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Effect of gamma irradiation on hydroxypropylmethylcellulose powders: Consequences on physical, rheological and pharmacotechnical properties

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Summary

In this paper, we describe a number of hydroxypropylmethylcellulose (HPMC) powders which were subjected to γ-irradiation and report the results obtained following investigation of their physical properties (coloration, UV and IR spectrometry, calorimetry) and rheological behaviour. The physical properties were not significantly modified on increasing the irradiation dose. In contrast, the rheological behaviour of the HPMC powders was modified: firstly, the solutions displayed pseudo-plastic behaviour, becoming Newtonian on rupture of the chains with increase in the irradiation dose. Concurrently to this polymeric transformation, the viscosity of the solutions decreased. HPMC powders, irradiated at different doses, were used in solution as a binding agent for granulation during tablet manufacture. The different production stages are also described, as well as physical controls (mass, friability, hardness, disintegration) dissolution tests of the active substance from the tablets. No clear modification can be noted.

Introduction

HPMC is a water soluble polymeric excipient extensively used in pharmaceutical technology (Hogan, 1988; Combes, 1989). Its different applications (tablet binder, viscosity increasing agent, gel base, ocular form, etc.) may require decontamination and/or sterilization, for instance, by γ-irradiation (Sebert et al., 1986, 1989).

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The aim of this study was to detect a possible effect, namely, the modification of structural and pharmacotechnical properties, when HPMC powders were subjected to treatment with increasing doses of γ-irradiation.

Materials and Methods

HPMC

Characteristics, irradiation, solutions HPMC is a semi-synthetic derivative of cellulose: cellulose, 2-hydroxypropyl methyl ether or hypromellose (Handbook of Pharmaceutical Excipients, 1986).

Three types of HPMC are commonly available (Seppic, 1987). The percentage of methoxy and hydroxypropoxy groups is variable but well defined. Each type presents various standard grades of different viscosity depending on the molecular weight and degree of substitution. Specifications of each type and study concentrations of HPMC used are listed in Table 1. Metolose® 60 SH 50 is most commonly used as a binding agent in granulation and was selected in the present study for preparing tablets.

Irradiation Dry powders of HPMC (relative humidity between 2 and 3%) were irradiated with γ-rays emitted by a radioactive isotope (^{60}Co). The power of the source and the dose rate were 1.7×10^6 GBq and 1.3 kGy/h, respectively. Samples of each HPMC received four irradiation doses: 1, 5, 15 and 25 kGy. One non-irradiated sample was kept as a reference.

Preparation of the solutions HPMC was dispersed in purified water at 20°C with a Baudard screw mixer (600 rpm). After swelling for 24 h at +4°C (structuration) it was homogenized at room temperature before use.

Tests

A visual examination was carried out on each aqueous solution in order to determine whether irradiation induced modifications. pH was measured at room temperature on diluted aqueous solution (1:10 or 1:3 w/w) as a function of samples.

Spectrometry UV spectra were recorded on a Beckman model 25 spectrophotometer, from 190 to 310 nm. Each solution was diluted according to its viscosity. IR spectra were recorded from 4000 to 200 cm^{-1} on a Perkin Elmer 1310 infrared spectrophotometer on dry films 10–25 μm thick. Films were obtained by evaporating water from HPMC solutions in a Petri box.

Calorimetry Differential scanning calorimetry was carried out on a Micro DSC Batch and Flow calorimeter (Setaram, 1991). Calorimetry is a method of thermal analysis in which heat exchanges between a sample and a thermally inert material are recorded as a function of temperature applied during programmation. Thermodynamic events in the sample can be due to exothermic transitions (e.g., oxidation, crystallization) or endothermic transitions (e.g., fusion, glass transition) (Blond and Simatos, 1991). In this study, the sample was a 5% water solution of Metolose® 60 SH 50 at 0, 5 and 25 kGy which was heated and cooled from 20 to 100°C at a rate of 0.2 or 1°C/min.

