RESEARCH PAPER

Enhanced Drug Release And Physicochemical Characterization Of Enalapril Nanosponges Using Emulsion Solvent Diffusion

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ABSTRACT

In the field of healthcare, nanotechnology has emerged as a transformative area with a wide range of applications, particularly in targeted drug delivery systems. The advancements in solubility, stability, bioavailability, and controlled release profiles achieved through nanoscale engineering of drug carriers enable more effective and patient-friendly treatments. The unique porous, sponge-like structure of nano-sponges facilitates high drug loading and extended release. This project aimed to develop and evaluate Enalapril-loaded polymeric nano-sponges to enhance the solubility and, critically, to achieve a sustained-release profile for Enalapril, an ACE inhibitor used for managing hypertension whose efficacy is limited by variable oral bioavailability and short dosing frequency. The nano-sponges were successfully fabricated using the emulsion solvent diffusion method with cross-linking agents and polymers, achieving optimal physicochemical properties. Comprehensive characterization included Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM), and particle size analysis. DSC analysis confirmed the presence of Enalapril within the formulation, exhibiting a distinct endothermic peak at 154.3ºC. SEM images revealed a smooth surface morphology and spherical shape. Particle size analysis showed formulations ranging from 175.2nm (F-10) to 684.8nm, with most promising results exhibiting homogeneous dispersion, such as the Polydispersity Index (PDI) of 0.140 (F-9). Zeta Potential values were consistently negative, ranging up to -28.92 mV (F-8), suggesting reasonable physical stability. The optimized formulations demonstrated high loading capacity, with formulation F-6 achieving the highest values of 92.87% drug content and 80.23% drug entrapment efficiency. In vitro dissolution studies confirmed the system's success in providing a significantly sustained release profile, extending drug release over 12 hours compared to the immediate release kinetics of the pure drug. This high performance, evidenced by the optimal physicochemical properties and high entrapment efficiency, strongly supports the potential for reduced dosing frequency and improved patient compliance in the long-term management of hypertension.

Keywords: Enalapril, Polymeric Nanosponges, Emulsion Solvent Diffusion, Sustained Release, Drug Entrapment Efficiency, Zeta Potential, Hypertension, Controlled Drug Delivery.

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1. INTRODUCTION

Designing and modifying materials and systems with dimensions usually between 1 and 100 nanometers are known as nanotechnology, and it has the potential to revolutionize several scientific fields. Nanotechnology has transformed drug delivery, diagnostics, and personalized therapy in the biomedical area by making it possible to create carriers that improve the solubility, stability, and targeted distribution of therapeutic substances that would otherwise be poorly soluble or

unstable. In addition to traditional drugs, nanosponges have shown encouraging outcomes in the delivery of proteins and enzymes, the creation of vaccines, anticancer therapy (with up to three to five times increased efficacy), and the immobilization of enzymes. Nanosponges are prepared using a variety of synthetic methods, including emulsion solvent diffusion, solvent evaporation, hyper-crosslinking of cyclodextrins, and ultrasound-assisted processes. The ratio of polymer to crosslinker is crucial in influencing encapsulation efficiency and release kinetics. Drug loading is typically accomplished through solvent diffusion or dispersion.

While nanoscience investigates phenomena at the molecular and atomic levels, nanomedicine, a significant subgroup of this subject, concentrates on the therapeutic and diagnostic applications of nanoscale materials. Because these systems can increase therapeutic efficacy while reducing systemic toxicity, they have proven very useful in the treatment of malignancies, cardiovascular illnesses, respiratory conditions, and disorders of the central nervous system (CNS). To accomplish site-specific drug administration and sustained release, a wide range of nanocarriers have been produced, including polymeric nanoparticles, solid lipid nanoparticles, magnetic nanoparticles, dendrimers, carbon nanotubes, metallic nanoparticles, and nanosponges. A kind of extremely porous, cross-linked colloidal carriers known as polymeric nanosponges can encapsulate both hydrophilic and lipophilic drugs, enhancing their solubility, bioavailability, and therapeutic efficacy. Their special three-dimensional structure has surface functional groups that allow chemical modification for targeted distribution, and inside cavities that can trap drug molecules. Numerous benefits are provided by nanosponges, such as regulated and prolonged drug release, resistance to deterioration, improved stability over a broad pH and temperature range, and less frequent dosing.

