Targeting Biotech Drugs
Nanosized Lipid Particles versus Drug Nanocrystals

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Nanotechnology and, in particular, the development of nanosized delivery systems for biotech drugs (namely peptides, proteins and oligonucleotides), is a multidisciplinary field undergoing exponential development in the latest years [1-3]. The rate of these developments has been dictated in parallel by the progress of biotechnology. Biotechnological techniques have expanded the variety of therapeutically active biotech drugs, which are nowadays the molecules of primary interest in the pharmaceutical market. Peptides, proteins and oligonucleotides have been formulated in innovative colloidal delivery systems with the aim to [4-7]: (i) achieve a modified-release profile (controlled, prolonged or targeted depending on the therapeutic needs), (ii) reduce adverse-side effects due to a non-targeted distribution and delivery to the site of action, (iii) increase drug bioavailability, (iv) increase patient compliance to the therapeutics, (v) optimize a more comfortable administration route, as well as to (vi) decrease the cost of the therapeutics if possible [3]. The present review presents the usefulness of nanosized lipid particles and the drug nanocrystal systems to target biotech drugs intended for different administration routes.

Nanosized lipid particles are derived from o/w emulsions by replacing the liquid lipid (oil) by a solid lipid, i.e. a lipid being solid at room and simultaneously at body temperature [2]. In the beginning of the nineties the so-called solid lipid nanoparticles (SLN™) have been developed. Due to their solid matrix, drug release from these particles can be modulated, which could be exploited to optimize the blood profile. The distinct advantage of SLN is that they fulfil the pre-requisites to market a product. The excipients used are of recognized status, i.e. all lipids and surfactants used for oral and parenteral dosage forms can be employed. The excipients are of low costs and large scale production is possible by high pressure homogenization lines, which are already approved for pharmaceutical industry, for example for the production of parenteral emulsions such as Intralipid®. At the turn of the millennium, a second generation of nanosized lipid particles was developed. These are the nanostructured lipid carriers (NLC™), which are prepared not from a solid lipid only but from a blend of a solid lipid with an oil and can be used for the same purposes as SLN. The main advantage of NLC over SLN is the higher loading capacity due to a less organized lipid matrix creating a higher number of voids and vacancies available for drug entrapment/encapsulation.

Another approach to formulate poorly soluble drugs for oral and parenteral administration is the development of drug nanocrystals [2,5]. This alternative can be used for drugs for which the dissolution velocity in water is an absorption/bioavailability limiting step. It is well known that micronization of a drug powder increases its dissolution velocity. For this purposes, drug nanocrystals decrease in size one dimension further by means of a nanonization process. Another interesting feature is the increased saturation solubility of nanonized drugs compared to micronized or larger sized powders. Both increased surface area and increased saturation solubility enhance the dissolution velocity. For some drugs, the drug nanocrystal principle proved to be highly effective. For example, the oral bioavailability of danazol could be improved from 5.1% to 82.3% when replacing the microsuspension by nanosuspension [8].
Precipitated drug particles exhibit very often the tendency to continue crystal growth to the size of micrometer crystals. Depending on the precipitation conditions these particles can be completely amorphous, partially amorphous or completely crystalline. To ensure the long term stability of the crystalline status, the easiest approach is to have particle in the low energy crystalline modification. Amorphous or partially amorphous particles bear the risk re-crystallization of this amorphous fraction followed by decrease in bioavailability. Both problems, avoidance of further crystal growth and uncertainty of crystalline/amorphous state, can be solved by combining the precipitation with a second high energy addition step. The precipitated particle suspension is subsequently homogenized which can basically preserve the size range of the particles obtained after the precipitation step. This annealing process converts all precipitated particles to crystalline material. This removes all concerns about physical stability of amorphous material. The drug nanocrystals possess a definite crystalline state. In comparison to the nanosized lipid particles, drug nanocrystals have the advantage of being easier to produce. Microsuspensions can be transferred to nanosuspensions simply by pearl milling or by high pressure homogenization [2]. On the other hand, both SLN and NLC are composed of a lipid matrix, and lipids are known to promote absorption of some drugs through e.g. oral route [9]. Therefore, another purpose of the present review was to compare the efficiency of nanosized lipid particles versus drug nanocrystals to enhance bioavailability of biotech drugs with practical relevance for potential market products. The various analytical techniques to characterise these colloidal carriers and to predict their long-term stability are also addressed, i.e. means Coulter Counter technology, photon correlation spectroscopy, laser diffractometry, light and electron microscopy and zeta potential measurements. The techniques are critically reviewed regarding advantages and limitations.

The authors present a new approach to formulate biotech compounds using nanosized lipid particles and the drug nanocrystal technology. The applications of such production procedures as feasible approaches systems for nanomedicine are emphasized. Parameters to control the nanosystem composition, its size, shape and functionality are discussed and the biological effects of well-optimized nanoparticulate systems are also addressed when delivered by different administration routes. The background knowledge of these studies will be of great relevance in the design of safer nanosystems for biotech drugs. Analysis of the theoretical and practical applications of these systems is an important aspect that will enable rapid development in this emerging field of nanotechnology.

References: