AAPS PharmSciTech 2005; 6 (4) Article 73 (http://www.aapspharmscitech.org).

Comparison Between Gamma and Beta Irradiation Effects on Hydroxypropylmethylcellulose and Gelatin Hard Capsules

Submitted: March 24, 2005; Accepted: September 17, 2005; Published: December 1, 2005

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ABSTRACT

The effects of electron beam or γ-irradiation on technological performances (capsule hardness, expressed as deforming work and dissolution time) of empty 2-shell capsules made of gelatin or hydroxypropylmethylcellulose (HPMC) were studied. Capsule structural changes induced by radiation treatment were investigated by capillary viscometry and atomic force microscopy (AFM). The capsules were irradiated in the air at 5, 15, and 25 kGy. The deforming work of nonirradiated HPMC capsules (0.06 ± 0.01 J) was lower than that of gelatin capsules (0.10 ± 0.01 J). The dissolution time of the HPMC capsules (414 ± 33 seconds) was slightly higher than that determined for gelatin hard capsules (288 ± 19 seconds). The hardness and dissolution time of gelatin and HPMC capsules were not significantly influenced by the irradiation type and the applied irradiation dose. As the viscometry analyses are concerned, irradiation caused a reduction of the intrinsic viscosity and water and dimethyl sulfoxide solvent power in both the cases. AFM analysis showed that the radiation treatment did not appreciably affect the surface roughness of the samples nor induce structural changes on capsule surface. However, measurements of force-distance curves pointed out a qualitative parameter for the identification of the irradiated capsules. On the bases of these preliminary results, empty gelatin or HPMC hard capsules can be sanitized/sterilized by ionizing radiation.

KEYWORDS: gelatin capsule, HPMC capsule, electron beam irradiation, gamma irradiation, AFM.

INTRODUCTION

Ionizing radiation processing at low dose plays an increasingly important role in the microbial decontamination of pharmaceutical and medicinal herbal products as well as health food and botanical health products. Nevertheless, irradiation has to be permitted only when it has been experimentally proved and well documented that no harmful side effects occur, owing to possible qualitative and quantitative alterations of the irradiated materials.

γ-rays emitted from nuclear source (^{60}Co or ^{137}Ce) or electron beam are the most frequently used ionizing radiation for the sanitization/sterilization of these products. Ionizing events cause a shower of secondary electrons that activate numerous chemical reactions, many of which induce oxidative degradations in the presence of oxygen. Although the main interactions between matter and γ-rays or high-energy electrons are based on the same reactions, minor differences still remain. In fact, γ-rays are electromagnetic radiation characterized by a very low dose rate (kGy/h), while β-rays are corpuscular radiation characterized by a very high dose rate (kGy/s). The different exposure time required to apply the same dose could have different effects on the performance of radiated dosage forms. As a matter of fact at the same applied dose, β-ray treatment may cause an overheating of the material, while γ-ray treatment could prolong the peroxidative radiolitic mechanisms owing to the longer exposure time.[1] Moreover, the electron beam irradiation process is faster, easier from an operative point of view, less expensive, and it does not incur environmental risks of nuclear irradiation.[1]

Hard capsules used in pharmaceutics, health food, and herbal preparations could be radiated to sanitize the products in the final step of manufacturing process. The final sterilization could also be an alternative to aseptic production of hard capsules used as pulmonary dosage forms.

