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New Approach for Administration of Doxazosin Mesylate: Comparative Study between Liquid and Solid Self-nanoemulsifying Drug Delivery Systems

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ABSTRACT

Self-nanoemulsifying drug delivery systems (SNEDDS) in both liquid and solid forms were suggested to improve water solubility of Doxazosin mesylate (DOX) a poorly water- soluble antihypertensive drug. Oleic acid: Smix (1:9 w/w) and Tween 80: co-surfactant mixture (Ethanol and PEG 400) (1:1, 2:1, 3:1 and 4:1) were chosen to prepare a liquid and solid forms of SNEDDS according to their solubility. TEM images revealed change in the crystalline nature of DOX into uniform particles with smooth surface. Characterization studies revealed droplet size ranges from 79.80±14.39 to 273.10±4.17 nm, zeta potential ranges from -5.57±0.10 to -21.13±0.46 mV and dissolution enhancement of more than two folds with more favorable properties for the solid forms. FTIR demonstrated significant physical changes in DOX crystalline structure. In conclusion, the solid SNEDDS containing oleic acid: Smix (1:9 w/w) and Tween 80: co-surfactant mixture (3:1 w/w) and adsorbent mixture of Avicel 101 and Aerosil 200 (40:1 w/w) might be a promising formula for better management of hypertension with expected shelf stability.

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INTRODUCTION

Poor aqueous solubility of drugs is considered one of the significant issues in pharmaceutical industry that results in low drug absorption and bioavailability. More than 90% of drugs had been approved since 1995 with 40% were practically water insoluble and hence many investigations for aqueous solubility enhancement had been emerged (Kalepu and Nekkanti, 2015; Savjani *et al.*, 2012).

Self-nanoemulsifying drug delivery systems (SNEDDS) are mixtures of various liquids mainly oil, surfactant and co-surfactant which are mixed with the drug (Cherniakov *et al.*, 2015). Bioavailability enhancement is achieved by self-nanoemulsifying drug delivery system formation by promotion of lymphatic transport with subsequent delivery of drug directly to the systemic circulation while avoiding hepatic first-pass metabolism (Balata *et al.*, 2016).

SNEDDS are filled into hard or soft gelatin capsules in order to be administrated; because of being liquid in nature which gave rise to some drawbacks including possible interactions with the capsule shell. Solid SNEDDS are fabricated to overcome these drawbacks. They possess high solubilizing ability for drugs; more stable and easier in handling than liquid SNEDDS (Date *et al.*, 2010).

Doxazosin Mesylate, α1-adrenergic receptor blocker, is an antihypertensive drug which

suffers from low bioavailability (65%) due to poor aqueous solubility and extensive first pass metabolism (Chung *et al.*, 1999). The aim of the study is to investigate the effect of either liquid or solid SNEDDS of Doxazosin mesylate on enhancement of its solubility.

MATERIALS AND METHODS

Materials

Doxazosin mesylate, poloxamer 407, PEG 400, Avicel 101 and Aerosil 200 were kindly supplied from Epico. Co., Egypt. Ethanol, Methanol and Tween 80 were purchased from Al Gomhouria Co, Egypt. Sesame oil was purchased from Choice Co., Egypt. Olive oil Terra Delyssa extra virgin was purchased from CHO Co., Tunisia. Oleic acid was purchased from Sigma Chemical Co., St. Louis, MO, USA. All the chemicals used were at analytical grade.

Saturation solubility of Doxazosin mesylate

Solubility of Doxazosin mesylate was screened in various oils (sesame oil, olive oil and oleic acid), surfactant (Tween 80 and poloxamer 407) and co-surfactants (PEG 400 and ethanol) in order to select SNEDDS components with highest solubilizing capacity for Doxazosin mesylate, the method was done according to (Nasr *et al.*, 2016).

