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Effect of Polysorbate 80 and Benzyl Alcohol on the Solubility of Amiodarone Hydrochloride

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Abstract

Amiodarone hydrochloride is an antiarrhythmic agent which has low aqueous solubility and presents bioavailability problem. These properties are a challenge for the pharmaceutical industry. Inclusion of lipophilic compound in the hydrophobic core of micelles, i.e. self-assembled structures based on surfactants in aqueous solution, is one way of increasing the solubility. Intravenous formulation of amiodarone hydrochloride with polysorbate 80 as a detergent and benzyl alcohol as a co-solvent is used in medical practice. This paper aimed to study the effect of polysorbate 80 and benzyl alcohol on the water solubility of amiodarone hydrochloride. Formation of mixed micelles consisting of nonionic surfactant polysorbate 80 and cationic amiodarone with chloride counterion was investigated by fluorescence spectroscopy. Benzyl alcohol was found to decrease the stability of the mixed micelles and lead to crystallization of amiodarone hydrochloride. The greatest amounts of crystals formed at 4°C for 30 days in the model drug solutions with polysorbate 80 concentrations of 100.1 mg/mL and 97.9 mg/mL. A change of the polysorbate 80 concentration and avoidance the use of benzyl alcohol are recommended to improve the stability of the parenteral dosage form. These results can open new perspectives in the optimization of amiodarone intravenous formulations.

Keywords: Amiodarone Hydrochloride, Solubility, Polysorbate 80, Mixed Micelles, Benzyl Alcohol, Fluorescence Spectroscopy.

Major classification: Health Science.

1. Introduction

Amiodarone hydrochloride (AMH), chemically known as (2-butyl-3-benzofuranyl)[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone hydrochloride, is widely used in treatments of heart diseases because of its antianginal and antiarrhythmic properties [Singh, 2006]. The structure of AMH is presented in Figure 1.

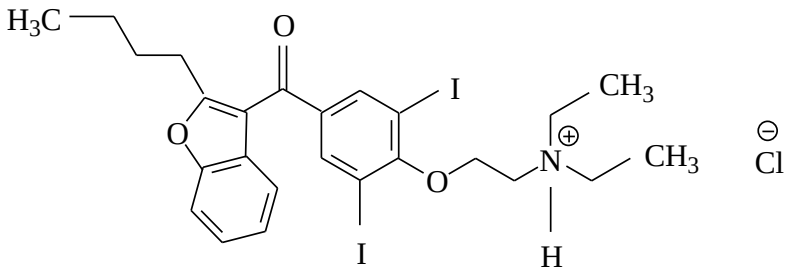

Figure 1: Structure of amiodarone hydrochloride

AMH is a cationic amphiphilic molecule that forms micelles in water. Each micelle contains approximately 150 monomeric units having a molecular weight in excess of 100 kDa [Souney *et al.*, 2010]. AMH is poorly soluble in water, at a possible maximum of 0.7 mg/mL at 25°C. The crystals of AMH have to be heated in water above 60°C to obtain a transparent liquid preparation (50 mg/mL and more) which remains stable for several days when cooled down to room temperature [Benedini *et al.*, 2010].

Owing to the low aqueous solubility of AMH, intravenous formulations require addition of surfactants and co-solvents. So, marketed formulations consist of AMH (50 mg/mL), polysorbate 80 (100 mg/mL), benzyl alcohol (20 mg/mL) and water for injection [Souney *et al.*, 2010].

The use of surfactants in the solubilization is attractive because they have both hydrophilic and hydrophobic moieties which allow them to reduce the interfacial tension. In aqueous solutions, surfactant molecules start to aggregate and form micelles in concentration called as critical micelle concentration (CMC), and it is one of the most important physical parameters of surfactants. The properties of a surfactant (like density, polarity, solubilization power etc.) vary markedly when its concentration is higher or lower than its CMC [Mahmood *et al.*, 2013]. If the molecules of the compound to be dissolved in aqueous solution are amphiphilic, then they are incorporated into surfactant micelles forming mixed micelles, the properties of which differ considerably from those of simple micelles [Azum *et al.*, 2017].

