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Preparation and Characterization of Olmesartan Medoxomil-Loaded Polymeric Mixed Micelle Nanocarrier

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Abstract

Olmesartan medoxomil (OLM) is a selective angiotensin II-receptor antagonist that effectively lowers blood pressure. It has low bioavailability when taken orally, around 26%, owing to limited solubility in water. OLM is therefore categorized as class II in the Biopharmaceuticals Classification System (BCS), suggesting that it has high permeability and low solubility. By generating nanomicelles, this work attempts to increase aqueous solubility and dissolution rate of OLM. Mixed polymeric nanomicelles made up of soluplus (SLP) with tween 80 (TWN80) and SLP with d-α tocopheryl polyethylene glycol 1000 succinate (TPGS) had been prepared in different gravimetric ratios. The nanomicelles holding OLM were developed using the film hydration technique and assessed for their particle size, polydispersity index (PDI), entrapment efficiency (EE%), and drug loading capacity (DL%), of the micellar dispersion. The optimized F4 formula comprising 100 mg SLP and 60 mg TWN 80, displayed a particle size of about 71.1±1.28 nm, PDI of 0.116±0.021, an EE% of 92±1.5, a DL% of 11.5±1.43, and enhanced in-vitro release compared to aqueous drug suspension. Using iodine as a hydrophobic probe, the critical micelle concentration (CMC) of F4 was determined to be 0.0112±0.001 mg/ml, which is lower than the theoretically computed CMC of 0.01284 mg/ml calculated using an equation. The preparation of F4 by the direct dissolution method was also established at different stirring periods (3,12, and 24 hours) and by two techniques, to evaluate the effect of the preparation method on particle size, PDI, EE%, and DL%. The results showed a significantly larger particle size, PDI, and lower EE% ($p<0.05$) than the thin film hydration method. Furthermore, the physical and chemical characteristics of F4 mixed nanomicelles were monitored over three months, both at room temperature and under refrigerated circumstances (4°C), and it was determined that the nanomicelles remained stable. The morphological analysis was conducted using a field emission scanning electron microscope (FESEM), which detected the presence of nanostructures with a spherical form and a diameter that matched the particle size measurements. The results of the existing study confirmed that OLM mixed nanomicelles are likely nanocarriers to improve solubility.

Key word: Mixed nanomicelle, Solubility, Critical micelle concentration

Introduction

Pharmaceutical compounds that exhibit inadequate solubility pose challenges for conventional formulation methods. These drugs manifest issues including delayed onset of action, suboptimal oral bioavailability, lack of dose proportionality, inability to attain steady state plasma concentration, and undesirable side effects [(1)]. By employing novel drug delivery systems that provide advantages such as decreased dosing frequency, reduced dosage magnitude, targeted drug delivery to specific sites, enhanced permeability, and improved oral bioavailability, these obstacles may be surmounted [(2)]. By increasing the surface area of drugs, nanosizing techniques have been implemented to enhance the oral bioavailability of substances that are difficult to solubilize in water and to accelerate drug dissolution. A large surface area facilitates enhanced interaction with the solvent, thereby leading to an increase in solubility [(3)]. Particularly promising in the discipline of drug delivery system development are nanotechnology-based approaches that target potent medications that have encountered hurdles in clinical trials resulting from suboptimal bioavailability, inadequate solubility, and low permeability, among other undesirable biopharmaceutical characteristics. Nanotechnology-based approaches that are frequently employed in the advancement of delivery systems include polymeric nanoparticle, solid lipid nanoparticles, nanoemulsion, dendrimers, micelles, and liposomes [(4,5)]. Extensive research has been conducted on nanotechnology-based solutions to enhance the oral bioavailability of antihypertensive medications [(6)]. Nano-micelles are being utilized as effective means to encapsulate pharmaceuticals that have limited solubility in water. The core–shell architecture of micelles hinders the access and existence of water within its internal core. The essential characteristic of micelles is that they

generate an appropriate environment for the entrapped drug when compared to the free drug [7]. Micellization refers to the spontaneous arrangement of amphiphilic copolymer molecules, or amphiphiles, into orientated colloidal aggregates called micelles in an aqueous solution. Polymeric micelles are nanoparticles that have a core-shell configuration and are formed by self-assembly in water above the critical micelle concentration (CMC). The hydrophobic core of these nano-carriers can serve as a microenvironment for solubilizing pharmaceuticals that have low water solubility, through hydrophobic interaction and/or hydrogen bonding. Additionally, it can protect the encapsulated compounds from becoming inactive in biological substances, while allowing their water-loving outer layers to be exposed to the external surroundings [8-10]. Polymeric micelles that are generated from a single polymer frequently suffer from instability, inadequate drug loading capacity, or wide size distribution, mainly because of limitations in the quantity of accessible building blocks [11]. Mixed micelles are mixes of amphiphile systems (which comprise surfactants, polymers, and copolymers) that form micellar aggregates. They display characteristics and features that set them apart from individual amphiphiles [12]. The combination of two or more block co-polymers in mixed micellar nanocarriers improves the qualities of single micelles in terms of carrier stability, precise size control, and easy surface modification with diverse components. This also enhances the effectiveness of drug encapsulation [13].

The polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus®) is a recently developed amphiphilic polymer that effectively improves the solubility of certain hydrophobic medicines [14]. The polymer has a low critical micellar concentration (CMC) of 0.76×10^{-3} % w/v, which imparts excellent stability to its aqueous micellar dispersions [15]. Another biomaterial that is commonly used for this purpose is D-α-tocopheryl polyethylene glycol (PEG) 1000 succinate. This substance is a water-soluble derivative of vitamin E and PEG, derived from natural sources. It is commonly used as a biomaterial to create micelles [16]. Tween 80, also known as Polysorbate 80, is a biocompatible nonionic surfactant that enhances the solubility of hydrophobic medicines in water by forming micelles. TWN80 can increase the permeability of certain medicines through biological membranes. TWN80 is selected as a surfactant because it demonstrates higher biosafety, biodegradability, and biocompatibility in comparison with high molecular weight polymeric surfactants. This is particularly relevant considering the extensive utilization of this surfactant in food and medicinal goods. They have received approval from the US Food and Drug Administration to be used in specified foods, with a maximum allowable concentration of 1% [17,18].

The drug compound OLM, is a highly effective angiotensin II receptor antagonist that can be administered orally. OLM is a type of prodrug that undergoes hydrolysis by esterase in the intestines and plasma. This process converts OLM into its active form, olmesartan, when it is taken orally. Angiotensin II receptor blockers are potent regulators of blood pressure that competitively impede the interaction between angiotensin II and its receptor, hence reducing vasoconstriction. Olmesartan has physiological effects that include lowering blood pressure, reducing cardiac activity, decreasing aldosterone levels, and increasing sodium excretion [19]. Because OLM has limited solubility in water, it has a low rate of absorption when taken orally and bioavailability (~ 26%). As a result, the Biopharmaceuticals Classification System (BCS) categorizes olmesartan as class II, indicating that it has low solubility and high permeability [20]. Several OLM nanoparticles were developed to solve this problem, including OLM nanostructured lipid carrier [21], OLM polylactic acid glycolic acid nanoparticle [22], OLM nanoemulsion [23] and others. These methods showed aptitude for improving OLM oral delivery.

The present work aims to develop a polymeric mixed micelle system that contains the lipophilic drug OLM and investigates the effect of carrier's type and concentration on preparation and characterization of nanomicelle. SLP, and TPGS, polymeric surfactant, and TWN 80 surfactant, biomaterials, were used to prepare mixed micelle in order to enhance OLM's dissolution rate.

Materials and methods

Material

From the company of Li (China), OLM was bought. BASF, (Germany) is the source where SLP was obtained. TWN 80 was provided by Indiamart (India). The source of (TPGS) was Hangzhou, Hyperchem (China). Methanol HPLC grade was provided by Chem-Lab (Belgium). The other compounds used are all classified as analytical.

Method

Preparation of OLM-loaded mixed micellar system

Preparation by thin film hydration method

Five ml of methanol was added to a round-bottom flask to dissolve 20 mg OLM and the necessary amount of SLP. TPGS or TWN 80 was dissolved in 10 ml methanol in another beaker. The temperature of these two solutions was raised to 40°C, and stirred for 30 minutes. With constant stirring, the second solution was added to the first solution. The resultant solution was evaporated at 60°C using a rotary evaporator and vacuum in order to obtain a thin film. Then the film was allowed to air dry overnight to remove any remaining moisture [24]. The film was then hydrated by stirring on a magnetic stirrer for two hours at 300 rpm and 50°C

with deionized water. The created dispersion was allowed to stay until a uniform transparent mixture could be realized at that point it was used, evaluated and characterized [25]. The component of micellar dispersion is represented in Table 1.

Table 1. The component of OLM mixed micellar dispersion in (mg)

Formulation code	OLM	SLP	TWN 80	TPGS	Deionized water(ml)
F1	20	40	60		10
F2	20	60	60		10
F3	20	80	60		10
F4	20	100	60		10
F5	20	120	120		10
F6	20	60	180		10
F7	20	180	60		10
F8	20	40		60	10
F9	20	60		60	10
F10	20	80		60	10
F11	20	100		60	10
F12	20	120		120	10
F13	20	60		180	10
F14	20	180		60	10

Preparation of OLM mixed micelle (selected formula) by direct dissolution method

Two different techniques were developed for the preparation of the selected formula by direct dissolution. The first one (T1), which involves adding an adequate quantity of the polymers described in the specified formula to 10 ml of deionized water, and then stirring the solution for three hours at a speed of 100 rpm. After obtaining a clear solution (it takes around three hours for polymers to be completely dissolved in water), 20 mg of OLM was added to the mixture, and it was stirred at a speed of 100 rpm for three, twelve, and twenty-four hours at a temperature of 25°C.

The second (T2) technique involves the simultaneous addition of 20 mg of the medication and an adequate quantity of the polymer to deionized water. The solutions were then agitated at a speed of 100rpm for three, twelve, and twenty-four hours at room temperature [8,26].

Characterization of mixed micellar dispersion particle size and poly dispersibility index measurement

Particle diameter and PDI possibly will be used to investigate the physical properties of OLM nanomicelles. Dynamic light scattering was used in this analysis at a temperature of 25°C and a backscatter angle of 173° using (Malvern Instruments, Zetasizer NanoZS, UK). All measurements were conducted in triplicate, and the mean ± standard deviation (SD) was determined.

Entrapment efficiency and drug loading capacity

The dialysis centrifugation method was used to calculate the EE% and DL% of OLM in nano micelles. The procedure involved centrifuging 2ml of formula for 30 minutes at 6000 rpm and 25°C in a bag of 10 KD molecular weight cut off dialysis membrane (Amicon®, Ultra -4Merck Millipore Ltd. Ireland) that was precisely fastened to the top of a centrifuge tube with a cup [27]. The amount of drug contained within micelle was determined by indirect method through exploring the unentrapped drug spectrophotometrically using calibration curve of OLM in methanol.

