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Research paper

Comparison of impact of the different hydrophilic carriers on the properties of piperazine-containing drug

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Abstract

The objective of this study was to determine the impact of a series of nonionic surfactants on the solubility of piperazine-containing drug (meclizine, MZ) in comparison to that of natural cyclodextrins (α-CD and β-CD) and dimethyl-β-cyclodextrin (DM-β-CD). The solubility of the drug was studied in either CDs solutions or nonionic surfactant solutions. Three classes of nonionic surfactants were used namely; polyoxyethylene (POE) sorbitan fatty acid esters (polysorbates), POE fatty acid esters (Myrjs) and polyethylene oxide (PEO) fatty alcohol ethers (Brijs and Eumulgins). The solubility of MZ was increased linearly with the increasing surfactant concentration, indicating that micellar solubilization follows the partition model. It was found that the longer the hydrocarbon chain in a homologous series, the more efficient is the solubilizing power of surfactant. For example, polysorbate 80 (Tween-80) is a more efficient solubilizer than polysorbate 20 (Tween-20), indicating that the drug was incorporated in the core of micelle more than the capsular region of the micelle. On the other hand, in case of POE fatty acid esters, the solubilizing power increased with decreasing polyoxyethylene chain as Myrj 53 was more efficient than Myrj 59. In class of PEO fatty alcohol ethers, the shorter the hydrophilic chain and longer lipophilic chain, the more efficient was the solubilizing capacity. Thus, Brij 58 was more efficient solubilizer than Brij 35 and Eumulgin C1000 was more active than Eumulgin C1500. Comparatively, Eumulgin C1000 had the highest solubilizing power for MZ among the studied PEO fatty alcohol ethers and other groups of surfactants. The solubility action of surfactants toward MZ was increased by raising the temperature of the surfactant solutions from 30 to 45°C. Hydrophilic macromolecules (PEG 1000 and PEG 6000) or cosolvents (glycerol and propylene glycol) have a very slight effect on the solubility of MZ and confirm the predominance of hydrophobic interaction between the drug and nonionic surfactants. A_L-type phase solubility diagrams were obtained for the drug with α-, β- and DM-β-CDs showing that the solubility of MZ was enhanced through inclusion complexation. Comparatively, DM-β-CD had the highest solubilizing efficiency for the drug among the investigated CDs, which could be attributed to its larger hydrophobic cavity size.

Keywords: Meclizine; Solubility; Nonionic surfactant; Micellar solubilization; Cyclodextrin; Complexation

1. Introduction

Transformation of water-insoluble drugs into solution is one of the main problems encountered in formulating such drugs in liquid dosage forms. Although several reports [1,2] have dealt with the solubilization of such drugs in nonionic surfactant solutions, more attention should be paid toward this phenomenon. Nonionic, rather than ionic, surfactant solutions have been employed in this aspect because of their lower toxicity, lower critical micellar concentration and their compatibility with body fluids [3]. Their micelles show a gradient of increased polarity from the core (the hydrocarbon chain) to the capsule (the polyoxyethylene chain)–water surface. The extended interfacial region between the core and aqueous solution, i.e. the polar mantle or capsule, is greatly hydrated. The anisotropic distribution of water molecules within the polar mantle favors the inclusion (solubilization) of a wide variety of molecules inside the micellar core [4].

Natural cyclodextrins (CDs), α-, β- and γ-CD, have been extensively employed to improve solubility dissolution, stability and bioavailability of various poorly water-soluble drugs [5,6]. The chemically modified cyclodextrins, such as dimethyl β-cyclodextrin (DM-β-CD) and trimethyl β-cyclodextrin (TM-β-CD), have received a considerable attention in pharmaceutical technology because of their advantageous physicochemical properties than the parent cyclodextrins [6], as they are much more soluble in both water and organic solvents. Both naturally occurring cyclodextrins and the chemically modified ones are subject of

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many research articles concerning various drugs inclusion complexation to achieve the required goals [7–12]. Meclizine hydrochloride (MZ) is slightly water-soluble drug, and is used in the treatment of motion sickness, nausea, pregnancy vomiting and allergy [13]. Therefore, improvement of its water solubility is desirable for formulating MZ in liquid dosage form and consequently its absorption and bioavailability.

