INTRODUCTION

Polycaprolactone (PCL) has been used as an implantation material since the early 1930s. It also became an environment-friendly agricultural product, as it could be degraded by microorganisms in vitro and in vivo. PCL (a hydrophobic semicrystalline polymer) displays the ideal solubility and plasticity needed for various applications and can be easily manufactured for medical uses.

The melting point of PCL is from 55°C to 60°C. PCL implants and scaffolds have been reported to exhibit a promising tunable porosity and controlled degradability. This tunable degradability is settled by the molecular weight (Mw) of PCL: longer-high Mw lasted longer than short-lower Mw. Therefore, PCL-M2 (Ellanse-M, Sinclair Pharmaceuticals, London, UK) was longer lasting than PCL-S1 (Ellanse S-version) after being injected into faces. Additionally, PCL filler showed neocollagenesis, neoelastinogenesis, and neovascularization in human studies.

For human studies, PCL-M2 was injected into the subdermis of the patients and biopsy specimens were obtained 1, 2, 3, and 4 years after the injections. Then, PCL diameter

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and PCL surface erosion were evaluated. PCL particles revealed various cutting cross-sections in the biopsy slides. Using various cutting cross sections, the real diameter (\(x^{\text{iso}}\)) was calculated using Equation of a circle (Equation\(^{10}\)) and Mean Value Theorem for Integrals (Integral\(^{\text{theo}}\)).\(^{11}\) The real PCL particle size can be calculated mathematically, and isovolumic phase-1 degradation property (how long the diameter lasts without changing in size) can be evaluated in vivo human biopsy studies.

With molecular weight, phase-1 degradation can be calculated using the formula \(M_\text{w} = M_\text{w}\exp(-k't)\).\(^{12}\) Phase-1 degradation times (\(t\)) of PCL fillers were 1, 2, 3, and 4 years in manufacturer’s planning. Therefore, \(M_\text{w}\) of PCL-S1, -M2, -L3, and -E4 can be estimated using this formula.

**METHOD**

All 8 patients underwent clinical evaluation after satisfying all study criteria related to previous medical and surgical history (including physical examinations). All patients, who had been to the author’s clinic in the past, were women, with the average age of 38.25 years. The patients were previously injected with botulinum toxin or were treated with an energy-based device such as high intensity–focused ultrasound (HIFU) and radiofrequency (RF). However, they were not treated within 6 months before the commencement of the study. Patients who had previously received any filler injections were excluded from this study. All 8 patients agreed to have not taken filler injection, have not been treated with HIFU, and have not undergone RF procedures during the follow-up period. These criteria were mandated because these would change the PCL particle size. In relation to these criteria, only Botox injection was allowed for the patients and was applied in the author’s clinic during the follow-up. Informed consent was obtained from the patients, in compliance with the Korean Society of Plastic and Reconstructive Surgeons standards. This study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and to the applicable local regulations. This is a single-clinic prospective study conducted from January 2013 to June 2019.

Using subdermal scraping skin tightening technique (SSSTT), PCL-M2 was injected for all patients just under the dermis with the help of a 25G-5cm blunt cannula. To evaluate immediately after injections, PCL-M2 fillers were injected under the skin and in muscle layer on fresh chicken breasts, and biopsy studies were conducted.

**Biopsy Study**

Specimens were obtained from 8 patients who had planned to undergo a face-lifting surgery after 1, 2, 3, and 4 years (random) after PCL-M2 injections. A 0.5 × 3 cm piece of soft tissue was excised from below the temporal hairline or preauricular area during the surgery.

A biopsy study was performed to measure the size of PCL particle in biopsy specimens, using a light microscope (Olympus BX41; Olympus, Tokyo, Japan) and a microscope digital camera (eXcope T300; Touptek, Zhejiang, China). Ten biopsy slides were selected from each of the 8 patients, amounting to a total of 80 slides. For each of the 80 slides, 5 photographs were taken in different areas, after observing them under a light-microscope (H&E stain) with 100× magnification so as to measure PCL size. Additionally, 5 photographs were taken with 200× magnification to evaluate PCL shape. Slide photographs with 100× magnification contained 30–100 PCL particles, and slide photographs with 200× magnification contained 5–45 PCL particles.