The following equations were used to compute the E E and DL [28]:

$$\mathbf{EE\%} = \frac{\textit{weight of OLM encapsulated in micelle}}{\textit{theoretical weight of OLM added}} \boldsymbol{x100} \quad \textbf{(1)}$$

$$\mathbf{DL\%} = \frac{\textit{weight of OLM encapsulated in micelle}}{\textit{Total weight of micelle (OLM+polymer)}} \boldsymbol{x100} \ \textbf{(2)}$$

Optimization of preparation conditions

The type of polymeric surfactants and their ratios (SLP/TWN 80 and SLP/ TPGS) were adjusted in this study, as the kind and ratio of pharmaceuticals and excipients take significant impact on the particle size, encapsulation effectiveness, and drug loading of the micelle. The indexes employed for optimization were particle size, PDI, and encapsulation efficiency [29].

In vitro release of OLM from mixed micellar dispersion

OLM micelles were examined for their in vitro release behavior utilizing the dialysis filter bag method and phosphate buffer pH 6.8 as the release medium [22].2.5 ml of micellar dispersion was added to the dialysis bag MWCO (12000-14000 Da) and both ends were sealed after it had been soaked overnight in phosphate buffer pH 6.8.

The bag was submerged in 500ml of the release media at 50 rpm and 37°C. At designated times (5, 10, 15, 30, 45, 60, 90, 120, and 180 minutes),5 ml was taken from the release media and fresh dissolution media was added for replacement [30]. Utilizing the calibration curve of OLM in phosphate buffer pH 6.8, the removed sample was spectrophotometrically analyzed at the absorbance wave length of 256 nm. The mean percentage of medication released was plotted versus time to compare the release patterns of these formulations. The release efficiency percentage (DE%) was computed to assess the improvement in release by mixed micelles. This was done by calculating the area under the release curve (AUC) at 60 minutes using DD solver software program. The expression is shown as a percentage of the rectangle's area, which corresponds to a 100% release, for a time of 60 minutes. This is determined by the following equation: [31,32]

$$DE\% = \frac{\int_0^t c.dt}{C100.T} x100 \qquad (3)$$

Where, C represents the drug released percentage as a function of time t, C100 represents the complete drug release (100%) and T represents the total time of drug release.

Critical Micelle Concentration CMC

Using iodine as a hydrophobic probe, the CMC of empty micellar dispersion of F4 and F11 with SLP/TWN 80 and SLP/TPGS respectively of the total concentration of (1.6%) in deionized water was assessed spectrophotometrically at 366 nm. In 50 ml of deionized water, 0.5 g of iodine and 1.0 g of potassium iodide (KI) were dissolved to produce the KI/I2 standard solution [33,34]. The aforementioned mixture of surfactant was created in various concentrations (between 0.00001% and 0.1%w/v). Each of the polymer mixtures, at varying concentrations, received 25 µl of the KI/I_2 standard solution. Following 12 hours of storage in dark at room temperature, the absorbance at 366 nm was measured. After three repetitions of each experiment, the mean absorbance was calculated. By graphing absorbance against the logarithm of polymer concentration, the CMC value of the polymer mixture can be determined to be the concentration of polymer at which a significant increase in absorbance was observed [35].

Theoretical Critical Micellar Concentration (CMC)

CMC theoretical value for the polymeric dispersion of F4 and F11 was calculated using the following equation [36]:

$$\frac{1}{CMC\ theoretical} = \frac{X\ SLP}{CMC\ SLP} + \frac{X(P)}{CMC(P)} \qquad (4)$$

where CMC_{SLP} and $CMC_{(P)}$ represent the published CMC values of SLP and TWN80 or TPGS, respectively, and X_{SLP} and $X_{(P)}$ denote the molar fractions of SLP and TWN80 or TPGS, respectively. The molar fractions of SLP and TWN 80 or TPGS were determined by dividing the number of moles of the constituent of mixed micelle by the sum of the moles of the mixture's components.

Micelle stability

The optimized OLM loaded mixed micellar dispersion was kept at 4°C and at room temperature for 90 days to test the storage stability of the ideal formulation. The drug-loaded micelles' EE%, PDI and particle size were inspected [37].

Morphological characterization by field emission scanning electron microscope (FESEM)

A drop of optimized micelle was placed and air dried onto aluminum stubs. Using double-coated adhesive tape, the slide was secured to the specimen holder. Next, a sputter coater was used to apply gold to the slide while it was under vacuum for ten minutes. This was done to establish a consistent coating that would allow for high-quality scanning electron microscopy photographs. Several magnifications were used to attain the images. (FESEM, INSPECT F50, Holland) [24,38].

Statistical analysis

To determine whether the variations in the factors that were applied are significant at the level of ($P < 0.05$), highly significant at level of ($P < 0.005$) and non-significant at the level of ($P > 0.05$), the research's findings were presented as the mean of three triplicate models ± (SD). One-way analysis of variance (ANOVA), and t-student test are employed to detect the difference in data [39].

Results and discussion

Particle size measurement and poly dispersibility index

Preparation of nanomicelle by thin film hydration method

The present work exploited SLP/TWN 80 and SLP/TPGS different ratios to determine their significance on micelle properties and behavior. (F1-F4) and (F8-F11) with total polymer concentrations of (1, 1.2, 1.4 and 1.6%) for formulas F1and F8, F2 and F9, F3 and F10, and F4 and F11 respectively, represent the effect of SLP concentration. While the formulas (F5-F7) and (F12-F14) with 2.4% total polymer concentration represent the effect of polymer ratio. The ratio of 2:2 was dependent for F5 and F12, the 1:3 ratio for F6 and F13, and 3:1 for F7 and F14 respectively. The results of particle size measurement, PDI, EE% and, DL% are given in Table 2.

