Journal of the Korean Physical Society, Vol. 66, No. 1, January 2015, pp. 17∼21

Poly(acrylic acid)/Polyethylene Glycol Hygrogel Prepared by Using Gamma-ray Irradiation for Mucosa Adhesion

Young-Chang Nho,* Jong-Seok Park,* Jung-Woong Shin, Youn-Mook Lim, Sung-In Jeong, Young-Min Shin and Hui-Jeong Gwon
Radiation Research Division for Industry and Environment, Korea Atomic Energy Research Institute, Jeongeup 580-185, Korea

Myung-Seob Khil
Department of Organic Materials and Fibers Engineering, Chonbuk National University, Jeonju 561-756, Korea

Deok-Won Lee
Department of Oral and Maxillofacial Surgery Dental Hospital, Seoul 134-727, Korea

Sung-Jun Ahn
JADAM Co., LTD., 39, Topyeongdong-ro, 139 beon-gil, Seogwipo 697-860, Korea

(Received 30 November 2013, in final form 20 February 2014)

A buccal delivery system provides a much milder environment for drug delivery compared to an oral delivery which presents a hostile environment for drugs, especially proteins and polypeptides, owing to acid hydrolysis. Local delivery in an oral cavity has particular applications in the treatment of toothaches, periodontal disease, and bacterial infections. Poly(acrylic acid) (PAA)-based hydrogels prepared using a chemical initiator have been attempted for a mucoadhesive system owing to their flexibility and excellent bioadhesion. In this experiment, PAA and polyethylene glycol (PEG) were selected to prepare using a radiation process a bioadhesive hydrogel for adhesion to mucosal surfaces. PAA and PEG were dissolved in purified water to prepare a homogeneous PAA/PEG solution, and the solution was then irradiated using an electron beam at dose up to 70 kGy to make the hydrogels. Their physical properties, such as gel percent, swelling percent, and adhesive strength to mucosal surfaces, were investigated. In this experiment, various amounts of PEG were incorporated into the PAA to enhance the mucoadhesive property of the hydrogels. The effect of the molecular weight of PEG on the mucoadhesion was also examined.

PACS numbers: 68.35.Gy
Keywords: Mucoadhesive, Polyacrylic acid (PAA), Drug carriers, Gamma- ray
DOI: 10.3938/jkps.66.17

I. INTRODUCTION

Controlled systems for drug delivery to mucosal surfaces, such as gastrointestinal, ocular, respiratory, bucall, nasal, and rectal vaginal path surface, have attracted wide interest around the world [1–3]. However, a viscose elastic and sticky mucus layer on all mucosal tissues has evolved to protect the body by rapidly removing foreign materials. Mucoadhesive polymers are utilized to immobilize a drug on a specific site for a targeted release and optimal drug delivery. Thus far, a considerable number of studies have been performed using hydrophilic polymers containing numerous hydrogen-bond forming groups, with a focus on the mucoadhesive properties of a wide range of polymeric materials. The interaction between the mucus and the mucoadhesive polymers has been proposed to be attributable to a physical entanglement and secondary bonding, mainly H-bonding and a van der Waals attraction, which are related to the chemical structure of the polymers. The surface chemical groups of mucoadhesive polymers that contribute to mucoadhesion include hydroxyl, carboxyl, amine and amide groups in the structure. Pepas *et al.* suggested that a polymer which had a mucoadhesion function would have the following characteristics; strong H-bonding groups, strong anionic charges, high molecular weight, sufficient chain flexibility, and surface-energy properties favoring a

*These authors contributed equally to this work.

spread onto mucus [4].

Typical polymers used as mucoadhesive drug carriers include poly(acrylic acid) (PAA), poly(methacrylic acid) (PMA), carboxymethyl cellulose (CMC), modified chitosan, and hydroxypropyl methylcelluose [5–9]. Of these polymers, PAA and its crosslinked commercial powder forms, Carbopol and Polycarbophil, usually show strong mucoadhesive properties. Carbopol is a crosslinked PAA-based polymer that has excellent bioadhesive properties over the short term when formulated as an aqueous system. However, rapid hydration can occur, leading to a breakdown of the gel's structure and finally adhesive failure. Also, PAA alone has limitations as a mucoadhesive drug carrier owing to its high water solubility, because of which it may be dissolved before the drug is delivered across the membrane. Many studies have been conducted to solve this problem by using copolymers, interpolymer complexes, or crosslinking [10–12].

