RESEARCH ARTICLE

Potential of Nitrofurantoin Cyclodextrin Nanosponge Complex to Enhance Solubility and Masking Bitter Taste

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ABSTRACT

This study aimed to produce b-cyclodextrin (β-CD) based nanosponges (NS) loaded with nitrofurantoin (NFN) to improve oral bioavailability, solubility, and dissolution rate while concealing bitter tastes. The cross-linker diphenyl carbonate and β-CD were reacted in various ratios (1:1, 1:2, 1:4, 1:6, and 1:8) to produce NFN-loaded NS. The developed NS were evaluated for phase solubility study, particle size, drug loading, polydispersity index, scanning electron microscope (SEM), zeta potential, fourier transform infrared (FTIR), differential scanning calorimetry (DSC), a study of phosphate buffer at pH 7.2 for *in-vitro* release and taste masking ability in human volunteers. Pure NFN showed nearly 100 mcg/mL solubility in ditilled water while at 1:8 (β-CD: DPC) ratio the solubility was found to be 250 mcg/mL, i.e., nearly 2.5 fold enhancement in solubility was observed. The SEM of the NFN-loaded NS (1:8 β-CD: DPC ratio) showed highly spherical surface morphology. For formulation containing a 1:8 proportion of β-CD to DPC, the average particle size was measured at 324.78 ± 10.45 nm, possessing a low polydispersity index of 0.196 ± 0.054. It was found that the zeta potential's value was -20.59 ± 0.4 mV, indicating sufficient electrostatic repulsion to maintain particle dispersion. FTIR, DSC study reveled excellent drug and excipient compatability. As compared to pure NFN, NFN-loaded NS showed faster release in pH 7.2 phosphate buffer. Research conducted *in-vitro* showed a gradual release of NFN from pure NFN throughout a two-hour period. The plain NFN suspension was found to have a pronounced bitterness. With 3.95 ± 0.57 as the average score, while the NFN nanosponges (1:8 ratio) had a mean bitterness score of only 0.10 ± 0.00. These findings suggest that the NFN (1:8 ratio) has the capacity to thoroughly cover up the bitter taste of NFN.

Keywords: Nitrofurantoin, Solubility, Taste mask, Nanosponge, Cyclodextrin.

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INTRODUCTION

Nitrofurantoin (NFN) is an antibiotic used to treat urinary tract infections caused by both gram-positive and gram-negative bacteria. Nitrofurantoin works by inhibiting the growth and replication of bacteria, preventing them from spreading and causing infection.[1] Nitrofurantoin is available in various dosage forms, including capsules and suspension, and it is typically taken orally. The drug is absorbed in the stomach and then excreted through the kidneys, making it particularly effective for treating urinary tract infections.[2] When nitrofurantoin is taken orally, it is partially eliminated unaltered in the urine. When 32 µg/mL is the minimal inhibitory concentration (MIC), it exhibits bacteriostatic activity, and beyond 2 MIC concentrations, it shows a bactericidal effect.[3,4] Nitrofurantoin is categorized as a class IV compound in light of its poor solubility in water, which is around 100 µg/mL at 25°C. As a result, the intestinal barrier's penetration and the substance's dissolution in gastrointestinal fluids are thought to be crucial time-dependent processes for its absorption after oral administration.[5, 6] Due to relatively poor solubility in water, it poses challenges in formulating the oral dosage form. Nitrofurantoin is a hydrophobic (water-repelling) compound with a limited ability to dissolve in aqueous solutions, which can limit its absorption and effectiveness in the body.[7] In addition to solubility issues, nitrofurantoin has been reported to be sensitive to pH changes in the stomach, which can affect its solubility and absorption.[8] Therefore, it is important to consider factors such as pH, particle size, and formulation components when developing nitrofurantoin products to ensure optimal solubility and therapeutic efficacy. To overcome solubility issues, different approaches have been utilized including micronization or processing into smaller particle sizes to increase its surface area and improve its aqueous solubility.[9] A solid dispersion approach was also used to enhance the solubility of nitrofurantoin.[10] Solubilizing agents such as surfactants or co-solvents and co-crystals have also been used to improve the bioavailability and solubility of nitrofurantoin.[8]

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Apart from solubility issues, Nitrofurantoin is known for its bitter taste, which can be unpleasant for some patients. The bitter taste is due to the chemical structure of nitrofurantoin, which contains a nitro group that can trigger the tongue's bitter taste receptors. Patients may find it difficult to take nitrofurantoin due to its bitter taste, especially young patients and older patients who may have trouble swallowing tablets or suspensions.[11] The bitter taste of nitrofurantoin can be lessened or covered by using a variety of techniques to solve this problem.

