Drug Development and Industrial Pharmacy, 25(4), 453–462 (1999)

RESEARCH PAPER

Effects of Thermal Neutron Irradiation on Some Potential Excipients for Colonic Delivery Systems

Sayeh F. Ahrabi,[1,*] Sverre A. Sande,[1] Tor Waaler,[1] and Christina Graffner[2]

[1]*Department of Pharmaceutics, School of Pharmacy, University of Oslo, Oslo, Norway*
[2]*Medical Products Agency, Uppsala, Sweden*

ABSTRACT

Different excipients, which are currently being studied for colon delivery systems, were examined with respect to their stability toward neutron irradiation as a potential method of radiolabeling the formulations for γ-scintigraphic studies. Three different pectin and four different hydroxypropyl methylcellulose (HPMC) types, in addition to two types of polymethacrylate films, were exposed to 1, 2, and 3 min of thermal neutron irradiation in a flux of 1.1×10^{13} *n* cm^{-2} s^{-1}. *The physicochemical characteristics of pectins and HPMCs and the mechanical properties of the polymethacrylate films were examined after the radioactivity of the samples had declined to background levels. Methods included ultraviolet (UV) and Fourier transform infrared (FTIR) spectroscopy, pH measurements, loss on drying, thermogravimetric analysis (TGA), viscosimetry, gas chromatographic (GC) analysis of pectin monosaccharides, and tensile strength testing of the films. The results suggest that pectins and HPMCs undergo degradation, as expressed by a significant reduction in the dynamic and intrinsic viscosities of the samples. Generally, HPMCs were more sensitive than pectins to neutron irradiation. However, calcium pectinate proved to be the most sensitive among all the investigated polymers. Both polymethacrylate films (Eudragit® L and S) resisted loss of mechanical properties following 1 and 2 min of neutron irradiation, whereas irradiation for 3 min implied significant changes in the appearance and the mechanical properties of Eudragit L films. As a conclusion, neutron irradiation results in dose-dependent degradation of the investigated polysaccharides and polymethacrylates. The consequences on the in vitro behavior of a formulation containing such polymers are discussed.*

* To whom correspondence should be addressed. School of Pharmacy, University of Oslo, P.O. Box 1068 Blindern, 0316 Oslo, Norway. Telephone: +47 22857905. Fax: +47 22854402. E-mail: s.f.ahrabi@farmasi.uio.no

INTRODUCTION

γ-Scintigraphy is a commonly used technique for observation of the transit of a dosage system through the gastrointestinal (GI) tract when the aim is to explain where and to what extent the system will dissolve or disintegrate (1). The most frequently used method of radiolabeling a formulation for this purpose is to admix the radioactive material during the production of the formulation. Another method is neutron activation, which is based on the incorporation of a stable lanthanide isotope (e.g., samarium-152). Subsequent irradiation of the final product by thermal neutrons activates the lanthanides to become γ-emittors. This method overcomes many of the drawbacks of the conventional radiolabeling techniques, such as the risk of radiation hazards during manufacturing, the batch size limitations, and the requirement of fast handling due to the short half-life of the radionuclides. The major disadvantage of the neutron activation technique is that the whole formulation is exposed to the ionizing radiation (both neutrons and the accompanying γ-radiation in the reactor), which might affect the stability of the ingredients and the in vitro behavior of the dosage forms (2). Therefore, it is essential that the residence time in the reactor is reduced to a minimum.

A colonic drug delivery system is designed to pass intact through the stomach and the small intestine and to disintegrate or release the active substance on arrival in the colon. There is a general agreement on the benefits of such a system for site-specific delivery of the active drugs in the treatment of the inflammatory bowel diseases (i.e., Crohn's disease and ulcerative colitis) (3). During the development of such a system, a γ-scintigraphic study will provide a unique opportunity to observe the passage of the dosage form through the GI tract and to determine the actual site of its disintegration or dissolution.

Several compositions of colonic delivery systems have been proposed that utilize the knowledge of the physiological characteristics of the GI tract. The most attractive systems to date seem to be based on utilization of pH-dependent coatings and polymers that undergo enzymatic degradation when exposed to the colonic bacteria.

Polymethacrylates have been extensively used as pH-dependent delayed-release coatings for colonic delivery, either for conventional tablets (4) or for matrix controlled-release systems such as hydroxypropyl methylcelluloses (HPMCs) (5).

Pectin is a naturally occurring polysaccharide that undergoes extensive microbial degradation in the colon (6). It has thus been the subject of several investigations in both natural and modified forms (7,8).

In the present study, some different qualities of polymethacrylate films, HPMCs, and pectins were exposed to varying doses of thermal neutron irradiation to determine their stability toward the radiation. The objective was to point out the more appropriate ones for a future colonic delivery system to be radiolabeled by neutron activation in a γ-scintigraphic study.