Hydrogels are macromolcular networks that swell, but do not dissolve, in water. Hydrogels can be synthesized by accomplishing crosslinking through radiation [13–16]. For the fabrication of hydrogels, the gamma-ray irradiation technique has several advantages, such as easy process control, the possibility of combining hydrogel formation and sterilization into one technological step, no necessity to add any initiators, and a crosslinker [17–19]. However, UV irradiation method requires additional photoinitiators to induce the formation of free radicals. Most photoinitiators are toxic and difficult to remove from a polymer [20, 21]. However, little work has been done on the mucoadhesion of hydrogels synthesized by irradiating of PAA or its copolymer solution.

The aim of the present study is to develop a suitable PAA-based mucoadhesive that might have a potential for localized prolonged delivery of active agents into an oral cavity. In this experiment, PAA and polyethylene glycol (PEG) were selected to prepare using a radiation process a bioadhesive hydrogel for adhesion to mucosal surfaces.

II. EXPERIMENTAL DETAILS

PAA with M.W. 100,000 that was purchased from Waco Pure Chemical Industries, Ltd (Osaka, Japan) was used without further purification. PEG with M.W. 10,000 was supplied by Sigma Aldrich (Missouri, USA) and was used without further purification.

In this experiment, hydrogels were prepared using PAA and PEG. PAA was dissolved in purified water to make a 7 wt% PAA solution, and $0.25 - 1$ wt% of PEG was then incorporated into the PAA solution. Three ml of a homogenous solution were put into a 35 mm Petri dish and were then irradiated by using an electron beam accelerator (10 MeV/1 mA, Jeongup site of Korea Atomic Energy Research Institute, Junbuk, Korea) at dose up to 70 kGy to make the hydrogels.

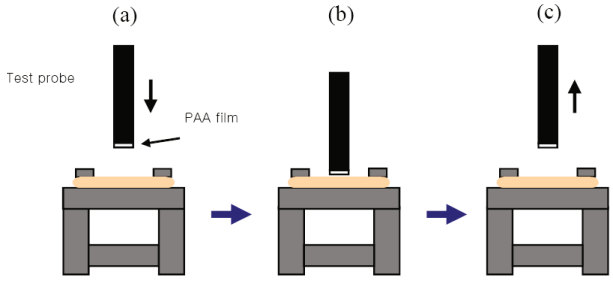

Fig. 1. (Color online) Procedure for mucoadhesive test by using a texture analyzer with a mucoadhesive holder; (a) the probe with hydrated PAA film was moved downward, (b) the dried PAA film was attached to the buccal mucosa of pig, (c) the probe is withdrawn at a specified rate.

The hydrogels prepared through irradiation were dried to measure the gellation. The dried hydrogels were extracted with water for 24 hr at room temperature to extract the insoluble part of the hydrogel. The insoluble part, *i.e.*, the gelled part, was taken out and washed with water to remove the soluble part, and were then dried and weighed. This extraction cycle was repeated until the weight became constant. The gel percent in the hydrogel was determined from the following equation:

$$\text{Degree of gelation } (\%) = (\mathrm{W_e}/\mathrm{W_d}) \times 100$$

where W_d and W_e represent the weights of the dried hydrogel and the gelled part after extraction, respectively.

The dried hydrogels, which were punched into discs, were weighed and allowed to swell in distilled water. The degree of swelling at equilibrium was calculated as follows:

$$\text{Swelling percent } (\%) = [(\mathrm{W_s} - \mathrm{W_d})/\mathrm{W_d}] \times 100$$

where W_d and W_s represent the weights of the dry and the wet hydrogel, respectively.

The buccal mucosa from a pig was used to determine the mucoadhesive properties of the hydrophilic crosslinked PAA-based specimens. Hydrogels, 3 mm in thickness, were dried, cut into 10 mm diameter circles, and then fixed to a cylindrical probe (10 mm in diameter) by using double-sided adhesive tape (Fig. 1(a)). A buccal mucosa specimen of a pig was cut into size of 30 $\times$ 30 mm^2, and were fixed to the surface of a stainless steel plate. Peel testing of the sample film was carried out using a universal mechanical tester equipped with a mucoadhesive holder. Figure 1 shows the procedure for the mucoadhesive test. The probe with a PAA-based polymer disc was pulled out at a speed of 0.5 mm/sec after attachment to the mucosa's surface at a contact force of 0.05 N for a contact time of 60 sec.

