Determination of Drug and Fatty Acid Binding Capacity to Pluronic F127 in Microemulsions

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We propose that one can deduce very insightful information regarding the drug and fatty acid binding capacity of microemulsions through simple turbidity experiments. Pluronic F127-based oil-in-water microemulsions of various compositions were synthesized and titrated to turbidity with concentrated amitriptyline, an antidepressant drug. We observed that, above certain Pluronic F127 concentrations, turbidity was never observed, irrespective of how much amitriptyline was added to the microemulsion. We also observed that whenever sodium caprylate fatty acid was not included in the microemulsion formulation, turbidity never occurred. On the basis of these findings, we were able to determine the point at which all sodium caprylate present in the microemulsion formulation was bound to the F127 in the microemulsion (i.e., no fatty acid was free in the bulk in monomer form). By the same logic we were also able to determine how much amitriptyline was binding to the microemulsions. We also measured the dynamic surface tension, foamability, and fabric wetting time of the microemulsion formulations to further prove the hypothesis that all fatty acid is bound to the F127 in the microemulsion above a critical Pluronic F127 concentration. On the basis of this research, we have concluded that there are approximately 11 molecules of sodium caprylate fatty acid bound per molecule of Pluronic F127 and approximately 12 molecules of amitriptyline bound per molecule of Pluronic F127 in the optimal microemulsion formulation. These findings give us valuable information about the charge density at the oil/water interface and about the mechanism of binding of the drug to the microemulsion.

Introduction

Drug overdose incidences are a common and problematic occurrence both nationally and globally. Many life-threatening drugs do not have specific pharmacological antidotes to reverse the toxic effects that result when an overdose occurs.[1] Attempts are currently under way to develop procedures to detoxify blood in a timely and efficient manner.[2−4] Therefore, the development of an effective methodology for the removal of free drug from the blood of an overdosed patient in a timely manner (less than 15 min) is critically important. In the past few years, efforts have been under way to utilize nanoparticulate systems to accomplish this task. Microemulsions are one of the systems that are currently under investigation. Upon injection of a biocompatible, nontoxic microemulsion in the blood of an overdosed person, the microemulsion, having extremely high interfacial area, can effectively adsorb and solubilize drug molecules, and thereby quickly decrease the concentration of free drug molecules in the blood. However, to fully grasp their function as toxicity reversal agents, one must understand the molecular mechanism of drug uptake and be able to determine and manipulate the contributing interfacial forces.

Preliminary results from pH studies have led us to believe that electrostatic forces can play a significant role in adsorption of drug onto the microemulsion. Amitriptyline hydrochloride, shown in Figure 1, is an antidepressant, and as of yet, there is no efficient method to reverse the effects of an overdose in a patient; therefore, it is the target drug for the experiments reported here. Amitriptyline (AMT) has a pK_a of approximately 9.4 so that, at physiological pH (∼7.4), it will be positively charged and can thereby interact through electrostatics with a negatively charged microemulsion. These microemulsions are composed of Pluronic F127, ethyl butyrate, and sodium caprylate fatty acid (which gives the negative charge) and are prepared in phosphate-buffered saline at pH 7.4. The objective of this study is to develop a better understanding of the important interactions that occur between the microemulsion and the drug.

We have shown, through turbidity analysis experiments, that there is a linear relationship between the amitriptyline hydrochloride solubilization capacity (i.e., the amount of amitriptyline that the microemulsion can accommodate before turbidity occurs) of the microemulsions and Pluronic surfactant concentration up to a certain Pluronic F127 concentration. Above that critical Pluronic F127 concentration, further titration with amitriptyline never yields turbidity. We have also seen that turbidity is not observed in systems that do not have sodium caprylate present. On the basis of these findings, we have concluded that, at the critical Pluronic concentration, there is no longer any free (unassociated) sodium caprylate molecules in the bulk phase, presumably due to binding of all fatty acid molecules with Pluronic molecules. Therefore, we are able to determine how many molecules of sodium caprylate and amitriptyline are associated with each Pluronic molecule. Each Pluronic F127 molecule can associate with approximately 11 molecules of sodium caprylate and 12 molecules of amitriptyline at the critical concentration (i.e., there appears to be a nearly 1:1 association of sodium

