Kayyali Chair for Pharmaceutical Industries[1], Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh, Kingdom of Saudi Arabia; Abbott Healthcare Products B.V[2], Weesp, The Netherlands; Department of Industrial Pharmacy[3], College of Pharmacy, Assiut University, Assiut, Egypt

Solidification of cinnarizine self-nanoemulsifying drug delivery systems by fluid bed coating: optimization of the process and formulation variables

A. Abdul-Wahhab Shahba[1,*], A. Riaz Ahmed[1,2], K. Mohsin[1], S. Ibrahim Abdel-Rahman[3], F. Kaed Alanazi[1]

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**Corresponding author: Ahmad Abdul-Wahhab Shahba, B.Pharm., M.Sc., Kayyali Chair for Pharmaceutical Industries, Department of Pharmaceutics, POBOX-2457, College of Pharmacy, King Saud University, Riyadh - 11451, Kingdom of Saudi Arabia*
shahba@ksu.edu.sa

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Self-nanoemulsifying drug delivery systems (SNEDDS) offer an efficient choice to improve the poor dissolution and erratic bioavailability of poorly-water soluble drugs. However, liquid SNEDDS experience some manufacturing and stability limitations. To overcome these limitations, the current study aims to investigate and optimize the solidification of cinnarizine (CN) liquid SNEDDS onto pellets by fluid bed coating. The study involved optimization of process and formulation variables. The coated self-nanoemulsifying pellets (SNEP) were characterized, their droplet size and dissolution profiles were compared to the corresponding liquid SNEDDS. Higher spray/microclimate air pressure led to minimal agglomeration and minimal spray drying. However, slight increase in inlet air volume above 35 m^3/h led to extensive spray drying. The optimized coating formula included oleic acid/Imwitor308/Cremophor El (25/25/50) as liquid SNEDDS, HPMC E3 as coating polymer and Plasacryl™T20 as anti-tacking agent. The optimum concentration of coating solution was 15% and optimum SNEDDS proportion in the coating layer was 40%. The droplet size of reconstituted SNEP was significantly ($p < 0.05$) higher than liquid SNEDDS, yet the SNEP aqueous dispersion was still within the nano-metric scale. Pure CN showed sharp precipitation upon shifting the media from pH 1.2 to 6.8. In contrast, Both SNEP and liquid SNEDDS maintained >85% CN in solution, even at pH 6.8. Therefore, CN-SNEP seems to be an excellent dosage form that maintains the solubilization benefits of liquid SNEDDS, overcomes their limitations along with the additional benefits of solid dosage form.

1. Introduction

Self-nanoemulsifying drug delivery systems (SNEDDS) have gained a lot of interest as excellent option for oral formulation of poorly-water soluble drugs (Date et al. 2010; Shahba et al. 2012a; Tang et al. 2008). Upon aqueous dilution in GI fluids, followed by mild agitation, SNEDDS spontaneously form an O/W nano-emulsion, introducing the drug in solubilized form ready for absorption (Gursoy and Benita 2004). Accordingly, SNEDDS possess unmatched potential in improving the rate, extent of absorption and reproducibility of plasma-time profiles (Singh et al. 2009). However, being liquid in nature, these systems need to be incorporated in soft or hard capsules. This might be associated with some limitations such as capsule aging, drug precipitation during fabrication and storage, formulation leakage and high production costs (Lei et al. 2011; Wang et al. 2010). Furthermore, some drugs may undergo chemical degradation in presence of lipids and related excipients (Gumaste et al. 2013). To overcome these limitations, the liquid SNEDDS could be transformed into a solid dosage form. Solid SNEDDS could retain all the advantages of liquid SNEDDS, including improved aqueous solubility and bioavailability, beside those of solid dosage forms, e.g. higher stability, more accurate dosing, better patient compliance and reduced production cost (Gupta et al. 2013). Most importantly, solid SNEDDS are very flexible to produce various dosage forms (Tang et al. 2008) such as self-nanoemulsifying tablets (Nazzal et al. 2002; Wei et al. 2007), solid dispersions (Vasanthavada and Serajuddin 2007), multiparticulate beads (Patil and Paradkar 2006) and pellets (Franceschinis et al. 2011). Therefore, solid SNEDDS have been extensively explored, in recent years, as effective alternatives to conventional liquid SNEDDS (Gupta et al. 2013).

The main techniques for converting liquid SNEDDS into solid form (Gupta et al. 2013) include lyophilization (Bamba et al. 1995), spray drying (Balakrishnan et al. 2009; Kallakunta et al. 2012), adsorption onto solid carriers (Ito et al. 2005), melt granulation (Seo et al. 2003), melt extrusion/spheronization (Iosio et al. 2011) and fluid bed coating (Lei et al. 2011). Among solid SNEDDS carriers, there has been emerging interest in multiparticulate pellet formulations due to their alluring properties. Pellets offer flexibility in dose dividing, reproducible drug plasma levels and hence improvement in efficacy/safety profile (Hoang Thi et al. 2015; Lei et al. 2011). Due to their small size and the hydrodynamics of GIT, pellets are able to leave the stomach continuously, even if the pylorus is partially closed. Therefore, their gastric emptying rate is more predictable and they are less likely to present dose dumping (Amrutkar et al. 2012; El-Malah and Nazzal 2008; Vervaeck et al. 2013). Fluid bed coating was recently introduced as an efficient technique to prepare solid self-nanoemulsifying pellets (SNEP). This technique is based on removing the solvent from the bulk coating solution, while the solid excipients simultaneously precipitate on the surface of non-pareil sugar cores (Lei et al. 2011). In fact, using this technique for SNEDDS solidification is very challenging due to the agglomeration tendency, stickiness and incomplete solidification experienced by liquid SNEDDS. On optimization, however, fluid bed coating could produce free-flowing, well-separated pellets with excellent content uniformity and high yield.

