

# Drug Delivery from Hyaluronic Acid–BDDE Injectable Hydrogels for Antibacterial and Anti-Inflammatory Applications

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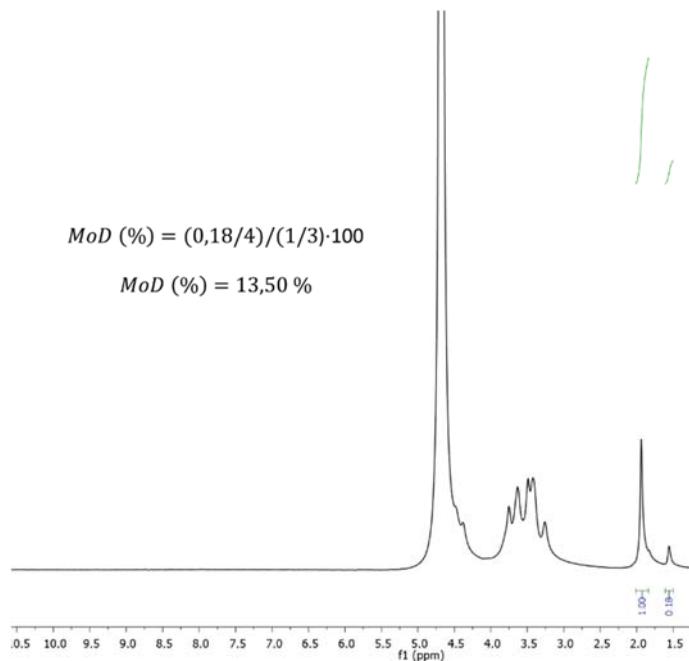
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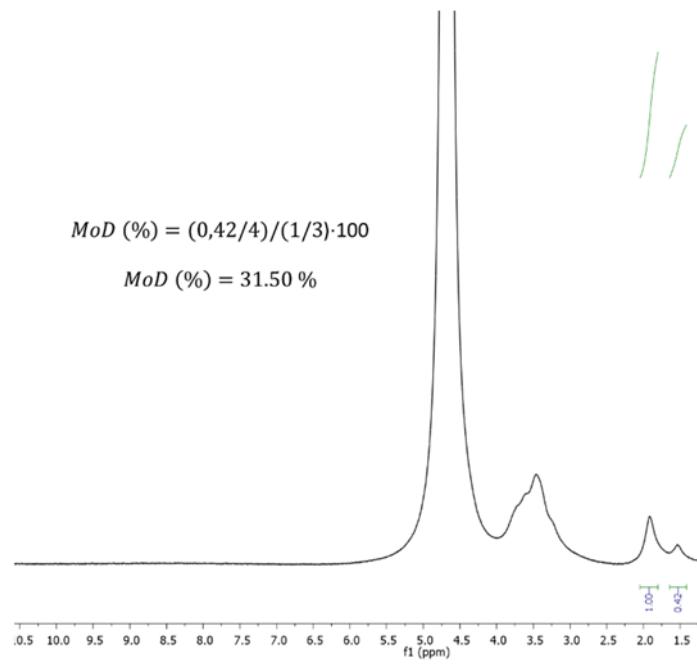
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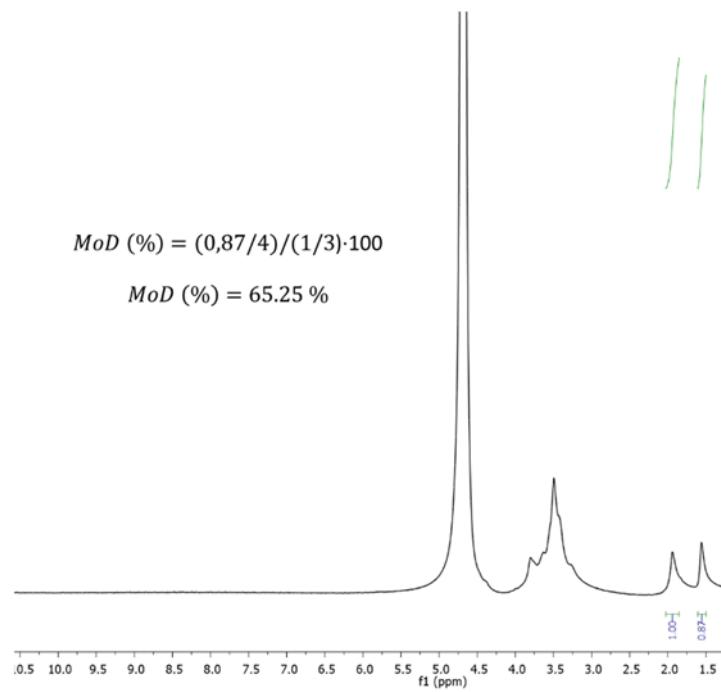
## Supplementary material



