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Drug targeting with nanoparticles

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SUMMARY

Nanoparticles are colloidal polymeric particles (size < 1000 nm) to which drugs are bound by sorption, incorporation, or chemical binding. After intravenous injection they normally distribute into the organs of the reticuloendothelial system (liver, spleen, lungs, bone marrow). However, their body distribution can be altered by coating with surfactants or with physiological components such as serum complement factors. The influence of these coatings on the body distribution and possible mechanisms for the alteration of this distribution are discussed. Differently coated nanoparticles can be used for the targeting of bound drugs to tumors, to the brain, and to inflamed areas in the body.

INTRODUCTION

Modern drug therapy requires that a drug is reaching the site of action in the most efficient way possible. This goal can be achieved to a great extent by site specific - targeted - delivery (1, 2). Drug targeting may be performed by using colloidal drug carriers (2). These carriers include microemulsions, liposomes, niosomes, and nanoparticles. Nanoparticles are colloidal polymeric particles ranging in size from 10 to 1000 nm. The polymers that may be employed include artificial as well as biopolymers. Drugs are bound to nanoparticles by ad- and absorption, incorporation, or chemical binding. The term nanoparticles includes monolithic matrix type systems (3) as well as nanocapsules with a shell-like wall (4). Nanoparticles posses the advantage over other colloidal drug systems that they are more stable, especially in body fluids after different ways of administration.

BODY DISTRIBUTION OF NANOPARTICLES AFTER I.V. INJECTION

In order to achieve effective drug targeting, the drug carrier has to reach the target area in sufficient concentrations while avoiding high levels in other parts of the body. For this reason, the body distribution of the carrier must be known and must be optimized. Carriers with particles sizes above 5-15 μm and large agglomerates of smaller particles are filtered out by the first capillary bed they traverse, i.e. after i.v. injection the lung. Dispersed smaller particles, including small emulsions and microemulsions, liposomes, niosomes, and nanoparticles, are removed by the cells of the reticuloendothelial system (RES) within 5 to 10 minutes, mainly by the liver (about 60 to 90%), the spleen (2-20%), a varying amount by the lungs, and about 0.05 to 1% by the bone marrow (5). As a consequence of this rapid removal by the RES, less than 1% of the injected dose stays in the blood circulation after 15 to 30 minutes.

The body distribution can be altered significantly by coating with certain substances including serum components (6) and surfactants (7-10) or by chemical alteration of the nanoparticle surface (11). Two lead substances for this alteration of the body distribution so-far have been identified - poloxamine 908 (7, 9, 10) and polysorbate 80 (9). Poloxamer 908 significantly reduces RES uptake, especially liver uptake (down to 25%) and drasticly increases the amount residing in the blood form below 1% to about 25% after 30 min (7, 9). The other lead substance - polysorbate 80 - increases the concentration in the non-RES organs and

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tissues (9).

These results show that the body distribution is governed by particle size and for colloidal particles by the surface properties. Rapidly after contact with serum nanoparticles are coated with serum opsonins. Opsonins are serum components that coat invading foreign particulates such as bacteria, etc. to promote their phagocytotic uptake by macrophages or their interaction with the immune system. As shown by PAGE, the type of opsonin that is absorbed is dependent on the surface properties of the particles (12).

Hence, particles with different surface properties will adsorb different opsonins. Uncoated particles adsorb a great variety of opsonins whereas coated particles adsorb much less but special opsonins (12).

TARGETING OF DRUGS AND PEPTIDES ACROSS THE BLOOD BRAIN BARRIER WITH NANOPARTICLES

As already mentioned, coating of nanoparticles with polysorbate 80 enhances their distribution to non-RES organs. This substance also leads to a rapid uptake by in vitro cultures of bovine blood vessel endothelial cells (13). Moreover, recently it was shown that a peptide - dalargin - was transported accross the blood brain barrier of mice after sorption to nanoparticles and overcoating with polysorbate 80 and exhibited a pharmacolocigal effect that was comparable to direct CNS injection (14). In contrast, after i.v. injection of dalargin in form of a simple solution this endorphine drug is not able to pass through the blood brain barrier and does not exhibit an analgesic effect. Without polysorbate 80-coating of the drug-loaded nanoparticles also no effect was achieved. The mechanism of the nanoparticle-facilitated transport was explained by using fluorescence and transmission electron microscopy: Isothiocyanate-dextran-labelled nanoparticles were observed by both types of microscopy within brain blood vessel endothelial cells as well as in Purkinje cells of the brain after i.v. injection to mice after coating with polysorbate 80. Without polysorbate 80-coating the particles remained in the blood vessels (14).

TARGETING TO TUMORS

Nanoparticles were shown to accumulate in a number of tumors (15, 16). The reason for this could be the high leakyness of tumor blood vessels and a possible higher endocytotic activity of tumor-associated cells in the blood vessels or in their vincinity. Nanoparticles of a number of antitumor drugs (17-20). Although in some cases (17, 19) the enhanced effiacy also were able to considerably enhance the efficacy was accompanied with an increase in toxicity, in other cases even a decrease in tocixity was observed (21, 22).

