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COMMUNICATION

The Role of Mixed Micelles in Drug Delivery. I. Solubilization

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ABSTRACT

The present study revealed that the solubilization of a poorly soluble drug, Amphotericin-B (AmB) can be improved by lipid–bile salt mixed micelles and it was also noted that mixed micellar systems are thermodynamically stable relative to micellar systems. It was observed that the degradation or precipitation of AmB was significantly reduced when stored at 8°C. The mixed micellar systems composed of sodium desoxycholate with monoolein increased the solubilization of AmB by more than seven-fold as compared to nonmicellar systems.

INTRODUCTION

The barrier permeation characteristics in relation to solubilization of poorly soluble drug could account for manifold increased bioavailability of poorly absorbable drug(s) when administered entrapped in mixed micelles (1–6). [Such lipid–bile salt mixed micelles are now recognized as solubilization potentiators for poorly soluble drugs(s) (7–12).] The therapeutic efficacy can be improved by delivering the drug with appropriate microcarrier systems which are able to change temporal spatial distribution of drug (13). Amphotericin-B (AmB), a lipophilic polyene antibiotic (14), was selected for the present investigation and an attempt has focused on improving the solubility of the poorly soluble drug by incorporating it into mixed micellar systems.

MATERIALS AND METHODS

Materials

Sodium taurocholate, sodium desoxycholate, and sodium cholate were obtained from Loba Chemie Pvt. Ltd., India. Oleic acid, glycerol, monostearate, and stearic acid were received from Fluka India Ltd.

Methods

The mixed micellar systems were prepared by dissolving the bile salt, 40 mM, in phosphate buffer at pH 7.4 with equimolar concentration of lipid. The drug, AmB, was added in excess to each system and sonicated for 3 min at 37°C. The solution was filtered through a 0.45-μm filter (Millipore) and assayed for AmB in micellar and

mixed micellar systems with the DB-G grating spectrophotometer (Beckman) at 382 nm.

The systems containing saturated concentration of AmB were stored at 8, 25, and 37°C in the dark for 2 weeks for stability studies. The amount of AmB precipitated or degraded during storage (15) was determined by analyzing AmB in the systems.

RESULTS AND DISCUSSION

All bile salts studied enhanced the solubility of AmB in phosphate buffer solution at pH 7.4. The solubility enhancement observed in each system is shown in Table 1. It was observed that sodium desoxycholate enhanced the dissolution characteristics of AmB by more than three-fold at 37°C compared to a nonmicellar system. A more than fourfold (280.64 ± 2.64 μg ml^{-1}) increase was observed in the solubility of AmB in the system MMS-DA2 composed of sodium desoxycholate and monoolein as compared to a nonmicellar system (62.84 ± 1.42 μg ml^{-1}) as shown in Fig. 1.

The maximum percent remaining of drug at 8°C was noted in the system prepared with sodium desoxycholate with monoolein. The degradation or precipitation of drug was significantly reduced when the mixed micellar system was stored at 8°C, and the precipitation was faster

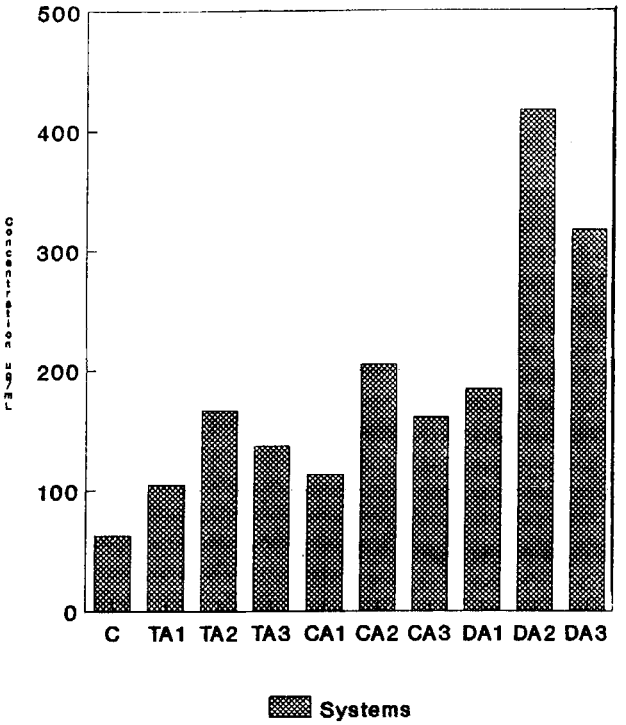

Figure 1. Solubility of AmB in mixed micellar systems after 1 hr at 37°C.

