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Original Research

Unlocking the Potential: Synergistic Effects of Solid SNEDDS and Lyophilized Solid Dispersion to Enhance Stability Attributes

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Abstract

Background: Among lipid-based formulations, self-nanoemulsifying drug delivery systems (SNEDDS) have captured a spotlight, captivating both academia and the pharmaceutical industry. These remarkable formulations offer a valuable option, yet their liquid form presents certain challenges for delivering poorly soluble drugs. Ensuring compatibility with capsule shells, maintaining physical and chemical stability, and understanding their impact on lipolysis remain vital areas of exploration. Therefore, the incorporation of this liquid formulation into a solid dosage form (S-SNEDDS) is compelling and desirable. S-SNEDDSs, prepared by adsorption, enhances formulation stability but retards drug dissolution. This study aims to design drug-free solid S-SNEDDS + solid dispersion (SD) as a novel combination to enhance cinnarizine (CN) stability upon storage while maintaining enhanced drug dissolution. **Methods**: Drug-free liquid SNEDDSs were solidified using Neusilin® US2 at a 1:1 ratio. CN-SDs were prepared using freeze-drying technology. The SDs that were developed underwent characterization using various techniques, including scanning electron microscopy (SEM), differential scanning calorimetry (DSC), X-ray powder diffraction (XRD), and Fourier transform infrared spectroscopy (FTIR). *In vitro* lipolysis studies were conducted to evaluate the effect of the combined system on the performance of the formulation upon exposure to enzymes within biorelevant media. **Results**: In agreement with the DSC and XRD results, FTIR confirmed the amorphization of CN within the freeze-dried solid dispersion (FD-SD) systems. The *in vitro* lipolysis studies showed that the drug-free S-SNEDDS + SD combination was able to maintain a significant portion of the initial CN in solution even in the presence of lipase for up to 30 min. The accelerated stability studies showed that the drug-free S-SNEDDS + SD combination maintained 96% intact CN in an amorphous state and more than 90% release at pH 1.2 for up to 6 months, while the dissolution profile at pH 6.8 showed a significant drop in CN release upon storage. **Conclusions**: Overall, the developed formulation could be a potential technique to enhance the dissolution of weakly basic drugs that possess challenging stability limitations.

Keywords: cinnarizine; S-SNEDDS; lipolysis; solid dispersion; stability improvement

1. Introduction

Cinnarizine (CN) is a weakly basic drug with poor solubility in water that poses certain challenges in regard to its formulation and delivery [1,2]. Additionally, it is chemically unstable after being formulated in liquid self-nanoemulsifying drug delivery systems (SNEDDS). Liquid SNEDDSs face limitations such as incompatibility with capsule shells, risk of formulation leakage, oil oxidation, drug precipitation, and potential chemical degradation of certain drugs [3,4]. These limitations can significantly impact the dissolution and effectiveness of the drug, especially under conditions of low stomach acid (hypochlorhydria/achlorhydria), where the drug is exposed to higher pH environments in the gastrointestinal tract [5].

On the other hand, solid SNEDDSs offer advantages such as overcoming the limitations of liquid SNEDDSs, maintaining enhanced drug solubilization, ensuring greater stability, and improving patient compliance with solid dosage forms [6]. The common approach for transforming liquid SNEDDSs into easily flowable powders involves adsorbing them onto high surface area inorganic silica materials [7]. However, this technique has been found to significantly retard drug release from the formulation [8,9]. In some studies, the adsorbents were shown to reduce drug release to as low as 20%, compared to over 80% release from liquid SNEDDS [10].

To overcome the challenges of poor drug release from solidified SNEDDSs, there is a pressing need for innovative approaches for CN. In response to this demand, the current study introduces an exciting and novel technique for solidifying SNEDDSs. The currently proposed technique combines drug-free S-SNEDDS with a drug-loaded solid dispersion (SD), which is prepared using the freeze-drying method. To the best of the authors' knowledge, this approach is relatively unexplored except in their own previous publications [5].

Integrating SNEDDSs with solid dispersions holds great potential for improving the dissolution rate, bioavail-

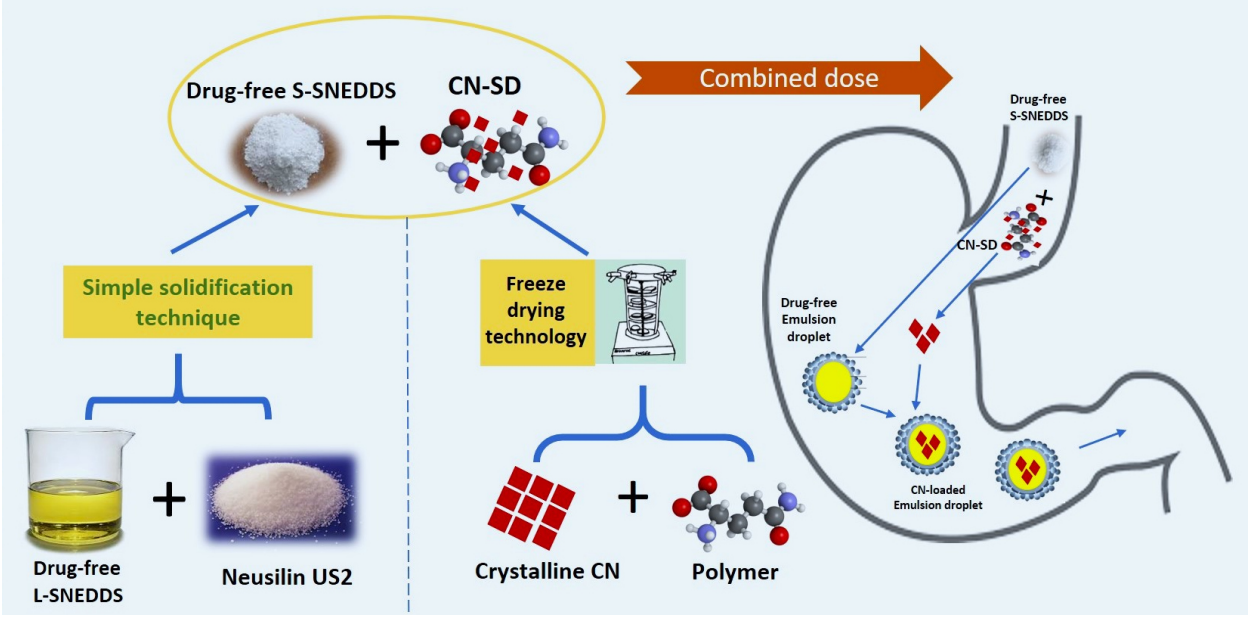

Fig. 1. Schematic diagram showcasing the manufacturing process and performance evaluation of the combined dosage form comprising cinnarizine-solid dispersion (CN-SD) and drug-free solid self-nanoemulsifying drug delivery systems (S-SNEDDS). L-SNEDDS, Liquid self-nanoemulsifying drug delivery systems.

ability, and stability of poorly water-soluble pharmaceuticals beyond using either system independently. Specifically, SNEDDS enable the swift formation of nanoemulsions potentially bypassing dissolution; a step that can limit absorption for poorly soluble compounds in the gastrointestinal tract (GIT) [11,12]. Meanwhile, solid dispersions utilize hydrophilic carriers to boost the wettability and dispersibility of drugs. Carriers in amorphous solid dispersions can stabilize the normally thermodynamically unstable solubilized or amorphous drug form upon storage [11]. Additionally, some polymers act as precipitation inhibitors for dissolved drugs, maintaining supersaturation upon dissolution in the GIT by inhibiting precipitation, known as the "parachute effect" [13]. Therefore, the SNEDDS + solid dispersion hybrid could potentially augment the concentration of dissolved drug in the SNEDDS preconcentrate, enhance the physical stability of the drug in storage, and improve absorption. Recent evidence, key to the current study, has shown high potential for improving the chemical and physical stability of conventional liquid SNEDDSs using a physically separate solid dispersion + drug-free SNEDDS format [5]. By converting liquid SNEDDS to solid powders via adsorption to solid carriers, the advantages of both delivery platforms can be harnessed, such as elevated solubility/dissolution while avoiding limitations such as low stability and the bulk of liquid SNEDDS [3,6].

The essence of this technique lies in the separation of the drug from S-SNEDDS during the manufacturing and storage processes. However, upon oral administration and when the formulation comes into contact with aqueous media, a remarkable transformation takes place as follows.

First, the drug-free S-SNEDDS undergoes self-emulsification, resulting in the formation of a drug-free nanoemulsion. Concurrently, in the second step, the amorphized drug partitions itself within the newly formed nanoemulsion droplets, leading to a significant enhancement in drug dissolution. This step is thought to be facilitated through drug amorphization with the SD [5]. In addition, this dynamic mechanism holds a distinct advantage, as it prevents any adverse interactions between the drug and the adsorbent during storage, which could safeguard against potential delays in the complete release of the drug from S-SNEDDS [14,15]. From another angle, CN was purposefully not incorporated into the liquid SNEDDS to prevent direct interaction between the drug and SNEDDS excipients during storage, as direct contact has been shown to cause significant degradation [16,17]. Instead, a drug-free liquid SNEDDS was developed first and then used to fabricate the subsequent drug-free solid SNEDDS (Fig. 1). This approach provides two key benefits: (1) the SNEDDS could still enable drug solubilization and nanoemulsification for improved absorption, and (2) encapsulating the CN separately from the liquid SNEDDS ingredients is expected to protect the drug from degradation that could occur with prolonged direct exposure to the excipients. Overall, this system presents a cutting-edge solution that could overcome the challenges faced in drug release from solidified SNEDDSs, offering promise for improved CN formulation and delivery along with improved stability.

Lipolysis is the process of lipid digestion that occurs in the presence of digestive enzymes and plays a crucial role in the absorption of lipophilic drugs, such as CN, in

Table 1. Formulation of Cinnarizine (CN) in the Liquid and Solid-states using lipid-based components and inorganic silica materials (adapted from reference [5]). All excipient proportions are presented as %w/w.

Excipient	CN	Oleic acid	Imwitor 308	Cremophor EL	Neusilin US2	HPMC E3	Total
Drug-free L-SNEDDS	-	25	25	50	-	-	100
Drug-free S-SNEDDS	-	12.5	12.5	25	50	-	100
FD-SD	20	-	-	-	-	80	100

HPMC, hydroxypropyl methylcellulose; SNEDDS, self-nanoemulsifying drug delivery systems; FD-SD, freeze-dried solid dispersion.

the gastrointestinal tract [18]. The lipolysis process aids in the absorption of lipophilic drugs by breaking lipids down into smaller lipid-based molecules, which can be more readily solubilized and absorbed through the intestinal mucosa. By evaluating the impact of the combined system on the *in vitro* lipolysis process, researchers can gain insights into the formulation's ability to potentially enhance the drug's solubility and dissolution within the body [19].

Moreover, the chemical and physical stability of CN and the drug-free solid SNEDDS are important factors to consider in formulation development. The chemical instability of CN in SNEDDS excipients even after solidification can lead to reduced drug efficacy or potential degradation. Therefore, it is necessary to assess the impact of the combined system on the stability of both CN and the drug-free solid SNEDDS to ensure the formulation's long-term effectiveness and shelf life.

The purpose of the current work is to evaluate the impact of the combined system of drug-free S-SNEDDS + CN-SD on the formulation performance in the *in vitro* lipolysis process as well as the chemical/physical stability of the CN and drug-free S-SNEDDS combined dosage form.

2. Materials and Methods

2.1 Materials

The medium chain monoglycerides known as Imwitor 308 (I308) were graciously provided by Sasol Germany GmbH, located in Werk Witten, Germany. Oleic acid (OL), a long-chain fatty acid with 18 carbon atoms, was acquired from Avonchem in Cheshire, UK. The Cremophor EL (Cr-El) came from BASF in Ludwigshafen, Germany. CN was obtained from The Fairdeal Corporation (FDC) Limited based in Maharashtra, India. Fish gelatin capsules (size 00) and hydroxypropyl methylcellulose HPMC capsules (size 2) were kindly donated by Capsugel, a company based in South Carolina, USA. Vivapharm® HPMC E3 was acquired from JRS Pharma in Rosenberg, Germany. Neusilin® US2 (NUS), on the other hand, was sourced from Grace in Germany.

2.2 Drug-Free L-SNEDDS Preparation

To ensure thorough melting and uniformity in the formulation preparation, waxy lipid excipients were preheated to 40 °C. Based on previous studies [1,20] that involved comprehensive self-emulsification assessments and solubility studies, the optimized formulation was developed by composing three excipients, namely, OL, Cr-EL, and Imwitor 308 (I308) in a 1:1:2 weight ratio. The excipients were combined and thoroughly mixed to achieve complete homogenization, resulting in the optimized SNEDDS. To prevent direct contact between the drug and SNEDDS excipients, CN was intentionally excluded from the drug-free SNEDDS [2].

2.3 Drug-Free S-SNEDDS Preparation

To solidify the drug-free L-SNEDDS, Neusilin® US2 was employed as an adsorbent (as indicated in Table 1, Ref. [5]). The L-SNEDDS that was prepared beforehand was combined with the adsorbent in a 1:1 (1× NUS) w/w ratio. The resulting mixture was thoroughly vortexed until a uniform solid powder was obtained, following the methodology described by Kazi *et al*. [21] in 2020. Afterward, the solidified SNEDDS were subjected to several characterization studies, as discussed further below.

2.4 Drug (CN) Loaded Freeze-Dried Solid Dispersion (FD-SD) Preparation

To prepare binary systems of CN and HPMC E3, the two components were dissolved together at a 1:4 w/w ratio in a 0.12 M HCl solution with a total solid concentration of 3%. The solution was vigorously stirred until a clear solution was obtained, ensuring complete solubilization of CN. Subsequently, the solutions were subjected to freeze-drying at a temperature of –60 °C using an Alpha 1-4 LD Plus freeze dryer (Osterode am Harz, Germany) for a minimum duration of 48 hours, following the methods described by Anwer *et al*. [22] in 2010 and Ibrahim *et al*. [23] in 2019. The resulting solidified residue was then ground using a mortar and pestle, followed by passing it through a 315 µm sieve to achieve a uniform and finely powdered size.

2.5 Combined Formulation (SD + S-SNEDDS) Preparation

The SD of cinnarizine (equivalent to 25 mg of CN) was combined with drug-free S-SNEDDS. This was done to ensure that cinnarizine remains at approximately 80% of its equilibrium solubility within the SNEDDS formulation to avoid the risk of increased precipitation tendency which might be triggered upon exceeding the saturation limit [11].

Table 2. The formulation of the mixture substance employed in *in vitro* digestion experiments.

Mixture substance	Amount	
CN-loaded liquid SNEDDS	40 mg CN + 460 mg SNEDDS (12.5% OL, 12.5% I308, 25% CrEL)	
FD-SD + drug-free S-SNEDDS	200 mg FD-SD + 460 mg SNEDDS (12.5% OL, 12.5% I308, 25% CrEL) + 460 mg NUS	
Pancreatic lipase	2 mL (800 TBU/mL)	
Lipolysis buffer	18 mL	
	Intestinal condition	
Composition of the lipolysis buffer	Fed State	Fasted state
Bile salt (BS, mM)	20	5
Phospholipid (PL, mM)	5	1.25
Tris maleate (mM)	0.5	0.5
Ca^{+} (mM)	0.05	0.05
Na^{+} (mM)	1.5	1.5

OL, Oleic acid; NUS, Neusilin® US2; TBU, Tributyrin unit.

An 80% loading was selected as a conservative threshold, leaving a 20% margin to account for any potential error in experimentally determined solubility values.

2.6 Combined Formulation: Characterization Studies

2.6.1 Scanning Electron Microscopy (SEM)

To assess the impact of solidification on the shape of adsorbent particles and identify any indications of incomplete solidification, the solid powder samples (consisting of pure Neusilin® US2, freeze-dried solid dispersion, and drug-free solid SNEDDS) were subjected to scanning electron microscopy (Carl Zeiss EVO LS10, Cambridge, UK). To secure the samples, double-sided adhesive carbon tape was used to affix them onto stubs. Then, a layer of gold was applied to the samples using a Q150R sputter coater unit (Quorum Technologies Ltd, East Sussex, UK) under vacuum for 60 seconds. The gold coating process took place in an argon atmosphere at 20 mA [7,21].

2.6.2 Fourier Transform Infrared Spectroscopy (FTIR)

To explore possible interactions between CN and the employed polymers, we conducted FTIR studies. The FTIR Spectrum BX instrument from Perkin Elmer LLC, Hopkinton, MA, USA, was used to analyze the chemical properties and complexation of powdered samples. Powdered samples of pure CN, pure HPMC, and CN-SD were compressed for 5 minutes at 5 bars on a KBr press. Subsequently, the spectra were scanned across the wavenumber range of 400–4000 cm^{-1} to obtain comprehensive information about possible interactions between the components [7,21].

2.7 In Vitro Lipolysis

To carry out the lipolysis experiment, two digestion buffer solutions were prepared under fed and fasted conditions. The composition and pH of the fed and fasted buffers were (101 mM NaOH, 144 mM glacial acetic acid, 203 mM NaCl, pH 5.0) and (10.5 mM NaOH, 28.6 mM NaH_2PO_4. H_2O, 105.9 mM NaCl, pH 6.5), respectively. The final digestion media was prepared by adding simulated intestinal fluid (SIF) powder containing taurocholate (bile salt, BS) and lecithin (phospholipid, PL) in a 4:1 molar ratio, which represents the secretion of bile ratio [24]. The concentrations of BS:PL were (20 mM:5 mM) for the Fed state and (5 mM:1.25 mM) for the Fasted state, respectively. For each sample run, 0.5 g CN-loaded liquid formulation (or an equivalent amount of S-SNEDDS) was dispersed in 18 mL of digestion media using a thermostatic jacketed glass reaction vessel (Table 2). Then, 2 mL of pancreatin extract (800 strength of tributyrin units) of pancreatic lipase was added to initiate lipolysis [18]. The formulations of relevant media and enzymes designed to mimic intestinal fluid, for *in vitro* digestion experiments, are presented in Table 2. During the lipolysis process, a constant pH of 6.8. and temperature of 37 °C were maintained using a pH-stat titration unit (902 Titrando by Metrohm AG, Herisau, Switzerland). Lipolysis was allowed to continue for a duration of 30 minutes. The resulting fatty acids (FA) generated during lipolysis were subsequently titrated using 0.2 M NaOH for all formulations.

Samples of the solution were withdrawn at 0 min, 5 min, 15 min, and 30 min. Each sample, measuring 1 mL, was then subjected to centrifugation at 15,000 rpm for a duration of 5 min. Then, a 100 µL aliquot was extracted from the supernatant and diluted with 900 µL of acetonitrile. The resulting solution was then subjected to analysis using Ultra High Performance Liquid Chromatography (UPLC), following a previously described method. The analysis of each sample was performed three times to ensure accuracy and reproducibility. Each formulation/lipolysis condition pair was compared in terms of drug solubilization efficiency which represents a modified calculation of the dissolution efficiency by the trapezoidal method reported earlier [5,25].

Initial Digestion Rate Evaluation

When comparing the digestion of various formulations, determining the initial rate of hydrolysis is a valuable parameter. This rate represents the release of FA per unit time during the initial stages of the reaction. To calculate the initial reaction rate, linear regression analysis was employed to determine the slopes of the hydrolysis curve

during the early stages of the reaction. The calculation of the slope involved considering multiple experimental points and employing the least-squares linear regression method. The slope value of the resulting straight line was determined until it started to decrease. The 0–3 min timeframe after introducing the lipase solution into the reaction vessel typically provided the most reliable estimate of the slope. This approach allows for a consistent and stable estimation of the hydrolysis rate for comparative analysis of different formulations [18].

