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Note

Exploring the potential of *N*-methyl pyrrolidone as a cosurfactant in the microemulsion systems

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Abstract

The effect of *N*-methyl pyrrolidone (NMP) on the phase behavior of two ternary systems, viz. PEG-35-castor oil (Cremophore®EL)–glyceryl caprylate/caprate (Capmul® MCM)–water and PEG-35-castor oil (Cremophore®EL)–isopropyl myristate–water was studied. The study indicated that NMP has considerable influence on the phase behavior of both the systems. NMP increased the area of microemulsion formation in both the systems. Moreover, it also led to reduction/disappearance in the gelling region of the Cremophore®EL–isopropyl myristate–water system. These observations allowed us to conclude that NMP can be considered as a cosurfactant for the development of biocompatible microemulsions.

Keywords: *N*-Methyl pyrrolidone; Microemulsions; Cosurfactant; Phase behavior; Microemulsion region; Gelling region

1. Introduction

Microemulsions (ME) are thermodynamically stable, transparent, isotropic, low-viscosity colloidal dispersions consisting of microdomains of oil and/or water stabilized by an interfacial film of alternating surfactant and cosurfactant molecules. They include swollen micellar (oil-in-water, O/W), reverse micellar (water-in-oil, W/O) and bicontinuous structures (Tenjarla, 1999). ME have received great attention as colloidal drug carriers during the past few years due to their versatility and attractive advantages such as high drug solubilization, long shelf life and ease of manufacture and scale-up by their virtue of spontaneous formation (Lawrence and Rees, 2000). Their applications in drug delivery are continuously being explored for the per-oral, ocular, parenteral, nasal and dermal routes (Lawrence and Rees, 2000; Kreilgard, 2002). However, one of the commonly encountered disadvantage of ME is the requirement of high concentration of surfactant for ME formation which may lead to issue of biocompatibility and tissue toxicity. One way to reduce the surfactant concentration required for ME formation is to incorporate an appropriate cosurfactant (Prince, 1977) that can hasten ME formation by their well-known interfacial or bulk effects. Moreover, cosurfactant, by its several interfacial effects, can profoundly influence the effect on the phase behavior and/or area of microemulsion existence of the system under investigation. Literature indicates that by and large, short chain amphiphiles like low molecular weight alcohols, alkanoic acids, alkanediols, alkyl amines, polyethylene glycol and polyethylene glycol alkyl ether have been explored for their potential to act as cosurfactants. Of these, medium chain alcohols and alkane diols have been extensively studied (Lawrence and Rees, 2000) and amongst them butanol and hexanediol were found to be the most effective (Alany et al., 2000). But, both these as well as the other short chain alcohols and alkane diols are not preferred in pharmaceutical systems. Hence, identification of pharmaceutically acceptable agents that can function as good cosurfactants and have good dermal, oral or parenteral acceptability is an ongoing process.

N-Methyl-2-pyrrolidone (NMP) is a short chain amphiphile that has been used as a permeation enhancer in transdermal formulations for a long time (Sasaki et al., 1988; Yoneto et al., 1995). Interestingly, it has been shown to improve the transdermal flux of both hydrophilic and hydrophobic drugs (Lee et al., 2005). It can also be used in parenteral formulations in certain cases (Strickley, 2004). However, to our knowledge, there are no

