Original Article

Co-surfactant effect of polyethylene glycol 400 on microemulsion using BCS class II model drug

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ABSTRACT

Microemulsions are an intriguing method for delivering poorly soluble drugs, protecting labile drugs, controlling drug release, and increasing drug bioavailability. They can be given topically, orally, or intravenously, and use polyethylene glycol (PEG-400) as a co-surfactant to improve the solubility and stability of biological classification system (BCS) class II drugs. The goal of this research is to develop and test an oil-in-water (O/W) microemulsion-based formulation to improve the solubility and possibly the stability of a hydrophobic medication (carvedilol) by using natural oil and PEG 400 as a co-surfactant. oil in water microemulsion was formulated using the water titration method. pH, particle size, zeta potential, and thermodynamic stability studies were carried out for optimization, followed by in vitro release experiments. Based on component solubility studies and pseudo-ternary phase diagrams, a 1:1 ratio of Tween80 to PEG400 (Smix) was chosen for the final microemulsion preparation. The optimized ME4 formula selected contains 10% oil, 42% Smix, and 48% water. The average globule size was found to be 58 nm, the pH was 6.95, the zeta potential was 28mV, and the percent transmittance was 97.1 percent. The thermodynamic stability study data shows better stability of the final formulation. The solubilization effect of the drug was enhanced by prepared ME formulation and hence confirms the utility of the ME system as a vehicle for better delivery of (BCS) class II.

Keywords: Microemulsion, Polyethylene Glycol 400, BCS Class II, Carvedilol

Introduction

The Microemulsion system (ME) is a type of colloidal drug carrier system that is thermodynamically stable, transparent, and extensively used by scientists to enhance the therapeutic efficacy of drugs [1]. The ME is considered a promising delivery system as it provides for both regulated and sustained drug release for a variety of routes of administration [2]. MEs have several distinct characteristics, the most notable of which are that they are less toxic, facilitate enhanced drug absorption, and regulate drug release rates [3]. In addition, they have a very small droplet size, which results in a large interfacial tension area for drug absorption and increased stability against sedimentation [4]. The ME system has received a lot of attention in the delivery of drugs due to their thermodynamic physical stability and ease of production.

Due to their low toxicity and irritant potential, non-ionic surfactants such as polyoxyethylene sorbitan esters (Tweens), and polyoxyethylene ethers are frequently used in pharmaceutical and cosmetic applications. Non-ionic surfactants are well-known for their safety and biocompatibility, as well as their resistance to pH changes due to their uncharged nature. The presence of hydroxyl groups in polyethylene glycol 400 (PEG 400) enables efficient intermolecular hydrogen bonding between oil components and glycol moieties [5]. PEG 400 is a non-toxic hydrophilic polymer that is used in a variety of pharmaceutical formulations to increase solubility and stability. It can be

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administered via oral, intravenous, or intranasal routes. Additionally, PEG 400 has been used to assess the BBB's permeability to a given substance. Mahajan *et al*. formulated nanoemulsion (NE) with tween 80 as the surfactant agent and polyethylene glycol 400 as a co-surfactant. It was found that brain drug delivery of saquinavir was enhanced through the use of excipients that had good inhibitory action on p-glycoprotein [6]. The Biopharmaceutics Classification System (BCS) has been founded in pharmaceutical drug development as an indicator of medication absorption, thereby facilitating the approval and formulation design processes [7]. BCS has been classified into four groups based on its solubility in water and permeability of the intestinal membrane. BCS Class II drugs and drug products have a low solubility and a high permeability, which means they would be entirely absorbed if they were in solution, exhibiting dissolution rate-limited absorption [8, 9]. Carvedilol belongs to BCS Class II and is a low molecular weight, non-selective beta-adrenoceptor blocker used to treat hypertension, reduces heart rate and myocardial oxygen demand by inhibiting beta-adrenergic receptors. Because of its alpha-adrenergic receptor blocking characteristics, carvedilol lowers systemic vascular resistance [10]. Low water solubility and short half-life are considered the primary reasons for the poor clinical efficacy of carvedilol in oral therapy [11]. The current study aims to improve the solubility and possibly the stability of a representative BCS class II carvedilol drug using a microemulsion approach with a variety of natural oils and polyethylene glycol 400 as a co-surfactant.

