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LOPERAMIDE LOADED POLYMERIC NANOSPONGES FOR ENHANCED BIOAVAILABILITY: FORMULATION DEVELOPMENT AND *IN-VITRO* EVALUATION

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Abstract

Loperamide HCl belongs to antidiarrheals group used for the treatment of variety of acute, chronic or traveler's diarrhea by slowing down an overactive bowel leading to the decreased number of bowel movements. This study involved loperamide loaded beta cyclodextrin-based nano sponges that were found to be effective for treating diarrhea. Beta-Cyclodextrin, polyvinyl alcohol and dimethylsulfoxide are employed to fabricate nanosponges through emulsion solvent diffusion technology with little modifications. Antidiarrheal drug loperamide HCl loaded beta cyclodextrin based nano sponges were formulated and evaluated for studying physiochemical characteristics. Fourier Transform Infrared spectroscopy and scanning electron microscopy were used for structural analysis. Drug compatibility with excipients used in the formulation was determined by FTIR analysis. The development of inclusion complexes with porous and spherical morphology was verified by FTIR without any chemical interaction between drug and polymer. Spherical, spongy, porous and nano sized three-dimensional structure was shown by scanning electron microscopy. Analysis of particle size, percent yield, drug loading and entrapment efficiency of nano sponges were also performed. The particle size of formulation was in nano size range. The percentage yield was in the range of 91 and 94%. The entrapment effectiveness and percent drug loading were between 89% and 90%. In the *in-vitro* release experiment, loperamide loaded beta cyclodextrin based nanosponge formulations revealed continuous drug release profile with the absence of burst release phenomenon. The findings of all the studies confirmed that encapsulation of drug in nanosponges led to improvement in its efficacy in terms of its solubility, dissolution , release and therapeutic applications.

Keywords: Anti-diarrheal, nanosponges, pharmaceutical technology, cyclodextrin based nanosponges, loperamide HCl

1. Introduction

The oral route is the most frequently used method for administering drugs into the gastrointestinal tract (GI tract). It is suitable for delivering medications throughout the body as well as for treating localized gastrointestinal conditions. Patients prefer this route because it is easy to use, non-invasive, and convenient for self-administration (1). Administering drugs orally can lead to slower absorption rates, which isn't ideal in emergency situations. Additionally, oral medications may have an unpleasant taste, cause irritation in the stomach, and undergo processes that reduce their effectiveness in both the intestines and liver. Moreover, the conditions within the gastrointestinal tract can influence drug solubility and stability (2).

These hurdles can be tackled through the application of innovative drug delivery methods, offering advantages such as reduced dosing frequency, smaller doses, precise targeting, improved permeability and enhanced oral absorption. Nanotechnology emerges as a promising approach in crafting drug delivery systems, particularly for potent medications whose clinical progress was hindered by issues like poor solubility, limited permeability, insufficient bioavailability, and other biopharmaceutical shortcomings (3). Among the commonly employed nanotechnology based approaches in delivery system development are nanoemulsions, dendrimers, micelles, liposomes, solid lipid nanoparticles, polymeric nanoparticles, carbon nanotubes, and similar technologies, which enable controlled, prolonged, and targeted drug delivery. Nanotechnology has immense potential to alter the pharmacokinetic characteristics as well as bioavailability of medications. Delivering the right dosage of the drug and directing the medications to specific target sites are challenging at the industrial level. The afore-mentioned technology addresses the formulation, development and delivery aspects of nanomedicines (4).

Among nano colloidal carriers, cyclodextrin nanosponges provide numerous advantages over other delivery systems. These include a high payload capacity, prolonged stability, enhanced solubilization ability, controlled release, and ease of large-scale production. These are microscopic scaffolds that reach the specific target and stick to the membrane and initiate the regulated and anticipated release of the medication (5). These are small nanometric particles having cavities that contain a broad range of compounds. Additionally, nanosponges improve the bioavailability of drugs and alter pharmacokinetic parameters. They are also an effective method for delivering both lipophilic and hydrophilic compounds because of their hydrophobic interior and hydrophilic exterior, providing exceptional versatility (6). They are stable in nature and can be administered orally, parentally, topically, or by inhalation. Research in this area demonstrates that nanosponges have the potential to transform the treatment of numerous diseases. Preliminary trials indicate that this technology could be up to five times more efficient in delivering breast cancer drugs compared to traditional methods (7,8).