MATERIALS

High-methoxylated calcium salt of a USP-grade pectin, Ca.P (X-5119, Copenhagen Pectin AS, Denmark); hydroxypropyl methylcelluloses K4M and E4M (Methocel® K4M and E4M, Colorcon, UK) and 60SH and 90SH (Metolose® 60SH-4000 and 90SH-4000, Shin-Etsu, Japan); and polymethacrylates Eudragit® L and S (Eudragit® L 100-55 and S 100, Röhm, Germany) were the generous gifts of the indicated sources. High-methoxylated pectin type USP (USP.P) and amidated low-methoxylated pectin type 920 (Am.P) were obtained from Citrus Colloids Limited, UK. Detailed characteristics of the polymers are presented in Tables 1, 2, and 3. All chemicals were analytical grade or better.

Table 1

Structural and Physicochemical Characteristics of the Different Pectin Types

	MW/1000[a]	pH[b]	DM[c]	DA[d]	Ca[e]	LOD[f]	Na[g]
USP.P	350–600	3.15–3.3	70	—	—	5.5–5.9	4.6
Am.P	350–600	4.45–4.5	23	24	—	8.8–9.5	5.4
Ca.P	100	4.15–4.3	65	—	20.2	9–9.15	9.5

[a] Reported by the supplier.
[b] 1% solution in water at 20°C as described under Methods.
[c] Degree of methoxylation (%) as reported by the supplier.
[d] Degree of amidation (%) as reported by the supplier.
[e] Calcium amount (mg/g) as reported by the supplier.
[f] Loss on drying (%) determined according to USP XXIII.
[g] Sodium impurity (mg/g) as described under Methods.

Table 2

Structural and Physicochemical Characteristics of Various HPMC Types

	Mw/1000	Viscosity (cP)[a]	pH[b]	%HP[c]	%M[d]	LOD[e]	Na[f]
K4M	88[g]	4000	5.3–5.8	8.1	22.1	3.9–4.2	1.6
E4M	92[g]	4000	6–6.5	8.5	29	2.4–2.9	2.2
60 SH	470[h]	3500–5600	6.2–6.3	7–12	28–30	2.3–2.5	1
90 SH	560[h]	3500–5600	5.6–5.9	4–12	19–24	2.4–2.7	0.5

[a] In 2% aqueous solution at 20°C, as reported by the suppliers.
[b] 1% solution in water at 20°C, as described under Methods.
[c] Percentage of the hydroxypropyl groups.
[d] Percentage of the methoxyl groups.
[e] Loss on drying (%) determined according to USP XXIII.
[f] Sodium impurity (mg/g) as described under Methods.
[g] Number: average mol. weight (M_n) reported by the supplier.
[h] As reported in Ref. 9.

METHODS

Pectins and Hydroxypropyl Methylcelluloses

Sodium Content Determination

Preweighed plain powders were irradiated for 1 min. The ^{24}Na gamma activity was measured and compared to that of an irradiated NaCl standard solution using a HPGe detector. This detector was connected to a multichannel analyzer (EG&G Ortec Spectrum ACE) via a spectroscopy amplifier (Canberra 2026), which was interfaced with a computer system. The areas under the photo peaks were calculated.

Fourier Transform Infrared Spectra

The KBr disks were made by mixing the vacuum-dried powders with dried KBr, and the spectra were obtained using a Fourier transform infrared (FTIR) spectrophotometer (Nicolet Magna-IR 550).

Table 3

Characteristics of the Investigated Polymethacrylate Aqueous Dispersions and Their Spraying Parameters

	Eudragit L	Eudragit S
Structure		
USP/NF	Type C	Type B
MW	250,000	135,000
Dissolution pH	>5.5	>7.0
Film dispersion		
Solid content (wt%)	16	16
Plasticizer type	TEC[a]	TEC[a]
Plasticizer content (wt% of polymer)	30	48
Spraying parameters		
Spray distance (cm)	20	20
Spray rate (g/min)	7.5	13.5
Atomizing air pressure (psi)	10	10
Vertical rotation of the nozzle (rpm)	10	30
Rotation of the cylinder (rpm)	20	20
Drying time after spraying (min)	15	15
Drying temperature (°C)	60 (±2)	60 (±2)

[a] Triethylcitrate.

Thermogravimetric Analysis and Loss on Drying

A Perkin-Elmer TGA7 with a heating rate of 20°C/min was used for the TGA analysis of the powders. Loss on drying (LOD) was determined according to the method of USP XXIII (1995).

Methanolysis-Gas Chromatographic Analysis of Pectins

The quantitative determination of the various monosaccharides in the pectins was performed according to the methanolysis-gas chromatographic (GC) analysis method described by Samuelsen and coworkers (10).

Preparation of Experimental Solutions

A solution of the irradiated and nonirradiated samples in deionized water was prepared by pouring the plain powder on the preheated solvent (50°C–60°C in the case of pectins and 80°C–90°C for HPMCs) under gentle stirring. The Ca.P powder was allowed to get thoroughly wet prior to stirring. The stirring was continued at room temperature until a clear and homogenous gel was formed. The solutions were kept in a refrigerator (4°C) for at least 12 hr. The evaporated water was replaced before the experiments were carried out.

Ultraviolet Absorbance and pH

A Shimadzu UV-160A and a Metrohm pH meter were used to obtain the ultraviolet (UV) absorbance spectra and the pH of the polymer solutions, respectively. The pH measurements were performed on 1% solutions at 20°C.

