ABSTRACT

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Nanomedicine allows application of nanoscaled drug delivery carriers to achieve a therapy that can be tailored in terms of e.g. controlled release, site-specific delivery and protection of an active substance. From multiple nanoplatforms available for drug delivery, advantage was taken of biocompatible and biodegradable polymers and lipids to enable targeted intracellular delivery, delivery of a poorly water-soluble drug and delivery of a sensitive macromolecule.

In the study with biodegradable polymeric nanomaterial we worked with experimental poly(lactic-co-glycolic acid) (PLGA) polymers. The formulations were optimised for targeting to phagocytic macrophages – of size up to 300 nm and negative surface charge. For this purpose, two linear and one branched PLGA were screened in combination with one of four surfactants in low concentrations (0.1-1%). These PLGA polymers were formulated into nanoparticles and loaded with a hydrophilic fluorescent dye Rhodamine B using nanoprecipitation (NPM) or emulsification solvent evaporation method (ESE). Increased concentration of employed surfactant decreased particle size more efficiently in ESE than in NPM. The lowest tested concentration of a surfactant (0.1%) was sufficient to formulate negatively charged nanoparticles of 200 nm using NPM. ESE yielded smaller particles of 100 nm when 1% surfactant solution was employed and larger ones, >200 nm, at 0.1% of surfactant. A release study in three different media (isotonic saline solution and buffered saline solutions at pH 4.5 and 7.4) was performed with nanoparticles prepared from all three experimental polymers combined with 0.1% Pluronic F127 using NPM. Rapid release (90% of Rhodamine B in 12 hours) in isotonic pH 7.4 medium was observed in all polymers. In the other media, less than 50% was released by 12 hours. This trend could be related to spontaneous cyclic swelling reported in the experimental polymers at pH 7.4. The swelling seemed to enhance the release of the hydrophilic dye Rhodamine B.

The same preparation methods were implemented into preparation of lipid nanoparticles. Lipid nanoparticles have the ability to increase solubility of poorly water-soluble drugs, such as indomethacin.

This anti-inflammatory drug was loaded into nanostructured liquid carriers based solid lipids either stearic acid or glycerol monostearate. Addition of a liquid lipid, isopropyl myristate, supported formation of unstructured matrix of the carriers, as assessed using differential scanning calorimetry. Nanostructured lipid carriers based on stearic acid were formulated utilising NPM and resulted in nanoparticles of 175 nm with zeta potential of about -35 mV, enhancing solubility of indomethacin 5-times relative to its solubility in water. Glycerol monostearate-based lipid carriers formed nanoparticles of about 140 nm with zeta potential of about -45 mV prepared using ESE enabled 10-fold solubility enhancement of indomethacin.

Another investigated lipid-based nanodelivery system is well-established in oral delivery. Self-emulsification drug delivery system (SEDDS) based on tight junction opening, and thus permeation enhancing, excipients was utilised for local delivery of an oligonucleotide through the intestinal Caco-2 monolayer. The fluorescently labelled oligonucleotide was ion-paired with either dimethyldioctadecylammonium bromide (DDAB) or 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP). The resulting hydrophobic complexes were loaded into one of two tested SEDDS formulation. Both SEDDS formulations readily dispersed forming nanostructures of about 200 nm in an aqueous environment. However, SEDDS can be distinguished by surface charge as neutral and negatively charged SEDDS. The neutral SEDDS offered a better protection of the sensitive nucleotide in the presence of nucleases, namely 58% remained intact in comparison to 16% of the protected oligonucleotide in the negatively charged SEDDS. Orlistat, a lipase inhibitor, slowed down lipolysis of this lipid-based drug delivery system. Both formulations enhanced permeability of the oligonucleotide through the Caco-2 monolayer into lamina propria. The permeability enhancement correlated with the decrease in transepithelial resistance that was more pronounced in the neutral SEEDS.

In summary, PLGA nanoparticles were optimised to act as promising intracellular macrophage-specific drug delivery systems. Nanostructured lipid carriers showed their ability to enhance solubility of a poorly water-soluble indomethacin. Lipid-based SEDDS can deliver an oligonucleotide across intestinal *in vitro* model. Drug delivery nanosystems offer multiple formulation approaches to maximise the potential of active substances.