Beta cyclodextrins (β-CDs) have been extensively studied for their ability to enhance drug bioavailability, owing to their distinct structure, low toxicity when administered locally or orally, and their stability when combined with crosslinking agents like carbonyl compounds, carboxylic acids, and epoxides. This combination results in the creation of nano-porous formulations. Within this realm, β-CD-based nanosponges (NSs) stand out as carriers characterized by a sponge-like structure and lipophilic nanochannels, which are formed by linking β-CD monomers together (9).

Loperamide (LPM) has antidiarrheal characteristic and is a μ-opioid receptor agonist. It was approved by the FDA to treat various types of diarrhea (acute, chronic, ileostomy, and traveler's diarrhea) as the primary indication, and chemotherapy-induced diarrhea (particularly when combined with irinotecan) as an off-label usage (10). It acts through various mechanisms that reduce peristalsis and fluids secretion, which leads to increased gastrointestinal transit time and higher gastrointestinal electrolytes and fluids absorption (11). It is offered in a variety of oral formulations for administration. However, its extremely bitter taste, low water solubility, significant first-pass effect and slow rate of

intestinal dissolution severely limit its therapeutic applications (12). Hence, this study is aimed to formulate beta-cyclodextrin-based nanosponges of loperamide HCl for enhancing the drug bioavailability by improving the solubility and sustained release profile for prolonged periods.

2. Materials and Methods

2.1 Materials

The following materials were used with the best possible grades available, supplied by the manufacturer. Loperamide HCl, polyvinyl alcohol (PVA), dimethyl sulfoxide (DMSO) and beta-cyclodextrin were used in the experiment. All other materials used of analytical grades. All the reagents and solvents used for study were of pharmacopeial and analytical grade.

2.2. Construction of Loperamide HCl Calibration Curve

To create the calibration curve, loperamide HCl dilutions were made in DMSO. Utilizing a UV spectrophotometer, absorbance readings of known concentrations ranging from 10 to 100 µg/ml were measured and graphed at the maximum wavelength (λmax) of 259 nm, establishing a correlation between concentration and absorbance. The mean value of triplicate measurements was calculated.

2.3. Development of Beta-Cyclodextrin Based Loperamide HCl Loaded Nano Sponges

Loperamide HCl loaded beta-cyclodextrin-based nanosponges were created using the emulsion solvent evaporation technology with modifications. Beta-cyclodextrin (40-100mg) and loperamide HCl (20 mg) were dissolved in 10 mL of dimethyl sulfoxide (DMSO) to prepare the organic phase. For the production of the aqueous phase, water was heated at 60°C with continuous stirring to dissolve PVA in 50 mL of deionized water (Table 1). As the aqueous phase's pH increased, more LPM was partitioned into the organic phase. Aqueous phase pH was adjusted with 0.1M NaOH to alkaline scale to make reaction possible.

The organic phase was emulsified drop wise into aqueous phase. PVA was used to stabilize nanosponges because it prevents particle agglomerations. The dispersion was then kept on a thermostatically controlled magnetic stirrer for 24 hours while being continuously stirred at 1000 rpm and at room temperature. Loperamide HCl was rinsed with ultrapure water to remove the adsorbed PVA after the organic solvent had completely evaporated. Next, nano sponges were collected by ultracentrifugation at 17,000 rpm and 4^{o}C for 30 min (13).

