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Isotropic medium chain mono–diglyceride/oil/water formulations for solubilization of lipophilic and hydrophilic drugs

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Abstract

The aim of the study was to investigate isotropic mono- and diglyceride (MCMDG)/oil/water systems as vehicles for combinations of hydrophilic and lipophilic drugs. For two-component systems, MCMDG was mixed with various masses of water. For MCMDG/oily vehicles/water systems, mixtures were prepared by mixing oil and MCMDG prior to the addition of the appropriate masses of water. The isotropic region was examined by visual inspection and confirmed using polarized light microscopy. Viscosities of the systems were determined. Solubilities of hydrophilic (levamisole HCl) and lipopohilic (abamectin) drugs were determined in the isotropic formulations by HPLC analysis. The isotropic regions in the two-component and three-component systems had water contents of up to 18% at 25 °C. The isotropic formulations exhibited Newtonion flow. The viscosity of formulations having the same percentage of water increased with increasing ratio of MCMDG to oil in three-component systems. The solubilities of the levamisole HCl and abamectin were higher in the isotropic MCMDG/sesame oil/water formulations than in equivalent MCMDG/water formulations. In some formulations, the solubility of levamisole HCl was higher in the absence of abamectin than in combination with abamectin. Isotropic MCMDG/oil/water systems were obtained without the use of co-surfactants. Increasing water content in the system did not proportionally increase the solubility of hydrophilic drug. Solubilization of hydrophilic drug was affected by lipophilic drug in the presence or absence of SO and lipophilic drug solubility was affected by hydrophilic drug in the absence of SO. These systems are suitable vehicles to deliver both hydrophilic and lipophilic drugs and could be of interest for pharmaceutical formulations.
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Keywords: Phase diagrams; Isotropic region; Formulation; Viscosity; Solubility

1. Introduction

The design and development of new drug delivery systems is an ongoing process in pharmaceutical research. Recently, some research has focused on clear, isotropic systems, microemulsions (Thevenin et al., 1996), and low viscosity monoglyceride-based systems (Chang and Bodmeier, 1998) as potential vehicles for injectable products.

Long chain monoglycerides, such as monoolein, show various types of phase behaviour depending on the water content and temperature (Lutton, 1965). Addition of small amounts of water to the lipids at 37 °C results in the formation of transparent isotropic reversed micellar solutions. As the water content and temperature increase, other phases, including lamellar (L), hexagonal (H), and cubic (C) are formed (Wyatt and Dorschel, 1992; Engstrom et al., 1992).

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An L2-phase isotropic solution was described by Friberg and Mandell (1970) for the system of the medium-chain glycerides tricaprylin/monocaprylin/water. Ekwall (1975) described a reversed micellar solution in the ternary system sodium caprylate/decanol/water. Pilman et al. (1982) obtained an L2-phase using sunflower oil monoglyceride/soybean oil/water at 30 °C. This isotropic phase consisted of water aggregates in a continuous lipid phase (Ekwall, 1975; Lindstrom et al., 1981; Pilman et al., 1982).

Therefore, examples of isotropic systems which are of interest for food products, pharmaceutical formulations and biotechnology are the ternary polar lipid/oil/water systems (Engstrom, 1990). They provide a possibility for solubilization of water-soluble and lipid-soluble substances in one phase (Pilman et al., 1982).

The aim of this study was to investigate the isotropic medium chain mono- and diglyceride (MCMDG)/oil/water systems to prepare potential formulations without cosurfactant, and demonstrate whether such systems could solubilize both lipophilic and hydrophilic drugs. The solubilities of lipophilic drugs in the presence of hydrophilic drug in the formulation and vice versa were studied. The solubilities of both lipophilic and hydrophilic drugs in MCMDG/sesame oil/water and MCMDG/water systems were compared and the effects of oil on the solubilities of the hydrophilic and lipophilic drugs were studied.

2. Materials and methods

2.1. Materials

Sesame oil (SO), a long chain triglyceride was obtained from Bronson and Jacobs Pty Ltd. (Auckland). Sesame oil contains triglycerides of palmitic acid 8.5%, stearic acid 4.5%, oleic acid 47.4%, linoleic acid 39% and hence comprises 10–15% saturated fatty acid, and 85–90% unsaturated fatty acid. Benzyl benzoate (BB) was purchased from Sigma Chemical Company. Ethyl oleate (EQ) was obtained from Inoue Perfumery MFG Co. Ltd.

Capmul MCM (MCMDG) (Abitec, Columbus, OH) comprises medium chain mono- and diglycerides of caprylic and caproic acids and has the following fatty acid distribution: caproic (C 6:0) 3.2%, caprylic (C 8:0) 55%, capric (10:0) 30%, palmitic (C 16:0) <1%, free glycerol 2%. The HLB of Capmul MCM is 5–6. Capmul MCM is used as an emulsifier, solubiliser and nonionic surfactant (Constantinides et al., 1994).

