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Microencapsulation of peptides and proteins

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Abstract

Microcapsules were prepared by using a double-emulsion technique. A new production method called 'induced phase separation method' was applied to encapsulate peptides and proteins. To find the optimal adjuvants a matrix was set up combining the appropriate organic solvents and the suitable surfactants. The polymer was chosen with regard to the required release period. The aqueous drug solution was intensively mixed with the organic polymer solution. An aqueous surfactant solution was slowly added to the O/W emulsion. The obtained W/O/W emulsion is stirred under partial vacuum conditions until the organic solvent was removed. After removing the solvent from the W/O/W emulsion the microcapsules were washed and lyophilized. The morphology of the microparticles (spheres, sponges, capsules, surplus polymer) was checked by microscopy, particle size distributions were measured by laser diffraction. © 2000 Published by Elsevier Science B.V. All rights reserved.

Keywords: Microencapsulation; Bioerodible polymers; Peptides; Proteins

Peptides and proteins gain more and more importance as drug substances. In most cases they are not stable and therefore not effective when given orally. To avoid infusions or to reduce the frequency of injections sustained release formulations have to be developed. Microparticles made of bioerodable polymers offer the possibility of creating tailor-made systems for controlled release.

The prepared formulations consist of Resomer, e.g. RG 752, RG 858 (poly-lactide-co-glycolide, Boehringer Ingelheim, Germany). The used organic solvents were alkyl acetates, alkyl formates and ketones, all of analytical grade.

The used surfactants were e.g. Tween 80 (Fluka, D), Synperonic F 68 (Serva, D), Synperonic F 127 and T-707 (ICI, GB).

Water for injection was used to prepare drug and surfactant solutions.

Microcapsules were prepared by using a double-emulsion technique. A new production method called 'induced phase separation method' was applied to encapsulate the peptides and proteins. To find the optimal adjuvants a matrix was set up combining the appropriate organic solvents and the suitable surfactants. The polymer was chosen with regard to the required release period (e.g. RG 585 or RG 752).

The aqueous drug solution was intensively mixed with the organic polymer solution. An aqueous surfactant solution was slowly added to the W/O emulsion. The obtained W/O/W emulsion was stirred under partial vacuum conditions

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until the organic solvent was removed. The microcapsules were separated from the surfactant solution, washed and lyophilized (Figs. 1 and 2). The morphology of the microparticles (spheres, sponges, capsules, surplus polymer) was checked by microscopy (Fig. 3), particle size distributions (Fig. 4) were measured with an LS 130 (Courter, GB). All IPC measurements were carried out with the double emulsions, the washed microparticles prior to lyophilization and the lyophilized, redispersed microparticles.

With all combinations of solvents and surfactants microcapsules could be achieved. The size of the capsules depended on the viscosity of the used solutions and on the velocity of the mixing processes (stirring duration and intensity of the W/O emulsion, addition of surfactant solution). The encapsulation efficiency could be varied for a given solvent/surfactant combination by adding salts or macromolecules to the surfactant solution.

Addition of PEG 6000 reduced the encapsulation of a model peptide whereas sodium sulfate increased the encapsulation efficiency from 10 to 40%.

The change in encapsulation efficiency depended on the concentration of additive. With sodium sulfate there seemed to be an optimum of additive as 10% led to a better result than 20%. We know that the pH of the organic phase has an important impact on the encapsulation (data not presented here). The influences of pH, polarity and viscosity of the surfactant phase still have to be determined.

Tests were made with insulin, bovine serum albumin and human serum albumin and other model drug peptides.

All tested peptides could be encapsulated into the PLA microparticles. Encapsulation efficiency up to 45% was found with the first compositions. From earlier encapsulation experiments with insulin we know that encapsulation efficiency up to 100% can be achieved with this method (Haeckel et al., 1998).

The drug substances showed bioactivity after encapsulation. The detected activity was only poor with peptides that were very sensible to water contact due to the use of standard production parameters (room temperature, intensive and long lasting contact with water), further investigations are in process.

