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Modelling structure-function relationships for diffusive drug transport in inert porous geopolymer matrices

Erik Jämstorp^{a,}, Maria Strømme^a, Göran Frenning^b*

^aDivision for Nanotechnology and Functional Materials, Department of Engineering Sciences, The Ångström Laboratory, Uppsala University, Box 534, SE-751 21 Uppsala, Sweden

^bDepartment of Pharmacy, Uppsala University, Box 580, SE-751 23 Uppsala, Sweden

*to whom correspondence should be addressed. E-mail address: erik.jamstorp@angstrom.uu.se

Abstract

A unique structure-function relationship investigation of mechanically strong geopolymer drug delivery vehicles for sustained release of potent substances is presented. The effect of in-synthesis water content on geopolymer pore structure and diffusive drug transport is investigated. Scanning electron microscopy, N₂ gas adsorption, Hg intrusion porosimetry, compression strength test, drug permeation and release experiments are performed. Effective diffusion coefficients are measured and compared to corresponding theoretical values as derived from pore size distribution and connectivity via pore network modelling. By solely varying the in-synthesis water content, mesoporous and mechanically strong geopolymers with porosities of 8–45% are obtained. Effective diffusion coefficients of the model drugs Saccharin and Zolpidem are observed to span two orders of magnitude ($\sim 1.6\text{--}120 \times 10^{-8} \text{ cm}^2/\text{s}$), comparing very well to theoretical estimations. The ability to predict drug permeation in and release from geopolymers, and materials alike, allows future formulations to be tailored on a structural and chemical level for specific applications, such as controlled drug delivery of highly potent substances.

Keywords: geopolymers, porosimetry, modelling, diffusion, permeation

1. Introduction

Proper treatment of chronic pain often requires a continuous supply of highly potent drugs such as opiates or synthetic opioids.¹ Controlled or sustained release formulations of these highly potent drugs would be of great value, provided that the safety issues associated with dose dumping could be overcome.² One option would be to use inert porous matrices of high chemical and mechanical integrity.^{3–5} Drug release from such matrix (or monolithic) systems is generally claimed to be diffusion controlled and, for matrices of a cylindrical shape, useful expressions for the amount of released drug exist in the literature, both when all drug is dissolved within the pore system⁶ and when solid and dissolved drug coexist as a result of solubility limitations.^{7,8}

We have previously suggested the use of inorganic amorphous aluminum-silicate gels,⁹ so called geopolymers,¹⁰ as potential drug carriers of highly potent opioids. Geopolymers are generally made at ambient temperatures by mixing thermally activated alumino-silicate precursor materials, such as clays, with an aqueous and highly caustic silicate solution. The harsh alkaline environment catalyses dissolution of the alumino-silicate precursor, whereby the dissolved species precipitate into a rigid and porous gel network.¹¹ The geopolymers set within a few hours and, once hardened, they have a number of attractive properties such as high compressive strength, high acid and heat resistance. Geopolymers have mainly been intended as an

environmentally friendly construction material substitute for Portland cement, or to be used in applications involving immobilization of toxic waste.^{10,12}

In recent years, a substantial amount of work on geopolymers has been devoted to the effect of synthesis parameters on geopolymerization and the resultant mechanical and chemical properties (Duxson et al^{11,12} and references therein). However, relatively few studies^{13,14} have specifically investigated their implication on the pore size distribution and diffusion rate within the geopolymer matrix.

In our previous report,⁹ it was shown that drug could readily be embedded into metakaolin based geopolymers in a one-pot synthesis. It was shown that by altering the compositional $\text{SiO}_2/\text{Al}_2\text{O}_3$, $\text{Na}_2\text{O}/\text{Al}_2\text{O}_3$ and $\text{H}_2\text{O}/\text{Al}_2\text{O}_3$ molar ratios of the final geopolymer, a considerable shift in pore size distribution followed, which had a major influence on drug release.

The aim of the present study is to investigate the effect of water as a pore forming agent in metakaolin based geopolymers on porosity, pore-size distribution as well as drug permeability and release rates. A link between the pore structure characteristics and diffusion will be established via pore-network modelling.¹⁵ In addition, the compression strength of the geopolymer compositions will be evaluated with regard to its appropriateness of use as a controlled release matrix.

2. Material and Methods

2.1 Materials

Kaolin ($\text{Al}_2\text{Si}_2\text{O}_5(\text{OH})_4$), fumed silica (SiO_2 , 7 nm particle size), reagent grade sodium hydroxide (NaOH) and potassium phosphate (KH_2PO_4) were purchased from Sigma-Aldrich, Sweden. The model drugs Sodium Saccharin ($\text{Na}\cdot\text{C}_7\text{H}_5\text{NO}_3\text{S}$, Aq. Solubility $\text{C}_s(37^\circ\text{C})\sim 1430$ mg/ml,¹⁶ from VWR, Sweden) and Zolpidem tartrate ($2\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}\cdot\text{C}_4\text{H}_4\text{O}_6$, Aq. Solubility $\text{C}_s(37^\circ\text{C})\sim 0.2$ mg/ml as measured in our laboratory, from Cambrex, Sweden).