Table 2. Particle size, poly dispersibility, entrapment efficiency and drug loading of OLM mixed micelles using thin film hydration method (mean ±SD, n=3)

Formula number	Particle size (nm)	PDI	EE%	DL%
F1	277±3.8*	0.2489±0.02	72.4±2.1	12.07±0.15
F2	189.4±3.7*	0.502±0.12	78.1±0.05	11.16±0.78
F3	125±1.2*	0.2413±0.01	84.9±0.5	10.6±1.09
F4	71.1±1.28*	0.116±0.02	92±1.5	11.5±1.43
F5	62.76±2.8**,***	0.1348±0.03	92.6±2.9	7.716±0.58
F6	68.1±1.3**	0.187±0.013	91.8±1.35	7.65±0.21
F7	58.12±4.2**	0.0943±0.01	95.45±1.8	7.916±0.11
F8	461.1±4.4*	0.2644±0.03	66.9±1.12	11.16±1.08
F9	311.7±3.1*	0.0525±0.01	70.4±0.60	10.08±1.56
F10	119.9±2.9*	0.2011±0.06	77.33±0.9	10.89±0.07
F11	95.5±2.4*	0.2341±0.03	87.1±0.86	9.68±0.33
F12	109.1±3.3**	0.195±0.02	84.2±0.31	6.48±0.06
F13	308.1±4.5**	0.693±0.2	70.4±0.09	5.42±0.11
F14	102.3±2.2**	0.2266±0.1	91±0.87	7.0±0.09

Note: *=significant difference by increasing SLP concentration, **=significant difference between different polymer ratio, *** =nonsignificant difference between (2:2) and (3:1) ratio.

The results revealed that as SLP concentrations increased the particle size significantly decreased ($p<0.05$) and the EE % increased concerning all formulations. The change in TWN 80 ratio has a significant effect on particle size and EE % values at ($p<0.05$). The particle size of SLP/TWN 80 nanomicelles is smaller than that of SLP/TPGS one, although the TPGS ratio had a considerable impact on particle size and EE% which is significant at $p<0.05$. Increasing concentration of TPGS and decreasing concentration of SLP resulted in an increase particle size. The same outcome was observed for SLP/TPGS silymarin nanomicelle; by increasing the concentration of TPGS, the particle size increased [40]. The DL% for SLP/TWN80 nanomicelle is larger than DL% of the corresponding SLP/TPGS micelle indicating greater percentage of mass of the nanoparticle that is due to the encapsulated drug. Low PDI confirms that every manufactured nanomicelle with a particle size of less than 100 nm is remarkably homogeneous. The particle size and PDI of drug-loaded nanocarriers are crucial factors that can influence their interactions with various cell types and play a substantial role in determining their behavior in vivo, regardless of the method of administration. The EE% and DL% were affected by the characteristics and concentration of polymers, as well as the properties and length of the core-forming block and shell-forming blocks in the micelle [41]. SLP has amphiphilic characteristics due to copolymer grafting. The backbone of polyethylene glycol stands in for the hydrophilic component, while the side chains of vinyl caprolactam and vinyl acetate represent the hydrophobic component. The hydrophobic segments of SLP constitute the central region of the micelle, which acts as a microenviroment for the inclusion and integration of the lipophilic molecules. The inclusion of TPGS in nanomicelles has an adverse impact. This phenomenon is likely attributed to the fact that TPGS can reduce the hydrophobic contacts between the polymer chains within the micellar core [36]. If there is insufficient affinity between the drug and the copolymer within the core, the drug will not be effectively loaded into the micelle. As a result, the likelihood of interactions between hydrophilic and hydrophobic segments increases, causing changes in the hydrophobic nature of the core and, subsequently, affecting its ability to encapsulate the drug. This can clarify the phenomenon of particle size enlargement. The observed increase can be credited to the positioning of TPGS within the micellar corona and the reduction in the EE% of the nanomicelle with increasing TPGS [42,43]. Oral administration of nanomicelles with an average hydrodynamic diameter below 100 nm can enhance intestinal medication absorption [40]. The micelles with particle size within 100 nm and less, and accepted technological parameters were selected for further study.

In vitro release of OLM from mixed micellar dispersion

To determine the optimal micellar dispersion (using previous findings from particle size measurements and EE%), this study examined the impact of surfactant concentration and type on in

vitro release. To examine the in vitro drug release pattern from the physically encapsulated OLM-containing micelles that were prepared, the release characteristics were assessed using the dialysis bag method in phosphate buffer pH 6.8 under sink conditions. This method was slightly modified from the one prescribed by the FDA (Food and Drug Administration) recommended method of dissolution for OLM oral tablets [31]. Figure.1 illustrates the release profile of OLM from the micelles composed of SLP/TWN 80. The steady rise in the cumulative release percentage over time suggests that the substance was continuously released into the medium. The release pattern that was observed was consistent with that documented in the literature for other micelle systems. The findings suggest that the amount of OLM released from the micellar dispersion is considerably greater than the amount released from the OLM pure drug powder suspension.

