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Gamma irradiation of carboxymethylcellulose: technological and pharmaceutical aspects

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Abstract

In this work, we have studied the stability of sodium carboxymethylcellulose (NaCMC) powder after irradiation. Its effect on the physical, chemical and pharmacotechnical properties has been investigated in order to determine the influence of such treatment on the functional properties of NaCMC, especially on the formulation of gels, suspensions, tablets and sustained release parenteral dosage forms.

Key words: Sodium carboxymethylcellulose; Gamma irradiation; Physical properties; Rheology; Binding agent

1. Introduction

Gamma irradiation is a suitable method to decontaminate or sterilize powdery raw materials and solid parenteral and ophthalmic preparations (Sébert et al., 1986, 1989). Sodium carboxymethylcellulose (NaCMC) is a water-soluble polymeric excipient widely used in pharmaceutical technology (Combes, 1989). NaCMC is frequently selected to participate in the formulation of these dosage forms; it can also enter into other preparations such as gel-base, binder or stabilizing agent and require decontamination.

The purpose of the present work was therefore to investigate the possible modifications of physical, rheological and pharmacotechnical properties when NaCMC powders were subjected to treatment with increasing doses of gamma irradiation. These alterations could modify the quality of pharmaceutical dosage forms.

2. Materials and methods

2.1. NaCMC

2.1.1. Characteristics

NaCMC is a cellulose carboxymethyl ether sodium salt (Merck Index, 1989). The material used in this study was a Blanose® cellulose gum (Aqualon, 1990). For the pharmaceutical grades, the degree of substitution (D.S.) spanned the range 0.60–1.00. The D.S. is determined by the number of hydroxyl groups substituted by anhydroglucose units. The type selected was Blanose 7 HCF which has a D.S. near 0.7 and a degree of polymerization (D.P.) close to 2000. The molecu-

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lar weight, dissolution and viscosity characteristics depend on the D.S. and D.P. The viscosity value (1%) at 25°C lies between 1500 and 2500 mPa s.

2.1.2. Irradiation

Dry powders of NaCMC (relative humidity 5%) were irradiated with gamma rays emitted by a radioactive isotope (^{60}Co). The radiation energies were 1.17 and 1.33 MeV. The power of the source and the dose rate were 2.0×10^5 GBq and 1.2 kGy/h, respectively. The samples of NaCMC received four irradiation doses: 1, 5, 15 and 25 kGy. One non-irradiated sample was kept as a reference.

2.1.3. Preparation of the solutions

NaCMC solutions (1.25% w/w) were prepared by dispersing the polymer in purified water at 20°C with an Ika-Werk spiral mixer (600 rpm). After swelling for 24 h at ±4°C (structuration) it was homogenized at room temperature before use.

2.2. Tests

2.2.1. Appearance: pH

A visual examination was carried out on each sample of NaCMC powder in order to determine the change in coloration under irradiation. The pH was measured at 20°C on diluted aqueous solutions with a Tacussel pH-meter.

2.2.2. Spectrometry

UV spectra were recorded on a Beckman model 25 spectrophotometer, from 190 to 310 nm, on diluted solutions. IR spectra were recorded from 4000 to 200 cm^{-1} on a Perkin Elmer 1310 infrared spectrophotometer on dry films 15–20 μm thick. Films were obtained by evaporating water from NaCMC solutions in a Petri box.

2.2.3. Calorimetry

DSC was carried out on a Micro DSC III Batch and Flow calorimeter (Setaram, 1993). With this apparatus, heat exchanges between a sample and a thermally inert material are recorded as a function of temperature applied during the thermal programming. Thermodynamic events in the sample can be due to exothermic transitions (e.g., oxidation, crystallization) or endothermic transitions (e.g., fusion, glass transition) (Ford and Timmins, 1989). In this study, the sample was a 1.75% (w/w) water solution of Blanose® 7 HCF at (0, 5 and 25 kGy) which was heated from 20 to 100°C at a rate of 1°C/min. The mass of sample introduced into the cell was about 750 mg.

2.2.4. Molecular weight

The molecular weight (M) of NaCMC was determined by using a viscosimetric method (Bardet and Alain, 1975). The intrinsic viscosity ($[\eta]$), evaluated according to a capillary tube method from polymer in diluted solutions, is related to the average molecular weight by the Mark-Houwink equation as follows:

$$[\eta] = KM^a$$

For NaCMC, K and a were calculated as described by Brown et al. (1963):

$$[\eta] = 8.1 \times 10^{-5} \cdot M^{0.92}$$

2.2.5. Rheology

Assessment of the rheological properties of NaCMC solutions was carried out on a coaxial cylinder viscosimeter (Searle system) using a Haake Rotovisco RV 12 fitted with an MVI rotor (Schramm, 1981). The solutions were prepared 24 h beforehand, stored at + 4°C and stored at room temperature until use. They were then introduced into the vessel of the viscosimeter, allowed to equilibrate for 10 min and studied at 25°C. During measurement, the shear rate (n) ranged from 1 to 512 rpm. Subsequently, the S value, related by a constant G (1374) to the shear stress, was registered (Couarraze and Grossiord, 1983).

