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NANOSPONGE LOADED HYDROGEL OF CEPHALEXIN FOR TOPICAL DELIVERY

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ABSTRACT: Cephalexin is a first generation cephalosporin antibiotic which is used for the treatment of skin and soft tissue infection, urinary tract infection and diabetic foot infection. Since cephalexin is not available as topical formulation, cephalexin was formulated into nanosponge loaded hydrogel as it can enhance skin permeation. Nanosponges of cephalexin were prepared using hydroxyl ethyl cellulose and poly vinyl alcohol by emulsion solvent evaporation method. The particle size and entrapment efficiency was found in the range of 200-400 nm and 88.5%- 95.6% respectively. Based on the characterization, nanopsonges with high entrapment efficiency and least particle size (NS2) was selected for hydrogel formulation. Five different formulations of hydrogels were prepared by using carbopol 934 with varying concentration of penetration enhancer (propylene glycol) and various evaluation studies were carried out. The *in vitro* release studies revealed that the formulation with higher concentration of penetration enhancer (15% propylene glycol) showed greater drug release. From the kinetic study, the best linearity was found with first order and Higuchi's equation. The permeation studies showed that the formulation having higher concentration of permeation enhancer showed good skin permeation. The histological investigation on porcine skin indicated a disruption of the stratum corneum, suggesting improved permeation of the drug.

INTRODUCTION: Drug delivery through skin is one of the most promising alternative route of drug administration which greatly helps in by- passing first pass metabolism and other side effects upon systemic administration of drugs.[1] The greatest challenge with topical drug delivery is the barrier nature of skin that restricts the entry of most of the drugs.[2]

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Nanosponge loaded topical formulations can serve as local depot for sustained drug release as well as rate- limiting membrane barrier for modulation of systemic absorption and thus overcoming the limitations of topical formulations. They are non-irritating, non- mutagenic, non- allergenic and non-toxic.[3] Nanosponges can be effectively incorporated in to a topical hydrogel drug delivery system for increased drug release and drug penetration across skin and reducing drug toxicity and improving patient compliance by prolonging dosage intervals.[4]

Cephalexin is a first generation cephalosporin antibiotic, used for the treatment of skin and soft

tissue infection, urinary tract infection and diabetic foot ulcer. It is bactericidal, active against both gram positive and gram negative bacteria with similar action of benzyl pencillin by inhibiting the synthesis of bacterial cell wall.[5] Cephalexin is commercially available as tablet, capsule and suspension dosage forms. Cephalexin on oral administration causes indigestion, stomach pain, vomiting and gastrointestinal distress.

The aim of the present investigation is to assess the applicability of nanosponge loaded hydrogel in delivering cephalexin through skin. For this purpose, cephalexin was entrapped in nanosponge and incorporated into hydrogel and evaluated the *in vitro* skin permeation. Since, the formulation was mainly focused on skin and soft tissue infection associated with diabetic foot infection; it was treated against organisms like *Staphylococcus aureus, Pseudomonas aeuroginosa* and *Enterobacteriaceae*. Diabetic foot infection is usually a mixed type infection; the major organism involved in the infection is *Staphylococcus aureus*.[6] *Pseudomonas* species are often isolated from the wounds. *Enterobacteriaceae* are also found in many patients with chronic infections. [7]

MATERIALS AND METHODS:

Cephalexin was the gift sample from Ranbaxy Laboratories Ltd, Haryana, India. Hydroxyl Ethyl Cellulose, Poly Vinyl Alcohol, Carbopol 934 and Triethanolamine were purchased from Loba Chemie Pvt. Ltd, Mumbai, India. Dichloromethane was purchased from Nice Chemicals, Kerala, India and Propylene Glycol was from Spectrum Reagents and Chemicals Pvt. Ltd. Kerala, India. All other ingredients used were of analytical grade.