2.2 Methods

2.2.1 Geopolymer synthesis

The precursor metakaolin was obtained by heating kaolin at 800°C for 2 h. The liquid water glass (sodium silicate solution) was prepared by vigorously mixing de-ionized water with fumed silica and sodium hydroxide until a clear and viscous solution was formed. The geopolymers were formulated by mixing metakaolin, water glass (diluted with de-ionized water) to match each individual composition ($\text{SiO}_2/\text{Al}_2\text{O}_3=3.6$, $\text{Na}_2\text{O}/\text{Al}_2\text{O}_3=1.1$, $\text{H}_2\text{O}/\text{Al}_2\text{O}_3=10.3, 12.3, 14.3, 16.3, 18.3$, expressed as molar ratio) and either of the model drugs (13 mg per gram metakaolin) into a homogeneous paste in a glass mortar. The thus formed systems will henceforth be referred to as Sac10–Sac18 and Zol10–Zol18 (for Saccharin and Zolpidem, respectively). The paste was transferred to pellet Teflon®-moulds having cylindrically shaped holes (1.5×1.5 mm, diameter $\times$ height). “Empty” geopolymer samples (henceforth referred to as Emp10–Emp18), i.e. without the model drug, were similarly prepared, whereby some of the paste was also transferred to disc-shaped Teflon®-moulds (20×1.2 mm) and cylindrical compression rod (6×12 mm) rubber moulds. After moulding, all moulds were sealed and subsequently placed in an oven set to 40°C for 48 h. This moderate heat treatment is considered to be sufficient for complete geopolymerization.¹⁷ The cured pellets, discs and rods were demoulded, air-dried and directly used for further experimental characterization. In addition to the five chosen samples, geopolymers with $\text{H}_2\text{O}/\text{Al}_2\text{O}_3$ ratios of 8.3 and 20.3 were prepared, but the former proved to be too

dry while the latter were too diluted to be poured, and kept within the Teflon pellet moulds.

2.2.2 X-ray powder diffraction (XRD)

XRD analysis was performed with a D5000 diffractometer (40 kV, 30 mA, Siemens/Bruker AXS Inc., US). The samples were pre-grinded with a mortar and pestle and the powder diffraction measurements were made from 15 to 45° in 2θ angle.

2.2.3 Scanning Electron Microscopy (SEM)

SEM imaging of pellets was performed with a Leo 1550 FEG microscope (Zeiss, UK) equipped with an in-lens detector. A thin gold/palladium layer was sputtered onto the non-conducting samples prior to analysis to avoid charging of the samples. The analysis was performed with 5 kV acceleration voltage.

2.2.4 Compressive strength test

The compressive strengths of the different compositions were tested with an Autograph AGS-H universal testing machine (Shimadzu corp., Japan). Eight to ten cylindrical rods of each composition with the dimensions 6 × 12 mm (diameter × height) were tested and the averages calculated.¹⁸

2.2.5 Mercury intrusion porosimetry

Hg intrusion porosimetry (MIP) was performed in duplicate on pellets without drug from different batches using a Micromeritics Autopore IV model 9520 (Norcross, GA, USA) with Autopore IV 9500 software version 1.06 by Particle Analytical ApS, Hørsholm, Denmark. The contact angle and surface tension used for the calculation were 130° and 0.485 N/m, respectively. The samples were degassed at 95 °C for at least 48 h prior to analysis. Mercury is assumed to penetrate all pores with a diameter larger than 3 nm. The bulk densities ρ_b (i.e. the sample mass divided by the total sample volume, V_{tot}^{Hg} , including all pore volume, V_{pore}^{Hg}) and apparent densities ρ_a (i.e. the sample mass divided by the skeletal volume, V_{skel}^{Hg} , excluding all accessible pore volume) of the Emp10–Emp18 samples were obtained from Hg intrusion data, with V_{tot}^{Hg} and V_{skel}^{Hg} determined as the measured sample volume when a minimum and a maximum amount of mercury had penetrated the sample, respectively. In effect, the apparent density, ρ_a , of a solid will always be larger than or equal to its bulk density, ρ_b . The porosities (in %) of the compositions, ε , were further calculated as:

$$\varepsilon = 100 \times \frac{V_{pore}}{V_{tot}} = 100 \times \left(1 - \frac{\rho_b}{\rho_a} \right) \quad (1)$$