The current study aims to investigate the solidification of liquid SNEDDS by fluid bed coating using cinnarizine (CN) as model drug. CN is an anti-histaminic and calcium channel blocker with a very low aqueous solubility (< 1 µg/ml) (Raghuvanshi and Pathak 2014; Shahba et al. 2012a). Recent studies (Larsen et al. 2012; Shahba et al. 2012a) have presented efficient liquid CN-SNEDDS with enhanced aqueous solubility and pH-independent dissolution that maintained

high percentage of CN in solution at both pH 1.2 and 6.8. However, such formulations experienced sharp discoloration upon storage. The observed poor physical stability was explained by the oxidation of formulation lipid portion (Shahba et al. 2012b). Also, CN showed considerable degradation in liquid SNEDDS and particularly, in oils (Shahba et al. 2012b; Shi et al. 2009). Solidification of CN-SNEDDS, by fluid bed coating, would be a novel approach because it could overcome the liquid SNEDDS limitations, enhance its physical stability and decrease CN degradation. The novelty of the current study arises from combining the advantages of liquid SNEDDS and multiparticulate pellets in one dosage form. However, solidification of liquid SNEDDS by fluid bed coating is quite challenging and, hence, scarce articles have explored utilization of fluid bed coating for SNEDDS solidification (Lei et al. 2011; Mukherjee and Plakogiannis 2012). This could be due to the agglomeration tendency and stickiness experienced by liquid SNEDDS during their fluid bed coating. In the current study, comprehensive process and formulation optimization has been carried out to achieve efficient SNEDDS solidification with minimal pellet agglomeration as well as minimal spray drying. Further, comparative studies were conducted to evaluate the performance of CN-SNEP versus their liquid counterparts.

2. Investigations, results and discussion

Solidification of SNEDDS by fluid bed coating is not a simple process since many variables must be optimized to achieve successful coating. Moreover, the oily nature of liquid SNEDDS turns its coating and solidification, by fluid bed, very challenging. In this work, process and formulation variables were optimized to achieve solidification of SNEDDS on top of non-pareil spheres. On optimization, free-flowing SNEDDS coated pellets were obtained. The optimized pellets exhibited minimal agglomeration, minimal spray drying and high yield.

2.1. Optimization of SNEP

2.1.1. Process variables

It was desirable to achieve the highest possible spray rate with no negative influence on pellet agglomeration. Spray rate had to be raised gradually accompanied with relevant rise in spray air pressure (SAP), microclimate air pressure (MAP), inlet air temperature and inlet air volume. Indeed, both SAP/MAP had a vital role in the atomization of the coating solution as well as protecting the product from spray drying. Increasing the SAP/MAP efficiently reduced the pellet agglomeration without causing spray drying. During spraying, SAP/MAP could be set upto (1.2/0.6) or (1.4/0.7) bar. However, special caution need to be paid to the inlet air volume. Increasing its value slightly more than 35 m^3/h often led to extensive spray drying. It was optimum to maintain the inlet air volume at (30-35 m^3/h) to ensure efficient pellet fluidization as well as minimal spray drying. Product temperature was optimized to ensure efficient film formation without causing spray drying. Optimum product temperature varied from 40 to 52.5 ºC depending on each formulation characteristics.

2.1.2. Formulation variables

It is worth mentioning that, for ensuring accurate optimization of formulation variables, one variable was changed at a time while the remaining variables were kept constant.

2.1.2.1. Type of coating polymer

The study involved screening two coating polymers; PVP K30 and HPMC E3. Preliminary results showed that PVP K30 produced very tacky pellets with several agglomerations that tend to co-agglomerate upon storage (Fig. 1A). This could be due to the hygroscopic nature of PVP K30 (Bühler 2008). In contrast, an earlier study (Lei et al. 2011) presented satisfactory coating outcomes upon using PVP K30 for SNEDDS coating. This might be because the latter study operated under low spray rate values and utilized different SNEDDS components. Moreover, Lei et al revealed that these PVP coated pellets couldn`t maintain their satisfactory outcomes within humid storage conditions (Lei et al. 2012). The PVP coated pellets exhibited significant agglomeration and moisture absorption, upon storage (Lei et al. 2012). On the other hand, HPMC E3 produced non-tacky, fully solidified pellets with much less agglomeration (Fig. 1B and C). Thus, HPMC E3 was further used as the standard coating polymer in the current study.

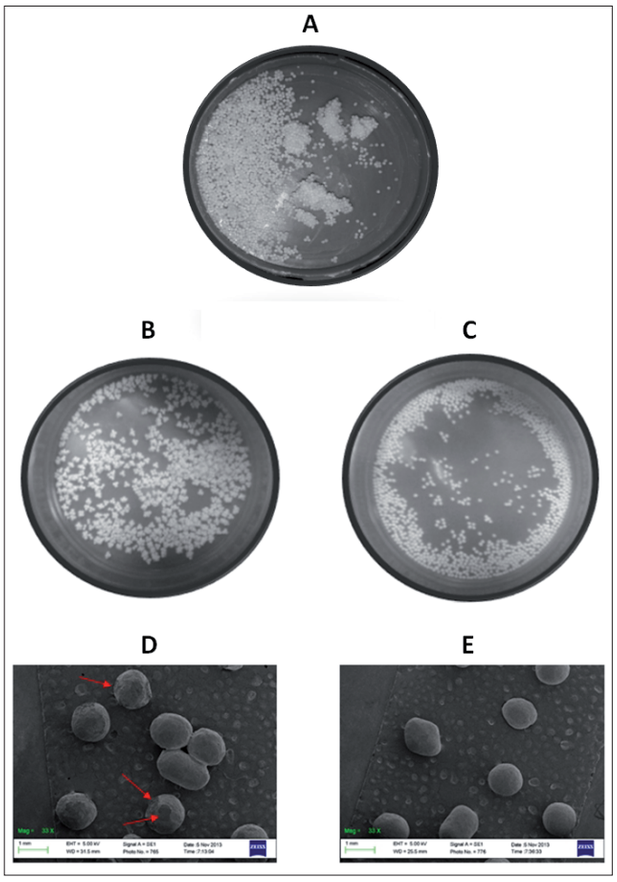

Fig. 1: Effect of coating polymer type and liquid SNEDDS composition on pellet agglomeration. (A), (B) and (C) represent digital imaging of SNEP prepared using PVP K30, HPMC (F1) and HPMC (F2), respectively. (D) and (E) represent SEM of SNEP prepared using HPMC (F1) and HPMC (F2), respectively. Arrows point to ruptured coat due to detachment of agglomerated pellets.