2.8 Stability Studies

To assess the performance during storage under accelerated conditions, both FD-SD and drug-free S-SNEDDS were included in the stability studies. The samples were placed in climatic stability chambers (KBF-ICH 240/720 series, Binder GmbH, Tuttlinger, Germany) maintained at a temperature of 40 °C ± 2 °C and a relative humidity (RH) of 75% ± 5% [26,27]. After a minimum storage period of 6 months, samples were withdrawn and allowed to reach room temperature before undergoing further examination. The assessment of the formulations' chemical and physical stability was conducted as follows: The chemical stability was evaluated by monitoring changes in the concentration of the intact drug. Each sample was analyzed in triplicate to ensure reliable results. The formulations were visually inspected for any indications of agglomeration or color alteration, taking note of their physical appearance. Additionally, crucial assessments were performed to evaluate the impact of storage on the dissolution behavior and drug crystallinity using *in vitro* dissolution, differential scanning calorimetry (DSC), and X-ray powder diffraction (XRD) studies,

2.8.1 Chemical Stability of CN

To assess the chemical stability of CN, the percentage of intact CN remaining in the formulation was determined. This involved weighing a CN-SD amount (equivalent to 4–5 mg CN) and transferring it into a 25 mL volumetric flask to measure the concentration of intact CN. The flask was then filled with 1% hydrochloric acid (HCl) solution up to the mark. To ensure complete solubilization of the drug, the mixture was sonicated for 45 minutes. Subsequently, an aliquot of the mixture was transferred into a 1.5 mL Eppendorf tube, and centrifugation was performed using a Benchtop centrifuge (PrO-Research K2015, Centurion Scientific Ltd., Chichester, UK) at a speed of 10,000 rpm for a duration of 5 min. The resulting supernatant (0.25 mL) was diluted in acetonitrile and analyzed using a validated stability-indicating UPLC assay, as described by Abdel-Hamid *et al*. in 2012 [28]. To ensure accuracy, a minimum of three replicates were performed for each sample.

2.8.2 In Vitro Dissolution Tests

The USP Type II dissolution apparatus (UDT-814, LOGAN Inst. Corp., Somerset, NJ, USA) was used to perform dissolution tests. The dissolution profile of FD-SD + drug-free S-SNEDDS was examined in both pH 1.2 and pH 6.8 dissolution media at a 50 rpm paddle speed. The dissolution medium used in the study consisted of either 500 mL of 0.1 N HCl solution with a pH of 1.2 or phosphate buffer at pH 6.8, both maintained at a temperature of 37 °C. For the experiment, drug-free SNEDDSs and FD-SDs equivalent to 25 mg of CN were weighed, and the experiment was performed with three replicates. At predetermined time points (5, 10, 15, 20, 30, 60, and 120 minutes), 2 mL serial samples were withdrawn. The samples were then centrifuged, and an aliquot of the supernatant was diluted in acetonitrile and analyzed using UPLC, following the methodology described by Abdel-Hamid *et al*. in 2012 [28]. The comparative assessment of formulation performance was conducted with regard to dissolution efficiency (DE%) [25].

2.8.3 DSC

A DSC-60 Shimadzu instrument from Kyoto, Japan, was utilized to examine the thermal characteristics of CN-SDs samples, for both freshly prepared and stored samples. The samples were placed in nonhermetically sealed aluminum pans and subjected to heating from 20 to 200 °C at a heating rate of 10 °C/min. The measurements were conducted under a nitrogen atmosphere with a flow rate of 40 mL/min, following the methodology outlined by Shahba *et al*. in 2017 [29].

2.8.4 XRD

Freshly prepared and stored samples of CN-SDs were subjected to evaluation using an Ultima IV diffractometer from Rigaku Corporation in Tokyo, Japan. The analysis was performed over a 3–30° 2θ range with a scan speed of 0.5 deg./min. A copper tube anode with a monochromatized wavelength of 0.154 nm, achieved with a graphite crystal, was used. The diffraction pattern was collected under a tube voltage of 40 kV and tube current of 40 mA, employing step scan mode with a step size of 0.02° and a counting time of 1 second per step. This methodology aligns with the approach described by Ahmad Abdul Wahhab Shahba *et al*. in 2018 [2].

2.9 CN Quantification by UPLC Assay

Quantification of CN was performed employing a validated UPLC reversed-phase technique, as outlined in the work by Abdel-Hamid *et al*. in 2012 [28], with slight adjustments made. To enhance the separation of peaks between the intact drug and degradation products, the composition of the mobile phase was modified to 0.5% trifluoroacetic acid in acetonitrile (60:40), and the duration of the run was extended to 5 min. To achieve peak separation, an Acquity® UPLC BEH C18 column (2.1 × 50

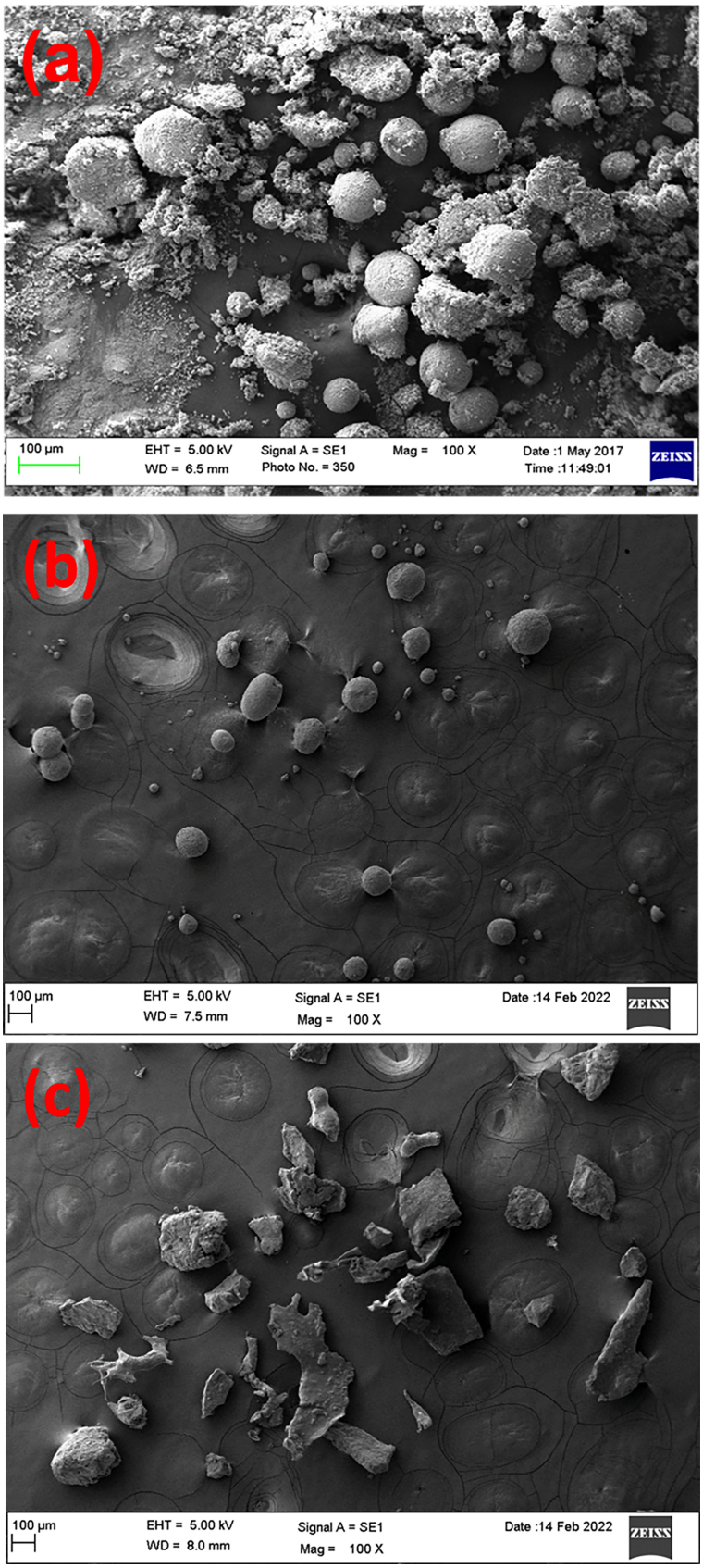

Fig. 2. Scanning electron microscopy (SEM) images of the drug-free S-SNEDDS + FD-SD formulation. (a) Denotes pure NUS. (b) Drug-free S-SNEDDS. (c) FD-SD. The magnification was fixed at 100×.

