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Chemical equivalence of two polyetherpolyurethane foams as a vehicle for povidone–iodine solution: kinetic model for the loss of available iodine

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Abstract: The loss of available iodine from povidone–iodine solution stored in contact with two different polyetherpolyurethane foams was monitored as a function of time and temperature. Statistical evaluation of the results for the four temperatures studied [ambient (25°), 30, 45 and 55°C] indicated the chemical equivalence of the two foams as storage and delivery systems for povidone–iodine solution in terms of solution stability. In addition, application of a first-order kinetic model to the data produced an acceptable fit. An Arrhenius-type evaluation of the resulting rate constants yielded a linear relationship which was shown to be useful for predicting loss of available iodine under ambient temperature conditions of storage.

Keywords: *Povidone–iodine; polyvinylpyrrolidone–iodine; stability; Arrhenius-type evaluation.*

Introduction

Povidone–iodine solution is a commonly used topical anti-infective agent which is widely applied in dialysis therapy facilities and hospitals. It is also often used to disinfect the set connections for patients undergoing continuous ambulatory peritoneal dialysis. The chemical structure of povidone–iodine is shown in Fig. 1. The antiseptic efficacy of povidone–iodine (polyvinylpyrrolidone–iodine, PVP-I) solution is attributed primarily to the free or available iodine which it contains [1]. The history of the development of PVP-I solution, its toxicity and therapeutic indications, as well as several case histories concerning its use, may be found in the classic work of Shelanski and Shelanski [2].

Polyetherpolyurethane (PEPU) foams used as sponges are commonly employed vehicles for the delivery of PVP-I solutions. The ability to substitute one commercial PEPU for another during manufacture of the product was considered to be a distinct advantage so long as product quality or efficacy was not compromised. In addition, a method by which long-term stability (in terms of loss of available iodine) of the product

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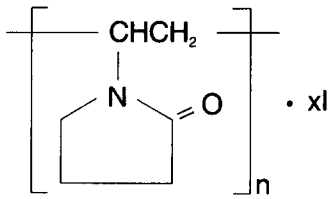

Figure 1
Chemical structure of povidone–iodine.

could be predicted was required in order to better understand the product and to allow for rapid stability evaluation of proposed product changes.

The aim of the study was 2-fold. First, the equivalence in terms of product stability of two commercially available polyetherpolyurethane foams was determined. Second, a first-order kinetic model was applied to the data for loss of available iodine followed by an Arrhenius-type evaluation. The first-order model was correlated with actual product performance under typical storage conditions to determine its utility.

Experimental

Two PEPU foams, foams A and B, were used as received from the suppliers. Table 1 lists the properties of the two foams. Povidone–iodine solution as stored and delivered from sponges made of these foams in a typical product was studied at each of four temperatures [ambient (25°C), 30, 45 and 55°C] over a period of time. In all cases, temperature in the storage chambers was maintained within ±2°C of the target temperature. Ambient humidity conditions existed at all temperatures. The typical product, in representative packaging consisting of a polyester-lined aluminium foil overwrap, was stored in packages, each containing one unit. Humidity was not monitored since the packaging provided a moisture barrier.

Assay of available iodine was performed by titration with 0.02 M sodium thiosulphate using starch as indicator as in the current USP specification [3]. Sodium thiosulphate and starch indicator solution were both obtained from Mallinkrodt Chemical Company (Paris, Kentucky). Preparation of samples for each titration comprised extracting two product units (sponge and plastic holder) with three 50-ml aliquots of methanol, diluting the combined extracts with 300 ml of water and acidifying the solution with 1 ml of 1 M HCl. Methanol and water were both HPLC grade and 1 M HCl was obtained from RICCA Chemical Company (Arlington, Texas). Control experiments demonstrated an extraction efficiency of 93% for the product containing either foam. All calculations were adjusted accordingly to accommodate this factor. Twelve product units (six