The first results prove the feasibility of the applied encapsulation method. As there are many parameters influencing the capsules it should be possible to develop optimal microcapsules for each drug.

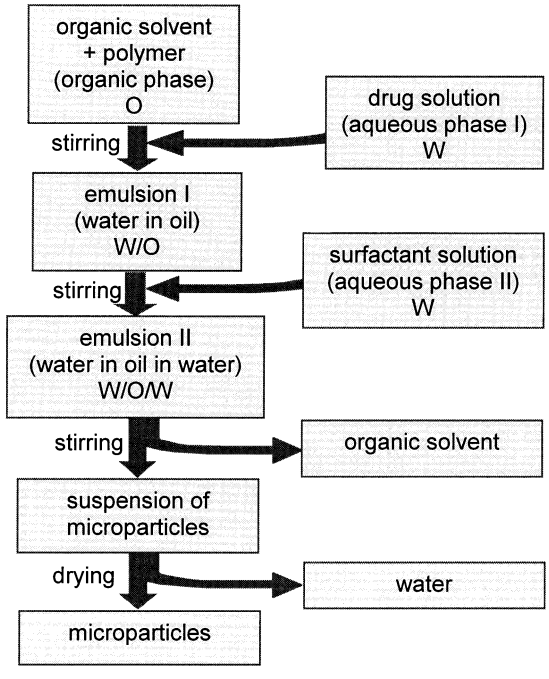

Fig. 1. Flowchart of microcapsule production according to the 'induced phase separation method'.

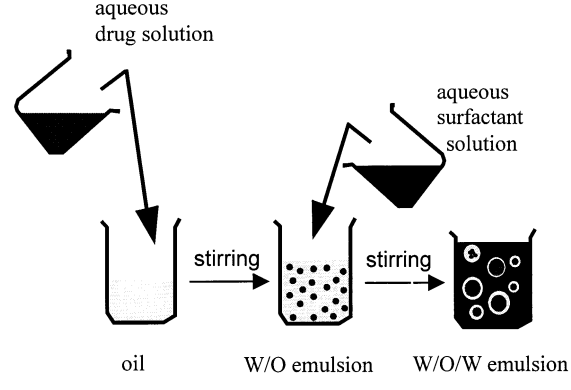

Fig. 2. Scheme of microcapsule production according to the 'induced phase separation method'.

