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Formulation, Evaluation and *In-Vitro* Characterization of Fenoprofen Loaded Nanosponges

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R. Gangadhara[1*], K. P. Satheesh[1], N. Devanna[2], T. Shobha Rani[3]

[1]Department of Chemistry, Jawaharlal Nehru Technological University, Anantapur, ATP, A.P., India,*

[2]Director, Oil Technological & Pharmaceutical Research Institute, ATP, A.P., India.

[3]Department of Chemistry, Dravidian University, Kuppam, Chittoor (DT), A. P., India.

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ABSTRACT

The present research was aims to assess the applicability of Fenoprofen nanosponge-loaded topical gel in delivering drug through skin into the body. For this purpose, Fenoprofen was entrapped in a nanosponge and incorporated into the gel then evaluated. A Fenoprofen nanosponge was formulated using Poloxamer, polymer, and β-Cyclodextrin by a solvent evaporation method. In this connection, the solubility, calibration of drug and drug entrapment efficiency of the nanosponges were investigated. Particle size analysis and surface morphology of nanosponges were performed. Also, physicochemical characteristics, drug content uniformity and *in-vitro* release studies have been evaluated for obtained nanosponge loaded hydrogel. The particle size was found in the range of 200-410 nm and entrapment efficiency was obtained in the ranges from 95.78 to 98.42%. Based on the characterization, nanosponges with high entrapment efficiency and least particle size (F3) were selected for gel formulation. Total 6 formulations are developed to know the sustained drug release by using Carbopol & HPMC K4M and evaluated for physicochemical studies and which show satisfactory results. From the nanosponge loaded hydrogel-drug release studies, it was observed that a formulation (F12) containing Carbopol shows maximum drug release at the end of 12 hrs than other formulations and it follows zero-order with case II transport mechanism.

INTRODUCTION

In recent years, there has been considerable emphasis given to the development of novel nanosponge-gel drug delivery systems for modifying and control the release behavior of the drugs. By incorporation into a carrier system, it is possible to alter the therapeutic index and duration of the activity of drugs[1]. Nanosponges are a novel class of hyper-cross linked polymer related colloidal structures consisting of solid nanoparticles with colloidal sizes and nano-sized cavities[2]. They enhance stability, reduce side effects, and modify drug release. The outer surface is typically porous, allowing the prolonged release of the drug. They are mainly used for topical drug delivery[3]. Conventional formulation of topical drugs accumulates excessively in the epidermis and dermis. Nanosponge prevents the accumulation of active substances in the dermis and epidermis. Nanosponge gels/systems reduce the irritation of effective drugs without decreasing their efficacy[4]. They can be used for targeting drugs to specific sites, prevent drug and protein degradation. These tiny sponges can pass to body until they encounter the specific target site and stick on the surface and began to release the drug in a controlled and predictable manner[5].

Drug delivery through the skin is one of the most promising alternative routes of drug administration which greatly helps in by passing into metabolism and other side effects upon systemic administration of drugs[6]. The greatest challenge with topical drug delivery is the barrier nature of skin that restricts the entry of most of the drugs[7]. Nanosponges can be effectively incorporated with a topical hydro gel to drug delivery system for increased drug release and drug penetration across the skin and reducing drug toxicity and improving patient compliance by prolonging dosage intervals[8].

Fenoprofen is an anti-inflammatory analgesic and antipyretic highly bound to plasma proteins. It is pharmacologically similar to aspirin but causes less gastrointestinal bleeding[9]. For this purpose, Fenoprofen was entrapped in Nanosponge and incorporated into the gel form and evaluated the *in-vitro* permeation studies[10]. The current study is aimed to prepare and evaluate a gel formulation based on Fenoprofen loaded nanosponges. Particle size, drug entrapment efficiency, and surface morphology of nanosponges were discussed in this article. In addition to this, Fenoprofen containing nanosponges loaded gel was characterized by *in-vitro* drug release and kinetic release mechanism. Also, the evaluated physicochemical studies for hydrogels.

MATERIALS AND METHODS:

MATERIALS

Fenoprofen was obtained as a gift sample from Sun Pharma, Hyderabad, India. Ethyl cellulose, Carbopol; HPMC K4M was procured from BMR Chemicals, Hyderabad. Polyvinyl alcohol, Dichloromethane, and methanol were purchased from SD fine chemicals and other suppliers. All other chemicals used were of analytical grade.

Pre-formulation study of Fenoprofen

Solubility studies

Approximately 10 mg of the compound was dissolved in 0.1 ml of each solvent at room temperature in glass test tubes. Test tubes were gently shaken and solubilities were observed. In case of any observed insoluble fraction, the known amount of solvent was further added to ascertain the solubility of the compound. After this period, the solutions were filtered, diluted and analyzed by a UV spectrophotometer. Three determinations were carried out for each sample to calculate the solubility of the drug. The results are shown in Table 1**.**

Table No. 1: Solubility studies of Fenoprofen

Buffer	Solubility (mg/ml)
0.1 N HCL	0.341
6.8 pH buffer	0.582
7.4 pH buffer	0.569
Ethanol	1.689
Methanol	2.045

