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International Journal of Pharmaceutics 130 (1996) 251–255

international journal of pharmaceutics

Notes

Compatibility of propofol diluted in 5% glucose with glass and plastics (polypropylene, polyvinylchloride) containers

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Received 22 June 1995; revised 14 August 1995; accepted 24 August 1995

Abstract

The compatibility of propofol diluted in 5% glucose with glass, polypropylene (PP) and polyvinylchloride (PVC) containers was evaluated after 30 days contact. The mixtures were exposed to several temperature and light conditions. Propofol was assayed by high performance liquid chromatography. Propofol interacted with PVC causing loss of 50% or more of the drug after 30 days contact. In contrast, containers made of PP or glass caused no noteworthy fall in propofol concentration. The best storage conditions were at +4°C irrespective of the container material.

Keywords: Propofol; Compatibility; Glass; Polypropylene; Polyvinyl chloride

Propofol (2,6-diisopropylphenol), marketed under the trade name Diprivan®, is an anaesthesic used intravenously to induce and maintain general anaesthesia (Ground et al., 1985). It is supplied as a lipid emulsion. It can be administered in continuous infusion after dilution in 5% glucose at a concentration of 2 mg/ml minimum; this is the limiting concentration above which the emulsion will not break up (Dictionnaire Vidal, 1995).

Some authors have shown that drugs, especially those with lipophilic properties, can interact with certain materials, in particular polyvinyl chloride (PVC) (Illum and Bundgaard, 1982; D'arcy, 1983; Martens et al., 1990; Arnaud et al., 1991; Trissel, 1994). These interactions can have important clinical consequences, particularly if the drug is administered by continuous infusion. As little information was available on the compatibility of propofol with plastics and glass (Bailey et al., 1991) we conducted a study of the behavior of this drug towards three materials: PVC, polypropylene (PP) and glass under various temperature and light conditions. We monitored the propofol concentration in the drug solution by high performance liquid chromatography (HPLC) using a method we developed based on the work of Guitton et al. (1992) and Chan and So (1990).

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SSDI 0378-5173(95)04295-L

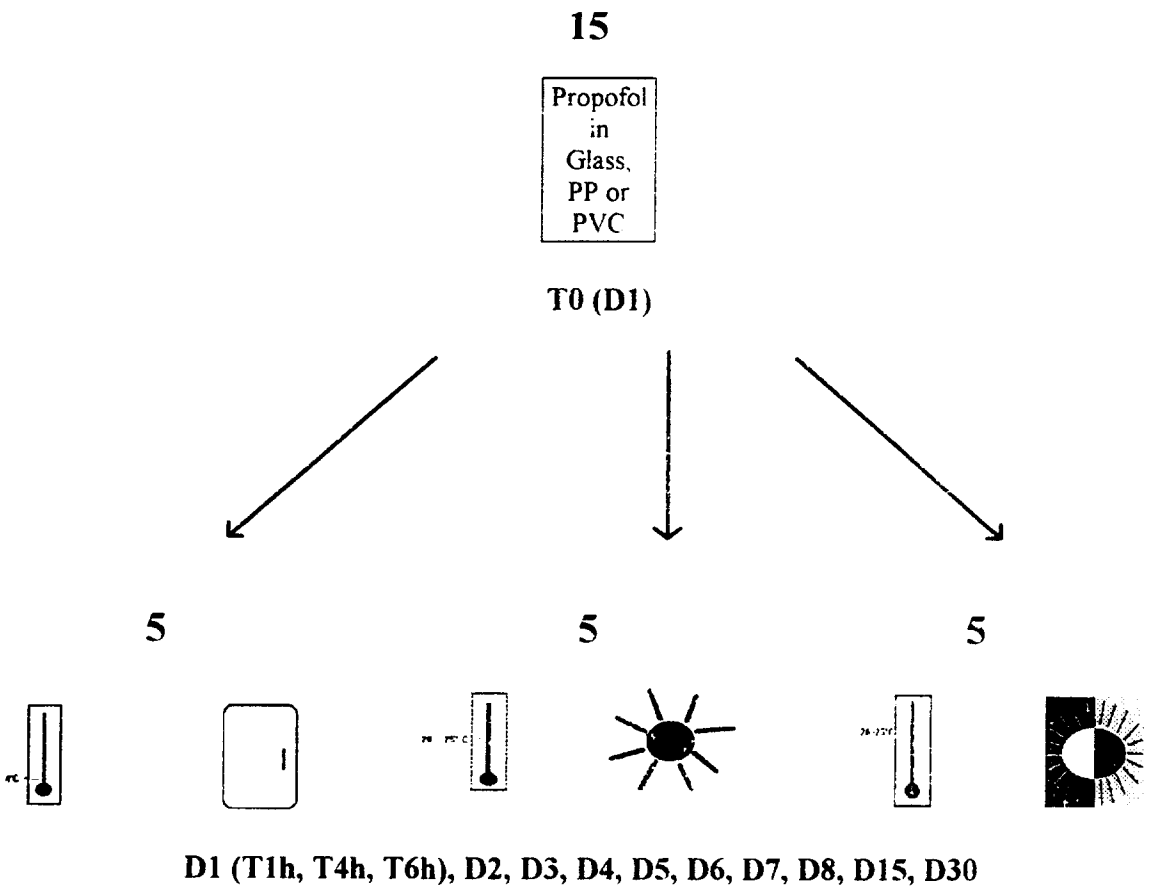

Fig. 1. Depiction of procedure for propofol stability study.