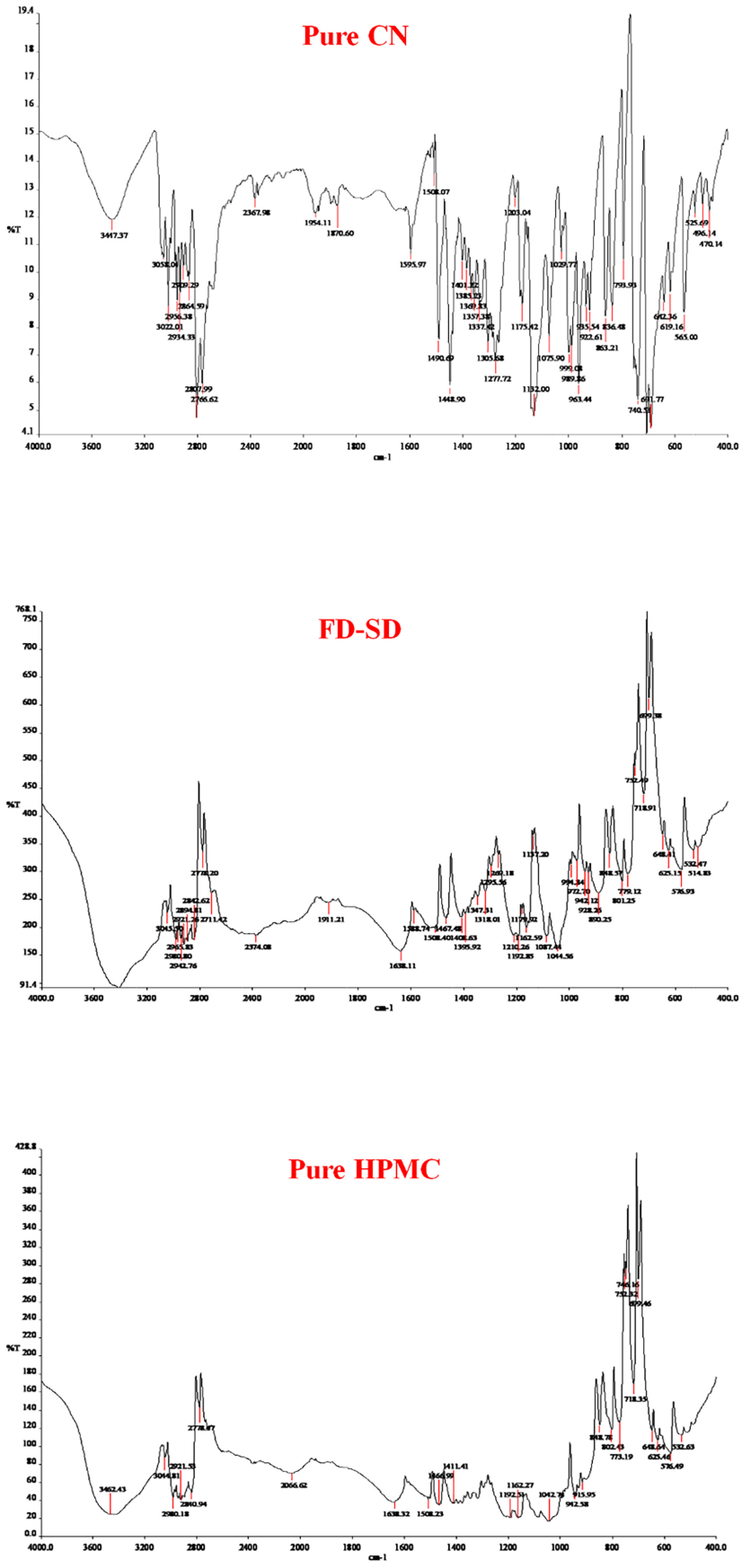

Fig. 3. Fourier transform infrared spectroscopy (FTIR) spectra of FD-SD formulations.

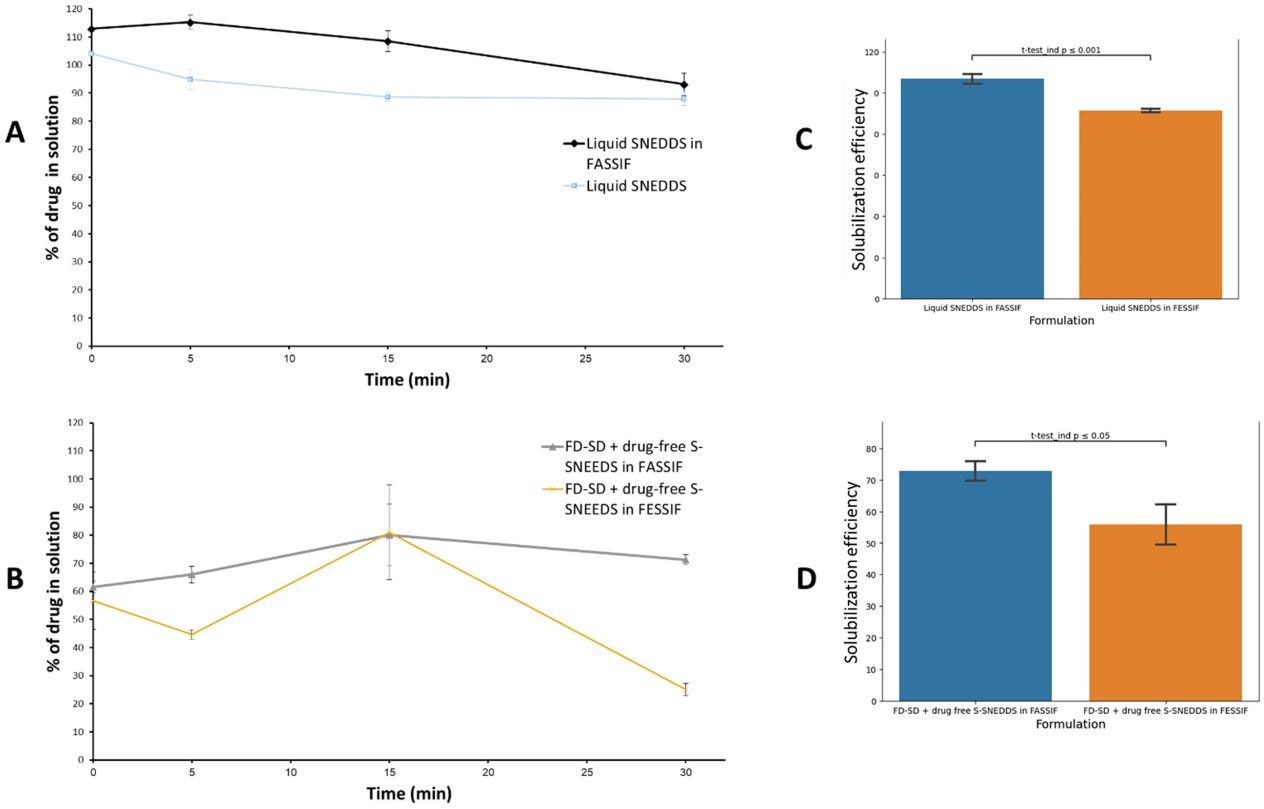

Fig. 4. Effect of *in-vitro* lipolysis on the percentage of drug in solution within Fad state simulated intestinal fluid (FASSIF) and Fed state simulated intestinal fluid (FESSIF). (A,C) Denotes the findings of liquid SNEDDS and (B,D) FD-SD + S-SNEDDS formulations. Data are presented as the mean ± standard deviation (SD), n = 3.

mm, 1.7 µm) with an accompanying Acquity guard filter was utilized while maintaining a constant flow rate of 0.25 mL/min. The UV detector was set to 251 nm to detect and quantify the CN peaks accurately [28].

2.10 Software

The data from the current study were analyzed using the Python programming language (version 3.9.13) within a Jupyter Notebook environment and SPSS 28 (IBM Corporation, Armonk, NY, USA). Portions of this article describing the data analysis methods and presenting results were composed with writing assistance from Claude (developed by Anthropic and operated by Poe) and Bing AI chat. Some Python scripts supporting the data analysis were also developed with input from these AI tools. However, the authors maintained overall responsibility for the direction, ideas, content, and finalization of the manuscript.

2.11 Statistical Analysis

Dissolution efficiencies of fresh and stored formulations were compared using independent samples *T* tests. In addition, the solubilization efficiencies in the lipolysis study were statistically compared using independent *T*-test (Scipy.stats and statannotations python package within the Jupyter Notebook environment). In the study, a significance level of $p < 0.05$ was considered to indicate statistical significance [1].

3. Results

3.1 Fabrication and Characterization of Solid SNEDDSs and Solid Dispersions

Based on our recent proof-of-concept study [5], the optimized solid SNEDDS + SD composition was directly selected and fabricated for the current work. The solid SNEDDSs were efficiently solidified into free-flowing powders without particle agglomeration.

3.2 Characterization of Solid SNEDDS and SDs

3.2.1 SEM

Pure NUS showed discrete and relatively spherical particles (Fig. 2a). Upon SNEDDS adsorption into NUS, no significant change in particle morphology was observed. The particles exhibited a spherical and distinct shape without any evidence of incomplete solidification or agglomer-

