

# Solubility Enhancement of Nevirapine Using B-Cyclodextrin Nanosponges

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## ABSTRACT:

**Aim:** Beta-cyclodextrin-based nanosponges were used to augment solubility and dissolution of Biopharmaceutical Classification System (BCS) class II drug Nevirapine. **Materials and Methods:** Nanosponges (NS) were prepared using  $\beta$ -cyclodextrin ( $\beta$ -CD) crosslinked with diphenyl carbonate and subjected to spray drying. Binary mixtures of NVP with  $\beta$ -CD, NS, & SDNS were prepared by solvent evaporation. Characterization was done by phase solubility studies and saturation solubility in different media and *in vitro* dissolution studies. Spectral analysis by Fourier transforms infrared spectroscopy, differential scanning calorimetry, powder X-ray diffraction, field emission scanning electron microscopy & stability studies were performed. **Results:** Spectral characterization confirmed the formation of inclusion complexes. The stability constant for the NVP-SDNS complex was found to be  $1584\text{m}^{-1}$ , indicating stable complex formulation. Saturation solubility was 2-4 folds more with NVP-SDNS complex in D.W. and 2-10 folds greater in 0.1N HCl. NVP displayed a noteworthy enhancement in solubility in relevant media. Binary mixtures show a 31-65% increase in dissolution in 0.1N HCl, with the highest dissolution rate compared to phosphate buffer pH 6.8, D.W, FaSSIF & FeSSIF. The percentage decrease in crystallinity of NVP- $\beta$ -CD, NVP-NS, & NVP-SDNS complexes was found to be in the range of 34-59%. Gas chromatography by solvent residue analysis indicated the evaporation of DCM from the NVP-SDNS complex. **Conclusion:** The NVP-SDNS binary mixture showed higher saturation solubility & Dissolution rate than other binary mixtures. It was inferred that the solubility of NVP was enhanced by using  $\beta$ -Cyclodextrin nanosponges.

**Keywords:** Beta-cyclodextrin Nanosponges, Nevirapine, Solubility enhancement.

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## INTRODUCTION

The oral route is one of the most popular routes for drug delivery.<sup>1</sup> However, 50% of drugs have high lipophilicity which is a challenge to oral administration. Biopharmaceutical Classification System Class (BCS) II and IV drugs suffer from low bioavailability due to poor water solubility. Consequently drug absorption is compromised.<sup>2</sup> Thus increasing drug solubility and oral bioavailability is a challenge to scientists.<sup>3</sup> Various approaches to improve solubilization and bioavailability of poorly water-soluble drugs include particle size reduction,<sup>4</sup> chemical modification,<sup>5</sup> microenvironmental pH modification,<sup>6</sup> solid dispersion,<sup>7</sup> complex formation,<sup>8</sup> co-solvency,<sup>9</sup> micellar solubilization,<sup>10</sup> hydrotrophy,<sup>11,12</sup>.

Nanosponges (NS) are a new type of polymer derivatized by crosslinking and comprising colloidal-sized particles with

nanosized cavities. The outer surface is usually porous, which allows for sustained drug release and topical drug delivery.<sup>13</sup> Lipophilic and hydrophilic substances can be entrapped by these particles, enhancing the solubility of weakly water-soluble substances.<sup>14</sup> Solvent evaporation, emulsion solvent evaporation, ultrasound-assisted synthesis, and interfacial phenomenon are some methods for NS preparation.<sup>15</sup> NS have been used to improve solubility and stability of telmisartan,<sup>16</sup> meloxicam,<sup>17</sup> curcumin,<sup>18</sup> and efavirenz,<sup>19</sup> NSs have effectively masked taste of drugs like oseltamivir phosphate<sup>20</sup> and gabapentin.<sup>21</sup> Controlled release formulations of drugs like camptothecin,<sup>22</sup> tamoxifen,<sup>23</sup> and quercetin,<sup>24</sup> have been successfully prepared using NS.<sup>25,26</sup>