Table 1. Composition of different formulations of loperamide HCl loaded β-cyclodextrin based nanosponges

Formulation Code	Drug (mg)	Beta-Cyclodextrin (mg)	Polyvinyl Alcohol	Dimethyl sulfoxide(ml)	Distilled Water (ml)
F1	20	40	0.25%	10	50
F2	20	60	0.75%	10	50
F3	20	80	1.5%	10	50
F4	20	100	2.5%	10	50

2.4. Characterization of Beta-Cyclodextrin Based Nanosponges of Loperamide HCl

2.4.1. Percent Yield

The actual yield of nanosponges was determined by weighing dried nanosponges. The weight of each solid ingredient utilized to formulate the nanosponges, including the drug, beta-cyclodextrin NS, was taken as the theoretical yield. Percent yield is calculated by the following formula (14).

$$\text{Percentage Yield} = \frac{\text{Actual Yield}}{\text{Theoretical yield}} \times 100$$

2.4.2. Percent Drug Loading

Accurately weighed NS (10mg) and 5ml of (0.1N NaOH) was taken in vortex tube (15ml) and shaken for 1 minute. With further addition of 0.1N NaOH, volume was made up to 10ml after shaking. 1ml

of filtered solution in volumetric flask was taken after filtration in order to calculate the concentration of loperamide HCl, absorbance was then determined at lambda max 259 nm (15).

$$\text{Drug Loading} = \frac{\text{Drug content of NS}}{\text{Weight of NS recovered}} \times 100$$

2.4.3. Entrapment Efficiency

In vortex tube (15ml), an accurately weighed amount of NS (10mg) and 5ml of (0.1N NaOH) were added, and then shaken for 1 minute. After shaking, volume was made up to 10ml with 0.1N NaOH. After filtration, 1ml of filtered solution was taken and volume was made up to 10ml with 0.1N NaOH. At lambda maximum 259 nm, absorbance was determined which was used to calculate the concentration of loperamide HCl (14).

$$\text{Entrapment efficiency} = \frac{\text{Drug content of NS}}{\text{Initial weight of NS}} \times 100$$

2.4.4. Zeta Analysis

Using a Malvern Zeta Sizer, the particle size of loperamide HCl nano sponges was determined. The samples were properly diluted with distilled water. All samples were analyzed using the same fixed angle of 90°. To evaluate the effect of particle size on drug release, a cumulative graph was plotted as particle size against time. Aqueous dispersion was diluted up to specified scattering at 25 ^{o}C. Dynamic light scattering with zeta sizer was used to determine the diameter of nanosponges. For the determination of zeta potential, nanosponge formulations were initially diluted with 0.1mol/l KCl and then placed in an electrophoretic cell and subjected to a 15V/cm electric field. Triplicate readings of zeta potential were taken (16).

2.4.5. Surface Morphology

Surface morphology of developed nanosponge formulations was determined with the help of scanning electron microscopy. Following a random scan of the samples, a photomicrograph was taken at a 20KV acceleration voltage. The average particle size was determined from the resulting image (17).

2.4.6. Drug Excipient Compatibility Study

To check the compatibility or interaction of loperamide HCl with polymer, Fourier transform infrared spectroscopy was used. Sample FTIR analysis was completed by ATR-FTIR spectrophotometer. Frequency range for verification of spectra was 4000-600cm^{-1}. To clarify the interaction, FTIR spectra of drug-free and drug-loaded Nano sponges were taken (18).

2.4.7. Drug Dissolution Studies

A section of dialysis membrane weighing 12,000–14,000 Da was cut prior to release study. It was then dipped in 2% sulfuric acid for 3-5 minutes, washed with distilled water, and then soaked in phosphate buffer solution for overnight. PBS pH 6.8 was put in the receptor compartment, and fresh formulation was placed in the donor compartment. The dialysis membrane, which is in contact with the receptor medium composed of phosphate buffer solution, filled with 3ml of the formulation. It was placed into a 250 ml vessel containing 100 ml of PBS pH 6.8. The entire assembly was set up on a thermostatically controlled magnetic stirrer at 1000rpm, and it was continuously stirred. The medium's temperature was maintained constant at 37 ± 0.5°. At specified intervals, 1ml of the sample was taken out of the receptor compartment and replaced with an equivalent volume of PBS 6.8. After the appropriate dilution, a UV-visible spectrophotometer was used to find the absorbance (19).