2.1.2.2. Liquid SNEDDS composition

SNEDDS composition could play an important role in the coating process-ability. Some SNEDDS excipients might increase/decrease the agglomeration tendency between the pellets. To optimize excipients which are suitable for SNEDDS layering, two liquid SNEDDS (M812/I308/T85) and (OL/I308/Cr-El) were investigated as shown in F1 and F2, respectively (Table 1). Both F1 and F2 presented excellent drug loading efficiency and coating recovery (CR)%. F1 required less product temperature and less process time compared to F2. However, F2 offered two critical advantages. This formulation presented ≈100% higher CN loading (80 mg/g in SNEDDS and 10.7 mg/g in pellets). This is certainly due to the superior CN solubility in OL (Tokumura et al. 1987). Moreover, F2 produced dry non-sticky pellets with minor agglomeration (99% mono-pellets), while F1 produced excessive duplicates and triplicates (34% mono-pellets) (Table 1, Fig. 1B and C). This was also evident in scanning electron microscopy (SEM) where F2 produced smooth mono-pellets without signs of previous agglomeration, while F1 showed triplicated pellets and mono-pellets with history of agglomeration (Fig. 1D and E). Based on previous data, OL/I308/Cr-El (25/25/50) was selected as the optimum SNEDDS for the current study.

Table 1: Formulation, process variables and characterization of F1-F3 formulations

	Formulation No.	F1	F2	F3
Formulation variables	Liquid SNEDDS	M812/I308/T85 (25/25/50)	OL/I308/Cr-El (25/25/50)	OL/I308/Cr-El (25/25/50)
	CN loading in SNEDDS [a] (mg/g)	40	80	80
	Coating solution composition	SNEDDS/HPMC/ Talc (40/40/20)	SNEDDS/HPMC/ Talc (40/40/20)	SNEDDS/HPMC/ Plasacryl (40/54.5/5.5)
	CN loading into final pellet [b] (mg/g)	5.3	10.7	10.7
	Concentration of the coating solution (%)	22%	22%	20%
	CWG (%)	50%	50%	50%
Process variables	Inlet temp. (ºC)	40-50	50-60	60-63
	Product temp. (ºC)	38-43	41-52.5	50-52.5
	Process time (h)	4.5	12.5	7.5
Characterization	CR (%)	94%	92%	93%
	Drug loading efficiency (%)	96%	98%	98%
	Mono pellets(%) [c]	34%	99%	90-92%

SNEDDS denotes: self-nanoemulsifying drug delivery systems, CWG: coating weight gain, CR: coating recovery, M812: miglyol 812, I308: Imwitor308, T85: tween 85, OL: oleic acid and Cr-El: cremophor El.
[a] CN loading in SNEDDS reflects drug concentration in liquid SNEDDS equal to ≈90% of equilibrium solubility.
[b] CN loading into final pellet was theoretically calculated assuming that CWG =50%.
[c] Mono-pellets (%) was calculated based on measuring % of pellets passing through 1.25 mm sieve.

2.1.2.3. Type of anti-tacking agent

The use of anti-tacking in the coating process is very crucial because it would efficiently decrease the agglomeration of the pellets. Talc is one of the most common anti-tacking agents and it was used as 50% based on dry polymer weight (Liu et al. 2009). Plasacryl™T20 is a relatively new anti-tacking agent (containing plasticizer) and it was used as 10% based on dry polymer weight (Ammar et al. 2016). Both talc-based (F2) and Plasacryl-based (F3) formulations exhibited high CR, drug loading efficiency and mono- pellets % (Table 1). F3 showed less process time compared to F2. Most importantly, F3 showed significantly ($p < 0.05$) higher dissolution compared with F2 (Fig. 2A). F3 was able to release > 96% CN in the acidic media compared with only 88% in case of F2. The lower dissolution in case of using talc might be due to the adsorption of some CN particles onto the surface of talc which hinders their dissolution. This explanation is supported by previous surface chemistry studies (Wallqvist et al. 2009) which have confirmed the interaction between talc and hydrophobic particles by bubble-induced attractive forces. Further, a follow-up study was conducted to investigate the influence of CN loading and talc presence on CN dissolution (Fig. 2B). The study revealed that decreasing CN loading (in SNEDDS) from 80 to 40 mg/g did not overcome the incomplete CN dissolution. On the other hand, formulation lacking talc showed significantly ($p < 0.05$) higher dissolution compared to formulations containing talc. Previous studies suggested that 10-15% of CN was adsorbed onto talc and hence CN was not completely released into solution. Therefore, Plasacryl™T20 was selected as the standard anti-tacking agent for CN-SNEDDS coating.

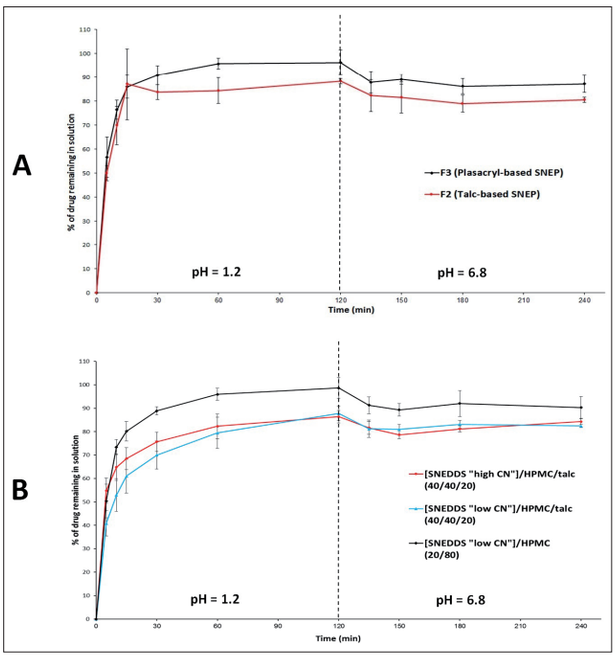

Fig. 2: Effect of anti-tacking agent on CN dissolution where (A) represents dissolution profile of CN from F2 (talc-based) and F3 (PlasacrylT20-based) SNEP and (B) Dissolution profile of CN from spray dried solidified SNEDDS. SNEP denotes: self-nanoemulsifying pellets, SNEDDS: self-nanoemulsifying drug delivery systems, SNEDDS "high CN": comprise 80 mg/g CN and SNEDDS "low CN": comprise 40mg/g CN. Liquid SNEDDS composition was fixed to OL/I308/Cr-El (25/25/50). Data are expressed as mean ± SD, n =3-6.

