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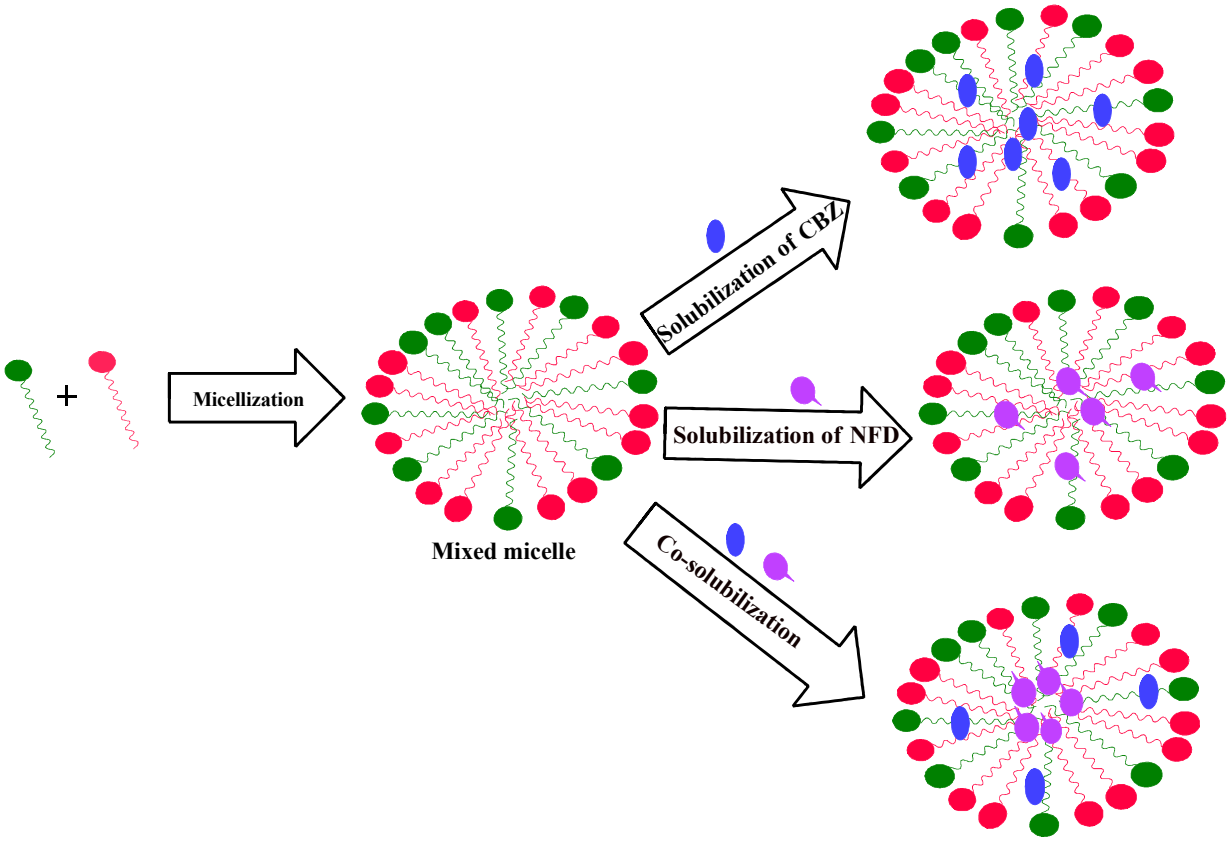
Graphical Abstract



We present single and simultaneous solubilization of Carabamezipine and Nifedipine in biocompatible binary and ternary mixed micelles

An investigation of solubilization and co-solubilization of Carbamazepine and Nifedipine in mixed micellar systems: insights from surface tension, electronic absorption, fluorescence and HPLC measurements.

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Abstract

Uv absorption spectral and HPLC study on the solubilization and co-solubilization behavior of antiepileptic drug Carbamazepine (CBZ) and calcium channel blocker Nifedipine (NFD) which are reported to have a synergistic potentiation was carried out in Cholic acid based binary and ternary mixed micellar systems with non-ionic polysorbate (Tween20, Tween40) and polyoxyethylene (Brij30, Brij35, Brij56 and Brij58) surfactants. The surfactant-surfactant interaction and its effect on aggregation number, solubility of drugs, solubilization site, surfactant-drug interaction and drug-drug interaction was evaluated and explained. Synergism in mixed micellization increases the aggregation number and decreases the polarity of palisade layer resulting in enhancement of core solubilization of drugs with concomitant decrease in palisade layer solubilization. In C_{12} series CBZ shows decrease in solubility upon surfactant mixing indicating its appreciable solubilization in palisade layer while in C_{16} series there occurs increase in its solubility than ideal mixing. For NFD decrease in solubility follows the trend of synergism in mixed micellization, it is more for strongly interacting surfactant systems. During co-solubilization since CBZ occupies preferentially the palisade layer, its solubility is decreased and the solubilization of NFD which mainly occurs within the micellar core is favored. The magnitude of drug-drug interactions increases in mixed micelles and is more for the surfactant systems showing more synergism in mixed micelle formation. The mixed micellar media used in the present study being biocompatible are expected to be employed as solubilization and drug delivery vehicles for co-administration of these two drugs *in vivo*.

Keywords*:* Solubilization; Co-solubilization; Micelle; Non-ionic surfactants; Hydrophobic Drugs

Introduction

Poor aqueous solubility paired with poor bioavailability of active pharmaceutical ingredients is a major challenge in pharmaceutical industry. These solubility problems led to the development of application vehicles like mixed micelles, a demanding research topic in pharmaceutical technology. Valium MM and Konakion MM are two mixed micelle based formulations currently available in the pharmaceutical market.[1] Mixed micelles usually have diameters less than 60nm, which prevent their uptake by the reticuloendothelial system (RES) and consequently increases their in vivo circulation and facilitates their extravasation in sites with leaky vasculature such as tumors.[2] The known classical mixed micellar systems are composed of bile salts and phospholipids but the fabrication of these mixed micelles involves use of organic solvents like chloroform and methanol which are required for solubilization of phospholipids.[3] So there arises a need to develop alternative mixed micelle formulations using components with good pharmaceutical acceptability. Bile salts are physiologically relevant, biocompatible and biodegradable molecules derived from cholesterol and can undergo aggregation in aqueous solution.[4] These are very safe and effective vehicle for medical applications and have been used in the solubilization of many poorly water soluble drugs like griseofulvin,[5] glutethimide,[5] digoxin,[6] leucotriene-D4 antagonists,[7] gemfibrozol[8] etc and also as delivery system for many other drugs and vitamins.[9,10] The ability of bile salts to enhance the oral bioavailability of poorly water-soluble drugs has been recognized.[11-13] They normally enhance the transport of lipophilic drugs across biological membranes and thereby enhance oral bioavailability.[14-16] Moreover, such micellar systems are known to improve the solubility of extremely lipophilic drugs.[17-19] Therefore, bile salts micelles and derived mixed systems are intensively investigated as drug carrier systems.[20-22] In addition, from an economic or commercial perspective, this technique of solubilizing drugs within micellar media simplifies the manufacturing process and allows for large-scale production of drugs.

Polysorbates (commonly known as Tween surfactants) are nonionic surfactants very effective in solubilizing drugs[23] and are used in the manufacture of a variety of pharmaceutical products.[24] They are known to enhance the permeability of phospholipid membranes causing leakage of low molecular mass compounds.[24] They induce alteration in the physicochemical properties of biomembranes and specifically increase the permeability of sarcoplasmic reticulum.[25] Alkyl

polyoxyethylene ether (Brij) surfactants have also been studied extensively in pharmaceutical systems[26-28] due to their minimum toxicity.

Carbamazepine (CBZ) is an antiepileptic drug used in the treatment of epilepsy, trigeminal neuralgia and bipolar disorders and Nifedipine (NFD) is a calcium channel blocker used for treatment of hypertension and angina pectoris.[29] CBZ and NFD have low aqueous solubility and hence irregular and delayed absorption. Several attempts using various techniques meant to increase the aqueous solubility of CBZ and NFD are reported in literature.[29] About 30% of the people with epilepsy have seizures that do not respond satisfactorily to the conventional antiepileptic drugs (CAEDs).[33] These limitations with the CAEDs highlight the need for exploring the drugs that could potentiate their action so as to make the treatment of epilepsy more effective. Medevite *et al*. has shown the presence of specific binding sites of calcium channel blockers (CCBs) which enable CAEDs to cross the blood brain barrier.[34] Desmedt *et al*.reported that CCBs like cinnarizine and flunarizine have anticonvulsive properties in rats and mice.[35] Rational polytherapy concept is based on the assumption that combining some antiepileptic drugs may results in supra-additive (synergistic) efficacy and infra additive (antagonistic) toxicity, resulting in an enhanced efficacy/toxicity profile. CCBs having antiepileptic property were combined with established antiepileptic drugs. Flunarizine, a CCB was given along with antiepileptic drugs as add-on therapy and has been found to reduce seizure significantly[36] and also nifedipine (NFD) was given along with carbamazepine (CBZ) to provide superior seizure control in maximal electroshock (MES)-induced and pentylenetetrazole (PTZ)-induced convulsions.[37] There are reports in literature where a patient with classical pattern of bipolar disorder with a cycle of mania and depression responds to a combination of CBZ and NFD.[38]

In our earlier work[29] we demonstrated that the single and simultaneous solubilization of CBZ and NFD in single surfactant based micellar media is highly sensitive to the hydrophilic-lipophilic balance (HLB) value and the concentration of surfactants. The present study aims to enhance the micellar solubilization/co-solubilization of these drugs with simultaneous reduction in the amount of surfactant used by employing technologically more efficient surfactant mixtures. The solubilization/co-solubilization of drugs in cholic acid based binary and ternary mixed micellar systems has not been reported. Therefore, as a part of our previous extensive work[29,39] on the

micelle mediated solubilization of pharmaceutically active molecules, we present here solubilization and co-solubilization of CBZ and NFD in biocompatible binary and ternary mixed micellar systems based on Sodium Cholate (Bile Salt), alkyl polyoxyethylene and alkyl polysorbate surfactants. . In general, this paper presents the model study for the alteration in solubility of drugs due to strong interaction between the component surfactants of mixed micellar system, co-solubilization of differently architectured drugs and the interaction between the drugs in the mixed micellar media being important both from industrial as well as research point of view.

Experimental Section

Materials

Tween20 (T20) was a Merck (India) product (purity > 99%) and Tween40 (T40) was obtained from Himedia laboratories (India) (purity > 99%). Brij30 (B30), Brij35 (B35), Brij56 (B56), Brij58 (B58) and Cholic acid, sodium salt hydrate (NaC) amphiphiles were Aldrich products (purity > 99%). CBZ and NFD were Himedia laboratories (India) products (purity > 98%). All the chemicals were used as received. The chemical structures of the materials used are presented in Scheme 1.

Methods

CMC Determination. The *cmc* values were determined from the surface tension (γ) vs. log [surfactant] plotted in Fig. 1. Kruss 9 tensiometer was used to measure the surface tension by the platinum ring detachment method having an accuracy of $\pm$ 0.1 dyne cm^{-1}. Surfactant concentration was varied by adding concentrated surfactant solution in small installments and reading were taken after thorough mixing and temperature equilibration. The temperature was maintained at 25^{o}C value (within ±0.1^{o}C) by circulating water from a HAAKE GH thermostat. The experiments were done in triplicate and the *cmc* values are presented as the mean of such measurements.

