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Improvement of dissolution of a class II poorly water-soluble drug, by developing a five-component self-nanoemulsifying drug delivery system

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ABSTRACT

Purpose of this study is to develop a self-nano emulsifying drug delivery system (SNEDDS) to improve the dissolution of tadalafil and to overcome two formulation challenges namely, increasing the tadalafil solubility in the preconcentrate using a cosolvent, as well as guarding against the drug precipitation upon dilution by adding a precipitation inhibitor (PI). The formulation steps included the choice of oil through examining the saturated solubility of tadalafil in the different oils. Then, a factorial design studying different surfactants/cosurfactants mixtures was done to determine the required hydrophilic-lipophilic balance (HLB), as well as the chemical nature suitable to the oil of choice (Capryol™ 90). A ternary phase diagram was constructed to identify the region of SNEDDS. The ability of various cosolvents to increase the tadalafil saturated solubility in the preconcentrate was investigated. Then, a factorial design was adopted to investigate the different PI types and concentrations. An *in-vitro* dissolution study was done to compare the percent drug dissolved from the SNEDDS, Cialis®, and the plain drug. Conclusion: 10% Capryol™ 90, Tween®80 and Transcutol®HP Smix 7:2 (HLB 12) were used to prepare the SNEDDS. PEG 400 and 3%HPMC were added. 80% of the drug was dissolved from the SNEDDS in 5 min.

1. Introduction

Tadalafil is a reversible, competitive, effective phosphodiesterase type 5 inhibitor [1]. It has a slower onset of action when compared to other drugs in the same class [2]. According to the Biopharmaceutics Classification System (BCS), tadalafil is a class two drug (low solubility and high permeability) [3]. Consequently, its delivery from the dosage form and solubility in the gastric fluid act as the rate-limiting step [4]. Additionally, drugs characterized by a log P equal to 2 [5] and a melting point above 200 °C are described as brick dust molecules [6]. Therefore, tadalafil might also be considered as a "brick-dust" drug, since it has a log P ≈ 2 [7] and a melting point value 301 °C [8]. According to Mehta et al. [9] drugs with log P value equal to 2 and administrated at a high dose are the most challenging to formulate as SNEDDS. This consequently presented an additional formulation challenge, to incorporate the 20 mg dose in the SNEDDS.

Several studies have approached the enhancement of dissolution of tadalafil through different techniques, such as nanosuspension [8], solid dispersion [10] and complexation [11]. SNEDDS has proven to be a successful tool to improve the solubility of lipophilic drugs [12]. SNEDDS exhibited several advantages over other delivery systems, such as ease of manufacture, ease of scale-up when compared to solid dispersions, liposomes and nanoparticles [13]. In addition, the drug molecules are pre-solubilized in lipid excipients, thus, overcoming the dissolution step in the GI tract [14,15]. SNEDDS exhibits small globule size, and excellent stability [16].

Since, the permeation and absorption of drugs from nanoemulsions are dependent on the various variables that include the rate of dispersion, the degree of emulsification, globule size as well as, the amplitude of drug solubilization and precipitation from the formula [17], therefore each of the aforementioned variables was taken into consideration during formulation.

The formulation steps were divided to firstly determine the solubility of the drug in the oil, which is a vital criterion since the maintenance of the drug solubilized by the nanoemulsion is highly influenced by the drug solubility in the oily phase [12,18–20]. Followed by the surfactant and cosurfactant selection based on the required HLB value and chemical compatibility, rather than the solubility results. The surfactant involved in the formulation of SNEDDS should facilitate the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media (good self-emulsifying performance) [13,20]. The cosurfactants were used since they tend to increase the flexibility and curvature of the interface [19] and consequently reduce the interfacial tension and bending stress [13,21]. Thus, cosurfactants enables the interfacial film to acquire different curvatures needed for the formation of nano/microemulsion [22]. Afterward, handling the

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miscellaneous problems was carried out. Since tadalafil exhibits properties of a brick-dust drug, therefore the use of cosolvent in this study was of particular interest to increase the solubility of tadalafil in the preconcentrate [14]. However, cosolvents could play other roles such as aiding in the dispersion of the surfactant and thereby reduce the probabilities of local irritation due to the high local concentration of surfactant [23]. Also, their addition facilitates increasing drug solubility by co-solvency and stability of the dispersed phase [24]. Finally, since the risk of precipitation increases if the surfactant and/or co-surfactant are contributing to the drug solubilization, as dilution of the nanoemulsion in the GIT would result in lowering of their solvent capacity [19], therefore PI was added.

In this study, the aim of work is to enhance the dissolution of tadalafil through developing tadalafil SNEDDS, using five-components in the formulation. This is significant because SNEDDS is a formulation drug delivery tool that exhibits appealing industrial advantages since its results are highly reproducible, is easy to scale-up, and presents a successful tool to overcome class II drug limiting step. Also, the challenge to incorporate the (20 mg) of tadalafil in the preconcentrate in a soluble form is approached using cosolvent addition. Moreover, the study followed a sequence of steps, to act as a suggested guide for the formulators to follow.