The aim of the present work was to study the impact of nonionic surfactants on the solubility of piperazine-containing drug (MZ) in comparison with that of CDs such as α-, β- and DM-β-CD. Furthermore, the mode of drug incorporation in the aforementioned solubilizing or complexing agents have been investigated and compared with each other.

2. Experimental

2.1. Materials

Meclizine hydrochloride (MZ): 1-(4-chlorobenzhydryl)-4-(3-methylbenzyl) piperazine dihydrochloride was generously supplied by Chemical Industrial Development (CID), Assiut, Egypt.

Polyoxyethylene (POE) sorbitan fatty acid esters (polysorbates): polyoxyethylene (20) sorbitan monolaurate (polysorbate 20) and polyoxyethylene (20) sorbitan monooleate (polysorbate 80) (Atlas Chemical Industries, Inc., Wilmington, DE, USA).

POE fatty acid esters (e.g. the Myrjs): polyoxyethylene (50) stearate (Myrj 53) and polyoxyethylene (100) stearate (Myrj 59) (Atlas Chemical Industries).

Polyethylene oxide (PEO) fatty alcohol ethers (e.g. Eumulgin's and Brij's): cetyl stearyl alcohol with (20) ethylene oxide units (Eumulgin C1000) and cetyl stearyl alcohol with (50) ethylene oxide units (Eumulgin C1500) (Henkle International, Dusseldorf, Germany).

Brij's: polyoxyethylene (23) lauryl ether (Brij 35) and polyoxyethylene (20) cetyl ether (Brij 58) (Atlas Chemical Industries). The number between brackets denotes the polyoxyethylene groups in the surfactant molecule.

Co-solvents: propylene glycol (Prolabo, Pelee, Paris, France), Glycerol (BDH, Poole, UK).

Macromolecules: polyethylene glycol 1000 (PEG 1000) and polyethylene glycol 6000 (PEG 6000) (BDH).

Cyclodextrins: α-cyclodextrin (α-CD) (Sigma Chemicals, MO, USA), β-cyclodextrin (β-CD) (Nakari Chemicals Ltd., Japan), dimethyl β-cyclodextrin (2,6-di-*O*-methyl β-cyclodextrin (DM-β-CD)) (Toshin Chemicals Co., Tokyo, Japan).

2.2. Equipment

Thermostatically controlled water bath with a shaker (GFL, Germany) and UV spectrophotometer (Melton Roy Spectronic 601, USA).

2.3. Methods

2.3.1. Solubilization of meclizine HCl by nonionic surfactants

Excess amount of the drug (100 mg) was added to distilled H_2O (10 ml) containing 0.3, 0.6, 0.9, 1.5 and 2% w/v of the investigated nonionic surfactants, namely polysorbates, POE fatty acid esters and PEO fatty alcohol ethers previously mentioned. The solutions were shaken in closed volumetric flasks (50 ml) in the thermostatically controlled water bath at different temperatures, 30, 37 and 45°C. After equilibrium was attained, aliquots were withdrawn using a 0.5-ml volumetric pipette fitted with a cotton plug. The filtered aliquots were diluted with distilled H_2O and assayed spectrophotometrically at 230 nm for the solubilized drug content using the same concentration of the surfactant as a blank. The solubility of MZ was also studied in the presence of cosolvents such as glycerol and propylene glycol or macromolecules such as PEG 1000 and PEG 6000. It was made certain that the presence of the surfactant, cosolvent or macromolecule in the dilution range did not interfere with the spectrophotometric assays of the drug.

