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Molecular weights of polycyanoacrylate nanoparticles

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Polycyanoacrylates represent a class of biodegradable polymers that can be obtained in the form of nanometer-sized particles by simple polymerization in aqueous medium (Couvreur et al., 1979a). These particles are called nanoparticles and are becoming more and more interesting as carriers for drug delivery systems or as adjuvants for vaccines (Brasseur et al., 1980; Kreuter and Speiser, 1976). A previous publication dealt with the determination of the molecular weights of poly(methyl methacrylate) nanoparticles using a HPLC method (Bentele et al., 1983). Poly(methyl methacrylate) is very promising for vaccination purposes. For drug delivery purposes, its biodegradability will be too slow (Oppenheimer et al., 1955). Polycyanoacrylates are much more rapidly biodegradable (Couvreur et al., 1979b), and therefore this material seems to be much more promising for the production of drug carriers. The objective of this report is the investigation of the influence of the polymerization conditions, such as the pH and the surfactant concentration, and of the monomer side-chain length on the molecular weight of the resulting nanoparticles.

Polyalkylcyanoacrylate nanoparticles were produced as follows: 1 ml of methyl cyanoacrylate (Schering, Bergkamen, F.R.G.), ethyl cyanoacrylate (Schering), butyl cyanoacrylate (Sichel Werke, Hanover, F.R.G.), or hexyl cyanoacrylate (Sichel Werke) was added drop by drop under stirring with a magnetic stirrer to the acidified solutions having the compositions shown in Tables 1 and 2. These mixtures were stirred for 2 h, resulting in the polymerization of the cyanoacrylates and thus forming the nanoparticles. Then these suspensions were neutralized with sodium hydroxide solutions and stirred for an additional 6 h. After this time, the nanoparticle suspensions were freeze-dried.

For the determination of the molecular weights, an HPLC-gel permeation chro-

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TABLE 1

MOLECULAR WEIGHT OF POLYCYANOACRYLATE NANOPARTICLES POLYMERIZED AT DIFFERENT HYDROCHLORIC ACID CONCENTRATIONS

Polymer	% Polysorbate 20	HCl (N)	M_{GPC}	$\overline{M}_w$	$\overline{M}_n$	Dispersity
Polymethylcyanoacrylate	0.5	0.01	2690/800 *	1270	1810	1.4
Polymethylcyanoacrylate	0.5	0.1	2430/720 *	1010	1510	1.5
Polymethylcyanoacrylate	0.5	1	3300/880 *	1270	1850	1.5
Polyethylcyanoacrylate	0.5	0.01	2690	1630	2100	1.3
Polyethylcyanoacrylate	0.5	0.1	1200	1330	1770	1.3
Polyethylcyanoacrylate	0.5	1	800	1060	1370	1.3
Polybutylcyanoacrylate	0.5	0.01	3300	2720	3790	1.4
Polybutylcyanoacrylate	0.5	0.1	3650	2340	3390	1.3
Polybutylcyanoacrylate	0.5	1	2690	1760	2330	1.3
Polyhexylcyanoacrylate	0.5	0.01	2980	2860	3570	1.2
Polyhexylcyanoacrylate	0.5	0.1	2690	1700	2250	1.3
Polyhexylcyanoacrylate	0.5	1	2200	2290	3240	1.4

* Bimodal distribution

matograph equipped with a refraction index detector was used (Waters R401, Milford, MA, U.S.A.). μ-Styragel 10^3 (Waters) served as column. Chloroform (PA, Merck, Darmstadt, F.R.G.) was used as eluent. 50 mg of nanoparticles were dissolved in 10.0 ml of chloroform and separated from inorganic material by centrifugation. The injection volume was 50 μl; the flow rate was 1 ml/min. The standards, polystyrene with molecular weights of 2350, 3600, 17,500, and 33,000 were obtained from Waters Ass. (Milford, MA, U.S.A.). The standard curve is shown in Fig. 1 and the results are shown in Tables 1 and 2. M_{GPC} represents the mode of the molecular weights taken from the chromatogram, $\overline{M}_w$ the molecular weight average, $\overline{M}_n$ the molecular weight number average, and $\overline{M}_w/\overline{M}_n$ the dispers-

