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Kinetics of Elution of Gentamicin from a Gentamicin-Loaded PMMA Bone Cement

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Abstract

Antibiotic-loaded poly (methyl methacrylate) bone cement (ALBC) is widely used for anchoring joint replacements as a means of reducing the potential for peri-prosthetic joint infection (primary cases) and treating a patient who has an infected joint replacement (revision cases). One shortcoming of the cement is the high maximum exothermic temperature experienced upon polymerization (T_{max}), a phenomenon that, it has been postulated, may cause or be implicated in thermal necrosis of peri-prosthetic tissues. There are many reports in the literature on methods of reducing T_{max}, with one such study involving the addition of a phase change material (microencapsulated paraffin) (MEPAR) to the cement powder or adding a chain-stopping chemical (1-dodecyl mercaptan) (DDM) to the liquid. In that report, the results of gentamicin elution tests were presented. In the present work, those results were used to calculate various indices of gentamicin elution kinetics, namely 1) diffusion coefficient (D_{gent}); and 2) values of the coefficients in four equations that are widely used to model antibiotic elution from ALBCs. We found 1) the difference in D_{gent} of either a MEPAR- or DDM-containing formulation, on the one hand, and that of the control cement, on the other, was not significant; and 2) a consistent trend in the value of only one coefficient in one of the four model equations, with this change suggesting insignificant difference in gentamicin elution mechanism between an experimental cement formulation and the control cement. The implications of these findings for guiding selection of additives that simultaneously produce significant reduction of T_{max} but minimal effect on gentamicin elution kinetics are discussed. This guide is a novel contribution to the literature.

Keywords

Poly (Methyl Methacrylate) Bone Cement, Gentamicin, Elution, Diffusion Coefficient, Kinetics Models

1. Introduction

For a total joint arthroplasty (TJA), its revision burden has been defined as the ratio of the number revised because of peri-prosthetic joint infection (PJI) to the total number of primary cases performed in a given period within a specific population [1]. The 2015 unweighted average burdens for total hip and knee arthroplasties between 6 arthroplasty registers are 0.97% and 1.03%, respectively [2]. In other words, the incidence of PJI is low; however, its impact is devastating. In fact, it is universally agreed that PJI is the most challenging complication of TJAs [3]. This is because of two reasons. First, a "gold standard" diagnostic test is lacking [3]. Second, even when diagnosed, it is difficult to treat/manage to the point of being intractable [3]. However, for patients who present with severe and persistent pain secondary to PJI diagnosis, the consensus is that the best treatment modality is two-stage exchange revision arthroplasty, which is a very painful and costly procedure (for example, in the United States, in 2010, annual hospital cost incurred for treating PJI cases was estimated to be between ~$769 million and ~$802 million, with it projected to rise to ~$1 billion by 2020) [4]. Thus, methods that aim to prevent PJI are an integral part of TJA practice. Arguably, the most widely used method is to anchor the joint replacement components in a bed of antibiotic-loaded poly (methyl methacrylate) bone cement (ALBC) [5]; for example, each year, in the United States, over the period 2010-2015, ~80% of total hip arthroplasties were cemented using an ALBC [6].

One of the shortcomings of the current generation of approved ALBC brands is that, upon polymerization, a high amount of heat is produced, which, some have postulated, may result in thermal necrosis of peri-prosthetic tissues [5]. Consequently, methods to reduce the maximum temperature reached during cement polymerization (T_{max}) have been the subject of many studies [7]-[12]. In one recent study, two experimental ALBC formulations were prepared, one in which a phase change material (microencapsulated paraffin (MEPAR)) was added to the cement powder and another in which a chain-stopping agent (1-dodecyl mercaptan (DDM)) was added to the cement liquid [12]. It was found that each of these additives was effective in that T_{max} was reduced by between 14% and 50% (with MEPAR additive) and between 31% and 47% (with DDM additive) compared to the corresponding value for the control ALBC [12]. However, in the study, although the cumulative gentamicin amount eluted obtained at different points during the test were determined, these results were only used to calculate CGE, which was defined as the cumulative mass of gentamicin eluted at the end of the test period (28 days) normalized by the product of the volume of phosphate buffered saline (PBS) solution used in the test and the initial mass of the test specimen [12].

