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# USE OF THERMOANALYTICAL METHODS IN QUANTIFICATION OF DRUG LOAD IN MESOPOROUS SILICON MICROPARTICLES

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Thermally carbonised mesoporous silicon microparticles were produced and loaded with two active pharmaceutical ingredients, ibuprofen and antipyrine. By combining the results measured with TG and DSC, reliable estimations for the degrees of the drug loads were obtained. To distinguish the drug adsorbed on the surfaces of the microparticles from that absorbed into the pores, the principle of thermoporometry on the DSC measurements was employed. According to the principle, the drug held in the capillaries of porous material has a depressed melting temperature because of the higher pressure of the drug in cavities with a curved interface. On the other hand, the drug located on the external surface of the microparticles exhibits the normal melting of bulk drug. The loading degrees obtained with the thermoanalytical methods (31 and 26 mass% for ibuprofen and antipyrine, respectively) were comparable with the results obtained with helium pycnometry (the corresponding values were 33 and 28 mass%). Nitrogen sorption studies were not reliable for quantitative determinations due to the inability of nitrogen to penetrate in all pores, which might be blocked by the drug on the surface of the microparticles.

***Keywords:*** *antipyrine, controlled drug release, drug loading, ibuprofen, mesoporous silicon microparticles, oral drug delivery, porosity, thermal analysis, thermoporometry*

## Introduction

Drug-loaded particles are reported to be particularly suited for controlled drug release and drug targeting offering interesting systems for oral drug delivery [1–5]. These systems are expected to enhance the bioavailability of poorly absorbed drugs via enhancing the solubility of the drug or the paracellular transport along the epithelial lumen of the small intestine. Usually, the systems consist of a polymeric matrix from which the drug is released [6]. However, these types of matrixes have disadvantages, e.g., inhomogeneous distribution of the drug through the matrix resulting in changes in the release rate between different samples. Non-erosive porous silicon microparticles possessing well-defined porosities and pore morphologies with desirable surface chemistry to accept organic guest molecule might offer an improved alternative.

Porous silicon (PSi) is a promising choice as a vehicle in oral dosing of drugs. With the drug-loaded PSi microparticles it is possible to control the drug release by varying the pore sizes and/or by functionalising the pore walls. Perhaps the most interesting feature of the PSi microparticles in oral drug delivery is their capability to enhance the drug permeation *in vitro* [3].

An important aspect in the development of the drug-loaded PSi microparticles with beneficial pharmacological features is to quantify and characterise the physicochemical nature of the drug loaded in the pores. A possibility for quantification is to combine the information obtained with thermogravimetry (TG) and differential scanning calorimetry (DSC). Normally, at high temperatures the organic drug molecules decompose and the subsequent desorbing of the volatiles can be measured with TG. The mass loss is proportional to the total drug content in the sample. On the other hand, when the drug is confined to small pores its melting temperature is depressed when compared with the melting of bulk drug. As the drug located on the external surfaces of the microparticles is regarded as bulk material it is possible to distinguish the drug located on the surface of the microparticles from that confined to pores with thermal analysis. The main objective of the present study is to explore the possibility and reliability of thermal analysis (DSC and TG) to quantify the drug substances loaded in porous material.

## Materials and methods

PSi was prepared by etching the Si (100) wafers electrochemically after which it was stabilised with an appropriate surface termination to obtain desirable chemical surface properties [7–9]. The thermally carbonised PSi (TCPSi) microparticles (1–38 μm) used in the present study were prepared by ball-mill-

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ing the etched PSi films before the actual stabilisation treatment that produced the SiC coverage. The temperatures applied in the thermal carbonisation processes were 500/850ºC and 850ºC for the porous microparticles into which ibuprofen and antipyrine were loaded, respectively. The two-step treatment (500/850ºC) was utilised in the case of ibuprofen since it stabilised the surface more efficiently and reduced less the pore size and the specific surface area of the etched material. Ibuprofen (Sigma Aldrich) and antipyrine (Sigma Aldrich) were used as the model drugs. The loading of the microparticles was made via immersing the TCPSi particles in saturated drug solution (ethanol for ibuprofen and water for antipyrine) at 22ºC for 1.5 h. After the subsequent filtering the microparticles were dried (at 65°C for ibuprofen and 105°C for antipyrine) for an hour [10]. The loading takes place through simple capillary action, which can be accelerated applying vacuum, but in the present study vacuum was not applied.

