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Research Article

Investigation of effect of complexing agent and processing method on solubility of Efonidipine

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Abstract

Nanosponges are versatile carriers due to their exceptional capability to improve the solubility of poorly water-soluble drugs, taste masking and enhancement of stability. This study investigates potential of nanosponges, prepared by crosslinking β-cyclodextrin with diphenyl carbonate in 1:4 ratio for enhancing solubility of Efonidipine. Nanosponges were characterized in terms of particle size. Phase solubility studies and solution state interaction studies were employed to understand the nature and strength of drug: nanosponge complexation. Complexes were prepared by kneading method and spray drying. Saturation solubility, *in vitro* dissolution studies and molecular modeling studies were performed. Complexes were characterized by differential scanning calorimetry (DSC), infrared spectroscopy, X ray powder diffraction (XRPD) and scanning electron microscopy. Phase solubility studies revealed 1:2 complexation between drug and carriers. Saturation solubility studies showed significant solubility increase with both beta CD and nanosponges. The increase was higher in case of spray dried complexes in all media. An 18 fold increase was observed in case of spray dried complexes in distilled water. DSC and PXRD confirmed amorphization of drug in the complexes. Thus solubility enhancement of EFD could be attributed to complexation and amorphization. Molecular modeling studies revealed the mode of entrapment of efonidipine in the carriers. In conclusion the versatility of nanosponges in encapsulating both hydrophilic and hydrophobic drug molecules holds immense promise for personalized medicine and targeted therapy, ultimately leading to improved patient outcomes. Moreover, the study introduces the efficacy of spray drying as a scalable and practical approach to maximize the solubility-enhancing benefits of nanosponges. This research highlights the potential of nanosponges to overcome a fundamental challenge in pharmaceuticals, opening new avenues for drug delivery and therapeutic advancement.

Keywords: Nanosponges, β -cyclodextrin, inclusion complexes, solubility enhancement, molecular modelling

INTRODUCTION

Nano-delivery systems have revolutionized the field of therapeutics, diagnostics and theranostics to achieve site specific controlled delivery[1].Novel biomaterials with nanosized structural properties has numerous applications in nanomedicine[2]. Nanosponges (NS) provide several advantages in this field which include holding great potential for personalized medicine, targeted therapy, and improved patient outcomes[3]. NS are multi cross-linked cyclodextrins (CD)[3] made by reaction between CD and suitable cross-linkers like carbonyl-di-imidazole or di-phenyl carbonate[4]. NS have sponges-like network that encapsulates a variety of compounds such as antineoplastics (e.g. camptothecin[5], docetaxel[6], flutamide[7]), proteins and peptides (e.g., bovine serum albumin[8]), and DNA[9].

CD-based NS form inclusive and non-inclusive complexes with drug molecules because of the cavities present in CD and also due to the porous structure of NS[10]. They entrap both hydrophilic (e.g. temozolomide[11], cephalexin[12]) and hydrophobic (e.g. ciprofloxacin[13], nifedipine, griseofulvin[14]molecules thereby enhancing aqueous solubility[15,16,17], increasing stability[18], and also masking taste[19-22]. β-CD is commonly used to prepare NS because to its low cost, excellent complexability and stability with crosslinkers[9]. Poor solubility and dissolution of pharmaceuticals are a major challenge in drug research. Literature includes number of methods to improve solubility, dissolution and hence their oral bioavailability. NS have been used for increasing the solubility (curcumin[23]), wettability (itraconazole[24]), rate of dissolution (lopinavir[25]), and also its bioavailability (propranolol[13])[26,27]. Guest molecules can be effectively encapsulated in the nanoporous structure of NS, leading to controlled release at designated site. This remarkable encapsulation capability eliminates the necessity for a dissolution step, thereby significantly increasing the apparent solubility of the drug[2, 28].

Efonidipine (EFD) is a cyclo-phosphorylation-derived 1,4-dihydropyridine and a calcium antagonist[29-31]. EFD

was first sold in Japan under the name of Landel®, a film-coated tablet prepared by solid dispersion[32,33]. It is used to treat hypertension by improving vascular dysfunction[34,35]. EFD belongs to the BCS class II, having log P of 5.44 and pKa value 2.33. Practically it is insoluble in water, and hence bioavailability (47.7%) and oral absorption need to be improved[36]. Various strategies explored include formulation of solid dispersions[36], solid lipid microparticles[37], and nanosuspensions[29].

In this study, complexes were prepared by solvent evaporation and spray drying. Phase solubility studies, compatibility studies, and solution state interactions were performed. The complexes were evaluated by saturation solubility, drug content, compatibility studies, differential scanning calorimetry, powder X-ray diffraction, scanning electron microscopy, molecular modeling, and *in-vitro* dissolution.

MATERIALS AND METHODS

Materials

EFD was a gift by Emcure Pharmaceutical Pvt. Ltd, β-Cyclodextrin (β-CD) from Analab Fine Chemicals Mumbai, diphenyl carbonate (DPC) from Loba Chemicals, dimethyl formaldehyde (DMF), Avicel, magnesium stearate from Loba Chemicals. All other reagents were of analytical grade.

Methods

Synthesis of CD NS

CD-based NS were synthesized with DPC as crosslinker. β-CD and DPC (1:4) were mixed using a magnetic stirrer (Remi Magnetic Stirrer 1MLH) and allowed to react at 100°C for 5 h. Resulting product was powdered and subsequently subjected to thoroughly washed with distilled water and acetone to remove any residual unreacted β-CD and DPC. The product was dried in a hot air oven (Biomedical Hot Air Oven) at 60°C for 2 h. It was triturated and passed through sieve no. 85. Particle size, polydispersity index (PDI), and zeta potential were evaluated using a Malvern zeta sizer ZS 90.