Cyclodextrins (CDs) have been widely used as a pharmaceutical excipient because of their ability to incorporate or adsorb guest molecules into their central cavity.<sup>27</sup> Crosslinking of CDs with crosslinkers such as carbonyl-diimidazole,<sup>28</sup> diphenyl carbonate (DPC),<sup>29</sup> hexamethylene diisocyanate,<sup>30</sup> and pyromellitic anhydride<sup>31</sup> have led to the formation of a diverse range of nanosponges which are nontoxic and temperature stable. Unlike plain CDs, NSs can develop supramolecular interactions with drug molecules by entrapping drug within the toroidal



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structure of CDs and also within the nanochannels created due to crosslinking.<sup>32</sup> The most common natural CDs used in the pharmaceutical industry are  $\alpha$ ,  $\beta$ , and  $\gamma$  CDs with varying numbers of glucopyranose units.<sup>33</sup> NS are usually made from  $\beta$ -CD because it has superior complexing ability and stability with cross-linking agents. The advantage of using  $\beta$ -CD for preparing NS is that it has cavity dimensions, minimal production costs, higher production rates, and is approved by the United States Food and Drug Administration as safe for consumers.<sup>34</sup> Van der Waals forces, lipophilic and hydrogen bonds are responsible for complexation.<sup>35</sup>

Non-nucleoside reverse transcriptase inhibitors (NNRTI) are frequently used along with high-activity antiretroviral therapy (HAART) to improve the lifespan of HIV patients. NNRTIs prevent uninfected cells from becoming infected by inhibiting the reverse transcriptase enzyme. Nevirapine (NVP), dolutegravir, efavirenz, rilpivirine, and etravirine are some of them.<sup>36</sup> NVP is classified as BCS class II (low solubility/high permeability). Its low intrinsic water solubility, weak base nature ( $pK_a=2.8$ ) and variable dissolution rates, compromise the drug bioavailability.<sup>37</sup> Chemically it comes under diazepam group.<sup>38</sup> It prevents various activities of DNA polymerases by binding directly with the allosteric site on reverse transcriptase.<sup>39</sup>

Solubility and dissolution rate of NVP was evaluated in this study by comparing binary mixtures of NVP with  $\beta$ -CD, NS crosslinked with DPC, and spray-dried NS. Phase solubility studies were performed to compute the stoichiometric ratio and stability constants. The complexes were characterized by solubility profile in different media, Fourier transform infrared spectroscopy, powder X-ray diffraction, differential scanning calorimetry, and field emission scanning electron microscopy, Gas Chromatography for solvent residue, *in vitro* dissolution and stability studies.

## MATERIALS AND METHODS

### Materials

NVP was gifted by Cipla Pharmaceuticals Ltd, Mumbai.  $\beta$ -Cyclodextrin ( $\beta$ -CD) gifted from Analab Fine Chemicals, Mumbai. Diphenyl Carbonate (DPC) was bought from Spectrochem Pvt Ltd, Mumbai. All other reagents used were of AR grade and procured locally.

### Synthesis of NS

Nanosponges of anhydrous  $\beta$ -CD and DPC in a 1:4 molar ratio prepared by a previously reported procedure.<sup>19</sup> Required quantities of  $\beta$ -CD (11.35g) and DPC (8.56g) heated to 100°C with continuous stirring. The crosslinking reaction results in the generation of phenol crystals separated carefully from the final product. The product was subjected to washings with distilled water (D.W.) and acetone to eliminate unreacted  $\beta$ -CD and phenol. Rinsings were checked for phenol residue using a ferric

chloride solution 10% w/v. The product was washed and dried for 2h at 60°C in a hot air oven.

### Preparation of spray-dried nanosponges (SDNS)

The NS was further subjected to spray drying (Make: LABULTIMA LU-222). Based on the solubility of NS, a 1:1 mixture of ethanol and D.W. was selected as the solvent system. NSs (25 g) dissolved in 200 ml of solvent system and spray dried with an inlet temperature 120°C and outlet temperature 60°C. The aspiration flow rate was 60 Nm<sup>3</sup>/h. The product was collected from the product collection chamber, and the percentage yield was calculated. Malvern Zeta sizer was used to determine the particle size, polydispersity index (PDI) & zeta potential of SDNS and NS (Model no: Nano ZS 90).