Methodology:

Preparation of Cephalexin Nanosponge:

Cephalexin nanosponge was formulated by emulsion solvent diffusion method. Four batches of nanosponges (NS1- NS4) with varying proportions of hydroxyl ethyl cellulose (HEC) and polyvinyl alcohol (PVA) were taken. The disperse phase consists of Cephalexin (100mg) and required quantity of HEC dissolved in 20ml of dichloromethane was slowly added to a specific quantity of PVA in 150 ml of aqueous continuous phase. Then the mixture was stirred at 1000 rpm for 2 hours on a magnetic stirrer (Kemi, India). The nanosponges formed were collected by filtration and dried in oven (Kemi, India) at 40^{o}C for 24 hours. Then the dried nanosponges were stored in vacuum desiccator to remove the residual solvent. The composition of nanosponge formulation was tabulated in **Table 1**. The prepared nanosponges were characterised based upon the entrapment efficacy and particle size.[8]

TABLE 1: COMPOSITION OF NANOSPONGE FORMULATION

Component (%w/w)	NS1	NS2	NS3	NS4
Drug	1.0	1.0	1.0	1.0
PVA	2.0	3.0	2.0	3.0
HEC	2.0	2.0	3.0	3.0
Dichloromethane	20	20	20	20
Distilled water	150	150	150	150

Characterization of Nanosponges:

Microscopic studies and particle size determination [9-12]

Analytical scanning electron microscope (JEOL, model JSM- 6490 LA) was used to study the particle size and surface morphology of cephalexin nanosponges. The particle size distribution study was evaluated by Dynamic Light Scattering Method (Malvern Instruments Ltd). The instrumental setting was fixed at a temperature, viscosity and refractive index of 25^{o}C, 0.887 cP and 1.33 respectively.

Entrapment efficiency:

The entrapment efficiency of nanosponges were determined by adding 10 ml of phosphate buffer of pH 7.2 and sonicated in a bath sonicator and filtered. 1 ml of filtrate is made up to 10 ml with phosphate buffer and was assayed spectrophotometrically at 262 nm (UV visible spectrophotometer, model UV-1601 PC, Shimadzu). The amount of entrapped drug was calculated from the equation:

$$\% EE = \frac{\text{Total amount of drug} - \text{Concentration of drug}}{\text{Total amount of drug}} \times 100$$

Formulation of Nanosponge loaded hydrogel:

Gel forming polymer was soaked in water for 2 hours and then dispersed by agitation with the aid of magnetic stirrer (Kemi, India) to get a uniform dispersion. The stirring was stopped and allowed to stand for 15 minutes to expel the entrapped air. To

this aqueous solution, 2%v/v triethanolamine was slowly added. At this stage, prepared nanosponge and different concentration of penetration enhancer (propylene glycol: 5%-15%) was added to get the hydrogel.[13] The composition was tabulated in **Table 2.**

TABLE 2: COMPOSITION OF NANOSPONGE LOADED HYDROGEL

Component (% w/w)	F0	F1	F2	F3	F4
Cephalexin nanosponges	-	6.0	6.0	6.0	6.0
Cephalexin	1.0	-	-	-	-
Triethanolamine	2.0	2.0	2.0	2.0	2.0
Propylene glycol	-	-	5	10	15
Carbopol 934	1.0	1.0	1.0	1.0	1.0
Distilled water (q.s)	100	100	100	100	100

Evaluation of Nanosponge Loaded Hydrogel:

Viscosity determination:

The viscosity of prepared hydrogels was measured using Brookfield viscometer (Prime Rheometer DV 1). Viscosity was measured at 25±1°C at 100 rpm using spindle no. 61.[14]

pH determination:

The pH of different hydrogel formulation was noted using calibrated pH meter. 1gm of cephalexin nanosponge loaded hydrogel was uniformly dispersed in 100 ml of distilled water and kept for 2 hours at room temperature. Then, pH of the dispersion was measured at 25±1°C.

