Opportunities and challenges for the development of polymer-based biomaterials and medical devices

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Abstract

Biomaterials and medical devices are broadly used in the diagnosis, treatment, repair, replacement or enhancing functions of human tissues or organs. Although the living conditions of human beings have been steadily improved in most parts of the world, the incidence of major human's diseases is still rapidly growing mainly because of the growth and aging of population. The compound annual growth rate of biomaterials and medical devices is projected to maintain around 10% in the next 10 years; and the global market sale of biomaterials and medical devices is estimated to reach $400 billion in 2020. In particular, the annual consumption of polymeric biomaterials is tremendous, more than 8000 kilotons. The compound annual growth rate of polymeric biomaterials and medical devices will be up to 15–30%. As a result, it is critical to address some widespread concerns that are associated with the biosafety of the polymer-based biomaterials and medical devices. Our group has been actively worked in this direction for the past two decades. In this review, some key research results will be highlighted.

Keywords: polymer-based biomaterials; antibacterial; plasticizer; ethylene oxide sterilization; anti-irradiation aging

Opportunities for the development of polymer-based biomaterials and medical devices

Biomaterials and medical devices industry have been rapidly developed in the past 10 years, thanks to the advances in science and technology and the tremendous clinical demand. The compound annual growth rate (CAGR) of biomaterials and medical devices is up to 15% in the 21st century. The global market sale of biomaterials and medical devices was about $203.5 billion in 2013. Although the living conditions of human beings have been steadily improved in most parts of the world, the incidence of major human's diseases is still rapidly growing, which is mainly attributed to population growth and aging. For example, the global cancer cases are projected to raise from 14 million in 2012–19 million in 2025 and 24 million in 2035, respectively. According to the International Diabetes Federation, the number of population worldwide with diabetes was around 382 million in 2013. More strikingly, this number is estimated to reach 522 million in 2035. As another example, according to World Health Organization, cardiovascular disease is the leading cause of death worldwide, accounting for 29% of the global mortality. The number of deaths will increase from about 17.5 million in 2013–25 million in 2020 and 36 million in 2035, respectively.

The CAGR of biomaterials and medical devices is projected to maintain ~10% growth in the next 10 years. The global market sales of biomaterials and medical devices will reach $400 billion in 2020. In particular, the market sale in China was $15.1 billion in 2013, which accounts for less than 8% of the worldwide sale; however, the number is estimated to rapidly grow to $71.5 billion in 2020 and $302.9 billion in 2035, respectively.

Among various biomaterials, the annual consumption of polymeric biomaterials is tremendous, more than 8000 kilotons [1]. However, only a few dozen species of polymeric materials, such
as polyolefin, polyvinyl chloride (PVC), medical engineering plastics and so forth, have been put into large-scale application to fabricate syringe, drug and blood storage and transfusion consumable, cathe
ter, orthopedic device and so forth. Currently, the annual consump
tion of polyolefin, PVC and medical engineering plastics reaches
more than 1500, 1000 and 200 kilotons, respectively. It is predicted
that the polymer-based biomaterial market will grow at a high rate
of 15–30% annually in the 21st century.

Challenges for the development of polymer-based biomaterials and medical devices

Recently, the safety of polymer-based biomaterials and medical de
vices in service, e.g. device-associated bacterial infections, the haz
ards of plasticized PVC biomaterials and the defects of ethylene
oxide (EO) sterilization, has caused widespread concerns. To ad
dress this, our group has been actively worked in this direction since
2000. In specific, two key scientific issues, i.e. the relationships be
 tween the modification methods of polymers and their performan ces, and the interactions between the surfaces of polymers and
blood, cell and microorganism, have been investigated. In this arti
cle, some key progresses are highlighted.

Bacteria-repellent materials and antibacterial polymers

Despite of sterilization and aseptic procedures, bacterial infection re
 mains a major impediment to theusage of medical devices (Table 1)

Table 1. Incidence of biomaterial-associated infection for different implants and devices [2]

| Tissue implant site | Implant or device | Infection incidence over lifetime (%) |
|---------------------|------------------|---------------------------------------|
| Urinary tract       | Catheter         | 33 (per week)                         |
| Percutaneous        | Central venous catheter | 2–10                           |
|                     | Temporary pacemaker | 4                                 |
|                     | Short indwelling catheter | 0–3                            |
|                     | Peritoneal dialysis catheter | 3–5                          |
|                     | Fixation pin or screw | 5–10                               |
|                     | Suture            | 1–5                                  |
|                     | Voice prosthesis  | 25 (per month)                      |
|                     | Dental implant    | 5–10                                 |
| Subcutaneous        | Cardiac pacemaker | 1–7                                 |
|                     | Penile prosthesis | 2–5                                 |
| Soft tissue         | Mammary prosthesis| 1–7                                 |
|                     | Abdominal wall patch | 1–16                          |
|                     | Intraocular lens  | 0.1                                 |
| Eye                 | Contact lens      | 0.1–0.5                             |
| Circulatory system  | Prosthetic heart valve | 1–3                         |
|                     | Vascular graft    | 1.5                                 |
| Bone                | Prosthetic hip    | 2–4                                 |
|                     | Prosthetic knee   | 3–4                                 |
|                     | Tibial nail       | 1–7                                 |

