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Preface

Pharmaceutical nanoparticles—From their innovative origin to their future

Prof. Speiser (right) receives the Life Time Achievement Award from Prof. Gurny/Geneva at the EWPS meeting in Berlin.

We use many objects useful in daily life whose origins we do not know, neither who invented them nor where they originated. With the passing of time such knowledge is often lost anyway. Ask just for fun your PhD students where and when were the first pharmaceutical nanoparticles invented?

It can be legitimately claimed that it all started at the ETH in Zurich, Switzerland in the laboratories of Prof. Peter P. Speiser. He became Associate Professor of Pharmaceutical Technology there in 1961 and full Professor some 7 years later. In the start up phase of his research in 1965 he concentrated on transferring emulsions from micrometer size to ultrafine nanodroplets by intensive emulsification, and he worked also on the chemical modification of surfactants and micelles and subsequently polymerised these systems.

It was by chance that Gerd Birrenbach applied for a PhD in the research group of Prof. Speiser. From the various topics proposed by Prof. Speiser, he selected the topic of the production of sera and vaccines with prolonged action by their incorporation in nanosized structures. After almost 4 years of intensive research Birrenbach presented his thesis: "Über Mizellpolymerisate, mögliche Einschlußverbindungen (Nanokapseln) und deren Eignung als Adjuvantien" (About polymerized micelles, potential inclusion complexes (nanocapsules) and their use as adjuvants) (Birrenbach, 1973). The word "nanocapsules" was used for the first time and pharmaceutical polymeric nanoparticles were born. Prof. Speiser continued intensively his research in nanoparticles until his retirement in 1998, capping more than a quarter of a century of successful research in nanoparticles. The details have been captured in a review by another co-worker Jörg Kreuter (Kreuter, 2007).

Prof. Speiser's work stimulated many activities in research of nanoparticulate systems in the broadest sense. Pharmaceutical industry took up his ideas with enthusiasm at the beginning of the 1980s and research centres were created. It became evident some years later that nanosystems are complex, and the way to the market longer than expected. Much basic academic research was required to establish these systems as clinically useful. Nevertheless, liposomes made it to the market with the first products around 1990 (e.g. Alveofact, a liposomal lung surfactant). The number of pharmaceutical products is however still lower than early expectations. One limiting factor is sometimes the high cost of daily treatment, which health systems are not prepared to cover. Nanotechnology can do much, but the technological advances must be paid for.

After the initial enthusiasm for nanoparticles in the 1980s, more sober assessments led to some disillusion. This changed around the millenium, when nanoparticles provided one solution for the formulation of patient-convenient or superior performing drugs. Traditional formulation approaches generally failed with the challenging new molecules such as very poorly soluble drugs. It was the return of nanotechnology, of course also stimulated by the success of nanotechnology in many other areas of daily life (from nanocoating of glass surfaces to nano polish for cars). With the preparation of drug nanocrystals a new nanoparticle entered the market in the year 2000 (product Emend). The product Tricor developed to a block buster with more than 1 billion $ annual sales in the US to one of the most successful pharmaceutical nano products. Nanoformulations have also been used as a tool for product life cycle management, an example of which is Tricor.

Pharmaceutical biotechnology is only possible in many areas by applying nanoparticles or nanotechnology. In gene therapy nanoparticulate vectors play a major role, and are also covered in this special issue. Transfection is achieved by positively charged liposomes, but also polymeric or lipid nanoparticles. In contrast to natural viruses, the synthetic systems are well defined and can be produced in a more controlled way.

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Prof. Speiser sees the future of nanotechnology mainly to formulate challenging, high value molecules, and for diseases for which no other treatment exists. Nanoparticles open the possibility to cross the blood–brain barrier and to treat diseases such as certain cancers for the first time efficiently. This was nicely proven by the Tween 80 surface-modified polymeric nanoparticles developed by Jörg Kreuter (Frankfurt), PhD student of Prof. Speiser and belonging to his academic family. Speiser's polyacrylcyanoacrylate nanoparticles were also further developed by Patrick Couvreur of the Université de Paris-Sud, a system at present in clinical trials in cancer patients.

Important pre-requisites for the introduction of nanoparticles are the accepted regulatory status of excipients, and the possibility of cost-effective large-scale production, using production lines acceptable by the regulatory authorities. This can easily fulfilled by nanoemulsions, previously used for parenteral nutrition (Lipofundin, Intralipid), and nowadays used for i.v. delivery of drugs such as diazepam, etomidate and propofol. A consequent next step was the exchange of the liquid lipid (=oil) of the nanoemulsions by solid lipids, leading to the solid lipid nanoparticles (SLN), at the beginning of the 1990s and nanostructured lipid carriers (NLC), developed at the turn of the millennium. Some of these systems are now undergoing Phase I first clinical trials.

Another important point, outlined by Prof. Speiser in his opening speech to the 2008 European Workshop on Particulate Systems (EWPS, www.ewps.org), is the intellectual property situation. Nobody can file for a second time general nanoparticle patents, but there is an unlimited field for filing special embodiments and variations of nanoparticles with special properties. No company will develop a non-protected nanoformulation if it can be immediately copied by competitors. Therefore scientists should protect their ideas to see them finally on the market for the benefit of patients.

What can we expect in the next decade from nanoparticles? Definitely there will be quite a number of nanocrystal drug products entering the market. Most likely we will have the first products based on lipid nanoparticles, especially because they have already entered the cosmetic market world wide, with the first products in 2005 (Dr. Rimpler, Germany). It should be recalled that liposomes first entered the market in a cosmetic product (1986, Capture, by Dior) before appearing in the clinic. Polymeric nanoparticles will also make it to the market, first limited to severe diseases like cancer. Nanoparticles will also play a major role in gene therapy, bearing in mind that gene therapy as routine treatment is a long way down the road. The next decade in pharma products will belong to pharmaceutical biotech products, nano products, and combinations of both of them.

A final point: the nanotoxicity discussion. There are increasing concerns about the toxicity of nanoparticles (e.g. EU cosmetic laws about declaration of "bioresistant" nanoparticles <100 nm in cosmetic products). Mankind tends to extremes, from recognising the ultimate good of nanotechnology to a condemnation of it. Here careful evaluation is necessary, scientists need to contribute to the debate through the provision of unbiased, neutral, realistic information to the public. Each technology has advantages and disadvantages. Nobody would abolish electricity because a child can be electrocuted by putting the fingers into a socket. Therefore the positive sides of nanotechnology need to be exploited for the benefit of patients, considering carefully the risks and the opportunities. By doing this, the future will belong to nanoparticles and nanotechnology. As he has been the father of many nanosystems and because it started in his laboratories Prof. Speiser was the appropriate first recipient of the "EWPS Life Time Achievement Award for Pioneering Work on Nanosystems" at the European Workshop on Particulate Systems held in Berlin 2008 (www.ewps.org). It was out of this meeting that the present special issue has grown, and we thank all those who contributed to it.

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