In 80 biopsy slides, thousand diameters from cutting cross sections follow normal distribution because measuring value was large enough. The author wanted to mathematically estimate the actual PCL particle size by cutting diameter of particles, and how long the diameter lasts without a change in diameter length (isovolumic degradation property). Also surface erosion without volume loss (phase-1 degradation) and bulk degradation showing volume loss (phase-2 degradation) were evaluated in long-term follow-up from human biopsy studies. The degradation features and shape of PCL particles were observed. (See Video [online], which displays the degradation features and shape of PCL particles.)

Using the Image-J program, all PCL particles were measured by 400 photographs (100×) from 80 slides. ImageJ is a Java-based image-processing program developed at the National Institutes of Health and the Laboratory for Optical and Computational Instrumentation (LOCI, University of Wisconsin).\(^{13,14}\) Using cross-section diameters of PCL particles in biopsy slides, real particle diameter was calculated mathematically using Equation\(^{\text{circle}}\) and Integral\(^{\text{theo}}\).\(^{11}\)

To measure immediately after injection, PCL-M2 fillers were injected under the skin and in muscle layer on fresh chicken breasts purchased from a usual market and biopsy slides were made (Tables 1 and 2).

**Mathematical Calculation to Estimate PCL Particle Size**

Particle sizes (all values) in 400 photographs (5 photographs from 80 biopsy slides) captured under 100× magnification were measured, and only top 20% of the largest particles can be used to calculate the actual size of PCL particle (\(P_{\text{size}}\)). Among all values, top 20% of the largest diameters were selected using Excel program and the average (Top\(^{20}\)) was calculated. The measured diameters (all values) were normally Gaussian distributed because the population size was large enough.

There are two methods to calculate \(P_{\text{size}}\) from Top\(^{20}\) in biopsy slides. One method is Equation of a circle and other is Mean Value Theorem for Integrals (see Video [online], which displays the degradation features and shape of PCL particles).

**Equation of a Circle**

Since all measured radii followed normal distribution, top 20% of the largest sizes (from \(x^{\text{iso}}\) to \(x^{w}\)) were selected. The actual radius of Ellansé was assumed to be 10 in the Equation of a circle. Then parameter\(^{14}\) can be calculated by the average diameter of top 20% (Top\(^{20}\)) using equation of a circle. By multiplying parameter\(^{41}\) to Top\(^{20}\), it is the actual size of Ellansé particle (\(P_{\text{size}}\)).
Equation of a circle

\[ r (\text{radius})^2 = x^2 + y^2 \]

If the radius of particle was assumed 10, \( x^{100} = 10 \)

\[ 10^2 = x^2 + y^2 \]

If actual particle size is assumed 10, then \( x^{100} \) is 10 in above graph of Figure 1.

“\( y \)” is the measured radius.

If the top 20% of the largest in size from all values were selected, “\( x \)” is between 0 (\( x^{100} \)) to 2 (\( x^{20} \))

\( x^{100} \) is the biggest radius among selected measured radius

\( x^{20} \) is the smallest radius among selected measured radius

\[ x^{80} = \sqrt{10^2 - x^{20}^2} = \sqrt{10^2 - 1^2} = 9.94987437 \] (Fig. 1)

The mean diameter of \( Top^{20} = x^{20} \)

\[ x^{80} = \sqrt{10^2 - x^{80}^2} = \sqrt{10^2 - 2^2} = 9.797958971 \] (Fig. 1)

Assumed radius of Ellansé: \( 10 = x^{20} \times \text{parameter}^{eq} \)

\[ \text{parameter}^{eq} = \left( \frac{10}{x^{20}} \right) = \left( \frac{10}{9.987492} \right) = 1.0050378 \]

Actual particle size \( (P_{\text{size}}) = Top^{20} \times \text{parameter}^{eq} = Top^{20} \times 1.0050378 \)

When top 20% of diameters were selected among all the measured values, the mean diameter \( (Top^{20}) \) turned out to be 99.4987437% of the actual diameter \( (P_{\text{size}}) \). When top 20% of diameters were selected from all values, particles were selected from 97.97958971% size \( (x^{80}) \) to 100% size \( (x^{100}) \) in normal distribution. If hypothetic radius is 10, the mean value of the selected top 20% will lie on top 10% \( (x^{20}) \). And parameter\(^{eq} \) can be calculated as above.

