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FORMULATION AND INVITRO EVALUATION OF FELODIPINE LOADED NANOSPONGES– A PROPITIOUS PLATFORM FOR ENHANCING ORAL BIOAVAILABILITY

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ABSTRACT

Hypertension is one of the most prevalent disorders in the world. Managing hypertension remains challenging due to the existing treatments' limited oral absorption and toxicity at higher dosages. Increasing the oral bioavailability of poorly water soluble drugs continues to be one of the most difficult areas of medical research. According to the Biopharmaceutical Classification System (BCS), felodipine is a class II drug with a low solubility and high permeability. It is therefore considered as the phase that limits the rate of the bioavailability process. Using the emulsion solvent diffusion approach and three different ethyl cellulose concentratisssssons, felodipine nanosponges were produced. This research project aims to increase felodipine's bioavailability. Particle sizes between 400 and 900 nm were confirmed by a DLS measurement. SEM photomicrographs were used to demonstrate the porous nature of the nanosponges, the solid surface of formulation F2 and the crystalline nature of the felodipine nanosponge confirmed by XRD study. In FTIR tests, no interactions between drugs and polymers were found. DSC thermograms were used to show that the drug's molecular dispersion in nanosponges was stable. The in vitro drug release from the nanosponges shown better solubility and higher bioavailability, with a burst release occurring within the first four hours and sustained drug delivery over the next twelve hours.

KEYWORDS: Nanosponges, Felodipine, Hypertension, Ethyl cellulose & emulsion solvent diffusion method.

INTRODUCTION

The calcium channel blocker felodipine comrs under the dihydropyridine (DHP) derivatives. Felodipine's vasodilatory actions cause a general drop in blood pressure.[14] Felodipine has the advantages of selective small artery dilation, no overt myocardial inhibition, no impact when used to treat mild to moderate essential hypertension, it has a positive impact on glomerular filtration rate and a reduced risk of organ damage.[12,13] However, the extremely poor oral bioavailability of felodipine (15%) is mostly a result of its inefficient liver metabolism and gastrointestinal absorption. It was established that the rate-limiting step in the stomach's capacity to absorb the felodipine and sluggish dissolution rate due to its poor solubility in gastrointestinal fluid, not gut permeability. They are porous, insoluble in both water and organic solvents, and stable at temperatures up to 300 °C, setting them apart from other nanoparticles. They feature a 3D structure with nanoscale voids and adjustable polarity, which enables them to carry and transport the drug molecules to the target site. Nanosponges have greater benefits than regular nanoparticles since they can be readily replenished using a variety of techniques, including cleaning with ecologically friendly solvents, mild heating, stripping with reasonably safe hot gases, or modifying ionic strength or pH.[5]

Due to felodipine's frequent administration, short half-life, and low bioavailability, there is a significant need for developing nano-particulate drug delivery systems. The felodipine was created as a Nano-sponge system in the current study, which increases the solubility and bioavailability of the medication while minimizing negative effects.[11]

The solubility of poorly water soluble drugs that increased by a special kind of hyper-cross linked polymer-based colloidal structure known as a "nano-sponge" that is hydrophilic and hydrophobic in nature and built of solid nanoparticles with colloidal sizes. Nanosponges are extremely small, mesh-like structures that have the potential to completely change how many diseases are treated, according to studies in this area of nanotechnology. With the use of particular linkers, nanosponges can bind to sick cells with great efficiency while minimizing adverse effects, lowering dose requirements, and increasing patient compliance. They remain stable at pH levels between 1 and 11.[2,4]

The solvent evaporation method was used to produce biocompatible and biodegradable/non-biodegradable polymer nanosponges, including PVA and ethyl cellulose polymer. The active pharmaceutical ingredient is dissolved in a polymeric solution that has been dissolved in a suitable water-miscible organic solvent in the solvent evaporation procedures. This is emulsified in an aqueous continuous phase using a surfactant, stabilizer, and emulsifying agent. A few of the factors that influence the formation of nanosponges include drug solubility, solvent diffusion rate, temperature, polymer type, viscosity, and pH of the external phase. This simple method makes it possible to capture a wide range of hydrophobic drugs.[2]

MATERIAL AND METHODS

MATERIALS

Pure felodipine was given as a gift by Biocon Research Limited. Dichloromethane, ethyl cellulose, and poly vinyl alcohol (PVA; M. Wt. 22000 Da) were bought from Zhuhai Chemico Industries and Himedia, Mumbai, respectively. Every other substance, including reagents, was of analytical grade. Milli Q water (Millipore) was utilized throughout the investigation.

Preparation of felodipine nanosponges by emulsion solvent diffusion method

Using an appropriate polymer and the emulsion solvent diffusion approach, felodipine-loaded nanosponges were produced. The drug (5 mg) and various polymer concentrations (10, 20, and 30 mg) were dissolved in 20 ml of dichloromethane to create the dispersion phase. A particular quantity of Polyvinyl alcohol (0.01%w/v) is dissolved in 100ml of water to create the aqueous phase. Using a magnetic stirrer for two hours at 2000 rpm, the dispersed phase was gradually mixed into the aqueous phase. The resultant nanosponges were filtered before being dried for 24 hours in an oven at 40°C. After that, they were put in vacuum desiccators to get rid of any leftover solvent. The felodipine nanosponges were made with ethyl cellulose polymers.[21]

The emulsion solvent diffusion technique was used to create three different formulations of felodipine nanosponges (F1-F3). The ingredients and amounts utilized to create felodipine nanosponge formulations are shown in (Table No.1).