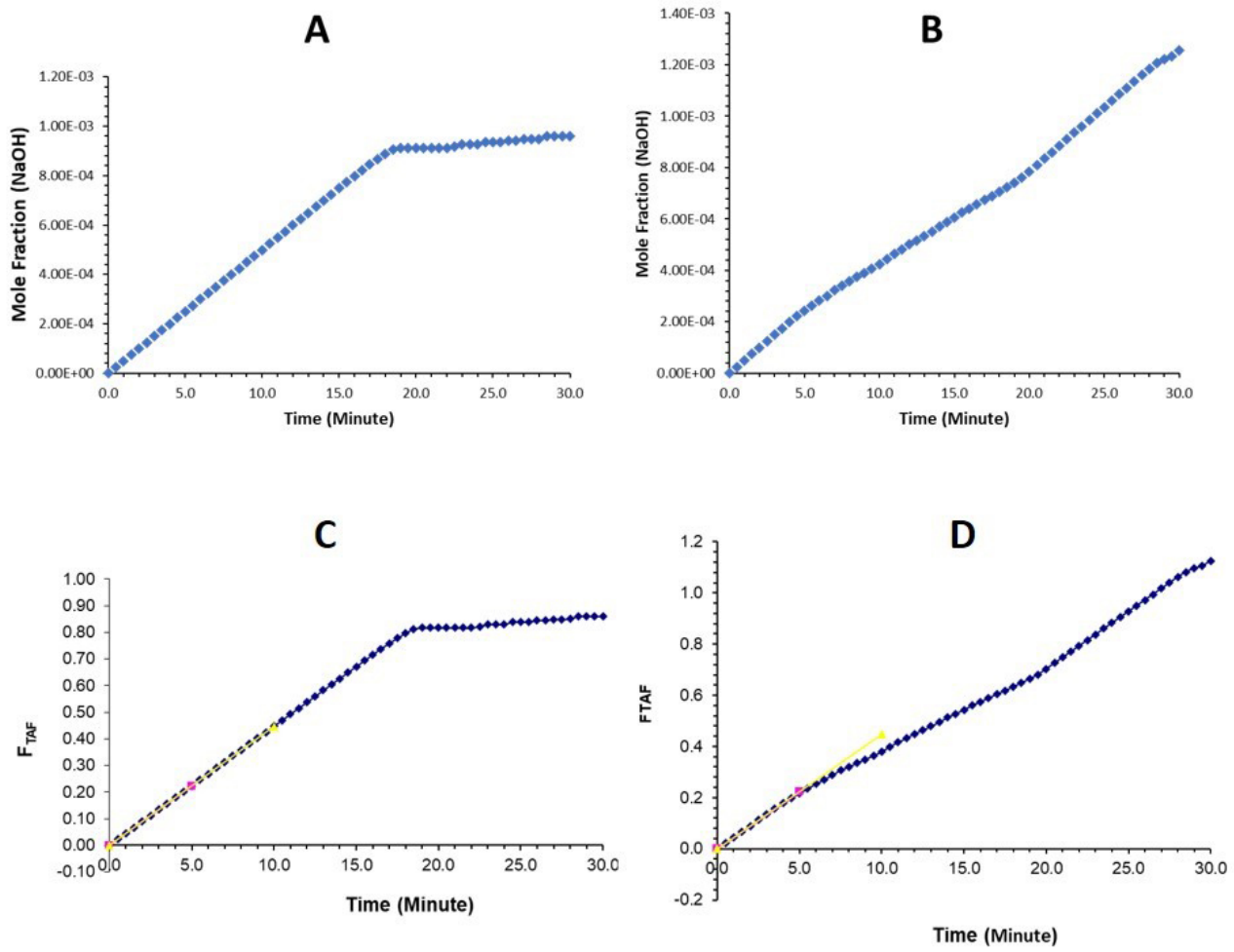

Fig. 5. NaOH titration and fatty acids (FAs) liberation during digestion under FESSIF. Number of NaOH moles (in mM) titrated and fraction of total available FAs liberated during the 30-minute digestion interval for drug-loaded L-SNEDDSs under (A,C) fed and (B,D) fasted conditions. The initial rate of digestion (C,D), represented by a yellow dotted arrow, was determined by measuring the amount of FAs (mmol/min) hydrolyzed during the first 0–5 min.

ation, as depicted in Fig. 2b. In contrast, FD-SD displayed irregular particles without indications of incomplete solidification, as shown in Fig. 2c.

3.2.2 Fourier Transform Infrared Spectroscopy (FTIR)

Distinct capsules were designated for the encapsulation of both the current SD and drug-free S-SNEDDS. Therefore, no interaction between the drug and S-SNEDDS was anticipated, and the FTIR samples were prepared by loading CN alone in the FD-SD formulation. Interestingly, FTIR showed similar spectra for FD-SD and HPMC E3. The CN characteristic peaks significantly disappeared in all FD-SD formulations (Fig. 3).

3.3 In Vitro Lipolysis

During the initial stage of the study, the liquid SNEDDS demonstrated excellent solubilization (>87%) of CN in both Fad state simulated intestinal fluid (FASSIF) and Fed state simulated intestinal fluid (FESSIF) conditions (Fig. 4A). However, drug solubilization was significantly higher in FASSIF than in FESSIF (Fig. 4C). Following the addition of pancreatin and the initiation of the lipolysis process, there was a slight decrease in the amount of solubilized CN in the aqueous phase. By the end of the study, the solubilized CN decreased to approximately 93% in FASSIF and 88% in FESSIF (Fig. 4A). On the other hand, the FD-SD + S-SNEDDS formulation was able to release 62% and 57% at the initial stage of the study in the FASSIF and FESSIF conditions, respectively (Fig. 4B). Similar to liquid SNEDDS, drug solubilization was significantly higher in FASSIF (Fig. 4D). Upon the addition of pancreatin, the lipolysis process was initiated, resulting in the solubilization of CN in the aqueous phase. At the conclusion of the study, the solubilized CN accounted for 71% in FASSIF and 25% in FESSIF (Fig. 4B).

In the lipolysis experiments, the advancement of lipid digestion was predominantly assessed by indirectly quantifying the rate and extent of digestion through titration of the

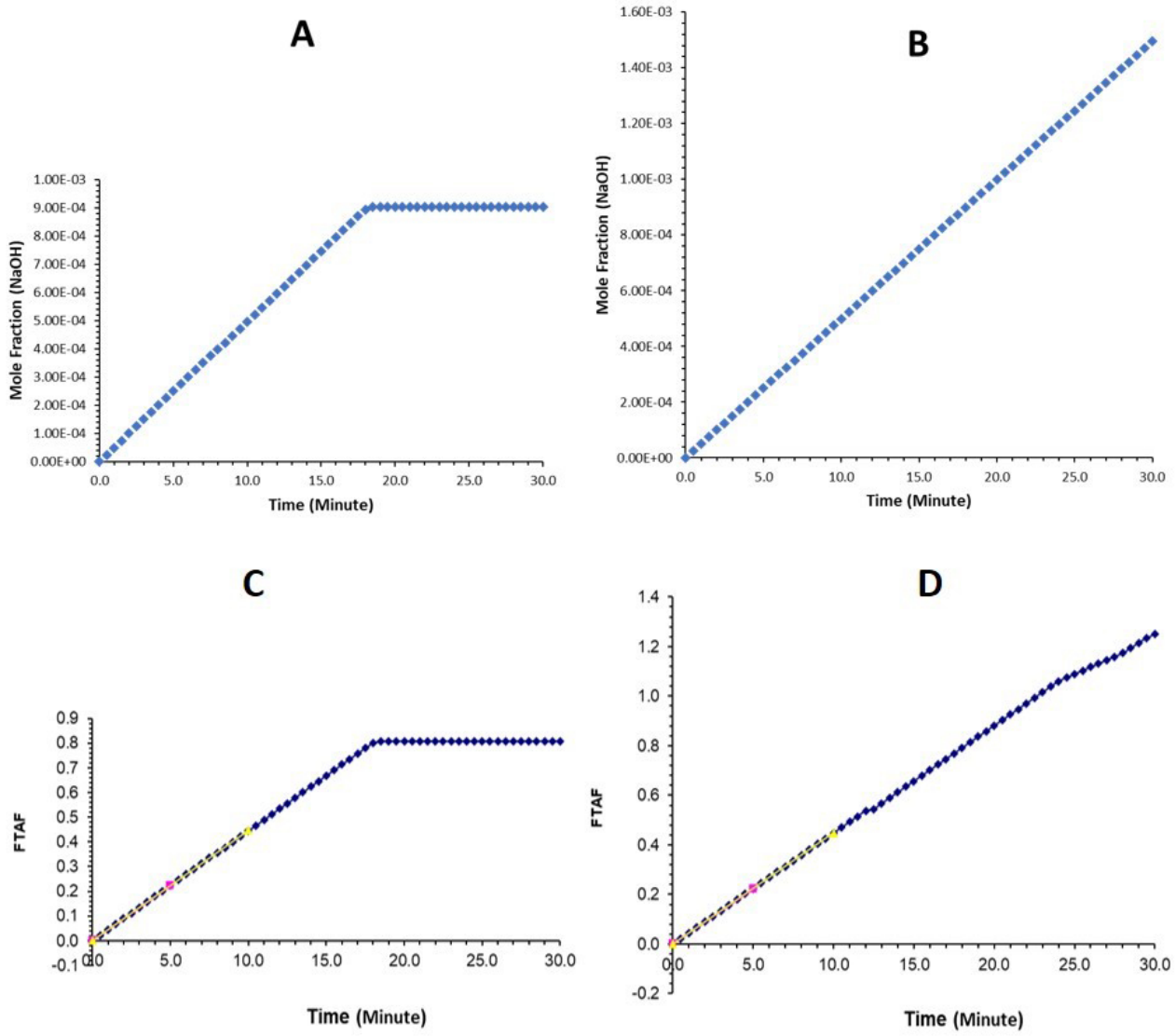

Fig. 6. NaOH titration and FAs liberation during digestion under FASSIF. Number of NaOH moles (in mM) titrated and fraction of total available FAs liberated during the 30-minute digestion interval for CN-SD + drug-free S-SNEDDSs under (A,C) fed and (B,D) fasted conditions. The yellow dashed arrow illustrates the initial digestion rate (C,D), quantified as the quantity of hydrolyzed FA (mmol/min) within the initial 0–5 minute period.

generated fatty acids. This approach allowed for the monitoring of the digestion process and provided valuable insights into the progress of lipid breakdown [18]. The digestion profiles depicted in Figs. 5,6 demonstrate the titrated NaOH mole fraction and the total available free FA content for both fasted and fed conditions. For both the liquid SNEDDS and solid dispersion-SNEDDS formulations, the reaction occurred rapidly in the first 5 minutes, accounting for over 25% of the total FAs released over 30 minutes. Under fed conditions, the digestion rate was initially rapid but experienced a sharp decline, transitioning to an approximately linear pattern after approximately 18 minutes (Fig. 5A,C, Fig. 6A,C). Conversely, under fasted conditions the digestion rate was slower initially than that in the fed state, but was more consistent and sustained over 30 minutes for both formulations (Fig. 5B,D and Fig. 6B,D). Interestingly, the extent of digestion was increased in the fasted versus fed state for both liquid SNEDDS and solid dispersion-SNEDDS. Overall, there were no marked differences observed in digestion extent between the liquid and solid dispersion-based formulations under either condition (Fig. 7).