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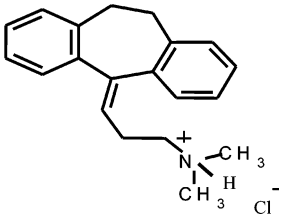

Figure 1. Amitriptyline hydrochloride, MW = 313.9.

caprylate to amitriptyline). This yields further credence to ultrafiltration studies that we have done as a function of pH which show that electrostatic interactions are important in amitriptyline binding to microemulsions produced by Pluronic F127 and fatty acid soap. The findings of this study will provide substantial information regarding the mechanism of reduction of overdosed drugs and will allow us to approximate the uptake capacity of a particular microemulsion system.

Experimental Section

Materials. Pluronic surfactants were obtained from BASF Inc. (Mount Olive, NJ). Pluronic was used as a nonionic surfactant composed of a symmetric triblock copolymer of propylene oxide (PO) and ethylene oxide (EO). The poly(propylene oxide) block was sandwiched between the more hydrophilic poly(ethylene oxide) blocks. The block copolymer was denoted by $(EO)_x(PO)_y(EO)_x$, where x and y are the number of units of EO and PO, respectively. Amitriptyline hydrochloride and sodium caprylate were purchased from the Sigma Chemical Co. (St. Louis, MO). Ethyl butyrate was purchased from ACROS Organics (New Jersey). Potassium phosphate monobasic, potassium phosphate dibasic, sodium chloride, and potassium chloride which were used to prepare the phosphate-buffered saline were purchased from Fisher Scientific Inc. (Suwanee, GA). Doubly distilled, deionized Millipure water was utilized for all solutions.

Microemulsion Preparation. Oil-in-water microemulsions were prepared by first solubilizing the appropriate concentration (3−9 mM) of Pluronic F127 surfactant in phosphate-buffered saline at pH 7.4 (physiological pH). Pluronic F127 was chosen because extensive studies have been performed which show that this surfactant is not harmful to the body.[5] Sodium caprylate (fatty acid surfactant) was then added to this Pluronic solution in concentrations ranging from 25 to 100 mM. Last, ethyl butyrate (oil) was added to the solution, and the system was stirred until it became clear. The ethyl butyrate concentration was fixed at 110 mM for all experiments in which microemulsions were used. The microemulsions were subsequently allowed to equilibrate for at least 1 day prior to use. Phosphate-buffered saline was prepared at pH 7.4 from 1.4 mM potassium phosphate monobasic, 8.7 mM potassium phosphate dibasic, 137 mM sodium chloride, and 2.7 mM potassium chloride.

Turbidity Analysis. Micelles, mixed micelles, and microemulsions were prepared with varying compositions of Pluronic F127 and/or sodium caprylate and/or ethyl butyrate. In the first case of micelles (i.e., systems without oil), only Pluronic F127 was prepared in concentrations ranging from 3 to 9 mM in phosphate-buffered saline (PBS) at pH ≈ 7.4. The second micellar solution was prepared with only sodium caprylate with concentrations ranging from 1 to 450 mM in PBS. The mixed micelles were of Pluronic F127 (3−9 mM) and sodium caprylate (25−125 mM) in PBS without oil. The microemulsion compositions are given in the previous section. Ten milliliters of the micelle, mixed micelle, or microemulsion sample was placed into a vial. The solution was titrated with 0.2 M amitriptyline (prepared in PBS) until the onset of turbidity was observed visually. The systems were sensitive enough that the transition from clear to turbid was very sharp (i.e., occurring over a change in volume of 50 μL or less). In some systems, prior to the system reaching turbidity, upon each incremental addition of amitriptyline, the solutions would exhibit a momentary cloudiness, but gentle swirling would lead to a return in clarity. During titration, if the initial cloudiness was not observed upon the additions of amitriptyline, copious amounts of drug were added to that system; if turbidity was not observed, then the system was categorized as one where turbidity would never occur.