### Primary Investigation of Binary Mixtures

#### Determination of stability constants

As proposed by Higuchi and Connors,<sup>40</sup> phase solubility studies were conducted to study supramolecular interactions between host and guest and determine stability constants. Excess amounts of the drug were added to 20 ml of DW with higher amount of  $\beta$ -CD, NS, and SDNS for binary mixtures of NVP with  $\beta$ -CD, NS, and SDNS. The mixture was swirled in orbital shaker (Remi CIS-24BL) for 48 h at 26°C, filtered using Whatman filter paper (0.45), and quantified at 280 nm using UV-Spectrophotometer (Make Model: Jasco V-730).

#### Drug loading

The solvent evaporation method was used to form binary mixtures (1:1) of NVP with  $\beta$ -CD, NS, and SDNS by dispersing in dichloromethane (1:1) and triturating until the solvent evaporated. To remove traces of dichloromethane, the moist SDs was dried at 50°C in an oven for 6h (Lab oven Biomedica). The complexes were characterized by saturation solubility studies, *in vitro* dissolution, thermal analysis, powder X-ray diffraction, gas chromatography for solvent residue, field emission scanning electron microscopy and stability studies.

### Evaluation and Characterization of Complexes

#### Saturation Solubility Studies

Saturation solubility studies were carried out by adding excess drug/binary mixtures to multiple media (20 ml each), including distilled water (D.W.), 0.1N HCl, phosphate buffer pH 6.8, biorelevant media.<sup>41</sup> The dispersions were subjected to swirling motion in an orbital shaker (Remi CIS-24BL) at 37±0.5°C for 24h at 100 rpm and then filtered by membrane filter paper (0.45), and the filtrate was quantified for NVP content by UV spectrophotometry at 280 nm to determine the amount of NVP in the filtrates. GraphPad InStat [DATASET1.ISD] was used to apply the Statistical *p*-test.

## Fourier Transform Infrared Spectroscopy (FESEM)

IR spectra of drug and binary mixtures were examined by SHIMADZU FTIR (version 2.26) spectrophotometer to assess the interaction between the NVP,  $\beta$ -CD, NS, and SDNS and to ensure the formation of the mixtures. The samples were studied from a frequency range of 3600-650  $\text{cm}^{-1}$ .

## Differential Scanning Calorimetry (DSC)

Thermograms for NVP and binary mixtures were recorded by differential scanning calorimeter (Instrument name: Mettler Toledo DSC 1), by exposing samples to 30-300°C at increments of 10°C/min in a nitrogen atmosphere (40-60 ml/min).

## Field Emission Scanning Electron Microscopy (FESEM)

The surface characteristics of plain NS, NVP loaded NS & NVP loaded SDNS were analyzed by Field Emission Scanning Electron Microscopy (FESEM) (Instrument name: FEI Nova Nano SEM 450). The magnification power of NS and NS-NVP was 30,000x, and SDNS and NVP-SDNS were 60,000x at a pressure of 1.5-4pa.

## Powder X-ray Diffraction (PXRD)

The PXRD spectra of NVP, NVP- $\beta$ -CD, NVP-NS & NVP-SDNS were examined using a high-power powder X-ray diffractometer (Rigaku Analytical XRD, India) using a K-beta filter at voltage of 40 kV and current of 40 mA. The scanning mode of  $2\theta/\theta$  was used. The degree of crystallinity was evaluated by below equation:

$$\text{Degree of crystallinity} = \frac{\sum c}{\sum c + \sum a} \times 100 \dots \text{Eq.1}$$

Where, c= crystalline peak intensities

a= amorphous peak intensities

## Gas chromatography (GC) for solvent residue

For the NVP-SDNS complex, a solvent residue test for DCM was performed using gas chromatography (Shimadzu GCMS QP2020). The sample was evaluated over a temperature range of 320/350°C using an SH-Rxi-5Sil column and Mass Spectroscopy detector.

## In vitro dissolution studies

The rate and extent of dissolution of plain NVP and binary mixtures of NVP with  $\beta$ -CD, NS, and SDNS were studied. Samples (equal to 100 mg of NVP) were subjected to dissolution studies

using a USP class II Paddle apparatus [Lab India Dissolution Test Apparatus, DISSO 2000, and India] at  $37 \pm 0.5^\circ\text{C}$  and paddle speed of 50 rpm with 900 ml of 0.1N HCl, phosphate buffer pH 6.8, FaSSIF and FeSSIF separately as dissolution media. Samples (10 ml) were taken from each dissolution vessel at 15, 30, 45, 60, 90, and 120 min intervals,<sup>39</sup> filtered using Whatman filter paper (0.45) and quantified by UV spectrophotometer (Make model: Jasco V-730) at  $\lambda_{\text{max}}$  280 nm.