Therefore, by multiplying 1.0050378 (parameter\(^{eq} \)) to \( Top^{20} \) in biopsy slides, it is possible to calculate the actual particle size \( (P_{\text{size}}) \).

Mean Value Theorem of Integrals

**Integral Theorem Using Top 20% Values**

Actual Ellansé radius can also be calculated by Integral\(^{\text{theorem}} \) with top 20% largest particles in biopsy slides instead of the Equation circle. Using Integral\(^{\text{theorem}} \), mean diameter from \( x^{80} \) to \( x^{20} \) can be calculated. The resulting integral can be computed using integration by parts or a double angle formula followed by one more substitution.

One can also note that the function being integrated is the upper right quarter of a circle with a radius of one, and hence integrating the upper right quarter from zero to one is the geometric equivalent to the area of one quarter of the unit circle, or \( \pi/4 \). Assuming that the radius of a circle is 10, the average of the top 20% of the radius is \( Top^{20} \) (Fig. 2).

With top 20% cross-section radius, real radius can be mathematically calculated using Integral\(^{\text{theorem}} \). The result is obtained through integral mean value theorem, where \( a = 0 \) and \( b = 2 \).

Integral Mean Value Theorem

\[ \frac{1}{b-a} \int_a^b f(x) \, dx \]

\[ \frac{1}{2-0} \int_0^2 \sqrt{100-x^2} \, dx \]

Manually computed antiderivative for

\[ f(x) = \sqrt{100-x^2} \]

\[ F^*(x) = 5x \sqrt{\frac{1-x^2}{100}} + 50 \arcsin \left( \frac{x}{10} \right) + C = \frac{x \sqrt{100-x^2}}{2} + 50 \arcsin \left( \frac{x}{10} \right) + C \]

To calculate the definite integral \( \int_0^2 \sqrt{100-x^2} \, dx \), the result follows:

\[ \int_0^2 \sqrt{100-x^2} \, dx = \left[ \left( \frac{2\sqrt{100-x^2}}{2} + 50 \arcsin \left( \frac{2}{10} \right) + C \right) - \left( 0 + 50 \arcsin \left( \frac{0}{10} \right) + C \right) \right] \]

\[ = 50 \arcsin \left( \frac{1}{5} \right) + 4\sqrt{6} \]

\[ = 19.86585501064925 \]

To achieve the final result in

\[ \frac{1}{2-0} \int_0^2 \sqrt{100-x^2} \, dx = \frac{1}{2-0} \times 19.86585501064925 = 9.932927505324625 \]

The calculated mean is 9.932927505324625, the \( Top^{20} \).

One can note that the function being integrated is the upper right quarter of a circle with a radius of 10. (Though needing the top 20%, a circle is symmetrical to the radius; therefore, it is logical to use only one quarter...
of the circle.) The actual radius of the PCL particle can be obtained through the ratio below after calculation of parameter_integ.

\[ 9.932927505324625 \times \text{parameter}_{\text{integ}} = 10 \] (assumed radius)

\[ \text{parameter}_{\text{integ}} = \left( \frac{10}{9.932927505324625} \right) = 1.006752540 \]

\[ F^{\text{size}} = \text{Top}^{20} \times \text{parameter}_{\text{integ}} \times 1.006752540 \]

**Integral Theorem Using All Measured Values**

To calculate the real PCL size, the average of all measured values (All\text{avrg}) can be used instead of the top 20% data, and these 2 results are the same. When calculating all measured size, \( a \) is 0 and \( b \) is 10 (Fig. 3).

Integral Mean Value Theorem

\[ \frac{1}{b-a} \int_{a}^{b} f(x) \, dx \]

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**Fig. 2.** Mean value theorem for integrals using top 20% values.