3.4 Accelerated Stability Studies

The FD-SD formulation was able to maintain ≈ 96.5% intact CN after 6 months of storage in accelerated conditions. Likewise, the FD-SD + S-SNEDDS formulation retained over 93% of CN in solution for both the initial

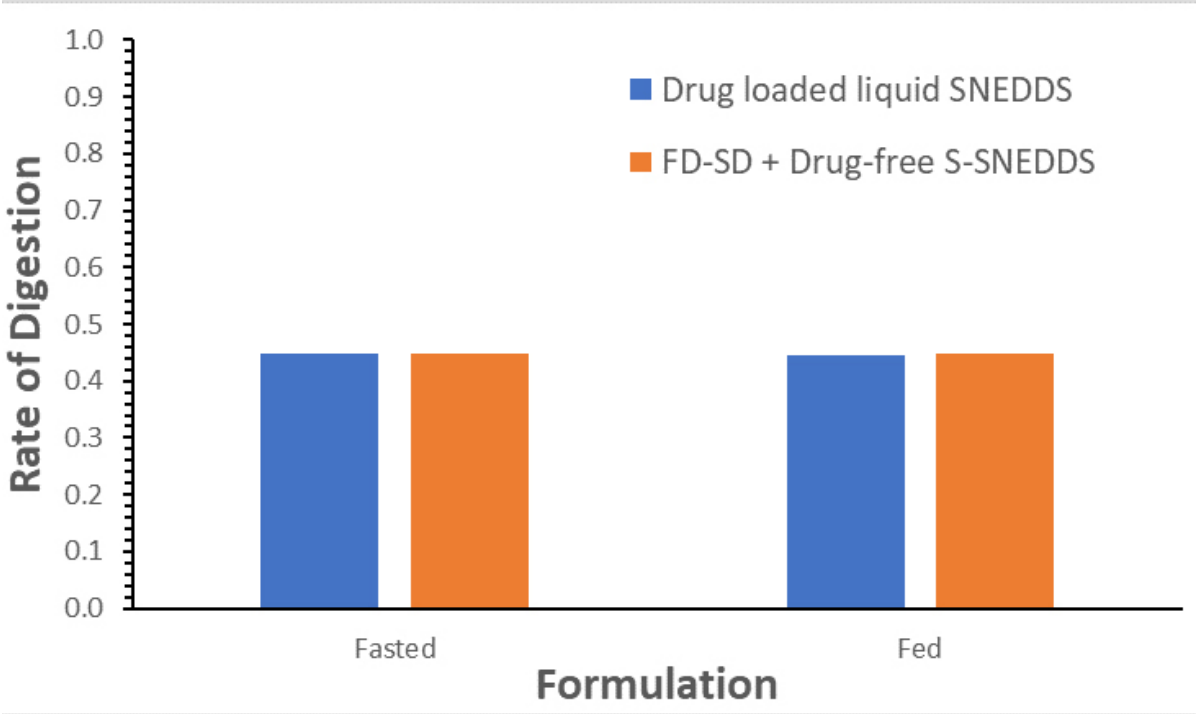

Fig. 7. The initial digestion rate of both liquid and solid SNEDDS formulations under fed and fasted (mmol FA/min) conditions. A mass of 500 mg of SNEDDS was utilized in the reaction vessel for the digestion process.

and 6-month samples at pH 1.2 (Fig. 8A). The two dissolution profiles were almost superimposed ($p > 0.05$, Fig. 8A). In contrast, the dissolution of CN was significantly reduced ($p < 0.001$) in the 6-month sample at pH 6.8. The initial sample of FD-SD + drug-free S-SNEDDS exhibited a dissolution of as much as 46%, whereas the 6-month sample demonstrated a maximum CN release of only 12.5% within 2 h (at pH 6.8) (Fig. 8B). Finally, the drug-free S-SNEDDS appeared as a white powder, while FD-SD appeared as beige powder at the initial stage (Fig. 9A). Upon storage for 6 months in accelerated conditions, no significant change in color or physical appearance was observed (Fig. 9B). Similarly, the DSC and XRD studies showed no significant difference between the initial and 6-month samples of FD-SD. The CN characteristic peaks were absent in both the initial and 6-month DSC and XRD samples Figs. 10,11.

4. Discussion

L-SNEDDSs that have been preloaded with drugs serve as an effective method for promoting pH-independent poorly water soluble drug (PWSD) dissolution. However, earlier research [16,17] has demonstrated considerable rancidity-related discoloration and CN degradation within L-SNEDDS formulations during storage. Therefore, recent research has concentrated on generating a novel solidification method to retain enhanced drug dissolution while also enhancing drug stability in the formulation to overcome these limitations.

Drug-loaded SNEDDSs often have a formulation step where the drug is dissolved into the SNEDDS components. The drug-loaded SNEDDS should spontaneously emulsify after being dissolved in water, attempting to maintain the drug in solution. Nevertheless, if the drug is not kept in a solubilized condition, this drug-loaded SNEDDS approach may be risky to use. In contrast, the PWSD was entirely separated from the solid SNEDDS in the current study's combination (SD + drug-free) SNEDDS, which was produced using a novel methodology, namely, FD-SD. This strategy was based on the hypothesis that drug-free SNEDDSs would self-emulsify to form nanosized micelles once the system was dissolved in water. The amorphized drug would simultaneously have a tendency to migrate inside the developing nanoemulsion droplets, whereas the crystalline drug would not be able to do so. This hypothesis is especially important when weakly basic PWSD is present in higher pH media [2,5].

In our recently published work [5], drug-free SNEDDSs were tested in terms of angle of repose, compressibility index, and Hausner ratio and showed fair-to-good flow properties. As expected, the drug-free SNEDDS maintained acceptable flow properties, even without incorporation of the drug. Furthermore, in the latter study, two solid dispersion techniques—freeze drying (FD-SD) and microwave irradiation (MW-SD)—were explored to determine the viability of this concept. The analysis of DSC and XRD data indicated the successful amorphization of CN within MW-SD and FD-SD formulations. This was

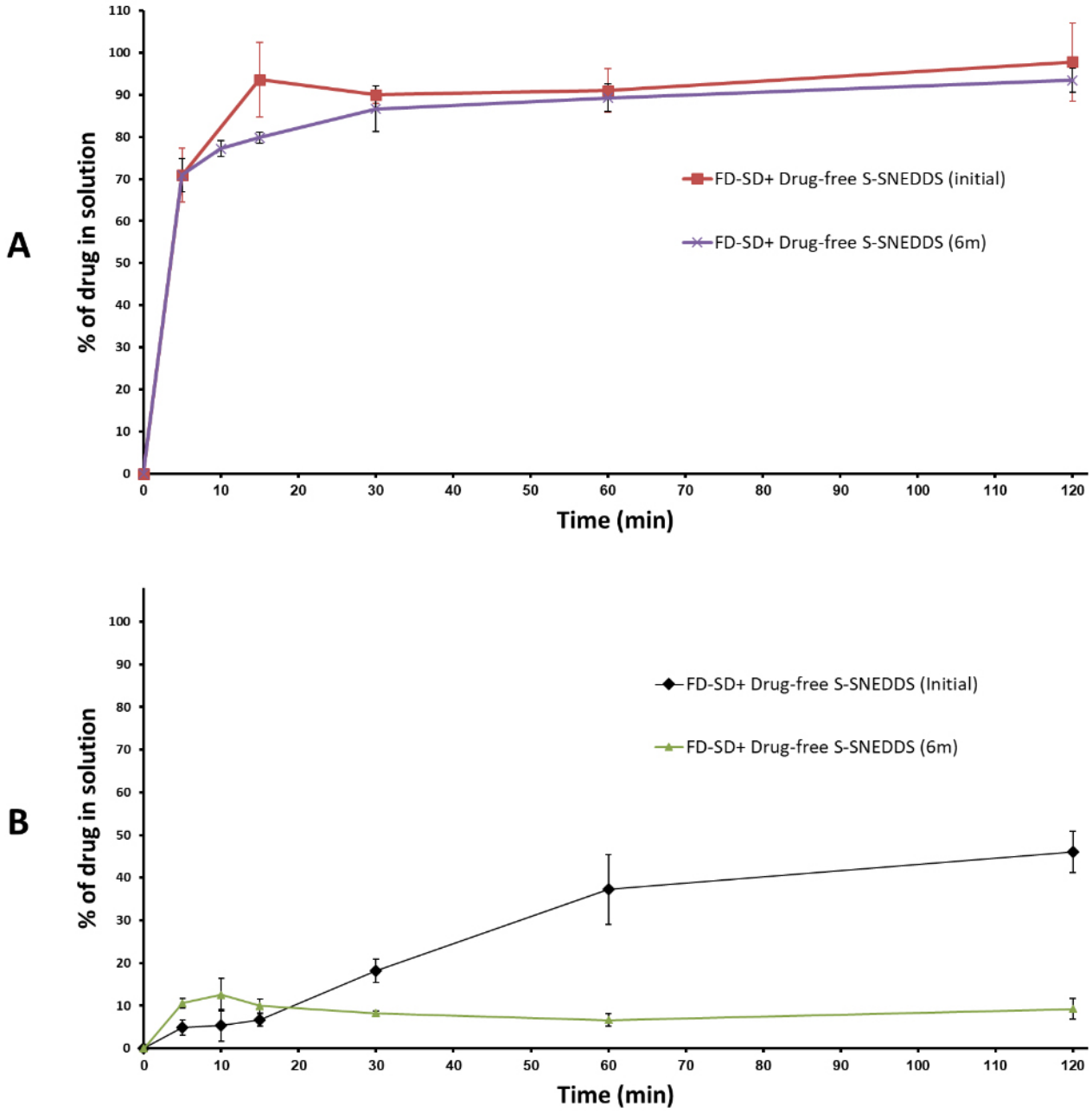

Fig. 8. *In vitro* dissolution of the FD-SD + S-SNEDDS formulation under accelerated stability conditions. The dissolution medium used consisted of (A) pH 1.2 and (B) pH 6.8. Data are expressed as the mean ± SD, n = 3.

evident as the characteristic endothermic peaks of CN and diffraction patterns disappeared completely from the DSC and XRD chromatograms, respectively [5]. The amorphized CN within both SDs was thought to migrate inside the formed drug-free nanoemulsion droplets, as proven by enhanced CN dissolution from these combined (drug-free SNEDDS + SD) systems. The crystalline CN could not show enhanced release, which was explained by its inability to migrate inside the formed nanoemulsion droplets.

In agreement with previous DSC and XRD results, the current study showed significant disappearance of CN characteristic peaks in the FTIR spectra of FD-SD samples, which implies that the drug was successfully captured inside the SD [31]. The resemblance observed in the FTIR spectra of both the polymers and their corresponding SDs indicates the absence of any chemical interaction between CN and the employed polymers. The results obtained from DSC, XRD, and FTIR analyses exhibit a strong correlation and confirm the successful amorphization of CN within the prepared solid dispersions FD-SD.