Dynamic Surface Tension. Dynamic surface tension was measured using the maximum bubble pressure technique. The pressure required to form a new bubble in solution is measured by a pressure transducer, and the reading is transmitted to an oscilloscope. For these experiments, the dynamic surface tension was measured for microemulsions consisting of fixed sodium caprylate (100 mM) and ethyl butyrate (110 mM) concentrations and increasing concentrations of Pluronic F127. All dynamic surface tension measurements were taken using an 18 gauge needle tip with a gas flow rate of 5 cm^3/min (which corresponds to 3−10 bubbles per second or approximately 100−333 ms per bubble residence time at the needle tip). We chose this flow rate because at higher flow rates the nitrogen gas forms a continuous jet in the surfactant solution at the needle tip. At lower flow rates, the results are similar to equilibrium surface tension results.

Foamability. Twenty milliliter samples of microemulsions consisting of fixed sodium caprylate (100 mM) and ethyl butyrate (110 mM) concentrations and increasing concentrations of Pluronic F127 were placed into 100 mL graduated cylinders and capped. Each cylinder was vigorously shaken 10 times by hand, and the volume of the foam was recorded immediately after shaking. Each solution was tested at least three times, and the reproducibility was better than ±2 mL.

Fabric Wetting. A commercially gained cotton fabric of 1 $in.^2$ was placed on the surface of the microemulsion solution at 25 °C. The microemulsions used consisted of fixed sodium caprylate (100 mM) and ethyl butyrate (110 mM) concentrations and increasing concentrations of Pluronic F127. The surfactant solution displaces air in the cotton surface by a wetting process, and when sufficient air has been displaced, the cotton starts sinking. The residence time of cotton fabric on the surface of the solution before it was completely immersed was measured as the wetting time in this study. This wetting time in each microemulsion solution was measured at least three times.

Results and Discussion

As previously reported,[1] we have taken a systematic approach to design a biocompatible microemulsion system that would effectively reduce the free concentration of target drugs in the blood. This microemulsion system is composed of Pluronic F127 as the surfactant, sodium caprylate (SC) fatty acid surfactant, and ethyl butyrate (EB) as the oil phase and is prepared in a phosphate-buffered saline solution at pH 7.4. Given that Pluronic F127 is a block copolymer and sodium caprylate is a surfactant, if we can understand the nature of the polymer−surfactant interactions in this microemulsion, then we can have a better understanding of the structure of the microemulsion and the molecular mechanism of uptake of the drug. For many years now, polymer−surfactant interactions have been studied extensively in relation to various interfacial processes.[6−13] One of the

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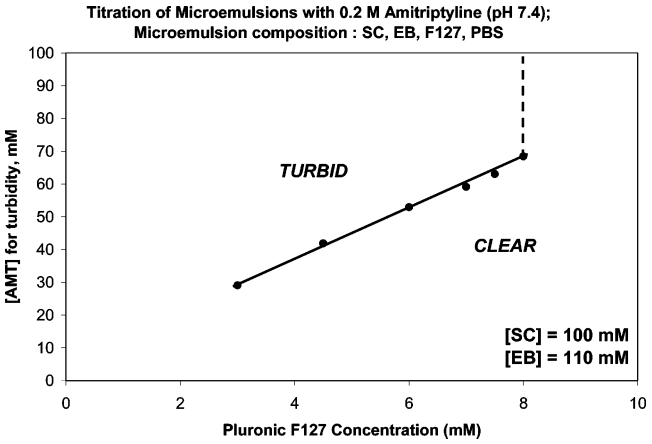

Figure 2. Titration of microemulsions with 0.2 M AMT. The solution is clear below the curve and turbid above the curve.