## Stability studies

The International Council for Harmonization guidelines were followed for accelerated stability studies.<sup>42</sup> The NVP-NS and NVP-SDNS were kept in a stability chamber (CHM-65 REMI) at 40°C and 70% RH. The complexes were evaluated for 3 months for their physical appearance and drug content with a sampling frequency of 1 month.<sup>43</sup>

## RESULT AND DISCUSSION

### Characterization of NS and SDNS

The practical yield of SDNS was 60% w/w yield of plain NS. The particle size of plain NS was 1589 nm and PDI was 0.493. Zeta potential was found to be -26.0 mV. Spray drying resulted in reduction in particle size and improved the particle size distribution by reducing the polydispersity. Particle size of SDNS was 601.7 nm with a PDI of 0.002. Zeta potential was found to be -23.7 mV. Spray drying is an energy-intensive process for producing free-flowing powders with well-defined particle sizes.<sup>44</sup> During spray drying, the droplet diameter is 10-100  $\mu\text{m}$ , which enables faster drying due to rapid heat and mass transfer.<sup>45-47</sup>

### Determination of stability constants

Phase solubility studies aid to determine the stoichiometry of complexation and stability of the inclusion mixtures. Phase solubility diagrams of NVP with all complexing agents showed AL-type curves (Table 1), as suggested by Higuchi and Connors' model. Inclusion complex formation was seen in a 1:1 stoichiometric ratio. The slope of linear part of phase solubility plot was calculated to determine the stability constant (Kc). Kc values greater than  $150 \text{ m}^{-1}$  indicate significant complexation activity. SDNS had the strongest interaction with NVP among all the complexes.<sup>40</sup> The stability constants reflect the strength of the interaction between host and guest. This will indicate the tendency for leakage of drugs from the complexes. Host-guest interactions involved various forces, like hydrogen bonding and van der Waal forces. The stability constant was with SDNS

**Table 1: Stability constants (Kc) for binary mixtures [Mean  $\pm$  SD, n=2]**

Sl. No.	Binary Mixtures	Type of curve	Stability constant (Kc) $\pm$ S.D.
1	NVP- $\beta$ -CD	$A_L$	$1169\text{M}^{-1} \pm 25.7$
2	NVP-NS	$A_L$	$1312\text{M}^{-1} \pm 33.1$
3	NVP-SDNS	$A_L$	$1584\text{M}^{-1} \pm 46.4$

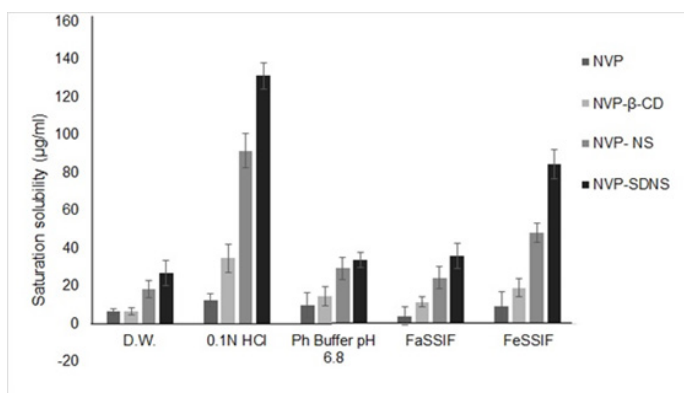


Figure 1: Saturation solubility.