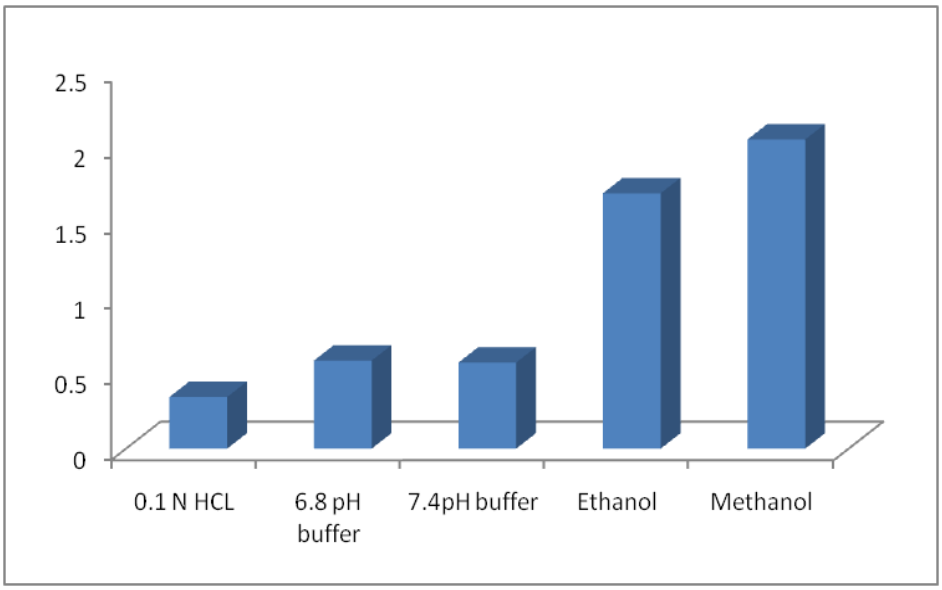


Figure No. 1: Solubility studies of Fenoprofen

It was observed that in Table 1 & Figure 1, more solubility is found in methanol i.e., 2.04 mg/ml while the lowest solubility can be seen in 0.1 N HCl buffer (0.34mg/ml) and in ethanol also find good solubility. From the above, it is understood that the solubility in 6.8 pH and 7.4 pH buffer are more or less equal. Among all the buffers, methanol, 6.8 pH, and 7.4 pH were suitable for Fenoprofen drug soluble and acquiring calibration.

Calibration curve of Fenoprofen in 6.8 pH buffer

Beer Lambert's plot of drug sample was prepared in 6.8 pH buffer. The results/curve on U.V. Spectrum of Fenoprofen (λ-max) in 6.8 phosphate buffer as shown in the Figure 2. A linear relationship was obtained between concentration (0-30 µg/ml) and the absorbance of the drug in 6.8 pH buffer with an R^2 value of 0.9991 at 273 nm is shown in the calibration curve shown in Figure 3 and line equation, y=0.0326x+0.0132. The concentration of the drug and corresponding absorbance values are mentioned in Table 2. The spectra absorbance value increases as increase of drug concentration. In view of calibration results, the 6.8 pH buffer has opted for Fenoprofen drug dissolution.

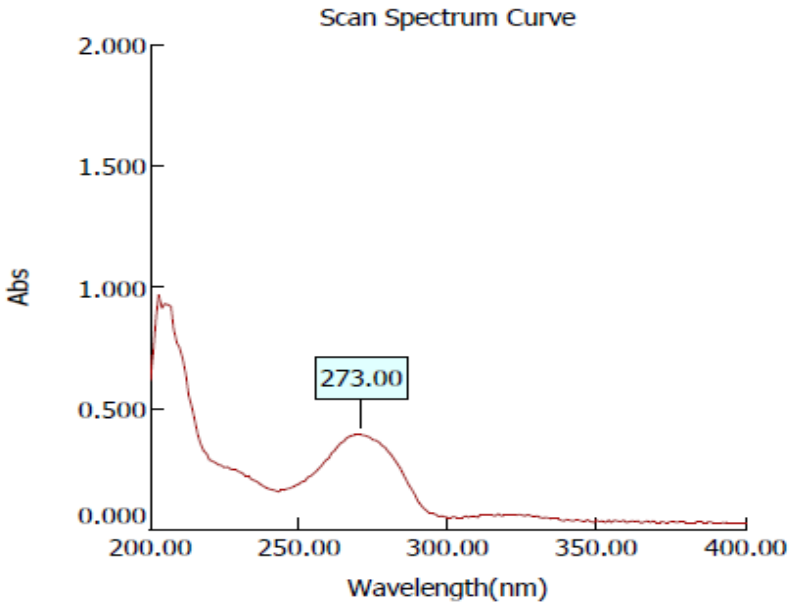


Figure No. 2: U.V. Spectrum of Fenoprofen (λ-max) in 6.8 phosphate buffer

Table No. 2: Calibration of Fenoprofen in 6.8 pH buffer

Concentration (µg/mL)	Absorbance
0	0
5	0.181
10	0.341
15	0.516
20	0.673
25	0.815
30	0.987