Drug content estimation:

The percentage drug content was estimated by weighing 100mg of the hydrogel and extracting with 5ml of 0.1 N HCl using mechanical stirrer (Kemi, India). The volume was made up to 10 ml and filtered and then diluted and concentration was determined spectrophotometrically at 262 nm. The viscosity, pH and percentage drug content was reported in **Table 3.**

TABLE 3: PHYSICOCHEMICAL EVALUATION OF HYDROGELS

Hydrogel code	Viscosity (cp)	pH	% Drug content
F0	7520	6.84	93.536
F1	9560	6.52	83.263
F2	11100	6.95	85.316
F3	12750	6.74	87.773
F4	13100	7.13	95.836

***In- vitro* drug release studies:**

The cephalexin nanosponge loaded hydrogels were permeated through an artificial cellophane membrane. 1gm of hydrogel was placed in the donor compartment. The receptor medium was filled with phosphate buffer of pH 7.2 and constantly stirred with a small magnetic bead. During the experiment, temperature was maintained at 37±0.5°C to simulate the human skin condition. 1 ml of samples were withdrawn at 0, 1, 2, 3, 4, 5, 6, 7, 8 and 24 hours and replaced with fresh receptor solution. The samples withdrawn were analysed spectrophotometricaly at 262nm. The amount of drug released was calculated and the percentage drug released was plotted against time.

Swelling studies:

Dried hydrogels were weighed accurately and kept immersed in 10 ml of phosphate buffer of pH 7.2. Hydrogels were taken carefully at 1, 2, 4, 6, 8, 10, 12 and 24 hours intervals. Blotted with filter paper and weighed accurately. Increase in weight was determined as time increases.[15] The percentage swelling was calculated from the equation:

$$\% \text{ swelling} = \text{wet weight} - \text{dry weight} / \text{wet weight} \times 100$$

***Ex- vivo* skin permeation studies:**

The histological and biochemical properties of porcine skin have been repeatedly shown to be quite similar to human skin.[16] For the penetration studies, pig ear skin was used, which was obtained from the local slaughter house. The hair on the skin and subcutaneous fatty tissues were removed and washed with Ringer's solution. The skin was allowed to dry and packed in aluminium foil and stored in a polyethylene bag at -2°C.[17, 18] The same *in vitro* drug release experimental set up was used here. Franz diffusion cells having surface area of 3.14 cm^2 were used for permeation studies.

The receptor compartment was filled with phosphate buffer of pH 7.2. To mimic the body condition during the experiment, the temperature was maintained as 37±0.5°C with an external constant water circulator. The receiver medium was continuously stirred with a small magnetic bead to prevent any boundary layer effects. The pig skin was placed between the donor and receptor

compartment. 1 gm of hydrogel was placed on the skin surface. 3 ml aliquots were collected at 1, 2, 3, 4, 5, 6, 7, 8 and 24 hours and replaced with fresh receptor solution. The withdrawn samples were analysed spectrophotometricaly at 262nm. The flux at 24 hours was observed and the release profile curves were drawn for all the formulations.[19]

In-vitro antimicrobial activity study:

The microbial culture *Staphylococcus aureus, Pseudomonas aeroginosa* and *Enterobacteriaceae* were used as the test strain, which was procured from the Eugreen Biolabs, Kochi, Kerala. These inoculums were spread onto nutrient agar plate by streak method, which was from Eugreen Biolabs, Kochi, Kerala. The optimized cephalexin nanosponge loaded hydrogel formulation (F4) was tested for antimicrobial activity using agar diffusion on solid media.

Determination of minimum inhibitory concentration (MIC) and zone of inhibition:

Sterile NA plates were prepared and 0.1 ml of the inoculums of test organism was spread uniformly. Wells were prepared by using a sterile borer of diameter 6 mm and the samples of different concentrations (0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg) were added in each well separately. The plates were incubated at 35-37^{o}C for 18-48 hours, a period of time sufficient for the growth. The zone of inhibition of microbial growth around the well was measured in cm. MIC was calculated from the fully grown plates.

