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Research paper

Increasing drug solubility by means of bile salt–phosphatidylcholine-based mixed micelles

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Abstract

Study of the solubilization of commercial grades of soya phosphatidylcholine (SPC) with different purities by bile salts (BS) indicated that only highly pure grades of SPC are suitable for the preparation of clear solutions of BS/SPC-mixed micelles (BS/SPC-MM). The solubilizing capacity of different BS towards SPC increased in the following order; Sodium cholate (SC) < sodium deoxycholate (SDC) < sodium glycocholate (SGC). Moreover, egg phosphatidylcholine (EPC) was solubilized to a higher extent than SPC. Furthermore, the solubility study of different drugs in the prepared MM showed substantial enhancement of solubility, the extent of which is essentially affected by the chemical nature of the drug and the composition of MM. Benzodiazepine drugs such as clonazepam, tetrazepam, diazepam, and lorazepam displayed higher affinity for MM compared with BS alone, whereas steroidal drugs, such as estradiol, prednisolone and progesterone, compared with benzodiazepines, displayed relatively higher affinity for BS alone. The solubilizing capacity of MM for the different drugs was increased to different degrees by the addition of benzyl alcohol which was comparable to the solubility of the drug in pure benzyl alcohol. The interaction between benzyl alcohol and the drug in MM could be proved by NMR.

Keywords: Bile salt–phosphatidylcholine-mixed micelles; Solubilization; Benzodiazepines; Steroidal drugs; Benzyl alcohol; NMR study

1. Introduction

Bile salt–phosphatidylcholine-based mixed micelles (BS/SPS-MM) were developed as drug carriers [1]. Their physiological compatibility and solubilizing capacity greatly encourage a wide spectrum of application as a vehicle for drugs with poor solubility. The formation, size, and structure of BS/SPC-MM were studied systematically using various techniques such as quasielastic light scattering [2–4], small-angle X-ray scattering [5], calorimetry [6,7], and nuclear magnetic resonance (NMR) [8]. The most widely accepted molecular model for the structure of BS/PC-MM is the 'mixed disc model' proposed by Mazer et al. [2]. In this model, the mixed micelle consists of a dislike portion of a lecithin bilayer surrounded on its perimeter by bile salt molecules, positioned with their hydrophilic surfaces in contact with the aqueous solvent and their hydrophobic surfaces interacting with the paraffin chains of the lecithin molecules. Moreover, bile salt molecules as hydrogen-bonded dimers are incorporated inside the lecithin bilayer.

Generalisations about the manner in which the structural characteristics of the surfactant affects its solubilizing capabilities are complicated by the existence of the different solubilization sites within the micelle [9]. For solubilizates which are located either in the micellar core or in a position of deep penetration within the micelle it might be expected that the solubilizing capacity would show a pronounced dependence on the alkyl chain length of the surfactant. Moreover, many factors can affect the amount of a given substance which can be solubilized. Polarity and polarizability, chain length and chain branching, molecular size, shape and structure have all been shown to have various effects. The effect of additives on the amount of solubilized drug in the micellar system was also reported [9].

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This study was undertaken to investigate the different parameters which could affect the preparation of MM and their solubilizing capacity for different drugs.

2. Materials and methods

2.1. Materials

SPC 95% and SPC 79% as Phospholipon® 100 and Phospholipon®80, respectively and sodium glycocholate (SGC) were a gift from Nattermann (Cologne, Germany). SPC 56% and SPC 24% as Epikuron® 145 V and Epikuron® 100 P, respectively were from Lucas Meyer (Hamburg, Germany). Egg phosphatidylcholine (EPC) 95% as Lipoid® E100 was supplied by Lipoid (Ludwigshafen, Germany). SDC was obtained from Sigma (Deisenhofen, Germany). Sodium cholate, NaH_2PO_4, Na_2HPO_4, KH_2PO_4, H_3PO_4 and methanol as HPLC grade, acetonitril as HPLC grade, and chloroform were purchased from Merck (Darmstadt, Germany). Diazepam was from Synopharm (Hamburg, Germany). Tetrazepam was from Sanofi (München, Germany). Lorazepam, clonazepam, estradiol and progesterone were purchased from Welding (Hamburg, Germany). Prednisolone was obtained from Mainland (Frankfurt, Germany). Deuterium oxide, 99.9 atom% D (D_2O) and methyl sulfoxide-d6, 99.9 atom% D (DMSO) were supplied by Sigma Aldrich GmbH (Deisenhofen, Germany). Water was double-distilled. All other reagents were of analytical grade.