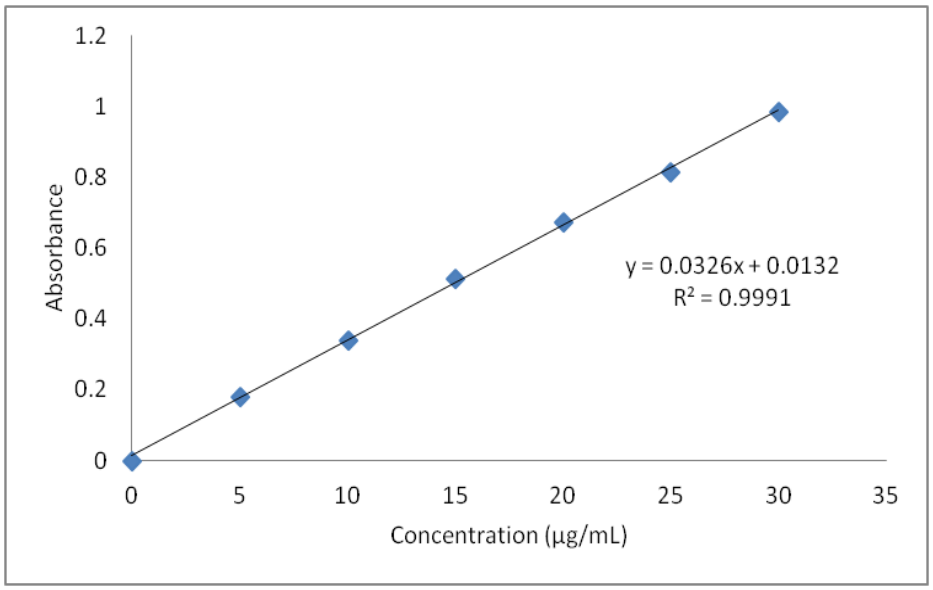


Figure No. 3: Calibration curve of Fenoprofen in 6.8 pH buffer

Calibration curve of Fenoprofen in 7.4 pH buffer

The solubility study of the drug sample was studied in different types of solvents and data shows that the drug was very slightly soluble in water, soluble in phosphate buffer (pH-7.4), and freely soluble in the rest of another solvent which is sown in Table 1**.** It was understood that from Table 3, the concentration of the drug increases, and the absorbance value also increases. In this view, the 7.4 pH buffer was optimized for drug dissolution.

Table No. 3: Calibration of Fenoprofen in 7.4 pH buffer

Concentration (µg/mL)	Absorbance
0	0
5	0.159
10	0.324
15	0.498
20	0.653
25	0.795
30	0.967

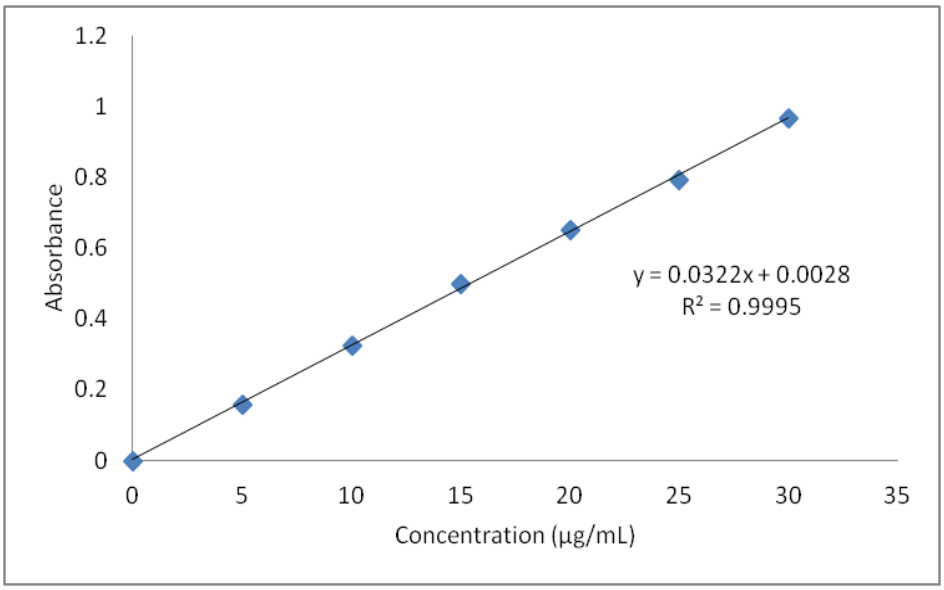


Figure No. 4: Calibration curve of Fenoprofen in 7.4 pH buffer

A linear relationship was acquired between concentration (0-30 µg/ml), and the absorbance of the drug in phosphate buffer (pH 7.4) with an R^2 value of 0.9995 at 276 nm is shown in the calibration curve of Figure 4 and line equation, y= 0.0322x+0.0028. Based on these results, a phosphate buffer pH 7.4 was chosen and calibrated for dissolution of the drug.

Formulation of Fenoprofen nanosponges

Nanosponges were prepared using different proportions of Poloxamer, β-cyclodextrin as rate retarding polymer, and co-polymers like polyvinyl alcohol by a solvent evaporation method. Disperse phase consisting of Fenoprofen and requisite quantity of polymer dissolved in 20 ml solvent (Methanol: Dichloromethane) was slowly added to a definite amount of PVA in 100ml of the aqueous continuous phase, prepared by using a magnetic stirrer. The reaction mixture was stirred at 1000 RPM on a magnetic stirrer for 2 hours and kept on a hot plate up to complete removal of organic solvent from the formulation. The nanosponges formed were collected by filtration through Whatmann filter paper and dried[9]. The prepared nanosponge formulations are listed in Table 4.

Table No. 4: Formulation of Fenoprofen loaded nanosponges

Excipients	F1	F2	F3	F4	F5	F6
Fenoprofen (g)	1	1	1	1	1	1
Poloxamer (g)	0.5	1	1.5	--	--	--
β-cyclodextrin (g)	--	--	--	0.5	1	1.5
PVA (mg)	500	500	500	500	500	500
DCM: methanol	20	20	20	20	20	20
Water (mL)	100	100	100	100	100	100

Formulation of Fenoprofen nanosponge loaded hydrogel[11]

The polymer was initially soaked in water for the gel for 2 hrs and dispersed by agitation at 600 rpm by using a magnetic stirrer to get smooth dispersion. Tri ethanolamine (2% v/v) was added to neutralize the pH. The previously prepared optimized nanosponge was thereby added and permeation enhancers (Propylene glycol) were added as a methanolic solution for the aqueous dispersion. The composition of nanosponge gels is shown in Table 5.

