Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 07, 2021

The Rise of Cephalexin Nanosponges as a Sustained Drug Delivery System: Formulation and Optimization

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Abstract- An antibiotic of the first generation called cephalexin is used to treat infections of the skin and soft tissues, the urinary system, and the feet of people with diabetes. Cephalexin was made into a nanosponge since topical formulations were not accessible, and the nanosponge can improve skin permeability. Ethylcellulose, polyvinyl alcohol, and Pluronic F68 were used to create six different cephalexin nanosponges utilizing the emulsion solvent evaporation method. Particle size and entrapment effectiveness were determined to be 200–400 nm and 88.5–95.6%, respectively. Studies on in vitro drug release demonstrated that formulations with higher penetration enhancer concentrations displayed increased drug release. The best linearity from the kinetic analysis was discovered using first order and Higuchi's equation. Studies on skin permeation revealed that formulations with increased permeation enhancer concentrations had better skin absorption.

Introduction-

One potential substitute medication administration method is through the skin, which significantly benefits in avoiding first-pass metabolism and other adverse effects associated with systemic medication delivery [1]. The skin's natural resistance function, which prevents most medications from entering, is the biggest obstacle to topical drug administration [2].

A contemporary substance known as a "Nanosponge" is composed of minute particulates with a small, nanometer-wide aperture. Such small particulates can transport hydrophilic and lipophilic medicinal molecules because of their shallow apertures that might be packed with different materials [3]. This could be highly beneficial to delivering the medication at the precise target place rather than letting it move throughout the body [4]. The development of nanosponges is an essential milestone in addressing the intricacy of freshly emerging structures. Nanosponge's compact size and permeable structure enable them to interact with 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. Such compositions are suitable with different carriers and components and are sustainable across a wide pH range in GI fluids [6]. By decreasing the regularity of dose while improving user convenience and adherence, this drug delivery technique can encapsulate a wide range of chemicals, minimizing complications, improving reliability, and increasing the aesthetics and composition versatility [7]. One of the complicated concerns in medicine formulation is the attempt to increase the dissolution and solubility of weakly and

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thoroughly water-insoluble medications. Several techniques have been developed to improve the oral absorption and bioavailability of such medications and their dissolution rate [8]. Nanosponges, among other methods, have produced excellent outcomes in increasing the drug's solubility, permeability, rate of drug dissolution, and ultimately its bioavailability [9]. Traditional medication regimens' specific drawbacks can be resolved using nanosponges [10].

Cephalexin is a first-generation cephalosporin that is used in the treatment of respiratory infections and other types of infections. It is administered orally, either in 250mg or 500mg capsules. 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 with upper respiratory tract or dental and heart conditions. It comes as a capsule, tablets, and a liquid to take by mouth. It has a similar bactericidal effect to benzyl pencillin and is effective against both gramme positive and gramme harmful bacteria by preventing the production of bacterial cell walls [12].

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

Material and Methodology-

Bio plus 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, Dipotassium 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 a continuous aqueous 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	F4	F5	F6
Cephalexin (mg)	100	100	100	100	100	100
Polyvinyl alcohol (mg)	200	300	400	500	600	800
Ethyl cellulose (mg)	300	250	200	150	100	50

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Pluronic F68 (mg)	100	100	100	100	100	100
Dichloromethane	15	15	15	15	15	15
Distilled water (ml)	100	100	100	100	100	100

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, odor, 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. The drug's taste and odor were examined by tasting and inhaling [15].

- **Melting Point-** It is employed to ascertain the drug's authenticity. A capillary tube was filled with a small 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 were noted [15].