One of the most common cardiovascular conditions in the world, hypertension significantly increases morbidity and death through consequences like myocardial infarction, heart failure, and stroke. Even though there are many antihypertensive drugs available, P-glycoprotein (P- gp) efflux, substantial first-pass metabolism, low oral bioavailability, and poor water solubility frequently restrict their therapeutic efficacy. Patient compliance is decreased because of these pharmacokinetic obstacles, which need frequent dosage. Drug delivery based on nanotechnology provides a novel solution to these problems. Antihypertensive drug encapsulation in nanoscale carriers (~100 nm) improves absorption, guards against enzyme breakdown, and encourages site-specific targeting. Nanocarrier-based approaches, such as nanoemulsions, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), polymeric nanoparticles, and nanosponges, provide significant advantages for prolonged and regulated drug delivery because many antihypertensive drugs fall under BCS Class II. Nanocarrier-based techniques, such as nanoemulsions, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), polymeric nanoparticles, and nanosponges, provide significant advantages for prolonged and regulated drug release because most antihypertensive drugs fall under BCS Class II. Biopharmaceutics Classification System (BCS) Class II drugs, which have high permeability and poor water solubility, benefit greatly from these nanostructures.

Angiotensin-converting enzyme (ACE) inhibitors like enalapril maleate, a prodrug of enalaprilat, are frequently used to treat heart failure and hypertension. Despite its therapeutic potential, enalapril's oral bioavailability is still below ideal (around 40%) because of its high first-pass metabolism, poor water solubility, and vulnerability to hydrolytic degradation. Variable absorption decreased therapeutic efficacy, and the requirement for frequent dosage to maintain constant plasma concentrations are the outcomes of these constraints. Therefore, it is crucial from a therapeutic standpoint to design an enhanced drug delivery system that may enhance the dissolving rate, stability, and controlled release of enalapril.

2. MATERIAL AND METHODS

2.1 Materials

Dhamtec Pharma and Consultant, located in Navi Mumbai, provided a gift sample of enalapril maleate, polyvinyl alcohol, and dichloromethane. Methanol and distilled water were supplied by the central store department of the college, but ethyl cellulose was bought from Rajesh Chemicals in Mumbai. Several polymers were purchased from commercial vendors and utilized as polymeric carriers, including Eudragit S100, Ethyl Cellulose, and Eudragit L100. The aqueous phase was stabilized with Kolliphor P188 and polyvinyl

alcohol (PVA). The organic solvent was analytical-grade dichloromethane (DCM).

2.2 Preparation of Nanosponges

Nanosponges were prepared by the emulsion solvent diffusion technique using ethyl cellulose as the polymeric carrier and polyvinyl alcohol (PVA) as the stabilizing agent. The procedure was optimized to obtain uniform, discrete, and stable nanosponge particles suitable for drug delivery applications.

2.3 Screening of different polymeric carriers by preparing various batches of nanosponges

To identify the most suitable polymer for nanosponge development, various polymeric carriers—Eudragit S100, Eudragit L100, and Ethyl Cellulose (EC)—were screened along with stabilizers such as PVA and Kolliphor P188. Dichloromethane served as the organic solvent. A total of twelve formulations (F1–F12) were prepared by altering the type and concentration of the carrier polymer while keeping the stabilizer and solvent ratios constant.

Table No. 1 Formulation of nanosponges

Material	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Eudragit (mg) S100	150	200	250	300	_	_	_	_	_	_	_	_
Eudragit L100	_	_	_	_	150	200	250	300	_	_	_	_
Ethyl cellulose (EC) (mg)	_	_	_	_	_	_	_	_	50	100	150	200
Polyvinyl Alchohol (PVA) (w/v)	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	_	_	_	_
Dichloromethan (DCM) (ml)	20	20	20	20	20	20	20	20	20	20	20	20
Kolliphor P188(w/v)	_	_	_	_	_	_	_	_	0.5%	0.5%	0.5%	0.5%
Distilled Water(ml)	100	100	100	100	100	100	100	100	100	100	100	100