Table No. 5: Composition of drug-nanosponge gels by solvent evaporation method

Ingredients	F7	F8	F9	F10	F11	F12
Optimize Nanosponge (% w/w)	1%	1%	1%	1%	1%	1%
HPMC K4M (gm)	1	2	3	--	--	--
Carbopol (gm)	--	--	--	1	2	3
Propylene Glycol (ml)	1	1	1	1	1	1
Distilled Water (ml)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Tri ethanol amine (2%v/v) (ml)	1	1	1	1	1	1

EVALUATION OF FENOPROFEN-NANOSPONGES

Scanning electron microscopy[12]

The morphological features of prepared nanosponges are observed by scanning electron microscopy at different magnifications. The samples were then randomly scanned and photomicrographs were taken at good resolution. From the resulting image, the particle size and shape were determined.

Particle size analysis[13]

The particle size of nanosponges was measured by particle size instrument [Horiba scientific SZ100]. For the measurement, 100µl of the formulation was diluted with a proper quantity of PBS pH 6.8, and vesicle diameter and zeta potential were determined. The sample was scanned for the determination of particle size. Each sample was measured three times, after which, the average value was used for further calculations.

Entrapment efficiency[14]

The amount of drug present in the Fenoprofen loaded nanosponges was determined by taking 10 mg of Fenoprofen-loaded nanosponges in 10 ml of phosphate buffer pH 7.4 and kept aside for 24 hrs and then after 24 hrs the solution was stirred using a magnetic stirrer at 1000 rpm for 30 min and filtered. The filtered solution absorbance was measured by using a UV Spectrophometer at 273 nm. It can be calculated by using the following formula.

$$\text{Entrapment efficiency} = \frac{\text{Practical yield}}{\text{Theoretical yield (drug + polymer)}} \times 100$$

In-vitro Characterization of Fenoprofen-Nanosponge loaded hydrogel

Drug content uniformity[15]

Drug content uniformity of prepared nanosponge gels was carried out using the spectrophotometric method. The assay of these formulations was carried out by pipetting 1 ml of all optimized formulations, and it was diluted up to 100 ml of pH 7.4. The formulations were shaken for 2-3 minutes until it gives a clear gel solution. The solution was filtered

through Millipore membrane filtrate (0.45um) and the drug content was determined by measuring the absorbance at 273 nm using a UV-Visible spectrophotometer. The measurement of the % of drug content of each formulation was carried out in triplicate and the average values are reported.

$$\% \text{ Drug content} = \frac{\text{Actual concentration of drug in the formulation}}{\text{Theoretical concentration of drug}} \times 100$$

Measurement of pH[16]

The pH of the prepared in-situ gelling system after the addition of all the ingredients was measured using a pH meter. One gram of gel was dissolved in 100 ml of distilled water and stored for two hours. Then, pH measurement was performed. The measurement of pH of each formulation was done in triplicate and average values were calculated.

Rheological studies

It is an important factor to determine the residence time of the drug in the eye by considering the viscosity of the instilled formulation. The prepared solutions were allowed to gel at physiological temperature and then the viscosity of different nanosponge gel formulations determination was carried out by using Brookfield viscometer (Brookfield DV^{+} Pro, Brookfield Engineering Laboratories, and Middleboro, MA, USA).

***In-vitro* Drug release studies of nanosponge gel formulations[17]**

The *in-vitro* evaluation/diffusion studies of the prepared gels can be carried out in Franz diffusion cell for studying the dissolution release of gels through a cellophane membrane. Gel sample (1g) containing 1% w/w of Fenoprofen was taken in cellophane membrane and the diffusion studies were carried out at 37 ± 1^{0} using 40 ml of phosphate buffer (pH 7.4) as the dissolution medium. One milliliter of each sample was withdrawn periodically at regular intervals of time and each sample was replaced with an equal volume of fresh dissolution medium. The drug analysis was done using UV Spectro photometrically at 273 nm. The dissolution studies were performed and the mean cumulative percentage of Fenoprofen was calculated and plotted against time.

Kinetic analysis of drug release[18]

In the present research, to study the drug release mechanism of nanosponge gel formulations, the release data of selected nanosponge formulations were fitted to zero-order, first-order, Higuchi and Korsmeyer Peppas kinetic models and release kinetic studies have been described. The kinetic model with the highest coefficient of correlation (R^2) value was considered to be the best fit model for describing the drug release from the nanosponge hydrogels.

RESULTS AND DISCUSSION:

The present study reported the development of Fenoprofen loaded nanosponges using cross-linker, and polyvinyl alcohol by the solvent evaporation method. In this connection, the morphology, particle size distribution, drug entrapment efficiency of nanosponges were evaluated then optimized the formulation and used for further process of analysis. The nanosponge-based gel formulation was prepared using Carbopol & HPMC K4M and estimated for pH, viscosity, drug content uniformity, *in-vitro* drug release, and release kinetics of Fenoprofen loaded nanosponge gels.

Morphology determination by scanning electron microscopy (SEM)

In this study, the drug-loaded nanosponges were prepared by solvent evaporation method and their surface morphology was determined by SEM analysis. The representative SEM photographs of the nanosponges are shown in Figure 5. It was observed that the nanosponges were spherical, and uniform with no drug crystals on the surface. The shape of the nanosponges affects the surface area and surface area per unit weight of spherical nanosponges. The irregular shape of the particles may affect the dissolution rate present in the dissolution environment. The size of the nanosponges was ranged from 113 -210 nm can be seen in Figure 5.