2.1.2.4. Proportion of SNEDDS in the coating layer

This parameter is very important for formulators, since it directly affects the drug loading level in the final coated pellets. The higher the proportion of SNEDDS in the coating layer, the higher the drug loading in coated pellet. The current study investigated F4, F5 and F6 formulations representing SNEDDS proportions 20%, 40% and 60%, respectively (Table 2). The study aimed to select the highest SNEDDS proportion giving adequate coating characteristics. All the formulations showed excellent CR%. However, due to its high SNEDDS proportion, F6 produced very sticky pellets with oily texture and incomplete solidification (Table 2). The latter has been confirmed by SEM where several pores are spreading in the coating layer (Fig. 3C,D). In contrast, both F4 and F5 produced dry and

Table 2: Formulation, process variables and characterization of F4-F6 formulations

	Formulation No.	F4	F5	F6
Formulation variables	Liquid SNEDDS	OL/I308/Cr-El (25/25/50)	OL/I308/Cr-El (25/25/50)	OL/I308/Cr-El (25/25/50)
	Coating solution composition	SNEDDS/HPMC/ Plasacryl (**20**/72.7/7.3)	SNEDDS/HPMC/ Plasacryl (**40**/54.5/5.5)	SNEDDS/HPMC/ Plasacryl (**60**/36.4/3.6)
	CN loading into final pellet [a] (mg/g)	5.33	10.66	16
	Concentration of the coating solution (%)	10%	10%	10%
Process variables	Inlet temp. (ºC)	55-75	55-69.5	53-76
	Product temp. (ºC)	42-52	50-52.5	41-52
Characterization	CR (%)	94%	90%	95.5%
	Mono pellets (%) [b]	94%	86-88%	84%
	Texture	Dry	Dry	Oily

SNEDDS denotes: self-nanoemulsifying drug delivery systems, CR: coating recovery, M812: miglyol 812, I308: Imwitor308, T85: tween 85, OL: oleic acid and Cr-El: cremophor El.
[a] CN loading into final pellet was theoretically calculated assuming that CWG =50% and CN loading in SNEDDS =80 mg/g.
[b] Mono-pellets (%) was calculated based on measuring % of pellets passing through 1.25 mm sieve.

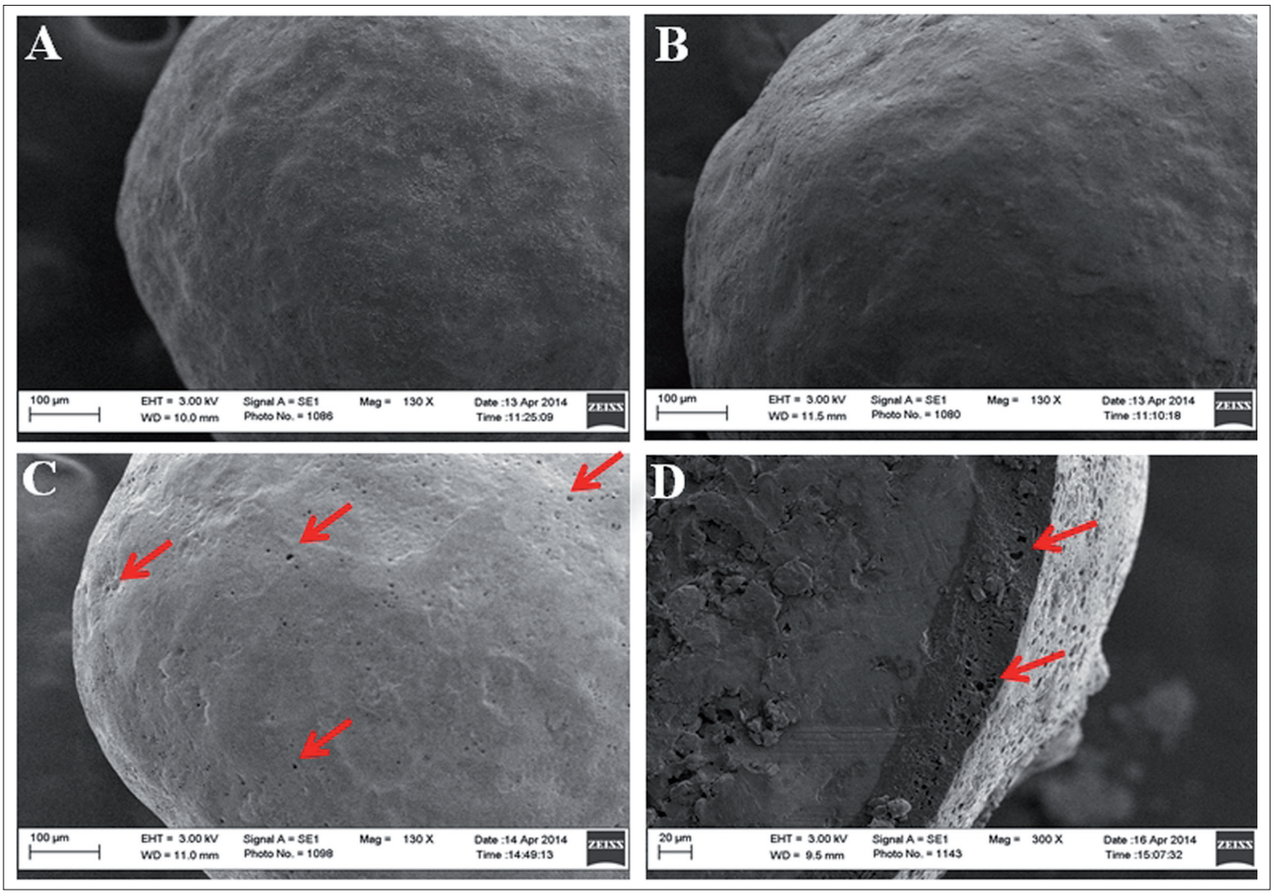

Fig. 3: SEM images showing (A) outer surface of F4 (20% SNEDDS), (B) F5 (40% SNEDDS), (C) F6 (60% SNEDDS) and (D) cross-section of F6 (60% SNEDDS). Arrows indicate pores in the coating layer.

fully solidified pellets with non-porous coating layer (Table 2, Fig. 3A,B). F4 (20% SNEDDS) presented relatively higher CR% and mono-pellets%. However, F5 (40% SNEDDS) was selected as the optimum SNEDDS proportion because it provides 100% higher drug loading (into pellets) compared to F4 (Table 2). These findings are in agreement with previous studies (Lei et al. 2011) that achieved successful SNEDDS coating upon loading a maximum of 40% liquid SNEDDS in the coating layer.