Flow Properties

The 10-ml samples of 1% w/w polymer solutions were tested in a Haake Rotovisco RV20 at 25°C. The shear time was programmed from 0 to 1 min and the shear rate from 0 to 2260 s^{-1}.

Polysaccharides are known to exhibit pseudoplastic flow normally. The theoretical relationship best describing this type of flow is

$$\tau^n = \nu' D \qquad (1)$$

where τ represents the shear stress (Pa), D is the shear rate (s^{-1}), ν' is the dynamic viscosity (Pa.s), and n is an index of pseudoplasticity. The effect of irradiation on n and ν' was evaluated by applying a multivariate analysis of the correlated parameters followed by a univariate analysis of variance (ANOVA) test of the most significant parameters.

Intrinsic Viscosity

The kinematic viscosities of the polymer solutions in the range 0.02–0.1% w/v were measured by means of a micro-Ostwald viscometer (Schott Geräte, Germany) at 25°C, and the intrinsic viscosity was calculated in accordance with the methods previously described (11,12).

Polymethacrylate Films

Sample Preparation

The aqueous dispersion of Eudragit L and Eudragit S were prepared as suggested in the information leaflets by the supplier. NH_3 solution was used for partial neutralization. Table 3 lists the characteristics of the film-forming polymers and the content of solids and plasticizer of the aqueous dispersions.

The films were prepared by a spraying technique using previously described equipment (13). A modification of the apparatus was introduced; the drying air was placed inside the cylinder to ensure a more homogeneous heating effect and to avoid any disturbance of the spraying pattern. The spraying parameters are presented in Table 3. The spraying time was adjusted to obtain films of a thickness of 30–50 μm. After storing the films at 40°C for 2 hr, their thicknesses were measured at several locations utilizing a micrometer (Clas Ohlson, Sweden). The films of acceptable thickness and appearance were stored at room temperature (25°C ± 3°C) in 60% relative humidity and protected from light until irradiation, which took place 4–7 days after the film preparation.

Tensile Strength Experiment

A Schenck Trebel RM 100 with a rate of 1 mm/min was used for the tensile strength testing. The samples were cut using a template. The test area of the samples was 60 mm^2 (length 15 mm, width 4 mm). The thicknesses of the samples were remeasured before the test. All samples with physical defects were discarded. The stress-strain curves were registered, and the fracture stress, the fracture strain, and the elasticity modulus were calculated as described by Arwidsson (13). A two-tailed Student's *t* test was applied for the statistical analysis of the data.

Irradiation

Samples were irradiated at the JEEP II reactor (Institute for Energy Technology, Kjeller, Norway) using thermal neutrons with a nominal neutron flux of 1.1×10^{13} n cm^{-2} s^{-1} (temperature approximately 57°C). The powders, as received, were sealed in polyethylene ampoules (diameter 10 mm, length 60 mm), placed in the larger transporting polyethylene tubes called ''rabbits'' (diameter 23 mm, length 80 mm), shipped to the reactor core, and irradiated for 1, 2, or 3 min. The films were packed in polyethylene bags before being placed in the rabbit.

Due to the 1–2% day-to-day fluctuations in the neutron flux inside the reactor, each material was exposed to various irradiation doses on the same day.

The samples were stored behind a lead shield until the radioactivity had declined to the background level. The powders were stored at ambient conditions and were protected from light until tested. The films were placed in a desiccator (60% relative humidity) at room temperature (25°C ± 3°C) and were protected from light. The tensile strength testing was done 7–10 days after the irradiation.

A thermal stress test was designed to examine a possible effect of the heat in the reactor on the polymers. Three samples of each polymer type were placed in an oven at 57°C for 3 min, corresponding to the maximum exposure time in the present study.

RESULTS

Matrix Components: Pectins and Hydroxypropyl Methylcelluloses

Appearance, TGA curves, FTIR and UV spectra, water content, and amount of the different carbohydrate entities in pectins (calculated using GC analysis) were identical for the nonirradiated and the irradiated samples.

The flow curves of pectin and HPMC solutions are presented in Figs. 1a, 1b, and 1c, 1d, respectively. The nonirradiated solutions showed a pseudoplastic flow, as expected. The dynamic viscosity ν′ of the polysaccharides changed significantly ($p < .05$) following 1 min of irradiation (Figs. 2a and 3a). A statistically significant reduction ($p < .05$) in the index of pseudoplasticity n was also observed for all the samples (Figs. 2b and 3b), which demonstrates that the irradiated samples become less pseudoplastic (more Newtonian). The extent of the change is a function of the irradiation dose. The flow curves remained unchanged up to 100 days after irradiation, indicating that no further degradation of the poly-