Preliminary Evaluation of Complexes

Phase solubility studies

Higuchi and Connors method was used to study phase equilibria between the carriers and EFD[38, 39]. Excess drug was added to aqueous solutions of β-CD/NS at 20-100 mg/ml. The dispersions were allowed to equilibrate in orbital shaker (Remi Instruments Ltd CIS-24 BL) at 37°C ± 0.5°C for 48 h, at80 rpm[40]. After standing at room temperature for an additional 24 h dispersions were filtered using Whatman filter paper no. 41. Quantification was done by UV spectrophotometric at 231 nm.

Solution state interaction studies[41]

A fixed amount of EFD (10 µg/ml) was added to increasing concentration of β-CD and NS (1, 2, 3, 4 µg/ml) in 20 ml of DW. This aqueous solution was kept overnight for interaction. Dispersions were filtered using Whatman filter paper no. 41 and scanned for absorbance at 231 nm. The spectral shift parameters were studied.

Drug Loading

EFD was loaded with β-CD and NS in a 1:2 molar ratio for each complex. Loading of drugs was done by two different methods:1. **Kneading method:** EFD was mixed with β-CD and NS (1:2 molar ratio) and was dissolved in DMF to form a slurry. Solvent evaporation was done by continuously triturating the slurry at room temperature. The complex was dried at 60°C in an oven to remove the traces of excess solvent and then passed through sieve no. 85 for further studies.2. **Spray drying method:** The complexes were spray dried (Labultima) to encapsulate EFD (1.9 gm) with β-CD (6.8 gm), and NS (7.5 gm) in 100 ml of DMF. Operating conditions were inlet temperature of 150°C and outlet temperature of 90°C. The flow rate was2ml/min. Loaded NS/β-CD was then collected and dried in a hot air oven (Biomedical Hot Air Oven) at 60°C for 1 h and passed through sieve no. 85. The percentage yield was calculated. Particle size, polydispersity index, and zeta potential of EFD complexes withβ-CD/NS were measured by Malvern Zeta Sizer ZS 90.

Evaluation of Complexes

Saturation Solubility Studies

Measured excess drug and complexes (300 mg) were added to 20 ml media (DW, 0.1 N HCl, phosphate buffer 6.8, FaSSIF (fasted state simulation intestinal fluid), and FeSSIF (fed state simulation intestinal fluid)) separately and stirred in an orbital shaker for 48 h at 37 ± 0.5°C at 80 rpm[42]. The dispersions were then filtered using a Whatman filter (0.45 µm) to obtain a clear solution and analyzed in UV spectrophotometry at 231 nm.

Drug Content

Accurately weighed amount of complexes (100 mg) was dispersed in DMF followed by filtration using Whatman filter paper no. 41. Samples were diluted suitably and analyzed at 231 nm using a UV spectrophotometer[43].

$$\text{Drug Content (\%)} = \frac{\text{Weight of the drug in nanosponges}}{\text{Weight of the nanosponges}} \times 100$$

Solvent residue studies using GC-MS

Solvent residue test targeting DMF was conducted by gas chromatography (GC). The analysis spanned a temperature range of 220°C to 250°C, facilitated by an Elite-624 column and a Mass Spectroscopy detector. This comprehensive approach aimed to detect and quantify any residual DMF.

FTIR Studies

Structural confirmation studies were done for EFD, complexes of EFD with β-CD and NS by performing FTIR of the samples using Shimadzu IR Spirit QARTS. Spectra were obtained in a range from 4000 cm^{-1} to 650 cm^{-1}. Complexes of EFD with β-CD and NS were kept in stability chamber at 40°C and humidity at 75%RHfor 1 month and FTIR spectra were recorded after 1 month between 4000 cm^{-1} to 650 cm^{-1} for compatibility studies.

Differential scanning calorimetry (DSC)

A HITACHI DSC 7020 instrument was used to acquire the thermograms of pure EFD and the complexes. Samples were sealed in aluminium crucibles and heated under controlled conditions at 10 °C/min, till 350°C, all while being exposed to a nitrogen atmosphere at a rate of 40 ml/min.

X-ray powder diffraction (XRPD)

An Ultima IVX-ray diffractometer was used to record the diffractograms of EFD and the complexes. The X-ray wavelength was tuned at λ = 2.28970 Å, and copper was utilized as the X-ray source at 40 KV and 40 mA current. With a scanning speed of 10°/min and scan step time of 0.8 seconds, the samples were scanned through2θ angle range from 0 to 80°. Operating temperature was 15 to 25°C and scintillation counter was used as a detector.

Scanning Electron Microscopy (SEM)

Structural morphology of EFD and the complexes were studied using SEM conducted on a Nova NanoSEM NPEP303 instrument. The study was employed to investigate and compare the structural morphology of pure EFD and its complexes with NS and β-CD.

Molecular Modeling Studies

This study was performed using Maestro Schrodinger 13.4 software[44] to study the complexes and interactions between host and guest. Structure of NS was drawn using Chem Draw software, and structure of EFD and β-CD was taken from PubChem[45]. Ligand preparation was done by ligprep for docking and a grid was generated around this ligand to find the interaction site and the drug was docked on this ligand[46]. EFD was docked with β-CD and NS. Results were evaluated by analyzing dock score and glide energy[47, 48].