**Fig. 3.** Mean value theorem for integrals using all values. With all cross-section radii, real radius can be calculated mathematically using Integral Theorem.
\[ \frac{1}{10-0} \int_{0}^{x} \sqrt{100-x^2} \, dx \]
\[ \frac{1}{10-0} \cdot 78.53982 = 7.853982 \]

If \( x^{100} \) assumed 10, integration of all radius is 7.853982.

\[ 10 \cdot (x^{100}) = 7.853982 \times \text{parameter}^{\text{Integ-All}} \]

\[ p_{\text{Size}} = \frac{\text{average of all measured values}}{\text{parameter}^{\text{Integ-All}}} \]

\[ p_{\text{Size}} = \text{All}^{\text{aver}} \times 1.273239485397344 \]

**Laser Diffraction Particle Size Analysis**

Additionally, PCL-M2 particle sizes were measured using a laser diffraction particle size analyzer (PSA) (PSA-1190).

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**Fig. 4.** Diffraction particle size analysis (PSA). Diffraction is when a wave goes through a small hole and has a flared-out geometric shadow of the slit. Reflection is when waves, whether physical or electromagnetic, bounce from a surface back toward the source. A mirror reflects the image of the observer. Refraction is when waves, whether physical or electromagnetic, are deflected when they go through a substance. The wave generally changes the angle of its general direction.

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**Table 1. PCL Particle Size Analysis from Biopsy Slide Using the Equation of a Circle**

|                  | Immediate* | 1 Year | 2 Years | 3 Years | 4 Years |
|------------------|------------|--------|---------|---------|---------|
| Top \( \mu \text{m} \) SD | 42.5525 ± 5.4737 | 42.8995 ± 6.6820 | 42.3365 ± 4.1930 | 40.6269 ± 4.1001 | 34.2361 ± 11.9927 |
| \times parameter\text{Circle} | | | | | |
| Calculated \( p_{\text{Size}} \) equation of a circle | 42.7668 | 43.1156 | 42.5497 | 40.8315 | 34.4085 |
| Changes in size | 100.00% | 100.81% | 99.49% | 95.47% | 80.45% |

The average of top 20% measured diameter \( (\text{Top}^{20}) \) and the calculated particle size \( (p_{\text{Size}}) \) using Equation of a Circle from \( \text{Top}^{20} \).

*To measure immediately after injection, PCL-M2 fillers were injected under the skin and in muscle layer on fresh chicken breasts purchased from a usual market and biopsy slides were made.

**Table 2. PCL Particle Size Analysis from Biopsy Slide Using Integral\text{theorem}.**

|                  | Immediate* | 1 Year | 2 Years | 3 Years | 4 Years |
|------------------|------------|--------|---------|---------|---------|
| Top \( \mu \text{m} \) SD | 42.5525 ± 5.4737 | 42.8995 ± 6.6820 | 42.3365 ± 4.1930 | 40.6269 ± 4.1001 | 34.2361 ± 11.9927 |
| \times parameter\text{Integral} | | | | | |
| Calculated \( p_{\text{Size}} \) Integral\text{theorem} | 42.8398 | 43.1892 | 42.6223 | 40.9013 | 34.4673 |
| Changes in size | 100.00% | 100.81% | 99.49% | 95.47% | 80.45% |

Measured Top \( \mu \text{m} \) in all slides, and \( p_{\text{Size}} \) was calculated using Integral\text{theorem} from \( \text{Top}^{20} \).

*To measure immediately after injection, PCL-M2 fillers were injected under the skin and in muscle layer on fresh chicken breasts purchased from a usual market and biopsy slides were made.
Anton-Paar, Graz, Austria). The PSA determines the particle size distribution based on laser diffraction exhibited by the sample. The angle of diffraction depends on the particle size. This diffraction pattern is detected and analyzed. The analysis compares the measured values with the expected theoretical values. This analyzer allows the measure of particles between 0.04 and 2500 μm by the diffraction pattern, using Fraunhofer or Mie theory\(^{15-18}\) (Fig. 4).

**RESULTS**

PCL particles maintained their diameters. The diameters after 1, 2, and 3 years were almost the same as the values obtained immediately after injection, showing phase-1 degradation. The changes in size were 100.81% (1 year), 99.49% (2 years), 95.47% (3 years), and 80.45% (4 years). Four years after injection, the diameter became 80%, showing phase-2 degradation. These changes in size were exactly the same in Equation of a circle and in Integral theorem (Tables 1 and 2).

On average, the calculated PCL size \(P_{Size}\) was 42.76 (immediately), 43.11 (1 year), 42.54 (2 years), 40.83 (3 years), and 34.40 μm (4 years) using Equation of a circle (Table 1 and Figs. 5–7).

