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Minireview

Nanoparticles and microparticles for drug and vaccine delivery

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ABSTRACT

Nanoparticles are polymeric particles in the nanometer size range whereas microparticles are particles in the micrometre size range. Both types of particle are used as drug carriers into which drugs or antigens may be incorporated in the form of solid solutions or solid dispersions or onto which these materials may be adsorbed or chemically bound. These particles have been shown to enhance the delivery of certain drugs across a number of natural and artificial membranes. In addition, the particles were shown to accumulate in areas of the intestine that appear to be the Peyer's patches. Possibly because of the combination of both effects these particles were able to significantly improve the bioavailability of some drugs after peroral administration in comparison with solutions. Recently nanoparticles coated with polysorbate 80 enabled the passage of small peptides and other drugs across the blood–brain barrier and the exhibition of a pharmacological effect after intravenous injection. Without the use of this type of nanoparticles the drugs did not cross this barrier and yielded no effect.

Key words: Gastrointestinal tract; Peyer's patches; blood–brain barrier.

INTRODUCTION

Nanoparticles are solid particles ranging in size from 10 nm to 1000 nm (1 μm). They consist of macromolecular materials in which the active principle (drug or biologically active material) is dissolved, entrapped, or encapsulated, and/or to which the active material is adsorbed or attached (Kreuter, 1994*a*, *b*). Microparticles are similar particles in the size range of 1 μm to 1000 μm (1 mm). The number of different types of these particles and of their manufacturing methods is even larger than that of nanoparticles. Microparticles have been described in a large number of detailed reviews before (Nixon, 1976; Deasy, 1984; Donbrow, 1992) and, therefore, will be reviewed here only marginally and in relation to nanoparticles. Nanoparticles can be made by a number of different manufacturing methods (Kreuter, 1994*a*, *b*). The most important methods are listed in the Table. Nanoparticles as well as microparticles are used as drug carriers or as adjuvants for vaccines. The drugs or antigens may be incorporated into the particles in form of a solid dispersion or a solid solution (Kreuter, 1983), or they may be bound to the particle surface by physical adsorption and chemical

Table 1. *Main manufacturing methods for nanoparticles*

Method	Polymers
Emulsion polymerisation	Poly(methyl methacrylate)
	Poly(alkyl cyanoacrylates)
	Poly acrylate-copolymers
Interfacial polymerisation	Poly(alkyl cyanoacrylates)
Desolvation	Albumin
	Gelatin
	Cellulose derivatives
Solvent evaporation	Polylactic acid
	Polylactic acid-copolymers
Solvent deposition	Polylactic acid
	Polylactic acid-copolymers

From Kreuter, 1994*a*, *b*.

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binding. Nanoparticles may be administered by different routes. These include intravenous, intramuscular, and subcutaneous injection, as well as peroral, ophthalmic and even transdermal administration (Cappel & Kreuter, 1991). Of special therapeutic interest is their ability to accumulate in certain solid tumours, inflamed areas of the body, macrophages (Kreuter, 1994*a*), lymphatic tissues (Maincent et al. 1992), and their ability to enable passage of peptides across the blood–brain-barrier (Alyautdin et al. 1995; Kreuter et al. 1995).

BODY DISTRIBUTION OF NANOPARTICLES

Nanoparticles like other colloidal drug carriers are able to pass through all capillaries after injection into the blood stream (Kreuter, 1994*a*). In contrast, microspheres with a size above about 4–10 μm are mechanically trapped and filtered out by the first capillary bed that they traverse which is the lung after intravenous injection. Nanoparticles and other colloids, however, in most cases are rapidly taken up by the macrophages of the reticuloendothelial system (RES). Alternatively, this system is also called the mononuclear phagocytic system (MPS). This latter expression, however, neglects the involvement of the endothelial cells in the process of particle removal from the bloodstream, a process that happens occasionally (Kreuter et al. 1995).