2.2. Methods

2.2.1. Preparation of MM

BS/SPC-MM were prepared by the coprecipitation method [4]. BS and PC (at different mol fractions) were dissolved in a mixture of methanol–chloroform (1:1 v/v). A film was formed after evaporation of the organic solvents at room temperature under vacuum until constant weight was reached (48–72 h). The resulting films were dispersed in a given amount of the dispersion medium (water or phosphate buffer 0.067 M, pH 7.4) to give clear micellar solutions with the required concentration.

2.2.2. Determination of PC solubility in BS

The maximum amount of PC that can be solubilized by BS was determined by measuring the light transmission at 660 nm in the prepared MM [10]. For this purpose, a double-beam UV spectrophotometer Uvikon 930 (Kontron Instruments, München, Germany) was used, and double-distilled water served as a blank. One hundred percent light transmission indicates complete solubilization of PC and formation of a clear mixed micellar solution. The inflection point corresponding to the sudden appearance of turbidity was considered as the saturation point of the system with respect to PC. The equilibrium was shown to be established a few minutes after the final preparation of MM as indicated by the constancy of the measurements over several days equilibration at 25°C under N_2.

2.2.3. Determination of drug solubility in different micellar systems

Excess amounts of the drug were added to 10 ml of the different micellar solutions in vials which were then tightly closed under N_2 and shaken in a thermostated shaking water bath SW-20C (Julabo Labortechnik, Seelbach, Germany) at 25°C until equilibrium, which was determined by repetitive sampling (24–72 h). Excess amounts of drug were separated by 5 min centrifugation at 13 000 rev./min on a Biofuge (Heraeus, Hamburg, Germany). Of the supernatant solutions, 0.5 ml was properly diluted and then subjected to HPLC analysis. Each run was repeated at least twice. For the calibration curve, different concentrations in a range (from 1 to 10 μg/ml for all drugs, except estradiol which had a range from 5 to 50 μg/ml) were prepared by dilution from a stock solution of the drug in methanol: water mixture (80:20 v/v). The dilution was made with the same solvent mixture. Addition of 20% water to methanol helped to achieve accurate pipetting of methanol. The concentration–absorption relationship obeyed the Beers–Lambert law (r^2 not less than 0.999).

2.2.4. HPLC analysis of drugs

The instruments consisted of an RP-18 5-μm column (150 × 4.6 mm) (Merck, Darmstadt, Germany), a high-precision pump Gynkotek 300C (Gynkotek, Munich, Germany), an autosampler Kontron 360 and a UV detector Kontron 742 (Konton Instruments, Munich, Germany), an integrator Shimadzu C-R6A chromatopac (Shimadzu, Kyoto, Japan). The analysis parameters for diazepam were: mobile phase acetonitril-H_2O (60:40 v/v), flow-rate 1 ml/min and wave-length 254 nm, for tetrazepam: mobile phase acetonitril-0.01M KH_2PO_4 buffer pH 4.2 (60:40 v/v), flow-rate 2 ml/min and wave-length 254 nm, for lorazepam: mobile phase acetonitril-H_2O-acetic acid (55:45:1 v/v/v), flow-rate 1 ml/min and wave length 254 nm, for clonazepam: mobile phase acetonitril-H2O (45:55 v/v), flow-rate 1 ml/min and wave-length 310 nm, for prednisolone: mobile-phase acetonitril-H_2O-methanol (30:50:20 v/v/v), flow-rate 1 ml/min and wave-length 240 nm, for progesterone: mobile phase acetonitril-H_2O-methanol (30:25:45 v/v/v), flow-rate 1.5 ml/min and wave-length 240 nm, for estradiol; mobile phase methanol-H_2O (80:20 v/v), flow-rate 0.8 ml/min and wave-length 280 nm.