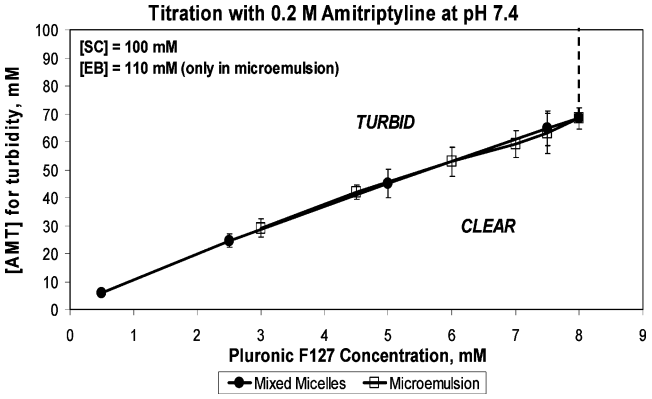

Figure 3. Titration of mixed micelles and microemulsion systems. The solution is clear in the area below the curve and turbid in the area above the curve.

methods of analyzing polymer−surfactant interactions is through titration studies.[14,15] Here, we take various microemulsion compositions and titrate them with concentrated amitriptyline solutions to turbidity. We are using the results of these studies to determine the pertinent stoichiometric ratios in our optimal microemulsion formulations.

For our initial titration studies we took the various microemulsion components and titrated them individually. Our first titrations were of SC solutions in PBS (pH 7.4). In this study, we found that, at 100 mM SC, turbidity occurred when 1 molecule of AMT was added for every 100 molecules of SC.

Next, we titrated systems containing only Pluronic F127 in PBS (pH 7.4) with 0.2 M AMT. In these systems we found that turbidity was never obtained, irrespective of how much AMT was added to the system. Then we added the ethyl butyrate oil to the Pluronic F127 systems and titrated these solutions with 0.2 M AMT. Once again, turbidity was never obtained. Finally, we added our last component, the sodium caprylate fatty acid,

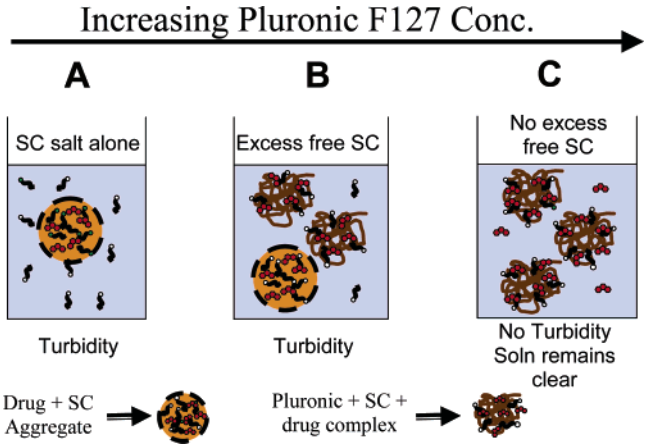

Figure 4. Schematic diagram of turbidity in various solutions. Surfactants with green heads represent the sodium caprylate. The red three-ring structure represents the amitriptyline drug. Black coils represent Pluronic F127. The light blue agglomerate system represents the complex that is formed between the free (monomeric) sodium caprylate in the bulk and the amitriptyline. This complex formation causes turbidity to appear in the system.

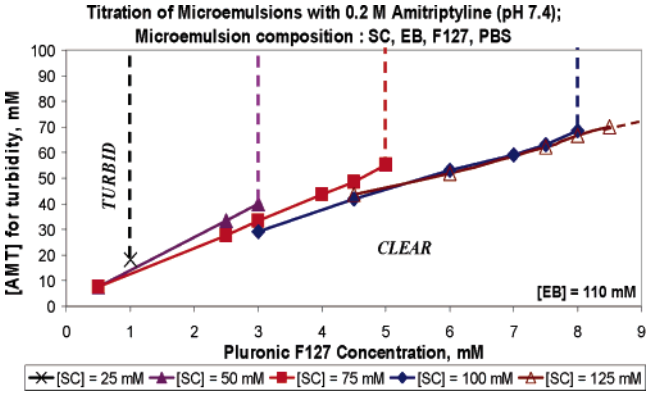

Figure 5. Titration of microemulsion systems with AMT. The sodium caprylate concentration is varied from 25 to 125 mM, and the F127 concentration is varied from 1 to 9 mM. The solution is clear in the area below the curve and turbid in the area above the curve.

to the system and found that, upon titration with 0.2 M AMT, turbidity was seen in these systems. For these systems, the sodium caprylate concentration was held fixed at 100 mM, the ethyl butyrate concentration was held fixed at 110 mM, and the Pluronic F127 concentration was varied from 3 to 9 mM. One of the interesting observations that we noticed in these titrations was that turbidity was achieved for every Pluronic F127 concentration up to 8 mM. Above 8 mM F127, turbidity was never achieved (see Figure 2).