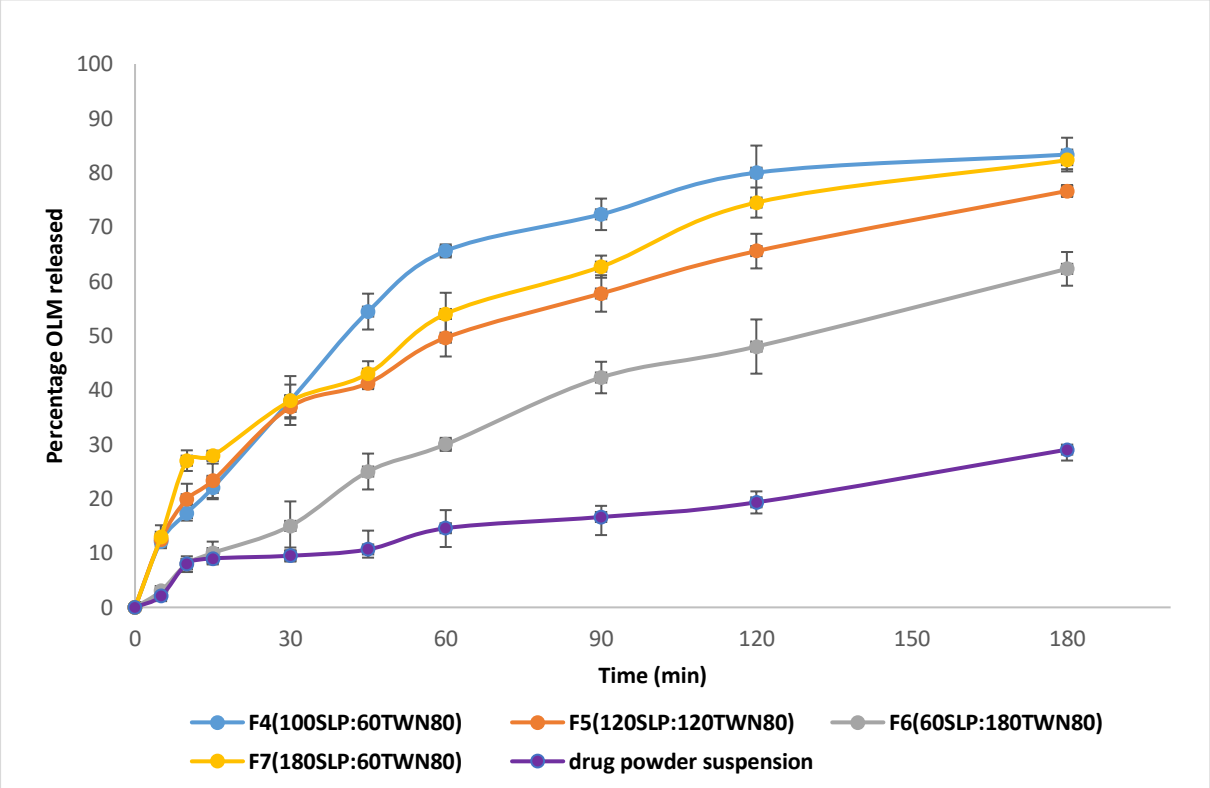

Figure 1. The release profile of OLM from micellar dispersions involving SLP/TWN80 and pure drug powder suspension in phosphate buffer (pH 6.8) at 37 °C (mean ± SD, n =3).

Table 3. The dissolution efficiency Data (mean ± SD, n =3)

Formula number	DE%
F4	70.02±1.5
F5	61.3±.98
F6	48.34±1.27
F7	67.1±2.9
F11	65.09±0.72
F12	42.45±1.88
F14	48±2.56
Drug powder suspension	18.9±1.57

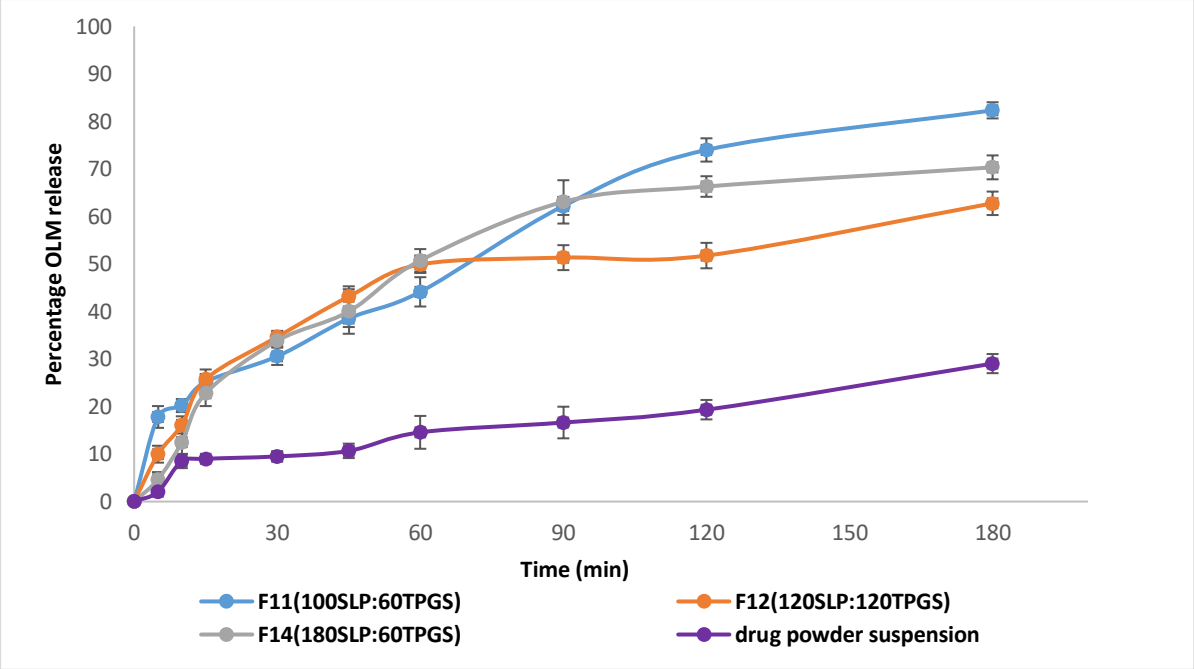

Figure 2. The release profile of OLM from micellar dispersion involving SLP/ TPGS and pure drug powder in phosphate buffer (pH 6.8) at 37 °C (mean ± SD, n =3).

