Comparison of the Biodistribution in Mice of ^{111}Indium Oxine Encapsulated into Poly(lactic-*co*-glycolic)-D,L-85/15 and Poly(epsilon Caprolactone) Nanocapsules

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Abstract □ Poly(lactic-*co*-glycolic)-D,L-85/15 (PLAGA) nanocapsules and poly(epsilon caprolactone) (PCL) nanocapsules were labeled with a relatively long half-life compound that is usually used in humans; that is, ^{111}In-labelled oxine (^{111}In oxine). This labeling technique led to a high ^{111}In oxine entrapment efficiency and good stability during dialysis against phosphate buffer and phosphate buffered albumin solution. Because of these characteristics, the nanocapsules biodistribution was followed up after intravenous administration for up to 96 h by determining the gamma activity in the tissues after sampling. The administration of the PCL-encapsulated ^{111}In oxine led to a decrease in the blood radioactivity and an increase in the liver radioactivity compared with the solution. This effect was even more pronounced with the PLAGA nanocapsules. Finally, the activity level in other tissues, such as the kidneys, the lungs, and the spleen, appeared to be rather low and only slightly affected by the encapsulation into one or the other polymer.

Introduction

Most research in the field of drug targeting is being carried out with either liposomes or polymeric micro- or nanoparticles. However, it has been demonstrated that submicron vesicular structures, the so-called nanocapsules, are of great interest for the delivery of lipophilic drug substances. The ability of nanocapsules to improve the biopharmaceutical properties of lipophilic drug substances has been studied using different routes of administration; namely, the intravenous (iv), oral, and ophthalmic routes.[1,2] Follow-up studies with nanocapsules made of different polymers after iv administration are useful to characterize the influence of physicochemical parameters on the ability of the carriers to escape the mononuclear phagocyte system (MPS). Nevertheless, the biodistribution of poly(lactic-*co*-glycolic)-D,L-85/15 (PLAGA) and poly(epsilon caprolactone) (PCL) nanocapsules in mice after iv administration has still not been described.

Biodistribution studies of colloidal carriers are usually performed with either liposomal lipids, polymers, or encapsulated drug labeled with beta emitters[3] or carbon-14.[4,5] For example, the biodistribution of radiolabeled cyclosporine incorporated into poly(isobutyl cyanoacrylate) nanocapsules has been described.[6] However, mainly because of safety reasons, preliminary phases of clinical trials can hardly be performed with such labeled dosage forms.

Therefore, colloidal carriers incorporating gamma emitters have been prepared and injected in humans by different routes of administration, such as the iv or the pulmonary route. Although most of these colloids are found in the MPS after iv administration,[7−9] the potential of gamma scintigraphy study techniques has been outlined by Rolland et al.[8] and by Gahnem et al. in humans[9] using poly(cyanoacrylate) nanoparticles labeled with Indium-111 and technetium-99m, as well as by Thanoo et al.[10] using ^{111}In oxine-labeled microspheres. In these studies, the particle distribution in the body was followed as a function of time.

Nevertheless, the labeling technique appears to be critical. Indeed, binding efficiency and radioactive half-life have a great impact onto the feasibility of the experiments, whereas stability of the labeling greatly influences the reliability of the data. For example, the binding efficiency of technetium-99m or iodide-125 to cyanoacrylates nanoparticles or to cellulose derivative microparticles, respectively, is poor; moreover, the technetium-99m gamma emitter has a relatively short half-life (6 h), which implies the use of highly radioactive preparations for a distribution follow-up of ≈12 h. Finally, noncovalent gamma emitter−carrier binding is susceptible to desorption due to dilution or particle degradation, especially in a blood protein environnement. Poly(butylcyanoacrylate) nanoparticles have been successfully labeled with ^{111}In by an adsorption process by Kreuter et al.,[11] but the stability of the binding has not been demonstrated. Discrimination between particles and the released free emitter biodistribution then appears to be difficult.

The objectives of the present work were to directly label polymeric nanocapsules with a relatively long half-life compound usually used in humans i.e., ^{111}In oxine (half-life, 2.8 days). Additionally, the labeling was to be done by an easy, fast, and reproducible method and the binding was to be stable in a blood environment. The potential of the labeling technique to follow up the distribution of the nanocapsules in the body after iv administration was evaluated in mice. Finally, the biodistribution of two different types of nanocapsules (PLAGA and PCL) were compared.