Our next experiment involved titration of Pluronic F127 and sodium caprylate mixed micellar systems (i.e., no oil is present). In this case, the sodium caprylate concentration was held fixed at 100 mM and the F127 concentration was varied from 1 to 9 mM. We were somewhat surprised to see that the lack of oil in these systems did not seem to affect the amount of AMT needed to induce turbidity (i.e., the graph for the mixed micellar system is nearly the same as that of the microemulsion system (see Figure 3). However, animal studies (living rats) have been performed to test the efficacy of both microemulsions and mixed micelles in the attenuation of drug molecules from the blood stream, and it has been shown that while the oil may not play

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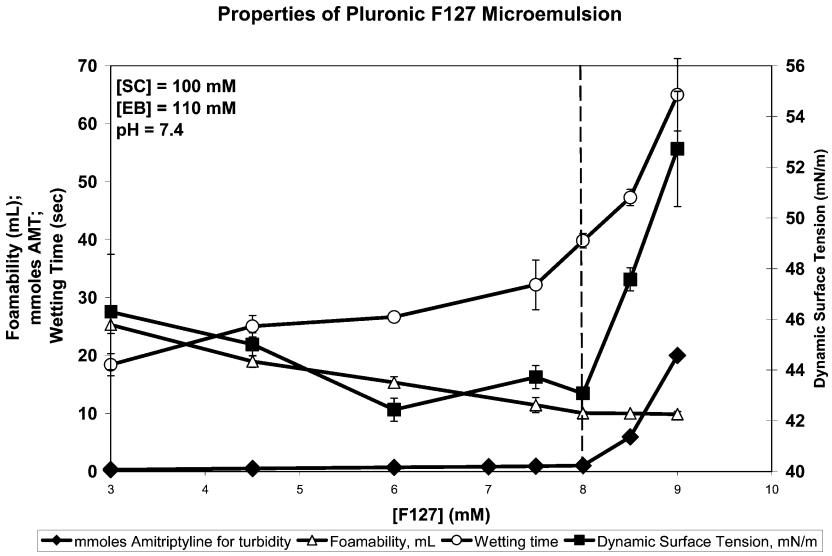

Figure 6. Graph of the turbidity, foamability, fabric wetting time, and dynamic surface tension of microemulsion systems with the SC concentration fixed at 100 mM, the EB concentration fixed at 110 mM, and varied F127 concentrations.

a major role in the initial uptake of drug, its presence is necessary to keep the drug from being re-released into the blood stream.[16]

These experiments provided us with two important insights. First, turbidity is only observed in the systems where the sodium caprylate is present. On the basis of this finding, we can conclude that the turbidity is arising from AMT forming a complex with the SC. Second, in the systems where Pluronic F127 is present with SC, turbidity is observed up to some critical F127 concentration, above which turbidity is no longer observed. Hence, we can conclude that the critical F127 concentration is the concentration at which no more SC exists as free monomers in the bulk solution and that the turbidity is a result of the AMT complexing with the free SC in the bulk. Figure 4 provides a schematic illustration of this hypothesis.

We have seen in our titrations of SC solutions (i.e., with no oil and no Pluronic present) that turbidity arises with very little addition of AMT (Figure 4A). However, when F127 is added to the system (both with and without oil present) more AMT can be added before turbidity occurs. This suggests that the F127/SC droplet acts as a sink for the drug molecules to partition into prior to interacting with the bulk SC (Figure 4B). At the critical F127 concentration, all SC is bound to the F127 and no longer exists freely in the bulk, so AMT first partitions to the F127/SC droplets until they become saturated and then begins to solubilize in the aqueous phase (Figure 4C).