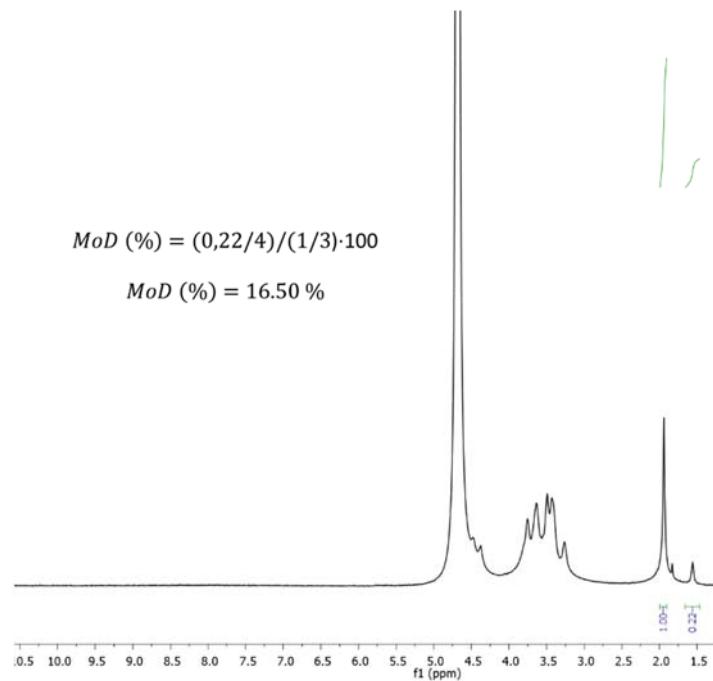
**Figure S1.** Proton nuclear magnetic resonance (<sup>1</sup>H-NMR) spectra of HA-BDDE-1 hydrogel for MoD determination.



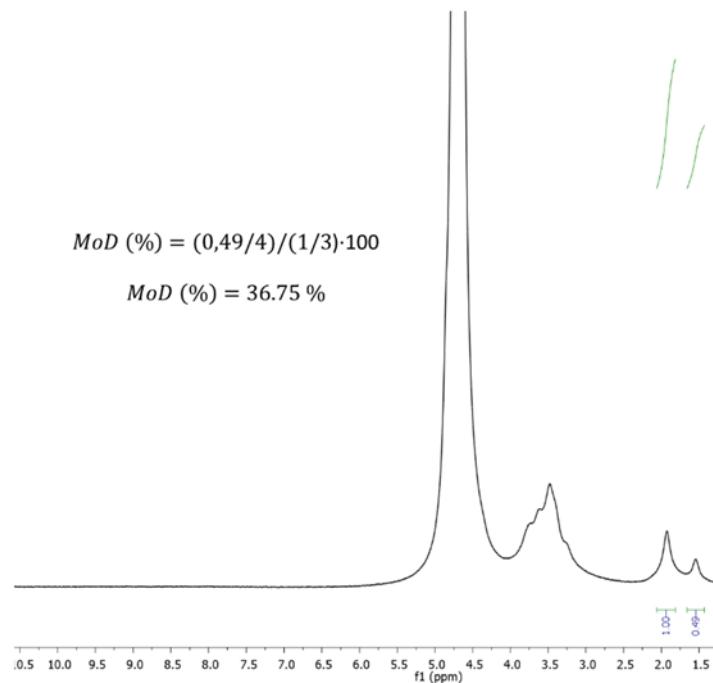
**Figure S2.** Proton nuclear magnetic resonance (<sup>1</sup>H-NMR) spectra of HA-BDDE-2 hydrogel for MoD determination.