Hence, it is important to investigate drug features, such as solubility, stability and compatibility of the pharmaceutical formulation, given that some changes may directly influence its bioavailability. Therefore, the aim of this paper was to study the effect of polysorbate 80 and benzyl alcohol on the solubility of AMH.

2. Material and methods

2.1. Apparatus

The spectrofluorometer FP-8500 (Jasco, Japan) with xenon lamp and 10-mm quartz cell was used. Excitation and emission wavelengths were set at 420 nm and 506 nm, respectively. Slit width for both monochromators was set at 5 nm.

Optical microscopy was performed with a digital microscope BIO 2 (Altami, Russia).

2.2. Reagents

AMH (purity > 99%) was obtained from Cambrex Profarmaco Milano Srl. (Italy). Polysorbate-80 was supplied by Oleon (Belgium). Benzyl alcohol was purchased from Sigma-Aldrich (USA). Distilled water was used in all experiments.

2.3. Determination of CMC for polysorbate 80

A series of solutions of various concentrations (10^{-6}–10^{-4} M) was prepared. The CMC was determined from a plot of fluorescence intensity versus concentrations of polysorbate 80 (log scale), using the point of intersection of the straight-line segments of the curve as the CMC value.

2.4. Model solutions of the drug

Model solutions of the drug containing AMH (50 mg/mL), polysorbate 80 (90.2–110.0 mg/mL, ±10% of its nominal content in the drug) and benzyl alcohol (20 mg/mL) were prepared. The control was a solution containing polysorbate 80 (100.1 mg/mL) and AMH (50 mg/mL) without benzyl alcohol.

3. Results and discussion

Since polysorbate 80 increases solubility of AMH in water, it was first advisable to determine the CMC of this surfactant. The dependence of fluorescence intensity on the concentrations of polysorbate 80 is illustrated in Figure 2. The CMC for polysorbate 80 in aqueous solution was approximately 2×10^{-5} M.

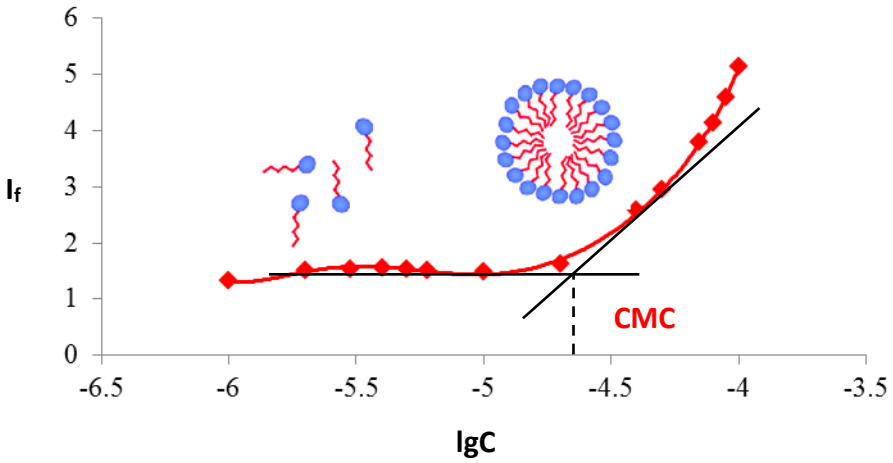

Figure 2: Determination of CMC for polysorbate 80

AMH and benzyl alcohol were added to the polysorbate 80 solutions, keeping the mole ratios of all components the same as in the parenteral drug solution and then measuring the fluorescence intensity (Figure 3). The results indicated that adding AMH to a polysorbate 80 solution increased the fluorescence intensity whereas subsequent addition of benzyl alcohol, which reduced the medium polarity, decreased it insignificantly.

