DEVELOPMENT OF RAMIPRIL-LOADED NANOSPONGES AND THEIR INCORPORATION INTO ORAL TABLET DOSAGE FORM: A NOVEL APPROACH TO ENHANCE ORAL BIOAVAILABILITY

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- Keywords: Ramipril, Drug-loaded nanosponges, Sustained release formulation, Oral tablet development, Stability studies

ABSTRACT

This study developed and evaluated a novel oral tablet of ramipril using drug-loaded nanosponges to improve solubility, stability, and bioavailability. Nanosponges were prepared by emulsion solvent diffusion with 1.0 g ramipril, 0.5 g ethyl cellulose, and 0.5 g polyvinyl alcohol. Among twelve batches, NS4 showed optimal properties: entrapment efficiency 92.13 ± 0.32 %, production yield 92.5 %, particle size 227.4 nm, PDI 0.204, and zeta potential –16.6 mV, indicating uniform, stable particles. Drug content of nanosponges ranged from 68.42 ± 0.21 % (NS1) to 96.12 ± 0.41 % (NS12), with NS4 showing 93.25 ± 0.28 %, confirming efficient drug loading. NS4 was compressed into tablets using HPMC K15M (20–60 mg), MCC pH102 (30 mg), colloidal silicon dioxide (2.5 mg), and magnesium stearate (2 mg). Pre-compression studies confirmed good flow (Carr's index 11–15 %, Hausner's ratio ~1.12–1.17, angle of repose ~25°). Tablets met pharmacopeial standards with weight ~173–210 mg, hardness ~7.7–7.8 kg/cm², friability <0.27 %, and acceptable thickness and disintegration. Drug content of tablets ranged from 4.78 ± 0.06 mg (F4) to 4.91 ± 0.03 mg (F3), ensuring dose uniformity. In-vitro dissolution showed sustained release: F3 (40 mg HPMC) released ~75 % drug over 8 hours and ~80 % over 12 hours, compared to pure drug (~96 % in 2 hours). Stability testing of F3 for 28 days confirmed consistent physical and release profiles. Incorporating ramipril-loaded nanosponges into tablets provided improved solubility, stability, and controlled release, offering a promising alternative to conventional formulations for better therapeutic outcomes and compliance.

KEYWORDS: Ramipril, Drug-loaded nanosponges, Sustained release formulation, Oral tablet development, Stability studies

1. INTRODUCTION

Targeted drug delivery systems like nanosponges deliver the medication to the intended location in a predictable and controlled manner. A wide range of chemicals and drug compounds can be encapsulated by nanosponges, which are tiny structures that resemble meshes [1]. They are spherical and colloidal, and they improve the solubilization of both lipid-soluble and water-soluble medicines. They improve the bioavailability of medications with extended release. No toxicity, allergic responses, irritations, or mutations are brought on by them. There are innumerable interconnecting voids, or empty spaces, inside these spongy spheres. By encasing a wide range of medications that are insoluble on their own, these voids serve to increase the bioavailability of such medications. They can contain both hydrophilic and lipophilic medicinal molecules because of their outside hydrophilic branching and interior lipophilic hollow. Because of their solid form, nanosponges can be safely delivered through alternative methods [2]. Drug containing nanosponges are incorporated into parenteral formulations using aqueous solutions such as sterile water and saline as solvents. To include nanosponges for topical medication administration, topical hydrogel is utilized. Topical nanosponges offer the benefits of decreased adverse effects, lower dosage, and increased patient compliance [3]. Unlike nanoparticles, nanosponges are porous, capable of withstanding temperatures of up to 300 °C, and insoluble in organic solvents or water. Drug release is triggered by their movement throughout the body without adhering to any surface.

1.1 Advantages of Nanosponges

- Nanosponges can contain drug moieties that are hydrophilic or lipophilic.
- The drug delivery methods for nanosponges are non-toxic, non-mutagenic, and non-irritating.
- Less frequent dosage; improved patient compliance; and stability of nanosponges complexes over a broad pH range (1–11) and at the higher temperature of 130 °C.
- Fewer negative effects (since less of the medication comes into contact with healthy tissue).
- Exhibit extended release of drug with continuous activity for up to 12 hours.
- Biodegradable in nature.
- Simple to scale up for commercial manufacturing [4,5]

2. RAMIPRIL

2.1 Background

Ramipril is a Second generation angiotensin converting enzyme (ACE) inhibitor. It is a prodrug and is hydrolysed in vivo to release the active metabolite, ramiprilat, which has a long elimination half- life, permitting once- daily administration. As it is soluble in water and shows first pass metabolism in liver hence, its oral bioavailability is affected, which is why, its administration is preferred by incorporation of drug loaded in nanosponges and taken by oral route.

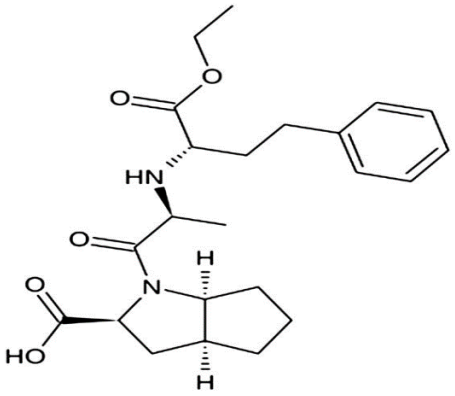


Figure 1.: Structural formula of Ramipril

2.2 Mechanism of action

Ramipril reduces the synthesis of angiotensin II and the breakdown of bradykinin by blocking the actions of the angiotensin converting enzyme (ACE). As blood is pushed via enlarged arteries, the relaxation of arteriole smooth muscle brought on by the drop in angiotensin II lowers blood pressure by lowering total peripheral resistance. The negative effects of dry cough are caused by its action on bradykinin. Carboxylesterase1 transforms the prodrug or precursor drug Ramipril into the active metabolite Ramiprilat. The kidneys are primarily responsible for excreting Ramiprilat. Its half-life varies from 3 to 16 hours, and renal, liver, and heart failure all lengthen it.

2.3 Pharmacokinetics

- **Absorption:** There is at least 50–60% absorption. Without changing the amount of absorption, food slows down the pace of absorption from the GIT. Ramipril and Ramiprilat have absolute bioavailabilities of 28 and 44%, respectively.
- **Protein binding:** Ramipril and Ramiprilat have roughly 73% and 56% protein binding, respectively.

3. AIM AND OBJECTIVE

Ramipril-loaded nanosponges will be prepared using suitable polymers and incorporated into matrix tablets for sustained drug release.

- To prepare ramipril-loaded nanosponges using suitable polymers and methods.
- To characterize the nanosponges for particle size, morphology, drug loading, and entrapment efficiency.
- To compress the nanosponges into tablets using hydrophilic polymers (e.g., HPMC) for sustained release.
- To evaluate the tablets for hardness, friability, weight variation, drug content, and in-vitro drug release.
- To perform stability studies of the formulation under accelerated conditions.

4. MATERIALS AND METHODS

4.1 Material: Ramipril API was procured from Loba Chemie Pvt. Ltd. Mumbai, Ethyl cellulose, Polyvinyl alcohol, Microcrystalline Cellulose pH 102, Magnesium stearate, Hydroxy Propyl Methyl Cellulose, Colloidal Silicon dioxide from Loba Chemie Pvt. Ltd. Mumbai and Dichloromethane, Methanol from Fisher Scientific India Pvt. Ltd., Mumbai.