2.2.6 N₂ gas sorption

Nitrogen adsorption–desorption isotherms at 77 K of geopolymer samples were measured in duplicate on pellets from different synthesis batches with a Micromeritics ASAP 2020 (Norcross, GA, USA) volumetric adsorption analyzer. The samples were degassed at 95 °C for at least 48 h prior to analysis. The cumulative mesopore volume $V_{pore}^{N_2}$ and pore size distribution f_{PSD} was calculated using BJH¹⁹ analysis of the adsorption branch of the isotherm. Assuming that all pores were filled with a condensed adsorbate in the normal liquid state at a relative pressure close to unity,²⁰ the geopolymer porosity was calculated from the pore volume $V_{pore}^{N_2}$ according to Eq. (1), using a total sample volume estimated from the bulk density ρ_b as measured by mercury intrusion. For the purpose of determining the connectivity, bulk

condensation experiments were performed, as described in Murray et al.²⁰ Briefly, the adsorption branch is measured in a regular manner but the pressure is kept at the N₂ saturation point ($p/p_0=1$) for 10 min before the equilibration at the first pressure point in the desorption branch, thus allowing nitrogen to condense in larger pores than probed during a normal run.

2.2.7 Drug permeation in diffusion cell

Disc-shaped geopolymer samples were mounted in a horizontal side-by-side diffusion cell (15mm, PermeGear, Riegelsville, PA-US). Donor and receptor compartments (34 ml) were initially filled with phosphate (50mM KH₂PO₄) buffer solution set to pH 6.8 with NaOH, and the donor compartment additionally contained 3 mg/ml dissolved Na-Saccharin. The phosphate anions are not expected to adsorb to the negatively charged geopolymer or to precipitate in an acid–base reaction due to the absence of suitable counterions, such as divalent or trivalent metals (e.g. Ca²⁺), in the solution.¹⁰ Experiments were performed at 37 °C and each compartment was kept under constant magnetic stirring (100 rpm). Changes in the concentration of Saccharin in the receptor compartment were monitored with a UV/VIS spectrophotometer (Shimadzu 1650PC, Japan) at regular time intervals by automatically withdrawing and returning small aliquots (1 mL) with a peristaltic pump. The diffusion coefficient was estimated by the time-lag (TL) method, which has been described mathematically in several books and articles.^{21,22} Briefly, in the TL method Fick's law may be solved²³ to give the total amount of solute $M(t)$ transferred through the membrane with time t as

$$M(t) = \frac{A\varepsilon DC_{d0}}{l} \left(t - \frac{l^2}{6\varepsilon D} \right) \quad (2)$$

where A , ε , C_{d0} , l and D are the effective membrane area, porosity, initial concentration of solute in the donor compartment, membrane thickness and diffusion coefficient, respectively. Here and henceforth, D represents the effective diffusion coefficient denoted by D' in Frenning et al.^{5,7} A variant quasi-steady-state (VQSS) model²³ was similarly used for verification. When applying the TL and VQSS models it is assumed that both compartments are well mixed to avoid any external mass transfer resistance.

2.2.8 Drug release measurements

The release of model drugs from the pellets was carried out in a USP-2 dissolution bath (Sotax AT7 Smart, Sotax AG, Switzerland) equipped with 1000 ml vessels (37 °C, 50 rpm). 400 mg of pellets were placed in each vessel containing 500 ml pH 6.8 phosphate buffer from which aliquots (1 mL) were withdrawn 8 to 9 times during the time of release. The concentration of drug in the liquid samples was analyzed with a UV/VIS detector (Shimadzu 1800, Japan).

When Saccharin is used as the model drug, the initial pellet drug concentration ($C_0 \sim 7\text{--}26$ mg/ml) is considerably below the solubility of the drug in the matrix ($\varepsilon C_s \sim 127\text{--}602$ mg/ml) and if the drug dissolution rate is assumed not to be a rate-limiting factor, the drug release would simply be governed by molecular diffusion (Fick's second law) through the network of pores of the geopolymer.²² The fraction of released drug $Q(t)$ as a function of time may then – for a uniform cylindrical body with zero concentration (perfect sink) boundary conditions – be expressed as^{22,6}

$$Q(t) = 1 - \frac{8}{(HR)^2} \sum_{i,j=1}^{\infty} \frac{1}{\alpha_i^2} \exp(-D\alpha_i^2 t) \frac{1}{\beta_j^2} \exp(-D\beta_j^2 t) \quad (3)$$

Here D is the diffusion coefficient of the drug molecules, $\alpha_i = \eta_i/R$, where η_i is the i :th zero of the Bessel function $J_0(r)$, $\beta_j = (2j-1)\pi/(2H)$, where R and H are the radius and half height of the cylindrical pellets, respectively. Equation (3) is applicable under the assumptions that uniformly dispersed solid drug rapidly dissolves in the liquid entering the pore system and that the subsequent release is governed by isotropic diffusion.

