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Targeted Drug Delivery of Diacerein Nanosponges for Treating Osteoarthritis with Enhanced Solubility

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ABSTRACT

Objectives: The aim of this research study was the formulation and characterization of Diacerein (DC) loaded Nanosponges (NSs) for enhancing oral solubility to treat Osteoarthritis (OA). **Methods:** NSs were prepared by emulsion solvent diffusion method by varying the concentration of Ethyl cellulose (EC) in different ratios. The prepared NSs were characterized in terms of entrapment efficiency, particle size, zeta potential, and surface morphology. Powder X-ray diffraction (PXRD) studies of selected NS formulations were performed. **Results:** The percent yield of the formulations varied from 75.00 ± 0.36% to 85.6 ± 0.78%. Particle size and percent capture efficiency ranged from 224.9 to 456.4 nm and from 61.20 ± 0.54% to 78.60 ± 0.55%, respectively. Scanning electron microscopy revealed that NSs were spherical and porous. F1 batch (1:1) showed good entrapment efficiency and particle size reduction. PXRD studies showed a decrease in the crystalline properties of DC. *In vitro* release studies demonstrated that the controlled release of the drug from the NSs increased the dissolution rate. **Conclusion:** This study concludes that DA-NSs are effective for drug delivery and DA-NSs improve oral solubility which helps therapeutic efficacy.

Keywords: *Diacerein, Nanosponges, Osteoarthritis, Controlled release, Therapeutic, Solubility.*

INTRODUCTION

The primary trends in the therapeutics field are target-oriented medication administration, improvements in therapeutic efficacy, a decrease in adverse effects, and improved dosing regimens.[1] Nanoparticle-based drug delivery systems like Nanosonge (NS) delivery plays a major role in targeting the drug to the required site of action. Nanosponges (NSs) are nano-sized particles having a tiny sponge-like structure. In this system, the core material or drug is encapsulated within a polymeric coat.[2,3] Both lipophilic and hydrophilic drugs can be encapsulated by this novel approach because of their inner hydrophobic cavities and external hydrophilic branching, thereby offering unparalleled flexibility. Because of their nonporous structure, NSs can advantageously carry water-insoluble drugs, especially for BCS class-II drugs.[4] These complexes are used to increase the solubility, dissolution rate, and stability of drugs.[5] These tiny sponges can circulate the body until they encounter the specific target site stick on the surface and begin to release the drug in a controlled and predictable manner.[6]

NSs are non-irritating, non-mutagenic, non-allergenic, and non-toxic, which reduces side effects and imparts improved stability.[7] They have a spherical colloidal nature and have a very high solubilization capacity for poorly soluble drugs by their inclusion and non-inclusion behavior. NSs have recently been developed and proposed for drug delivery. NS can solubilize poorly water-soluble drugs, prolong release, and improve drug bioavailability.[8,9] NS closely resembles a three-dimensional network or scaffold. The backbone is a long polyester that is mixed in solution with small molecules called crosslinkers, which act like tiny hooks and connect different parts of the polymer.[10] Compared to other nanoparticles, NSs are soluble in water and organic solvents. It is porous, non-toxic, and stable at high temperatures up to 300 °C. NSs have advantages over traditional nanoparticles.[11] These can be easily regenerated by various treatment methods such as cleaning with environmentally friendly solvents, removal with moderately hot gases, gentle heating and pH adjustment, and ionic strength.[12] NSs are the type of nanoparticle that encapsulates drug molecules in its core. These fuse in solution with small molecules that act as crosslinkers and help break down different parts of the polymer.[13,14]

Osteoarthritis (OA) is one of the most common forms of arthritis. It is a degenerative joint disease characterized by destruction of articular cartilage, subchondral bone changes, and synovitis.[15] Diacerein (DC) is a novel connective tissue structure modifier intended for the treatment of OA. It belongs to the class of anthraquinone derivatives. DC is classified as class II in the biopharmaceutical classification system, with low solubility and high permeability. Currently, DC capsules, tablets, and powders are commercially available. Due to poor solubility, oral doses are generally much higher to achieve the required drug plasma levels, increasing treatment costs.[16,17]

Therefore, there is a need to develop newer DC formulations that dissolve more rapidly and are likely to have improved bioavailability. The purpose of this study was to develop and evaluate the properties of DC-NSs to improve oral solubility for the treatment of OA.