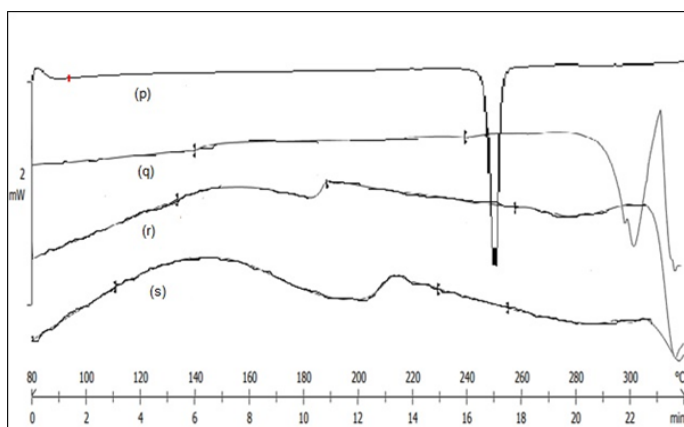


Figure 3: DSC thermogram of (p)-NVP, (q)-NVP-β-CD, (r)-NVP-NS, (s)-NVP-SDNS

non-inclusion complexes due to the cross-linking, hence a greater degree of van der Waals forces of attraction.<sup>35</sup> It can be presumed between NVP and NS. The smaller particle size of SDNS also provides a greater interfacial area for interaction between NVP and NS. The increments in stability constants can be attributed to these factors.<sup>40</sup>

## Evaluation and Characterization of Binary Mixtures

### Saturation Solubility Studies

Maximum solubility of NVP, NVP-β-CD, NVP-NS, and NVP-SDNS mixture in D.W. was found in the range of 6.4 to 45 µg/ml, respectively. Solubility of NVP binary mixture with NS and SDNS ( $p < 0.01$ ) was increased by 2 to 4-fold, respectively as compared to NVP. The binary mixture with β-CD indicated the same solubility in D.W. as plain NVP. In phosphate buffer pH 6.8, the solubility of binary mixtures with NS and SDNS ( $p < 0.01$ ) was enhanced by 3-3.5 fold, respectively, compared with plain NVP. Compared to plain NVP in FaSSIF (pH 6.5), the solubility of binary mixtures with β-CD, NS, and SDNS ( $p < 0.001$ ) were increased by 2-8 folds, respectively. When compared to plain NVP in FeSSIF (pH 5), the solubility of binary mixtures with β-CD, NS, and SDNS ( $p < 0.001$ ) was enhanced by 2-8 folds, respectively. Compared to plain NVP in 0.1N HCl, binary mixtures of SDNS ( $p < 0.001$ ) obtained a solubility increase of 10-fold while binary

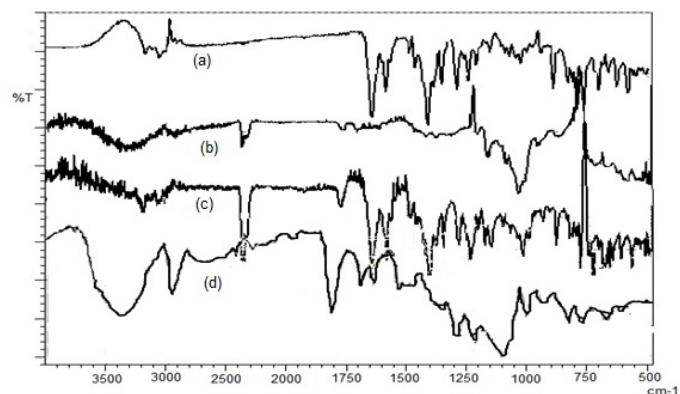


Figure 2: FTIR Spectra of (a)-NVP, (b)-NVP-β-CD, (c)-NVP-NS, (d)-NVP-SDNS mixtures of β-CD and NS showed a solubility increase of 2 to 7fold, respectively. The solubility of NVP is pH-dependent, as noted by the observation that it was most soluble in 0.1 N HCl (Figure 1). NVP has a pKa of 2.8, suggesting it is weakly basic.<sup>48</sup> According to studies, NVP has high solubility at pH 3.<sup>49</sup>

### FTIR

FTIR spectra of NVP showed stretching vibrations of characteristic functional groups like -NH at 3310-3360  $\text{cm}^{-1}$ , -CH at 2862-2882  $\text{cm}^{-1}$ , C=N at 1250-1340  $\text{cm}^{-1}$ , and C=O at 1705-1725  $\text{cm}^{-1}$ .<sup>31</sup> Peaks at 3311, 2925, 1019, and 1642  $\text{cm}^{-1}$  in the FTIR spectra of β-CD correspond to the stretching vibrations of -OH, -CH<sub>2</sub>, C-O, and C=O, respectively.<sup>50</sup> The spectra of NVP-NS and NV-SDNS displayed a C=O stretching peak at 1643  $\text{cm}^{-1}$ . FTIR studies confirmed the complexation between NVP, NS, and SDNS (Figure 2). The specific peaks observed in the IR spectra of plain NS and NVP were dislodged in complexes. NVP was compatible in drug-excipient compatibility studies with both β-CD and NS.