Gelatin is the most widely used material in capsule manufacturing. However, after the outbreak of bovine spongiform encephalopathy (BSE), there has been increased interest in the use of hydroxypropylmethylcellulose (HPMC) as a way to avoid risks associated with the use of animal-derived ingredients. HPMC capsules available on the market contain a low percentage of a gelatinizing agent, namely, kappa-carrageenan, to decrease HPMC thermal gelation temperature.[2]

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According to the level of exposure, ionizing radiation may change the molecular weight and its distribution of all shell components. The viscosity of irradiated solutions containing bovine powder gelatin was significantly affected by both β- or γ-rays when doses higher than 5 kGy were administered.[3] The effects of γ-irradiation on HPMC raw material were studied by calorimetry, spectrometry, rheology,[4] electronic paramagnetic resonance analysis and capillary viscometry.[5] In these studies it has been demonstrated that the main radiolytic process is based on HPMC chain scission events. The degradation mechanism is in agreement with the results of viscosity measurements that showed a progressive decrease of the average molecular weight by increasing the radiation dose.[4,5] Similarly, the viscosity of irradiated carrageenan solutions decreased as the irradiation dose increased, as a consequence of the depolymerization of basic units.[6]

Although the effects of ionizing radiation on components of hard capsule have been already described, the effects of their degradation on the technological performances of irradiated capsules are not reported in literature.

In the present study, empty gelatin and HPMC hard capsules were irradiated at doses of 5 kGy, 15 kGy, and 25 kGy by using either electron beam or γ-irradiation, and the technological performances in terms of dissolution time and hardness were evaluated. The maximum dose of 25 kGy was selected as it ensures overkill condition.[7] The intrinsic viscosity of dissolved hard capsules was also determined by capillary viscometry aiming to detect possible changes in polymer molecular weight.

Morphological and topographical modifications of sample surface were studied measuring the surface roughness by atomic force microscopy (AFM). Possible changes in adhesion response related to induced surface modifications between irradiated and nonirradiated capsules were evaluated by the analysis of force-distance curve.

Materials and Methods

Materials

HPMC, colorless, hard capsule, size 0 (batch number: E0004403, Shionogi Qualicaps SA, Madrid, Spain) and gelatin, colorless, hard capsule, size 0 (batch number: E9905211, Coni-Snap, Capsugel, Bornem, Belgium) were purchased from Prodottigianni (Milan, Italy). According to the data sheet, the HPMC capsules contained 2% κ-carrageenan. The capsules, as received, were sealed in aluminum blisters.

All solvents unless specified were of analytical grade.

β- and γ-Irradiation of 2-Shell Hard Capsules

γ-Irradiation

Gelatin and HPMC hard capsules were irradiated by using ^{60}Co as irradiation source (Gammacell, Nordion Inc, Vancouver, Canada). Irradiation was performed in the presence of air at the doses of 5, 15, and 25 kGy, applied at a dose rate of 865 Gy/h; irradiation temperature, 25°C ± 1°C.

β-Irradiation

Gelatin and HPMC hard capsules were irradiated by using an electron beam accelerator (Bioster, Dalmine, Italy). Irradiation was performed in the presence of air, calorimetry doses 5, 15, and 25 kGy, energy 10 MeV; irradiation temperature, 25°C ± 1°C.

Viscosity Measurements

Theoretical Consideration

Using the dynamic viscosity of solution (η) and that of pure solvent (η_o), several dimensionless parameters may be calculated.

The relative viscosity (η_{rel}) is expressed as

$$\eta_{rel} = \frac{\eta}{\eta_0} = \frac{\rho k t}{\rho_0 k t_0}, \quad (1)$$

where t and t_0 are the efflux times for the polymeric solution and for the solvent respectively; ρ and ρ_0 are their densities; and k is a constant that includes the viscometer characteristics. In diluted solutions ρ and ρ_0 can be considered equivalent and Equation 1 can be simplified as follows:

$$\eta_{rel} = \frac{t}{t_0} \quad (2)$$

Considering the concentration of the polymer (c), the inherent viscosity (η_{in}) can be calculated from the following equation:

$$\eta_{in} = \frac{(ln\ \eta_{rel})}{c} \quad (3)$$

The fractional increase in viscosity, due to the presence of the solute, is defined as specific viscosity (η_{sp}):

$$\eta_{sp} = \frac{(\eta - \eta_0)}{\eta_0} = \eta_{rel} - 1 = \frac{t}{t_0} - 1 \quad (4)$$