TABLE 2

MOLECULAR WEIGHT OF POLYCYANOACRYLATE NANOPARTICLES POLYMERIZED AT DIFFERENT SURFACTANT CONCENTRATIONS

Polymer	% Polysorbate 20	HCl (N)	M_{GPC}	$\overline{M}_w$	$\overline{M}_n$	Dispersity
Polybutylcyanoacrylate	0.1	0.1	1800	2020	2300	1.1
Polybutylcyanoacrylate	0.5	0.1	3650	2340	3390	1.3
Polybutylcyanoacrylate	1.0	0.1	2980	2420	2820	1.2
Polyhexylcyanoacrylate	0.1	0.1	2690	2290	2840	1.2
Polyhexylcyanoacrylate	0.5	0.1	2690	1700	2250	1.3
Polyhexylcyanoacrylate	1.0	0.1	3300	3210	4410	1.4

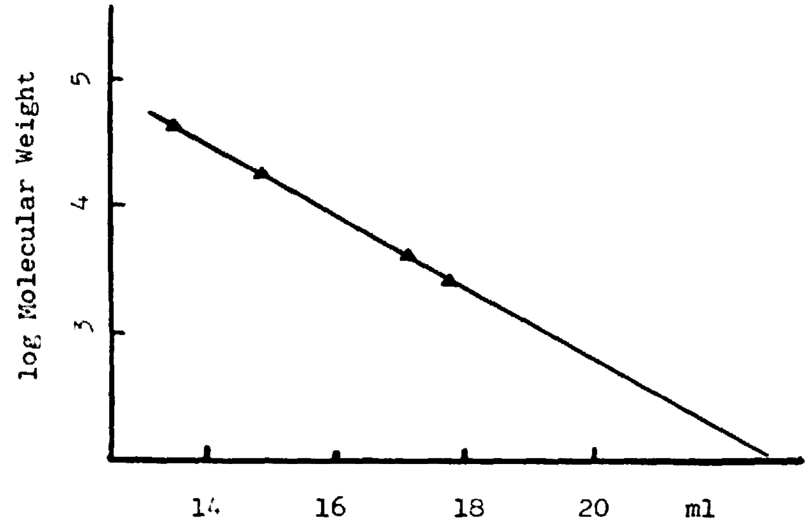

Fig. 1. Calibration curve of μ-Styragel 10^3 nm gel permeation column with polystyrene standards.

ity. For details in the calculations see the previous publication by Bentele et al. (1983).

The molecular weights of polycyanoacrylate nanoparticles were much lower than those of poly(methyl methacrylate) nanoparticles. The molecular weight differences between polycyanoacrylate nanoparticles with different side-chain lengths as well as the molecular weight differences of polycyanoacrylate nanoparticles produced at different hydrochloric acid concentrations or surfactant concentrations appear to be not very pronounced. Nevertheless, the following trends can be observed: an increase in side-chain length led to increasing molecular weights. Increasing hydrochloric acid concentrations reduced the molecular weights. The latter observation is completely the opposite of what would be expected: cyanoacrylate polymerization is initiated by hydroxyl ions, whose concentration decreases with decreasing pH. Normally, a decrease in initiator concentration leads to increasing molecular weights. Possibly, the fact that the solvent generates the initiator may be responsible for the abnormality observed with polycyanoacrylate nanoparticles. The increase in molecular weight of the polycyanoacrylate nanoparticles with increasing surfactant concentration was probably caused by the stabilizing effect of the surfactants. The molecular weight distribution of polymethylcyanoacrylate nanoparticles was bimodal, which was possibly caused by degradation products, which may already result during the stirring at neutral pH with this least stable polycyanoacrylate.

This communication may appear to be somewhat premature in that it cannot explain some of the anomalous results. However, because of the great interest in nanoparticles as drug delivery systems and because the molecular weight measurements require some expertise and equipment that is not necessarily available in all laboratories, it was felt that these results are of interest to a number of research groups.

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