Materials and Methods

Carvedilol was purchased from the Wadi Al-Rafidian factory for pharmaceutical products, (Baghdad, Iraq). Tween 80, PEG400, Ethanol, Methanol, propylene glycol, peppermint oil, and sesame oil were purchased from Sigma Chemical Co. (St. Louis, USA).

Characterization of carvedilol

Determination of melting point of carvedilol

The melting point was determined by the capillary method according to British Pharmacopeia (BP). An appropriate amount of carvedilol powder was added to a capillary tube to form a compact column with a height of 4-6 mm. The tube was placed in electrical melting point equipment, which gradually raised the temperature. The temperature at which the final solid particle of carvedilol in the tube transitioned to the liquid phase was recorded as the melting point [12].

Determination of λ max of carvedilol

To determine the maximum wavelengths (max) of carvedilol, a UV-Visible Spectrophotometer in the range of 200-400 nm scanned the drug solution in methanol against a blank, and the spectrum for carvedilol was recorded [13].

Preparation of calibration curve of carvedilol

A standard solution of the model drug (carvedilol) was made by dissolving 20 mg of the medication in 100 ml of methanol to generate a solution with a 200µg/ml concentration. The stock solution was further diluted using the same solvent to obtain a 25µg/ml stock solution, from which four dilutions (5, 10, 15, and 20 µg/ml) were prepared [14].

Solubility determination

Carvedilol powder was added in excess (about 200mg) to 2ml of different vehicles, which included oils (Peppermint oil, sesame oil), surfactant (Tween 8o), and co-surfactants (Propylene glycol, Ethanol, PEG 400). After shaking with a thermal shaker at 30 °C for 48h, samples were collected and centrifuged at 3000 rpm for 15 min, and then the supernatant layer was separated and filtered with a filter syringe (0.22µ) to remove any drug precipitate. Samples of these solutions were then collected and the concentration of the drug was measured by a UV-spectrometer at 285nm [15].

Phase diagram construction

The pseudo-ternary phase diagrams of oils, surfactants,co-surfactants, and water were constructed using the aqueous titration technique. The mixtures of oil, surfactant, and co-surfactant at defined weight ratios were diluted with H_2O in a drop-wise manner. The phase diagram was prepared with Tween 40: PEG400 weight ratios defined at 1:0.5, 1:1, and 1:2. A homogenous mixture of peppermint oil and Smix (Tween 80: PEG400) at different concentrations was formed under uniform hand mixing. Then, each mixture was titrated with H_2O and visually observed for phase clarity. No heating was applied during the preparation. The ME region in the phase diagram was identified.

Thermodynamic stability studies

The prepared MEs were centrifuged at 6000 rpm for thirty minutes and examined for phase separation creaming, cracking. This was followed by a heating-cooling cycle in which the formulated ME was kept at 40°C and 4°C alternately for less than 48 hours. Finally, it was put through a freeze-thaw cycle. The formulation was subjected to three freeze-thaw cycles between 21°C and +25°C with storage at each temperature for not more than 48 hours to determine the optimized formulation's thermodynamic stability [16].

Particle size and zeta potential measurements

The dynamic light scattering (DLS) technique was used routinely to measure the particle size of all optimized MEs at 25 °C in a detection angle of 90 degrees using the Malvern Nanosizer (Malvern Instruments USA). Malvern Zetasizer is often used to examine the surface charge (Zeta potential) of the formulation by

using the approach of Electrophoretic Light Scattering (ELS). All samples were measured in triplicate and the data were expressed as mean ± SD.