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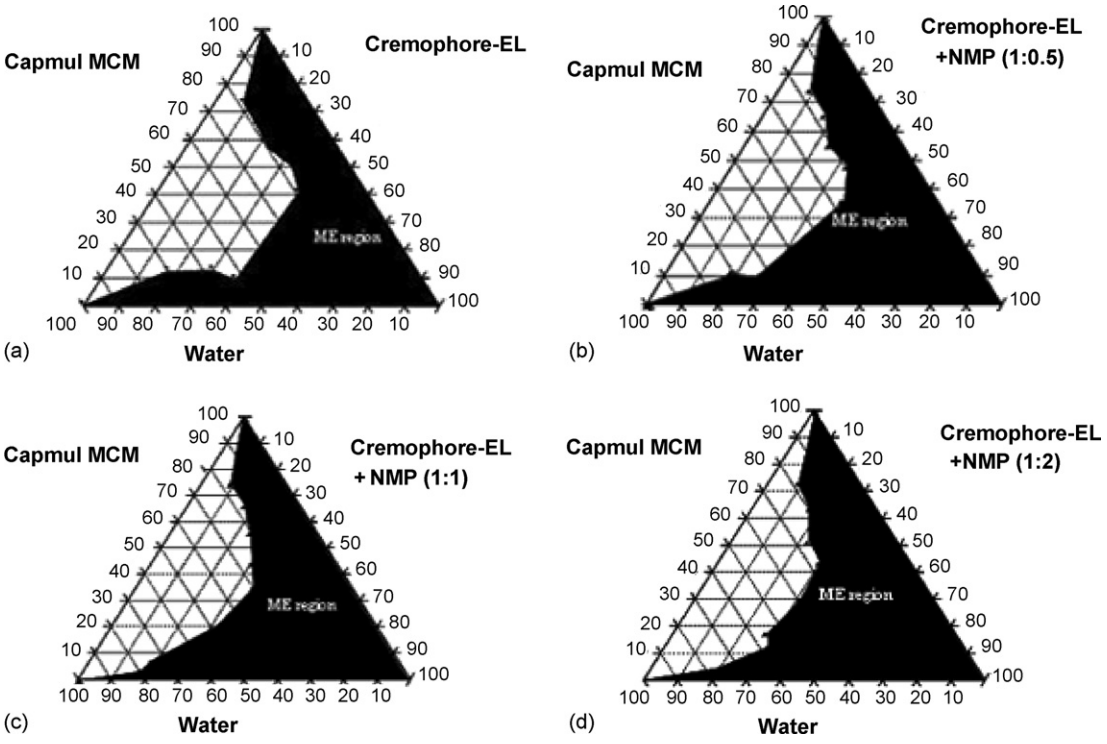

Fig. 1. Phase behavior of Capmul®MCM:Cremophore® EL:water system in the absence of NMP (a) or in the presence of NMP at various K_m values (ratio of Cremophore® EL:NMP) 2 (b), 1 (c) and 0.5 (d).

reports on use of NMP as a cosurfactant in formulation of ME. Hence, in the present investigation, we have tried to evaluate the potential of NMP to act as a cosurfactant for yielding completely biocompatible ME mainly for dermal/transdermal delivery.

The potential of NMP to act as a cosurfactant was evaluated for the following systems.

1. Glyceryl caprylate/caprate (Capmul® MCM):PEG-35-castor oil (Cremophore® EL):water.
2. Isopropyl myristate (IPM):Cremophore® EL:water.

Cremophore® EL, Capmul® MCM and IPM were selected for the investigation mainly due to their biocompatibility and excellent acceptability for dermal, oral or parenteral applications. The effect of NMP on the phase behavior of aforementioned systems was studied by mixing NMP with Cremophore® EL in various ratios (w/w). The ratio of Cremophore® EL to NMP was regarded as K_m. The K_m values in the investigation were varied from 0 to 2 for both the systems.

The pseudo-ternary phase diagrams of oil (Capmul® MCM or IPM), Cremophore® EL:NMP and water were plotted using water titration method. The phase behavior of both the systems was studied at K_m (ratio of Cremophore® EL to NMP) values of 0, 0.5, 1 and 2. Briefly, mixtures of the oil (Capmul® MCM or IPM) with surfactant and cosurfactant were prepared at ratios (w/w) of 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, 0:10 in different vials. A small amount of water in 5% (w/w) increment was added into the vials. Following each water addition, the mixtures in vials were vortexed for 2–3 min and allowed to equilibrate. The resulting mixtures were evaluated by visual observation and by polarizing microscope. In the phase diagram, ME was the region of monophasic, clear and isotropic solutions that might also contain micellar solutions. Gels were claimed for those mixtures that did not show a change in the meniscus when tilted to an angle of 90°. All the experiments were performed at 25 °C.

Fig. 1(a) shows the ternary phase diagram of Capmul®MCM:Cremophore® EL:water without cosurfactant (NMP). Fig. 1(b–d) shows effect of cosurfactant on the phase behavior of the system. It is evident that the addition of cosurfactant significantly increased the area of ME formation at all the K_m values greater than 0 (Table 1). Moreover, the area of microemulsion existence was highest for $K_m = 0.5$ as compared to the other K_m values but the difference between %ME area was not very significant.

Fig. 2(a) shows the pseudo-ternary phase diagram of IPM:Cremophore®EL:water without cosurfactant (NMP). Unlike earlier system, this system, to a considerable extent, showed the presence of gelling region. Interestingly, it is evident from Fig. 2(b–d) that NMP is able to reduce the gelling region

Table 1
Effect of NMP on area of ME formation of Capmul®MCM:Cremophore® EL:water system

Figure	%Non-ME area	%ME area	K_m value
Fig. 1a	43	57	0
Fig. 1b	37	63	2
Fig. 1c	36	64	1
Fig. 1d	34	66	0.5

%ME area: area of ME formation.