Because the degree of viscosity enhancement is dependent on the amount of dissolved material as well as molecular

size, a more fundamental parameter is the reduced viscosity (η_{red}):

$$\eta_{red} = \frac{\eta_{sp}}{c} \quad (5)$$

Because specific viscosity (η_{sp}) is dimensionless (being a ratio between viscosities), the reduced viscosity, as well as the inherent viscosity, has the dimension of a specific volume, which may be considered as the sum of the effective hydrodynamic volumes (EHV) of the number of molecules that make up 1 g of the polymer. When the solution is infinitely diluted, the molecules have no influence on each other and the EHV is simply the addition of the effective hydrodynamic volumes of the separate molecules. The limit of infinite dilution of the reduced viscosity (Equation 5) represents the intrinsic viscosity [η] that is the EHV in this situation and characterizes the fractional increase in viscosity owing to each isolated molecule of solute:

$$[\eta] = \lim_{c \to 0} (\eta_{sp}/c) \quad (6)$$

At higher concentrations, the reduced viscosity (η_{red}) increases because of mutual interference in the solvent's flow patterns around the solute, as expressed by the Huggins equation:

$$\eta_{red} = [\eta] + k'[\eta]^2 c \quad (7)$$

Equation 7 can be illustrated as a linear plot in which the intercept is the intrinsic viscosity and the Huggins constant, k', is a dimensionless parameter related to solvent-polymer interactions. Both parameters [η] and k' are indirect means of the ability of the solvent to solvate a polymer, in particular the intrinsic viscosity is an expression of the hydrodynamic interference between the polymer and the solvent, thus reflecting the ability of the solvent to swell the polymer.

The constant k' can be considered independent of the molecular weight and/or the rigidity of polymer chain, and therefore suitable for the selection of a good solvent for a particular polymer. The constant k' describes the interaction resulting only from differences in the chemical structure of the polymer and/or the nature of the solvent. A low interaction among the dissolved macromolecules, expressed by low value of k', reflects a high solvent power for the specific polymer. Nevertheless, to obtain an accurate measure of [η], k' values in the range 0.3 to 0.4 are desirable.[8,9]

An alternative extrapolation of intrinsic viscosity is the Kraemer equation:

$$\eta_{in} = \frac{(ln\ \eta_{rel})}{c} = [\eta] - k''[\eta]^2 c \quad (8)$$

Combined application of both Huggins and Kraemer extrapolations may allow the determination of the intrinsic viscosity, [η], with greater precision. Moreover, the evaluation of k'' can be also useful in the determination of the good solvent. Indeed, combining Equation 7 with Equation 8, the theoretical value of the sum of k' and k'' should be 0.5.[8] Values near this number are an indication of the suitability of the experiments.

Experimental Set Up

The solutions used for the viscometric experiments were prepared by cutting the capsule in little specimens. The samples were dried and specimens weighting ~250 mg were dissolved in an appropriate solvent at 40°C ± 0.1°C; the solution was cooled down to 20°C ± 0.1°C and diluted using the same solvent in order to obtain a concentration of 1 g/dL. The solutions were maintained under gentle stirring overnight at 20°C ± 0.1°C.

Viscosity was measured by an Ubbelohde viscometer 100 seconds (Permax, Italy). The measurements were performed at constant temperature of 35°C ± 0.1°C in a thermostated water bath (Haake F6, Karlsruhe, Germany) after 15 minutes of storage.

The results were expressed as the mean of 6 determinations, and the single data were accepted if the coefficient of variation (CV) was lower than 2%. The experiment was performed in replicate.

Considering the solubility of gelatin and HPMC hard capsules, the following solvents were tested: deionized water, phosphate buffered solution (PBS) pH 7.4, and dimethyl sulfoxide (DMSO).

Atomic Force Microscopy

Root mean squared (Rms) of surface roughness of capsules, resulting from radiation treatment, were investigated by an AutoProbe CP Research atomic force microscope with microfabricated rectangular silicon cantilever with silicon conical tip of measured spring constant k = 0.01 N/m and curvature radius of 10 nm (ThermoMicroscopes, Sunnyvale, CA).