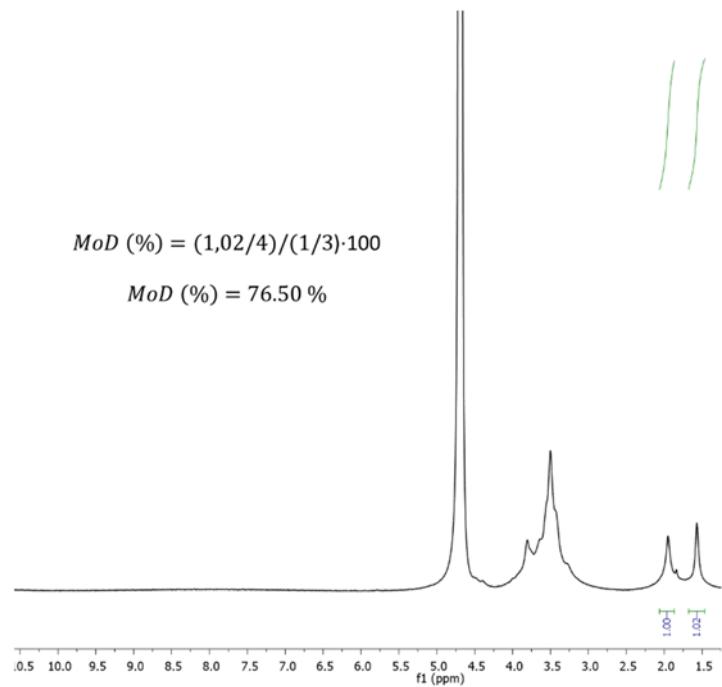
**Figure S3.** Proton nuclear magnetic resonance (<sup>1</sup>H-NMR) spectra of HA-BDDE-3 hydrogel for MoD determination.



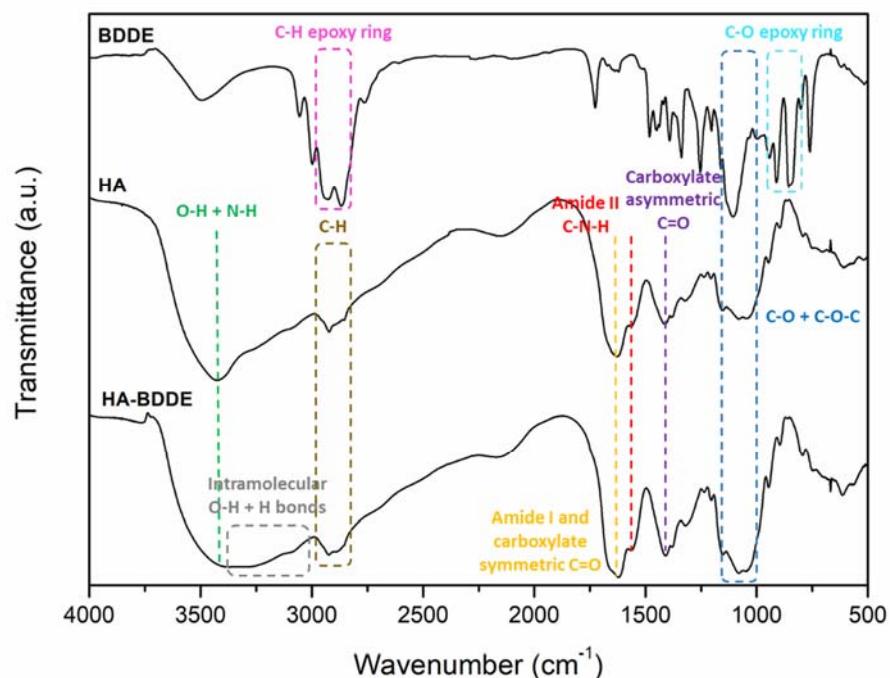
**Figure S4.** Proton nuclear magnetic resonance ( $^1\text{H}$ -NMR) spectra of HA-BDDE-4 hydrogel for MoD determination.



**Figure S5.** Proton nuclear magnetic resonance ( $^1\text{H}$ -NMR) spectra of HA-BDDE-5 hydrogel for MoD determination.



**Figure S6.** Proton nuclear magnetic resonance ( $^1\text{H}$ -NMR) spectra of HA-BDDE-6 hydrogel for MoD determination.