MATERIAL AND METHODS

Chemical reagents

DC and Polyvinyl alcohol (PVA) were obtained from Yarrow Chem Products, Mumbai, India. Ethyl cellulose (EC) was procured from Hi-Media Laboratory Pvt Limited, Mumbai, India. Dichloromethane (DCM) was purchased from Loba Chemie Products, Mumbai, India. All other materials used were analytically pure.

Pre formulation studies

Determination of solubility

An excess amount of drug was added to 10 ml of solution and determined by dissolving DC in 0.1 N HCl, Dimethyl sulfoxide (DMSO), and water. The sample was then placed on a magnetic stirrer and stirred for 24 hours. At 37±0.5℃. Samples were filtered and diluted accordingly. Samples were analyzed spectrophotometrically at λ max for DC. [18]

Standard platform for DC in 0.1N HCl

To create a standard plot for DC, a UV spectrophotometric estimation procedure was performed. 10 mg of pure DC was transferred to a 100 ml volumetric flask, dissolved in 10 ml of DMSO and the volume was adjusted to the mark with 0.1 N HCl to obtain a concentration of 100 µg/ml. This is A stock. Stock solution B was prepared at a concentration of 20 µg/ml. Prepare aliquots ranging in concentration from 2 to 12 µg/ml from the stock solution (B). Absorbance was recorded against 0.1 N HCl as blank. [19]

Drug-excipient compatibility studies:

All physicochemical interactions between different excipients can be studied and predicted using FTIR. An IR spectral matching approach was used to identify possible chemical interactions between drugs and excipients. The drug–excipient mixture was scanned in an FTIR spectrophotometer in the range of 4000-400 cm^{-1}. The IR spectrum of the mixture is compared with that of pure DC, and peak matching is performed to detect the appearance or disappearance of peaks. [20]

Formulation of NS

NSs were prepared using the emulsion solvent diffusion method. The NSs were formulated by varying the concentration of EC and keeping the drug concentration constant (**Table No. I**). The weighed EC and DC are dissolved in 10 ml of DCM with constant stirring. This dispersed phase is treated in an ultrasonic bath for 30 minutes. The above-dispersed phase is slowly added to an aqueous solution containing PVA with continuous stirring of 1000 to 1500 rpm for 2 hours in a magnetic stirrer. The NSs were collected by centrifugation and dried in an oven at 40°C for 12 hours. The dried NSs were stored in vacuum desiccators to facilitate the removal of residual solvent.[21]

Characterization of DC-loaded NSs:

Percentage yield

The percentage yield of the NSs was calculated by following the equation after determining the accurate initial weight of the raw materials and the final weight of the NS obtained.[22]

% yield = (Initial weight / Theoretical weight of NSs) * 100

Table 1. Formulation chart of DC-loaded NSs.

Formulation	F1	F2	F3	F4	F5
DC: EC (mg)	1:1	1:1.5	1:2	1:2.5	1:3
PVA (mg)	100	100	100	100	100
DCM (ml)	10	10	10	10	10
Dist. Water (ml)	100	100	100	100	100

Drug entrapment efficiency (%)

NSs equivalent to 50mg of the drug were taken and transferred into a beaker containing 100 ml of 0.1N HCl. Kept for 1hr with frequent stirring in Magnetic stirrer. Then it was filtered, and the absorbance of the filtrate was measured at 257.5nm after suitable dilutions. The drug content was calculated from the standard curve and expressed as the free drug content in the NS.[23] The drug entrapment efficiency (%) of the NSs was calculated according to the following equation:

%Entrapment efficiency = Drug added- free drug/ Total drug * 100

Particle size analysis

The particle size of DC-loaded NSs was determined using a Malvern zeta sizer. Measurements were made at the fixed angle of 90˚ for all the samples (F1 to F5). From this, the mean diameter, and the average particle size of the NSs are measured.[24]

Surface morphology

Morphological studies of selected NS formulations (F1) were performed using a scanning electron microscope with an automated imaging system. The particles were placed on an aluminum stub and coated with gold using a sputter coater operated under a vacuum at 40 mA for 25 seconds. The shape and morphology were determined from the obtained images. [25]

Zeta potential

The zeta potential of the NSs was measured using a Malvern Zeta Sizer instrument. Measurements were performed on the selected NS formulation (F1). Zeta potential represents the degree of repulsion between adjacent similarly charged particles in dispersion and the stability of the formulation. [26]

Powder X-ray diffraction analysis (PXRD)

