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RESEARCH ARTICLE

Effect of tocopherol on microemulsions: turbidity studies and Dynamic light scattering and dynamic surface tension measurements

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ABSTRACT

The development and design of the biocompatible and biodegradable thermodynamically stable micellar and microemulsion transparent dispersions to reduce the free and unbounded drugs concentration in the blood is a basic challenge in field of drug efficacy and bioavailability of drugs. In the current work, solubilization capacity of the drug (Tocopherol), oil (Ethyl Butyrate), and oil+drug (1:1 molar ratio) into F127 pluronic microemulsions was studied as a function of F127 concentration by using turbidity or transparency experiments. F127-based oil-in-water microemulsions with different compositions were synthesized and titrated with drug (Tocopherol), oil (Ethyl Butyrate), and oil+drug (1:1 molar ratio), separately, to determine clear /turbid transition zone. It was observed that at certain concentration of Pluronic F127, microemulsion samples were gel-like. This specific concentration of F127 was different for three systems mentioned. It also observed that by increasing concentration of fatty acid of sodium caprylate (SC) in the system, solutions became transparent. By the current experiments, it was possible to determine the optimal binding ratio of F127 and/or sodium caprylate to ethyl butyrate oil, Tocopherol drug, and oil+drug (1:1 molar ratio) in microemulsion. To study the bounding process of the fatty acid to the F127 within microemulsion, the microemulsion formulations were characterized by means of the dynamic surface tension and dynamic light scattering. According to this effort, we have concluded that there are approximately 1 molecule of oil for every 2 molecule of F127 (for system titration with oil), approximately 4 molecules of Tocopherol Drug for every 100 molecule of F127 (for system titration with drug), and approximately 4 molecule from the oil+drug (1:1 molar ratio) for every 5 molecule of F127 (for system titration with oil+drug (1:1 molar ratio) in the optimal microemulsion formulation. These results highlight the useful information about the mechanism of binding of the tocopherol, oil, and oil:drug mixture (1:1 molar ratio) to the F127 microemulsion.

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INTRODUCTION

The design of the effective and thermodynamically stable drug delivery systems in the field of nano-medicine based on surfactant-stabilized oil-in-water microemulsions as ideal nano-carrier systems to deliver the hydrophobic drugs with the aim of increasing the efficacy of therapeutic agents including higher bioavailability, lower toxicity, and lower side effect of drug in living system has received widespread attention in recent years [1-14].

Literature survey reveals that the PEO–PPO–PEO (poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) triblock copolymers (known as pluronics) as stabilizing agent, are one of the best options for the encapsulation of hydrophobic drugs within oil-in-water microemulsion owing to their low toxicity and high environment-friendly [1-14].

α-Tocopherol is a hydrophobic drug with wide applications in the cosmetic, pharmaceutical, and food industry due to its anti-tumor and antioxidant

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properties [15-17].

The conducted studies reveal disadvantages along with drug delivery by solubility of tocopherol in bulk oil including the lower stability, lower solubility, non-effective drug release, and lower bioavailability of drug [16-17]. These factors have limited its use in the drug delivery systems, especially topical drug delivery [16-20].

On the other hand, the reported studies confirm increase in solubility, stability, bioavailability, and effective drug release of α-Tocopherol by incorporating the α-Tocopherol into oil-in-water microemulsion [16-20].

Besides, it must be pointed out that the stability of a drug-loaded oil-in-water microemulsion is affected by concentration of oil, surfactant, co-surfactant, and drug [1-8]. In field of surfactants, for pharmaceutical applications, it is widely believed that Pluoronic (non-ionic surfactants) are preferred in Nano-colloidal systems of oil-in-water microemulsion because of higher stability and less toxicity compared to ionic surfactants [1-14].

So, it is necessary to select components to make a stable and safe oil-in-water microemulsion containing hydrophobic drug (here Tocopherol) by turbidity experiment.

With this in mind, the aim of our present study is to understand the important interactions that occur between the F127 microemulsion and/or mixed micelles and the Tocopherol drug in the presence of sodium caprylate to increase bioavailability of Tocopherol drug by turbidity/transparency experiments.

The conducted studies focus on pH parameter indicate that electrostatic interactions can play a important role in adsorption of Tocopherol onto the microemulsion. Tocopherol that is shown in Fig.1, has a pKa of approximately 10.8 [29-30], so that at physiological pH of 7.4, it can be positively charged and resulting interacts with a negatively charged SC within microemulsion.

The results related to the turbidity analysis experiments indicated that there is a linear relationship between the tocopherol and/or oil and/or oil:drug solubilization capacity of the microemulsions up to a certain concentration of F127.

