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Functionalized calcium carbonate (FCC) as a novel carrier to solidify supersaturated self-nanoemulsifying drug delivery systems (super-SNEDDS)

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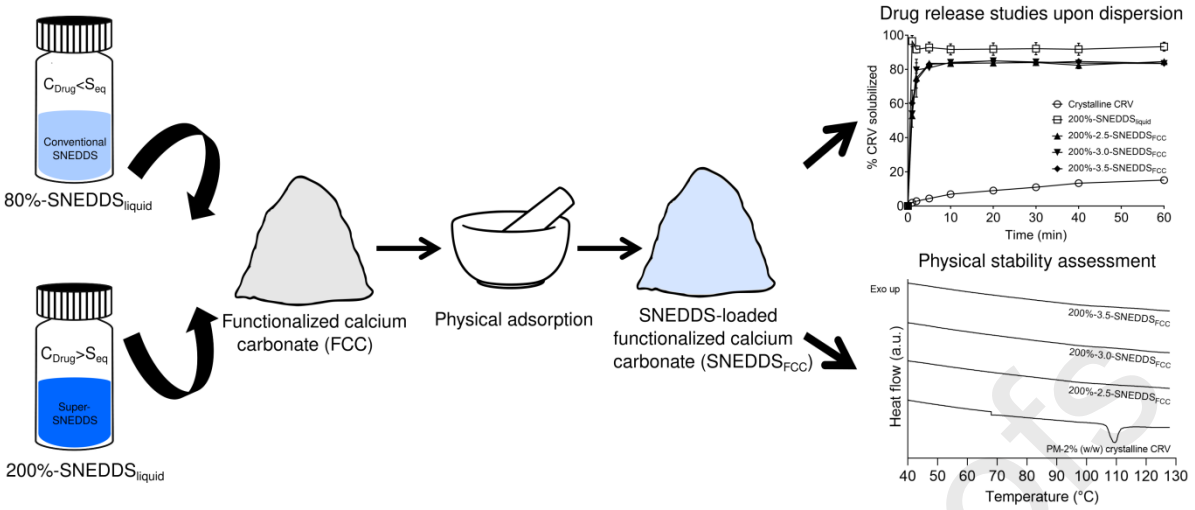
Abstract

Functionalized calcium carbonate (FCC), a novel pharmaceutical excipient, has shown promising properties in the field of oral drug delivery. The current study aimed at evaluating the feasibility of FCC as a carrier for the solidification of self-nanoemulsifying drug delivery systems (SNEDDS) containing the poorly water-soluble model drug carvedilol (CRV). Conventional, subsaturated SNEDDS (80%-$SNEDDS_{liquid}$) and supersaturated SNEDDS (200%-$SNEDDS_{liquid}$) were loaded onto FCC via physical adsorption at three ratios; 2.5:1, 3.0:1 and 3.5:1 (w/w) of FCC:$SNEDDS_{liquid}$, respectively, generating free-flowing powders ($SNEDDS_{FCC}$) with drug loading ranging from 0.8% to 2.6% (w/w) CRV. The emulsification of $SNEDDS_{FCC}$ in a USP II dissolution setup (in purified water) was characterized using dynamic light scattering, resulting in similar droplet sizes and PDIs as observed for their liquid counterparts. The morphology and physical state of the obtained $SNEDDS_{FCC}$ were characterized using scanning electron microscopy and differential scanning calorimetry. The physical stability and drug release upon dispersion were assessed as a function of storage time. The 200%-$SNEDDS_{liquid}$ were physically stable for 6 days, however, solidification using FCC stabilized the supersaturated concentrations of CRV for a test period of up to 10 weeks (solidification ratios 3.0:1 and 3.5:1 (FCC:$SNEDDS_{liquid}$)). $SNEDDS_{FCC}$ achieved an improved rate and extent of drug release upon dispersion compared to the crystalline CRV in tap water (pH 7.5), however, to a lesser extent than their liquid counterparts. After 8 weeks of storage (25 °C at dry conditions), FCC was still able to rapidly release the $SNEDDS_{liquid}$ and demonstrated the same rate and extent of drug release as freshly prepared samples. The solidification of 200%-$SNEDDS_{liquid}$ in presence of FCC greatly improved the drug loading and showed an enhanced drug release profile compared to the conventional systems. In conclusion, FCC showed potential as a carrier for solidification of SNEDDS and for the development of novel supersaturated solid SNEDDS for the oral delivery of poorly water-soluble drugs.

Keywords

Oral drug delivery, Lipid-based drug delivery, Self-nanoemulsifying drug delivery systems, Functionalized calcium carbonate, Solidified lipid-based systems, Carvedilol, Solid-state analysis

Graphical Abstract



Introduction

Oral drug delivery is the most favored route of drug administration due to its potential advantages including patient compliance, cost-effectiveness and non-invasiveness [1]. In a recent report (2021), 90% of the new drug candidates emerging from the pharmaceutical industry were classified as poorly water-soluble [2], leading to low and erratic bioavailability from conventional dosage forms after oral administration [3]. Hence, enabling formulation strategies are needed to improve the bioavailability of poorly water-soluble drugs after oral administration [4].

Lipid-based formulations (LBF) offer a solution by mitigating the inherently slow dissolution process of poorly water-soluble drugs due to their ability to pre-dissolve lipophilic drugs and thus circumvent the dissolution step in the gastrointestinal tract [5–7]. Amongst the various LBF, the use of a self-nanoemulsifying drug delivery system (SNEDDS) has attracted significant attention [8]. SNEDDS consists of drugs dissolved in an isotropic mixture of lipids, surfactants, co-surfactants and co-solvents from which a nanoemulsion is formed upon dispersion in aqueous media [7]. Conventional SNEDDS usually have a drug load between 50% to 90% of the drug's equilibrium solubility (S_{eq}) in the SNEDDS preconcentrate to avoid drug precipitation during storage and after administration [9]. The low drug loading of conventional SNEDDS potentially results in the administration of several dosage units, negatively affecting patient compliance [10]. To increase the drug loading in SNEDDS preconcentrate, Thomas et al. [9,11] developed the concept of supersaturated SNEDDS (super-SNEDDS). Super-SNEDDS are characterized by containing drug concentrations well beyond the drug's S_{eq} in the SNEDDS preconcentrate and have been demonstrated to be suitable alternatives to conventional SNEDDS [9,11,12].

Despite the mentioned advantages, some limitations still exist for SNEDDS. They are usually filled in soft gelatin capsules, therefore limiting the drug loading by the fill weight and the drug solubility in the formulation [13,14]. Furthermore, nearly all development and manufacturing activities involving soft gelatin capsules are outsourced to contract manufacturing organizations since most pharmaceutical companies lack in house capability leading to high production costs [15]. In an attempt to overcome these limitations, the solidification of liquid SNEDDS using chemically inert solid carriers to enable the production of solid dosage forms has attracted substantial interest in recent years [16].

The general hypothesis applied is that the development of solidified SNEDDS could combine the advantages of liquid SNEDDS with the high physical stability of solid dosage forms while enhancing or retaining the biopharmaceutical performance of the poorly water-soluble drugs compared to their liquid counterparts [17]. Moreover, the ease of manufacturing associated with low costs and the possibility of producing a wider range of dosage forms, e.g., powder filled in sachets or capsules or compressed into tablets, makes solidification attractive from an industrial perspective [16,18,19].

A plethora of research is devoted to the transformation of liquid LBF into solid dosage forms with a focus on various solidification methods as well as on the selection of solid carrier excipients. The solidification methods most commonly employed are physical adsorption, spray drying and melt extrusion [18]. A wide range of inorganic porous carriers for the solidification of LBF has been investigated including magnesium aluminometasilicate (e.g. Neusilin®), colloidal silicon dioxide (e.g. Aerosil®), porous amorphous silica gels (e.g. Sylysia® and Syloid®), and calcium silicate (e.g. Hubersorb®) [20]. An appropriate selection of the solid carrier for the solidification of LBF should enable the highest possible lipid (and drug) loading efficiency, adequate flowability, compactability, as well as an efficient re-dispersibility after administration [21,22].