2.5. Statistical Analysis

The data were analyzed statistically using one-way ANOVA with SPSS software (version 18.0) to determine significant differences between groups. A p-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Calibration Curve of Loperamide HCl

To construct the calibration curve, dilutions of loperamide HCl were prepared. Using UV spectrophotometer, by measuring and plotting absorbance of known concentration from 10 to 100mg/ml the calibration curve was prepared at λ maximum of 259 nm, and between concentrations versus absorbance a curve was plotted. The average of triplicate was taken. Loperamide HCl calibration curve showed a straight line with a regression equation.

$$y = 0.0192x - 0.0048, R2 - 0.976$$

For the determination of concentration in unknown samples, this curve was used.

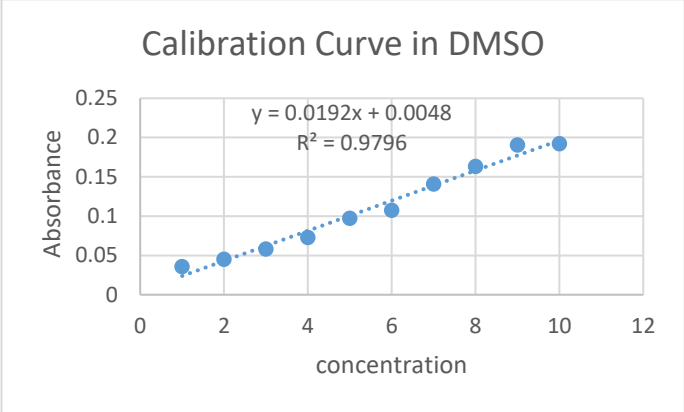


Figure 1. Calibration curve of loperamide HCl (Dimethyl sulfoxide DMSO)

3.2. Development of Nanosponge Formulations

Four different nanosponge formulations were prepared according to the method as already mentioned in the methodology section by taking the accurately weighed fraction of all the ingredients. The results revealed successful stable nanosponge formulations of batch F3 and F4, as presented in Table 2. These successful batches were further run for various characterization analysis.

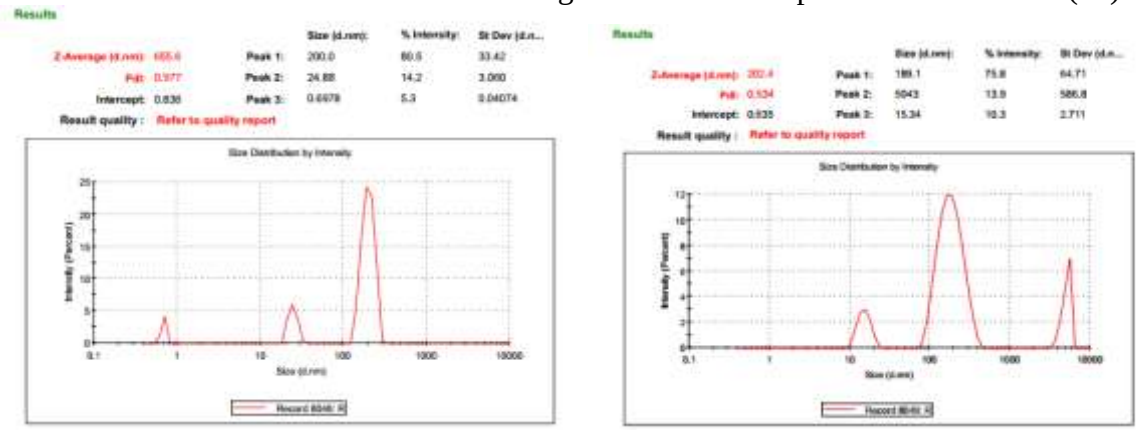
Table 2. Pictorial display of various nanosponge formulations (stable & unstable)