The complex formation of the drug-polymer was analyzed by X-ray diffraction analysis. Powder X-ray diffraction analysis of pure drug and selected formulation (F1) was performed in an X-ray diffractometer using Cu-Kα radiation (λ = 1.789 Å). The scanning speed was 70/min and the diffraction angle of 2° was 3 – 80. [27]

***In vitro* dissolution studies**

In vitro, drug release studies were performed in 900 ml of 0.1 N HCl at 50 rpm and 37±0.5° C. using a USP device II (paddle). The NS tablet was inserted into the device, 5 mL samples were taken at predetermined time intervals, and the same amount of fresh medium was returned to the basket to maintain the submerged state. Samples were taken at specific intervals of time to study the controlled release of DC from the NSs. The collected samples were diluted accordingly and analyzed spectrophotometrically. [28]

RESULTS AND DISCUSSION

Solubility study

A solubility study of DC was performed, and the drug solubility was found to be 0.011 mg/ml in water, 0.018 mg/ml in 0.1 N HCl, and 14.86 mg/ml in dimethyl sulfoxide (DMSO). Ta. Solubility in all solvents was within the specified literature limits. The results show that DC is freely soluble in DMSO and partially soluble in water and 0.1 N HCl.

Standard calibration technique for DC

The absorption spectrum of pure DC was scanned from 200 to 400 nm using a UV spectrophotometer against 0.1 N HCl as a blank. From the obtained spectrum, the absorption maximum of DC was found to be 257.5 nm.

The absorbance of pure DC at different concentration ranges was scanned at λ max of 257.5 nm. Absorbance values at different concentration ranges (2–12 µg/ml) in 0.1 N HCl. The absorbance values remained linear and followed Lambert's law in the range of 2–12 µg/mL with a regression coefficient (R2) of 0.9996.

Drug-polymer compatibility study

The FTIR spectra of DC, drug-polymer mixture (EC, PVA), and selected formulations are shown in **Figure 1**. The spectrum of DC is 2870 cm^{-1}

Table 2. Evaluation parameters of DC NSs

Formulation	Percentage yield (%) *	Entrapment efficiency(%EE) *	Particle size(nm)	PDI
F1	75.00±0.36%	78.60±0.55%	224.9	0.390
F2	78.60±0.22%	73.10±0.15%	291.1	0.665
F3	81.4±0.14%	70.86±0.28%	362.5	0.417
F4	83.4±0.54%	65.40±0.41%	416.1	0.715
F5	85.6±0.78%	61.20±0.54%	456.4	0.728