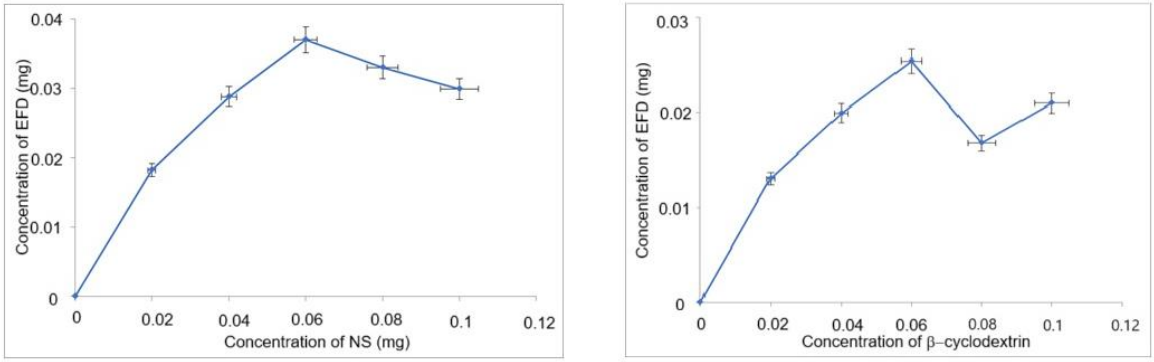
Invitro dissolution studies

Dissolution studies were carried on complexes equivalent to 100 mg EFD. The studies were conducted in USP type 2 dissolution apparatus at 70 rpm and 37°C, with 900 ml of distilled water, phosphate buffer (PB) pH 6.8, and 0.1 N HCl. At pre-defined time intervals (15 minutes), 5 ml of each sample was collected over a 2hperiod;5 ml of fresh media was added after each collection. Samples were filtered through a 0.45 µm Whatman filter. Concentration of EFD was determined using UV spectrophotometry at 231 nm.

RESULTS AND DISCUSSION

Phase Solubility Studies

These studies based on Higuchi and Connors model enable the determination of ratio of host-guest complexation and the strength of physical interactive forces in the complex. In present studies an A_N type of curve for both NSs andβ-CD was evident (Figure 1), which suggested a 1:2 inclusion complexation between EFD and NS and β-CD[49]. Stability constant, calculated from the slope of linear segment of phase solubility plot indicates the strength of complexation. Values between the 100–5000 M^{-1} indicate strong supramolecular interactions[50].Stability constant for NS-EFD andβ-CD-EFD was found to be 553.70 and337.94 M^{-1}, which suggests moderately strong interactions between the host and guest. Relatively stronger interactions were seen between NS and EFD than with β-CD. Too strong interactions may retard the drug's release in its biologically active, free form[20]. This feature could be used as a strategy for controlled release of drugs.

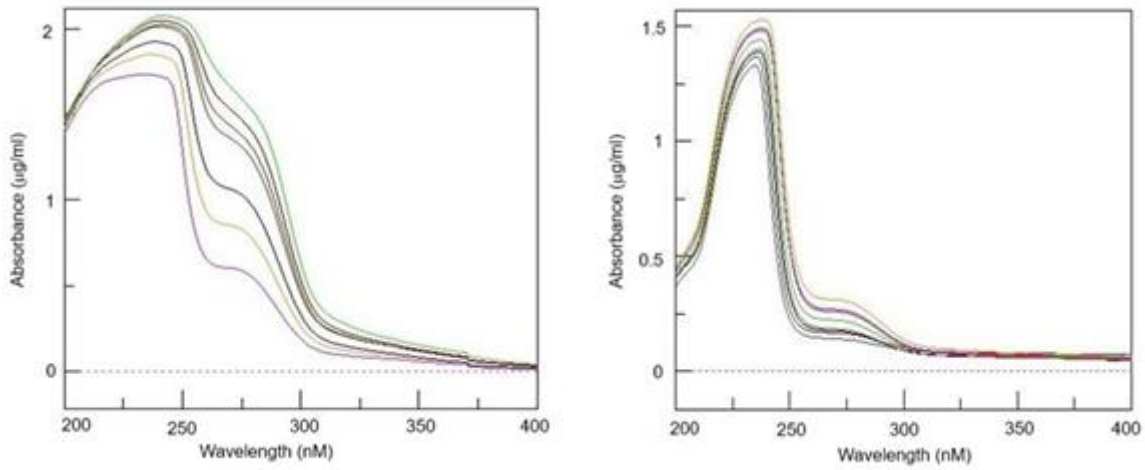


a **b**

Figure 1: Phase solubility diagram of a. EFD-NS b. EFD-β-CD, (Mean ± SD, n=3)

Solution State Interaction Studies

Solution state interaction studies are conducted to understand and characterize molecular interactions in liquid systems, providing insights into chemical and physical properties. EFD showed maximum UV absorption at 231 nm. Increase in concentration of β-CD/NS from1 to 4 µg/ml resulted in shift in wavelength of maximum absorption of EFD. This confirms the inclusion complexation of EFD in β-CD/NS. At 10 ppm the characteristic peak of EFD at 231 nm was masked in both β-CD/NS (Figure 2). This phenomenon can be attributed to weak interactions between complexing agents and EFD. β-CD/NS and EFD. Another possibility is that a hydrophobic moiety (i.e., 4-tert-butyl-dimethyl-biphenyl group within EFD might be masked due to these interactions[51]. This could potentially play a role in the improved solubilization of EFD facilitated by the β-CD/NS.