2.2.5. NMR study

The NMR study in this paper was carried out using a Bruker ARX 300 MHz H^1 NMR spectrometer (Bruker, Rheinstatten, Germany). The MM solution for NMR study was prepared as mentioned above, except that the redispersion was carried out in D_2O. Diazepam was chosen as the drug to study interaction with SGC/SPC-MM in the pre-

sence and absence of BA and was added as methanolic solution during the first stage of MM preparation. For samples not containing MM, either D_2O or a mixture of D_2O (approx. 60% v) and DMSO (approx. 40%) was used as solvent. The concentration of diazepam in MM was 0.5 mg/ml, whereas the concentration in D_2O. In the presence of DMSO, enough concentration of diazepam could be used as it had greater solubility. Of each sample, 0.5 ml was placed in the measurement tube of the NMR apparatus and then subjected to NMR measurement at 25°C.

3. Results and discussion

3.1. Solubilization of PC by BS

The inflection points for the abrupt decrease in the % light transmission corresponded to the maximum mol fractions of PC which could be incorporated in the different BS solutions to form clear mixed micellar solutions (Fig. 1). For SPC, the maximum mol fractions were 0.5, 0.52 and 0.55 in the case of SC, SDC and SGC, respectively, whereas EPC in a maximum mol fraction of 0.6 could be incorporated in SGC to form a clear mixed micellar solution. The extent of SPC solubilization by either SDC or SGC is in agreement with the result of Dürr et al. [10] who used SPC of the same purity. Moreover, Smidt et al. [11] solubilized phospholipon 100 with SC to approximately the same extent found in this study. The higher solubilizing capacity of SGC is probably in part due to its higher degree of ionisation at pH 7.4 compared with the other two bile salts. The pK_a values of the conjugated bile acid of SDC, SC, and SGC are 6.58, 6.4, and 4.4 and the pH at which these acids are precipitated were found to be 6.8, 6.5, and 4, respectively.

The greater extent of EPC solubilization compared with SPC may be due to the nature of trace amounts present as impurities, which can significantly affect the solubility of PC by BS. It was found that the presence of non-polar substances such as cholesterol, even at a lower concentration,

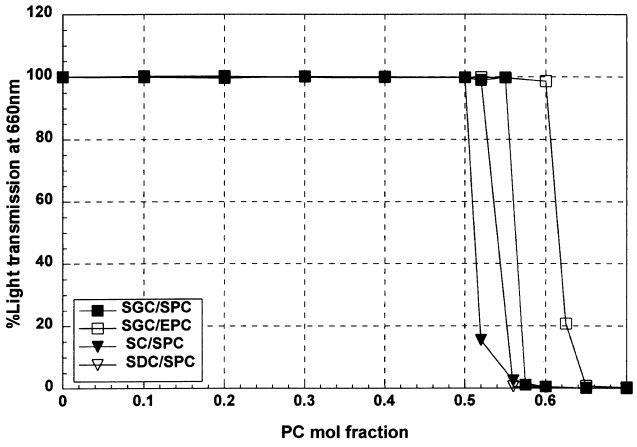

Fig. 1. Change of light transmission as function of PC mol fraction in different MM (total conc. 5% w/w in phos. buff. pH 7.4, 0.067 M).

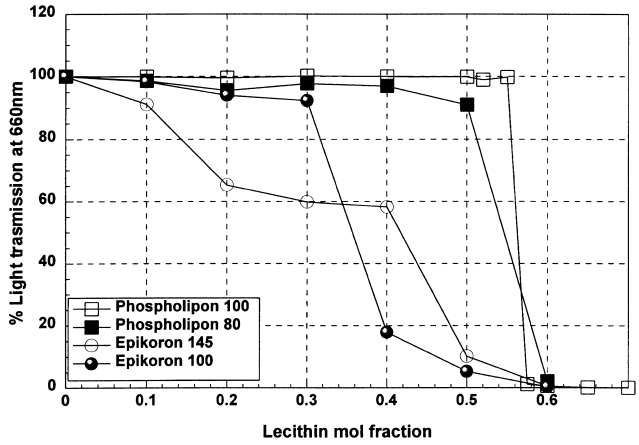

Fig. 2. Change of light transmission as function of SPC grade (total conc. 5% w/w in phos. buff. pH 7.4, 0.067 M).

greatly limited the solubilization of EPC by SC [12].

To investigate the effect of the present impurities on the solubilization of PC by BS, the solubility of different grades of soya lecithin (with different percentages of PC) in SGC was studied. Fig. 2 shows that the solubility of lecithin in SGC is dramatically limited when using grades with a lower percentage of PC in their compositions. The most proper grade for formulation of MM is that containing 95% PC. This decrease in lecithin solubility in SGC is thought to be due to the increasing amounts of impurities, especially neutral oils and sterol which are difficult to solubilize by BS. Moreover, other impurities which are present with high amounts are phosphatidylethanolamine, phosphatidylinositol and phosphatidic acid. These phospholipids induce the formation of inverted hexagonal phase and non-bilayer structures (in contrast to PC) [13].