Rheology Rheological examination was carried out on a coaxial cylinder viscosimeter (Searle system). A Haake Rotovisco RV 12 with an MVI rotor was used (Schramm, 1981). Solutions were prepared 24 h beforehand, stored at +4°C and placed at room temperature until use. They were then studied at +25°C in the thermostatic vessel of the viscosimeter. 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 calculated at a shear rate chosen to correspond to the linear portion of the plot, using the formula:

$$\eta = GS/n$$

TABLE 1

Types, grades and study concentrations of HPMC used

Types grades	% methoxy	% hydroxy-propoxy	Viscosity (2%) (mPa s)	Study concentration (%)
Pharmacoat ® 606	28–30	7–12	4.8–7.2	11
Pharmacoat ® 615	28–30	7–12	12.0–18.0	7
Metolose ® 60 SH 50	28–30	7–12	50.0	6
Metolose ® 60 SH 4000	28–30	7–12	4000.0	1.25
Metolose ® 65 SH 4000	27–29	4– 7.5	4000.0	1.25
Metolose ® 90 SH 4000	19–24	4–12	4000.0	1.25

Pharmacoat® and Metolose® are trade names of different types and grades of HPMC (Shin Etsu Chemical Co., Ltd, and Seppic).

Tablet formulation and preparation

Tablet formulations The tablet formulations were as follows (a 5% HPMC solution was prepared by blending 300 g for every batch of 1 kg): sodium salicylate, 15%; microcrystalline cellulose (Avicel®), 30%; lactose, 48%; colloidal silica (Aerosil® 200), 0.5%; sodium starch glycolate (Primojel®), 3%; HPMC (Metolose® 60 SH 50), 1.5%; magnesium stearate, 1%; talc, 1%.

Preparation of tablets A pseudo-planetary mixer (Erweka MKS) was used to perform dry mixing (5 min at 40 rpm) with all internal phase components except HPMC, wetting (5 min at 40 rpm) with progressive addition of HPMC solution and final kneading (5 min at 80 rpm). An Erweka FAG granulator was then used and the granulate obtained 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-DR oscillating mill with a 1000 μm opening sieve. Sifting was carried out with an Erweka VT vibrating sieve for 10 min. Particles of diameter less than 160 μm were eliminated. Addition of 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. Initial setting was carried out on the non-irriadiated reference batch. Mass was adjusted from 400 to 450 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.

Granulate and tablet controls (Le Hir, 1986)

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. Granulate moisture level was measured on a Cenco infrared thermobalance.

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.

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 a Erweka TAP friabilator apparatus for 10 min. The percentage loss was calculated. This instrument was designed to assess the ability of tablets to withstand abrasion.

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. 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. Sodium salicylate was released and dissolved, then dosed with an UV spectrophotometer at 3000 Å.

Results

Characteristics of HPMC

Coloration; pH For Pharmacoat® 605 and Metolose® 60 SH 50, gradual discoloration was observed with increasing irradiation dose (non-irradiated solutions were slightly yellow). In contrast, for the other HPMC, no change could be detected. Acidification took place when the rate of irradiation increased (pH 6.65 to 4.3 for Metolose® 60 SH 50).

Spectrometry During UV analysis, for Pharmacoat® 606 and 615, we observed a progressive attenuation of the 257 nm peak on irradiation at 15 kGy and subsequently. No modification was observed for the other peak. In the case of IR spectrometry, comparison of the spectra at 0, 5 and 25 kGy demonstrated the absence of modifications.

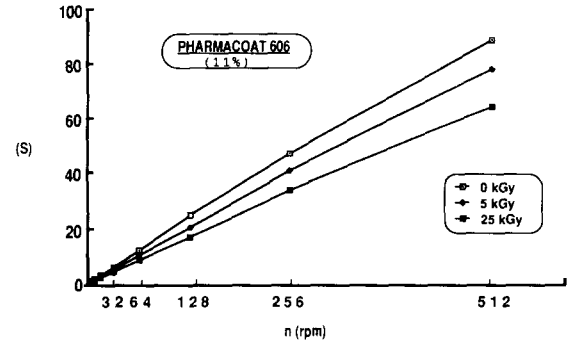

Fig. 1. Flow curves before and after irradiation.