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

- **Fourier transform infrared spectroscopy (FTIR) -** The infrared spectrum of any chemical can reveal insight regarding the available functional groups. 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 in 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 was 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

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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. According to Beer's rule, Lambert's this max is a distinctive quality of a particular molecule and provides essential details on the "Qualitative and Quantitative aspects." 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, create the Cephalexin standard calibration curve in phosphate buffer pH 7.2 systems. Drugs need to be maintained and weighed precisely. Before experimenting, the solvent solution should be purified and double-filtered. If buffers are utilized, they should be newly made and double-filtered for purity. With the aid of a pH meter, its proper pH should also be checked. The steps for preparing various buffer solutions about 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 stock above 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 compared to a standard blank, we can 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. The following is a calculation of the 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 analyzing

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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 a zeta sizer, 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 analyzed for the average size and PDI after diluting with deionized water (1:9 v/v) [24].

- **Shape and surface morphology**- Scanning electron microscopy (IISER, Bhopal) 68-69 was used to analyze 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 on scaffolds with carbon glue. Then, 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 time needed to prepare 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 is in vitro drug release investigations were carried out for 12 hours utilizing 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 the 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 simplified by applying

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mathematical formulae that reflect dissolve outcomes due to specific dosage form parameters [25].

- **Zero Order Kinetics-** It is the optimal way of drug release to create an extended pharmacological action because the dosage forms that adopt particular characteristics deliver the exact quantity of medication by time unit. This model can be expressed by the relation below:

$$\mathbf{Q_t = Q_o + K_o t}$$

Here, Q_t = the quantity of drug dissolved in time t,
Q_o= the preliminary extent of the drug in the solution (most often, Q_o=0),
K_o= the zero-order release constant [25].

- **First Order kinetics-** The subsequent relationship states this paradigm:

$$\log Q_t = \log Q_o + \frac{K_1 t}{2.303}$$

Here, Q_t = the quantity of drug dissolved in time t,
Q_o = the starting amount of drug in the solution,
K_1 = the zero-order release constant [27].

- **Higuchi Model-** The Higuchi paradigm describes drug transfer as Fick's law-based time-dependent diffusion technique. This connection can describe how drugs dissolve when administered in many pharmaceutical dosage forms with changed absorption, such as transdermal systems and matrix tablets incorporating water-soluble drugs. The Higuchi model is expressed as follows:

$$Q = K_H t^{1/2}$$

Q = the quantity of medication released in time t
KH represents the Higuchi dissolving constant [28]

- **Korsmeyer Peppas Model:** Only systems with a drug diffusion coefficient that is slightly concentration independent could use this formula.

$$\frac{M_t}{M_\infty} = a\, t^n$$

To obtain the exponent n, just the portion of the distribution curve where M_t/M_∞ 0.6 should be used. Using this formula, you also need a one-dimensional release and a network width-thickness or length-thickness correlation of at least 10. A revised form

$$\frac{M_{t-l}}{M_\infty} = a\,(t-l)^n$$

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of this equation was created to compensate for the lag time (l) at the beginning of drug release from the pharmaceutical dosage form:

This equation changes when the burst effect probability, b, is present: If there is no lag time or burst effect, the l and b values are 0, and merely at n is used. Numerous pharmacological controlled release dosage forms have been released according to this mathematical formula, commonly known as the Power Law [28].

- **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 examinations such as organoleptic properties, melting point, and loss on drying. The results of the evaluated studies have been given in the table. 3

Table.3 Preformulation Evaluation of Cephalexin

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

Solubility- To achieve the necessary amount in the systemic circulation and provide the best possible therapeutic reaction, solubility is a critical aspect to perform. The solubility of the drug has been evaluated in various 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	++++

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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. Figure 6.1 shows the IR spectrum, which was captured using an FTIR spectrophotometer.