4.2 Method of Preparation: Emulsion Solvent Evaporation Method

Ramipril-loaded nanosponges were prepared using the emulsion solvent diffusion method. While the amount of drug (i.e., 1 g) remained constant, various ratios of ethyl cellulose (EC) and polyvinyl alcohol (PVA) were employed. Drug and EC were added to 20 mL of dichloromethane, and the mixture was sonicated for about 10 minutes to dissolve the drug completely. This created the disperse phase. PVA was dissolved in 100 milliliters of distilled water in a water bath set at 60 degrees Celsius to create a continuous phase. The continuous phase was continuously stirred at 1000 rpm for two hours while the dispersion phase was added drop by drop. The dispersion was dried in an oven set to 40ºC for 24 hours after being filtered through a millipore filter with pore size 0.45 µm. Once the formulations had dried, they were sealed in containers and kept in a desiccator until they could be further examined [6].

5. FORMULATION OF RAMIPRIL-LOADED NANOSPONGES

Table 1.: Formulation composition of Ramipril - loaded Nanosponges

Formulation Code	Drug (g)	Ethyl cellulose (g)	Polyvinyl Alcohol (%w/v)	Dichloromethane (mL)
NS 1	1.0	0.5	0.50	20.0
NS 2	1.0	1.0	0.50	20.0
NS 3	1.0	1.5	0.50	20.0
NS 4	1.0	2.0	0.50	20.0
NS 5	1.0	0.5	0.75	20.0

NS 6	1.0	1.0	0.75	20.0
NS 7	1.0	1.5	0.75	20.0
NS 8	1.0	2.0	0.75	20.0
NS 9	1.0	0.5	1.00	20.0
NS 10	1.0	1.0	1.00	20.0
NS 11	1.0	1.5	1.00	20.0
NS 12	1.0	2.0	1.00	20.0

5.1 EVALUATION PARAMETERS OF RAMIPRIL LOADED NANOSPONGES

5.1.1 Drug Content

A known weight of Ramipril-loaded nanosponges was dissolved in phosphate buffer (pH 6.8) and sonicated to extract the drug completely. The solution was filtered to remove any particles, and the filtrate was diluted suitably. The absorbance of the solution was measured at 208 nm using a UV–Visible spectrophotometer against a blank. The amount of drug present was calculated using the calibration curve of Ramipril. The drug content was expressed as the percentage of the theoretical drug present in the nanosponges.

$$\textbf{Drug Content (\%)} = \frac{\text{Theoretical amount of drug in sample}}{\text{Actual amount of drug determined}} \times 100$$

5.1.2 Estimation of Entrapment Efficiency

Ramipril-loaded nanosponges were weighed, dissolved in phosphate buffer (pH 6.8), and centrifuged for 30 minutes at 1000 rpm. After that, the supernatant was taken out, suitably diluted with phosphate buffer (pH 6.8), and its absorbance was measured using UV spectroscopy in comparison to a blank [7].

$$\textbf{\% Drug Entrapment} = \frac{\text{Calculated drug content}}{\text{Theoretical drug content}} \times 100 \text{……..Eq (1)}$$

5.1.3 Production Yield

The final weight of the produced nanosponges was compared to the initial weight of the raw materials to calculate the production yield (PY) [8].

$$\textbf{Production Yield:} \frac{\text{Practical mass of Nanosponge}}{\text{Theoretical mass (Polymer+drug)}} \times 100 \text{……Eq (2)}$$

5.1.4 Optical Microscopy

Optical microscopy was used to characterize the generated nanosponges for morphology, or shape uniformity [9].

5.1.5 Particle Size Analysis

The dynamic light scattering (DLS) approach, which yields precise measurements of the average particle size and polydispersity index (PDI), was used to assess the particle size of Ramipril-loaded nanosponges. One important factor affecting medication release, surface area, and absorption is particle size. Water was used as the dispersions medium in order to determine the NS4 formulation's particle size and shape. The temperature at which the size distribution analysis was conducted was 25.0 C. A disposable sizing cuvette was used to measure the particle size. The sample was scanned 100 times to determine the particle size in order to calculate the size of the optimal batch.

5.1.6 Zeta Potential

Zeta potential is a crucial metric for assessing the stability and surface charge of nanosponge compositions. Particle dispersion and aggregation are inhibited by electrostatic repulsion, which is reflected in this phenomenon. Zeta potential was calculated for the NS 4 formulation with water serving as the dispersion medium. The zeta cuvette used for the measurement was disposable. To get a trustworthy zeta potential value, the optimized batch was scanned 100 times to guarantee accuracy.

5.1.7 Field Emission Scanning Electron Microscope (FE-SEM)

The surface topography and morphology of nanoscale materials are frequently studied using the sophisticated imaging method known as field emission scanning electron microscopy, or FE-SEM. Nanoparticulate drug delivery methods benefit greatly from FE-SEM analysis since it offers important information on particle shape, surface roughness, and porosity. This method is essential for verifying that nanoscale structures are successfully fabricated and for comprehending how they might behave in drug delivery applications.

5.1.8 In- Vitro Release Studies

A vessel containing 900 milliliters of phosphate buffer with a pH of 6.8 was used to assemble the USP apparatus type II (Paddle Method). The medium was left to reach an equilibrium temperature of 37 ± 0.5°C. The powdered nanosponges were put in the tea bag, put in the vessel, and run for eight hours at fifty rpm. 5 ml of the receptor fluid were extracted, filtered, diluted, and subjected to spectrophotometric analysis at predetermined intervals [10].

6 RESULTS AND DISCUSSION

6.1 Drug Content

Table 2: Drug content of prepared Ramipril - loaded Nanosponges

Formulation Code	% Drug Content (Mean ± SD)
NS 1	68.42 ± 0.21
NS 2	78.35 ± 0.34
NS 3	88.91 ± 0.45
NS 4	93.25 ± 0.28
NS 5	69.85 ± 0.52
NS 6	82.74 ± 0.38
NS 7	90.52 ± 0.19
NS 8	94.02 ± 0.27
NS 9	73.16 ± 0.23
NS 10	83.87 ± 0.65
NS 11	91.73 ± 0.29
NS 12	96.12 ± 0.41

*Values expressed as mean ± SD (n = 3)

6.2 Entrapment efficiency

Better entrapment efficiency was found to result from increased ethyl cellulose (EC) and polyvinyl alcohol (PVA) concentrations. Since NS12 had greater concentrations of both polyvinyl alcohol and ethyl cellulose, it was determined to be the ideal formulation.

Table 3: Percentage entrapment efficiency of prepared Ramipril - loaded Nanosponges

Formulation code	Percentage Entrapment efficiency (Mean ± SD)	Formulation code	Percentage Entrapment efficiency (Mean ± SD)
NS 1	65.03 ± 0.15	**NS 7**	89.09 ± 0.15
NS 2	77.53 ± 0.35	**NS 8**	92.09 ± 0.21
NS 3	87.77 ± 0.59	**NS 9**	71.97 ± 0.21
NS 4	92.13 ± 0.32	**NS 10**	81.80 ± 0.92
NS 5	67.87 ± 0.58	**NS 11**	90.27 ± 0.25
NS 6	80.57 ± 0.40	**NS 12**	95.17 ± 0.42

*Values expressed as mean ± SD (n = 3)

6.3 Production Yield

The production yield was found to be directly correlated with the concentration of the polymer; higher concentrations of ethyl cellulose and polyvinyl alcohol (PVA) resulted in higher production yields.