In order for the loaded poorly water-soluble drug to be released from the solid carrier, the liquid lipid phase of the solid dosage form has to desorb from the solid carrier and partition into the aqueous phase, or the solid carrier itself has to dissolve within the gastrointestinal tract [16]. Over the past years, various solid carriers have been investigated with respect to their role in retaining or enhancing the biopharmaceutical performance of solidified LBF. However, conflicting evidence has been reported as to whether the solidified formulations will preserve, enhance, or decrease the biopharmaceutical performance compared to their respective liquid counterparts. While several studies reported complete drug release from the solidified LBF [23–26], others observed incomplete desorption from solidified formulations translating to a reduced *in vivo* performance [14,27–29].

Neusilin®, a mesoporous magnesium aluminometasilicate, demonstrated significant potential as a solid carrier for LBF due to its ability to generate solidified LBF by simple physical adsorption and direct compactability allowing the manufacturing of tablets [30]. However, the suitability of Neusilin® as a solid carrier for LBF has been discussed controversially. Incomplete drug release was identified to be a major issue with formulations containing Neusilin® as a solid carrier due to the formation of gels by lipid-surfactants mixtures once in contact with water, hindering the drug release from deeper pores of Neusilin® [14,15,30]. A further reduction of drug release from the solidified LBF upon storage has been a concern, possibly due to the progressing migration of the mobile fractions of liquid LBF to deeper unwetted regions of the carrier during storage, entrapping the drug deeper within the pores [20].

The above-mentioned limitations drive the need to investigate the potential of new solid carriers for the solidification of LBF. In a previous study, solid supersaturatable SNEDDS loaded with glipizide were developed using conventional calcium carbonate, in combination with talc and hydroxypropyl methylcellulose (HPMC-E5) as polymeric precipitation inhibitor (PPI). However, the primary objective of the study was to evaluate the potential of HPMC-E5 in stabilizing the resulting supersaturated drug concentrations following dispersion [31].

Functionalized calcium carbonate (FCC) was recently identified as a novel pharmaceutical excipient for the oral delivery of poorly water-soluble drugs [32]. FCC is a microparticulate material ranging from 5-15 µm in diameter [33]. The small pore diameter (0.01-1 µm) and thus resulting high specific area of FCC enables water absorption at a faster rate and 10 times higher extent than conventional calcium carbonate [32,34]. The physical attributes of FCC led to the exploration of this material in the field of pharmaceutical excipient research, resulting in the development of several innovative drug delivery systems. FCC has been investigated as mucoadhesive delivery systems for colon targeting [35], oral protein delivery systems [36], orally dispersible tablets [34,37], floating tablets [38] and as a carrier for increasing the physical stability of amorphous drugs [39].

Since FCC has not been studied as a pharmaceutical excipient for the solidification of SNEDDS, the overall objective of this study was to investigate the feasibility of FCC to serve as a solid carrier for conventional SNEDDS and super-SNEDDS. It was hypothesized that the adsorption of super-SNEDDS onto FCC would increase the physical stability of the utilized BSC II model drug carvedilol (CRV) and help to achieve a greater CRV load. The developed solid (super-)SNEDDS and their liquid counterparts were characterized with respect to their *in vitro* performance including droplet size measurements and drug release upon dispersion. The developed solid (super-)SNEDDS were further characterized for drug release upon dispersion as a function of storage time.

Materials and Methods

Materials

Functionalized calcium carbonate (FCC) (Omyapharm® 500 – OG) was obtained from Omya International AG (Oftringen, Switzerland). Carvedilol (CRV) was purchased from Cipla Ltd. (Mumbai, India). Capmul MCM C8 EP/NF (medium chain (MC) mixed glycerides) and Captex 300 EP/NF (MC triglycerides) from Abitec (Columbus, OH, USA) were provided by Barentz (Odense, Denmark). Kolliphor RH40 (polyoxyl 40 hydrogenated castor oil) was donated by BASF (Ludwigshafen, Germany). Transcutol was donated by Gattefossé (Saint Priest, France). Potassium phosphate monobasic and potassium chloride were purchased from Sigma Aldrich (St Louis, MO, USA). Hydrochloric acid 37% (HCl) and acetonitrile (HPLC grade) were purchased from VWR Chemicals (Herlev, Denmark). Purified water was obtained from a SG Ultraclear water system (SG Water GmbH, Barsbüttel, Germany). Tap water (pH 7.5) was used through the course of the study.

Methods

Preparation of liquid SNEDDS ($SNEDDS_{liquid}$)

The MC mixed glycerides (Capmul MCM C8 EP/NF) and the surfactant (Kolliphor RH40) were molten at approximately 50 °C before they were blended in a vortex mixer with the MC triglycerides (Captex 300 EP/NF). After equilibration to room temperature, the co-solvent (Transcutol) was added to the mixture followed by a second mixing step forming an isotropic mixture consisting of 51% (w/w) lipid (18% (w/w) Capmul MCM C8 EP/NF and 33% (w/w) Captex 300 EP/NF), 43% (w/w) surfactant (Kolliphor RH40) and 6% (w/w) co-solvent (Transcutol). The generated blank-$SNEDDS_{liquid}$ (drug-free) were subsequently left for overnight stirring at 37 °C and were stored at 25 °C until use.

The S_{eq} of CRV in the blank-$SNEDDS_{liquid}$ was determined at room temperature using a shake flask method adapted from Thomas et al. (2012) [9]. Samples were withdrawn at regular intervals and S_{eq} was assumed to have been achieved when consecutive solubility values differed by less than 5%, resulting in an S_{eq} of 47 ± 0.5 mg/g. Conventional SNEDDS (80%-$SNEDDS_{liquid}$) and super-SNEDDS (200%-$SNEDDS_{liquid}$) were produced using a heating-cooling cycle at levels corresponding to 80% and 200% of the drugs S_{eq}, respectively. Based on the drug load, the required amounts of CRV and blank-$SNEDDS_{liquid}$ were accurately weighed into dust-free glass vials containing a magnetic stirring bar. The mixtures were vortexed at room temperature for 30 s and subsequently ultrasonicated for 15 min at room temperature in a Branson 5510 ultrasonic bath (Branson Ultrasonics, Danbury, CT, USA). To facilitate complete dissolution of the drug, the obtained suspensions were placed in a silicon oil bath (60 °C) and stirred for 1 h (Arex Digital PRO, Heating Magnetic stirrer, VELP® Scientifica, Usmate (MB), Italy). After the heating cycle, the prepared formulations were allowed to slowly equilibrate to 25 °C inside the oil bath resulting in isotropic 80%-$SNEDDS_{liquid}$ and 200%-$SNEDDS_{liquid}$. The magnetic stirring bar was removed, and the vials were stored at 25 °C. The complete dissolution of the CRV after the heating-cooling cycle in all formulations was assessed using polarized light microscopy (PLM) (see below). After the heating-cooling cycle, the chemical stability of CRV in 200%-$SNEDDS_{liquid}$ was determined and an average of 99.7 ± 3.3% of the added CRV content was detected, indicating chemical stability of CRV during the drug loading procedure. Samples were stored in sealed glass vials at 25 °C and produced in triplicates to assess their physical stability. The vials were analyzed at regular intervals for possible precipitation of the dissolved drug by both visual observation and PLM (see below).