The samples were characterised with TG (TGA 7, Perkin Elmer, 10ºC $min^{-1}$, $N_2$ gas purge of 50 mL $min^{-1}$), DSC (Pyris Diamond DSC, Perkin Elmer, 2ºC $min^{-1}$, aluminium pans with pinholes, $N_2$ gas purge of 40 mL $min^{-1}$), helium pycnometer (AccuPyc 1330, Micromeritics) and $N_2$ ad/desorption studies (TriStar 3000, Micromeritics). DSC was calibrated with indium, TG with alumel and nickel, and pycnometer with calibration standards (Micromeritics) according to the operator's manual. The function of TriStar was verified with reference materials (Micromeritics). All the measurements were made at least in duplicate and representative mean values has been reported. The pore volumes were calculated from the $N_2$ desorption values on the basis of BJH theory [11].

When the loading of the TCPSi microparticles is performed, a part of the drug is absorbed into the pores and some of the drug is adsorbed on the surface of the particles. The model drug molecules employed in the present study decompose at high temperatures under nitrogen atmosphere. Nitrogen was used as the purge gas in the thermal analysis to prevent oxidation of TCPSi that could interfere the interpretation of the results above 300°C. The drug itself can also chemically react with the microparticles, which must be taking into account. Consequently, TG was used to quantify the total amount of the drug in the TCPSi microparticles. When a solid substance is confined to small pores the melting temperature of the substance is depressed. The relationship between the pore diameter and the melting temperature depression is described by the Gibbs-Thomson equation [12]; the smaller pores the larger melting temperature depression. The equation is valid for a porous medium with an average pore size much greater than the size of the confined molecules [13, 14], and it forms the basis for the widely used thermoporometry to determine simultaneously the sizes and shapes of the pores. Thermoporometry has been utilised previously in some studies in the field of pharmaceutical research, e.g. [15, 16].

In the present study the relationship between the pore size and the melting temperature depression was utilised to distinguish the drug adsorbed on the surface from that absorbed within the pores. The other methods of the study were used for verification.

## Results and discussion

### *Ibuprofen*

As the result of the TG measurements, the total amount of ibuprofen in the TCPSi microparticles was 30.8 mass% (Fig. 1). The mass loss was attributed solely to the drug decomposition and the subsequent desorption since the decomposition temperature was high compared with the boiling temperature of ethanol (79ºC) and due to the prolonged drying time of the ibuprofen loaded TCPSi microparticles (ch. chapter Materials and methods). Also, as ibuprofen was separately precipitated from ethanol any formation of solvates was observed. Only a fraction (0.2 mass%) was located on the surface of the particles according to the DSC measurements (Fig. 2) since only a minor endotherm (1.60 mJ) was observed at the melting point of bulk ibuprofen. Due to the melting of the ibuprofen confined to the pores, a broad endotherm in the DSC curve was observed before the sharp melting of bulk ibuprofen (Fig. 2). With the drug load of 30.6 mass% within the pores, the obtained heat of fusion for the ibuprofen confined to the pores was 53.1 J $g^{-1}$. The corresponding value for bulk ibuprofen was 124.2 J $g^{-1}$. Thus, the heat of fusion is obviously decreased when the size of crystallites are decreased and the heat values