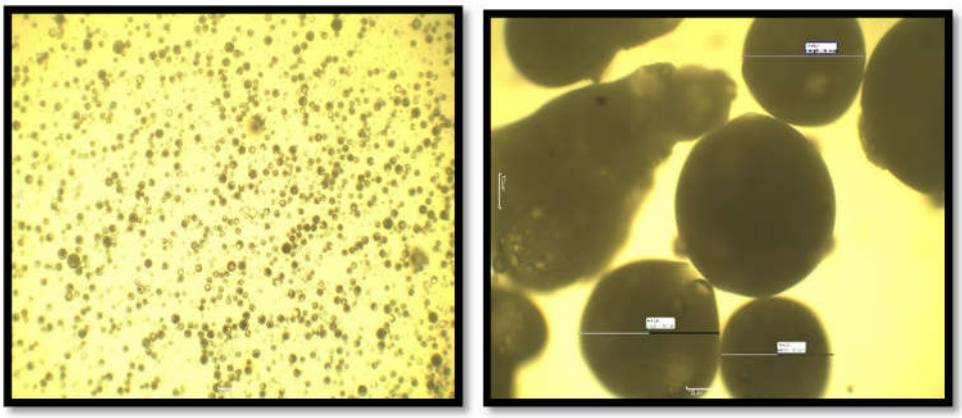
Table 4: Percentage production yield of prepared Ramipril - loaded Nanosponges

Formulation code	Percentage Production Yield	Formulation code	Percentage Production Yield
NS 1	82.1 ± 0.28	**NS 7**	82.3 ± 0.19
NS 2	83.6 ± 0.31	**NS 8**	80.2 ± 0.45
NS 3	79.1 ± 0.65	**NS 9**	78.5 ± 0.40
NS 4	92.5 ± 0.42	**NS 10**	78.0 ± 0.66
NS 5	79.6 ± 0.59	**NS 11**	79.9 ± 0.59
NS 6	81.6 ± 0.21	**NS 12**	86.0 ± 0.44

*Values expressed as mean ± SD (n = 3)

6.4 Optical Microscopy

Optical microscope images at 10x magnification demonstrating the development of nanosponges throughout the batch.



NS 4 **NS 12**

Figure 2.: Optical Microscopy of NS 4 and NS 12 Formulation

6.5 Particle Size Analysis

Dynamic light scattering (DLS) was used to determine the particle size distribution of the NS 4 nanosponge formulation, which is shown in the graph above. Given that values below 0.3 indicate monodispersity, the Z-Average particle size was determined to be 227.4 d.nm with a polydispersity index (PDI) of 0.204, suggesting a narrow and uniform size range. The measurement's correctness was confirmed when the result quality was rated as "Good." Two notable peaks can be seen in the intensity distribution graph: Peak 1 at 148.4 d.nm (76.6% intensity) indicates the dominating particle population, whereas Peak 2 at 13.69 d.nm (23.5% intensity) indicates the presence of smaller particles or perhaps drug residues or degraded nanosponges. Peaks 1 and 2's respective standard deviations were 48.18 d.nm and 2.43 d.nm, indicating that the particle sizes were consistent.

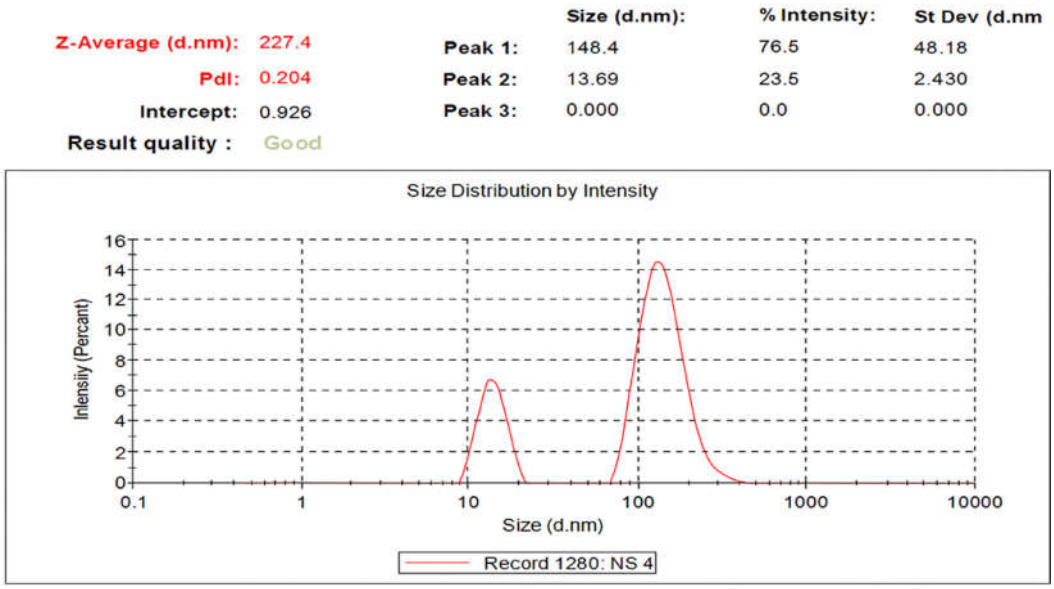


Figure 3.: Particle size analysis of Formulation (NS 4)

6.6 Zeta Potential

The nanosponge formulation (NS4) was found to have a conductivity of 0.485 mS/cm, a zeta potential of –16.6 mV, and a zeta deviation of 8.18. The existence of a negatively charged surface is indicated by the negative zeta potential, which is most likely caused by anionic functional groups

from the stabilizers or polymers included in the formulation. Particle aggregation is somewhat reduced by a zeta potential of –16.6 mV, which indicates considerable electrostatic stability even though the value is below the ±30 mV threshold usually linked to good colloidal stability. The distribution of particle surface charges is reflected in the zeta deviation, which was within a reasonable range. Crucially, "Good" was the overall result quality rating, indicating that the collected data was reliable, repeatable, and appropriate for interpretation.

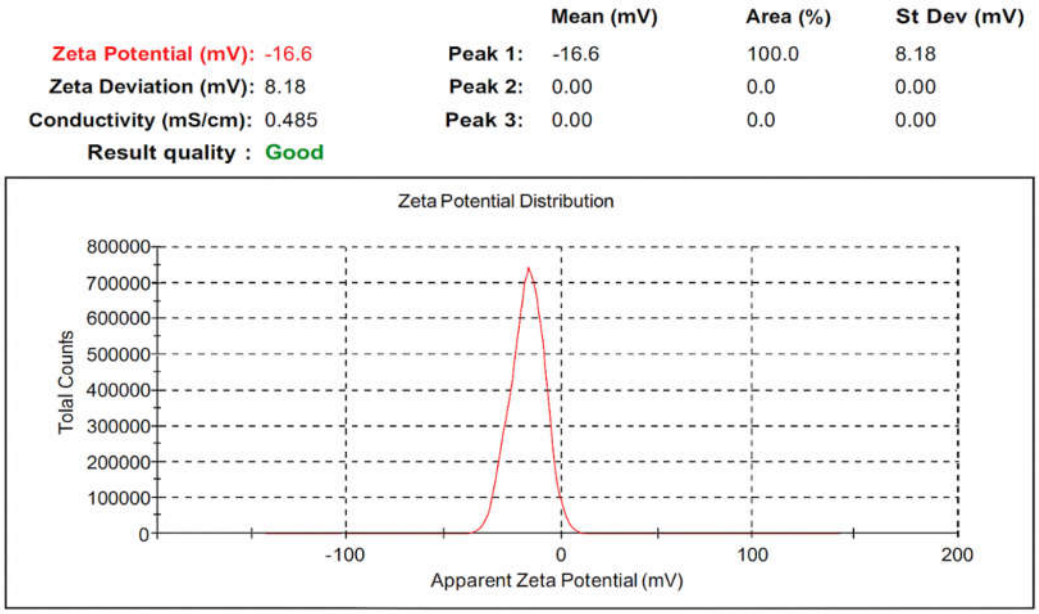


Figure 4.: Zeta Potential of Formulation (NS 4)

6.7 Field Emission Scanning Electron Microscope (FE-SEM)

Using FE-SEM at various magnifications, the surface morphology of the produced ramipril-loaded nanosponges was investigated. With a rough and porous surface structure, the well-defined spherical nanosponge was visible in the high-magnification image (Figure A, ×25,000). The successful development of nanosponges, which are essential for increasing drug loading capacity and regulating drug release, is indicated by these surface holes and abnormalities. On the other hand, a group of spherical particles with consistent diameters and comparatively smooth surfaces were seen in the lower magnification image (Figure B, ×130). A robust and well-optimized formulation process is suggested by the consistent shape and lack of particle aggregation.