Table No.2 Preparation of nanosponges using Emulsion solvent Diffusion Method

Step	Operation/Phase	Input Materials & Conditions	Output/Result
1	Preparation of Organic Phase	Drug (Enalapril maleate) + Polymer (Ethyl Cellulose) dissolved in Dichlorometha	Clear Organic Solution

		ne (Organic Solvent).	
2	Preparation of Aqueous Phase	Stabilizer (PVA or Kolliphor P188, 0.5-1% w/v) dissolved in Water (Aqueous Medium).	Aqueous Solution (Temperature controlled at 25-30ºC
3	Emulsification (Formation of O/W Emulsion)	Organic Solution added dropwise to Aqueous Solution. Continuous Stirring (1000-200rpm)	Emulsion (Nanosized droplets formed)
4	Solvent Evaporation/Diffusion	The system is continuously stirred until complete evaporation of the organic solvent (Dichloromethane).	Nanosponges Suspension (Spherical, porous nanosponges)
5	Purification and Isolation	Nanosponges Suspension undergoes: Filtering, followed by Washing.	Washed Nanosponges
6	Drying	Washed Nanosponges are subjected to Lyophilization (Freeze-Drying).	Final Nanosponges Powder

Table No. 3 Formulation of Drug Loaded Nanosponges

Sr. No.	Ingredients	Formulations											
		F1	F2	F3	F4	F5	F6	F7	F8	F8	F10	F11	F12
1.	Enalapril (Mg)	100	100	100	100	100	100	100	100	100	100	100	100
2.	Ethyl Cellulose (Mg)	50	10	15	30	20	15	50	30	30	30	15	15
3.	Poly Vinyl Alcohol (mg)	100	150	200	400	300	400	100	200	400	100	200	200
4.	Dichloromethane (ml)	30	30	30	30	30	30	30	30	30	30	30	30
5.	Distilled Water (ml)	100	100	100	100	100	100	100	100	100	100	100	100

2.4 Characterization Techniques

a. **The estimation of the maximum absorbance (λmax):** Using a blank solution of phosphate buffer pH 6.8, the standard stock solution was scanned in the UV spectrophotometer between 200 and 400 nm. The highest Enalapril absorption levels were measured at 234 and 360 nm, and they were compared to the highest levels of the reference samples specified in the Indian Pharmacopoeia.

b. **Physical Characteristics:** To verify conformity with established specifications, the drug's appearance, color, and odor were assessed. The capillary method was used to determine the melting point, which offers information about the compound's identity and purity.

c. **Solubility Test:** The solubility profile of Enalapril was examined in several solvents, such as methanol, water, dichloromethane, and chloroform.

d. **Fourier Transform Infrared (FTIR) Spectroscopy:** Fourier Transform Infrared (FTIR) Spectroscopy: This technique was used to examine the chemical compatibility of Enalapril with the chosen polymers. To find any possible shifts, peaks that would suggest chemical interactions, or peaks that might disappear or form, the spectra were compared.

e. **Percentage Yield:** The practical weight of the final product was compared to the theoretical weight of each ingredient employed in the formulation to determine the prepared nanosponges' percentage yield.

f. **SEM Analysis:** Scanning electron microscopy (SEM) was used to analyse the surface morphology and structural features of the created nanosponges.

g. **Particle Size:** After being dispersed in an appropriate medium, the average particle size of the produced nanosponges was determined using Dynamic Light Scattering (DLS).

h. Zeta Potential: Zeta Potential was determined using the Horiba SZ-100 zet sizer instrument. The surface charge and electrostatic stability of the nanosponge suspension were ascertained using zeta potential analysis. Nanosponges with zeta potential value greater than 17.5 mV or less than -40.7 mV typically have high degrees of stability.

i. **Entrapment Efficiency:** Using UV-visible spectrophotometry, the amount of unentrapped Enalapril in the supernatant following centrifugation was measured to assess the drug entrapment efficiency of the nanosponge formulation.

$$\% \, Percentage \, entrapment = \frac{Entrap}{Total \, d}$$

j. In Vitro Release: The amount of unentrapped Enalapril that remained in the supernatant after centrifugation was measured using UV-visible spectrophotometry to determine the drug entrapment efficiency of the nanosponge formulation.

k. Release Kinetics: To clarify the drug release mechanism, the in vitro release data were further examined using mathematical models such the zero-order, first-order, Higuchi, and Korsmeyer–Peppas equations. According to the best-fitting model, Enalapril was released from the nanosponges via a sustained, diffusion-controlled process. This suggests that the total release process is controlled by drug diffusion across the polymeric network. Predicting formulation performance, maximizing polymer composition, and customizing release characteristics for intended therapeutic results are all made easier with an understanding of kinetic behavior.

