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MOLECULAR DYNAMICS IN POLYMERIC NANOCAPSULES. NMR INVESTIGATIONS

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Abstract

Understanding the dynamics of molecules confined in nanocapsules dispersed in liquid environments is important both for obtaining of theoretical scientific knowledge and for designing of new nanocapsules to be used in controlled drug delivery [1]. Obtaining of information on Brownian motion of the confined molecules, as well as on the molecular exchange through capsule membrane can be favorably accomplished using nuclear magnetic resonance (NMR) diffusometry, a completely noninvasive technique [2].

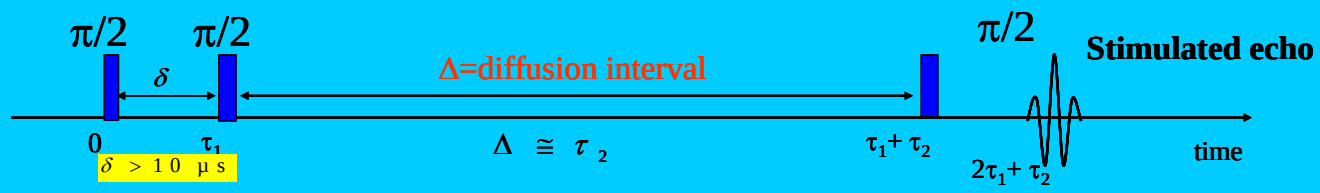
Among the wide variety of NMR diffusometry techniques [3] the fringe field stimulated echo (FFStE) technique was proved to be a versatile one [4]. It consists of three radiofrequency pulses that are applied in the presence of a steady gradient. The time interval between the second and the third radiofrequency pulse defines the diffusion interval. In our experiments the gradient was obtained by shifting the probe21 mm below the homogeneous region. Under such conditions the gradient was 22 T/m and the resonance frequency 375 MHz. This value of the gradient allowed us diffusion measurements for diffusion times between 1ms and 300ms.

Time dependent diffusion studies were performed on miglyol and hexadecane molecules encapsulated in polymeric capsules prepared by two different methods based on emulsification – diffusion technique. These two methods are described in detail in Refs. [5,6]. The diffusion experimental data obtained using the FFStE technique indicate an exchange of encapsulated molecules through the capsules walls. In order to obtain a correct interpretation of the experimental data Monte Carlo simulations will be done.

[1]. V.R. Kumar, J.Pharm. Pharmaceut Sci. **3**, 234(2000)
[2]. C.Mayer, Prog. Nucl. Magn. Reson. Spectroscopy, **40**, 307(2002)
[3]. I.Ardelean and R.Kimmich, Annu. Rep. NMR Spectrosc. **48**, 43(2003)
[4]. G.Farrher, I.Ardelean, and R.Kimmich, J. Magn. Reson. **182**, 215 (2006)
[5]. H.Wassenius, M.Nyden, and B.Vincent, J.Coll.Interf.Sci.**264**, 538(2003)
[6]. D.Quintanar, H.Fessi, E.Allemann, and E.Doelker, Int.J.Pharm.**143**, 133(1996)

The fringe field stimulated echo technique for diffusion measurements

•The RF pulse sequence



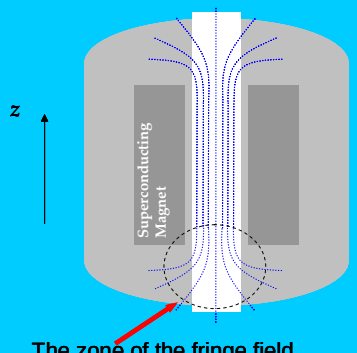
•The gradient

•The echo attenuation formula in the case of unrestricted diffusion

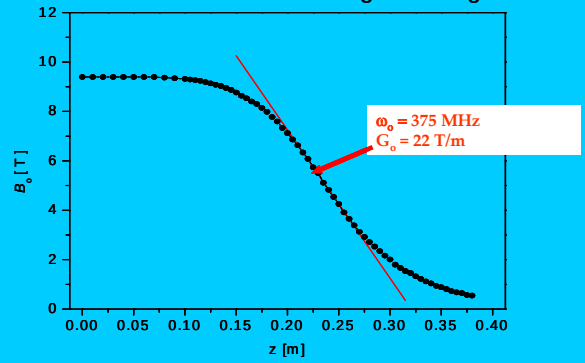
$$A = A_0 e^{-D(\gamma G)^2 \delta^2 (\Delta + \frac{2}{3}\delta)}$$

