International Journal of Pharmaceutics, 13 (1983) 109–113
Elsevier Biomedical Press

Molecular weights of poly(methyl methacrylate) nanoparticles

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(Received March 15th, 1982)
(Modified version received June 12th, 1982)
(Accepted June 15th, 1982)

Nanoparticles are colloidal particles ranging in size between 10 and 1000 nm. They consist of macromolecular materials in which the biologically active material is dissolved, entrapped, and/or to which the active material is adsorbed or bound. Nanoparticles are promising drug delivery systems; they have been shown to enhance the activity of cytostatics, and they were able to improve the effectivity of vaccines considerably (Brasseur et al., 1980; Couvreur et al., 1979; Kreuter and Speiser, 1976; Kreuter et al., 1976; Kreuter and Liehl, 1978, 1981). For the latter purpose, poly(methyl methacrylate) seems to be the material of choice (unpublished observation). The molecular weights of these nanoparticles were so far not determined. The molecular weight, however, is not only of significance for the evaluation of the mechanism and kinetics of the polymerization process and as a parameter for the process control, but seems also to have an important influence on the elimination from tissue and from the whole body (Schindler et al., 1977).

The nanoparticles were produced after purification from polymerization inhibitors as described by Riddle (1954) and Tessmar (1961) and dissolution in the polymerization medium (Table 1) either by gamma-ray initiated polymerization with 500 krad in a ^{60}Co-source at a rate of 2.2 krad/min or by chemically initiated polymerization keeping up the conditions specified in Table 1 for 2 h.

The molecular weights of polyacrylic nanoparticles were determined with HPLC-gel permeation chromatography. An HPLC-gel permeation chromatograph equipped with a refraction index detector was used (Waters R 401, Milford, MA, U.S.A.). μ-Styragel 10^3 as well as μ-Styragel 10^4 (Waters Ass., Milford, MA, U.S.A.) served as columns. Chloroform (PA, Merck, Darmstadt, F.R.G.) was used as eluent. 50 mg of nanoparticles were dissolved in 10.0 ml of chloroform and if necessary separated from inorganic material by centrifugation. In two cases (Sample 1 + 2) 1% aqueous

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0378-5173/83/0000-0000/$03.00 © 1983 Elsevier Biomedical Press

TABLE I

MOLECULAR WEIGHT OF POLY(METHYL METHACRYLATE) NANOPARTICLES

Sample no.	Polymerization medium	M_{GPC}	$\overline{M}_w$	$\overline{M}_n$	Dispersity
γ-Ray-initiated polymerization					
1	100 mmol/l MMA [a] in phosphate-buffered saline; 4°C	20,280	42,400	5655	7.5
2	100 mmol/l MMA [a] in water; 4°C	18,370	37,500	5680	6.6
3	100 mmol/l MMA [a] in water; freeze-dried; 4°C	18,350	36,400	3920	9.3
Chemically initiated polymerization					
4	80 mmol/l MMA [a] in water; 3 mmol/l $K_2S_2O_8$; 65°C	145,900	289,300	75,800	3.8
5	80 mmol/l MMA [a] in water; 3 mmol/l $K_2S_2O_8$; 85°C	130,000	220,600	54,900	4.0
6	80 mmol/l MMA [a] in water; 0.3 mmol/l $K_2S_2O_8$; 85°C	210,800	434,100	134,000	3.2
7	156 mmol/l MMA [a] in water; 3 mmol/l $K_2S_2O_8$; 85°C	206,600	398,900	76,400	5.2
Commercial sample					
8	Poly(methyl methacrylate) beads; diameter 10 μm	51,800	274,900	73,900	3.5

[a] Monomeric methyl methacrylate.

suspensions of the particles were injected. The injection volume was 50 μl; the flow rate was 1 ml/min. Poly(methyl methacrylate) as well as styrene standards were used for calibration because only poly(methyl methacrylate) standards of a molecular weight of 75,000 and 160,000 were available. The standards, polystyrene with molecular weights of 2350, 3600, 17,500, 33,000, 110,000, 233,000, 470,000 and 650,000 were obtained from Waters Ass. (Milford, MA, U.S.A.) and poly(methyl methacrylate) from Polyscience (Warrington, PA, U.S.A.). The calibration curve is shown in Fig. 1 and the chromatograms of the nanoparticles are shown in Fig. 2.

