observed in pluronic F68, BS, sugar ether, and BS/SPC-MM, respectively. The results showed that BS/SPC-MM systems displayed the highest solubilizing capacity, while pluronic F68 showed the lowest. The authors believed that lower solubilizing capacity of pluronic F68 could be explained by the fact that it has a semipolar micelle core that is not suitable for the accommodation of the lipophilic side of clonazepam molecules that would be responsible for interaction and orientation of the drug in the micelle. Moreover, water may penetrate into the oxypropylene region of the micelle. This effect would render this region too polar for solubilizate molecules (Elworthy and Patel, 1983). In addition, incomplete micellization is expected from the structural features of pluronic surfactants which could be another reason for the decreased solubilizing capacity of these surfactants for this drug. On the other hand, higher solubility could be achieved in MM probably owing to the simultaneous presence of both the charged palisade layer (the charges of PC and BS) and lipophilic core (PC fatty acids residue and the lipophilic side of BS) in the MM, which result in enhanced interaction with polar and nonpolar regions, respectively, of the clonazepam molecule. Lower solubility in sodium glycocholate (SGC) micelles compared with that in BS/SPC-MM was thought to be due to its smaller micelle size and higher hydrophilicity. Balzer (1996) showed that sugar ether or glucoside 81s forms anisometric *worm-like* micelles with high aggregation numbers favoring higher solubilization. However, it has a lower solubilizing capacity compared with that of BS/SPC-MM. This can be explained by lower lipophilicity of the micelle core (C8–10) compared with that of BS/SPC-MM. In addition, the bulky hydrophilic palisade layer of the glucose units is expected to hinder interaction of clonazepam molecules with the micelles.

However, only slight differences in solubilizing capacity were observed among MM prepared from different bile salts, sodium cholate (SC) and SGC. The slight difference between SC/SPC-MM and SGC/SPC-MM is accounted for by the small difference in micellar size, as these two BS are trihydroxy bile salts and expected to form more or less similar micelles.

Moreover, increasing SPC ratio in MM led to a parallel increase in solubility due to the parallel increase of both size and lipophilicity of the formed BS/SPC-MM. This effect has also been noted during the solubility study of diazepam in MM from SC and egg phosphatidylcholine (Rosoff and Serajuddin, 1980).

Additive Effect on Solubilization of Mixed Micelles

Hammad and Muller (1998) studied the effect of addition of alcohols with different hydrophilicity, such as ethanol, propanol, butanol, pentanol, cyclohexanol, and benzyl alcohol, as well as 2-phenylethanol, on clonazepam solubility in MM. Addition of alcohols with ascending lipophilicity, beginning with ethanol, propanol, and up to butanol, insignificantly affected clonazepam solubility in MM. Addition of pentanol cyclohexanol, benzyl alcohol, or 2-phenylethanol increased the solubility to different degrees. The increase in the lipophilicity of alcohol increased its affinity to the micellar phase and hence a higher concentration of the alcohol in the micellar phase is expected.

It has been reported that water-soluble alcohols (methanol to butanol) are predominantly dissolved in the water phase and may decrease or increase the micellar aggregation number, n, depending on the alcohol concentration. Moderately soluble alcohols (pentanol and hexanol) are distributed between the aqueous and micellar phases and may increase the association number (Backland et al., 1981). Moreover, more hydrophilic alcohols were found to increase the CMC, while more lipophilic alcohols were found to decrease the CMC (Green, 1972). Although the decrease in CMC could partially contribute to the increase in the solubilizing capacity, it could also be considered as an indication of the formation of micellar species with larger size. These results furnish a basis that agrees with the explanations of Hammad and Muller (1998). In addition, Roe and Barry (1982) reported that addition of 2-phenylethanol at concentrations in the same range used in this study to different bile salt solutions showed an increase in the micellar size. The increase in the size of bile salt micelles as a function of 2-phenylethanol concentration occurred in a more or less similar fashion to the increase of clonazepam solubility in MM.