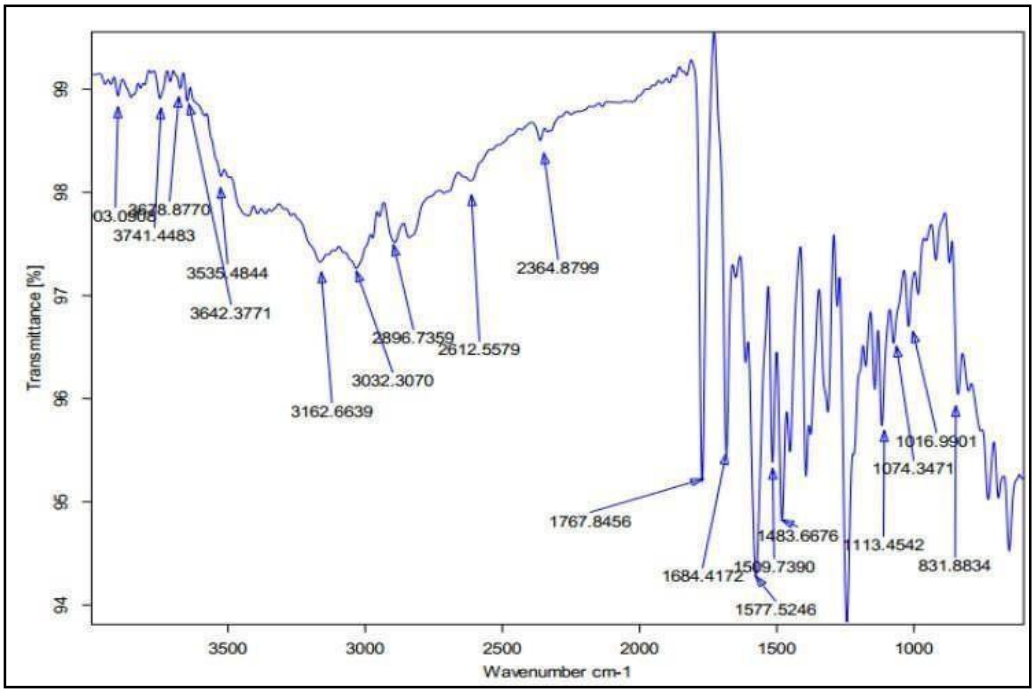

Figure 1: Infrared spectrum of Cephalexin

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 utilized were either freshly synthesized (in the case of buffers) or other organic solvents were filtered before use.

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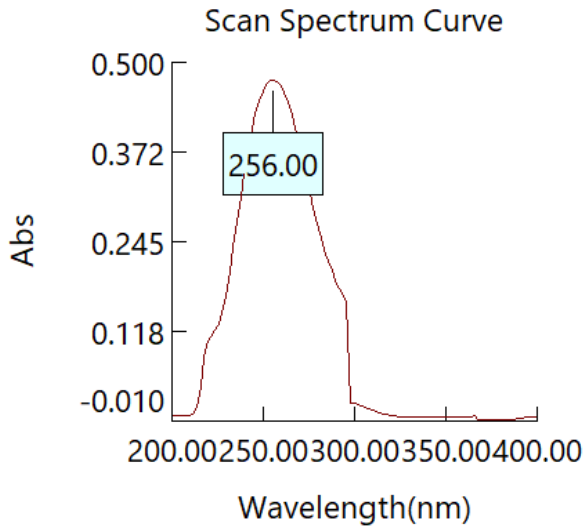

Figure 2: Calibration curve of Cephalexin in phosphate buffer pH 7.2

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 was 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

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F4	71.14±0.24
F5	69.98±0.36
F6	70.74±0.41

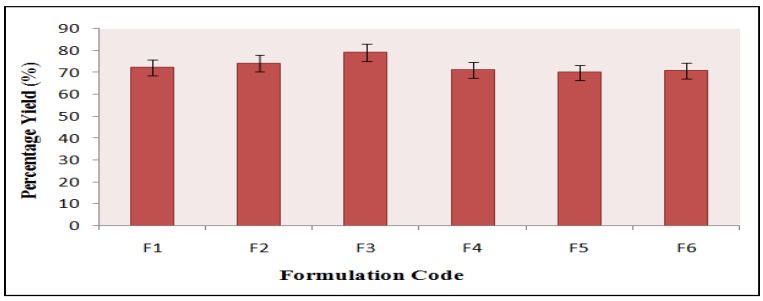

Figure 3: Graph of Percentage Yield for Different Formulation

Entrapment Efficiency- The formulation F3's percent drug entrapment efficacy has been 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 the 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