Formulation code	NS Formation
F1	unstable
F2	unstable
F3	stable
F4	stable

3.3. Physico-chemical Characterization

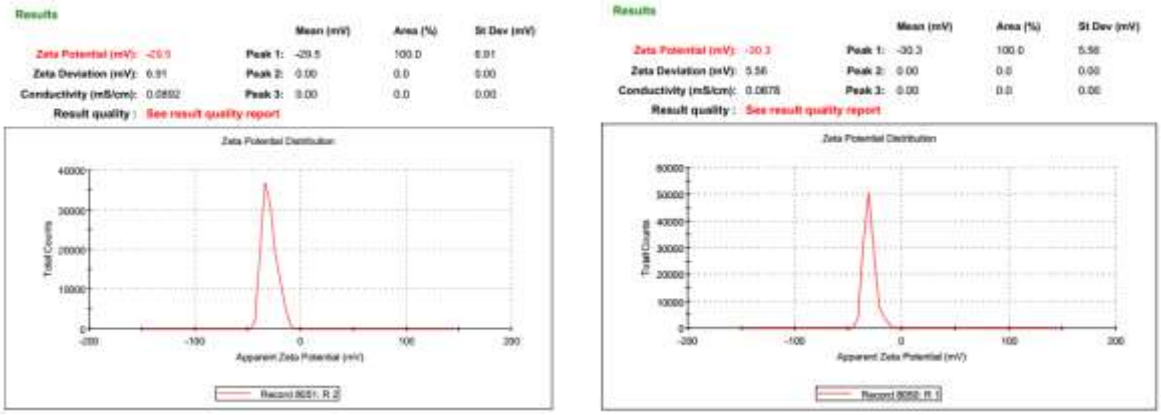
Among all the prepared formulations, F3 and F4 were stable and opted for further analysis of their respective physico-chemical tests. The particle size of F3 was found to be 655.6 nm whereas the F4 has particle size of 202.4 nm (Figure 2). This may be attributed to the fact, as supported by the previous literature, that increasing the PVA content in the formulation can cause reduction in the particle size (20). A statistically significant difference was observed in the particle size of formulations F3 and F4 ($p<0.05$). Zeta potential of nanosponges enables us to understand more about the stability of formulation and extent of agglomeration. Selected formulations were led forward to perform analysis of zeta potential measurement. The zeta potential of NS F3 and F4 was found to be

-30.3 mV and -29.5 mV respectively (Figure 3), indicating absence of agglomeration due to the steric hinderance (21), lacking any significant difference ($p>0.05$). The resulting yields of formulation F3 and F4 were found to be 91 % and 94 % respectively. Similarly, the resulting entrapment efficiencies of prepared formulations F3 and F4 were 89 % and 90 % respectively. The higher drug loading as well as entrapment efficiency values in F4 formulation were strongly correlated to the higher PVA contents in the formulation. Our results are in agreement with the previous researchers (22).



(A) **(B)**

Figure 2. Particle size of NS F3 (A) and F4 (B)