Five samples of either gelatin or HPMC capsules for each type of treatment were imaged and for each sample, 6 squares

of 10-μm side were scanned under constant applied force conditions operating in contact mode, and all AFM images were collected in air. To prevent possible sample deformations induced by the AFM probe, the vertical force applied to the cantilever was adjusted at values lower than 500 pN. Images of 512 × 512 pixels^2 were recorded at typical line frequencies of 4 Hz. The Image Processing and Data Analysis software (Version 2.0, ThermoMicroscopes) was used for the surface roughness analysis. Capsule adhesion and elastic properties were investigated using force-distance curves.

Since AFM imaging requires flat samples, special care was devoted to the preparation of flat patches of capsules firmly fixed to the AFM sample holder.

Capsule Water Content

The water content of the nonirradiated and irradiated capsules was determined by Karl Fisher volumetric titration (Metter Toledo DL50 Graphix, Mettler Toledo, Sweden). A capsule cap—exactly weighted—was suspended in methanol and titrated with a Karl Fisher pyridine-free solution. Each value was obtained from triplicate determination.

Capsule Hardness

The hardness of the nonirradiated and irradiated capsules was obtained by texture profiles using a software-controlled dynamometer (AG/MC1, Acquati, Italy) equipped with a 5-DaN force cell.

Each capsule was attached to a stainless steel plate by an adhesive tape and compressed by a flat stainless steel punch (diameter 1.3 mm) at the constant rate of 10 mm/min until the shell was broken or completely compressed. The area under the curve of the compression force versus the punch movement was determined to represent the work or energy required to deform the capsule. The results are expressed as the mean ± SD of 6 samples.

Dissolution Time

The dissolution time was determined by using the *European Pharmacopoeia* 4th edition apparatus for "Disintegration of tablets and capsules—test A″ (Pharma Test Ptz 9162, Pharma Test, Hainburg, Germany) using purified water as medium. Dissolution was considered achieved when the capsule appeared completely dissolved by visual inspection. The results are expressed as the mean ± SD of 6 samples.

RESULTS AND DISCUSSION

Viscosity Measurements

Determination of the Good Solvent

In the case of HPMC capsules, when the ionic strength of aqueous solution was increased by using PBS, the resulting $[\eta]$ decreased, indicating a reduction of effective hydrodynamic volumes and an increasing of k', which reflects a reduction of the solvent power of the HPMC (Table 1).

Water did not demonstrate a good solvent nature to dissolve gelatin capsules, as shown in Table 1. Indeed, the k' value was negative and did not permit the estimation of $[\eta]$. In the case of PBS, the gelatin solutions showed a reduction of the η_{red} values in function of the storage time. As a matter of fact, the η_{red} decreased from 1.71 (t = 0 hours, solution stirred overnight) to 0.24 (t = 72 hours). This feature can be due to the presence of polymer-polymer aggregates whose formation was reversible over time. Indeed, by cooling down a gelatin solution from 60°C to 35°C, the molecular weight of polymeric chains doubled, implying a strong association of this polypeptide.[10] It is probable that the number of aggregates decreased over time as a consequence of stirring.

Based on these preliminary findings, the following solvents were selected to evaluate the effects of ionizing radiations on capsule shells:

- water and DMSO for HPMC hard capsules, and
- DMSO for gelatin hard capsules.

Effects of β- and γ-Irradiation

As expected, the treatment with ionizing radiation caused a modification of the hydrodynamic properties of both gelatin and HPMC capsule solutions expressed as $[\eta]$ and k' (Table 2).