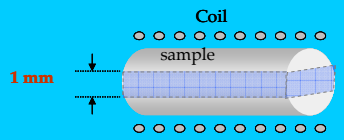
D=diffusion coefficient
γ=magnetogyric ratio
δ=encoding time
G=gradient strength
Δ=diffusion time

•The experimental setup



Measured magnetic induction as a function of the distance from the homogeneos region





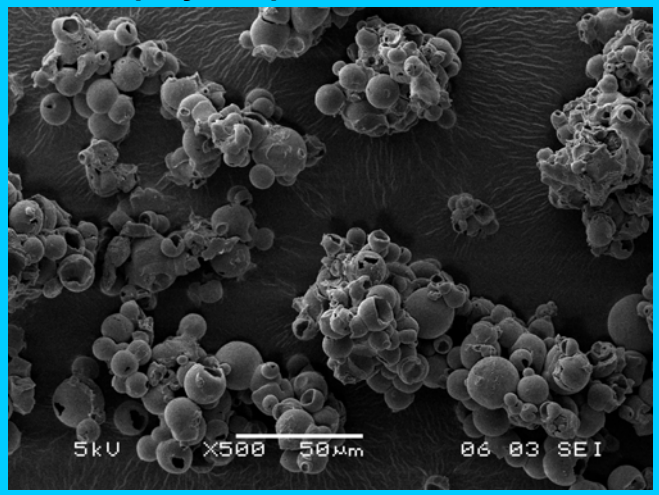
•Due to the high magnetic field gradient (G=22 T/m) only a thin slice will be excited

Observations:

•A constant gradient of **22T/m** is obtained at a position between 22-26 cm bellow the homogeneous region.
•The operation frequency of the spectrometer will be 375 MHz and the probe has to be tuned accordingly
•There are no special hardware requirements for implementing this technique.

Sample preparation and characterization

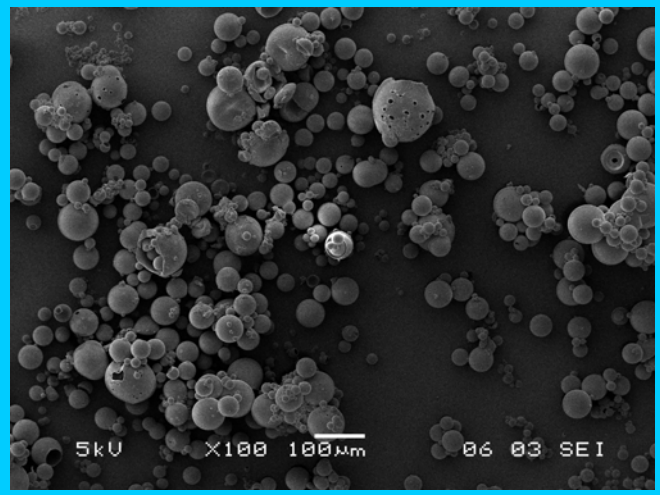
The SEM image of poly ε-caprolactone capsules
- **liquid core: miglyol**
- **solid shell: poly ε-caprolactone**



Preparation:

The poly ε-caprolactone capsules were prepared by an emulsification – diffusion technique. First, two mutually saturated phases were prepared. The saturated water contains 9% of solvent (ethylacetate) and the saturated solvent containts 2.5 % of water. The stabilizer (Pluronic F68) was dissolved at a concentration of 2.5 % in satured water. The oil (Mygliol 812) and the polymer (poly ε caprolactone) were dissolved in satured ethyl acetate. The resultant organic solution was poured into satured water containing stabilizer and stirred at 8000 rpm. An oil in water emulsion was formed. The dispersed droplets were converted in capsules by addition of a large volume of water in order to induce the solvent diffusion under stirring at 300 rpm. The solvent and part of the water were removed by evaporation under reduced pressure to get a concentrated suspension. Finally the suspension was frozen at -55 oC and freeze dried under 0.05 mbar vacuum for 24 h.