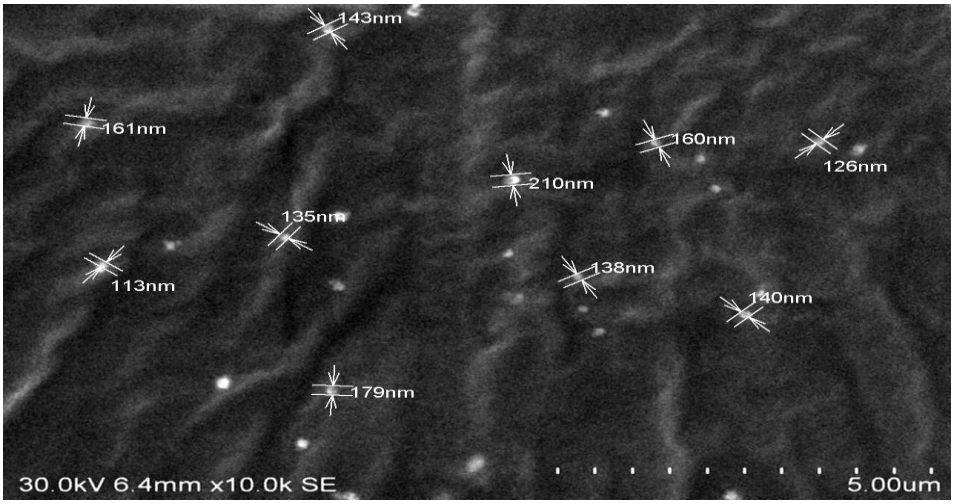
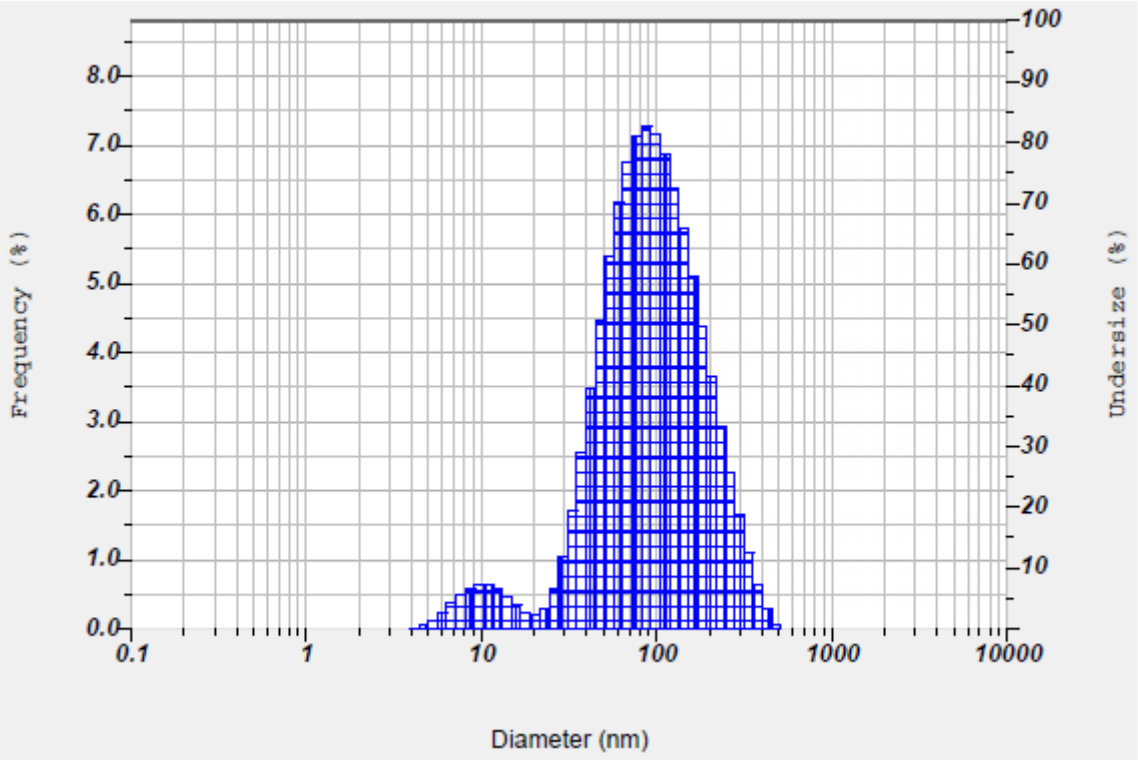


Figure No. 5: Nanosponges structure of optimized formulation (F3) [SEM]

Particle size distribution and analysis

The particle size distribution was characterized for Fenoprofen loaded nanosponges. The particle size distribution of Fenoprofen loaded nanosponge for F3 formulation is shown in Figure 6. The particle size of the optimized nanosponge formulation (F3) was found to be 86.4 nm. The mean particle size was found to increase with the decrease in polymer amount because zeta potential plays a major role. The mean particle size of nanosponge formulations should be in the range of 10-300 nm. As the average particle size of the F3 formulation nanosponge was found to be less than 100 nm, and PI is 0.26 nm, the pore size of these nanosponges could be smaller than 1 nm. Due to the smaller pore size bacteria cannot penetrate it which makes the nanosponges can self sterilized[19].

A nanosponge product with a size of 86.4 nm (F3) was chosen for topical gel formulation to avoid a gritty feeling in the final product[20]. Moreover, the nanosponge of formulation F3 showed promising results in parameters such as Drug content/uniformity, entrapment efficiency, and average particle size. An increase in the concentration of polymer leads to an increase in the particle size of nanosponges [21].



