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Use of radiation in the production of hydrogels

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Abstract

The first hydrogel for wound dressing processed by radiation left the laboratories in Poland in 1986 by the hands of its inventor Janusz M. Rosiak and soon, after formal tests, arrived in the local market (1992). It was a technological breakthrough due to its product characteristics as pain reliever and enhanced healing properties besides its clever production process combining sterilization and crosslinking in a simultaneous operation. IAEA invited professor Rosiak to support the transference of his technology for many laboratories around the world. The laboratories of developing countries, which face all kinds of restrictions, were seduced by the simplicity of the process and low cost of its raw materials. This was the seed of the flourishing activities in hydrogel dressings in Brazil and other developing countries. The technology transfer of the radiation production of hydrogel dressings and other hydrogels to the Brazilian industry is under way. The usual issues associated with radiation processing arise from this experience, i.e. capital costs, misinformation about radiation and lack of expertise on radiation processing. Some other issues concerning local market and social peculiarities also add to the problem. Notwithstanding, many different opportunities arise from those challenges. These technical and commercial issues are roughly: (i) There are plenty of new hydrogels in the market and all say the same. What else radiation processed hydrogels can say? (ii) Regarding to hydrogels and its industrial production as market product, what are the unique characteristics of radiation processing? It was shown that the radiation is a powerful tool for producing hydrogels the same basic formula with improved flexibility, control and purity.

Keywords: Biomaterials; Hydrogels; Dressings; Wound healing; Radiation sterilization; Crosslinking of polymers; Drug delivery system

1. Introduction

The first hydrogel for wound dressing processed by radiation left the laboratories in Poland in 1986 by the hands of its inventor Janusz M. Rosiak [1,2] and soon, after formal tests, arrived in the local market (1992). It was a technological breakthrough due to its product characteristics as pain reliever and enhanced healing properties besides its clever production process combining sterilization and crosslinking in a simultaneous operation. IAEA invited professor Rosiak and supported the transference of this technology for many laboratories around the world. The laboratories of developing countries, which face all kinds of

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restrictions, were seduced by the simplicity of the process and low cost of its raw materials. This was the seed of the flourishing activities in hydrogel dressings in Brazil and other developing countries.

Naturally, the development achievements are like a chain reaction; one starts the other, so many other products based on hydrogels are being developed. The authors' group (cf. [3–6]) has been studying the radiation processing of hydrogels and its various applications in medicine. Some products are already in the market, but we are developing ours, like an intra-vaginal device, which releases prostaglandin to relax the muscles during the induction of labor. Others original products are being developed in our laboratories, such as special dressings for wounds in the hands, special gels for bedsore and other pressure sore. There are important challenges such as to improve the mechanical strength of dressings without decreasing its softness, since, in general, the more resistant dressing will not touch the wound perfectly in some points, increasing pain.

Besides the technical approach one has to think of the commercial side if the product is realized to reach the market. These technical and commercial issues are commented on below. This paper will deal mostly with hydrogel dressings produced according to Rosiak's process, i.e. mixture of PVP(K-90 from GAF), PEG (from Oxiteno), agar(Oxoid) and water irradiated to 25 kGy as it is the best established product in the market.

2. Properties of hydrogels wound dressings

Hydrogel dressings are new products; they are in fact a revolution in the traditional area of the wound care management. The important qualities are:

1. The most important feature is the pain relief, this effect is achieved by the gentle touch of the very soft membrane surface with the nerves terminations (see Fig. 1).
2. The other key feature is the absorption of exudates; each kind of wound has a different rate of exudation, hydrogels dressings have different rates of absorption according to its polymeric structure, but as they are usually sold swelled by water, they are not useful for highly exudative wounds. Some dried dressing can be used for highly exudative wounds.

