Analysis of the Shelf Life of Nano-Two Solution Bone Cement (η-TSBC)

+1Jariwala, S H; 1Hasenwinkel, J M; 1Gilbert, J L... 
Mather, professor at the Dept. of BMCE, Syracuse University, Syracuse, NY

gilbert@syr.edu

Introduction:
A novel two-solution bone cement (TSBC) has been developed as an alternative to the commercially available powder-liquid bone cement used clinically to stabilize implants. The TSBC was further modified by addition of a cross-linked phase, polymethylmethacrylate (PMMA) nanoparticles, to tailor the viscosity of the cement for applications such as vertebroplasty and kyphoplasty and was called nano-two solution bone cement (η-TSBC). A significant difference in the TSBC system in comparison to commercial systems is that the initiator, benzoyl peroxide (BPO), is dissolved into the PMMA-methylmethacrylate (MMA) solution and is directly in contact with the monomer. This renders the cement susceptible to spontaneous polymerization during storage due to heat or light, thus affecting the clinically useful shelf-life of the cement. The goal of this study was to determine the effect of storage time and temperature on the spontaneous polymerization of BPO-containing η-TSBC using isothermal differential scanning calorimetry (Iso-DSC).

Method:
The TSBC, used as controls, were prepared at a polymer (P) to monomer (M) ratio 0:9:1 following the technique described by Hasenwinkel and co-workers. The modified η-TSBCs were made up of two polymer phases: (1) dissolved linear PMMA (P), and (2) dispersed cross-linked PMMA nanospheres (P2). PMMA nanospheres were synthesized via boiling temperature soap-free emulsion polymerization of MMA (6.25% v/v). This technique resulted in monodisperse nanospheres ranging in size from 300 to 330 nm. For the η-TSBC, the desired ratio of cross-linked nanospheres to linear PMMA (P2/P1) was determined and these two components were mixed to form the powder phase (P). The MMA was first mixed with BPO (1.25g/100ml MMA) and then with the powder phase in polypropylene cartridges. The cement cartridges were then sealed and mixed on a rotating drum for 18 hrs. The cartridges were then stored at 4°C prior to use. The P2/P1 ratios used for this study were 1:1 and 1.5:1 and P:M ratios used were 1:1, 1:1.1.

Iso-DSC (DSC-7, Perkin Elmer) was used to investigate the shelf-life of the different cement compositions over a temperature range of 45-70°C. Approximately 10-20 mg of sample was directly placed in the DSC pan and tested isothermally at several temperatures (45, 50, 55, 60, 65 and 70°C) and the power vs. time data was obtained. Three DSC runs were collected at each temperature for each cement composition. The power vs. time plots reflected the changes in the heat given off (or taken up) by the sample, which was determined by fitting a baseline and integrating the plots to get the area under the peak. The setting time (t_s) was determined as the time to reach the maximum exothermic power. Decomposition of BPO could become a rate controlling mechanism of thermal polymerization during storage and was hypothesized to be governed by an Arrhenius-type behavior, k = A exp (-E/RT), where k is the rate of decomposition of BPO, A is a frequency factor, E is the activation energy for decomposition, R is the ideal gas constant (8.314 J/mol K) and T is the temperature in degrees Kelvin. However conversion of the monomer is concerned with the propagation rate constant (k_p), and k_p is proportional to (1/t_s), so the Arrhenius equation becomes ln(1/t_s) = ln A - E/RT

The setting behavior of BPO containing η-TSBC was monitored by plotting ln(1/t_s) vs. 1/T (experimental temperature). Long term shelf-life analysis was also planned for a year, where the cement cartridge was stored at 4°C and tested at 70°C every 2 weeks under the Iso-DSC in order to obtain the amount of heat given out. The long-term shelf-life testing is ongoing.

Results:
The results of Iso-DSC testing are shown in Figure 1(a). The setting time increased exponentially with decreasing experimental temperature, suggesting the reaction is governed by the Arrhenius equation. Figure 1(b) shows the Arrhenius plots of the cements tested. It can be seen that there is a high correlation between shelf life and storage temperatures. The shelf life of η-TSBC was predicted by using regression analysis and extrapolating to 4°C as shown in Table 1. Statistical analysis on the regression lines revealed the 95% confidence and prediction levels which allowed for a range of shelf lives at a given temperature, as shown in Figure 2(a).

(b) Long term shelf-life analysis of η-TSBC. Setting time as a function of storage time.

Figure 1. Iso-DSC of η-TSBCs. (a) Setting time as a function of temperature. (b) Setting time of η-TSBC analyzed using Arrhenius expression. The regression lines are extrapolated to find the setting time at 4°C (cement storage temperature).

Discussion:
As seen from Figure 1(a), there was a clear dependence of setting time on temperature, with longer setting times at lower temperatures. We have found that introduction of nanospheres in TSBC increases the cement setting time. Since the exothermic heat developed during the polymerization is due to the propagation step (monomer conversion), longer setting time means a slower polymerization rate and hence longer shelf life, as can be observed from the results obtained in Table 1. Thus the modified cements have a significantly longer shelf-life at 4°C compared to TSBC. However, the prediction levels indicate a very broad range of values that this shelf life could take at 4°C. Hence a long term analysis would give a better approximation about the shelf life of the cements, where shortened setting times and lower heats would indicate that partial setting of the polymer had occurred. This study is ongoing and as can be seen from Figure 2(b), there is not a significant drop in TSBC or η-TSBC (P:M 1:1; P2/P1 1:1) setting time during the first 16 weeks of the study.

Conclusions:
Spontaneous polymerization of BPO-containing η-TSBC obeys an Arrhenius expression and depends on storage temperature. The η-TSBCs had longer shelf lives at 4°C compared to the TSBC. These results also indicate that temperatures below 4°C will significantly increase shelf life (shelf life at freezer temperature (-20°C) for TSBC is 90.5 years). Shelf life of η-TSBC can be simply determined by Iso-DSC method.

References:

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