Preparation of Doxazosin mesylate self nanoemulsifying drug delivery systems (SNEDDS)

Based on the results of saturation solubility study, oleic acid was chosen as oil, Tween 80 as a surfactant and a mixture of (1:1) Ethanol and PEG 400 as co-surfactant for preparation of four Doxazosin mesylate SNEDDS as illustrated in Table 1. SNEDDS were prepared at fixed ratio (1:9 w/w) of oil: Smix and four Smix ratios (1:1, 2:1, 3:1 and 4:1 w/w) of Tween 80: co-surfactant respectively, the method was done according to (Ali and Hussein, 2017).

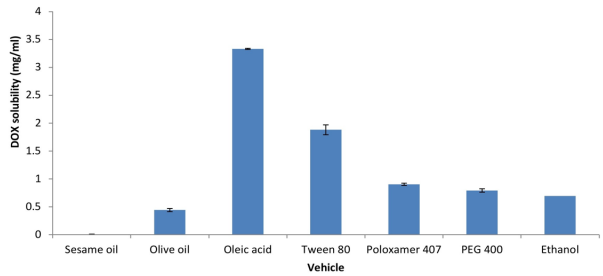

Figure 1: Solubility chart of Doxazosin mesylate in oils, surfactants and co-surfactants.

Preparation of Doxazosin mesylate solid (SNEDDS)

Four Solid SNEDDS formulae were prepared by manual mixing of 0.6 g of each liquid SNEDDS with adsorbent mixture of Avicel 101 and Aerosil 200 (40:1 w/w) in a porcelain mortar as shown in Table 2. (Ali and Hussein, 2017).

Characterization of liquid & solid SNEDDS

Transmission electron microscopy (TEM)

The morphology of selected liquid and solid (Doxazosin mesylate) SNEDDS compared with pure Doxazosin mesylate was observed using TEM (JEOL-JEM 1010, Tokyo, Japan). Each sample was diluted with distilled water at 10 times dilution, then one drop of 2% phosphotungstic acid was further added and examined under microscope after being air dried (Nasr *et al.*, 2016).

Measurement of droplet size, polydispersity index (PDI) and zeta potential

Characterization of the prepared liquid and solid SNEDDS was done in terms of droplet size, PDI and zeta potential using dynamic light scattering (DLS) (Zetasizer Nano ZS-90, Malvern Instruments, Worcestershire, UK). Each sample was diluted 10 times with distilled water and measurements were done in triplicates (Nasr *et al.*, 2016).

Drug entrapment efficiency

An accurate amount of either liquid or solid SNEDDS (each equivalent to 2 mg Doxazosin mesylate) was properly diluted with methanol and assayed by UV spectrophotometer at 266 nm for Doxazosin mesylate, measurements were done in triplicate (Nasr *et al.*, 2016).

Fourier transform infrared spectroscopy (FTIR)

Different samples of pure components as well as selected liquid and solid SNEDDS were examined at a wave number range 4000-400 cm^{-1} using FTIR (Perkin-Elmer 1600 FTIR Spectrophotometer, Norwalk, USA) by KBr disc method at a resolution of 4 cm^{-1} (Aiswarya *et al.*, 2015).

In-vitro dissolution

The *in vitro* dissolution studies were done for pure Doxazosin mesylate, all liquid and solid SNEDDS, using a Pharma Test dissolution tester type II (Paddle Apparatus, SP6-400 Hamburg, Germany). About 2 mg of pure Doxazosin mesylate or its equivalent amount was filled in a hard gelatin capsule (size 3) and placed in dissolution vessel containing 500 ml 0.1 N HCL buffer (pH 1.2) at 37°C ± 0.5 at 100 rpm (Ahmad *et al.*, 2017). Samples (3 ml) were withdrawn after 3, 5, 7, 10 and 20 min and replaced by an equal volume of fresh buffer. Absorbance values were measured using UV Spectrophotometer at

Table 1: Composition of Doxazosin mesylate liquid SNEDDS (%w/w)

