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Nanosponges: A Game-Changer in Drug Delivery Design and Assessment for Sustained Release

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ABSTRACT

Cephalexin, the first generation antibiotics has been employed for the treatment of infectious disease associated with skin and soft tissues, the urinary system, and the feet of diabetics. Cephalexin has been made into a novel nanosponge because topical formulations were not accessible and these preparations can improve skin permeability. Ethyl cellulose, polyvinyl alcohol, and Pluronic F68 were used to create various different cephalexin nanosponges employing the emulsion solvent evaporation method. Particle size and entrapment effectiveness were determined to be in the range of 200–400 nm and 88.5–95.6%, respectively. Analysis on in vitro drug release revealed that designs with advanced penetration power exhibited higher drug release. Studies on skin permeation revealed that formulations with increased permeation enhancer concentrations had better skin absorption.

Keywords- Cephalexin, Nanosponge, Antibiotics, Topical formulation.

Introduction-

Skin is the potential substitute medication administration methods is through the skin, because it avoids first-pass metabolism and other negative effects associated with systemic medication delivery [1]. The skin's natural resistance function that prevents few medications from entering, is the principal hurdle for topical drug administration [2].

A novel existing element known as a "Nanosponge" is made up of infinitesimal particulates with a small, nanometer-wide orifice. Such small particulates have the capacity to transport both hydrophilic and lipophilic medicinal molecules because of their shallow apertures that might be packed with different kinds of materials [3].This could be highly beneficial to deliver the medication at the precise target place rather than letting it travel throughout the body [4]. Nanosponge's compact size and permeable structure enable them to interact insoluble medicines within the matrix, increasing their dissolution rate and tolerability [5]. Due to their internal hydrophobic voids and exterior hydrophilic twisting, nanosponges offer exceptional elasticity and can implicate both hydrophilic and lipophilic medicative ingredients [6]. By decreasing the regularity of dose while improving user convenience and adherence, this drug delivery technique is capable of encapsulating a wide range of chemicals, minimising complications, improving reliability, and increasing the aesthetics and composition versatility [7]. One of the really difficult concerns in medicine formulation continues to be the attempt to increase the dissolution and solubility of weakly and completely water insoluble medications. To improve oral absorption and bioavailability of such medications as well as their dissolution rate, a

number of techniques have been developed [8]. Nanosponges, among other methods, had produced excellent outcomes in increasing the drug's solubility, permeability, rate of drug dissolution, and ultimately its bioavailability [9]. Certain drawbacks of the traditional medication regimens can indeed to be resolved using nanosponges [10].

Cephalexin is a first-generation cephalosporin which is used in the treatment of respiratory infections and other types of infections. It is administered orally as solid capsule dosage 250mg or 500mg. It is usually taken at the same time every day between 6 to 12 hours [11]. It is also sometimes used for penicillin allergic patients who have upper respiratory tract or dental and heart conditions. It comes in the form of capsules, tablets and liquids. It has a similar bactericidal effect to benzyl pencillin and is effective against both gramme positive and gramme negative bacteria by preventing the production of bacterial cell walls [12].

The current experiment's goal is to determine whether nanosponges technology can be used to administer cephalexin via skin. Cephalexin was examined after being confined in a nanosponges for this reason. The preparation has been addressed against microbes because it was primarily targeted on the skin [13].

Material and Methodology-

Bioplus Lifesciences Pvt Ltd., Bangalore India, provided the gift sample of cephalexin. The following items were bought from Qualigens fine Chemical, Mumbai, India: Ethanol, Dichloromethane, Methanol and Chloroform; Sodium Chloride, Di sodium hydrogen phosphate, Di potassium hydrogen orthophosphate from S.D. fine Chem Pvt. Ltd, Mumbai, India; Sodium Hydroxide from Loba Chemie Pvt. Ltd, Mumbai, India; Eudragit S- 100 from Evonik industries, Mumbai, India; and Ethyl cellulose from Research Lab fine Chem industries, Mumbai, India.

Methodology-

Various concentrations of ethyl cellulose, polyvinyl alcohol, and Pluronic F68 had been used to develop cephalexin nanosponges adopting the emulsion solvent diffusion approach. A certain proportion of PVA in 100 mL of an aqueous continuous phase has been gradually introduced following the dispersion phase, which contained 100 mg of Cephalexin and a predetermined proportion of ethylcellulose dissolved in 30 mL of dichloromethane. On a magnetic stirrer, this specimen was swirled for two hours at a speed of 1000 rpm. Vacuum filtration was used to gather the developed Cephalexin nanosponges, which were then dried for 24 hours at 400°C in an oven [14].