Incidence data are given over the entire implant or device lifetime, unless stated otherwise

3. An infection-resistant slippery surface through infusing fluo
carbon-tethered wrinkling surface with fluorocarbon liquid [12].
Inspired by the liquid-infused porous slippery surface [13], a fluoro
carbon-tethered wrinkling surface was facilely prepared by combing
photo-graft polymerization with osmotically driven wrinkling,
followed by infusing with perfluorooctyl methacrylate liquid lubri
cant to obtain a fluorocarbon liquid-infused wrinkling surface
(Fig. 3) [12]. Fluorocarbon liquid-infused wrinkling surface is char
acterized by the following features. The affinity between the perfluor
ocarbon liquid and the fluorocarbon-tethered surface is much
higher than that between the ambient fluid and the surface. The per
fluorocarbon lubricating fluid is locked in place to form a stable,
defect-free, self-healing and inert slippery surface, because the
roughness of the surface is greatly increased by the osmotically
driven wrinkling. The slippery surface repels various liquids, thus
can resist infection and thrombus formation.

Plasticizer-free polymers for biomedical applications

Biomedical soft PVC is used in the production of a wide range of dis
posable medical devices including blood bag, infusion device,
respiratory mask, peritoneal dialysis bag and catheter. About 2.4 million ton of PVC is consumed per year which accounts for 28% of the total polymer-based biomaterials [14]. In particular, diethylhexyl phthalate (DEHP) is the most commonly used plasticizers in biomedical PVC. In general, DEHP is not chemically bound to PVC backbone and may leach from materials upon contacting with blood, drugs and intravenous injection fluids in service (Table 2) [15]. Available toxicological testing in animals and in vitro tests provide evidences for the association of DEHP and its metabolites with a wide range of adverse effects in multiple organ systems such as liver, reproductive tract (testes, ovaries and secondary sex organs), kidney, lung and heart [15].

Because of the potential hazard of soft PVC, various non-PVC alternatives have been investigated and developed in our group since 2000. In one study, styrene thermoplastic elastomers (TPE) were first chemically modified with acrylate through vinyl pyrrolidone intermediary bridge, followed by reactive blending with polypropylene to obtain TPE alloy (Fig. 4) [16–19]. According to Chinese National Standard GB 15593-1995 and GB 8368–2005, most of the biomedical properties of the as-prepared TPE alloys and associated medical devices were much better than those of the soft PVC ones (Table 3). Platelet storage period in TPE blood bag was up to 3–5 days, in stark contrast to 1–3 days in soft PVC one (Table 4). The TPE biomaterials and medical devices have been put into large-scale industrial production in WEGO HOLDING CO., LIMITED (China). Representative pictures of the TPS medical devices are shown in Fig. 5.

Radiation-resistant polymer-based biomaterials

Medical sterilization has become increasingly complex because of the need to prevent patient exposure to infections caused by instruments and devices [20]. Significant institutional costs related to nosocomial infections and mortality/morbidity concerns arise from the inadequate sterilization of medical devices [21]. Currently, the widely used industrial sterilization technologies of medical devices are steam, EO and irradiation. Each technology has its undeniable advantages over the other technologies. Notably, the defects of EO sterilization have aroused widespread concerns, mostly related to potential hazards of carcinogenic and mutagenic EO to patients, staffs and the environment, as well as risks associated with handling a flammable gas [22]. An investigation of symptoms in EO sterilization workers in hospital has confirmed that the daily sterilization work with EO can induce acute or chronic symptoms in EO sterilization workers [23]. Radiation sterilization is proven to be an effective method to kill the microorganism on material through
Figure 2. (a) Illustration of the DNase coating to cleave DNA and (b) bacterial adhesion, biofilm formation and cytotoxicity

Figure 3. Illustration of the fluorocarbon liquid-infused wrinkling slippery surface to repel bacteria