**Data expressed as a mean ± SD, n=3*

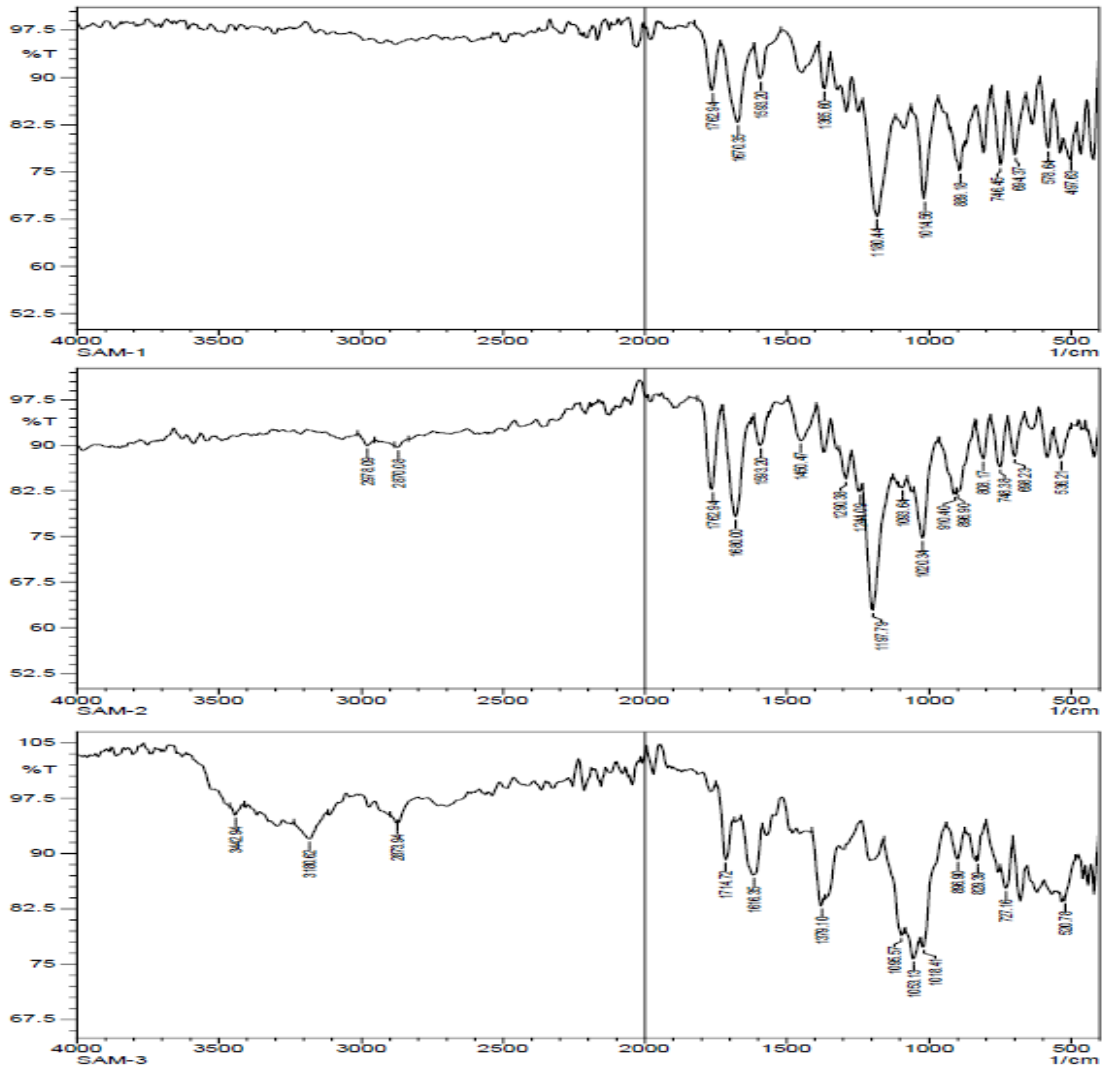

Figure 1. FTIR of Pure drug (a), Polymer mixture (b), and Formulation (c)

(C-H stretching), 1762 cm^{-1} (C=O stretching, ester), 1670 cm^{-1} (C=O stretching, COOH), 1593 cm^{-1} (C= C stretching aromatic family), 1014 cm^{-1} (C-O stretching), and 746 cm^{-1} (m-substituted benzene). The presence of these peaks indicates the purity of DC. In addition to the characteristic peaks, DC-specific peaks were also present in the fingerprint region of the spectrum. Physical mixtures of DC and excipients were prepared by mixing in equimolar ratios (1:1:1). FTIR of the physical mixture revealed that all the characteristic peaks of the DC were found in spectra and no significant shifts were observed. This indicates that there are no chemical interactions between drugs and excipients used in the NS formulations. The spectrum of NS formulation exhibited the broadening and disappearance of identical peaks of the DC with a reduction in intensity in the fingerprint region of the drug. This indicates that the DC was physically encapsulated within the polymer matrix.

Percentage yield

The percentage yield for all the batches of prepared DC NSs was determined and the result is given in **Table no II**. The percentage yield of formulation F1-F5 was found to be in the range of 75.00±0.36% to 85.6±0.78%. This indicates that with the increase in polymer concentration, the Percentage yield also increased. Reduction in the percentage yield can be due to rotation speed and polymer concentration. Hence, it reveals that EC concentration and crosslinking time affect the production yield of NSs.

Entrapment efficiency

The entrapment efficiency of all formulations (F1-F5) showed the value ranging from 61.20±0.54% to 78.60±0.55% and were listed in **Table No. II**. The formulations F1 and F2 showed good entrapment efficiency (78.60±0.55% and 73.10±0.15%) compared to other formulations F3, F4, and F5. The F1 batch with 78.6±0.55% showed the best entrapment efficiency. As there was an increase in polymer concentration the entrapment efficiency of formulation was decreased. This shows polymers and drugs with the same concentration achieve high drug loading which helps in drug delivery and to improve oral bioavailability.

Particle size

The average particle size of DC NSs was measured using a Malvern Zeta sizer. The particle size of the entire formulation (F1 to F5) was measured, and the results were displayed in the range of 224.9 to 456.4 nm (**Table No. II**). Formulation F1 had an average particle size of 224.9 nm and a PDI of 0.390 (**Figure 2**). The particle size of NSs increased as the drug-to-polymer ratio increased. Formulation F1 with an active ingredient-to-polymer ratio of 1:1 showed a reduction in particle size. Increasing the drug-to-polymer ratio reduces the particle size of NS. This shows that the particle size changes depending on the ratio of active ingredient concentration to the polymer.

