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Regular Article

Permeability profile of poly(alkyl cyanoacrylate) nanocapsules

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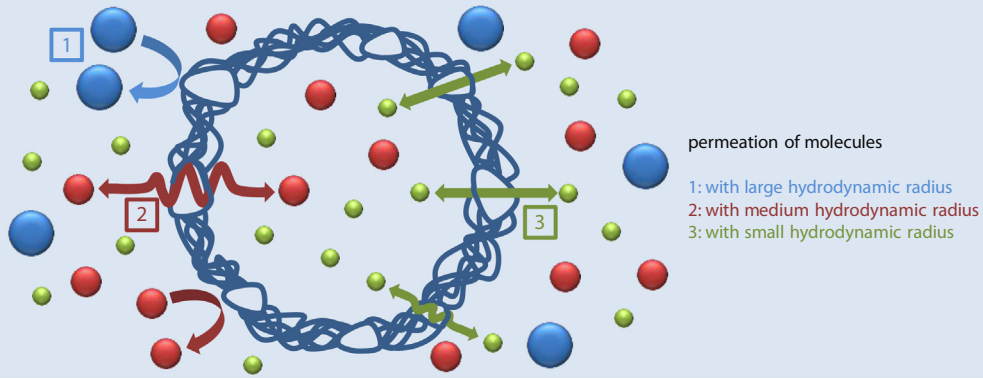
GRAPHICAL ABSTRACT



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ABSTRACT

The permeability profile of poly(alkyl cyanoacrylate) nanocapsules is studied using pulsed-field gradient NMR on a variety of tracer molecules of different size and polarity. In addition, the influence of the surfactant layer and of organic tracer molecules on the capsule membrane permeability for water is examined. The aim of the study is a detailed understanding of the dependencies between molecular properties of a given tracer and its capability to permeate the polymer membrane.

As expected, the results clearly show that the capsule membrane permeability depends on the size of the tracer molecule: the exchange rate of polyethylene glycols continuously decreases with increasing chain length. However, the permeation rate also varies with the polarity of the tracer molecule: molecules of lower polarity exchange faster than more polar ones.

In turn, the capsule membrane permeability is influenced by added organic compounds. Focusing on water as a characteristic permeate and depending on the type of the additive, the permeability can be varied by almost an order of magnitude, offering an opportunity to reversibly switch the uptake and release properties of the capsules.

1. Introduction

Following a common definition, nanocapsules (NCs) consist of a sub-micrometer sized spherical polymer membrane with a liquid core. Typical applications for NCs are drug carrier and release systems in medical environments [1,2] or, in technical environments, material surface functionalizations [3,4].

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A typical polymer material which is used for the nanocapsule membranes is poly(alkyl cyanoacrylate) (PACA). The first PACA NCs have been prepared since the seventies by Florence et al. [5] and Al Khouri Fallouh et al. [6]. PACA NCs fulfill basic requirements for use as medical or pharmaceutical products: they are biodegradable [7] and of low toxicity [8] and they are discussed for the controlled release of calcitonin [9], doxorubicin [10] or for peroral administration of insulin [11–13]. Another possible application is their use as oxygen carriers in liquid dispersion as an artificial blood replacement [14–16]. Different choices for the alkyl side chain open some variability for the physical and physiological properties of the capsules. The alkyl side chains may be partially equipped with terminal alkyne groups which allows for covalent binding of various side chains via click chemistry and hence opens the pathway for a chemical variation of the capsule surface [17,18].

Generally, four approaches lead to the generation of nanocapsules [19]: interfacial polymerization, interfacial precipitation [20,21], self-association of amphiphilic molecules [22] or the layer-by-layer technique [23]. In the layer-by-layer approach, anionic and cationic polyelectrolytes are adsorbed alternatingly onto a solid core which later is replaced by a liquid [23]. The self-association process leads to unilamellar vesicle-like structures [22]. For the two interfacially-induced capsule preparation methods, the polymer is either formed or precipitated at the interface of small emulsion droplets [20,21].

For PACA nanocapsules, Al Khouri Fallouh introduced a preparation method using interfacial polymerization which leads to NCs with thin polymeric walls and a narrow size distribution [6,24–26]. A suitable choice of the emulsion components and of the stabilizing agents used during the NC preparation opens a wide variety of surface structures and properties for medical applications [27]. Initially, a water in oil or oil in water emulsion is formed, either under high-shear conditions or by spontaneous nucleation (“Ouzo effect” [28,29]). Due to their amphiphilicity, the alkyl cyanoacrylate molecules accumulate at the interface of the dispersed droplets. Triggered by hydroxide ions, interfacial polymerization of the reactive cyanoacrylate is started, leading to a spherical capsule membrane with a diameter in a range of 200–600 nm dispersed in an aqueous or organic continuous phase. At this stage, all components of the discontinuous phase which either is or contains the active ingredient arrive in an encapsulated state [5,6,16,24].