2.1.2.5. *Concentration of the coating solution*

Formulators usually prefer to use high concentration of coating solution to decrease the process time and save energy required for solvent removal. However, attention need to be paid keeping the solution with adequate viscosity to avoid nozzle blockage or intermittence of the coating solution flow. The current study investigated three levels of coating solution concentrations; 10, 15 and 20% represented by F5, F7 and F3, respectively (Table 3). Upon solidification, the three formulations would have the same coating layer composition, hence similar dissolution profiles, droplet size and reconstitution properties would be expected. Moreover, the three formulations showed excellent CR%. However, with respect to coating process-ability, F3 (20% coating solution) exhibited frequent nozzle blockage. This finding is matching with previous studies that showed increased clogging tendency upon rising HPMC concentration in solution (Sangalli et al. 2004). This could be related to the sharp increase of solution viscosity upon increasing the HPMC concentration in solution (Kokubo and Obara 2008). On the other hand, Both F5 (10% coating solution) and F7 (15% coating solution) presented flexible and shorter coating process without any nozzle blockage. Furthermore, F7 showed superior mono-pellets(%) and hence the optimum concentration of coating solution was considered 15%.

In the current study, it is worth mentioning that the process time decreased upon decreasing the solution concentration. This is opposing expectation from previous data, since less solution concentration would require high amount of solution to be sprayed and hence longer process time (Sangalli et al. 2004). However, in the current study, the spray rate enhancement (upon decreasing solution concentration) was high enough to overcome the time required for excess solvent removal (Table 3).

2.1.3. *Optimized formula for CN-SNEP*

According to the study findings, the optimized formula for CN-SNEDDS solidification is suggested to be:

1. Type of coating polymer: HPMC E3
2. Liquid SNEDDS composition: OL/I308/Cr-El (25/25/50)
3. Type of anti-tacking agent: PlasacrylTM T20.
4. Proportion of SNEDDS in the coating layer: 40%
5. Concentration of the coating solution: 15%

The optimized CN-SNEP were free flowing, completely solidified with minor agglomeration. Further, they could present high CR% and reasonable process time.

2.2. *Differential scanning calorimetry (DSC) and x-ray diffraction (XRD)*

The DSC study showed that pure CN exhibited a sharp endothermic peak at 125 ºC (Fig. 4). This peak is corresponding to the reported melting point (Abouelatta et al. 2015) and confirms the crystalline state of pure CN. In contrast, CN peak completely disappeared in case of CN-loaded solid SNEDDS suggesting the absence of CN crystallinity (Tian et al. 2013). This finding is in agreement with XRD results (Fig. 5) in which the crystalline pure CN exhibited typical X-ray diffraction peaks at 3° to 30° (2θ). The (3/97) physical mixture showed few diffraction peaks corresponding to crystalline CN, with low intensity due to the low CN concentration in the mixture. Subsequent physical mixture with higher CN ratio (50/50) showed well defined CN diffraction peaks. In contrast, the CN-loaded solid SNEDDS presented complete absence of CN diffraction peaks. The above-mentioned data confirm that CN did not exist in crystalline form, within solid SNEDDS, which ensures that the solidification process would not cause drug precipitation (Lei et al. 2011; Tian et al. 2013).

2.3. *Morphology of SNEP*

The average diameter for uncoated non-pareil spheres was 974±8 µm while SNEP (50% CWG) showed considerable growth to reach an average diameter of 1082±5 µm. SEM images showed comparable results (Fig. 6A) and the high magnification view showed a layer of tightly coated SNEDDS around the core, with ≈77 µm thickness (Fig. 6B).

Table 3: Formulation, process variables and characterization of F3, F5 and F7 formulations

	Formulation No.	F3	F5	F7
Formulation variables	Liquid SNEDDS	OL/I308/Cr-El (25/25/50)	OL/I308/Cr-El (25/25/50)	OL/I308/Cr-El (25/25/50)
	Coating excipients composition	SNEDDS/HPMC/ Plasacryl (40/54.5/5.5)	SNEDDS/HPMC/ Plasacryl (40/54.5/5.5)	SNEDDS/HPMC/ Plasacryl (40/54.5/5.5)
	CN loading into final pellet[a] (mg/g)	10.66	10.66	10.66
	Concentration of the coating solution (%)	20%	10%	15%
	CWG (%)	50%	50%	50%
Process variables	Inlet temp. (ºC)	60-63	55-69.5	58-65
	Product temp. (ºC)	50-52.5	50-52.5	50-52
	Spray rate[b](g/min)	0.8-2.6	2.1-4.5	1.1-3.1
	Process time (h)	7.5	5.0	6.5
Characterization	CR (%)	93%	90%	92%
	Mono pellets(%)[c]	90-92%	86-88%	97%
	Nozzle blockage	Yes	No	No

SNEDDS denotes: self-nanoemulsifying drug delivery systems, CWG: coating weight gain, CR: coating recovery, M812: miglyol 812, I308: Imwitor308, T85: tween 85, OL: oleic acid and Cr-El: cremophor El.
[a] CN loading into final pellet was theoretically calculated assuming that CWG =50% and CN loading in SNEDDS =80 mg/g.
[b] Spray rate was gradually increased to achieve the maximum possible rate without causing significant agglomeration or disturbing pellet fluidization.
[c] Mono-pellets (%) was calculated based on measuring % of pellets passing through 1.25 mm sieve.

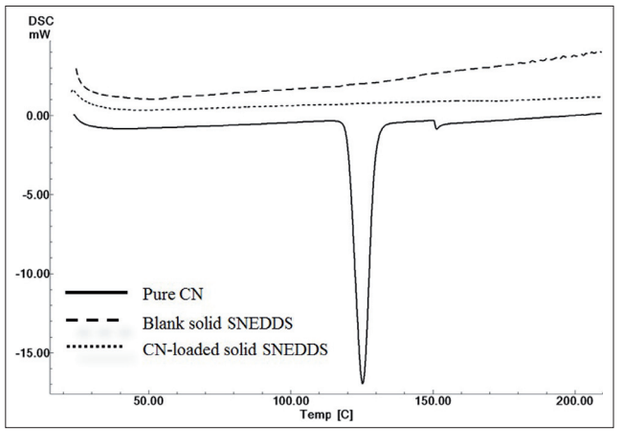

Fig. 4: DSC of pure CN, blank solid SNEDDS and CN-loaded solid SNEDDS. CN denotes: cinnarizine and SNEDDS: self-nanoemulsifying drug delivery systems.

2.4. SNEP vs. liquid SNEDDS

It was critical to investigate whether the solidification process could cause any negative influence on SNEDDS performance including reconstitution properties, droplet size and *in-vitro* dissolution.