Table 1

Concentration of Amphotericin-B in Various Micellar and Mixed Micellar Systems After 1 hr at 37°C

System Code	Composition	Concentration μg/ml (±SD)
C	Control	62.84 ± 1.42
MS-TA	Sodium taurocholate	107.92 ± 2.12
MS-CA	Sodium cholate	109.86 ± 2.34
MS-DA	Sodium desoxycholate	216.84 ± 4.11
MMS-TA1	Sodium taurocholate + oleic acid	104.63 ± 4.12
MMS-TA2	Sodium taurocholate + monoolein	166.97 ± 4.62
MMS-TA3	Sodium taurocholate + soya lecithin	136.85 ± 3.68
MMS-CA1	Sodium cholate + oleic acid	112.84 ± 4.64
MMS-CA2	Sodium cholate + monoolein	204.60 ± 4.16
MMS-CA3	Sodium cholate + soya lecithin	160.70 ± 4.25
MMS-DA1	Sodium desoxycholate + oleic acid	184.40 ± 3.16
MMS-DA2	Sodium desoxycholate + monoolein	416.92 ± 6.22
MMS-DA3	Sodium desoxycholate + soya lecithin	316.70 ± 1.22

All systems were prepared in phosphate buffer solution at pH 7.4 without sodium chloride. The concentration of each component in the system was 40 mM.

Table 2

Average Percentage of Amphotericin-B Relative to Initial Level Remaining in the Micellar and Mixed Micellar Systems After Storage for 15 days at 8, 25, and 37°C

System Code	Composition	% Remaining of AmB, Mean ± SD		
		8°C	25°C	37°C
C	Control	60.22 ± 4.28	22.36 ± 6.36	10.64 ± 2.66
MS-TA	Sodium taurocholate	71.80 ± 6.42	42.60 ± 4.38	28.56 ± 1.08
MMS-TA1	Sodium taurocholate + oleic acid	88.96 ± 0.66	56.80 ± 1.16	39.42 ± 4.22
MMS-TA2	Sodium taurocholate + monoolein	91.50 ± 3.22	74.87 ± 6.04	55.66 ± 0.28
MMS-TA3	Sodium taurocholate + soya lecithin	88.82 ± 3.88	60.71 ± 3.88	26.02 ± 3.26
MS-CA	Sodium cholate	70.40 ± 8.22	34.28 ± 5.44	17.70 ± 2.40
MMS-CA1	Sodium cholate + oleic acid	87.12 ± 5.24	52.28 ± 2.36	52.15 ± 3.44
MMS-CA2	Sodium cholate + monoolein	94.25 ± 1.82	78.57 ± 0.42	69.23 ± 3.22
MMS-CA3	Sodium cholate + soya lecithin	95.28 ± 2.24	71.28 ± 5.62	49.52 ± 2.16
MS-DA	Sodium desoxycholate	89.62 ± 4.22	47.94 ± 2.42	16.56 ± 2.40
MMS-DA1	Sodium desoxycholate + oleic acid	68.78 ± 4.22	57.44 ± 3.44	46.20 ± 3.42
MMS-DA2	Sodium desoxycholate + monoolein	96.53 ± 1.66	83.11 ± 2.06	68.12 ± 0.26
MMS-DA3	Sodium desoxycholate + soya lecithin	87.13 ± 2.16	76.55 ± 3.22	50.42 ± 1.20

Initial level concentration of AmB in each system was determined on the first day of study.
The concentration of each component in the system was 40 mM.

when stored at 37°C. These observations could be due to a change in the thermodynamic equilibrium of inter- and intramicellar salt monomer concentration at different temperatures.

It was noted that the solubilization potential of mixed micellar systems was more than that of plain micellar systems. This could be because the critical micelle concentration (CMC) of each salt in the mixed micellar system is lower than that of the bile salt alone and also because of an increased affinity of the drug for the lipophilic mixed micellar interior. In mixed micellar systems, bile salts possess the ability to solubilize fatty acids, because they are likely to be solubilized within the hydrocarbon portion of the micelles. As a result, these mixed micelles swell appreciably to accommodate a greater proportion of poorly soluble drug molecules (Table 2).

CONCLUSION

The solubilization potential of mixed micellar systems was shown to be greater than that of plain micellar systems. This could be because the CMC of bile salt in mixed micellar systems is lower than that of the bile salt alone, and because in a mixed micellar system, bile salt possesses the ability to solubilize fatty acids; as a result, these mixed micellar systems appreciably accommodate a greater proportion of drug molecules.

Degradation or precipitation of AmB was significantly reduced when stored at 8°C. It was noted that the mixed micellar system did not appear to be very stable as a solution; these preparations should be freeze-dried and can be stored as powder for clinical application until use. Thus, a mixed micellar system can be used as a vehicle for designing drug delivery systems for poorly soluble drugs.

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