3.2. Solubilization of drugs by MM

3.2.1. Effect of the type of BS, PC and dispersion medium

The effect of the type of BS, PC and dispersion medium on the solubility of diazepam in either BS alone or in BS/PC-MM is shown in Table 1. SDC alone or in mixed micelle

Table 1
Effect of type of BS, PC and dispersion medium on diazepam solubility in BS or BS/PC-MM (mol fraction 0.5, total conc. 5% w/w)

System	Dispersion medium	Solubility (mg/ml)[a]
SGC	Phosphate buffer	$0.97 \pm 1.41 \times 10^{-2}$
SGC	Water	$0.85 \pm 0.7 \times 10^{-2}$
SC	Water	$1.08 \pm 3.5 \times 10^{-2}$
SDC	Water	$1.35 \pm 2.12 \times 10^{-2}$
SGC/EPC-MM	Phosphate buffer	$1 \pm 1.41 \times 10^{-2}$
SGC/SPC-MM	Phosphate buffer	$1.11 \pm 1.41 \times 10^{-2}$
SC/EPC-MM	Phosphate buffer	$1.1 \pm 2.12 \times 10^{-2}$
SC/EPC-MM	Water	$1.03 \pm 2.12 \times 10^{-2}$
SDC/EPC-MM	Phosphate buffer	$1.11 \pm 2.83 \times 10^{-2}$
SDC/SPC-MM	Phosphate buffer	$1.31 \pm 7.8 \times 10^{-2}$

[a]Mean value ± SD, $n \geq 2$.

with PC displayed the highest solubilizing capacity for diazepam. This observation has also been reported for diazepam and other drugs [14,15]. The formation of larger micelles by dihydroxy bile salt could be partly responsible for this behaviour [2,16]. The solubilizing capacity of BS/SPC-MM is higher than that of BS/EPC-MM which is in agreement with the result of Alkan-Onyuksel and Son for the solubilization of teniposide in MM [17]. This higher solubilizing capacity of SPC containing MM could be interpreted as resulting from the presence of more unsaturated double bonds which could result in more preferable interaction with the aromatic moieties of diazepam. In addition the increased unsaturation in case of SPC leads to higher mobility of the lipophilic interior of MM which can facilitate interaction with the drug molecules. Moreover, SPC is composed of fatty acids with longer chain lengths [18] which could result in the formation of MM with larger size and hence higher solubilizing capacity.

The use of an aqueous buffer as dispersion medium resulted in an additional increase of diazepam solubility in both BS or BS/PC-MM, the effect is more pronounced in the case of BS alone. This effect could result from the increase in the micellar size due to neutralisation of part of their charges especially in the case of BS. This effect is clearly observed in the case of SDC which formed a gel in the presence of phosphate buffer pH 7.4, a phenomenon which is also reported by Marten et al. [19] and is interpreted to be due to the dramatic increase in the micellar size at this pH [9]

3.2.2. Effect of PC mol fraction and concentration on solubility of different drugs in MM

The course of the solubility profile for drug substances with different chemical structures as a function of SPC mol fraction in MM is shown in Fig. 3. The effect of increasing the mol fraction of SPC in MM on the solubility of different drugs was different. For benzodiazepines, increasing the SPC mol fraction is accompanied by an increasing affinity

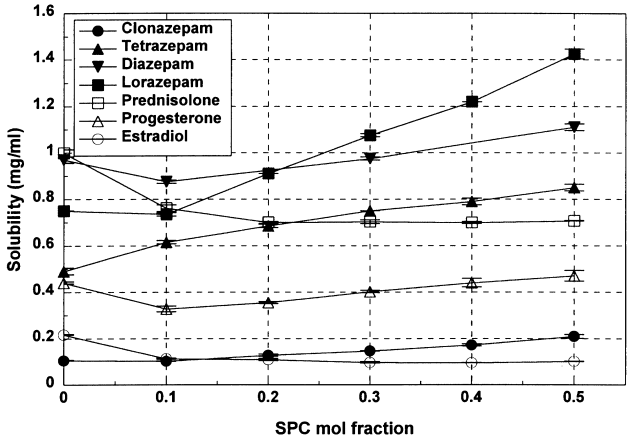

Fig. 3. Effect of SPC mol fraction on the solubility of different drugs in SGC/SPC-MM (total conc. 5% w/w, in phos. buff. pH 7.4, 0.067 M) at 25°C.

of the drug to MM. On the other hand increasing the SPC mol fraction shows relatively lower affinity to MM, compared with benzodiazepines, of steroidal drugs in MM. The extent of solubility is greatly influenced by the chemical structure of the drug and the composition of MM.