Fluorescence Measurements: The aggregation numbers of pure and mixed surfactant systems were determined by steady-state fluorescence quenching experiments at 25±0.1 ^{o}C. Pyrene was used as a probe with cetylpyridinium chloride (CPC) as quencher. The fluorescence emission

spectra of pyrene were obtained with Shimadzu, Japan, Model RF-5301 spectrofluorometer at excitation wavelength 336 nm and emission wavelength 373 nm. Measurements were made in 1 cm path length quartz cuvette using a 3 mm excitation and emission slit width and the fluorescence emission spectra were recorded in the range of 350-450 nm.

Solubility Experiment. The solubility and co-solubility of CBZ and NFD was measured in a range of (1-5 mM) mixed micellar concentrations. Excess amounts of drugs were added to the vials containing 3ml of micellar solutions to ensure maximum solubility. The 5ml sample vials were sealed with screw caps and then were agitated for a period of 24 hours on a magnetic stirrer at a temperature of (25±0.5) ^{o}C using magnetic teflon pieces previously placed in the vials. The solutions were subjected to centrifugation at 13400 rpm to remove the un-dissolved drug. The concentration of solubilized drug was determined spectrophotometricaly with a ShimadzuSpectrophotometer (model UV-1650) following appropriate dilution of an aliquot of the supernatant with corresponding surfactant concentration. The surfactant concentration was kept the same in both the reference and the measurement cells to eliminate the effect of surfactant on UV absorbance. The solubility of CBZ was determined at its characteristic wavelength of 286 nm, at which its extinction coefficient calculated from the calibration curve of the drug in methanol was 1.4335 $mM^{-1}cm^{-1}$. Using this extinction coefficient the solubility of CBZ in water was confirmed to be 6.98×10^{-1}mM which tallied well with the literature value.[40] The solubility of NFD was determined at 355 nm and was equal to 3.3×10^{-3} mM in conformity with the earlier studies[41] using extinction coefficient 3.28 $mM^{-1}cm^{-1}$ determined from the calibration curve of the drug in methanol. The solubilities of CBZ and NFD in the mixture were determined at the above mentioned wavelengths using their respective extinction coefficients. CBZ and NFD absorptions at 286 nm and 355 nm respectively were non-interfering with each other as depicted by their prototype absorption curves in methanol (Fig.2a) and in 2 mM (B35+T20) binary surfactant solution (Fig.2b). The concentration of drugs are presented as the mean of three independent measurements corresponding to each surfactant concentration.

HPLC of CBZ and NFD during solubilization and co-solubilization. The liquid chromatography system consisted of a Shimadzu LC-20A with a SPD-M20A variable-wavelength UV detector (set at 237 nm), a CBM-20A/20Alite system controller, LC-20AB pump and an injection valve with a 25μl loop (Shimadzu, Kyoto, Japan). Separation was achieved

using Enable C18G column (250mm×4.6 mm, 5μm) and CTO-10ASvp column oven. The mobile phase used consisted of water: methanol (40:60, v/v), flowing at a rate of 0.5 ml min^{-1}. The instrument was operated at 40°C. Drugs solubilized in mixed micellar solutions were first centrifuged and then filtered using 0.2μm filter paper. 20 μl of the drug solution was injected and the separation was carried out for 45 minutes.

Results and Discussion

Surfactant-Surfactant interactions in mixed micelles

The *cmc* values of NaC and mixed micellar systems for both the series of surfactants are given in Table 1. The cmc values of T20, B30, B35, T40, B56 and B58 are 0.036, 0.033, 0.039, 0.029, 0.036 and 0.003 mM respectively reported earlier by us.[29] The ideal *cmc* values, cmc_{ideal} for mixed surfactant systems calculated using Clint equation[42] are also given in Table 1. All the observed *cmc* values were found to be lower than cmc_{ideal} values, indicating negative deviation from ideal behavior for mixed micelle formation. The estimate of negative deviation of experimental *cmc* values from cmc_{ideal} and hence non-ideality of mixed binary surfactant systems was made in light of Rubingh's equation[43] based on of regular solution theory. The interaction parameter, β is an indicator of the degree of interaction between two surfactants in mixed micelles and accounts for deviation from ideality and a negative β value implies an attractive interaction. The values of β along with micellar mole fraction, X_i^M and the activity coefficients, f_i, of the *i*th surfactant calculated using Rubingh treatment are presented in Table 1. For ionic-nonionic mixed surfactant systems, the electrostatic self-repulsion of ionics and weak steric self-repulsion of nonionics are reduced by dilution effects after mixing[39] besides the ion-dipole interaction between the hydrophilic head groups of anionic and nonionic surfactants favors the micellization and results in synergism.[44-47] The favorable possibility of hydrogen bonding in addition to the polar attractions of the hydrophilic head groups of these two surfactant systems and the strong hydrophobic interactions of their tail groups may account for the obtained degree of non-ideality which is in conformity with some earlier studies on such types of mixed micellar systems.[39] The absolute magnitude of β increases with decrease in chain length of nonionic surfactant, a fact attributed to the more favorable self-interaction in longer T40, B58 and B56 surfactant systems and hence higher propensity to form micelles. [44]The large negative value of β

for B30+NaC (β = -8.77) and B56+NaC (β = - 10.42) binary mixed micellar systems in their respective series is owed to lesser steric hindrance between the two surfactant systems involved and hence ease of micellization. The value of β for B35+NaC (β = -7.97) is almost equal to that for T20+NaC (β = -8.08) binary system and also β for T40+NaC (β = - 8.9) binary system is close with that of B58+NaC (β = -9.11) binary mixed micellar system due to the comparable steric effects of surfactants involved. Among Brij-Tween binary systems, the larger interaction between B35+T20 (β = -2.67) and B58+T40 (β = -2.67) system is attributed to more polar-polar interaction between large number of ethoxyl and hydroxyl groups present when compared to interaction of B30+T20 (β = - 0.59) and B56+T40 (β = - 1.36) binary surfactant systems. Moreover these mixed micelles are dominated by non-ionic surfactants as indicated by X_i^M values (Table 1) in conformity with the results of other studies on different ionic+non-ionic mixed micellar systems.[48,49]

Holland and Rubingh have proposed a generalized multi-component non-ideal mixed micelle model based on pseudophase separation approach. It has been successfully applied in the case of many ternary surfactant systems[50] for evaluation of micellar composition, activity coefficients and *cmc* values. It makes an effective use of net interaction parameters determined experimentally from *cmc* measurements on binary systems. In the present study values of binary interaction parameters β_{12}, β_{13} and β_{23} following Rubingh's method and *cmc* values of pure surfactants were used in the equations of Rubingh-Holland (RH) formulation[50] to evaluate activity coefficients, f_1, f_2 and f_3 and the micellar mole fractions X_1^M X_2^M and X_3^M These values were then used to predict the *cmc* of ternary system, cmc_{RH}, according to Rubingh-Holland (RH) formulation. The results are presented in Table 1. The composition of mixed micelles (X) differs from the bulk composition (α),X_{anionic} values are much lower than α_{anionic} but X_{nonionic} values are fairly higher than α_{nonionic} values in both surfactant series. The activity coefficients of anionics are very low but are close to unity for nonionics. The cmc_{RH} values are found to be in good agreement with experimental *cmc* values, but both are lower than the cmc_{ideal} values, indicating the synergistic non-ideal nature of mixed ternary micellar systems. The agreement between cmc_{RH} and experimental *cmc* in both the series indicates fair applicability of the RH method for such systems.

Aggregation number

The mean aggregation number of pure and various binary and ternary surfactant systems were determined from steady state fluorescence data[51] using the equation

$$\ln\left(\frac{I_o}{I}\right) = N\frac{[Q]}{(C_t - cmc)} \qquad (1)$$

where ,[Q] C_t and *cmc* are quencher concentration, total surfactant concentration and critical micelle concentration of the pure/mixed surfactant systems. *Io* and *I* are the fluorescence intensities in the absence and presence of quencher, respectively, for the first vibronic peak in the pyrene emission spectra. A representative plot of decrease in fluorescence intensity of pyrene by addition of CPC and that of $ln(I_o/I)$ versus [Q] for pure and equimolar binary and ternary mixed micellar systems are shown in Fig 3a and 3b respectively. The total surfactant concentration was kept constant at 10 mM and values of *N* (aggregation number) obtained for NaC,T20, and B30 were 12 , 79 and 97 comparable to the earlier reported values [29,39]of 11, 86 and 101 respectively in aqueous phase. The aggregation number increases for binary and ternary micellar systems indicating micellar growth. A correlation is observed between aggregation number and interaction factor, a huge interaction corresponds to favorable micellization resulting in the formation of larger micelles. Bile salt micelles due to the steric hindrance of the large steroidal skeleton are small with a low aggregation number, the addition of Brij/Tween surfactants favors the intermolecular hydrogen bonding between carboxyl, hydroxyl and ethoxy groups with partial hydrophobic interaction resulting in micellar growth as reported in earlier studies.[39] The much favorable interactions (β = -8.77) leads to the higher aggregation number of 167 for B30+NaC binary micellar system. The aggregation number of T20+NaC is 157 due to slightly less favourable interactions of the surfactants (β = -7.97) in mixed micelles than B30+NaC binary surfactant system. The magnitude of interaction is even lesser for T20 and B30 surfactant system leading to lower aggregation number (N=127) than other two systems. The aggregation number of ternary surfactant system (T20+B30+NaC) is 131, more than that of the corresponding single surfactant systems but less or equal to that of their binary surfactant systems indicating a balance between electrostatic and steric effects.

Molar Solubilization Ratio (MSR)

Molar solubilization ratio (MSR) is equivalent to increase in solubilizate concentration per unit increase in micellar surfactant concentration. It is measure of the effectiveness of a surfactant in solubilizing a given solubilizate. MSR is given by the equation[44]

$$MSR = \frac{S_t - S_{cmc}}{C_t - cmc} \qquad (2)$$

It is obtained from the slope of curve between solubilizate concentration and surfactant concentration. S_t is the total apparent solubility of a drug (CBZ or NFD) in either single state or in their binary mixture at a particular total single and/or mixed surfactant concentration, C_t, above *cmc*, and S_{cmc} is the apparent solubility of drugs at *cmc*, which is taken as their water solubility since it changes only very slightly up to *cmc* of surfactant. The aqueous solubilities of drugs increases linearly over the range of single and/or mixed surfactant concentrations above *cmc* indicating their solubility enhancement in water due to solubilization within the micelles. As a prototype, variation of S_t for CBZ in its single and mixed states vs C_t in given mixed surfactant systems is shown in Fig.4. The MSR values of CBZ and NFD individually as well as in combined states in the studied mixed surfactant systems calculated using above procedure are presented in Table 2.

For NaC micelles there occurs slight increase in solubilizate concentration by increasing the surfactant concentration below the *cmc* [Fig.5(a)] due to weak interactions between the solubilizate monomer and the bile salt monomer, in accordance with earlier studies.[52,53] The formation of micelles causes the solubilizate concentration to increase rapidly above the *cmc* [Fig.5(b)]. Bile salt micelles provide nonpolar hydrophobic interior and polar hydrophilic surface for solubilization of polar steroids,[54] so here in present study the amphiphilic drugs CBZ and NFD also seems to occupy both solubilization sites. The MSR plots of CBZ and NFD during solubilization and co-solubilization in NaC micelles are shown in Fig.5 (b). NaC proves out to be more promising medium for the solubilization of CBZ than all other non-ionic surfactant systems studied[29] due to more provision for the solubilization of CBZ in the outer hydrophilic corona owing to favorable electrostatic interactions attributed to the presence of charge on the micellar

surface. For NFD, the MSR values obtained in NaC are less than that of CBZ, this difference in the solubility of two drugs could be attributed to the difference in their chemical structure. The incorporation of NFD into NaC micelles of relatively small aggregation number may need much energy in order to make a large space inside the micelle owing to its non-planer structure, higher molecular weight and more molecular volume resulting in its lesser solubilization within the micelle. The MSR value of NFD obtained in NaC is more than the MSR values obtained for C_{12} series of non-ionic surfactants[29] which could be attributed to higher palisade layer solubilization of more polarizable NFD due to favorable polar interactions between the charged micelle-water interface of NaC and polar groups of NFD. However the MSR value of NFD in NaC is lesser than its MSR value in C_{16} series of non-ionic surfactants probably due to lesser aggregation number of NaC. This decreases micellar core volume available for NFD solubilization which outplays the higher magnitude of solubilization at hydrophilic surface of NaC. During co-solubilization of the two drugs in NaC, the solubility of CBZ is decreased probably due to the preferential occupation of NaC micellar core by NFD. CBZ solubilized in the palisade layer of NaC micelle decreases the micelle-water interfacial tension and hence increases the micellar core volume thereby increasing the solubilization of NFD.