2. Materials and methods

2.1. Materials

Tadalafil, MW = 389.41, batch no. TV005K05; was obtained as a gift from Dr. Reddy's Laboratories, India supplied by Luna pharmaceuticals company, Egypt. Capryol™ 90 (propylene glycol monocaprylate type II), Capryol™ PGMC (propylene glycol monocaprylate type I), Labrafil® M 2125 CS (linoleoyl polyoxyl-6 glycerides), Labrafac™ PG (propylene glycol dicaprylate/dicaprate), Labrasol® (PEG-8 glyceryl caprylate/caprate), Labrafil® M 1944 CS (oleoyl macrogol glycerides), Labrafac™ Lipophile WL 1349 (caprylic/capric triglyceride), Transcutol® HP (diethylene glycol monoethylether) were supplied as a gift from Gattefosse Pharmaceuticals, Gennevilliers, France. Methocel® E15 LV (Hydroxypropyl methylcellulose 15cp) was obtained as a gift from Colorcon (UK). Polyvinylpyrrolidone MW = 10,000 (PVP K-17), Span® 80 (sorbitan monooleate) were bought from Sigma Aldrich, St. Louis, USA. Cialis® tablets labeled to contain 20 mg tadalafil, batch no. 23,725; manufactured by Lilly del Caribe Inc., Puerto Rico released by Lilly, Spain. Potassium chloride, anhydrous disodium hydrogen phosphate B.P. 2001, Potassium dihydrogen orthophosphate, Sodium chloride, Hydrochloric acid, Tween® 80 (polyoxytheylene-20-sorbitan monooleate), Propylene glycol, Polyethylene glycol 400, Ethanol, Glycerin; were supplied from El-Nasr pharmaceutical chemicals company, Abu – Zaabal, Cairo, Egypt. All other reagents were of analytical grade and used as received. Used water was deionized, distilled water.

3. Methods

3.1. Determination of the equilibrium solubility of tadalafil in different media

Equilibrium solubility measurements of tadalafil in the various oils namely; Capryol™ PGMC, Capryol™ 90, Labrafac™ PG, Labrafil® M 2125 CS, Labrafac™ Lipophile WL 1349, surfactants (Tween® 80, Span® 80, Labrasol®), cosurfactants (Labrafil® M 1944Cs, Transcutol® HP) and co-solvents (glycerin, ethanol, propylene glycol (PG) and polyethylene glycol 400 (PEG 400)) were determined in duplicates. Excess amounts of tadalafil (50 mg) were added to 3 mL volumes of each vehicle in a well-stoppard glass vial. The vials were mixed (100 rpm) [25] and incubated in thermostatically controlled shaking water bath at 37 ± 0.5 °C for 72 h to reach equilibrium [26]. The equilibrated samples were withdrawn and centrifuged for 15 min at 5000 rpm to precipitate the undissolved tadalafil. The supernatant was filtered through Millipore® filter 0.45 μm (type μstar LB; Costar Corp., Cambridge, USA). After appropriate dilution with ethanol (0.1 mL of the filtrate of the sample was diluted to 10 mL with ethanol), spectrophotometric absorbance using UV/VIS spectrophotometer, (UV-1800 PC; Shimadzu, Kyoto, Japan) of the filtrates were measured at λmax of 284.4 nm. Their tadalafil content was calculated using the procedural constant obtained from the tadalafil calibration curve in ethanol. A blank was done for each mixture using the tested vehicle diluted with ethanol. Each experiment was done out in duplicate and the findings were represented as mean values (mg/mL) ± S.D.

3.2. Determination of surfactant/cosurfactant type and required hydrophilic-lipophilic balance (HLB) for emulsification of Capryol™ 90

3.2.1. Design of the experiment

A full mixed $7^1*3^1*2^1$ factorial design was used for the determination of surfactant/cosurfactant type and HLB required for the emulsification of Capryol™ 90. The design resulted in a total of 84 preparations. The study design included the evaluation of the impact of three independent factors namely; the surfactant type (Tween® 80 and Labrasol®) and the cosurfactant type which included, Span® 80, Transcutol® HP and Labrafil® M199, as well as the HLB values (6, 7, 8, 9, 10, 12 and 13) on the percent transmittance at 638.2 nm. Each experiment was done out in duplicate.

3.2.2. Preparation of different surfactants and cosurfactants in different ratios

The different mixtures of surfactant and cosurfactant were prepared in various ratios to obtain the predetermined HLB values of 6, 7, 8, 9, 10, 12 and 13 in glass vials. The vial was placed for 30 min in a thermostatic shaker with the temperature kept constant at 37 ± 0.5 °C at 100 rpm. The HLB mixture values could be calculated from the following equation:

$$\text{HLB mix} = \text{fa. HLBa} + \text{fb. HLBb}$$

Where HLBa presented the values of surfactant HLB and HLBb presented the HLB values of cosurfactant. fa and fb is the weight fraction of surfactant and cosurfactant, respectively [27].

3.2.3. Formation of the emulsion and assessment of the percent transmittance

Briefly, 300 mg of the surfactant and cosurfactant mixture with the assigned HLB value was added to 300 mg Capryol™ 90. Gentle heating to the mixture was done in a thermostatic water bath to 37 ± 0.5 °C to obtain homogenous components. Afterward, 50 mg were taken from each oil/surfactant mixture and diluted with distilled water to 50 mL in a conical flask. Emulsions were allowed to stand for 2 h. Finally, at 638.2 nm the percent transmittance was measured using distilled water as a blank. The results obtained were an average of two measurements [26].

3.3. Construction of ternary phase diagram

The oil, surfactant, and cosurfactant were plotted in a ternary phase diagram using SigmaPlot Software (Systat Software Inc., San Jose, CA, USA). Ternary mixtures were performed by varying the concentrations of oil, surfactant, and cosurfactant. However, the mixture of the components always added up to 100%. The selected oil (Capryol™ 90), surfactant (Tween® 80), and cosurfactant (Transcutol® HP) were investigated to recognize the regions where each point can emulsify spontaneously by dilution. The experiments were established in duplicates.