Table 1: Formulation of different batches of felodipine nanosponges.

S.No	Formulation code	Weight of drug (mg)	Weight of polymer (mg)	Weight of PVA (mg)
1	F1	5	10	10
2	F2	5	20	10
3	F3	5	30	10

Characterization of felodipine nanosponges

The estimation of the maximum absorbance (λmax)

The standard stock solution was scanned in the UV spectrophotometer between 200 and 400 nm using a blank solution of phosphate buffer pH 6.8. The maximum levels of felodipine absorption at 238 and 361 nm were observed and contrasted with the maximum levels of the reference samples listed in the Indian Pharmacopoeia.

Fourier Transform Infra-Red (FTIR) spectroscopy

FT-IR spectrophotometer was used to record the drug's FT-IR spectra. The diffuse reflectance approach was used to conduct investigations on the mid-IR 4000-400 cm-1 spectral region. The spectrum was recorded and the characteristic peaks of the functional group were explained using the KBr pellet technique.[20]

Particle Size Determination

The mean particle size and the breadth of the particle size distribution, which are important characterisation factors, control the saturation solubility, dissolving velocity, physical stability, and even biological performance of nanosponges. With the changing drug particle size, there has been a noticeable variation in the saturation solubility and dissolution. Using the dynamic scattering method created by Malvern Zetasizer at 25°C, the average mean diameter and size distribution of nanosponges are determined. The dried nanosponges were dispersed in water to produce the requisite light scattering intensity for felodipine nanosponges.[17]

Zeta potential evaluation

Zeta potential measures surface charge. A zetasizer (Malvern instrument) outfitted with zeta cells, a polycarbonate cell with gold-plated electrodes, and nanosponge dispersions that have been diluted to 1 to 100 using double-distilled water can be used to measure the surface charge of nanosponges. In order to achieve the best electrophoretic velocity measurement, the dispersion was charged in the zeta meter cell and the voltage was set at 50-100V. Direct

readings from the device were used to determine the charge on the nanosponge and its average zeta potential value with standard deviation (SD). Its indicating the stability of nanosponges.[17]

Determine the effectiveness of entrapment

The amount of unentrapped felodipine in nanosponges are separated by ultracentrifugation at 8000 rpm for 10mins at 4◦C, then supernatant liquid assayed spectrophotometrically at 364nm for free drug content. Amount of entrapped drug was obtained by subtracting amount of unentrapped drug from the total drug incorporated.[19]

$$\%\ Percentage\ entrapment = \frac{Entrapped\ drug\ (mg)}{Total\ drug\ added\ (mg)} \times 100$$

Saturation solubility studies

Both the pure medication and several batches of nanosponges that had been specially prepared were examined in the saturation solubility investigations. Weighed separately, 10 ml of HCl and Phosphate buffer were poured to a 25 ml stoppered conical flask holding 5 mg of unprocessed drug and nanosponges corresponding to 5 mg of felodipine. The flasks were sealed and maintained in a rotary shaker at 37℃ for 24 hours before reaching equilibrium for 2 days. After the predetermined amount of time, the samples were membrane-filtered and submitted to UV spectrophotometric analysis at 364 nm. The samples were then collected, and the findings were recorded.[8]

Study on *In Vitro* release

At a rotational speed of 100 rpm, the USP Dissolution Test Device was utilized to examine the dissolution profile of felodipine and its nanosponges. In-vitro release procedures were carried out in freshly made phosphate buffer PH 6.8. The equivalent of 5 mg of the pure medication and felodipine nanosponges were taken and added to the dissolving medium. The dissolving media was 900 ml in volume, and the temperature was maintained at 37℃. At regular intervals, samples were changed out and filtered. A UV spectrophotometer was used to analyze the filtered samples at 364 nm. The results of every calculation were triple checked. The cumulative percentage release was computed using the calibration equation.[7]

Scanning Electron Microscopy study

The morphological characteristics of the created felodipine-loaded nanosponge was investigated using SEM analysis. A scanning electron microscope (SEM) (CARL ZEISS,

BRUKER) was put on the sample and used to analyze it under various magnifications. Using a sputter coater unit running at 15 kV acceleration voltage, samples were placed on vacuum-sealed glass slides and coated with a thin coating of gold.

Thermal analysis

Drug, polymer, and copolymer interactions are clarified through thermal study. Using a cooling accessory made of liquid nitrogen, DTA and TGA were performed. Dry nitrogen gas was used as a purge during the study. A sufficient seal was achieved by tightly crimping the lid after placing the sample, weighing between 2 and 5 mg, in an aluminum crucible cell. The sample was heated at a preset heating rate of 10℃/min from room temperature to 30℃.[15,16]

X-ray powder diffraction

Using an efficient X-ray diffractometer, felodipine nanosponges was analysed with a target filter of cu and a voltage/current of 40KV/40Ma at a scan speed of 1 second, an X-ray diffractometer will be used to study the felodipine nanosponges' X-ray diffraction patterns (XRD). Two angles, spanning from 4 to 90 degrees each, will be used to analyze the material.[18]