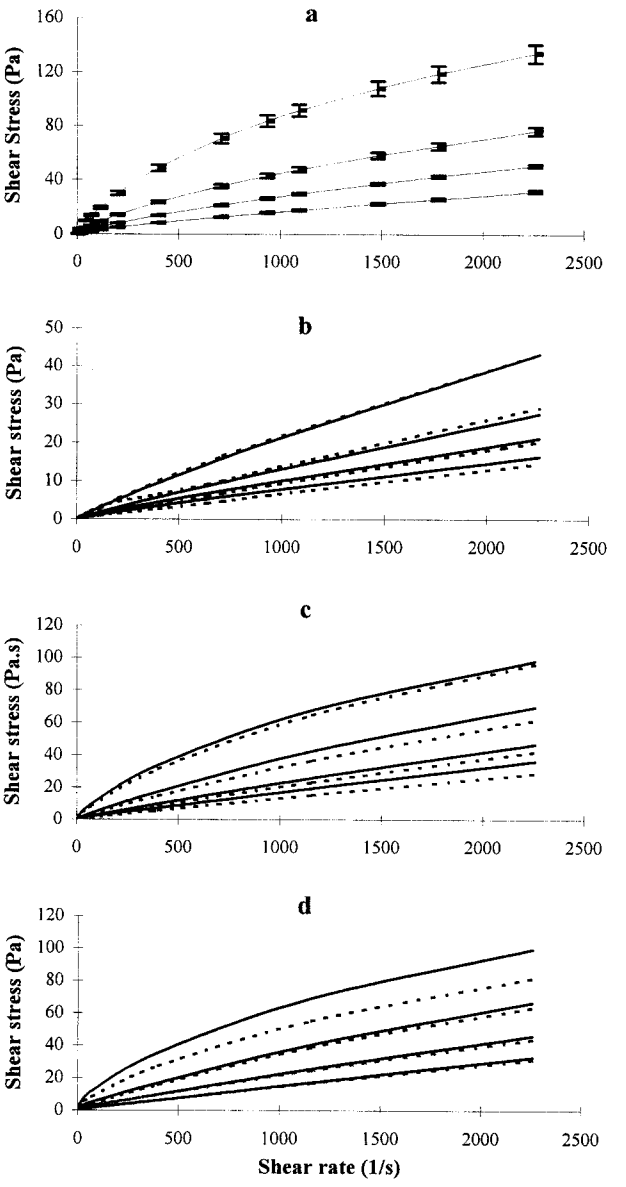

Figure 1. Flow curves for the nonirradiated and irradiated matrix-forming polymers: (a) Ca.P; (b) USP.P (---) and Am.P (——); (c) K4M (---) and E4M (——); and (d) 60 SH (---) and 90 SH (——). For each polymer, the upper curve represents the nonirradiated sample and the three consecutive curves represent the samples irradiated for 1, 2, and 3 min, respectively ($n = 3$).

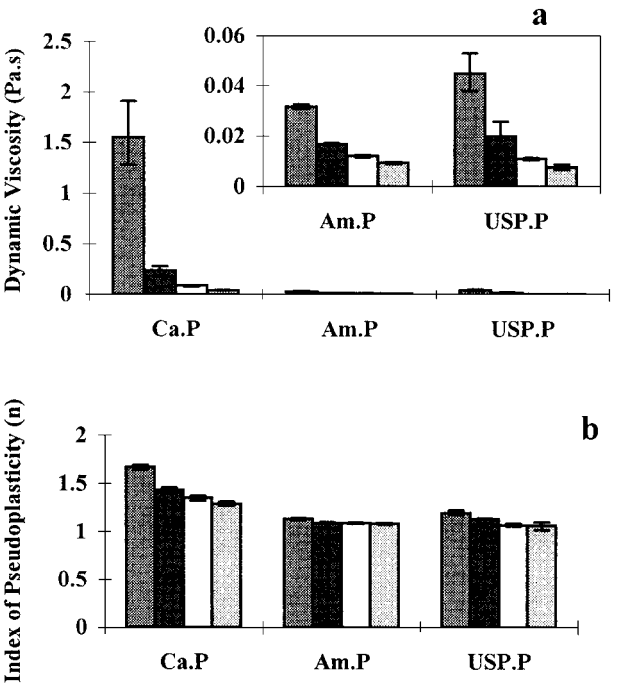

Figure 2. (a) Dynamic viscosity and (b) index of pseudoplasticity for pectin samples as a function of neutron irradiation dose. The four columns within each polymer type represent, from left to right, 0, 1, 2, and 3 min of neutron irradiation. Error bars are the maximum and minimum values ($n = 3$).