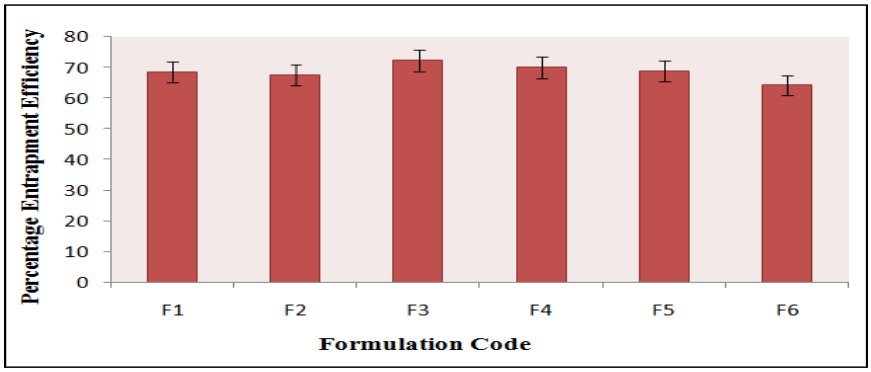

Figure 4: Graphical Representation of Entrapment Efficiency for Different Formulation

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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 used 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.

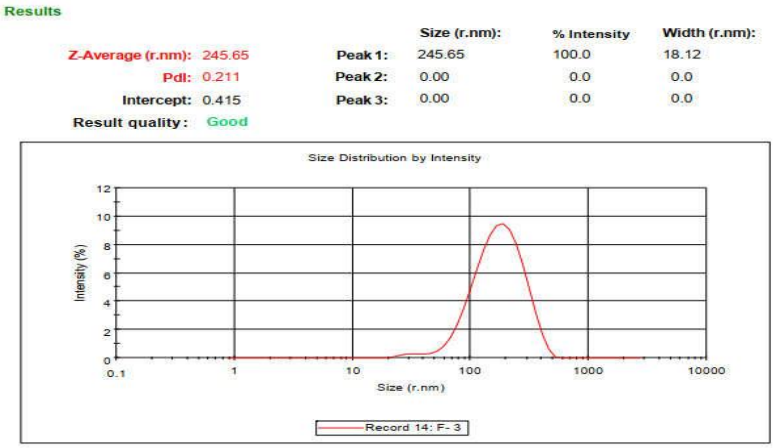

Figure 5: Graphical Presentation of Mean Particle size

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 were evaluated in water at 25°C. Zeta potential measurements of optimized 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 negative sign indicates the stability of nanosponges.

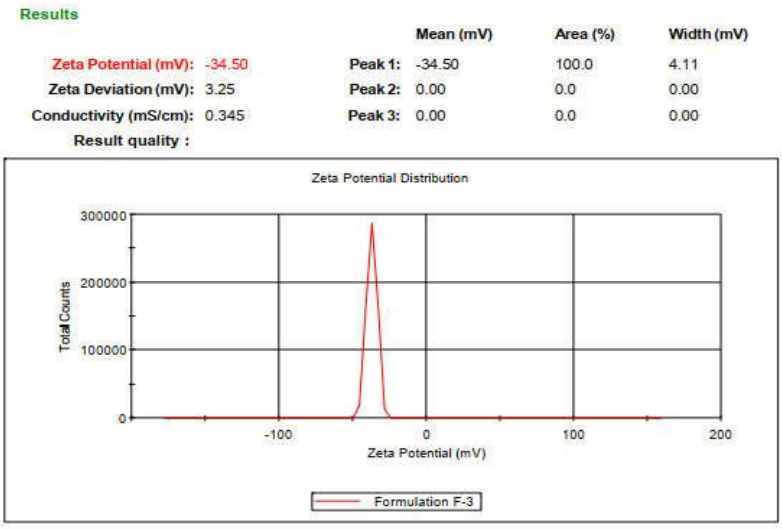

Figure 6: Graphical Representation of Zeta Potential

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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 of drug releases were evaluated. This was done using a scanning electron microscope (Japan 6000) to examine 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.