Histological Studies:

The pig ear skin was treated for 6 hours with water, normal saline, drug containing hydrogel and optimized formulation. Then the skin was washed and kept in 10% formalin solution. Then cut this section vertically and dehydrated using ethanol, embedded in paraffin for fixing and stained with haematoxylin and eosin. These samples were observed under light microscope and the changes in the skin after treatment were evaluated.[20]

Stability studies:

The optimized formulation were kept for stability studies for 3 months at room temperature (30 ± 2°C), at refrigerator temperature (4 ±2°C) and at accelerated condition (40±2°C, 75%RH) in programmable environmental test chamber (Remi) to determine physical and chemical stabilities. The formulation was evaluated visually and for entrapment efficiency and drug release after 15, 30, 45, 60 and 90 days.[22, 23]

RESULT AND DISCUSSION: Cephalexin nanosponge was prepared by emulsion solvent diffusion method and incorporated into hydrogel by continuous stirring in a magnetic stirrer. The formulations were prepared to study the applicability of nanosponge loaded hydrogel for delivering cephalexin through skin and to study the effect of penetration enhancer used in the formulation. Various evaluation studies were carried out for cephalexin nanosponge and hydrogels.

Microscopic studies and particle size determination:

The particle size distribution study was determined by Dynamic Light Scattering (DLS). The particle size of prepared cephalexin nanosponges were found to be between 288- 386nm and tabulated in table 4. The SEM micrographs gave an idea about the morphological structure of nanosponge (**Fig.1**). From the figure, it was evident that the surface of nanosponge is porous. The presence of pores was due to the impression of diffusion of the solvent dichloromethane.

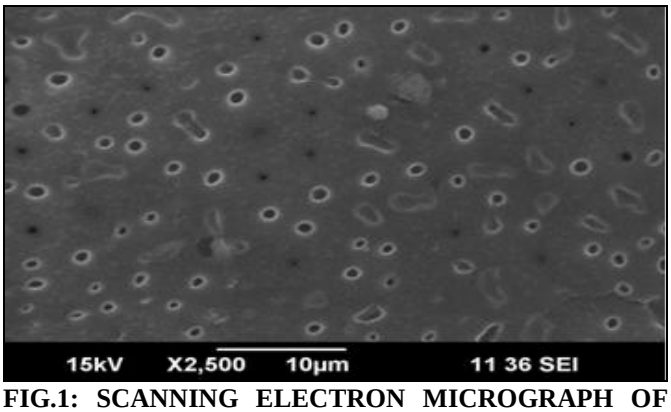

FIG.1: SCANNING ELECTRON MICROGRAPH OF CEPHALEXIN NANOSPONGE

Entrapment efficiency:

The entrapment efficiency was determined for all nanosponge formulations as listed in **Table 4**. The variation in entrapment efficiency was due to the changes in the polymer concentration and difference in degree of cross linking. The

entrapment efficiency was highest for NS 2 which can be possibly attributed to the higher concentration of polyvinyl alcohol and lower concentration of hydroxyl ethyl cellulose. The formulation having least particle size and maximum entrapment efficiency were taken to formulate hydrogels. The particle size of NS2 formulation was found to be 288nm and entrapment efficiency was found to be 95.63%. Hence, the formulation code NS2 was taken as the optimised cephalexin nanosponge formulation.

TABLE 4: PARTICLE SIZE AND ENTRAPMENT EFFICIENCY OF CEPHALEXIN NANOSPONGE

Formulation code	Z-average (nm)	% Entrapment Efficiency
NS1	294	90.54
NS2	288	95.63
NS3	367	88.52
NS4	386	93.26

Five hydrogel formulations were prepared using Carbopol 934 as gelling agent with variable concentration of penetration enhancer and evaluation studies were carried out. Carbopol 934 is hygroscopic in nature and is the best choice for gel formulations, owing to its good thermal stability and optimum rheological properties.[21]

Physicochemical evaluation of hydrogels:

The physicochemical properties of all prepared hydrogels were evaluated. The prepared hydrogels were transparent and smooth in appearance. These were uniform in color and gel like appearance. The physicochemical properties like viscosity, pH and drug content of hydrogel formulations were determined and tabulated in **Table 4**. The viscosity affects the spreadability, extrudability and release of drug. The gels with high viscosity may not extrude from the tube easily whereas low viscosity gels may flow quickly. Hence, there should be an optimum viscosity.