Propofol (Diprivan®) was marketed by Zeneca Pharma (Cergy, France) as a lipid emulsion in 20-ml vials at 10 mg/ml.

The dilution solvent was 5% glucose in glass bottles (Biosedra, Louviers, France), PVC bags (Tuliflex, Aguettant, Lyon, France) and PP bottles (Biosedra, Louviers, France).

Propofol assay was performed using an HPLC apparatus (Merck-Hitachi, Darmstadt, Germany) comprising the following elements: L5000 LC Gradient controller, 655 A-11 pump, Rheodyne 7125 20-μl injection loop, L4250 UV-Vis detector, D2000 Chromato-Integrator. The analysis column was a C18 type: Lichrospher 100 RP18 (5 μm) 125 × 4 mm ID) (Merck). Thymol (Sigma, St. Louis, MO, USA) was used as internal standard.

The mobile phase was a 75-25 (v/v) mixture of acetonitrile and phosphate buffer, pH 6.8. The flow rate was 0.8 ml/min. The detection wavelength was set at 270 nm. The injection volume was 20 μl.

The standard solutions were made up by dilution in methanol of the commercial 10-mg/ml solution. They contained 0.1, 0.2 and 0.3 mg/ml of propofol for a concentration of internal standard (thymol) of 100 μg/ml. These solutions were used to plot the calibration curve. The calibration curve is a plot of the ratio of the areas under the propofol peak and the internal standard peak versus propofol concentration. The propofol concentration of an unknown sample is calculated by extrapolation from the calibration $y = ax + b$ describing the plot.

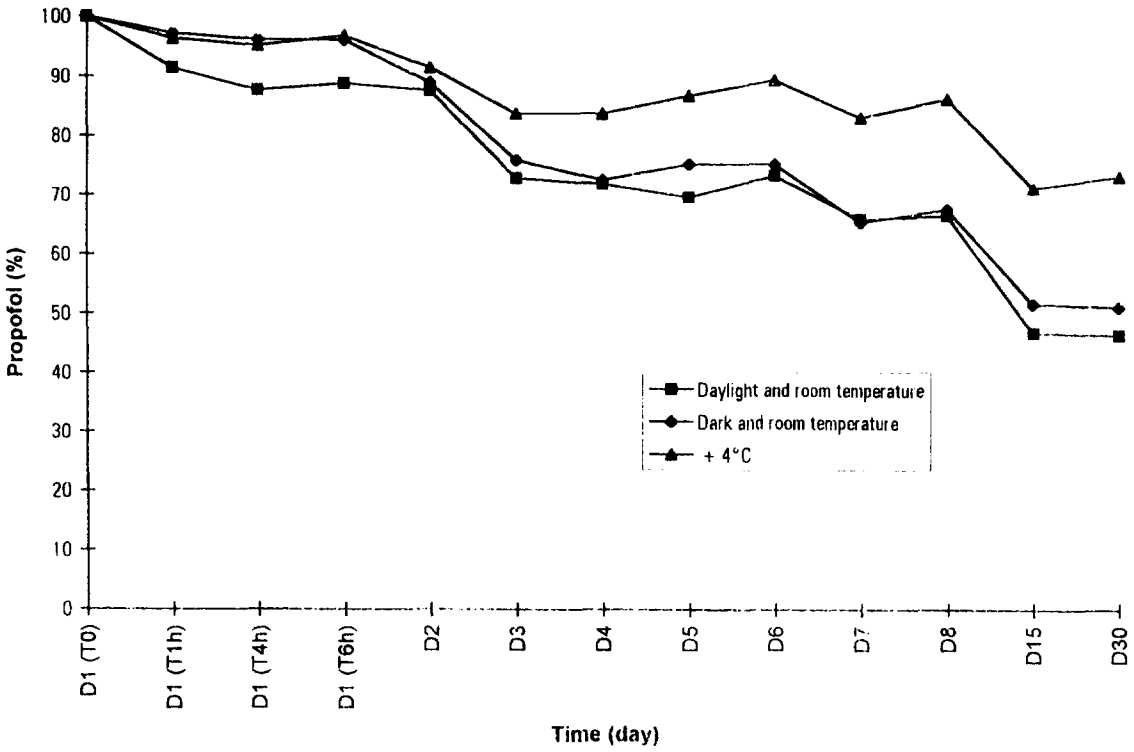

Fig. 2. Stability of propofol in 5% glucose in PVC bags.