Percent of light transmittance assay

The % transmittance of the manufactured MEs was determined at 600 nm using UV- dual-beam spectrophotometer with deionized water used as blank. The tests were done in triplicate [17].

pH measurements

The pH value of the MEs was measured by dipping the pH electrode in the formulation contained in a ten-milliliter glass vial. For each sample, measurements were made in triplicate.

In vitro release studies

The In vitro drug release profile of Carvedilol ME was assessed utilizing a dialysis bag method. The dialysis membrane was hydrated in distilled water before use. In this test, we used a dialysis membrane with a pore diameter of 2.4 nanometers and molecular mass cut off between 12000-14000 Dalton. The phosphate buffer of 6.8 pH was used as a release medium. Three milliliters of freshly prepared carvedilol loaded ME and free carvedilol solution were placed individually in the dialysis bag and then sealed on both sides with plastic clips. The in vitro release study was conducted in a USP dissolution apparatus type – II, set to 37°C and rotating at 60 pm. At various time points, aliquots of the release medium were taken and replaced with a freshly prepared solution to maintain optimum sink conditions. The experiment was repeated three times. The drug concentration and cumulative percentage release were determined using a UV-visible spectrophotometer operating at a wavelength of 285 nm [18, 19].

Results and Discussion

Pre-formulation studies

Pre-formulation studies are preliminary studies to understand the physicochemical properties of the selected drug and possible obstacles in the development of the final dosage form. These studies include the determination of the melting point, λ max, and the solubility of the drug in different vehicles.

Melting Point of carvedilol

The melting point of carvedilol powder was 117-123 °C. This result is about 2-5^{0}C higher than the reported melting point in the references, which was found to be 115 degrees Celsius [20]. The variation in melting point could be due to differences in raw materials used to synthesize carvedilol, which varies from company to company. The melting point determines the purity of the drug sample. If there is any impurity present, the melting point of the given substance will change.

Determination of λ max of carvedilol

The UV scans of carvedilol in methanol revealed a peak absorbance at 285 nm, which is consistent with the results of several investigations that demonstrate absorption maxima of Carvedilol in the region of 284 and 286nm [21, 22].

Calibration curve of carvedilol

The calibration curve of carvedilol in methanol using absorbance and concentrations of standard solutions shows a straight line with a high correlation coefficient (0.9967) using regression analysis the linear equation 0.0058x + 0.0373y that indicates the curve obeys Beer-Lambert law over the concentration between 5-25 µg/ml as shown in **Figure 1**.