Adsorption of $SNEDDS_{liquid}$ onto FCC ($SNEDDS_{FCC}$)

Adsorption of $SNEDDS_{liquid}$ onto FCC was achieved by manual mixing using a mortar and pestle. First, FCC and $SNEDDS_{liquid}$ were mixed at a ratio of 1:1 (expressed as the weight ratio of FCC:$SNEDDS_{liquid}$). The amount of FCC was gradually increased until a free-flowing powder was obtained. The following ratios of FCC:$SNEDDS_{liquid}$ were evaluated: 2.5:1, 3.0:1, 3.5:1 (w/w). The

resulting mixtures were gently mixed in a mortar for 3 min to obtain a free-flowing powder. The efficiency of the loading procedure was evaluated based on visual inspection of the powder's appearance and flowability. Accordingly, 100 mg of $SNEDDS_{liquid}$ (corresponding to 3.76 mg CRV for 80%-$SNEDDS_{liquid}$ and 9.4 mg CRV for 200%-$SNEDDS_{liquid}$) were loaded onto 250 mg, 300 mg and 350 mg of FCC. Hence, six $SNEDDS_{FCC}$ were produced as follows: (A) 80%-2.5-$SNEDDS_{FCC}$; (B) 80%-3.0-$SNEDDS_{FCC}$; (C) 80%-3.5-$SNEDDS_{FCC}$; (D) 200%-2.5-$SNEDDS_{FCC}$; (E) 200%-3.0-$SNEDDS_{FCC}$; (F) 200%-3.5-$SNEDDS_{FCC}$ with CRV loading ranging from 0.8% to 2.6% (w/w).

Drug loading efficiency

The CRV loading efficiency after adsorption of $SNEDDS_{liquid}$ onto FCC was assessed by HPLC. Powder samples of 80%-$SNEDDS_{FCC}$ and 200%-$SNEDDS_{FCC}$ were collected from three different parts of the powder, placed in volumetric flasks and suspended in a mixture of phosphate buffer (0.02M, pH 2) and acetonitrile (55:45% (v/v)). The samples were subsequently ultrasonicated for 20 min in a Branson 5510 ultrasonic bath (Branson Ultrasonics, Danbury, CT, USA). The obtained $SNEDDS_{FCC}$ suspensions were centrifuged for 15 min at 13,300 rpm (17,000*g*) (MicroCL 17 Centrifuge, Thermo Scientific, Waltham, MA, USA) followed by HPLC quantification of the CRV concentration in the clear supernatant. Each formulation was prepared in triplicates and sampling was done from three parts of the $SNEDDS_{FCC}$ powder; thus, the total number of measurements was n=9. The CRV contents are represented as quantified mass of CRV (mg) obtained from HPLC analysis compared to the theoretical mass of CRV (mg).

Solid-state characterization

The surface morphology of neat CRV, neat FCC and $SNEDDS_{FCC}$ (80% and 200%) was studied by scanning electron microscopy (SEM) using a Hitachi TM3030 tabletop microscope (Hitachi High Technologies Europe GmbH, Krefeld, Germany) operated at an accelerating voltage of 15 kV. Samples were sputter coated with gold (Cressington 108 auto, Cressington Scientific Instruments, Watford, UK) prior to SEM analysis.

X-ray powder diffraction (XRPD) measurements were performed for neat CRV, neat FCC, physical mixtures, and $SNEDDS_{FCC}$ (80% and 200%) using an X'Pert PANalytical PRO X-ray diffractometer (PANalytical, Almelo, The Netherlands). Physical mixtures were prepared by manually mixing CRV and FCC at different drug to excipient weight ratios (2.5%–20% CRV). Cu Kα radiation (λ= 1.54187 Å) was generated using a 45 kV acceleration voltage and current of 40 mA. Samples were scanned in reflectance mode from 5–16° 2θ with a scan rate of 0.016834° 2θ/s and a step size of 0.0065652° 2θ. The data was collected and analyzed using the software X'Pert Data Collector (version 2.2.4) (PANalytical, Almelo, The Netherlands).

Neat CRV, neat FCC, individual SNEDDS excipients, $SNEDDS_{FCC}$ (80% and 200%) and physical mixtures (PM) were analyzed using differential scanning calorimetry (DSC) using a Discovery DSC (TA Instruments, New Castle, DE, USA). The PM were prepared by mixing 100 mg of blank-$SNEDDS_{liquid}$, 350 mg FCC and the corresponding amount of CRV. All the $SNEDDS_{FCC}$ were stored in a desiccator under dry conditions over silica gel at 25 °C and checked for potential CRV recrystallization over a period of 10 weeks. Samples were regularly analyzed by DSC (weekly for the first 4 weeks, and every 2 weeks thereafter) until a CRV melting endotherm was detected. All $SNEDDS_{FCC}$ used for the physical stability assessment were produced in triplicates. A sample mass of 3-5 mg was transferred to Tzero aluminium pans and sealed with pierced hermetic Tzero lids. All measurements were carried out using a heating rate of 10 °C/min from a starting temperature of 10 °C (isothermal for 2 min) to an end temperature of 130 °C under a nitrogen gas flow of 50 mL/min. The obtained thermograms were analyzed using TRIOS software (TA Instruments, New Castle, DE, USA).

Droplet size measurements

The droplet size after dispersion of the $SNEDDS_{FCC}$ (80% and 200%) and their respective liquid counterparts was measured by dynamic light scattering (DLS) using a Zetasizer Nano (Malvern, Worcestershire, UK) operated at 37 °C. A USP type II dissolution apparatus consisting of a set of mini glass vessels with rotating mini paddles (Erweka DT600 dissolution tester, Erweka GmbH, Heusenstamm, Germany) was used to promote emulsification in two media, i.e. purified water and HCl solution (0.2M, pH 1.6).

Approximately 100 mg of $SNEDDS_{FCC}$ (80% and 200%) and their respective $SNEDDS_{liquid}$ were weighed into the vessel and 100 mL of pre-heated purified water or HCl solution (0.2M, pH 1.6) was added. The dispersions were stirred at 100 rpm for 30 min at 37 ± 0.5 °C. After 30 min, 1 mL aliquots were withdrawn from the vessel. For all $SNEDDS_{FCC}$ dispersed in purified water, the turbid dispersions were centrifuged at 13,300 rpm (17,000*g*) for 15 min. After centrifugation, the particle size in the obtained supernatant was immediately analyzed without further dilution. The droplet sizes of the resulting dispersions from $SNEDDS_{FCC}$ dispersed in HCl solution (0.2M, pH 1.6) and $SNEDDS_{liquid}$ were immediately analyzed from aliquots directly taken from the vessel, without further dilution. In the case of $SNEDDS_{FCC}$ dispersed in HCl solution (0.2M, pH 1.6), no centrifugation step was necessary due to the apparent solubility of FCC in acidic media. Additionally, droplet size measurements for blank-$SNEDDS_{liquid,}$ and blank-$SNEDDS_{FCC}$ were performed as controls. The measured droplet size and PDI of three independent measurements per formulation are reported as mean z-average (nm) and PDI, respectively.

Drug release upon dispersion

Drug release upon dispersion of $SNEDDS_{FCC}$ (80% and 200%), $SNEDDS_{liquid}$ (80% and 200%) and crystalline CRV was quantified in 100 mL of tap water (pH 7.5) using a USP type II apparatus consisting of a set of mini glass vessels with rotating mini paddles (Erweka DT600 dissolution tester, Erweka GmbH, Heusenstamm, Germany) under sink conditions. A sample amount corresponding to 3.76 mg of CRV was used corresponding to a lipid content of 100 mg for 80%-$SNEDDS_{FCC}$ and 40 mg for 200%-$SNEDDS_{FCC}$. The paddle rotation speed was set to 100 rpm and the temperature of the media was maintained at 37 ± 0.5 °C. Aliquots (3 mL) were withdrawn at predetermined time points (1, 2, 5, 10, 15, 20, 30, 40 and 60 min) and the volume was replaced by fresh, pre-heated media. The samples were centrifuged at 13,300 rpm (17,000*g*) for 1 min and the obtained supernatant was diluted appropriately and subsequently analyzed by HPLC (see below). All measurements were carried out in triplicates.