2.3.2. Solubility study of meclizine HCl using CDs

The solubility of meclizine HCl in the different concentrations of α-, β- and DM-β-CD was carried out according to Higuchi and Connors procedures [14]. Excess amount of the drug (100 mg) was added to aqueous solution containing various concentrations (mol/l) of the investigated CDs, and were shaken in thermostatically controlled water bath at 30°C. The solubilized drug was determined spectrophotometrically as mentioned above. The solubility phase diagrams were constructed and the 1:1 stability constants (K) were calculated from the Higuchi equation

$$K = \text{slope}/\text{intercept}(1 - \text{slope}) \quad (1)$$

3. Results and discussion

Figs. 1 and 2 show the solubility profiles of MZ in aqueous nonionic surfactant solutions at 30°C. The solubility of the drug increased linearly with increasing the surfactant concentration indicating that the solubility obeyed the partition model [1,2] of solubilization. The systems investigated were always one liquid plus solid indicating true micellar solubilization of MZ. The solubility of the drug was expressed in grams of the drug per gram of the surfactant, as shown in Table 1, which represents the slopes of the regression lines of the solubility isotherms (Figs. 1 and 2). It was evident from Fig. 1 and Table 1 that polysorbate 80 (Tween-80) from the class POE sorbitan fatty acid esters, with longer hydrocarbon chain, was more efficient as a solubilizer for MZ than polysorbate 20 (Tween-20). It is worth noting that polysorbate 80 has an HLB value of 15 less than that of polysorbate 20 (16.7). From the class PEO fatty alco-

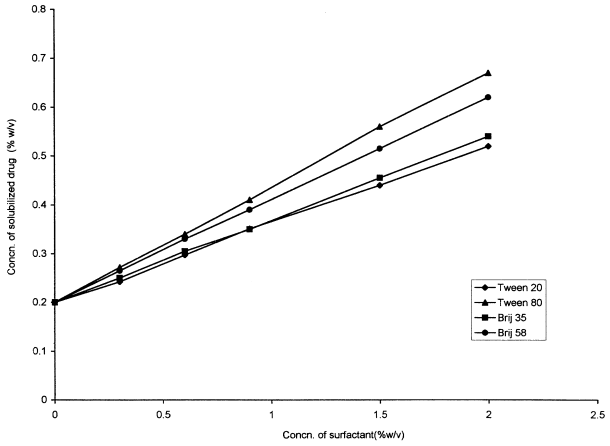

Fig. 1. Solubility profile of meclizine HCl in nonionic surfactant solutions at 30°C.

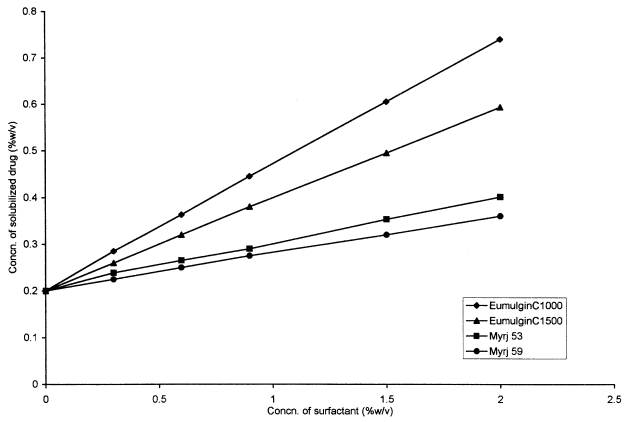

Fig. 2. Solubility profile of meclizine HCl in surfactant solutions at 30°C.

hol ethers, Brij 58, of longer hydrocarbon chain and shorter polyoxyethylene chain, was more efficient as a solubilizer than Brij 35. The HLB value of Brij 58 is less than that of Brij 35, which confirmed the importance of HLB in the solubilizing power of the surfactant. These results suggested that the hydrocarbon chain or the micellar core played the most important role in the solubilization of MZ. They also provided evidence of the hydrophobic interaction between MZ and core of the micelle. On the other hand, Eumulgin C1000 from the class of PEO fatty alcohol ethers, with shorter polyoxyethylene chain, has higher solubilizing power than Eumulgin C1500 with a longer polyoxyethylene chain (Fig. 2). Also in the group of POE fatty acid esters, Myrj 53, with a shorter polyoxyethylene chain; in a homologous series, was more efficient than Myrj 59 (Fig. 2). These results confirmed that the capsular region or the mantle of the micelle (hydrophilic part) contributed in drug solubilization only a minor role beside the major role of the micellar core (lipophilic part). The solubilizing efficiencies of the investigated surfactants in the class PEO fatty alcohol ethers toward MZ can be arranged in the following order: Eumulgin C1000 > Brij58 > EumulginC1500 > Brij 35 (Table 1 and Figs. 1 and 2). In general Eumulgin C1000 gave the highest solubilizing power and highest stability constant with MZ among the studied nonionic surfactants (Table 2). This could be attributed to its longer hydrocarbon chain (cetostearyl group) and shorter ethylene oxide units (20) among others.