Experimental Section

Chemicals—Copolymer of lactic and glycolic acid (PLAGA MW 40 000) was kindly furnished by Medisorb (Cincinnati, OH). Polyepsilon caprolactone (MW 60 000) was purchased from Aldrich Chemical (Saint Quentin Fallavier, France), olive oil and ^{111}In

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Table 1—Mean Diameter, Zeta Potential, and ^{111}In Oxine Encapsulation Ratio of PLAGA and PCL Nanocapsules

nanocapsules	mean diameter ± standard deviation, nm	zeta potential ± standard deviation, mV	^{111}In oxine encapsulation ratio, %
PLAGA	340 ± 12	–25 ± 1.1	94
PCL	454 ± 8	–29 ± 1.1	95

oxine (^{111}In oxine, 1 mCi/mL) were purchased from Cooper (Melun, France) and Oris Industrie (Saclay, France), respectively. Pluronic F68 was a gift from BASF (Paris, France). All reagents were analytical grade and used as received.

Preparation of Labeled Nanocapsules—the commercial indium oxine is an aqueous solution containing <0.1 μg of radioactive indium atoms complexed by 50 mg of hydroxy-8-quinoleine (i.e., oxine). According to the first step of the preparation process, the lipophilic marker was partioned upon shaking for 20 min between the aqueous radioactive phase (0.25 mL) and olive oil (0.7 mL). Up to 80% of the radioactive compound transferred into the olive oil. After separation by centrifugation, 0.5 mL of olive oil was used for further processing.

PLAGA and PCL nanocapsules were prepared according to the method of Fessi et al.[12] Briefly, 0.125 g of polymer was dissolved in 20 mL of acetone. After dissolution of the polymer, the radioactive oily phase was mixed with the acetonic phase. This radioactive organic solution was mixed with 50 mL of an aqueous solution containing 0.25 g of Pluronic F68 as a stabilizer. Acetone was evaporated under reduced pressure, and the final volume of the suspension was adjusted to 15 mL. The final polymer concentration in the suspension was 0.83% (w/v).

Indium Oxine Incorporation Ratio—Gel permeation chromatography was performed to assess the incorporation ratio of the radioactive compound in the nanocapsules. Briefly, an aliquot (0.1 mL) of the suspension was passed through a Sephadex G75 column (3 × 16 cm). The suspension was eluted with a 0.9% NaCl solution at a rate of 1 mL/min. Samples were collected at the bottom of the column, and the radioactive content of each sample was counted with a gamma counter. An aliquot of 0.1 mL of pure indium oxine solution was also eluted at the same conditions and served as a reference. The activity of each sample was expressed as a percentage of the total activity of the suspension counted before the sample was passed through the column.

Characterization of the Nanocapsules—The particle diameter was determined by photon correlation spectroscopy (Malvern 4600, Malvern, France) and the zeta-potential by LASER doppler velocimetry (Zetamaster, Malvern, France). All suspensions were diluted with a 10^{-6} M NaCl, pH 6.5 aqueous solution to maintain a constant ionic strength and an adequate concentration of particles.

Biodistribution Studies of the Indium Oxine Formulations—Studies were carried out in Swiss male mice weighing ≈20 g. A 0.1 mL volume of ^{111}In-labelled nanocapsules was injected by iv bolus into the tail vein. After various time intervals up to 96 h after administration, five mice per time point were sacrified by cervical fracture. The blood, liver, spleen, lungs, and kidneys were removed, washed with 0.9% NaCl solution, and accurately weighed. A group of five mice also received a 0.1 mL bolus dose of ^{111}In oxine aqueous solution by the same administration route. Along with standards prepared from the injected materials, the total radioactivity in the blood and the organs was measured on an auto-gamma well counter (Beckman Gamma 4000, Munich, Germany). The raw radioactive data were corrected for the half-life of the marker and presented as the percentage of the administered dose per gram of tissue. Statistical analysis was performed using the ANOVA test (Fischer, $p < 0.05$). The ^{111}In oxine half-life in the blood was calculated with a noncompartmental model.