The drug release studies were performed for freshly prepared samples (week 0) and after 3, 6 and 8 weeks of storage. The samples were stored in a desiccator under dry conditions over silica gel at 25 °C and analyzed for CRV drug release upon dispersion. All the $SNEDDS_{FCC}$ used for the drug release assessment during storage were produced in triplicates.

HPLC analysis

Quantification of CRV in samples obtained from the S_{eq} quantification, solidification efficiency assessment, chemical stability study and drug release studies were performed using an Ultimate 3000 Ultraviolet (UV) detector, UltiMate 3000 autosampler and UltiMate 3000 pump (Thermo Scientific, Waltham MA, USA) equipped with an ACE Excel 5 C18AR column (Advanced Chromatography Technologies Ltd., Aberdeen, Scotland). The mobile phase consisted of phosphate buffer (0.02 M, pH 2) and acetonitrile (55:45% (v/v)). The injection volume was 20 µL at a flow rate of 1.0 mL/min. The eluted CRV was detected at a wavelength of 240 nm.

Polarized light microscopy

$SNEDDS_{liquid}$ (80% and 200%) were analyzed for undissolved crystalline CRV after the heating and cooling cycle and for precipitation of CRV upon storage using a Leica DM LM microscope equipped with cross polarizers (Leica Microsystems, Wetzlar, Germany). Images were acquired using a Media

Cybernetics Evolution MP digital camera and the ImagePro Insight software version 8.0 (Media Cybernetics).

Statistical analysis

Statistical analysis was carried out using GraphPad Prism (Version 9.5.0, GraphPad Software, San Diego, CA, USA). Unpaired Student's t-tests were applied to determine statistically significant differences ($p = 0.05$) between two groups, whereas analysis of variance (ANOVA) followed by Tukey's post-test were utilized for differences between more than two groups ($p = 0.05$).

Results and discussion

Drug loading efficiency

To ensure a uniform drug distribution after the adsorption of $SNEDDS_{liquid}$ onto FCC, the content uniformity of CRV was studied. As shown in Figure 1, for both drug loadings (80%-$SNEDDS_{FCC}$ and 200%-$SNEDDS_{FCC}$) and their corresponding solidification ratios (2.5:1, 3.0:1, and 3.5:1 (w/w)) no statistically significant difference between the theoretical mass of CRV and the corresponding quantified mass of CRV was observed ($p > 0.05$). This indicates that the employed solidification method by manual mixing using a mortar and pestle resulted in a uniform distribution of CRV in $SNEDDS_{FCC}$.

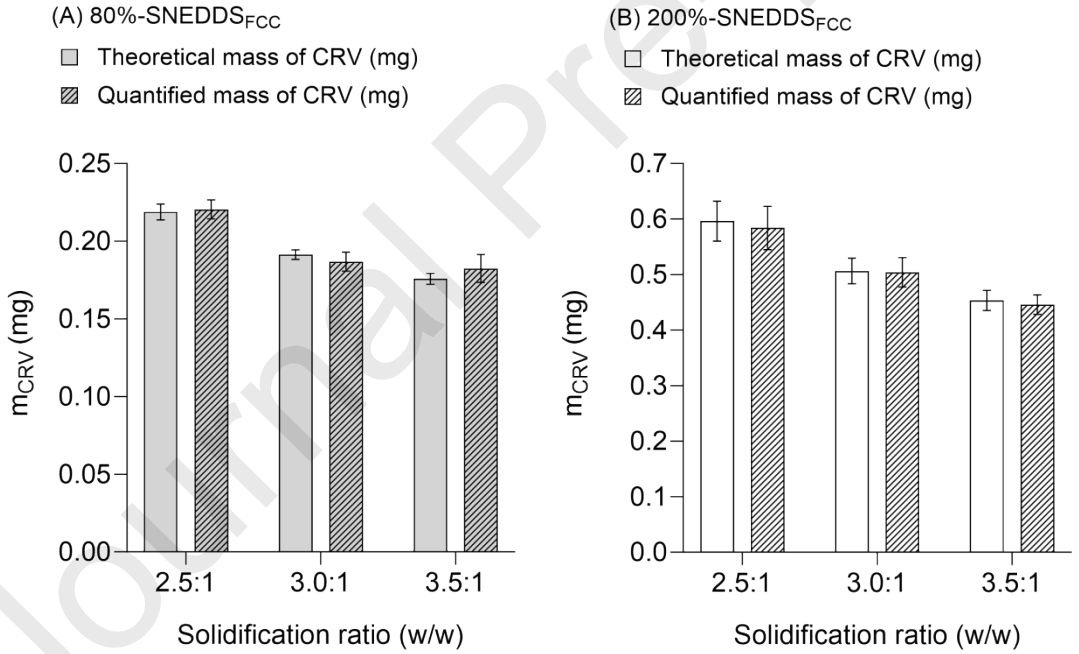


Figure 1. Quantified mass of CRV *(dashed columns)* compared to the theoretical mass of CRV *(solid columns)* for (A) 80%-$SNEDDS_{FCC}$ *(light grey columns)* and (B) 200%-$SNEDDS_{FCC}$ *(white columns)* at solidification ratios of 2.5:1, 3.0:1, and 3.5:1 (w/w). Results are represented as mean ± SD (n=9).

Solid state characterization

SEM analysis of $SNEDDS_{FCC}$ was carried out to study the surface morphology of FCC particles before and after loading with $SNEDDS_{liquid}$. The morphology of neat CRV, neat FCC, blank-$SNEDDS_{FCC}$ and $SNEDDS_{FCC}$ are shown in the SEM images in Figure 2. Blank-$SNEDDS_{liquid}$ was loaded onto FCC as a reference (blank-$SNEDDS_{FCC}$, Figure 2 (C)) to study the surface morphology of FCC particles after

lipid-loading (drug-free) and enable a comparison with neat FCC particles (Figure 2 (B)). $SNEDDS_{FCC}$ for both drug loadings and the corresponding solidification ratios (2.5:1, 3.0:1, and 3.5:1 (w/w)) retained the original shape of the neat FCC particles while showing no signs of CRV crystals (Figure 2 (A)). The developed $SNEDDS_{FCC}$ formulations appeared no different to the neat FCC and the blank-$SNEDDS_{FCC}$ particles at CRV loading of 0.8% to 2.6% (w/w), suggesting a complete adsorption of drug-loaded $SNEDDS_{liquid}$ onto FCC.

