

Production of Tablet-Like Solid Bodies Without Pressure by Sol-Gel Processes

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Abstract: A sol-gel and a freeze-casting process are used to produce tablet-like bodies without the standard compression. The advantage is that temperature sensible materials can be produced in tablet-like forms, thus other cost intensive production processes like capsulation or freeze drying are avoided. Different ways are introduced to characterize the suspension and the tablet. Herewith the influences of parameters like composition of the materials or freezing conditions on the final products should be clarified.

Keywords: Sol-gel, Freeze casting, Tablet, Pressure free tableting, Tablet-like body, Cold compression.

INTRODUCTION

Standard tablet compression requires high pressures which may therefore induce high temperatures [1]. Such a process is not applicable in case of temperature sensible materials. Drug ingredients which can be harmed by high temperatures are currently not producible in a tablet form. Such drugs are only available e.g. as capsules which are more expensive in production than tablets. A different possible form to deliver those drugs are injections. Injections are, indeed, not very comfortable for the patients [2].

There are already freeze drying processes existing to produce tablets. Nevertheless, tablets produced with those techniques have a very low strength against breakage. Furthermore the sublimation of water is a very energy-consuming process, therefore those techniques are very cost intensive [3].

The advantage of a sol-gel process is the irreversibility of this procedure [4]. A sol is a stable dispersion of solid colloidal particles in a liquid. Stable means here that there is no settling or agglomeration of the particles. If the concentration of this sol is increased or the temperature decreased, it transforms to a gel [5]. A gel is a continuous solid skeleton made of colloidal particles/ polymers enclosing a continuous liquid phase. As this phase transformation is irreversible, a sublimation is not necessary to remove the water from the sample but a simple drying is sufficient. The experiments show that the tablet-like bodies produced by a sol-gel process show a better hardness than freeze dried samples [3]. The hardness can even be increased by the addition of a binder such as ascorbic acid. The use of a binder has, however, an enormous influence on the dissolution behaviour of such tablet-like bodies.

The sol-gel process is used in combination with a freeze-casting process. Therefore the dissolution behaviour as well as the mechanical strength are influenced by the way of

processing. As the pores in the tablets are the negative images of the ice crystals created during the freezing step of the freeze-casting process [6, 7, 8, 9, 10], the importance of the processing is obvious.

MATERIAL AND METHODS

The tablet-like bodies were produced with active ingredients, colloidal silica and binding agents. The active ingredient applied was paracetamol (Merck, Germany), used as crystalline powder (density 1.293 g/cm³ at 21 °C, melting point 169 - 171 °C, molecular weight 151.17 g/mol, d₅₀=89.98 µm). Two types of silica-sol (EKA Chemicals, Germany) were used. The characteristics of those materials are shown in Table 1:

Table 1. Used sol Types (Bindzil®) with their Characteristics [11]

Bindzil Grade	830	1440
SiO ₂ [wt %]	30	40
Particle size [nm]	10	14
Na ₂ O [wt %]	0.6	0.5
pH	10.5	10.4
Density [g/cm ³]	1.2	1.3
Viscosity [cPs]	8	16

The requirements to the binding agent were a good water solubility, an easy and cheap availability and of course an applicability in a dosage form (e.g. non toxic). As ascorbic acid is used as additive in some analgesics (e.g. ASPIRIN® Plus C) for the support of the convalescence, it was chosen as binding agent (L(+)-Ascorbic acid, NORMAPUR, C₆H₈O₆, molecular weight 176,13 g/mol, melting point 190-192°C) for the investigations. The function of the binding agent is to improve the hardness of the tablet body. Furthermore, the dissolution behaviour was regulated by the amount of binder.

The experimental procedure is as follows: an aqueous suspension of the above mentioned materials was poured