And \(P_{Size}\) was 42.83 (immediately), 43.18 (1 year), 42.62 (2 years), 40.90 (3 years), and 34.46 μm (4 years) using Integral theorem (Table 2).

In laser diffraction particle size analysis, the mean diameter was 42.42 μm (29.10–59.72 μm), with the median at 41.26 μm. And this value was close to the calculated size, that is, 42.76 μm (Equation of a circle) and 42.82 μm (Integral theorem) (Fig. 5) (Tables 1 and 2).

The results obtained using mathematical calculation by Equation of a circle and Integral theorem in biopsy slides were almost the same as the result gained through the laser diffraction method in vitro.

**Equation of a Circle**

The average of top 20% measured diameters in biopsy slides \((\text{Top}^{20})\) were 42.5525 (immediately after injection), 42.8995 (1 year), 42.3365 (2 years), 40.6269 (3 years), and 34.236 μm (4 years).

The calculated diameter is \(\text{Top}^{20} \times \text{parameter}_{\text{Circle}}\).

\[ P_{Size} = \text{Top}^{20} \times \text{parameter}_{\text{Circle}} = \text{Top}^{20} \times 1.006752540 \]

The diameter calculated using the equation of a circle was 42.8398 (immediately), 43.1892 (1 year), 42.6223 (2 years), 40.9013 (3 years), and 34.4673 μm (4 years) (Table 1).

**Mean Value Theorem for Integrals**

**Integral theorem Using Top 20% Values**

\(\text{Top}^{20}\) were 42.55 ± 5.47, 42.89 ± 6.68, 42.33 ± 4.19, 40.62 ± 4.10, and 34.23 ± 11.09.

The calculated diameter is \(\text{Top}^{20} \times \text{parameter}_{\text{Integ}}\).

\[ P_{Size} = \text{Top}^{20} \times \text{parameter}_{\text{Integ}} = \text{Top}^{20} \times 1.006752540 \]

The calculated diameter using mean value theorem for integrals was 42.8398 (immediately), 43.1892 (1 year), 42.6223 (2 years), 40.9013 (3 years), and 34.4673 (4 years) (Table 2).

**Fig. 5.** Particle size and shape 2 years after PCL injection in subdermis (H&E ×200). All particles were circular with smooth surfaces.

**Fig. 6.** Particle size and shape 3 years after PCL injection in the subdermis (H&E ×200). Some particles had a smooth surface (arrow head). Other particles had a slightly rough surface showing surface erosion (arrow). F, fibrocyte; FGC, foreign body giant cell; Mp, macrophage.

**Fig. 7.** Particle size and shape 4 years after PCL injection in subdermis (H&E ×200). All particles had a rough surface showing surface erosion, and particle size decreased, showing bulky degradation (phase-2 degradation). Matured collagen bundles were seen, which were found to mimic a hypertrophic scar tissue pattern.
Integral Mean Value Theorem Using All Values

Diameters of PCL particles ($d_{av}$) can be calculated with all measured PCL sizes in biopsy slides.

$$
\frac{1}{b-a} \int_{a}^{b} f(x) \, dx
$$

$$
\frac{1}{10-0} \int_{0}^{10} \sqrt{100-x^2} \, dx = \frac{1}{10-0} \int 78.53982 = 7.853982
$$

If $x^{100}$ assumed 10, integration of all radius is 7.853982.

$$
10 \text{ (assumed)} = 7.853982 \times \text{parameter}_{\text{Integ-All}}
$$

$$
\text{parameter}_{\text{Integ-All}} = \left( \frac{10}{7.853982} \right) = 1.273239485397344
$$

$$
P_{\text{Size}} = \text{All}_{\text{av}} \times \text{parameter}_{\text{Integ}}
$$

$$
= 32.2893617 \times 1.273239485397344 = 41.11209028
$$

The average of all measured particle sizes (immediately after the injection) was 32.2893617 ± 10.76050592 µm. Using all measured values, calculated particle size was 41.11 µm. There was a very small difference between calculations using all measured values (41.11 µm) and using the top 20% (42.83 µm).