Results and Discussion

Preparation and Labeling of the Nanocapsules—as shown in Table 1, the preparation method led to the production of PLAGA and PCL nanocapsules of 340 ± 12 and 454 ± 8 nm, respectively, as well as a high gamma emitter encapsulation efficiency. Both PLAGA and PCL nanocapsules gel permeation elution profiles show that >90% of the total ^{111}In oxine radioactivity was associated with the combined fractions of nanocapsules. Thus, the manufacturing process of labeled nanocapsules appears to be fairly independent of the polymer used. Although the gamma emitter is water soluble at this low concentration, most of it did not diffuse from the oil into the acetone/water phase during the manufacturing process, nor during the elution of the nanocapsules from the gel permeation column. The release of ^{111}In oxine upon high dilution in aqueous medium is fairly low. These results are not in favor of a diffusion process driven by Fick's Law but rather by the partition effect. The partitioning effect has also been considered as one of the driving force of the release process of drugs from the oily core of nanocapsules into outer phases, such as blood or intestinal fluids.[13] Moreover, it has been proposed that the intraocular penetration of drugs encapsulated in PCL nanocapsules after topical application is partly related to the partition of the drug between the oily inner phase of the capsules and the lipophilic corneal epithelium.[2]

The in vitro stability of the labeling of PCL nanocapsules in an albumin or buffer environment was investigated, earlier in our laboratory[14] and was shown to be high. The release kinetics of ^{111}In oxine from PCL nanocapsules during dialysis against albumin aqueous solution or phosphate buffer were compared with the free ^{111}In oxine solution, and the results showed that ^{111}In oxine diffuses very slowly out of the capsules into the albumin solution or the buffered outer phase. After 4 h, <5% of the aqueous (i.e., nonencapsulated) solution of the gamma emitter is still present into the dialysis bag compared with 100% of the encapsulated gamma emitter. This labeling technique, therefore, leads to high ^{111}In oxine entrapment efficiency and good stability against dilution and partitionning. The method is easy, fast, and reproducible. Because of these characteristics, the nanocapsules biodistribution can be followed-up after iv administration either by gamma scintigraphy imaging or by determining the gamma activity in the tissues after sampling. Moreover, the study can be performed for up to 96 h because of the relative long half-life of indium oxine. Finally, the gamma dose used under these conditions is relatively safe because the same low dose is used for diagnosis purposes in humans.

Biodistribution of Indium Oxine after Intravenous Administration—Depending on the drug dosage form (solution or nanocapsules), the distribution of the ^{111}In oxine appears to be very different. A comparison of the radioactivity detected in the blood and the other tissues at the earlier sampling time shows that most of the ^{111}In oxine solution was distributed into the blood and the liver (Figures 1 and 2). However, the administration of the PCL-encapsulated ^{111}In oxine led to a decrease in the blood activity and an increase in the liver activity compared with the solution (Figures 1 and 2). This effect was even more pronounced after administration of the PLAGA nanocapsules. In that latter case, 60−70% of the administered dose reached the liver. The activity level in other tissues, such as kidneys, lungs, and spleen, appeared to be unaffected by the encapsulation into one or the other polymer (Tables 2, 3, 4). These results are in good agreement with results obtained with ^{14}C-labeled colloidal carriers. Indeed, it was previously shown that a high proportion of the nanoparticles were quickly taken up by the liver after iv administration.[1,7−10,15] The plasma half-life of such carriers usually ranges from 1 to 10 min,[15] but could be extended up to >10 h if nanoparticles are precoated with Pluronic F108.[16]

In addition, it appears that the ^{111}In oxine radioactivity kinetics in the blood as well as in the liver are, quite similarly, independent of the dosage form. Indeed, the blood

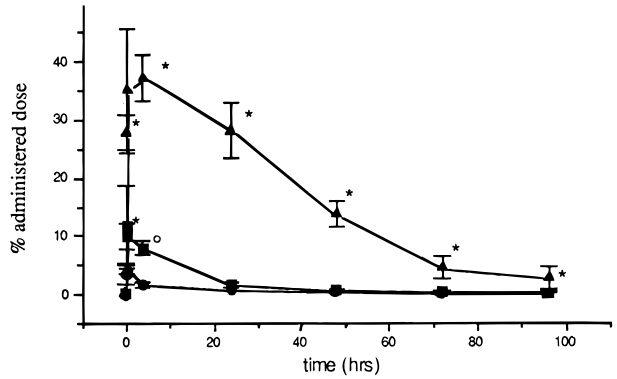

Figure 1—Chronological blood ^{111}In oxine activity after iv administration of the ^{111}In oxine solution, the PLAGA nanocapsules, and the PCL nanocapsules. Key: (●) PLAGA nanocapsules, (■) PCL nanocapsules, (▲) ^{111}In oxine solution; (*) = statistically different at 95% compared with PLAGA and PCL nanocapsules; (○) statistically different at 95% compared with PLAGA nanocapsules (one-factor ANOVA *F* test).