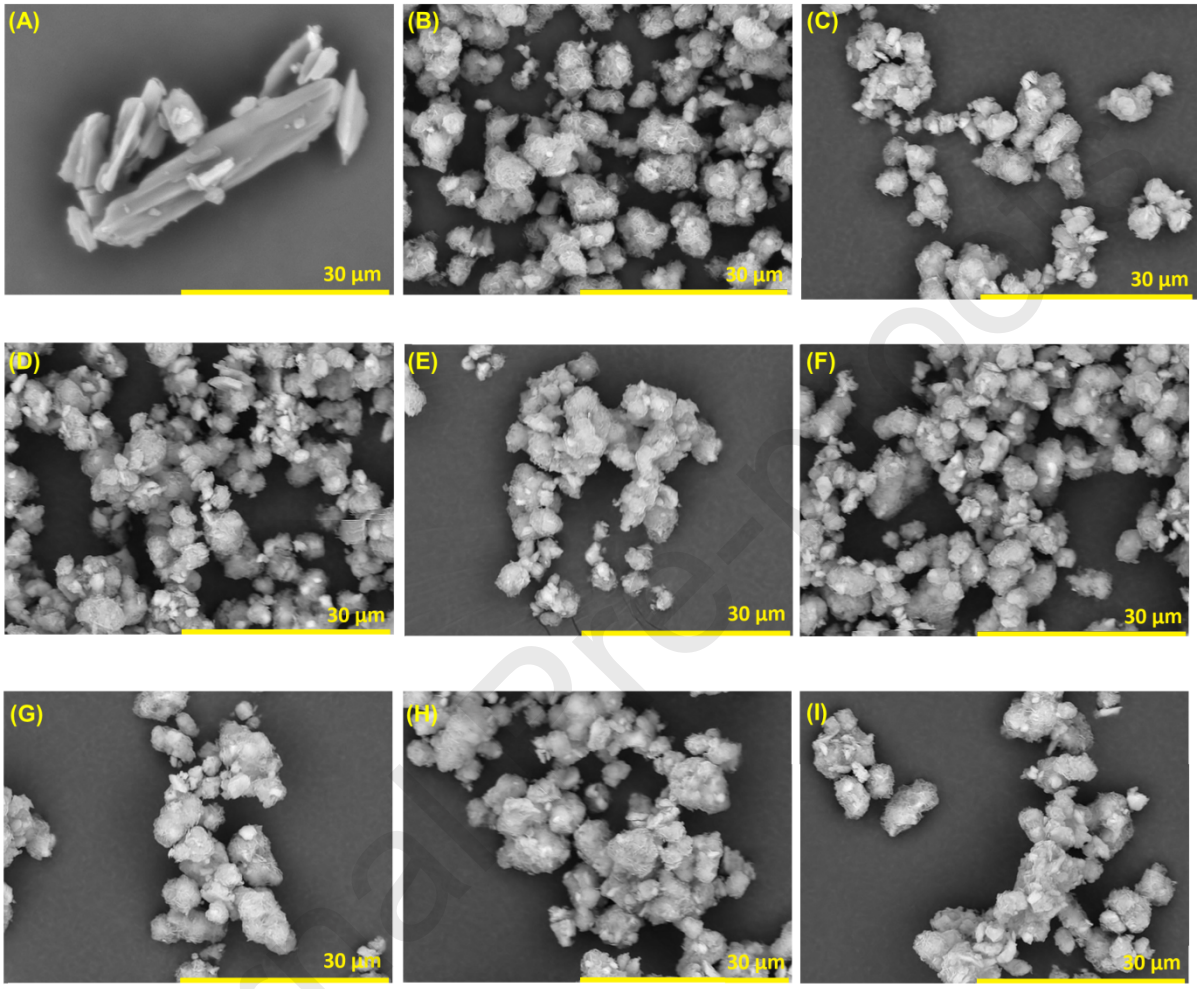


Figure 2. SEM images of (A) neat CRV; (B) neat FCC; (C) blank-$SNEDDS_{FCC}$; (D) 80%-2.5-$SNEDDS_{FCC;}$ (E) 80%-3.0-$SNEDDS_{FCC}$; (F) 80%-3.5-$SNEDDS_{FCC}$; (G) 200%-2.5-$SNEDDS_{FCC}$; (H) 200%-3.0-$SNEDDS_{FCC}$; (I) 200%-3.5-$SNEDDS_{FCC}$ loaded via physical adsorption. All SEM images were obtained at a magnification of x3000.

As the amount of CRV present in the developed $SNEDDS_{FCC}$ ranged from 0.8% to 2.6% (w/w), XRPD showed an insufficient limit of detection (LOD) to detect potentially recrystallized CRV (see supplementary information, Figure S1). Thus, the feasibility of using DSC for the detection of low amounts of crystalline CRV in $SNEDDS_{FCC}$ during the physical stability study was investigated.

DSC thermograms of the individual excipients and neat CRV are presented in Figure S2 (supplementary information). Neat crystalline CRV displayed a sharp melting endotherm with an onset temperature of 115.4 °C, corresponding to its characteristic melting point [40]. PMs ranging from 2%-0.04% (w/w) of crystalline CRV were analyzed using DSC to determine the LOD for CRV in the FCC matrix (supplementary information, Figure S3). The PM containing 2%, 0.8%, 0.52%, 0.2%, and 0.08% (w/w) of crystalline CRV in FCC displayed an endothermic peak corresponding to the melting of crystalline CRV. However, no melting endotherm was observed for the PM containing 0.04% (w/w) of crystalline

CRV. Consequently, the LOD of crystalline CRV using DSC was found to be 0.08% (w/w) CRV, demonstrating a sufficient sensitivity to detect the recrystallization of 3% of the loaded CRV in 200%-2.5-SNEDDS$_{FCC}$ (or 10% recrystallization of the loaded CRV in the 80%-3.5-SNEDDS$_{FCC}$).

The DSC thermograms of freshly prepared samples of 80%-SNEDDS$_{FCC}$ and 200%-SNEDDS$_{FCC}$ are shown in Figure 3(A) and Figure 3(B), respectively. The DSC thermograms of 80%-SNEDDS$_{FCC}$ and 200%-SNEDDS$_{FCC}$ displayed no characteristic CRV melting endotherm for freshly prepared samples, indicating the presence of dissolved CRV in the SNEDDS$_{FCC}$. The obtained results demonstrate the ability of FCC to act as a solid carrier maintaining CRV in a dissolved state even at supersaturated concentrations of CRV in the adsorbed 200%-SNEDDS$_{liquid}$ after the initial loading procedure.

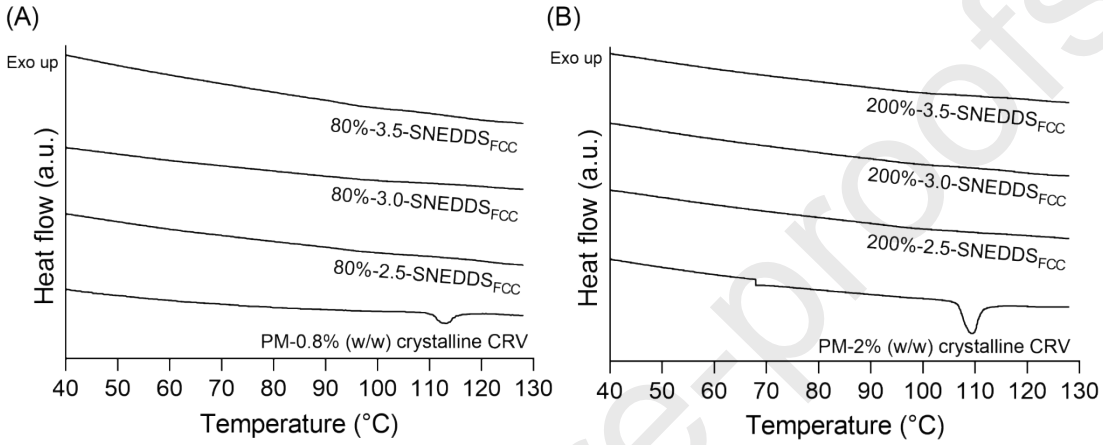


Figure 3. DSC thermograms of freshly prepared samples of (A) 80%-SNEDDS$_{FCC}$ and (B) 200%-SNEDDS$_{FCC}$ and their corresponding PM containing 0.8% (w/w) and 2% (w/w) crystalline CRV, respectively. The DSC thermograms shown for the developed SNEDDS$_{FCC}$ are representative results for one of the triplicate samples.

Physical stability studies

The SNEDDS$_{liquid}$ were inspected on a regular basis by PLM, and the onset of CRV precipitation in SNEDDS$_{liquid}$ was defined as the time point when crystals were detected by PLM in at least one of the prepared triplicate samples. Since the 80%-SNEDDS$_{liquid}$ contained CRV concentrations below the drug's $S_{eq,}$ they were found to be thermodynamically stable throughout the course of the study for 8 months, and no CRV precipitation was observed. However, due to the supersaturated concentrations of CRV in 200%-SNEDDS$_{liquid}$ the potential precipitation during storage is of interest. Therefore, the 200%-SNEDDS$_{liquid}$ were inspected on a regular basis by PLM, and needle-shaped crystals of CRV were observed after 6 days (see supplementary information, Figure S4).