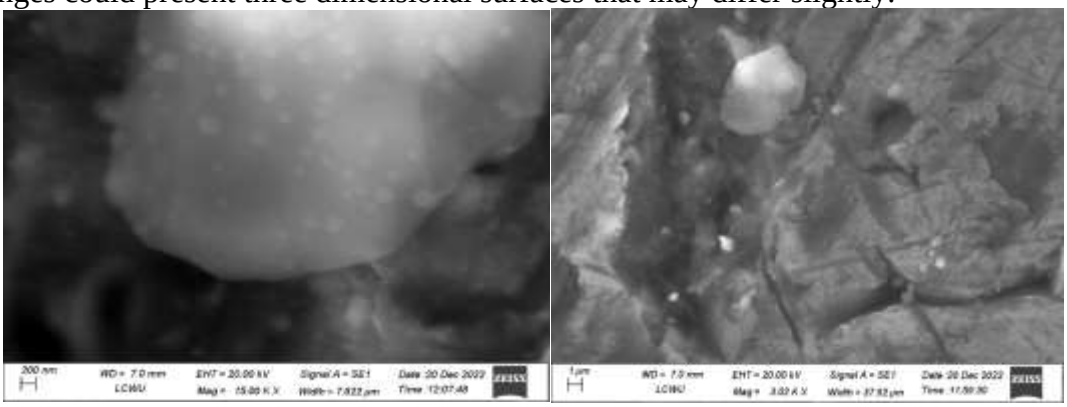


(A) **(B)**

Figure 3. Zeta potential NS F3 (A) and NS F4 (B)

3.4. Scanning Electron Microscopy

SEM was performed to assess morphological features of F3 and F4 nanosponge formulations. Figure 4 depicted porous and spongy nature having orange peel like appearance. It is evident that polymeric nanosponges could present three dimensional surfaces that may differ slightly.



(A) **(B)**

Figure 4. SEM analysis of (A) NS F3 and (B) NS F4

3.5. Drug Excipient Compatibility Analysis

FTIR spectra of pure drug, beta-Cyclodextrin, polyvinyl alcohol, dimethyl sulfoxide and loperamide HCl loaded NS formulations are demonstrated in Figure 5. The FTIR spectrum of loperamide HCl displayed distinct absorption peaks consistent with previously reported data (23), confirming the presence of specific functional groups. A broad peak observed around 3211 cm−1 signifies the presence of an exchangeable proton stretch (-OH). Around 2980 cm−1, new peaks emerged, signifying the presence of saturated carbons, thereby confirming the –CH group. In the region below 2000 cm−1, known as the fingerprint region, several characteristic peaks corresponding to different functional groups of the molecule were seen, including -CO, -CH3 and -R-Cl that corresponded to 1463 cm−1, 1379 cm−1 and 1040 cm−1, respectively, and a distinct area between 760 to 740 cm−1 for aromatic hydrocarbons. FTIR analysis revealed no new peak formation or absence of actual peaks, indicating no incompatibility among drug and excipients of the formulation. However, the broadening and masking of drug peaks was observed, which confirmed the encapsulation of loperamide HCl in nano sponge core.