The distribution coefficient (K_m) of MZ which was expressed by the ratio of the solubilized drug in the micelle of surfactant solution to that present in the aqueous phase is listed in Table 1. There is a good relationship between the solubility of the MZ and the K_m value, in the manner of the higher the incorporation of the drug within the surfactant micelle, the higher will be its solubility and higher its K_m value. Thus, the order of the K_m values was the same order of the solubilizing efficiencies of the investigated nonionic surfactants.

Fig. 3 shows the solubility diagrams of MZ in aqueous solutions of certain macromolecules and cosolvents at 30°C. The investigated macromolecules were PEG 1000 and PEG 6000, while the cosolvents were propylene glycol and glycerol. The solubility of MZ was slightly increased by the action of cosolvent; glycerol or propylene glycol, and was not affected or slightly decreased by the presence of PEG 1000 or PEG 6000. These findings explained the tendency of MZ to be solubilized in a hydrophobic environment rather than in a hydrophilic phase. Thus, the above results confirmed the mode of interaction between MZ

Table 1
Solubility (g/g) and distribution coefficient of meclizine hydrochloride between micellar and aqueous phases at different temperatures

Surfactant	Solubility (g/g surfactant)			Distribution coefficient (K_m)		
	30°C	37°C	45°C	30°C	37°C	45°C
Polysorbate 20	0.1612	0.1666	0.1900	80	64	63
Polysorbate 80	0.2360	0.2363	0.2370	119	90	78
Brij 35	0.1698	0.1710	0.1740	86	57	47
Brij 58	0.2090	0.2440	0.2700	107	96	90
Eumulgin C1000	0.2690	0.2530	0.3040	138	100	100
Eumulgin C1500	0.1960	0.2090	0.2640	100	83	88
Myrj 53	0.0987	0.0979	0.1787	55	40	56
Myrj 59	0.0796	0.0690	0.0768	42	21	27

Table 2
Comparison between the solubilizing efficiencies of non-ionic surfactant solutions and cyclodextrins for meclizine HCl at 30°C

Solubilizer	Solubilized amount (g% w/v)			Stability constant K (g^{-1})
	0.9	1.5	2.0	
Polysorbate 20	0.351	0.440	0.520	97
Polysorbate 80	0.410	0.560	0.670	155
Brij 35	0.350	0.450	0.540	102
Brij 58	0.390	0.515	0.620	131
Eumulgin C1000	0.445	0.605	0.740	182
Eumulgin C1500	0.380	0.495	0.593	121
Myrj 53	0.290	0.353	0.401	54
Myrj 59	0.275	0.320	0.360	43
α-CD	0.430	0.590	0.691	165 (240)[b]
β-CD	0.430	0.604	–[a]	167 (338)[b]
DM-β-CD	0.500	0.670	0.781	171 (580)[b]

[b] Stability constants are expressed as M^{-1}.
[a] β-CD itself is insoluble in this concentration.

and the studied surfactants to be mainly hydrophobic interaction.