Abamectin was purchased from Zhejiang Hisun Pharmaceutical, China. It is a lipophilic antiparasitic semi-synthetic drug of the macrocylic lactone group. Levamisole HCl obtained from Hanjiang Pharmaceutical Ltd., China is a highly water soluble widely used imidazothiazole anthelmintic.

2.2. Phase diagrams

For two-component systems, MCMDG (Capmul MCM) was mixed with various masses of water. For the three-component systems, the samples were prepared by mixing the oils (SO, BB or EO) with MCMDG prior to the addition of varying masses of water. The samples were vortexed and equilibrated for 24 h at 25 °C. The isotropic region was identified where clear and transparent formulations were obtained based on visual inspection of samples. For an initial identification of various phases within the entire phase diagram, 50–100 samples were prepared and once the isotropic phase was identified additional samples were prepared to determine boundary regions. The formulations were prepared by weighing all components (% w/w). For comparison of the different systems, the isotropic region of each was expressed as a percentage of the total area of the phase diagram. This was determined by cutting and weighing.

2.3. Polarized light microscopy

Samples were examined by polarizing light microscopy (Optiphot Nikon PFX microscope) equipped with camera to confirm absence of birefringence in isotropic samples.

2.4. Viscosity

Viscosity measurements were carried out at 25 °C using a Brookfield viscometer model DV-III with CP-42 cone and spindle calibrated with water. Rheocalc for Windows Software (used with the DV-III Rheometer) was run under Windows® 3.1 and provided full control of all DV-III Rheometer functions,

including the Brookfield Thermosel controller (Model 106 or HT-104) and water-bath controllers (Model 107 or HT-105).

2.5. Physical stability evaluation

The physical stability of formulations maintained at 25 °C was evaluated initially daily and later on a weekly basis. Stable systems were identified as those free of any physical change under visual inspection.

2.6. Solubility of hydrophilic and lipophilic drugs

Weighed amounts (500 mg) of abamectin and/or levamisole HCl were added to tubes containing 5 g of formulations. The systems were vortexed to ensure that the drug was fully dispersed in the vehicle. Tubes were incubated in a waterbath (25 °C) and shaken at 120 strokes per minute. After 48 h, tubes were centrifuged at 10,000 rpm (14,000 rcf) (Eppendorf Centrifuge 5804) for 10 min at 25 °C to sediment excess drug and aliquots (0.5 ml) were diluted with HPLC mobile phase prior to analyses.

2.7. HPLC analysis

The HPLC system consisted of a Shimadzu LC 6A pump and SPD-6A variable-wavelength UV absorbance detector (253 nm) (Shimazdu, Japan), a Rheodyne 7125 injector (Rheodyne Inc., California, USA), 20 μl injection loop and a Hitachi D-2500 integrator (Hitachi, Tokyo, Japan). A Zorbax ODS column, 7 μm particle size, 4.6 i.d. × 250 mm (Phenomenex, Torrance, CA, USA) was used.

The mobile phase was developed to determine levamisole and abamectin simultaneously in formulations. The mobile phase consisted of acetonitrile, water, and ammonia 1.0N solution (80:20:0.1) and the flow rate was 2 ml/min. The HPLC system was operated at ambient temperature. Retention times of levamisole and abamectin were 2.46 and 5.80 min, respectively. The maximum interday and intraday coefficients of variation were 1 and 0.7% at 13.5 μg/ml for levamisole, and 5.8 and 2.2% at 0.5 μg/ml for abamectin, respectively. Accuracies were 98.9 ± 5.2% and 96.2 ± 3.1% (mean ± S.D., $n = 14$) for levamisole and abamectin, respectively at concentrations of 27.3 μg/ml of levamisole and 1 μg/ml of abamectin.

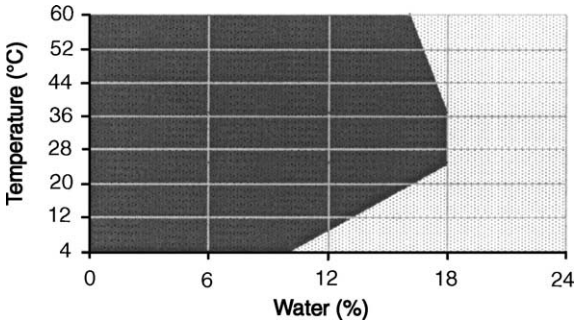

Fig. 1. Phase diagram of MCMDG (Capmul MCM)/water system: (■) isotropic region; (▒) two phase region.

2.8. Statistical analysis

The data were evaluated for statistically significant differences by a balanced analysis of variance (ANOVA) using Minitab Release 12.1.