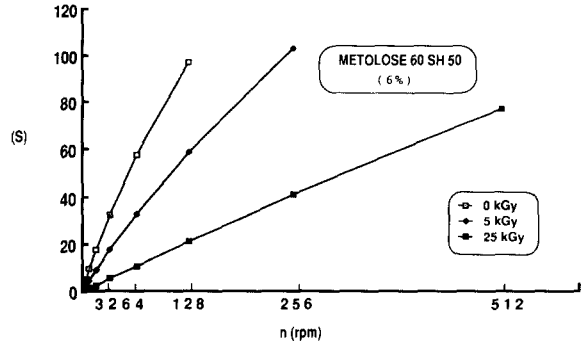

Fig. 3. Flow curves before and after irradiation.

Calorimetry The thermograms obtained with Metolose® 60 SH 50 were not significantly different when the irradiation rates were increased: the glass transition temperatures ('fusion') were similar, the energy related to the endothermic peaks was almost identical and all the phenomena observed were reversible.

Rheology Figs 1–6 show the evolution of flow curves after irradiation of HPMC powders at doses from 0 to 25 kGy. In non-irradiated samples, HPMC solutions of the highest grades showed a greater extent of pseudo-plastic behaviour. With increasing irradiation dose, this pseudo-plastic behaviour became Newtonian. This modification appeared at 5 or 15 kGy. Thixotropy or rheopexy phenomena were not observed. Using flow curves and viscosimeter constants, the viscosities were calculated for a shear rate of 128 rpm. The results are presented in Fig. 7. Irrespective of the type of HPMC, the viscosity was observed to decrease on increase in the irradiation dose, and the percentage loss was found to be proportional to the grade (41–96%).

Granulate and tablet controls The particle size distribution is demonstrated in Fig. 8 as weight percentage. The granulate moisture content was maintained at 1.5–3%. The results obtained for average mass, mass uniformity, hardness, friabil-

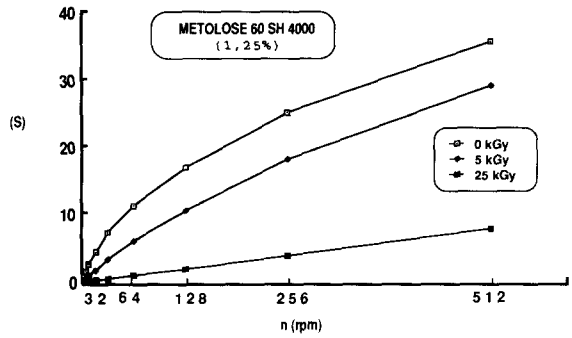

Fig. 4. Flow curves before and after irradiation.

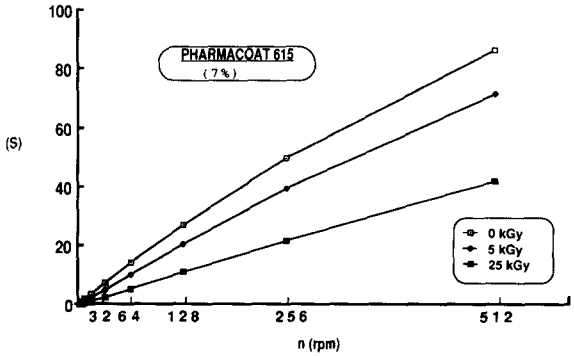

Fig. 2. Flow curves before and after irradiation.

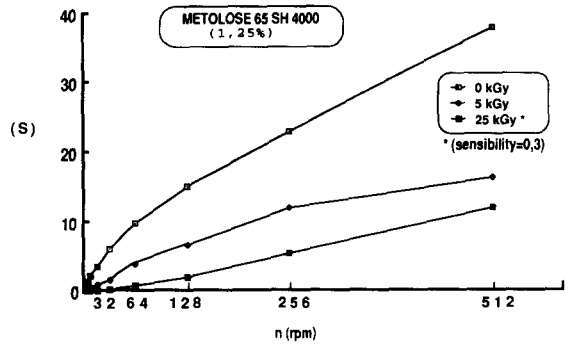

Fig. 5. Flow curves before and after irradiation.