As a consequence of their rapid removal from the circulation, after 30 min after i.v. injection about 60–90 % of the particles end up in the liver, 2–20 % in the spleen, a varying amount in the lungs, and about 0.1–1 % in the bone marrow. A decrease in RES-uptake and especially in liver uptake, combined with a considerable enhancement in blood circulation time, can be achieved by coating the particles with surfactants (Tröster et al. 1990; Kreuter, 1994*a*) or by PEGylation of the nanoparticle polymer (Gref et al. 1994). The lead substance in decreasing liver uptake and increasing blood circulation time is the surfactant poloxamine 908 (Kreuter, 1994*a*). Another lead substance for altering the body distribution is polysorbate 80. This surfactant is not as efficient in enhancing the blood circulation time, but overall is the optimal substance in enhancing the uptake into other organs (Jani et al. 1990; Kreuter, 1994*a*). It has to be noted, however, that uptake in this context does not necessarily mean passage across the blood capillary walls into this organ. It can also mean adhesion to the blood capillary wall in these organs or endocytosis by the endothelial cells. As will be discussed below, polysorbate 80 also leads to the uptake of nanoparticles by brain–blood vessel endothelial cells and enables a delivery of peptides across the blood–brain barrier (Kreuter et al. 1995). The coating of nanoparticles by surfactants also monitors the uptake of the particles into solid tumours (Beck et al. 1993) and into blood macrophages (Schäfer et al. 1992). Both processes are of paramount therapeutic importance but so far have not been studied in sufficient detail.

PERORAL ADMINISTRATION

Nanoparticles can improve the peroral delivery of a number of drugs (Maincent et al. 1986; Beck et al. 1994; Kreuter, 1994*a*). Accordingly, the bioavailability of vincamine was enhanced 1.75-fold (Maincent et al. 1986) and that of avarol even 9-fold (Beck et al. 1994) in comparison with a solution after binding to nanoparticles. In addition, the encapsulation of insulin into poly(butylcyanoacrylate) nanocapsules enabled the peroral delivery of insulin and lead to a significant prolonged reduction of the blood glucose levels in fasted diabetic rats (Damgé et al. 1988; Kreuter, 1994*a*).

There are 3 possibilities for the mechanism of gastrointestinal uptake of nanoparticles: (1) intracellular uptake; (2) intracellular/paracellular uptake; and (3) uptake via the M-cells and Peyer's patches in the gut (Kreuter, 1991, 1994*a*). The extent and pathway of nanoparticle uptake was different in different parts of the intestine (Michel et al. 1991). Nevertheless, although all 3 above-mentioned uptake pathways are involved in the gastrointestinal uptake of intact nanoparticles, the major pathway seems to be uptake via the M cells and Peyer's patches in the gut (Kreuter, 1991, 1994*a*). The uptake into the Peyer's patches seems to be restricted to particles below 10 μm (Eldridge et al. 1990). Particles above 5 μm remained in the Peyer's patches, whereas those below this size were transported within macrophages through the efferent lymphatics. The uptake increased with increasing hydrophobicity (Eldrige et al. 1990) and decreasing particle size (Jani, 1989, 1990; Kreuter, 1994*a*). In addition to drug delivery via uptake of intact particles, enhanced drug delivery was also observed through a direct interaction of the nanoparticles with a membrane without transport of the particles through this membrane (Kreuter et al. 1983). Peroral drug delivery with nanoparticles, therefore, may be further enhanced by addition of mucoadhesive substances to the nanoparticles (Kreuter, 1994*a*).

DELIVERY OF PEPTIDES ACROSS THE BLOOD–BRAIN BARRIER WITH NANOPARTICLES

Poly(butylcyanoacrylate) nanoparticles coated with polysorbate 80 enabled the delivery of a hexapeptide, dalargin, across the blood–brain barrier following intravenous injection (Alyautdin et al. 1995; Kreuter et al. 1995). The endorphin dalargin exhibits an analgesic effect after direct injection into the brain but is not able to cross the blood–brain barrier. Dalargin adsorbed to the nanoparticles and overcoated with polysorbate 80 exhibited a similar, dose-dependent analgesic effect in mice after intravenous injection. Analgesia could be totally blocked by pretreatment with naloxone. All controls, including a simple mixture of the 3 component nanoparticles, dalargin, and polysorbate 80 without allowing sufficient time for the drug and for the surfactant to adsorb on the nanoparticles, exhibited no effect (Alyautdin et al. 1995). Similar observations were made with other potentially analgesic drugs that normally are unable to cross the blood–brain barrier such as loperamide and a tetrapeptideamide.

Fluorescence microscopy and transmission electron microscopy using FITC-dextran 70000-labelled nanoparticles indicated occurrence of an endocytotic uptake of these particles by the brain blood vessel endothelium (Kreuter et al. 1995). Tissue culture experiments with bovine blood vessel endothelial cells using ^{14}C-labelled nanoparticles lead to similar conclusions (Borchard et al. 1994).

CONCLUSIONS

Nanoparticles represent promising delivery systems for a number of applications especially after parenteral and peroral administration. They may allow an improvement of the peroral bioavailability of a number of poorly absorbable drugs as well as the delivery of peptides and other drugs to the brain following intravenous injection.

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