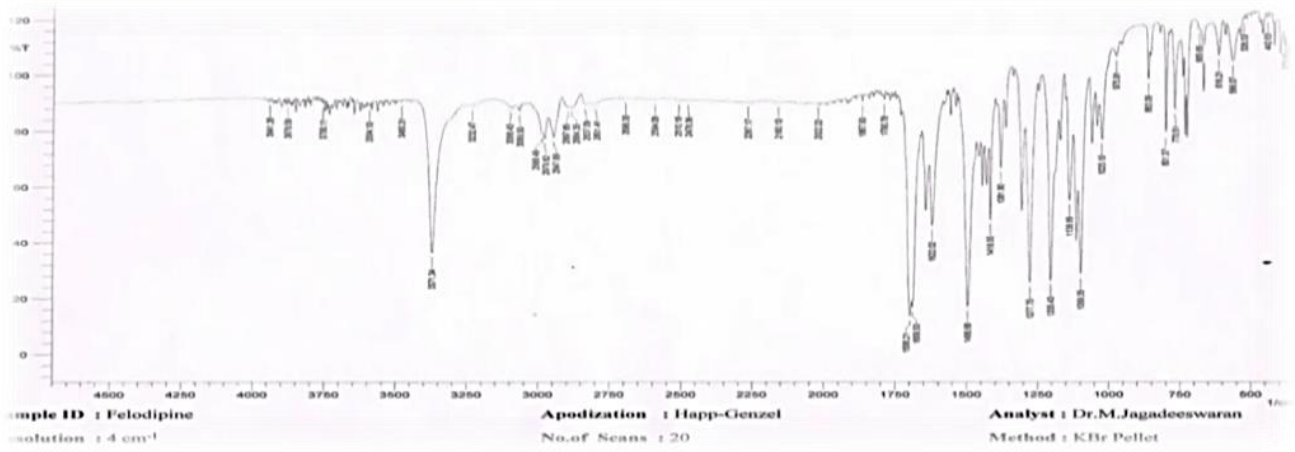
RESULT AND DISCUSSION

Ultra-Violet (UV) absorption spectra

The spectrophotometric evaluation of felodipine was done between 200 and 400 nm. At 364nm, the maximum absorbance (max), which was discovered using a quantitative approach, was found.

IR spectroscopy

To find any potential interactions between pure drugs and polymers, FTIR spectrum was utilized. The unique peaks can be seen in formulations, polymers, and pure drugs. Peaks in the polymer and felodipine were comparable. All of the polymers were determined to be appropriate for the formation of nanosponges since there was no discernible shift, disappearance, or reappearance of peaks in the combined spectra shown in Figure 1 (a,b,c,d), which indicated good drug-polymer compatibility and no change in felodipine's chemical structure.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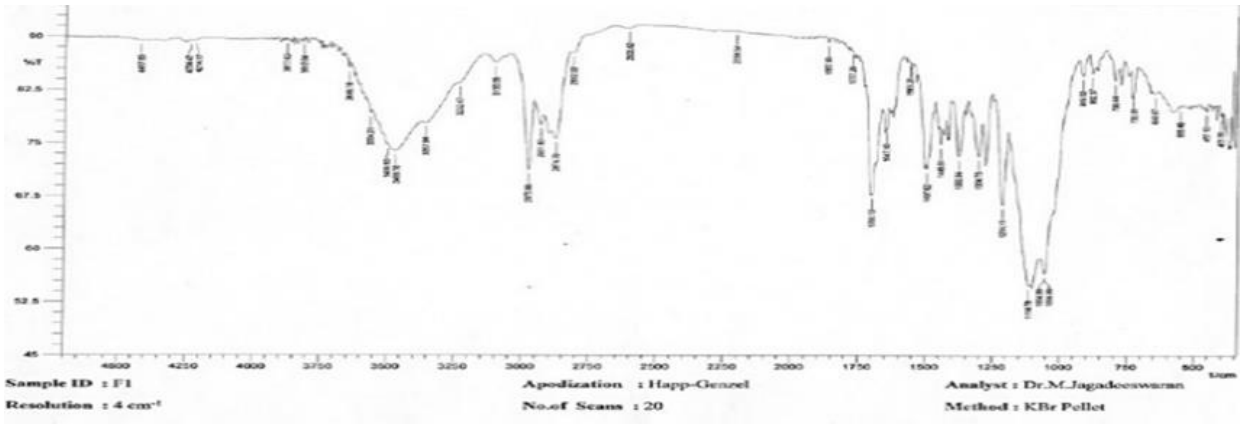
Analyst : Dr.M.Jagadeeswaran
No.of Scans : 20
Method : KBr Pellet


Sample ID : F1
Resolution : 4 cm-1
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No.of Scans : 20
Analyst : Dr.M.Jagadeeswaran
Method : KBr Pellet