To test our hypothesis, we did the turbidity experiments for various sodium caprylate concentrations. If our hypothesis is correct, we would expect for the critical F127 concentration to decrease proportionally to the decrease in SC concentration. As can be seen in Figure 5, the decrease in the critical concentration of F127 is indeed nearly proportional to the decrease in the SC concentration. The critical F127 concentration is never reached in the system where the SC concentration is 125 mM because above an F127 concentration of 9 mM, the solution becomes a gel.

We also decided to test our hypothesis by analyzing various characteristics of the microemulsion system that would be sensitive to the presence of bulk surfactant. We tested the dynamic surface tension, fabric wetting time, and foamability of the microemulsion systems having fixed SC and EB concentrations ([SC] = 100 mM and [EB] = 110 mM) and varying concentrations of F127 ([F127] = 3−9 mM).

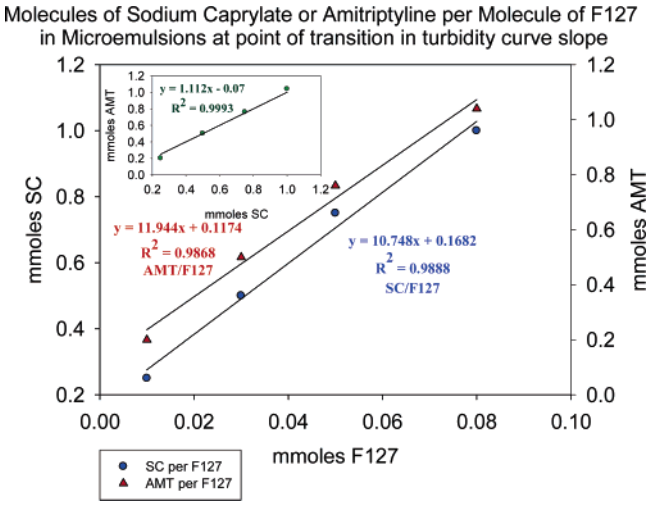

Figure 7. Optimal binding ratio of SC to F127 in microemulsions (shown by blue points) and optimal binding ratio of AMT to F127 (shown by red points). The inset shows the binding ratio of SC to AMT.

Dynamic surface tension (DST) is a measure of the availability of surface-active species to partition to a newly created surface and stabilize it. Dynamic surface tension is an important quantity in any process in which a new gas/liquid or liquid/liquid interface is rapidly generated.[17] A high DST value is reflective of the fact that any surface-active species that are present in the system are not readily available to diffuse to the newly created interface, whereas a low DST reflects that the species can quickly diffuse to the surface. Therefore, we would expect that, as the F127 concentration is increased, the amount of free SC in the bulk decreases, and as such, the DST value should increase.

The fabric wetting time is a measure of the time that it takes for a fabric to be completely wetted by a liquid. For a hydrophobic fabric, this time could be relatively long, depending upon the weight of the fabric. There are three forces at play in this situation: hydrophobicity, buoyancy, and gravity. The hydro-

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phobic and the buoyancy forces oppose the fabric sinking into the solution, whereas gravity promotes the fabric to sink into the solution. The hydrophobic force can be minimized if surface-active species are present in the solution to adsorb onto the fabric and make it hydrophilic. In this situation, the hydrophobic tail of the surfactant adsorbs onto the fabric and the hydrophilic head is exposed to the solution, hence making the fabric appear to be hydrophilic. On the basis of this knowledge, the fabric wetting time can be used as a relative measure of the amount of free sodium caprylate in the microemulsion solution. One would expect that, as the F127 concentration is increased, the SC concentration decreases and the fabric wetting time increases.

Foamability is a measure of the relative ability of a solution to generate foam. As foam is being formed, a new air/liquid interface is generated. If this new air/liquid interface can be rapidly stabilized (i.e., if surfactant molecules are available to rapidly diffuse to the interface), then the foam volume will be high. This solution would be considered as one having a high foamability. If no surfactant is available to stabilize this newly created interface, as the foam is generated, it will almost instantaneously collapse, and the foam volume will be very low. This solution would be considered to have a low foamability. Given this information, one would expect that, as the F127 concentration is increased, the SC concentration decreases and as such the foamability should decrease.