EXPERIMENTAL SECTION

Materials

Pluronic F127 and sodium caprylate (SC) were provided from BASF Inc. (Mount Olive, NJ). Tocopherol, sodium caprylate, sodium deconate, and ethyl butyrate were purchased from Sigma Chemical Co. (St. Louis, MO). Potassium phosphate monobasic, potassium phosphate dibasic, sodium

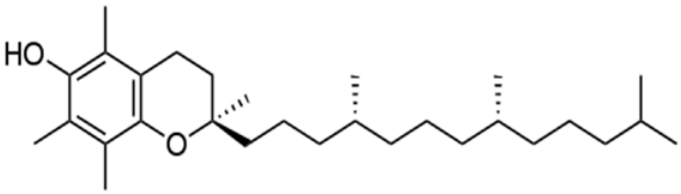

Fig. 1. molecular structure of Tocopherol

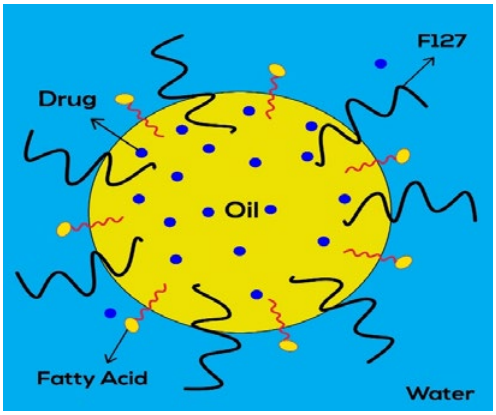

Fig. 2. Schematic of a microemulsion droplet

chloride, and potassium chloride which were purchased from Fisher Scientific Inc. (Suwanee, GA). Doubly distilled, deionized Millipore water was used.

Microemulsion Preparation

Initial oil-in-water microemulsions were prepared as 1% w/w solutions of ethyl butyrate by dissolving certain concentrations of Pluronic (F127), fatty acids of sodium caprylate (SC), oil of ethyl butyrate, and drug of Tocopherol into solution of normal saline (pH 7.4) [5-7] .

Then, the F127-based oil-in-water microemulsions and micelles were titrated with components of Tocopherol, Ethyl Butyrate, and oil+drug (1:1 molar ratio), separately, to determine turbid/clear area.

Turbidity Analysis

Microemulsion samples prepared by varying components of Pluronic F127 and/or sodium caprylate and/or ethyl butyrate and/or Tocopherol drug and/or oil:drug (1:1 molar ratio) in the system.

Our research to obtain oil-in-water F127 microemulsions containing Tocopherol were done in three cases based on turbidity experiments.

In the first case, at the first, we prepared a solution containing Pluronic F127, ethyl butyrate, and PBS in the absence of drug.

Then, we titrated the solution with sodium caprylate (SC) at different concentrations to transparency (to obtain oil-in-water F127 microemulsion).

In result, an oil-in-water F127 microemulsion sample was obtained in the presence of sodium caprylate (SC) at a certain concentration (please see Table 1). Then, to the oil-in-water F127 microemulsion, oil (in addition to the initial oil that we added) was added more and more to find upper limit for solubilization of oil within oil-in-water F127 microemulsion (please see Table 2).

In final step, F127 pluronic along with oil (pure liquid) were added more and more to the turbid solution with aim determining region of turbid and clear (please see Table 3).

In the second case, at the first, we prepared a solution containing Pluronic F127, drug, and PBS in the absence of oil that was turbid.

Then, we titrated the solution with sodium caprylate (SC) at different concentrations to transparency (to obtain a micelle).

In result, a micelle sample was obtained in the presence of sodium caprylate (SC) at a certain concentration (please see Table 4).

Then, drug of Tocopherol was added more and more to the micelle to find upper limit for solubilization of drug in the micelle (please see Table 5).

In final step, F127 pluronic along with drug were added more and more to turbid solution with aim determining region of turbid and clear (please see Table 6).

In the third case, at the first, we prepared a solution containing F127 Pluronic, sodium caprylate (SC), and PBS.

Then, the solution titrated with oil+drug solution (1:1 molar ratio) to turbidity (please see Table 7).

Then , F127 pluronic along with oil+drug solution (1:1 molar ratio) were added more and more to the turbid solution with aim determining region of turbid and clear (please see Table 8).

It is important to mention that the solutions were titrated with certain concentrations of SC and/or oil and/or drug and/or oil and/or oil:drug until the turbidity and/or transparency of solutions were observed visually.

Theory of Dynamic Light Scattering

Dynamic Light Scattering (DLS) is a useful measurement to characterize the dynamic parameters of colloidal nanoparticles such as the diffusion coefficient and particle size. The scattered light intensity of time-dependent is a fluctuating quantity depends on the size, Brownian motion and diffusive behavior of nanoparticles in solution and viscosity of solvent. The fluctuations can be measured according to the normalized autocorrelation function, $g^1(\tau)$, of the scattered electrical field for a given delay time, τ [35-42].

$$g^1(q,\tau)=\frac{\langle E(q,t)E^*(q,t+\tau)\rangle}{\langle I(q,t)\rangle} \quad (1)$$

Experimentally, the intensity autocorrelation function of $g^2(q, \tau)$ is determined as following [33-40]:

$$g^2(q,\tau)=\frac{\langle E(q,t)E^*(q,t)E(q,t+\tau)E^*(q,t+\tau)\rangle}{\langle I^2(q,t)\rangle} \quad (2)$$