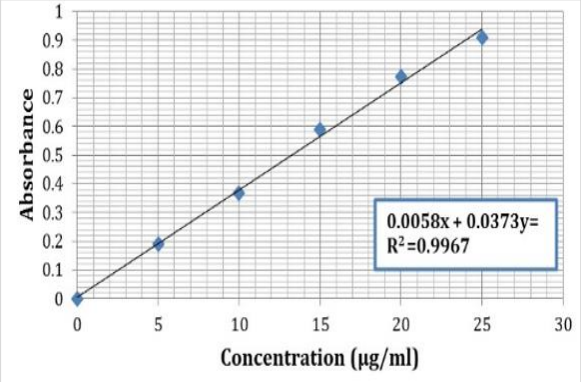


Figure 1. Calibration Curve of Carvedilol with Regression line equation

Solubility of carvedilol drug

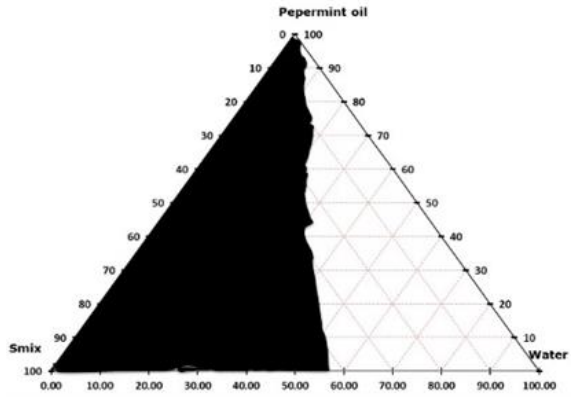
The measured solubility of the model drug (carvedilol) in different vehicles was higher in peppermint oil than in sesame oil, while the solubility in co-surfactant was in the following descending order: PEG 400 > Ethanol > Propylene glycol as shown in **Table 1**. Based on solubility studies, peppermint oil, Tween40, and PEG400 were chosen for the preparation of the ME system, as higher solubility is critical for developing microemulsion formulations with high drug loading efficiency.

Table 1. Saturated Solubility of Carvedilol in Different Solvents

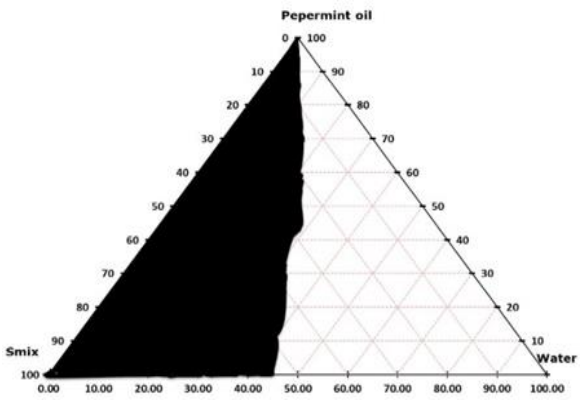
Microemulsion components	Carvedilol solubility (mg/ml)
Sesame oil	4.22
Peppermint oil	65.47
Tween 80	25.58
PEG 400	110.77
Ethanol	22.65
Propylene glycol	6.14

Construction of Ternary phase diagram

Pseudo ternary phase diagrams were created to identify ME regain to choose the ideal concentration of peppermint oil material, Tween 80, polyethylene glycol 400, and Water. The diagram was mapped by altering the ratio of Tween 80: PEG 400 as shown in **Figures 2a-2c**. The shaded area displays the ME region that represents one phase system while the clear area shows a non-ME region of a two-phase system.it seems that the ternary phase diagram with Tween 80:PEG 400 (1:1) was optimum for developing ME formulation as it shows the largest size of ME Area **(Figure 2b)**. No increase in the transparent microemulsion area was noted when the ratio of Tween 80 to PEG 400 was changed from 1:1 **(Figure 2b)** to 2:1 **(Figure 2c)**. This observation may be due to the inability of Polyethylene glycol 400 to incorporate the water or because the H- bond between the glycol moiety of Polyethylene glycol 400 and the hydroxyl moiety of the water molecule was not strong enough. Surfactants and co-surfactants contribute to the reduction of interfacial tension between the two phases layers through adsorption at their interface and act as a mechanical barrier against coalescence, therefore, increasing the ratio of co-surfactant to surfactant can improve micelle formation and increase the solubilizing capacity of MEs [23]. In addition the effect of co-surfactant on the fluidity of interfacial film by reducing the bending stress of interface and give more flexibility to the interfacial film to take more curvature resulting wider ME area [24].



a)



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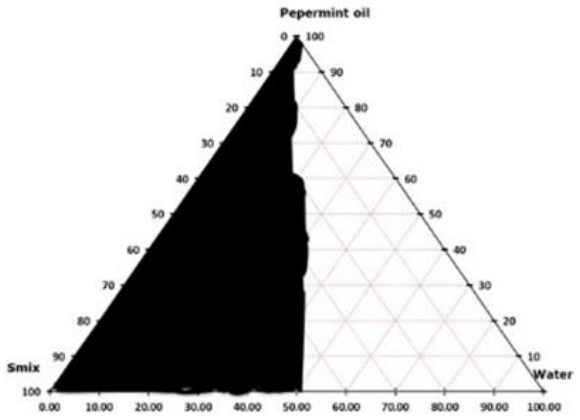

c)