Table 1
Mean saturated solubility of tadalafil in different media.

Medium	Component	Saturated solubility (mg/mL) ± SD
Oil	Capryol 90	4.754 ± 0.100
	Capryol PGMC	3.599 ± 0.092
	Labrafac PG	0.453 ± 0.035
	Labrafac Lipophile WL 1349	0.465 ± 0.007
Surfactant\Cosurfactant	Tween 80	4.885 ± 0.347
	Labrasol	17.975 ± 0.176
	Span 80	0.578 ± 0.186
	Transcutol HP	21.145 ± 1.336
	Labrafil M 1944 CS	1.315 ± 0.106
Cosolvents	Ethanol	1.544 ± 0.056
	Glycerin	0.392 ± 0.105
	PG	2.301 ± 0.113
	PEG 400	29.303 ± 0.282

Data are the mean values (n = 2) ± SD.

3.3.1. Preparation of different mixtures used in the ternary phase diagram

One gram of each mixture was prepared by the addition of variable proportions of the oil, surfactant, and cosurfactant into a 10 mL capped glass vial. The components were mingled till homogenous in a shaking water bath at 37 ± 0.5 °C for 10 min. To test the efficiency of nanoemulsion formation of each point resulting from the phase diagram, dilution of one gram of the ternary mixture to 10 mL using distilled water, in a capped vial was done. Afterward, the mixture was gently agitated by inversion, to give a minimal amount of shear for self-emulsification/dispersion [16], till a homogeneous emulsion was formed. Visual observation was carried out immediately for the diluted nanoemulsions to investigate the occurrence of self-emulsification. Clear dispersions (≤200 nm) were used to draw the nanoemulsion area of the diagram. The boundaries of the self-nanoemulsification areas in phase diagrams were constructed using Sigma-plot 2000 software (Systat Software Inc., San Jose, CA, USA). The experiments were established in duplicates.

3.4. Characterization of the selected SNEDDS

Further investigations for the selected preconcentrates presented in Table 2 were carried out.

3.4.1. Rate of emulsification of the prepared systems

The ease of formation of emulsions was detected by tracking the time [22,28] while inverting the sample, required for the disappearance of the preconcentrate and formation of uniform emulsion upon adding 10 mL distilled water to one gram of the respective preconcentrate [26]. Each experiment was done out in duplicate.

3.4.2. Determination of the dilution effect on globule size

One gram from each of the selected formulation was diluted with either 10 mL or 250 mL of water and was gently inverted. Globule size was computed by photocorrelation spectroscopy using Zetasizer Nano ZS Zeta-globule sizer: Model nanoZS, Zetasizer nanoseries; (Malvern Instruments, UK). All values were established on the measurements of the intensity distribution, made at 25 °C and angle 173°. Each measurement was done in duplicates.

Table 2
Composition of the selected preconcentrates.

Code	Capryol 90	Tween 80	Transcutol HP
T1	10%	40%	50%
T2	10%	50%	40%
T3	10%	60%	30%
T4	10%	70%	20%
T5	10%	80%	10%
T6	10%	90%	0%

3.5. Optimization of the resultant SNEDDS

3.5.1. Addition of cosolvent

A full mixed 2^1*4^1 factorial design was used for further optimization of the saturated solubility of tadalafil in the selected preconcentrate (T4, and T5). The design resulted in a total of 16 preparations. The study design involved the investigation of the effect of two factors namely; the selected formula (T5 and T4) and the type of cosolvent (ethanol, glycerin, PEG 400, PG) on the globule size as detailed in the determination of the dilution effect on globule size, where one gram was diluted with 10 mL of water. In addition, tadalafil saturated solubility in one gram of the preconcentrate was measured as in the determination of the equilibrium solubility of tadalafil in different media. The cosolvent tested was added to the SNEDDS in 10% w/w. Each experiment was done out in duplicate.

3.5.2. Effect of precipitation inhibitor

Design of the experiment. A full mixed 3^1*2^1 factorial design was used to investigate the impact of two factors namely; the precipitation inhibitor type (PVP K-17 and HPMC 15cp) and % of PI (0%, 1.5%, 3%) on the percent cumulative drug dissolved at 5 min and 90 min from the *in-vitro* precipitation test. The design resulted in a total of 12 preparations.

Preparation of the SNEDDS containing PI. Preconcentrates with drug loads equivalent to approximately 80% of the equilibrium solubility (Seq), 20 mg tadalafil in 1.5 gm preconcentrate, were ultrasonicated for 15 min to aid the drug dissolution. The SNEDDS-PI formulation was obtained by dispersing either 0% or 1.5% or 3% w/w of the PI tested. The precipitation inhibitors used were either HPMC or PVP K-17 into the SNEDDS. The mixture was re-sonicated for 10 min using a bath sonicator (Model 275T, Crest Ultrasonic Corp, New York, USA) to acquire a homogenous dispersion.

*3.5.2.1. Characterization of the SNEDDS containing PI. **In-vitro precipitation test***. 20 mg tadalafil was loaded in 1.5 gm of the five investigated systems containing 0% PI, 1.5% PI, 3% PI (either HPMC or PVP). The SNEDDS-PI was added to 700 mL of 0.1 N HCl of pH 1.2. The *in-vitro* precipitation test was conducted using USP Dissolution Tester (Apparatus II, Model VK 700; Vankel Corp., USA), USP XXVIII rotating paddle apparatus, at a paddle speed of 100 rpm preserved at a temperature of 37 ± 0.5 °C. The paddle was placed at 2.5 cm from the bottom of the vessel. 5 mL solution samples were taken from the medium without replacement of the volume withdrawn (thus done in non-sink condition) at 5,10,15,20,30,40,50,60,75,90,120 and 240 min. The withdrawn samples were centrifuged at 5000 rpm for 10 min at 25 °C [29] and the supernatant was tested for its tadalafil concentration by measuring their UV absorbance at 283.2 nm against a blank formulation. Experiments were done in duplicate.