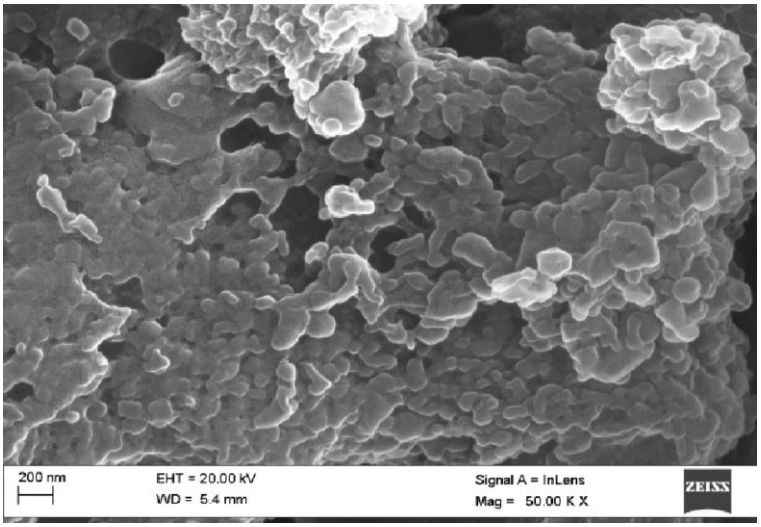

Figure 7: Scanning Electronic Microscopy of optimized formulation (F3)

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

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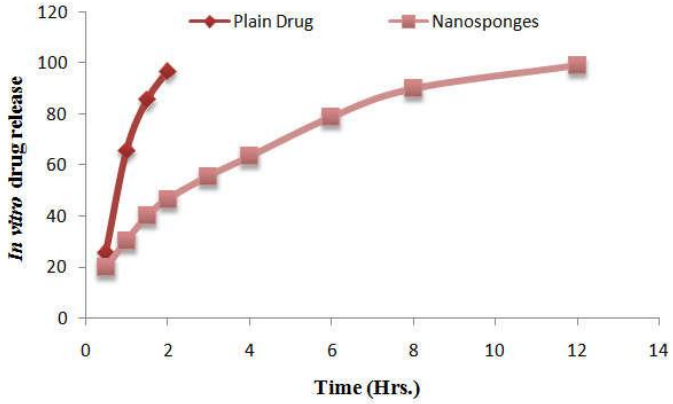

