SUPRAMOLECULAR ULTRA-SHORT DEHYDROPEPTIDE-BASED HYDROGELS AS POTENTIAL AFFORDABLE NANOCARRIERS

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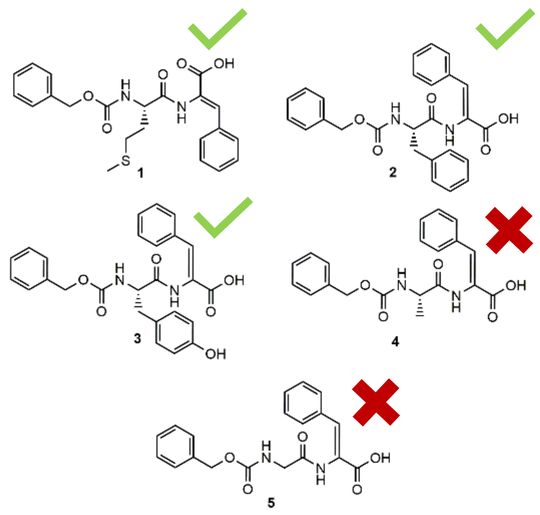
Why using **dehydropeptide**-based **supramolecular** hydrogels?

- ❑ **Easy** chemical functionalization
- ❑ **Tuneable** mechanical properties
- ❑ **Biocompatibility**
- ❑ Proteolytic **stability**



Chemical structure of the synthesised compounds: **1** (Cbz-*L*-Met-*Z*-ΔPhe-OH); **2** (Cbz-*L*-Phe-*Z*-ΔPhe-OH); **3** (Cbz-*L*-Tyr-*Z*-ΔPhe-OH); **4** (Cbz-*L*-Ala-*Z*-ΔPhe-OH); **5** (Cbz-*L*-Gly-*Z*-ΔPhe-OH) [1]

Supramolecular hydrogels have shown promising **encapsulation** and **delivery** of drugs:

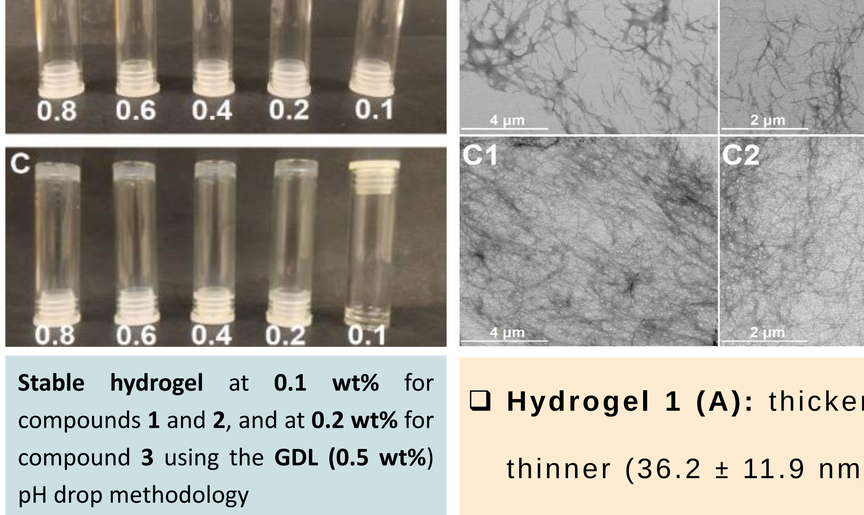
- ❑ **New antitumor thienopyridine derivatives** [2]
- ❑ **Model drug curcumin** [2-4]
- ❑ **Chemotherapeutic drug doxorubicin** [5]

CHALLENGES

Make supramolecular gels affordable to research community:

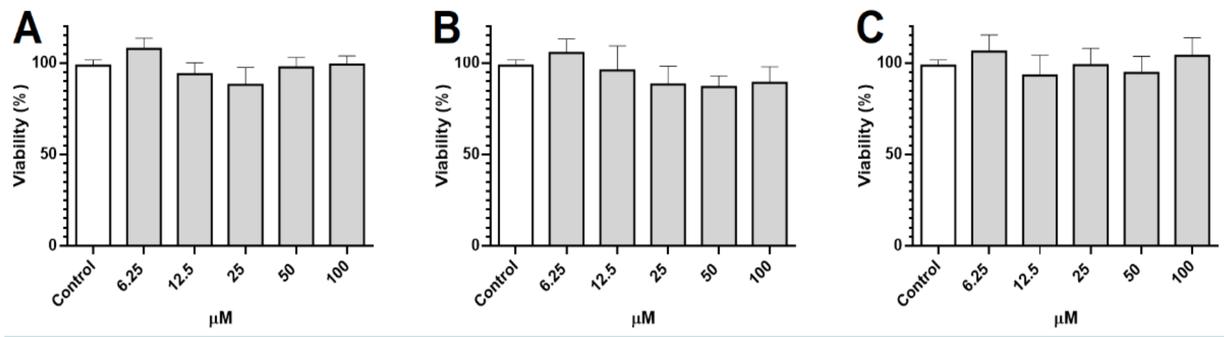
- ❑ **Reduce cost** of production
- ❑ **Facile** synthesis
- ❑ **Suitable properties** for biomedical applications

SYNTHESIS STRATEGY 1



Synthesis of compounds **1-5**. (a) DCC, HOBt, Et_3N, MeCN, rt (for **7a**,**b**); (b) HBTU, Et_3N, MeCN, rt (for **7c**-**e**); (c) (i) Boc_2O, DMAP, dry MeCN, rt, (ii) TMG; (d) TFA, rt (**8c** only); (e) (i) NaOH (1M), 1,4-dioxane, rt, (ii) $KHSO_4$

CYTOTOXICITY 3



Evaluated for their potential toxicity against the **keratinocyte cell line HaCat**

- ❑ **No toxicity** was detected in the **6.25 uM-100 μM range**
- ❑ Molecules do **not elicit significant changes** in the overall **morphology** of cells, both in the case of **actin filaments** and **chromatin status**

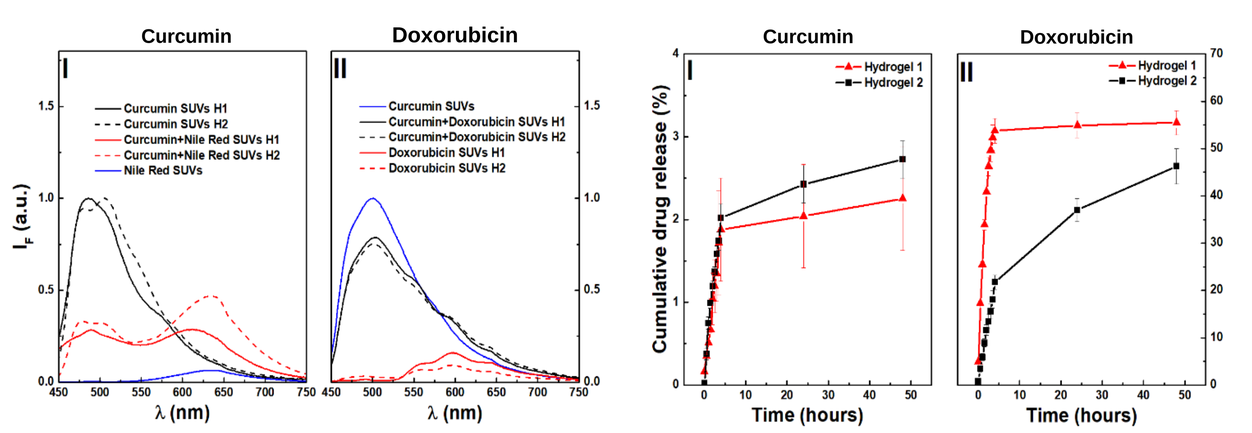
GELATION CHARACTERIZATION 2

Stable hydrogel at **0.1 wt%** for compounds **1** and **2**, and at **0.2 wt%** for compound **3** using the **GDL (0.5 wt%)** pH drop methodology