With regards to the stability assessment of the SNEDDS$_{FCC}$, since PLM could not be employed as a method to investigate a possible CRV recrystallization during storage from the SNEDDS$_{FCC}$, the use of DSC was continued for the physical stability assessment of SNEDDS$_{FCC}$ over a storage period of 10 weeks.

The DSC thermograms of 80%-SNEDDS$_{FCC}$ over a storage period of 10 weeks displayed no melting endotherm for all three solidification ratios (2.5:1, 3.0:1 and 3.5:1 (w/w)) (data not shown). This confirms that adsorption onto FCC did not cause a loss in the solvent capacity of the SNEDDS$_{liquid}$ over the storage duration of 10 weeks.

The DSC thermograms of 200%-2.5-SNEDDS$_{FCC}$ showed an endothermic event after 3 weeks of storage with an onset temperature of 110-111 °C corresponding to the onset temperatures of crystalline

CRV melting obtained from the thermograms of the PM (Figure 4(A)). In contrast, the $SNEDDS_{FCC}$ with a higher FCC:$SNEDDS_{liquid}$ ratio (200%-3.0-$SNEDDS_{FCC}$ and 200%-3.5-$SNEDDS_{FCC}$) did not show a melting endotherm even after 10 weeks of storage (Figure 4(B) and Figure 4(C)). It is thus possible that the presence of a higher amount of FCC in the formulation led to a complete incorporation of the 200%-$SNEDDS_{liquid}$ inside the pores of FCC and correspondingly a lower amount of 200%-$SNEDDS_{liquid}$ being present on the FCC surface, thus having an improved stabilizing effect against drug recrystallization, possibly due to spatial confinement of the 200%-$SNEDDS_{liquid}$ in the pores. In summary, comparing the physical stability results from $SNEDDS_{FCC}$ and $SNEDDS_{liquid}$, it can be concluded that FCC was able to increase the physical stability of the supersaturated concentrations of CRV in the adsorbed $SNEDDS_{liquid}$ when compared to its liquid counterpart (200%-$SNEDDS_{liquid}$). When comparing the three solidification ratios, the ratio 2.5:1 (w/w), having the lowest amount of FCC, could not retain the supersaturated concentration of CRV in the dissolved state and was found to be stable for only 3 weeks. Thus, the amount of FCC present in the formulation plays a role in stabilizing the supersaturated concentration of CRV against recrystallization.

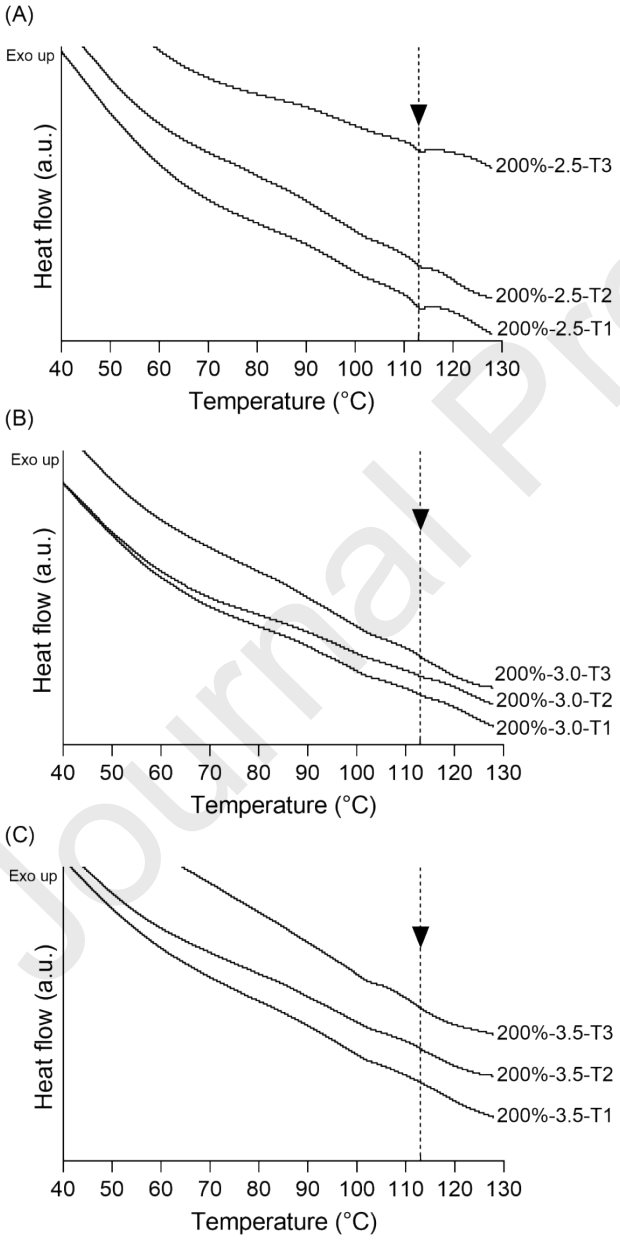


Figure 4. Enlarged DSC thermograms for the triplicate samples (T1/T2/T3) of (A) 200%-2.5-SNEDDS$_{FCC}$ after 3 weeks; (B) 200%-3.0-SNEDDS$_{FCC}$ after 10 weeks; and (C) 200%-3.5-SNEDDS$_{FCC}$ after 10 weeks of storage under dry conditions at 25 °C. The dashed line with an arrow guides the eye for the melting endotherm of CRV observed in 200%-2.5-SNEDDS$_{FCC}$ and its absence for 200%-3.0-SNEDDS$_{FCC}$ and 200%-3.5-SNEDDS$_{FCC}$.

Droplet size measurements

Droplet size measurements for SNEDDS$_{FCC}$ were carried out in purified water to assess their ability to form nano-sized emulsions in a comparable way to SNEDDS$_{liquid}$. Blank-SNEDDS$_{liquid}$ and 80%-SNEDDS$_{liquid}$ emulsified completely after 1 min in purified water forming a translucent dispersion. In contrast, dispersions of 200%-SNEDDS$_{liquid}$ had a slightly bluish appearance, but there were no signs of CRV precipitation after 30 min when investigated by PLM. The droplet size for both blank-SNEDDS$_{liquid}$ and 80%-SNEDDS$_{liquid}$ were found to be around 30 nm, and no statistical difference was observed in the droplet sizes between the blank-SNEDDS$_{liquid}$ and 80%-SNEDDS$_{liquid}$ ($p > 0.05$) demonstrating the formation of nano-sized emulsions (Figure 5 (A)). However, the increased drug load for 200%-SNEDDS$_{liquid}$ resulted in a small but significant increase in droplet size ($p < 0.05$) to 40 nm. This is in agreement with the studies previously performed by Bannow et al. (2020) showing a slight, but significant, increase in the droplet size for drug loadings above the S_{eq} [41].

For the SNEDDS$_{FCC}$, both 80%-SNEDDS$_{FCC}$ and 200%-SNEDDS$_{FCC}$ dispersions had a turbid appearance due to undissolved FCC, hence the dispersions were centrifuged to obtain a clear supernatant prior to DLS analysis. The 80%-SNEDDS$_{FCC}$ and 200%-SNEDDS$_{FCC}$ exhibited a droplet size in the range of 30-35 nm and 40-50 nm, respectively indicating the formation of nano-sized emulsions. Additionally, no statistical difference ($p > 0.05$) in the droplet sizes amongst the three solidification ratios (2.5:1, 3.0:1, and 3.5:1) (w/w) was observed. The PDI for 80%-SNEDDS$_{FCC}$ and 200%-SNEDDS$_{FCC}$ was found to be approximately 0.1 and 0.2 respectively, resulting in similar monodisperse systems as observed for the respective SNEDDS$_{liquid}$ (Figure 5 (A)). Overall, the SNEDDS$_{liquid}$ were released from FCC and rapidly dispersed in purified water, demonstrating the ability of SNEDDS$_{FCC}$ to form nano-sized emulsions.