CBZ is an amphiphilic drug molecule while NFD is slightly polar but polarizable drug molecule and hence these drugs can be solubilized both in the core and in the palisade layer of the micelle.[29] The surfactant systems which exhibit synergism on mixing not only show decrease in *cmc* values but also an increase in aggregation number. In strongly interacting surfactant systems the aggregation number is higher (as observed in mixed systems of B30, T20 and NaC) indicating micellar growth compared to their single surfactant micelles.[55,57] The change is sensitive to those solutes which solubilize by incorporation in the micellar hydrocarbon core. The application of laplace pressure to the mixed micelle situation predicts an increase of micellar solubilization upon micellar growth. Further the electrostatic attraction between polar head groups of surfactants in the mixed micellar system reduces the interaction between surfactants and amphiphilic solubilizates.[55-57] The larger increase of aggregation number in the mixed micelle results in enhanced solubilization in micellar core whereas the strong interaction between the surfactant head groups lowers the solubilization in the palisade layer. So the occurrence of synergism in solubilization of substances in mixed micelles will depend on the relative strength

of the two opposing effects. When a larger part of the solubilizate is located in the micellar core, a positive synergism is expected. In contrast if the palisade layer solubilization exceeds then the solubilization capacity of mixed micelle is smaller than that of pure micelles.

CBZ solubilized in C_{12} series of surfactants shows decrease in MSR values when compared to ideal MSR values (MSR_{ideal}) calculated as

$$MSR_{ideal} = X_1 MSR_1 + X_2 MSR_2 \qquad (3)$$

Where X_1 and X_2 are mole fractions of the two surfactants and MSR_1 and MSR_2 are the molar solubilization ratios for CBZ[29] in the two surfactant solutions involved. The MSR_{ideal} values of CBZ and NFD calculated using eq.2 are given in Table 2. Since an appreciable amount of CBZ is solubilized in the palisade layer[29] so the decrease in MSR values could be attributed to the decrease in polar interaction between the surfactants and CBZ due to mixing effect of surfactants. The results are quite in conformity with the solubilization of polar hydrophobic molecules like barbituric acid, [55]n-hexanol, [56] 1-petanol[57] and n-octanol[58] solubilized in the mixed micelles with larger negative β value. The decrease in solubilization of CBZ occurs much more for B35+ NaC binary surfactant system owing to the larger interaction between the surfactants involved as indicated by larger negative value of β. Also the main solubilization site of CBZ in B35 is the palisade layer[29] where polar interactions between the amide group of CBZ and OE groups of B35 determine its solubility. Since mole fraction of B35 in mixed micelle is more as calculated by Rubingh method [Table 1], so the decrease in these interactions due to mixing effect of surfactants decreases the MSR value of CBZ. The difference between the experimental MSR and MSR_{ideal} is least for B30+ T20 surfactant systems attributed to least negative value of β for the two surfactant systems and since the surfactant mixing approaches ideal behavior the solubilization behavior also approaches ideality. Due to larger core volume of C_{16} series of surfactants, CBZ is mainly solubilized in the micellar core[29]so a further increase in aggregation number and hence micellar core volume increases its solubility. The MSR values of CBZ obtained in C_{16} series of surfactants are more than the ideal values due to the higher aggregation number upon surfactant mixing leading to favourable solubilization in the hydrocarbon core as predicted by the basic laplace pressure equation. Toluene slightly polar but polarizable molecule[59] and other slightly soluble benzenoid[60] compounds show similar behavior in surfactant

systems with longer chain lengths where the increase in solubilization occurs due to increase of aggregation number in the mixed micellar system. In C_{16} series the interaction parameter has larger negative value for B56+NaC binary surfactant system, so the increase in micellar core volume will be maximum and hence the solubility of CBZ is large. As mentioned earlier B56+NaC binary mixture is dominated by B56, as result we expect higher core volume for such binary system. Moreover, the main solubilization site for CBZ in B56+NaC binary mixture being micellar core the higher core volume favors the solubilization of CBZ explaining the more difference in the magnitude of experimental MSR than MSR_{ideal} for this binary surfactant system. The difference between the experimental MSR value and the MSR_{ideal} is least for B56+ T40 binary surfactant system corresponding to the lowest interaction between the surfactant systems involved. The difference between the MSR_{ideal} and experimental MSR values follows the trend of β values; it is less for the systems with lower negative values of β and more for the systems with more negative β values. In the ternary mixed micellar systems, a negative synergism in solubilization is observed for B30+T20+NaC, B35+T20+NaC and B58+T40+NaC surfactant systems probably due to the more favorable interaction between the surfactants involved which decreases the palisade layer solubilization and hence the total solubility of CBZ in these systems. For B56+T40+NaC mixed micellar system the increase in aggregation number and hence the micellar core solubilization seems to override the effect of decrease in palisade layer solubilization. Synergism in solubilization greatly depends on the molecular structure and polarity of solubilizates.[59-61] For NFD there occurs decrease in solubility when compared with the ideal solubilization in both the surfactant series due to its higher polarizability and hence appreciable solubilization at the palisade layer.[29] However for B30+T20 and B35+T20 binary surfactant systems there occurs increase in solubility of NFD due to relatively more increase in micellar core solubilization than decrease in palisade layer solubilization as the surfactants involved have lesser interaction indicated by the higher absolute magnitude of β. The difference between the experimental MSR and MSR_{ideal} values is higher for the surfactant systems with more interactions as the probability for hydrophilic interactions between the drugs and surfactants of mixed micelle decreases with decrease in the magnitude of β. The decrease in solubility of NFD is more for B35+ NaC and B58+ NaC surfactant systems than its decrease in B30+ NaC and B56+NaC binary surfactant systems respectively due to more appreciable palisade layer solubilization of NFD in B35 and B58 surfactant systems and hence more

provision of decrease in its solubility due to strong interactions between the surfactants in binary mixed micellar system. For NFD solubilized in ternary surfactant systems, an ideal solubilization of NFD is obtained in B30+T20+NaC mixed micellar system where the increase in core volume and decrease in palisade layer solubilization seem to balance the each other. For the rest of ternary mixed micellar systems, negative synergism in solubilization is observed due to less solubilization in dense hydrophilic corona associated with these surfactant systems where the provision for solubilization is less owed to surfactant-surfactant interactions and steric effects.

Co-solubilization of CBZ and NFD

MSR values of CBZ and NFD during their co-solubilization are also presented in Table2. It is observed from the data that MSR values of CBZ during its co-solubilization are reduced in all surfactant systems relative to its MSR values during single solute solubilization. It has been suggested that the location of solutes within micelles is an important factor influencing the micellar partitioning of solutes in multi-solute systems.[62-64] If the solutes compete with each other for a location in the interior of micelle, it will lead to decrease in the solubility of one solute in the presence of others. However, during co-solubilization of two solutes with different hydrophobicities, the less hydrophobic compound gets solubilized in the palisade layer of the micelle resulting in increase in the micellar core volume allowing synergistic increase in MSR value of more hydrophobic compound which prefers the micellar core solubilization.[62-64]CBZ being more polar is appreciably solubilized at palisade layer, while its solubilization within the micellar core is decreased during co-solubilization due to preferential occupation of micellar core by more hydrophobic NFD resulting in net decrease in CBZ solubility. The experimental MSR values of CBZ during co-solubilization are less when compared with MSR_{ideal} values calculated for co-solubilization. The deviation from ideal solubility is more during co-solubilization, reason being the less potency of palisade layer towards the solubilizates in mixed micellar media due to favorable polar interactions between the component surfactants of mixed micelles. Since during co-solubilization, palisade layer is the main occupation site of CBZ[29] so its solubility is affected the most. The decrease in solubility follows the order of increase in interaction between the surfactants involved; it is more for B35+NaC and B58+NaC surfactant systems which show more synergism in mixed micellization besides more mole fractions of B35 and B58 present in mixed micelle offers more palisade layer solubilization. The decrease in solubility is least for

B30+T20 and B56+T40 binary surfactant systems exhibiting the minimum synergism as indicated by higher magnitude of β and less potency of B30 and B56 towards palisade layer solubilization. In case of ternary surfactant systems, the MSR value of CBZ obtained during co-solubilization is lower than the MSR value of CBZ obtained for single solute solubilization due to the competitive solubilization behavior exhibited by the two drugs. The decrease is more in B30+T20+NaC and B56+T40+NaC ternary micellar systems due to the higher mole fractions of Brij30 and Brij56 respectively obtained by Rubingh-Holland model and hence more provision for micellar core solubilization which is occupied by NFD during co-solubilization. When the experimental MSR values obtained are compared with the MSR_{ideal} values calculated using eq. 2, a net decrease in solubility of CBZ is observed in all ternary surfactant systems due to the preferential occupation of palisade layer by CBZ during co-solubilization and more of the decrease is observed in ternary mixed micellar system of B35 and B58 due to more interaction between the surfactants involved. Moreover, higher *cmc* and hence lower palisade layer area than the individual surfactants also decrease the solubility of CBZ.

There occurs an increase in MSR value of NFD during co-solubilization which is attributed to increase in micellar core volume by solubilization of less hydrophobic CBZ in the palisade layer of the micelles which decreases the interfacial tension. CBZ would be replaced from the core of micelle by more hydrophobic NFD during its co-solubilization in the two solute system which results in drastic decrease in MSR value of CBZ on one hand and on the other hand CBZ solubilized in the palisade layer makes the stay of NFD in the micellar core more favorable. In general, the experimental MSR values obtained for NFD in all the surfactant systems are higher than MSR_{ideal} values obtained using eq.2 except for B30+NaC, B56+T40 and B58+T40 binary surfactant systems where the experimental MSR values are slightly lower than MSR_{ideal} values probably due to decrease in palisade layer solubilization and more competition with the carbamazepine for micellar core solubilization.. For the increase in solubility of NFD in all other mixed micellar systems studied during co-solubilization when compared with the ideal solubilization, two phenomena occur which cause the micellar core volume to increase, thereby increasing the solubilization of NFD.

1. Due to the favorable interactions between the surfactants involved in mixed micellar systems, the propensity of micellization increases. Large micelles with larger core

volume are formed and hence an enhancement in solubilization of NFD is observed when compared with the solubilization of NFD in single surfactant systems during co-solubilization.[29]

2. CBZ solubilized in the palisade layer decreases the interfacial tension at micelle-water interface, thereby increasing the micellar core volume and hence solubility of NFD.