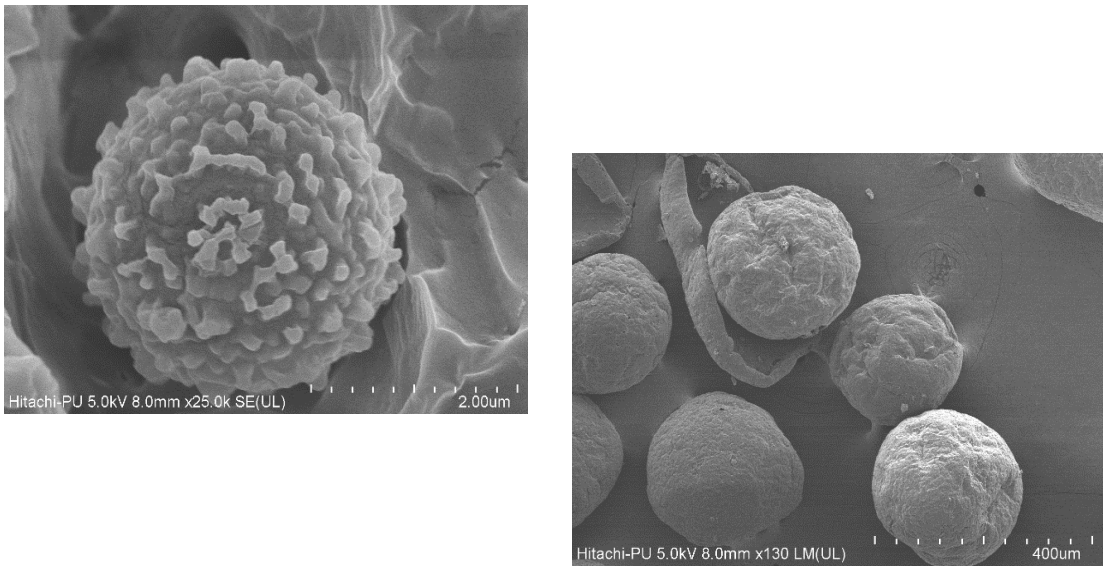


Figure 5.: FE-SEM of Optimized formulation (NS 4)

6.8 In- Vitro Release Studies

Table 5.: *In vitro* % cumulative drug (Ramipril) released data vs time intervals of pure drug vs different prepared Nanosponges (Formulation code.: NS 1, NS 2, NS 3 and NS 4)

Time intervals (minutes)	Pure drug	NS 1	NS 2	NS 3	NS 4
	% Cumulative drug release (Mean ± SD)				
0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
15	45.9 ± 0.5	45.9 ± 0.6	41.7 ± 0.6	32.4 ± 3.4	18.4 ± 1.6
30	62.5 ± 0.9	57.2 ± 0.7	50.5 ± 0.5	46.2 ± 2.9	28.4 ± 1.8
45	76.6 ± 0.4	63.9 ± 0.8	55.9 ± 1.2	52.4 ± 1.5	38.8 ± 1.5
60	85.9 ± 0.9	69.1 ± 0.3	61.5 ± 1.5	58.7 ± 0.9	46.7 ± 2.3
90	93.1 ± 0.8	74.8 ± 0.2	65.9 ± 1.9	60.8 ± 0.8	51.4 ± 2.0
120	96.6 ± 0.5	78.8 ± 0.5	70.4 ± 0.9	64.0 ± 0.5	57.4 ± 1.9
240	-	83.4 ± 0.6	75.7 ± 0.1	69.6 ± 0.3	61.9 ± 0.3
360	-	87.8 ± 0.3	80.0 ± 0.0	73.9 ± 0.2	65.4 ± 0.1
420	-	89.4 ± 0.1	81.0 ± 0.2	75.9 ± 0.1	68.8 ± 0.5
480	-	90.2 ± 0.8	82.0 ± 0.2	77.1 ± 0.1	72.4 ± 0.6

*Values expressed as mean ± SD (n = 3)

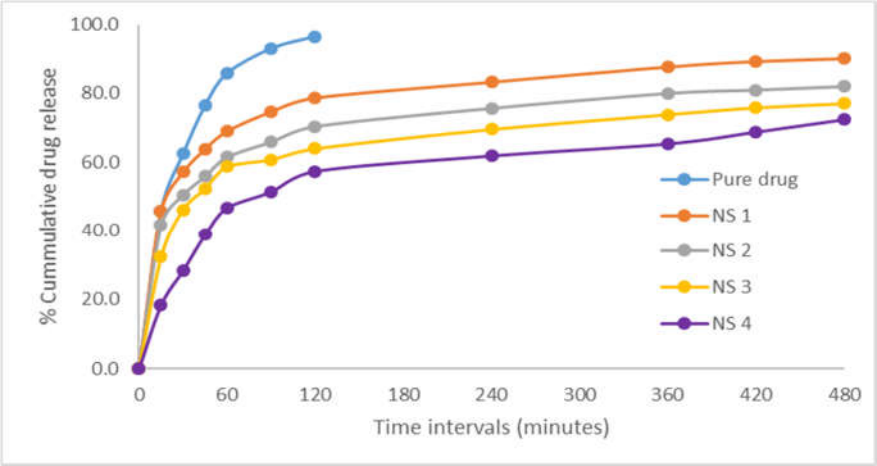


Figure 6.: *In vitro* % cumulative drug (Ramipril) released data (Formulation code.: NS 1, NS 2, NS 3 and NS 4)

Table 6.: *In vitro* % cumulative drug (Ramipril) released data vs time intervals of pure drug vs different prepared Nanosponges (Formulation code.: NS 5, NS 6, NS 7 and NS 8)

Time intervals (minutes)	Pure drug	NS 5	NS 6	NS 7	NS 8
	% Cumulative drug release (Mean ± SD)				
0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
15	45.9 ± 0.5	49.9 ± 3.4	45.2 ± 0.6	35.4 ± 1.6	24.5 ± 0.6
30	62.5 ± 0.9	59.4 ± 2.9	52.6 ± 0.7	47.4 ± 1.8	35.9 ± 0.5
45	76.6 ± 0.4	65.2 ± 1.5	58.4 ± 0.8	53.8 ± 1.5	46.6 ± 1.2
60	85.9 ± 0.9	71.9 ± 0.9	62.6 ± 0.3	59.1 ± 2.3	50.8 ± 1.5
90	93.1 ± 0.8	76.9 ± 0.8	69.3 ± 0.2	61.2 ± 2.0	55.9 ± 1.9
120	96.6 ± 0.5	80.4 ± 0.5	71.7 ± 0.5	65.6 ± 1.9	59.7 ± 0.9
240	-	85.4 ± 0.3	78.5 ± 0.6	71.9 ± 0.3	63.3 ± 0.1
360	-	88.0 ± 0.2	82.9 ± 0.3	74.7 ± 0.1	70.8 ± 0.0
420	-	93.0 ± 0.1	84.0 ± 0.1	76.6 ± 0.5	72.9 ± 0.2
480	-	93.2 ± 0.1	85.5 ± 0.8	78.2 ± 0.6	75.6 ± 0.2