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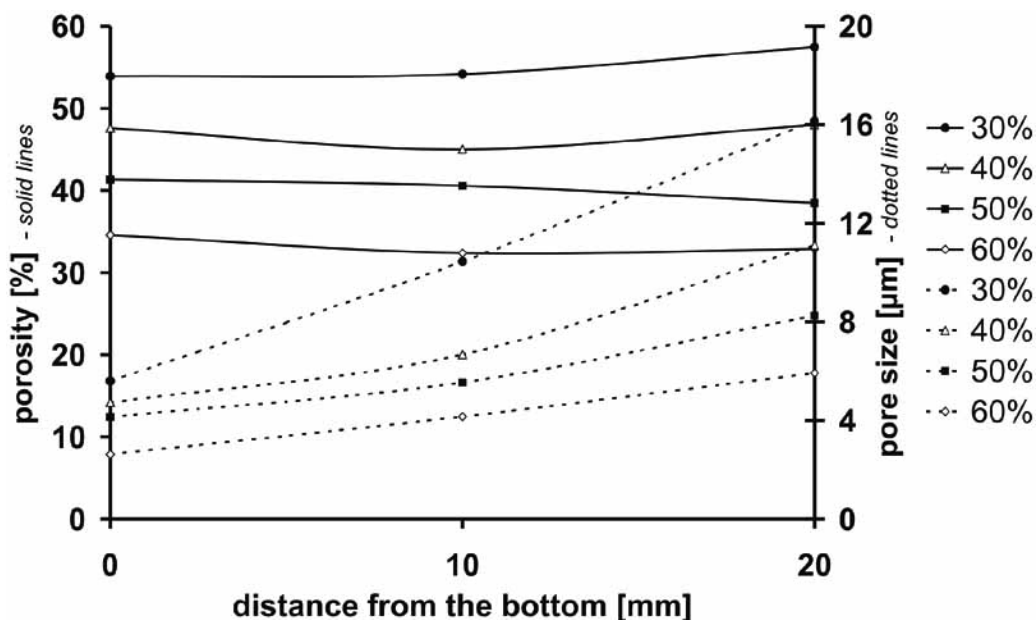


Fig. (1). Porosity (solid lines) and pore size (dotted lines) depending on the height of the sample and the paracetamol concentration. The suspension consisting of paracetamol and Bindzil 830 was frozen at -30°C .

into a cylindrical casting mould which was placed on a cooled freezing cell. The only contact area between suspension and freezing cell is at the bottom of the moulds. As the top of the moulds is open to ambient conditions, a temperature gradient is created which forces the ice crystals to grow as dendrites from the bottom to the top. After the water in the samples is removed by drying, a porous matrix with pores as negative image of the ice crystals remains [6].

The suspension was investigated, among others, with respect to density, viscosity, freezing rate and metastable zone width. At the dried tablet bodies were investigated concerning their properties: porosity, average pore size (mercury porosimeter Pascal 140+440 Series, Porotec), dissolution behaviour (paddle dissolution tester, Erweka DT6, Erweka, uv-vis analyser spectrophotometer SPEKOL[®] 1200, Analytik Jena) and tensile strength (TBH 30, Erweka).

RESULTS AND DISCUSSION

Due to the temperature difference between the bottom and the top of the sample of the suspension in the mould, the porosity and the pore size in the sample changes with the height in the sample. On the bottom, where the temperatures are the lowest, many ice crystals appear. With increasing heights and therefore rising temperatures (but still clearly below 0°C), the ice crystals grow slower and slower. The pores created are therefore bigger in size. The porosity stays constant over the whole sample, as can be seen from Fig. (1). The shown sample is produced by a suspension consisting of paracetamol and Bindzil 830, frozen at -30°C . It can clearly be seen that the porosity as well as the pore sizes decrease with an increasing paracetamol content.

The increasing size of the pores with increasing distance from the bottom of the freezing cell can also be clarified by

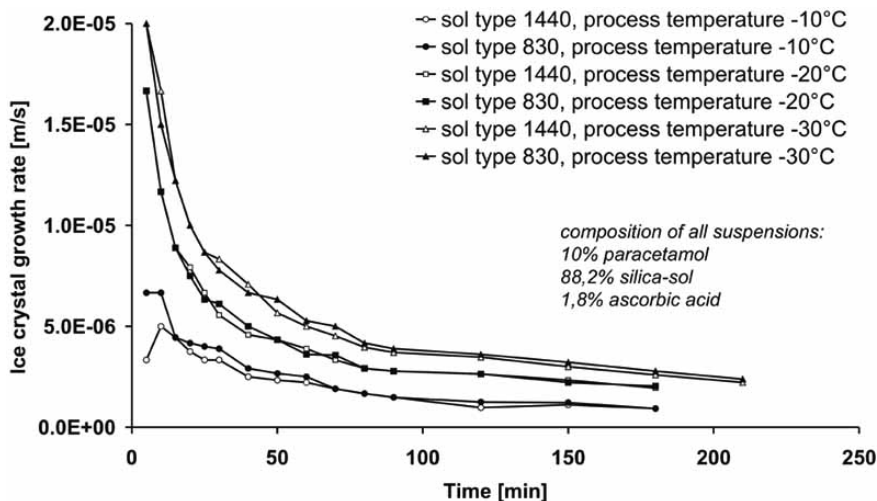


Fig. (2). Ice crystal growth rates depending on experiment time, sol types and process temperatures.