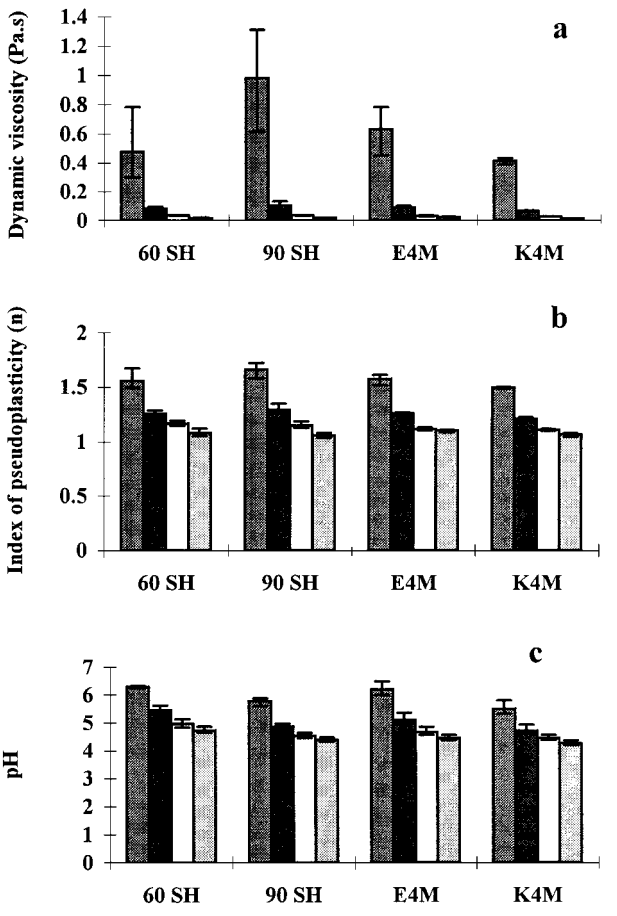

Figure 3. (a) Dynamic viscosity, (b) index of pseudoplasticity, and (c) pH values for HPMC samples as a function of neutron irradiation dose. The four columns within each polymer type represent, from left to right, 0, 1, 2, and 3 min of neutron irradiation. Error bars are the maximum and minimum values ($n = 3$).

mers will occur. The thermal stress alone did not change the flow properties of the polymers.

The pH of the pectin solutions did not change as a result of irradiation; however, a reduction up to one unit was observed following neutron irradiation of HPMCs (Fig. 3c).

The intrinsic viscosity of the samples dropped significantly ($p < .05$) following 1 min of neutron irradiation (Figs. 4a and 4b).

Polymethacrylate Films

The mechanical properties of the free films of polymethacrylates are presented in Table 4. The two types of the polymethacrylate dispersions resulted in strong and clear films. However, those based on the Eudragit S grade were softer than the ones made of the Eudragit L grade, as expressed by the former's lower elasticity modulus.

Irradiation up to 3 min did not have any visible effect on Eudragit S films. The results of the mechanical property analyses also revealed a stable fracture stress and elasticity modulus. The fracture strain, however, was significantly reduced following only 1 min of neutron irradiation.

The appearance and the mechanical properties of Eudragit L films were unchanged following neutron irradiation doses for up to 2 min. On the other hand, 3 min of exposure resulted in sticky films with some cracks. A statistically significant reduction in the thickness, the fracture stress, and the elasticity modulus of these films was observed.

An earlier study performed in our laboratories (14) demonstrated that a thermal stress of up to 15 min at 60°C did not have any impact on the appearance or release properties of tablets coated with Eudragit L 30 D. Hence, the effect of the heat in the reactor on the polymethacry-

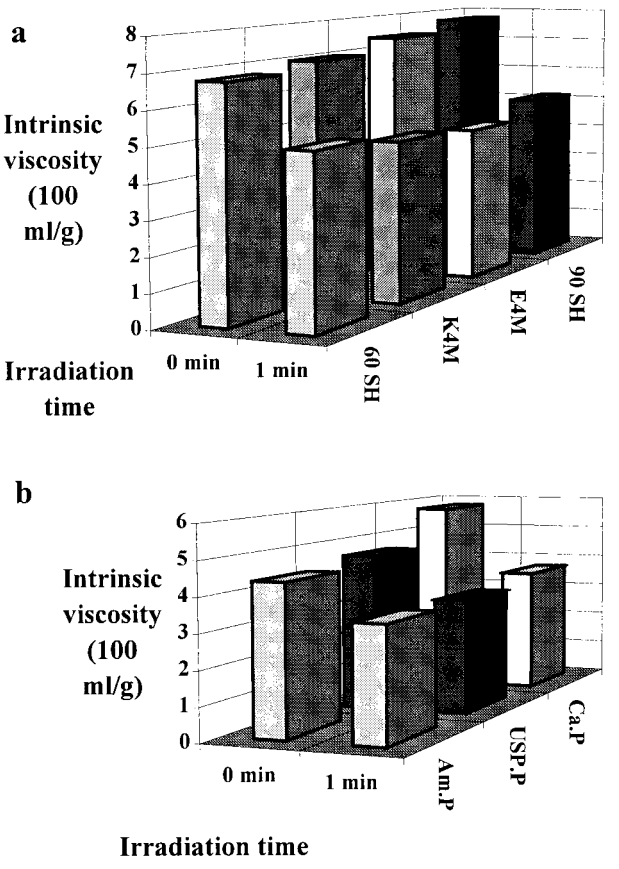

Figure 4. Reduction in the value of intrinsic viscosity as a result of neutron irradiation: (a) HPMCs; (b) pectins.

late films investigated in the present study should be marginal.

DISCUSSION

Choice of Irradiation Dose

The transit time of a dosage form in the GI tract is expected to be more than 24 hr. To be able to study the behavior of an oral colonic delivery system, it is thus necessary to choose a radionuclide with a suitable half-life. One must also consider that the radioactivity should be within an acceptable range for humans, but at the same time high enough to allow detection by the γ-camera until the dosage form is expelled from the body. Samarium-153, with a half-life of 46.7 hr, has been the isotope of choice in several γ-scintigraphic studies. A γ-activity of 1.5 MBq at the time of administration of an oral colon-targeted system has been suggested for this isotope (15).