Recent results with mitoxantrone showed that the efficacy against different types of tumors may be dependent on the delivery system (20). Mitoxantrone nanoparticles made of poly(butyl cyanoacrylate) were more effective against a solid B 16 melanoma tumor, whereas mitoxantrone liposomes were more effective against P 388 leucemia. Again the targeting to these tumors may have depended on the surface properties of these carriers.

TARGETING TO HIV-INFECTED CELLS

Macrophages represent a major target cell of HIV after infection and may represent a reason for the long course of AIDS. Since nanoparticles accumulate especially in HIV-infected macrophages (23) they seem to represent a promising delivery system for the cure of this desease.

TARGETING TO INFLAMED AREAS OF THE BODY

The enhanced accumulation of nanoparticles in inflamed areas of the body was observed in the eyes (24) as well as in anthritic joints (25), and artificial air pouches (26). For this reason, they also hold promise for inflammation targeting.

OTHER USES OF NANOPARTICLES

Other uses of nanoparticles include peroral (27), ophthalmic (28), lymphatic administration (29), and their use as adjuvants of vaccines (1, 2). After peroral administration they enhanced the bioavailability of a number of drugs including vincamine, insulin (1,2) and avarol (30). In the eye the reduction of the intraocular pressure was prolonged very considerably after administration of pilocarpine bound to nanoparticles compared to the aqueous solution (28). The use of nanoparticles as an adjuvant for vaccines enhanced the antibody response against a number of antigens and the protection against infection (1,2). The enhancement of the antibody response was especially pronounced with inactivated HIV-1 and HIV-2 split whole virus vaccines. Nanoparticles also increased the in vitro stability of influenza vaccines. These results demonstrate that nanoparticles

hold promise as colloidal drug carriers for a variety of therapeutical and preventive medical applications.

REFERENCES

1. Kreuter, J. (1992) Nanoparticles - preparation and applications, in Donbrow, M. (ed.) Microcapsules and Nanoparticles in Medicine and Pharmacy, CRS Press, Boca Raton, pp. 125-148.
2. Kreuter, J. (ed.) (1994) Colloidal Drug Delivery Systems, M. Dekker, New York.
3. Couvreur, P., Kante, B., Roland, M., Guiot, P., Bauduin, P., and Speiser, P. (1979) Polycyanoacrylate nanocapsules as potential lysosomotropic carriers: preparation, morphological and sorptive properties, J. Pharm. Pharmacol. **31**, 331-332.
4. Al Khouri Fallough, N., Roblot-Treupel, L., Fessi, H., Devissaguet, J.Ph., and Pusieux, F. (1986) Development of a new process for the manufacture of polyisobutylcyanoacrylate nanocapsules, Int. J. Pharm. **28**, 125-132.
5. Kreuter, J. (1983) Evaluation of nanoparticles as drug delivery systems II: Comparison of the body distribution of nanoparticles with the body distribution of microspheres (diameter > 1 μm), liposomes, and emulsions, Pharm. Acta Helv. **58**, 242-250.
6. Borchard, G. and Kreuter, J. (1993) Interaction of serum components with poly(methyl methacrylate) nanoparticles and the resulting body distribution after intravenous injection in rats, J. Drug Target. **1**, 21-27.
7. Illum, L. and Davis, S.S. (1984) The organ uptake of intravenously administered colloidal particles can be altered using a non-ionic surfactant (poloxamer 338), FEBS Letters **167**, 79-82.
8. Illum, L., Davis, S.S., Müller, R.H., Mak, E., and West, P. (1987) The organ distribution and circulation time of intravenously injected colloidal carriers sterically stabilized with a blockpolymer - poloxamine 908, Life Sci. **40**, 367-374.
9. Tröster, S.D., Müller, U., and Kreuter, J. (1990) Modification of the body distribution of poly(methyl methacrylate) nanoparticles in rats by coating with surfactants, Int. J. Pharm, **61**, 85-100.
10. Tröster, S.D. and Kreuter, J. (1992) Influence of the surface properties of low contact angle surfactants on the body distribution of ^{14}C-poly(methyl methacrylate) nanoparticles, J. Microencapsul. **9**, 19-28.
11. Borchard, G., Brandriss, S., Kreuter, J., and Margel, S. (1994) Body distribution of ^{75}Se-radiolabeled silica nanoaparticles covalently coated with ω-functionalized surfactants after intravenous injection in rats, J. Drug Target. **2**, 61-77.
12. Blunk, T., Hochstrasser, D., Sanchez, J.-C., Müller, R.H. (1993) Colloidal carriers for intravenous drug targeting - plasma absorption patterns on surface-modified latex particles evaluated by 2-D-polyacryamide gel electrophoresis, Electrophoresis **14**, 1382-1387.
13. Borchard, G., Audus, K.L., Shi, F., and Kreuter, J. (1994) Uptake of surfactant-coated poly(methyl methacrylate) - nanoparticles by bovine brain microvessel endothelial cell monolayers, Int. J. Pharm. **110**, 29-35.
14. Alyautdin, R., Gothier, D., Petrov, V., Kharkevich, D., and Kreuter, J. (in press) Analgesic activity of the hexaptide dalargin adsorbed on the surface of polysorbate 80-coated poly(butyl cyanoacrylate) nanoparticles, Eur. J. Pharm. Biopharm.
15. Grislain, L., Couvreur, P., Lenaerts, V., Roland, M., Deprez-Decampeneere, D., and Speiser, P. (1983) Pharmacokinetics and distribution of a biodegradable drug carrier, Int. J. Pharm. **17**, 335-345.
16. Gipps, E.M., Arshady, R., Kreuter, J., Groscurth, P., and Speiser, P.P. (1986) Distribution of polyhexyl cyanoacrylate nanoparticles in nude mice bearing human osteosarcoma, J. Pharm. Sci. **75**, 256-258.
17. Brasseur, F., Couvreur, P., Kante, B., Deckers-Passau, L., Roland, M., Deckers, C., and Speiser, P. (1980) Actinomycin D adsorbed on polymethylcyanoacrylate nanoparticles: Increased efficiency against an experimental tumor, Eur. J. Cancer **16**, 1441-1445.
18. Kattan, J., Droz, J.-P., Couvreur, P., Marino, J.-P., Boutan-Laroze, A., Rougier, P., Brault, P., Vranckx, H., Grognet, J.-M., Morge, X., and Sancho-Garnier, H. (1992) Phase I clinical trial and pharmacokinetic evaluation of doxorubicin carried by polyisohexylcyanoacrylate nanoparticles, Invest. New Drugs **10**, 191-199.
19. Kreuter, J. and Hartmann, H.R. (1983) Comparative study on the cytostatic effects and the tissue distribution of 5-fluorouracil in a free form and bound to polybutylcyanoacrylate nanoparticles in sarcoma 180-bearing mice, Oncology **40**, 363-366.
20. Beck, P., Kreuter, J., Reszka, R., and Fichtner, I. (1993) Influence of polybutylcyanoacrylate nanoparticles and liposomes on the efficacy and toxicity of the anticancer drug mitoxantrone in murine tumor models, J. Microencapsul. **10**, 101-114.
21. Couvreur, P., Kante, B., Grislain, L., Roland, M., and Speiser, P. (1982) Toxicity of polyalkylcyanoacrylate nanoparticles II: Doxorubicin-loaded nanoparticles, J. Pharm. Sci. **71**, 790-792.
22. Couvreur, P., Grislain, L., Lenaerts, V., Brasseur, F., Guiot, P., and Biernacki, A. (1986) Biodegradable polymeric nanoparticles as drug carrier for antitumor agents, in Guiot, P. and Couvreur, P. (eds.) Polymeric Nanoparticles and Microspheres, CRC Press, Boca Raton, pp. 27-93.