The purpose of the present study was to determine more information about the kinetics of elution of gentamicin from the two aforementioned experimental ALBC formulations; specifically, 1) determine the diffusion coefficient (D_{gent}), 2) determine the best-fit equation (from a collection of equations) for modeling the

kinetics, and 3) use the results obtained in items 1) and 2) to provide guidelines for the selection of T_{max}-reducing agents. There are very few literature reports that present diffusion coefficient for elution of an antibiotic from an ALBC and there are no reports that utilize the combination of diffusion coefficient and best-fit equations for antibiotic release to provide guidance on materials to be added to the powder and/or liquid of an ALBC to influence cement properties. Both of these aspects are covered in this present work, underscoring its novelty.

2. Materials and Methods

2.1. Materials

The control cement used was a commercially-available gentamicin-loaded ALBC brand (Table 1). The additive to the cement powder was MEPAR (Microtek Laboratories, Moraine, OH, USA) and the additive to the cement liquid was DDM (98% purity; Acros Organics, ThermoFisher Scientific, Pittsburgh, PA, USA) (Table 2). Details of methods used to blend MEPAR with the cement powder and to dissolve DDM in the cement liquid are given in the previous report [12].

2.2. Specimen Preparation and Elution Test

Details of the methods used to obtain a homogenous cement dough and prepare the test specimens and the protocol used in performing the gentamicin elution test are given in the previous report [12]. After each measuring time-point (t) (1, 2, 5, 7, 10, 14, 21, and 28 d), a chemical derivatization method and a configurable microplate reader were used to determine the cumulative mass of gentamicin

Table 1. Composition of control cement brand [12].

Powder (40.0 g)		Liquid (15.7 mL)	
Poly (methyl methacrylate) beads (g)	33.11	Methyl methacrylate (mL)	15.42
$BaSO_4$ (g)	4.00	N,N-dimethyl-*p*-toluidine (mL)	0.27
Benzoyl peroxide (g)	1.20	Hydroquinone (ppm)	75
Gentamicin sulfate (g)	1.69		

Table 2. Compositions of the cements in the study groups [12].

Study group	Cement powder (g)	MEPAR (g)	Cement liquid (mL)	DDM (mL)	Powder-to-liquid ratio ($g \cdot mL^{-1}$)
Control	10.00	----	3.9	----	2.56
5MEPAR	8.00	0.42	3.3	----	2.55
15MEPAR	8.00	1.41	3.7	----	2.54
25MEPAR	8.00	2.67	4.2	----	2.54
1DDM	10.00	----	3.9	0.04	2.54
2DDM	10.00	----	3.8	0.08	2.58
3DDM	10.00	----	3.7	0.12	2.61

eluted (in μg) after which it was normalized by the product of the volume of the PBS solution used (3 mL) and the initial mass of the test specimen (321 ± 38 mg) leading to a final result (in $\mu g \cdot mL^{-1} \cdot mg^{-1}$). For each cement group, 3 replicate specimens were used for each value of t. Further details of this computation are given in the previous report [12].

2.3. Calculation of Diffusion Coefficient

The applicable governing equation for the elution of gentamicin out of the test specimen (for release ratio ≤ 0.8) was taken to be that for diffusion of a drug out of a long, cylindrical specimen; thus, it is [13]:

$$\frac{M_t}{M_\infty} = 4\left[\frac{D_{gent}t}{\pi a^2}\right]^{\frac{1}{2}} - \pi\left[\frac{D_{gent}t}{\pi a^2}\right] - \frac{\pi}{3}\left[\frac{D_{gent}t}{\pi a^2}\right]^{\frac{3}{2}} + 4\left[\frac{D_{gent}t}{\pi l^2}\right]^{\frac{1}{2}} - \frac{2a}{l}\left[8\left(\frac{D_{gent}t}{\pi a^2}\right) - 2\pi\left(\frac{D_{gent}t}{\pi a^2}\right)^{\frac{3}{2}} - \frac{2\pi}{3}\left(\frac{D_{gent}t}{\pi a^2}\right)^2\right], \quad (1)$$

where M_t is the cumulative amount of released gentamicin at a given time-point, M_∞ is the equilibrium amount of released gentamicin (defined as the value of M_t at which the M_t-versus-t plot flattened), D_{gent} is the gentamicin diffusion coefficient, t is time, l is the length of the test specimen (0.062 m), and a is the mean radius of the specimen (0.00374 m). With the aid of a commercially-available software package (Wolfram Mathematica, version 11; Citrix StoreFront, Citrix Corp., Fort Lauderdale, FL, USA), the M_t/M_∞-versus-t results and Equation (1) were used to compute D_{gent}.