M_{GPC} represents the mode of the molecular weights taken from the chromatogram. $\overline{M}_w$ represents the molecular weight average that was calculated according to the method proposed by Waters Ass. (1974) using Eqn. 1,

$$\overline{M}_w = \frac{\sum_{i=1}^{i=\infty} w_i \cdot M_i}{\sum_{i=1}^{i=\infty} w_i} \qquad (1)$$

where w_i represents the amount of molecules of a certain molecular weight M_i given by the height in the chromatogram curve (Hoffman et al., 1977); $\overline{M}_n$ is the molecular

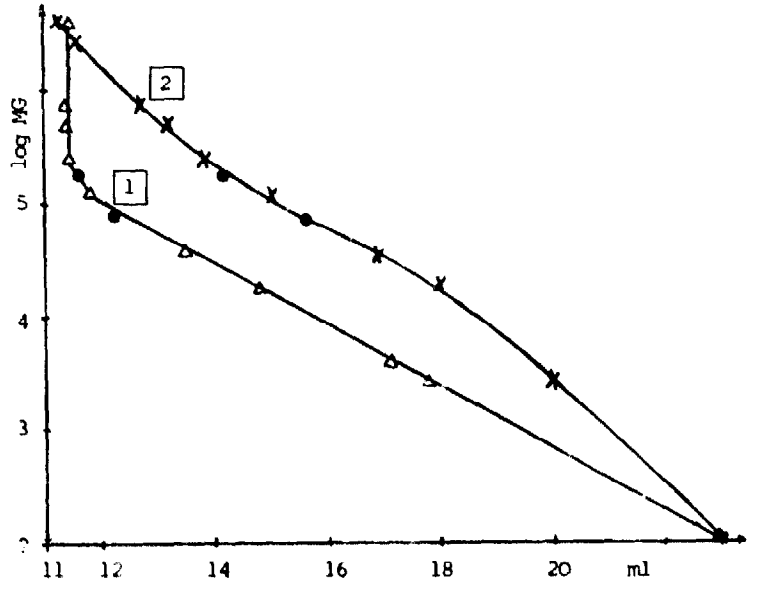

Fig. 1. Calibration curves of μ-Styragel gel permeation column combination. (1) μ-Styragel 10^2 nm + 10^3 nm. (2) μ-Styragel $10^3 + 10^4$ nm. Eluent: chloroform. ×, calibration standards; △, polystyrene; ●, poly(methyl methacrylate).