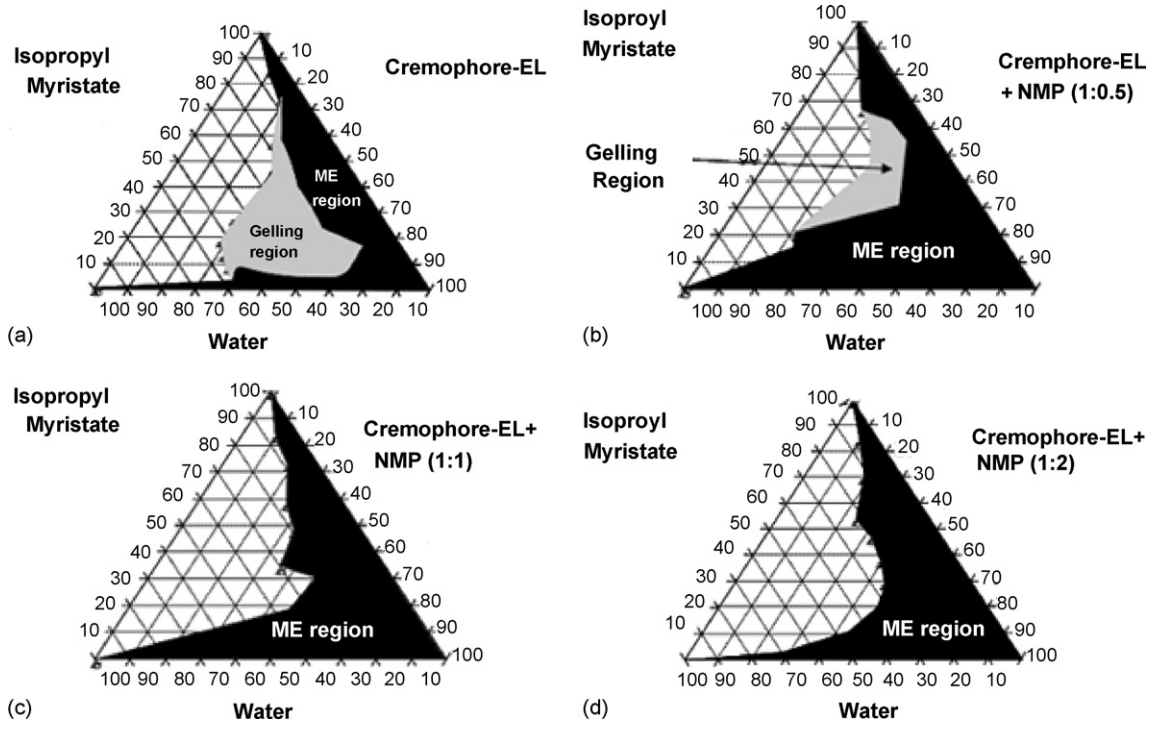

Fig. 2. Phase behavior of IPM:Cremophore® EL:water system in the absence of NMP (a) or in the presence of NMP at various K_m values (ratio of Cremophore® EL:NMP) 2 (b), 1 (c) and 0.5 (d).

of the system resulting in the increase in the area of microemulsion existence. The gelling region disappeared at $K_m = 1$ and 0.5 and there was clear cut increase in the area of ME formation (Table 2).

The reduction in the gelling region may be due the increased fluidity at the interface caused by NMP resulting in increase in the entropy of the system. Moreover, due to its amphiphilic nature, like short chain alcohols, it might be increasing the solubility of the aqueous and oily phases due to its partitioning between these phases thereby altering the relative hydro/lipophilicity. This observation to some extent, confirms the cosurfactant like activity of the NMP.