*Values expressed as mean ± SD (n = 3)

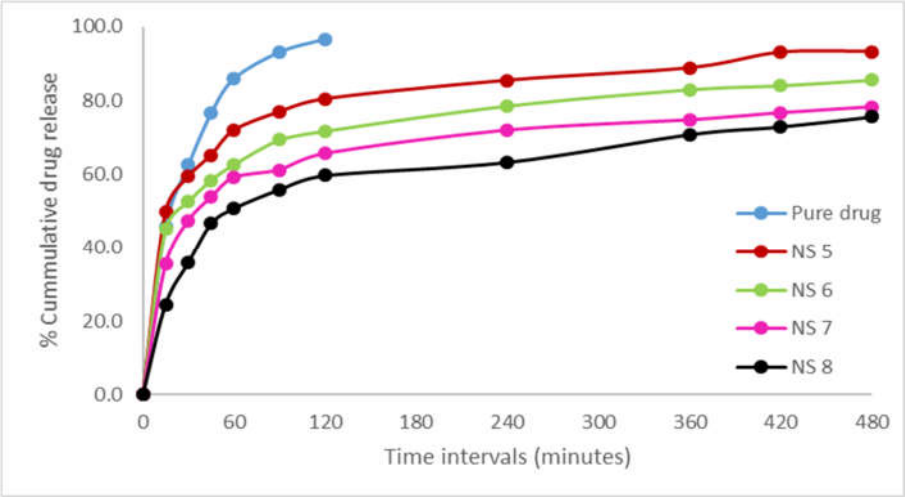


Figure 7.: *In vitro* % cumulative drug (Ramipril) released data (Formulation code.: NS 5, NS 6, NS 7 and NS 8)

Table 7.: *In vitro* % cumulative drug (Ramipril) released data vs time intervals of pure drug vs different prepared Nanosponges (Formulation code.: NS 9, NS 10, NS 11 and NS 12)

Time intervals (minutes)	Pure drug	NS 9	NS 10	NS 11	NS 12
	% Cumulative drug release (Mean ± SD)				
0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
15	45.9 ± 0.5	50.2 ± 1.6	45.6 ± 0.6	38.8 ± 0.6	30.3 ± 3.4
30	62.5 ± 0.9	62.5 ± 1.8	55.7 ± 0.5	48.6 ± 0.7	45.6 ± 2.9
45	76.6 ± 0.4	69.2 ± 1.5	59.2 ± 1.2	54.9 ± 0.8	51.6 ± 1.5
60	85.9 ± 0.9	75.9 ± 2.3	65.2 ± 1.5	60.9 ± 0.3	57.2 ± 0.9
90	93.1 ± 0.8	80.9 ± 2.0	71.6 ± 1.9	63.8 ± 0.2	60.1 ± 0.8
120	96.6 ± 0.5	84.2 ± 1.9	75.4 ± 0.9	68.0 ± 0.5	63.4 ± 0.5
240	-	88.4 ± 0.3	81.0 ± 0.1	73.1 ± 0.6	65.4 ± 0.3
360	-	92.9 ± 0.1	85.0 ± 0.0	77.3 ± 0.3	72.4 ± 0.2
420	-	94.6 ± 0.5	86.6 ± 0.2	78.4 ± 0.1	75.4 ± 0.1
480	-	94.9 ± 0.6	87.2 ± 0.2	79.5 ± 0.8	75.4 ± 0.1

*Values expressed as mean ± SD (n = 3)

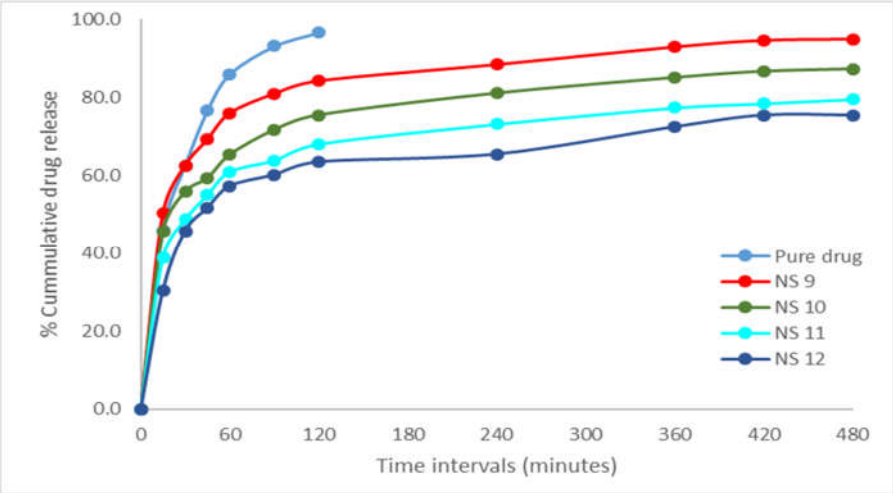


Figure 8.: ***In vitro*** **% cumulative drug (Ramipril) released data (Formulation code.: NS 9, NS 10, NS 11 and NS 12)**

7. FORMULATION OF TABLET OF RAMIPRIL NANOSPONGES

7.1 Preparation of tablet of ramipril nanosponges

The direct compression approach was used to create tablets with pure drug and drug-loaded nanosponges. Accurately weighed amounts of Ramipril-loaded nanosponges (equivalent to 5 mg of drug, or 117.5 mg of nanosponge formulation) were combined with 2 mg of colloidal silicon dioxide, 30 mg of microcrystalline cellulose (MCC pH 102), and Hydroxypropyl Methylcellulose (HPMC K15M) to create drug-loaded nanosponges tablets. To get a homogenous mixture, the mixing was done in a mortar and pestle for ten to fifteen minutes. To finish the lubrication process, 2.5 mg of magnesium stearate was added as a lubricant and gently stirred for an additional three to five minutes after everything had been thoroughly combined. A single-punch tablet compression machine fitted with an 8 mm flat-faced punch was used to compress the finished blend into tablets.

Table 8.: Formulation composition of prepared Ramipril tablets

Formulation code	Nanosponges (mg)	HPMC K15M (mg)	MCC Ph 102 (mg)	Colloidal Silicon Dioxide (mg)	Magnesium Stearate (mg)
F1	117.5	20.0	30.0	2.0	2.5
F2	117.5	30.0	30.0	2.0	2.5
F3	117.5	40.0	30.0	2.0	2.5
F4	117.5	50.0	30.0	2.0	2.5
F5	117.5	60.0	30.0	2.0	2.5

Note:

1. Formulation code of Nanosponge used for preparation of final Ramipril tablets is NS 4, basis of percentage entrapment efficiency and *in vitro* drug release profile data.
2. Nanosponges 117.5 mg is equivalent to 5.0 mg of Ramipril.