Although the two phenomena lead to the same result but a strong interaction between the surfactants involved in mixed micelle decreases the palisade layer solubilization of CBZ; so an overall effect of the two phenomena seems to be operative where a stronger interaction between the surfactant systems and a higher magnitude of CBZ solubilized in the palisade layer in a given micelle favors the solubilization of NFD, which explains the more difference between the experimental MSR values and MSR_{ideal} values in T20+NaC, B35+NaC and T40+NaC surfactant systems than the rest of binary surfactant systems. For ternary surfactant systems an enhancement in solubility of NFD is observed during co-solubilization and also experimental MSR values are more than the MSR_{ideal} values more prominent in ternary surfactant systems involving B35 and B58 due to an appreciable amount of CBZ solubilized at micelle-water interface.

HPLC of CBZ and NFD during solubilization and co-solubilization

The HPLC profiles of CBZ and NFD during solubilization and co-solubilization in binary (T20+ NaC) and ternary (B30+T20+NaC) surfactant system are given in Fig.6. It is pertinent to mention that the surfactants didn't elute in the time range presented in HPLC profiles (Supplementary material, Fig. S1). Some important results were obtained from the HPLC plots. Since the molar absorbance coefficient is different for the two drugs so the intensity of the peaks cannot be directly correlated with their concentration, but when the relative concentration of drugs during single solute solubilization and co-solubilization is considered, the intensity of the peaks corresponding to both the drugs decreases during simultaneous solubilization indicating competition between the drugs for solubilization sites. Further the relative amount of drugs solubilized in (T20+NaC) binary surfactant system is more than that of (B30+T20+NaC) ternary surfactant system quite in conformity with the results presented in Table 2. During co-solubilization the retention time of NFD was increased from 1.51 to 2.9 minutes and 1.03 to 2.7

minutes while that of CBZ was slightly decreased from 3.3 to 3.14 minutes and 3.4 to 3.25 minutes in binary and ternary surfactant mixture respectively which confirms that the drugs show interaction within the mixed micellar systems. The magnitude of interaction is lesser in ternary surfactant system when compared to binary micellar system where the two drugs have tendency to get eluted together (Fig.6(c)) appreciating the results presented in Table 3.

Partition coefficient

The effectiveness of solubilization can also be expressed in terms of the partition coefficient, K_m, of the drug between the micelle and aqueous phases and is defined as the ratio of mole fraction of the drugs in the micellar phase, X_m, to that in the aqueous phase, X_a.

$$K_m = \frac{X_m}{X_a} \qquad (4a)$$

The value of X_m in terms of MSR can be written as

$$X_m = \frac{MSR}{1 + MSR} \qquad (4b)$$

During co-solubilization of two species '*i*' and '*j*', the mole fraction of the drug '*i*', X_{mi}, is given by[53]

$$X_{mí} = \frac{n_i}{n_i + n_j + n_{surf}} = \frac{MSR_i}{MSR_i + MSR_j + 1} \qquad (4c)$$

where n_i, n_j *and* n_{surf} are respectively the number of moles of solutes (*i* and *j*) and surfactant in micellar pseudo-phase. X_a can be expressed as $X_a = [S_{cmc}]V_m$. V_m is the molar volume of water equal to 0.01805 L/mol at 25°C. With these expressions, K_m for solubilization becomes

$$K_m = \frac{MSR}{(S_{cmc})V_m(1 + MSR)} \qquad (5a)$$

For co-solubilization partition coefficient, K_{mi}, of the drug *i* would be given by

$$K_{mi} = \frac{MSR_i}{(S_{cmc})V_m\left(1 + MSR_i + MSR_j\right)} \qquad (5b)$$

The K_m and K_{mi} values of the two drugs are given in Fig. 7 & 8 for all mixed micellar systems.

According to Treiner et. al.[65] the partitioning of a neutral nonpolar solute between a pseudo binary micellar solution and water is represented by the relationship.

$$\ln K(x) = x_m ln K_1 + (1 - x_m) ln K_2 + x_m(1 - x_m)B \qquad (6)$$

K_1 and K_2 are mole fractional partition coefficients of the solute in the single surfactant solutions and $K(x)$ is the same parameter in the mixed micelles. B[66] is an empirical parameter and is given by

$$B = 0.194 + 0.343\beta \qquad (7)$$

where β is the interaction parameter appearing in the regular solution model for the *cmc* of surfactant mixtures in the absence of any solubilizate.

For the solubilization of CBZ, the *K(x)* values calculated using eq.6 are smaller than the partition coefficient for the single surfactant micelles[29] so there occurs decrease in solubilization of CBZ due to strong interaction between the surfactants leading to decreased palisade layer solubilization both during its solubilization and co-solubilization in mixed micellar systems. The results are in conformity for other amphiphilic solubilizates in anionic-nonionic mixed micellar system having negative β value. [67,68] *K(x)* values obtained were compared with the K_m and K_{mi} values calculated using eq.5a and 5b for solubilization and co-solubilization of CBZ (Fig. 7). A good correlation was attained though *K(x)* values obtained were smaller than the K_m and K_{mi} values apparently due to polar nature of CBZ as the eq. 6 has been developed for the partitioning of a neutral nonpolar solute between a pseudo binary micellar solution and water.[65] NFD seems to follow the ideal solubilization behavior with the *K(x)* values calculated using eq.6 very close to the partition coefficient for the pure component micelle.[29] The solubilization of pentanol[69] in an anionic+non-ionic mixed micelle system is found to follow ideal behavior with $\beta = 0$ due to small aggregate structural changes. For NFD solubilization in mixed micelles, $\beta \neq 0$ but the increase in solubilization due to larger aggregate structural change is balanced by the decrease in solubilization in the palisade layer due to appreciable surfactant interactions. A good correlation was also observed between *K(x)* values calculated for NFD using eq. 6 and K_m and K_{mi} values calculated using eq.5a and 5b for its solubilization and co-solubilization (Fig. 8). For NFD the *K(x)* values obtained were greater than K_m and K_{mi} attributed to its appreciable polarizability. The

variation of ideal partition coefficients and the experimental partition coefficients could be attributed to the tunability of the solubilizate between two opposite effects of increase in its solubilization in the micellar core and decrease in its solubility in palisade layer depending on the polarity and other physico-chemical properties of solubilizates.

Drug-drug interaction in the micellar pseudophase

Solubilized amounts of CBZ and NFD during solubilization and co-solubilization as well as total solubilized amount of both the drugs during co-solubilization were plotted against surfactant concentration as shown in representative Fig.9. The total solubilized amount of drugs (CBZ+NFD) solubilized during co-solubilization is greater than both the amount of CBZ and NFD solubilized during single solute solubilization in all surfactant systems indicating the synergistic solubilization of CBZ and NFD during co-solubilization. To reveal the nature of interaction between drugs inside the micelles, the formulation proposed by Sugihara et al.[70] has been adopted:

The solubilization equilibrium when drug is used in excess can be written as

$$\text{Drug Crystal} \xleftrightarrow{K_d} \text{Singly Dispersed Species in Bulk} \xleftrightarrow{K_m} \text{Solubilized Species in Micelle}$$

where, K_d = activity of singly dispersed drug/ activity of solid drug and is equal to activity of singly dispersed drug because activity of solid drug is unity. Since the drug solubility is very low K_d approximates to molarity of drug solubilized below *cmc*, which is taken equal to its water solubility, S_{cmc}. The equilibrium constant of solubilization for translation from solid phase to solubilized state in micelles is, therefore, given by

$$K_{eq} = K_d \times K_m \qquad (8)$$

whereK_m is the partition coefficient of the drug between aqueous phase and micellar phase. Values of K_m were calculated from equation 4a for single solubilizate system. The molar Gibbs free energy change upon solubilization,ΔG°, will therefore be given as

$$\Delta G^{\circ} = -\mathrm{RT}\ln K_{eq} \qquad (9)$$

For co-solubilization of two solid solubilizates, A and B, the total equilibrium constant of cosolubilization for translation from solid phase to solubilized state in micelles will be given by

$$K_{eq}^{mix} = ({K^A}_d \times {K^A}_m) \times ({K^B}_d \times {K^B}_m) \quad (10)$$

where K_d^A andK_d^B are the respective activities of the two drugs A and B dispersed in bulk and${K^A}_m$ and${K^B}_m$ are their respective partition coefficients in mixed solubilization systems. Taking the ${K^A}_m$ and${K^B}_m$ from equation 4b the Gibbs energy change, $\Delta G°_m$, accompanying the translation of two solubilizates from bulk phase to micellar phase would be given by:

$$\Delta G_{mix}^{\circ} = -RTlnK_{eq}^{mix} \quad (11)$$

If the mixture is ideally formed, the molar Gibbs energy of ideal mixing $\Delta G_{mix}^{S}(ideal)$ should satisfy the additivity rule as

$$\Delta G_{mix}^{S}(ideal) = \chi^A \Delta G_A^{\circ} + \chi^B \Delta G_B^{\circ} \quad (12)$$

Whereχ^A and $\chi^B$are the mole fractions of the two species 'A' and 'B' within the micelles on the solubilizate only basis and were calculated from the equation

$$\chi^A = \frac{MSR_A}{MSR_A + MSR_B} \quad (13)$$

where the MSR_i were taken as their MSR values during co-solubilization. The difference between the real value of the free energy change ΔG_{mix}° and $\Delta G_{mix}^{S}(ideal)$ gives the excess Gibbs energy

$$\Delta G_{excess}^{S} = \Delta G_{mix}^{\circ} - (\chi^A \Delta G_A^{\circ} + \chi^B \Delta G_B^{\circ}) \quad (14)$$

Since the total amount of two drugs solubilized during co-solubilization is more than the amount of CBZ and NFD solubilized during single solute solubilization ΔG_{excess}^{S} is negative for all surfactant systems.

The interaction parameter 'ω/RT', activity coefficients of the two drugs inside the micelles 'γ_c' and 'γ_n' are calculated from the excess Gibbs energy[70] ΔG_{excess}^{S} as,

$$\omega = \Delta G_{excess}^{S} / (\chi^A \chi^B) RT \quad (15)$$

$$ln\gamma_i = \omega(1 - \chi^A)^2 / RT \quad (16)$$

The values of ΔG_{excess}^{S}, ω/RT and $\gamma_{i's}$ calculated in different surfactant systems for the drugs are presented in Table 3. The interaction parameter 'ω/RT' gives the cohesive forces between the unlike solubilizates. The negative values of 'ω/RT' obtained signify that the interaction between CBZ and NFD were enhanced and the two drugs are spontaneously miscible in all mixed micellar systems studied. The absolute magnitude of ω/RT obtained in mixed micelles is more

than that of single surfactant systems[29] indicating that there is more favorable interaction between the two drugs in the mixed micellar media, the results obtained are quite obvious as the surfactants in the mixed micellar system interact among themselves firmly and hence their interaction with the drugs is less which enforces the intermolecular interaction between the drugs. Also due to negative β value, the palisade layer solubilization of drugs is less in all the mixed micellar systems studied and there occurs an increase in micellar core volume and hence an appreciable and more sterically favored drug solubilization in the micellar core, the two drugs are in close proximity in the micellar core where there are more chances of favorable polar interactions between the two drugs within the nonpolar environment of the micellar core. The trend obtained for interaction parameter 'ω/RT' is same as that for β values. A larger negative value of β corresponds to more interaction between the surfactants and hence a larger increase in micellar core volume which results in more favorable interaction between the drugs. The interaction parameter 'ω/RT' is higher for T20+NaC, B35+NaC and T40+NaC binary mixed micellar systems attributed to more increment in core volume and weaker hydrophobicity within these mixed micelles owed to their higher HLB value both of which favor the interaction between the drugs. The interaction parameter 'ω/RT' has lesser value for B30+T20, B56+T40 and B58+T40 binary surfactant systems owing to lower negative value of β value and more hydrophobicity within this mixed micellar system. In case of ternary surfactant systems the interaction between the drugs is more in B35+T20+NaC mixed micellar system owed to its lesser hydrophobicity due to the presence of higher mole fraction of B35 in the mixed micelle and the interaction between the drugs is less in B30+T20+NaC owed to more hydrophobicity of B30 which is present in higher mole fraction in mixed micelle.