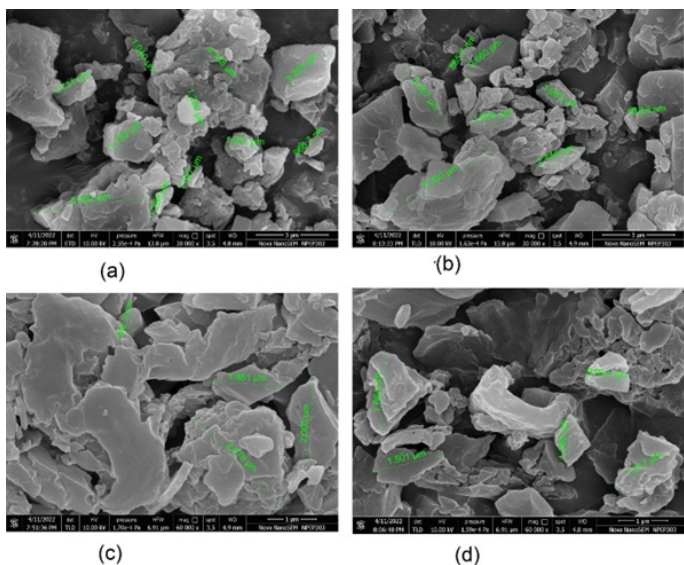
### DSC

DSC Thermogram of NVP displayed a sharp endotherm at 249°C, and β-CD showed at 300°C,<sup>51</sup> which correlates to their melting point (Figure 3). The absence of endotherm's in binary mixtures showed that NVP is distributed in the NS in the molecular form. At temperatures between 140-200°C, the thermogram of binary mixtures showed broadened and shallow peaks. We can hence conclude that drug is molecularly distributed in the NS, with hydrophobic functional groups of NVP entrapped within lipophilic cavities.

### Field Emission Scanning Electron Microscopy (FESEM)

Using FESEM, the surface characteristics of plain and drug-loaded NS and SDNS with NVP was determined. According to FESEM results, NVP-NS and NVP-SDNS exhibit NVP crystals entrapped in channels inside the NS structure. SEM analyses revealed that the form was flat plate-like crystals (Figure 4).





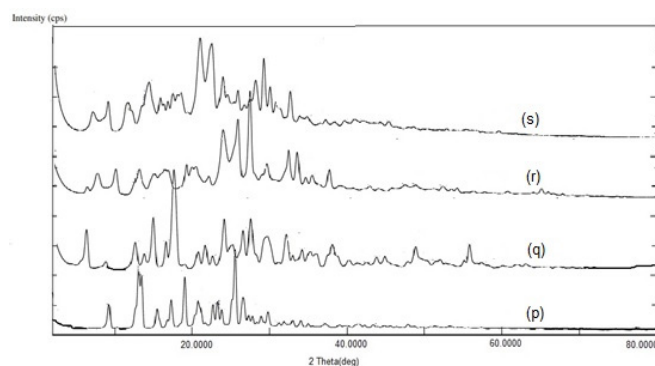
**Figure 4:** FESEM: (a) Plain NS (30,000x), (b) NVP-NS (30,000x), (c) Plain SDNS (60,000x), (d) NVP-SDNS(60,000x).