3. Results

3.1. Phase diagrams

The two-component systems (MCMDG/water), accommodated 10% (w/w) water at 4 °C and the isotropic region increased with increasing temperature up to 37 °C (Fig. 1). In the three-component systems, although a cosurfactant (such as Tween 80) was not used, a maximum of 18 % water was incorporated at 25 °C (Fig. 2). The ternary phase diagrams showed that the isotropic region increased with increasing percentage of MCMDG (Fig. 2). Formulations have been observed for more than 2.5 years and are still clear.

The system containing EO had a slightly larger isotropic area compared with that of other oily vehicles, the areas being 10.4, 12.8 and 14.5% for MCMDO/BB/water, MCMDG/SO/water and MCMDG/EO/water, respectively at 25 °C. Two-component MCMDG/BB or SO or EO mixtures, represented on the axis between oils and MCMDG, were miscible in all proportions (Fig. 2).

3.2. Viscosity of the systems

All formulations exhibited Newtonion behaviour. The viscosity of MCMDG/water systems reduced

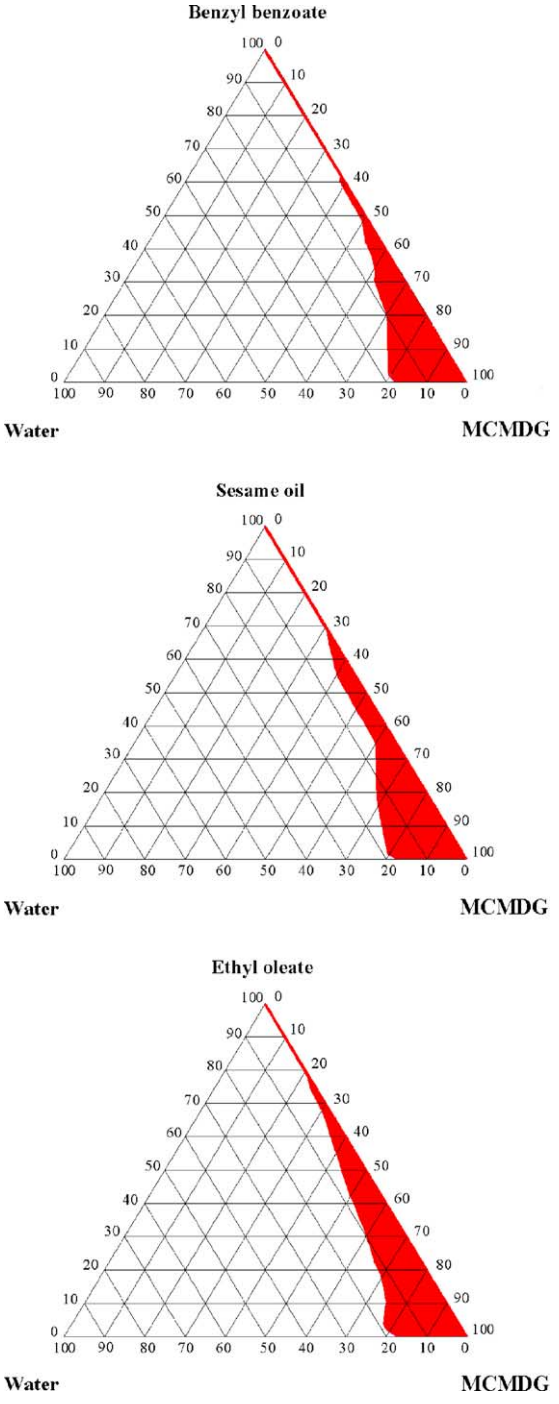

Fig. 2. Ternary phase diagrams showing the isotropic phase in systems comprising MCMDG and SO or BB or EO in the presence of water at 25 °C. The clear, isotropic phase is represented by the shaded region.

with increasing water level (Fig. 3A). The viscosity of the isotropic systems having the same ratio of MCMDG and oil did not change significantly with increasing water content (Fig. 3B). Increasing the MCMDG content increased the viscosity of the systems with a constant ratio of water to oil (Fig. 3C). MCMDG/EO/water systems exhibited the lowest viscosities. These systems with low viscosities would be suitable for subcutaneous or intramuscular injections using standard gauge needles.

3.3. Solubility of hydrophilic and lipophilic drugs in the systems

Solubilities of levamisole HCl or abamectin alone and solubilities of a mixture of both drugs were evaluated in MCMDG/SO/water and MCMDG/water formulations (Table 1). In the text below, "No SO" refers to formulations without sesame oil. "SO" refers to formulations containing sesame oil. "Mixture" refers to a combination of levamisole HCl and abamectin. "Alone" represents only levamisole HCl or abamectin alone in formulations (Table 1).