Conclusions

An estimation of the interaction between the surfactants in mixed micelles is important to understand the role of a number of amphiphiles in biological systems. In the present study solubilization and co-solubilization of drugs in aqueous amphiphillic solutions containing Bile Salt surfactant micelles and its mixed micelles with non-ionic surfactants viz Tweens and Brijs were investigated. The solubilization of drugs depends on the interaction between the surfactants in mixed micelles; it increases with increase in interaction between the surfactants when the location of solubilization is the micellar core and decreases with increase in surfactant interaction when the solubilization occurs in palisade layer. From experimental measurements of the surfactant-surfactant interaction during mixed micellization, amount of drugs solubilized during single solute solubilization and co-solubilization, interaction between the drugs and thermodynamic analysis provide a quantitative understanding of the solubilization of these drugs with mixed micellar systems. This work also emphasizes the importance of mixed surfactant systems that can be frequently used for transport and drug delivery purposes.

Acknowledgment

We are thankful to the head of the Department of Chemistry, University of Kashmir, for providing the laboratory facilities and his constant encouragement and inspiration.

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Figures and Tables

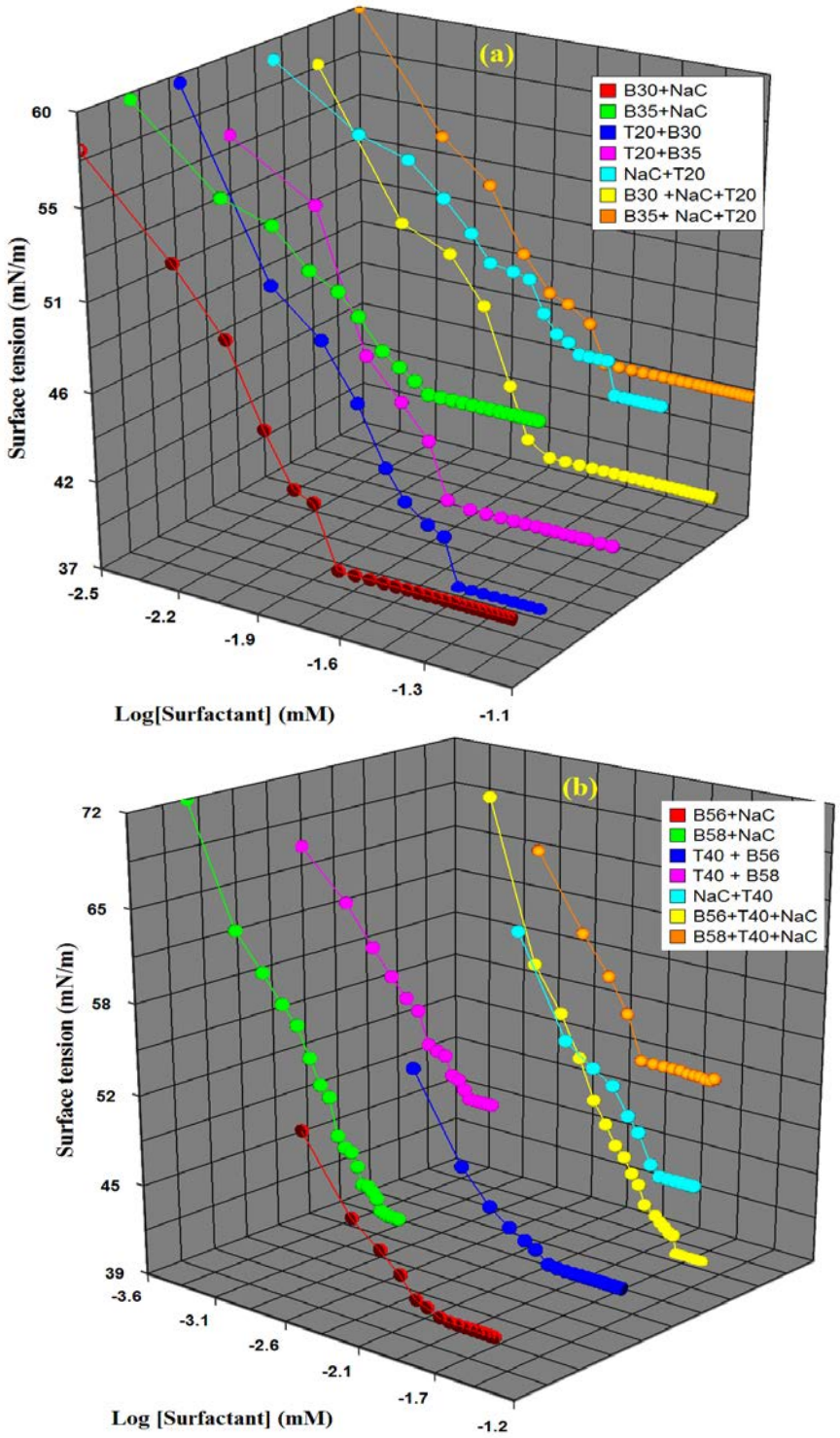


Fig.1. Variation of surface tension with surfactant concentration at 25^{o}C a) C_{12} series b) C_{16} series.

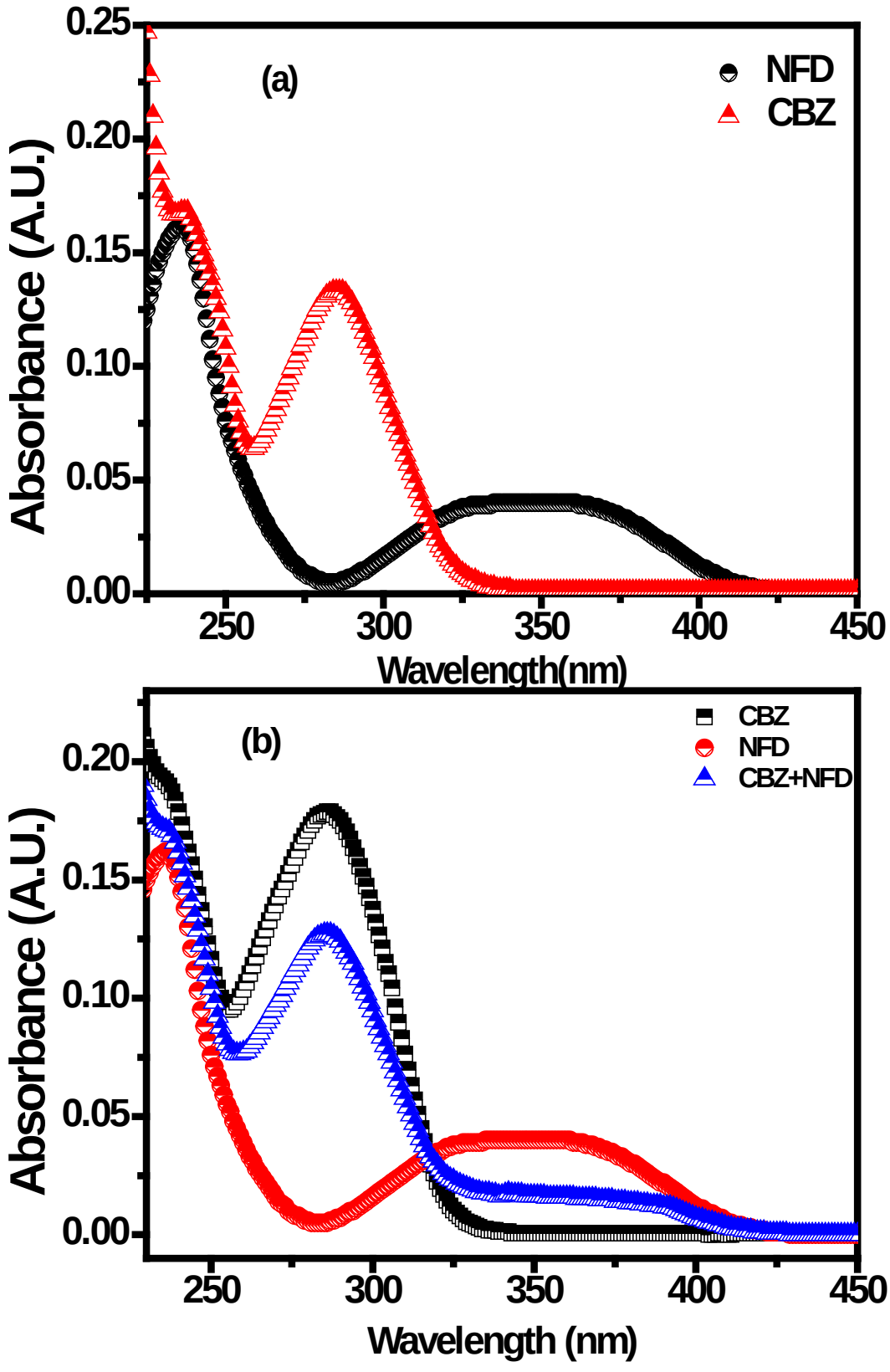


Fig.2. Absorbance vs wavelength of 1 mM a) CBZ and NFD in methanol, and b) CBZ, NFD and CBZ+NFD mixture in 2 mM B35+T20 solution.