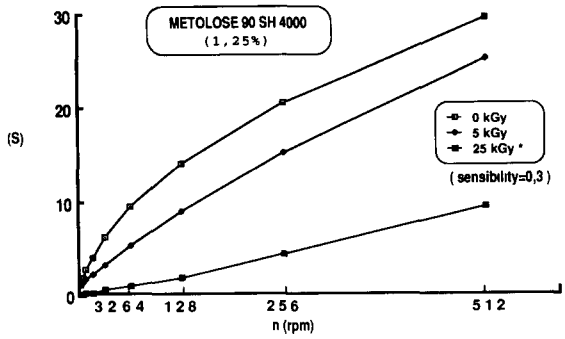

Fig. 6. Flow curves before and after irradiation.

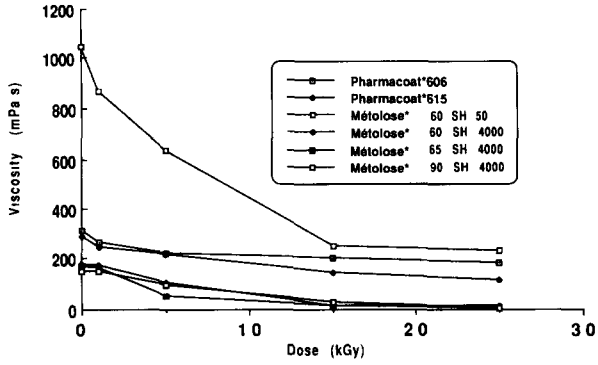

Fig. 7. Solution viscosity before and after irradiation.

ity and disintegration are listed in Table 2. The percentage liberation of tracer (sodium salicylate) is depicted in Fig. 9.

TABLE 2

Tablet characteristics

Tests	Dose (kGy)				
	0	1	5	15	25
Mass (mg)	423	448	424	414	432
σ	9.1	3.1	5.9	5.6	4.5
C.V. (%)	2.15	0.69	1.39	1.35	1.04
Hardness (N)	56.1	68.6	55.8	54.7	62.5
σ	4.3	5.1	3.0	4.6	4.6
C.V. (%)	7.7	7.4	5.4	8.4	7.4
Friability (loss %)	0.78	0.65	0.92	0.66	0 85
Disintegration time (min)	19	18.5	16.5	15.5	15.5

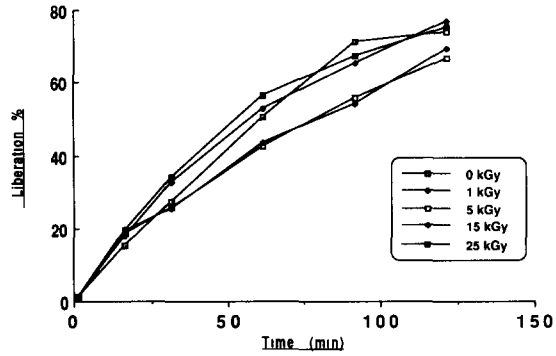

Fig. 9. Tracer liberation.

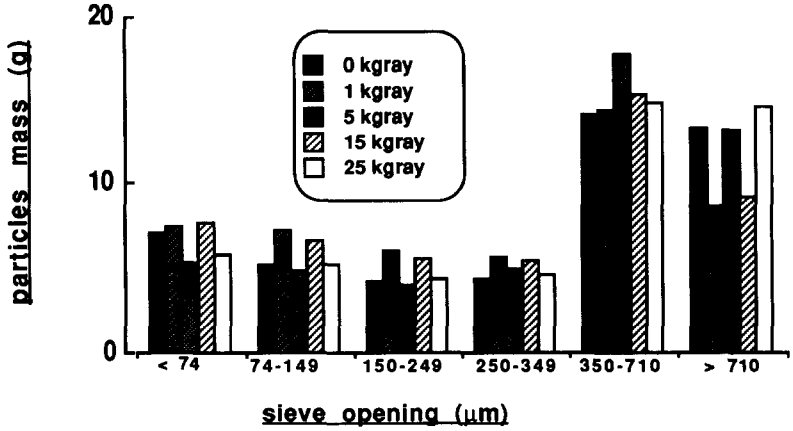

Fig. 8. Particle size distribution after grinding.