3. RESULTS AND DISCUSSION

A comparative assessment of formulations F1–F12 (Table 1) demonstrated a substantial influence of the carrier polymer on the physicochemical attributes of the prepared nanosponges. Formulations incorporating Eudragit S100 and L100 (F1–F8) produced turbid and visually unstable dispersions exhibiting marked particle aggregation and broad particle size distributions (200–700 nm).

a. Physical Characteristics: The physical and organoleptic properties of Enalapril were evaluated to confirm its identity and suitability for formulation. The drug appeared as an amorphous, light-yellow, odorless powder, consistent with reported literature. Melting point determination using Thiele's tube method yielded a value of **142 °C**, which falls within the official range of **141–145 °C**, thereby confirming the purity and authenticity of the sample.

b. Solubility

Table No. 5 Solubility test for Enalapril in different solvents

Sr. No	Solvent	Soluble	Sparing Soluble	Insoluble
1.	Ethanol	+	-	-
2.	Dichloromethane	+	-	-
3.	DMSO	+	-	-
4.	Water	-	-	+

c. Selection of Wavelength: UV–Visible spectroscopic analysis revealed a distinct absorption maximum at 271 nm, attributed to π→π* electronic transitions of the aromatic and conjugated functional groups within Enalapril. This sharp and well-resolved peak offered superior sensitivity and reproducibility, and therefore 271 nm was selected as the analytical wavelength for subsequent quantitative estimations of Enalapril in nanosponge formulations (Figure 2).

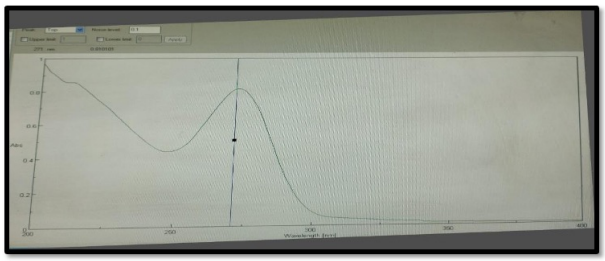

Figure No. 2 Ultra-Violet (UV) absorption spectra of Enalapril

3.4 Construction of Calibration curve of Enalapril: A calibration curve constructed over the concentration range of **3–15 µg/mL** exhibited excellent linearity, yielding a regression coefficient of **R^2 = 0.998**. These results confirm adherence to Beer–Lambert's law within this concentration range, validating the method for accurate quantification of Enalapril in dissolution and entrapment studies (Table 6, Figure 3)

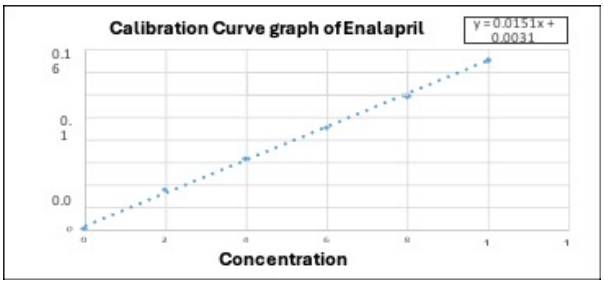

Figure No. 3 Calibration Curve graph of Enalapril API

Table No. 7 Optical parameters for calibration curve of Enalapril

Sr. No.	Parameter	Values
1.	Absorbance maximum (λmax) nm	271 nm
2.	Regression coefficient (R2)	0.9987
3.	Slope	0.0151
4.	Intercept	y= 0.0151x + 0.0031

3.5 Compatibility Studies:

a. FTIR Analysis:

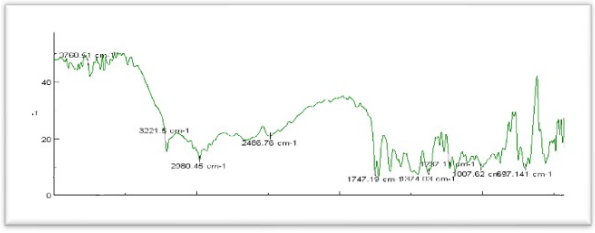

Figure No.4 FTIR analysis of the physical mixture containing Enalapril, PVA, and Ethyl Cellulose

b. DSC Studies: DSC thermogram of the optimized nanosponge formulation exhibited a broadened endothermic peak at 222.52 °C, attributed to the melting of entrapped Enalapril. The reduction in peak intensity and broadening, compared with the sharp melting endotherm of the pure drug, suggests successful entrapment and partial amorphization or molecular dispersion of Enalapril within the polymeric network. This transformation is favorable for improved dissolution performance (Figure 5).