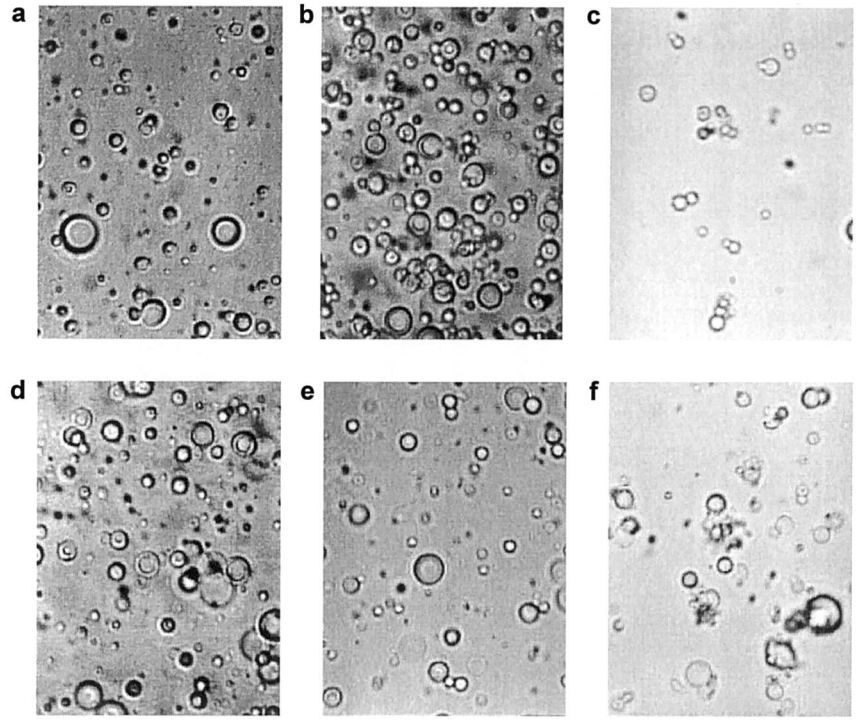

Fig. 3. IPC of microcapsules containing model drug complex (1st row) or pure model drug (2nd row), a/d: after production; b/e: after washing prior to lyophilization; c/f: redispersed lyophilized microparticles.

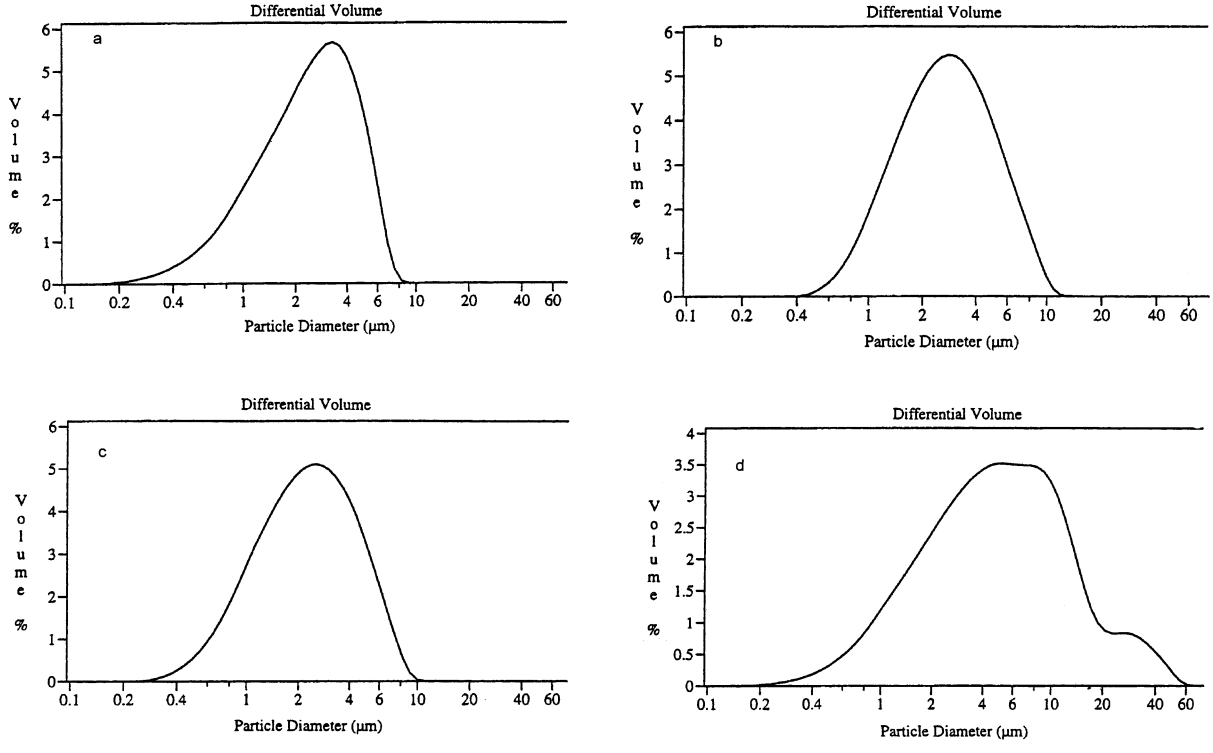

Fig. 4. Particle size measurements prior to lyophilization and after lyophilization, a/b: model drug complex; c/d: pure model drug.

References

Haeckel, S., Sachse, A., Albayrak, C., Müller, R.H., 1998. Preparation and characterization of insulin-loaded microcapsules produced by the induced phase separation method. In: Proceedings of The Second World Meeting APGI/APV, Paris.