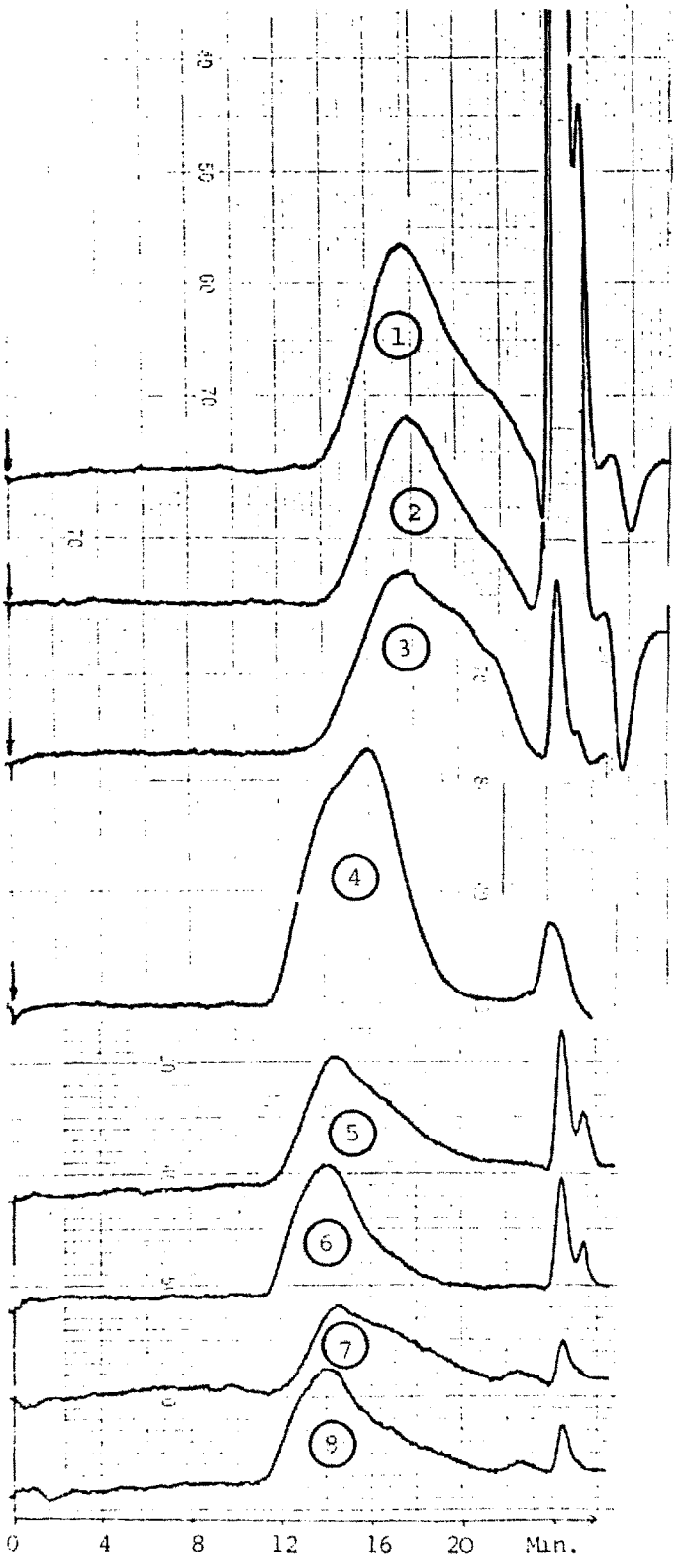

Fig. 2. Chromatograms of poly(methyl methacrylate) nanoparticles: γ-Ray initiated polymerization: (1) 100 mmol/l MMA [a] in phosphate-buffered saline, 4°C; (2) 100 mmol/l MMA [a] in water, 4°C; (3) 100 mmol/l MMA [a] in water, 4°C, freeze-dried. Commercial sample: (4) poly(methyl methacrylate) beads; diameter 10 μm. Chemically initiated polymerization: (5) 80 mmol/l MMA [a] in water, 3 mmol/l $K_2S_2O_8$, 65°C; (6) 80 mmol/l MMA [a] in water, 0.3 mmol/l $K_2S_2O_8$, 85°C; (7) 80 mmol/l MMA [a] in water, 3 mmol/l $K_2S_2O_8$, 85°C. (8) 156 mmol/l MMA [a] in water, 3 mmol/l $K_2S_2O_8$, 85°C.

[a] Monomeric methyl methacrylate.

weight number average that was calculated using Eqn. 2:

$$\overline{M}_n = \frac{\sum_{i=1}^{i=\infty} w_i}{\sum_{i=1}^{i=\infty} w_i/M_i} \qquad (2)$$

The dispersity, showing the wideness of the molecular weight distribution, is the quotient of $\overline{M}_w/\overline{M}_n$.

The molecular weights of the poly(methyl methacrylate) nanoparticles polymerized by initiation with gamma-rays were considerably lower than the molecular weights of those initiated by the decay of potassium peroxodisulphate. As expected, the molecular weight of the freeze-dried product (Sample 3) did not differ significantly from the sample injected directly in the aqueous phase (Sample 2). The nanoparticles produced by polymerization in phosphate-buffered saline yielded a slightly higher molecular weight, indicating a higher degree of coagulation of macroradicals prior to the termination of the polymerization in the salt-containing medium than in pure water. The nanoparticles produced by polymerization initiation using the decay of potassium peroxodisulphate had a much lower dispersity than the nanoparticles produced by gamma-irradiation. The dispersity of the chemically initiated nanoparticles was comparable to that of commercial polymeric beads with a diameter of 10 μm. A low starter concentration yielded the highest molecular weight. An increase in monomer as well as a reduction in temperature also increased the molecular weight, however, to a lesser degree, confirming the theoretical expectations.

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