Propofol was diluted in 5% glucose to obtain a final concentration of 2.5 mg/ml. The container was glass, PVC or PP. For each container material, 15 preparations of propofol at 2.5 mg/ml were made up. Of these 15 preparations, five were kept at room temperature and exposed to daylight, five were kept in the dark at room temperature (bottles and bags were wrapped in aluminium foil), and five were stored in a refrigerator at +4°C. A sample was taken immediately after diluting the propofol in the 5% glucose. This served as the reference value corresponding to the initial propofol concentration (i.e., T_0). Samples were then taken on the first day (D1) and then on D2, D3, D4, D5, D6, D7, D8, D15, D30.

This procedure is depicted in Fig. 1. Each sample was diluted and the internal standard was added in the following sequence: 80 μl of sample; 100 μl of 1 mg/ml thymol solution; 820 μl of methanol.

This dilution was necessary to obtain a propofol concentration in the range of the calibration curve. After dilution each sample was analysed by HPLC.

The propofol concentration chosen for the study (2.5 mg/ml) was a therapeutic concentration close to the limiting dilution in 5% glucose specified by the supplier Zeneca (2 mg/ml); below this concentration the emulsion is liable to break up.

Means were calculated for the five values obtained at each sampling time for each container material and each storage condition. The mean propofol concentrations were then expressed in percent relative to the initial concentration at T_0, taken as 100%.

The results obtained were analysed statistically by analysis of variance to evaluate the significance of any differences between materials and storage conditions. Whenever an overall significant difference was revealed, a Student's t-test was applied to compare means two by two. The significance threshold was taken as $p < 0.05$.

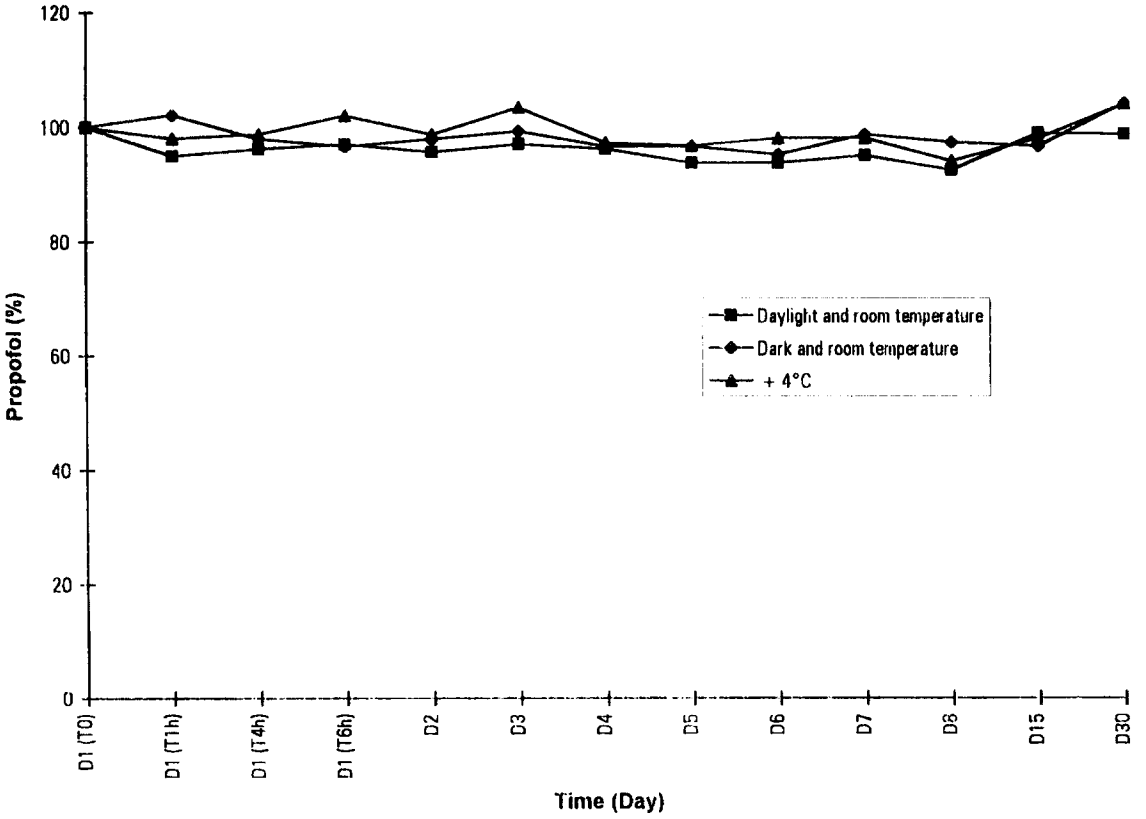

Fig. 3. Stability of propofol in 5% glucose in glass bottles.