A further factor to consider is the amount of sodium in the samples presented in Tables 1 and 2. This is a common impurity that is simultaneously activated during the neutron irradiation procedure ($t_{1/2}$ ^{24}Na = 15 hr). Unlike the lanthanide salts, sodium is absorbed into the blood circulation following oral administration. The time between irradiation and administration (lag time) must therefore be adjusted to allow its radioactivity to reduce to a safe level. Generally, the amount of sodium was found to be larger in the pectin samples than in the HPMC ones (Tables 1 and 2). This means that a longer lag time should be considered for pectin formulations.

The choice of the irradiation dose was based on

1. A lag time of 1–4 days. An exposure of 1 mg ^{152}Sm for 1, 2, or 3 min to a thermal neutron flux

Table 4

Results for Tensile Strength Testing of Polymethacrylate Free Films ($n \geq 12$)

Film	Irradiation (min)	Thickness (μm)	Fracture Stress (MPa)	Fracture Strain (%)	Elasticity Modulus (MPa)
Eudragit L	0	50 (6)	8.278 (1.08)	10.128 (3.265)	454.67 (210.9)
	1	45 (4)	8.46 (0.58)	8.28 (1.32)	458.02 (157.04)
	2	50 (6)	9.033 (0.85)	9.41 (2.56)	570.79 (245.82)
	3	40 (4)[a]	6.873 (0.72)[a]	13.61 (3.33)	274.09 (129.97)[a]
Eudragit S	0	35 (7)	7.889 (1.22)	8.139 (1.68)	333.52 (107.07)
	1	35 (7)	8.362 (0.99)	6.69 (1.31)[a]	300.75 (84.53)
	2	30 (7)	8.039 (0.81)	6.75 (1.39)[a]	332.86 (91.72)
	3	35 (11)	8.036 (1.03)	6.698 (1.39)[a]	354.53 (90.08)

[a] Significant effect compared to nonirradiated sample ($\alpha = .01$).
Numbers in parentheses are standard deviations.

of 1.1×10^{13} n $cm^{-2}s^{-1}$ will produce the required 1.5 MBq ^{153}Sm activity after 27, 74, and 100 hr, respectively.

2. Utilization of samarium oxide with the naturally abundant samarium (27.6% ^{152}Sm) instead of the enriched version (about 98% ^{152}Sm) since the price of the latter is more than 100 times higher (16). Obviously, in an industrial-scale production, this price difference would be of importance. As a consequence, either larger amounts of the samarium oxide powder or higher neutron irradiation doses would be necessary to achieve the desired ^{153}Sm activity. On the other hand, the amount of samarium oxide should be limited minimum, due to the technological problems associated with its incorporation into the dosage forms. Hence, the objective of the study was to investigate to what extent the irradiation dose can be increased without damaging the polymers.

Matrix Components

Viscosity Reduction

The significant reduction in the dynamic viscosity and the index of pseudoplasticity (Figs. 2, 3a, 3b) strongly suggests that a chain scission along the glycosidic bonds is the predominant reaction following neutron irradiation of both the pectin and the HPMC qualities. This observation was supported by the reduced values of the intrinsic viscosity (Figs. 4a, 4b). The relationship between intrinsic viscosity and molecular weight (MW) of polymer homologue samples in a given solvent at a given temperature is given in the Mark-Houwink-Sakurada equation:

$$[\nu] = KM^{\alpha} \qquad (2)$$

where [ν] represents the intrinsic viscosity (100 ml/g), M is the average MW, α describes the shape of the molecule, and K is a constant. For the polysaccharides, the value of α is close to one. Thus, it is possible to estimate the degree of degradation by direct comparison of the intrinsic viscosity of the nonirradiated samples and the irradiated ones.

The swelling and the solubility of the homologue polymers are direct functions of the MW. The release of a drug incorporated in an uncoated pectin matrix is completely controlled by the matrix during its passage through the GI tract. If the degree of polymer degradation is too high, the consequence might be premature release of the active substance in the intestine. On the other hand, in the case of HPMC matrices, which usually have a surrounding coating layer, the release is initially controlled by the coating. The coating will start to disintegrate when the pH of the environment reaches a critical value. A Eudragit S coating, as an example, dissolves at a pH greater than 7. Therefore, a HPMC-controlled drug release in such a formulation is not expected to start until the ileum or the colon. In vivo, an accelerated release as a result of a degradation of the polymer might not be as critical.

Chemical Versus Physical Changes

Small and undetectable chemical changes produced by moderate radiation doses may cause significant changes in the physical properties of polymers. One broken bond in a polymeric chain consisting of several thousand monomers corresponds to less than 0.1% chemical change, causing techniques such as FTIR spectroscopy or UV absorbance to suggest perfect structural stability. However, even smaller changes can profoundly modify the viscosity of a polymer (17). It therefore could be concluded that the primary structure of the polymers was maintained although the MW was significantly reduced as a result of radiation. Similar results have been observed by Mumper and Jay (18) on poly(L-lactic acid) microspheres following considerably higher doses of neutron irradiation than employed in the present study.