Figure 2. a) Smix (1:0.5) Tween80:PEG400. b) Smix (1:1) Tween80:PEG400. c) Smix(1:2) Tween 80: PEG400

Preparation of drug loaded microemulsion

10 mg of carvedilol was added to peppermint oil in a test tube and vortexed using a vortex mixer until the drug was completely dissolved. The Smix of all optimized systems **(Table 2)** was added to the oil phase mixture with continuous stirring. Finally, Deionized water is added drop by drop to the oil and Smix (surfactant and co-surfactant) till a transparent ME is obtained as showed in **(Figure 3)**.

Figure 3. optimization formulations of one phase system

Table 2. Formulation optimization of carvedilol loaded MEs

Formulation	Drug (mg)	Peppermint oil %w/w	Smix(1:1) Tween80:PEG400 w/w%	Water w/w%
ME1	12.5 mg	10	30	60
ME2	12.5 mg	10	33	57
ME3	12.5 mg	10	36	64
ME4	12.5 mg	10	42	48

Thermodynamic stability studies

The selected formulations ME1, ME2, ME3, ME4 didn't show any signs of phase separation or drug precipitation or phase inversion, or even flocculation. These types of studies were done to confirm the physical stability of the prepared MEs and differentiate them from the emulsion system. Some alcohols, such as polyethylene glycol PEG400 and propylene glycol as co-

solvents, are deemed promising for the stability of the prepared formulation. Co-solvents could also increase the dissolution of hydrophilic surfactants in large quantities in the oil base [25].

pH and % transmittance

The physicochemical features of acceptable MEs formulations were chosen based on their clear or translucent appearance, lack of precipitation, low viscosity, and lack of phase separation. The optimized MEs (ME1.ME2, ME3, ME4) showed more than 94 % transparency at 600 nm confirming the homogenous mixture and the clarity of the prepared MEs.

The pH value is not affect only on the bioavailability and activity of the drug in the final formulation but also affects its stability [26]. The pH range in these formulations is indicative of stability because variability in this parameter can indicate the presence of contaminants, chemical hydrolysis, or decomposition of MEs components, all of which cause instability issues. The pH values of drug-loaded MEs were found to be in the range of 6.9-7.35 indicating that this value is optimum for the final dosage forms to be administered through different routes such as oral or non-oral routes.

Particle size distribution and zeta potential

The most valuable consideration to differentiate the MEs from the other systems is to measurement their particle size that should be in nano-range. Because of their submicron sizes, MEs appear as translucent solutions. As shown in **Table 3** as the amount of surfactant and co-surfactants increase, the particle size of MEs is decreases it is most likely explained by the fact that when the concentration of surfactant is increased, more micelles are produced, favoring the dispersion of more active species. Condensation reaction among particles results in smaller particle size and wider size distribution. When the emulsifier content is lower, fewer particles are produced, and the particles are more likely to grow on the quondam molecular chain, resulting in larger particle size distribution [27].

All the optimized drug formulations (ME1, ME2, ME3, and ME4) had particle size in the nanoscale. Carvedilol loaded ME (ME4) containing 10 % of peppermint oil and 42% of water had the lowest globule size due to the effect of Tween80 and PEG 400 in decreasing particle size through increasing their concentration at a fixed percentage of oil.

The zeta potential is an analytical parameter used to determine the surface charge of particles in a colloidal solution. When the zeta potential is greater than ±30mV, a stable dispersion may emerge. This is owing to the presence of repulsion forces between particles, which prevent aggregation [28]. The highest value of zeta potential was found with ME-4 that could confirm the physical stability of the optimized formulation ME4 was chosen as the best formulation because it exhibited optimal features such as 97.1 percent optical transparency, the smallest globule size (58nm), and zeta potential of −28 mv.