Figure 9.: Ramipril-loaded nanosponge tablets prepared by direct compression method

7.2 Evaluation of Pre-compression characterizations of powder [11]

7.2.1 Angle of Repose: The funnel method was used to determine the angle of repose (α). A vertically movable funnel was used to pour the mixture until the desired maximum cone height (h) was reached. The angle of repose was computed and the heap's radius (r) measured:

$$\alpha = \tan^{-1}(h/r)$$

7.2.2 Bulk Density*:* The mix of preserved medicine excipients was put into a graduated cylinder, and the weight and volume were measured "as it is" in order to calculate the apparent bulk density.

$$\text{Bulk density} = \frac{\text{Weight of dry powder}}{\text{Bulk volume}}$$

7.2.3 Tapped Density: The measuring cylinder was tapped for a predetermined number of times while holding a certain mass of blend. In addition to the blend's weight, the cylinder's minimum volume was measured. The formula below was used to determine the tapped density:

$$\text{Tapped density} = \frac{\text{Weight of dry powder}}{\text{Tapped volume}}$$

7.2.4 Hausner's Ratio: Hausner's ratio, a measure of powder flow ease, is computed using the formula below:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

7.2.5 Carr's Index: Compressibility is the most straightforward method of measuring a powder's free flow property. Compressive strength, which is determined as follows, indicates how easily a material may be made to flow.

$$C = \frac{Tapped\ density}{Bulk\ density} \times 100$$

7.3 Evaluation of prepared ramipril tablets

7.3.1 Tablet thickness and size: For tablets to have a consistent size, their thickness and diameter were crucial. Vernier Calipers were used to measure the diameter and thickness.

7.3.2 Tablet Hardness: A Monsanto Hardness tester was used to measure the hardness of the tablets in each formulation. Kg/cm2 was used to measure the hardness.

7.3.3 Friability: After ten precisely weighted tablets were put in the tumbling device, which rotates at 25 rpm, the tablets were dropped six inches at a time. The tables were weighed after four minutes, and the percentage decrease in tablet weight was calculated.

$$Friability\ (\%) = 100 \times (W1 - W2)/W1$$

where, W1- Initial weight

W2- Final weight

7.3.4 Weight variation: The average weight of ten randomly chosen pills was determined. The weight difference was computed and contrasted with I.P. norms.

7.3.5 Drug content: The drug content of the tablets was determined to check the amount of Ramipril present in each formulation. One tablet from each batch was powdered, and an amount of powder equivalent to one tablet was weighed and dissolved in phosphate buffer (pH 6.8). The solution was sonicated to extract the drug completely, then filtered and suitably diluted. The absorbance of the solution was measured at 208 nm using a UV spectrophotometer, and the amount of drug was calculated using the calibration curve. The drug content was expressed as the percentage of the theoretical amount of 5 mg per tablet.

7.3.6 *In-vitro Drug Release Study*

The IP Dissolution Test Apparatus Type II (basket type) was used to measure the rate at which Ramipril was released from the tablet. At 50 rpm, 900 cc of phosphate buffer with a pH of 6.8 was filled with Ramipril Nanosponges that were inserted into tablets. The bath's temperature was kept at 37 ± 0.5 °C. For eight hours, 5 ml were taken out at one-hour

intervals. Whatman filter paper no. 41 was used to filter the samples. A UV-Visible spectrophotometer was used to test the absorbance of these solutions at 208 nm. An equation derived from a standard curve was used to compute cumulative percentage medication release.

8. RESULTS AND DISCUSSION

8.1 Pre-compression characterizations of powder

The flow characteristics of the powder blends were assessed by evaluating the pre-compression parameters of all formulations (F1–F5). The formulations' tapped density values varied between 0.652 ± 0.018 g/mL and 0.688 ± 0.015 g/mL, while their bulk densities ranged from 0.517 ± 0.008 g/mL to 0.544 ± 0.012 g/mL. The powder's compressibility, as measured by Carr's Index, was found to be between 11.897 ± 0.042% and 15.056 ± 0.247%, indicating good flow characteristics. Since values below 1.25 typically indicate adequate flow, Hausner's ratio values for all formulations were found to be between 1.121 ± 0.016 and 1.167 ± 0.004, which likewise suggested satisfactory flowability. The powder blends' good flow qualities were further confirmed by the angle of repose, which varied from 25.180 ± 0.287° to 25.582 ± 2.127° for all blends.

Table 9.: Pre-compression characterizations of powder

S. No.	Formulation	Bulk Density (g/mL)	Tapped density (g/mL)	Carr's Index (%)	Hausner's ratio	Angle of repose (θ)
1.	F1	0.517 ± 0.008	0.652 ± 0.018	12.670 ± 1.021	1.121 ± 0.016	25.535 ± 1.355
2.	F2	0.544 ± 0.012	0.688 ± 0.015	11.897 ± 0.042	1.164 ± 0.001	25.582 ± 2.127
3.	F3	0.517 ± 0.011	0.655 ± 0.016	15.056 ± 0.247	1.167 ± 0.004	25.180 ± 0.287
4.	F4	0.517 ± 0.008	0.652 ± 0.018	14.670 ± 1.021	1.161 ± 0.016	25.535 ± 1.355
5.	F5	0.517 ± 0.011	0.655 ± 0.016	13.056 ± 0.247	1.167 ± 0.004	25.180 ± 0.287

*Values expressed as mean ± SD (n = 3)

8.2 Post compression data for Ramipril Tablets

With an increase in HPMC K15M concentration, the average weight of the tablets rose from 172.9 ± 3.0 mg (F1) to 210.3 ± 3.7 mg (F5), which was in line with the amount of polymer added. The tablets had a thickness of 4.47 ± 0.03 mm to 4.72 ± 0.03 mm and a hardness of 7.7 ± 0.5 to 7.8 ± 0.6 kg/cm², which demonstrated good mechanical strength appropriate for handling and packaging. All of the formulations had friability levels below 1%, ranging from 0.209 ± 0.099% to 0.265 ± 0.109%, which verifies the tablets' resilience and meets with I.P. standards.

Table 10.: Post compression data for Ramipril Tablets

Formulation	Average weight (mg)	Drug content (mg)	Thickness (mm)	Hardness (kg/cm)	Friability (%w/w)
F1	172.9 ± 3.0	4.82 ± 0.05	4.52 ± 0.03	7.8 ± 0.6	0.245 ± 0.031
F2	183.0 ± 2.3	4.87 ± 0.04	4.55 ± 0.03	7.7 ± 0.7	0.209 ± 0.099
F3	194.0 ± 3.7	4.91 ± 0.03	4.59 ± 0.02	7.8 ± 0.5	0.232 ± 0.061
F4	201.3 ± 2.9	4.78 ± 0.06	4.72 ± 0.03	7.7 ± 0.8	0.259 ± 0.042
F5	210.3 ± 3.7	4.85 ± 0.05	4.47 ± 0.03	7.7 ± 0.6	0.265 ± 0.109

8.3 In-vitro Drug Release Study

Table 11.: *In vitro* % cumulative drug (Ramipril) released data vs time intervals of pure drug vs different prepared formulations (Formulation no.: F1, F2, F3, F4 and F5)

