Preparation of polymeric microcapsules for application as ultrasound contrast agents and for ultrasound-mediated delivery of lipophilic drugs

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Ultrasound is the most widely used imaging technique in the world, and for this technique, contrast agents are needed, which are micro gas bubbles covered with a thin polymer or protein shell. In the study presented here, we aim to design polymeric ultrasound contrast agents with well-defined size, size distribution, and mechanical properties of the shell. Besides, we will show how an oil soluble drug can be incorporated in the UCA and released locally through ultrasound.

The microcapsules or UCA's are prepared by pre-mix membrane emulsification of a biodegradable polylactide dissolved in dichloromethane (solvent) to which dodecane is added (poor solvent) and a nonsolvent solution that consists of water or water-alcohol mixtures with surfactant. The pre-mix emulsion is repeatedly passed through a glass fibre membrane, and the formed droplets solidify onto the dodecane droplet through extraction of the solvent to the non-solvent phase. The dodecane is subsequently removed by freeze-drying, and hollow UCA's are obtained.

It was found that especially the amount and the type of alcohol could be used to fine-tune the particle size and size distribution; addition of alcohol speeds up the solvent removal rate and reduces the interfacial tension, which decreases the size and the span of the microcapsules. Besides, addition of alcohol enhanced emulsification efficiency; it reduced the number of emulsification passes, and had a pronounced effect on surface morphology, and capsule strength.

Besides used direct as UCA, these microcapsules can also be partially loaded with lipophilic drugs that can subsequently be released through ultrasound, which is an interesting new development in medicine. Fluorinated end-capped poly(L-lactic acid) was used as polymer, and the bubbles contained, apart from a gaseous phase, different amounts of hexadecane oil as a model drug-carrier reservoir. At low acoustic pressures (1 MHz, 0.24 MPa) microcapsules compressed but remained intact, while at higher diagnostic pressures of 0.51 MPa, microcapsules cracked, thereby releasing the encapsulated gas and model lipophilic drug (experiments performed at Rotterdam MC in collaboration with Philips).

In conclusion, pre-mix emulsification can be used to fine-tune microcapsule properties, while ultrasound can be used for diagnostics and to fine-tune of the local delivery of drugs and this is expected to ultimately lead to earlier diagnosis and milder treatments.