Effect of Polymer Grade, Structure, and Water Content

The degradation of the pectins and HPMCs as a result of the neutron irradiation is a direct function of their grade. The explanation is that it takes only one bond break to cut the average MW of a polymeric chain in half regardless of the initial MW. Therefore, for larger molecules, a bond break leads to a larger decrease in the MW (and thereby the derived properties such as viscosity) than for smaller molecules (19). This fact can be visualized by considering two hypothetical polymers with one having half the MW of the other so that 10 molecules of polymer A weigh exactly the same as 20 molecules of polymer B. One bond break would result in 11 and 21 molecules for polymers A and B, respectively. This means a 9.09% reduction in the average MW for polymer A and a 4.76% reduction for polymer B. Polymer B needs two bond breaks to reduce its MW by 9.09%.

In our investigation, the viscosity reduction, as an indirect measure of the MW, was more significant for the HPMCs than for the pectins, except for Ca.P. The fact that this effect diminishes with an increase of the radiation dose supports the above-mentioned theory. Another factor that can explain the relative physical stability of

the pectins compared to the HPMCs is the water content of the polymers. When water is present in solid polysaccharides, it is proposed to have a protective effect against ionizing irradiation (20). The amount of water in the pectin samples was generally found to be higher than in the HPMC ones (Tables 1 and 2).

The excessive sensitivity of Ca.P to the irradiation (Fig. 2a) is most probably due to its special structure. The interaction of calcium ion with the acidic groups on the pectin chains (21) has been suggested to form an ''egg-box'' structure (as is explained for alginates in ref. 22) and accounts for the considerably higher viscosity of Ca.P solutions. If the ionizing radiation damages this particular structure, a ''double effect'' can be expected (i.e., degradation of the pectin chain and destruction of the egg-box). This might account for the extraordinary reduction in the viscosity following irradiation of Ca.P for only 1 min.

pH Reduction

The observed reduction in pH of the HPMC solutions as a function of the irradiation dose (Fig. 3c) is attributed to the cleavage of the glycosidic bonds, leading to formation of acidic end groups. Such a pH reduction was not observed for pectins since the pH values of these lie in an acidic area in which a strong increase in the amount of protons is needed to produce a detectable pH reduction. The pH values of the HPMCs, on the other hand, are located in a more sensitive part of the scale (pH = 5–7), for which even a minor change in the amount of acidic groups will influence the pH.

Film-Forming Polymers

With respect to the mechanical properties, both polymethacrylate grades were stable toward 1 and 2 min of neutron irradiation. Eudragit S films were more stable toward the irradiation than the Eudragit L ones. A statistically significant reduction was only found in the fracture strain (the ductility parameter) of Eudragit S films. The magnitude of the reduction, however, was not big enough to affect the inversely related elasticity modulus parameter. The fracture strain is known to be the most sensitive parameter for studying changes in the mechanical properties of the films (23). But, since the other two important parameters expressing strength and softness of the films did not change, the reduction in the fracture strain should have negligible practical consequences.

Neutron irradiation up to 2 min was also well tolerated by the Eudragit L films. However, 3 min of irradiation caused visible structural damage, that is, some areas became brittle while the crack-free parts were soft and sticky. The last parts of the films, which were chosen for the tensile strength testing, were weaker (lower fracture stress) and softer (lower elasticity modulus) than the nonirradiated samples (Table 4). An increase in the mean value of the fracture strain was also observed, although this effect was nonsignificant due to large standard deviations. The significant reduction in the thickness values of these films is most probably due to the measuring method, that is, since the films became softer, they exhibited less resistance to being pressed by the micrometer.

These results might be induced by any phenomenon that promotes better cohesion and coalescence in the films, such as an increase in the amount of the plasticizers used in the films (23) or a degradation of the polymer to smaller chains (24). It can be hypothesized that, in this study, both effects have occurred. Polymer degradation, as well as a possible migration and accumulation of the plasticizer, promotes the excessive softness of some parts of the films, whereas loss of the plasticizer and degradation/cross-linking of the polymer results in the brittleness of the other parts. Watts and coworkers (2) suggested a complex set of reactions due to degradation and cross-linking of Eudragit RS microspheres as a result of neutron irradiation. Nevertheless, the dissolution rate of the microspheres was higher following irradiation, which suggests that degradation is the predominant reaction. This is in accordance with the study of Lawton, Bueche, and Balwit (25) on the effect of ionizing radiation on different polymers.

The above observations suggest that a formulation coated with Eudragit L exposed to 3 min of neutron irradiation will not be able to exhibit the expected enteric coating properties due to the surface cracks and the weakness and excessive softness of the coating.

Eudragit L proved to be more sensitive than Eudragit S due to its higher MW (Table 3) and its thicker films, which means that a higher polymer density in the film was available for the neutrons.

