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Review

Biodegradable inflatable balloons for tissue separation

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ABSTRACT

Confining radiation to a specific region (during radiation therapy) minimizes damage to surrounding tissues. Biodegradable inflatable balloons (bio-balloons) were developed. The device protects the normal tissues by increasing the gap between radiation source and critical structures. The radiation fades away while passing through the inflated balloon preventing the surrounding tissues from harmful radiation. These bio-balloons have also found clinical use to treat massive rotator cuff tear. This review summarizes the chemistry, engineering, and clinical development of these biomedical devices. These balloons are made of biodegradable polymers folded into the edge of a trocar and inserted between the tissues to be separated, and inflated by normal saline in the site of the application. The inserted balloon protects the tissues from radiation or mechanical stress. They remain inflated on site for two months and are finally eliminated within 12 months.

1. Introduction

Biodegradable and biocompatible polymeric implants significantly influenced treatment approaches [1]. Typical biomedical implants include: (i) Cardiovascular implants like stents, vascular grafts, heart valves, defibrillators, pacemakers, etc. [2]. (ii) Neural implants like prostheses for the central nervous system, cochlear and retinal implants [3]. (iii) Orthopedic implants like bone grafts, bone plates, fins and fusion devices [4]; bone tissue engineering scaffolds [5] and dental implants [6]. This review focuses on balloons as a new implantable device used as an aid in cancer treatment and in orthopedic applications.

Overcoming foreign body reaction is the main challenge in implant technology [7]. Degradation performance classifies implant material in two groups: bio-inert and biodegradable. Bio-inert materials stay in the body forever or may remain in the body for a time period and surgically removed. Biodegradable implants are eliminated from the body with time after serving their purpose [8]. Minimally invasive implantation procedures for medical devices (wherever applicable) are preferable.

Biodegradable balloons (bio-balloons) are inflatable fluid-filled devices fabricated from biodegradable polymers. These balloons are portable in a deliverable device that unfolds *in vivo*, and then inflates and is sealed off. The resulting balloon remains inflated in the body for 1–4 months, serving its designated purpose, and gradually degrading and being eliminated with time. Fabricating such systems is an engineering challenge. The balloon should be elastic with significant mechanical strength, and they should stay inflated for the desired time, yet be biocompatible and biodegradable.

Prostate cancer is treated through a combination of chemo- and radiation therapy. Radiation treatment invariably damages adjacent tissues in these patients, especially tissues around the rectum [9,10]. Injectable *in situ* forming hydrogels and other polymeric materials have been used to protect the radiation effect. However, these methods are inefficient, cumbersome, and with significant subject variation [11]. *In vivo* inflatable balloons provide a robust, biodegradable yet minimally invasive alternative, by enlarging the distance between radiation source and critical structures. They are a single structure of a fixed volume and width, providing a predictable and defined protection.

2. Engineering

The device must fulfill the following criteria:

i) Balloons must be made of a biocompatible polymer whose safety and biodegradation are well characterized. The

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structural polymer should fully degrade and eliminated within a defined period such as one year, leaving no residuals at the implant site or the body.

ii) Balloons should be made as a continuous single unit with minimal connecting parts, gluing points or welding lines, surface defects, or mechanical weak points that are prone to deform and deflate the device.

iii) Balloons must be made of highly homogeneous flexible and elastic material that retains its mechanical properties during folding. Moreover, the wall thickness of the balloon cannot exceed a certain thickness, preferably <200 μm, as the balloon must be easily rolled up to be inserted through the catheter dispenser system.

The following sections compile the fabrication method and characterization of the device.

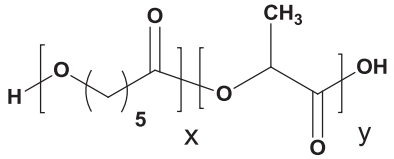
2.1. Choice of polymer

Bio-balloons should be biocompatible, biodegradable, mechanically robust, elastic, malleable, stable to sterilization, and easy to fabricate. Polyhydroxyacid based biomaterials, such as polylactide (PLA), polyglycolide (PGA) and polycaprolactone (PCL), have been used in urothelial tissue engineering with favorable results [12,13]. However, the mechanical properties of PGA or PLA membranes are not optimal, because these materials are inelastic and are too stiff for the intended application. Additionally, the degradation rate of PGA is relatively rapid [14]. PCL is highly elastic, and its strain is >700% at breakage [8]. The degradation rate of PCL is also slow, sometimes up to 2 years [15]. Combined with lactides, their properties are tunable. Poly-L-lactide-*co*-ε-caprolactone (PLCL) compositions (Scheme 1) have been studied [16–19], but the focus has been on producing electrospun nanofibrous membranes. PLCL degrades slowly, having desirable mechanical strength, hydrophobic, easier to cast [20,21]. Therefore, it is an obvious polymer of choice.