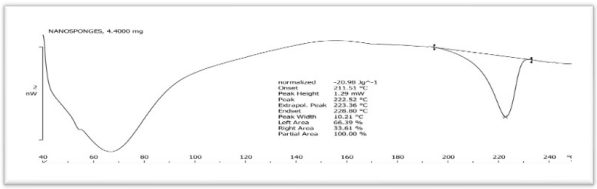

Figure No. 5: DSC Thermogram of Nanosponges (Batch F 6).

3.6 Percentage Yield: The highest yield was obtained for formulation F6 (98.16%), likely due to optimal polymer–drug ratios and efficient emulsification.

Table No. 8 Percentage yield of Enalapril nanosponges

Sr. No	Formulation code	Percentage yield (%)
1.	F1	84.3±0.32
2.	F2	91.11±0.15
3.	F3	84.45±0.34
4.	F4	90.4±0.31
5.	F5	94.17±0.26
6.	F6	98.16±0.17
7.	F7	82.64±0.48
8.	F8	78.29±0.71
9.	F9	83.3±0.43
10.	F10	92.55±0.27
11.	F11	88.06±0.63
12.	F12	75.53±0.51

3.7 Surface Morphology (SEM): SEM analysis revealed that the prepared nanosponges exhibited spherical, discrete, and uniformly formed particles with smooth surfaces and porous internal structures (Figure 6). The morphological attributes suggest improved drug entrapment capacity and enhanced solvent permeability, supporting sustained drug release from the nanosponge matrix.

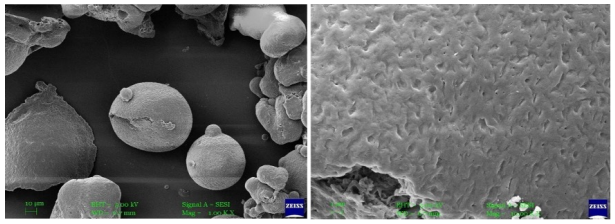

Figure No. 6 SEM images of F-6 formulation

3.8 Particle Size Analysis & Polydispersity Index (PDI): Particle size significantly influences nanosponge stability, release kinetics, and biological performance. Measurements using the Horiba SZ-100 instrument indicated that the mean particle size ranged from 175.2 nm to 684.8 nm across formulations. Specific particle sizes were recorded as follows: 658.4 nm (F1), 614.6 nm (F2), 636.4 nm (F3), 338.2 nm (F4), 205.5 nm (F5), 175.2 nm (F6), 229.8 nm (F7), 433.1 nm (F8), 396.8 nm (F9), 684.8 nm (F10), 412.9 nm (F11), and 431.6 nm (F12). PDI values ranged from 0.165 to 0.389, indicating acceptable size uniformity, with several formulations exhibiting near-monodisperse behavior (PDI < 0.3). The specific PDI value of formulations was found to be 0.199 nm (F1), 0.218 nm (F2), 0.389 nm (F3), 0.165 nm (F4), 0.300 nm (F5), 0.273 nm (F6), 0.353 nm (F7), 0.293 nm (F8), 0.174 nm (F9), 0.239 nm (F10), 0.223 nm (F11) and 0.230 nm (F12).

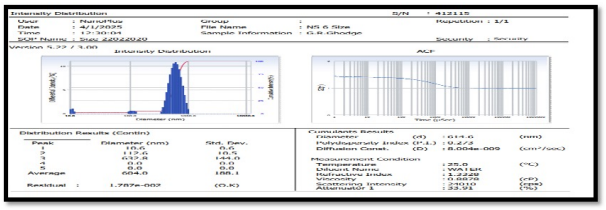

Figure No. 7: Particle Size and PDI of Nanosponges (F-6)

3.9 Zeta Potential: Zeta potential measurements revealed values ranging between −10.59 mV and −28.92 mV across formulations F1–F12. Zeta potential profiles of optimized batch F6 are illustrated in Figure .