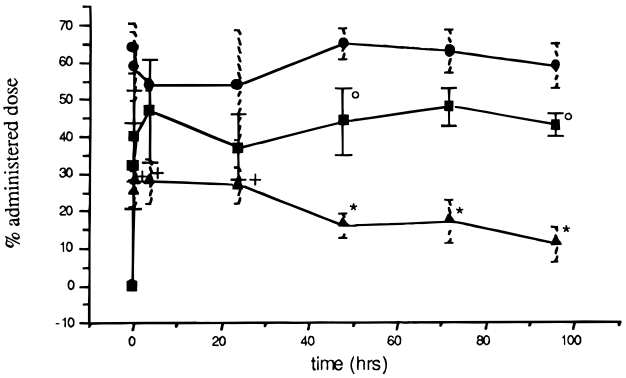

Figure 2—Chronological liver ^{111}In oxine radioactivity after iv administration of the ^{111}In oxine solution, the PLAGA nanocapsules, and the PCL nanocapsules. Key: (●) PLAGA labeled nanocapsules; (■) PCL nanocapsules; (▲) ^{111}In oxine solution; (*) statistically different at 95% compared with PLAGA and PCL nanocapsules; (○) statistically different at 95% compared with PLAGA ; (+) statistically different at 95% compared with PCL nanocapsules (one-factor ANOVA *F* test).

Table 2—Mean Percentages of ^{111}In Oxine Administered Dose in Lungs As a Function of Time after Administration[a]

	lungs		
time (h)	solution (SD)	PCL (SD)	PLAGA (SD)
0.00	0	0	0
0.25	7 (1.1)	18.5 (9.2)	6 (2.6)
0.50	5.4 (1.4)	7.5 (6.8)	4.8 (1.4)
4.00	4.7 (2.0)	4.8 (1.7)	4.0 (1.3)
24.00	5.1 (1.7)	2.9 (0.8)	1.5 (1.1)
48.00	2.9 (0.6)	1.1 (0.6)	1.6 (0.2)
72.00	1.2 (0.7)	0.9 (0.2)	1 (0.6)
96.00	0.8 (0.4)	0.8 (0.3)	1 (0.5)

[a] $n = 5$, values have been corrected according to the half-life of ^{111}In.

radioactivity after administration of the solution, the PCL nanocapsules, and the PLAGA nanocapsules followed a monoexponential decline with a half-lives of 23, 25, and 28 h, respectively. In the kidneys, the marker radioactivity declined slowly after administration of either the solution or the encapsulated forms. It has been previously demonstrated that after iv administration of an indium oxine solution, the indium oxine is quickly bound to the plasma transferin. After adsorption, the marker is taken up by the liver cells through the transferin receptor, and a progressive elimination of the marker from the blood occurs. Indeed, the elimination of the marker from the blood is driven by the availability of free transferin receptors. The

Table 3—Mean Percentages of ^{111}In Oxine Administered Dose in Spleen As a Function of Time after Administration[a]

	spleen		
time (h)	solution (SD)	PCL (SD)	PLAGA (SD)
0.00	0	0	0
0.25	8 (2.3)	1.6 (1.4)	2.8 (0.2)
0.50	7.9 (3.6)	1.4 (0.6)	2.7 (0.6)
4.00	13.3 (2.9)	1.8 (0.2)	2.9 (0.5)
24.00	4.8 (2.2)	1.7 (0.4)	3.4 (0.8)
48.00	2.5 (0.7)	2.3 (0.4)	3.6 (0.9)
72.00	9.4 (5.5)	2.2 (0.2)	3.6 (0.9)
96.00	7.2 (6.6)	2.0 (0.9)	3.3 (0.4)

[a] $n = 5$; values have been corrected according to the half-life of ^{111}In.