2.4.1. Reconstitution properties and droplet size analysis

The SNEP (represented by F3) were readily dispersed in distilled water. The resulting aqueous dispersion was slightly turbid while the corresponding liquid SNEDDS (OL/I308/Cr-EL [25/25/50]) produced bluish aqueous dispersion. The droplet size of the reconstituted nanoemulsions (from SNEP) was 118±23.9 nm, which was significantly (P <0.05) higher than the droplet size (22±1.5 nm) of dispersed liquid SNEDDS. The significant increase in droplet size might be arising from the coating excipients (especially the anti-tacking agent). Most importantly, the SNEP aqueous dispersion was still within the nano-metric scale (20-200 nm) (Date et al. 2010).

2.4.2. *In-vitro* dissolution studies

In contrast to droplet size variation, the dissolution of SNEP (represented by F3) and liquid SNEDDS were comparable (Fig. 7). Both formulations exhibited superior (P < 0.05) dissolution compared to pure CN at pH 1.2 and pH 6.8. Upon shifting to pH 6.8, pure CN showed sharp precipitation while both SNEP and liquid SNEDDS maintained > 85% CN in solution. The superior dissolution of SNEP and liquid SNEDDS could be explained by their ability to provide a microenvironment that favors the formation of nanoemulsion introducing the drug in solution within the nanosized oil droplets (Piao et al. 2014; Shahba et al. 2012a). The formed nanoemulsion could resist the sharp drug precipitation resulting from shifting into higher pH environments. The latter dissolution data are harmonizing with recent study (Piao et al. 2014) that showed similar findings with another weakly basic drug. These results confirm that the solidification process did not cause a serious drawback on SNEDDS performance. Indeed, the dissolution of SNEP was not practically influenced by droplet size increase. Therefore, CN-SNEP could be considered as efficient alternative that combine the advantages of liquid SNEDDS and those of solid dosage form.

2.5. Conclusion

CN Liquid SNEDDS were efficiently solidified using fluid bed coating. The solidification process involved optimization of the process and formulation variables. On optimization, the best formula involved OL/I308/Cr-El (25/25/50) as liquid SNEDDS, HPMC E3 as coating polymer and Plasacryl^{TM}T20 as anti-tacking agent. The optimum concentration of coating solution was 15% and the optimum proportion of excipients (liquid SNEDDS/HPMC/Plasacryl) was (40/54.5/5.5). The optimized CN-SNEP were free flowing, completely solidified with excellent coating outcomes. Further, CN-SNEP presented excellent dissolution performance maintaining >85% CN in solution, even at higher pH media. Accordingly, CN-SNEP could be a potential dosage form that circumvents the limitations of liquid SNEDDS, combine their efficient solubilization along with the additional benefits of solid dosage forms.

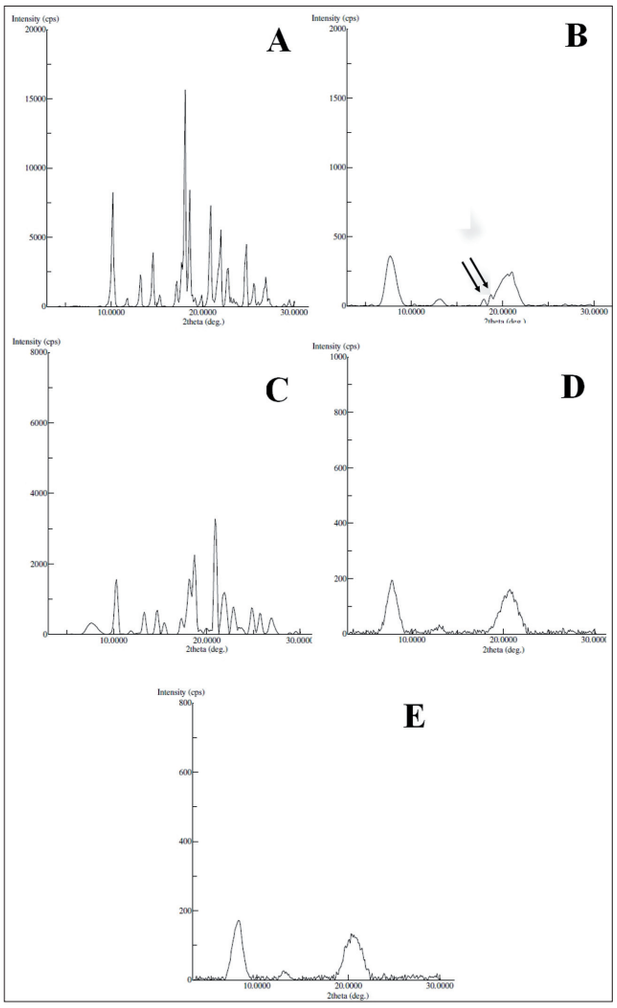

Fig. 5: XRD of (A) pure CN, (B) physical mixture of CN/blank solid SNEDDS (3/97) (C) physical mixture of CN/blank solid SNEDDS (50:50), (D) Blank Solid SNEDDS and (E) CN-loaded solid SNEDDS with 3% CN. The arrows point to few CN diffraction peaks with low intensity.

3. Experimental

3.1. Materials

CN was donated by FDC Limited, Maharashtra, India. Miglyol 812 (M812, medium chain triglycerides) and Imwitor 308 (I308, medium chain mono-glycerides) were donated by Sasol Germany GmbH (Werk Witten, Witten-Germany). Oleic acid (OL, long chain fatty acid) was purchased from Avonchem (Cheshire, England). Tween 85 (T85) was purchased from Merck-Schuchardt OHG (Darmstadt, Germany). Cremophor El (Cr-El) was donated by BASF (Ludwigshafen, Germany). Vcaps Plus® HPMC capsules (size 0) were donated by Capsugel (South Carolina, USA). Vivapharm® (HPMC E3) and non-pareil sugar spheres (850-1000 µm) were purchased from JRS Pharma (Germany). Kollidon® Polyvinylpyrrolidone (PVP K30) was purchased from BASF (Ludwigshafen, Germany). Plasacryl^{TM}T20 [20% aqueous suspension, containing GMS (antitacking agent), triethyl citrate (plasticizer), and polysorbate 80 (stabilizer)] was donated by Evonic Industries (Germany).