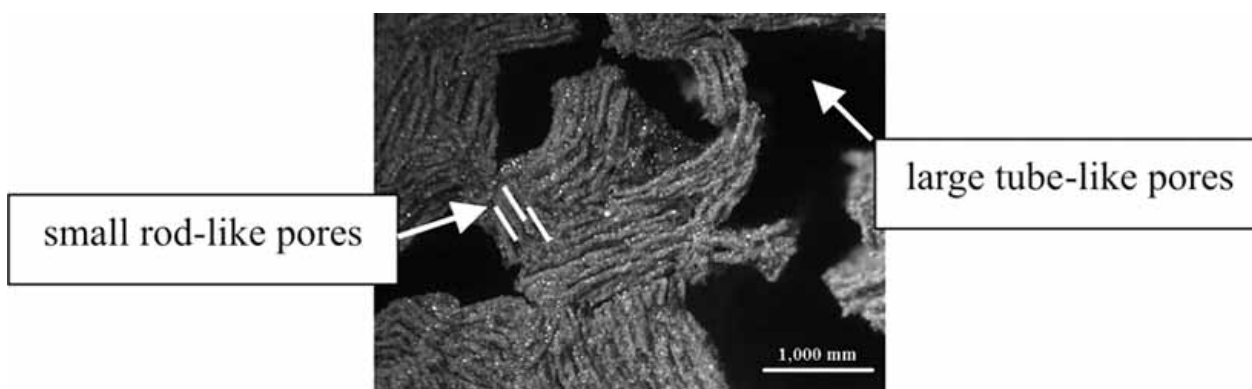


Fig. (3). Micrograph of the top of a dried tablet body ($h=1,6\text{cm}$) perpendicular to the ice growth direction. The sample was created from a basic suspension consisting of 25% paracetamol, 71,25% Bindzil 830 and 3,75% ascorbic acid (after drying: 49,88% paracetamol, 42,64% SiO_2 , 7,48% ascorbic acid), which was frozen at -30°C . The big black areas are the large tube-like pores, the small dark areas, marked eg. by the dark lines, are the small rod-like pores.

Fig. (2), where the ice crystal growth rates are shown depending on time of the experiment, sol types and process temperatures. The composition of all suspensions was 10wt% paracetamol, 88,2wt% silica-sol and 1,8wt% ascorbic acid. The longer the suspension was exposed to the freezing, the higher the ice crystals have been grown. With increasing height of the ice layer the driving force to freeze the remaining suspension, decreases due to the increasing insulation of the already frozen layer. The ice crystal growth rate decreases and each growing ice crystal becomes larger. Fig. (2) shows moreover that different sols (e.g. 1440 or 830) do not influence the ice crystal growth rate, the corresponding curves match very precisely. With lower process temperatures the ice crystal growth rate increases (from -10°C to -30°C).

Fig. (3) shows a micrograph of the top of the a dried tablet body perpendicular to the ice growth direction. The sample was created from a basic suspension consisting of 25% paracetamol, 71,25%, Bindzil 830 and 3,75% ascorbic acid. It was frozen at -30°C . After the drying, the composition accords to 49,88% paracetamol, 42,64% SiO_2 and 7,48% ascorbic acid.

In Fig. (3) is visible clearly a regular pattern of big, flat, rod-like pores. In tablet bodies being created with such a small paracetamol content in the suspensions (here 25wt%), besides this regular pores also large tube like pores appear, which start at the bottom of the tablet bodies and lead vertically through the whole sample. Such holes do not appear in higher concentrated samples. At the same time the rod-like pores are much smaller.