Cyclodextrins (CD) are cyclic oligosaccharides made up of glucose units with an exterior surface that is hydrophilic and an inner cavity that is hydrophobic. The pharmaceutical industry frequently uses them because of their capacity to improve the solubility of weakly soluble pharmaceuticals and to mask undesirable tastes and odor. When cyclodextrins are used to enhance solubility, inside the hydrophobic cyclodextrin cavity, the medication molecule is enclosed, forming an inclusion complex.[12] This inclusion complex makes the medication more soluble in water, allowing it to be more easily absorbed by the body. Drugs with limited water solubility can benefit greatly from the addition of cyclodextrins to their solubility, which is a common problem in drug development. Cyclodextrins can also be used for taste masking, which is particularly important for pediatric and geriatric formulations. By encapsulating the drug molecule within the cavity of cyclodextrin, the taste and odor of the drug can be masked, making it more palatable and increasing patient compliance.[13] However, utilizing native cyclodextrins to create inclusion complexes does have its limitations. For example, separating the complex upon dilution may not be a straightforward process, and drug molecules with increased molecular weight or solubility in water may not be suitable for complexation. Additionally, a strong hydrogen bonding between molecules in the crystal state limits cyclodextrins' solubility in water.

A kind of crosslinked polymer nanoparticle known as cyclodextrin-based nanosponges (NS) is produced when cyclodextrins and a crosslinking agent react. They have a three-dimensional, porous structure that allows them to absorb and encapsulate a wide range of substances, such as drugs, dyes, and heavy metals. Lately, there has been a considerable rise in interest in the application of cyclodextrin-based nanosponges for medication delivery. Since they are porous and have a vast area of surface, they can carry a large amount of drug molecules, which makes them ideal for targeted drug delivery. Additionally, they can enhance drug solubility, improve bioavailability, and protect drugs from degradation.[14]

The inclusion capacity of cyclodextrins is enhanced by the nanosponge structure, which allows for a greater number of cyclodextrin molecules to be present in each volume. The pores in the nanosponge provide additional surface area for drug molecules to interact with the cyclodextrin, increasing the likelihood of inclusion complex formation. This results in a higher loading capacity for drugs within the nanosponge structure.[15] Furthermore, when crosslinking agents are used to generate cyclodextrin-based nanosponges, functional groups can be incorporated, which can improve the cyclodextrins' ability to be included.[16]

The aim of the study was to produce nanosponges loaded with nitrofurantoin and analyze their physicochemical characteristics to improve the solubility, dissolution, and bitter taste of nitrofurantoin to improve patient compliance.

MATERIALS AND METHODS

Materials

Tooba Pharmaceuticals (located in Aurangabad) provided a gift sample of nitrofurantoin. The β-CD was acquired from S.D. Fine Chemicals Ltd. located in Mumbai, India. Diphenyl carbonate (DPC), DMF, and ethanol were acquired from Spectrochem Pvt. Ltd. Mumbai India.

Formulation of Nitrofurantoin loaded β- CD NS

In this study, using DPC as a cross-linker, distinct β-CD to DPC ratios (1:1, 1:2, 1:4, 1:6, and 1:8) were used to produce β-CD-based nanosponges (NS). DPC and anhydrous β-CD were homogenized and then added to a conical flask. The mixture was magnetically stirred, heated gradually to 100°C, and then allowed to react for five hours. During the process, phenol crystals developed at the flask's neck. The product was roughly broken up and repeatedly washed with distilled water after cooling down to get remove of any unreacted β-CD. Acetone was then used to wash away any remaining unreacted DPC and phenol by-products. The purified nanosponges were then stored at 25°C until needed for further experimentation.