2.4. Model Equations

For each of the study groups, four kinetics equations that have been widely used to gain insight into the mechanism(s) involved in the release of an antibiotic from ALBC specimens were fitted to the M_t/M_∞-versus-t results. These equations, in order, are those given by Korsmeyer *et al.* [14], Lindner and Lippold [15], Frutos *et al.* [16], and Hesaraki *et al.* [17]; namely

$$M_t/M_\infty = k_1 t^{n_1} \quad (2)$$

$$M_t/M_\infty = b + k_2 t^{n_2} \quad (3)$$

$$M_t/M_\infty = A + B\left(1 - e^{-n_3 t}\right) + Ct^{0.5} \quad (4)$$

$$M_t/M_\infty = k_3\left[1 - e^{-(t/\tau)d}\right] \quad (5)$$

The physical meanings of the coefficients (k_1, n_1, b, k_2, n_2, A, B, n_3, C, k_3, τ and d) in Equations (2)-(5) are given in **Table 3**, and their values were determined using a nonlinear least squares method contained in a commercially-available software package (OriginPro 8.6; OriginLab Corp, Northampton, MA, USA).

2.5. Statistical Analysis

The D_{gent} results are presented as mean ± population standard deviation and the mean values are reported for the coefficients in the model equations. For D_{gent} and each of the aforementioned coefficients, intergroup comparison was carried out using the Kruskal-Wallis test, with Bonferroni correction (SAS Version 11.5; SAS Institute, Inc., Cary, NC, USA). Significance was denoted when $p < 0.05$.

3. Results

The gentamicin elution test results are presented in **Figure 1** [12]. The computed

Table 3. Physical meanings of coefficients in Equations (2)-(5).

Coefficient	Physical meaning
k_1; k_2	Each is related to the characteristics of the macromolecular network of the cement matrix and the gentamicin
n_1; n_2; C; d	Each denotes that the mechanism of release of the gentamicin from the cement matrix is a diffusion process
b; A	Each is a term that characterizes the initial burst of the gentamicin from the cement
B; n_3	Each term is associated with a Noyes-Whitney dissolution process [18] of the gentamicin within the cement matrix
k_3	A term whose value is related to the initial loading of the gentamicin in the cement
τ	A time constant related to the mechanism of release of the gentamicin from the cement

