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Notes

Effect of 2-hydroxypropyl-β-cyclodextrin on the aqueous solubility of the anaesthetic agent propofol (2,6-diisopropylphenol)

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Abstract

The inclusion complexation of Propofol (2,6-diisopropylphenol), an intravenous anaesthetic agent in clinical use, with 2-hydroxypropyl-β-cyclodextrin (HPβCyD) was investigated for the purpose of improving the low aqueous solubility and developing a potentially acceptable aqueous formulation. The aqueous solubility of propofol was increased as a function of HPβCyD concentration affording a linear phase-solubility profile.

Keywords: Propofol; Intravenous anaesthetic agent; Solubility; Complexation; 2-Hydroxypropyl-β-cyclodextrin

Propofol (2,6-diisopropylphenol) is a short-acting, rapidly metabolized intravenous anaesthetic agent that can be used to induce and maintain general anaesthesia (Langley and Heel, 1988). However, despite its popularity, the neurochemical mechanism of action remains to be clarified. In this regard, recent electrophysiological and biochemical studies (Concas et al., 1992) have shown a possible interaction of propofol with the GABA receptor complex similar to that observed for other general anaesthetics.

Due to the very limited aqueous solubility of propofol an early formulation was prepared as a 1% solution in 16% 'Cremophor EL'. However, an unexpectedly high occurrence of pain on injection and some observed cases of anaphylactic reactions (Langley and Heel, 1988) prompted the development of an alternative formulation for propofol which is now produced as 1% w/v of

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oil/water emulsion of soya bean oil, glycerol and purified egg phosphatide (Diprivan®). Unfortunately, this formulation too has its drawbacks as proved by the high frequency of infections observed with a non-strictly aseptic use of the lipid-based anaesthetic agent (Bennett et al., 1995).

In an effort to develop a potentially acceptable aqueous formulation for propofol we investigated the interaction of the anaesthetic agent with 2-hydroxypropyl-β-cyclodextrin (HPβCyD) whose properties of stability, enhancing solubility, and the possibility of being tolerated parenterally in high doses is well documented (Pitha et al., 1986; Brewster et al., 1990, 1991, 1992). This paper deals with the preparation of an inclusion complex between propofol and HPβCyD in order to improve the water solubility of the drug.

Propofol was of extra pure reagent grade and chromatographically pure (TLC) samples of propofol were stored under nitrogen. 2-Hydroxypropyl-β-cyclodextrin (average molecular weight 1380) and propofol were purchased from Aldrich Chemical Co. (USA).

The aqueous solubility of propofol was determined at 25 ± 0.5°C using various aqueous solutions of HPβCyD (4.05%, 8.1%, 16.2%, 24.3%, 32.4%, and 40.5% w/v) in deionized water. A large excess of the anaesthetic agent was added to 2 ml of the appropriate HPβCyD solution in screw-capped test tubes. The mixture was vortexed for ~ 5 min and kept in a bath at 2.5 ± 0.5°C under magnetic stirring for 5 days. Then the mixtures were filtered through a 0.45 μm membrane filter and analyzed using UV spectrophotometry. The data are the mean of three separate experiments.

The apparent 1:1 stability constant (K_c) was estimated from the slope of the initial straight line portion of the phase-solubility diagram and the solubility (S_0) of propofol in water (Higuchi and Connors, 1965):

$$K_c = \text{slope}/S_0(1 - \text{slope})$$

The quantitative determination of propofol was performed using a Varian 2000 UV-Vis spectrophotometer. A standard curve was prepared using deionized water at a wavelength of 270 nm and was linear ($r^2 > 0.998$) over a concentration range of 8.10^{-5} M–8.10^{-4} M. For analysis of the solubilized propofol in the presence of HPβCyD, known volumes of the filtrate solutions were appropriately diluted, the absorbances at 270 nm were recorded and the concentrations determined using a standard Beer's law plot. Compensation of the HPβCyD background absorbance was made by using a solution of HPβCyD at an appropriate concentration as a blank. The solubility of propofol in 0.05 M phosphate buffer (pH 7.4) was also determined by using HPLC. The system configuration consisted of a Water Associates Model 600 pump equipped with a Water 990 variable wavelength UV detector and a 20 μl loop injection valve (Rheodyne). For analysis, a reversed phase μBondapack C_{18} (30 cm × 3.9 mm; 10 μm particles) column in conjunction with Guard-Pak precolumn module with μBondapack C_{18} insert was eluted with mixtures of methanol and 0.05 M phosphate buffer (pH 7.4). The flow rate of 1 ml/min was maintained. The column effluent was monitored continuously at 229 nm. A standard curve was prepared at a wavelength of 229 nm using methanol as the solvent and was linear ($r^2 > 0.998$) over a concentration range of interest. UV and HPLC methods were quite consistent, e.g. in separate experiments, the solubility of propofol in water was 146 ± 8.9 μg/ml (UV) and 154 ± 10 μg/ml (HPLC).