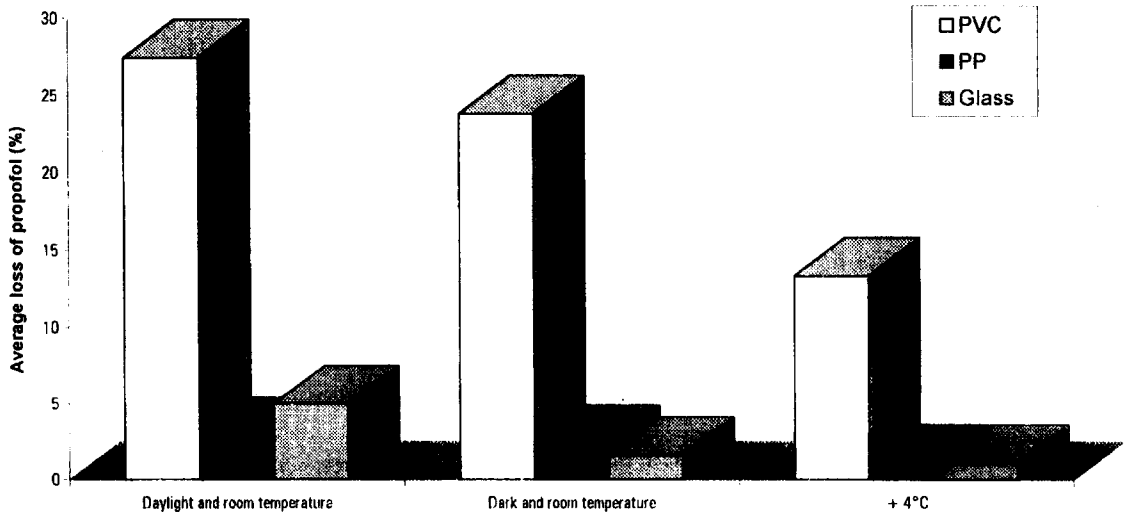

Fig. 4. Average loss of propofol over 30 days according to container material and storage conditions.

The propofol assay method was validated. The precision (intra- and inter-day variabilities) was correct with coefficient of variation inferior to 5%. Each result represents the mean of 10 values (n = 10). The method displayed high linearity for the range of concentrations from 0.1 to 0.3 mg/ml with a correlation coefficient r = 0.9999 (r^2 = 0.9999).

In PVC bags, propofol concentration fell over time, apparently being absorbed by the plastic (Fig. 2). This effect has often been observed with lipophilic substances like propofol. Some authors (Illum and Bundgaard, 1982; Roberts et al., 1983) have even demonstrated a relationship between the binding of active substances to PVC and their hexane/water or octanol/water partition coefficients.

Temperature also seems important for the stability of propofol in PVC bags. As shown in Fig. 2, loss of propofol is lower when the bags are stored in a refrigerator. This is confirmed by the average loss of propofol over 30 days, which was significantly lower at +4°C than at room temperature (Fig. 4).

No significant difference ($p < 0.05$) in mean propofol concentration was found between solutions exposed to daylight and those kept in the dark.

Propofol was much more stable in PP than in PVC containers. After 30 days, regardless of the storage conditions, propofol concentration did not vary more than 10% of its initial concentration at T_0. The mean percentage of propofol in the solution at D30 was 94% (light and room temperature), 96% (dark and room temperature) and 100% (refrigerator).

Average loss after 30 days was low, under 3%. there was no significant difference ($p < 0.05$) according to conditions of storage.

Propofol was highly stable in glass (Fig. 3) The variations in propofol concentration did not exceed 10% of initial values irrespective of storage conditions.

There was a significant difference between solutions exposed to daylight and those stored in the dark (at room temperature or +4°C), suggesting a light sensitivity. This may be more evident with glass bottles since these were the least opaque of the three materials. However, the variations in concentration were too slight for them to have any clinical impact.

In conclusion, propofol is demonstrably incompatible with PVC. The histogram in Fig. 4 shows the differences in compatibility of propofol and PVC, PP and glass. Analysis of variance shows no significant difference ($p < 0.05$) between glass and PP bottles under any of the storage conditions.

The same histogram also shows that the best conservation of propofol diluted in 5% glucose is at +4°C. The widest variations in propofol concentration were observed when the mixtures were exposed to light. This difference was more marked for the mixtures in the glass bottles, which were the least opaque. It therefore seems advisable to protect bottles from light for optimal conservation of propofol in 5% glucose.

Acknowledgements

The authors thank the members of the association Perfuverre who supported this work.

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