Calculation Results

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	0.05	10.6 nm	3.3 nm	10.9 nm
2	0.95	114.3 nm	72.1 nm	87.5 nm
3	—	— nm	— nm	— nm
Total	1.00	109.3 nm	73.8 nm	87.5 nm

Cumulant Operations

Z-Average : 86.4 nm
PI : 0.263

Molecular weight measurement

Molecular weight : ---
Mark-Houwink-Sakurada parameters : ---

Figure No. 6: Particle size distribution of Fenoprofen loaded nanosponges F3 formulation

Entrapment efficiency of Fenoprofen nanosponges

It is calculated to know about the efficiency of any method, thus it helps in the selection of the appropriate method of production. After the preparation of formulations, the practical yield was calculated as nanosponges recovered from each preparation with the sum of starting material (Theoretical yield).

Table No. 6: Entrapment efficiency of F1-F6 formulations

Formulation code	% Entrapment efficiency
F1	96.52±1.02
F2	95.78±0.08
F3	98.42±1.11
F4	97.63±0.06
F5	98.25±0.58
F6	98.01±0.12

The **%** of entrapment efficiency is calculated for F1-F6 formulations using the above-mentioned formula and the results acquired are presented in Table 6. The entrapment efficiency was measured for formulations F1-F6 and the amount of drug entrapped was found to be in the range of 95.78 to 98.42%. It was seen from Table 6 and the percentage of entrapment efficiency was found to be more for F3 formulation (Fenoprofen: Poloxamer, ratio 1:1.5) which is 98.42% and the less entrapment efficiency was found for F2 formulation (Fenoprofen: Poloxamer, ratio 1:1). The entrapment efficiency was affected for the drug and the variation in entrapment efficiency was due to the changes in the polymer/cross-linker concentration and difference in the degree of cross-linking. The higher efficiency for formulation means a good amount of drug was encapsulated.

Results and Discussion of Fenoprofen-Nanosponge loaded hydrogel

Drug content uniformity of nanosponge gels

The drug content of the formulated nanosponge gels was found satisfactory ranging from 95.25 to 98.96 % and given in Table 7. This is considered an acceptable range for topical drug release and reduces skin irritation.

Table No. 7: Drug content of formulated gels

Formulation Code	Drug content
F7	96.35±0.22
F8	98.96±0.18
F9	95.27±0.58
F10	95.25±0.36
F11	96.34±0.22
F12	98.04±1.12

PH determination of drug loaded nanosponge gels

The Fenoprofen nanosponge gels were found to have a smooth appearance and texture. The pH of all nanosponge gels was found to be between 7.2 and 7.6 that lie in the normal pH range of skin 4.0 to 6.8. Hence the preparations were non-irritant. An increase in pH values may lead to skin irritation. All the prepared gels were homogenous and clear. The pH values of all nanosponge gel formulations were tabulated in the following Table.

Table No. 8: PH measurements of all formulations (F7- F12 nanosponge gels)

Formula	pH
F7	7.2±0.22
F8	7.6±0.16
F9	7.4±0.24
F10	7.3±0.85
F11	7.4±0.22
F12	7.4±0.34

All the formulations have satisfactory pH ranging from 7.2 to 7.6, which is acceptable for topical delivery.

Rheological studies of nanosponge gel formulations

The viscosity of the formulations was evaluated by a Brookfield DV 3 programmable rheometer, using varying angular velocities or shear rate. The viscosity studies for all nanosponge gel formulations F7-F12 were carried out and viscosity was noted on cps. The viscosities of all formulations are shown in Table 9. The viscosity of formulations F7- F12 ranged from 414.0-1327.0 cps at 100 rpm. As the angular velocity increased, viscosity decreased which indicating no thixotropic property.

Table No. 9: Viscosity studies of formulations [F7-F12]

Angular Velocity (rpm)	F7	F8	F9	F10	F11	F12
10	675±1.08	892±1.02	968±1.08	1342±1.22	1522±1.69	1654±1.28
100	414±1.25	521±0.85	757±1.59	1002±1.04	1245±1.24	1327±1.08

***In-vitro* Drug release studies of nanosponge gel formulations**

The diffusion studies of the prepared gels can be carried out in Franz diffusion cell for studying the dissolution release of gels through a cellophane membrane. The drug analysis was done using UV Spectro photometrically at 273 nm. *In-vitro* release studies of Fenoprofen nanosponges for a period of 12 hrs were carried out to formulations F7 to F12 and the percentage of drug release of nanosponge gels as listed in Table 10. The results obtained in *in-vitro* release studies were plotted as percent cumulative drug Vs time and shown in Figure 7.

Table No. 10: Percentage of drug release of gels loaded with Fenoprofen nanosponges (F7-F12)

Time (hrs)	% of Cumulate Drug release					
	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
1	30.42±0.18	26.04±0.42	23.54±0.11	32.04±1.05	20.54±0.14	16.24±0.54
2	39.86±0.05	35.86±0.52	32.15±0.12	40.96±0.22	30.56±0.19	23.48±0.26
3	47.15±0.48	46.79±0.44	42.15±0.45	49.86±0.19	39.86±0.58	32.17±0.35
4	59.26±0.12	52.08±0.16	50.24±0.22	56.32±0.18	47.25±0.36	39.52±0.33
5	70.25±0.26	60.56±0.27	59.35±0.31	62.75±0.18	56.35±0.35	46.72±0.64
6	82.68±0.22	72.86±0.16	65.12±0.64	69.34±0.11	68.53±0.28	60.21±0.28
7	89.76±0.54	83.94±0.14	69.53±0.19	78.25±0.16	76.31±0.92	69.86±0.33
8	98.45±0.19	91.05±0.22	82.35±0.27	84.07±0.19	83.62±1.00	75.01±0.27
9		97.02±0.16	92.34±0.82	96.24±0.28	90.75±0.19	80.34±0.19
10			97.21±0.11		98.04±0.36	89.63±0.48
11						93.34±0.66
12						98.19±0.72