The solubility profiles of MZ in aqueous nonionic surfactant solutions at the higher temperatures, 37 and 45°C, are shown in Figs. 4–7. Raising the temperature of the investigated solutions from 30 to 37 or 45°C led to an increase in the amount of the solubilized drug. This positive temperature effect might be due to the increasing of the inherent solubility of the drug in the aqueous phase in addition to the increased amount of the drug solubilized by the surfactant micelles. The latter aggregates more monomers to form larger micelles of larger volumes by increasing the temperature, which accommodated more drug [1]. When the temperature of the investigated solutions was raised, a decrease in the K_m value of the MZ between the micellar and aqueous phases occurred (Table 1). This could be attributed to the temperature effect which modified the ratio of distribution of the drug between the micellar and aqueous phases.

The inclusion complexation of MZ with α-, β- and DM-β-CD in aqueous solutions at 30°C was investigated by the solubility method. The solubility of MZ increased linearly with increasing cyclodextrin concentrations (Fig. 8), showing A_L-type phase solubility diagrams with no precipitation of the inclusion complex formed [14]. The stability constant (K) values of the 1:1 inclusion complexes were calculated for the drug with α-, β- and DM-β-CD and were found to be 240, 338 and 580 M^{-1}, respectively (Table 2). The highest stability constant and highest solubilized amount of the drug were obtained with DM-β-CD (Table 2). It is interesting to apply the Higuchi equation for the calculation of stability constant between the drug and CDs per gram for inclusion complexation in the solution state. The order of solubilizing efficiencies of the investigated CDs toward MZ was as follows: DM-β-CD > β-CD > α-CD. The highest efficiency of the first member could be attributed to the larger hydrophobic cavity size compared with other CDs [15]. Therefore, hydrophobic interaction as well as other forces may be responsible for the inclusion complexation of MZ with the investigated CDs [16].

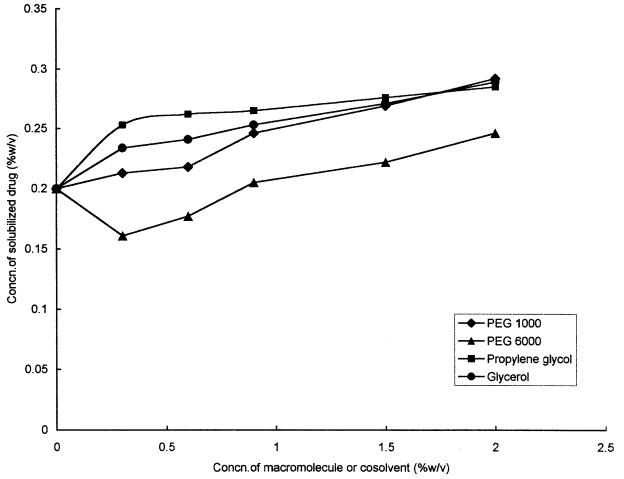

Fig. 3. Solubility profile of meclizine HCl in macromolecule or cosolvent solutions at 30°C.

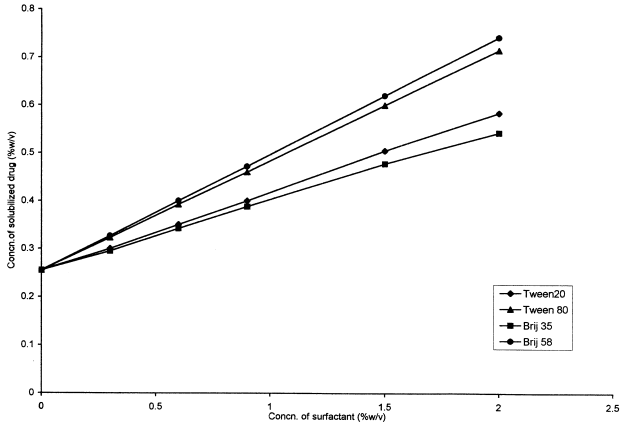

Fig. 4. Solubility profile of meclizine HCl in nonionic surfactant solutions at 37°C.