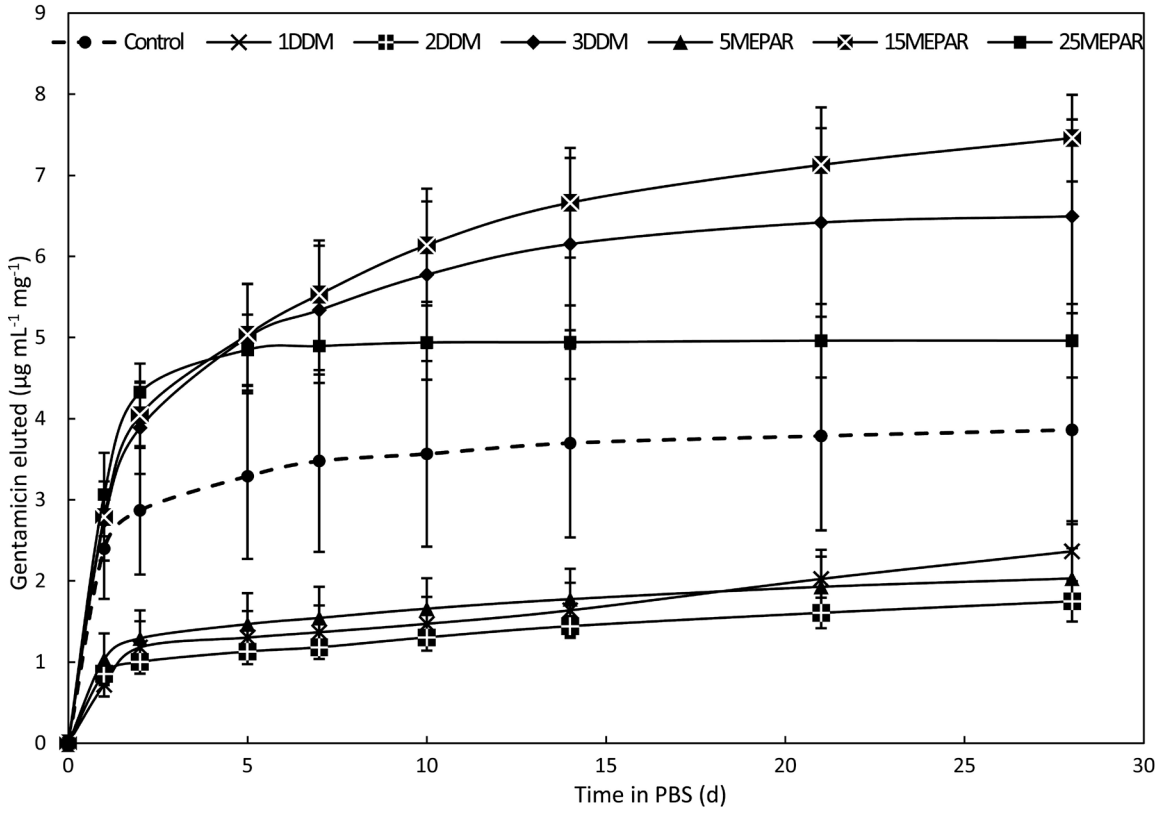

Figure 1. Summary of the gentamicin elution test results [12].

values for D_{gent} are given in Table 4 and the best-fit values of the coefficients in the model equations in Equations (2)-(5) are given in Table 5, from which it is seen that the fits were excellent (as an example, see Figure 2).

The difference between D_{gent} of an experimental cement formulation and that of the control cement was not significant ($p = 0.06$). The difference in D_{gent} among the experimental cement formulations was not significant ($p = 0.109$). Only one coefficient in one of the model equations displayed a consistent trend in going from the control cement to the experimental cement formulations; that is, coefficient n_2 in Equation (3). It was found that n_2 of an experimental cement formulation was greater than the corresponding value for the control cement but not significantly so ($p = 0.534$). The difference in n_2 among the experimental cement formulations was not significant ($p = 0.625$).

Table 4. Summary of computed values of D_{gent}.

Group	D_{gent} (10^{-12} $m^2 \cdot s^{-1}$)
Control	26.5 ± 7.6
5MEPAR	19.7 ± 5.7
15MEPAR	12.6 ± 4.4
25MEPAR	28.9 ± 5.2
1DDM	17.3 ± 2.1
2DDM	21.1 ± 7.7
3DDM	14.8 ± 1.9

Table 5. Summary of best-fit mean values of parameters: fits between release kinetics models and experimental results.

Cement	Equation (2)			Equation (3)				Equation (4)					Equation (5)			
	k_1	n_1	Adjusted R^{2*}	b	k_2	n_2	Adjusted R^{2*}	A	B	C	n_3	Adjusted R^{2*}	k_3	τ	d	Adjusted R^{2*}
Control	0.68	0.13	0.988	0.0066	0.68	0.16	0.985	0.0067	−0.64	0.25	1.21	0.989	2.04	1.333	0.29	0.998
5MEPAR	0.50	0.21	0.995	0.0008	0.50	0.21	0.994	0.0029	−0.59	0.25	1.32	0.993	4.23	1.77×10^4	0.28	0.995
15MEPAR	0.44	0.25	0.980	−0.0067	0.44	0.26	0.977	0.00027	0.48	0.10	1.37	0.993	3.26	1.73×10^4	0.48	0.996
25MEPAR	0.78	0.10	0.940	−0.0053	0.76	0.21	0.930	0.0033	−1.23	0.32	0.57	0.988	0.99	0.99	1.15	0.998

Cement	Equation (2)			Equation (3)				Equation (4)					Equation (5)			
	k_1	n_1	Adjusted R^{2*}	b	k_2	n_2	Adjusted R^{2*}	A	B	C	n_3	Adjusted R^{2*}	k_3	τ	d	Adjusted R^{2*}
1DDM	0.31	0.35	0.949	0.02	1.41	0.29	0.945	0.0031	1.72	0.45	0.08	0.975	40.63	0	0.37	0.941
2DDM	0.40	0.22	0.989	0.006	0.49	0.22	0.984	0.0057	0.01	0.18	7.45	0.995	6.55	2.63×10^4	0.29	0.987
3DDM	0.44	0.21	0.964	-0.009	0.53	0.21	0.958	0.0028	0.69	0.06	0.74	0.994	1.05	3.04	0.62	0.997

*Adjusted R^2 = coefficient of multiple determination, adjusted for the degrees of freedom of the equation. Control: no additive to powder or liquid; 5MEPAR: 5 wt./wt.% MEPAR in cement powder; 15MEPAR: 15 wt./wt.% MEPAR in cement powder; 25MEPAR: 25 wt./wt.% MEPAR in cement powder; 1DDM: 1 vol./vol.% DDM in cement liquid; 2DDM: 2 vol./vol.% DDM in cement liquid; 3DDM: 3 vol./vol.% DDM in cement liquid.