Characterisation of Nitrofurantoin loaded β- CD NS

Phase solubility study

To investigate the phase solubility equilibrium between the drug and β-CD or NS, equilibrium plots were generated with distilled water at 25°C. The protocol recommended by Higuchi and Connors was adhered to in the experimental procedure. A 20 mL aqueous solution containing a progressively increasing concentration of either β-CD or NS was mixed with an excess of the drug to conduct the experiments. The mixture was agitated for 48 hours at a temperature of 25 ± 0.5°C until equilibrium was reached. Following the filtering of the samples, a Jasco UV-vis spectrophotometer was used to detect the absorbance at 324 nm.

Percentage drug loading

The nitrogenfurantoin-loaded freeze-dried nanosponges were weighed meticulously and then dissolved in a suitable amount of DMF. The drug content was ascertained using a UV spectrophotometer (Jasco, Japan) in order to calculate the drug loading capacity percentage for each preparation.

Quantitative determination of NFN

The HPLC method was used to quantify resveratrol. The chromatographic system was comprised of an LC-250 pump and an LC-95 detector (HPLC system). An analytical column (4.6 x 250 mm) called Microsorb MV 100-5 C18 from Varian Analytical Instruments was employed for the chromatographic

separation. The mobile phase, which comprised 0.5% (v/v) acetic acid in methanol and water (52:48 v/v), was filtered using a 0.45 µm nylon membrane that had been ultrasonically degassed before use. The flow rate of the mobile phase was 1-mL/min, the attenuation was 0.001, the injection volume was 100 µL, and the detection wavelength was 324 nm. The HPLC method's linearity, quantitation, and detection limit were all confirmed.

Scanning electron microscopy

Under high vacuum, the physical appearance of a freeze-dried formulation with NFN-loaded NS were examined using a Holland's filed emission-scanning electron microscopy (FE-SEM) quanta FEG 250 scanning electron microscope. A gold layer was applied to the samples employing a SPI-Module sputter coater. At an accelerating voltage of 20 kV, digital photos of the samples were taken.

Polydispersity index, zeta potential, and particle size

The average polydispersity index (PDI), zeta potential, and particle size of the formulations were measured using a Malvern Zetasizer (Worcestershire, UK). Prior to the measurements, distilled water was used to appropriately dilute each sample. The temperature of 25 ± 0.5°C was maintained during all three measurements, standard deviation (± SD) and the mean value of the data were reported.

Fourier transform infrared spectroscopy

The stability of the drug through the nanosponge loading procedure and possible interactions between NFN and the excipients were examined using FTIR spectroscopy. To conduct the analysis, the potassium bromide disc method was utilized, which involved mixing samples (about 2–3 mg) with KBr, palletizing them under vacuum, and utilizing an FTIR spectrophotometer to measure the signals across a 4000 to 400 cm^{-1} range.

Differential scanning calorimetry

Scanning calorimetry (DSC) was conducted to confirm any potential interactions between NFN and the excipients used in the nanosponge loading process and to assess the drug's ability to withstand this process. A computerized data station and a Shimadzu DSC-50 device were used for the analysis. Five-milligram samples were heated between 33 and 300°C at a rate of 100°C/min in aluminum pans with a flat bottom and 30 mL/min flow of nitrogen is being observed. Aluminum pans that were empty were used as a point of comparison.

In-vitro release study

USP dissolving tester equipment II (Hanson Research, Chatsworth, California, USA) using the paddle method was used to assess the release characteristics of both the pure drug and NFN-loaded NS. The temperature was kept at 37 ± 0.5°C while at 50 rpm, the paddles rotated. A molecular weight threshold of 12,000 to 14,000 Da (Spectra/Pro, Spectrum Laboratories, Inc., USA) was used to determine the equivalent amounts of NFN-loaded NS and pure drugs, each weighing 10 mg. The dialysis bags were then sealed to the paddle before being submerged in the release medium. Phosphate buffer with a pH of 7.2 (900 mL) was used for the initial release experiments. The samples were taken out and replaced with an equivalent volume of fresh media every 3 mL at predetermined intervals. After filtering, the samples' NFN content was measured spectrophotometrically at 324 nm. The cumulative percent of the drug released against time was shown using the mean data from each of the three release studies, which were carried out in duplicate.