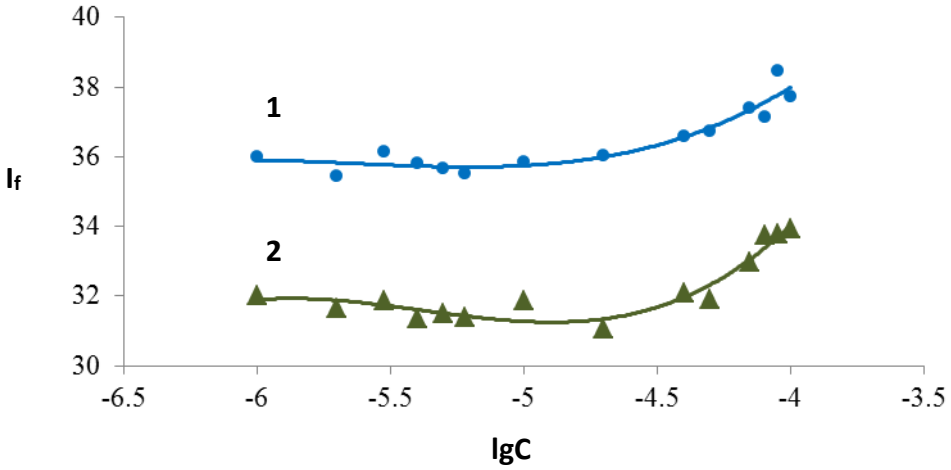

Figure 3: Fluorescence intensity as a function of polysorbate 80 concentration in the range 10^{-6}–10^{-4} M:
1 – polysorbate 80 with AMH; **2** – polysorbate 80 with AMH and benzyl alcohol

However, adding AMH and benzyl alcohol in the same mole ratios as in the intravenous formulation to a solution of polysorbate 80 in the range of concentrations $6.9 \times 10^{-2} – 8.4 \times 10^{-2}$ M (±10% of its nominal content in the drug) showed different features. Firstly, plots of fluorescence intensity versus concentrations of polysorbate 80 were linear. Secondly, it led to a significant decrease in fluorescence intensity (Figure 4). In this instance, it could be suggested that the polysorbate 80 micelle structure changed and that mixed micelles had formed because the AMH concentration was two orders of magnitude greater than its solubility in water.

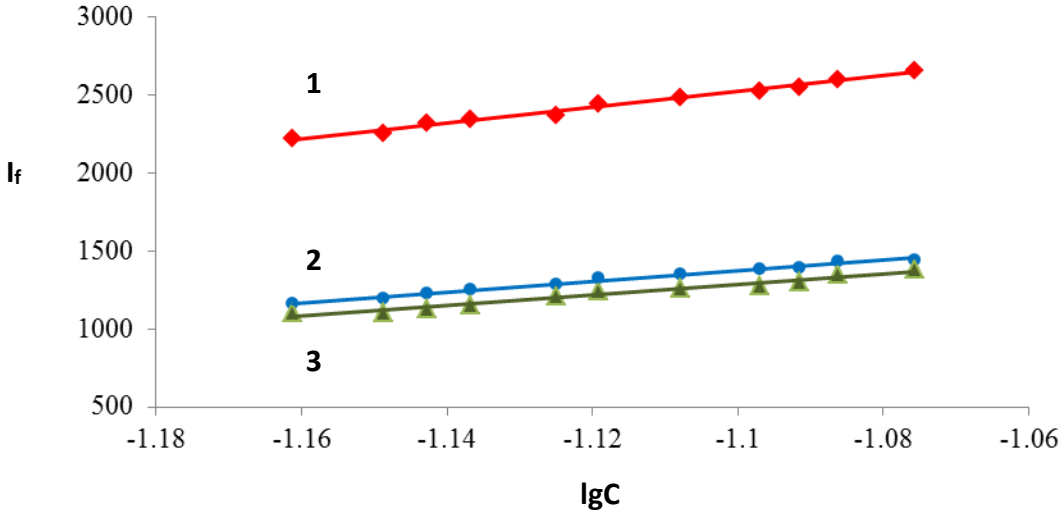

Figure 4: Fluorescence intensity as a function of polysorbate 80 concentration in the range $6.9 \times 10^{-2} – 8.4 \times 10^{-2}$ M: **1** – polysorbate 80; **2** – polysorbate 80 with AMH; **3** – polysorbate 80 with AMH and benzyl alcohol

Polysorbate 80 molecules have very bulky hydrophilic heads and short hydrophobic tails. Therefore, the hydrophobic regions in micelles formed by them are small. The bulkier hydrophobic regions of AMH seek into the micelles displacing molecules of surfactant. The resulting mixed micelles increase in size. Positive charge appears on their surface (Figure 5).