When Zolpidem is used as the model drug, the initial pellet drug concentration ($C_0 \sim 7\text{--}13$ mg/ml) is considerably above the drug solubility in the matrix ($\varepsilon C_s \sim 18\text{--}84$ $\mu\text{g/ml}$). As the dissolution liquid penetrates the pellet structure, a distinct boundary between the completely dissolved and (partially) solid drug will form, that exists until all excess of drug ($C_0 - \varepsilon C_s$) has been removed by diffusion. The well-known Higuchi equation,²⁴ valid for planar systems, has been extended^{7,8} to describe drug release from a finite-sized cylindrical geometry. The fraction of released drug $Q(t)$ as a function of time may, for a uniform cylindrical body with zero concentration (perfect sink) boundary conditions on all surfaces, be expressed as⁷

$$Q(t) = 1 - (1 - c_s)\xi\kappa^2 + c_s \frac{(1 - \kappa^2)(1 + \xi)}{4 \ln \kappa} \quad (4)$$

where $c_s = \varepsilon C_s / C_0$. The time-dependent variables ξ and κ are defined as

$$\xi = 1 - \sqrt{\frac{4c_s D t}{(2 - c_s)H^2}} \quad (5)$$

and

$$\frac{4c_s D t}{R^2} = (1 - 2c_s)(1 - \kappa^2) + 2(1 - c_s)\kappa^2 \ln \kappa + c_s [E_1(-2 \ln \kappa) + \ln(-2 \ln \kappa) + \gamma] \quad (6)$$

where R and H again denote the radius and half height of the cylinder, respectively, D the diffusion coefficient, $\gamma \approx 0.577$ is the Euler constant and E_1 is an exponential integral (see Frenning et al⁷). Nonlinear curve fitting to the experimental data was performed by using MATLAB[®].

2.2.9 Pore connectivity

The pore connectivity, Z , was determined from bulk nitrogen adsorption/desorption data according to the procedure described by Seaton and co-workers.^{20,25,26} The analysis is based on the observation that a certain nitrogen filled pore cannot empty during desorption unless it is connected to the exterior by open pores, resulting in a percolation-type desorption process, from which inferences about the connectivity can be made. If we let X be the fraction of pores in which nitrogen is below its condensation pressure (that hence would be empty in the absence of percolation effects) and X_A be the fraction of pores that indeed are empty, ZX_A is expected to be a universal function of ZX (and the lattice size N for finite lattices),²⁶

$$ZX_A = f(ZX, N) \quad (7)$$

The connectivity Z may thus be extracted by fitting Eq. (7) to the experimental data. No analytical expression for $f(ZX, N)$ is known, however, and this function was therefore determined by simulations according to the procedure described by Liu et al.,²⁶ effectively reproducing Fig. 3 in this reference.

2.2.10 Pore network model

In order to relate the pore structure to the ensuing diffusional drug release, we consider a three-dimensional pore-network model that is based on the simple cubic lattice. Each lattice node thus represents a pore junction and each nearest-neighbour bond a pore that may be either open or closed. The simple cubic lattice is convenient to work with as long as the connectivity Z does not exceed 6 (the number of nearest neighbours in the network), and has previously been shown to provide results that are practically indistinguishable from those obtained from random networks of the same average connectivity.²⁷

The open pores are assumed to have a cylindrical shape, with varying radii r and fixed length L . Although a translated Rayleigh distribution typically has been postulated for the pore radii,²⁸ we here use a standard Weibull distribution, of the form

$$f = \frac{\alpha}{\beta} \left(\frac{r}{\beta} \right)^{\alpha-1} \exp \left[- \left(\frac{r}{\beta} \right)^{\alpha} \right], \quad (8)$$

where the parameters α and β govern the shape and the width of the distribution. The mean pore radius, μ , is calculated as $\beta \Gamma(1+1/\alpha)$, where Γ is the Gamma function. As shown below, the Weibull distribution, Eq. (8), provided an excellent description of the experimental data, enabling values of α and β to be extracted by nonlinear curve fitting. The Weibull distribution reduces to a (non-translated) Rayleigh distribution when the shape parameter $\alpha = 2$. The pore length L is finally determined so that the porosity of the resulting pore network matches the experimental values (attributing all pore volume to the cylindrical pores and none to their junctions).

Consider a pore with radius r_{ij} (cross-sectional area $a_{ij} = \pi r_{ij}^2$) that connects two neighbouring sites i and j . If C_i and C_j are the drug concentrations at the two sites, the flux along the pore may, during steady state, be expressed as

$$I_{ij} = - \frac{D_0 a_{ij}}{L} (C_i - C_j) \quad (9)$$

where D_0 is the diffusion coefficient of the drug in the liquid within the pores. Consistent with the fact that no volume is assigned to the nodes, it makes sense to demand that no drug accumulates at the nodes. For each node i , it thus holds that

$$\sum_{j \in \text{nn}\{i\}} I_{ij} = 0, \quad (10)$$

where the sum extends over all nearest neighbours to i , as indicated. When concentrations are assigned to the nodes on two opposite boundaries – corresponding to a concentration gradient in one spatial direction – Eqs. (9) and (10) between them form a linear equation system for the drug concentrations at all nodes in contact with either boundary. This equation system was solved numerically by using routines for sparse computation implemented in the Sun Performance Library (Oracle Solaris Studio 12.2, Oracle, USA). Networks of size $30 \times 30 \times 30$ (in units of L) were studied and all reported values are the average of 16 independent simulations.