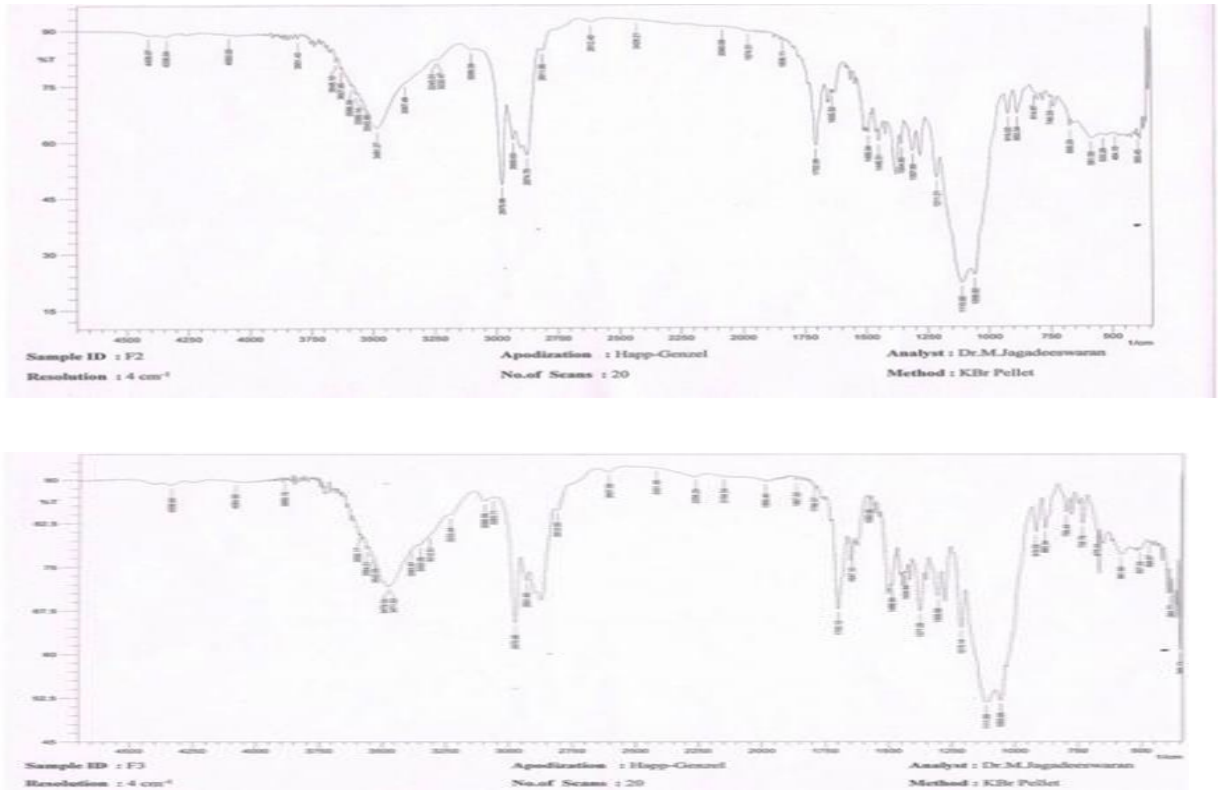


Figure 1: (a) FTIR spectrum of felodipine; (b) FTIR spectrum of F1 formulation; (c) FTIR spectrum of F2 formulation; (d) FTIR spectrum of F3 formulation.

Particle size and poly Dispersibility index

The average diameter of the particle size was measured in nanometers, and the polydispersity index was used to assess the particle size distribution. Figure 2 gives data information on polydispersity index, and particle size.The average particle size of nanosponges range of (F1) 670.8, (F2) 486.6 and (F3) 989.02 d. nm respectively. The physical stability of nanosponges is increased by the polydispersity index, which provides a measure of particle size distribution. The polydispersity index of formulation ranges from (F1) 0.026, (F2) 0.376 and (F3) 0.167 respectively (figure 2-a,b,c). The formulation F3 indicates smallest particle size (92.02) which suggests nano size and good uniformity in particle size distribution. The result indicates that nanosponges particle size increased with increasing polymer concentration.