a b

Figure 2: Solution State Interaction Study a. NS-EFD, b. β-CD-EFD

Saturation solubility studies

Saturation solubility of both spray-dried and non-spray-dried complexes, namely EFD-β-CD and EFD-NS, compared to plain EFD, exhibited significant improvements across various media, including distilled water (DW), phosphate buffer pH 6.8 (PB pH 6.8), 0.1 N HCl, fed state simulated intestinal fluid (FeSSIF), and fasted state simulated fluid (FaSSIF) (Figure 3). The solubility of EFD ranged from 8.3 ± 0.249 ($p<0.002$) to 49.02 ± 0.142 ($p<0.001$) µg/mL in different media. Notably, the highest solubility was observed in 0.1 N HCl (49.02 ± 0.142 µg/mL), while the lowest was in distilled water (8.3 ± 0.249 µg/mL). Both EFD-β-CD and EFD-NS demonstrated remarkable enhancements in solubility than plain EFD. In the case of spray-dried EFD-β-CD, the most substantial increase occurred in DW, with an 18-fold rise, while the least increase was in 0.1 N HCl, at 3.45 folds. Similarly, non-spray-dried EFD-β-CD exhibited a 17-fold increase in DW and a 2.99-fold increase in 0.1 N HCl. For spray-dried EFD-NS, the highest solubility improvement was seen in DW, with an 18-fold increase, and the least in 0.1 N HCl, with a 3.40-fold increase. Non-spray-dried EFD-NS displayed a solubility increase by a factor of 16 in DW and 2.98 in 0.1 N HCl. Remarkably, the most significant solubility enhancement was observed in 0.1 N HCl, where the solubility of EFD in binary complexes was approximately 7.5 times higher than that of plain EFD. Although EFD has a pKa value of 2.33, indicating its acidic nature, it paradoxically exhibited higher solubility in acidic media (0.1 N HCl) within all binary complexes. Furthermore, EFD's log P of 5.44 suggests its lipophilicity, which may contribute to its low solubility[52]. This enhanced solubility can be attributed to entrapment of drugs within the hydrophobic core of β-CD and NS, effectively boosting its solubility. However, it was noted that the increase in solubility was similar in both β-CD and NS, possibly due to EFD's molecular size (molecular weight 631 g/mol), which may limit its effective entry into the NS structure. Solubility of drug in FeSSIF when compared with FaSSIF is higher. The bile salts in FeSSIF may be forming mixed micelles and entrapping some of the drug, leading to higher solubility in FeSSIF[53]. Solubility of EFD in FeSSIF was higher than all other media. Additionally, the spray-dried complexes display increased solubility when compared to their non-spray-dried counterparts. This is due to larger surface area during spray-drying process by virtue of atomization of sample and the rapid drying, which leads to amorphization[54]. Amorphous forms are more soluble than crystalline solids. Thus uniform and smaller particle size and amorphization lead to enhanced solubility of the spray-dried complexes[55, 56].

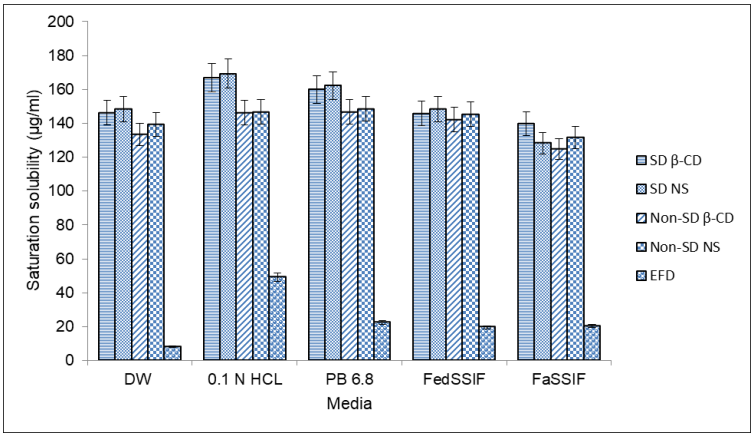


Figure 3: Saturation solubility studies of plain EFD, EFD-β-CD, and EFD-NS in different media, mean ± Std n=3

Particle size, Zeta potential, and PDI

All the complexes had particle sizes smaller than 1000 nm. Plain NS and β-CD had particle sizes of 279 and 207 nm, with zeta potentials of -19.4 and -10.0 mV. However, when EFD was loaded into these complexes, both the particle size and zeta potential increased. For spray-dried and non-spray-dried NS, the particle size ranged from 905.5 to 948.1 nm, with zeta potentials of -13.9 and -17.9 mV. Similarly, for spray-dried and non-spray-dried β-CD, the particle size ranged from 667.1 to 715.1 nm, with zeta potentials of -14.9 and -21.6 mV. The polydispersity I index (PDI) of plain NS and β-CD fell within the range of 0.525 to 0.529. In contrast, the PDI for spray-dried and non-spray-dried EFD-NS ranged from 0.129 to 0.782, while for EFD-β-CD, it ranged from 0.206 to 0.450.

Drug content

Drug content in formulations was determined by dissolving 10 mg complexes in DMF. The drug content was within the range of 25-30% w/w for both the spray-dried (SD) and non-spray-dried (Non SD) samples. Percentage yield for the SD and non-SD NS complexes was 36% and 85% w/w, respectively, while for β-CD, it was 35% and 80% w/w, respectively.

Solvent residue studies

The results of the solvent residue test for DMF using GC on the SD EFD-NS complex reveal that there is no detectable residual DMF in the sample (Figure 4). Retention time for DMF was 7.4 min (Figure 4). Absence of peak at 7.4 min in the gas chromatogram of sample confirms the absence of DMF thereby indicating the suitability of the complex for its intended applications.