23. Schäfer, V., v. Briesen, H., Andreesen, R., Steffan, A.-M., Royer, C., Tröster, S., Kreuter, J., and Rübsamen-Waigmann, H. (1992) Phagocytosis of nanoparticles by human immunodeficiency virus (HIV)-infected macrophages: A possibility for antiviral drug targeting, Pharm. Res. **9**, 541-546.

24. Diepold, R., Kreuter, J., Guggenbuhl, P., and Robinson, J.R. (1989) Distribution of poly-hexyl-2-cyano-[3-^{14}C] acrylate nanoparticles in healthy and chronically inflamed rabbit eyes, Int. J. Pharm. **54**, 149-153.

25. Illum, L., Wright, J., and Davis, S.S. (1989) Targeting of microspheres to sites of inflammation, Int. J. Pharm. **52**, 221-224.

26. Alpar, H.O., Field, W.N., Hyde, R., and Lewis, D.A. (1989) The transport of microspheres from the gastrointestinal tract to inflammatory air pouches in the rat, J. Pharm. Pharmacol. **41**, 194-196.

27. Kreuter, J. (1991) Peroral administration of nanoparticles, Adv. Drug Deliv. Rev. **7**, 71-86.

28. Diepold, R., Kreuter, J., Himber, J., Gurny, R., Lee, V.H.K., Robinson, J.R., Saettone, M.F., and Schnaudigel, O.E. (1989) Comparison of different models for the testing of pilocarpine eyedrops using conventional eyedrops and a novel depot formulation (nanoparticles), Gre afe's Arch. Clin. Exp. Ophthalmol. **227**, 188-193.

29. Maincent, P., Thouvenot, P., Amicabile, C., Hoffman, M., Kreuter, J., Couvreur, P., and Devissaguet, J.P. (1992) Lymphatic targetting of polymeric nanoparticles after intraperitoneal administration in rats, Pharm. Res. **9**, 1534-1539.

30. Beck, P.H. Kreuter, J., Müller, W.E.G., and Schatton, W. (1994) Improved delivery of avarol with poly-butylcyanoacrylate - nanoparticles, Eur. J. Pharm. Biopharm. **40**, 134-137.