Compound **2** critical gelation concentration of **0.3 wt%** in **phosphate buffer (0.1 M, pH=7.3)**

- ❑ **Hydrogel 1 (A):** thicker (104.6 ± 24.5 nm) and thinner (36.2 ± 11.9 nm)
- ❑ **Hydrogel 2 (B):** homogeneous (26.1 ± 4.6 nm)
- ❑ **Hydrogel 3 (C):** homogeneous (34.5 ± 6.8 nm)

DRUG DELIVERY 4



Interaction with biomembrane models monitored by FRET

Drug release

Curcumin transport

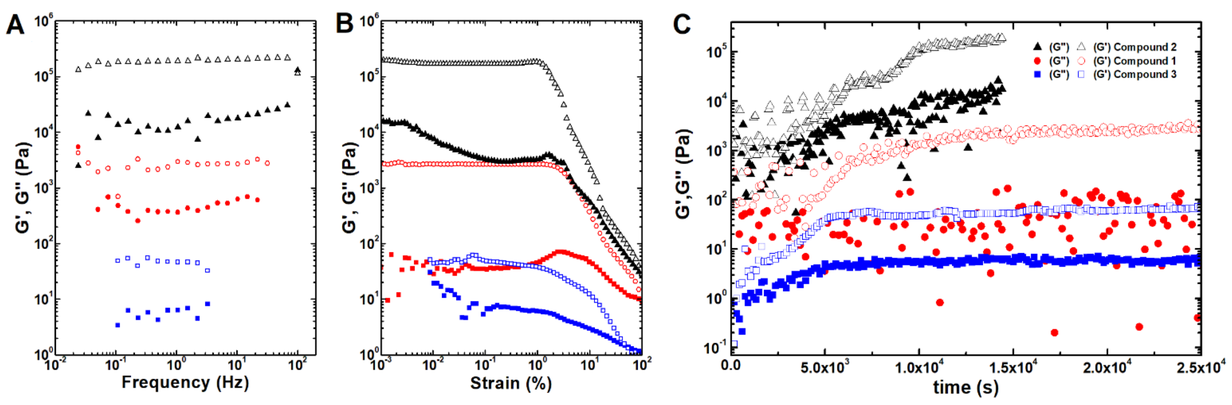
- ❑ Nile Red-labelled vesicles (Nile Red as energy acceptor) interacted with curcumin-loaded gels (curcumin as donor)

Doxorubicin transport

- ❑ Curcumin-labelled vesicles (curcumin as energy donor) interacted with doxorubicin-loaded gels (DOX as acceptor)

The energy transfer between the loaded drug and the lipid-labelling fluorescent probe evidences the **transport of the drug into the membranes**

- ❑ **Hydrogel 2** is **more efficient** on **controlling** release than **hydrogel 1**
- ❑ The loaded **drug** is **not completely released** after **three days**
- ❑ Combination of **erosion** and **diffusion** drug **release**



Hydrogels **1** and **2** elastic modulus falls in the **range of** the native tissues, 0.1 kPa (brain) to 100 kPa (cartilage) that covers soft tissues such as skin, pancreas, spleen, glands and muscles

HIGHLIGHTS

- ✓ **Elastic** properties **matching** the elasticity of biological **soft tissues**
- ✓ Proper **encapsulation** of drugs
- ✓ **Ensure** the **drug delivery** to **biomembrane** models
- ✓ **Outperform similar** low molecular weight **peptide-based hydrogels** regarding gelation and rheological properties
- ✓ **Expedite synthesis** in 3 steps

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