Radiation Physics and Chemistry 145 (2018) 19–25

Contents lists available at ScienceDirect

Radiation Physics and Chemistry

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

# Rheological effect of gamma radiation on gel-like formulation: Appraisal for the construction of radiopharmaceuticals for cutaneous application

Vivian Saez[a], Helen Jamil Khoury[b], Maria Isabel Barbosa da Silva[c], Claudia Regina Elias Mansur[a], Ralph Santos-Oliveira[c,d,*]

[a] FederalUniversityof Rio de Janeiro,Institute of Macromolecules (IMA/UFRJ), Av. Horácio Macedo, 2030, 29141598 RJ, Brazil
[b] Federal University of Pernambuco, Department of Nuclear Energy, Pernambuco, Brazil
[c] Brazilian Nuclear Energy Commission, Nuclear Engineering Institute, Rio de Janeiro, Brazil
[d] Brazilian Association of Radiopharmacy, Presidency, Rio de Janeiro, Brazil

ARTICLE INFO

*Keywords:*
Rheology
Melanoma treatment
Irradiation
Hydrogel
Carbopol

ABSTRACT

Skin cancer affects a lot of people being a malignant cutaneous melanoma one of the most aggressive neoplasms. Nowadays, the FDA-approved drugs to treat them are not as efficient as needed. Thus, the development of new agents or treatments is quite urgent. In that sense, the use of radioactive materials could represent a good alternative and especially Radium-223 is already been explored with promising results. Here, a Carbopol gel-like formulation was designed and irradiated with different doses in order to prove that it is suitable to include Radium-223 for its combined application by topic route. A formulation was obtained by the addition of triethanolamine to the Carbopol solution until pH 5.0. Physical and rheological tests showed that the formulation is a weak gel with a proper consistence to be administered by both routes. The formulation kept its appearance of transparent gel without change in color, presence of grits or syneresis after all tratments. The microstructure of gels was only slightly modified when the irradiation was made with 1000 Gy while the spreadability and viscosity were more deeply affected. Since the properties of this Carbopol gel-like formulation were maintained under irradiation doses until 100 Gy it is possible to consider that the formulation is suitable to include Radium-223 in order to evaluate its performance as localized drug delivery system for topical administration.

## 1. Introduction

Skin cancer is a very common type of malignance that affects a lot of people and every year many cases are detected (Simões et al., 2015). There are two known types of skin cancer: i) the non-melanoma that consists of basal cell carcinomas and ii) squamous cell carcinomas, and melanomas, which originate in melanocytes (Lo and Fisher, 2014; Biswas et al., 2015; Dummer et al., 2016). Currently, malignant cutaneous melanoma has been described as one of the most aggressive neoplasms and its incidence is increasing (Lo and Fisher, 2014; Biswas et al., 2015). Thus, it has been considered as the most serious form of skin cancer (Lin and Fisher, 2007; Lo and Fisher, 2014).

There are few therapeutic alternatives for the treatment of cutaneous melanoma and the only drugs approved by the Food and Drug Administration (FDA) for the treatment of advanced melanoma were Dacarbazine (DTIC) and high doses of interleukin-2 (HIL-2). Both of them have low response rates (10–20%). Until recently, none of the agents used for the treatment of melanoma have demonstrated an increase in overall survival. Consequently,the development of new agents or treatments is quite urgent (Kirkwood and Legha, 1997; Lo and Fisher, 2014).

Recently, the use of radioactive materials has been taking on unimaginable proportions and their applications have been growing exponentially. Specially, the use of Radium-223 (Ra-223) in cancer therapy has been increasing by virtue of its characteristics. It is an alpha emitter radioisotope with half-life of 11.4-day that has chemical similarity to calcium. There are some encouraging results related to the application of Ra-223 in bone cancer metastases in the skeleton that result from advanced prostate and breast cancer (Parker et al., 2013; Coleman et al., 2014; Shore, 2015; Takalkar et al., 2015). The use of Ra-223 may be expanded to other applications. For example, intratumoral applications, as well as a cutaneous application, in particular as an adjuvant form in the treatment of skin cancer.

Consequently, and foreseeing the expansion of the use of Ra-223 in cutaneous formulations to treat melanomas, it could be convenient to develop a proper pharmaceutical dosage form which could be

* Corresponding author at: Brazilian Nuclear Energy Commission, Nuclear Engineering Institute, Rio de Janeiro, Brazil.
*E-mail address:* presidenciaradiofarmacia@gmail.com (R. Santos-Oliveira).

https://doi.org/10.1016/j.radphyschem.2017.12.008
Received 5 September 2017; Received in revised form 20 November 2017; Accepted 10 December 2017
Available online 13 December 2017
0969-806X/ 

administered topically. In that sense, hydrophilic gels could be a good alternative. They are commonly used in pharmaceutical and cosmetic products as dermatological base since they are easy to spread, exhibit low occlusion effect and support the delivery of several active agents (Li and Mooney, 2016; Zakaria et al., 2016). Among the diverse materials than can be used to form gels, polymers are preferred because they allow to obtain a great variety of gel properties. There are a lot of polymers available to produce pharmaceutical formulations and cosmetics, but the group of carboxyvinylic acids (i.e. Carbopols®) is the most popular. They have been used in different pharmaceutical dosage forms taking advantages of their capacity to: *i)* form clear and homogeneous hydrogels (Roberts and Barnes, 2001), *ii)* give a wide range of gel properties by varying the type of Carbopol and the specific conditions to prepare the hydrogels (Di Giuseppe et al., 2015), *iii)* provide bioadhesive character to formulations (Sareen et al., 2011; Tejada et al., 2017), *iv)* have good compatibility with a variety of other compounds to form hybrid materials with new properties (Junqueira et al., 2016; Singh and Dhiman, 2017), *v)*form tissue film and, *vi)* modulate the release rate of different active agents included directly on a gels (Sareen et al., 2011) or previously encapsulated in nanoparticles (Bharadwaj et al., 2016).