3. Results and Discussion

3.1 Geopolymer structure

Figure 1 shows XRD spectra of kaolin, metakaolin and the Emp10–Emp18 samples. Apart from the XRD peaks which are thought to be associated with mica (M) impurities in the kaolin powder, the spectra show the transition of crystalline kaolin to amorphous metakaolin due to the heat treatment. The metakaolin, as well as the synthesized geopolymers spectra, display broad humps, which are typical for amorphous materials, with maxima located at $\sim 20\text{--}22^\circ$ and $\sim 28\text{--}30^\circ$ in 2θ (Fig. 1), respectively. The XRD spectra of the different geopolymer compositions (Emp10–Emp18) were very similar, and the varying amount of water did not seem to have any influence with regard to crystallinity. This is consistent with previously reported results,^{13,29} which indicated that the compositional effect on the chemistry of the structure due to different water ratios was negligible, as probed with ^{29}Si and ^{27}Al MAS NMR, as long as the Si/Al ratio was kept constant. Figure 2 shows SEM micrographs of the precursor metakaolin (Fig. 2a) and fracture surfaces (Fig. 2b–f) of fully reacted regions of the different geopolymer compositions (Emp10–Emp18). The well-known sheet-like microstructure of crystalline kaolin³⁰ is preserved in the transition to amorphous metakaolin as observed by SEM in Fig. 2a.

The geopolymers are synthesized as monoliths, where the water required in synthesis is distributed in the geopolymer gel network. The space taken up by water constitutes the pores after drying. The microstructure (Fig. 2b–f) is seen to consist of a nanoparticulate meshwork of clusters resulting from dissolution of the aluminosilicate precursor, followed by nucleation and growth of nanometer-sized particles that aggregate at a critical concentration, causing the geopolymer to solidify. The water used in synthesis is expelled to the pore network, which has a non-uniform morphology with a distribution of sizes as is evident from the micrographs (Fig. 2b–f). However, on larger length scales, the porosity appears uniformly distributed throughout the microstructure, where unreacted sheets of metakaolin are also sometimes visible.³⁰

The size and packing of the gel clusters as well as the pore size and morphology are seen (Fig. 2) to be affected by the varying processing conditions ($\text{H}_2\text{O}/\text{Al}_2\text{O}_3$ ratio). Apart from the in-synthesis water fraction, additional processing conditions such as the relative amounts of the other synthesis constituents ($\text{SiO}_2/\text{Al}_2\text{O}_3$, $\text{Na}_2\text{O}/\text{Al}_2\text{O}_3$), synthesis temperature and pressure, have previously been reported^{11,12,17,30} to greatly affect the geopolymer microstructure. When (Fig. 2b–f) the $\text{H}_2\text{O}/\text{Al}_2\text{O}_3$ ratio increases from 10.3, 12.3, 14.3, 16.3 to 18.3 (while keeping the remaining conditions constant), the particulate network appear to turn more open. Water is necessary during gelation to enable the dissolution, hydrolysis, transfer and subsequent condensation of the various Al^{3+} and Si^{4+} species. An increase in the $\text{H}_2\text{O}/\text{Al}_2\text{O}_3$ ratio is seen (Fig. 2b–f) to produce coarser cluster structures. This observation has previously been related³⁰ to the geopolymerization reaction proceeding more slowly with more water present, as a result of the reduction in pH of the paste, allowing more time for the dissolution and re-precipitation. Such precipitation would occur as bridging material rather than as individual nuclei (Ostwald ripening).³¹ After gelation, transformation occurs, due to continued reaction or structural reorganization, which causes the expulsion of fluid from the interstices of the structure into larger pores. This process, syneresis,¹¹ would be promoted by an increased matrix permeability with larger water fraction.

The compression strengths of the Emp10–18 samples were fairly high ($\sim 40\text{--}80$ MPa) as compared to previously reported values⁹ and were seen to decrease with an increase in the $\text{H}_2\text{O}/\text{Al}_2\text{O}_3$ ratio (see Supporting Information). A more open pore

structure (Fig. 2), reduce the volume fraction of load-bearing material and increases the probability of crack formation. This is expected and has earlier been thoroughly discussed.⁹

3.2 Porosity

The porosity of the Emp10–Emp18 samples, shown in Fig. 3, ranges from ~8–43% as estimated (Eq. (1)) from bulk density ρ_b (from Hg intrusion) and apparent density ρ_a (from Hg intrusion porosimetry and N₂ sorption). The reduction in bulk density ρ_b (from 1.74 to 1.28 g/mL), and the consequent increase in porosity, is mainly a result of the higher water content used in synthesis, which leaves more and larger pores in the matrix after evaporation. Furthermore, the increase in apparent density ρ_a (from ~1.89 to 2.23 g/mL), is most likely an effect of pores being more accessible³² due to the reorganization process mentioned above, leading to a larger total pore volume being obtained from the Hg intrusion and N₂ sorption data.