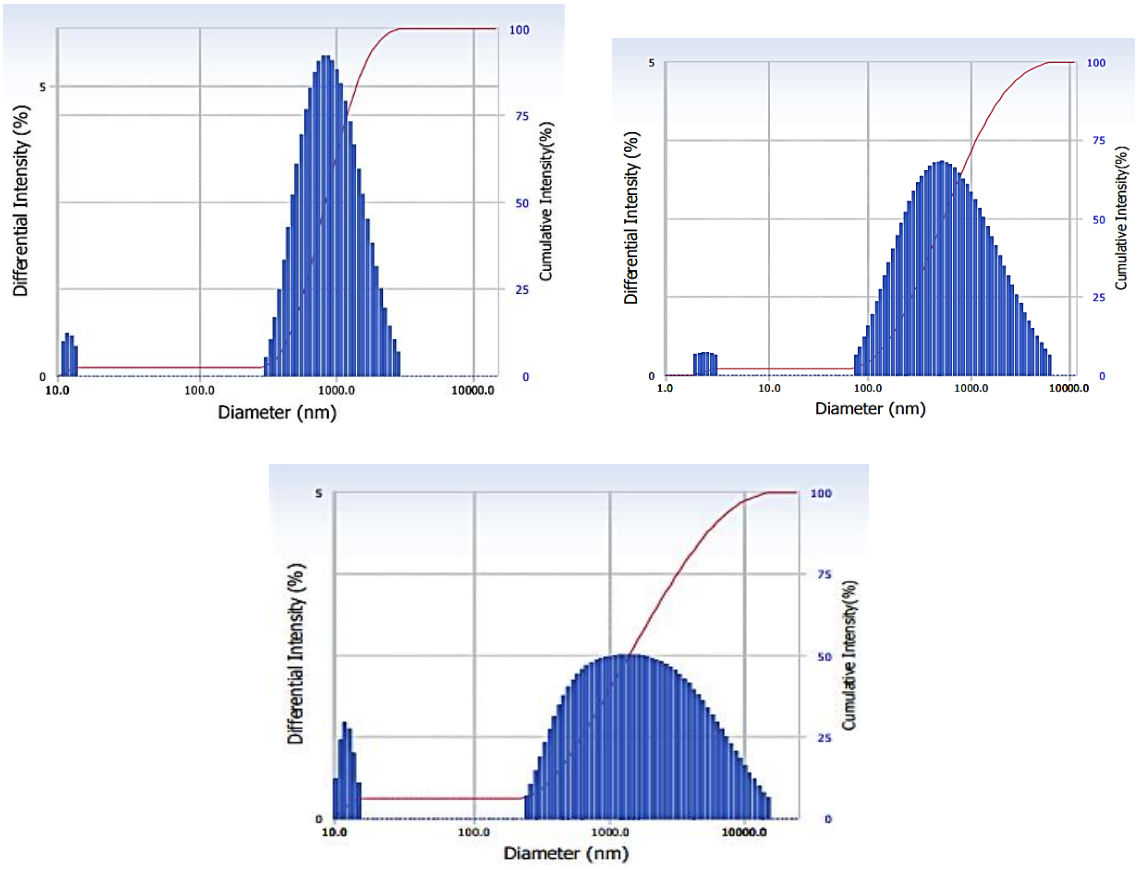


Figure 2: a) particle size and poly-dispersibility index of Nanosponge F1; b) particle size and poly-dispersibility index of Nanospong F2; c) particle size and polydispersiblity index of Nanosponge F3.

Determination of zeta potential

Stronger repelling forces are produced by extremely positive or negative zeta potential levels, although repelling oppositely charged particles keeps them from congregating and promotes re-dispersion. In order to combine electrostatic and steric stability, a zeta potential of at least 20 mV was necessary. Zeta potential analysis is done to determine a particle's surface charge in order to determine its stability during storage. In the examination of nanosponges zeta potential, it was discovered that the formulations F1 to F3 had zeta potentials in the range of F1 (-14.1 mV), F2 (-21.3 mV), and F3 (-27.2 mV), respectively (figure 3-a,b,c). This indicates strong physical stability of nanosponges. Stabilizer absorption on the drug particles produced the negative charge, which causes the negative zeta potential in drug nanosponges.

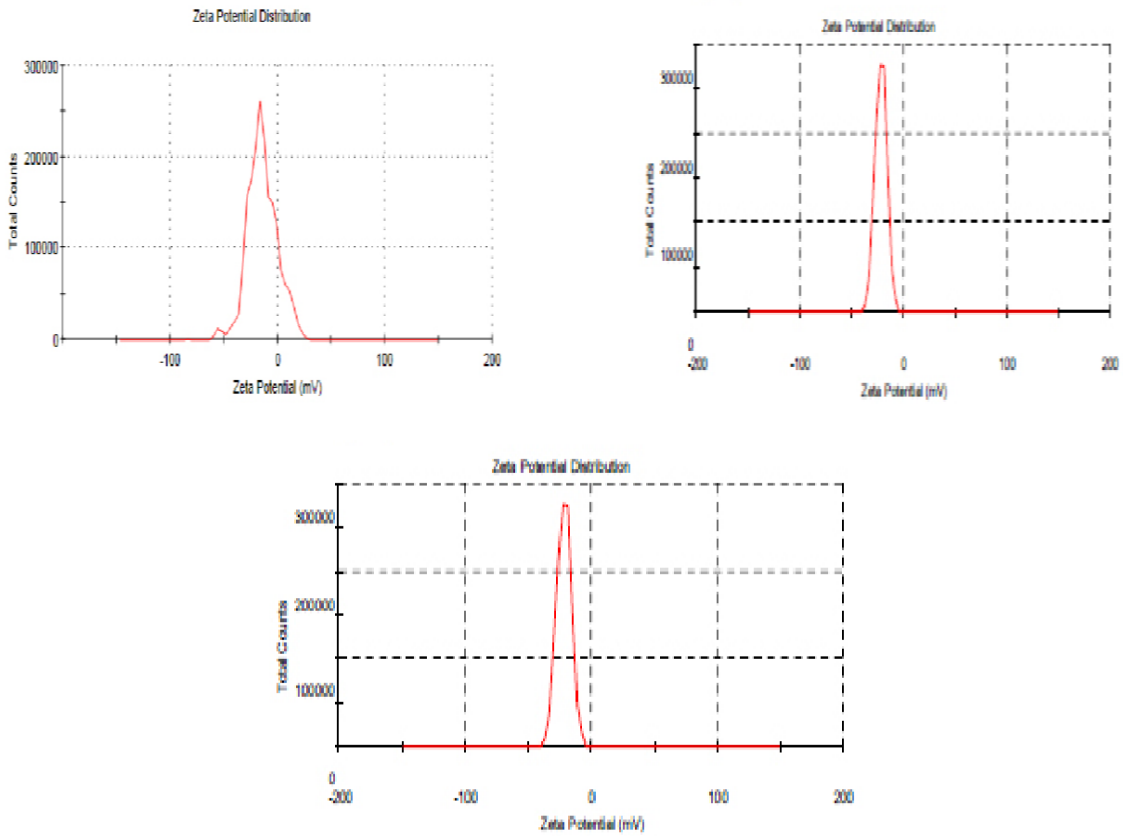


Figure 3: (a) zeta potential distribution of formulation F1; (b) zeta potential distribution of formulation F2; (c) zeta potential distribution of formulation F3.

