Radiation Physics and Chemistry 81 (2012) 1249–1253

Contents lists available at SciVerse ScienceDirect

Radiation Physics and Chemistry

journal homepage: www.elsevier.com/locate/radphyschem

Pilot scale-up and shelf stability of hydrogel wound dressings obtained by gamma radiation

Dulce María Soler [a,*], Yanet Rodríguez [a], Hector Correa [a], Ailed Moreno [b], Lila Carrizales [b]

[a] National Center for Animal and Plant Health (CENSA), Development and Industrial Biotechnology Group, San José de las Lajas, Mayabeque, Cuba
[b] Venezolan Institute of Scientific Research (IVIC), Nuclear Technology Unit, Altos de Pipe, Caracas 1020A, Venezuela

ARTICLE INFO

Article history:
Received 1 July 2011
Accepted 16 February 2012
Available online 24 February 2012

Keywords:
Hydrogel
Poly(vinyl pyrrolidone)
Wound dressing
Scale-up
Stability

ABSTRACT

This study is aimed of producing pilot batches of hydrogel wound dressings by gamma radiation and evaluating their shelf stability. Six batches of 3L capacity were prepared based on poly(vinyl pyrrolidone), agar and polyethylene glycol and they were dispensed in polyester trays, covered with polyester films and sealed in two types of materials: polyethylene bags and vacuum polyethylene bags. Dressings were formed in a single step process for the hydrogel formation and sterilization at 25–30 kGy gamma radiation dose in a JS-9500 Gamma Irradiator (Nordion, Canada). The six batches were initially physicochemical characterized in terms of dimensions and appearance, gel fraction, morphology analysis, hydrogel strength, moisture retention capability and swelling capacity. They were kept under two storage conditions: room temperature (T: 30 ± 2 °C/RH: 70 ± 5%) and refrigerated temperature (T: 5 ± 3 °C) during 24 months and sterility test was performed. The appearance of membranes was transparent, clear, uncut and flexible; the gel fraction of batches was higher than 75% and the hydrogel surface showed a porous structure. There was a slow decrease of the compression rate 20% until 7 h and about 70% at 24 h. Moisture retention capability in 5 h was similar for all the batches, about 40% and 60% at 37 °C and at room temperature respectively. The swelling of hydrogels in acidic media was strong and in alkaline media the weight variation remains almost stable until 24 h and then there is a loss of weight. The six batches remained sterile during the stability study in the conditions tested. The pilot batches were consistent from batch to batch and remained stable during 24 months.

1. Introduction

Hydrogels are bi or multicomponent systems consisting in a permanent three-dimensional network of linked polymer chains, and molecules of a solvent filling the pores of this network. They are obtained by polymerization with crosslinking agents, by chemical crosslinking of polymers or by radiation-induced crosslinking of polymers. The radiation processing has several advantages such as the simultaneous crosslinking and sterilization in one step and the easy control of physical properties of hydrogels by combining dose with polymer composition; it allows to fabricate a pure and human-friendly product non-contaminated with ballast materials or the residuals of toxic initiators (Lugao and Malmonge, 2001; Rosiak et al., 1995).

Hydrogels based on polyvinylpyrrolidone (PVP), agar and poly(ethylene glycol) (PEG) firstly developed as wound burn dressings by Dr. Rosiak from Poland (Rosiak et al., 1989) have had a successfully wide application for medical treatment of other types of wounds and illnesses since their market introduction in 1992. These biomaterials should fulfill some requirements that are mentioned by Rosiak et al. (1995): absorb effectively the body fluids and prevent their loss, act as an efficient barrier against bacteria, adhere well to the wound but stronger to healthy skin, exhibit high elasticity but also some mechanical strength, show good transparency, enable the oxygen to penetrate through the volume of dressing to the wound surface, enable to control drug dosage and offer good handling (i.e. easy placement and replacement) without pain. In addition they should be sterile, easy to store, relatively cheap and generally accelerate healing. The International Atomic Energy Agency (IAEA) has supported the technical cooperation related to the development of this kind of product in the laboratories of developing countries like Cuba. To develop the total production process of our product, it is necessary to follow the product life cycle that goes through multiple phases, involves many professional disciplines, and requires many skills, tools and processes (Westkämper, 2000). After the laboratory tests, it is important to demonstrate the scalability of the process and the product stability. Scale-up is generally defined as the process of increasing the batch size. In moving from R&D to production scale, it is sometimes essential to have an intermediate

* Corresponding author. Tel.: +53 047863653.
E-mail address: dmsoler@censa.edu.cu (D.M. Soler).

0969-806X/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.radphyschem.2012.02.024

batch scale. This is achieved at the so-called pilot scale, which is defined as the manufacturing of drug product by a procedure fully representative and simulating that used for full manufacturing scale (Levin, 2005). During product development, stability studies are conducted to establish an expiration-dating period that would be applicable to all future batches of the product manufactured under similar circumstances (FDA, 1998).