Formula no.	Smix ratio	Oil: Smix ratio	Oleic acid%	Tween 80%	PEG 400	Ethanol
L1	1:1	1:9	10	45	22.5	22.5
L2	2:1	1:9	10	60	15	15
L3	3:1	1:9	10	67.5	11.25	11.25
L4	4:1	1:9	10	72	9	9

Table 2: Compositions of Doxazosin mesylate solid SNEDDS

Formula no.	Smix Ratio	Oil: Smix ratio	Avicel 101 (mg)	Aerosil 200 (mg)
S1	1:1	1:9	600	15
S2	2:1	1:9	600	15
S3	3:1	1:9	600	15
S4	4:1	1:9	600	15

Table 3: Droplet/Particle size, Zetapotential, Polydispersity index, Entrapment efficiency and Dissolution parameters of DOX liquid and solid SNEDDS.

Formula no.	Droplet/ Particle size (nm)	Zeta potential (mv)	Polydispersity index (PDI)	Entrapment efficiency (%)	Dissolution% after 20 min (DR_{20min})	Dissolution efficiency% (DE_{20min})	Dissolution enhancement ratio (DER)
Pure DOX	——	——	——	——	41±1.02	24.59 ±1.25	1.00
L1	273.10±4.17	-7.81±0.47	0.448± 0.00	99.99±0.01	81±2.28	50.64±1.34	2.05
S1	233.84±139.19	-9.47±1.74	1.00±0.00	99.99±0.02	99±1.57	62.27±0.36	2.53
L2	230.70±6.38	-7.12±0.49	0.323±0.03	99.99±0.01	89±1.89	55.84±2.99	2.27
S2	215.60±89.90	-15.16±0.80	1.00±0.00	99.99±0.05	100±1.87	64.28±0.66	2.61
L3	224.40±15.55	-5.57±0.10	0.470±0.01	99.99±0.04	93±4.47	58.68±2.02	2.38
S3	79.80±14.39	-18.10±0.26	1.00±0.00	99.99±0.03	100±2.72	65.78±0.96	2.67
L4	263.00±4.29	-6.07±0.14	0.424±0.03	99.99±0.02	86±3.10	53.54±0.87	2.17
S4	165.03±35.83	-21.13±0.46	1.00±0.00	99.99±0.06	100±3.84	62.99±1.36	2.56

266 nm. Dissolution parameters in terms of dissolution% after 20 min (DR_{20min}), dissolution efficiency % after 20 min (DE_{20min}) and dissolution enhancement ratio (DER) were then calculated.

RESULTS AND DISCUSSION

Saturation solubility of Doxazosin mesylate

Solubility study is a crucial testing in order to choose SNEDDS components having good solubilizing capacity of Doxazosin mesylate to ensure maximum drug entrapment into SNEDDS droplets (Figure 1) (Debnath *et al.*, 2011). Oleic acid was chosen as an oily phase as it possessed the highest ability to solubilize Doxazosin mesylate arising from its ion pairing capability with amine group of Doxazosin mesylate as it will be explained later by FTIR study (Patel *et al.*, 2013). Doxazosin mesylate solubility in oleic acid was (3.33±0.01 mg/ml) compared to only 0.0004±0.01 and 0.44±0.03 mg/ml