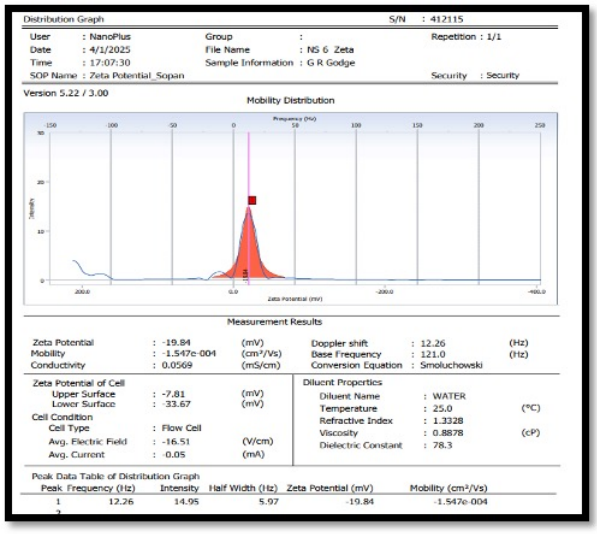

Figure No. 8: Zeta Potential of Nanosponges (F-6)

Table No. 9 List of particle size, polydispersity index, zeta potential of all batches

Sr.	Batch	Particle	Polydispersity	Zeta
1	**F-1**	658.4nm	0.199	-12.59
2	**F-2**	614.6nm	0.218	-12.27
3	**F-3**	636.4nm	0.389	-12.83
4	**F-4**	338.2nm	0.165	-10.75
5	**F-5**	205.5nm	0.300	-19.35
6	**F-6**	175.2nm	0.273	-19.84
7	**F-7**	229.8nm	0.353	-25.04
8	**F-8**	433.1nm	0.293	-28.92
9	**F-9**	396.8nm	0.174	-15.24
10	**F-10**	684.8nm	0.239	-10.59
11	**F-11**	412.9nm	0.223	-14.42
12	**F-12**	431.6nm	0.230	-15.23

3.9 Entrapment Efficiency: Entrapment efficiency of all nanosponge formulations (F1 to F12), determined spectrophotometrically, ranged from 67.15% to 80.23%. Formulation F6 demonstrated the highest entrapment (80.23 ± 0.54%), which may be associated with smaller particle size and optimal polymer–drug interactions. The uniform distribution of Enalapril within the nanosponge matrix is evident from the consistency across batches Table 10.

Table No. 10: Entrapment Efficiency of Enalapril loaded Nanosponges.

Sr	Formula	Entrapment
1.	F1	67.
2.	F2	70.
3.	F3	69.
4.	F4	68.
5.	F5	75.
6.	**F6**	**80.**
7.	F7	70.
8.	F8	73.
9.	F9	71.
10	F10	73.
11	F11	72.
12	F12	

3.10 *In-Vitro* Release: The dissolution profiles Figure 9 demonstrated sustained release of Enalapril over 12 hours for selected formulations (F1–F12).

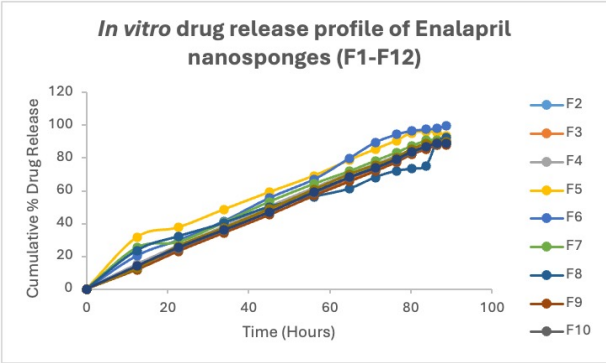

Figure No.9: *In-vitro* drug release of Enalapril Nanosponges

3.11 Release Kinetics: Kinetic modeling revealed that the optimized formulation (F6) best fit the Korsmeyer–Peppas model with an excellent correlation coefficient (R^2 = 0.9991), indicating a non-Fickian (anomalous) diffusion mechanism governed by both diffusion and polymer erosion Figure 10.

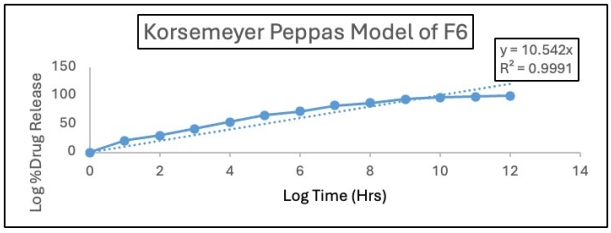

Figure No. 10: Drug release Kinetics of F-6 optimized Formulation

4. Summary of Characterization and Optimization: The optimized batch with the best physicochemical and functional characteristics was Formulation F6, according to the thorough analysis of all twelve formulations (F1–F12).