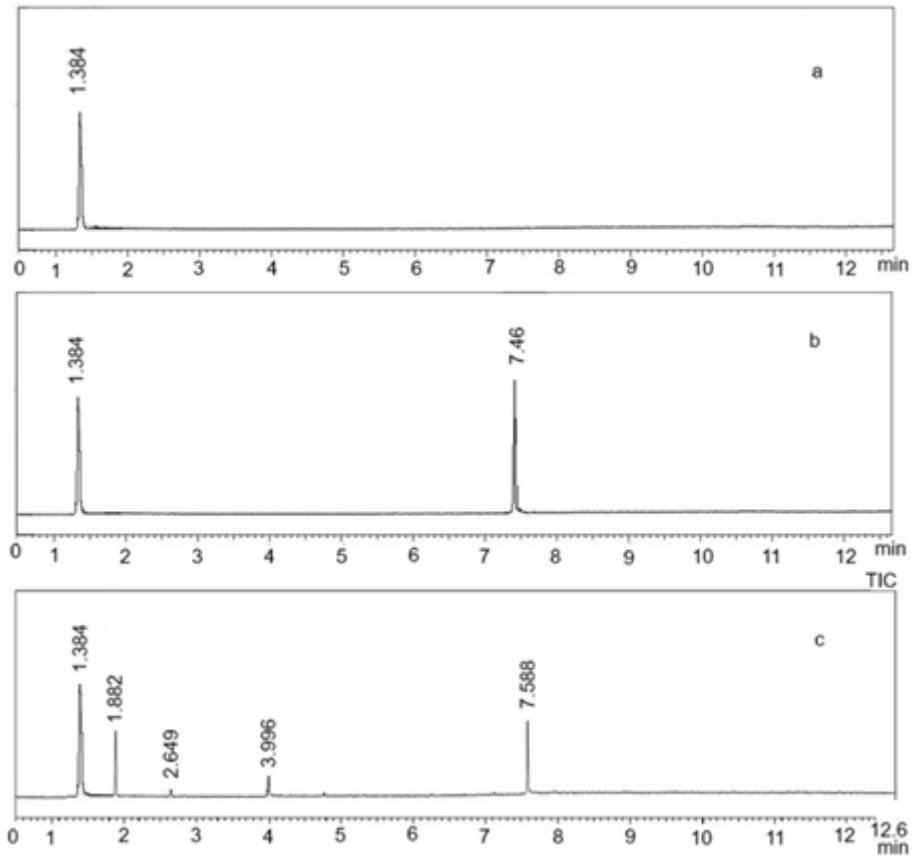


Figure 4: Solvent residue analysis by gas chromatography a) pure water b) DMF in water c) EFD complex

FTIR Studies

FTIR spectra of the pure EFD, SD-EFD-NS, and SD-EFD-β-CD were recorded (Figure 5). NS complexes revealed a characteristic peak at 1741 cm^{-1}, demonstrating the formation of the carbonate ester group. Furthermore, The FTIR peaks of EFD are C=O stretching (1697.29 cm^{-1}), C-O-C ester (1246.58 cm^{-1}), and aromatic C=C (1491.90 cm^{-1}), and -NO_2 (1337.86 and 1597.82 cm^{-1}). Among the listed EFD peaks, the 693.18 cm^{-1} peak was concealed, while peaks at 2467.48 cm^{-1}, 1697.29 cm^{-1}, 1640.23 cm^{-1}, and 895.71 cm^{-1} were displaced upon complexation with NS and β-CD. This shift in FTIR peaks confirms the complexation of EFD with β-CD/NS. These outcomes affirm the successful complexation of EFD and also the retention of vital structural elements necessary for its functional attributes.