Laser Diffraction Particle Size Analysis

In laser diffraction PSA, the actual mean diameter of PCL particles was 42.42 µm (29.10–59.72 µm), and median diameter was 41.26 µm (Fig. 5). The measured diameter (42.42 µm) using PSA in vitro was almost the same as the diameter (42.76 µm) by Equation circle and 42.83 µm by Integral theorem calculated from biopsy slides (Fig. 8).

**DISCUSSION**

From molecular weight phase 1, *phase-1 degradation time* ($t$) can be calculated using the formula $M_n = M_w \exp(-k't)$. Also reversely, if phase-1 degradation can be 1, 2, 3, and 4 years, molecular weight can be calculated as wished.

$$
M_n = M_w : \exp(-k't)
$$

where

$$
k' = k(\text{HzO}[\text{EI}])
$$

This kinetic expression holds surprisingly well for an extended degradation period, during which $M_w$ decreases to <10% of its initial value, and the crystallinity increases from 45% to about 80%. The observation that the kinetic expression (1) incorporates the first power of the carboxylic acid end group concentration is unexpected. The hydrogen ion concentration of a weak acid is proportional to the square root of the acid concentration.

Regardless of the initial $M_w$ or its geometry of the sample, a linear relationship between In $M$ or In [n] and the time until the $M_w$ decreases to about 5000. Thereafter, there was a consistent but slower increase in crystallinity with chain cleavage to a value of about 80% after 120 weeks ($M_n = 4600$). The rate constant $k'$ derived from the initial part of the linear plot in Figure 2 (up to 110 weeks) is $3.07 \times 10^{-3}$ day$^{-1}$, that is, the number of ester groups cleaved per day corresponds to about 0.31% of the carboxylic acid end groups present (Fig. 9).

$$
M_n = M_w \times e^{-kt}
$$

$$
e = \sum_{n=0}^{\infty} \frac{1}{n!} = 2.71828
$$

Using the given formula and putting 784 days (112 weeks) for $t$,

$$
k = 3.07 \times 10^{-3} \text{ day}^{-1} \quad M_w = 51,000 \times e^{-3.07 \times 10^{-3} \times 784}
$$

$$
M_n = 4,600
$$

Therefore, the equation is matched to time and molecular weight.

The consistency of the data in Figure 9 demonstrates that the value of the rate constant is not affected by the presence of drug and dispersing agent. From this formula, manufacturer’s developmental background can be guessed. If they wanted to make 2 year of phase-1 degradation, it will be 730 days (2 year). The *original molecular weights* ($M_w$) can be calculated by 1, 2, 3, and 4 years of phase-1 degradation ($t$) inverting the confidence interval procedure. The unit of $t$ is day.

$$
M_n = M_w \times e^{-kt}
$$

$$
4600 = M_w^{M_2} \times e^{-kt}
$$

$$
e = 2.71828
$$

$$
k = 3.07 \times 10^{-3} \text{ day}^{-1}
$$

$$
t = 730 \text{ day} (2 \text{ year})
$$

$$
4600 = M_w^{M_2} \times e^{-0.00307 \times 730}
$$

$$
M_w^{M_2} = 4600 / e^{-0.00307 \times 730} = 43,256.88
$$

In the manufacturer guideline, PCL-S1 lasts for 1 year, PCL-M2 for 2 years, PCL-L3 for 3 years, and PCL-E4 for 4 years. They must have used the formula above. Then, we can derive the molecular weight of PCL particles.

Using the method above, the author’s estimation of the *original molecular weight* ($M_w$) of Ellansé product series follows:

To make exactly 1, 2, 3, and 4 years of *phase-1 degradation time* ($t$)

$$
T = \text{S1, M2, L3, E4 (1, 2, 3, 4 year)}
$$

$$
(t = 365, 730, 1095, 1460)
$$

$$
M_n = M_w \times e^{-kt}
$$

$$
4600 = M_w^{T} \times e^{-0.00307 \times t}
$$

$$
e = 2.71828, k = 3.07 \times 10^{-3} \text{ day}^{-1}
$$

$$
M_w^{T} = 4600 / 2.71828^{-0.00307 \times t}
$$
The result follows: for 1 year, $M_w$ will be 14,106; for 2 years, 43,265; for 3 years, 132,648; and for 4 years, 406,773.