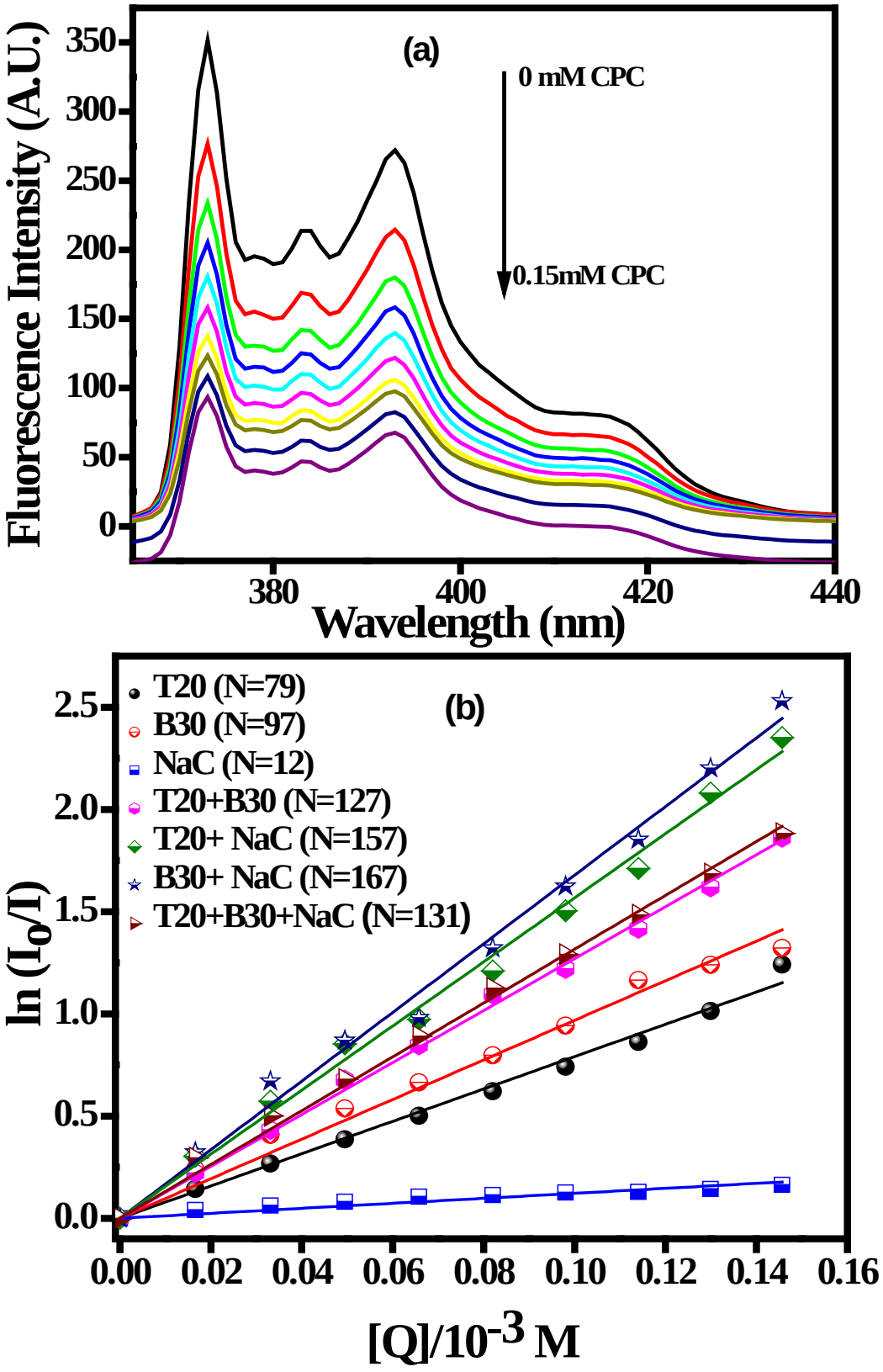


Fig. 3. Representative plot of a) decrease in fluorescence intensity of pyrene with increase in [CPC] b) ln*(Io/I)* vs [quencher] for determination of aggregation number of T20, B30, NaC and their equimolar binary and ternary combinations at 25 ˚C.

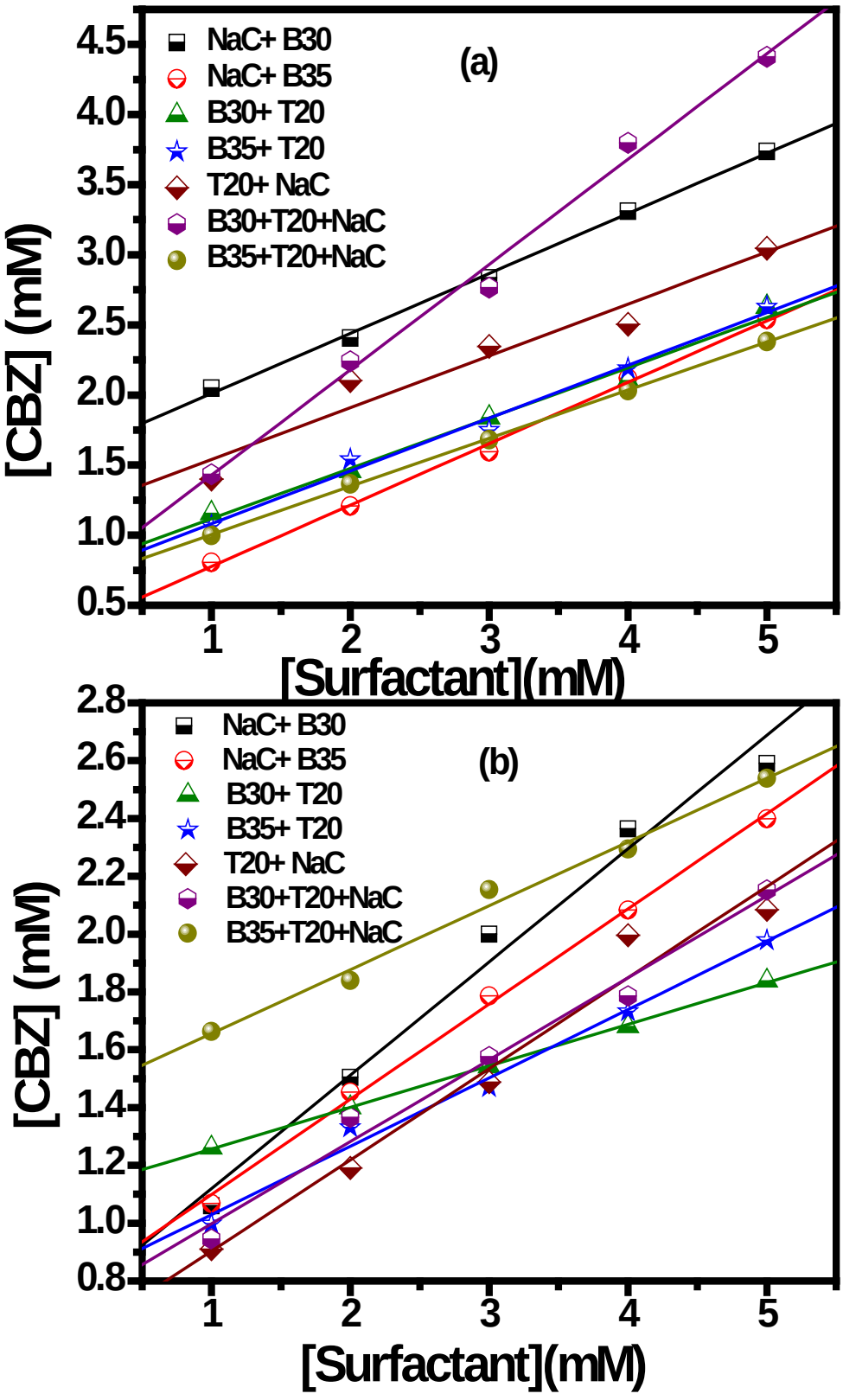


Fig. 4. Variation of CBZ concentration with surfactant concentration at 25°C during a) solubilization b) co-solubilization.

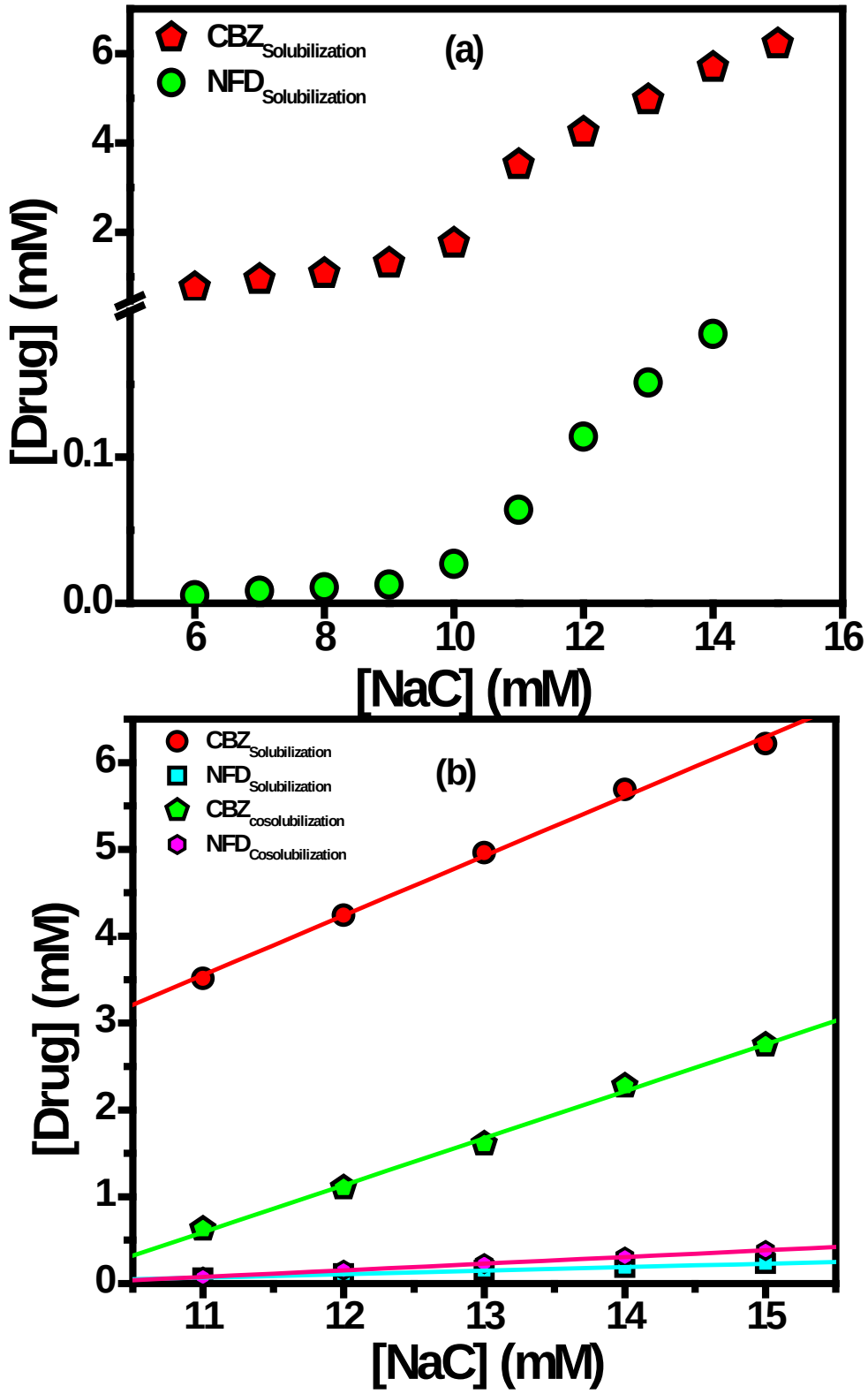


Fig. 5.a) Plot showing increase in solubility of drugs with increase in NaC concentration in pre and post micellar regions b) Variation of concentration of CBZ and NFD during solubilization and co-solubilization with NaC surfactant concentration.

