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Visualization and analysis of the release mechanism of shellac coated ascorbic acid pellets

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Shellac coated sustained release ascorbic acid containing pellets were investigated using scanning electron microscopy in order to visualize the release mechanism and to establish a correlation to dissolution data. Scanning electron micrograph pictures revealed different drug release profiles of individual pellets. Single pellet dissolution measurements demonstrated that the release profile of the encapsulated dosage form, containing approximately 400 pellets per capsule, is a combination of different release profiles of all individual pellets. The release of ascorbic acid occurred only in some small spots on the surface area of the pellets and could be visualized by the reduction of silver ions from an aqueous silver nitrate solution. These spots could be identified as defects in the shellac sustained release film using scanning electron microscopy. In further trials, the dissolution rate of an individual pellet could be related to the number and dimension of holes in its membrane. In conclusion, the release is characterized by surface defects and scanning electron microscopy studies are a useful tool to get new information for a better understanding of the drug release.

1. Introduction

Multiple unit peroral sustained release dosage forms are of increasing importance. Compared to single units they offer the following advantages: lower transit times in the stomach and reduced intra- and inter-individual variations in bioavailability (Bogentoft et al. 1978; Scheidel et al. 1994; Hosny et al. 1998). Pellets are the most widely used multiple units. For sustained release purposes pellets can be coated with a water insoluble polymer or they can be of the matrix type. Drug dissolution from coated pellets normally is membrane controlled and follows Fick's law. As long as solid drug is present in the pellet zero order kinetic results (Lippold 1984). In case of a matrix the liberation of the active follows the Higuchi equation (Higuchi 1963). The aim of the present study was to investigate the mechanism of drug liberation from a shellac coated sustained release pellet preparation containing ascorbic acid as the active ingredient and being on the market as a drug and a food supplement. The methods used were: secondary electron microscopy for visualization and drug dissolution studies using the paddle method.

2. Investigations, results and discussion

During the dissolution experiments some of the pellets were deformed while others remained intact (Fig. 1). With increasing dissolution time the number of deformed pellets increased. SEM is a useful tool to visualize the drug release from the pellets. Intact pellets did not show any ascorbic acid dissolution, while highly deformed pellets lost the active drug almost completely. The view onto the cross sectional area of the pellets demonstrates the differences (Fig. 1): deformed pellets are like holes containing only the outer shellac coat, the residual shellac used as binder in the powder layering process and fragments of the nonpareil core. Intact pellets do not show a loss of ascorbic acid.

In some cases the initial dissolution of ascorbic acid could be visualized (Fig. 2). Obviously this initial dissolution occurs at surface defects of the coating. In Fig. 2, a hemispherical area is shown, where no longer ascorbic acid crystals are visible. This highly porous area indicates the section from where the dissolution of ascorbic acid starts. Therefore the dissolution is not a membrane controlled process, it is controlled by the number and size of the defects in the coating.

SEM studies of the surface of untreated pellets showed defects of several μm in diameter (SEMs not shown here). They were caused by accumulated talc particles not incorporated completely into the shellac film and sticking out of the film surface. These membrane defects could be visualized and identified during the dissolution testing by a second method using an aqueous solution of silver nitrate as dissolution medium. The argentous ions were reduced by ascorbic acid to metallic silver settling on the surface of the pellets at regions with coating defects. Therefore the dissolution of vitamin C could be observed by the proliferation of silver on the pellet-surface (Fig. 3). A semiquantitative correlation between the silver being present on the surface of the pellets and the residual ascorbic acid content at the end of the dissolution experiment could be established. Single pellets were treated with 10 ml silver