Table 1. Values of Intrinsic Viscosity ($[\eta]$), Huggins Constant (k'), and Kraemer Constant (k'') of HPMC and Gelatin Capsules Dissolved in the Selected Solvents*

Capsule Type	Solvent	$[\eta]$ (dL/g)	k'	k''
HPMC	Water	1.40 ± 0.02	0.24	0.12
	PBS	0.80 ± 0.01	0.69	0.03
	DMSO	0.76 ± 0.02	0.25	0.19
Gelatin	Water	-†	−0.30	0.40
	PBS	1.35 ± 0.01	0.19	0.17
	DMSO	0.37 ± 0.01	0.35	0.14

* HPMC indicates hydroxypropylmethylcellulose; PBS, phosphate buffered saline; and DMSO, dimethyl sulfoxide. The results are expressed as the mean ± SD (n = 6).
† Not determinable.

Table 2. Values of Intrinsic Viscosity ([η]), Huggins Constant (k') and Kraemer Constant (k'') of Irradiated HPMC and Gelatin Capsules Dissolved in the Selected Good Solvent*

Capsule Type	Solvent	β Dose (kGy)	γ Dose (kGy)	[η] (dL/g)	k'	k''
HPMC	Water	5		1.13 ± 0.06	0.21	0.10
		15		0.95 ± 0.01	0.54	0.09
		25		0.60 ± 0.00	0.41	0.13
			5	1.14 ± 0.05	0.21	0.09
			15	0.83 ± 0.01	0.51	0.09
			25	0.73 ± 0.00	0.42	0.12
	DMSO	5		0.73 ± 0.01	0.19	0.19
		15		0.59 ± 0.01	0.28	0.06
		25		0.22 ± 0.00	0.83	0.21
			5	0.62 ± 0.01	0.51	0.08
			15	0.59 ± 0.01	0.83	0.09
			25	0.48 ± 0.00	0.64	0.00
Gelatin	DMSO	5		0.36 ± 0.01	0.34	0.22
		15		0.34 ± 0.00	0.49	0.08
		25		0.28 ± 0.00	0.41	0.13
			5	0.38 ± 0.01	0.31	0.21
			15	0.32 ± 0.01	0.51	0.09
			25	0.27 ± 0.00	0.42	0.12

* HPMC indicates hydroxypropylmethylcellulose; and DMSO, dimethyl sulfoxide. The results are expressed as the mean ± SD (n = 6).

Changes in viscosity values for both types of capsules were not significantly influenced by the exposure to γ- or β-irradiation source (Table 2). HPMC hard capsules appeared to be more sensitive to ionizing treatments than gelatin hard capsules. Indeed, administering a dose of 5 kGy, only the [η] values of HPMC hard capsule solution in water and DMSO were statistically different (Student t test, $P < .05$) from the values of the corresponding nonirradiated capsule solutions. In the case of HPMC capsules, the higher reduction of [η] could be attributed to a major sensitivity of all the constituents to irradiation treatment. Nevertheless, the different behavior could be also explained considering that the spatial extension of the gelatin chains are not large[10] and consequently the reduction in molecular weight did not affect the hydrodynamic interferences between the polypeptide and the solvent.

Even if [η] is mainly related to the molecular weight, the differences measured in irradiated HPMC and gelatin capsules provided only a qualitative description of the variations that occurred after sterilization or sanitization treatment by ionizing radiation because the corresponding k' values were higher than 0.35, and consequently the selected solvents, namely, water and DMSO, ceased to demonstrate a good solvent nature. The decrease of water and DMSO solvent power can be justified in terms of capsule composition. Indeed, HPMC capsules are made of HPMC/κ-carrageenan blend and gelatin capsules are made of type A gelatin/type B gelatin blend. The Huggins constant (k') would be a source of information of the interactions in a ternary polymer/polymer-solvent system whose properties underwent marked variations upon irradiation.[11,12]

The decrease of solvent power (k') was evident in the case of DMSO solutions of HPMC capsules (Table 2), which was more sensitive to the ionizing treatment than aqueous solution. Since water did not demonstrate a good solvent nature to dissolve gelatin capsules and variations of [η] and k' values were amplified when DMSO was used to dissolve HPMC capsules, DMSO should be regarded as the suitable solvent to perform the viscosity analysis of these materials.