The inclusion complex between propofol and HPβCyD was prepared by two different methods: (i) cosolvent evaporation and (ii) freeze-drying. In preparing the inclusion complex by the cosolvent evaporation method, an excess of propofol was equilibrated, at room temperature and under stirring, in 10 ml of 40.5% w/v solution of HPβCyD for 4 days under nitrogen atmosphere; then the mixture was filtered through a 0.45 μm filter and evaporated under reduced pressure in a rotatory evaporator at 40°C. In preparing the inclusion complex by the freeze-drying method, the same procedure reported for the coevaporation method was followed until filtration through a 0.45 μm filter; then the filtrate was frozen in liquid nitrogen and lyophilized by using an Edwards model type 680 freeze-drier. The solid complex obtained by both methods was kept under vacuum at room temperature up to constant weight.

Table 1
Effect of various concentrations of HPβCyD on propofol solubility

HPβCyD (% w/v)	S (mg/ml)
0.00	0.154 ± 0.010
4.05	3.59 ± 0.14
8.10	6.95 ± 0.19
16.2	14.47 ± 0.42
24.3	22.75 ± 0.64
32.4	31.53 ± 0.42
40.5	39.73 ± 0.74

The propofol is a lipophilic drug with a log P value of 3.38 calculated according to the method of Morigushi et al., 1992. Such high lipophilicity limits the water solubility of the anaesthetic agent which was determined to be 146 ± 8.9 μg/ml (UV) and 154 ± 10 μg/ml (HPLC). As shown in Table 1, the aqueous solubility of propofol was notably improved in the presence of HPβCD. Interestingly, a 40.5% HPβCyD provided for a 39.73 mg/ml solution of propofol corresponding to a ~ 266-fold increase in solubility of propofol with respect to that observed in deionized water. The phase-solubility profile was linear in the range of HPβCyD concentrations investigated (Fig. 1). Using the linear portion of the phase solubility diagram, the apparent 1:1 stability constant (K_c) was estimated to be 3972 M^{-1}.

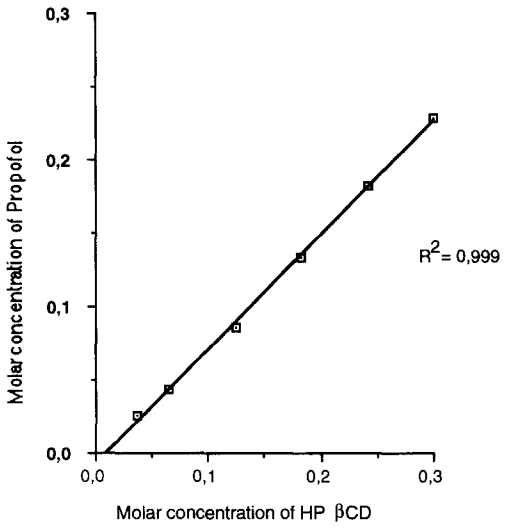

Fig. 1. Phase-solubility profile of propofol as function of 2-hydroxypropyl-β-cyclodextrin (HPβCyD) concentration.

The degree of propofol incorporation in the solid complex with HPβCyD was determined by UV spectrophotometry to be 17.41 mg/g of complex.

In conclusion, the data suggest that HPβCyD may be useful for the development of a potentially acceptable aqueous formulation of propofol. The emulsion-based formulation currently used (Diprivan®) contains 10 mg/ml. Using a HPβCyD-based formulation a similar system could be accomplished by employing HPβCyD concentrations ranging between 8.1 and 16.2% w/v.

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