The viscosity ranged between 7520- 13100 cps. The viscosity variation was based on the varying concentration of penetration enhancer, since the concentration of gelling agent was kept constant for all hydrogel formulations. The pH of all hydrogel formulation was ranged between 6.5- 7.1 which are considered acceptable to avoid the risk of irritation upon application to the skin. The drug content was found to be between 83.26-95.83%.

***In- vitro* drug release studies:**

The *in vitro* release studies were carried out in phosphate buffer of pH 7.2 using cellophane membrane in a Franz diffusion cell apparatus (Orchid Scientifics). Amongst all formulations, F4 formulation showed highest drug release compared to other formulations. The F4 formulation showed drug release of 75.57±0.2048% at the end of 24th hour. The highest *in vitro* release of cephalexin from F4 formulation may be attributed to the solubility of drug within the gel matrix due to permeation enhancer that consequently facilitated the drug to release from the hydrogel network in to the test media. The *in vitro* release data were plotted in **Fig. 2**.

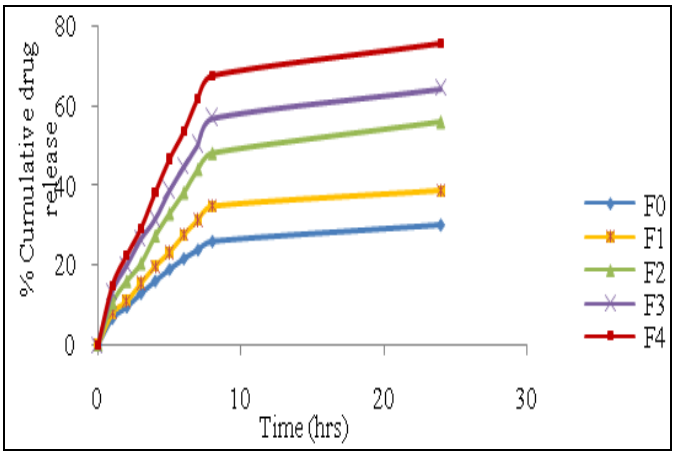

FIG.2: *IN VITRO* RELEASE PROFILE OF CEPHALEXIN NANOPSONGE LOADED HYDROGEL FORMULATION

Kinetic data modelling studies:

The data obtained from the *in vitro* release study was used for kinetic modelling. This was done to find out the mechanism of drug release from cephalexin nanosponge loaded hydrogel. In the present study the release was not linear that the drug release from the formulation was not linear, hence not followed zero order kinetics. The *in vitro* release model best fitted to Higuchi release order. This was confirmed by plotting percentage cumulative drug release and square root of time and R^2 value ranges between 0.936- 0.958.

The Korsmeyer- Peppas release exponent (n) ranged between 0.326-0.473 and hence confirmed diffusion as the principal of mechanism of drug release. The values of kinetic studies were tabulated in **Table 5**.

TABLE 5: KINETIC MODELLING DATA

Hydrogel code	Zero order	First order	Higuchi model	Korsmeyer-Peppas	
	R^2	R^2	R^2	R^2	n
F0	0.622	0.976	0.936	0.943	0.417
F1	0.646	0.952	0.941	0.933	0.326
F2	0.656	0.963	0.943	0.945	0.347
F3	0.740	0.974	0.949	0.947	0.426
F4	0.762	0.978	0.958	0.953	0.473

Swelling studies:

The study of swelling study was important as it is the one of the main mechanism for drug release from gel formulation. As water penetrates to gel and allow the drug to dissolve in the water and thus by this mechanism drug is released.[23] In the present study, swelling studies of all formulations were carried out in phosphate buffer of pH 7.2. Here, gel on contact with the buffer, this buffer penetrates into the gel and then become swell and allow the drug to dissolve and the drug gets released. Amongst all formulations, F4 formulation showed highest percentage swelling within 24 hours.