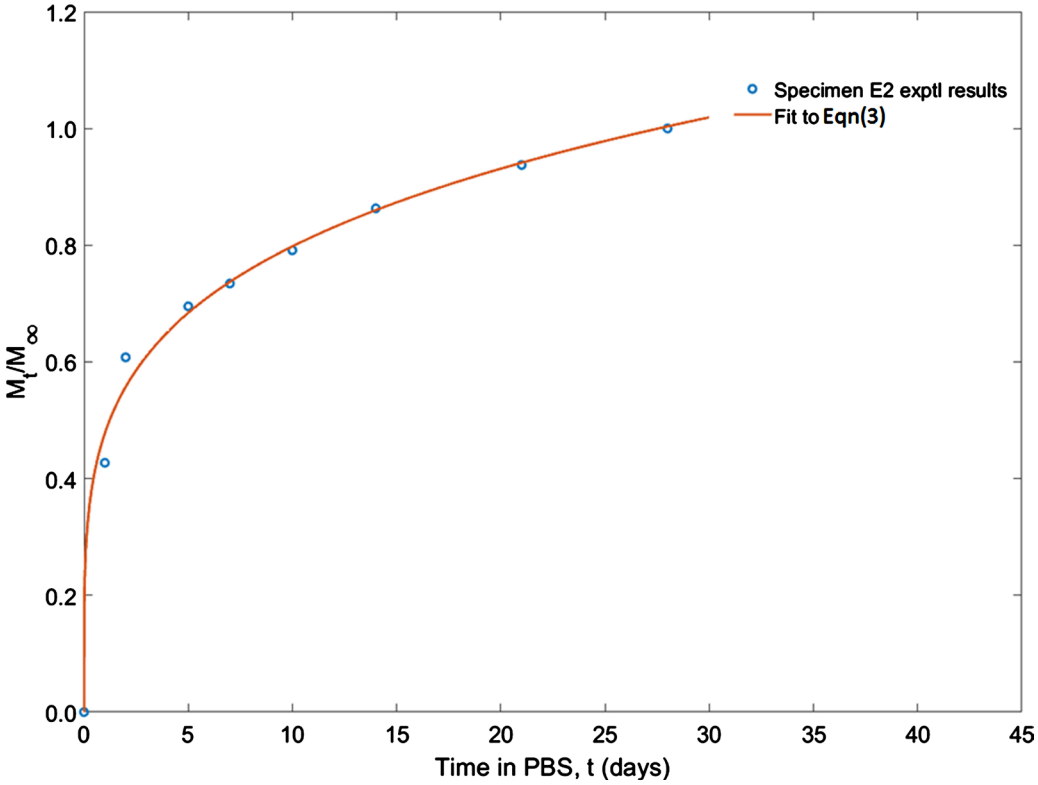

Figure 2. Sample fit between experimental results and Equation (3): specimen E2 (specimen #2 in the 5MEPAR group; for compositional details of the group, see **Table 2**).

4. Discussion

Many TJAs are grouted in the contiguous bone in an ALBC bed as a way of reducing the likelihood of PJI, which is the most challenging complication of TRJs (primary cases), or of treating a patient from whom an infected TJA has been removed (2-stage revision cases) [3].

There is a sizeable body of literature on research into methods of addressing one of the shortcomings of ALBCs, namely, high T_{max} [7]-[12]. In one such study, the relative influence of addition of a phase change material to the cement powder or of a chain-stopping agent to the cement liquid was investigated [12]. As part of that study, T_{max} and other cement properties were determined, among which was cumulative amount of gentamicin eluted over the test period of 28 days. No other index of gentamicin elution kinetics was determined. The purpose of the present study was to determine some of these indices, specifically, the coefficient for the diffusion of gentamicin (D_{gent}) and values of coefficients in four equations that have been postulated to be relevant to modeling the kinetics of elution of an antibiotic from an ALBC.

