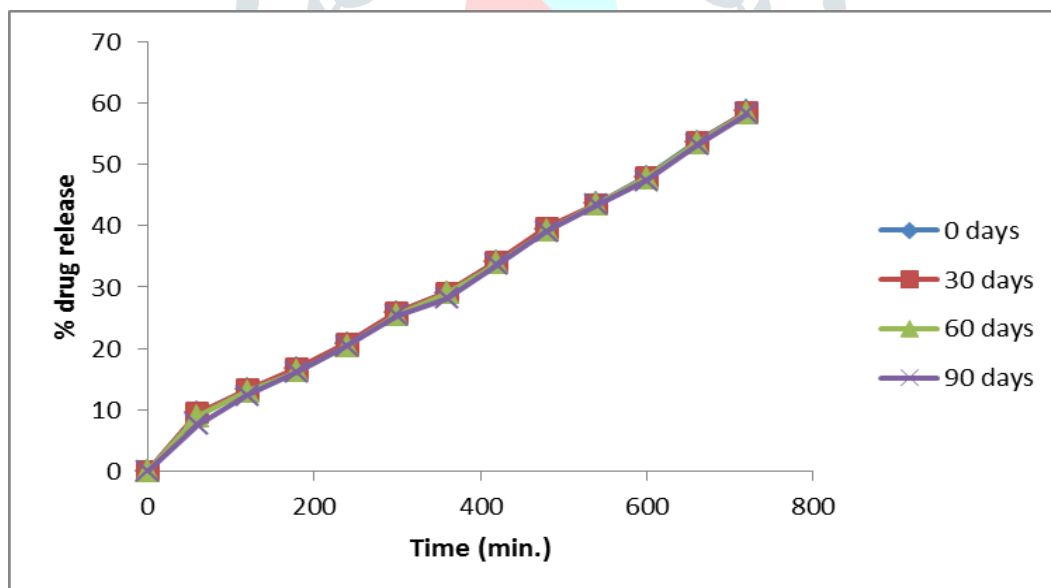
Figure: Comparative release profile of Niosomal gel on stability

Conclusion

The present worker carried out the research work aiming at enhance residence time of drug at the site of application and prevent severe gastrointestinal side effects associated with its oral administration as well as to improve the residence time of drug into skin for enhance antifungal activity.

The selected drug (Mupirocin), studied for physicochemical characteristics, was run on U.V-Visible Spectrophotometer (in different concentrations) and wavelength maxima was recorded which was further

confirmed from overlain spectra thus obtained. Standard calibration curves were also prepared using different solvent media i.e. distilled water, pH 7.4 phosphate buffer.

FTIR & densitometry TLC studies were carried out for testing the compatibility of the drug with selected surfactant & co-surfactant and other excipients. The characteristic peaks of the pure drug were compared with that obtained with the drug-excipients combinations, which remained nearly same and the thin layer chromatographs of pure drug and that of the drug-excipients combinations, resulted approximately equivalent R_f values. Conclusively, Mupirocin was found to be compatible with excipients used in gel formulations.

Initially nine batch containing different surfactant along with cholesterol on different ratio were prepared and evaluated for different parameters. The best batch (A1) containing Span 20 and cholesterol in 0.5:0.5 ratio was selected for formulating as Niosomal gel.

Prepared Niosomes were subjected to evaluation and the results inferred were; Vesicle diameter (51.4-500), drug content (88.08±1.2-98.9±1.5), Drug entrapment efficiency (Drug entrapment efficiency 80.371-99.68).

Similarly Niosomes gels thus prepared were evaluated an results were (Clarity), (Homogeneity all formulation were found clear and vesicle were uniformly dispersion medium which was confirmed by homogenesity), Spreadability (7.2±0.25-10.3±0.3), Extrudability (75.67±0.67-97.56±1.56), pH (5.56-6.77), Drug content (96.44±3.1-99.9±1.9), viscosity (5556-8470).

Based on the results obtained from evaluation F3 formulation was considered as optimized batch as it showed maximum drug release than other batches.

In-vitro release of the optimized formulation (F3) in pH 7.4 Phosphate buffer was found to be 84.480 % in 720 min.

The stability study was performed with the optimized formulation as per ICH guidelines under officially prescribed condition ($40^0 \pm 2^0$C/75%±5%RH) which showed that the formulations were stable and thus complied with dose conformity criterion.

The present worker suggested that such a formulation design could be extrapolated to many potential therapeutic candidates causing gastric irritation targeting overwhelming demands of better permeability encompassing utmost economic relevance.

CONFLICT OF INTEREST: NIL

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