Table.1 Formulation of Cephalexin Nanosponges

Ingredients	F1	F2	F3
Cephalexin (mg)	50	50	50
Polyvinyl alcohol (mg)	15	20	25
Ethyl cellulose (mg)	25	15	20
Pluronic F68 (mg)	5	5	5
Dichloromethane	5	5	5
Distilled water (ml)	qs	qs	qs

Preformulation studies of Drug-

It is the examination of the physicochemical characteristics of a drug ingredient both on its own and in conjunction with excipients [9].

Physical Characteristics-

- **Organoleptic Parameters-** The drug has been tested for its color, odour and taste. The color of the drug was determined by taking a small quantity of a powdered drug into butter paper and viewed under an illuminated area. By tasting and inhaling the taste and odour of the drug had been examined [15].

- **Melting Point-** It is employed to ascertain the drug's authenticity. A capillary tube was filled with a little amount of powder. The melting point equipment was used to position that tube, and the temperature ranges between when the powder began to melt and when it finished melting was noted [15].

- **Solubility Analysis-** By gradually introducing solvent to a test tube having a set concentration of solute, or vice versa, it was possible to determine the solubility qualitatively. The device was violently agitated and manually checked it after every insertion [16].

- **Fourier transform infrared spectroscopy (FTIR) -** The infrared spectrum of any chemical can reveal insight regarding the functional groups that are available. The KBr pellet approach has been used to collect an infrared spectrum of the medication [17].

- **Loss on Drying-** Loss on drying is the weight loss, given as a fraction of weight, brought on by water and any volatile material which can be carried out at certain circumstances. The IR moisture balance immediately measures loss on drying. Initially, the equipment was calibrated using the knob. Next, 5 grammes of powdered was taken, the temperature was held constant at 100°C to 105°C for 15 minutes, the knob has been rectified, and the percentage of moisture was checked by the given formula [18]:

$$\text{Loss on drying (\%)} = \frac{\text{initial weight of sample - weight of sample after drying x 100}}{\text{Initial weight of sample}}$$

- **UV – Spectroscopic Analysis-** The λ_{max} was exposed to UV radiation for this study. The distinctive "Absorption Maxima (max)" peak of the Cephalexin medication sample's FTIR spectrum transitions from the ground state to the excited state at wavelengths between 200

and 400 nm, and this particular occurrence results in a specific UV-absorption spectrum curve. This maximum was established using the following technique: as part of regular operations, 10 mg of Cephalexin were precisely measured and solubilized in phosphate buffer solution with a pH of 7.2 in a 10 ml volumetric flask. In the next stage, 1 ml of the mixture from above was removed, and 100 ml of phosphate buffer with a pH of 7.2 was added to create a solution with a strength of 10 g/ml. Then, using the UV/Vis spectrophotometer Labindia 3000+ to examine this solution from 200 to 400 nm while comparing it to a blank for the reagent, we were able to produce a specific UV absorption spectrophotometric curve [19].

First and foremost, to create the Cephalexin standard calibration curve in phosphate buffer pH 7.2 systems. Drugs need to be maintained and weighed precisely. Prior to conducting the experiment, the solvent solution to be utilised should be purified and double-filtered. If buffers are being utilised, they should be newly made and double-filtered for purity. With the aid of a pH meter, its proper pH should also be checked. Following are the steps for preparing various buffer solutions in reference with I.P [20].

- **Calibration curve of Cephalexin in phosphate buffer pH 7.2-** Typically, a precise dosage of the drug—about 10 mg—was weighed and then dissolved in 10 ml of phosphate buffer, pH 7.2, in a volumetric flask, yielding a solution with a strength of 1 mg/ml (or 1000 g/ml). Then, 1 ml of the previously mentioned solution was taken out and appropriately diluted up to 10 ml of phosphate buffer pH 7.2 to create a solution with the strength of "100 g/ml stock solution". Then, from the aforementioned stock solution, 0.5 ml, 1.0 ml, 1.5 ml, 2.0 ml, and 2.5 ml were removed and diluted up to 10 ml, yielding a solution with a strength of 5–25 g/ml. Then, using a "U.V/Vis Spectrophotometer Labindia 3000+" to evaluate these serial dilutions in comparison to a standard blank, we are able to produce our standard calibration curve in a variety of solvents. We have created a standard calibration curve in phosphate buffer at pH 7.2 for our prospective experiment [21].