It appears that the presence of the planar aromatic rings in the case of benzodiazepines facilitate the interaction of the drug molecule with the lipophilic part of the micelle by insertion between the molecules of the surfactant. Such interaction of deep penetration is expected to increase as the lipophilic part of the MM is increased by increasing the SPC mol fraction. In the case of clonazepam, the presence of the bulky polar NO_2 group attached at position 7 is expected to greatly limit the interaction with the lipophilic part of either BS or BS/SPC-MM which will result in highly-reduced solubility compared with the other benzodiazepines. In the case of tetrazepam compared with diazepam, the partially-saturated ring attached at position 4 is not planar and can display conformational changes. Accordingly, its interaction with the lipophilic part of the micelle is expected to be less. Although it has a hydrophilic OH group at position 3, lorazepam was solubilized at a higher extent with increasing SPC mol fraction than either diazepam or tetrazepam. The presence of an OH group at the hydrophilic side of the molecule beside the carbonyl group does not limit the lipophilic interaction with micelles and instead of this it increases the hydrophilic interaction through formation of hydrogen bonds with the hydrophilic portion of MM. This reflects how important the distribution of the lipophilic and hydrophilic moieties in the molecule is, in affecting the association with micelles.

In comparison with benzodiazepines, steroidal drugs, with their linear structure, possibility of conformational changes and the distribution of a polar groups at each end of the molecule displayed lower degrees of association with micelles. The absence of a polar group-free end in the molecule resulted in the limitation of the lipophilic interaction with the micelle and suggests that these drugs are solubilized in the palisade layer between BS molecules. This could explain the enhanced solubility of these drugs in BS alone compared with MM. In the case of progesterone, the polar carbonyl group at one end is not directly attached to the steroidal nucleus and hence there is more freedom for the lipophilic part of the molecule to interact with the lipophilic part of MM. This may explain the slight increase in the solubility of progesterone at increasing SPC mol fraction. The structural similarity between the steroidal drugs and the bile salts could also result in more favourable orientation of the drug molecules with that of BS. This could also account for the relative decrease in solubility at lower BS mol fractions.

In Fig. 4 the extent of solubility for different drugs at increasing MM concentration indicates the reproducibility of the results which are shown in Fig. 3. For benzodiazepine drugs, the solubility increases in the following order; clonazepam $<$ tetrazepam $<$ diazepam $<$ lorazepam whereas

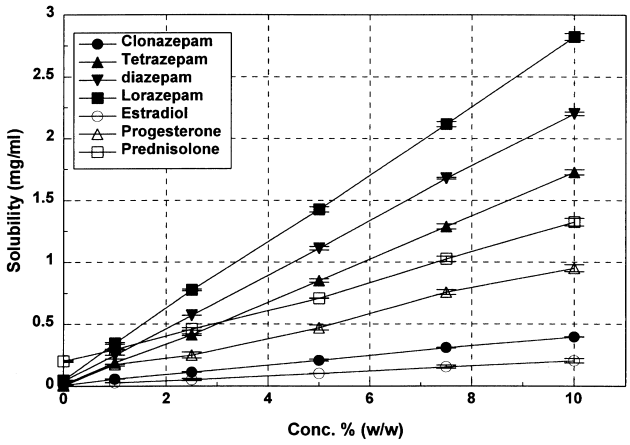

Fig. 4. Effect of SGC/SPC-MM (mol fraction 0.5) concentration on the solubility of different drugs (dispersion medium phos. buff. pH 7.4, 0.067 M) at 25°C.

for steroidal drugs the order is estradiol < progesteron < prednisolone. The linear increase in the solubility with an increase in concentration of MM is common for the solubility of drugs in surfactant solutions.