Time intervals (minutes)	Pure drug	F1	F2	F3	F4	F5
	% Cumulative drug release (Mean ± SD)					
0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
15	45.9 ± 0.5	25.6 ± 0.6	21.6 ± 0.6	15.9 ± 3.4	12.6 ± 1.6	8.4 ± 0.6
30	62.5 ± 0.9	30.9 ± 0.7	27.4 ± 0.5	19.6 ± 2.9	15.4 ± 1.8	12.6 ± 0.8
45	76.6 ± 0.4	39.5 ± 0.8	33.4 ± 1.2	22.4 ± 1.5	17.9 ± 1.5	13.4 ± 0.3
60	85.9 ± 0.9	42.9 ± 0.3	38.4 ± 1.5	30.4 ± 0.9	21.6 ± 2.3	14.0 ± 0.5
90	93.1 ± 0.8	50.9 ± 0.2	47.1 ± 1.9	34.8 ± 0.8	25.9 ± 2.0	20.6 ± 0.6
120	96.6 ± 0.5	60.7 ± 0.5	55.4 ± 0.9	42.6 ± 0.5	30.0 ± 1.9	25.0 ± 0.3
240	-	77.4 ± 0.6	70.0 ± 0.1	55.4 ± 0.3	48.0 ± 0.3	38.0 ± 0.1
360	-	85.4 ± 0.3	77.1 ± 0.0	67.4 ± 0.2	60.0 ± 0.1	50.0 ± 0.8
420	-	89.5 ± 0.1	80.4 ± 0.2	72.6 ± 0.1	66.6 ± 0.5	55.9 ± 0.1
480	-	92.4 ± 0.8	82.4 ± 0.2	75.4 ± 0.1	70.0 ± 0.6	60.0 ± 0.8

*Values expressed as mean ± SD (n = 3)

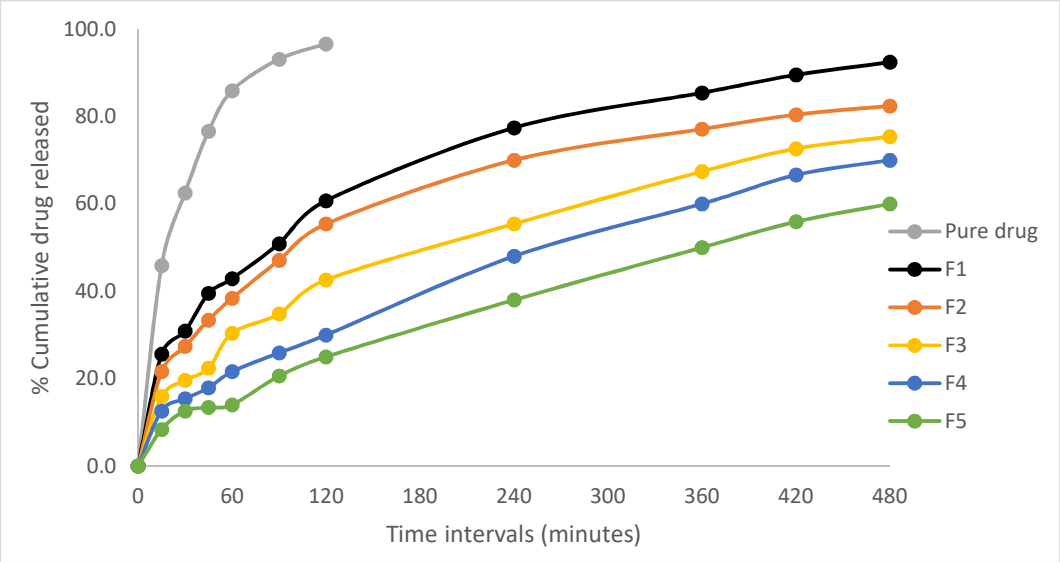


Figure 10.: ***In vitro*** **% cumulative drug (Ramipril) released data (Formulation no.: F1, F2, F3, F4 and F5)**

8.4 In Vitro Drug Release Kinetic Modeling

Several kinetic models were used to assess the drug release profile of ramipril-loaded nanosponge tablets in order to comprehend the underlying release mechanism. First-order, zero-order, and Korsmeyer-Peppas models were fitted to the dissolution data.

Table 12.: In vitro drug release kinetics studies data of F3 Formulation

Model	Kinetics parameter	Observed values
Zero Order Kinetics	**K_0 (% min^{-1})**	0.1261
	R^2	0.9574
First Order Kinetics	**K_1 (min^{-1})**	-0.0012
	R^2	0.985
Korsmeyer-Peppas Model	**K**	0.4733
	R^2	0.9904
	n	0.6362

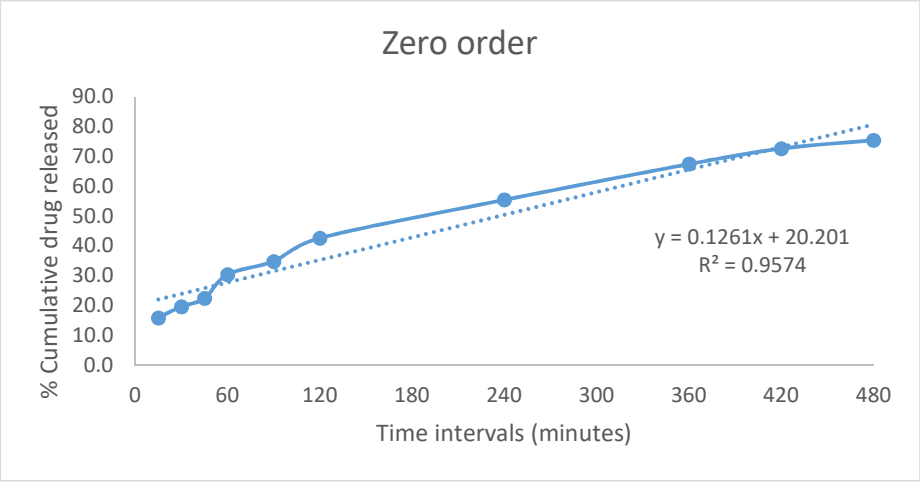


Figure 11.: % Cumulative drug released *vs* time intervals profile (Zero Order Kinetics)

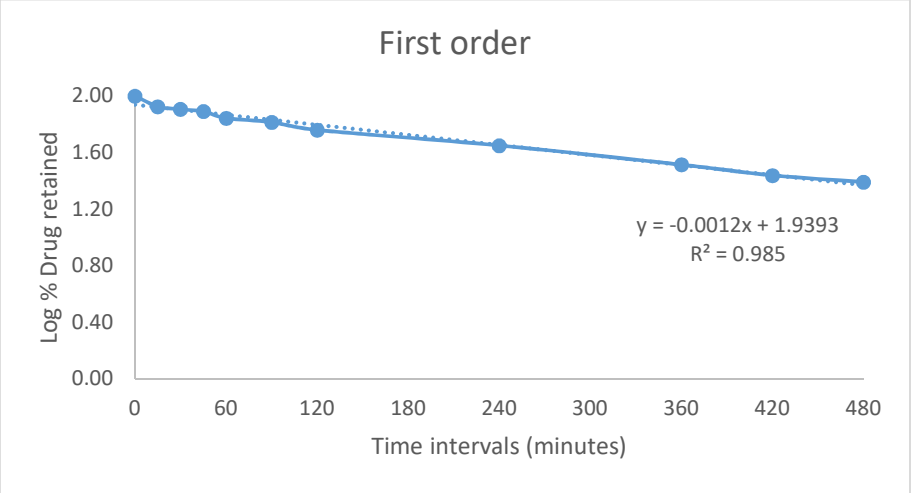


Figure 12.: Log % Cumulative drug released *vs* time intervals profile (First Order Kinetics)