### Powder X-ray Diffraction (PXRD)

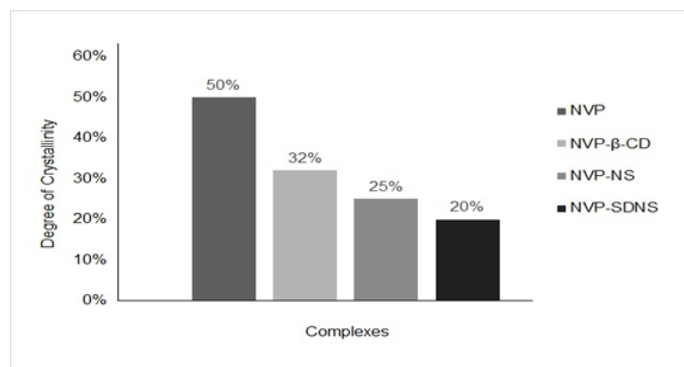
PXRD of NVP exhibited sharp peaks at  $2\theta$  angles of  $13.1^\circ$ ,  $25.5^\circ$ ,  $19^\circ$ , and  $9.2^\circ$ , confirming its crystalline nature (Figure 5). Decreased peak heights and the loss of few peaks in the diffractograms of binary mixtures with  $\beta$ -CD, NS, and SD-NS confirmed formation of inclusion complexes. Compared to plain NVP, the crystallinity of NVP in the binary mixtures was significantly reduced. The degree of crystallinity of plain NVP was 50.04% (Figure 6). A percent decrease in crystallinity was found in 34-59% of NVP- $\beta$ -CD, NVP-NS, and NVP-SDNS complexes. We can infer from these findings that a reduction in peak sharpness and height in the diffractogram indicate inclusion complexation. During the process, guest molecules entrapped in CD cavities may undergo partial amorphization. Partial amorphization of the drug may be caused by the complexifying agent's presence which restricting the crystal building phenomena.<sup>52</sup> Poorly soluble drugs show improved solubility due to amorphization. Thus, we may conclude that NVP has undergone amorphization, which could be an additional factor responsible for solubility enhancement.<sup>2,41</sup>

### In vitro dissolution Studies

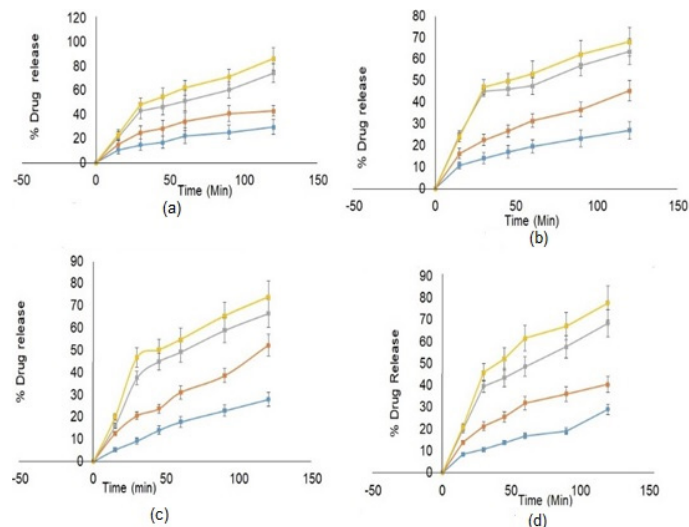
The dissolution profiling of plain NVP and binary mixtures of NVP- $\beta$ -CD, NVP-NS, and NVP-SDNS were carried out in various dissolution media. The percent release of NVP in 0.1N HCl and phosphate buffer pH 6.8 was observed to be 29.63% and 27.04%, respectively, in 120 min (Figure 7(a)). Percent drug release of NVP- $\beta$ -CD, NVP-NS, and NVP-SDNS complexes in 0.1N HCl was found in the range of 42.97% to 86.33%, respectively, in 120 min. Cumulative percent drug release was enhanced by approximately 31-60% for NVP- $\beta$ -CD and NVP-NS complexes, respectively, and approximately 65.67% for the NVP-SDNS complex in 0.1N HCl at 120 min.,