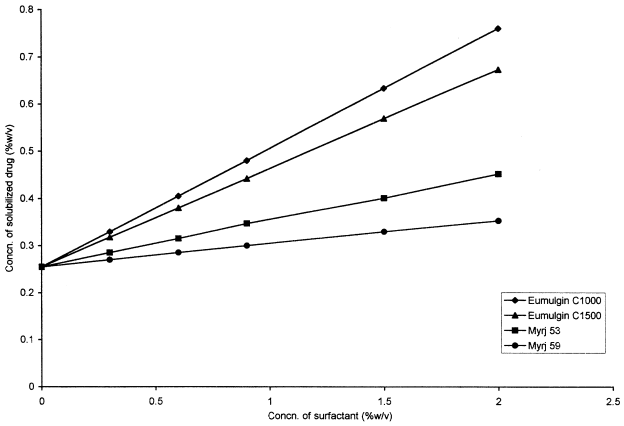

Fig. 5. Solubility profile of meclizine HCl in nonionic surfactant solutions at 37°C.

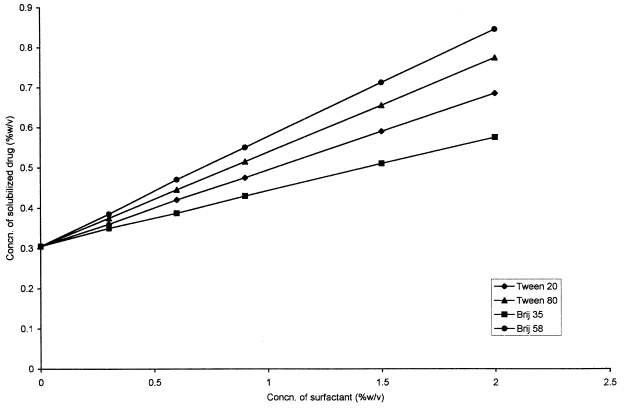

Fig. 6. Solubility profile of meclizine HCl in nonionic surfactant solutions at 45°C.

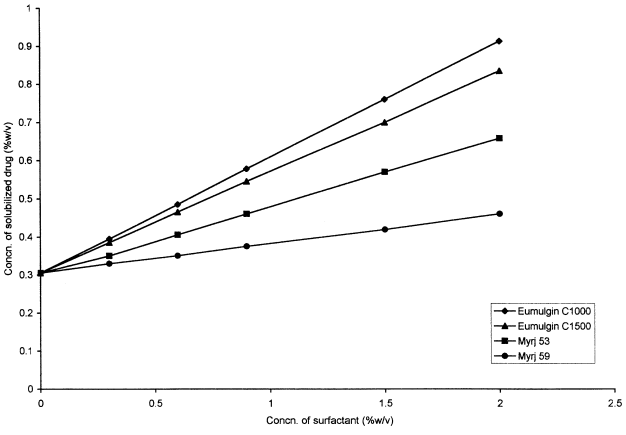

Fig. 7. Solubility profile of meclizine HCI in nonionic surfactant solutions at 45°C.

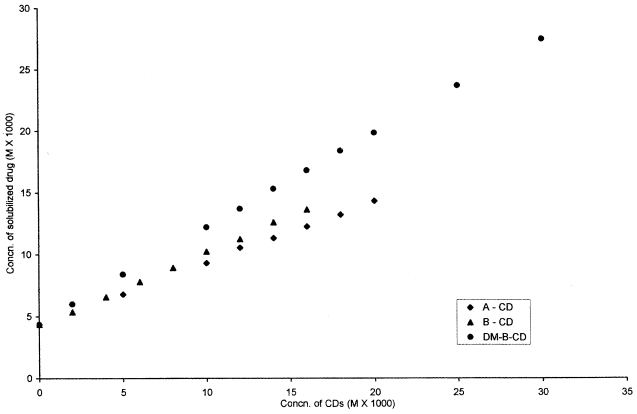

Fig. 8. Phase solubility diagram of meclizine HCl with CDs in water at 30°C.

A comparison of the solubilizing efficiencies of the different investigated solutions, including nonionic surfactants or cyclodextrins, toward MZ at 30°C and their stability constants (K) are shown in Table 2. It was apparent that DM-β-CD showed the highest solubilizing efficiency for the drug among the investigated CDs by inclusion complexation. Eumulgin C1000 was the most efficient solubilizer among the studied nonionic surfactants for MZ by micellar solubilization.

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