3.2. Preparation of liquid self-nanoemulsifying drug delivery systems (SNEDDS)

Optimum liquid SNEDDS should be able to solubilize sufficient drug amount, maintain it in solution upon aqueous dispersion and avoid possible precipitation during drug transit in GIT. Based on previous studies (Shahba et al. 2012a, 2016), the selected CN-SNEDDS

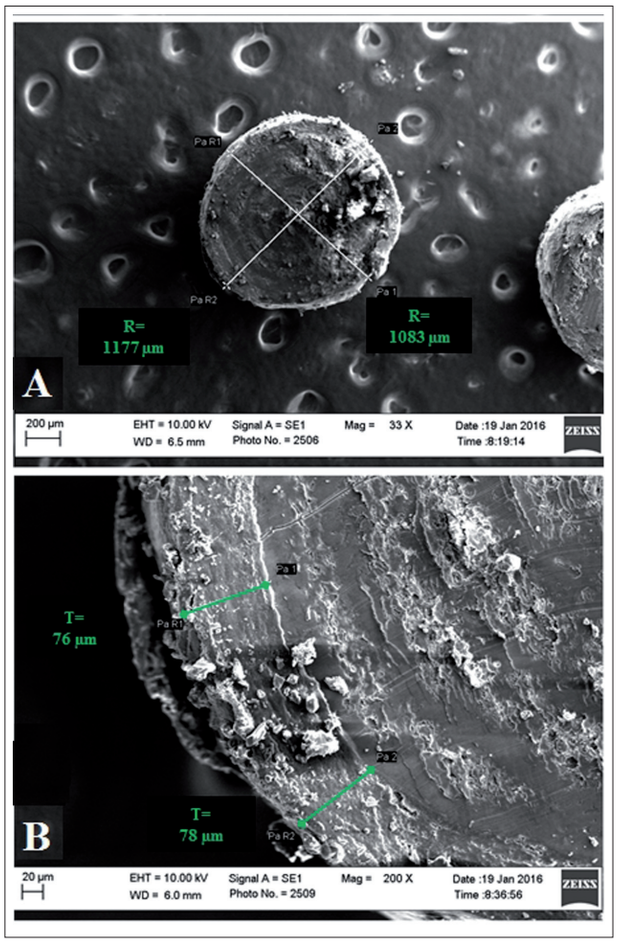

Fig. 6: SEM images of optimized SNEP showing (A) cross section at magnification 33x (displaying pellet diameter) and (b) cross-section at magnification 200x (displaying the coating layer thickness).

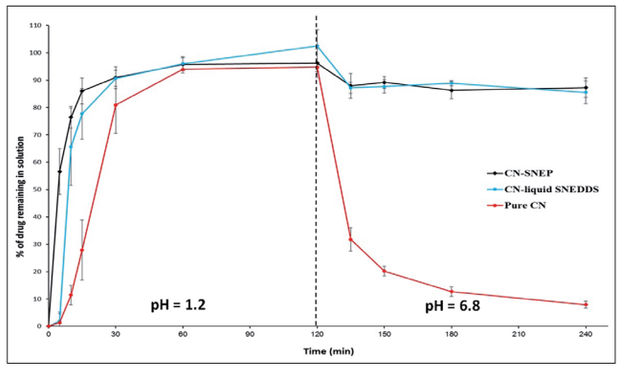

Fig. 7: Comparative dissolution of CN-SNEP (F3), CN-liquid SNEDDS and pure CN. Data are expressed as mean±SD, n =3-6. CN denotes: cinnarizine, SNEP: self-nanoemulsifying pellets and SNEDDS: self-nanoemulsifying drug delivery systems.

Table 4: List of process and formulation variables

Process		*Formulation*	
Variables	Value[a]	Variables	Type/Value
Spray air pressure (SAP) bar	0.6 - 1.4	Coating polymer	1) PVP K30 2) HPMC E3
Microclimate air pressure (MAP)[b] bar	0.3 - 0.7	Liquid SNEDDS composition	1) M812/I308/T85 (25/25/50) 2) OL/I308/Cr-El (25/25/50)
Inlet air volume (m^3/h)	30-50	Anti-tacking agent	1) Talc 2) Plasacryl™T20
Spray rate (g/min)	0.5 - 7.0	Proportion of SNEDDS in the coating layer	1) 20% 2) 40% 3) 60%
Inlet air temperature (°C)	40.0 - 76.0	Concentration of the coating solution	1) 10% 2) 15% 3) 20%
Product temperature (°C)	29.0 - 53.5		

SNEDDS denotes: self-nanoemulsifying drug delivery systems, M812: miglyol 812, I308: Imwitor308, T85: tween 85, OL: oleic acid and Cr-El: cremophor El.
[a]: The value of process variables depended on the formulation characteristics and coating stage.
[b]: The set value for MAP was fixed to be 50% of SAP

were M812/I308/T85 (25/25/50) and OL/I308/Cr-El (25/25/50). Recent studies have reported the equilibrium solubility of CN in M812/I308/T85 (25/25/50) = 46.7±0.3 mg/g and OL/I308/Cr-El (25/25/50) = 88±1.8 mg/g (Shahba et al. 2016). The selected CN-SNEDDS were prepared by mixing the oil, surfactant and co-surfactants at optimized ratio. In case of drug-loaded formulations, CN was added at value ≈90% of its equilibrium solubility in the formulation. Finally, the components were thoroughly mixed ensure complete drug solubilization and homogenization (Christiansen et al. 2014).

3.3. Preparation of solid self-nanoemulsifying pellets (SNEP)

SNEP were prepared using a bottom-spray fluid-bed coater (Mycrolab, Oystar Huttlin, Germany) (Lei et al. 2011; Mukherjee and Plakogiannis 2012). The coating solution was prepared in three steps: 1) Preparation of 20% aqueous solution of the coating polymer. 2) Addition of freshly prepared SNEDDS and anti-tacking agent into polymer solution, under mechanical stirring. 3) Addition of distilled water to achieve the required concentration of the coating solution. The non-pareil sugar spheres were charged into preheated fluid bed chamber, 10 min prior to coating. Further, the coating solution was bottom-sprayed on the fluidizing spheres using a peristaltic pump. Finally, the coated pellets were dried for at least 10 minutes (Mukherjee and Plakogiannis 2012).

3.4. Optimization of CN-SNEP

The optimization of fluid bed coating aimed to achieve successful coating process with minimal agglomeration, minimal spray drying and high yield. The coating optimization involved investigating process variables and formulation variables, which are listed in Table 4.

3.5. Characterization of SNEP

3.5.1. Coating recovery (CR%)

This parameter was calculated as (de Souza et al. 2014):

$$CR\% = \frac{Actual\ coating\ layer\ weight}{Theoretical\ coating\ layer\ weight} \times 100$$

The actual coating layer weight was calculated by subtracting the initial core weight from the final weight of coated pellets. The theoretical coating layer weight was calculated by the sum weight of coating polymer, liquid SNEDDS and anti-tacking excipients. CR% could be used to evaluate the coating efficiency and the spray drying extent. Generally, high CR values reveals minimal spray drying.