RESULTS AND DISCUSSION

Study of Phase Solubility

The phase solubility investigation was conducted on both pure NFN and NFN-loaded β-CD NS in distilled water. The comparative phase solubility study with different NFN: β-CD NS are presented in Figure 1. The solubility of NFN was found to be β-CD concentration dependent. A linear relation was observed between the solubility of NFN and β-CD to DPC concentration. Pure NFN showed nearly 100 mcg/mL solubility in distilled water while at 1:8 (β-CD: DPC) ratio the solubility was found to be 250 mcg/mL, i.e., nearly 2.5 fold enhancement in solubility was observed.

The phase solubility plot of NFN showed an AL curve, which meant that an inclusion complex of NFN and β-CD had formed at a stoichiometric ratio of 1:8 for β-CD: DPC. Based on the linear section of the phase solubility curve, the stability constant of the complex at 25°C was determined to be 370.120 M^{-1} for β-CD: DPC, indicating a stable complex. This suggests that NFN and β-CD make a more stable complex with NFN having a stronger affinity.

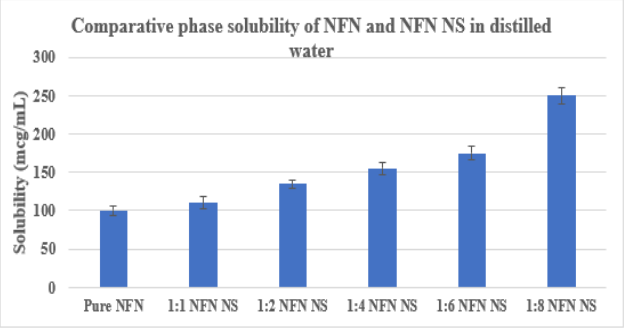

Figure 1: The comparative phase solubility study of pure NFN and different concentrations of NFN: β-CD NS.

Table 1: NFN loading with respect to β-CD: DPC ratio

S. No	*β-CD: DPC ratio*	*%drug (NFN) loading*
1	1:1	20 ± 1.8
2	1:2	25.14 ± 0.22
3	1:4	29.77 ± 0.47
4	1:6	37.11 ± 0.20
5	1:8	45.96 ± 0.71

Percentage Drug Loading

The %drug (NFN) loading was determined for all formulations of nanosponges which is presented in Table 1.

The amount of medication loaded increased linearly with an increase in DPC concentration. It was discovered that β-CD's capacity to encapsulate can be increased by the formation of ternary complexes with DPC. These complexes, which are made up of three different molecular entities, can enhance the guest molecules' physicochemical, chemical, and bioavailable characteristics. In some circumstances, a third element has the potential to enhance encapsulation or release while reducing the quantity of β-CD needed to produce the aforementioned outcomes. This will allow for the final product's bulk formulation, cost, and toxicity to be optimized.[17] Out of all the generated NFN-loaded nanosponges in this study, the formula with a 1:8 β-CD: DPC ratio attained the greatest proportion of drug loading, 45.96 ± 0.71%. For further evaluation studies, this formula was selected.

Scanning Electron Microscopy

The SEM of the NFN-loaded NS (1:8 β-CD: DPC ratio) showed highly spherical surface morphology as presented in Figure 2. The nanosponge formulation possesses nano-sized dimensions and exhibits a structure resembling that of a sponge. Effective drug penetration inside the nanosponge's interpenetrating network is made possible by its porous nature.[18]

Polydispersity Index, Zeta Potential, and Particle Size

Particle size and charge have a significant impact on the behavior of oral nano-platforms, influencing their toxicity, metabolism, distribution, stability, and bioavailability. The average particle size for formulations with a 1:8 ratio of β-CD to DPC was measured to be 324.78 ± 10.45 nm, and the polydispersity index was found to be low, at 0.196 ± 0.054. The measured zeta potential was -20.59 ± 0.4 mV, which suggests that there is enough electrostatic repulsion to keep the particles dispersed. The negative charge in β-CD is caused by the presence of free hydroxyl and carbonyl groups. The comparative PDI, zeta potential, and particle size of the different NS are presented in Table 2.