Rheological curves were plotted, $S = f(n)$, and viscosities, η, were determined at a suitable shear rate, using the following formula: $\eta = GS/n$.

2.3. Tablet formulation and preparation

2.3.1. Tablet formulation

Tablet formulation was performed as follows (a 1.25% (w/w) NaCMC solution was prepared

by blending 272 g for every batch of 1 kg): sodium salicylate, 15%; microcrystalline cellulose (Avicel®), 27.5%; lactose, 51.66%; colloidal silica (Aerosil® 200), 0.5%; sodium starch glycolate (Primojel®), 3.0%; NaCMC (Blanose® 7 HCF), 0.34%; magnesium stearate, 1%; talc, 1%.

2.3.2. Preparation of tablets

A pseudo-planetary mixer (Erweka MKS) was used to perform dry mixing (5 min at 40 rpm) with all internal components except NaCMC, wetting (5 min at 40 rpm) with progressive addition of the NaCMC solution and final kneading (5 min at 80 rpm). An Erweka FAG granulator was then used and the resulting granulate was placed on a tray. Drying was carried out on a drying stove (60°C) for 4 h and dry grinding on a Frewit GLA-OR oscillating mill with a 1000 μm opening sieve. Sifting was performed with an Erweka VT vibrating sieve for 10 min. Particles of diameter less than 160 μm were eliminated. The addition of the external phase was carried out on an Erweka UG cubic mixer of suitable volume, for 10 min at 30 rpm.

An alternative Frogerais (Esstic 55) press with flat punches (11 mm diameter) was used for compression. The initial setting was carried out on the non-irradiated reference batch. Mass was adjusted from 600 to 650 mg and hardness from 60 to 70 N. For the other batches (1–25 kGy), no modification of the initial setting was effected. The manufacture of each batch lasted 30 min, however, only the central stabilized portion was retained in order to avoid initial and final modifications.

2.4. Granulate and tablet controls (Le Hir, 1986)

2.4.1. Particle size distribution after grinding

This operation was carried out on a Hosokawa PTE powder analyzer. Screen analysis was performed on a vibrating sieve column with 50 g of powder. The amplitude of vibration was 1 mm in width over 210 s. The granulate moisture level was measured on a Cenco infrared thermobalance.

2.4.2. Average mass; mass uniformity

20 tablets were cut off and individually weighed on a Sartorius 1212 MP balance (mg) coupled with a Hewlett Packard 97S calculator. The tolerance limits for average weight variation were taken from the P.F.X.

2.4.3. Hardness; friability

50 tablets were cut off and tested on a Schleuniger 2E apparatus in which radial hardness was measured (N). 10 tablets were weighed before and after passage in an Erweka TAP friabilitor apparatus for 10 min. The percentage loss was calculated. This instrument was designed to assess the ability of tablets to withstand abrasion.

2.4.4. Drug release

For disintegration tests, six tablets were used according to the P.F.X protocol on an Erweka ZT3 apparatus. The sodium salicylate dissolution test was carried out on the apparatus described in P.F.X. A Prolabo Dissolutest apparatus with stirring blades was used. Six tablets of each batch were precisely weighed and placed in a vessel. This study was carried out in 500 ml of artificial gastric medium (without enzymes) at pH 1.4 for 2 h. The rotational speed was 60 rpm and the temperature was 37 $\pm$ 1°C. Samples were taken at 15, 30, 60, 90 and 120 min and filtered. The sodium salicylate was released and dissolved, then dosed with an UV spectrophotomer at 300 nm..

3. Results

3.1. Properties of NaCMC

3.1.1. Coloration; pH

As a function of the irradiation dose, a slightly yellow discoloration of the powder from 5 kGy appeared. No change in pH of the solution occurred; the values were stable (6.3–6.4). Since the aqueous solutions of NaCMC are stable between pH 2 and 10, the solubility will not be modified.