An indication of an increase in accessible porosity may also be seen if an estimation of the total porosity is performed. A plot can be made (Fig. 3) by assuming that the most porous composition (H₂O/Al₂O₃=18.3) had a porosity of ~43% and that each decrement in water content would give a decrease in the corresponding pore volume (considering the density of water being ~1g/mL). The values thus derived agree fairly well with the most porous samples (Emp16–Emp18), but deviate increasingly for the samples with decreasing porosity (Emp10–Emp14), which is interpreted as an effect of an increased volume of closed pores. The porosities are in the same range as has been reported before.^{14,32} The reasonable agreement of results obtained from the different techniques has already been reported²⁰ and is here similarly observed.

Figure 4a shows the cumulative intrusion volume and differential intrusion pore volume vs. pore diameter d for the Emp10–Emp18 samples as recorded by mercury intrusion porosimetry. Again, the increase in total pore volume (and porosity) with an increase in in-synthesis water is here seen in the maximum Hg intrusion volume (the high-pressure plateau in Fig. 4a). This technique offered an estimate of the pore-size distribution in the range from 0.003 to 300 μm (Fig 4a), and the pores of the Emp10–Emp18 samples were nearly all to be found in the mesoporous range ($d < 50 \text{ nm}$).

Figure 4b shows the nitrogen sorption data for the Emp10–Emp18 samples together with the pore size distribution (inset) obtained by BJH analysis¹⁹ of the adsorption isotherms. Since the N₂ isotherms all show a slight indication of a plateau at high relative pressure ($p/p_0 \sim 0.8\text{--}0.9$), they may be regarded as Type IV.³³ The hysteresis loops for all recorded isotherms are of an intermediate type between the H2 and H3 hysteresis loops described in the IUPAC classification. This shape is typical for many inorganic oxide gels and is related to their complex pore structures.³³

For analysis of pore size distribution, the adsorption branch was adopted (inset Fig. 4b), even though there is a risk of overestimating the pore sizes (delayed condensation effects).³³ However, the presence of a broad distribution of interconnected pores (Fig. 4) renders the location of the desorption branch to be largely controlled by network percolation effects and thus less suitable.³³ The increase in average pore size with increasing water ratio, which was anticipated from the inspection of the SEM micrographs (Fig. 2), is quantitatively accounted for in Fig. 4. As seen in the inset in Fig. 4b, the Weibull distribution (Eq. (8)) was found to provide an excellent description of the major part of the pore-size distribution. The parameter values extracted from the fits are collected in Table 1.

The average pore diameter (2μ) was observed to increase from 10.1 nm (Emp12) to 12.4 nm (Emp14) to 17.1 nm (Emp16) and 26.9 nm (Emp18) for every increment in water ratio. Emp10 was an exception to this trend, with $2\mu \approx 11.8 \text{ nm}$. The reason

for this could be related to incomplete geopolymerization under the insufficient water condition, resulting in partially dissolved or undissolved metakaolin with interstitial pore space as mentioned in Sec. 3.1 above (See Fig. 2b).

These observations are in line with those presented by Kriven et al.²⁹ and in a recent study by Okada et al.,¹³ where it was observed that both pore volume and pore size increased with an increase in the $\text{H}_2\text{O}/\text{Al}_2\text{O}_3$ (but also the $\text{Na}_2\text{O}/\text{Al}_2\text{O}_3$) ratio.

Results from the bulk condensation experiments are exemplified by the sorption isotherms of Emp14 displayed in Fig. 5a. As expected, the major part of the adsorption branch coincides with the one shown in Fig. 4b, but a rapid increase in amount adsorbed is seen to occur in the vicinity to the saturation pressure. As a consequence, the desorption branch differs from the one seen in a standard N_2 sorption experiment. In the inset of Fig. 5a, the fraction of accessible pores (X_A) – calculated from the difference between the adsorption and desorption branches – is shown as a function of the fraction of pores (X) that would have been empty in the absence of percolation effects. The solid line in the figure represents a fit of Eq. (7) to the experimental data, from which inferences about connectivity were made.

An analogous analysis of data for the remaining “empty” geopolymer samples indicated that the connectivity increased from about 2.5 for Emp10 to slightly less than 6 for Emp18 (see Fig. 5b). A few bulk condensation experiments were performed on extracted Sac and Zol systems. The results generally confirmed the increase in connectivity seen for the “empty” samples.