Fourier Transform Infrared Spectroscopy

According to the NFN API's FTIR spectra, the following groups' notable peaks were found: C–H bond at 2855.57 cm^{-1}, C=O group at 1725.79 cm^{-1}, C-O-C group at 1107.84 cm^{-1}, N–H stretching at 3276.75 cm^{-1}, HC=N bond at 2367.98 cm^{-1}, and N-O asymmetric stretching at 1516.12 cm^{-1} (Figure 3). Functional groups and the drug's purity were verified and identified by the FTIR spectra that were detected. The NFN-loaded NS also showed similar peaks as that of pure NFN indicating excellent compatibility between NFN and other excipients used. While plain nanosponge did not show any IR spectra corresponding to any functional group of NFN. These observations clearly indicate that the proper complexation of NFN was achieved with excipients used in the formulation.

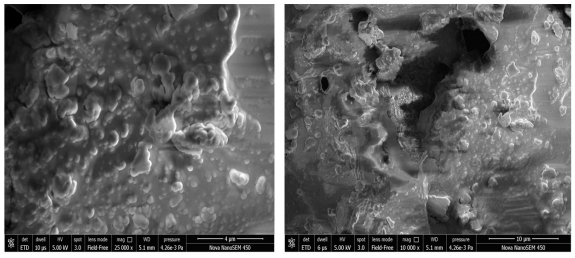

Figure 2: SEM of the NFN loaded NS with 1:8 β-CD: DPC ratio

Differential Scanning Calorimetry

The melting point of NFN (272°C) corresponds to a sharp endothermic peak seen in raw NFN at 269.43°C. A slight shifting of the endothermic peak (265.24°C) was observed in NFN-loaded NS confirming the encapsulation of NFN in NS. The plane NS i.e. without NFN did not show any endothermic peak in between 260-272°C. A sharp endothermic peak at 255.62°C was observed which was not corresponding to the NFN. These observations clearly indicated that the drug NFN was found intact and stable in NS formulation. The comparative DSC thermograms of pure NFN, NFN-loaded NS and plain NS are presented in Figure 4.

In-vitro Release Study

As compared to pure NFN, NFN-loaded NS showed faster release in pH 7.2 phosphate buffer. Studies conducted *in-vitro* showed that pure NFN released NFN gradually over a two-hour period. The ternary complexes formed with β-CD, DPC and NFN at different ratios showed excellent enhancement in dissolution rate as shown in Figure 5. Ternary complex with 1:8 ratio of β-CD to DPC showed comparatively faster release than any other complex studied. The initial burst release of nearly 40% was observed due to surface-bound NFN that was not properly encapsulated in NS or complex.

By trapping poorly soluble medications inside their nanochannels and cavities, nanosponges may be able to enhance the solubility of certain medications. This process

Table 2: Comparative particle size, PDI and zeta potential of NFN-loaded NS

S. No	*β-CD: DPC ratio*	*Particle size (nm)*	*PDI*	*Zeta potential (mV)*
1	1:1	746.8 ± 10.9	0.355 ± 0.027	35.97 ± 0.8
2	1:2	651.84 ± 12.4	0.387 ± 0.015	34.51 ± 0.9
3	1:4	513.51 ± 10.12	0.301 ± 0.021	32.78 ± 0.7
4	1:6	452.67 ± 11.71	0.294 ± 0.034	-31.12 ± 0.9
5	1:8	324.78 ± 10.45	0.196 ± 0.054	-20.59 ± 0.4