To further investigate the effect of the presence of dissolved FCC during the emulsification process on the resulting droplet size and PDI, the dispersion medium was changed from water to HCl solution (0.2M, pH 1.6). All SNEDDS$_{liquid}$ and SNEDDS$_{FCC}$ emulsified completely within 1 min and 5 min respectively and had a translucent appearance. The droplet size for SNEDDS$_{liquid}$ was found to be in the range of 30-40 nm (Figure 5 (B)) similar to the results obtained for the dispersion in purified water. However, for all SNEDD$_{FCC}$ the presence of dissolved FCC increased the droplet size of the emulsions to 100-120 nm and the PDI to 0.3-0.35. Blank-SNEDDS$_{FCC}$, 80%-SNEDDS$_{FCC}$ and 200%-SNEDDS$_{FCC}$ thus showed a significant increase ($p < 0.05$) in droplet sizes when compared to their respective liquid counterparts. Additionally, a PDI of 0.3-0.35 indicated the generation of a polydisperse system compared to the monodisperse systems observed under neutral conditions in purified water. However, no statistical difference ($p > 0.05$) in the droplet sizes was observed amongst the three solidification ratios (2.5:1, 3.0:1, and 3.5:1 (w/w)) further confirming no significant impact of the amount of FCC present in the formulations on self-emulsifying properties (in contrast to the above discussed influence on physical stability). However, dispersion of SNEDDS$_{FCC}$ resulted in droplet sizes in the range of 100-120 nm, indicating that the droplet size is still in the nanoemulsion range and solidification with FCC enabled the formation of a nano-sized emulsion.

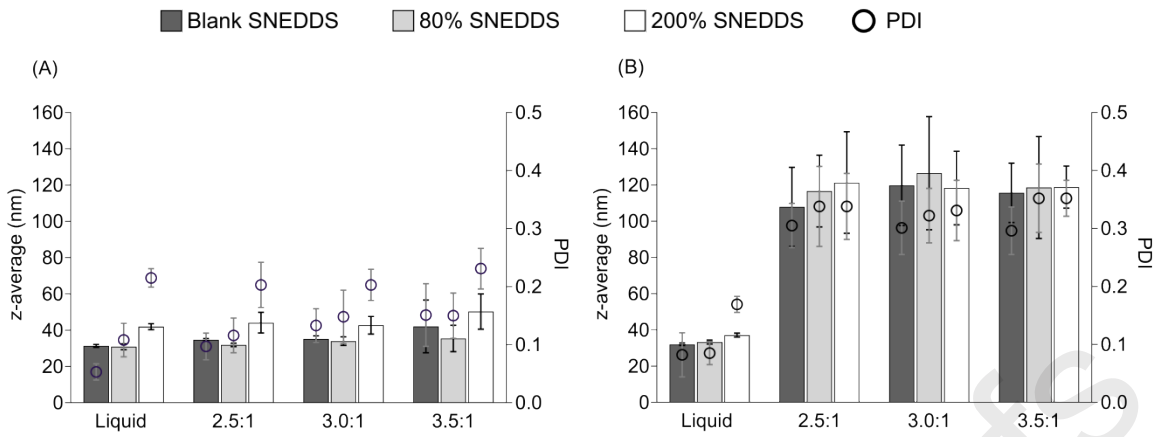


Figure 5: Droplet size *(columns)* and PDI *(circles)* measured after dispersion of 100 mg of formulation at 37 °C in 100 mL of (A) Purified water and (B) HCl solution (0.2M, pH 1.6). The data is grouped according to CRV drug load, starting from $SNEDDS_{liquid}$ to $SNEDDS_{FCC}$ according to the solidification ratio (2.5:1, 3.0:1, and 3.5:1 (w/w)), from left: blank SNEDDS *(dark grey columns)*, center: 80%-SNEDDS *(light grey columns)* and right: 200%-SNEDDS *(white columns)*. Results are represented as mean ± SD (n=9).

Drug release upon dispersion

As mentioned earlier, incomplete release of drug from formulations containing Neusilin® as the solid carrier is a concern during the development of solidified LBF [20]. Complete drug release may be obtained initially in freshly prepared formulations; however, the drug release was found to be reduced to less than 5% for SEDDS absorbed on neat Neusilin® after 60 days of storage [15].

The term 'dispersion test' rather than 'dissolution test' is used in this study since CRV was released from FCC along with the $SNEDDS_{liquid}$ and then dispersed in the media as part of a nanoemulsion. The $SNEDDS_{FCC}$ and their respective $SNEDDS_{liquid}$ were freshly produced before the dispersion studies.

A fixed dose of 3.76 mg of CRV was added to the dissolution vessel resulting in varying amounts of total formulation dosed based on their drug load. The dispersion test was carried out in tap water (pH 7.5) to compare the drug release performance of $SNEDDS_{FCC}$ with their respective $SNEDDS_{liquid}$ and crystalline CRV. Due to FCC's poor solubility in tap water (pH 7.5), the employed set-up investigates the degree of release of the drug-loaded $SNEDDS_{liquid}$ from the FCC carrier. Furthermore, the dispersion tests were carried out in order to demonstrate the solubility advantage of pre-dissolved CRV in SNEDDS against the solubility of crystalline CRV at neutral pH, since CRV has a pH-dependent solubility and shows fast and complete release at acidic pH [42].

As shown in Figure 6, crystalline CRV exhibited a slow and incomplete dissolution, resulting in a drug dissolution of about 15% of the dosed amount of crystalline CRV after 60 min. The $SNEDDS_{liquid}$ and both $SNEDDS_{FCC}$ with drug loading at their corresponding different solidification ratios (2.5:1, 3.0:1, and 3.5:1 (w/w)) showed an enhanced rate and extent of drug release compared to crystalline CRV. Both $SNEDDS_{liquid}$ and $SNEDDS_{FCC}$ demonstrated the same immediate release kinetics, reaching a plateau of maximum concentration within the first 5 min of the dispersion with no precipitation after 60 min.

However, when compared to the respective $SNEDDS_{liquid}$, the $SNEDDS_{FCC}$ were not able to reach the same extent of drug release. A possible reason for this could be residual $SNEDDS_{liquid}$ being trapped inside the pores of FCC and thus not being available during the dispersion process. The total drug release for 80%-$SNEDDS_{liquid}$ by the end of 60 min was 90%. However, 80%-2.5-$SNEDDS_{FCC}$ showed a release of 80% in 5 min, while only 70% of drug was released from 80%-3.0-$SNEDDS_{FCC}$ and 80%-

3.5-SNEDDS$_{FCC}$ within the same period of time (Figure 6 (A)). These observations suggest that the amount of FCC present in the formulation plays an important role in governing the drug release behavior.

The 200%-SNEDDS$_{liquid}$ showed a total drug release of 90% after 5 min, which was maintained over the complete test duration. All 200%-SNEDDS$_{FCC}$ showed a drug release of more than 80% after 5 min and this level was again maintained for the rest of the study (60 min). No difference in drug release behavior was observed among the formulations at the three solidification ratios (Figure 6 (B)).