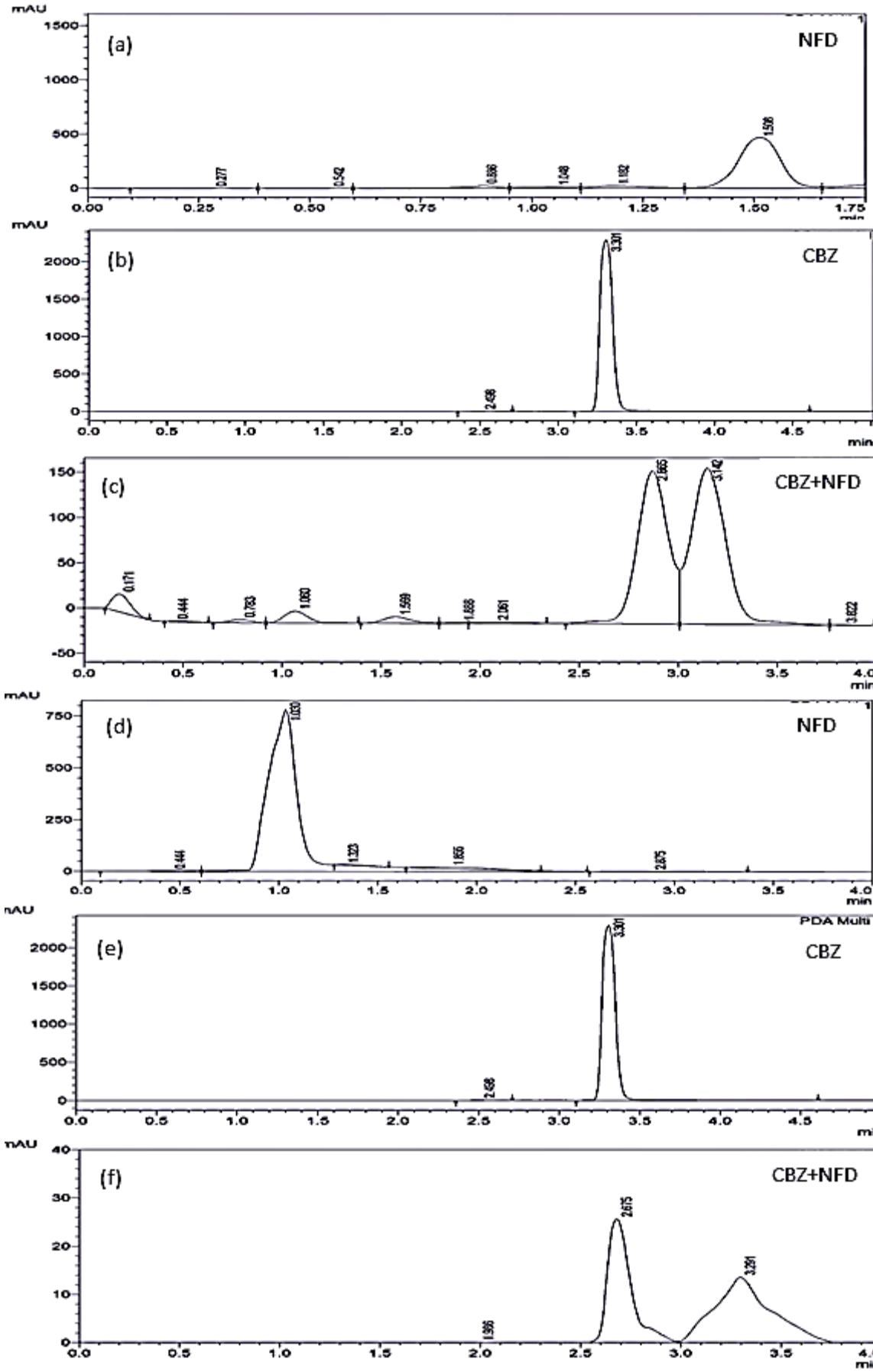


Fig. 6. HPLC profile a) NFD b) CBZ c) NFD+CBZ in (T20+NaC) binary surfactant system d) NFD e) CBZ and f) CBZ+NFD in (B30+T20+NaC) in ternary surfactant system.

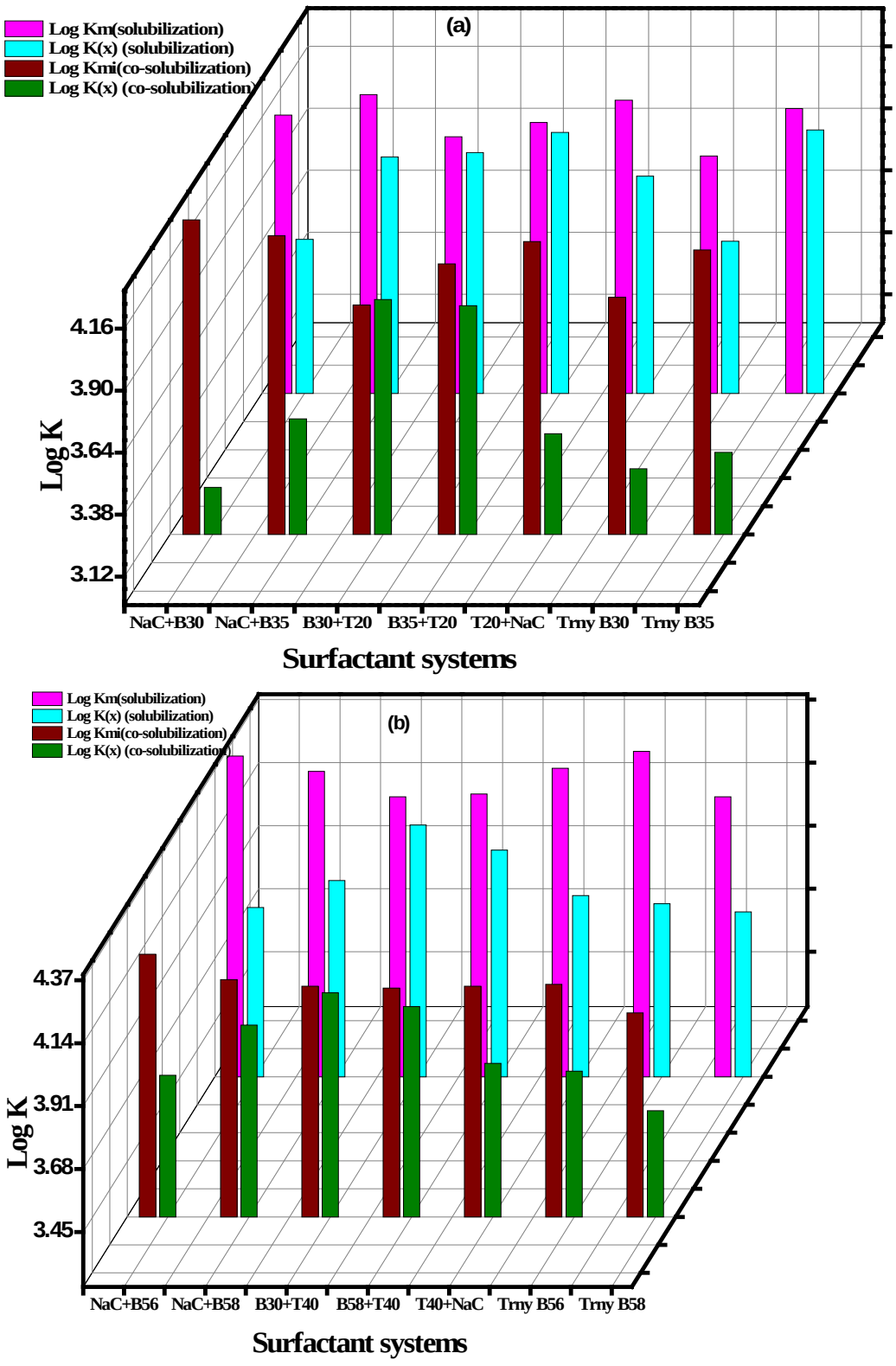


Fig. 7.*Comparison of log Km and logK(x) of CBZ during single solute solubilization and co-solubilization a) in C_{12} series b) in C_{16} series.*

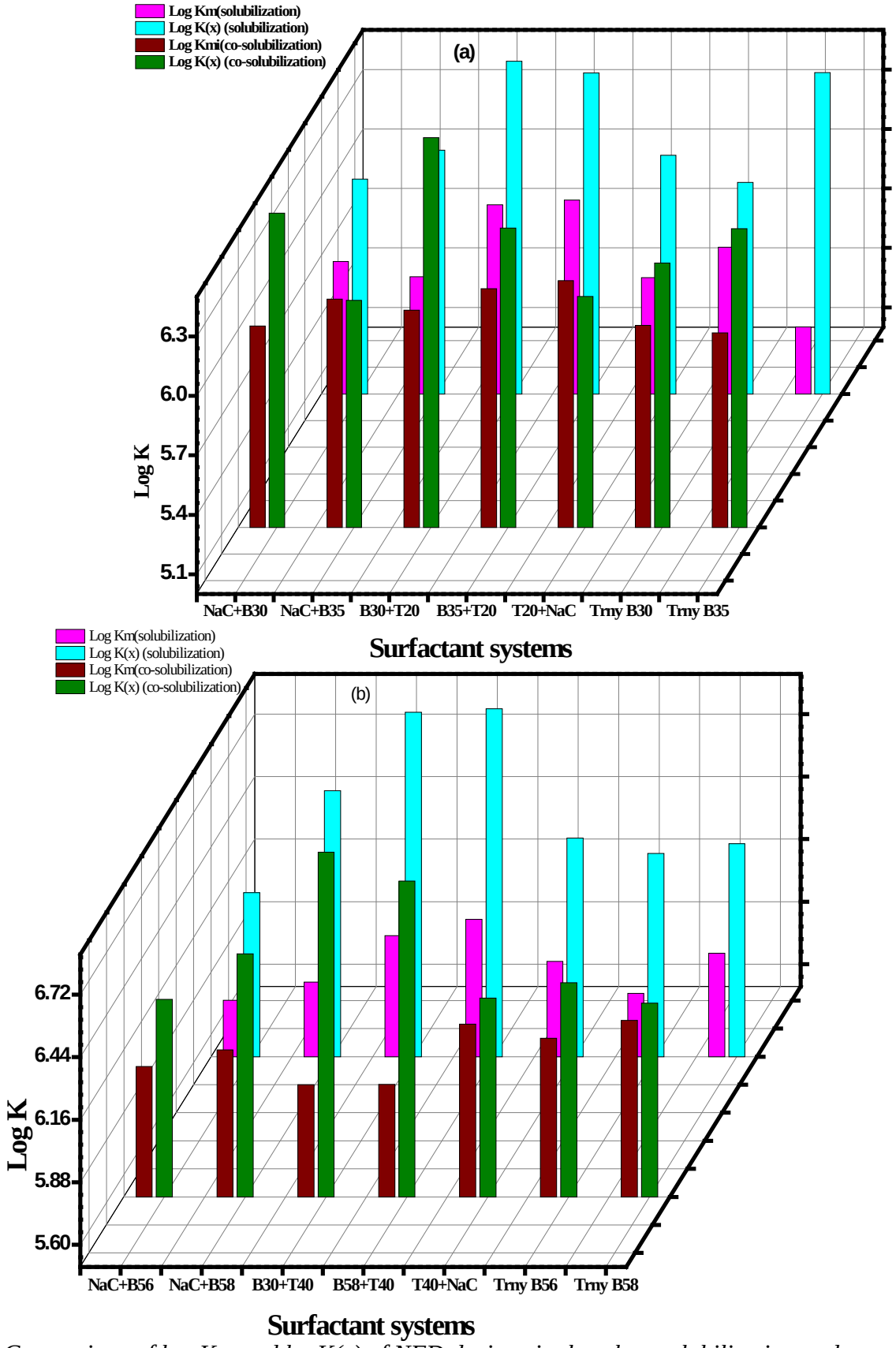


Fig.8. *Comparison of log Km and logK(x) of NFD during single solute solubilization and co-solubilization a) in C_{12} series b) in C_{16} series.*