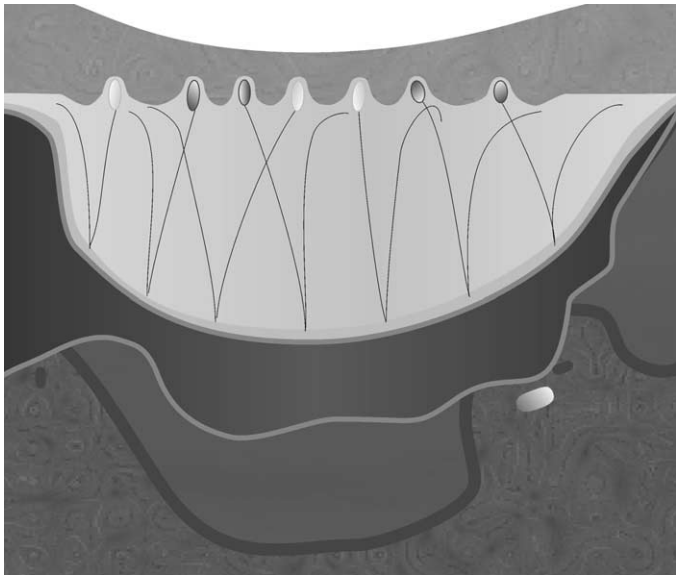

Fig. 1. Schematic drawing of a cross-section of a wound, showing the gentle touch of the dressing over the nerves tips.

Others important features are:

3. barrier for bacteria, keeping the wound clean;
4. it provides access of oxygen to the wound;
5. it is soft and elastic, allowing an easy contour to the wound in difficult areas;
6. it shows adhesion to the skin without the tendency to stick, allowing a painless replacement of dressings;
7. its transparency allows the observation of the healing process;
8. it allows the application of drugs without dressing replacement;
9. its water evaporation decreases the temperature of the wound, helping to control the inflammatory process and decrease the pain also.

Those features are common to almost all dressings, but some can have the most important features improved. The question is:

- There are plenty of new hydrogels in the market and all say the same. What else radiation processed hydrogels can say?

The dressings do not have initiators and they are sterile, but others are also safe for the users. The unique features are linked with the characteristics of optimum painkiller and good absorption rate. The radiation-processed dressings can be made in only one operation with very soft surface, usually by means of oxidative degradation, very tough in the core and resistant in the surface free from oxygen.

The membrane can be obtained with very good mechanical properties, but with a completely pasty surface, produced by oxidation and the dressings can be optimized to absorb more exudates, depending on the polymeric composition and amount of water.

3. Advantages of radiation processing for hydrogel production

- Regarding hydrogels and its industrial production as market product, which are the advantages of radiation processed hydrogels in respect to its characteristics and industrial production?
    1. Simultaneous sterilization and crosslinking; one should understand that this feature is really important as the combination of sterilization and polymer modification in just one industrial procedure simplifies the process and reduces costs.
    2. Take advantage of the electron penetration profile to produce hydrogels with a sandwich structure, i.e. the crosslinking density depends on the depth of electron penetration. This characteristic can be very important for wound care management, as for instance, the main advantage of hydrogels dressings are its tender contact with nerves points, reducing the pain, so softer surfaces can achieve this effect much better.
    3. For matrices designed to slow release of drugs sometimes is important to compound monomers with polymers, in that case, radiation can show all its usefulness, as is the technique that reduces at minimum level the amount of toxic residual monomers; Figs. 2(a)–(d) show the swelling properties of different compositions of hydrogels; the addition of monomer or HEMA, increase the crosslinking level, decreasing the swelling.
    4. Easy control of physical properties by combining dose with polymer composition; for instance, the same basic formula of dressings can produce solid, elastic ones and fluid gels (see Fig. 3).

Although radiation proves itself a very versatile tool to fit compositions to different mechanical properties, the radiation chemistry sometimes is very complex. We have been studying the effects of PEG for the gel formation without the addition of agar. Figs. 4 and 5 show the gel fraction for samples with different molecular weights and concentrations of PEG 6000, respectively.