Table 1
Comparison of physical properties of two PEPU foams

	Foam A	Foam B
Colour	White	White
Density [kg(m^{-3})]	20–23	19–21
Tensile strength (kPa)	>100	>96
Elongation (%)	>200	>150
Tear strength [N(cm^{-1})]	*	2.1
Compression (%)	10	15

*Value not available.

titrations) were assayed to establish available iodine levels at initial time. Immediately after the completion of this determination, the remaining samples were divided and placed under the specified storage conditions. Eight product units (four titrations) were assayed at all other time intervals for all temperatures studied. For each point, a mean and a relative standard deviation (RSD) were calculated and reported. Historical data generated using the described method for this and similar products indicated a typical precision of ±5% (RSD).

Results and Discussion

Figures 2, 3, 4 and 5 depict the data collected for product containing one of the two PEPU foams for all temperatures studied. The difference between the initial potency of available iodine of the two foams can be explained by the fact that the products made using these foams were manufactured at different times and experienced different storage and transportation conditions prior to this study. This difference remained essentially constant throughout the study at all temperatures. As previously noted, the initial potency of available iodine was identical for the four study temperatures for each foam, respectively.

The general profile of the stability curves for PVP-I solution in the two foams shows an initial rapid decline in available iodine (I_a) followed by a period of relatively constant I_a potency. Although this shape is more apparent at higher temperatures, the fact that it is observed at all temperatures lends credence to the assumption that a similar reaction mechanism for loss of I_a exists for the temperature range studied. This general profile is also seen in typical long-term data collected over a period of ≈12 months for products stored at ambient temperature.

The parallel nature of the curves for PVP-I in the two foams at a given temperature indicates an equivalence of behaviour of PEPU foams A and B in terms of I_a stability. In order to confirm this statistically, however, several tests were applied to the data. Results of a Wilk–Shapiro test of normality and an F-test for variance ratio, both conducted at a

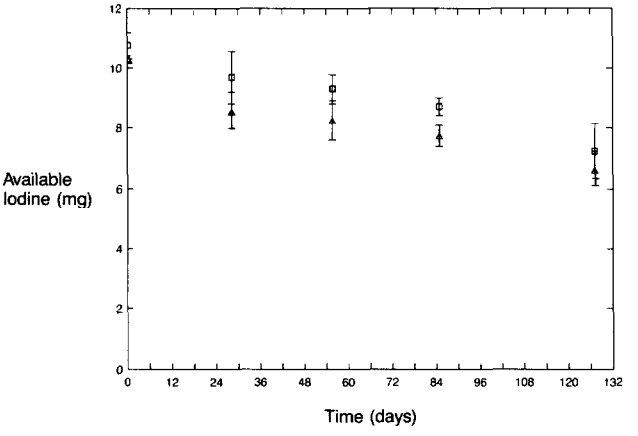

Figure 2
Loss of available iodine from povidone–iodine solution in two foams as a function of time at ambient (≈25°C) temperature. □, Foam A; △, foam B. Error bars represent the standard deviation about the mean (n = 6 at t = 0, n = 4 at all other times).

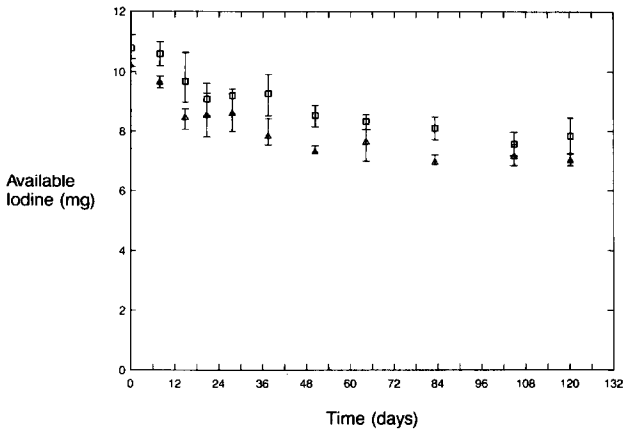

Figure 3
Loss of available iodine from povidone–iodine solution in two foams as a function of time at 30°C. □, Foam A; △, foam B. Error bars represent the standard deviation about the mean ($n = 6$ at $t = 0$, $n = 4$ at all other times).