In-vitro Dissolution Study. A comparison of the *in-vitro* dissolution of tadalafil was carried out between the selected formula which is prepared by the addition of 3% HPMC to (10% Capryol™ 90, 62.2% Tween® 80, 17.8% Transcutol® HP, 10% PEG 400), the market product Cialis® (20 mg) and the tadalafil pure drug. The *in-vitro* dissolution was done as previously mentioned with the *in-vitro* precipitation test. However, some modifications were made where the dissolution from the selected formulations was done in 1000 mL, 0.1 N HCl [11]. The aliquots of 5 mL were taken at time intervals of 5, 10, 15, 20, 30, 45, 60, 90 and 120 min and were substituted with an equivalent amount of fresh dissolution medium to maintain a fixed dissolution volume. A blank, drug-free, was prepared likewise and was used as a reference to guard against the interference from the formulation components if present [30]. The supernatant solution was analysed spectrophotometrically for its tadalafil content by measuring the absorbance at

λmax 283.2 nm against a blank formulation in case of SNEDDS while against 0.1 N HCl in case of pure drug and market tablet. The experiment was done in duplicate. The percent cumulative drug dissolved was plotted against time.

3.6. Statistics

A statistical analysis applying one-way ANOVA followed by Duncan post hoc test was carried out. Statistical analysis was implemented using the SPSS® software, version 17 (SPSS Inc., Chicago, IL). The findings were considered significantly different when p-values were < 0.05. All preparations and assays were done in duplicate.

4. Results and discussion

4.1. Determination of the equilibrium solubility of tadalafil in different media

The convenient solubility of a drug in different excipients is a vital variable in the development of SNEDDS [31].

4.1.1. Saturated solubility of tadalafil in different oils

The mean concentration of tadalafil saturated solubility in each oil is shown in Table l. Drug solubility in the oil is an essential requirement in the SNEDDS formulation [12,18]. Consequently, the choice of suitable oil is based on which oil displays the maximal solubilizing potential for the drug [12].

The lipid class (fatty acid, monoglyceride, diglyceride, and triglyceride) plays an important factor in the formulation of SNEDDS [32]. Therefore, this study focused on the solubility of tadalafil in medium chain lipids (MC), since they offer various advantages. Medium chain lipids have higher drug solubilities when compared to long chain lipids (LC) [33], as a result of the higher polarity of MC lipids with respect to LC lipids [34]. Thus, Medium chain monoglycerides, fatty acids and monoesters of fatty acids are favoured vehicles for lipid delivery systems [18]. Additionally, Deckelbaum et al. [35] reported that medium chain triglycerides (MCT) were more soluble and mobile in the lipid/water interfaces. Also, Prajapati et al. [33] concluded that MCT, at a highly diluted concentration (1:100) could still form nanoemulsions. This ratio is typically present in the GIT after ingestion of a SNEDDS. Moreover, at room temperature medium chain lipids are liquids [33], which ease their use in the formulation.

The digestion of the lipid used in the formulation is another factor that is in favour of MCT. The more digestible the lipid used, the higher the drug dispersion, consequently, promoting its absorption and bioavailability from the SNEDDS [24]. Qian et al. [36] confirmed this finding. They observed higher rate and extent of drug dissolution in nanoemulsions prepared using MCT than those containing LCT, as a result of the superiority of MC mono, di and triglycerides as substrates for pancreatic lipase than LC triglycerides [37].

One-way (ANOVA) was applied for the drug-saturated solubility in each oil in order to statistically evaluate the differences among oils. It was evident that a notable difference ($p < 0.0001$) existed between the drug solubility in each oil, Duncan post hoc test was utilized to find where the significant variations occurred between groups, where it presented that tadalafil solubility significantly increased in the order of Labrafac™ PG and Labrafac™ Lipophile WL 1349 (homogenous subset) < Capryol™ PGMC < Capryol™ 90. Capryol™ 90 showed the highest ability to dissolve the drug in all of the medium chain oils investigated. This is because Capryol™ 90, a low molar volume oil, exhibits high polarity as indicated by its HLB (6) [13] and it has been reported that poor water-soluble drugs polarity makes them favour the solubilization in small/medium molar volume oils such as medium chain mono, di or triglycerides [19]. Albeit lipophile WL 1349 was also considered a medium chain triglyceride yet, they didn't efficiently solubilize tadalafil, probably as they lacked the amphiphilic nature of both Capryol™ 90 and Capryol™ PMG [26].

4.1.2. Saturated solubility of tadalafil in different surfactants and cosurfactants

In this study, the surfactants examined were Labrasol® and Tween® 80. The cosurfactants were Transcutol® HP, Span® 80 and Labrafil® M 1944 CS. Table 1 shows the mean tadalafil saturated solubility in each surfactant/cosurfactant. It is evident that Labrasol® had significantly ($p < 0.0001$) higher tadalafil saturated solubility than Tween® 80. The difference in tadalafil solubility in Tween® 80 and Labrasol® could be credited to the differences between them in both the length of the chain and the chemical structure [38].

