^{1}H HRMAS NMR: drug motion in hydrogel systems

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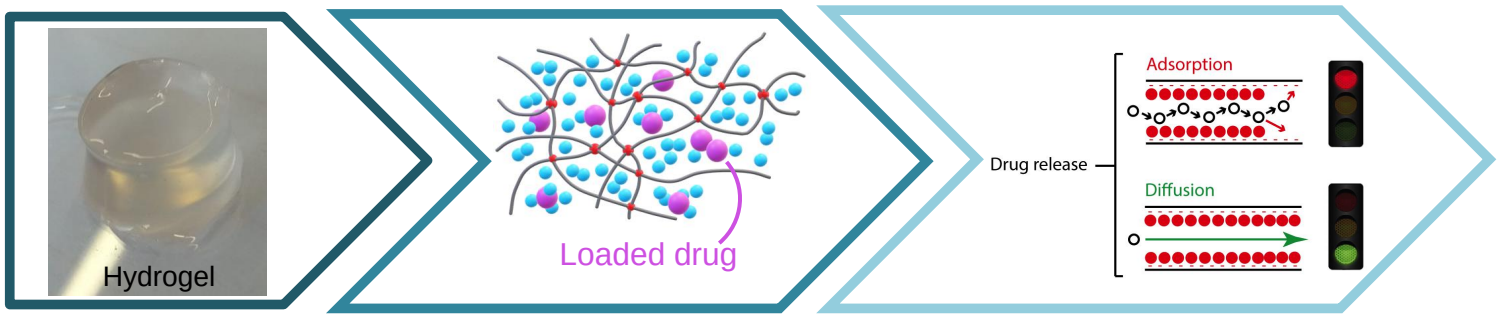
GIDRM Gruppo Italiano Discussione Risonanze Magnetiche

POLITECNICO MILANO 1863

Laboratorio Grandi Strumenti
Risonanza Magnetica Nucleare
Spettrometria di Massa
LGS
Large Scale Facilities

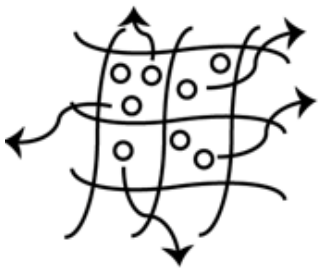
MOLECULAR DYNAMICS OF DRUGS IN HYDROGEL NETWORKS

- Hydrogels are three-dimensional, cross-linked networks of water-swellable polymers
- They may be used as drug delivery and controlled drug-release systems
- Self-diffusion arises from random translational (Brownian) motion of molecules (or aggregates) driven by thermal energy
- Why study molecular diffusion? Molecular size, Aggregation phenomena, Encapsulation, Hydrogen bond, …
- Comparison of molecular diffusion with macroscopic release kinetics



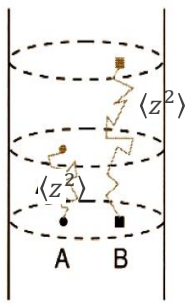
MOTION OF SMALL MOLECULES

Motion of small molecules confined in a hydrogel system with different pore dimensions



Small molecules dissolved in isotropic solutions: diffusion coefficient can be measured

$$\langle z^2(t_d)\rangle = 2\,D t_d^{\alpha}$$



The diffusion regime can be defined according to the different values of α:

1) Unrestricted diffusion (mono-exponential decay)

$\alpha = 1$ **Gaussian motion**

2) Restricted diffusion

$\alpha > 1$ **Superdiffusive regime**

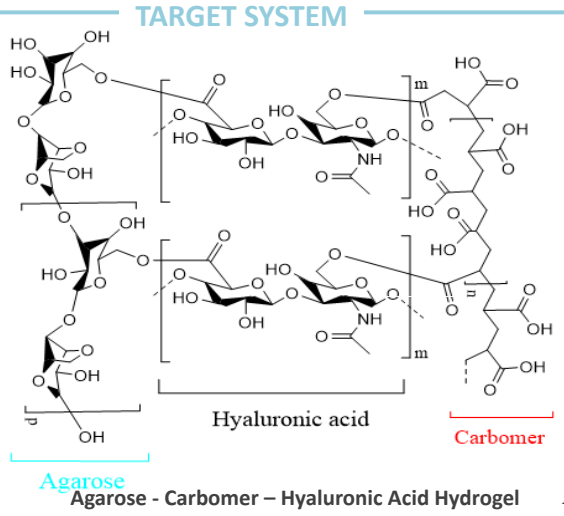
$\alpha < 1$ **Subdiffusive regime**

TARGET SYSTEM

HYDROGEL NETWORK

SYSTEM	MESH SIZE
AC1 (no hyaluronic acid)	**90 µm**
AC-HA (L)	**245 µm**
AC-HA (M)	**481 µm**
AC-HA (H)	**3026 µm**

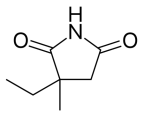
Different hydrogels were prepared starting from an agarose-carbomer system (AC1) and increasing the mesh size replacing part of the carbomer with hyaluronic acid.