By subjecting the lipolysis product to ultracentrifugation, researchers were able to determine the distribution of the drug in the aqueous phase fractions. This analysis provided insights into the probable destiny of the drug follow-

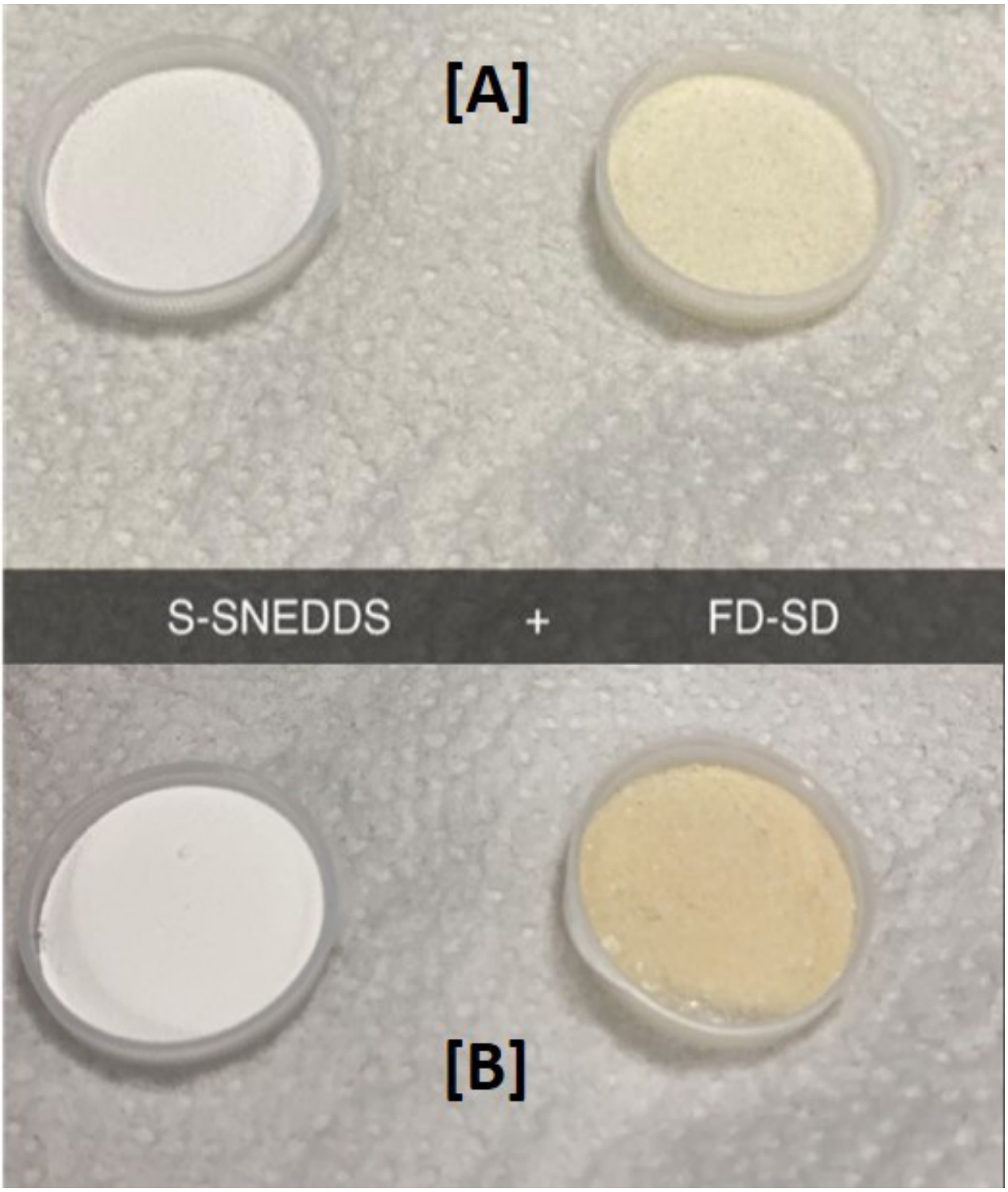

Fig. 9. Images of S-SNEDDS and FD-SD. The image of S-SNEDDS and FD-SD captured (A) initially and (B) after 6 months of storage under accelerated storage conditions.

ing lipolysis. Accordingly, drug molecules dissolved in the aqueous phase of the lipolysis medium were anticipated to be accessible for absorption, while drug particles present in the sediment might not be readily available for absorption under *in vivo* conditions [18]. Liquid and solid SNEDDSs of similar oil/surfactant/cosurfactant composition were assessed upon lipid digestion to assess whether the solidification process adversely affected the lipolysis process.

The results of the *in vitro* lipolysis experiments exhibited a strong correlation with the corresponding *in vitro* dis-

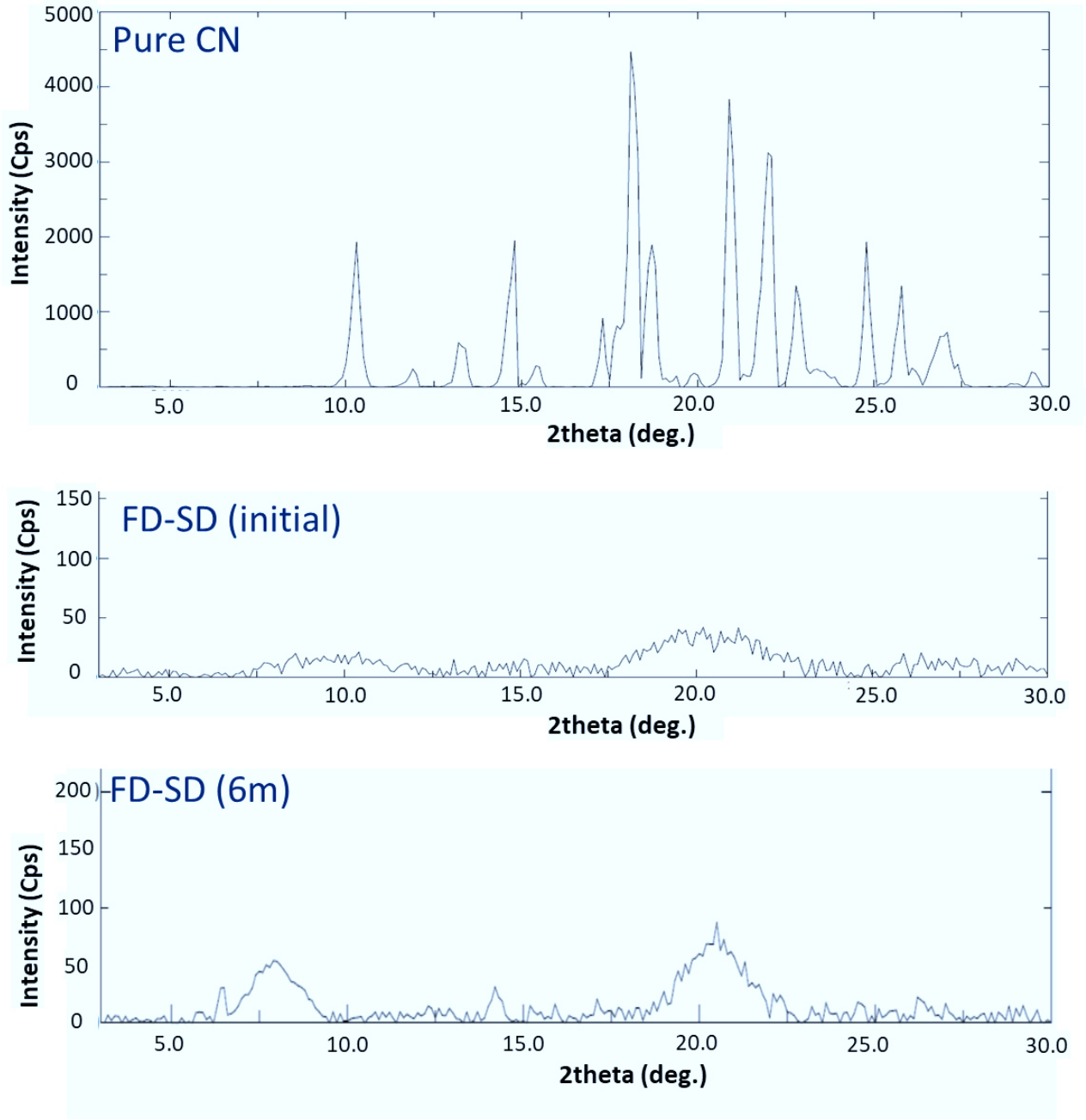

Fig. 10. The effect of accelerated storage conditions on the X-ray powder diffraction (XRD) profile of FD-SD.

solution studies [31]. The *in vitro* lipolysis study also revealed key differences in digestion and solubilization behavior between the liquid SNEDDS formulation and the combined solid dispersion-solid SNEDDS system. The liquid SNEDDS exhibited near complete initial cinnarizine solubilization in both fasted and fed states, aligning with its enhanced dissolution. This can be attributed to micellar solubilization by oleic acid and stabilization by the surfactant Cremophor El and cosurfactant Imwitor 308 in the SNEDDS composition. A slight decrease was seen later likely because of lipase degrading these colloidal structures.