As shown in Figure.2 the release of OLM is largely reserved by the incorporation of TPGS in the nanomicelle in contrast to the release from the SLP/TWN80 nanomicelle although it is better than pure drug powder suspension. From the results of DE% in Table 3, it seems that formulas with SLP/TWN80 mixed micelle structures have better release than SLP/TPGS one having the same ratio and concentration. At the same time, it is shown that as the SLP concentration increased the DE% increased, indicating that the polymer is not only involved in forming more micelles but the micelles are formed by more SLP units [44]; also, it suggests the formation of progressively more micelles containing the host molecules with increasing SLP concentration. It became apparent from Figure. 1 and 2 that increasing polymer concentration from 1.6% to 2.5% have a undesirable effect and was inversely correlated with the rate of drug release from the micelles [7]. This may be suggested by the phenomenon of saturation of micellar structure [14]. Retardation of the release by using TPGS may be due to incorporation of drug in the core firmly remains inside the micelle, which causes the slower release. The same delay release effect was detected by TPGS via Deoxycholate-TPGS mixed nanomicelles and diocin naomicelle [45,46]. The formulation F4 shows the higher amount of drug release about 66% within one hour and higher DE% about 70% compared with other formulations. Because increased surface area that results from reducing the drug particles to nanosized, the dissolving velocity will be significantly accelerated [47]. Accordingly, F4 was selected as best formula regarding small particle size and PDI, faster drug release so it was subjected to further investigation.

Critical micelle concentration CMC

The CMC value was determined by using iodine as hydrophobic probe. F4 and F11 which have the same SLP: surfactant ratio (100:60mg) with total surfactant concentration of (1.6% w/v) were selected as comparison between the two polymer TWN 80 and TPGS in combination with SLP since they have optimal physical features of low particle size and PDI and consume lower concentration of polymer. Table 4 represents the measured CMC values.

Table 4. Calculated and theoretical CMC value for F4 and F11

Formula code	Calculated CMC mg/ml	Theoretical CMC mg/ml
F4	0.0112±0.0001	0.01284
F11	0.0385±.00021	0.1332

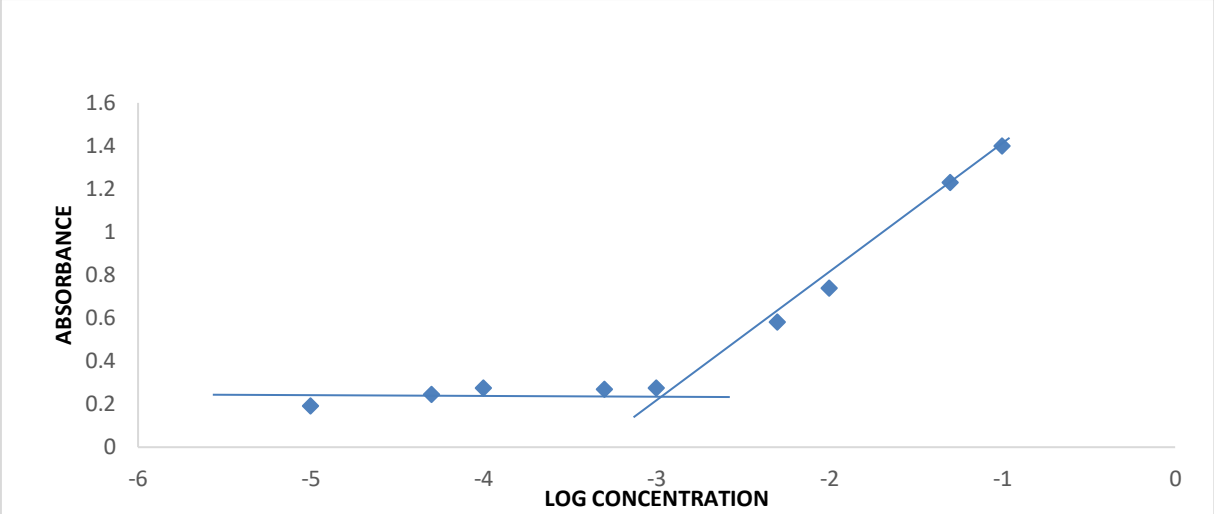

Figure 3. The calculated CMC value of F4(mean ± SD, n =3).

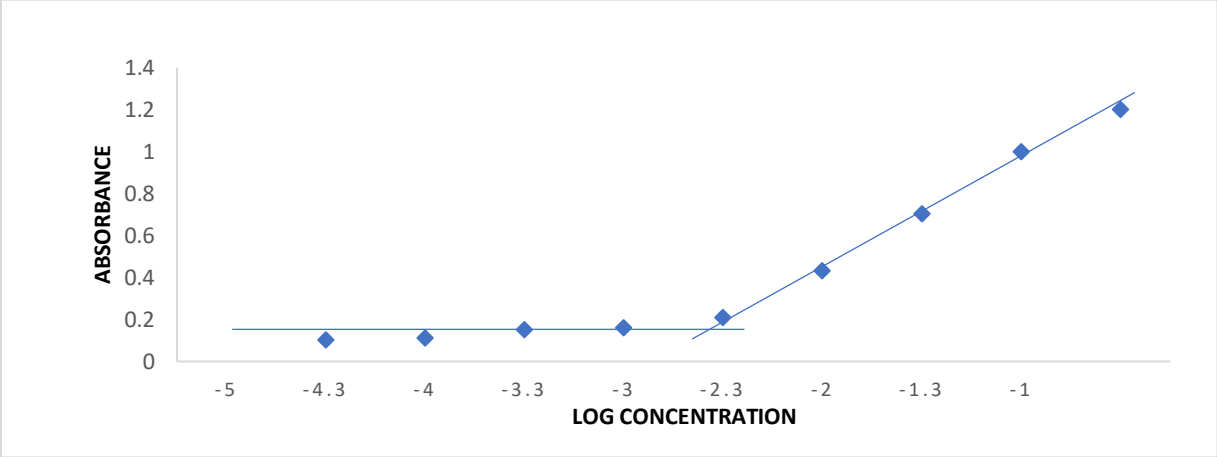

Figure 4. The calculated CMC value of F11 (mean ± SD, n =3)