3.1.2. Spectrometry

For UV spectrometry, absorption measurments between 170 and 340 nm gave similar

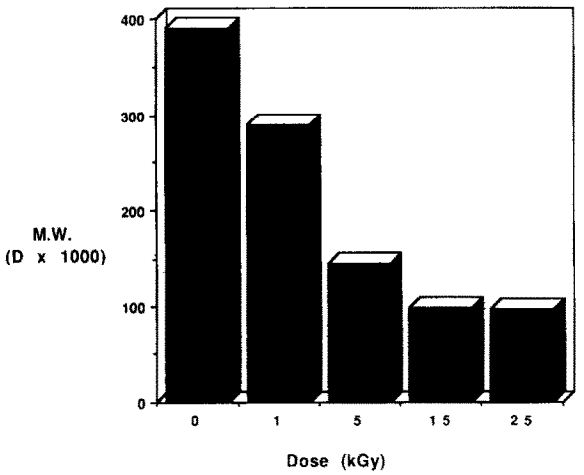

Fig. 1. Molecular weight (M.W.) before and after irradiation.

spectra. NaCMC solutions exhibited a maximum near 205 nm. However, at 2600 Å, we observed an increase in the weak absorption from 5 kGy. In the case of IR spectrometry, no modification appeared; the registered spectra were identical at 0, 5 and 25 kGy. These results demonstrated structural stability.

3.1.3. Calorimetry

The difference in energy plotted as a function of the temperature recorded by the programming device gave similar thermograms. However, the absence of an endothermic peak at 47°C on the irradiated samples was marked although the energy of this endothermic peak was of very weak intensity (0.08 mW). The study of thermodynamic events demonstrated no significant modification.

3.1.4. Molecular weight

The values of the 'viscosity average molecular weight' are reported in Fig. 1. We found that the molecular weight decreased with increasing irradiation doses. This observation shows that gamma rays induce depolymerization of NaCMC by breaking the glucosidic linkage. The side effects of radiation are important, since a considerable percentage loss was noted: 63% at 5 kGy and 75% at 25 kGy. The effect of radiation appears to be stabilized for high doses (15 and 25 kGy).

3.1.5. Rheology

The non-irradiated solution of NaCMC presents pseudo-plastic behaviour. Greater shearing rates cause the chains to become more linearly orientated and the apparent viscosity decreases. Depending on the intensity of irradiation, the flow curves demonstrate evolution toward Newtonian behaviour (completely from 15 kGy). Irrespective of the dose, no thixotropy or rheopexy phenomena could be noted. Fig. 2 shows the flow curves before and after irradiation. A rapid decrease in the viscosity values was evident with increasing irradiation doses (Fig. 3). The percentage loss in viscosity was 92% at 25 kGy. The mechanism by which this phenomenon occurs is discussed at the molecular level in relation with chain-length. The transition from pseudo-plastic to Newtonian behaviour can be interpreted as indicative of a change from a disperse structure to a globular form as a result of the influence of chain rupture. It is not difficult to correlate the decrease in viscosity with the depolymerization of NaCMC.

3.2. Granulate and tablet controls

The granulate moisture content was maintained at 2–4%. The particle size distribution of tabletting mass is illustrated in Fig. 4. We can

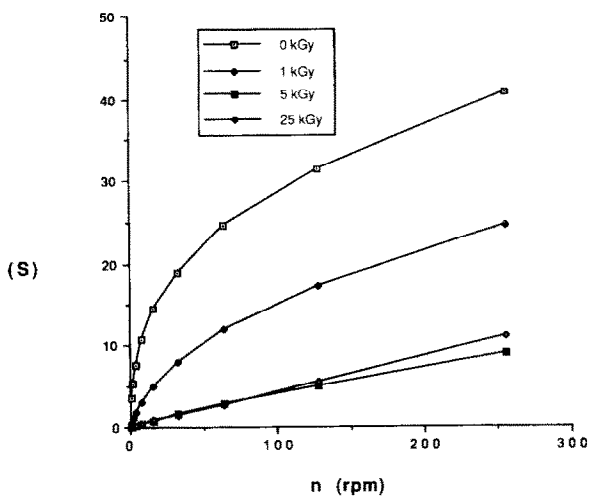

Fig. 2. Flow curves before and after irradiation.