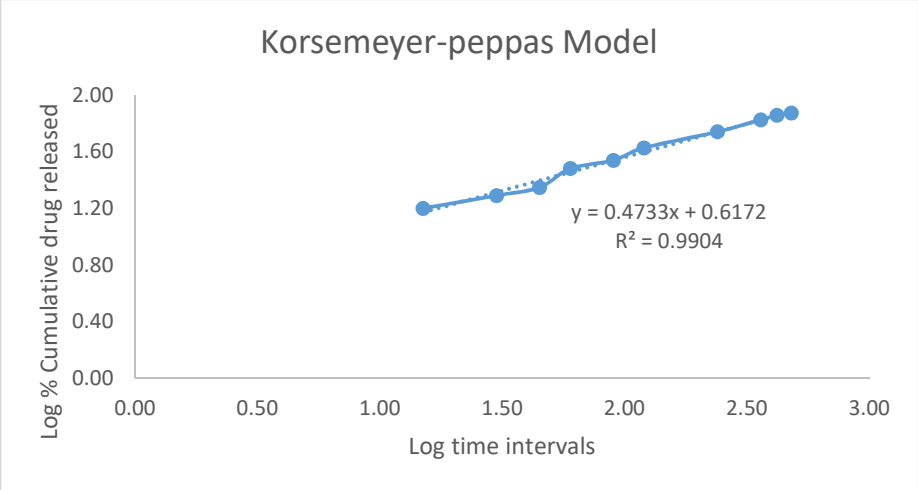


Figure 13.: Log % Cumulative drug released *vs* Log time intervals profile (Korsmeyer-Peppas model kinetics)

9. STABILITY STUDIES

9.1 Purpose of study

This study aimed to assess the stability profile of the generated nanosponge-based tablet formulation (F3) under conditions of accelerated storage. The study sought to evaluate:

- Tablet hardness and appearance
- Weight variation
- Friability
- In vitro drug release (percentage of cumulative drug release)

Table 13.: Storage conditions and period for stability studies

Formulation code	Storage condition	Storage Period
F3	Accelerated condition (40 ± 2 °C / 75 ± 5% RH)	28 days

9.2 Testing Plan

Formulation F3's tablets were kept in airtight containers wrapped in aluminum foil to keep out light. At predetermined intervals of 0, 7, 14, 21, and 28 days, samples were taken out and assessed using approved techniques.

Table 14.: Sampling Intervals During Stability Study

Storage Conditions	Sampling Intervals
Accelerated condition (40 ± 2 °C / 75 ± 5%RH)	7^{th}, 14^{th}, 21^{st}, 28^{th} day

9.3 Evaluation of Stability Samples

During the storage period, every tested parameter stayed within allowable bounds. There were no indications of deterioration in the tablets' consistent physical characteristics or drug release capabilities.

- Physical characteristics: No mottling, surface cracking, or color change were noticed.
- Tablet hardness: Showed constant mechanical strength, remaining steady.
- Friability: The tablet's durability was confirmed by all values staying well below 1%.

- Weight variation: Within pharmacopeial bounds, showed homogeneity.

Table 15.: Stability Data of Tablet Formulation (F3)

Accelerated condition (40 ± 2 °C / 75% ± 5%RH)						
S.No.	**Parameter**	**0 day**	**1 week**	**2 week**	**3 week**	**4 week**
1.	Physical appearance	No change	No change	No change	No change	No change
2.	Hardness (Kg/cm^2)	7.8 ± 0.5	7.7 ± 0.4	7.8 ± 0.2	7.8 ± 0.3	7.8 ± 0.2
3.	Friability (%)	0.232 ± 0.061	0.232 ± 0.042	0.231 ± 0.061	0.232 ± 0.099	0.232 ± 0.109
4.	Weight variation (mg)	194.0 ± 3.7	194.1 ± 2.9	194.0 ± 3.1	194.0 ± 2.8	194.0± 3.0
5.	Drug content	4.80 ± 0.05	4.88 ± 0.04	4.90 ± 0.03	4.77 ± 0.06	4.83 ± 0.05

9.3.1 Dissolution Profile Comparison

Additionally, the Formulation, F3, was subjected to a comparative dissolution profile examination. To assess variations in release over time, the in vitro dissolution data collected on day 28 was compared to the initial dissolution data collected on day 0. Model independent statistical methods for comparison include the similarity factor (f_2) and difference factor (f_1). Both the FDA and the ICH recommend these for comparing the dissolving profiles of pharmacological dosage forms. In order to demonstrate minimal disparity, the difference factor (f_1), which indicates the percentage difference between two curves at each time point, should ideally be less than 15. The similarity factor (f_2), which indicates how closely two dissolution profiles match, ranges from 0% to 100%; profiles are considered dissimilar if the value is less than 50 [12].

Table 16.: *In vitro* drug release data of Formulation, F3 at Accelerated conditions (40 ± 2 °C / 75% ± 5%RH)

% Cumulative drug released		
Time intervals (minutes)	**Initial**	**After**
0	0.0 ± 0.0	0.0 ± 0.0
15	15.9 ± 3.4	13.6 ± 0.6
30	19.6 ± 2.9	18.4 ± 0.8
45	22.4 ± 1.5	20.0 ± 0.3
60	30.4 ± 0.9	28.4 ± 0.5
90	34.8 ± 0.8	33.9 ± 0.6
120	42.6 ± 0.5	42.4 ± 0.3
240	55.4 ± 0.3	53 ± 0.1
360	67.4 ± 0.2	65.8 ± 0.8
420	72.6 ± 0.1	71.9 ± 0.1
480	75.4 ± 0.1	75.2 ± 0.8

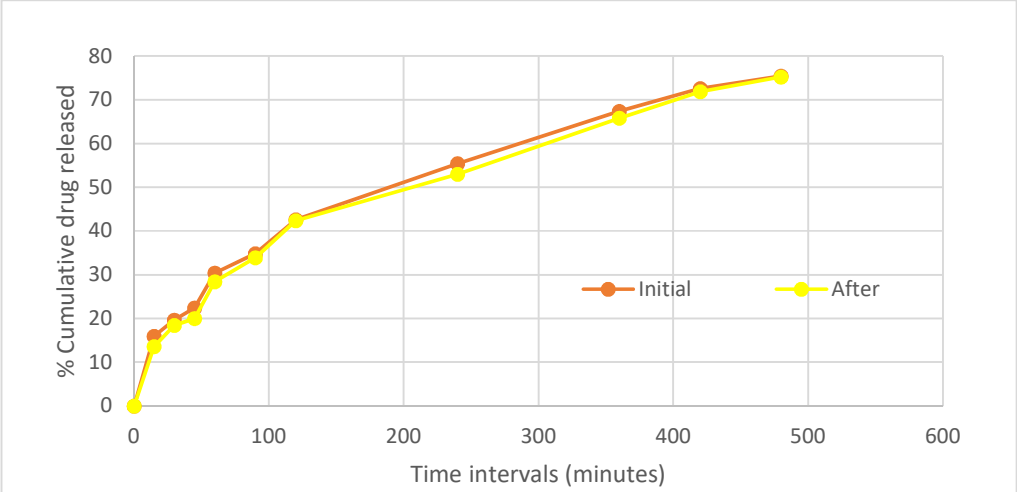


Figure 14.: Dissolution profile comparison of Formulation, F3 at t = 0 days and 28 days evaluated under accelerated stability conditions (40 ± 2 °C / 75 ± 5%RH)

Result: Under accelerated stability conditions (40 ± 2°C / 75 ± 5%RH), the dissolution profile of Formulation (F3) was assessed and compared from day 0 to day 28. The similarity factor (f2 = 86.77) and difference factor (f1 = 3.18), which are model-independent statistical metrics, verified that the drug release behavior did not significantly alter with time. These numbers show that the

two profiles are very comparable, indicating that the formulation is stable and performs consistently during the course of storage.

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