The other evaluation method of mucoadhesion in this experiment was examining the amount of time the adhesion was maintained between a PAA-based specimen and the buccal mucosa in phosphate buffered saline solution under stirring. Hydrogels, 3 mm in thickness, were

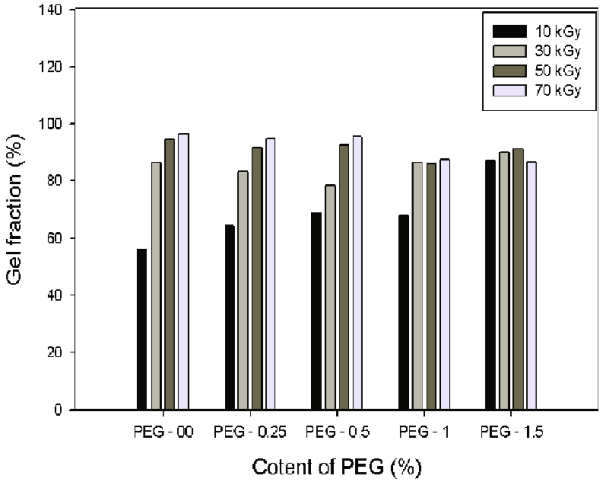

Fig. 2. (Color online) Effect of irradiation dose on the gel fraction of the crosslinked PAA-based hydrogel for various amounts of PEG.

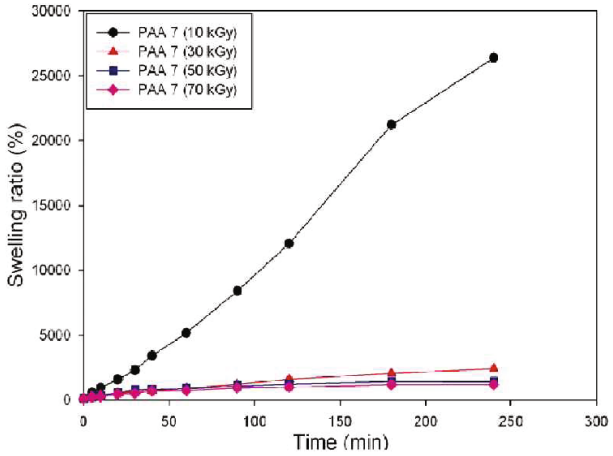

Fig. 3. (Color online) Effect of irradiation dose on the swelling ration of the crosslinked PAA-based hydrogels.

dried, and cut into 10 mm-diameter circles. They were attached to the buccal mucosa specimen of a pig at a contact force of 0.05 N for a contact time of 60 sec, and were then immerged in a phosphate buffered saline solution under stirring until they were separated.

III. RESULTS AND DISCUSSION

1. Gel Percent and Swelling Behavior

Radiation technology can be effectively used to prepare hydrogels because their properties are easily controlled by using the irradiation dose, which influences their crosslinking density and structure [22]. The method of radiation-induced crosslinking has been utilized to prepare hydrogels based on different types of polymers.

When a polymer solution is subjected to radiation, reactive sites are formed on macromolecules by direct radiation or its indirect effect. The action of ionizing radiation on a polymer in an aqueous solution is known to occur mainly through an indirect effect [23]. Radiation energy absorbed mostly by water causes reactive species such as hydroxyl radicals, hydrogen atoms, and hydrated electrons; subsequently, the hydroxyl radicals and hydrogen atoms react rapidly with the polymer, leading to hydrogen abstraction from the polymer. Macroradicals formed by these progresses are combined to form hydrogels.

The effect of the irradiation dose on the gel fraction of PAA for various concentrations of PEG is shown in Fig. 2. The gel fraction was observed to increase with increasing irradiation dose. Also, the addition of 1.5 wt% PEG led to a high gel fraction at a low dose of 10 kGy. These hydrogels are assumed to have a semi-IPN structure, where PEG chains are diffused into the crosslinked network of PAA, forming a complex between PAA and PEG [24,25]. Inter-polymer complexes are known to be formed between a proton donor group like poly(carboxylic acids) and a proton acceptor group like PEG, poly(propylene oxide), poly(vinyl pyrolidone), poly(vinyl alcohol), *etc.* Crosslinking by radiation transforms a linear polymer into a three-dimensional molecule, resulting in a significant increase in the molecular mass, a lower solubility in organic solvents, and improved mechanical properties. Therefore, it is explained that the increase in gel fraction by irradiation as shown in Fig. 2 mostly due to the crosslinking of the polymer.