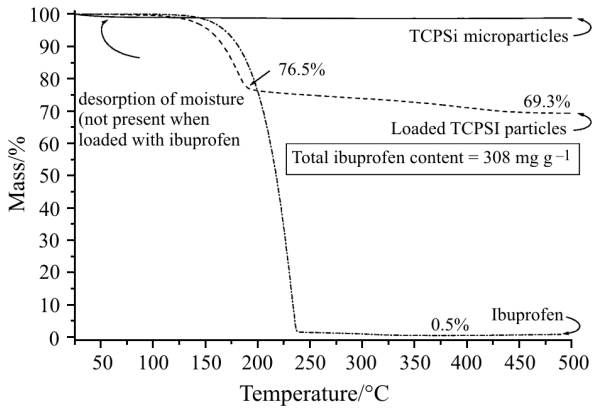


**Fig. 1** TG curves of TCPSi microparticles (solid line), ibuprofen loaded TCPSi (500/850°C) particles (dashed line) and ibuprofen powder (dotted line). Heating rate=10ºC $min^{-1}$, gas purge=$N_2$

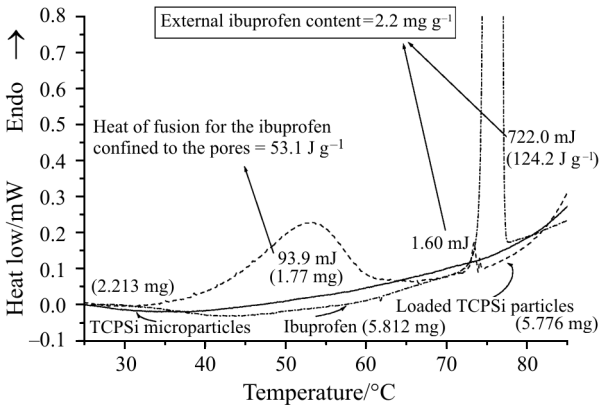


**Fig. 2** DSC curves of TCPSi microparticles (solid line), ibuprofen loaded TCPSi (500/850ºC) particles (dashed line) and ibuprofen powder (dotted line). Heating rate=2ºC $min^{-1}$, gas purge=$N_2$

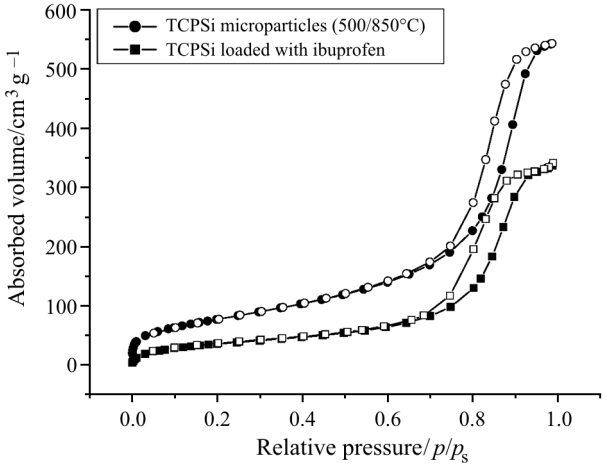


**Fig. 3** $N_2$ adsorption (solid symbols) and desorption (open symbols) isotherms of TCPSi microparticles (circles) and ibuprofen loaded TCPSi particles (squares)

of the broad melting endotherm cannot be applied to calculate the amount of ibuprofen within the pores. The low heat value for melting could be caused by the pseudoliquid layer bound to the walls of pores [14, 17]. This thin layer does not undergo any phase transition. Even though the layer is thin its volume fraction is significant for smaller pores.

The densities of the TCPSi microparticles, the bulk ibuprofen and the loaded microparticles were 2.439, 1.120 and 1.757 g $cm^{-3}$, respectively. The obtained drug load was 51.71 volume% (33.0 mass%). The value was in good agreement with the value obtained with the thermoanalytical methods. The value calculated from the densities could be an overestimation because of two possible reasons. First, the density of the drug confined to pores is presumably lower than that of the bulk drug. Second, helium may be unable to penetrate in all pores especially if they are isolated by the drug solidified on the surface of the microparticles. As the porosity of the TCPSi microparticles was determined to be 65 volume% (gravimetrically), it could be concluded the pores being 80% fulfilled by volume. To determine the porosity of the porous silicon (etched film), the porous film was weighed and the mass was divided by the density. When the value was compared with the volume of the film calculated on the basis of physical dimensions the porosity was obtained.