Naturally, the suitability of the NCs as nanoscopic containments is determined by the permeability profile of the capsule membrane. While most applications for drug carriers will require low permeability constants for the active ingredient, the contrary may be desired for other uses (as e.g. for oxygen and carbon dioxide carriers in artificial blood replacements [16,30]). In any case, the membrane permeability marks one of the most important capsule properties.

In the past, multiple studies on the permeability of capsule membranes have been performed [31–37]. For microcapsules with diameters in the order of several μm, fluorescent labels have been applied extensively. In this case, the permeation process is followed on a labeled permeate in a time-resolved experiment, often using confocal laser microscopy as a tool [31–35]. If the capsules are of macroscopic size with diameters in the order of several mm, the permeation can be observed by photometry on the adjacent aqueous phase [36] or, in a very recent approach, by NMR micro-imaging (NMR microscopy) [37].

In case of nanocapsules, the observation of the permeation process is much more demanding, as the passage through the membrane cannot be optically resolved. Under these circumstances, a perfect approach to monitor permeation processes is pulsed field gradient-assisted nuclear magnetic resonance (PFG-NMR). This technique not only allows for the assignment of all system components to either the encapsulated or the free state in the capsule dispersion, but also gives access to the observation of the trans-membrane exchange processes [38–43]. Similar techniques have been applied to analyze the membrane permeability of living cells [44,45].

In this study, PFG-NMR is applied to determine a full permeability profile of PACA nanocapsules for a wide variety of organic substances. Further, a separate series of measurements is meant to reveal how organic constituents of the fluid medium affect the membrane permeability. Hereby, we want to achieve a general understanding on how the permeation rates for different molecules depend on their individual properties and how they - in turn - influence permeation. With the knowledge of these fundamental dependencies, it should be possible to predict the permeability constants for potential active ingredients and to (reversibly) influence them in order to control uptake and release in a system with dispersed capsules.

2. Materials and methods

2.1. Basic chemicals

n-Butyl cyanoacrylate (nBCA) was purchased under the name of “Vetbond” from 3M (St. Paul, USA). 1-Propanol was bought from Acros Organics (New Jersey, USA). 1,4-Dioxane, 1-butanol, cyanoacetic acid, D,L-serine, ethanediol, ethanolamine chloride, methansulfonic acid, paraformaldehyde, propargyl alcohol and 2-methylpropan-2-amine were purchased from Alfa Aesar (Karlsruhe, Germany). Phosphorous pentoxide was bought from AppliChem (Darmstadt, Germany). Sodium chloride was purchased from Bernd Kraft (Duisburg, Germany). Acetone, chloroform, cyclohexane, diethyl ether and methanol were purchased from Fisher Chemical (Loughborough, United Kingdom). Sulfuric acid was purchased from Fisher Scientific (Loughborough, United Kingdom). 1,2-Butanediol, 1,4-butanediol, dodecyltrimethylammonium chloride, hydroquinone, L(−)-fucose, polyethylene glycol 200 and polyethylene glycol 8000 were purchased from Fluka (Buchs, Switzerland). Sodium-1-dodecane sulfonate was purchased from Merck (Darmstadt, Germany). Polyethylene glycol 600 and 2000 were bought from Merck-Schuchardt (München, Germany). D(+)-glucose and magnesium sulfate were purchased from Riedel de Haen (Seelze, Germany). Acetonitrile, dimethyl sulfoxide and glycerol were bought from Roth (Karslruhe, Germany). 1,2-Pentanediol, 1,6-hexanediol, L-alanine and D(+)-mannose were purchased from Sigma Aldrich (St. Louis, USA). Span 60 (sorbitan monostearate) was purchased from Sigma Life Science (St. Louis, USA). Ethanol was obtained from VWR (Fontenay Sous Bois, France).

2.2. Propargyl cyanoacetate

Cyanoacetic acid (25.5 g, 300 mmol, 1.0 eq.) and porpargyl alcohol (23.5 g, 420 mmol, 1.4 eq.) are dissolved in chloroform. After addition of 2 mol% sulfuric acid the mixture is stirred for 5 h at 60 °C. After cooling down to room temperature the reaction mixture is washed with saturated sodium chloride solution and the organic phase is dried over magnesium sulfate followed by filtration. The solvent is evaporated and the residue is distilled under vacuum resulting in a clear colorless oily liquid.

^{1}H NMR (300 MHz, $CDCl_3$, d): [ppm] = 2.56 (t, 1H, CH), 3.53 (s, 2H, CH_2), 4.74 (d, 2H, CH_2).