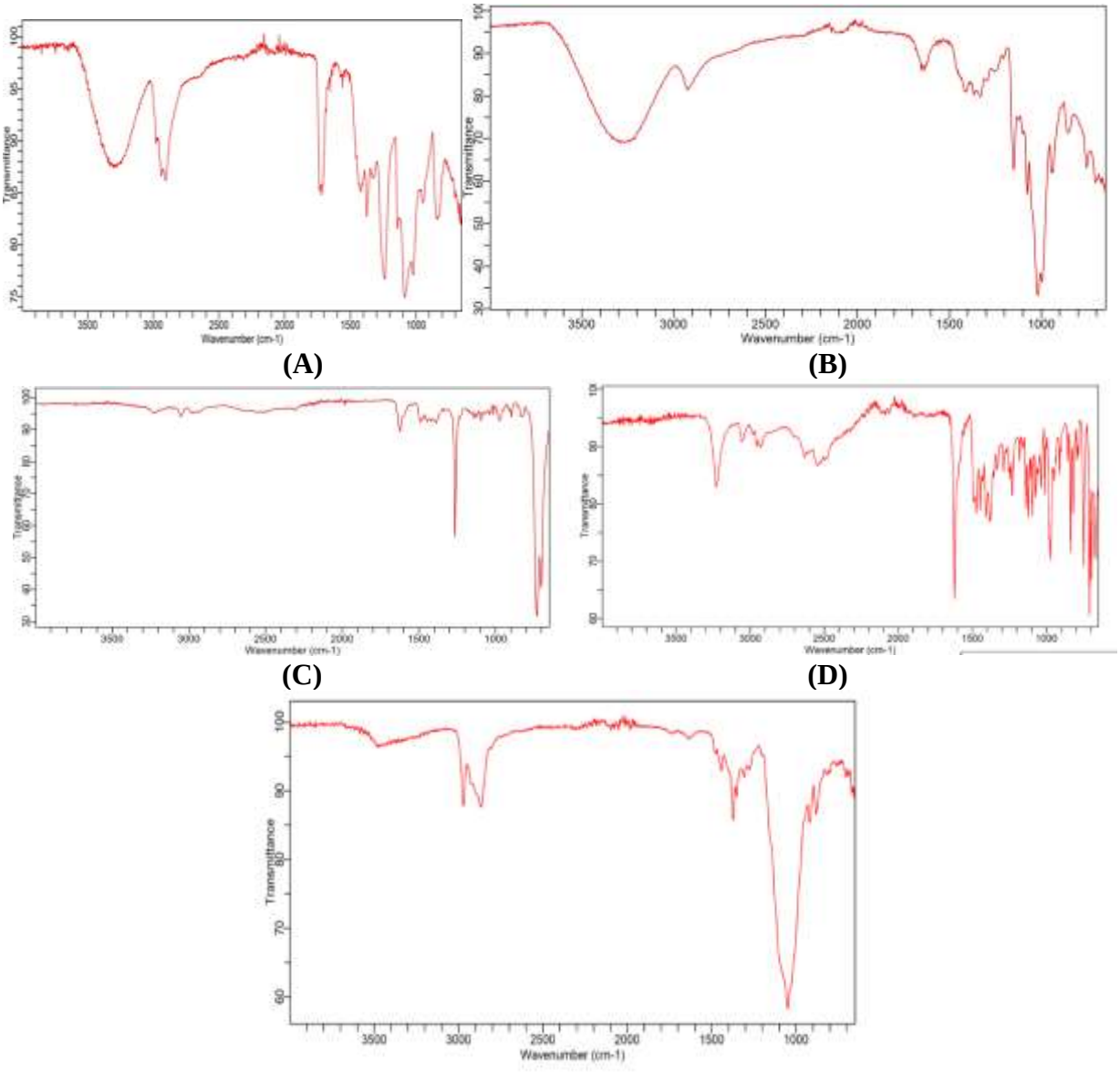


Figure 5. FTIR spectra of (A) PVA, (B) Beta-cyclodextrin, (C) DMSO, (D) Loperamide, (E) Loperamide Loaded Nanosponges

3.6. *In-vitro* Drug Release

Loperamide nanosponge formulation F4 exhibited no initial burst release at pH 6.8, indicating minimal drug presence over nanosponge surface. A steady release profile was noted at this pH. Over a 24-hour period, approximately 90 % of the loperamide was released from the nanosponges in PBS (pH 6.8), suggesting effective encapsulation within the nanosponges. This encapsulation likely protects the drug from the harsh acidic conditions in the stomach, allowing for its release in the small intestine (24). The drug release profile is illustrated in the accompanying Figure 6.

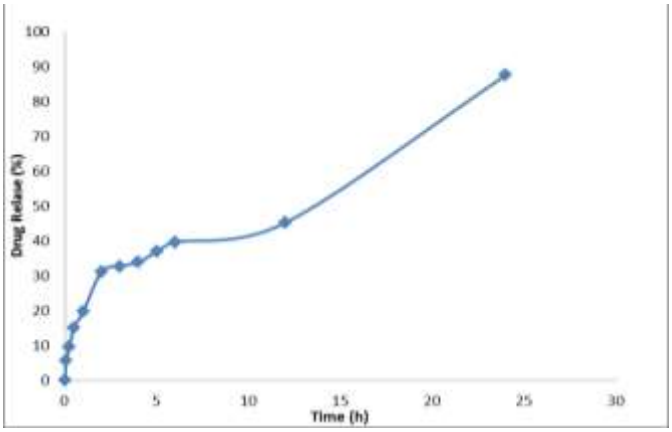


Figure 6. *In-vitro* drug release profile of loperamide HCl nanosponge formulation F4 in PBS pH 6.8.