Here, E^* is the complex conjugated of E. The normalized autocorrelation function of $g^2(q,\tau)$ is converted to the autocorrelation function of the

scattered electrical field of g1 (q, τ) by the Siegret relationship [33-40].

$$g^2(q,\tau) = 1 + |A \exp(-\Gamma\tau)|^2 \quad (3)$$

Where, A is an instrumental constant. For a system containing monodisperse particles, the function of g1 (q, τ) is illustrated by the single exponential decay curve as following [33-40].

$$g^1(q,\tau) = A \exp(-\Gamma\tau) \quad (4)$$

The decay rate of Γ is converted to diffusion coefficient by using [33-40]:

$$D=\Gamma/q^2 \quad (5)$$

Here q is the scattering vector by particles [59-63]. Finally, the diffusion coefficient of nanoparticles can be measured as the hydrodynamic size of R_h according to the stokes-Einstein relation [33-40]:

$$R_h = \frac{KT}{6\eta\pi D} \quad (6)$$

Where K is Boltzmann's constant, T is the temperature in K, and η is the viscosity of solvent.

Dynamic Surface Tension

Dynamic surface tension of samples was characterized by using the maximum bubble pressure tool. In the current characterization, the pressure required to form a new bubble in solution is characterized by a pressure transducer and resulting transmission of result to an oscilloscope.

RESULTS AND DISCUSSION

As mentioned earlier, development of a systematic method to design the biocompatible mixed micelle and microemulsion to increase stability, solubility of drug as well as the more effective drug release and drug delivery in living system is an important challenge in field of pharmacy sciences. In the current study, Tocopherol-loaded oil-in-water F127 microemulsions were synthesized by mixing the different components including Pluronic F127 as the surfactant, fatty acid of sodium caprylate (SC) as co-surfactant, ethyl butyrate (EB) as the oil phase, and Tocopherol as drug in solution of the phosphate-buffered saline (PBS) at pH 7.4 [5-7, 21-27]. In the current work, the different micelles with various compositions were synthesized and titrated with certain component to turbidity or transparency studies [5-7].

Study of upper limit for solubilization of oil (Ethyl Butyrate) in F127 microemulsions in the absence of drug (Tocopherol)

In the first case, at the first, we prepared a solution containing F127, ethyl butyrate, and PBS in the absence of drug.

Then, the solution titrated with sodium caprylate (SC) at different concentrations ranging from 0.114 to 2.641 M to obtain oil-in-water microemulsion in the absence of Tocopherol drug (Table1).

In result, an oil-in-water F127 microemulsion sample obtained in the presence of sodium caprylate (SC) at a certain concentration (2.641 M).

In this case as is shown in Table 1, transparency occurred when 0.02641 mole of sodium caprylate (SC) was added to the solution of Pluronic F127 and ethyl butyrate (oil) in PBS with the fixed concentrations of F127 and oil. In other word, an oil-in-water F127 microemulsion in the absence of drug obtained by using SC at a certain concentration (2.641 M).

Then , to the oil-in-water F127 microemulsion in the absence of drug, oil (in addition to initial oil) was added more and more from concentration of 4.304 to 42.183 M to find upper limit for solubilization of oil in F127 microemulsions (Table 2).

In this case as shown in Table 2, we found that for the oil-in-water F127 microemulsion in the absence of drug, turbidity occurred when 0.42183 mole of oil (EB) was added to the F127 microemulsion solution.

Table 1. The added co-surfactant concentration (SC) to the solution of Pluronic F127 and ethyl butyrate in PBS to find a transparence solution in the absence of drug ([F127]=0.009 M , [Ethyl butyrate]= 4.304 M)

system	Added SC amount (mole)	Added SC amount (Molar)	Turbidity
PBS+oil+F127	0.00114	0.114	Turbid
PBS+oil+F127	0.00542	0.542	Turbid
PBS+oil+F127	0.01191	1.191	Turbid
PBS+oil+F127	0.01203	1.203	Turbid
PBS+oil+F127	0.01799	1.799	Turbid
PBS+oil+F127	0.02641	2.641	Transparent

In this section the turbidity for the oil-in-water F127 microemulsions (in the absence of drug) occurred when approximately 16 molecule of oil was added for every 1 molecule of SC, and approximately 4 molecules of oil were added for every 1 molecule of F127 .

So, high limit for solubilization of oil in the F127 microemulsions will be at 42.183 M.

In final step, F127 pluronic along with oil (pure liquid) were added more and more to the turbid solution with aim determining region of turbid and clear (please see Table 3).

Curve related to titration of oil-in-water F127 microemulsion (without drug) with oil and F127 according to data in Table 3 to determine turbid/ clear region in the absence of drug is shown in Fig. 3.

It is clear from Fig. 3 that there is a linear relation between solbulization capacity of oil and F127 surfactant in the solution.