The CMC value is an essential indicator of micellar stability and micellization capacity; a lower value signifies easier preparation and greater stability of the micelles. Iodine was used in this work as a hydrophobic probe to determine the mixed micelle's CMC value. The experiment produced the scatter plots depicted in Figures. 3 and 4, from which fitted linear curves were created. The point where the two fitted curves intersection is where the mixed micelle's CMC value can be found. The CMC values for F4 and F11 were found to be 0.01122 and 0.0148 mg/ml, respectively, exceeding the manufacturer's stated CMC value of 7.6×10^{-3} mg/ml for pure Soluplus® without providing any technique details [9]. The incorporation of TWN 80 in F4 and TPGS in F11, which resulted in a considerably higher CMC value, may be the reason of the rise in CMC. The self-aggregation of Soluplus® is adversely affected when TPGS is added to the micelles. This impact is the most likely caused by TPGS's potential to reduce the hydrophobic contacts between the polymer chains at the micellar core, which would raise CMC [36]. For TWN 80 and TPGS, the published CMC values are 0.015 and 0.2 mg/ml, respectively [48,49]. According to testimony from another report [10], the CMC value of combined micelles SLP/TPGS (molar ratio 11:1) is roughly 0.0477 mg/ml. The value would also be affected in different ways by the conditions and methodology used to estimate the CMC. This could be the cause of the discrepancy between the measured and theoretical CMC, as determined by applying equation (4). There was a negative departure from the ideal behavior in the experimental CMC values, which were smaller than the theoretical one. A comparable pattern was noted in mixed systems composed of Pluronic® F88 and P123 [50]. A positive mixing process is indicated by a negative divergence from ideality [36].

Preparation of OLM mixed micelle (selected formula) by direct dissolution method

An alternative method of preparation was tested to investigate the effect of the method of preparation on particle size, PDI, EE% and DL% of the optimized formula, F4. The results of preparation by the direct dissolution method are listed in Table 5.

Table 5. Influence of formulation techniques and mixing time on mixed micelle particle size PDI, EE% DL%, prepared by the direct dissolution method

Tested Parameter	T1-3 hr	T1-12 hr	T1-24 hr	T2-3 hr	T2-12 hr	T2-24 hr
Particle size (nm)	84.67±4.8	162.3±5.7	184.1±4.5	117.8±6.3	240.3±8.4	233.8±9.5
PDI	0.254±0.011	0.484±0.11	0.66±0.021	0.539±0.43	0.510±0.07	0.7549±.21
EE%	90.1±2.9	77.6±2.7	76.5±3.43	83.6±3.8	73.4±4.7	72.5±3.66
DL%	10 ±0.21	8.56±2.1	8.5±0.93	9.29±1.77	8.16±0.56	8.06±3.2

T1: First technique, T2: second technique,3hr:3 hours mixing,12hr:12hours mixing, 24:24 hours mixing.

The data demonstrate that the application of T1 consistently leads to a smaller particle size compared to T2, regardless of the stirring period. This indicates that the initial dissolving of the polymer, followed by the inclusion of the drug, resulting in a reduction in particle size, polydispersity index (PDI), and an increase in encapsulation efficiency (EE%). When considering the impact of stirring time, it is important to note that stirring for 3 hours led to a significantly smaller particle size and higher EE% ($p<0.05$) compared to stirring for 12 and 24 hours using the two techniques. However, increasing the stirring time from 12 to 24 hours did not have a significant effect on particle size, EE%, and DL% ($p>0.05$). The reduced particle size of 84.67±4.8nm was achieved by utilizing T1 and stirring period of 3 hours. This method of generating nanomicelles eliminates the need for organic solvents, which is commonly employed in the thin film hydration approach. However, it does lead to a considerable increase in particle size for the same formula. The block copolymer is often self-assembled into nanomicelles using the direct dissolution approach, also known as the simple equilibrium method. This involves dissolving both the drug and copolymer in the correct ratio in an aqueous solution, which triggers the production of nanomicelles [51].

Micelle stability

The results of stability study for F4 represented inTable (6) indicated that micelle dispersion after storage for three months is stable which mean SLP/TWN 80 mixed micelle can maintain its integrity upon storage.

Field emission scanning electron microscope (FESEM)

The morphology of the micelles was observed by FESEM. As shown in Figure.7, the micelles exhibited a spherical shape and smooth surface. The size of F4 mixed micelle was found to be 71.1±1.287 nm Table 2. The size calculated from FESEM comparable to the size observed by zeta sizer by dynamic light scattering DLS. There is no change in size and shape due to accumulation [52].