Evaluation Parameters of Nanosponges-

***In Vitro* Characterization of Nanosponges-**

- **Percentage yield-** Weighing was done on the dried Cephalexin nanosponges. Following is a calculation of percentage yield value [22].

% yield = Weight of nanosponges×100/Total solids weight

- **Entrapment Efficiency-** The effectiveness of Cephalexin nanosponges in entrapping particles was calculated using a UV spectrophotometric method. For Cephalexin in 0.1 N HCl in the 5–25 g/mL (Beer's Lambert's range) range, a calibration curve was plotted at 256 nm. The concentration of Cephalexin and its absorbance showed an excellent linear connection (r2=0.999, m=0.032, n=3). Each batch's 10 mg of Cephalexin nanosponges were chosen, ground in a mortar, and added to 10 mL of 0.1 N HCl. After the appropriate dilution, cephalexin was recovered by centrifuging at 1000 rpm for 30 min, filtering, and analysing concentration using calibration curve data. Following is how percentage entrapment was determined [23]:

$$\% \text{ Entrapment efficiency} = \frac{\text{Weight of initial drug} - \text{Weight of free drug}}{\text{Weight of Initial drug}} x100$$

- **Particle size, polydispersity index-** Using zetasizer, the average particle size and polydispersity index (PDI) of the produced nanosponges were determined (DTS were 4.10, Horriba instrument, India). The nanosponges formulation was analysed for average size and PDI after being diluted with deionized water (1:9 v/v) [24].

- **Shape and surface morphology**- Scanning electron microscopy (IISER, Bhopal) 68-69 was used to analyse the interface morphology and form of the nanospongess. A high-vacuum evaporator with a gold sputter module was used to cover the nanospongess with gold after they had been placed to scaffolds with carbon-glue. Following that, specimens were examined using a scanning electron microscope set at 10 kV [25].

- ***In-vitro* drug release from nanosponges-** It is a changing dynamic property that describes how a homogeneous solution of a solid or liquid can be created in a solvent. The test establishes the amount of time needed for the preparation to release a particular amount of the medication [26].

Table.2 *In-Vitro* Test Procedure

Medium	**900ml, 0.1N HCl**
Apparatus	Paddle (USP-II)
RPM	55
Temperature	37^0C±0.5
Time Points	0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hrs.

- **Procedure-** The in vitro dissolution analysis for oral dosage regimens must be carried out in a dissolution medium that mimics in vivo settings (actual physiological conditions). The developed formulation's in vitro drug release investigations were carried out for a duration of 12 hours utilising a Labindia DS 8000 model dissolution tester USP Type-2 apparatus (spinning paddle) set at 100 rpm and a temperature of 37 0.5°C. To maintain the volume constant, 5 ml specimens were taken out of the dissolution medium at predetermined periods and filled with new medium. Using a UV-visible spectrophotometer, the absorbance of the specimen solution was examined at 256 nm for the availability of the simulated medication [27].

- **Mathematical treatment of *in-vitro* release data-** Quantitative evaluation of the findings collected in dissolution/release testing has been made simplified by applying mathematical formulae that reflect dissolve outcomes as a consequence of certain of the dosage form parameters [25].

- **Stability of a composition for improved nanosponges-** According to ICH requirements, the produced nanosponges underwent stability testing at 40 °C/75 % RH and 30 °C/60 % RH for a time frame of three months. At 1-month durations, specimens were taken out and examined for physical condition and drug content [29].

Result and Discussion-

Preformulation Studies-

The preformulation analysis of the drug has been examined by adopting different physical examination such as organoleptic properties, melting point and loss on drying. The results of the evaluated studies has been given in Table 3.

Table.3 Preformulation Evaluation of Cephalexin

Sr. No.	Properties	Experimental Value
1.	Appearance	White – off white
2.	Taste	Bitter
3.	Odour	Unpleasant breath
4.	Melting point	322-325 ^{o}C
5.	State	Crystalline
6.	Loss on Drying	0.285±0.001%.

Solubility- In order to achieve the necessary amount in the systemic circulation and to provide the best possible therapeutic reaction, solubility is a critical aspect to perform. The solubility of the drug has been evaluated in various different solvents. The table below shows the results obtained.