Fig. 5 shows that the gel content of the sample without PEG, only PVP and water, shows about the same results as the samples with PEG of various molecular weights (MW). So the amount of PEG in the range of 0.5 balanced way, i.e. the increase in distance, is been compensated in some way, maybe by the increase in mobility. It is easy to see that MW does not show any trend, however, Fig. 4 shows that the increase in PEG concentration, increases the gel formation up to 0.5 steadily

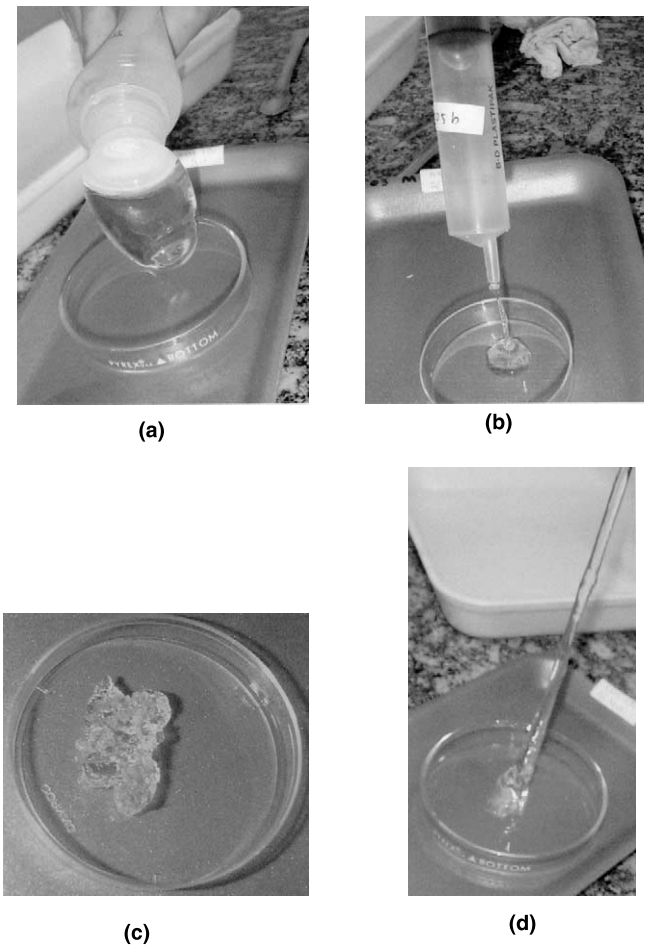

Fig. 2. Four different mechanical behavior of hydrogels produced by irradiation from the same basic formula, i.e. PVP, PEG and water. (a), (d) Very elastic, (b) more fluid, (c) brittle.

to higher PEG concentrations. The decrease is so noticeable, that for even higher PEG concentrations the amount of gel goes to zero. The decrease in gel formation is easy to explain, as the PEG acts mostly as plasticizer, increasing the distance between the PVP molecules. So, the overall effect of PEG is to decrease the gel content, mainly, at higher concentrations.

4. Transference of radiation technology to industry

The first approach is very important when one wants to sell a development to potential clients from government or industry. This product has a very strong appeal due to its use for people with serious injuries such as burns. So the government and industry easily accept it as an important new product.

One has to sell an idea that is easily understood by the technical staff as well as by administrators as usually if one tries to sell very advanced technology, this will possibly scare the potential client, at least in developing countries. The idea will become even more attractive if the client understands that this could easily become "his" project.

Also very important is the right choice of the counterpart industry, the industry ideally should

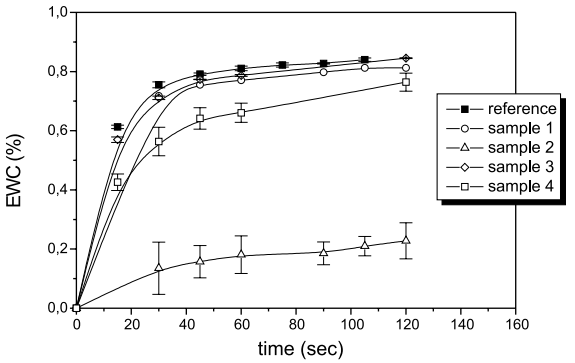

Fig. 3. Swelling in water (RT) of different compositions cross-linked at 25 kGy designed to act as a drug delivery system. Reference is a commercial device for prostaglandin release. Sample 1 is PVP 5%, sample 2 is HEMA 90% + PVP 10%, sample 3 is PVP 10% + PEG 10% and sample 4 is NVP + PEG 1%.