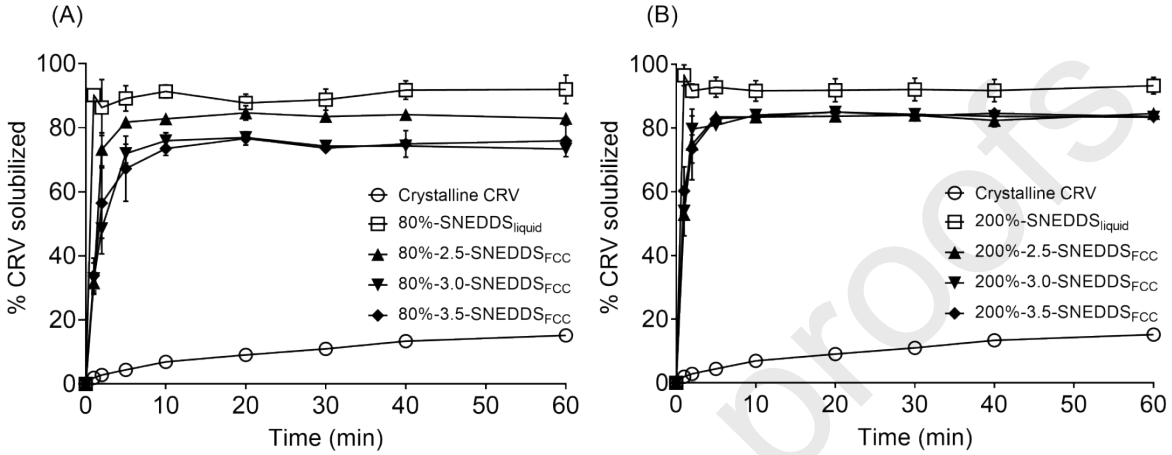


Figure 6. (A) Dispersion profiles of freshly prepared 80%-SNEDDS$_{FCC}$, 80%-SNEDDS$_{liquid}$ and dissolution profile of crystalline CRV (all samples dosed at 3.76 mg of CRV). (B) Dispersion profiles of freshly prepared 200%-SNEDDS$_{FCC}$, 200%-SNEDDS$_{liquid}$ and dissolution profile of crystalline CRV (all samples dosed at 3.76 mg of CRV). Tests were carried out in 100 mL tap water (pH 7.5, 37 °C) stirred at 100 rpm. Results are represented as mean ± SD (n=3).

Figure 7 shows the extent of drug release during 60 min of dispersion testing for 80%-SNEDDS$_{FCC}$ and 200%-SNEDDS$_{FCC}$ after storage under dry conditions at 25 °C for up to 8 weeks, compared to the drug release observed from freshly prepared samples (week 0). All investigated SNEDDS$_{FCC}$ formulations showed no significant differences in drug release over a period of 8 weeks of storage ($p > 0.05$). Drug release from all investigated formulations reached a plateau of maximum concentration within 5 min of dispersion irrespective of the storage period. Even after 8 weeks of storage, the SNEDDS$_{FCC}$ rapidly releases the SNEDDS$_{liquid}$ upon contact with the dissolution media and showed spontaneous emulsification.

As discussed above, 200%-2.5-SNEDDS$_{FCC}$ showed an onset of CRV recrystallization after 3 weeks of storage, which was assumed to influence the *in vitro* drug release behavior. However, the dispersion profiles indicated no changes in the total amount of CRV released even after 8 weeks of storage. Based on the LOD of the employed DSC method, the amount of recrystallized CRV after 3 weeks of storage was estimated to be around 0.08% (w/w) CRV of the total drug amount present (i.e. for 200%-2.5-SNEDDS$_{FCC}$ approximately 0.08% (w/w) of 2.6% (w/w) CRV), which was not sufficient to have an effect on the resulting *in vitro* drug release performance of the supersaturated SNEDDS$_{FCC}$.

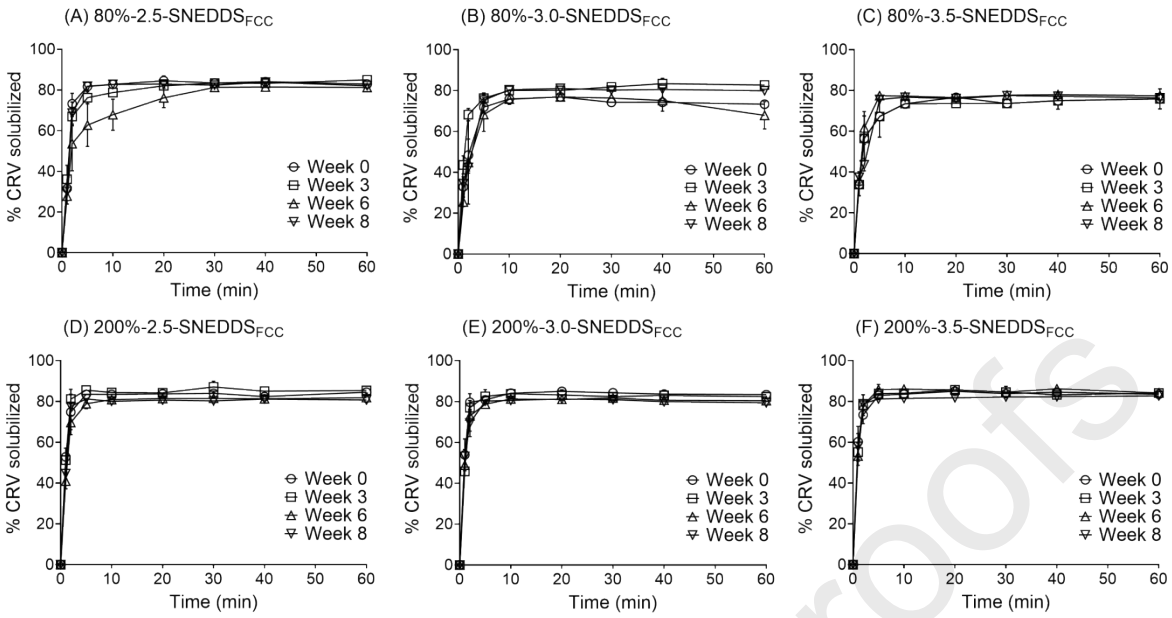


Figure 7. Dispersion profiles of (A) 80%-2.5-SNEDDS$_{FCC}$; (B) 80%-3.0-SNEDDS$_{FCC}$; (C) 80%-3.5-SNEDDS$_{FCC}$; (D) 200%-2.5-SNEDDS$_{FCC}$; (E) 200%-3.0-SNEDDS$_{FCC}$ and (F) 200%-3.5-SNEDDS$_{FCC}$ of freshly prepared samples (week 0) and after storage under dry conditions at 25 °C for 3, 6 and 8 weeks. The formulations were dosed at 3.76 mg of CRV in 100 mL of tap water (pH 7.5, 37 °C) stirred at 100 rpm. Results are represented as mean ± SD (n=3).

Conclusion

In this study, FCC was successfully loaded with conventional SNEDDS$_{liquid}$ and super-SNEDDS$_{liquid}$ via physical adsorption generating free-flowing powders (SNEDDS$_{FCC}$) with drug loadings ranging from 0.8% to 2.6% (w/w) of CRV. FCC stabilized the supersaturated CRV concentrations in the 200%-3.0-SNEDDS$_{FCC}$ and 200%-3.5-SNEDDS$_{FCC}$ over a storage period of 10 weeks (25 °C at dry conditions), compared to the observed precipitation of CRV after 6 days of storage in 200%-SNEDDS$_{liquid}$. Both the SNEDDS$_{FCC}$ achieved an increased *in vitro* drug release compared to pure crystalline CRV, however slightly less than their liquid counterparts, indicating that residual SNEDDS$_{liquid}$ might be trapped in the pores of FCC. FCC as a solid carrier stabilized the supersaturated solidified SNEDDS and demonstrated the same rate and extent of drug release as freshly prepared samples even after 8 weeks of storage. The thermodynamic instability of supersaturated LBF, resulting in the precipitation of drug during storage, has hindered a more widespread application of super-SNEDDS$_{liquid}$ in the field of oral drug delivery. However, the results of the current study indicate that loading super-SNEDDS$_{liquid}$ on FCC can greatly improve their physical stability.

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