CONCLUSION

The release-controlling excipients of an oral colon delivery system must be carefully chosen if the dosage form is meant to be radiolabeled by neutron activation. The commonly used polymers will undergo degradation as a result of the irradiation procedure, and the degradation will probably affect the drug release properties of the dosage forms. The degree of degradation will strongly de-

pend on the type and the grade of the polymer, with the higher grades being more sensitive. The investigated HPMC qualities were more sensitive to neutron irradiation than those of the pectins. The calcium pectinate was the least stable of all the polymers investigated in this study, and this was explained by its molecular structure. A neutron irradiation of up to 2 min was well tolerated by the investigated polymethacrylate films. The Eudragit L grade was more sensitive to the higher doses of neutron radiation than the Eudragit S grade.

For neutron activation purposes, amidated pectin and USP pectin seem to be the most suitable matrix-forming polymers, and both Eudragit L and S aqueous dispersions can be utilized as coatings.

ACKNOWLEDGMENTS

This work was partly presented at the CRS conference on Advances in Controlled Delivery, Baltimore, Maryland, August 1996. We would like to thank Dr. K. Redford, Mr. K. Olafsen, and Mr. R. Kalland, Sintef, Oslo; Mr. P. O. Bremer and Mr. O. Johansen, Institute for Energy Technology, Kjeller, Norway; Ms. P. Dietrich, Ms. A. Tiedt, and Ms. C. Starch, Christian-Albrechts University, Kiel, Germany; and Mr. H. Gundersen, School of Pharmacy, University of Oslo, for their contributions to this work. Special thanks to Mrs. A. B. Samuelsen, School of Pharmacy, University of Oslo, for the valuable discussions and for providing the working facilities for the methanolysis and GC analysis of pectins. The financial support of the Norwegian Pharmaceutical Society to S. F. A. is gratefully acknowledged.

REFERENCES

1. G. A. Digenis and E. Sandefer, Crit. Rev. Ther. Drug Carrier Sys., 7, 309 (1991).
2. P. J. Watts, C. G. Wilson, M. C. Davies, and C. D. Melia, Int. J. Pharm., 98, 63 (1993).
3. M. Campieri, P. Gionchetti, A. Belluzzi, C. Brignola, M. Miglioli, and L. Barbara, Curr. Opin. Gastroenterol., 8, 663 (1992).
4. M. Ashford, J. T. Fell, D. Attwood, H. Sharma, and P. J. Woodhead, Int. J. Pharm., 95, 193 (1993).
5. K. P. Steed, G. Hooper, P. Ventura, R. Musa, and I. R. Wilding, Int. J. Pharm., 112, 199 (1994).
6. W. D. Holloway, C. Tasman-Jones, and K. Maher, Am. J. Clin. Nutr., 37, 253 (1983).
7. A. Rubinstein and R. Radai, Eur. J. Pharm. Biopharm., 41, 291 (1995).
8. Z. Wakerly, J. T. Fell, D. Attwood, and D. A. Parkins, Int. J. Pharm., 129, 73 (1996).
9. T. Kato, H. Maeda, and A. Takahashi, Kobunshi Ronbunshu, 44, 179 (1987).
10. A. B. Samuelsen, B. S. Paulsen, J. K. Wold, H. Otsuka, H. Yamada, and T. Espevik, Phytother. Res., 19, 211 (1995).
11. P. E. Christensen, Food Res., 19, 163 (1954).
12. T. Østberg, L. Vesterhus, and C. Graffner, Int. J. Pharm., 97, 183 (1993).
13. H. Arwidsson, Acta Pharm. Nord., 3, 25 (1991).
14. T. Waaler, S. A. Sande, B. W. Müller, and G. Schüller Lisether, The influence of neutron irradiation on Eudragit® coated tablets. Validation of neutron activation II., Eur. J. Pharm. Sci., in press.
15. P. J. Watts, C. G. Wilson, M. C. Davies, and C. D. Melia, Int. J. Pharm., 102, 101 (1994).
16. M. B. Awang, J. G. Hardy, S. S. Davis, I. R. Wilding, and S. J. Parry, J. Labelled Comp. Radiopharm., 33, 941 (1993).
17. J. E. Wilson, *Radiation Chemistry of Monomers, Polymers, and Plastics*, Marcel Dekker, New York, 1974, p. 370.
18. R. J. Mumper and M. Jay, Pharm. Res., 9, 149 (1992).
19. J. Guillet, *Polymer Photophysics and Photochemistry*, Cambridge University Press, Cambridge, UK, 1985, p. 75.
20. P. S. Elias and A. J. Cohen, *Radiation Chemistry of Major Food Components*, Elsevier/North Holland, Amsterdam, 1977, p. 154.
21. G. O. Philips, P. A. Williams, and D. J. Wedlock, *Gums and Stabilisers for the Food Industry 7*, IRL Press, 1994, p. 413.
22. G. T. Grant, E. R. Morris, D. A. Rees, P. C. J. Smith, and D. Thom, FEBS Lett., 31, 195 (1973).
23. D. Hutchings, S. Clarson, and A. Sakr., Int. J. Pharm., 104, 203 (1994).
24. G. S. Banker, Film coating theory and practice, J. Pharm. Sci., 55, 81 (1966).
25. E. J. Lawton, A. M. Bueche, and J. S. Balwit, Nature, 172, 76 (1953).