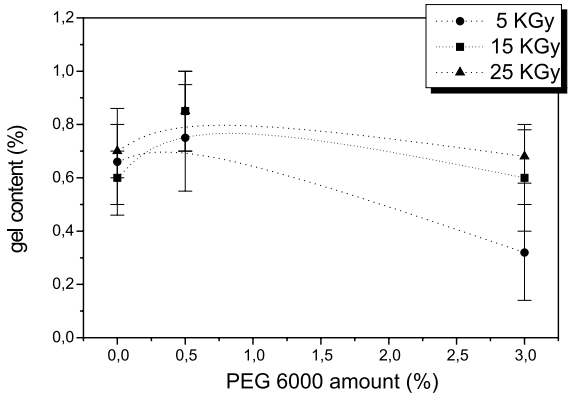

Fig. 4. Gel fraction for samples with 5% PVP and different PEG concentrations irradiated at 25 kGy.

have a R&D team to support the technology transfer and the highest directive level should be committed to this development.

The transference of the technology for the production of hydrogel dressings and other hydrogels by radiation to the Brazilian industry is under way. The usual issues associated with radiation processing arise from this experience, i.e. capital costs, misinformation about radiation and lack of expertise on radiation processing. Some other issues concerning local market and social

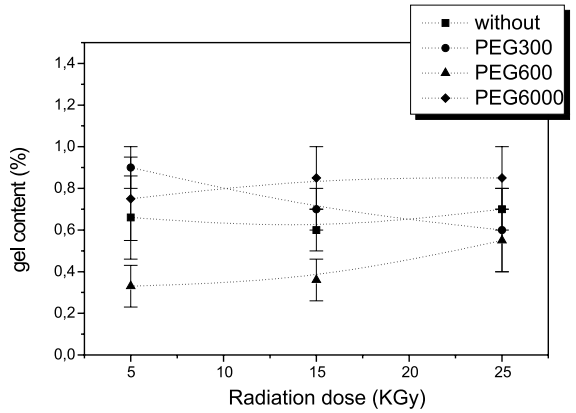

Fig. 5. Gel fraction for samples with 5% PVP and different PEG molecular weights (300, 600 and 6000).

peculiarities also add to the problem. Notwithstanding, many different opportunities arise from those challenges.

The relationship among industry and research group to perform the technology transfer is like a marriage. The main steps of this relationship are:

- The period of partner's search – the group is always looking for funds and it is certainly a pleasure to see the products and process approaching the market; the company is looking for a group committed with short to medium time development and also committed with deadlines and confidentiality.
- The agreement time – it is very important to formalize the relationship.
- The period for the development of mutual confidence – the time when the research team, preferable having staff from both partners, will work together pursuing well defined goals, having a well defined bench mark; it is necessary to achieve a final product after some time, otherwise the relation will deteriorate, the will for the optimum will be against the clock.

In order to properly evaluate the development risks or possibilities of product success, it is necessary to construct a decision tree to evaluate the risks, foresee the profits and technology value and it even is a basic decision tool to establish the royalties to be paid by the industry.

5. Conclusion

The "end of line" of product development is always the market approach. These barriers are greater than technical issues. The main points are outlined below.

- The difference of the physician perspective from developed countries as compared with well developed ones regarding the proper care to the first and second degree burns, and even the third degree–second degree burns are not considered important enough to demand special care in Brazil.
- The difference in approach for clinical trials; typically conservative for the medical societies all over the world, but it is not so strong as in developed countries, i.e. physicians are willing for more effective solutions at higher risks – some problems are so hopeless due to the lack of medical care structure, which stimulates the physician to search for alternative solutions.
- Legislation is not so rigorous for experiments under strict ethical codes – there is not a culture to take all problems to the justice court.
- The effectiveness of the new drug carriers and or dressing is not the central point if the main concern is just to have profits in all the production and commercialization chain.
- In developing countries, the national industries do not have quality standards and technology to approach the global market as they still think "local".

Acknowledgements

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