Incase of cosurfactants, there was no significant difference between Span® 80 and Labrafil® M 1944 CS, whereas Transcutol® HP (HLB 4.2) [13] had significantly higher tadalafil saturated solubility than either.

4.1.3. Saturated solubility of tadalafil in different cosolvents

Table 1 shows the mean tadalafil saturated solubility in each cosolvent. The one-way ANOVA results presented a significant difference ($p < 0.0001$) between the tadalafil saturated solubility in each cosolvent. There was a significant difference between all cosolvents used in the order of glycerin < ethanol < PG < PEG 400. The cosolvents results could be attributed to the difference in their structure as indicated by their different dielectric constant value (δ) at room temperature, where glycerin has the value of 42.5, PG 32, PEG 400 12.4 [39], and ethanol 24.2 [40]. As the solvent polarity decreased the solubilization of tadalafil increased with the exception of PG. This exception in behavior indicates that there are other factors influencing the solubilization of tadalafil in the cosolvent other than the polarity of the solvent.

4.2. Determination of surfactant/cosurfactant type and required HLB for emulsification of Capryol™ 90

Many studies relied on both the drug solubility and self-emulsification efficiency to choose the surfactant/cosurfactant [13], however, if the two targets conflicted, self-emulsification properties were given priority [13]. Selection of the surfactant on the bases of highest drug solubility is questionable as it is not necessary that the surfactant with highest drug solubility exhibits the required oil solubilization [19]. In fact, each type of oil would require a particular HLB value to formulate a stable emulsion [19], as well as the surfactant/cosurfactant chemical compatibility with the oily phase [41]. Thus, the selection of surfactant or cosurfactant in this study was determined primarily by their emulsification efficiency rather than their capability to solubilize tadalafil. Yet, it would have been an extra privilege if the surfactant and cosurfactant of choice showed also high solubilization to tadalafil.

The construction of a stable self-emulsifying preparation demands a suitable combination of low and high HLB surfactant [13], thus mixtures of surfactants are used to provide the required HLB [21]. Various references concluded that the formulation of SNEDDS requires emulsifiers with HLB higher than 10 [19] as well as co-emulsifiers with HLB values extending from 4 to 6 [18]. In this study, it was taken in attention that an HLB value between 8 and 14 is mandatory to obtain an aqueous emulsion [42]. The surfactant choice is critical since it affects the resultant globule size of the emulsion [12].

Moreover, non-ionic surfactants show numerous advantages such as, being less toxic than ionic surfactants [18], reported minimal effect by pH and ionic strength changes [18], ability to produce reversible alteration in the intestinal mucosa [20], thereby enhancing drug permeability and absorption [43], in addition to the reported relatively stable lipid droplets (coated with non-ionic surfactants) to exposure to simulated oral and gastric fluids [36]. Furthermore, o/w nanoemulsion prepared using non-ionic surfactants are more likely to be stable *in-vivo* [19].

With respect to the importance of the chemical compatibility

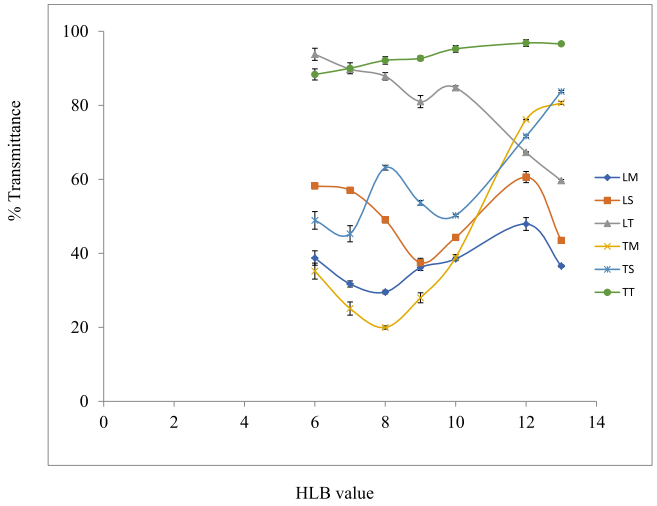

Fig. 1. The percent transmittance of the different emulsions prepared using different surfactant/cosurfactant mixtures at different HLB values.

between the surfactant/cosurfactant mixture and oil, Wang et al. [27] recognized that the surfactant structure had an extensive impact on the resultant emulsion, as was also reported by multiple references.

In conclusion, since a stable emulsion requires an emulsifying agent with an ideal HLB value, as well as, a chemical nature suitable for the emulsion components, therefore the emulsifier of choice is concluded mainly by experimental methods [41].

4.2.1. Formation of the emulsion and assessment of the percent transmittance

Percent transmittance was used as a response factor to assess which surfactant/cosurfactant mixture and HLB value would improve the nanoemulsification ability. The percent transmittance is an optical property used to assess the transparency of formulations. Since SNEDDS is characterized by oil globule size less than 100 nm and a dispersion that is optically clear, consequently the high values (towards 100%) indicated a transparent and isotropic SNEDDS, while the low values indicated a turbid formulation [44].

Fig. 1 presents the percent transmittance versus surfactant/cosurfactant mixture and HLB value, respectively, where the mean percent transmittance for the different formulae ranged from 19.95 ± 0.43% to 96.83 ± 0.91%.