Entrapment efficiency

According to figure 4, the Entrapment Efficiency of nanosponge formulations F1, F2, and F3 was 74.57%, 87.97%, and 84.49%, respectively. In comparison to other formulations, formulation (F2) had a greater entrapment efficiency. This might be as a result of the different levels of cross linking and changes in polymer concentration causing variations in entrapment efficiency.

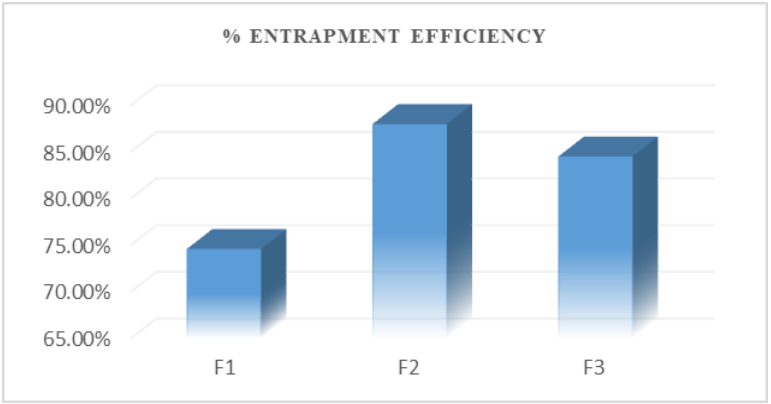


Figure 4: Entrapment efficiency of FDP nanosponges.

Studies on saturation solubility

The saturation solubility study results showed the enhancement of solubility of felodipine by development of nanosponges. The solubility of prepared felodipine nanosponges in 0.1N and phosphate buffer was higher than that of pure felodipine (10.02% ± 0.01 and 33.45% ± 0.06) and was more than threefold higher (28.26% ± 0.16 and 86.01% ± 0.16). The reduction in particle size may be due to the enhanced solubility of felodipine from developed felodipine nanosponges. In comparison to pure medication and other formulations, the findings show that F2 achieved 28.26% and 86.87% of high saturation solubility in 0.1N HCl and phosphate buffer pH 6.8 (figure 5).

The reduction of particle size from micron to nano scale may enhance the surface area and also greatly increases the solubility, as seen by the formulation F2 of nanosponges, which has the greatest solubility compared to other formulations and pure medication. This significant improvement in saturation solubility was due to the twin characteristics of the presence of surfactant and decreased particle size, which led to an increase in surface area. Fenomenodipine is a BCS class II medication with poor aqueous solubility and high permeability; hence, an increase in solubility is expected to increase absorption and, in turn, bioavailability.

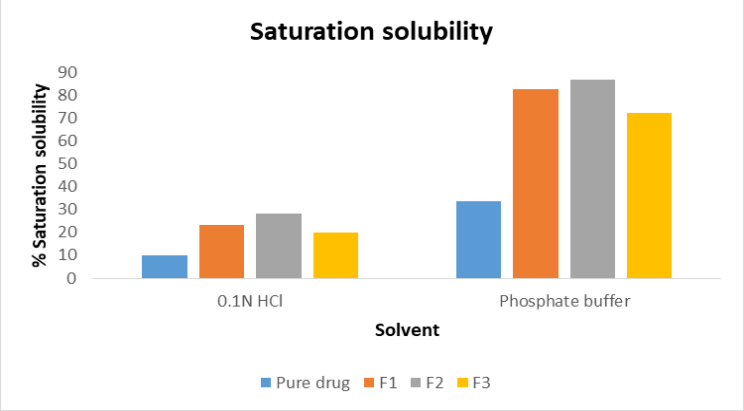


Figure 5: saturation solubility of pure drug and FDP nanosponges.

***In Vitro* Drug Release Studies**

In vitro dissolution studies of Felodipine plain drug by the different formulations of Felodipine is loaded as nanosponges by using phosphate buffer pH (6.8) as dissolution media for Formulations F1, F2, F3. Approximetly 16.88% of the drug release of pure drug at the end of 120 min, which is an poor dissolution rate. A marketed formulation shows approximately 28.4% of drug release and formulation F1 shows 66.97%, F2 shows 89.8% and F3 shows

83.21% respectively. From the results the formulation F2 shows better cumulative drug release compared to other formulations, marketed product and pure drug. The result suggests that smaller the size of nanosponges the surface area was more and the drug release is faster due to the addition of the stabilizer, all the formulations were stabilized by stabilizer. From the overall dissolution result concluded that the release rate of felodipine nanosponge higher (89.8%) in phosphate buffer pH 6.8. Hence formulation F2 shows better release from the felodipine nanosponges that indicates efficiency of nanosponges in bioavailability enhancement. *In vitro* release profiles of felodipine nanosponges are shown in (Figure 6).