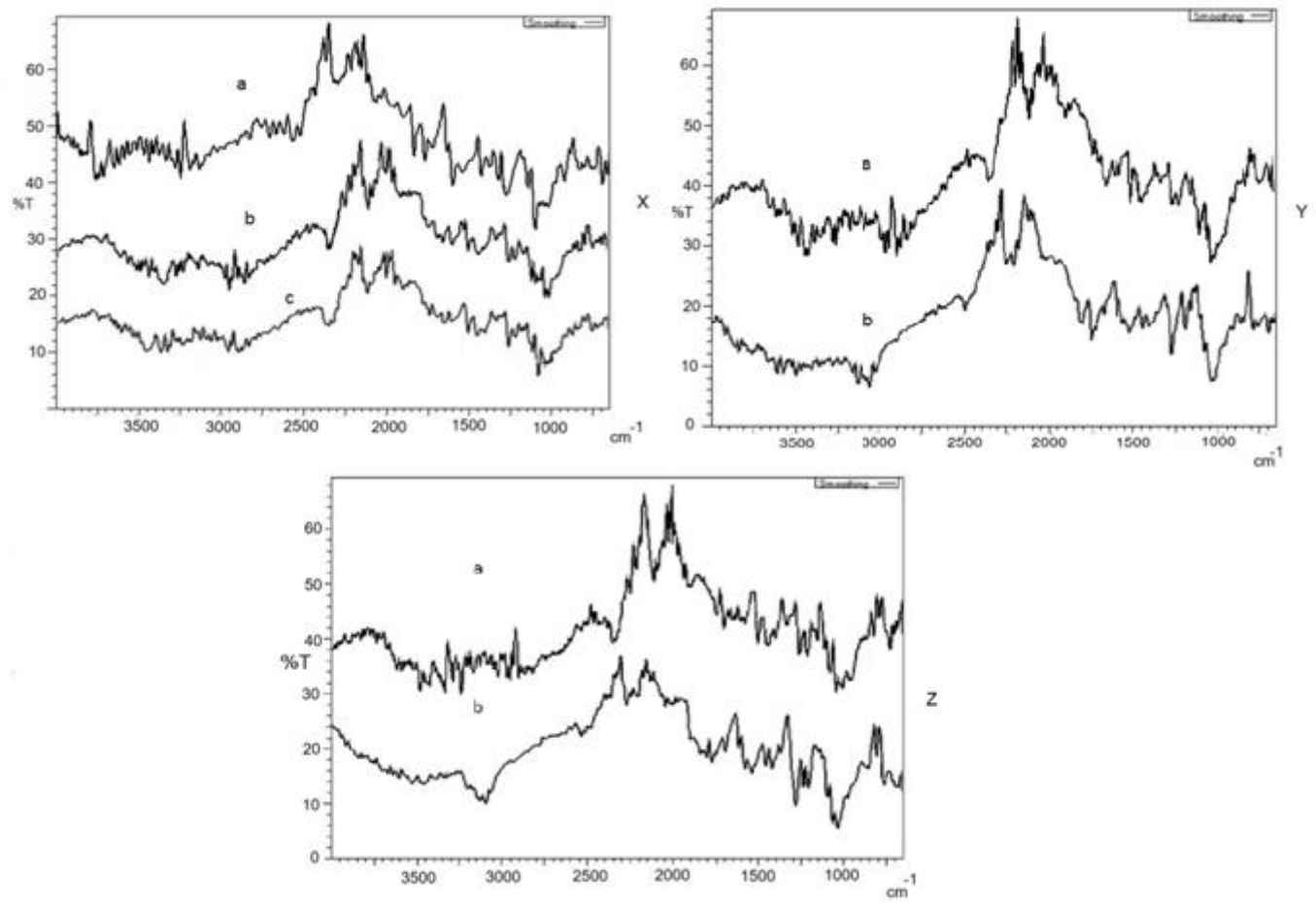


Figure 5: FTIR studies of X: a) Pure Drug (EFD) b) Complex EFD+NS c) Complex EFD+β-CD

Y: Complex EFD-β-CD a) FTIR of complex at 30-37°C b) FTIR at 40°C and 75% RH

Z: Complex EFD-NS a) FTIR of complex at 30-37°C b) FTIR at 40°C and 75% RH

Compatibility studies

Compatibility studies of the complexes were conducted by FTIR analysis. The complexes were subjected to 40°C and 75% RH for 1 month. The peaks observed, for the complex of EFD-β-CD such as C-O-C stretching at 1250-1020 cm^{-1}, and -NH stretching at 3500-3350 cm^{-1}at room temperature was found to align with the peaks obtained after the 1-month stability period in the controlled environment, depicted in Figure 5. Similarly, the complexes of EFD-NS show consistent peaks such as C-O-C stretching at 1250-1020 cm^{-1}, C=O bonding at 1650-1750 $cm^{-1}$when subjected to the stability chamber conditions for 1 month. This observation provides compelling evidence that the complexes remained stable throughout the one-month period under the specified conditions.

DSC

DSC thermogram of EFD displayed a sharp endotherm at 172.02°C. This indicates the melting of the crystalline drug (Figure 6). The peak vanished in SD EFD-NS, indicating that the drug's crystallized form had changed to an amorphous state[57]. This also is an indication of incorporation of EFD as inclusion or non-inclusion complexes within the NS (Figure 6b). The SD complexes of EFD with both β-CD and NS displayed a broad melting endotherm around 85°C (Figure 6c)[58] The drastic decrease in the melting temperature points to dilution effect, inclusion complexation and amorphization of EFD. The enthalpy of pure EFD during melting is 68.01 KJ/mol [59] but for the complexes the enthalpy was 5.46 KJ/mol and 2.9 KJ/mol for SD EFD-NS and SD EFD-β-CD, respectively. This decrease in the enthalpy further validates the inference that crystalline EFD was converted to amorphous form. Degrees of crystallinity obtain for β-CD is 8.02% and for NS is 4.2%. A reduction in enthalpy, indicating an exothermic process, is crucial for solubility because it signifies favorable interactions between the solute and solvent[60]. This results in improved dissolution, as the energy released promotes stable molecular interactions and facilitates the dispersion of the solute[60, 61]. This thermodynamic driving force reduces activation barriers, enhancing molecular mobility and accelerating the rate of dissolution. Ultimately, the enthalpy decrease plays a pivotal role in enhancing solubility[60-62].

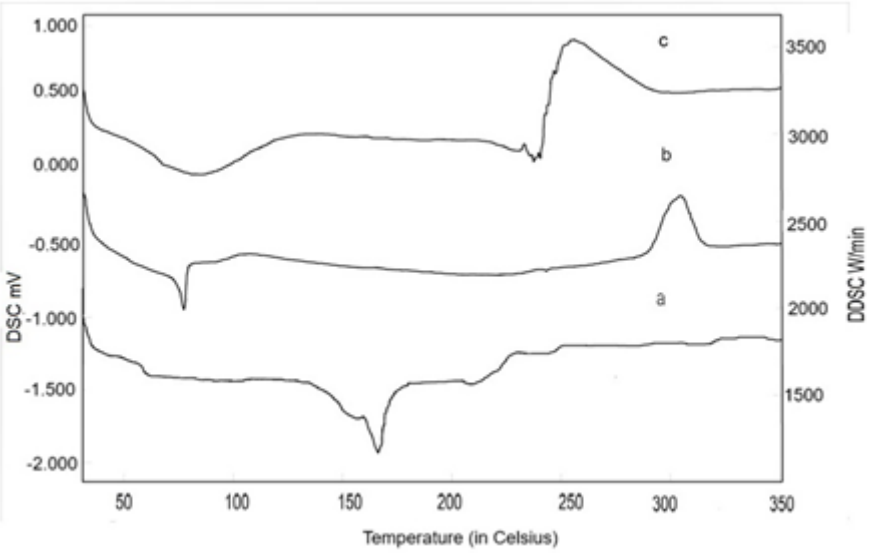


Figure 6: DSC of a) Pure Drug b) SD EFD+NS c) SD EFD+β-CD

PXRD

EFD XRD pattern revealed noticeable strong peaks at 2θ angles 5.6,7.4, 10.6, 12.4, 13.0, 13.9, 18.06, 20.4, 23.14, 24.14, and 26.5°which indicates crystallinity of the drug. This was noticeably diminished, as shown in Figure 7 by dispersed peaks with low intensities in the diffractograms of the drug in NS, indicating loading of drugs into NS inside the polymeric matrix in an unstructured, solid-state-solubilized, or disorganized crystalline phase[12]. These results also support the DSC results. In essence, reduced crystallinity disrupts the well-defined crystal lattice, making it easier for the drug molecules to dissociate from the solid matrix and enter the surrounding solvent. As a result, the drug can dissolve more readily, leading to an improved solubility profile[63]. Degree of crystallinity for EFD was found to be 73% and for complexes it was 0.87% for EFD-NS and1.76% for EFD-β-CD which suggested that the drug had converted to amorphous state, which is the reason for higher solubility of the drug in the complexes. These results also support the DSC results.