Percent transmittance values were increasing as the HLB value increased except for Labrasol® group. This could be endorsed to the decreased mean globule size with increasing the HLB value, as a result of the presence of the surfactant at the aqueous-oil interface, hence stabilizing the oil droplets. However, in some occasions, the average globule size might grow with incrementing the surfactant concentrations, as a result of the interfacial rupture induced by increased water penetration into the oily phase [9]. Another explanation attributed this phenomenon of globule size increment to the decrease of the cosurfactant ratio. The decrease of cosurfactant could have resulted in higher bending stress and rigidity of the interface, with a concomitant decrease in the flexibility of the interfacial film, which in turn fails to withstand the curvatures needed to form nanoemulsion [13], leading to emulsions with larger globule size.

The effect of the formulation variables namely; surfactant type, cosurfactant type and HLB values on the percent transmittance were assessed with analysis of variance of the factorial design. The ANOVA results showed that all the tested variables had a significant effect on the percent transmittance.

The percent transmittance was significantly ($p < 0.0001$) affected by the surfactant type, where Tween® 80 had significantly higher percent transmittance. This indicates that Tween® 80 emulsification ability was better than Labrasol® although Labrasol® had higher tadalafil solubilizing power. This could be attributed to the structural difference between the two surfactants since they both have similar HLB values.

The percent transmittance was significantly affected by the cosurfactant type. Duncan post hoc test showed that there was a significant difference in percent transmittance between the three cosurfactants used (Labrafil® M1995 < Span® 80 < Transcutol® HP).

Transcutol® HP showed the highest percent transmittance. This could be associated with the decrease in globule size as a result of the better emulsification, as a consequence of decreasing the surface tension, leading to higher interfacial stabilization. It is worth mentioning, that although Span® 80 had a similar oily part (oleate) as the Tween® 80, yet it didn't exhibit the best emulsifying mixture with Tween® 80. This could be explained by Wang et al. [27] results that suggested that nanoemulsion with smaller globule size is favoured by inequality in the hydrocarbon chain length. The unequal surfactant chain length is expected to lead to a more disarranged surfactant/oil interface, hence, producing a region of enhanced oil mixing [42].

Therefore, Transcutol® HP was selected as the cosurfactant of choice in the development of SNEDDS since it could form spontaneous nanoemulsions, as well as improve the tadalafil saturated solubility in the preconcentrate [13].

The HLB value also had a significant effect on the percent transmittance where the HLB 12 had the highest percent transmittance with all surfactant mixtures.

4.3. Construction of ternary phase diagrams

Ternary phase diagrams were established in the absence of tadalafil [13]. The aim of the phase diagram was to identify the self-emulsifying regions and to optimize the oil percentage in the SNEDDS formulations [45]. For simplicity, the effect of the aqueous phase was neglected (considered as a constant factor). The oil, surfactant and cosurfactant components were used to identify the self-nano emulsifying region post-dilution on the ternary phase diagrams [13]. The ternary phase diagram is presented in Fig. 2. The development of self-emulsifying formulations with high surfactant ratio has become increasingly common [46].

4.4. Characterization of the selected SNEDDS

To evaluate the ability of the preconcentrate mixture to self-emulsify into SNEDDS, two factors were tested namely; the rate of emulsification [14] and the resultant globule size [20].

4.4.1. Rate of emulsification of the prepared systems

The SNEDDS required only few flask inversions for homogenous emulsion formation. The emulsification rate was swift within few seconds with no significant difference between formulations to be measured accurately [22].

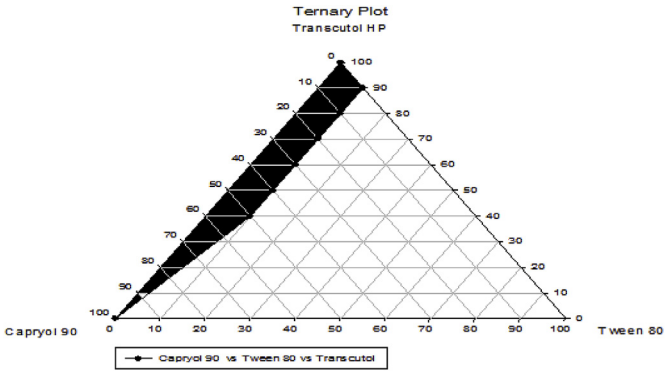

Fig. 2. Ternary phase diagram between tween 80, transcutol HP and capryol 90. The shaded area indicates the formation of clear microemulsion.

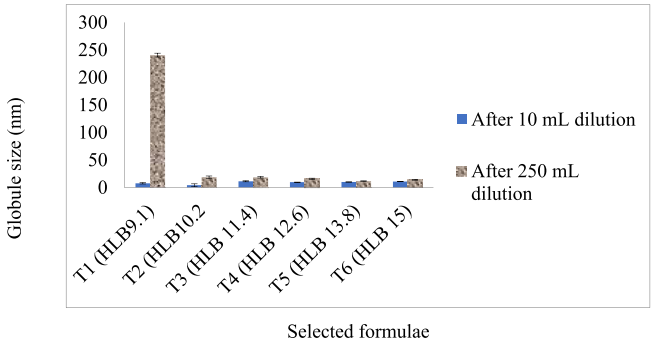

Fig. 3. Mean globule size of selected formulae systems after dilution with 10 and 250 mL using distilled water.

4.4.2. Determination of the dilution effect on globule size

Globule size is one of the vital factors that significantly affect drug absorption [30], as well as the rate and extent of drug dissolution [47].