In these case, we observed that at a critical

Table 2. The added oil to the oil-in-water F127 microemulsion to determine upper limit for solubilization of oil in microemulsions in the absence of drug ([F127]=0.009 M , [Sodium Caprylate (SC)]= 2.641 M).

system	Added oil amount (mole)	turbidity
PBS+SC+F127+oil	0.04304	Transparent
PBS+SC+F127+oil	0.08609	Transparent
PBS+SC+F127+oil	0.13774	Transparent
PBS+SC+F127+oil	0.18079	Transparent
PBS+SC+F127+oil	0.22383	clear
PBS+SC+F127+oil	0.27548	clear
PBS+SC+F127+oil	0.33574	clear
PBS+SC+F127+oil	0.34435	clear
PBS+SC+F127+oil	0.36157	clear
PBS+SC+F127+oil	0.40461	Turbid-like clear
PBS+SC+F127+oil	0.42183	turbid

Table 3. Titration of turbid solution of F127, SC, oil in PBS with Ethyl butyrate oil and F127 surfactant ([Sodium Caprylate (SC)]= 2.641 M) with aim determining region of turbid and clear

SYSTEM	F127 (Molar)	Added OIL amount (Molar)	
PBS+SC+F127+oil	0.00891	0.08609	
PBS+SC+F127+oil	0.3572	0.259	
PBS+SC+F127+oil	0.8113	0.4869	
PBS+SC+F127+oil	1.118	0.639	
PBS+SC+F127+oil	1.1643	0.6619	gel-like

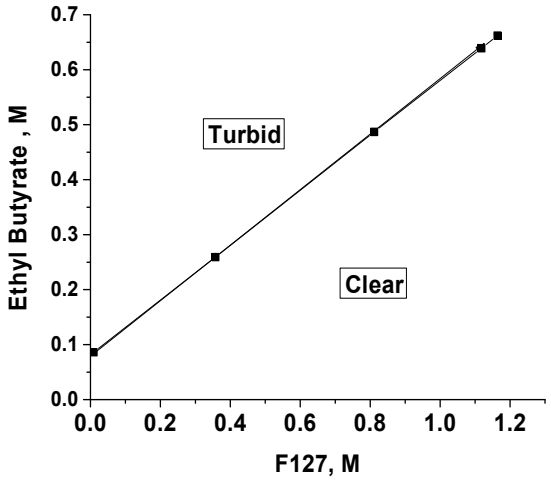

Fig. 3. Titration of microemulsions with Ethyl butyrate oil and F127 surfactant. The solution is clear below the curve and turbid above the curve.

Pluronic F127 concentration (1.1643 M), system was gel-like transparence

It can be said that as concentration of F127 increases, the viscosity of the solution also increases.

We also plotted the concentration of oil versus F127 to determine the optimal binding ratio of F127 to oil according to data in Table 3. Fig. 4 shows the result of this plot.

As can be seen in the Fig. 4, the optimal binding ratio of oil and F127 is approximately 1 molecule of oil for every 2 molecules of F127.

It can be said when F127 is added to the solution more oil can be added before gel-like status occurs. This observation suggests that the F127/SC nanomicelles act as a sink for molecules of oil within system prior to interacting with molecules of SC present in bulk solvent. At the critical concentration of F127, all molecules of SC are bound to the F127 and no longer exists in the bulk solvent, freely [5-7].

Study of upper limit for solubilization of drug (Tocopherol) in the micelle in the absence of oil (Ethyl Butyrate)

In the research second case, solution of Pluronic F127 and drug (pure liquid) in PBS (without oil)

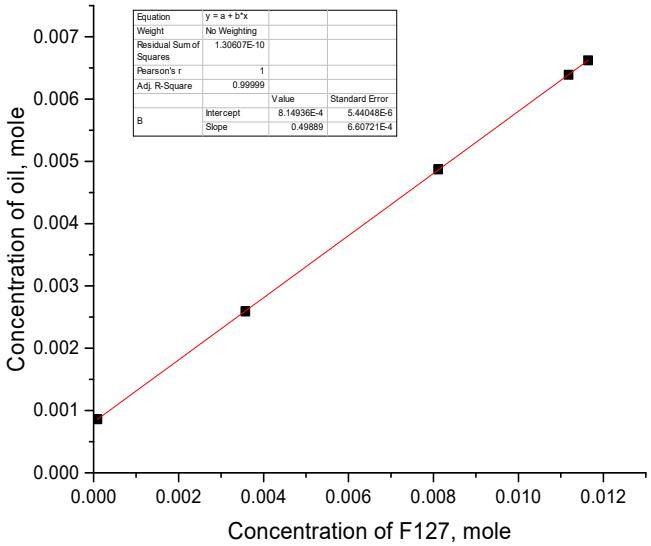

Fig. 4. Optimal binding ratio of oil to F127 in microemulsions

Table 4. The added SC amount to the solution of Pluronic F127 and drug in PBS (without oil) to transparency ([F127]=0.009 M, [*Drug]= 0.09984 M).