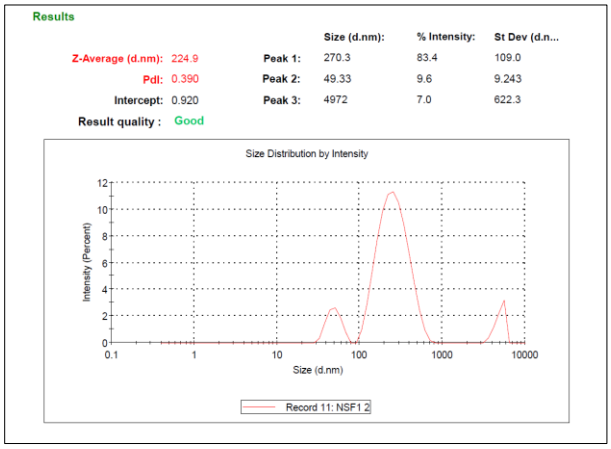

Figure 2. Particle size and PDT of F1 formulation

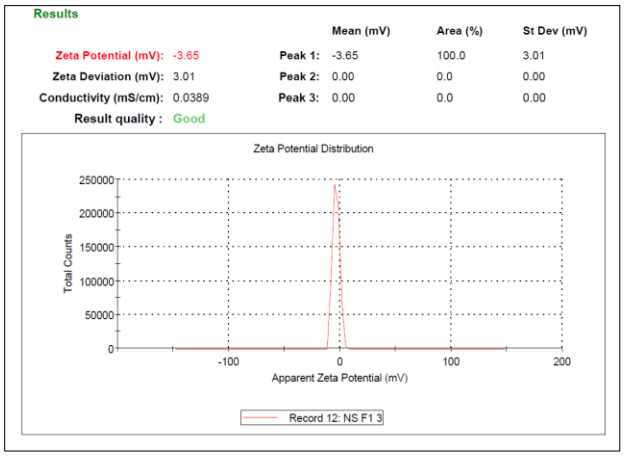

Figure 3. Zeta potential of F1 formulation

Surface morphology

The shape and surface morphology of the prepared NSs were observed by scanning electron microscopy (SEM) and are shown in **Figure 4**. SEM studies showed that the DC-loaded NS formulations were spherical, porous, and uniform in size, confirming the NS properties and particle size measurements.

Zeta potential

Zeta potential indicates the stability of NS formulations. The high absolute value of zeta potential suggests that there is a charge on the surface of the drug-loaded NSs, which may generate a large repulsive force

between the particles and hinder the aggregation of the NSs. The zeta potential of NS formulation F1 was negative -3.65 mV (**Figure 3**). Negative values indicate good physical stability of the prepared NS formulations.

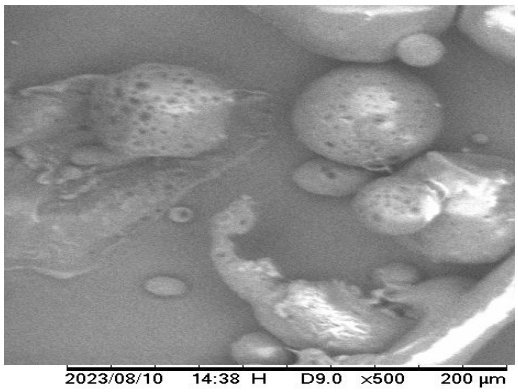

Figure no. 4: SEM image of NS

Powder X-ray diffraction analysis

XRD spectra of pure drug DC and selected NSs (F1) are shown in **Figure 5**. The XRD diffractogram of DC showed various characteristic sharp and strong peaks at 2-theta 10.5°, 17.3°, 19.1°, 22.1°, 25.8°, and 28.5°. The diffraction pattern of pure DC indicates the crystallinity of the drug. The diffraction grams of the NSs show sharp diffraction peaks with slightly lower intensity, with 2Ɵ values almost the same as pure DC. A sharp diffraction peak of the drug is observed at 19.1° (62210 cps), while the intensity became lower (33715 cps) and some peaks disappeared for the NS. Disappearance/reduction in peak intensity indicates a decrease in the crystalline properties of DC.