3.2.3. Effect of benzyl alcohol on the solubility of different drugs in MM

The effect of BA on the solubility of different drugs in MM is illustrated in Fig. 5. Dramatic increases in the solubility of different drugs were obtained as a result of BA addition to MM especially at concentrations near the saturation solubility of BA (approx. 5% w/w) in MM. Although it is expected that the size of MM is increased by the addition of BA, the rate of increasing drug solubility was different among different drugs. A more-or-less parallel increase in solubility was observed for diazepam, tetrazepam and progesterone. These drugs also displayed higher solubility in pure BA compared with the other drugs (Table 2). On the other hand, lorazepam and prednisolone showed parallel curves of lower rates of increasing solubility as a function

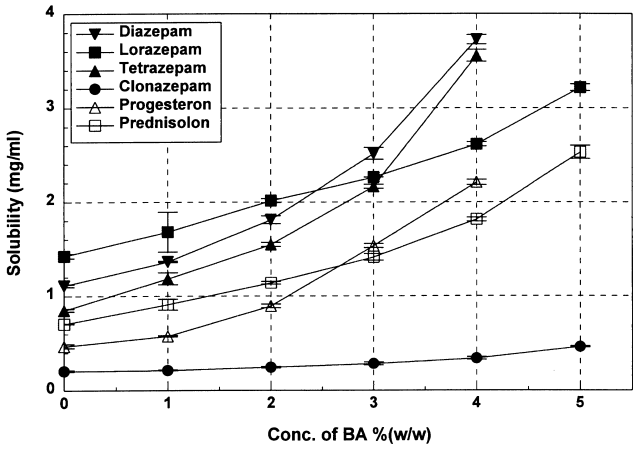

Fig. 5. Effect of benzyl alcohol (BA) on the solubility of different drugs in SGC/SPC-MM (mol fraction 0.5, total conc. 5% w/w in phos. buff. pH 7.4, 0.067 M) at 25°C.

Table 2
Solubility of different drugs in pure benzyl alcohol

Drug	Solubility (mg/ml)[a]
Diazepam	369.3 ± 0.771
Tetrazepam	332.7 ± 2.43
Lorazepam	206.2 ± 1.06
Clonazepam	33.5 ± 0.219
Progesterone	423.2 ± 1.63
Prednisolone	118.0 ± 1.36

[a]Mean value ± SD, $n \geq 2$.

of added BA to MM as well as lower solubility in pure BA compared with the above three drugs. In the case of clonazepam, which showed the lowest solubility in pure BA, the lowest rate of increase in solubility in MM as a function of added BA was also observed. These results suggest that as well as the increase in micellar size, the interaction of BA with the drug in MM is another important factor which could contribute to the extent of drug solubility in MM.

3.3. NMR spectra of drug in MM and in MM containing benzyl alcohol

The NMR spectra of diazepam at different concentrations of MM as well as in the presence of BA in comparison with that in solvent alone is illustrated in Fig. 6. Due to the very low solubility of diazepam in D_2O (approx. 0.05 mg/ml) it was difficult to characterise the different signals corresponding to different protons. Accordingly, the spectra of diazepam in mixture from D_2O and DMSO were determined in order to increase the amount of diazepam in the sample. The shift of aromatic protons from diazepam was used to

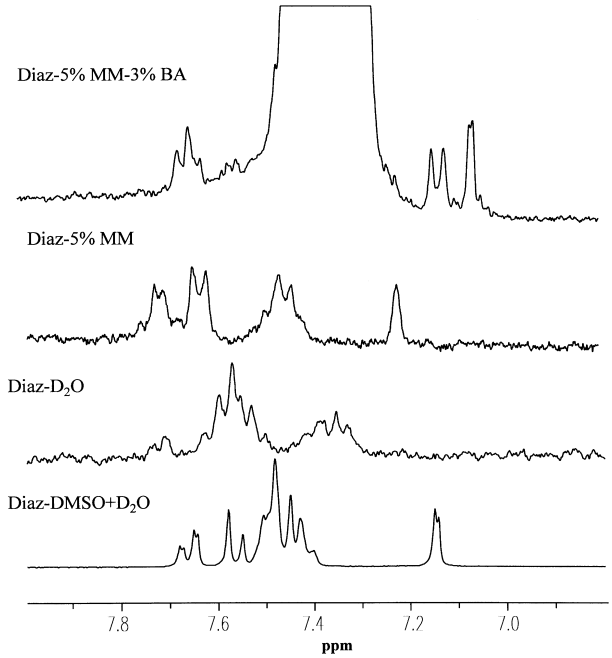

Fig. 6. NMR spectra of diazepam at different concentrations of SGC/SPC-MM as well as in presence of benzyl alcohol.

