

A GENERAL SURVEY OF RESEARCH ON BIOMEDICAL APPLICATIONS OF RADIATION TECHNOLOGY IN CHINA

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ABSTRACT This paper reviewed the progress of research on biomedical products and synthesis of biomaterials by radiation technology. The promising prospect and some proposals have been discussed as well.

KEYWORDS γ -sterilization, Synthesis of biomaterials, Immobilization, Hydrogel, Radiation processing

Since 1980, especially late 80's, the radiation technology for biomedical application in China have rapidly developed and its hopeful prospect has been of a great attention. This presentation reviewed the progress in γ -sterilization of biomedical products and synthesis of biomaterials in China.

1 Progress on γ -sterilization of biomedical products

1.1 Evaluation of irradiated herbs^[1]

Having studied the γ -radiolysis of 124 types of herbs and evaluated the pharmacological efficacy of 40 types irradiated herbs, fruitful results were obtained subsequently, hopeful prospect to sterilize herbs by γ -ray becomes available, but important measure and step should be applied:

- (1) The herbs must be existed in dry state.
- (2) It is preferred to make bolus by mixing powdered Chinese medicine and honey because the latter can inhibit the radiolysis of herbs.
- (3) the producer must pay attention to execute strictly manufacture procedure to reduce the microbiological contamination and thus, subsequently lower the applied dose.

1.2 Improvement in hygienic quality of glucoamylase^[2]

γ -sterilization of industrial glycoamylase under 2kGy can greatly reduce the contamination of gemma bacillus and other putrefactive microbes, thus stabilize the pH value during its preparation. Glucoamylase can be preserved in good quality without antiseptic.

1.3 New treatments for enhancing the radiation to lurance of polypropylene

Systematic study of radiation effect on PP has been undertaken, such as on the morpho-

logy of polypropylene with some additives^[3]. To compete with ETO method, the price of new treatment PP must be cheaper, more over, it should be safer than conventional treatment. A lot of trials have been performed. Some treatments of PP present good radiation tolerance in the absence of additive Trinuvin 770, a well-known photo oxidant stabilizer, which might have blocking effect on autonomic nerve.

2 Progress on the use of radiation processing for synthesis of biomaterials

There is a great interest in focusing on immobilization synthesis of hydrogel, grafting hydrophilic monomer to biocompatible polymer matrix and fundamental studies.

2.1 Immobilization of drugs, enzymes and cells

Slow release anticancer drugs(5-Fluorouracilum, Mitomycinum, Bleomycinum and Ara-C) were prepared by radiation copolymerization of monomer such as HEMA. The release rate and amount of drug can be controlled by regulating the content of hydrophilic or hydrophobic monomer ($MMA < EMA < BMA$) and crosslinking reagent in drug-copolymer composite and by changing the radiation dose and drug content. The pore structure of composite may accelerate the release rate^[4,5]. The radiation polymerization was used for immobilizing testosterone propionate into crosslinked network of polyhydroxyethyl methacrylate to prepare slow release male sex hormone drug which is used for testicular prosthesis. Its evaluation in vivo has also been made. The testosterone level in serum of the castrated male rabbits rises significantly and finally stabilizes at the level of 429 ± 36 mg/100 ml after transplantation^[6].

The immobilization of enzymes(horseradish peroxidase, glucoseoxidase), cells(baker's yeast, E. Coli), proteins(bovine serum albumin) by radiation polymerization was studied. The monomers used were 2-hydroxyethyl methacrylate, acrylic acid, acrylamide and N-isopropylacrylamide^[7-10].

Generally, two methods have been applied for immobilization. The carrier can be synthesized by radiation polymerization. Adding crosslinking agent will obviously decrease the dose applied for gel formation and modify other properties. The other was graft copolymerization, for example, the acrylic acid was grafted via radiation onto segmented polyetherurethane (SPEU) film which is a kind of biocompatible material. Then the peroxidase was immobilized on the grafted SPEU film through chemical binding^[11].

Immobilized cells membranes of E. Coli by radiation technique was successful prepared. The Nylon 6 was grafted with HEMA, which has survival free radicals. The matrix containing free radicals was used to prepare for immobilized cells membranes with E. Coli by radiation entrapment at low temperature^[9].

It should be noticed that a number of irradiated oxidoreductases (catalase and horseradish peroxidase) are able to be of post deactivation, especially in the presence of air^[12].

2.2 Hydrogels

Recently, a lot of attention has been paid on radiation synthesis of thermo-sensitive polymer and the hydrogel dressing. An activated copolymer, poly(N-isopropylacrylamide-co-N-acryloxy succinimide) has been prepared. The active ester group of NASI has good chemical stability, physical properties and shows both high reactivity and selectivity toward amino nucleophiles, thus, the BSA or HRP has been immobilized onto the active copolymer. The BSA (or HRP)/copolymer conjugates still maintain the original thermally

sensitive properties of the linear poly NIPAAm^[13]. Other reports revealed that NIPAAm was grafted onto the surface of ethyl-vinylacetate (EVA slice) by means of preirradiation grafting due to poly-NIPAAm's weak mechanical strength, and the surface of EVA slice grafted with NIPAAm appears thermosensitivity similar to poly NIPAAm gel, while the mechanical strength is high. The response to the change of temperature through the lower critical solution temperature (LCST) of the graft is more swift than that of the gel. The LCST of the grafted surface shifts to higher and the drop of swelling around the LCST diminishes with increasing hydrophilicity of the graft when cografing NIPAAm with acrylic acid or acrylamide^[14].