Table 3. Physicochemical characteristics of MEs (ME1-ME4)

Formulations	Particle size	% Transmittance	pH	Zeta potential
ME-1	91nm±2.21	96.3	6.89±0.11	− 20.3± 1.09
ME-2	84 nm±1.04	96.5	7.03±0.08	−25± 1.97
ME-3	69± 1.81 nm	98.9%	7.2± 0.21	−26.9± 2.04
ME-4	58 ±2.1 nm	97.1	6.95±0.36	−28.2± 1.5

In vitro release study

The usual structure of MEs, which consists of scattered droplets surrounded by a surfactant film in a dispersion medium, presents a major hurdle to drugs dissolved in the inner phase preventing rapid spread to the outer phase. The drug release profile from the selected carvedilol incorporated ME formulation and free drug solution is depicted in **(Figure 4)**. As shown in the diagram, approximately 100% of the drug content of the optimized ME-4 was released in six hours. The results show the microemulsion system containing Tween 80:PEG400 (1:1) significantly increases the percentage of the drug release and this type of release could be continuous and slow compared to plain drug solution which may be owing to a solubilizing enhancing constituent of the Tween and PEG400. Surfactants material and co-surfactants are capable of dissolving the oil by producing micelles lowering the interfacial tension between oil and water. As a result, the solubility of the drug in oil will be improved [29]. It is evident that optimized carvedilol ME had a better in-vitro release profile than marketed formulation.

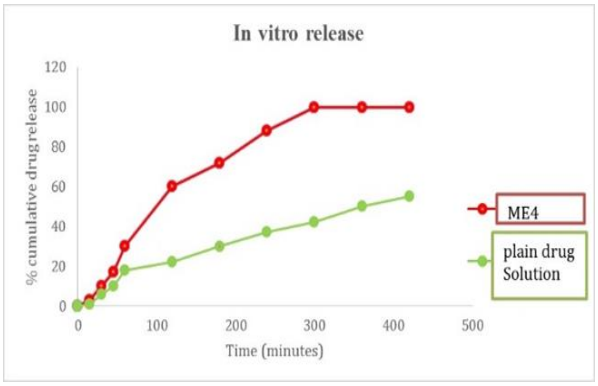

Figure 4. In vitro release profile of carvedilol ME and carvedilol solution

The in vitro release data was translated into several graphical forms according to different kinetic models to elucidate the process and type of drug release from ME formulations. The kinetics of the dissolution data were well suited to the zero-order model, first-order model, Higuchi model, and 60% of the drug release were well fitted to the Korsmeyer-Peppas equation.

The R square of different kinetic models (Zero order, First order, Higuchi model , Korsmeyer Pappas model) of ME-4 was found to be 0.9653, 0.9617, 0.9523, 0.9789 Consecutively while for free carvedilol solution is 0.9707, 0.9902, 0.9728, 0.9017). The kinetic release data of the ME-4 formulation revealed that drug release across the cellulose membrane fitted

to the Korsmeyer Pappas model and this was confirmed by a high regression coefficient parameter (R^2).

Conclusion

Microemulsion systems comprised of peppermint oil as the oil dispersed phase, Polysorbate 80(Tween 80) as a surfactant, and polyethylene glycol 400 as a co-surfactant were successfully manufactured and characterized which increased the solubility and possibly the stability of a representative BCS class II Carvedilol drug. The optical brightness and centrifugation studies revealed that the created ME systems with Smix of 1:1 ratio (Tween 80:PEG400) were thermodynamically stable and transparent single-phase solutions. The chosen formulation (ME4) demonstrated a high solubility of carvedilol drug in experimental oil, as well as a high percent cumulative of drug release as compared to crude drug solution. Thus, all characterizations have revealed that the formed ME could be a viable formula to improve BCS class II Carvedilol water solubility and thus bioavailability for usage as an efficient drug carrier for administration via various delivery routes.

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Ethics statement: None

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