In contrast, the solid dispersion-solid SNEDDS combination showed lower initial solubilization, releasing approximately 60% cinnarizine, but was able to maintain higher solubilization by the end of the experiment with FASSIF conditions. This observation also correlates with the *in vitro* dissolution results, which showed an initial release of only 46% from the freshly prepared solid dispersion-solid SNEDDS system. The reduced early performance could be attributed to two potential mechanisms: (1) Entrapment of SNEDDS within the small pores of the silica carrier, which can impede emulsification and drug release compared to the liquid SNEDDS. (2) The time needed

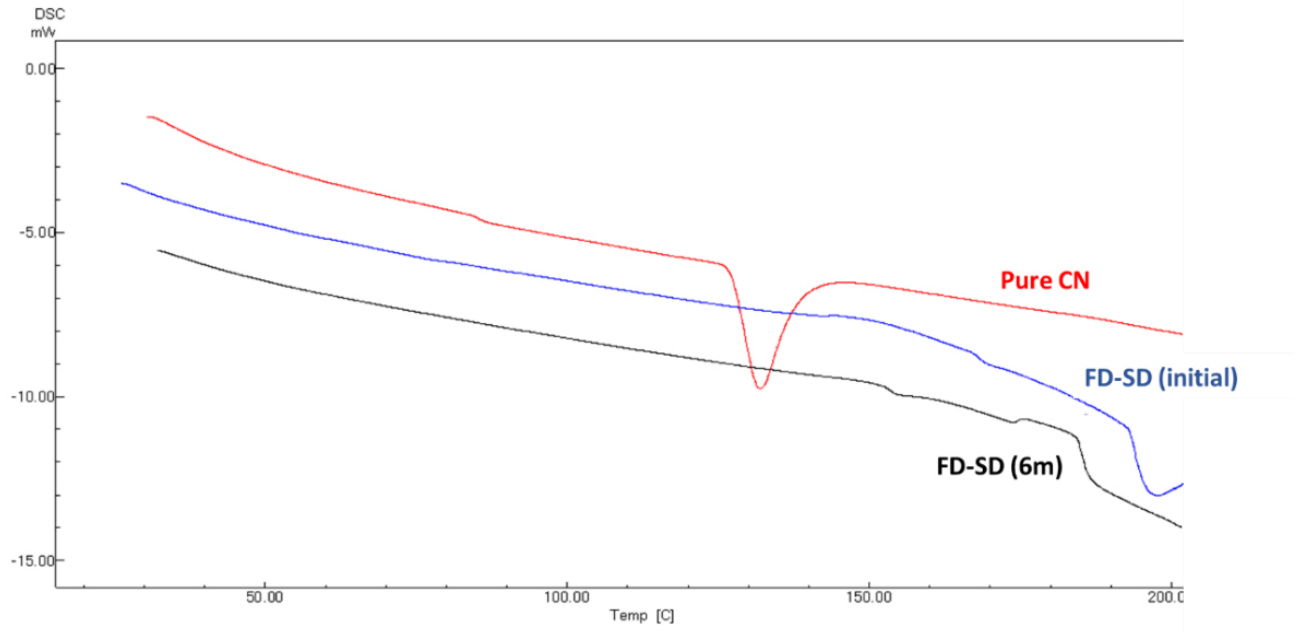

Fig. 11. The effect of accelerated storage conditions on the differential scanning calorimetry (DSC) profile of FD-SD.

for the amorphous drug in the solid dispersion to partition into the solid SNEDDS nanoemulsion droplets, compared to the faster release of molecularly dissolved drug in the liquid SNEDDS.

While the solid combination demonstrated slower initial solubilization, its ability to sustain higher levels over time suggests that the solid-state provided some stability against precipitation. The hydrophilic HPMC polymer in the solid dispersion not only enhances wetting and dispersion, but also inhibits precipitation by providing a "parachute" effect during lipolysis [13]. This helps sustain supersaturation and counteracts decreases in solubilization.

Under fed conditions however, the solid combination exhibited significant precipitation, with the solubilized drug decreasing to 25%. An interesting observation was the formation of a creamy layer on top of the aqueous phase during lipolysis of the SD + S-SNEDDS formulation under fed state conditions. This unique finding suggests potential disruption of the nanoemulsion integrity that might have exposed CN to unfavorable aqueous media and led to precipitation. This proposed mechanism is further supported by the high variability in solubilized drug amounts seen exclusively with the SD + S-SNEDDS formulation.

From another angle, lipid digestion was monitored by titrating the liberated fatty acids, which allowed assessment of the rate and overall extent of digestion. Oleic acid acts as a lipid component and is a readily available source of FFAs. The high percentage of MG (98% monocaprylate) in Imwitor 308 enhanced the solubility of lipids and facilitated formulation emulsification during digestion [32]. This process generated additional FA on top of the FA available in OL, which couldpromote the formation of mixed micelles. Cremophor EL, also known as polyoxyl 35 castor oil, is a nonionic surfactant that is used in SNEDDSs to promote refined nanoemulsion formation. Its primary composition consists of the tri-ricinoleate ester of ethoxylated glycerol which might be a potential substrate for digestive lipases [33].

The more sustained digestion in the fasted state could be attributed to weaker inhibition of lipase activity compared to the fed state. In the fasted state, the stomach is relatively empty, and there is minimal secretion of bile and digestive enzymes. When a SNEDDS formulation is administered in a fasted state, it encounters fewer obstacles to emulsification and drug release. The low presence of bile and food in the stomach could allow for efficient self-emulsification and drug solubilization, leading to enhanced drug absorption.

Intriguingly, the extent of digestion for both liquid SNEDDS and the SD + S-SNEDDS combination was comparable under both fed and fasted conditions. This similarity suggests that digestion is likely to be fully accomplished within the gastrointestinal (GI) tract, as a significant amount of fatty acids were liberated. This could be attributed to the available digestible glycerides present in the Imwitor 308 and/or Cremophor El, while oleic acid resembled a source of free fatty acids. Overall, the similar digestion patterns between liquid and solid SNEDDS suggest that lipid conversion to the solid form did not substantially impact lipase access or activity.

In drug-loaded SNEDDS, it was hypothesized that the drug is still exposed to SNEDDS excipients even at the solid stage, so it may actually undergo a slower rate of CN degradation, but this solidification alone is unlikely to entirely

stop the degradation. This hypothesis has been confirmed according to another recent article that showed significant drug degradation within drug-loaded solid SNEDDS after 3 months of storage [31]. In contrast, the present study demonstrated the excellent chemical stability of CN, with over 96% of CN remaining intact during storage for up to 6 months under accelerated conditions. This remarkable stability can be attributed to the complete separation between the drug-free SNEDDS and CN during storage. Moreover, the FD-SD + drug-free S-SNEDDS formulation ensures optimal isolation of the drug from the adsorbent, thereby preventing the formation of undesirable physical bonds between the drug and the adsorbent during storage.

The current study attempted to evaluate the formulation performance from several aspects in accelerated conditions rather than testing only chemical stability. The accelerated stability study showed excellent CN chemical stability in addition to maintaining a similar physical appearance, amorphization, and dissolution profile at pH 1.2 upon storage for up to 6 months. These findings show significant improvement of CN chemical stability in formulation compared to recently published data that reported a significant loss of the intact CN within the drug-loaded liquid and solid SNEDDS after storage in similar conditions [2,17,31]. Due to the amorphization of CN within FD-SD, it was critical to assess the recrystallization of CN within SD upon storage by DSC and XRD. While the formulation demonstrated excellent chemical stability by retaining over 96% of intact CN, the decline in the dissolution profile at pH 6.8 warrants further discussion.

The decrease in CN release could be due to several potential mechanisms that were reported for silica-based solid dispersions:

- Migration of lipophilic SNEDDS excipients into the silica carrier over time, reducing wettability and drug release from the smaller mesopores [5,8,10,34].
- Entrapment of SNEDDS in narrow mesopores (<50 nm) impedes emulsification compared to macropores (>50 nm) [34].
- Storage at elevated temperature decreased SNEDDS viscosity enabling deeper penetration into the smaller pores [34].
- The minor impact at pH 1.2 versus the pronounced effect at pH 6.8 correlates (Fig. 8) with the pH-dependent solubility of cinnarizine [1] and suggests that the mechanism involves hindered dissolution rather than degradation.

Accordingly, the decline in performance sheds light on formulation-carrier compatibility challenges to guide future studies.

The data presented demonstrate the potential impact of combining SDs with drug-free S-SNEDDSs in the development of a solidified SNEDDS formulation with an enhanced drug stability profile. However, the use of silica adsorbents and their curing process for SNEDDS solidification needs more attention, as the area is still largely unexplored. In the future, it is recommended to employ a lipophilic fluorescent probe for an in-depth exploration of the mechanism underlying partial drug release from both freshly formulated and long-term stored S-SNEDDSs. These investigations could shed light on the primary factors contributing to incomplete drug release in freshly prepared and aged S-SNEDDS formulations. In future studies, it is essential to thoroughly explore the potential advantages of using hydrophilic polymers such as PVP-k30 for precoated adsorbents, aiming to mitigate dissolution delays during storage. Subsequently, FD-SD could be combined with drug-free SNEDDS (prepared by precoated adsorbent) to combine the benefits of the two recently investigated techniques. Characterization of the pellets, obtained after lipolysis sample centrifugation, with XRD and light microscopy could offer interesting information for the solid-state of cinnarizine. Alternative approaches, such as freeze-drying S-SNEDDS without silica, adsorbent curation or optimization of pore sizes/excipient levels, could maintain robustness. To bridge the gap between *in vitro* findings and real-world performance, it is crucial to complement these investigations with *in vivo* pharmacokinetic and pharmacodynamic studies.

5. Conclusions

The preparation of S-SNEDDSs through adsorption provides a viable approach for improving drug dissolution and stability. Nevertheless, the use of adsorbents such as Neusilin® in this technique noticeably slows down the release of the drug from SNEDDS formulations during storage. In the present study, the combination of drug-free S-SNEDDSs with FD-SD offered a promising approach to overcome the stability limitations associated with liquid SNEDDSs. Furthermore, the developed dosage form design exhibited remarkable chemical and physical stability. Nonetheless, it is worth highlighting that the dissolution of the formulation notably decreased when tested at pH 6.8. Overall, the developed formulation could be a potential technique to enhance the dissolution of weakly basic drugs that possess challenging stability limitations.

Availability of Data and Materials

Samples of the compounds CN are available from the authors. The data utilized and/or examined in the present study can be obtained from the corresponding author upon a reasonable request.

Author Contributions

Conceptualization, AYT, AAWS and FKA; Formal analysis, AAWS; Funding acquisition, MK; Investigation, AYT and AAWS; Supervision, MK and FKA; Validation, AAWS and MK; Writing — original draft, AYT and AAWS; Writing — review & editing, FKA and MK. All authors have read and agreed to the published version of the manuscript. All authors have participated sufficiently in the

work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity. All authors contributed to editorial changes in the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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