4. Discussion

Loperamide HCl is a potent anti-diarrheal agent used specifically for the management of variety of diarrheal etiologies like traveler's diarrhoea as well as chemotherapy induced diarrhoea. The implication of this drug is limited due to its low solubility profile, significant hepatic first pass metabolism and low intestinal dissolution. In order to address these drawbacks, loperamide HCl was loaded into nanosponge formulation for its improved solubility as well as intestinal dissolution profiles. Loperamide loaded nanosponges were effectively produced using the emulsion solvent evaporation method, which involves allowing the organic solvent to evaporate from the mixture through vigorous stirring overnight (25). The polymer concentration for nanosponge development was fine-tuned to achieve the desired characteristics of the nanosponges, such as particle size, zeta potential, and *in-vitro* drug dissolution. Various polymers were considered for the formulation, including Eudragit L 1000, ethyl cellulose and beta-cyclodextrin. Of these, beta-cyclodextrin proved to be the most suitable with the chosen preparation method, demonstrating promising results in drug entrapment, and was therefore selected for further development.

Entrapment efficiency was found to be associated with polymer concentration. An enhanced polymer concentration resulted in increased entrapment efficiency. A similar trend has been found in case of particle size, however PVA content has substantial impact on the particle size i.e. increasing PVA content leads to decreased particle size. This could be attributed to increased porosity of the nanosponges that retained the drug more inside, leading to reduction in the particle size (20).

Diffusion coefficient and electrophoretic mobility are taken into consideration while measuring zeta potential. When determining the zeta potential, the pH and electrolyte concentration must be taken into consideration. Zeta analysis can be used to evaluate the stability of the manufactured Nano sponges. The values of zeta potential were within the appreciable range of ± 30 mV, indicating formulation stability due to steric hinderance (26).

For the analysis of structure and morphology of prepared NS formulations, SEM and FTIR were used. Higher drug loading and entrapment efficiency formulations were selected for structural analysis. The SEM technique also offered a qualitative evaluation of the particle size, size distribution, shape, porosity, morphology, consistency and crystal form of the nanosponge formulation (27). The data

provided by SEM can help ensure the precise quality characterization of nanosponges. By using vacuum with a focused electron beam, SEM involves imparting conductivity to the developed particles. Even after the drug was encapsulated within the nano sponges, their size and shape remained unaltered (28).

FTIR is a crucial technique for identifying the existence of functional groups. The existence of functional group peaks in the FTIR spectrum following polymer synthesis is a sign that bonds between the polymer's monomer units are formed. A vibrational spectrum for crystalline structure is obtained in FTIR. The fingerprint region, or 900 to 1400 cm^{-1}, experienced significant changes in the spectra of loperamide HCl and complex, indicating drug loading in the nanosponges. Employing spectroscopic techniques like FTIR in pre-formulation has greatly enhanced the early identification and analysis of potential physical or chemical interactions between the drug and excipient. This approach aids in the logical selection of the most suitable excipients for designing dosage forms (29). There was no burst release rather continuous release was exhibited by loperamide HCl loaded nanosponge formulations. This could be attributed to the porous nature of the nanosponges which enabled the drug to be released through their pores. The findings showed that the drug release was regulated by the rate at which the solvent penetrated a non-swellable, water-insoluble polymer like β-cyclodextrin, which controls the drug release through the micropores in its structural framework (30).

5. Conclusion

Beta-cyclodextrin, a well-known polymer for its release retarding properties, was used in crafting sustained release nano sponges of loperamide HCl with the help of the emulsion solvent diffusion approach using PVA as surfactant. Polymer ratio affected the physiochemical parameters of NS including production yield, entrapment efficiency and particle size. Spherical and spongy structures were observed by morphological analysis. These nano sponges were characterized and results encouraged this approach for modification of loperamide HCl for conventional capsules to novel dosage form of nanosponges.

6. References

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