Table 2. Human exposure to DEHP following treatment with PVC medical devices [16]

| Treatment                      | Total exposure (mg) per patient | Time period       | Body weight (mg/kg) |
|--------------------------------|---------------------------------|-------------------|--------------------|
| Hemodialysis                   | 0.5–360                         | Dialysis session  | 0.01–7.2           |
| Blood transfusion              | 14–600                          | Treatment         | 0.2–8.0            |
| Extracorporeal oxygenation     | –                               | Treatment period  | 42.0–140.0         |
| Cardiopulmonary bypass        | 2.3–168                         | Treatment day     | 0.03–2.4           |
| Artificial ventilation        | 0.001–4.2                       | Hour              | –                  |
| Exchange transfusions          | –                               | Treatment         | 0.8–4.2            |
electromagnetic radiation. Because of its outstanding effect in eliminating toxic and problematic residues, radiation sterilization of disposable medical devices has captured a large and still rapidly growing segment of the market in many industrialized countries [24]. However, irradiation sterilization usually causes the chain cracking of polymers and the creation of macro-radicals, resulting in the stiffening, discoloration and decreasing of mechanical properties of polymer-based materials [25–28]. Anti-irradiation agents are

Table 3. Chemical and biological performances of TPE infusion device

| Item                           | TPE device | PVC device |
|--------------------------------|------------|------------|
| Reducing substance (ml/l)     | 0.1        | 1.2        |
| pH change                      | 0.2        | 1.0        |
| Heavy metals (ppm)            | Undetected | 1.0        |
| UV absorbance                 | 0.001      | 0.03       |
| Alcohol extraction (µg/ml)    | Undetected | 170        |
| Cell toxicity                 | 1 class    | 2 class    |
| Intracutaneous stimulation    | 1 class    | 2 class    |
| Hemolysis ratio (%)           | 0.2        | 2          |

Table 4. Storage performances of platelets in TPE blood bag

| Item                           | TPE device | PVC device | t value |
|--------------------------------|------------|------------|---------|
| Number (x 10^7/l)              | 820 ± 140  | 688 ± 159  | 2.9     |
| pH value                       | 6.93 ± 0.08 | 5.59 ± 0.04 | 45.1   |
| Platelet aggregation (%)       | 10.0 ± 8.8  | 0.4 ± 0.8  | 2.9     |
| Hypotonic shock (%)            | 75.1 ± 4.2  | 0.3 ± 0.7  | 7.3     |
| CD62P positive expression (%)  | 32.0 ± 4.6  | 83.1 ± 2.9 | -18.8   |
| Lactic acid (mmol/l)           | 14.84 ± 1.85 | 23.68 ± 8.14 | -2.7   |
| Glucose (mmol/l)               | 15.8 ± 1.0  | 5.8 ± 0.4  | 32.5    |

Figure 4. The chemical modification (left) and blending (right) principles

Figure 5. Representative TPE medical devices
commonly mixed or added into bulk polymers to obtain irradiation-resistant capability [29]. Although this strategy is simple and efficient, the anti-irradiation agent may leach from materials, threatening the long-term anti-irradiation performance. To solve this issue, we invent a pre-irradiation graft technology that produce macromolecular peroxide R–O–O–R or R–O–O–H to initiate the efficient graft polymerization of the double-bond-containing anti-irradiation agents in twin-screw extrusion (Fig. 6)[30, 31]. It is shown that, after being subjected to 25 kGy radiation dose and stored for 3 months, the tensile strength, yellowness index and haze of the as-prepared radiation-resistant PP material are obviously superior to the reference sample (Table 5).

Table 5. Performances of radiation-resistant polymers*

| Material            | Tensile strength (MPa) | Flexural modulus (MPa) | Yellowness index | Haze (%) |
|---------------------|------------------------|------------------------|------------------|----------|
| PP                  | 8.2                    | 837                    | 16               | 21.2     |
| Anti-irradiation PP | 27.2                   | 971                    | 8                | 1.8      |

*Twenty-five-kilogram radiation dose, stored for 3 months.

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References
1. Vert M. Polymeric biomaterials: strategies of the past vs. strategies of the future. Prog Polym Sci 2007;32:755–61.
2. Busscher HJ, van der Mei HC, Subbiahdoss G et al. Biomaterial-associated infection: locating the finish line in the race for the surface. Sci Trans Med 2012;4:e153ev10.
3. Hetrick EM, Schoenfisch MH. Reducing implant-related infections: active release strategies. Chem Soc Rev 2006;35:780–9.
4. Darouiche RO. Treatment of infections associated with surgical implants. New Engl J Med 2004;350:1422–9.

5. Campoccia D, Montanaro L, Arciola CR. A review of the biomaterials technologies for infection-resistant surfaces. Biomaterials 2013;34:8333–54.

6. Ferreira L, Zumbühl A. Non-leaching surfaces capable of killing microorganisms on contact. J Mater Chem 2009;19:7796–806.

7. Banerjee I, Pangule RC, Kane RS. Antifouling coatings: recent developments in the design of surfaces that prevent fouling by proteins, bacteria, and marine organisms. Ado Mater 2011;23:690–718.