Discussion

General properties

In spite of a few modifications, probably due to depolymerization, the physical and chemical characteristics examined were generally stable with increase in irradiation rate.

Rheological properties

Rheological behaviour was found to be modified on irradiation at 5 or 15 kGy. 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. This hypothesis was supported by the observed decrease in viscosity which was most noticeable with HPMC of higher grades.

Tablet characteristics

According to the above results, with increasing irradiation rates, a small decrease in disintegration time and relative stability of the other properties could be noted. In the particle size distribution of tabletting mass, any modification could indicate a change in binding capacity. Concerning the average mass, a marked improvement can be achieved by an increase in the irradiation dose. The hardness (in relation to mass variability) and friability (consistently below 1%) remained unmodified. The kinetic order of the release of sodium salicylate was the same and the availability of comparable value.

The greater uniformity in mass with increasing irradiation dose would appear to be linked to a change in the viscosity of the solution of binding agent. Indeed, the homogeneous wetting of powders during granulation can result in better granulate densification and a greater extent of filling of compression room. Such higher granulate quality was favourable for batch production using a heavy duty machine.

Conclusions

Gamma irradiation of HPMC appears to have a stronger effect on secondary structure (conformation of polymerized molecule) than on primary structure (polymer functions and chemical groups). The main effect was depolymerization. The irradiation of HPMC might have been expected to exert an influence on the technical properties of this binding agent. This study has demonstrated not only that there was a lack of any significant modification, but also that a small trend toward improved binding capacity could be observed.

Gamma irradiation rays appears to be promising as a method for decontaminating HPMC raw material or sterilizing pharmaceutical dosage forms (sustained release suspensions, pellets) containing HPMC.

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References

Blond, G. and Simatos, D., Analyses thermiques in Techniques d'analyse et de contrôle dans l'industrie alimentaire, Tec. et Doc. Paris, 1991, pp. 141–161.

Combes, A., Etude d'excipients utilisés dans l'industrie pharmaceutique. *STP Pharm.*, 5 (1989) 766–790.

Couarraze, G. and Grossiord, J.L., Initiation à la rhéologie, Tec. et Doc., Paris, 1983, p. 219.

Handbook of Pharmaceutical Excipients, 'HPMC', The Pharmaceutical Press, Washington, 1986, p. 138.

Hogan, J.E., HPMC substained release technology. *Drug Dev. Ind. Pharm.*, 6 (1988) 975–999.

Le Hir, A., *Abrégé de Pharmacie Galénique,* Masson, Paris, 1986, p. 377.

Schramm, G., *Introduction to Practical Viscosimetry, Haake Viscosimeter,* Gebrüder Haake, Karlsruhe, 1981, p. 119.

Sebert, P., Bardon, J., Robelin, N., Chaumat, C. and Rollet, M., Formes pressurisées: stérilisation par les radiations ionisantes: III. Radiostérilisation des excipients et des produits actifs. *STP Pharm.*, 2 (1986) 1010–1014.

Sebert, P., Lombard, E., Barthelemy, P. and Rollet, M., Radiodécontamination d'excipients pharmaceutiques: étude du comportement de la gélatine. *5th International Conference on Pharmaceutical Technology,* Paris, IV (1989) 381–389.

Seppic, Documentation technique. Metolose-Pharmacoat. Shin-Etsu Chemical Co., Ltd, 1987, p. 25.

Setaram, Documentation technique. Société d'Etudes d'Automatisation, de Régulation et d'Appareils de Mesure. Lyon-Caluire, 1991, p. 4.