Table. 4 Solubility Evaluation of Cephalexin

Sr. No.	Solvent Used	Experimental Value
1.	Water	++--
2.	Ethanol	+++-
3.	Methanol	+++-
4.	0.1 N Hcl	++++
5.	0.1 N NaoH	++++
6.	Chloroform	+---
7.	Phosphate buffer (pH 7.2)	++++

++++ = Soluble; +++- = Sparingly soluble; ++-- = Slightly soluble; +--- = Very slightly soluble.

Fourier transform infrared spectroscopy (FTIR) - Distinct peaks in the IR spectra were believed to indicate the availability of certain groups in the drug's configuration.

UV Spectrophotometric method- UV- 0.680 g of potassium dihydrogen phosphate, 0.100 g of sodium hydroxide, and 100 milliliters of distilled water were used to make the phosphate buffer, which has a pH of 7.2. In order to prevent the potential of any minuscule contamination, it was observed that all of the solvent systems utilised were either freshly synthesized (in the case of buffers) or other organic solvents were filtered before use. The phosphate buffer (pH 7.2) was used to generate the standard drug solution in various concentrations, and the relationship between concentration and absorbance was graphed. The linear line was established on the absorption point in the plot of absorbance vs. concentration. Beer's lambert law is applied here. On the Absorbance data points, the linear regression analysis was performed. Slope, Intercept, and Correlation Coefficient were found to have values of 0.032, -0.002, and 0.999, respectively.

Table. 5 Absorbance Evaluated

S. No.	Concentration (µg/ml)	Absorbance
1	5	0.158
2	10	0.325
3	15	0.476
4	20	0.649
5	25	0.812

Assessment of developed nanosponges compositions-

Percentage Yield- The optimum nanosponge percentage yield value for F3 was discovered to be 78.980.21 (table.6). It was found that the percentage yield also grows when the formulation's polymer ratio does. The drug-polymer solution being wasted could be the cause of some formulations' low yield percentages.

Table.6 Percentage Yield

Formulation	Percentage Yield* (%)
F1	72.32±0.45
F2	74.25±0.23
F3	78.98±0.21
F4	71.14±0.24
F5	69.98±0.36
F6	70.74±0.41

Entrapment Efficiency- The formulation F3's percent drug entrapment efficacy has been observed to be the highest, ranging from 64.120.22 to 72.210.14. The outcomes showed that ethyl cellulose concentration is directly proportional to entrapment efficiency, but polyvinyl alcohol concentration is only indirectly proportional because polymer is poorly soluble in water (Table.7).

Table.7 Entrapment Efficiency Results

Formulation	Entrapment Efficiency of prepared Nanosponges
F1	68.54±0.25
F2	67.45±0.32
F3	72.21±0.14
F4	69.95±0.36
F5	68.84±0.41
F6	64.12±0.22

Measurement of mean particle size- By using photo correlation spectroscopy (PCS) on a submicron particle size analyzer (Particle Size Analyzer from Malvern) at a scattering angle of 90°C, the mean size of the optimized nanosponges formulation F3 was ascertained. The study was performed using a sample of the nanosponges (0.5 mg) suspended in 5 ml of distilled water. The mean particle size of improved formulation F3 nanosponges was measured and determined to be 245.65 nm

Determination of zeta potential- By assessing the electrophoretic mobility in a micro electrophoresis flow cell, the zeta potential of the drug-loaded nanosponges was calculated using a

zeta sizer (Malvern Instruments). In triplicate, the specimens have been evaluated in water at 25°C. Zeta potential measurements of optimised formulation F3 nanosponges revealed a value of -34.50 mV. The nanosponges' zeta potential was discovered to be at -34.50 mV. (Figure 8.4). The stability of nanosponges is indicated by the negative sign.

Assessment of nanosponges by Scanning Electron Microscopy (SEM)- The surface morphology and shape of formulations (F3) from the nanosponges formulation batches that demonstrated a suitable balance between the percentage drug releases were evaluated. This was done using a scanning electron microscope (Japan 6000) to look at the surfaces. A high vacuum evaporator was used to apply fine gold sputtering after the sample had been attached on carbon tape. During scanning, the acceleration voltage was set to 10 KV.