Fig. (4) shows the $t_{50\%}$ -values of the dissolution of tablet bodies with different concentrations of paracetamol, SiO_2 and ascorbic acid, calculated by the dose-response-function [12]. The concentrations in Fig. (4) represent those in the suspension before drying. Bindzil 830 was used as sol and the sample was frozen at -30°C . $t_{50\%}$ is the time, at which 50% of the active ingredient paracetamol in the sample is dissolved. The higher the paracetamol concentration is the longer the sample needs for dissolution. Moreover, the higher the ascorbic acid amount is the slower is the dissolution. In the low concentration range of ascorbic acid (lower than 5% ascorbic acid) suddenly a jump appears which involves a much longer dissolution time. This behaviour tails off with lower paracetamol contents.

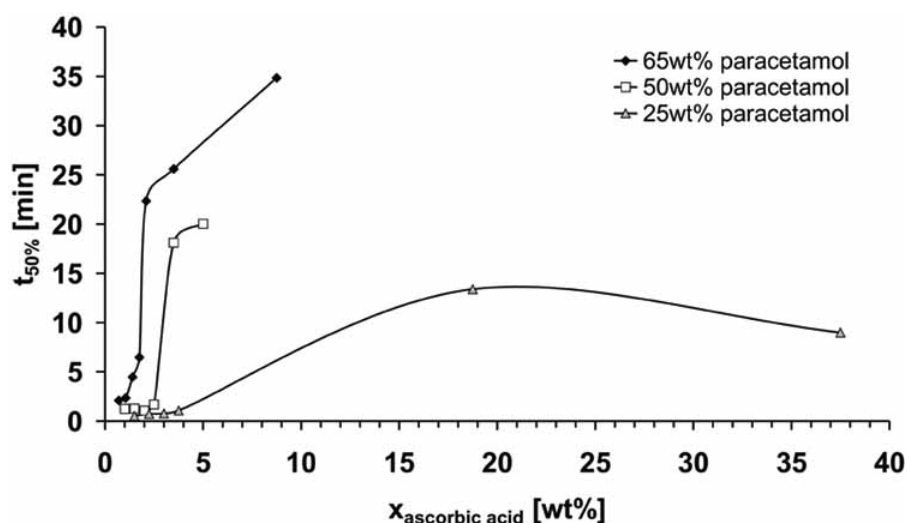


Fig. (4). Dissolution of paracetamol from tablet-like bodies with different concentrations. The concentrations in the figure represent those in the suspension before drying. Bindzil® 830 was used as sol and the sample was frozen at -30°C .

The reasons for the behaviour of the samples in Fig. (4) are the following: Lower paracetamol concentrations in the suspensions mean also a higher water content. After the drying those samples have a higher porosity and offer therefore a bigger surface to the dissolution medium. Moreover, the mechanical strengths were higher in the higher concentrated samples. The increase of the amount of ascorbic acid had two effects. On the one hand the ascorbic acid connected the paracetamol and SiO₂ particles after crystallisation, on the other hand the paracetamol particles fill the pores, whereby in both cases the dissolution time is extended. With knowledge of this behaviour the dissolution rate of tablets can be regulated easily by the composition of the tablet-like bodies.

Further experiments showed that samples without ascorbic acid dissolve extremely fast, even faster than the commercial available paracetamol ratiopharm® 500, which exhibits a t_{50%} value of 72.17 seconds. Moreover, it was shown that by the presented process a high breaking strength of the tablets is achievable [13]. As example a sample is mentioned, produced from a suspension containing 50% paracetamol, 25% ascorbic acid and 25% Bindzil® 830 and frozen at -30°C, with a tensile strength of 2.054 N/mm. In comparison, paracetamol ratiopharm® 500 exhibits just a tensile strength of 1.583 N/mm.

CONCLUSIONS

As some pharmaceutical materials are due to their temperature sensibility not compressible to tablets, a sol-gel-process was investigated. This process is applicable for those materials without using a cost-intensive freeze-drying. Experiments showed that by the composition of the basic suspensions the ice crystal growth rates and thereby the pore sizes, the morphology and the dissolution behaviour of the dried tablet bodies can be regulated. The pore sizes increase with increasing heights of the sample and decrease with increasing paracetamol contents. It was furthermore shown that different sols do not influence the ice crystal growth rate. With lower process temperatures the ice crystal growth rate increases.

Micrographs showed clearly a regular pattern of big, flat, rod-like pores.

Dissolution experiments clarified that the higher the paracetamol concentration is the longer is the sample dissolution time. Moreover, the higher the ascorbic acid amount is the slower is the dissolution rate.

The presented process has the capabilities for the development of interesting alternatives to regulate the hardness, the structure and the dissolution behaviour of the tablet-like bodies.

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