system	Added SC amount (mole)	Added SC amount (Molar)	Turbidity
PBS+drug+F127	0.00114	0.114	Turbid
PBS+drug+F127	0.00542	0.542	Turbid
PBS+drug+F127	0.01191	1.191	Turbid
PBS+drug+F127	0.01203	1.203	Turbid
PBS+drug+F127	0.01799	1.799	Turbid
PBS+drug+F127	0.02641	2.641	Transparent

Table 5. The added drug to the micelle to determine the upper limit of solubilization of drug in F127 micelle ([F127]=0.009 M, [Sodium Caprylate (SC)]= 2.641 M).

system	Added drug amount (mole)	turbidity	Added drug amount (Molar)
PBS+SC+F127	0	Transparent	
PBS+SC+F127+drug	9.98352E-4	Transparent	0.09984
PBS+SC+F127+drug	0.00209	Transparent	0.209
PBS+SC+F127+drug	0.00406	Transparent	0.406
PBS+SC+F127+drug	0.00464	Transparent	0.464
PBS+SC+F127+drug	0.07685	turbid	7.685

titrated with sodium caprylate (SC) at different concentrations ranging from 0.114 to 2.641 M in PBS to transparency (Table 4).

In this study, we found that for solution of Pluronic F127 and drug (pure oil) in PBS (without oil), transparency occurred when 0.02641 mole of sodium caprylate (SC) was added to the solution.

In other word, a micelle in the absence of oil obtained by using SC at a certain concentration (2.641 M).

Then, to the micelle in the absence of oil, drug (Tocopherol) was added more and more from concentration of 0.09984 to 7.685 M to find upper limit for solubilization of drug in F127 micelle (Table 5).

In this case, we found that for F127 micelle system in the absence of oil, turbidity occurred when 0.07685 mole of drug (Tocopherol) was added to the the mentioned transparence solution with certain concentrations of F127 and SC.

In other words, we found that, for F127 micelle system turbidity occurred when approximately 3 molecules of Tocopherol was added for every 1 molecule of SC, and approximately 853 molecules of drug was added for every 1 molecule of F127.

In this case, so, high limit for solubilization of drug in the F127 micelle system in the absence of oil will be at 7.685 M.

Then, to obtained turbid solution, F127 along with drug was added mor and more to determine region of turbid and clear (Table 6).

Curve related to titration of PBS+SC+F127+drug with drug and F127 according to data in Table 6 to determine turbid/clear region in the absence of oil is shown in Fig. 5.

It is clear from Fig. 5 that there is a linear relation between solbulization capacity of drug and F127 surfactant in the solution.

In these titrations, we observed that at a critical Pluronic F127 concentration, system was gel-like transparence (0.5803M).

We also plotted the concentration of drug versus F127 to determine the optimal binding ratio of F127 to drug. Fig.5 shows the result of this plot.

As can be seen in the Fig. 6, the optimal binding ratio of drug and F127 is approximately 4 molecules of drug for every 100 molecule of F127.

This suggests that the electrostatic interactions

Table 6. Titration of turbid solution of F127, SC, drug in PBS with F127 and drug ([PBS]=Const., [Sodium Caprylate (SC)]= Const.).

SYSTEM	F127 (Molar)	Added drug amount (Molar)	
PBS+SC+F127+drug	0.00891	9.98352E-4	
PBS+SC+F127+drug	0.167	0.00768	
PBS+SC+F127+drug	0.3678	0.0163	
PBS+SC+F127+drug	0.559	0.02482	
	0.5803	0.0255	gel-like

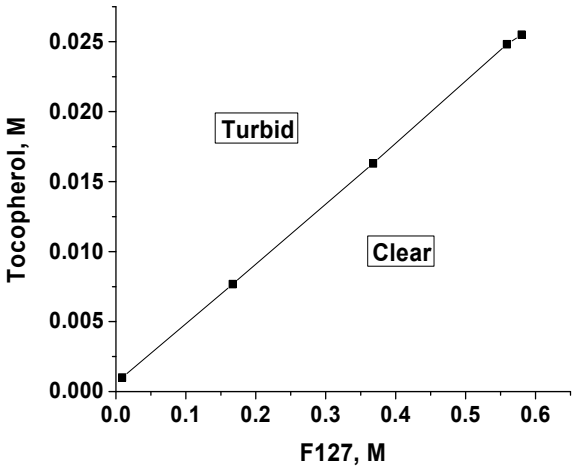

Fig. 5. Titration of solution of F127, SC, drug in PBS with Tocopherol drug and F127 surfactant. The solution is clear below the curve and turbid above the curve.

between molecules of the SC and drug play a major role in the binding process of the Tocopherol to the F127 molecules within microemulsion.

However, when F127 is added to the solution, more Tocopherol can be added before gel-like status occurs. This observation suggests that the F127/SC nanomicelles act as a sink for molecules of Tocopherol within system prior to interacting with molecules of SC present in bulk solvent. At the critical concentration of F127, all molecules of SC are bound to the F127 and no longer exists in the bulk solvent, freely [5-7].