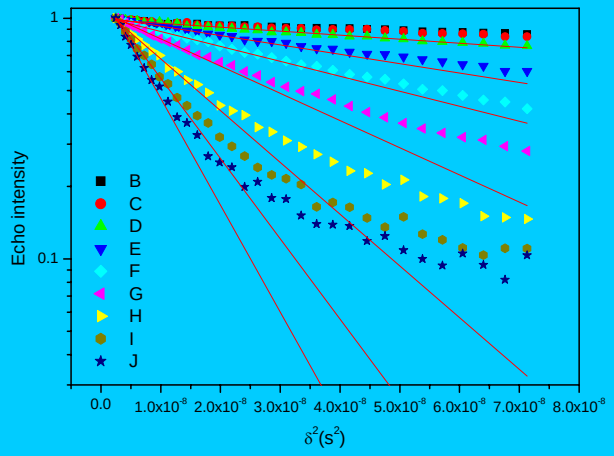
The SEM image of polystyrene capsules
- **liquid core: hexadecane**
- **solid shell: polystyrene**



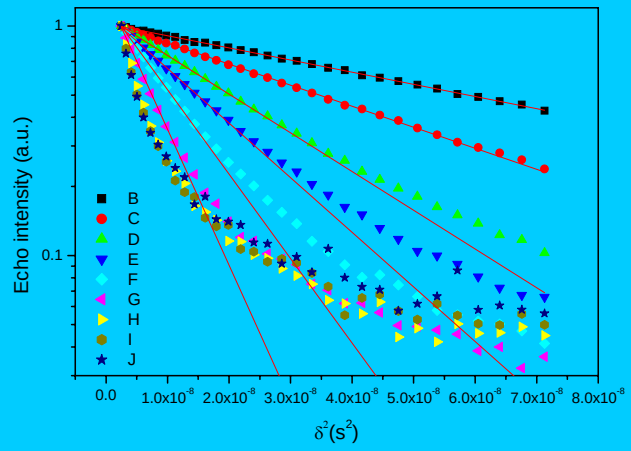
Preparation:

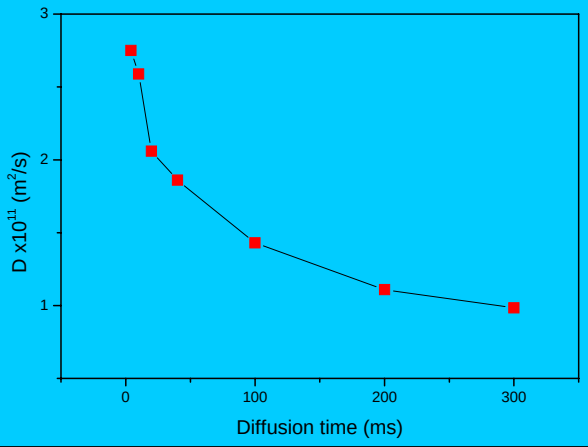
Polystyrene was dissolved in dichloromethane and then hexadecane was added. The relative amounts of each ingredient were chosen so that the system was in one – phase region of the ternary phase diagram, and well away from the phase boundary. Acetone was added to this solution in order to aid emulsification. An equal volume of aqueous surfactant solution (PVA) was prepared and maintained at 20 ^{o}C. This aqueous phase was stirred vigorously and the oil phase was added over to from an oil in water emulsion. Agitation was maintained for at least 1 h before pouring the emulsion into further 100 ml of aqueons surfantant solution. The diluted emulsion was rotary evaporated at ambient temperature to remove the last remainders of solvents and then lyophilized.

Experimental results

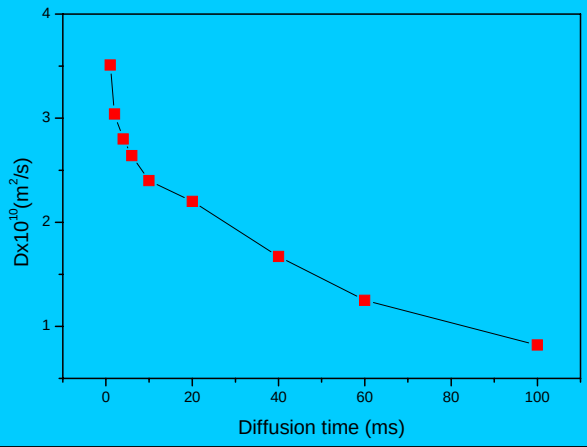


•Echo attenuation versus δ^2 for different diffusion times





•Effective diffusivity as a function of diffusion time



Conclusions

- FFStE technique can be successfully used for diffusion measurements of molecules confined in polymeric nanocapsules.
- The shape of echo decay indicates an exchange of molecules thorough capsules membrane
- The time dependence of the effective diffusivity for low gradient areas also indicates an exchange

Aknowledgements

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