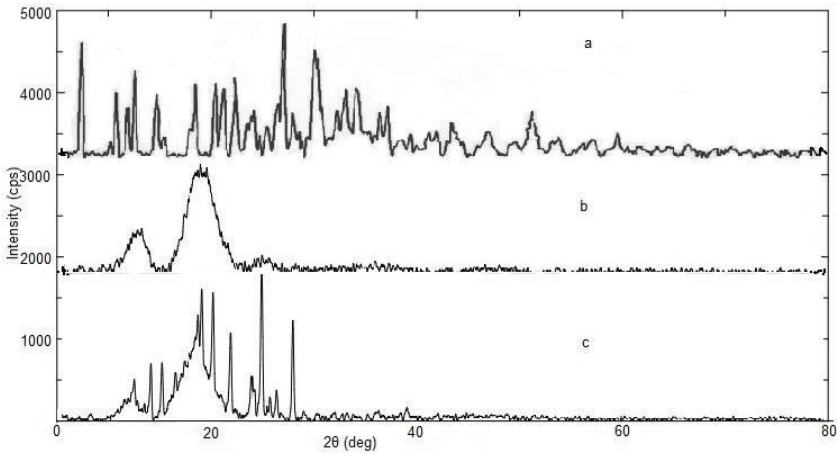


Figure 7: XRPD graph of a) Pure Drug b) SD EFD+β-CD c) SD EFD+NS

Scanning Electron Microscope (SEM)

SEM images of the complexes of EFD-NS and EFD+β-CD are displayed in Figure 8. The particles appear relatively small and almost spherical, showcasing numerous surface pores. Comparatively, the surface morphology of the pure drug is quite different, as illustrated in Figure 8a. In contrast to the relatively uniform and porous appearance of the complexes, the surface of the pure drug particles appears to be equant shape and possibly rough, which may be attributed to its crystalline nature. SEM images also revealed that the particles of interest are effectively dispersed within the β-CD/NS under investigation, and no significant agglomeration or clustering is observed. This dispersion is visually evident from the images, where individual particles appear distinct and separate from each other.

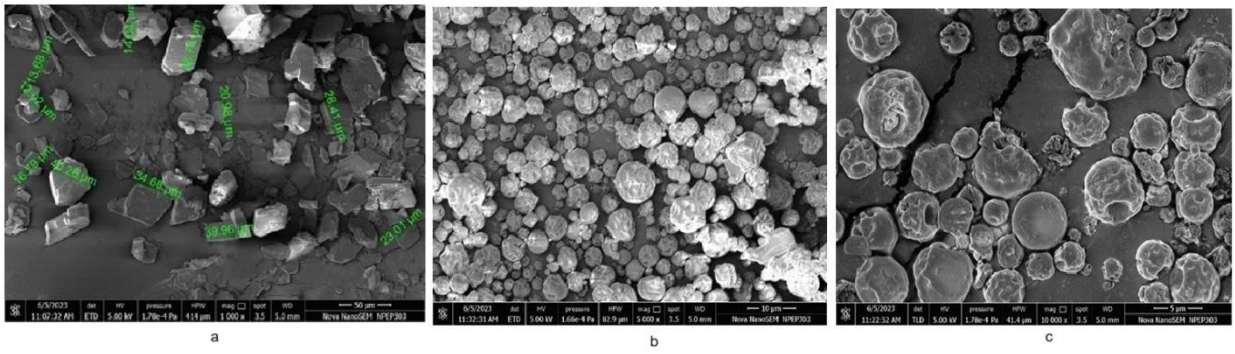


Figure 8: a) SEM images of pure drug b) SEM images of SD EFD+β-CDc) SEM images of SD EFD+NS

Molecular docking

This study was performed using Maestro Schrodinger 13.4 software [59] to study the interaction between EFD and β-CD and NS. Molecular modeling reveals types of interaction (H-bond, hydrophobic, etc.) and the binding affinity between target and ligand. β-CD and NS displayed two hydrogen bonds involving the hydroxyl groups present on both molecules as shown in Figure 9. This interaction yielded a docking score of -2.69 and glide energy of -32.30. Subsequently, the same complex underwent further docking with EFD to investigate its binding mode. This analysis indicated formation of three hydrogen bonds between oxygen and hydrogen atoms of NS with EFD, resulting in a -2.88-docking score and glide energy of -34.0. These results collectively suggest a moderate binding affinity based on the docking score, while the glide score indicated a strong binding interaction and a stable binding pose. In this study, EFD-NS shows stronger hydrogen bonding than β-CD complex. Docking scores help prioritize ligands by ranking them based on their potential to bind to the receptor. A low docking score suggests that a ligand is likely to have strong binding affinity and could be a promising lead compound[64].Glide energy provides a comprehensive estimation of supramolecular interactions between complexing agent and drug[65]. Lower glide energy values indicate stronger binding interactions and more stable binding poses[66]. The glide energy can be used to rank ligands and evaluate the quality of binding modes predicted by the docking simulation. These results are in line with the results of solubility studies, wherein both β-CD and NS complexes yielded nearly similar effect on solubility of EFD.

