A Smart Approach to Evaluate Drug Diffusivity In Injectable Agar-Carbomer Hydrogels for Drug Delivery

M. Santoro[§], P. Marchetti[§], F. Rossi, G. Perale*, F. Castiglione, A. Mele and M. Masi

Dipartimento di Chimica, Materiali ed Ingegneria Chimica "G. Natta", Politecnico di Milano,

Via Mancinelli 7, 20131 Milano, Italy

Supporting Information:

A)Flory-Rehner calculation and structural parameters

Swelling experiments were performed in order to characterize the hydrogel structure. Samples were first immersed in excess PBS for about 24 hrs, then freeze-dried, weighted (W_d) and poured in excess PBS to achieve complete swelling, while being kept at 37 °C in a 5% CO_2 atmosphere. Samples were removed from PBS at regular intervals. Hydrogel surfaces were then wiped with moistened filter paper in order to remove the excess of solvent and then weighted (W_t). Swelling ratio (Q_m), was calculated as:

$$Q_m = \frac{W_t}{W_d} \cdot 100 \quad (1)$$

Q_m was corrected to give the volumetric swelling ratio Q_V through the expression:

$$Q_V = 1 + \frac{\rho_p}{\rho_s} \cdot (Q_m - 1) \quad (2)$$

where ρ_p is the density of the dry polymer and ρ_s the density of the solvent. Following the Flory-Rehner calculations,[1] Q_V were used to calculate the three most important hydrogel structural parameters, that are:

1) Average molecular weight M_C, defined as the chain average molecular weight between two following cross-links;
2) Mean cross-linkage density ν_e, expressed as the ratio between the average number of moles between two following cross-links and the volume of dry polymer;
3) Mean mesh size ζ, defined as the average length of polymer chain between two following cross-links.[2-6]

The average molecular weight (M_C) was indirectly calculated as in Eq.3, using a simplification of Flory-Rehner equation[1,7]:

$$Q_V^{5/3} = \frac{\nu \cdot M_C}{V_1} \cdot (0.5 - \chi) \tag{3}$$

where ν is the specific volume of dry polymer, V_1 is the specific volume of solvent (PBS) and χ the Flory interaction parameter between polymer and solvent.

Cross-linking density and the swollen hydrogel mesh size were calculated applying the equations:

$$\nu_e = \frac{\rho_p}{M_C} \tag{4}$$

$$\zeta = Q_V^{1/3} \cdot \left(\overline{r_0^2}\right)^{1/2} \tag{5}$$

where $\left(\overline{r_0^2}\right)^{1/2}$ is the root-mean-squared end-to-end distance of network chains between two adjacent crosslinks in the unperturbed state.

B)NMR spectra for sodium fluorescein

The fast rotation of the sample at the so called magic-angle (54.7 ° with respect to the z-direction of the stray field of the NMR magnet) cancels out the Hamiltonian components related to interactions between nuclear magnetic moments, averages the dipole-dipole interactions and susceptibility distortions, as can be seen in Figure B1.

This results in spectra in which signal is not jammed by hydrogel matrix's interferences, with well resolved peaks for the investigated molecule, in this case sodium fluorescein.

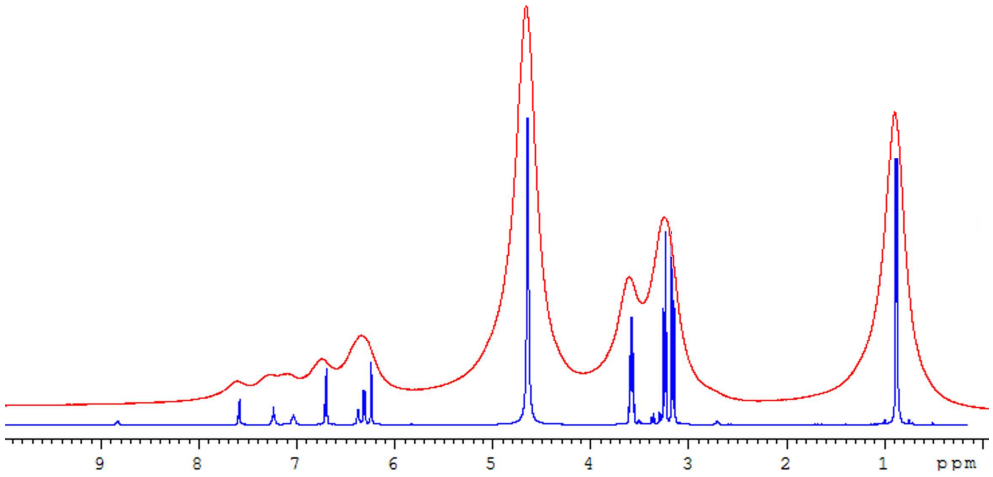

Figure B1. NMR spectra of sodium fluorescein obtained with conventional method (red line), and with HR-MAS technique (blue line)

References

(1) Flory, P. J.; Rehner, J. *J. Chem. Phys.* **1943**, *11*, 512.

(2) Flory, P. J. *Principles of polymer chemistry*: Cornell University Press: Ithaca (NY), 1953.

(3) Hu, B. H.; Su, J.; Messersmith, P. B. *Biomacromolecules* **2009**, *10*, 2194.

(4) de Jong, S. J.; van Eerdenbrugh, B.; van Nostrum, C. F.; Kettenes-van den Bosch, J. J.; Hennink, W. E. *J. Controlled Release* **2001**, *71*, 261.

(5) Rammensee, S.; Huemmerich, D.; Hermanson, K. D.; Scheibel, T.; Bausch, A. R. *Appl. Phys. A: Mater Sci. Process.* **2006**, *82*, 261.

(6) van de Manakker, F.; Vermonden, T.; El Morabit, N.; van Nostrum, C. F.; Hennink, W. E. *Langmuir* **2008**, *24*, 12559.

(7) Flory, P. J. *J. Chem. Phys.* **1951**, *74*, 2718.