2.2. Balloon preparation by a dip coating technique

Biodegradable balloons were prepared from PLCL using a dip coating methodology, because they should not contain any bonding parts along their surface. Such areas are highly delicate and therefore susceptible to structural failure and leakages. Balloon fabrication consists of two steps: a casting step of the mold and a dip-coating step (Fig. 1). A brief description of the procedure is as follows [22,23]:

- A balloon shaped agar or gelatin template mold (shape may be fabricated as required) generated by pouring hot 5% w/v aqueous agar solution into a metallic or silicon mold.When the agar mold is liquid, a stainless steel pin is inserted into the mold. The pin serves as the balloon nozzle template, and supports or grips the template. When cooled to room temperature, an agar mold for the desired shape and volume of the desired balloon is created,



Scheme 1. Poly(L-lactide-*co*-ε-caprolactone) was used for fabricating "bio-balloons." They are significantly elastic with desired mechanical strength and biodegradability.

- The balloon mold is dip coated in a polymer solution (14% w/v of PLCL in dichloromethane) at a constant speed. The process has to be carried out under a dry nitrogen atmosphere to minimize moisture interference.
- Coated molds are allowed to dry at room temperature for solvent evaporation. Subsequently, a second layer is dip coated on top of the first one. Three cycles of coatings achieved a desired balloon wall thickness of ~100 micro-meters.

After dip coating is completed and dried properly, agar is removed by immersing the coated cast in distilled water at 90 °C for 2 min. The agar mold becomes liquid and gently squeezed-out of the nozzle. After drying the empty balloon under vacuum, residual values of dichloromethane are determined by gas chromatography to conform below toxic levels (<0.3 ppm).

2.2.1. Sleeve and plug preparation

Sleeves are prepared with an outer diameter of 2.5 mm and an inner diameter in the range of 2.0 and 1.5 mm. The sleeve are prepared using poly(L-lactide-*co*-ε-caprolactone) (PLCL) solution by a dip-coating technique, on a metal template. The sleeves are joined onto the balloon nozzle using a thin gluing film of 20% w/v PLCL solution.

The implant dispensing kit includes a needle, guiding wire, a 3–4 mm dilator with a sheath passed over the dilator, and the folded balloon inside a second sheath that can be introduced through the dilator sheath. The needle, guide wire, and dilator are commonly used as part of a method known as the Seldinger technique [24].

A minimally invasive technique (harnessed in a retractable sheath) has been developed to enable access for the device to a specified location in the body. When the sheath is in place, the balloon is deployed, inflated, and sealed. The balloon is exposed by retracting the sheaths, and then it is inflated at the proper location and orientation by physiological saline to the desired volume. It is sealed to prevent deflation by using a biodegradable plug made of the same polymer.

2.3. Evaluation and characterization of the device [25]

The developed devices were incubated under physiological conditions (0.1 M PBS pH 7.4, for a period of 120 days) to assess the implant stability. The incubated balloons were evaluated at regular intervals for integrity and leakage. The integrity of the balloons was dependent on their wall thickness. Nearly 50% of the 75-μm group balloons failed after 1 week, while the 100-μm group remain inflated over 90 days of incubation. The weight loss of the inflated balloons was minimal during 60 days, supporting the intactness profiles of the balloons. Molecular weight steadily decreased for over a period of 150 days. An increase in polymer polydispersity index was also recorded until 117 days. The minimum wall thickness at which balloons do not deflate were determined as 100 μm which were sufficiently thin to be easily rolled up to a final diameter of <3 mm for insertion in the trocar tip.

The polymeric PLCL films were highly flexible with elongation of nearly 650% of their original length (upward velocity of 30 cm/min). The films preserved the majority of their mechanical properties during the first 60 days of incubation. After 120 days, the mechanical properties of the films were less than 10% of their initial values. Despite the gradual decrease in mechanical properties, films were left with sufficient mechanical strength after 6 weeks of incubation ultimate stress of ~63% and ~400% elongation relative to the original value (Fig. 2c).

Differential scanning calorimetry analysis revealed a marginal increase in heat capacity for all samples after ~100 days of incubation. In addition, films changed their transparency and became opaque. The changes in thermal properties and in color were an