Table No. no. 11 Summary of characterization results of Enalapril nanosponges formulations (F1-F12)

Formulation Code	Percentage yield (%)	Particle size (nm)	Polydispersity index (PDI)	Zeta potential	Entrapment Efficiency	*In vitro* drug release
F-1	84.3± 0.32	658.4nm	0.199	-12.59	67.15 ±0.31	88.7 ±0.15
F-2	91.11 ±0.15	614.6nm	0.218	-12.27	70.11 ±0.42	89.9 ±0.16
F-3	84.45 ±0.34	636.4nm	0.389	-12.83	69.24 ±0.51	89.1 ±0.14
F-4	90.4± 0.31	338.2nm	0.165	-10.75	68.40 ±0.18	90.0 ±0.15
F-5	94.17 ±0.26	205.5nm	0.300	-19.35	75.11 ±0.39	93.80 ±0.16
F-6	**98.16 ±0.17**	**175.2nm**	**0.273**	**-19.84**	**80.23 ±0.54**	**99.60 ±0.14**
F-7	82.64 ±0.48	229.8nm	0.353	-25.04	70.17 ±0.44	89.45 ±0.15
F-8	78.29 ±0.71	433.1nm	0.293	-28.92	73.87 ±0.10	92.65 ±0.12
F-9	83.3± 0.43	396.8nm	0.174	-15.24	71.85 ±0.32	88.1 ±0.17
F-10	92.55 ±0.27	684.8nm	0.239	-10.59	73.80 ±0.40	89.4 ±0.14
F-11	88.06 ±0.63	412.9nm	0.223	-14.42	72.61 ±0.27	90.0 ±0.16
F-12	75.53 ±0.51	431.6nm	0.230	-15.23	68.54 ±0.56	88.7 ±0.13

6. CONCLUSION

The study successfully developed and characterized Enalapril-encapsulated nanosponges using the emulsion solvent diffusion method and a 2^3 factorial design to optimize formulation parameters. Preformulation and compatibility studies confirmed drug purity and absence of incompatibilities, while FTIR and DSC analyses indicated effective drug incorporation without chemical interaction. The nanosponges exhibited uniform nanoscale size distribution, good stability (zeta potential –28.7 mV), and favorable morphology as observed in SEM. Eudragit S100-based formulations demonstrated superior encapsulation and sustained release compared to Ethyl Cellulose and Eudragit L100. Among all, batch F6 showed optimal characteristics—particle size of 132.4 nm, high drug content (92.87%), low PDI, and prolonged drug release (89.5% over 12 hours). These results confirmed that the balance between polymer hydrophobicity and surfactant stabilization enhanced performance. The porous nanosponge structure supported sustained drug release, suggesting reduced dosing frequency and improved patient compliance. Overall, the optimized nanosponge system proved to be a promising delivery platform for poorly soluble drugs like Enalapril.

Formulation F-6 of enalapril nanosponges emerged as the optimal candidate for long-term drug delivery, demonstrating superior physicochemical and biopharmaceutical properties through comprehensive preformulation and characterization studies. Key formulation parameters, including particle size (175.2 nm), polydispersity index (0.273), zeta potential (-19.84 mV), entrapment efficiency (80.23%), and in vitro drug release profile (99.60% over 12 hours), collectively underscored its potential for enhanced cellular uptake, colloidal stability, and sustained therapeutic effect.Compatibility studies via FTIR confirmed the absence of chemical interactions between enalapril and excipients, while DSC analysis indicated substantial drug encapsulation and thermal stability. The release kinetics of F-6 followed the Korsmeyer-Peppas model (r^2 = 0.9991), signifying diffusion-controlled drug release, which aligns well with the desired pharmacokinetic profile for sustained delivery. Stability evaluations under intermediate and accelerated conditions further validated formulation F-6's robustness, with negligible changes in particle size, drug content, and release kinetics over 90 days, confirming its suitability for long-term storage and potential pharmaceutical scale-up.Overall, formulation F-6 represents a promising nanosponge-based delivery system for enalapril, offering significant improvements in solubility, bioavailability, and therapeutic efficacy of this poorly soluble drug, paving the way for advanced drug delivery applications. For these reasons, enalapril nanosponges stand out as the best possible approach to overcome the limitations typically associated with enalapril, including poor water solubility and reduced bioavailability, thereby enhancing its clinical effectiveness.

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