In the case of hydrogels containing radiopharmaceuticals, the interaction of them with the polymeric matrix could be considered since some modifications might occur as a consequence of the radiation emitted by the radionuclide. In general terms, these modifications can include scission of polymeric chains and cross-linking (Sintzel et al., 1997). Such transformations on the polymeric material could lead to changes on the physico-chemical stability of the formulation, as well as its skin behavior, especially in the release of the active principle, as well as its adhesion, and finally, in the formation of the tissue film (Sintzel et al., 1997; Silindir and Özer, 2012). Consequently, this work was aimed to study physical and rheological properties of a Carbopol gel-like formulation exposed to different rates of gamma radiation. This study simulates the behavior of this pharmaceutical formulation containing the radionuclide for topical application.

## 2. Materials and method

### 2.1. Materials

Carbopol 940 P, methylparaben, propylparaben and triethanolamine was obtained from (Sigma-Aldrich (St. Louis, MO). All reagents were used as received.

### 2.2. Gel formulation

The gel was made using Carbopol 940 P (2%, w/w), methylparaben (0.3%, w/w), propylparaben(0.1%, w/w), triethanolamine (qs to assure pH 5.0), and purified water (qs for 100 mL of formulation). Briefly, the polymer was carefully weighted and then added to a vessel containing purified water. This mixture was gently stirred overnight. Gel was formed by adding triethanolamine slowly until the pH was stabilized at 5.0. The formulation process was carried out under GMP's conditions, i.e. under sterile conditions, in order to guarantee the microbiological stability.

### 2.3. Irradiation

Irradiation was performed at room temperature using a 60-Co Gamma Cell 220 available at the Federal University of Pernambuco with a dose rate of 2.25 $kGyh^{-1}$ (2.255 $kGyh^{-1}$). All samples were placed in Eppendorf vials (2 g of gel in each vial) and then irradiated at different doses (1, 5, 10, 100 and 1000 Gy). All samples were irradiated in duplicate at all doses. Non-irradiated samples were used as controls to detect physicochemical changes resulting from the action of ionizing radiation on the gel.

It is important to notice that the sample treated with the lowest dose was irradiated in a 60-Co Gamma Cell 220 also available at Federal University of Pernambuco, with a dose rate of 1.709 $Gyh^{-1}$.

### 2.4. Physical evaluation of materials

The appearance of gel-like materials was examined through observation for any change in color, presence of grits or syneresis. To detect changes in their microarchitecture all samples were analyzed with an optical microscope AxioVision(Carl Zeiss Vision GmbH, Germany). The spreadability was evaluated by adapting the methodology described by Parente*et al* in 2015 (Parente et al., 2015). Briefly, 25 mg of samples was carefully deposited in a glass slide previously placed over a millimeter paper. The material was covered with another glass slide and a piece of 1 g was allowed to rest over this plate during one minute. The diameter of the circle occupied by the spread formulation was then measured. The pH of gels before and after irradiation was also measured using a digital pH-meter.

### 2.5. Rheological analysis

Measurements were performed in a HAAKE™ MARS™ 60 Rotational Rheometer(HAAKE, Germany) using the cone and plate geometry with an angle of 2° and a diameter of 35 mm. The gap between the plate and cone was adjusted to 0.098 mm. The quantity of samples required for filling the space between the plate and cone was approximately of 0.4–0.5 mL. The temperature control ( ± 0.1 °C) was guaranteed by a Peltier unit assisted with a cryostat. After the sample be placed in the space of the device 10 min were waited in order to allow the gel reach the equilibrium temperature with the measuring system.

The oscillatory analysis was made keeping the frequency constant at 1 Hz and sweeping the strain between 0.01% and 100%. The viscosity curves were obtained as a function of the shear rate which varied from 0.01 until 500 Hz. Temperature was maintained at 25.0 ± 0.1 °C for all tests.

### 2.6. FTIR analysis

The IR spectra of the formulations were obtained with an Excalibur Varian 3100 FTIR spectrometer(Varian, USA). The Spectrum was collected between 4000 and 600 $cm^{-1}$). The spectrometer has an attenuated total reflection (ATR) accessory with a ZnSe crystal. A thin film of each sample was spread directly on the ZnSe crystal for measurement. Non additional sample preparation was required. The resolution was 4 $cm^{-1}$ and 120 scans were used to form the spectrum.

## 3. Results and discussion

Carbopols are cross-linked polyacrylic acid polymers containing a fraction of carboxyl groups. They are physical hydrogels since their structure are supported by physical interactions such as molecular entanglement, ionic interaction and hydrogen bonding, among the polymeric chains (Pal et al., 2009). The acceptable properties (viscosity and clarity) of Carbopol gels start by pH values between 4.5 and 5, having a maximum at pH 7 and start to decrease again at pH 11. The materials used in this work were prepared under a fine tuning of final pH in order to obtain a semisolid gel-like formulation having a gel appearance but with a lowest viscosity for making possible to inject it topically. It means that the interactions between polymeric chains could be not as strong as in a real gel. On the other hand, it is well known that syneresis of these materials can occur when interactions between particles of the dispersed phase becomes great at the equilibrium state, the dispersing medium is then squeezed out in form of droplets and the gel shrinks. At low pH values, hydrogels with carboxylic acid groups could suffer syneresis probably due to the suppression of ionization of the carboxylic groups, loss of hydration water and the formation of intramolecular