So, at the first, drug of Tocopherol partitions to the F127/SC nanomicelle before saturation and resulting solubilization into the bulk phase of microemulsion.

Study of upper limit for solubilization of Oil+Drug (1:1 molar ratio) in F127 microemulsions

In the third case, at the first, we prepared a solution containing F127 Pluronic, sodium caprylate (SC) , and PBS.

Then, the solution was titrated with oil+drug solution (1:1 molar ratio) to turbidity (please see Table 7).

It is important to mention that the oil+drug solution containing oil (pure liquid) and drug (pure liquid) prepared with 1:1 molar ratio.

For this system, the F127 and Sodium Caprylate (SC) concentrations were held fixed at 0.009 and 2.641 M, respectively, and the oil+drug concentration was varied from 0.02124 to 0.125 M.

In this case as shown in Table 7, turbidity the

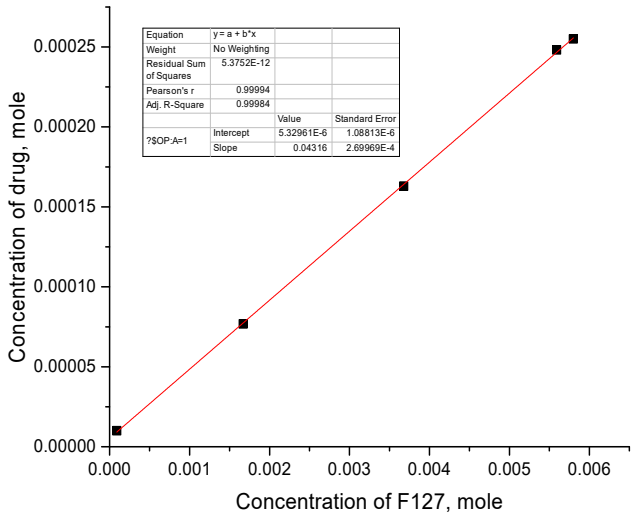

Fig. 6. Optimal binding ratio of drug to F127 micelle.

Table 7. the added oil+drug (in 1:1 molar ratio) amount into the solution of Pluronic F127 and sodium caprylate (SC) in PBS to find the upper limit of solubilization the oil+drug in the solution ([F127]=0.009 M , [Sodium Caprylate (SC)]= 2.641 M)

system	Added drug+oil (mole)	turbidity	Added drug+oil (Molar)
PBS+SC+F127	0	Transparence	micelle
PBS+SC+F127	2.12409E-4	Clear	0.02124
PBS+SC+F127	4.24818E-4	Clear	0.04248
PBS+SC+F127	0.00125	Turbid	0.125

Table 8. Titration of turbid solution of F127, SC, oil+drug in PBS with F127 and Oil+Drug (1:1 molar ratio) ([PBS]=Const. , [Sodium Caprylate (SC)]= Const.).

SYSTEM	F127 , Molar	Added Oil+Drug , Molar	
PBS+SC+F127+oil:drug	0.00891	4.24818E-43	
PBS+SC+F127+oil:drug	0.2348	0.1825	
PBS+SC+F127+oil:drug	0.4932	0.4039	
PBS+SC+F127+oil:drug	0.7966	0.6484	
PBS+SC+F127+oil:drug	0.822	0.6656	Jel-like

solution (containing Pluronic F127, sodium caprylate (SC), and PBS) occurred at a certain concentration of the drug+oil solution (0.125 M).

In other word, we found that turbidity occurred when approximately 4 molecule of oil+drug mixture (1:1 molar ratio) was added for every 100 molecules of SC, and approximately 14 molecule of oil+drug mixture (1:1 molar ratio) was added for every 1 molecules of F127 .

In this case, high limit for solubilization of oil+drug solution (1:1 molar ratio) within F127 microemulsions was at concentration of 0.125 M.

Then, F127 pluronic along with oil+drug solution (1:1 molar ratio) were added more and more to the turbid solution with aim determining region of turbid and clear (Table 8).

Curve related to titration of the PBS+SC+F127+ oil:drug solution (with 1:1 molar ratio) with F127 and the oil:drug according to data in Table 8 to determine turbid/clear region is shown in Fig. 7.

It is clear from Fig. 7 that there is a linear relation between solbulization capacity of oil:drug and F127 surfactant in the solution.

In these titrations, it was observed that at a critical pluronic F127 concentration, system was a gel-like transparence liquid (0.822 M).

We also plotted the concentration of oil:drug mixture (1:1 molar ratio) versus F127 to determine the optimal binding ratio of F127 to oil:drug mixture (1:1 molar ratio). Fig. 8 shows the result of this plot.