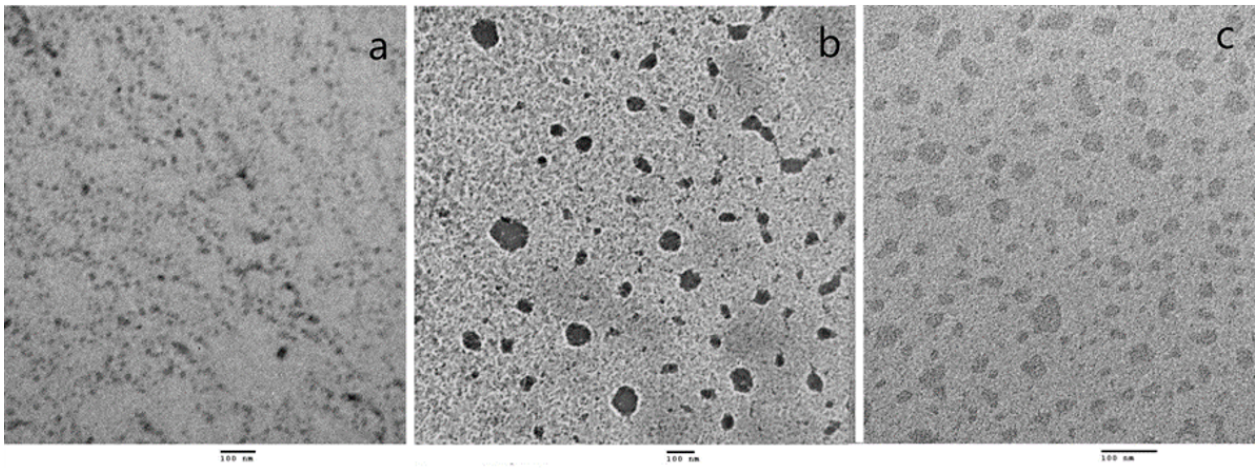

Figure 2: TEM images using 100 nm scale of (a) pure Doxazosin mesylate (b) liquid Doxazosin mesylate SNEDDS (L3) and (c) solid Doxazosin mesylate SNEDDS (S3).

for sesame oil and olive oil, respectively. The solubility of Doxazosin mesylate using Tween 80 and poloxamer 407 was 1.88 and 0.9±0.09 mg/ml respectively. Being non-ionic hydrophilic surfactant (HLB = 15) giving rise to small fine droplets with high surface area and improved dissolution rate, Tween 80 was chosen as a surfactant in SNEDDS preparation (Balata, 2018). Poloxamer 407 was excluded because it gave rise to non-homogenous formulation. The Solubility of Doxazosin mesylate in both hydrophilic co-surfactants (Ethanol and PEG 400) was (0.69±0.01 and 0.79±0.03 mg/ml) respectively, so a mixture of both was chosen as a co-surfactant (Larsen *et al.*, 2012).

Transmission electron microscopy (TEM)

TEM images of pure Doxazosin mesylate compared with selected liquid and solid SNEDDS are illustrated in Figure 2. Pure Doxazosin mesylate, which was appearing as crystalline particles, was changed into uniform particles with smooth surface in both liquid and solid SNEDDS (Bhagat *et al.*, 2013). It is worthy mentioned that TEM image of solid SNEEDS is not identical to liquid SNEDDS which may be due to uniform coating of solid SNEDDS particle surfaces by adsorbents (Izham *et al.*, 2019).

Measurement of droplet/particle size, polydispersity index (PDI) and zeta potential of liquid and solid SNEDDS

Values of droplet/particle size as well as polydispersity index (PDI) and zeta potential are summarized in Table 3.

It was found that, increasing surfactant concentration up to 67.5 % (L3) resulted in a decrease in droplet size of liquid SNEDDS to 224.40±15.55 nm. Further increase in Tween 80 concentration to 72 % (L4) resulted in a significant increase ($P < 0.05$) in droplet size to 263 ± 4.29 nm. This result may be ascribed to formation of closely attached surfactant film with subsequent formation of stable nano-sized droplets at lower surfactant concentration (Ali and Hussein, 2017; Nasr *et al.*, 2016), Further increase in surfactant concentration resulted in increase in water permeation inside the oil droplets; disrupting this film lead to an increase in the droplet size, also the increase in viscosity slow down the self-emulsifying process giving rise to larger droplets (Tong *et al.*, 2018). Similarly, solid SNEDDS exhibited decreased particle size to 79.80 ± 14.39 with increased Tween 80 concentration up to 67.5 % (S3) but with further reduction in droplet size than liquid formulations. This result could be explained by the small particle size of both adsorbents as the particle size of Aerosil 200 is 15 nm offering high surface area about (100–400 m^2 /g) and the particle size of Avicel 101 is 50 μm, giving rise to porous structure (Ali and Hussein, 2017; Nazzal *et al.*, 2002).