Table 4—Mean Percentages of ^{111}In Oxine Administered Dose in Kidneys As A Function of Time after Administration[a]

	kidneys		
time (h)	solution (SD)	PCL (SD)	PLAGA (SD)
0.00	0	0	0
0.25	11.2 (3.9)	5.5 (2.9)	4.1 (0.9)
0.50	8.1 (1.0)	7.9 (5.3)	3.5 (1.7)
4.00	10.4 (2.7)	8.8 (4.6)	2.8 (1.0)
24.00	11.2 (3.5)	7.5 (1.1)	3.3 (0.7)
48.00	7.5 (2.2)	5.1 (0.6)	2.4 (0.5)
72.00	4.8 (1.1)	5.5 (0.2)	2.0 (0.5)
96.00	4.0 (0.7)	4.5 (1.3)	2.0 (0.5)

[a] $n = 5$, values have been corrected according to the half-life of ^{111}In.

marker is continuously internalized and released into the liver cells where the complex is disrupted and the hydrophilic indium molecule is eliminated. However, the biodistribution process of encapsulated indium oxine appears to be very different. It seems that it mainly proceeds through a rapid liver uptake. The uptake of nanocapsules by the liver is nonspecific, mediated by the opsonization of the particles after contact with the plasma proteins, and leads to a higher uptake of the marker compared to the solution. After internalization of the nanocapsules, the indium oxine is released and reduced to its hydrophilic form. This form is then eliminated, as demonstrated by the activity in the kidneys.

Although a high proportion of both PLAGA and PCL nanocapsules were quickly taken up by the liver after iv administration, the biodistribution profiles of the two carriers were different. These differences are apparent in the blood and the liver distribution, whereas the distribution of the carriers in the other tissues does not seem to depend on the polymer used. Both the proportion of the carrier that was detected in the tissues as well as the elimination rate of the carrier from the tissues have to be considered. Indeed, until 20 h after administration of the nanocapsules, a higher gamma activity was detected in the blood after administration of PCL nanocapsules compared with PLAGA nanocapsules. However, the gamma emittor encapsulated either in PLAGA or in PCL nanocapsules was eliminated at a similar rate from the blood (25 and 28 h, respectively). In the liver, we found a higher proportion of ^{111}In oxine after administration of PLAGA nanocapsules than after administration of PCL nanocapsules but, again, both were eliminated at a slow and similar rate. Previously, it was demonstrated that particle size, zeta potential, and surface hydrophilicity greatly influence the kinetics of the elimination of particles from the blood.[4,5,13,15–18] Because following internalization into the liver the release rate from the two types of nanocapsules are similar, one can assume that the longer residence time of PCL nanocapsules in blood compared with that of the PLAGA nanocapsules

results from the lower liver uptake mediated by the adsorption of opsonins onto the carriers. Budhi et al.[5] have shown that larger polystyrene particles were eliminated from the blood faster than smaller ones. In our study, the size as well as the zeta potential of the two types of nanocapsules are similar. In addition, both polymers are considered to be hydrophobic. However, the glass transition temperature of the PCL is far lower that of the PLAGA (−53 and +42 °C, respectively). The PCL nanocapsules surface is therefore less rigid than the PLAGA nanocapsules surface at temperatures <42 °C (e.g., 37 °C, body temperature). Both types of nanocapsules have been prepared in the presence of Pluronic F68 as stabilizer, but the interaction of the stabilizer with the polymer during the formation of the polymeric wall could be influenced by the physical state of the polymer. The rubbery state of PCL at room temperature (≈20 °C, manufacturing temperature) could facilitate the anchor of the stabilizer into the polymeric wall. As already demonstrated,[19−21] the presence of block copolymers, such as Pluronic F68, promotes a decrease in the interaction with liver-specific opsonins, which in turn leads to a slower blood clearance and a lower liver uptake. Because the uptake of the two types of nanocapsules is similar in the spleen, it seems that the difference in the interaction with spleen-specific opsonins is less pronounced. The preferential adsorption of liver- and spleen-specific opsonins onto polymeric colloidal carriers has nevertheless not been demonstrated. Polymers with a glass transition temperature lower than the manufacturing temperature and/or 37 °C, like PCL, appear therefore to be a potential interesting polymer in the development of colloidal carriers. Because of its rubbery state at 37 °C, this polymer could be an alternative to PLAGA. In particular, higher plasma drug level could be achieved for a prolonged period of time after administration of PCL colloidal carriers prepared only with hydrophilic surfactant. This procedure could be an alternative to stealth PLAGA colloidal carriers, at least for the first 24 h, during which the hydrophilic part is covalently bound onto the polymer.

References and Notes

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