The aim of this work was to produce pilot batches of hydrogel wound dressings by gamma radiation and to evaluate their shelf stability.

2. Materials and methods

2.1. Materials

Polyvinylpyrrolidone (PVP: Povidone K 90) was supplied by BASF, polyethylenglycol (PEG, MW 400) and agar were supplied by Merck. These ingredients were used as received.

Double distilled water was used for the preparation of batches and hydrogels were contained in polyester trays of 10 cm $\times$ 12 cm $\times$ 0.7 cm dimensions.

2.2. Preparation of Hydrogel batches

Six batches with a total volume of 3L were manufactured following the next steps: preparation of aqueous solution of PVP (7%), PEG (1%) and agar (1.5%) at 85 °C for about 1 h, filling the trays with the hot solution, cooling at room temperature until the solution becomes a solid gel, covering with polyester films and sealing in bags made from two different materials: polyethylene of 0.07 mm supplied by Chader S.L., Spain and vacuum polyethylene packaging of 0.14 mm supplied by Multivac, Mexico. Gamma irradiation at 25–30 kGy of the trays packed in carton boxes was carried out in a JS-9500 tote irradiator (Nordion, Canada) having a dose rate of 6 kGy/h. The absorbed doses were measured using red polymethalmethacrylate dosimeters.

Circular samples of around 15 mm diameter from hydrogel batches were cut for running the characterization.

2.3. Dimensions and appearance

Size and the thickness of hydrogel wound dressings were determined using a micrometer with a resolution of 0.001 mm. Shape and the appearance was described through the visual inspection.

2.4. Gel fraction

Dried samples were weighed (W_o) and put in a beaker containing excess distilled water for 24 h. After that, water was discarded and swelled gel was boiled in fresh water for 5 min. The gel was washed again in distilled water and then dried to constant weight (W_E). Gel fraction was calculated using the following formula:

$$GF(\%) = \frac{W_E}{W_0} \times 100 \quad (1)$$

where W_o is the weight of dried gel after irradiation and W_E is the weight of dry gel after removing sol.

2.5. Morphology analysis

The surface of the hydrogel was sputter coated with gold to obtain the desirable contrast. The surface morphology of the freeze dried hydrogel samples was examined with a Phillips serie XL 30 scanning electron microscopy (SEM).

2.6. Hydrogel strength

Circular samples were subjected to a pressure of 50 g/cm^2 during 24 h using a 50 g calibration weight, according to the method described by Wang et al. (2007). The gel strength of the hydrogel determined by the relative change in circular samples height under pressure was evaluated by its compression ratio (CR) at initial time and at 1,2,3,4,5,6 and 24 h which were calculated by the following formula:

$$CR(\%) = \frac{L}{L_o} \times 100 \quad (2)$$

where L_0 is the initial height of the circular samples before pressing and L is the height under pressure at different times.

2.7. Moisture retention capability

Circular samples from the six batches put into Petri dishes were placed during 24 h under two storage conditions: incubator (37 °C) and at room temperature (T: 30 $\pm$ 2 °C). The samples were weighed at initiation (m_0) and at different time intervals (m_t). Moisture retention capability (Rh) was measured by the following formula:

$$R_h(\%) = \frac{m_t}{m_o} \times 100 \quad (3)$$

2.8. Swelling capacity

Circular samples were weighed (G_d) and immersed in aqueous medium with different pH values (pH=1, 5.7, 10) at room temperature during 48 h. They were removed from the medium at 1,2,4,6,8,24 and 48 h, wiped with filter paper and weighed (G_i). The degree of swelling ratio was calculated according to formula (4):

$$\text{Degree of swelling} = G_i - G_d / G_d \quad (4)$$

2.9. Shelf stability study

The six batches were kept under two storage conditions: room temperature (T: 30 $\pm$ 2 °C/RH: 70 $\pm$ 5%) and refrigerated temperature (T: 5 $\pm$ 3 °C) during 24 months. The sterility test of the hydrogel batches was conducted at initial time and at 6, 12, 18 and 24 months according to USP (2009), by the direct transfer method.

3. Results and discussion

3.1. Dimensions and appearance

The membranes obtained from all batches had rectangular shape, size of 105 $\times$ 85 mm and thickness of 5–7 mm. The appearance of membranes were transparent, clear, uncut and flexible. Also a few drops of visible condensed water drops and some small burbles inside hydrogel were acceptable.

3.2. Gel fraction

The gel fraction of the six hydrogel batches is shown in Table 1. The batches show a gel fraction higher than 75% of gelling (75–86%), which is a good value for this characteristic. While the degree of crosslinking the amount of water that can be absorbed is smaller (Rosiak et al., 1995b), tensile strength is higher and elongation is smaller, that is why it is important to