Agarose - Carbomer – Hyaluronic Acid Hydrogel
anionic polymer network

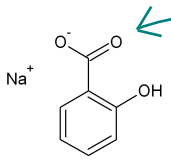
SMALL DRUGS

Ethosuximide (ESM): no net charge



Two concentrations: **40** and **80 mg/ml**

Sodium salycilate Negative charge



GOALS

Study the diffusion coefficient of small drugs in hydrogel systems varing:

- Mesh size
- Drug concentration
- Drug charge

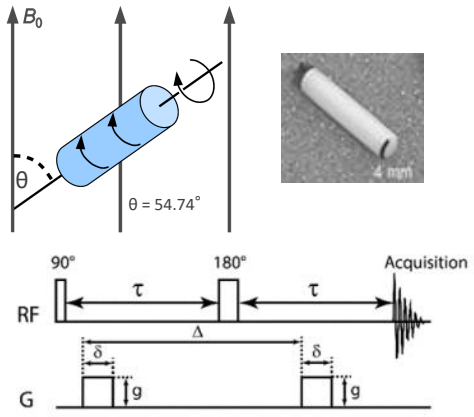
FUTURE GOALS

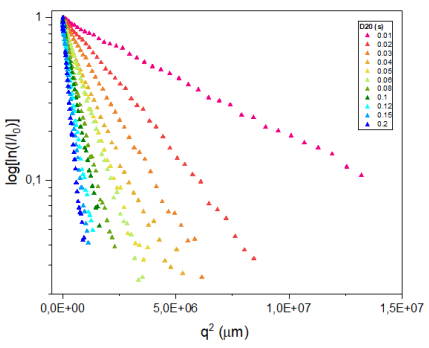
- Negative charged drugs
- Codelivery of different drugs
- Macroscopic release studies

HRMAS NMR SPECTROSCOPY FOR SEMI-SOLID SAMPLES

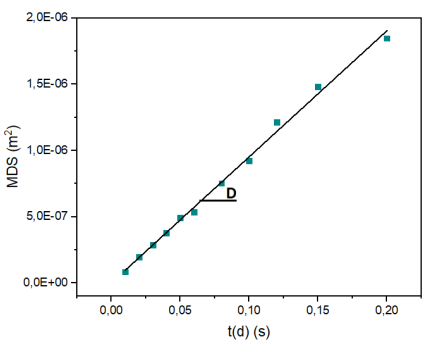
PGSE experiment using HRMAS probehead

$$\ln\frac{I(q,t_d)}{I(0,t_d)} = -\frac{1}{2}q^2\langle z^2(t_d)\rangle;\quad q = \gamma\delta g;\quad t_d = \Delta - \frac{\delta}{3};\quad \langle z^2(t_d)\rangle = \text{MSD}$$



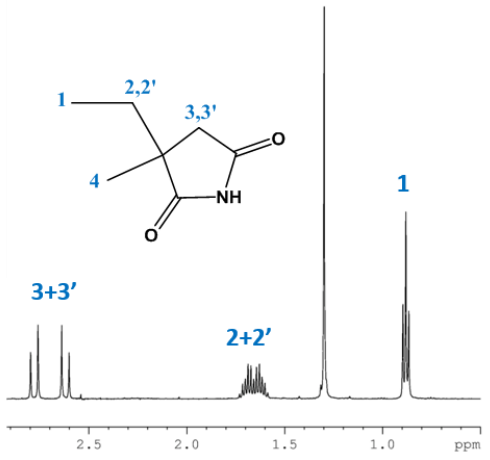


Linear regression of $\ln(I/I_0)$ *vs* q^2: the slope gives the molecular MSD for each defined t_d value



Plot of MDS values over t(d): the slope provides the experimental diffusion coefficient (D) values

^{1}H HRMAS NMR SPECTRA IN GEL 4kHz spinning

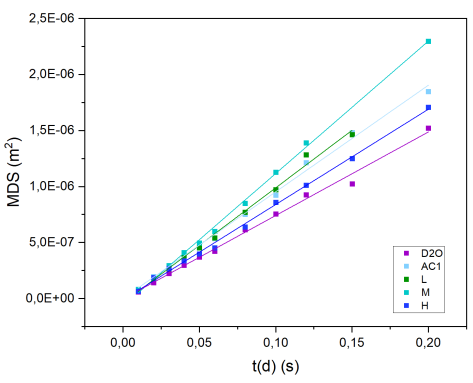


CONCLUSIONS

HRMAS spin-echo NMR spectroscopy provides experimental data on the **molecular dynamics** of drugs entrapped in 3D hydrogel networks.

Drugs show a superdiffusive behaviour in hydrogels, according to the mesh size.

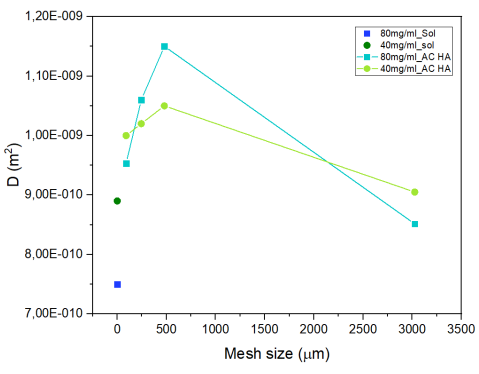
DIFFUSION OF SMALL DRUGS



Plot of MSD vs t(d) of ethosuximide in different hydrogels compared to the ones in solution.

The trend of the diffusion coefficient is the same for both concentrations.
The difference arises when considering the mesh size:

- In the mesh from 90 to 480µm the D increases compared to the values in solution, suggesting a superdiffusive behaviour of the drug;
- In the mesh of 3000mm the D decreases with a more solution-like behaviour.



Plot of D values over ζ of both samples with concentrations of 40mg/ml and 80mg/ml.

References:
[1] F. Rossi, F. Castiglione, M. Ferro, M. Moioli, A. Mele, and M. Masi *Chem. Phys. Chem.*, **17**, 1-9, (2016)
[2] F. Castiglione, M. Casalegno, M. Ferro, F. Rossi, G. Raos, and A. Mele *J. Controlled Release*, **305**, 11-119, (2019)