“Production of Microcapsules”
Introduction

Sulfathiazole is an antibioticum belonging to the class of sulfonamides. The azo-dye Prontosil is known as the precursor of all sulfonamids and was first used as broad-band antibiotic in 1935. Nowadays, it is mostly used in veterinary medicine. Sulfathiazole is a white, cristalline powder, hardly soluble in water.

![Sulfathiazole](image)

**Fig. 2: Sulfathiazole**

Micro-encapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small capsules of many useful properties. These capsules have a diameter of 5 to 5000 µm. Advantages are, e.g. a slower release of a substance over a longer period of time, the change of physical parameters of powders, protection from light and oxidation or lamination of tastes or smells. Examples of microencapsulation are entericcoated capsules or capsules with a slower release of a pharmaceutical drug.

Coacervation is a unique type of electrostatically-driven liquid-liquid phase separation, resulting from association of oppositely charged macro-ions. The coacervation procedure was first described by Kruyt and Bungenberg de Jong in 1930. During the coacervation, colloidal solubilized macromolecules become insoluble due to change of physical conditions, such as temperature, and form a colloid-rich phase (coacervate). In the example of Fig. 3, upon becoming insoluble the gelatin encloses the dispersed material (sulfathiazole). Coacervation proceeds generally in four steps:

1.) Distribution: The dispersed, water-insoluble material (sulfathiazole) is resuspended in the aqueous phase (gelatin).
2.) Phase separation: The cover material is emulsified by suitable measures (stirring in paraffin oil).
3.) Encapsulation/Coating: The liquid cover material engulfs the substance.
4.) Solidification: The liquid cover material is solidified by suitable measures (decreasing temperature)
Gelatin is a natural polymer with a molecular weight of 30 to 200 kDa and is obtained upon hydrolytic degradation of collagen. Gelatin has the property of swelling in water, taking up water 5-10 times of its own weight. At temperatures above 50 °C, gelatin liquefies. Its solidification point is around 25 °C. In the pharmaceutical industry gelatin is used for generation of hard and soft capsules.

**Task**
Production of gelatin microcapsules with the model medicinal agent sulfathiazole (by coacervation). A visual evaluation, a measurement of the microcapsule’s size and a photometric determination of the active ingredient should be performed.

Amount of sulfathiazole to be used: 1.5 g
Experimental procedure:

Material: beaker (100 ml, 250 ml high form), stirring rod, heating magnetic stirrer, magnetic stirrer, feeding bottle, suction filter, thermometer, water bath, vacuum pump, gelatin, sulfathiazole, acetone, 2-propanol (isopropanol)

Give 6.0 g gelatin and 20 g water in a 100 ml beaker. Allow the gelatin to swell for 30 minutes and stir it from time to time. In the meanwhile heat 60 g of paraffin oil in a 200 ml beaker fixed with a stand in a water bath. Liquefy the gelatin in a 60 °C water bath and suspend 1.5 g sulfathiazole. Inject the suspension quick with a 20 ml syringe through a needle in the paraffin oil stirred by a magnetic stirrer at high frequency. Stir for 5 min.

Put the beaker in an ice-water-mixture on a stirrer (the stirring should be interrupted as short as possible). When the suspension reaches a temperature of at most 5 °C stir for another 60 min (max. speed). Add 30 ml of 5 °C-cold isopropanol and stir for 5 minutes.

Filtrate the microcapsules using a suction filter and a vacuum pump. After complete suction of the liquid the capsules are washed with 30 ml acetone and 80 ml isopropanol.

The isopropanol rheumy microcapsules are dried overnight in thin layers on absorbent paper.

Investigation of the microcapsule size:

The microcapsules are initially evaluated eye-minded whether they are small enough to perform the size determination with a microscope or if the diameter can be measured in a different way (e.g. using test sieves).
Photometrical determination of the active ingredient:

Material: 100 ml volumetric flask, test tubes, quartz cuvette, photometer, water bath, 0.1 N HCl, sulfathiazole, microcapsules

Standards: 40 mg sulfathiazole (weigh in precisely) are dissolved in a 100 ml volumetric flask in 0.1 N HCl at 40°C. Subsequent the flask is filled up to 100 ml. Take 0.2 ml of this solution and dilute it with 9.8 ml 0.1 N HCl (= 8 mg/l). Based on this solution a sulfathiazole standard curve with 0, 2, 4, 6, and 8 mg/ml is prepared.

Dissolve three samples of 40 mg microcapsules each (weigh in precisely) in a 100 ml volumetric flask in 0.1 N HCl at 40 °C. Avoid foaming! Subsequent the flask is filled up to 100 ml. Take 0.5 ml of this solution and dilute it with 9.5 ml 0.1 N HCl.

Table 2: Determination of sulfathiazole concentration

<table>
<thead>
<tr>
<th>Sulfathiazole concentration (mg/l)</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume stock solution (0.8 mg/100 ml)</td>
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<tr>
<td>Volume 0.1 N HCl</td>
<td>1 ml</td>
<td>1 ml</td>
<td>1 ml</td>
<td>1 ml</td>
<td>1 ml</td>
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<td>( E_{283} )</td>
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The absorption of the solutions is determined with a spectral photometer at \( \lambda = 283 \text{ nm} \) and 0.1 N HCl as reference solution. From the sulfathiazole calibration curve the substance contents of the microcapsules samples are calculated (results in mg and percent of microcapsules initial weight). The estimated values are compared with the theoretical maximum yield.

Microscopical investigation of the particle size:

Material: Microscope, stage micrometer, micrometer eyepiece, object plates, microcapsules

The particle size of the microcapsules is investigated microscopically using a micrometer eyepiece. The diameter of the biggest and the smallest microcapsules, as well as the most common diameter should be determined.

The size measurements are performed using a measuring eyepiece which has to be calibrated with a stage micrometer in advance (Fig. 5).
Fig. 5: Calibration of a measuring eyepiece. (a) stage micrometer, (b) micrometer eyepiece

The stage micrometer has a minor division dividing 1 mm into 100 scale lines. The distance between two scale lines is 10 µm. The micrometer eyepiece is calibrated by applying the scale of the stage micrometer.

Caution! This proportion varies depending on magnification and type of microscope.

Literature:


Lerneinheit Mikroverkapselung – Koazervation.
http://www.chemgapedia.de/vsengine/vlu/vsc/de/ch/16/tc/microcaps/microcaps.vlu/Page/vsc/de/ch/16/tc/microcaps/microcaps07.vscml.html
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