Figure 3 shows the swelling behavior of the PAA-based specimens obtained by drying the hydrogels. In this experiment, the concentration of PAA in water was 7 wt% excluding PEG. The polymer swelling was observed to decrease with increasing in the irradiation dose. This is attributable to the fact that more irradiation leads to a tighter three-dimension network of the polymer in water, resulting in a further restriction in the mobility of the polymer chains.

2. Mucoadhesive Properties

Bioadhesion is the general term describing adhesion between any biological and synthetic surface. Mucoadhesion is a specific term describing the particular interaction of a mucosal membrane with a synthetic surface. There is no universally agreed test method to determine the bioadhesion; however, the large majority of studies report the work of adhesion and the maximum force of detachment as the preferred bioadhesion parameters [26–29]. The majority of in-vitro bioadhesion studies have employed animal mucosas as model substrates [30–32].

Figure 4 shows the effect of addition of PEG on the mucoadhesive strength for the PAA-based specimen irradiated at a dose of 50 kGy. A probe with a PAA-based

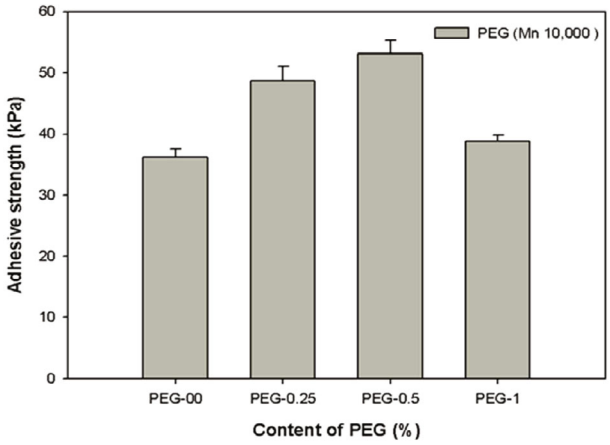

Fig. 4. Effect of PEG content on mucoadhesive strength.

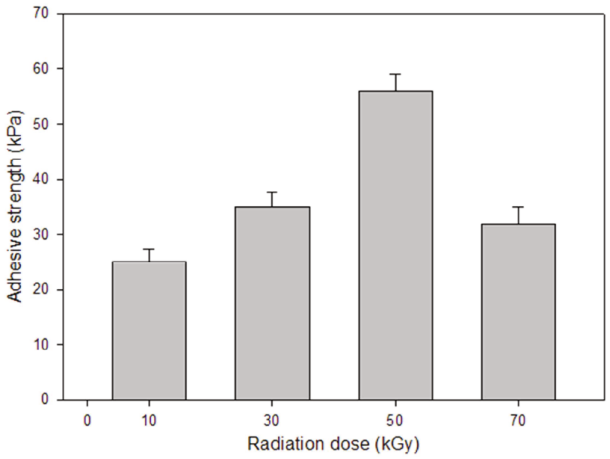

Fig. 5. Effect of irradiation dose on mucoadhesive strength.

specimen was pulled out at a speed of 0.5 mm/sec after attachment to the mucosa's surface at a contact force of 0.05 N for a contact time of 60 sec. As shown in Fig. 4, the addition of 0.5 wt% PEG had a significant effect on the mucoadhesive strength, which was 52 kPa. In contrast, the addition of 1 wt% PEG resulted in no additional effect, with a similar value to a virgin PAA specimen.

Figure 5 shows the effect of irradiation dose on the adhesive strength of a PAA-based specimen involving 0.5 wt% PEG. The adhesive strength increased with increasing irradiation dose up to 50 kGy and decreased at 70 kGy. Modest gamma-ray irradiation is needed to improve the bioadhesion of a hydrogel [5]. This indicates that the appropriate crosslinking structure induces an effective chain entanglement between the glycoproteins of the mucus and the mucoadhesive polymer; however, higher crosslinking prevents such as a chain entanglement.