Atomic Force Microscopy

Roughness Analysis

At a first glance, the morphology appeared to be different between the 2 types of capsules. Nevertheless, this qualitative observation has not been supported by the roughness analysis: the values of gelatin (rms = 9.7 ± 2.9 nm) and HPMC (rms = 15.9 ± 6.5 nm) capsules were not statistically different ($P = 0.0514$). Moreover, the rms roughness values did not disclose the possibility of discriminating the effects of different irradiation doses and their nature. As an example, AFM error signal images of gelatin capsules in the following conditions are reported: (1) not irradiated, (2) after γ radiation at the dose of 25 kGy, and (3) after β radiation at the dose of 25 kGy (Figure 1). The surface morphology appeared to be mainly dominated by the presence of grooves due to the manufacturing process of the capsules rather than irradiation-induced surface modifications. This qualitative inspection was confirmed by the evaluation of rms surface roughness and the relative statistical analysis. The measured values of rms roughness of irradiated samples (rms = 11.6 ± 5.9 nm for γ-radiated

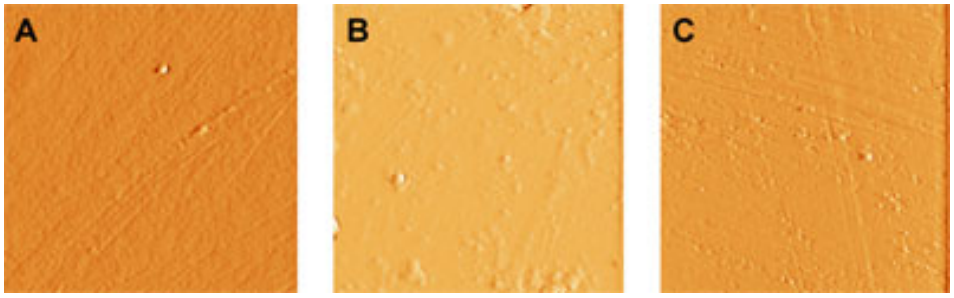

Figure 1. AFM (10 × 0 μm^2) error signal of gelatin capsules: (A) untreated; (B) irradiated at 25 kGy by using γ-ray; and (C) β-ray.

sample and rms = 11.4 ± 3.8 nm for β-radiated sample) were not statistically different from the nonirradiated samples (1-way analysis of variance [ANOVA], $P > .05$). Also in the case of HPMC capsules (rms = 17.4 ± 4.5 nm for γ-radiated sample and rms = 16.1 ± 4.4 nm for β- radiated sample), it was not possible to highlight the irradiation effects (1-way ANOVA, $P > .05$).

Force-distance Curves

In addition to morphological measurements, the AFM can be used to record force-distance curves. In this configuration, the AFM′s tip is moved toward the sample at a fixed position. The interaction forces are measured as a function of the distance of the tip from the sample surface either in approach curve or in withdrawal curve. This technique allowed us to investigate the attractive and repulsive forces between the probe tip and the sample surface and then provided information on the local surface properties, for instance, adhesion response.

Aiming to ascertain if a force-distance curve can be considered a proper marker of the irradiation of hard shell capsules, several irradiated and nonirradiated specimens were examined taking force-distance curves in 15 different