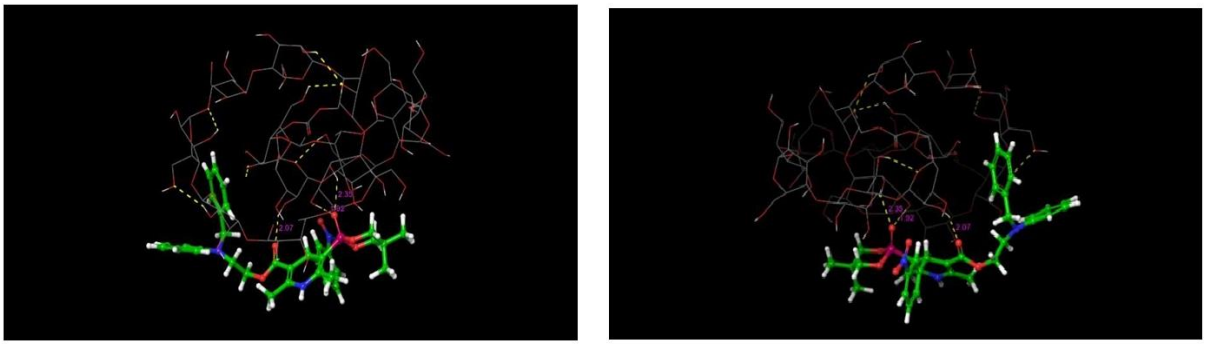


Figure 9: Molecular Docking of EFD-NS0

In vitro dissolution studies

In vitro dissolution studies showed that EFD was released from NS over a span of 2h. The release of the pure drug in different media were found to be 50% in D.W., 52% in phosphate buffer pH 6.8, and 54% in 0.1 N HCL ($P<0.0001$). Notably, binary complexes containing β-CD, both spray drying and non-spray dried, exhibited significantly improved release profiles as shown in Figure 10. In distilled water, spray dried EDF-β-CD displayed a 69% release rate, marking an 18% increase compared to non-spray drying. In 0.1 N HCl, it achieved an 81% release in D.W., a 19% increase, and at pH 6.8, a 76% release, an 18% increase. Similarly, EFD-NS, prepared using the same methods, showed enhanced release with a 70% release in D.W., 24% increase, 73% at pH 6.8, 20% increase, and 78% in 0.1 N HCl, 14% increase compared to their non-spray dried complexes. Comparatively, β-CD exhibited higher drug release than NS and the pure drug. Spray dried EFD-NS/EDF-β-CD exhibit significantly high solubility in comparison to their non-spray dried complexes. This improvement can be attributed to increased surface area and amorphization due to spray drying procedure[58]. The values for spray dried and non-spray dried differences were found to be statistically significant ($p < 0.02$).

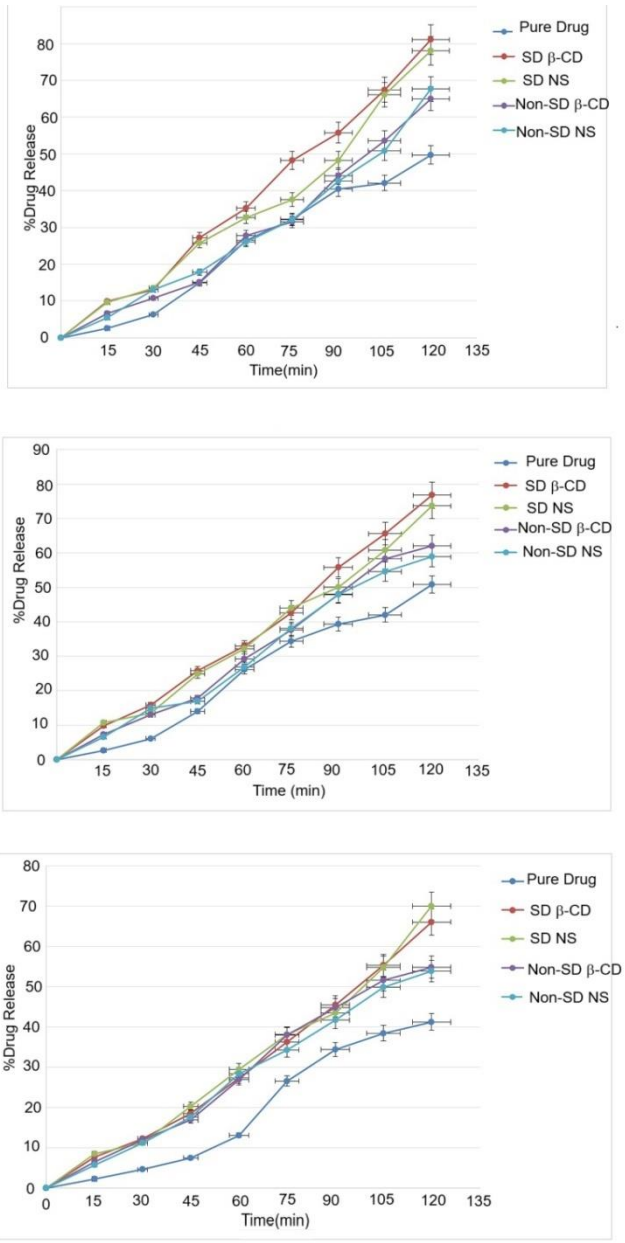


Figure 10: *In-vitro* drug release in a) 0.1 N HCl b) PB pH 6.8 c) DW, (Mean ± SD, n=2)

CONCLUSION

Inclusion complex of EFD with β-CD and NS were prepared by kneading and spray dried method. Phase solubility studies revealed 1:2 complexation with both carriers. Saturation solubility and *in vitro* dissolution studies revealed that there was a marked improvement in solubility of EFD in all media than pure EFD. Comparing between solubility in β-CD and NS did not show a significant difference. However among all complexes spray dried complexes caused a remarkable increase in drug solubility as compared to non-spray dried complexes. This can be attributed to increased surface area and amorphous characteristics. Overall, these findings hold great promise for advancing drug delivery systems, potentially leading to improved therapeutic outcomes and patient benefits in the field of pharmaceutical research. Further investigations are warranted to explore the translational potential of complexation approaches.

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Conflict of Interests

The authors report no conflict of interest, financial or otherwise.

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