All liquid SNEDDS had PDI values ranged from 0.323±0.03 to 0.470± 0.01 which reflected that samples possessed uniform particle size distribution, while solid SNEDDS had PDI values of 1 which indicated that samples possessed different particle size populations this may be due presence of adsorbents with different sizes as mentioned before (Ige *et al.*, 2013; Nazzal *et al.*, 2002).

Liquid SNEDDS had moderate zeta potential ranged from -5.57±0.10 to -7.81±0.47 mv. Negative zeta potential values were mainly due to the oil content and the values varied according to droplet size (Khames, 2019). Interestingly, solid SNEDDS exhibited higher zeta potential values of -9.47±1.74 to -21.13±0.46 mv confirming the more stable

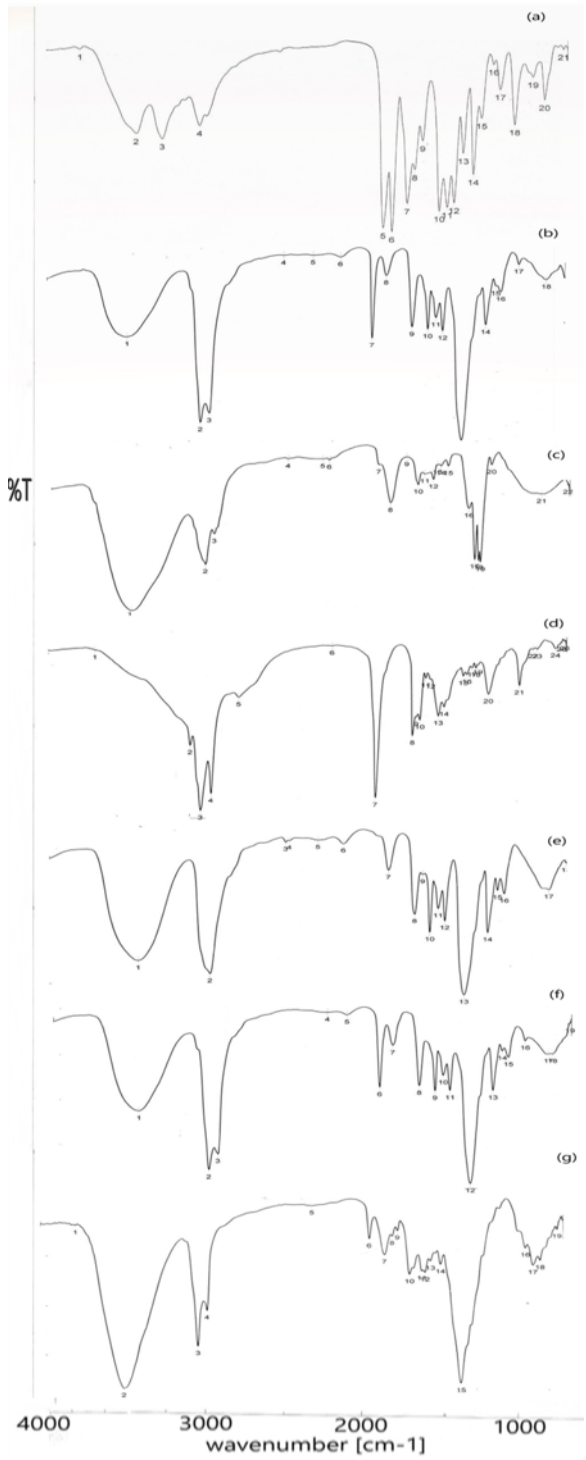

Figure 3: FTIR spectra of (a) pure Doxazosin mesylate, (b) Tween 80, (c) Ethanol, (d) Oleic acid, (e) PEG400, (F) (L3) Liquid SNEDDS, and (g) (S3) Solid SNEDDS.

nature of solid SNEDDS rather than liquid formulations. The increase in zeta potential was mainly due to presence of adsorbents. Aerosil 200 contributed to surface negative charge by adsorption of protons on its surface resulting in ionization of its silanol groups (Farooq *et al.*, 2011) and Avicel 101 by adsorption of sulfate anions on its surface (Du *et al.*, 2017).