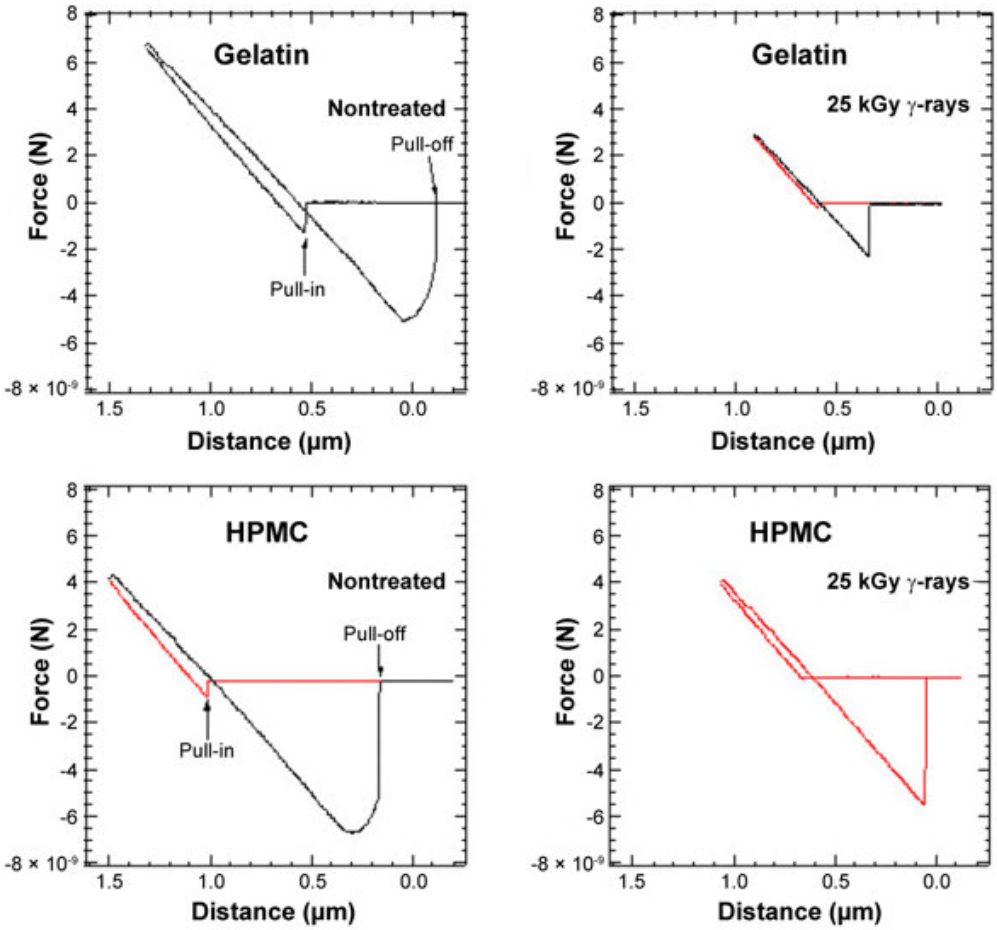

Figure 2. Approach and withdrawal curves of gelatin and HPMC samples, before and after γ-ray treatment at the dose of 25 kGy.

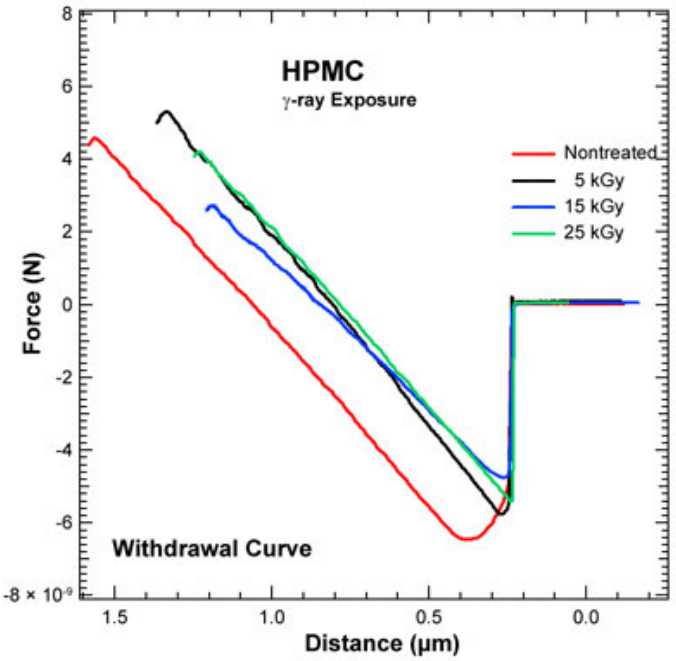

Figure 3. Effect of different γ-irradiation doses on withdrawal curves of HPMC capsules.