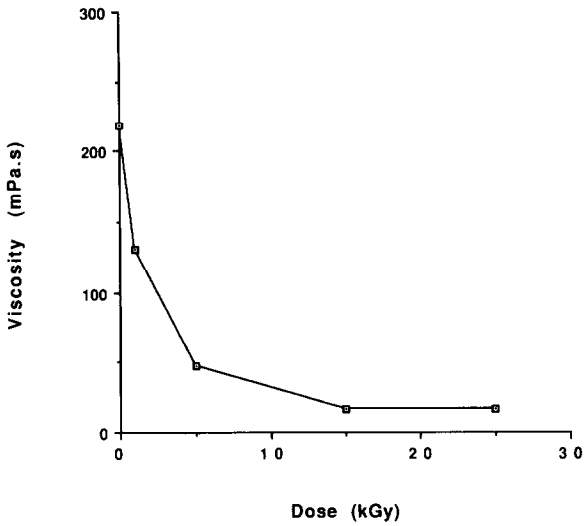

Fig. 3. Solution viscosity before and after irradiation.

observe that fractions of different size remain almost unchanged (slight increase in coarse particles and slight decrease in fines). This could indicate no greater modification in binding capacity. The results obtained for average mass, hardness, friability and disintegration are listed in Table 1. The percentage of tracer (sodium salicylate) liberated is presented in Fig. 5. We were able to establish that, following irradiation, the

Table 1
Tablet characteristics

Tests	Dose (kGy)				
	0	1	5	15	25
Mass (mg)	611	605	625	634	658
Hardness (N)	6.6	5.4	6.5	7.9	9.5
Friability (loss %)	0.91	1.1	0.88	0.68	0.53
Disintegration time (min)	12.5	12.0	11.5	13.5	13.0

average mass was raised and that uniformity in mass had been attained. This could indicate better densification of granulate particles and greater filling of the compression chamber. Similarly, the hardness was increased and the friability reduced. This pattern of behaviour is consistent and demonstrates the greater cohesive force of the particles in the tablets. The disintegration time was not modified. The kinetic order of the release of sodium salicylate was similar, however, the in vitro availability was reduced from 15 kGy. Statistically, significant modifications confirm the decrease in tracer dissolution speed. During granulation, better distribution of the NaCMC binding solution on the particle surface, as a result of lower viscosity, could explain these results and demonstrate the improvement in binding force.

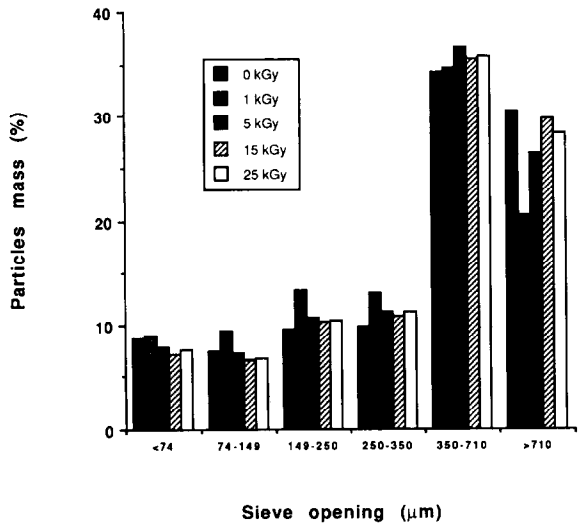

Fig. 4. Particle size distribution after grinding.

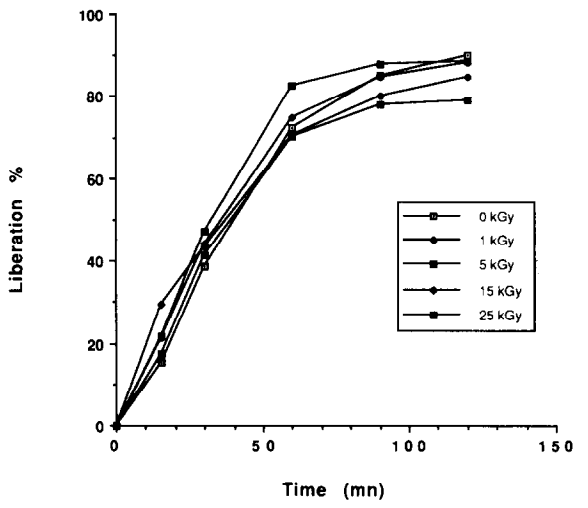

Fig. 5. Tracer liberation.

4. Conclusions

The impact of gamma rays on NaCMC powder is particularly marked from 15 kGy. The main consequence appears to be rupture of the glucosidic linkages. This depolymerization induces a modification of the rheological behaviour causing especially a noticeable decrease in viscosity. This change could involve different repercussions on pharmacotechnical applications. The stability of suspensions could be impaired by facilitating particle sedimentation and gel formation could be disturbed. On the other hand, we have demonstrated that the NaCMC binding capacity is improved. Accordingly, the obtaining of higher granulate quality could be favourable for batch tablet production. Moreover, the release of drugs from sustained release parenteral dosage forms based on diffusion could be modified and should be considered.

Finally, even if the effects of irradiation are clear at the level of the physical and chemical properties, the influence on the functional properties of NaCMC appears to be moderate.

5. Acknowledgements

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