Figure 8: Graphical Representation of *in vitro* drug release study

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

Time (h)	the 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

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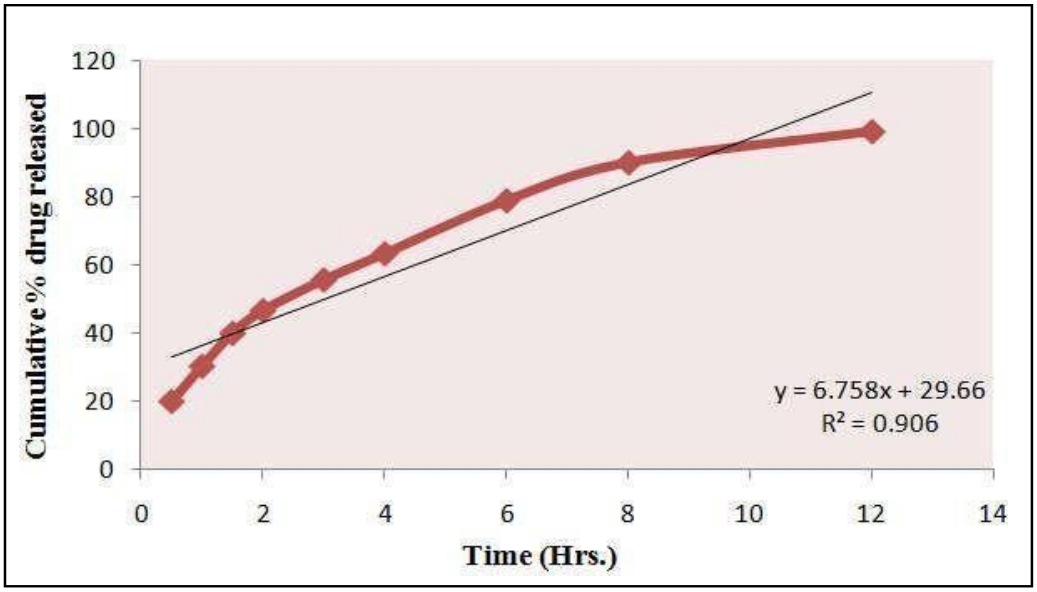

Figure 9: Cumulative % drug released Vs. Time (Zero Order Kinetics)

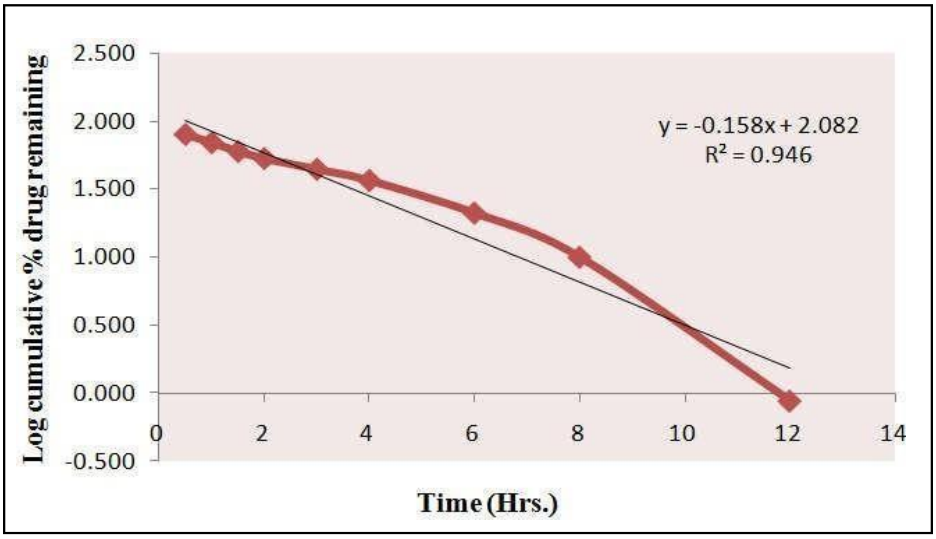

Figure 10: Log cumulative % drug remaining Vs. Time (First Order Kinetics)

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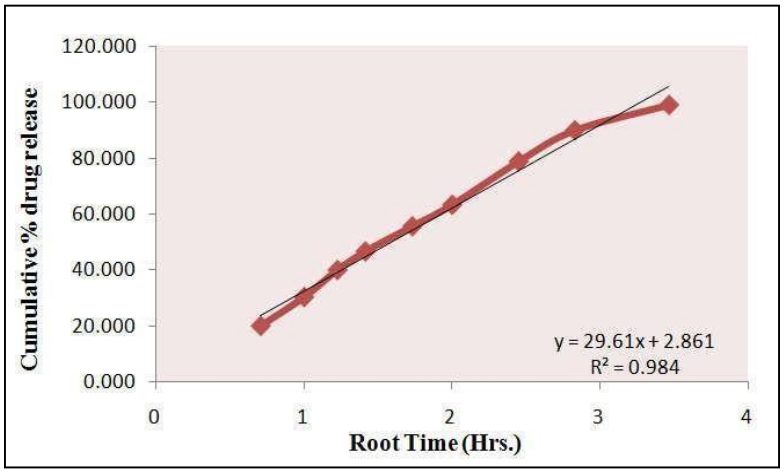