Table 6. Stability of F4 mixed micelle during storage

Storage condition	Particle size	PDI	EE%
4°C after 3 months	71.1±2.11	0.09±0.002	90.6±3.1
25°C after 3 months	72.15±1.87	0.04228±0.0012	90.0±2.2

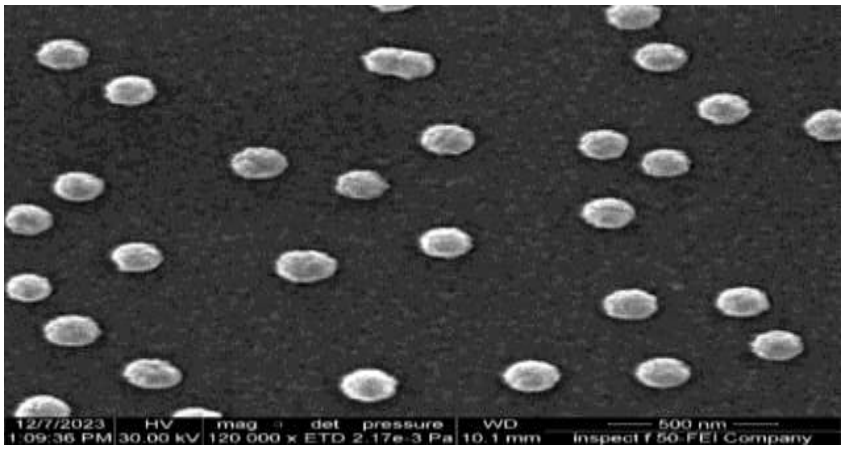

Figure 5.FESEM image of selected polymeric mixed micelle (F4)

Conclusion

Surfactant mixtures were tested at various weight ratio to solubilize the low solubility drug olmesartan medoxomil. The optimization and evaluation of micelles' physicochemical features, such as particle diameter, encapsulation efficiency, and drug release, were carried out through research. The optimized mixed micelle Soluplus/tween 80 (F4) has small particle size, low critical micelle concentration, stability upon storage and enhanced dissolution rate compared to that of pure drug powder of olmesartan medoxomil. In contrast to the thin film hydration method, the direct dissolution method of nanomicelle preparation produced particles of significantly larger size.

In conclusion, the physical properties and stability of soluplus /tween 80 drug-loaded nanomicelles make them an attractive candidate for investigation as a carrier for oral drug delivery and an appropriate technique to increase the solubility of BCS-class II drugs.

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Conflicts of Interest

Authors have declared that there is no conflict of interest exist.

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Ethics Statement

No animal or human study.

Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: Nawal A.Rajab , Halah Talal Sulaiman ; data collection: Halah Talal Sulaiman ; analysis and interpretation of results: Halah Talal Sulaiman; draft manuscript preparation: Halah Talal Sulaiman. All authors reviewed the results and approved the final version of the manuscript.

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تحضير وتقييم الناقل النانوي مختلط البوليمر المحمل بمذيلات الاولميسارتان ميدوكسوميل

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الخلاصة

اولميسراتان ميدوكسوميل (OLM) هو مضاد انتقائي للأنجيوتنسين II فعال في خفض ضغط الدم لديه توافر حيوي قليل عندما يؤخذ عن طريق الفم يبلغ حوالي ٢٦٪، وقابلية ذوبان محدودة في الماء. لذلك يتم تصنيف OLM على أنه من الفئة الثانية في نظام تصنيف الصيدلانيات البيولوجي (BCS)، مما يشير إلى أنه يتمتع بنفاذية عالية وقابلية ذوبان منخفضة. من خلال توليد مذيلات نانوية، يحاول هذا البحث زيادة الذوبان وسرعة التحلل بالماء. تم تحضير مذيلات نانوية مختلطة مكونة من soluplus (SLP) مع توين ٨٠ (TWN80) وSLP مع d-α توكوفيرل بولي إيثيلين جلايكول ١٠٠٠ سكسينات (TPGS)، بنسب وزنية مختلفة. تم تحضير المذيلات النانوية التي تحتوي على OLM باستخدام تقنية ترطيب الغشاء الرقيق وتقييمها من حيث حجم الجسيمات، ومؤشر تعدد التشتت (PDI)، وكفاءة الانحباس (EE٪)، وقدرة تحميل الدواء (DL٪). التركيبة المحسنة F4 تتكون من ١٠٠ ملغ من SLP مع ٦٠ ملغم من TWN 80. بلغ حجم المذيلة في هذه التركيبة حوالي ٧١,١ ± ١,٢٨٧ نانومتر، كما بلغ PDIحوالي ٠,١١٦، EE٪ بلغت ٩٢، DL٪ ١١,٥, مع تحسن في قابلية التحرر في المختبر مقارنة بالمعلق الدوائي المائي. تم حساب تركيز المذيلة الحرج (CMC) بطريقة التجربة باستعمال اليود كقطب كاره للماء للصيغة F4 ووجد أنه ٠,٠٠١±٠,٠١١٢ ملغم/مل وهو أقل من CMC المحسوب نظريا بالمعادلة والذي كان مساويا الى ٠,01284 ملغم/مل. كما تم تحضير F4 بطريقة الذوبان المباشر عند فترات تحريك مختلفة (٣،١٢،٢٤ ساعة) وبواسطة تقنيتين، وذلك لتقييم تأثير طريقة التحضير على حجم الجسيمات، PDI، EE ٪، DL٪ وكانت النتائج ذات دلالة احصائية حيث أظهرت النتائج حجم جسيم أكبر، وزيادة PDI($p<0.05$) وانخفاض٪ EE مقارنة بطريقة ترطيب الأغشية الرقيقة. علاوة على ذلك، تم فحص الخصائص الفيزيائية والكيميائية للمذيل النانوي F4 لفترة ثلاثة أشهر، في درجة حرارة الغرفة وتحت ظروف التبريد (٤ درجة مئوية)، وتبين ان المذيلات النانوية ظلت مستقرة. وقد أجري فحص الشكل باستخدام جهاز المجهر الإلكتروني الماسح بالانبعاث الميداني (FESEM)، الذي كشف عن وجود هياكل نانوية ذات شكل كروي .

وقطر يطابق قياسات حجم المذيلات. بذلك أكدت نتائج الدراسة الحالية أن المذيلات النانوية المختلطة لعقار OLM تعتبر حاملة نانوية محتملة لتحسين قابلية الذوبان.

الكلمات المفتاحية: مذيلات نانوية مختلطة,الذوبانية,التركيزالمذيلي الحرج .