In our experiments, a polymer specimen prepared by drying hydrogel was used for the bioadhesive test. The

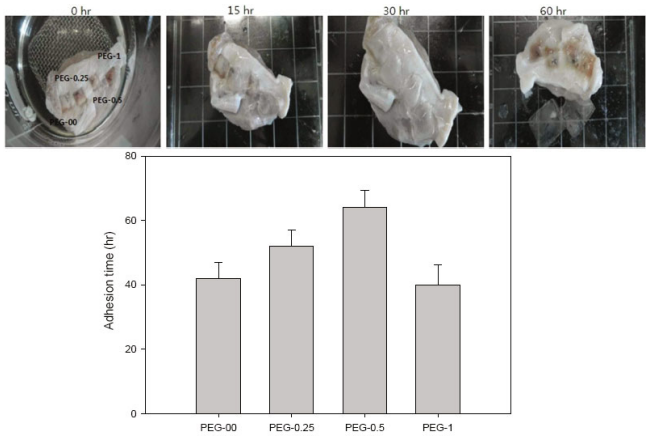

Fig. 6. (Color online) Amount of time the adhesion was maintained between the PAA-based specimen and the buccal mucosa in phosphate buffered saline solution; Photographs shows the adhesion test between the PAA-based specimen and buccal mucose.

dried specimen had much higher adhesive strength than the hydrogel. The moment the dried specimen made contact with the wet mucus surface, its hydration occurred, leading to increased mobility in the polymer chains to enhance the interpenetration between the polymer and the mucin. Therefore, the hydration process is considered to be one of the important factors in this mucoadhesion mechanism.

Figure 6 shows the amount of time the adhesion was maintained between the PAA-based specimen and the buccal mucosa in a phosphate buffered saline solution until they were separated from each other. With a maximum adhesion time of 60 hr, the addition of 0.5 wt% PEG had a significant effect on the adhesion time between a PAA-based specimen and buccal mucosa. These data show properties similar to the adhesive strength values obtained in Fig. 4. The photographs in Fig. 6 show the effect of PEG on the mucoadhesion between the PAA-based film-type disk and fresh buccal mucosa specimen from a pig. Even after 60 hr, a PAA-based film-type disk involving 0.5 wt% PEG remained attached to buccal mucosa while others were completely separated.

The crosslinking and the hydration of a polymer chains occur at the same time during gamma-ray irradiation [33, 34]. The results from this experiment involving a PEG/PAA system indicate that a critical degree of hydration of the mucoadhesive polymer exists where the optimum crosslinking and bioadhesion occurs. Bioadhesion starts with the diffusion of polymer chains into the interfacial region. Therefore, it is important that the polymer chains contain a substantial degree of flexibility to achieve the desired entanglement with the mucus. The increased chain interpenetration is believed to be attributed to the incorporation of poly(ethylene glycol). In general, the mobility and flexibility of polymers can be related to their viscosities and diffusion coefficients,

where the higher flexibility of a polymer causes greater diffusion into the mucus network.

IV. CONCLUSIONS

In this experiment, PAA and PEG were selected to prepare, by using a radiation process a bioadhesive hydrogel for adhesion to mucosal surfaces. An aqueous PAA/PEG solution was irradiated with an electron beam with doses up to 70 kGy to make hydrogels. Their physical properties, such as gel percent, swelling percent, and adhesive strength to mucosal surfaces, were investigated.

The gel fraction was observed to increase with increasing irradiation dose. Also, the addition of 1.5 wt% PEG led to high gel fraction even at low dose of 10 kGy. These hydrogels are assumed to have a semi-IPN structure where PEG chains are diffused into the crosslinked network of PAA to form a complex between PAA and PEG.

The adhesive strength increased with increasing irradiation dose up to 50 kGy, but decreased at 70 kGy. With a maximum adhesion time of 60 hr, the addition of 0.5 wt% PEG had a significant effect on the adhesion time between a PAA-based specimen and buccal mucosa when prepared at an irradiation dose of 50 kGy. These results suggest that radiation processing may be one of most efficient methods to make mucoadhesives.

ACKNOWLEDGMENTS

We would like to thank the nuclear R&D program of the Ministry of Science, ICT and Future Planning for Korea for its financial support.