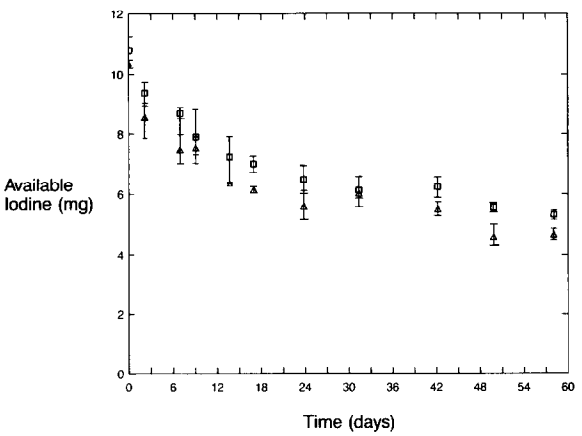

Figure 4
Loss of available iodine from povidone–iodine solution in two foams as a function of time at 45°C. □, Foam A; △, foam B. Error bars represent the standard deviation about the mean ($n = 6$ at $t = 0$, $n = 4$ at all other times).

significance level of 0.05, indicated that all sample populations were normal and that equal variances existed for the data for the two foams at each temperature. Subsequent correlation of the data obtained for foams A and B at 25, 30, 45 and 55°C produced correlation coefficients (r) of 0.9782, 0.9532, 0.9838 and 0.9950, respectively. All these values indicate similar behaviour of the two foams. In addition, a two-way analysis of variance was performed by temperature using time as a discrete factor. The results of this test, also conducted at the 0.05 significance level, were identical for all temperatures. Namely, at a given temperature, the mean I_a value for the two foams differed (the constant difference described above), I_a varied as a function of time, and there was no type–time interaction, i.e. the behaviour of one foam in terms of I_a stability was indistinguishable from that of the other.

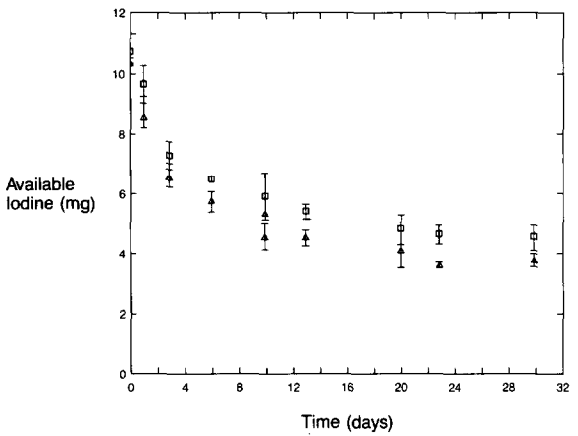

Figure 5
Loss of available iodine from povidone–iodine solution in two foams as a function of time at ambient 55°C. □, Foam A; △, foam B. Error bars represent the standard deviation about the mean ($n = 6$ at $t = 0$, $n = 4$ at all other times).

The shape of the stability curves in Figs 2–5 indicates a period of active reaction followed by a pseudo-steady state in terms of I_a. Available iodine concentration at the pseudo-steady state appears to be a function of temperature, with higher temperatures resulting in lower steady-state values. It was thus shown that the extent of the reaction period essentially determined the total extent of I_a loss in the product. In order to predict long-term product stability, it was deemed necessary to only model behaviour prior to the establishment of the pseudo-steady state. Models of kinetic behaviour were applied to all data generated at or before 130, 60, 27 and 12 days for 25, 30, 45 and 55°C, respectively. Initial time data were included in the regression analysis of 25°C data only, so as not to artificially increase the significance of these values. An empirical approach to kinetic modelling was taken with models of kinetic order 1, 3/2, 2, 5/2 and 3 being applied to the data. Based on the correlation coefficient and a residuals analysis, a first-order kinetic model was considered most appropriate. This model produced the rate constants listed in Table 2.