The pore volumes of the TCPSi microparticles and the loaded TCPSi particles were 0.8335 $cm^3/g_{TCPSi}$ and 0.3555 $cm^3/g_{TCPSi+ibu}$, respectively (Fig. 3). By setting the drug load degree as 31 mass%, the total pore volume of the drug loaded TCPSi microparticles was 0.575 $cm^3/g_{TCPSi+ibu}$ (0.8335 $cm^3/g_{TCPSi}$ · (1–0.310) $g_{TCPSi}/g_{TCPSi+ibu}$). The value includes the empty pore volume together with the volume of ibuprofen in the pores. By subtracting, the volume of ibuprofen within the pores was obtained as 0.220 $cm^3/g_{TCPSi+ibu}$, and this value now equals to 310 $mg/g_{TCPSi+ibu}$ (31 mass%). These values gave (by dividing) the density value of 1.41 g $cm^{-3}$ for the ibuprofen confined to the pores. This was an unrealistically high value when compared with the density of bulk ibuprofen (1.120 g $cm^{-3}$) and was obviously due to the incorrect pore volume value measured with nitrogen desorption for ibuprofen loaded TCPSi microparticles.

*Antipyrine*

The same procedure in the calculations was performed with antipyrine as with ibuprofen. The total antipyrine content in the TCPSi microparticles was 25.6 mass% according to the TG measurements

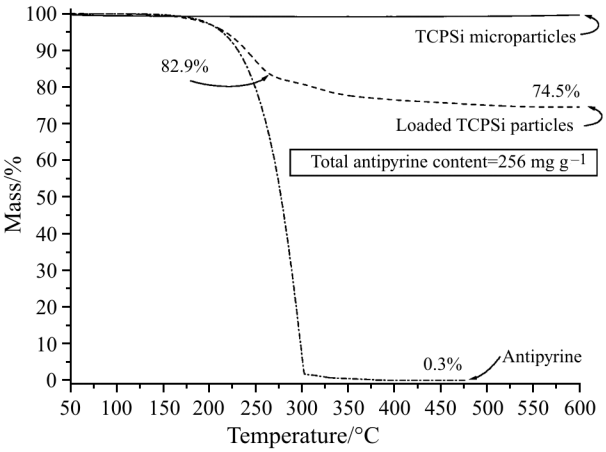


**Fig. 4** TG curves of TCPSi microparticles (solid line), antipyrine loaded TCPSi (850ºC) particles (dashed line) and antipyrine powder (dotted line). Heating rate=10ºC $min^{-1}$, gas purge=$N_2$

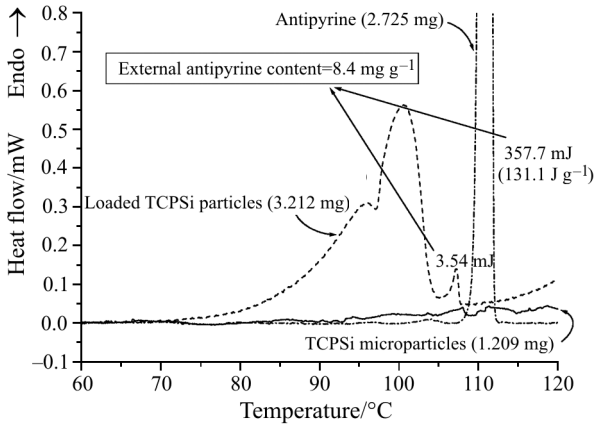


**Fig. 5** DSC curves of TCPSi microparticles (solid line), antipyrine loaded TCPSi (850ºC) particles (dashed line) and antipyrine powder (dotted line). Heating rate=2ºC min$^{-1}$, gas purge=$N_2$