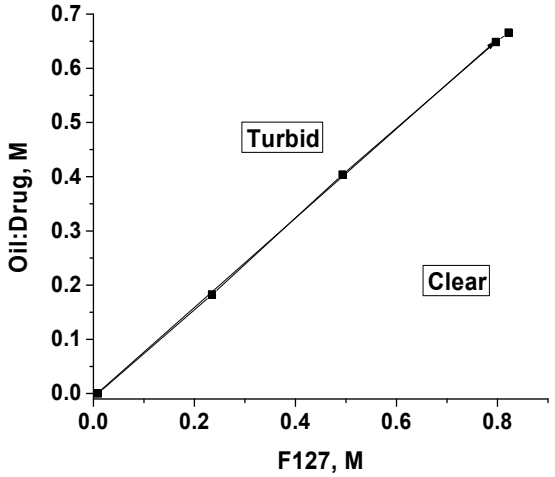

Fig. 7. Titration of turbid solution of F127, SC, oil+drug in PBS with oil+drug and F127 surfactant. The solution is clear below the curve and turbid above the curve.

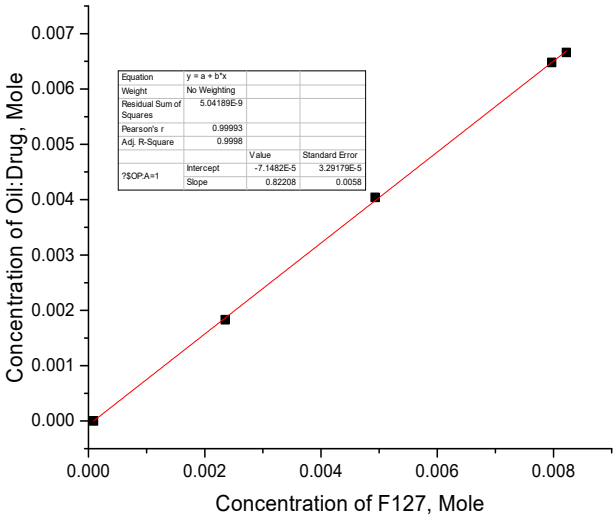

Fig. 8. Optimal binding ratio of Oil+Drug to F127 in microemulsions

As can be seen in the Fig. 8, optimal binding ratio of oil:drug mixture (1:1 molar ratio) and F127 is approximately 4 molecule of oil+drug (1:1 molar ratio) for every 5 molecule of F127.

This result suggests that the electrostatic interactions among the components involved in solution play a key role in binding the molecules of the oil:drug mixture (1:1 molar ratio) to the F127 molecules within microemulsion.

Titration of solutions in PBS with different components versus F127 pluronic is shown in Fig. 9.

By comparing results in above Figure, it is resulted that gelling threshold for microemulsions is depends on type of titration of system with oil, drug, and oil+drug (1:1 molar ratio) component.

It is clear from Figure that solubilization capacity of oil and oil+drug (1:1 molar ratio) with F127 in microemulsion is more considerable than solubilization capacity of Tocopherol with F127 within microemulsion.

In other word, solubilization capacity of Tocopherol with F127 in microemulsion is nearly constant than solubilization capacity of oil and oil+drug (1:1 molar ratio) with F127 in microemulsion.

Dynamic Light Scattering

The autocorrelation function of F127 microemulsions as a function of relaxation time obtained by DLS tool is shown in Fig. 10.

The Diffusion and hydrodynamic size of the of F127 micro-emulsions according to analysis of the autocorrelation function of F127 microemulsions is shown in Fig. 10.

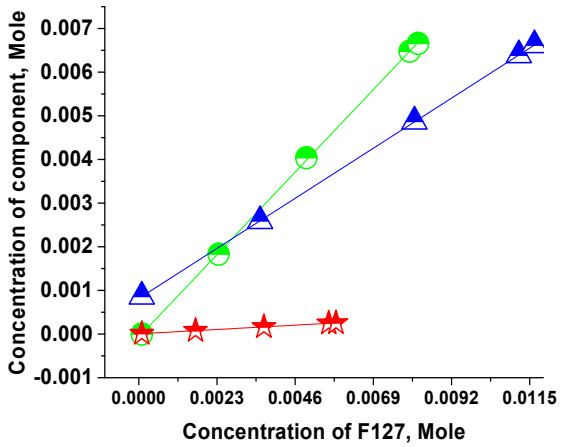

Fig. 9. Titration of solutions in PBS with component versus F127 pluronic: (star) Tocopherol drug, (circle) oil+drug (1:1 molar ratio), and (up triangle) oil and F127 surfactant. The solution is clear below the curve and turbid above the curve.

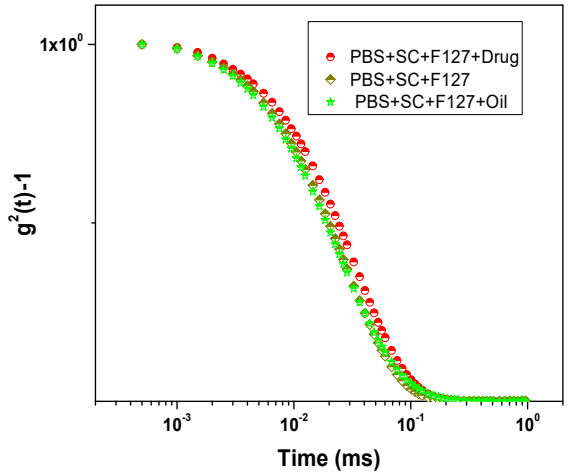

Fig. 10. the autocorrelation function of F127 microemulsions as a function of relaxation time at RT.