positions for each sample. In Figure 2 the curves before and after a γ-ray treatment at the dose of 25 kGy are compared both for gelatin and for HPMC samples. It is clearly evident that there is a marked difference concerning the pull-off region. The irradiated samples presented a right angle squared pull-off, while the nonirradiated samples showed a completely different round pull-off. The overall situation for the HPMC capsules is detailed in Figure 3. Lowering the applied dose to 5 kGy, a round trend began to be foreseen. These results were independent of the β- or γ-irradiation treatment. The same features were evident in the case of the gelatin capsules. No correlations between the values of force measured by AFM (Figure 3) and the irradiation conditions (ie, dose and irradiation type) can be individuated because of the heterogeneity of the surface. Nevertheless, the presence of a squared pull-off in the force-distance measurements can be established as a marker of irradiation without any doubt.

Table 3. Values of Energy (J) Required Deforming 2-shell Hard Capsules and Empty Capsule Dissolution Time*

Capsule Type	β Dose (kGy)	γ Dose (kGy)	Deforming Work (J)	Dissolution Time (seconds)
HPMC	-	-	0.06 ± 0.01	414 ± 33
	5	-	0.05 ± 0.01	439 ± 61
	15	-	0.06 ± 0.00	416 ± 40
	25	-	0.06 ± 0.00	368 ± 65
	-	5	0.06 ± 0.00	417 ± 23
	-	15	0.06 ± 0.01	325 ± 52
	-	25	0.06 ± 0.01	336 ± 35
Gelatin	-	-	0.10 ± 0.01	288 ± 19
	5	-	0.09 ± 0.01	319 ± 32
	15	-	0.11 ± 0.00	257 ± 46
	25	-	0.10 ± 0.01	225 ± 29
	-	5	0.11 ± 0.01	330 ± 44
	-	15	0.12 ± 0.01	237 ± 21
	-	25	0.13 ± 0.01	259 ± 38

* HPMC indicates hydroxypropylmethylcellulose. The results are expressed as the mean ± SD (n = 6).

Technological Performances

The moisture content was 9.96% ± 1.22% for HPMC capsules and 11.38% ± 1.70% in the case of gelatin capsules. As expected it did not change after the irradiation.

All the capsules submitted to hardness testing were completely deformed without rupture of the hard shell. The capsule-deforming work determined for nonirradiated HPMC capsules was less than that measured for gelatin capsules (Table 3). The dissolution time of the HPMC capsules was slightly higher than that determined for gelatin hard capsules (Table 3), confirming the data reported in the literature.[13] Both the capsule hardness and the dissolution time did not seem to be significantly affected (1-way ANOVA, $P > .05$) by the nature of radiation used and the applied irradiation dose (Table 3).

The reduction of the average molecular weight of the hard shell components,[3,5,6] confirmed by the [η] reduction and the alteration in the AFM distance-force curves, did not affect the technological performance of the irradiated capsules at doses lower than or equal to 25 kGy.

CONCLUSION

Empty gelatin or HPMC hard capsules can be sterilized or sanitized by means of ionizing radiations at doses lower than or equal to 25 kGy as their technological performances are not affected by the treatment. Nevertheless, the use of γ-rays or β-rays to sanitize or sterilize gelatin or HPMC hard capsules may alter the chemical integrity of the functional excipients of the shell. The detrimental effects on both polymeric-blend-forming gelatin or HPMC capsules could be indirectly evidenced by means of AFM and capillary viscosity. In particular, AFM can be proposed as a technique able to discriminate qualitatively between radiated and nonirradiated samples because a variation of the shape of the pull-off step in the force-distance curves was evident in both HPMC and gelatin capsules after γ- and β-ray treatment.

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