Figure 6 shows how the experimental results of the DST, fabric wetting time, and foamability support our hypothesis. One point to note is that, as the F127 concentration is increased, the viscosity of the solution also increases. The viscosity would also effect each of these processes (DST, fabric wetting time, and foamability), but the fact that each of these properties exhibits a distinct change in their curve around 8 mM supports the fact that there must be some change in the system around this concentration range. This is the point at which there is no free SC in the bulk solution.

Now that we have some confidence that our hypothesis is correct, we can plot the concentration of F127 at which turbidity is no longer observed versus the SC concentration and determine the optimal binding ratio of F127 to SC in our microemulsions. We can also plot the concentration of F127 at which turbidity is no longer observed versus the AMT concentration and determine the optimal binding ratio of F127 to AMT. Figure 7 shows the results of these plots. As can be seen in the figure, the optimal binding ratio of SC and F127 is approximately 11 molecules of SC for every 1 molecule of F127, and the optimal binding ratio of AMT and F127 is approximately 12 molecules of AMT for every 1 molecule of F127. When plotting the millimoles of AMT for turbidity versus the millimoles of bound SC, as shown in the inset of Figure 7, we see that there is nearly a 1:1 association between the two molecules.

This suggests that the electrostatic interaction between the negatively charged SC and the positively charged AMT plays a significant role in the AMT binding to the microemulsion. Ultrafiltration experiments have also been performed in which the drug is introduced to the microemulsion system and filtered through nanoporous membrane filters and the AMT concentration in the filtrate is subsequently measured. We observed that the AMT extraction by the microemulsion is very high at pH values that are equal to or lower than the pK_a of AMT (9.4) and is very low above the pK_a. This verifies that electrostatic forces are indeed the predominant force in the initial uptake of AMT into the microemulsion, thereby giving us further proof of the molecular mechanism of AMT uptake by Pluronic microemulsions.

Conclusion

Here, we have shown how one can use turbidity analysis to gain valuable insight into the molecular structure of Pluronic F127-based microemulsion systems. We have shown that the uptake of AMT by the microemulsion increases with F127 concentration. We also found that the addition of AMT to the Pluronic F127 microemulsions produced turbidity in all systems up to a critical F127 concentration. Above this critical concentration, turbidity is no longer observed irrespective of how much AMT is added. Other titration experiments proved that turbidity would only occur when there was free SC fatty acid for the AMT to interact with. On the basis of these findings, we concluded that, above the critical F127 concentration, there is no longer any free SC available for the AMT to interact with. This allowed us to determine the optimal binding ratios of SC to Pluronic F127 and of AMT to F127. These ratios were found to be approximately 11 molecules of SC per molecule of F127 and approximately 12 molecules of AMT per molecule of F127. We also found the ratio of SC to AMT to be very nearly 1:1, which indicates that electrostatic interactions play a major role in the uptake of AMT by the microemulsions due to the negatively charged SC interacting with the positively charged AMT.

We also performed foamability, fabric wetting, and dynamic surface tension studies to correlate with our theory that above a critical F127 concentration there are no longer any free SC molecules present in the bulk. These experiments exhibited a lower foamability, longer fabric wetting time, and higher dynamic surface tension at the critical F127 concentration. These findings support our turbidity analysis conclusions because they indicate that there is less surfactant monomer to partition to the interfaces that are present in these experiments (i.e., air/water for foamability, solid/liquid for fabric wetting, and air/water for dynamic surface tension).

The findings of this research suggest that microemulsions of Pluronic F127 + SC + EB are effective for binding of amitriptyline. However, one might venture to ask why a microemulsion is necessary (i.e., why a micellar or mixed micellar solution cannot be used). We have shown through this study that the SC is necessary to provide the charge at the interface so that the AMT will be attracted to the droplet. Testing of these systems has also been done on living rats to measure their relative effectiveness as toxicity reversal medium.[16] These tests have shown that the oil, EB, is necessary to keep the drug molecules sequestered (i.e., to prevent the drug molecules from being re-released into the blood). Therefore, a most effective system for detoxification should contain the Pluronic F127, which can be used in high enough concentrations to form microemulsions without becoming toxic, EB, and SC.

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