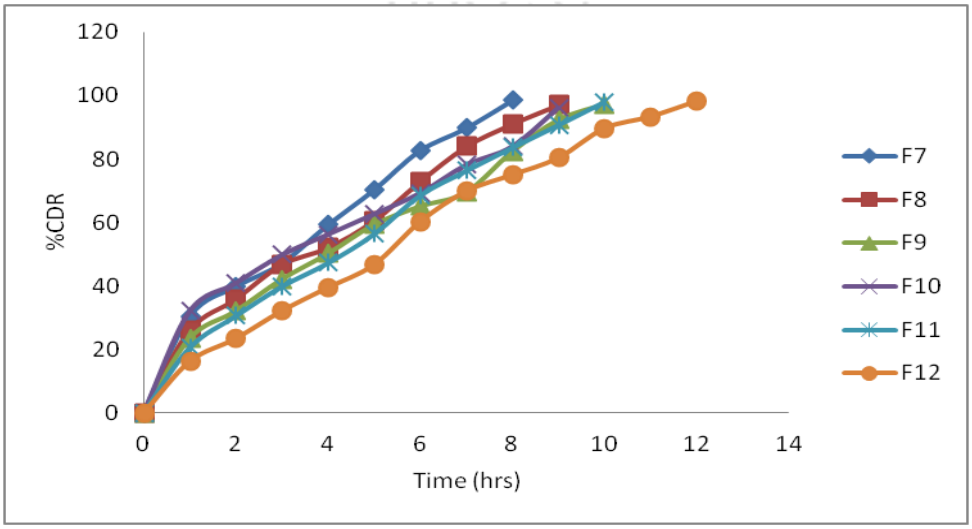


Figure No. 7: Percentage of cumulative drug release graph of F7- F12

In the 12 hrs duration, the release was found to be in the ranges from 96.24 to 98.45% for formulations F7 to F12 which can be observed in Table 10 and Figure 7. It was observed that from Table 10, the more percentage of drug release was found to be 98.45% for F7 formulation in 8 hrs period while lowest is 96.24% at 9 hrs, this may be accredited because of

the high solubility of the drug. The average drug release was seen to F9 formulation i.e., 97.21 % for 10 hrs period spans whereas for F12 formulation 98 % of drug release was observed up to 12 hrs. Moreover, the release profiles of all formulations were significantly different from that of pure drug. As results showed that F12 gel formulation sustained the release for more duration when compared to others (Table 10, and Figure 7). The concentration of polymer played an important role in the release characteristics [22].

Release kinetics of Fenoprofen nanosponges loaded gels

The *in-vitro* drug release data of all the Fenoprofen loaded nanosponge hydrogel formulations were subjected to the goodness of fit test by linear regression analysis according to zero-order and first orders kinetic equations, Higuchi's and Korsmeyer–Peppas models to ascertain the mechanism of drug release. The plot/profiles were obtained between points in time in hrs on X-axis Vs cumulative % drug release on Y-axis of selected formulation as shown in Figures 8-11. The slopes and regression coefficient values (R^2) of various mathematical models for the optimized formulation, 0.9862, 0.8626, 0.9569, 0.7401 for zero-order, first order, Higuchi and Peppas model respectively. Good linearity was observed with the zero-order and regression coefficient value close to 1. Hence this formulation is best fitted into the zero-order release kinetics model and the regression coefficient value shows linearity as shown in Figure 8. The mechanism of drug release was found to be a case II transport mechanism.