This indicates that higher the percentage swelling, higher will be the drug release. Hence, from swelling studies it was again confirmed that F4 formulation showed higher drug release. The percentage swelling of different hydrogel formulations within 24 hours were tabulated in **Table 6**.

TABLE 6: PERCENTAGE SWELLING

Formulation code	% swelling
F0	64.23
F1	71.57
F2	76.31
F3	81.92
F4	93.45

***Ex- vivo* skin permeation studies:**

The *ex-vivo* permeation study gives the information about the behaviour of the molecule *in-vivo*. The amount of drug permeated gives the information about the amount of drug absorbed into the blood. In the present study, *ex-vivo* skin permeation studies for all formulations were carried out in phosphate buffer of pH 7.2 using pig ear skin obtained from local slaughter house in a Franz diffusion cell apparatus (Orchid Scientifics). The permeation data showed that the increase in concentration of permeation enhancer caused increased permeation. Amongst all formulations, F4 formulation showed highest drug permeation through the skin within 24 hours. The *ex- vivo* skin permeation data were plotted in **Fig.4.**

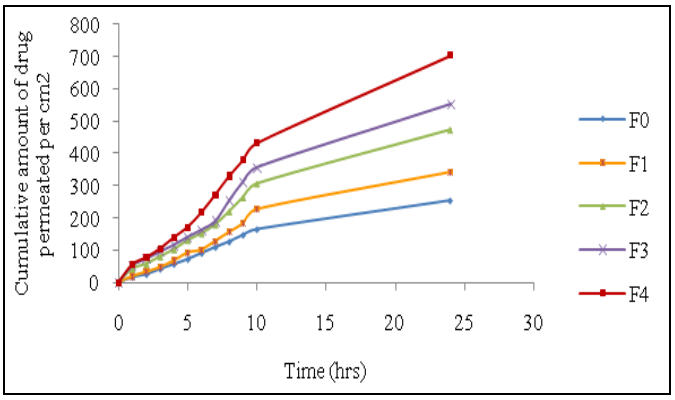

FIG. 4: *EX- VIVO* SKIN PERMEATION STUDIES

***In-vitro* antimicrobial activity study by zone of inhibition**

The antimicrobial activity of optimized formulation (F4) was determined against *Staphylococcus aureus*, *Pseudomonas aeroginosa* and *Enterobacter*. The antimicrobial activity was carried out at different concentrations (0.1 mg, 0.2 mg, 0.3mg, 0.4mg). The minimum inhibitory concentration (MIC) was calculated and reported in **Table 7** and represented in **Fig. 5.**

TABLE 7: EVALUATION OF ANTIMICROBIAL ACTIVITY BY ZONE OF INHIBITION

Microorganism	Volume added (mg)	Zone of inhibition (cm)
Staphylococcus aureus	Control	0
	0.1	1.3
	0.2	1.3
	0.3	1.2
	0.4	1.3
Enterobacter	Control	0
	0.1	1.2
	0.2	1.3
	0.3	1.3
	0.4	1.3
Pseudomonas aeroginosa	Control	0
	0.1	1.3
	0.2	1.2
	0.3	1.2
	0.4	1.3

Histological Studies: The histology of pig ear skin treated with normal saline, drug solution, drug containing hydrogel (F0) and optimized formulation (F4) is represented in **Fig. 6**. From the figure, it was clear that the stratum corneum, dermis and epidermis were closely packed in case of drug solution. But in case of optimized nanosponge loaded hydrogel

formulation, the stratum corneum is disrupted. Hence, improves the permeation of drug into the deeper layers of skin.