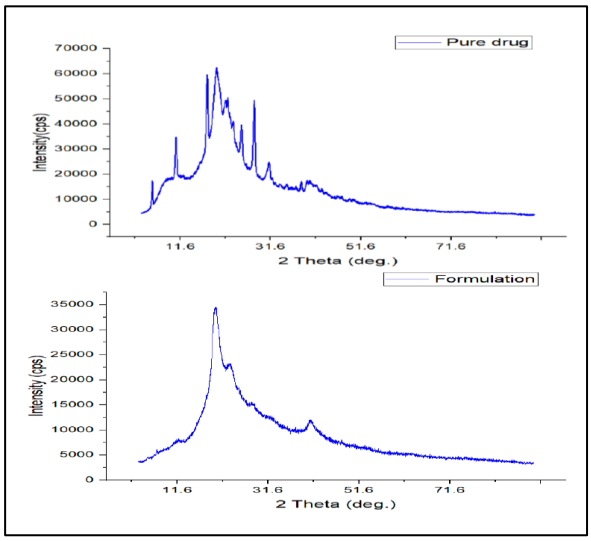

Figure 5. XRD graph of Pure drug and formulation

***In vitro* solution studies**

In vitro drug release studies were performed using a USP device II (paddle) at 50 rpm and 37 ± 0.5 °C in 900 ml 0.1 N HCl. Samples were taken after 0.5, 1, 2, 3, 4, 5, 6, and 7 hours. These samples were diluted and analyzed spectrophotometrically at 257.5 nm. The cumulative drug release percentage of the NS tablets was 75.02 ± 0.95% at 7 h (**Table 3**). A graph of %CDR vs. time was created and shown in **Figure No. 6**. The results showed that drug release from the DC-NSs was controlled and improved. As the polymer concentration increases, the rate of drug release decreases. The increased dissolution rate is due to the potential of NSs to improve the dissolution of poorly soluble drugs.

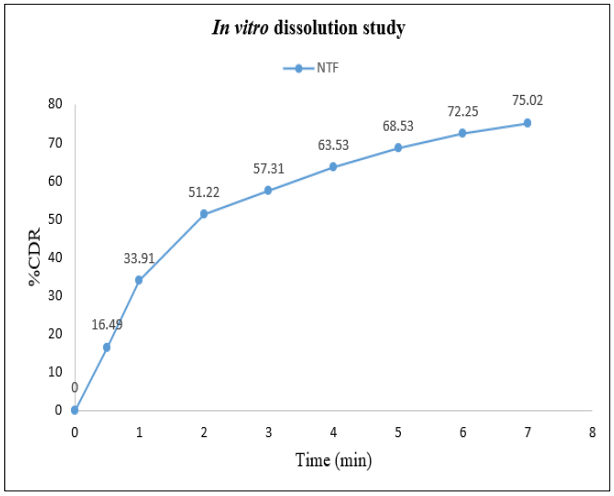

Figure 6. *In vitro* dissolution study of NSs

Table 3. Evaluation parameters of DC NSs

Time (hr.)	% Cumulative drug release* (DC-NSs)
0	0.00
1	33.91±0.52
2	51.22±0.34
3	57.31±0.68
4	63.53±0.21
5	68.53±0.93
6	72.25±0.66
7	75.02±0.95

**Data expressed as a mean ± SD, n=3*

CONCLUSION

DC is observed to be easily soluble in DMSO and partially soluble in water and 0.1N HCl. The FTIR of the physical mixture showed no chemical interaction between DC and the polymer. Therefore, these polymers can be used in NS formulations. FTIR spectra of the NS formulations showed that DC was physically encapsulated in the polymer matrix. DC-loaded NS formulations with different drug-polymer ratios showed good yields. This indicates that the emulsion solvent diffusion method is suitable for the development of NSs. It was observed that as the polymer concentration increased, the entrapment efficiency of the NSs decreased. The capture efficiency of NSs with smaller particle sizes was higher. F1 batch (1:1) showed the highest capture efficiency (78.60 ± 0.55%) and particle size reduction (224.9 nm) with a yield of 75.00 ± 0.36%. SEM images of DC-filled NSs confirmed the NS's properties of being spherical and porous. Zeta potential studies have shown that DC is stable, and the surface charge is cationic. The PXRD peak intensity of DC NSs indicated a decrease in the crystalline properties of the drug. This demonstrated that DC is physically encapsulated and increased solubility can occur due to decreased crystallinity. *In vitro* release studies showed controlled and enhanced drug release with a %CDR of 75.02±0.95 at 7 h. This indicates that DC NS tablets enhance solubility and control drug release. Therefore, this study concludes that DC NSs are effective for drug delivery and DC NSs improve solubility.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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