study the interaction with MM as the absorption of these protons is not affected by the absorption of MM components. In D_2O–DMSO mixtures, the peaks from right to left are as follows; the peak at about 7.15 ppm corresponds to C-6 proton, the broad multiplet peak at the range 7.4–7.55 ppm corresponds to protons of the unsubstituted aromatic ring, the doublet peak at about 7.58 ppm corresponds to C-9 proton, and the doublet at about 7.68 ppm corresponds to the C-8 proton. The absorption of these protons has been reported to occur approximately in the same range [20].

In the case of pure D_2O as solvent, the broad peak corresponding to the unsubstituted aromatic ring showed downfield shift and probably fuses with the peak of C-9 proton. The peak corresponding to the C-3 proton is difficult to characterise in D_2O. In the presence of MM all peaks could be characterised accurately. The broad peak of the aromatic ring showed an upfield shift which is expected to result from the interaction with the lipophilic part of MM. Changing the concentration of MM insignificantly affected the positions of the different peaks. The changes in the peak of the aromatic ring protons which result in the presence of BA could not be observed due to the interference with the very large peak of aromatic protons from BA. Fortunately, the peaks of C-6, C-8 and C-9 protons absorb at a range

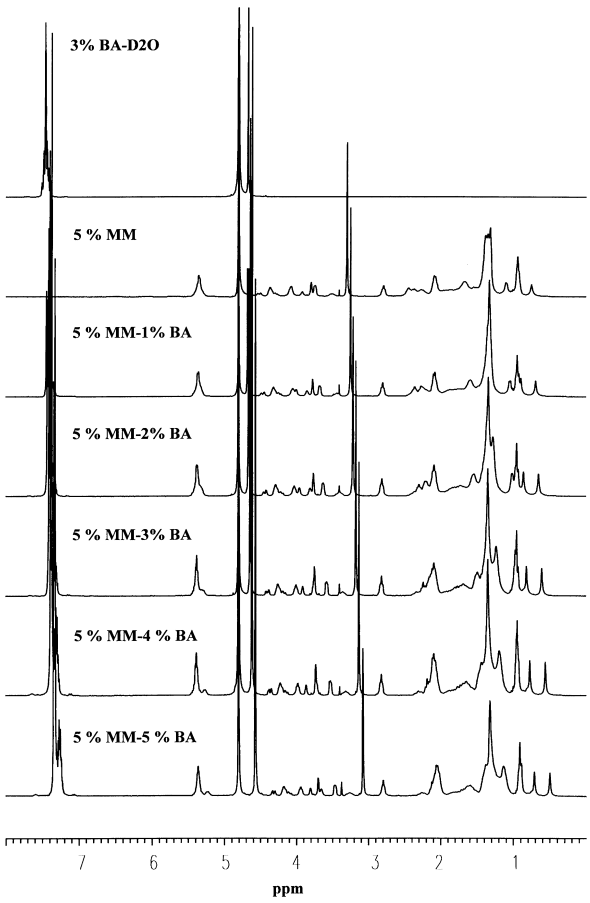

Fig. 7. NMR Spectra of SGC/SPC-MM in presence of different concentrations of benzyl alcohol (BA).

Table 3

Chemical shift (ppm) of different protons from either SPC, SGC or benzyl alcohol (BA) as function of BA concentration added to SGC/SPC-MM

BA% w/w	C-18 (SGC)	C-19 (SGC)	N (CH3)3 (SPC)	CH2 (BA)
0	0.7396	0.9324	3.2928	4.6692
1	0.6881	0.8902	3.2438	4.6779
2	0.6466	0.853	3.2072	4.6593
3	0.6038	0.8134	3.1694	4.6388
4	0.556	0.7675	3.1266	4.6134
5	0.4955	0.7081	3.0699	4.5658

which is quite far from that peak. These latter three protons showed an upfield shift due to the interaction of BA with diazepam in MM. From the structural characteristics of either benzyl alcohol or the drugs studied, it is to be expected that their sites of solubilization are very close to each other. This provides the chance for the interaction between the molecules of benzyl alcohol and that of either of these drugs with a consequent increase in drug solubility.