But, no powder with the exact molecular weight exists. The company would normally use ready-made powder with the molecular weight ($M_w$) of 10k, 15k, 20k, 25k, 30k, 37k, 40k, 43k, 50k, 60k, 80k, 100k, and 190k. The longevity of powders can be found in Figures 10 and 11.

Biodegradables are solid polymeric materials that break down due to macromolecular degradation with dispersion in vivo but no proof for the elimination from the body. Bioresorbables show bulk degradation and further resorb in vivo. Bioerodibles show surface degradation and resorb in vivo. Bioresorbables and bioerodibles reflect total elimination of the initial foreign material and of surface degradation by-product with no

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**Fig. 8.** PCL-M2 particle size measurement using laser diffraction particle size analyzer.
residual side effects. Bioabsorbables dissolve in body fluids without any polymer chain cleavage or molecular mass decrease.\textsuperscript{19,20}

PCLs can be biodegraded by outdoor living organisms with enzyme.\textsuperscript{21} The process in human body, which can be divided into 2 phases, takes much longer.\textsuperscript{22} Phase 1 involves nonenzymatic hydrolytic cleavage of the ester linkages. The mass and volume of the implant remain unchanged during this process.\textsuperscript{12,23,24} The phase shows controlled, predictable, first-order, and linear bioresorption pattern. Phase 2 starts at a specific chain length with approximate chain molecular weight of about 5000 Da.\textsuperscript{25} Bulk degradation occurs in this phase when water penetrates the entire polymer bulk, causing hydrolysis throughout the entire polymer matrix. In this case, the internal concentration of auto-catalysis product can produce an acidic gradient.\textsuperscript{26}

The nonbacterial inflammatory reactions in vivo such as swelling or redness after the PCL filler injection is due to this acidic gradient and the rapid release of the oligomers. This also results in accelerated speed of internal degradation compared with that in the surface; an outer-layer’s molecular weight becomes higher than that of the interior. When the inner oligomers become small enough, they diffuse rapidly through the outer layer, accompanied by an onset of weight loss and a decrease in the rate of chain scission. During this phase, rate of chain scission decreases. It is also characterized by the onset of controlled and predictable total mass loss via bioresorption of the microspheres and excretion through the normal metabolic pathways.\textsuperscript{7,23}

\textbf{Fig. 9.} In vivo degradation of PCL capsule in Pitt’s study\textsuperscript{12}: (•) PCL-FRL-3 with Silastic insert; (▲) PCL-RRL-5B containing norgestrel insesame oil; () PCL*-1 unfilled.

\textbf{Fig. 10.} Estimated “phase-1 degradation time (t)” from commonly sold PCL powders. (The unit of t is day.) If molecular weight (Mw) of 15,000 was used to make PCL-S1 (Ellanse-S version; Sinclair Pharmaceuticals, London, UK), phase-1 degradation time (t) will be 385.01 days (1.05 years). For 40,000 Mw, it will be 704.50 days (1.99 years); for 100,000 Mw, 1002.97 days (2.74 years); and for 1,900,000 Mw, 1212.04 days (3.32 years) (Figs. 10 and 11).
Under isothermal conditions, the mass of PCL remained constant for 2 hours at temperatures ranging from 100 to 250°C. Therefore, temperature cannot be used to remove PCL fillers because 50–60°C do not effect thermal degradation.

PCL particles lasted for 3 years, maintaining its diameter, and isovolmic phase-1 degradation property of PCL was proved by this study. In cases such as HA fillers and calcium hydroxyapatite filler (Radiesse), they have a property of constant volume reduction immediate after injection. Therefore, the isovolmic degradation property is very different from other fillers; thus it is crucial for the surgeon to be aware of the change in volume after each filler injection (see Video [online], which displays the degradation features and shape of PCL particles).

CONCLUSIONS

For 3 years in subdermis, PCL particles maintained 95.47% (40 µm) of their original diameter (42 µm). This proved for the first time the isovolmic degradation property of PCL particles in human biopsy study, PCL particles maintained their diameter and volume for a minimum of 3 years in phase-1 degradation.

Four years after the injection, the PCL diameter became smaller, to 80% of its size (34 µm), showing phase-2 degradation, and the surface of particles became very rough and eroded. The transition from phase 1 to 2 is between 3 and 4 years. The longevity of PCL-M2 was greater than 4 years.

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