A special drug carrying hydrogel base wound dressing by radiation preparation is developed for hospital uses. Main chemical materials used are (1) polymer (PVA, PVP, PEG etc) (2) Difunctional monomer (Itaconic diallyl ester etc.) (3) Chloramphenicol. The dressing possesses high water absorption property and standard tests for biomedical material were made. Results obtained from clinical test were acceptable^[15]. The hydrogel dressing has been produced in author's laboratory by Rosiak's method^[16], but it has to pass the examination of concerning department-standard test and clinical test are required.

The kinetics of the radiation synthesis of poly-2-hydroxyethylmethacrylate hydrogel has been studied. The results showed that (1) the PHEMA gel is formed when 20% HEMA is polymerized by γ -radiation, (2) the polymerization crosslinking of HEMA is proceed by the free radical mechanism: $V_0 \propto I^{0.6}$ (3) a low dose such as 2 kGy (dose rate 55 Gy·s⁻¹) is able to initiate the radiation crosslinking, high gel content (>90%) can be obtained at 4 kGy^[17].

The radiation graft kinetics of HEMA and HEMA and DGDA (diglycol diacrylate) mixture have been investigated. It has been found that grafting was different in different atmospheres. The findings show that the depth distribution of HEMA/DGDA monomer units in grafting layer is heterogeneous^[18]. The phase transition process of radiation synthesized hydrogels PAM and polyacrylamide-sodium acrylate has been studied in detail^[19].

3 Prospect and Proposal

Proposals for promoting the rapid growth of biomedical applications of radiation technology are as follows:

3.1 Enhancing the international cooperation especially in field of pilot scale studies and standard test, clinical test of biomedical material

3.2 Great attention should be focused on going research and development of the use of radiation processing for modification of natural biomaterial

(a) *Modification of carbohydrates* For example, acrylonitrile has been grafted on starch by γ -irradiation. The structure characterization on hydrolysed product of graft copolymers of acrylonitrile onto starches has been performed with IR spectrum, X-ray diffraction and SEM. There are various sizes of cavities and random crosslinking in the state of aggregation, which is associated with water retention. It may be developed as a super water absorbent^[20]. Modification of chitin has bright prospect, it can be processed to prepare hydrogel dressing, special membrane etc.

(b) *Modification of natural medicine by radiation processing* It has been reported that^[21] hydroxymethylation of 1,3-dimethyluracil by radiolysis of CH₃OH-1,3 dimethyl-

uracil solution provides a convenient and useful method for the introduction of a hydroxymethyl group into the 6 position of the pyrimidine and potential use for the analogous synthesis of biological importance. In author's laboratory, hydroethylation and diethylation of baicalin by γ -radiolysis of $\text{CH}_3\text{CH}_2\text{OH}$ -baicalin solution have been performed. Eight ethylation compounds have been separated by HPLC. Those compounds have higher polarity than original ones. It is expected that the baicalins will have different pharmacological efficacies.

(c) *Controlled release of Chinese medicine for brain research*^[22] Chinese and oriental medicines include a lot of smell substances and also physiologically and psychologically active substances for brain-nervous system. Radiation may be able to contribute to this subject with sterilization of medicine and immobilization for controlled release system. We hope to have a nice cooperation with Prof. Isao Kaetsu.

3.3 On fundamental research much attention should be paid

In the field, the fundamental research is closely connected with industrial application. Some important examples are listed as follows,

(a) *The role of trapping and peroxide radical in preirradiation grafting or polymerization process* Two methods of radiation induced polymerization or grafting are currently used, which are irradiation at low temperature (-78°C) method and preirradiation grafting or polymerization method. In latter method two types of radical-trapping radical and peroxide radical-play important roles in radiation synthesis^[23]. For initiating the polymerization reaction, some authors preferred to the peroxide radical, however, temperature control should be concerned, as at lower temperature the grafting yield is low, while a number of enzymes or cells can be deactivated or killed as increasing temperature. Some improvements have been made by use of UV light at 0°C ^[24] to initiate the polymerization of γ -preirradiated methacrylates. The superfine structures of embedded biological materials were observed under electron microscopy.

It has been reported that peroxide formed by preirradiating acrylamide can initiate polymerization at room temperature, but which seems ambiguous.

Above discussion demonstrates clearly that to distinguish trapping radical from peroxide radicals is very important in use of preirradiation technique. More efforts are still needed to study the behaviour of these radicals in detail because their activities directly linked with industrial process.

(b) *The characterization of grafting* The characterization of grafting is still poor, it is difficult to estimate the confidence limit of grafting yield. The grafting mechanism is uncertain, for example, why Al foil can inhibit the formation of homopolymer. What is the role of H^+ on grafting etc.. In author's laboratory, it was found that some monomer such as N-vinyl-pyrrolidone, acrylamide could be grafted by radiation technology onto segmented polyetherurethane (SPEU) or silicone rubber, which contains the electrically negative heteroatoms in their main chains, only in basic medium or in a medium with higher pH value. The results show that the acid effect in grafting systems, in fact, depends on many factors such as component of matrix, type of monomer and solvent, method of radiation grafting, total dose and so on. It can not be considered simply that just acid could enhance the grafting yield in any grafting system^[25,26].

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我国在生物医学中应用辐射加工技术的研究进展和展望

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摘要 综述我国八十年代以来, 辐射加工技术在生物医学中应用的研究进展: (1) 生物医学材料或制品 γ 辐射消毒研究的进展, (2) 利用辐射技术制备生物材料的进展。还讨论了应用前景及今后发展方向。

关键词 γ 辐射消毒, 生物材料合成, 固定化, 水凝胶, 辐射加工