The literature on diffusion coefficient for elution of an antibiotic from ALBCs is very sparse, with the only reports being those by Shen *et al.* [19], Salehi *et al.* [20], and Shen *et al.* [21]. The values, computed by Shen *et al.* for gentamicin eluting from an approved brand (SmartSet GHV) and an experimental formulation (Simplex P (an approved plain brand) to which 3.4 wt./wt.% gentamicin was

mixed with the cement powder) were 4.9×10^{-15} $m^2 \cdot s^{-1}$ and 1.2×10^{-15} $m^2 \cdot s^{-1}$, respectively [19] [21]. These values are not on the same order as the present D_{gent} result for the control cement, which may be a consequence of a difference in the method of computation used. Salehi *et al.* [20] determined the diffusion coefficient of daptomycin (D_{dapt}) from an experimental cement formulation (1.36 g of daptomycin per 40 g of cement powder) to be $(37.50 \pm 2.10) \times 10^{-12}$ $m^2 \cdot s^{-1}$. While the present value of D_{gent} for the control cement ($(26.5 \pm 7.6) \times 10^{-12}$) is comparable to D_{dapt}, a difference in antibiotic incorporation method (that is, method used to mix/blend the antibiotic into the control cement powder) in the two studies should be noted; namely, proprietary (in the present study) and via a manual mixing device (in the study by Salehi *et al.* [20]). Various curing and cured properties of a commercially-available gentamicin-loaded bone cement (1.69 g of gentamicin per 40 g of cement powder; proprietary antibiotic incorporation method group (Cement A)) and two experimental formulations, each with the same powder as in Cement A but gentamicin incorporation method being mixing in an open bowl (Cement B) or mixing in a cement powder mixer (Cement C) have been reported [22]. It was found that while the difference in gentamicin elution rates (into PBS, at 37˚C) between Cement A and Cement B specimens was not significant, elution rate from Cement C specimens was significant higher than from either Cement A or Cement B specimens [22]. These results point to the likelihood that antibiotic incorporation method would exert a significant influence on D_{gent}.

Lack of significant difference in both D_{gent} and n_2 between experimental cement formulations, on the one hand, and the control cement, on the other, suggests that there is no significant difference in gentamicin elution mechanism between these two groups [5] [23]. In other words, addition of either MEPAR or DDM to the control cement powder and liquid, respectively, does not interfere with or alter the gentamicin elution mechanism of the control cement [5] [23]. It is worth noting that for both control cement and experimental cement formulations, $n_2 < 0.5$, consistent with the postulate of Fickian diffusion of gentamicin through pores in the matrix of the cement [24]. Thus, among the possible gentamicin elution mechanisms are diffusion of the gentamicin through the solid part of the cement matrix or through channels of cracks and voids in the cement matrix [5] [23]. Furthermore, lack of significant difference in n_2 between experimental cement formulations, on the one hand, and the control cement, on the other, indicates similarity in porosity among the specimens from these two groups.

Taken together, the trends in the D_{gent} and n_2 provide a guide with regard to selection of additives to incorporate in an ALBC from the perspective of reducing T_{max} without simultaneously affecting the kinetics of diffusion of the antibiotic. An appropriate additive is one that does not significantly affect the porosity of the cement specimen.

We recognize two limitations of our study. First, the gentamicin elution tests

were conducted in a medium (1X PBS solution, at 37˚C) whose ionic composition is similar to that of synovial fluid (the medium to which a joint and a TJR is exposed *in vivo*) but differs from it in terms of other constituents, such as proteins and cells and, additionally, the test conditions do not account for key *in vivo* features, such as the response of the host [25]. Second, the study was only on one approved ALBC brand, and, as such, generality of the applicability of the results to other approved ALBC brands cannot be claimed.

5. Conclusions

Based on the results obtained on one gentamicin-loaded PMMA bone cement brand, we conclude that:

- Addition of either a phase change material to the cement powder or a chain-stopping chemical to the cement liquid does not have a significant influence on the coefficient of diffusion of the gentamicin.
- A consistent trend was found in one coefficient in one of the four gentamicin elution kinetics equations tested for fit to the experimental elution test results, with this trend suggesting that 1) gentamicin elution mechanism in the control cement is not different from that in an experimental cement formulation and 2) the experimental cement formulation and control cement specimens have similarity porosity.
- Taken together, the present results provide guidance in selecting an additive to an ALBC that will simultaneously significantly reduce T_{max} but have an insignificant influence on antibiotic elution kinetics.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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