3.3.1. Solubility of levamisole HCl

As expected, the solubility of levamisole HCI was higher in formulations with higher water content (Table 1). However, the situation was more complex than this. Balanced ANOVA showed highly significant ($P < 0.001$) two-factor interactions (No SO/SO*formulation and No SO/SO*alone/mixture). The three factor interaction (No SO/SO*formulation* alone/mixture) was marginally significant ($P \approx 0.0l$) and is not considered further. The two-factor interaction (No SO/SO*alone/mixture) indicates that SO increased the solubility of levamisole HCl in levamisole alone to a greater extent (5 mg/ml) than in the levamisole HCl abamectin mixture case (2 mg/ml) (Fig. 4A). The No SO/SO*formulation interaction indicates that SO increased the solubility of levamisole HCl in Formulations 4 and 5 but had no effect in Formulations 1–3 (Fig. 4B). The two-factor interaction formulation*alone/mixture indicates that the solubility of levamisole HCl in formulations with a high water content (e.g. Formulations 4 and 5) was lower in the presence of abamectin but abamectin had no effect in formula-

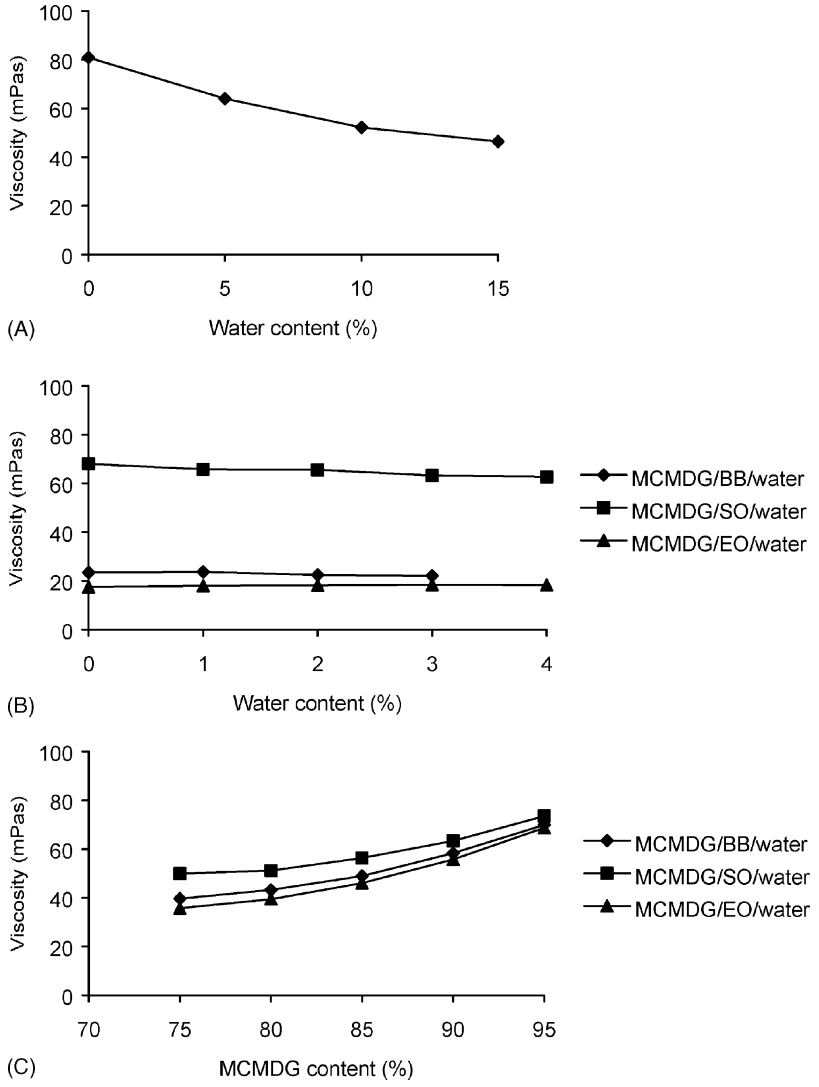

Fig. 3. Effect of water content and MCMDG content on viscosity of the isotropic MCMDG water and MCMDG/oil/water formulations (% w/w) at 25 °C. (A) MCMDG/water system, (B and C) MCMDG/oil/water.

tions with the lower water content (Formulations 1–3) (Fig. 4C).

3.3.2. Solubility of abamectin

As expected, the solubility of the lipophilic drug, abamectin decreased, as water content of formulations increased. However, as noted for levamisole HCI, the situation was more complex. Balanced ANOVA showed highly significant two-factor interactions ($P < 0.001$) for No SO/SO*formulation, and $P < 0.006$ for No SO/SO*alone/mixture). The two-factor interaction No SO/SO*alone/mixture indicates that the solubility of abamectin was affected by levamisole HCl in the absence of SO but levamisole HCl had no affect in the presence of SO (Fig. 5A). The two-factor interaction No SO/SO and alone/mixture indicates that although SO increased the solubility of abamectin in all formulations its effect was greater in formulations with a lower water content (Fig. 5B).