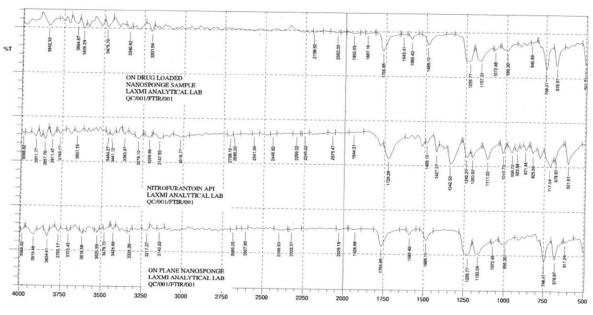

Figure 3: FTIR spectra of NFN loaded NS; Pure NFN and plane NS

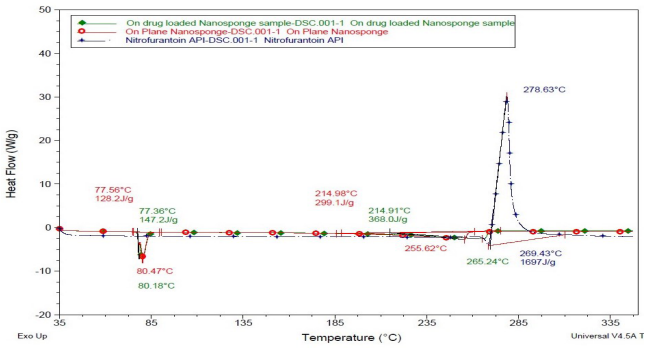

Figure 4: DSC thermograms of the pure NFN, NFN loaded NS and plain NS formulation

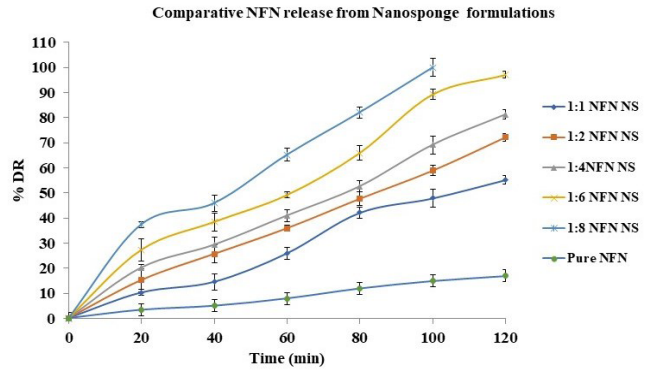

Figure 5: Comparative dissolution profile

masks the hydrophobic moieties of the drug and increases its apparent solubility. Additionally, encapsulating hydrophobic drugs in NSs reduces their crystallinity and enhances their wettability, leading to increased solubility and maintenance of a greater proportion in a condition of molecular dispersion.[19, 20] The NFN loaded NS (1:8 ratio) in vitro release results indicate that it might be useful in increasing the bioavailability of NFN by boosting its poor solubility following administration.

Evaluation of Taste Masking Potential of NFN loaded Manosponges

According to the findings of gustatory response palatability studies conducted with a human panel, there was a significant difference ($p < 0.05$) in the bitterness score between the conventional NFN suspension and the NFN nanosponges formula (1:8 ratio). The results showed that the NFN nanosponges (1:8 ratio) had a mean bitterness score of only 0.10 ± 0.00, compared to an average score of 3.95 ± 0.57 for the plain NFN suspension. These results imply that the bitter taste of NFN may be entirely concealed by the NFN (1:8 ratio).

CONCLUSION

In order to increase NFN's solubility and rate of dissolution while also masking its bitter taste, NFN-loaded nanosponges were created for this investigation. The use of a 1:8 b-CD to crosslinker diphenyl carbonate ratio, aided by a solubility phase diagram, proved to be the most suitable for NFN loading. The optimized formulation exhibited the highest drug loading capacity of 45.96 ± 0.71 and a notable acceleration in the rate of dissolution and solubility. The potential of NFN-loaded nanosponges for masking bitter tastes was proven by investigations on the gustatory response and palatability of human panels. As a result, the formula with the beta CD and DPC ratio of 1:8 could be utilized as a dry suspension for reconstitution, which would be an efficient NFN dose form for pediatric patients. To confirm these findings, however, more in vivo absorption research on humans and patient-centered clinical studies are required.

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