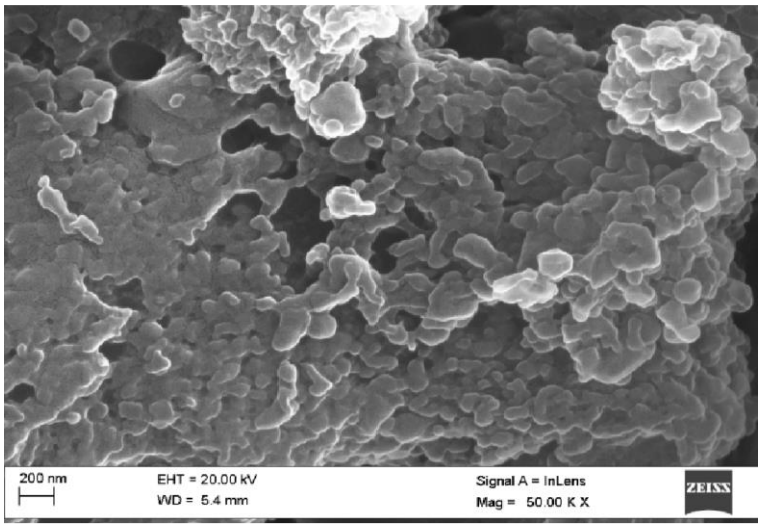

Figure 7: Scanning Electronic Microscopy of optimized formulation (F3)

Cephalexin-loaded nanosponges' release analysis-

Table. 8 *In vitro* drug release study of Cephalexin loaded nanosponges

S. No.	Time (hrs.)	Plain Drug	Nanospongs
1	0.5	25.65	19.98
2	1	65.58	30.32

3	1.5	85.45	39.98
4	2	96.65	46.65
5	3	-	55.65
6	4	-	63.32
7	6	-	78.85
8	8	-	89.98
9	12	-	99.12

Table.9 *In-vitro* drug release data for optimized formulation F3

Time (h)	square Root of time (h)1/2	Log Time	Cumulative % drug Release	Log cumulative % drug release	cumulative % drug remaining	Log cumulative % drug remaining
0.5	0.707	0.301	19.98	1.301	80.02	1.903
1	1	0	30.32	1.482	69.68	1.843
1.5	1.225	0.176	39.98	1.602	60.02	1.778
2	1.414	0.301	46.65	1.669	53.35	1.727
3	1.732	0.477	55.65	1.745	44.35	1.647
4	2	0.602	63.32	1.802	36.68	1.564
6	2.449	0.778	78.85	1.897	21.15	1.325
8	2.828	0.903	89.98	1.954	10.02	1.001
12	3.464	1.079	99.12	1.996	0.88	0.056

Stability Studies- The improved nanosponges formulation (F3) was shown to be stable after three months of storage at 4°C, but the preparation was found to be unstable at 25-282°C. Based on the percentage of EE, the average particle size, and physical appearance, the formulation's consistency has been determined.

After 1, 2, and 3 months of storage at 4.0 0.2°C, the average particle size of nanosponges was found to be 225.65±0.25, 220.36±0.25, and 219.85±0.33 nm, whereas at 25-282°C, the average vesicle size was found to be 245.65±0.36, 285.69±0.25, and 295.65±0.35 nm. After 1, 2, and 3 months of storage

at 4.00.2°C, the percent EE in the nanosponges composition was 74.65±0.45, 73.25±0.32, and 73.15±0.74 percent, whereas after 3 months of storage at 4oC, there were no appreciable changes in the percent EE and physical attributes.

Table.11 Optimized formulation of nanosponges F3

Characteristic			Time (Month)			
		1 Month	2 Month		3 Month	
Temperature	4.0 ±0. 2°C	25-28±2°C	4.0 ±0. 2°C	25-28±2°C	4.0 ±0. 2°C	25-28±2°C
Average particle size (nm)	225.65±0.25	245.65±0.36	220.36±0.25	285.69±0.25	219.85±0.33	295.65±0.35
% EE	74.65±0.45	65.58±0.65	73.25±0.32	60.85±0.25	73.15±0.74	55.78±0.63
Physical Appearance	Normal	Normal	Normal	Normal	Normal	Normal

Conclusion-

The majority of the optimal characteristics needed for an oral controlled release dosage form were present in the cephalexin-containing nanosponges. It has proven possible to create nanosponges with a smaller particle size of 245.65 nm thanks to a negatively charged surface charge. Continuous regulated release up to 12 hours was suggested by the release profile. Since the nanosponge systems have been shown to have a good potential for sustained drug release, they can be advantageous in terms of lowering dosages, reducing delivery regularity, and preventing associated systemic side effects. Thus, it can be said that the oral nanosponges of Cephalexin that have been produced are thought to be excellent and successful in the therapy of ulcer and related conditions.

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