Drug entrapment efficiency

Both liquid and solid SNEDDS exhibited nearly 100% entrapment efficiency as illustrated in Table 3. This result could be due to high HLB value of tween 80 which created o/w micelle structure with the hydrophobic core enhancing the entrapment of Doxazosin mesylate, thus increasing its solubility (Cho *et al.*, 2016; Debnath *et al.*, 2011).

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of pure components as well as a selected liquid (L3) and solid SNEDDS (S3) are illustrated in Figure 3. The characteristic peaks of Doxazosin mesylate at 3357, 3180 cm^{-1} corresponding to NH2 group disappeared in both liquid and solid SNEDDS, the peak at 1651 cm^{-1} corresponding to C=N group was shifted to 1644 and 1631 cm^{-1} in liquid and solid SNEDDS respectively, the peak at 1039 cm^{-1} corresponding to C-O group was shifted to 1248 cm^{-1} in both liquid and solid SNEDDS, the peak at 1490 cm^{-1} corresponding to C=C group was shifted to 1460 cm^{-1} in both liquid and solid SNEDDS. These changes suggested the protonation between -COOH group of oleic acid and –NH2 group in quinazoline ring of Doxazosin mesylate and hence electrostatic attraction and formation of doxazosin oleate salt. This result explained the increased solubility of Doxazosin mesylate in oleic acid more than other investigated oils. In addition, FTIR spectra suggested the presence of intermolecular hydrogen bonding between Doxazosin mesylate basic nitrogen and O-H groups of Aerosil 200 and Avicel 101 in solid SNEDDS which explained the further reduction in droplet size of solid than liquid SNEDDS. Similar results were obtained by (Mardiyanto *et al.*, 2020).

In vitro dissolution

Dissolution profiles of Doxazosin mesylate from different formulations compared with its pure form are summarized in Table 3. Because of its hydrophobic nature, pure Doxazosin mesylate exhibited low DR_{20min} of 41 % ±1.02 and DE_{20min} of 24.59% ± 1.25. Incorporation of Doxazosin mesylate in SNEDDS either in liquid or solid state enhanced its dissolution by more than 2 folds owing to the remarkable size reduction with high surface area for dissolution as explained before in FTIR and DSC studies. It is worthy to mention that there is strong negative correlation between DE_{20min} and droplet size (Pearson coefficient = -0.952 & -0.786 for liquid and solid SNEDDS, respectively).

Solid SNEDDS exhibited significant ($P < 0.05$) higher dissolution parameters than liquid formulations. Different factors contributed to this result including: smaller droplet size, presence of hydrophilic adsorbants (Avicel 101 and Aerosil 200) with large surface area exposed to dissolution medium and hydrogen bonding formation between Doxazosin mesylate and the adsorbents as mentioned before in FTIR study (Ali and Hussein, 2017; Nazzal *et al.*, 2002).

CONCLUSIONS

SNEDDS were successfully prepared in liquid and solid forms to enhance the dissolution and antihypertensive effect of Doxazosin mesylate. The formulation (S3) containing Smix of 3:1 (67.5% Tween 80, 11.25% Ethanol and 11.25% PEG 400) and adsorbent mixture of Avicel 101 and Aerosil 200 (40:1 w/w) showed droplet size of 79.80±14.39 nm, zeta potential of -18.10 ±0.26 mv and dissolution efficiency % after 20 min of 65.78±0.96 % with dissolution enhancement ratio of 2.67.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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