REFERENCES

[1] N. Salamat-Miller, M. Chittchang and T. P. Johnston, Adv. Drug Deliver. Rev. **57**, 1666 (2005).
[2] V. Grabovac, D. Guggi and A. Bernkop-Schnurch, Adv. Drug Deliver. Rev. **57**, 1713 (2005).
[3] S. K. Lai, Y. Y. Wang and J. Janes, Adv. Drug Deliver. Rev. **61**, 158 (2009).
[4] N. A. Peppas and P. A. Buri, J. Control Release **2**, 257 (1985).
[5] J. O. Morales and J. T. McConville, Eur. J. Pharm. Biopharm. **77**, 187 (2011).
[6] Q. R. Cao, Y. Liu, W. J. Xu, B. J. Lee, M. Yang and J. H. Cui, Int. J. Pharm. **434**, 325 (2012).
[7] A. Abruzzo, F. Bigucci, T. Cerchiara, F. Cruciani, B. Vitali and B. Luppi, Carbohyd. Polym. **87**, 581 (2012).
[8] M. K. Chun, C. S. Cho and J. K. Choi, J. Control. Release **81**, 327 (2002).
[9] L. Juntapram. N. Praphairaksit, S. Puttipipatkhachorn and P. Sriamornsak, Carbohyd. Polym. **87**, 2399 (2012).
[10] P. Haesun and R. Joseph, Pharm. Res. **4**, 457 (1987).
[11] C. James, T. Pugh, A. L. Johnson, T. A. Jenkins, Euro. Polym. J. **47**, 1338 (2011).
[12] L. Bromberg, M. Temchenko, V. Alakhov and T. A. Hatton, Int. J. Pharm. **282**, 45 (2004).
[13] Y. M. Lim, S. J. An, L. K. Kim, Y. H. Kim, M. H. Youn, H. J Gwon, J. H. Shin and Y. C. Nho, Radiat. Phys. Chem. **71**, 239 (2009).
[14] H. J. Gwon, Y. M. Lim, H. N. Chang and Y. C. Nho, J. Appl. Polym. Sci. **116**, 3682 (2010).
[15] Z. A. Othman and J. M. Rosiak, Nucl. Instrum. Meth. B **229**, 375 (2005).
[16] N. Yusof, A. H Ainul Hafiza, R. M. Zohdi and M. Z. A. Bakar, Radiat. Phys. Chem. **76**, 1767 (2007).
[17] J. H. Lee, Y. C. Nho, Y. M. Lim and T. I. Son, J. Appl. Polym. Sci. **96**, 1138 (2008).
[18] J. Rosiak and F. Yoshii, Nucl. Istrum. Meth. B **151**, 56 (1999).
[19] Y. C. Nho, J. S. Park and Y. M. Lim, Radiat. Rhys. Chem. **94**, 176 (2014).
[20] N. T. Nguyen and J. H. Liu, Euro. Polym. J. **49**, 4201 (2013).
[21] J. Berger, M. Reist, J. M. Mayer, O. Felt, N. A. Peppas and R. Gurny, Eur. J. Pharm. Biopharm. **57**, 19 (2004)
[22] N. Nagasawa, T. Yagi, T. Jume and F. Yoshii, Carbohyd. Polym. **58**, 109 (2004).
[23] F. Hutchison and D. A. Ross, Radiat. Res. **10**, 477 (1959).
[24] E. A. Bekturov, V. A. Frolova and G. K. Mamytekov, Macromol. Chem. Phys. **201**, 1031 (2000).
[25] C. Alkan, E. Gunther, S. Hiebler and M. Himpel, Energ. Convers. Manage. **64**, 364 (2012).
[26] C. A. Santos, J. S. Jacob, B. A. Hertzog, B. D. Freedman, D. L. Press, P. Harnpicharnchai and E. Mathiowitz, J. Control Release **61**, 113 (1999).
[27] H. K. Batchelor, D. Banning, P. W. Dettmar, F. C. Hampson, I. G. Jolliffe and D. Q. M. Craig, Int. J. Pharm. **238**, 123 (2002)
[28] M. A. Zaman, G. P. Martin and G. D. Rees, J. Dent. **38**, 757 (2010).
[29] C. A. Santos, B. D. Freedman, S. Ghon, J. S. Jacob, M. Scarpulla and E. Mathiowitz, Biomaterials **24**, 3571 (2003).
[30] K. Vermani, S. Garg and L. J. Zaneveld, Drug. Dev. Ind. Pharm. **28**, 1133 (2002).
[31] A. Jaipal, M. M. Pandey, A. Abhishek, S. Vinary and S. Y. Charde, Colloid Surface B **111**, 644 (2013).
[32] I. G. Needleman and F. C. Smales, Biomaterials **16**, 617 (1995).
[33] B. Han, J. K. Kim, Y. Kim, J. Korean Phys. Soc. **61**, 180 (2012).
[34] C. O. Yang, E. K. Park and H. J. Kim, J. Korean Phys. Soc. **61**, 297 (2012).