Table 9. The Diffusion and hydrodynamic size of the of F127 micro-emulsions according to analysis of Fig. 10 at RT.

Sample	Diffusion (m^2/s)	Hydrodynamic size (nm)
PBS+SC+F127+Drug	2.39535E-11	9.9665
PBS+SC+F127	2.71473E-11	8.79397
PBS+SC+F127+oil	3.03411E-11	7.86829

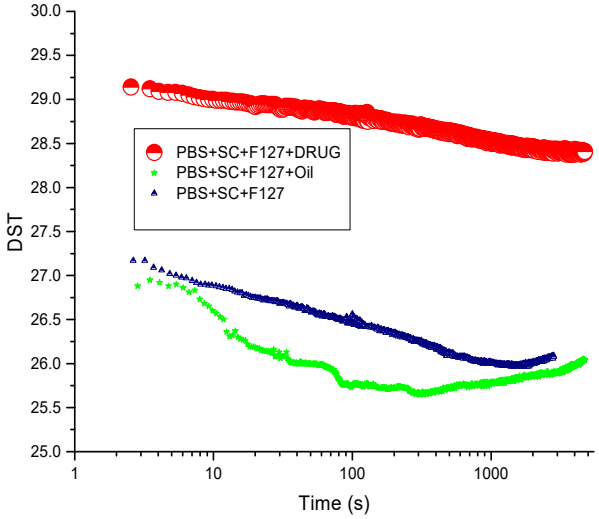

Fig. 11. surface tension of different mixtures with time from up to bottom: solution of F127, SC, drug in PBS, solution of F127, SC, oil in PBS, and solution of F127, SC in PBS.

Dynamic surface tension (DST)

It is widely believed that Dynamic surface tension (DST) is a key parameter to measure the surfactants molecules available to participate to a newly created surface and in result stabilizing new surface.

The obtained results related to characterize the samples by Dynamic surface tension measurement is shown in Fig. 11.

Presented results in Fig. 11 shows that behavior of surface tension is depends on type of mixture.

It is well-known that through DST of microemulsions, as the new surface creates as a result of production of bubble, potential locations to supply the surfactant molecules for stabilization new interface will be from the bulk, micelles, and interface of droplet microemulsion within system [5-8].

Through results in Fig. 11, it is clear that for the solution of F127, SC, and Drug in PBS, the surface tension is higher than that of the solution of F127, SC, and Oil in PBS at the same time.

This observation can be assigned to lower stability of new interface formed for the solution of F127, SC, drug in PBS than the solution of F127, SC, Oil in PBS due to low supply of surfactant molecules from the system in solution of F127, SC, Drug in PBS than other solution [5-8].

In other word, this result suggests higher stability of droplet microemulsions in the solution of F127, SC, and Drug in PBS than the solution of F127, SC, and Oil in PBS as a result of low supply of surfactant molecules from the system in solution of F127, SC, and Drug in PBS than other solution [5-8].

On the other hand, the presented results in Fig. 11 indicate a nearly constant DST value at higher times for all samples, which this event can be rationalized in term of the fact that molecules of surfactant existing in the system are not available to diffuse to the newly created interface at the higher time [5-8].

Also, decrease in DST at lower times for all samples reflects that the surfactant molecules can fast diffuse to the new surface from the system including bulk or interface of the droplet micro emulsion and/or micelles [5-8].

CONCLUSION

In the current work, solubilization capacity of the hydrophibic drug (Tocopherol), oil (Ethyl

Butyrate), and oil+drug (1:1 molar ratio) into F127 pluronic microemulsions was studied as a function of F127 concentration through simple turbidity or transparency experiments. Pluronic F127-based oil-in-water microemulsions of various compositions were synthesized and titrated with concentrated Tocopherol drug, Ethyl Butyrate oil, and oil+drug (1:1 molar ratio), separately, to determine clear / turbid transition zone. We found that the addition of Tocopherol, oil, and oil:drug to the Pluronic F127 microemulsions produced turbid/clear region in microemulsion up to the critical concentration of F127. At this concertation of F127, the solutions were gelled. Other experiments indicated that turbidity occurs when of free SC molecules there are in the system to interact with the drug, oil, and oil:drug mixture (1:1 molar ratio). According to the our results, it was concluded that at the critical concentration of F127, there is molecules of SC within bulk phase, freely, to interact with molecules of Tocopherol, oil, and oil:drug. This approach was used to determine the optimal binding ratios SC to F127 and the drug, oil, and oil:drug to F127. Results indicated that the electrostatic interactions play an important role in the uptake of Tocopherol by the oil-in-water microemulsion according to the positively charged drug and the negatively charged SC.

The dynamic surface tension experiments of samples indicated a higher DST for PBS+SC+F127+drug than other compositions.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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