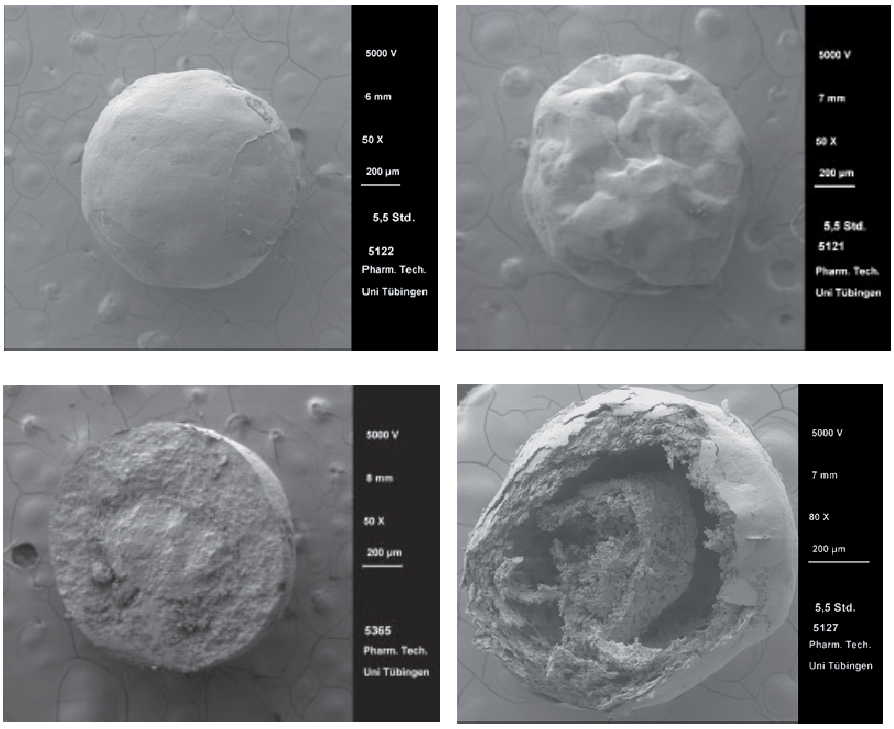

Fig. 1:
Pellets after 5.5 h release time. Left: Unchanged pellet, right: deformed pellet. Top: pellet surface, bottom: cross sectional area

nitrate solution (4.25 g/100 ml water) and the formation of silver was documented by photography under the microscope. After two hours the silver nitrate solution was decanted, the pellet was washed with water and the residual ascorbic acid was determined spectrophotometrically. The results are presented in Fig. 4 and show a fairly good correlation between the increase of silver on the surface of the pellets and the residual ascorbic acid content.

Finally the ascorbic acid liberation from 20 single pellets over time was investigated. The results are shown in Fig. 5. Single pellets show extremely different dissolution rates, indicating again that there is no passive diffusion mechanism. Some pellets liberate the drug within two hours while others showed a liberation of only 20% during this time period. The mean ascorbic acid liberation from these 20 pellets showed a dissolution curve being in the same order of magnitude as the drug liberation from a capsule containing 500 mg ascorbic acid in approx. 400 pellets (Fig. 5, right). The dissolution of ascorbic acid from the sustained release pellets under investigation is therefore the sum of individual liberation curves of the single pellets, which do not follow a membrane controlled process. The high number of pellets per unit dose leads by statistical means to a reproducible drug liberation.

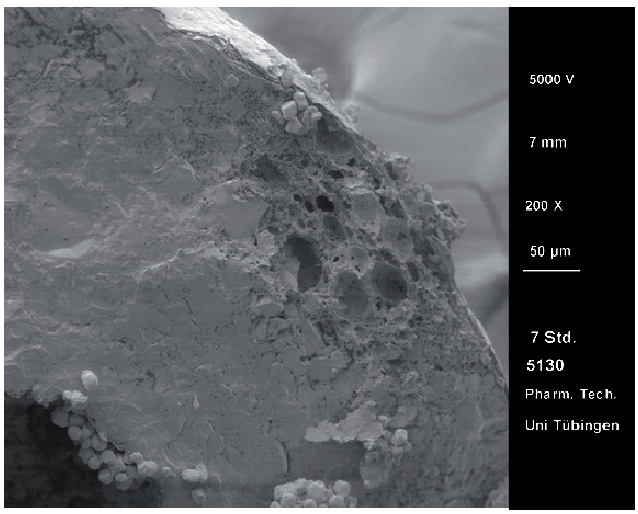

Fig. 2: Initial dissolution of ascorbic acid from a surface defect of the shellac coating. The hemispherical porous area indicates the section from where ascorbic acid crystals were dissolved

3. Experimental

3.1. Materials

The ascorbic acid sustained release pellets were provided by GSK Consumer Healthcare, Herrenberg, Germany. All reagents were of analytical grade (Merck KGaA, Darmstadt, Germany and Carl Roth GmbH, Karlsruhe, Germany).

3.2. Methods

3.2.1. Preparation of pellets

The pellets were prepared by powder layering of ascorbic acid on nonpareil pellets in a conventional coating pan. An ethanolic shellac-solution was used as binder. In a final step the pellets were coated with an ethanolic shellac solution containing 10% of tartaric acid as a plasticizer, resulting in film thickness of 2–3 µm. Purified talc powder was used as antiadherent.

3.2.2. In vitro dissolution testing

Dissolution testing of the vitamin C pellets was performed in 1000 ml water, containing 0.49 g Titriplex V and 0.24 g sodium disulfite. An automated paddle dissolution tester (Sotax AT7 Smart, Sotax AG, Basel, Switzerland) was used at a speed of 100 rpm. At different time intervals samples were taken and spectrophotometrically analyzed at 249 nm (Beckmann spectrometer DU 640, Beckmann Instruments GmbH, Munich, Germany). Calibration was done with a solution of ascorbic acid standard (Merck KGaA, Darmstadt, Germany) from 1 µg/ml to 12 µg/ml.