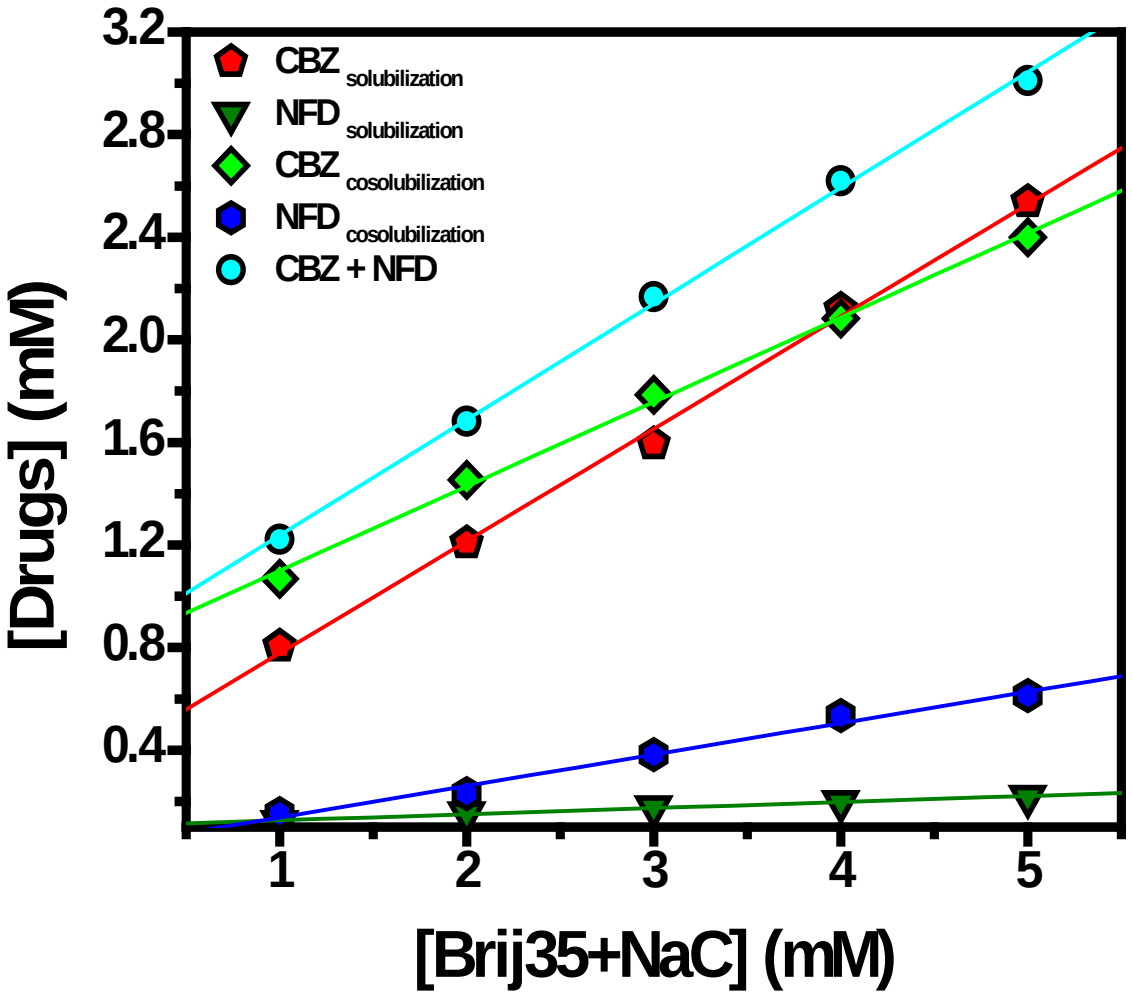
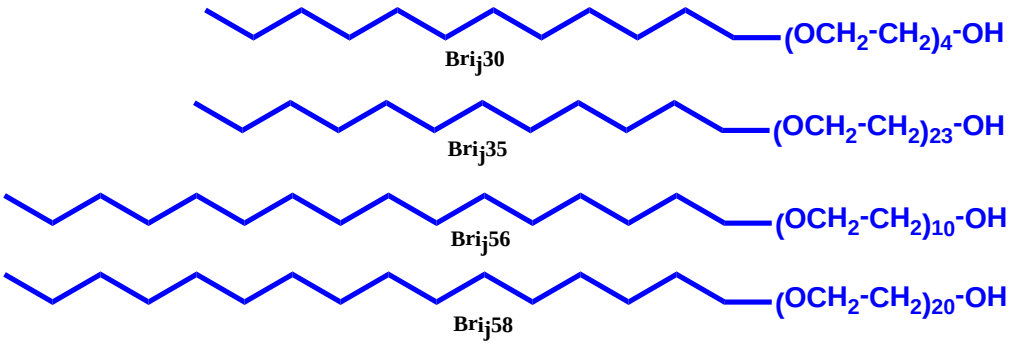
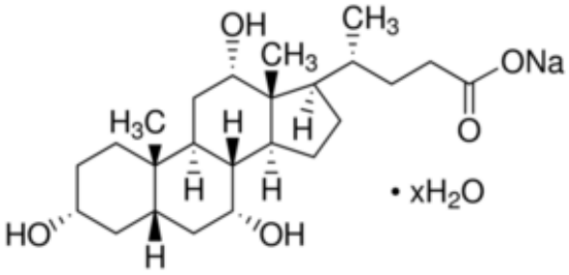


Fig. 9. Comparison between solubilized amounts of CBZ and NFD during solubilization and co-solubilization in addition to total amount of the two drugs solubilized in B35+NaC binary surfactant system at 25 ^{o}C.

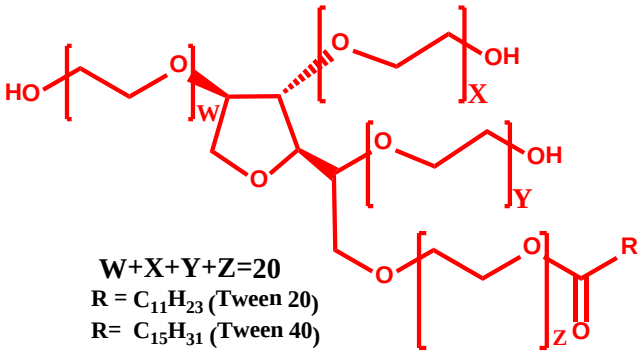


[A]. Polyoxyethylene Surfactants



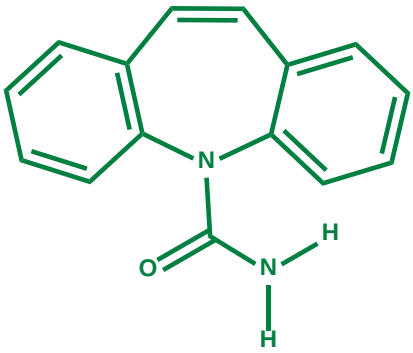
Sodium Cholate

[B]. Bile Salt

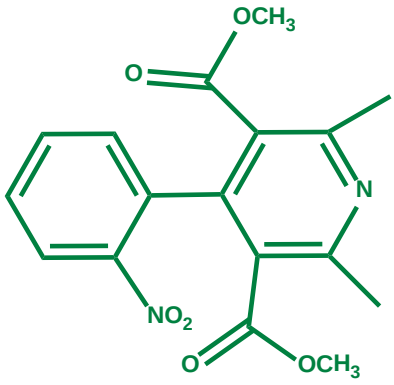


W+X+Y+Z=20
R = $C_{11}H_{23}$ (Tween 20)
R= $C_{15}H_{31}$ (Tween 40)

[C]. Polysorbate Surfactants



Carbamazepine



Nifedipine

[D]. Drugs

Scheme 1. Chemical Structure of materials

Table 1: ***Critical Micelle Concentration (cmc_{exp}), Ideal Critical Micelle Concentration (cmc_{ideal}) Micellar Composition (X_i^M), interaction parameter (β) and activity coefficients (f_i) of equimolar binary surfactant mixtures using Rubingh's method and equimolar ternary surfactant mixtures using Rubingh's Pseudobinary and Rubingh-Holland methods at 25 °C for both C12 and C16 Surfactant Series.***

System	cmc_{exp} *(mM)*	cmc_{ideal} */cmc_{RH}(mM)*	β	$X_1^M/X_2^M/X_3^M$	$f_1/f_2/f_3$
NaC	9.8				
B30+NaC	0.030	0.065	-8.77	0.76/0.24/-	0.60/0.01
B35+NaC	0.039	0.078	-7.97	0.77/0.23/-	0.65/0.01
B30+T20	0.030	0.034	-0.59	0.48/0.52/-	0.87/0.85
B35+T20	0.019	0.038	-2.67	0.51/0.49/-	0.50/0.53
T20+NaC	0.036	0.072	-8.08	0.77/0.23/-	0.65/0.01
B56+NaC	0.023	0.072	-10.42	0.72/0.28/-	0.44/0.01
B58+NaC	0.005	0.007	-9.11	0.76/0.25/-	0.80/0.01
B56+T40	0.023	0.032	-1.36	0.53/0.47/-	0.74/0.68
B58+T40	0.004	0.006	-2.67	0.73/0.27/-	0.82/0.25
T40+NaC	0.026	0.058	-8.90	0.75/0.25/-	0.59/0.01
B30+T20+NaC	0.023	0.052/0.026		0.44/0.36/0.20	0.60/0.66/0.01
B35+T20+NaC	0.026	0.057/0.025		0.59/0.41/~0.00	0.36/0.56/0.56
B56+T40+NaC	0.018	0.049/0.018		0.41/0.38/0.21	0.41/0.54/0.01
B58+T40+NaC	0.005	0.009/0.005		0.65/0.23/0.12	0.71/0.23/0.01

Error limits of cmc, X_1 , β and f are ±5%, ±0.02, ±0.05 and ±0.02 respectively

Table 2: ***Experimental Molar Solubilization Ratio (MSR) and Ideal Molar Solubilization Ratio (MSR_{ideal}) calculated for CBZ and NFD during solubilization and co-solubilization in various mixed surfactant systems at 25 °C.***

Surfactant system	CBZ_{pure}		CBZ_{mix}		NFD_{pure}		NFD_{mix}	
	MSR_{ideal}	*MSR*	MSR_{ideal}	*MSR*	MSR_{ideal}	*MSR*	MSR_{ideal}	*MSR*
B30+NaC	0.621	0.428	0.260	0.249	0.032	0.029	0.094	0.092
B35+NaC	0.574	0.348	0.364	0.329	0.039	0.024	0.045	0.122
B30+T20	0.431	0.424	0.204	0.194	0.032	0.057	0.068	0.092
B35+T20	0.392	0.376	0.274	0.236	0.037	0.060	0.035	0.130
T20+NaC	0.351	0.369	0.310	0.315	0.037	0.024	0.044	0.154
B56+NaC	0.408	0.496	0.331	0.284	0.067	0.035	0.096	0.100
B58+NaC	0.344	0.411	0.313	0.221	0.094	0.042	0.091	0.115
B56+T40	0.263	0.308	0.234	0.200	0.085	0.070	0.089	0.076
B58+T40	0.266	0.317	0.256	0.196	0.100	0.084	0.089	0.077
NaC+T40	0.343	0.427	0.300	0.214	0.078	0.053	0.076	0.153
B30+T20+NaC	0.489	0.351	0.268	0.154	0.034	0.034	0.071	0.076
B35+T20+NaC	0.421	0.343	0.282	0.266	0.038	0.013	0.035	0.076
B56+T40+NaC	0.358	0.527	0.301	0.214	0.074	0.038	0.088	0.130
B58+T40+NaC	0.366	0.308	0.326	0.165	0.088	0.058	0.088	0.153

Error limits in the measurement of MSR are ± 6%.

Table 3: **Excess Gibbs energy changes (ΔG^{S}_{excess}), interaction parameter (ω/RT) and activity coefficients (γ_i) of CBZ and NFD during Co-solubilization in different mixed surfactant systems at 25 ^{o}C.**

System	ΔG^{S}_{excess}	ω/RT	γ_{CBZ}	γ_{NFD}
B30+NaC	-3.69	-0.0076	0.999	0.996
B35+NaC	-5.10	-0.0104	0.999	0.995
B30+T20	-3.07	-0.0057	0.999	0.997
B35+T20	-4.36	-0.0077	0.999	0.997
T20+NaC	-5.77	-0.0106	0.999	0.995
B56+NaC	-3.71	-0.0078	0.999	0.996
B58+NaC	-4.12	-0.0074	0.999	0.997
B56+T40	-2.82	-0.0057	1.000	0.997
B58+T40	-2.65	-0.0053	1.000	0.997
NaC+T40	-4.74	-0.0079	0.999	0.997
B30+T20+NaC	-2.11	-0.0038	1.000	0.998
B35+T20+NaC	-3.85	-0.009	1.000	0.995
B56+T40+NaC	-4.34	-0.0075	0.999	0.997
B58+T40+NaC	-4.77	-0.0077	0.998	0.998

ΔG^{S}_{excess} is in kJmol^{-1} with error limits ± 4%.