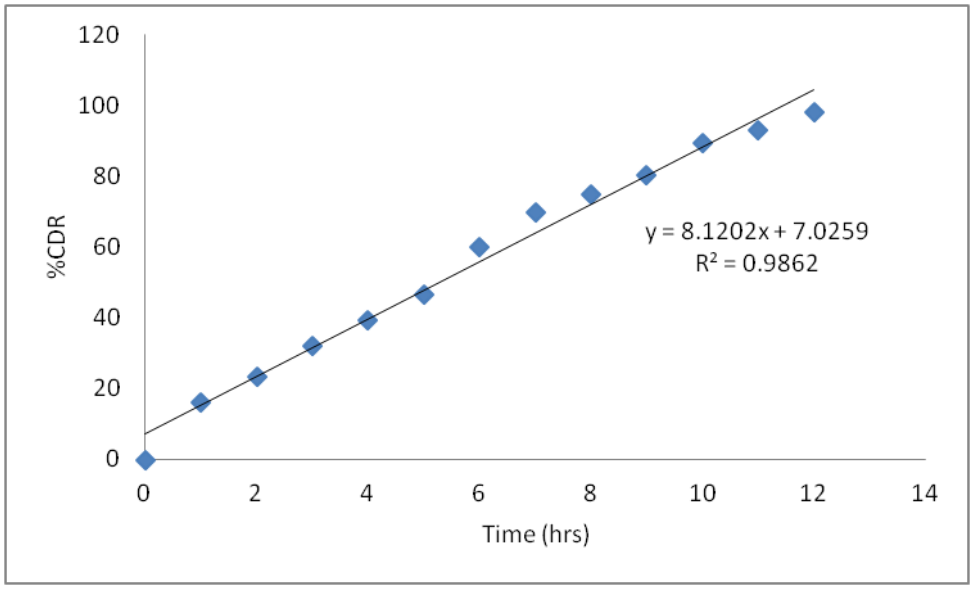


Figure No. 8: Zero-order release kinetics profile of formulation F12

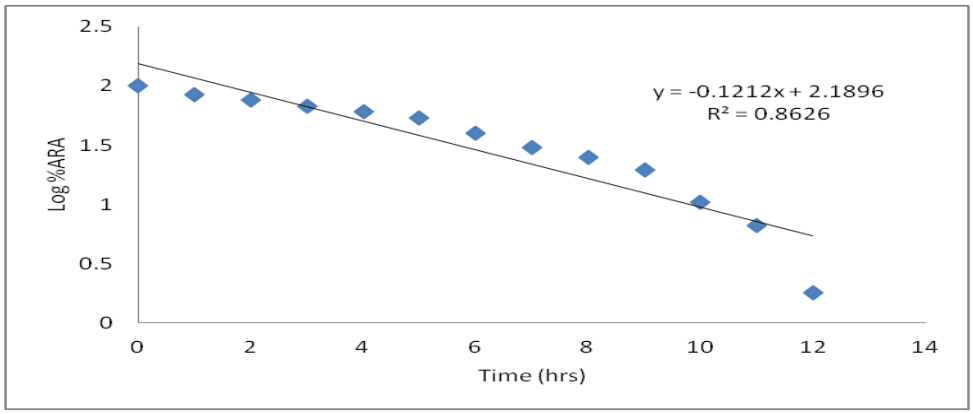


Figure No. 9: First-Order release kinetics plot for F12 formulation

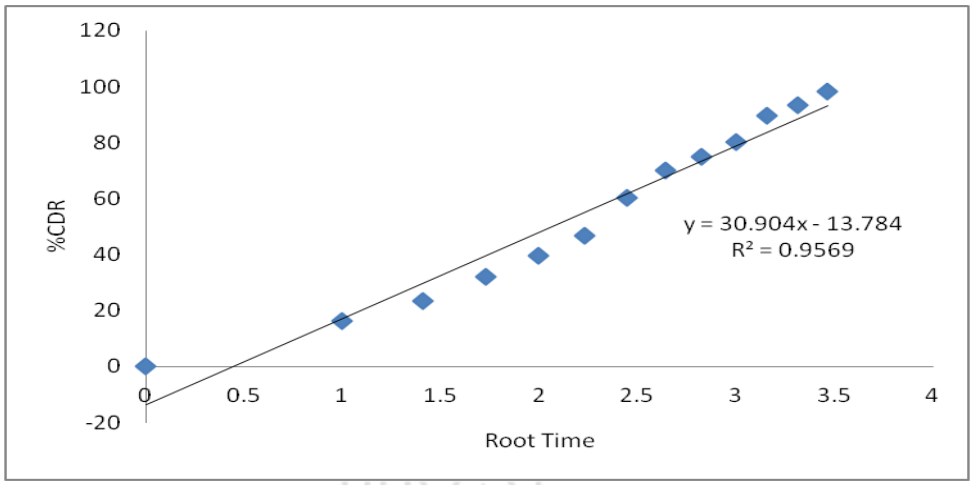


Figure No. 10: Higuchi release kinetics plot for F12 formulation

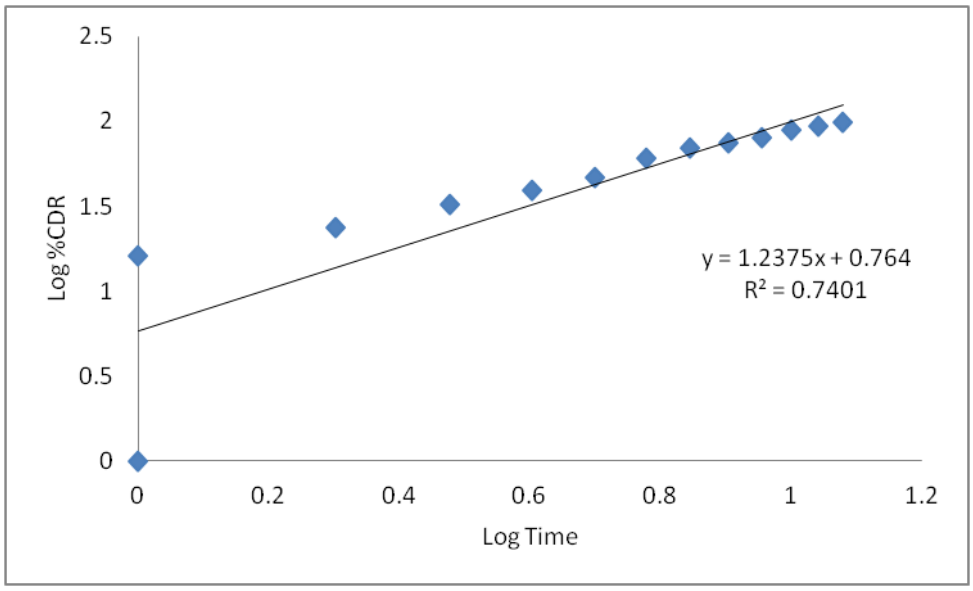


Figure No. 11: Peppas release kinetics plot for F12 formulation

CONCLUSION

The present work was aimed to develop Fenoprofen nanosponges loaded gels for targeting drug delivery systems. The solvent diffusion method used for the preparation of the nanosponges was simple, reproducible, and rapid. Fenoprofen nanosponges were formulated using Poloxamer and β-Cyclodextrin with different ratios. The developed nanosponges were further evaluated for particle size, morphology, in which F3 formulation containing Poloxamer shows the spongy structure with minute pores and shows good entrapment efficiency than remaining formulations. So further optimized F3 formulation was incorporated as a topical gel by using 3 different rates retarding polymers in which formulation (F12) containing Carbopol revealed sustained drug release up to 12 hrs and follows zero-order with case II transport mechanism. Based on the observations the optimized formulation (F12) was safe and effective for topical use as Fenoprofen nanosponge loaded gel.

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