K_m value did influence the area of ME formation confirming the known fact that the ratio of surfactant to cosurfactant has influence on the phase behavior of the system (Gao et al., 1998; Kim et al., 2000; Debuigne et al., 2001; Kang et al., 2004; Li et al., 2004). The area of ME formation was highest at $K_m = 1$. It has also been observed that the area of ME formation is maximum only at a particular K_m value which is unique for each quaternary system (Gao et al., 1998; Kim et al., 2000; Debuigne et al., 2001; Kang et al., 2004; Li et al., 2004). Our observations are in line with these observations. The area of ME formation was found to be highest at $K_m = 0.5$ for Capmul® MCM:Cremophore® EL:NMP:water system and at $K_m = 1$ for IPM:Cremophore® EL:NMP:water system. The study also revealed that both O/W and W/O microemulsions can be achieved in case of both the systems containing NMP as cosurfactant. Moreover, physicochemical properties of NMP were quite in line with most of the physicochemical characteristics of a classical cosurfactant [C No. 4–6, C (%) 60–65, O (%) 20–30, log P 0.2–0.9 and log 1/S close to zero] as stated by Alany et al. (2000). To our knowledge, this is the first report stating the use of NMP as a cosurfactant for producing biocompatible microemulsions. The need of hour is to explore the potential of these systems for various routes of delivery with special focus on dermal and transdermal delivery.

Table 2
Effect of NMP on area of ME formation of IPM:Cremophore® EL:water system

Figure	%Non-ME area	%Gelling area	%ME area	K_m value
Fig. 2a	44	19	37	0
Fig. 2b	32	9	59	2
Fig. 2c	46	0	64	1
Fig. 2d	52	0	48	0.5

%ME area: area of ME formation.

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References

Alany, R.G., Rades, T., Agatonovic-Kustrin, S., Davies, N.M., Tucker, I.G., 2000. Effects of alcohols and diols on the phase behaviour of quaternary systems. Int. J. Pharm. 196, 141–145.

Debuigne, F., Cuisenaire, J., Jeunieau, L., Masereel, B., Nagy, J.B., 2001. Synthesis of nimesulide nanoparticles in the microemulsion Epikuron/Isopropyl Myristate/Water/n-Butanol (or Isopropanol). J. Colloid Interface Sci. 243, 90–101.

Gao, Z.G., Choi, H.G., Shin, H.J., Park, K.M., Lim, S.J., Hwang, K.J., Kim, C.K., 1998. Physicochemical characterization and evaluation of a microemulsion system for oral delivery of cyclosporine A. Int. J. Pharm. 161, 75–86.

Kang, B.K., Lee, J.S., Chon, S.K., Jeong, S.Y., Yuk, S.H., Khang, G., Lee, H.B., Cho, S.H., 2004. Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. Int. J. Pharm. 274, 65–73.

Kim, H.J., Yoon, K.A., Hahn, M., Park, E.S., Chi, S.C., 2000. Preparation and in vitro evaluation of self-microemulsifying drug delivery systems containing idebenone. Drug Dev. Ind. Pharm. 26, 523–529.

Kreilgard, M., 2002. Influence of microemulsions on cutaneous drug delivery. Adv. Drug Deliv. Rev. 54, S77–S98.

Lawrence, M.J., Rees, G.D., 2000. Microemulsion-based media as novel drug delivery systems. Adv. Drug Deliv. Rev. 45, 89–121.

Lee, P.J., Langer, R., Shastri, V.P., 2005. Role of N-methyl pyrrolidone in the enhancement of aqueous phase transdermal transport. J. Pharm. Sci. 94, 912–917.

Li, P., Ghosh, A., Wagnera, R.F., Krill, S., Joshi, Y., Serajuddin, A.T.M., 2004. Effect of combined use of nonionic surfactant on formation of oil-in-water microemulsions. Int. J. Pharm. 288, 27–34.

Prince, L.M., 1977. Schulman's microemulsions. In: Prince, L.M. (Ed.), Microemulsions Theory and Practice. Academic Press, New York, pp. 1–20.

Sasaki, H., Kojima, M., Mori, Y., Nakamura, J., Shibasaki, J., 1988. Enhancing effect of pyrrolidone derivatives on transdermal drug delivery I. Int. J. Pharm. 44, 15–24.

Strickley, R.G., 2004. Solubilizing excipients in oral and injectable formulations. Pharm. Res. 21, 201–230.

Tenjarla, S., 1999. Microemulsions: an overview and pharmaceutical applications. Crit. Rev. Ther. Drug Carrier Syst. 16, 461–521.

Yoneto, K., Li, S.K., Ghanem, A.H., Crommelin, D.J., Higuchi, W.I., 1995. A mechanistic study of the effects of the 1-alkyl-2-pyrrolidones on bilayer permeability of stratum corneum lipid liposomes: a comparison with hairless mouse skin studies. J. Pharm. Sci. 84, 853–860.