The ratio of drug to polymer altered the rate of release. As a result of the drug:polymer ratio, the drug release increased. It was shown that when polymer concentration increased, medication release reduced. This could be the case because drug release from the polymer matrix happens after the polymer has fully inflated, and the time required to swell increases with the amount of polymer in the formulation.

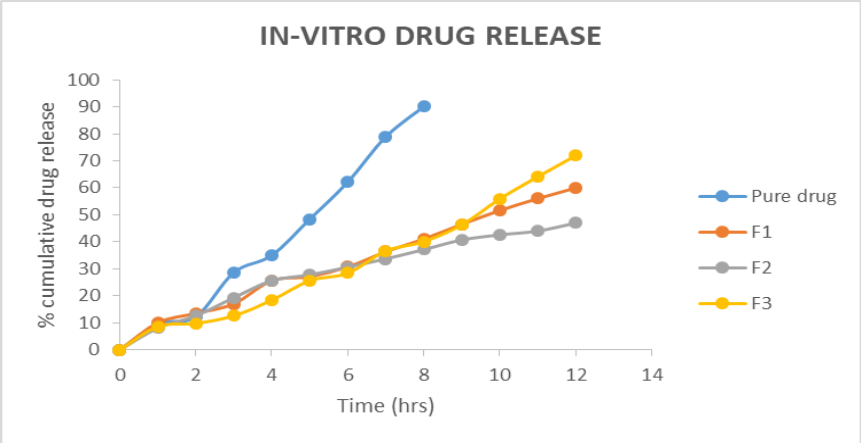


Figure 6: In vitro release profile of pure drug and FDP nanosponges.

Thermal analysis

The thermograms of the pure drug and the felodipine nanosponge (F2) are displayed in Figure 7. A melting exothermic peak was visible on the DTA curve of pure felodipine at 143.3°C. Thus, it was determined that the drug-polymer combination had an acceptable compatibility for further formulation by comparing the thermograms of the two compounds. Thermal study of drug-loaded nanosponges revealed a reduction in the drug's crystallinity, an increase in thermodynamic energy, and an improvement in the drug's amorphous characteristic.

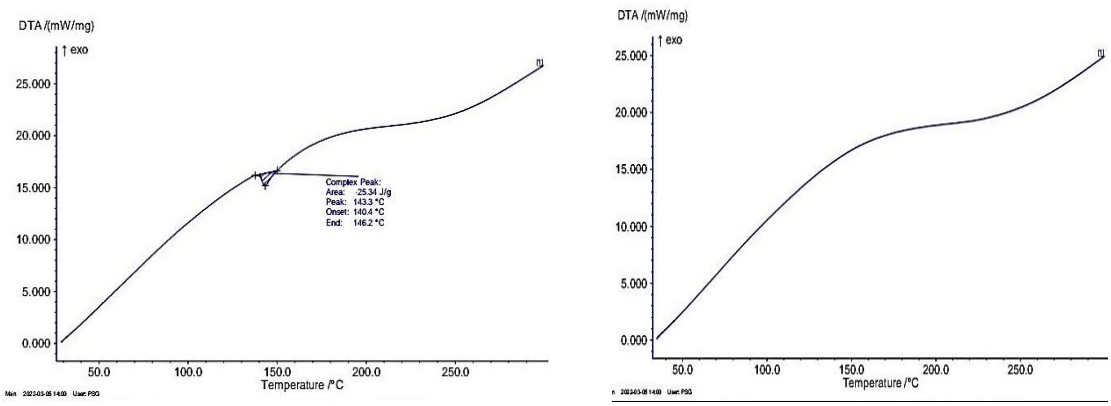


Figure 7: Thermogram of pure felodipine and formulation F2 by DTA.

X-Ray powder diffraction

Drug loading, solubility, dissolution, and release kinetics are greatly affected by changes in crystallinity, which are utilized to anticipate the crystalline form of manufactured nanosponges and their capability for complexation. Figure 3 shows an XRPD diffractogram of a felodipine nanosponge.Fenomenodipine nanosponge has a low crystalline content, according to its XPRD profile. A diffractogram showed three large peaks at about 10.1°C, 11.4°C, and 23.9°C. The crystalline form of nanosponges indicates high loading capacity with felodipine.

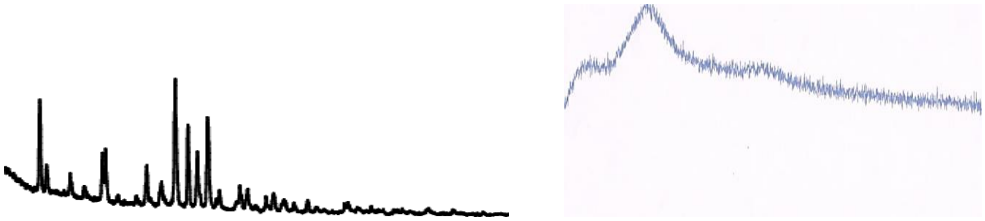
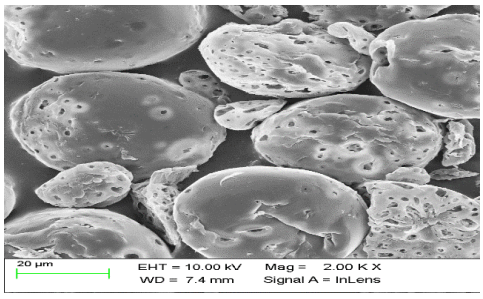


Figure 8: X-Ray of (a) pure felodipine, (b) formulation F2.