**Figure S7.** FTIR spectra of BDDE, HA and HA-BDDE hydrogels between 4000–500  $\text{cm}^{-1}$ .

**Table S1.** Acute systemic toxicity results of HA-BDDE-4 (●) hydrogel and control group.

| HA-BDDE-4 hydrogel – Treated group |                  |                |  |   |    |    |    |
|------------------------------------|------------------|----------------|--|---|----|----|----|
| Animal number                      | Start weight (g) | End weight (g) | Clinical symptoms at different times (h) |   |    |    |    |
|                                    |                  |                | 0  | 4 | 24 | 48 | 72 |
| 1                                  | 23.6             | 27.5           | 0  | 0 | 0  | 0  | 0  |
| 2                                  | 22.8             | 27.4           | 0  | 0 | 0  | 0  | 0  |
| 3                                  | 20.4             | 23.2           | 0  | 0 | 0  | 0  | 0  |
| 4                                  | 21.5             | 25.3           | 0  | 0 | 0  | 0  | 0  |
| 5                                  | 23.4             | 27.0           | 0  | 0 | 0  | 0  | 0  |

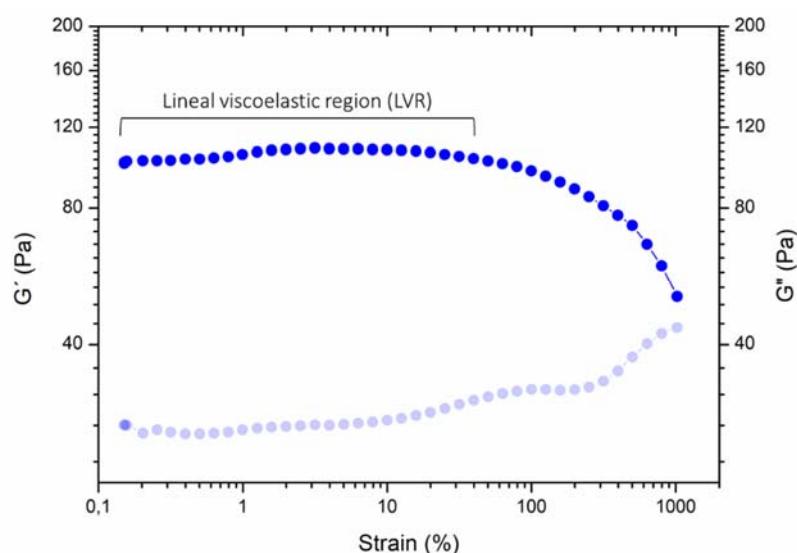
  

| Cottonseed oil - Control group |                  |                |  |   |    |    |    |
|--------------------------------|------------------|----------------|--|---|----|----|----|
| Animal number                  | Start weight (g) | End weight (g) | Clinical symptoms at different times (h) |   |    |    |    |
|                                |                  |                | 0  | 4 | 24 | 48 | 72 |
| 1                              | 23.6             | 27.6           | 0  | 0 | 0  | 0  | 0  |
| 2                              | 21.7             | 25.5           | 0  | 0 | 0  | 0  | 0  |
| 3                              | 21.3             | 26.3           | 0  | 0 | 0  | 0  | 0  |
| 4                              | 23.5             | 26.1           | 0  | 0 | 0  | 0  | 0  |
| 5                              | 20.2             | 24.4           | 0  | 0 | 0  | 0  | 0  |

0: no symptoms.

**Table S2.** Physicochemical properties of CFX, TCN, AMX and ASS drugs.

| Drug | Molecular weight (g/mol) | Water solubility (mg/mL, 25 °C) | log Kow | pKa          | Net charge (pH 7.4) |
|------|--------------------------|---------------------------------|---------|--------------|---------------------|
| CFX  | 446.4                    | > 100                           | - 0.80  | pKa (1) 2.5  | --                  |
|      |                          |                                 |         | pKa (1) 3.3  |                     |
| TCN  | 480.9                    | 22.0                            | - 1.30  | pKa (2) 7.7  | +                   |
|      |                          |                                 |         | pKa (3) 9.5  |                     |
|      |                          |                                 |         | pKa (1) 2.4  |                     |
| AMX  | 365.4                    | 4.0                             | 0.87    | pKa (2) 7.4  | -                   |
|      |                          |                                 |         | pKa (3) 10.6 |                     |
| AAS  | 180.2                    | 3.3                             | 1.19    | pKa (1) 3.5  | --                  |



**Figure S8.**  $G'$  and viscous  $G''$  versus strain of HA-BDDE-1 (●) for LVR determination by amplitude sweep.