3.2.3. Sample preparation for scanning electron microscopy (SEM)

The dissolution experiments run over 8 h. Every 30 min one dissolution vessel was displaced, the dissolution medium decanted and the pellets collected on a filter. The pellets were dried in a desiccator at room temperature for 24 h and were sputtered with gold in a sputter coater (Bio-Rad Laboratories GmbH, Munich, Germany) 4 times 60 s at 2.1 kV and 20 mA.

3.2.4. Scanning electron microscopy (SEM)

Pellets were fixed on aluminium stubs using double-sided adhesive tape. SEM pictures were taken using a DMS 940 A apparatus (Carl Zeiss, Oberkochen, Germany) before and after dissolution testing.

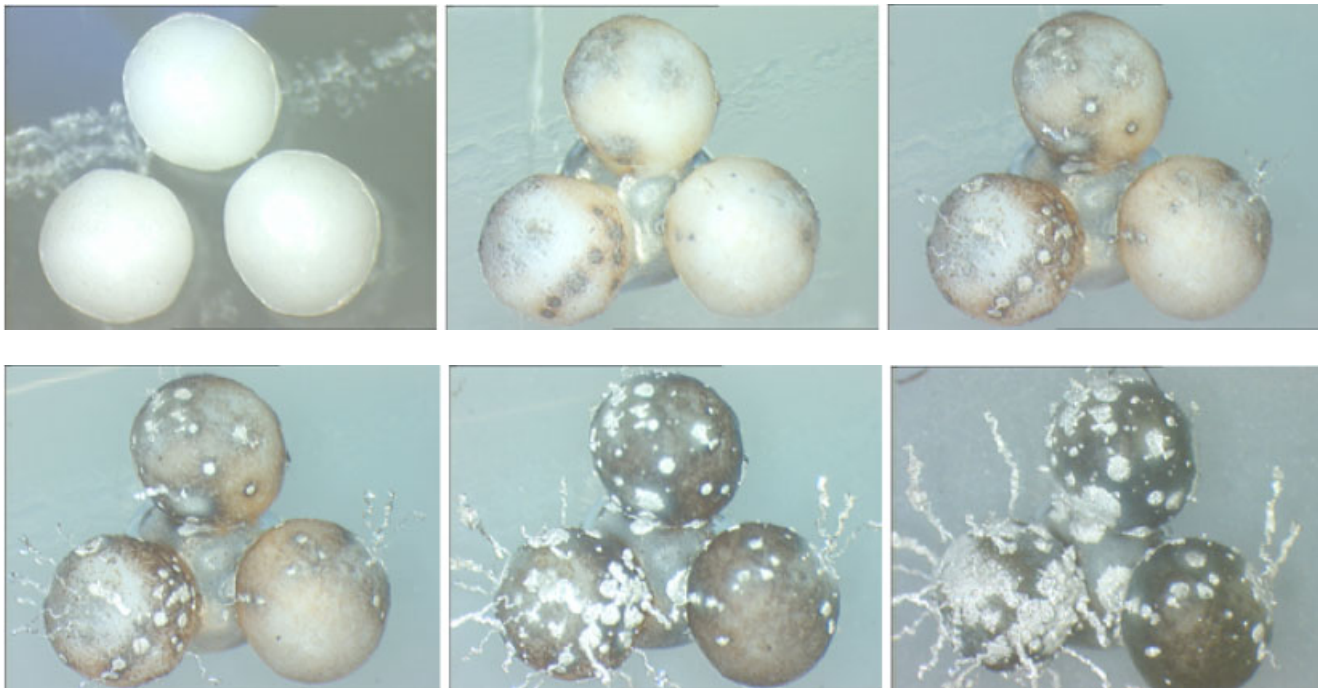

Fig. 3: Dissolution of ascorbic acid pellets in silver nitrate solution R1. From top left to bottom right: pellets before dissolution and after 5, 30, 60, 180 and 360 min dissolution time