3.4. NMR spectra of BA in MM

The NMR spectra of both SGC/SPC-MM and benzyl alcohol showed significant changes on the addition of the latter to MM (Fig. 7). Continuous upfield shifts were recorded for some protons from either SPC or SGC on the addition of benzyl alcohol to SGC/SPC-MM (Table 3).

The peaks of C-18 and of C-19 methyl protons of SGC appeared at 0.7396 and 0.9324 ppm, whereas upfield shifts to 0.4955 and 0.7081 ppm were observed in the presence of 5% benzyl alcohol. The protons of the choline head group ($N^+(CH_3)_3$) of SPC also showed an upfield shift from 3.2928 to 3.0699 ppm upon the addition of 5% benzyl alcohol to MM. The broad peak corresponding to $(CH_2)_n$ of SPC showed interesting changes upon the addition of benzyl alcohol to MM. With gradual addition of benzyl alcohol to MM this peak became more sharp and separated into two peaks.

The changes which were observed for the different proton absorption peaks from SGC and SPC can be explained as follows: the incorporation of benzyl alcohol molecules between the lipophilic chains of SPC leads to an increase in the size of MM and gives some degree of freedom to the chains, so the peaks become more sharp. The presence of the methyl protons of SGC associated with the lipophilic chains of SPC makes it possible that these protons will be affected by the incorporated benzyl alcohol molecules in MM.

The splitting of the broad peak at about 1.4 ppm can be explained by the interaction of benzyl alcohol molecules only with SPC lipophilic chains which constitute the outer layers of MM and hence give the upfield shift. These continuous upfield shifts displayed by the spectra of the different protons from either SPC or SGC indicate that the

concentration of BA is increasing in the micellar structures with concomitant increase in the micellar size.

The splitting of the $(CH_2)_n$ proton peak which was observed upon the interaction of benzyl alcohol with MM was also reported for other systems studied. Different degrees of $(CH_2)_n$ proton peak splitting were noted on solubilization of pyrene, pyrene butyrate and pyrene sulphate in CTAB [21] with pyrene giving the highest degree of resolution. This was interpreted to arise when the aromatic ring of the solubilisate is located in close proximity to the inner methylene groups.

The above chemical shifts which were observed for different protons of different chemical groups from SPC and SGC on the addition of benzyl alcohol to MM indicated that the molecules of benzyl alcohol were inserted between the molecules of SGC (covering the perimeter of MM) with their aromatic rings partially incorporated in the outer part of lipophilic core of MM. Moreover, the upfield chemical shift which was observed for the choline head suggests that the molecules of benzyl alcohol were also incorporated in MM with the aromatic rings inserted between the methyl groups of the choline residue.

Changes were also observed for the peaks corresponding to protons from benzyl alcohol. The most interesting changes are those of the peak corresponding to the aromatic protons which absorb at about 7.45 ppm (Fig. 7). Upon addition of benzyl alcohol to MM the broad multiple peaks present on each side of the higher intensity peak are shifted to the right side (upfield). With a gradual increase in the amount of added benzyl alcohol to MM, an increasing upfield shift was observed without further change of the position of the different peaks relative to each other. These changes are suggested to occur due to the insertion of the aromatic ring of benzyl alcohol molecules between the lipophilic chains of SPC. In this position the meta and para protons penetrate more deeply in the lipophilic part of MM than the ortho protons which are shifted to a more hydrophilic medium. The noted upfield shift with increasing amounts of benzyl alcohol to MM probably results from the interaction between the benzyl alcohol molecules themselves.

There are published works which have dealt with the interaction of solubilizates having aromatic rings with micellar structures using the NMR technique. Jacobs et al. have studied the solubilization of phenol by micelles of sodium dodecyl sulphate (SDS) using NMR [22]. They found that the aromatic protons showed an upfield shift. The meta and para protons showed a greater shift than the ortho protons indicating an environmental change for the latter. On the basis of the obtained results it was concluded that phenol was solubilized in such a way that the hydroxy group was closest to the polar micellar surface. This arrangement is in agreement with assumption for the interaction of benzyl alcohol with MM. CH_2 of BA showed an insignificant shift, indicating that these protons do not interact with the same component of MM as for the aromatic protons.

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