Table 1
Solubilities (mg/ml) of levamisole HCl and abamectin in formulations of MCMDG/water and MCMDG/SO/water (mean ± S.D., $n = 3$)

Formulations	Levamisole HCl[a]	Abamectin[a]	Levamisole HCl[b]	Abamectin[c]
MCMDG/water (w/w)				
97.5/2.5	32.9 ± 1.7	54.4 ± 1.1	31.0 ± 0.9	57.7 ± 4.1
95/5	38.5 ± 0.9	46.8 ± 1.3	38.7 ± 2.8	49.1 ± 2.1
92.5/7.5	46.4 ± 1.0	47.7 ± 1.4	44.4 ± 2.7	48.2 ± 1.0
90/10	53.0 ± 1.9	42.0 ± 3.2	48.1 ± 0.9	47.6 ± 3.8
87.5/12.5	59.0 ± 2.6	43.3 ± 2.1	55.2 ± 1.1	46.6 ± 2.7
MCMDG/SO/water (w/w/w)				
95/2.5/2.5	33.7 ± 0.4	68.9 ± 3.5	31.4 ± 0.7	66.0 ± 0.0
90/5/5	42.6 ± 1.3	63.0 ± 2.3	38.5 ± 1.0	59.9 ± 2.0
85/7.5/7.5	48.2 ± 1.4	55.0 ± 1.4	45.3 ± 2.3	57.2 ± 3.3
80/10/10	59.9 ± 1.1	54.1 ± 1.4	52.2 ± 0.7	52.6 ± 1.4
75/12.5/12.5	71.9 ± 1.5	47.3 ± 1.7	59.0 ± 0.9	49.5 ± 2.7

[a] Levamisole HCl or abamectin alone.
[b] Levamisole HCl in the presence of excess abamectin.
[c] Abamectin in the presence of excess levamisole HCL.

4. Discussion

4.1. Two-component systems

The isotropic regions of two-component MCMDG/water systems were examined. The area of the isotropic regions increased with increasing water content to a limit, and with increasing temperature up to 37 °C (Fig. 1). Similarly, Engstrom (1990) and Engstrom et al. (1992) reported that an isotropic phase solution was formed at 37 °C when a small amount of water was added to long chain monoglycerides (glyceryl monooleate) and this phase was defined as a reversed micellar system. The increased miscibility in these non-ionic surfactant systems on temperature increases from 4 to 37 °C is due to increasing micellar size as the cloud point is approached (Florence and Attwood, 1988). It has been suggested that at the higher temperature, interaction between nonionic surfactant polar groups is more favoured than the nonionic surfactant polar group and water interaction and this results in increased aggregation numbers (Nilsson et al., 1983).

4.2. Three-component systems

In this study, the isotropic phase obtained by mixing oils, amphiphilic lipid (MCMDG) and water (Fig. 2) was similar to that described by Pilman et al. (1982) who constructed the phase diagram of the ternary system of sunflower oil monoglycerides/soybean oil/water at 30 °C. For use as vehicles for hydrophilic drugs, it is of interest to use an L2-phase with as high a water content as possible. Pilman et al. (1982) found a blend of sunflower oil monoglyceride/soybean oil of ratio 7:3 (w/w) could incorporate water up to 21% (w/w) at 30 °C. In the present study, it was found that the maximum water content was 18% in the L2-phase region at 25 °C and the system yielded a clear, transparent solution which has remained stable for more 2 years. Based on the X-ray data, Engstrom (1990) reported that the L2-phase in a system of water, triglyceride oil (soybean) and amphiphilic lipid (sunflower oil monoglyceride) is an isotropic solution with reversed micelles. In this case, the maximum level of water in the system was approximately 14% (w/w) (Engstrom, 1990). In addition, the reversed micellar phase in the mono-olein/oil/water system has been reported as a microemulsion, since it is an isotropic liquid system containing oil, water and surfactant (Engstrom, 1995).

4.3. Viscosity of the systems

Viscosity characteristics of vehicles are important determinants of functional properties such as injectability. In this study, the viscosity of L2-phase formulations showed Newtonian flow. The viscosity of the L2-phase of MCMDG/oils/water systems having the same water weight fraction increased