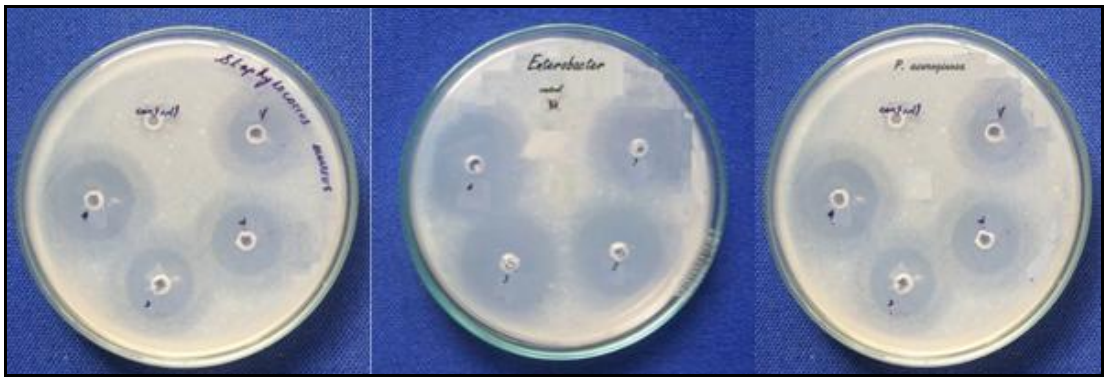

FIG. 5: *IN VITRO* ANTIMICROBIAL ACTIVITY BY ZONE OF INHIBITION

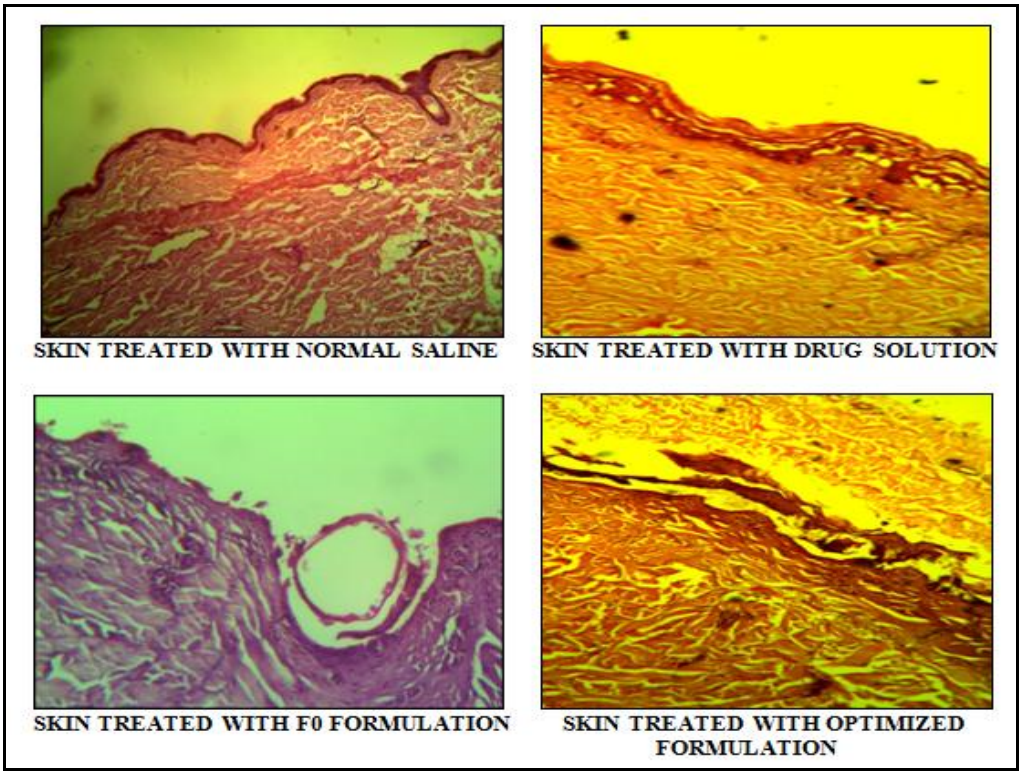

FIG.6: HISTOLOGY OF SKIN TREATED WITH VARIOUS FORMULATIONS

Stability studies:

The stability studies of optimized formulation at room temperature (30±2°C), at refrigerator temperature (4 ±2°C) and at accelerated condition (40±2°C, 75±5%RH) were carried out for 3 months. The physical appearance and drug content were determined and tabulated in **Table 8.** It did not show any changes in physical appearance when compared to the freshly prepared formulation. The percentage drug content were evaluated and shows that there was no significant changes in the percentage drug content during the storage for 3 months in all conditions. The *in vitro* release studies were carried out at the end of 7^{th}, 15^{th}, 30^{th}, 60^{th} and 90^{th} day and compared with initial in vitro drug release data for any significant changes. The results obtained were tabulated in **Table 9** and represented graphically in **Fig.7**. From the data, it was evident that there was no significant changes in the *in vitro* release as compared to initial drug release during the storage for 3 months in all conditions. Hence, based upon the stability studies carried out for 3 months, it was concluded that the optimised formulation is stable under ambient conditions.

TABLE 8: STABILITY STUDY OF OPTIMIZED FORMULATION

Temperature	Room temperature (30 ± 2°C)		Refrigerator (4 ± 2°C)		Accelerated (40 ± 2°C, 75 ± 5% RH)	
Parameters	Physical appearance	Percentage drug content (%)	Physical appearance	Percentage drug content (%)	Physical appearance	Percentage drug content (%)
Freshly prepared	Transparent and smooth	95.836	Transparent and smooth	95.836	Transparent and smooth	95.836
7th day	Transparent and smooth	94.512	Transparent and smooth	95.421	Transparent and smooth	95.515
15th day	Transparent and smooth	94.123	Transparent and smooth	95.053	Transparent and smooth	95.098
30th day	Transparent and smooth	93.883	Transparent and smooth	94.899	Transparent and smooth	95.001
60th day	Transparent and smooth	93.338	Transparent and smooth	94.788	Transparent and smooth	94.879
90th day	Transparent and smooth	93.063	Transparent and smooth	94.593	Transparent and smooth	94.749

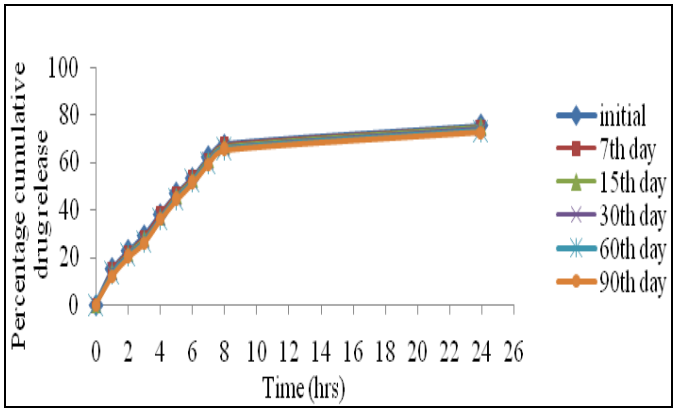

FIG.7: STABILITY STUDY OF OPTIMISED FORMULATION (*IN VITRO* RELEASE)

CONCLUSION: The prepared nanosponges were successfully incorporated into topical hydrogel. The nanosponge based formulation showed better drug release and good stability. The nanosponge system was found to have better penetration of drug through the skin and hence we can speculate that cephalexin nanosponge loaded hydrogel formulation is a good candidate for topical drug delivery in the treatment of skin and soft tissue infection associated with diabetic foot infections.

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