8. Tuson HH, Weibel DB. Bacteria-surface interactions. Soft Matter 2013;9:4368–80.

9. Yuan SS, Zhao J, Luan SF et al. Nuclease-functionalized poly(styrene-b-isobutylene-b-styrene) surface with anti-infection and tissue integration bifunctions. ACS Appl Mater Interfaces 2014;6:18078–86.

10. Whitchurch CB, Toller-Nielsen T, Ragaas PC et al. Effect of bacterial biofilm formation. Science 2002;295:1487.

11. Ghaz-Jahanian MA, Khodaparastan F, Berenjian A et al. Influence of small RNAs on biofilm formation process in bacteria. Mol Biotechnol 2013;55:288–97.

12. Yuan SS, Luan SF, Yan SJ et al. Facile fabrication of lubricant-infused wrinkling surface for preventing thrombus formation and infection. ACS Appl Mater Interfaces 2015;7:19466–73.

13. Wong TS, Kang SH, Tang SKY et al. Biospired self-repairing slippery surfaces with pressure-stable omniphobicity. Nature 2011;477:443–7.

14. FDA Safety Assessment of Di(2-ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080457pdf. 21 February 2008, date last accessed.

15. Tickner JA, Schettler T, Guidotti T et al. Health risks posed by use of di-2-ethylhexyl phthalate (DEHP) in PVC medical devices: a critical review. Am J Ind Med 2001;39:100–11.

16. Yang HW, Luan SF, Zhao J et al. Improving hemocompatibility of styrene-b-(ethylene-co-butylene)-b-styrene elastomer via N-vinyl pyrrolidone-assisted grafting of poly(ethylene glycol) methacrylate. Polymer 2012;53:1675–83.

17. Yang HW, Luan SF, Zhao J et al. N-vinyl pyrrolidone-assisted free radical functionalization of glycidyl methacrylate onto styrene-b-(ethylene-co-butylene)-b-styrene. React Funct Polym 2010;70:961–6.

18. Luan SF, Zhao J, Yang HW et al. Surface modification of poly(styrene-b-(ethylene-co-butylene)-b-styrene) elastomer via UV-induced graft polymerization of N-vinyl pyrrolidone. Colloid Surface B 2012;93:127–34.

19. Luan S, Yin J, Li Z et al. Resin compound containing a functionalized poly(propylene and a functionalized styrene-thermoplastic elastomer. U.S. Patent 8119702, 2012.

20. Mendes GGC, Brandao TRS, Silva CLM. Ethylene oxide sterilization of medical devices: a review. Am J Infect Control 2007;35:574–81.

21. Rutala WA, Weber DJ. Infection control: the role of disinfection and sterilization. J Hosp Infect 1999;43:543–55.

22. Lucas AD, Merritt K, Hitchins VM et al. Residual ethylene oxide in medical devices and device material. J Biomed Mater Res B 2003;66B:548–52.

23. Yahata K, Fujihiro K, Horii H et al. An investigation of symptoms in ethylene oxide sterilization workers in hospitals. J Occup Health 2001;43:180–4.

24. Clough RL. High-energy radiation and polymers: a review of commercial processes and emerging applications. Nucl Instrum Methods B 2001;185:8–33.

25. Steller R, Zachowska D, Meissner W et al. Crystalline structure of polypropylene in blends with thermoplastic elastomers after electron beam irradiation. Radiat Phys Chem 2006;75:259–67.

26. Luan SF, Shia H, Yao ZH et al. Effect of electron beam irradiation sterilization on the biomedical poly (octene-co-ethylene)/polypropylene films. Nucl Instrum Methods B 2010;268:1474–7.

27. Luan SF, Yang HW, Shi HC et al. Stabilization of polypropylene, polypropylene blends with poly (styrene-b-(ethylene-co-butylene)-b-styrene) under irradiation: a comparative investigation. Nucl Instrum Methods B 2011;269:94–9.

28. Alariqi SAS, Kumar AP, Rao BSM et al. Stabilization of gamma-sterilized biomedical polyolefins by synergistic mixtures of oligomeric stabilizers. Polym Degrad Stab 2006;91:2451–64.

29. Alariqi SAS, Kumar AP, Rao BSM et al. Stabilization of gamma-sterilized biomedical polyolefins by synergistic mixtures of oligomeric stabilizers. Part II. Polypropylene matrix. Polym Degrad Stab 2007;92:299–309.

30. Cai CH, Shi Q, Li LL et al. Grafting acrylic acid onto polypropylene by re-active extrusion with pre-irradiated PP as initiator. Radiat Phys Chem 2008;77:370–2.

31. Shi HC, Shi DA, Yin LG et al. Preparation of PP-g-PEG by using partial pre-irradiated polypropylene as initiator and its properties. Polym Bull 2010;65:929–40.