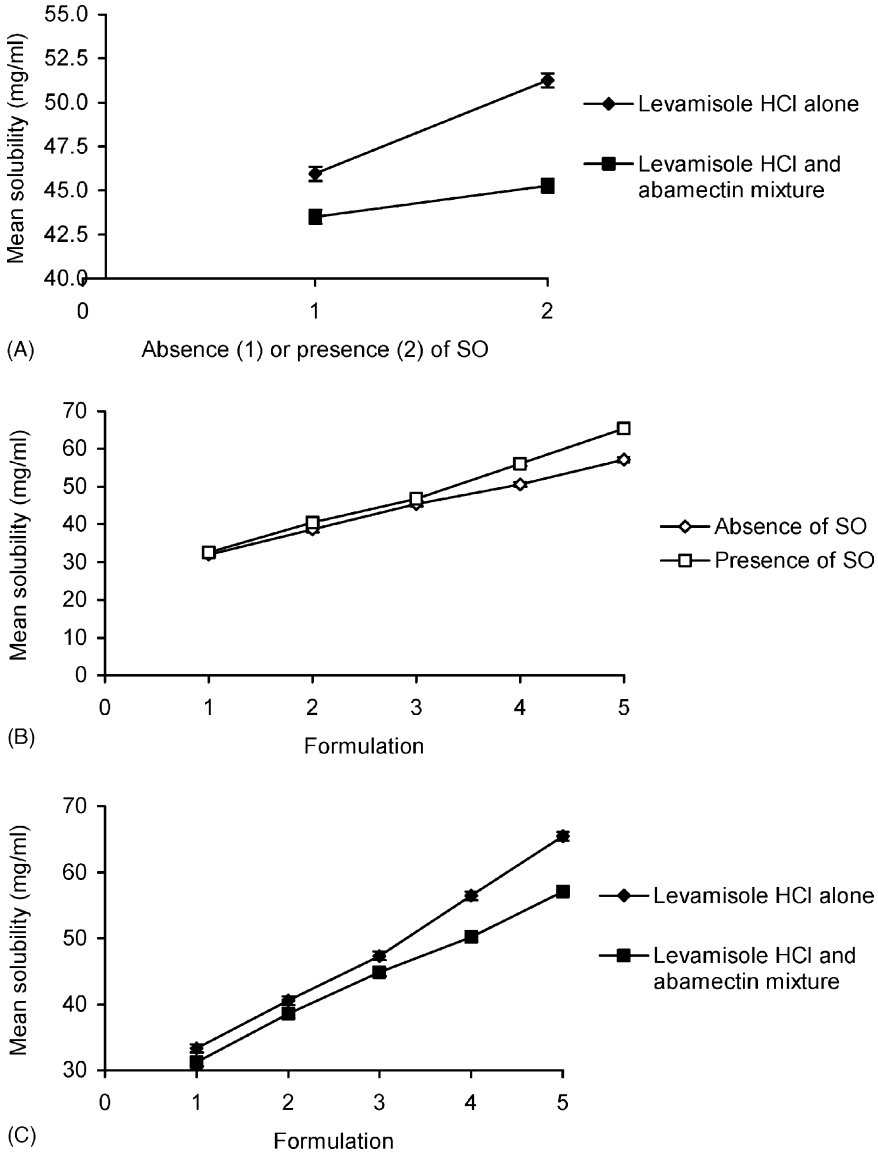

Fig. 4. Interaction plots showing mean solubilities of levamisole HCl. (A) Effect of SO on the mean solubility of levamisole HCl alone and in the presence of abamectin; (B) effect of SO on the mean solubility of levamisole HCl in various formulations; and (C) effect of abamectin on the mean solubility of levamisole HCl in various formulations. Bars show the pooled standard errors from ANOVA.

with increasing concentration of MCMDG in the present study (Fig. 3C). Similarly, Baker et al. (1984) reported that the viscosity of the isotropic systems (sodium alkyl benzene sulfonate as a surfactant and hexanol/xylene/water) having the same water weight fraction increased with increasing concentration of surfactant. The low viscosity formulations could be injected easily. Syringeability of oil formulations which is an important property for use in practice has been shown to be inversely related to the vehicle viscosity (Dexter and Shott, 1979).