3.3 Diffusion coefficients from drug permeation and release

Figure 6 presents the results from the drug permeation and release experiments. After an initial lag time, the Saccharin permeation through the geopolymer discs (Emp10–Emp18 with $\text{H}_2\text{O}/\text{Al}_2\text{O}_3=10.3\text{--}18.3$) reached a steady-state,²¹ demonstrated by the linearly increasing amount of Saccharin Q transferred to the donor compartment (Fig 6a). This is typical for an inert porous matrix providing a constant barrier to diffusion during the time course of an experiment. Any temporal change in porosity, such as swelling or degradation during drug diffusion, is not expected due to the mechanical and chemical stability of the high-density geopolymer gel at neutral pH.¹⁰ The larger amount of Saccharin transferred per unit time with increasing $\text{H}_2\text{O}/\text{Al}_2\text{O}_3$ ratio may thus be related to the shift in pore size distribution towards more and larger pores with higher connectivity. A more open pore structure enables a higher mass transfer rate. This explanation may likewise account for the similar trend found in the release experiments. Figure 6b and c show the fraction of Saccharin and Zolpidem, respectively, released from the geopolymer pellets (Sac10–Sac18 and Zol10–Zol18) with time. A higher $\text{H}_2\text{O}/\text{Al}_2\text{O}_3$ ratio results in a higher rate of release for both Saccharin (Fig. 6b) and Zolpidem (Fig 6c). The role of drug solubility is apparent when comparing Fig. 6b and c. The markedly higher solubility of Saccharin as compared to Zolpidem is greatly affecting the cumulative amount of drug released per time $Q(t)$. Diffusive mass flow is limited by the highest attainable concentration gradient according to Fick’s law. Apart from this, a larger amount of water in synthesis yields a larger total fraction of drug being released. This has been more thoroughly discussed before⁹ and is thought to be due to trapping of drug in closed pores, which amount is expected to increase with lower $\text{H}_2\text{O}/\text{Al}_2\text{O}_3$ ratio and decreasing pore connectivity (Fig. 5b).

The rate of the mass transfer in the porous geopolymer structures may be quantified by an effective diffusion coefficient D . Figure 6d shows a plot of D obtained from the diffusion cell and release experiments as well as from simulations. The experimental values of D were extracted by fitting of Eqs. (2)–(4) to the data with a good fit quality (viz. solid lines in Fig. 6a–c). For Saccharin permeation, the

diffusion coefficients were obtained from the slope dQ/dt via a fit of Eq. (2) of the TL method (VQSS model values differed in average about 5%). The diffusion coefficients are all found to increase, spanning over two orders of magnitude, from $\sim 1.6 \times 10^{-8}$ to $\sim 120 \times 10^{-8} \text{ cm}^2/\text{s}$, with higher $\text{H}_2\text{O}/\text{Al}_2\text{O}_3$ ratio.

The average values of D obtained from the Saccharin permeation and release and the Zolpidem release were all comparable (Fig. 6d), showing that there is a good agreement between the results of the two methods. However, slight discrepancies in D , e.g. for $\text{H}_2\text{O}/\text{Al}_2\text{O}_3=10.3$, could be due to a difference in distribution of the drugs inside the matrix caused by dissimilar drug dissolution and particle size during synthesis. The influence of embedding drugs during pellet synthesis on the structure and the consequent effect on D was examined by doubling the in-synthesis drug amount (0.7 wt% to 1.4 wt%) for all compositions followed by subsequent drug release measurements (see Supporting Information). The diffusion coefficients were found to be unaffected by doubling the drug concentration except for compositions with $\text{H}_2\text{O}/\text{Al}_2\text{O}_3=10.3$, for which D increased from 1.6×10^{-8} to $6.8 \times 10^{-8} \text{ cm}^2/\text{s}$.

Also included in Fig. 6d are the results obtained from pore-network modelling, using the parameters α and β from the pore-size distribution, the porosity ε and the connectivity Z of the Emp systems as input. To enable a direct comparison with experimental data, the unhindered drug diffusion coefficient D_0 was set to $5 \times 10^{-6} \text{ cm}^2/\text{s}$. As observed in the figure, the theoretical results follow the same trend as the experimental, and a good quantitative agreement is found, demonstrating that the effective diffusion coefficients indeed may be inferred from pore-network modelling.

The observed broad range in apparent diffusion coefficients is a product of differences between samples in pore radii and connectivity of the pore network. A percolation threshold exists at a connectivity of about 1.5, and the effective diffusion coefficient vanishes when the connectivity approaches this value.⁵ With a distribution in pore sizes, one would expect the smallest pores to contribute insignificantly to the overall flux, making the connectivity of those pores that make a significant contribution somewhat smaller than the values presented in Fig. 5b.