Since according to the BCS, the GI fluid volume is considered to be 250 mL [33], therefore the mean globule size of the selected SNEDDS was determined after dilution with distilled water (10 mL and 250 mL). The results are presented in Fig. 3 showing the range of globule size after 10 mL dilution to be from 4.09 ± 2.48 nm to 11.2 ± 0.92 nm. However, the mean globule size after 250 mL dilution ranged from 11.65 ± 0.19 nm to 240.5 ± 3.42 nm. The globule size analysis results revealed that all of the selected systems, except T1 had an average globule size value < 50 nm (after both the 10 ml and 250 mL dilution), thus fulfilling the SNEDDS criteria. This could indicate that the usage of the appropriate surfactant/cosurfactant mixture, which effectively diminished the free energy of the system, lead to a small globule size [48]. In the present study, the globule size was shown to be kept stable at the different dilution volumes over the HLB range (11.4–15).

4.5. Optimization of the resultant SNEDDS

4.5.1. Addition of cosolvent

The main reason cosolvents are investigated in this study is to promote the solubility of tadalafil in the preconcentrate [13]. It was reported that drug absorption was related to the amount of solubilized drug rather than the fraction suspended. Thus, efficient absorption due to improved dissolution and solubilization of the drug occurs when the drug is dissolved rather than suspended as a solid drug in the lipid phase [47]. Consequently, the aim was to investigate the effect of addition of ethanol, propylene glycol, glycerin, and PEG 400 on the tadalafil saturated solubility in the SNEDDS as well as on the globule size of the SNEDDS.

4.5.1.1. Determination of the globule size of tadalafil in the optimized SNEDDS containing different cosolvents. Fig. 4 (a) shows the mean globule size for the formulae. The mean globule size range was from 7.41 ± 2.28 nm to 30.01 ± 2.11 nm.

The ANOVA shows that the formula type had a significant effect ($p < 0.0001$) on the globule size, where T4 was significantly smaller than T5. This could be attributed to the fact that Smix ratio (7:2) was nearer to the HLB 12, which had the highest percent transmittance i.e. smallest globule size, in comparison to the 8:1 ratio.

The cosolvent type had a none-significant effect on the globule size which could indicate that none of the used cosolvents affected the globule stability.

4.5.1.2. Determination of the tadalafil saturated solubility in the optimized SNEDDS containing different cosolvents. Fig. 4 (b) shows the mean tadalafil saturated solubility for the different formulae. The mean tadalafil saturated solubility range was from 10.855 ± 0.431 mg/mL to 16.65 ± 0.593 mg/mL. The ANOVA shows no significant difference

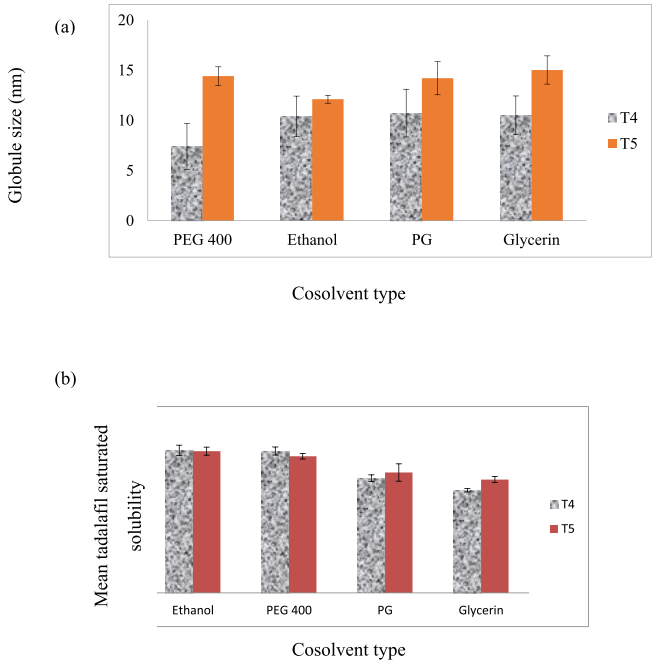

Fig. 4. Addition of cosolvent effect on mean globule size and mean tadalafil saturated solubility: (a) Mean globule size of the different formula types with different cosolvents. (b) Mean tadalafil saturated solubility in different formula types with different cosolvents.

between the formula types tested on the tadalafil saturated solubility.

However, the cosolvent type had a significant effect on the drug-saturated solubility. It is apparent that PEG 400 had the highest tadalafil saturated solubility in the preconcentrate, this could be credited to the evident high solubilization of the drug in PEG 400.

4.5.2. Effect of precipitation inhibitor

Effective absorption might be hindered by drug precipitation in the GI lumen. Thus, precipitation should be minimized and the drug should be maintained in a solubilized form for a duration long enough at the site of absorption [20]. Oral nanoemulsions are subjected to dilution by the GI fluids, where gradual desorption of the surfactant occurs [49]. Cosolvent solubilization capacity could be reduced due to dilution in the bulk phase [15]. It is worth mentioning that drug precipitation is affected by the extent of the contribution of hydrophilic surfactant and cosolvent in the drug solubility in the preconcentrate [50]. The PI could inhibit and/or hinder the drug precipitation through interrupting the nucleation and/or crystal growth process [43]. The selection of polymeric precipitation inhibitor is still based on experimental trials as no structure-activity correlations have been yet established [51].

4.5.2.1. Characterization of the SNEDDS containing PI. ***In-vitro precipitation test.*** *In-vitro* precipitation assay was done in non-sink condition to study the precipitation inhibiting capacity of hydrophilic polymers. To estimate drug precipitation behavior precisely, it is mandatory to remove the precipitated tadalafil from the dispersion system. Chen et al. [52] reported the superiority of centrifugal separation over filtration in terms of the recovery and repeatability probably due to eliminating the waste of the drug by adsorption to the filter, thus centrifugation was used in this study.