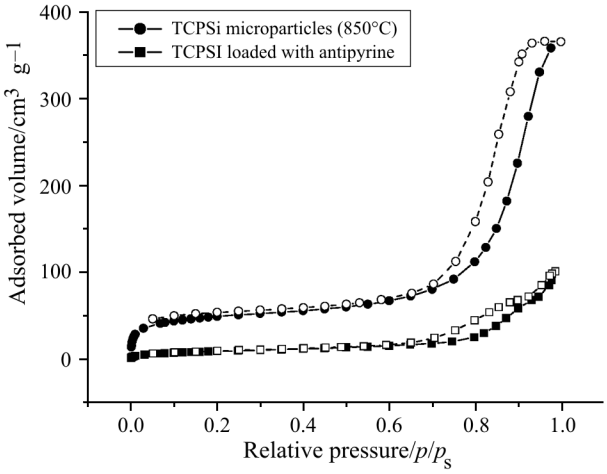


**Fig. 6** $N_2$ adsorption (solid symbols) and desorption (open symbols) isotherms of TCPSi microparticles (circles) and antipyrine loaded TCPSi particles (squares)

(Fig. 4). The fraction of the drug on the surface of the particles was 0.8 mass% calculated from the DSC traces (Fig. 5). Also for antipyrine, a broad endotherm was observed before the sharp melting of bulk antipyrine. The minor shift in the melting temperature with respect to bulk antipyrine was due to the precipitation of antipyrine in the form of thin layer on the surface of the TCPSi microparticles. The interpretation was verified via DSC measurements made with unporous silicon particles, on which antipyrine was precipitated (data not shown). Contrary to ibuprofen, the heat of fusion for the antipyrine confined to the pores was abnormally high, namely 199 J g$^{-1}$, when compared with the corresponding values of the bulk material (131.3 J g$^{-1}$). The explanation for the high heat values might be the evaporation of the loading solution residue, but as the TG curves did not show any mass loss at that temperature range the discrepancy remained unresolved during the present study.

The densities of the TCPSi microparticles, the bulk antipyrine and the loaded microparticles were 2.549, 1.246 and 1.979 g cm$^{-3}$, respectively. The obtained drug load was thus 43.75 volume% that equals to 27.5 mass% agreeing well with the result obtained by thermal analysis.

The pore volumes of the TCPSi microparticles and the loaded TCPSi microparticles were 0.5688 $cm^3/g_{TCPSi}$ and 0.1516 $cm^3/g_{TCPSi+ant}$, respectively (Fig. 6). When the drug load was approximated as 25 mass%, the total pore volume of the drug loaded TCPSi microparticles was 0.427 $cm^3/g_{TCPSi+ant}$. This gave the value of 0.275 $cm^3/g_{TCPSi+ant}$ for the volume of antipyrine within the pores. Dividing of 250 $mg/g_{TCPSi+ant}$ (25 mass%) by 0.275 $cm^3/g_{TCPSi+ant}$ yielded the density value of 0.909 g cm$^{-3}$ for the antipyrine confined to the pores. The density of bulk antipyrine was 1.246 g cm$^{-3}$. The calculated density value was reasonable since the molecules of the solids substance occupy more room in a limited space where the disordered surface structure constitutes a great fraction of the whole substance [4]. Thus, it is expected that the smaller the pores are the lower values the density (molar volume) reaches. Another reason for the low density could be the inability of the nitrogen molecules to penetrate into the isolated pores blocked by the drug in the timescale of the measurement.

## Conclusions

Combination of the information obtained from TG and DSC measurements gave a reliable estimation for the amount of the drug confined to the pores of mesoporous materials. To distinguish the drug in the pores from that on the surface, thermoporometry provided a beneficial principle since the drug loaded within the pores possessed depressed melting temperature. A simple method to verify the results was helium pycnometry that gave the total content of the drug in the TCPSi sample as well. Nitrogen ad/desorption data could be used to estimate the degree of drug load but with cautions, since the capability of the nitrogen molecules to penetrate in the isolated pores might be incomplete.

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