SEM analysis

To assess the surface shape of the synthesized felodipine nanosponges, SEM examinations were carried out. (Figure9) displays the SEM images of formulation (F2).



In-vitro Drug Release Kinetics

The in vitro release data were analyzed using the simplified Higuchi model for zero order, first order, and diffusion controlled mechanisms in order to identify the release model. The choice of a particular mechanism was made based on the coefficient of determination (r2) for the parameters under investigation; as the Higuchi model had a higher r2 value, it was chosen as the best matched model. By charting the % cumulative drug release, the square root of time, and a r2 value range of 0.989, this was validated. Figure 10-a,b,c,d shows that the formulation (F2) followed non-Fickian dissemination.

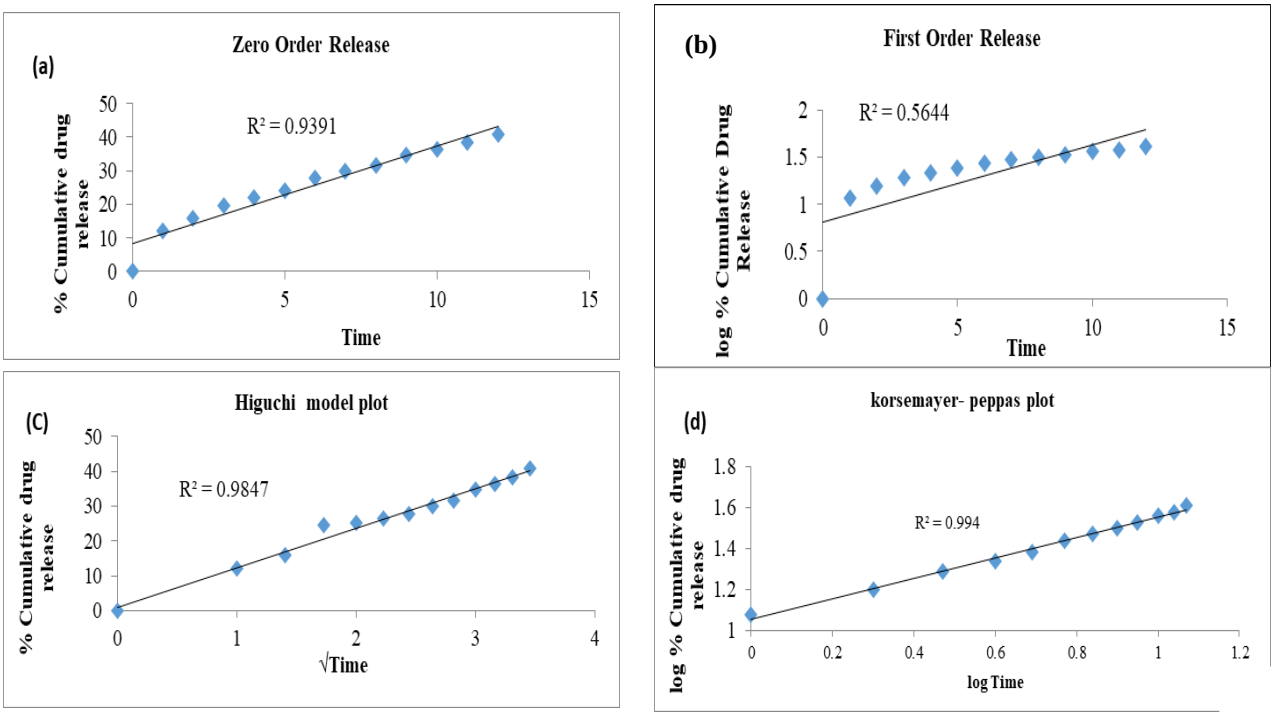


Figure 10: Drug release data of formulation F2 fitting to various kinetics models, (a) zero order release, (b) first order release, (c) Higuchi model plot, (d) korsemayer-peppas plot.

CONCLUSION

By using the emulsion solvent diffusion process, felodipine nanosponges were effectively created with three different concentrations of the hydrophobic polymer (Ethyl cellulose). They were then tested for entrapment effectiveness, saturation solubility, and in-vitro release studies. The improved formulation was determined to be felodipine-loaded nanospomges (F2) based on early evaluation. At the conclusion of 12 hours, the improved formulation F2 shown superior sustained release (figure 6), saturation, solubility (figure 5), and increased entrapment efficiency (figure 4). For DSC, XRD, and SEM investigation, the optimized

formulation F2 was assessed (figures 7, 8, and 9). Thus, it was determined that the created nanosponges had porous character, which is conducive to greater therapeutic efficiency. The planned study looked at whether felodipine-loaded nanosponges may be useful in treating high systolic blood pressure. As the drug:polymer ratio increased, an increase in drug release was seen. For each formulation, it was shown that the drug release reduced as the amount of polymer increased. It was investigated how the ratio of drug to polymer affected the way felodipine nanosponges released the drug. It was discovered that the drug release pattern is significantly influenced by the drug to polymer ratio. The amount of drug released from the nanosponges reduces as the drug:polymer ratio rises. The Korsemeyar-Peppas model (figure 10) is best suited by the in-vitro release model. This model's r2 value range is 0.994.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest regarding this investigation.

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