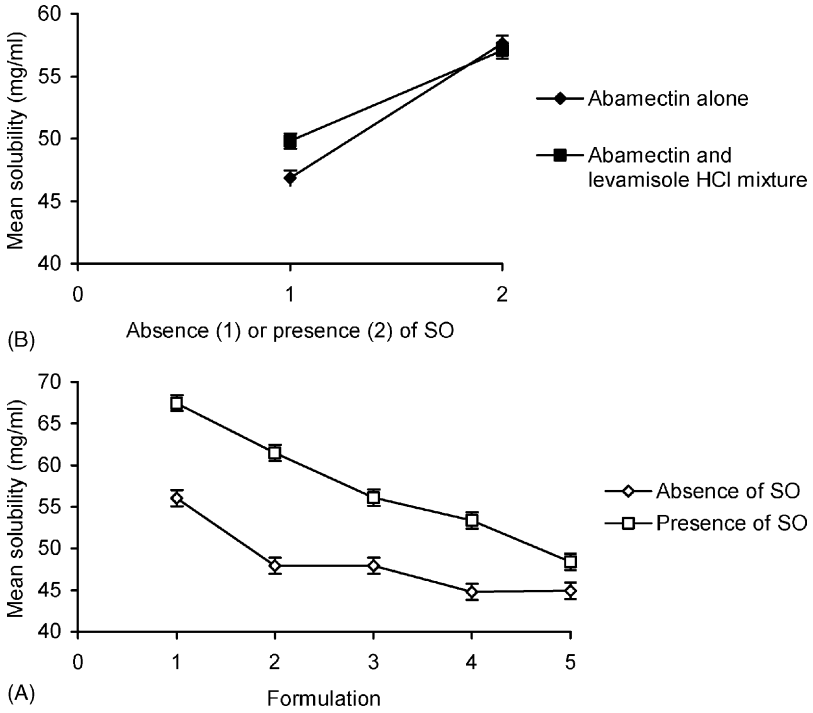

Fig. 5. Interaction plots showing mean solubilities of abamectin. (A) Effect of SO on the mean solubility of abamectin alone and in the presence of levamisole HCl and (B) effect of SO on the mean solubility of abamectin in various formulations. Bars show the pooled standard errors from ANOVA.

4.4. Solubility of hydrophilic and lipophilic drugs

MCMDG/SO/water systems exhibited significant increase in solubilization of both levamisole HCl and abamectin over equivalent MCMDG/water formulations. For example, the increases in solubility of levamisole HCl and abamectin alone in MCMDG/SO/water was 21.9 and 9.6%, respectively greater in the presence of SO at the maximum tested water level (12.5%), than in the equivalent MCMDG/water systems (Table 1). For potassium oleate/l-hexanol/benzene/water isotropic solution (water-in-oil (w/o) microemulsions), Hansen (1974) reported that there were low mobility water molecules associated with the surfactant polar groups at the aqueous interface in addition to free water, which was similar to ordinary liquid water. Kumar and Balasubramanian (1980) indicated that the hydration of surfactant increased slowly as water was added to an isotropic solution (w/o microemulsion) comprising Triton X-100, 1-hexanol, cyclohexane and water. But they suggested that there was a limiting ratio of one water molecule bound per two oxyethylene units in this system. Consequently, free and bound water could have an important role in solubilization of hydrophilic drugs. Malcolmson et al. (1998) reported that higher solubilization of the lipophilic drug testosterone propionate in a non-ionic isotropic system (non-ionic oil-in-water microemulsions) than the equivalent micellar solution. They suggested that this was related to the solubility of the drug in the dispersed phase. The oil influenced the system by dehydrating the polyoxyethylene region in the system, and it is this region which is thought to be one of the main sites of solubilization of lipophilic drugs.

The solubility of abamectin in SO was found to be only 1.7 ± 0.1 mg/ml (mean $\pm$ S.D., $n = 3$) at 25 °C. However, the solubilites of abamectin in the MCMDG/water system at 2.5% water was 54.4 mg/ml. This differs from the solubility of 68.9 mg/ml in the equivalent MCMDG/SO/water systems. This difference of 14 mg/ml far exceeds the additive increase

expected based on the solubility in the SO. This situation was similar in systems containing other percentages of water. Similarly, Malcolmson et al. (1998) indicated that there was no strong relationship between the solubility of the lipophilic drug in oil and the bulk oil in the non-ionic oil-in-water microemulsions and micellar solutions. This suggests that the low level of SO changes the nature of the system thereby affecting solubility.

The solubility of levamisole HCl increased with increasing water levels (from 2.5 to 12.5%) but the increase was not proportional to water added to the systems. Abamectin solubility was reduced with increasing water content (Table 1). This effect has been found previously for other drugs (Skodvin et al., 1993). They reported that the solubility of chloramphenicol, a lipophilic drug decreased when water content was increased. Also, they found that the solubility of pilocarpine hydrochloride, a hydrophilic drug did not increase in proportion to the increasing water level in the isotropic sodium octanoate/octanoic acid/water systems (w/o microemulsions). It is apparent that solubility in these systems is probably dependent on the colloidal structures, which depend on the components present. Also the presence of one drug may thereby affect the solubility of another by altering the colloidal structures.

The solubilization of levamisole HCl was affected by abamectin in presence or absence of SO and abamectin solubility was affected by levamisole HCl in absence of SO. Skodvin et al. (1993) reported that the addition of pilocarpine hydrochloride and chloramphenicol modified the packing conditions in AOT/octanoic acid/water and sodium octanoate/octanoic acid/water systems. Therefore, they concluded that the hydrophilic drug interacted with the colloidal structures and affected the solubility of the lipophilic drug located in the interfacial region. It is suggested that levamisole HCl and abamectin modify the colloidal structure in the present system and so affect each others solubility.Usual dosing levels of levamisole RCI and abamectin are 7.5 mg/kg and 200 μg/kg, respectively in animals. Therefore, based on solubilization data in this experiment either system (MCMDG/water or MCMDG/SO/water) could be used for preparation of solution dose forms containing usual dosages of these drugs.