Table 2
Rate constants for loss of available iodine from povidone–iodine solution stored in two PEPU foams at various temperatures: first-order kinetic model

Temperature (°C)	Foam	Rate constant ($days^{-1}$)
25	Foam A	2.00×10^{-3}
25	Foam B	2.26×10^{-3}
30	Foam A	2.75×10^{-3}
30	Foam B	3.67×10^{-3}
45	Foam A	2.18×10^{-2}
45	Foam B	2.41×10^{-2}
55	Foam A	6.45×10^{-2}
55	Foam B	7.90×10^{-2}

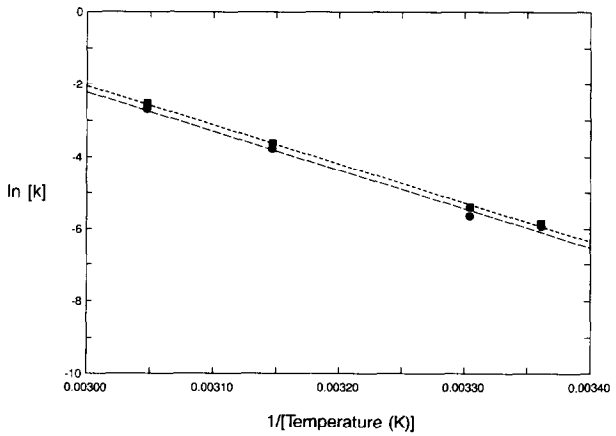

Figure 6
Arrhenius-type evaluation of rate information obtained from a first-order kinetic model applied to the stability of available iodine in povidone–iodine solution in two foams. ●, Foam A; ■, foam B. Linear regression analysis of the data yielded: foam A, $y = -11770x + 33.15$, $r = 0.9930$; foam B, $y = -11720x + 33.17$, $r = 0.9981$.

A plot of the logarithm of the rate constant versus the reciprocal of absolute (K) temperature (Arrhenius-type evaluation) produced a linear relationship yielding an activation energy of 2100 cal mol^{-1} for the reaction. Figure 6 depicts this relationship as well as the results of a linear regression analysis of the data. Note that the slope of the regression lines for the two foams is essentially identical, again indicating equivalence of stability behaviour. Based on this analysis, rate constants ±95% confidence limits of 1.75×10^{-3} $days^{-1} \pm 0.16 \times 10^{-3}$ $days^{-1}$ and 2.10×10^{-3} $days^{-1} \pm 0.19 \times 10^{-3}$ $days^{-1}$ were predicted for PVP-I solution stored at 25°C in foams A and B, respectively. Consequently, the time ±95% confidence limits required for I_a to drop from 10 to 4 mg (current product in-house limit) is 523 ± 43 days (1.4 ± 0.1 years) for foam A, and 436 ± 36 days (1.2 ± 0.1 years) for foam B. These estimates correlate well with actual acceptable commercial product data for the two foams. In addition, since the model ignores the occurrence of a plateau on the stability curve, it represents a more conservative estimate of actual product performance.

Conclusions

Sponges made from one of two PEPU foams and used in a typical dialysis therapy product were shown to be equivalent storage and delivery systems for povidone–iodine solution in terms of the stability of available iodine. The general shapes of plots of available iodine potency with time, based on storage at 25, 30, 45 and 55°C, respectively were shown to be identical, indicating the likelihood of similar reaction mechanisms in this temperature range. Since this profile consisted of an initial rapid loss of potency followed by an apparent steady state, a kinetic model was developed to predict long-term stability based solely on points on the profile decline. Using this assumption, the loss of available iodine with time in a typical product was shown empirically to follow a first-order kinetic profile. Comparisons of shelf-life predictions resulting from the model and actual long-term ambient temperature storage data showed a good correlation, thus indicating the utility of the model as a predictive tool.

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