3.5.2. Coating weight gain (CWG %)

This parameter was used to define the percent increase in pellet weight relative to initial core and was calculated as (Lei et al. 2011; Tian et al. 2013):

$$\mathbf{CWG\ \%} = \frac{Theoretical\ coating\ layer\ weight}{Initial\ core\ weight} \times 100$$

3.5.3. Drug loading efficiency (%)

This parameter reflects the ability of the coating process to efficiently load the claimed drug doses within the coated pellets. It was calculated as (Kayaert et al. 2011):

$$\text{Drug loading efficiency (\%)} \frac{Actual\ drug\ load}{Theoretical\ drug\ load} \times 100$$

To calculate the actual drug load, a sample of the coated pellets was initially crushed using a mill, then (1 g) aliquot was dissolved in acetonitrile, sonicated for at least 10 min and centrifuged (Kayaert et al. 2011). Supernatant (1 ml) was diluted in acetonitsile and subsequently assayed by UPLC (Abdel-Hamid et al. 2012). Each sample was analyzed at least three times.

3.5.4. Mono-pellets (%)

This parameter was used to reflect the pellets agglomeration and was calculated based on % of pellets passing through 1.25 mm sieve. Pellets larger than 1.25 mm were considered as agglomerates (de Souza et al. 2014).

3.5.5. Scanning electron microscopy (SEM)

The surface and cross-section morphology of SNEP were examined under a scanning electron microscope (Carl Zeiss EVO LS10; Cambridge, United Kingdom). Samples were fixed on stubs using double-sided adhesive carbon tape. Then, they were gold-coated by Q150R sputter coater (Quorum Technologies Ltd, East Sussex, United Kingdom). The process was conducted in an argon atmosphere, at 20 mA for 1 min. The examination involved applying an excitation electron energy of 3-10 KV (Lei et al. 2011).

3.5.6. In-vitro dissolution studies

The *in-vitro* dissolution studies was conducted using USP dissolution apparatus II (Model: UDT-804, LOGAN Inst. Corp., USA) at 50 rpm paddle stirring rate and 37±0.5 °C. To ensure accurate comparison, all the tested formulations were utilized in amounts equivalent to 25 mg CN. Due to the weakly basic nature of CN, it was vital to conduct the dissolution studies in both acidic (pH 1.2) and neutral (pH 6.8) media. Initially, the dissolution medium was composed of 500 ml 0.1N HCl (pH 1.2). Consecutive samples were withdrawn at 5, 10, 15, 30, 60 and 120 min then centrifuged and assayed by UPLC (Shahba et al. 2012a). After the "120 min" sample, the dissolution medium was adjusted to pH 6.8 by adding 250 ml of 120 mM tribasic sodium phosphate. In the new pH, samples were collected at 15, 30, 60 and 120 min, centrifuged and assayed as mentioned earlier (Shahba et al. 2012a). A minimum of three replicates were considered for each sample.

3.5.7. Differential scanning calorimetry (DSC)

To exclude interference of non-pareil cores with DSC and XRD, CN-loaded and blank (CN-free) solid SNEDDS were prepared as free films. The coating solution was casted and the solvent was evaporated to obtain a sample of the solidified coating layer (Felton 2007; Lei et al. 2011). Later, the film was crushed into fine particles and utilized for physical characterization. DSC Samples were analyzed using a DSC-60 Shimadzu instrument (Kyoto, Japan). Samples (≈ 7 mg) were weighed in a non-hermetically sealed aluminum pan. The samples were heated from 25 to 200 °C at a heating rate of 10 °C/min. The measurements were carried out in nitrogen atmosphere at 40 ml/min flow rate (Tian et al. 2013).

3.5.8. X-ray diffraction (XRD)

XRD samples (pure CN, blank solid SNEDDS, physical mixture, and CN-loaded solid SNEDDS) were evaluated by Ultima IV diffractometer (Rigaku, Japan) over the 3–30° 2θ range at a scan speed of 0.5 deg./min. The tube anode was Cu with Ka = 0.154 nm monochromatized with a graphite crystal. The pattern was collected at tube voltage (40 kV) and tube current (40 mA) in step scan mode (step size 0.02°, counting time 1 second per step) (Tian et al. 2013; Zhang et al. 2008). The physical mixtures were prepared by mixing CN with blank solid SNEDDS at ratios (3/97) and (50/50), respectively. The (3/97) physical mixture was utilized to simulate CN-loaded Solid SNEDDS that contained 3% CN.

3.5.9. Pellet sizing

The average diameter of uncoated and coated pellets was measured using laser light diffraction particle sizer (Mastersizer Scirocco 2000, Malvern instruments, Grovewood Road, U. K). For a typical experiment, pellets (≈ 2 g) were loaded in the sample micro feeder. Each sample was analyzed in triplicate (Elzayat et al. 2016).

3.5.10. Reconstitution study and droplet size analysis

The liquid SNEDDS and solid SNEP were dispersed in distilled water at ratio 1:1000 w/w, stirred for 2 min and incubated for 1 h, prior to examination (Atef and Belmonte 2008; Kommuru et al. 2001; Mukherjee 2010). The dispersion was then observed visually and characterized for droplet size. The average droplet size of the dispersed formulations were examined by dynamic light scattering (Zetasizer Nano ZS, Malvern, UK). In case of solid SNEP, the aqueous dispersion was centrifuged using EBA 20 Centrifuge (Hettich Zentrifugen, Germany) at 865×g for 2 min, prior to examination. The centrifugation step aimed to exclude the interference of insoluble particles with the droplet size of the aqueous dispersion. Each sample was repeated three times and the average value was considered.

3.6. CN quantification by UPLC

CN was analyzed by reversed-phase UPLC (Abdel-Hamid et al. 2012), with minor modifications. The mobile phase composition was altered to 0.5% trifluroaceticacid: acetonitrile (55:45) and the run time was increased to 1.5 min, to allow for higher resolution of the intact drug peak. The system involved Acquity® UPLC BEH C18 (2.1 x 50 mm, 1.7 µm) column along with Acquity guard filter, maintained at 50 ºC, and flow rate of 0.5 ml/min. The injection volume was 1.0 µl and the UV detector was set at 251 nm.

3.7. Statistical analysis

SPSS 22® software was utilized to explore the significance of the data. Droplet size data were compared using Paired T-test. *In-vitro* dissolution profiles were compared using two-way ANOVA followed by post hoc tests (LSD). A value of $p < 0.05$ was considered significant (Atef and Belmonte 2008; Shahba et al. 2012a).

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