4. Conclusions

Five geopolymer compositions ($\text{SiO}_2/\text{Al}_2\text{O}_3=3.6$, $\text{Na}_2\text{O}/\text{Al}_2\text{O}_3=1.1$) with varying water content ($\text{H}_2\text{O}/\text{Al}_2\text{O}_3=10.3, 12.3, 14.3, 16.3, 18.3$) were prepared. The porosity, average pore size, drug permeation and release rate were all found to increase with increasing water ratio, while the compression strength decreased. However, all compression strengths can be considered sufficiently high to hinder possible dose dumping due to mechanical impact in highly potent drug delivery applications. Effective diffusion coefficients, as extracted from experimental data and modelling, compared very well and were seen to span over two orders of magnitude (~ 1.6 – $120 \times 10^{-8} \text{ cm}^2/\text{s}$). The ability of this approach to predict and control molecular permeation and release characteristics of geopolymers may also equally well be extended to many other inert disordered porous materials alike. Future formulations could thus be tailored on a structural and chemical level to suit relevant applications thereof, such as controlled drug delivery, or conversely, immobilization of toxic waste.

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Figures and tables

Figure 1. X-ray powder diffraction spectra of crystalline kaolin (green), amorphous metakaolin (brown), and the amorphous Emp10 geopolymer. The positions of kaolinite (K) and mica (M) diffraction peaks are indicated. The inset shows spectra of all Emp compositions under study.

Figure 2. SEM images displaying the microstructure of metakaolin (a) and geopolymer pellets Emp10–18 (b–f) with increasing water concentration. All bars represent 100 nm.

Figure 3. Average porosity ϵ versus water ratio H_2O/Al_2O_3 of samples Emp10–Emp18 as estimated theoretically and obtained experimentally via Eq. 1 from the measured bulk (ρ_b) and apparent (ρ_a) densities (c.f. inset). Error bars represent total ranges.

Figure 4. (a) Mercury intrusion data plotted as cumulative intrusion volume and differential intrusion pore volume (inset) versus pore diameter for sample Emp10–Emp18. (b) Nitrogen sorption isotherms. The inset shows the BJH pore size distribution calculated from the adsorption branch (symbols) and fits of Eq. 8 to the experimental data (lines).

Figure 5. (a) Nitrogen bulk sorption isotherms for Emp14. The inset shows the corresponding accessibility plot, in which symbols represent experimental data, the solid line a fit of Eq. 7, and the dashed line illustrates the response in the absence of percolation effects ($X_A = X$). (b) Connectivity, Z , of pore networks extracted from bulk condensation experiments with the dashed line as a guide to the eye. An illustration of the cubic lattice cylindrical pore network is included.

Figure 6. Plot of the results from (a) Saccharin permeation, (b) Saccharin release, (c) Zolpidem release, and the extracted (d) diffusion coefficients. Error bars indicate standard deviations.

Table 1: Parameters α and β obtained by fitting the Weibull distribution (Eq. (8)) to the experimental pore-size distributions. The corresponding average pore diameter 2μ is also provided.

Sample	α [-]	β [nm]	2μ [nm]
Emp10	2.99	6.59	11.8
Emp12	3.21	5.66	10.1
Emp14	3.01	6.95	12.4
Emp16	2.67	9.60	17.1
Emp18	2.31	15.17	26.9

Supporting information:

Modeling Structure-function relationships for diffusive drug transport in inert porous geopolymer matrices

Erik Jämstorp, Maria Strømme, Göran Frenning

S1. Compression strength

Figure S1 presents the results from the compression strength tests. An increase in water amount in synthesis results in a decrease in compression strength. A larger amount of water present in synthesis induces a higher porosity, which reduces the volume fraction of load-bearing material and increases the probability of crack formation. See Ref. [S1] for a more extended discussion thereof.

The Emp10-18 geopolymer compositions had fairly high compression strengths (~40-80 MPa) if a comparison with ordinary Portland cement (~35 MPa [S2]) is made. This is an important and promising aspect in order to prevent a controlled release geopolymer pellet from breakage and a subsequent “dose-dumping” during patient administration.

Figure S1 Average compression strength of samples Emp10-18. Error bars represent the standard deviation for at least 8 compression tests.

S2. Drug release from pellets with doubled drug concentration

Figure S2 presents the results of drug release measurements from pellets containing twice as much drug as the ones described in the main text (1.4wt% Saccharin). Similar release profiles and rates as for the single loaded pellets (0.7wt% Saccharin) were found (cf. Fig. 6b of the main text), except for the geopolymer composition with H₂O/Al₂O₃=10.3 where the diffusion coefficient increased from $\sim 1.6 \times 10^{-8}$ to $\sim 6.8 \times 10^{-8} \text{ cm}^2/\text{s}$. An explanation for the higher release rate may be found in the effect of the drug itself on the porosity and connectivity of this very dense geopolymer

composition. The precipitated drug may during a drug release experiment gradually open up pores as it dissolves by letting the dissolution media penetrate the volume it previously occupied.

Figure S2 Results of Sacharin release from geopolymer pellets loaded with twice the amount of drug as those described in the main text (1.4%), with the extracted diffusion coefficients shown in the inset. Error bars indicate standard deviations.

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