Fig. 5 (a) shows the percent cumulative drug dissolved for the drug formulae. The decline in the amount of dissolved drug reveals that precipitation had occurred [52]. The effect of various formulation variables namely; the PI type and concentration on the percent cumulative drug dissolved at 5 and 90 min were assessed with analysis of variance of the factorial design.

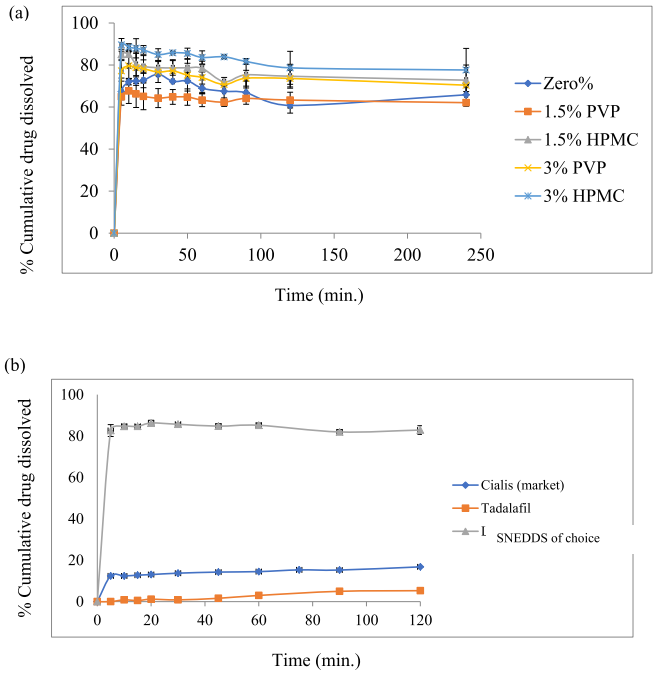

Fig. 5. (a) *In-vitro* precipitation test of tadalafil from the different formulae. (b) I*n-vitro* dissolution profiles of pure drug tadalafil, market product and selected SNEDDS formula.

The ANOVA results show that the PI type and concentration significantly affect the percent cumulative drug dissolved at 5 ($p < 0.008$) and 90 min ($p < 0.05$), where HPMC was significantly better than PVP K-17. In addition, the 3% was better than 0% and 1.5% which had no significant difference in between (homogenous subset) as indicated by the Duncan post hoc test results. Thus, the addition of 3% HPMC significantly increased the rate of dissolution at time 5 min and delayed the precipitation over the 90 min of dissolution.

The difference in behavior between HPMC (a more hydrophobic polymer) and PVP (a more hydrophilic polymer) is mostly related to their variation in hydrophilicity. This may be due to the substantial substitution of methyl groups in case of HPMC rendering it more hydrophobic when compared to PVP. Also, the methyl group might preferably adsorb on the surface of the nuclei during the nucleation phase, resulting in amorphous nuclei instead of crystalline nuclei [45]. Moreover, HPMC molecular structure offers more hydrogen bonding groups per monomer unit than PVP [52].

An optimum formulation of choice was obtained by dissolving 20 mg tadalafil in a mixture containing 10% Capryol™ 90, 10% PEG 400 and 80% of a mixture composed of (Tween® 80 to Transcutol® HP (7:2)), after which 3% HPMC was dispersed in the preconcentrate). 10% of Capryol™ 90 was used as indicated from the ternary phase diagram and the saturated solubility of tadalafil in different oils. 10% PEG 400 was used since it had the highest tadalafil solubility in the preconcentrate. 80% of the mixture composed of (Tween® 80 to Transcutol® HP (7:2)) was used as concluded from the percent transmittance results as well as the ternary phase diagram results. 3% HPMC was used as indicated by the *in-vitro* precipitation test.

4.5.3. In-vitro dissolution study

Fig. 5 (b) shows the tadalafil mean percent cumulative drug dissolved from each formula (pure drug, market tablet and the selected SNEDDS). It could be observed that the *in-vitro* dissolution of the drug from the SNEDDS formula was significantly superior ($p<0.0001$) to the other two formulae investigated. The *in-vitro* dissolution assay revealed that 80% of the drug was dissolved from the SNEDDS formula in 5 min, while about 12% of the drug was dissolved from the market Cialis® tablet. Prajapati et al. [33] considered the cumulative drug release of 80% a complete release. In addition, tadalafil was dissolved from SNEDDS formula within 5 min with no observed lag time. The absence of lag time could probably be a result of using monoglyceride [33] as an oily phase, as well as the absence of gel formation in the phase diagram. This enhancement in tadalafil dissolution could be a result of increasing the surface area as a result of the formation of nanoemulsion droplets during the dissolution process. The dissolution of tadalafil from the pure drug and the marketed product was relatively low and this might be resulting from the poor solubility of the drug in water.

5. Conclusion

The poor dissolution of tadalafil was significantly improved through formulating it into SNEDDS, which included five main components that provided various advantages. SNEDDS enhanced the solubility of tadalafil due to the distinct surface area increment as a result of nanosized emulsion droplets formation. Additionally, the use of Capryol™ 90, and the suitable surfactant/cosurfactant mixture of Tween® 80 and Transcutol® HP resulted in a quickly and easily dispersed nanoemulsion. The use of PEG 400 as a cosolvent enabled the dissolution of tadalafil (20 mg) in the preconcentrate, while the PI resulted in a significant decrease in the expected drug precipitation.

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