5. Conclusions

Mixtures of amphiphilic lipid (MCMDG) and oil in the presence of water produced isotropic solutions without the use of cosurfactants. The solubility of levamisole HCl was higher in the isotropic MCMDG/SO/water systems than in equivalent MCMDG/water systems. The solubility of the hydrophilic drug was lower in some formulations (Formulations 4 and 5) in the presence of lipophilic drug. The solubility of the hydrophilic drug did not increase in proportion to the increasing water level in systems. Solubilization of lipophilic drug affected the hydrophilic drug solubility in the presence or absence of SO and lipophilic drug solubility was affected by hydrophilic drug in the absence of SO. Based on solubilization of levamisole HCl and abamectin, both drugs can be formulated at usual concentrations in these isotropic systems and such systems could be of interest for pharmaceutical injection.

References

Baker, R.C., Florence, A.T., Ottewill, R.H., Tadros, T.F., 1984. Investigations into the formation and characterization of microemulsions. 2. Light scattering conductivity and viscosity studies of microemulsions. J. Colloid Interface Sci. 100, 332–349.

Chang, C.M., Bodmeier, R., 1998. Low viscosity monoglyceride-based drug delivery systems transforming into a highly viscous cubic phase. Int. J. Pharm. 173, 51–60.

Constantinides, P.P., Scalart, J.P., Lancaster, C., Marcello, J., Marks, G., Ellens, H., Smith, P.L., 1994. Formulation and intestinal absorption enhancement evaluation of water-in-oil microemulsions incorporating medium-chain glycerides. Pharm. Res. 11, 1385–1390.

Dexter, M.B., Shott, M.J., 1979. The evaluation of the force to expel oily injection vehicles from syringes. J. Pharm. Pharmacol. 31, 497–500.

Ekwall, P., 1975. In: Brown, G.H. (Ed.), Advances in Liquid Crystals, vol. 1. Academic Press, New York, pp. 1–142.

Engstrom, L., 1990. Aggregation and structural changes in the L2-phase in the system water/soybean oil/sunflower oil monoglycerides. J. Disp. Sci. Techn. 11, 479–489.

Engstrom, S., Lindahl, L., Wallin, R., Engblom, J., 1992. A study of polar lipid drug carrier systems undergoing a thermoreversible lamellar-to-cubic phase transition. Int. J. Pharm. 86, 137–145.

Engstrom, S., 1995. Law and order in lipid-water systems- from drug delivery to the barrier properties of skin. B.T. Gattefosse 88, 27–35.

Florence, A.T., Attwood, D., 1988. Physicochemical Principles of Pharmacy, 2nd ed. MacMillan, London, pp. 221–224.

Friberg, S., Mandell, L., 1970. Phase equilibria and their influence on the properties of emulsions. J. Am. Oil Chem. Soc. 47, 149–152.

Hansen, J.R., 1974. High-resolution and nuclear magnetic resonance studies of microemulsions. J. Phys. Chem. 78, 261–265.

Kumar, C., Balasubramanian, D., 1980. Structural features of water-in-oil microemulsions. J. Phys. Chem. 84, 1895–1899.

Lindstrom, M., Ljusberg-Wahren, H., Larsson, K., Borgstrom, B., 1981. Aqueous lipid phases of relevance to intestinal fat digestion and absorption. Lipids 16, 749–754.

Lutton, E.S., 1965. Phase behavior of aqueous systems of monoglycerides. J. Am. Oil Chem. Soc. 42, 1068–1070.

Malcolmson, C., Satra, C., Kantaria, S., Sidhu, A., Lawrence, M.J., 1998. Effect of oil on the level of solubilization of testosterone propionate into nonionic oil-in-water microemulsions. J. Pharm. Sci. 87, 109–116.

Nilsson, P.G., Wennerstrom, H., Lindman, B., 1983. Structure of micellar solutions of nonionic surfactants. Nuclear magnetic resonance self-diffusion and proton relaxation studies of poly(ethylene oxide) alkyl ethers. J. Phys. Chem. 87, 1377–1385.

Pilman, E., Larsson, K., Tornberg, E., 1982. Interfacial tension between and inverse micellar phase of lipid components and aqueous protein solutions. J. Disp. Sci. Techn. 3, 335–349.

Skodvin, T., Sjoblom, J., Saeten, J.O., 1993. Solubilization of solubilization of drugs in microemulsions as studied by dielectric spectroscopy. J. Colloid Interface Sci. 155, 392–401.

Thevenin, M.A., Grossiord, J.L., Poelman, M.C., 1996. Sucrose esters/cosurfactant microemulsion systems for transdermal delivery: assessment of bicontinuous structures. Int. J. Pharm. 13, 177–186.

Wyatt, D.M., Dorschel, D., 1992. A cubic-phase delivery system composed of glyceryl monooleate and water for sustained release of water-soluble drugs, Pharm. Tech. 116–130.