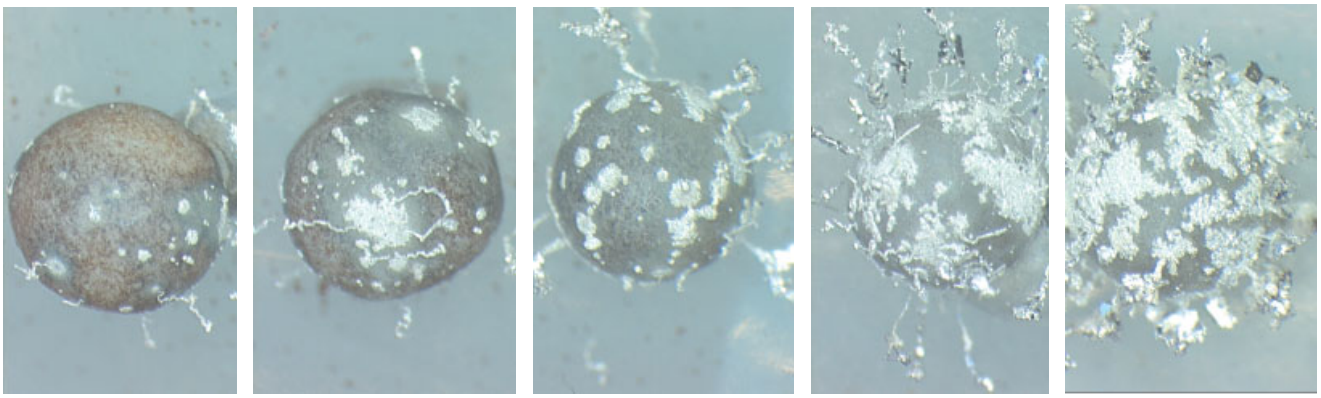

Fig. 4: Five different pellets after 120 min dissolution time in silver nitrate solution R1 in correlation to the residual amount of ascorbic acid in the single pellet at this time. Residual amount of ascorbic acid in the single pellets from left to right: 1.79 mg; 1.52 mg; 1.13 mg; 1.01 mg; 0.14 mg

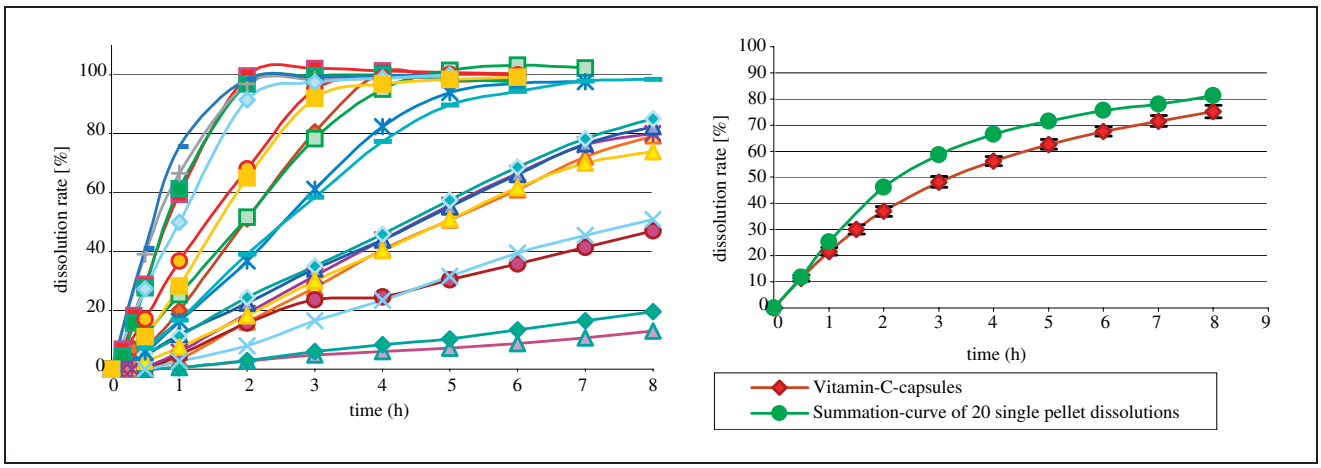

Fig. 5: Left: Ascorbic acid release profiles of 20 single pellets. Right: Comparison of the mean release profile of 20 single pellets and the release profile of the encapsulated dosage form containing approx. 400 pellets with 500 mg ascorbic acid in a hard gelatine capsule

3.2.5. Pellet dissolution in silver nitrate solution R1 (Europäisches Arzneibuch 2002)

The pellets were fixed on adhesive tape and placed in a Petri-dish. 10 ml Silver nitrate solution R1 were added and at different time intervals microscopic pictures were taken at a magnification of 60 (Olympus SZH, Olympus Optical Co. GmbH, Hamburg, Germany, with 3-CCD Color Camera, HV-C29, Hitachi Denshi, Rodgau, Germany). For the determination of the remaining content of ascorbic acid the solution was decanted and the pellets were rinsed with water. Then single pellets were destroyed by a pestle and dissolved in water. The samples were spectrophothometrically analyzed at a wavelength of 249 nm.

3.2.6. Single pellet dissolution

Dissolution testing of single ascorbic acid pellets was performed in 100 ml of water by a Sotax AT 7 dissolution tester at a paddle speed of 150 rpm. The samples were spectrophotometrically analyzed at 249 nm.

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