Figure 11: Cumulative % drug release Vs. Root time (Higuchi Release Kinetics)

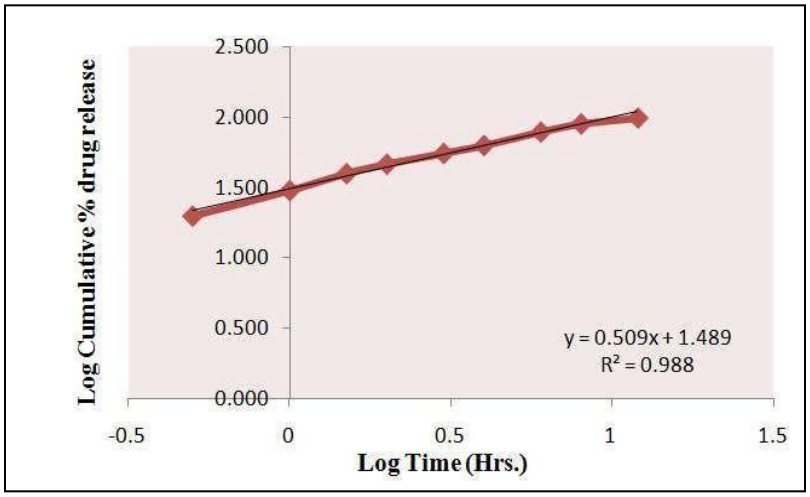

Figure 12: Log Cumulative % drug release Vs. Log time (Korsmeyer Peppas Model)

Regression Analysis- Once the regression constants have been analyzed, it was revealed that the Korsmeyer Peppas model's "r" value, which was the highest, yields 0.988, demonstrating that the kinetics of drug release from preparations were determined to follow this model.

Table. 10 Regression analysis data of Cephalexin loaded nanosponges

Batch	Zero Order	First Order	Higuchi	Korsmeyr Peppas
	R^2	R^2	R^2	R^2

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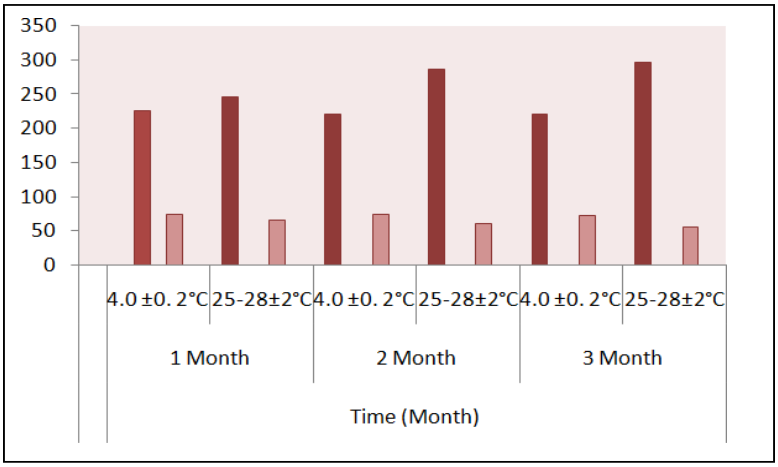
F3	0.906	0.946	0.984	0.988

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

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 three 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



ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 01, 2021

Figure 13: Graphical Representation of stability study of Optimized formulation of nanosponges F3

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. The release profile suggested continuous regulated release up to 12 hours. Since the nanosponge systems have been shown to have a good potential for sustained drug release, they can be advantageous in 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 thriving in the therapy of ulcer and related conditions.

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ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 01, 2021

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