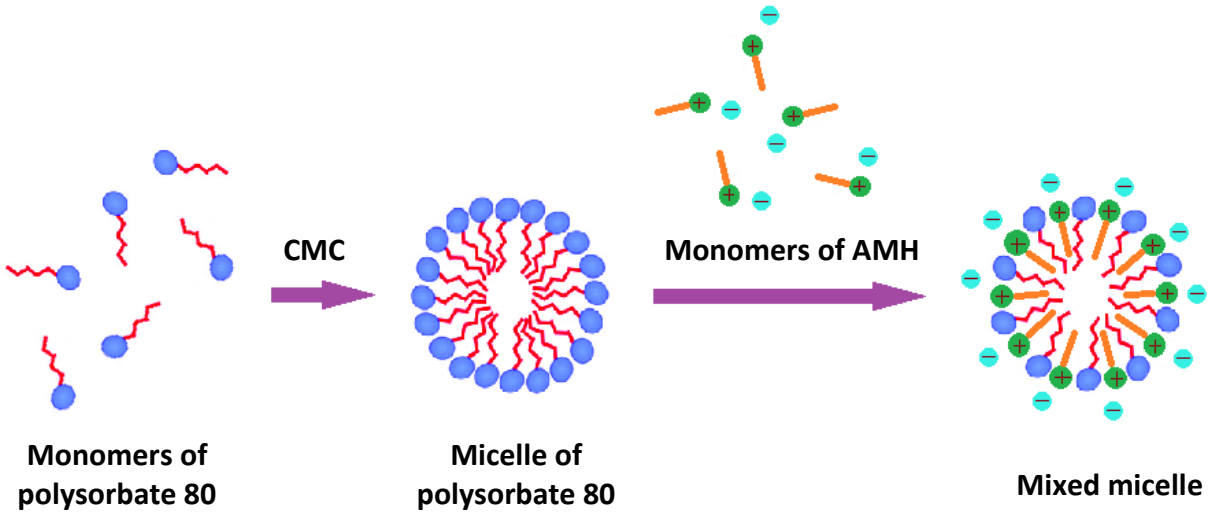

Figure 5: Formation of simple micelle of polysorbate 80 andincorporation into it of AMH to form mixed micelle

The stability of the mixed micelles depends on temperature, reduction of which leads to crystallization of the dissolved compound.

Model solutions of the drug were used to study the crystallization. The model solutions were stored at 4°C for 30 days. The results indicated that the greatest amounts of crystals formed in the model drug solutions with polysorbate 80 concentrations of 100.1 mg/mL and 97.9 mg/mL. Microphotography of AMH crystals is shown in Figure 6. Decreasing and increasing the polysorbate 80 content relative to the nominal value decreased the AMH crystallization rate. This was due to a change of the mixed micelles composition and the different effect on them of benzyl alcohol.

Crystals did not form in the control at 4°C. Hence, it was benzyl alcohol that lowered the stability of the mixed micelles in the model drug solutions and led to crystallization of AMH.

Figure 6: Microphotography of AMH crystals formed during storage of model drug solutions at 4°C for 30 days

Thus, changing the mole ratio of AMH, polysorbate 80 and benzyl alcohol (1:1:2.5) used in parenteral drug solutions increased their stability. Furthermore, excluding benzyl alcohol from the drug composition increased even more the stability of the micellar solutions at low temperatures.

4. Conclusions

The pharmaceutical importance of this study is apparent, and the implication of solubility to drug availability in a dosage form is obvious. When formulating this drug, the pharmacist must exercise extreme care in the selection of the proper excipients and also in the concentration of these ingredients. A study of this type points out that a thorough understanding of the physical-chemical behavior of complex drug molecules is extremely important.

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