**Figure 5:** PXRD Spectra (p): NVP, (q): NVP- $\beta$ -CD, (r): NVP-NS, (s): NVP-SDNS.



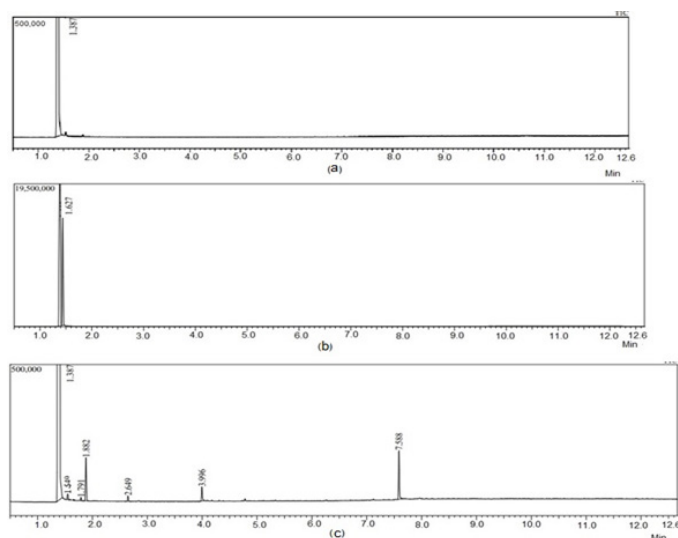
**Figure 6:** Degree of Crystallinity



**Figure 7:** In vitro dissolution Studies (a) NVP, (b) NVP- $\beta$ -CD, (c) NVP-NS, (d) NVP-SDNS

Percent drug release of NVP in NVP- $\beta$ -CD, NVP-NS, and NVP-SDNS complexes in phosphate buffer pH 6.8 were found between 45 to 68%, respectively, in 120 min (Figure 7(b)). Percent drug release increased by approximately 40 to 57% for NVP- $\beta$ -CD and NVP-NS complexes, respectively, and approximately 60% for the NVP-SDNS complex at 120 min in phosphate buffer pH 6.8 than plain NVP.

The percent drug release from NVP- $\beta$ -CD, NVP-NS, and NVP-SDNS complexes in FaSSIF ranged from 52 to 73 % in 120



**Figure 8:** Gas Chromatograms (a-D.W., b-DCM, c-NVP-SDNS). Graphical Abstract

min (Figure 7(C)). Compared to plain NVP in FaSSIF, the percent drug release was enhanced by 40-58 % for NVP- $\beta$ -CD and NVP-NS complexes, respectively, and by 62 % for the NVP-SDNS complex at 120 min. Percent drug release of NVP- $\beta$ -CD, NVP-NS, and NVP-SDNS complexes in FeSSIF was found in the range of 40 to 77%, respectively, in 120 min (Figure 7(d)). Compared to plain NVP in FeSSIF, the percent drug release was increased by approximately 28-57% for NVP- $\beta$ -CD and NVP-NS complexes, respectively, and approximately 62% for the NVP-SDNS complex at 120 min. An increase in dissolution is associated with an increase in saturation solubility. This could be attributed to loading of drug molecules in the lipophilic cavity of  $\beta$ -CD in the NS and the interstitial spaces created due to crosslinking.<sup>53</sup>

### Gas Chromatography for solvent residue analysis

Solvent selection for preparing solid dispersions depends upon their solubility in various solvents. In present study DCM was used. As per ICH guidelines Q3C, it belongs to the Class 2 solvents (R6). From these guidelines, the permissible daily exposure (PDE) is 6 mg/day, and the concentration limit is 600 ppm.<sup>54</sup> Solvent residues also harm drug stability. The spray-drying and freeze-drying methods ensure complete removal of solvents.<sup>55</sup> In current study, the SDs were dried in an oven, therefore samples were analyzed for solvent residues. The retention time of DCM is 1.62 min evident in the chromatogram. The absence of peak at 1.62 min in the chromatogram of sample is indicative of absence of solvent residues. (Figure 8).

### Stability studies

There were no significant changes in the complexes' physical appearance and drug loading after three months under accelerated conditions (40°C/75%RH). These results were confirmed by evaluating the nanosponges' stability at in both acidic and basic

environments. Compared to the basic environment, which did not affect the nanosponges' physical appearance and drug content, which is 90% of NVP-SDNS and 80.1% of NVP-NS, acidic conditions (0.1 N HCl) caused a restricted release from cyclodextrin units after 2h.<sup>56</sup>

## CONCLUSION

Beta-cyclodextrin-based nanosponges are newer carriers used for solubility and dissolution enhancement of many poorly soluble drugs. Spectral studies of SDs of nevirapine with  $\beta$ -CD, NS, and SDNS demonstrated stability of inclusion complexes. Phase solubility plots indicated a linear relationship between aqueous solubility of nevirapine and concentrations of nanosponges. The binary mixtures of nevirapine with SDNS showed maximum saturation solubility and *in vitro* drug release. The enhanced solubility can be connected to the presence of molecularly dispersed drug in the nanocarrier.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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