

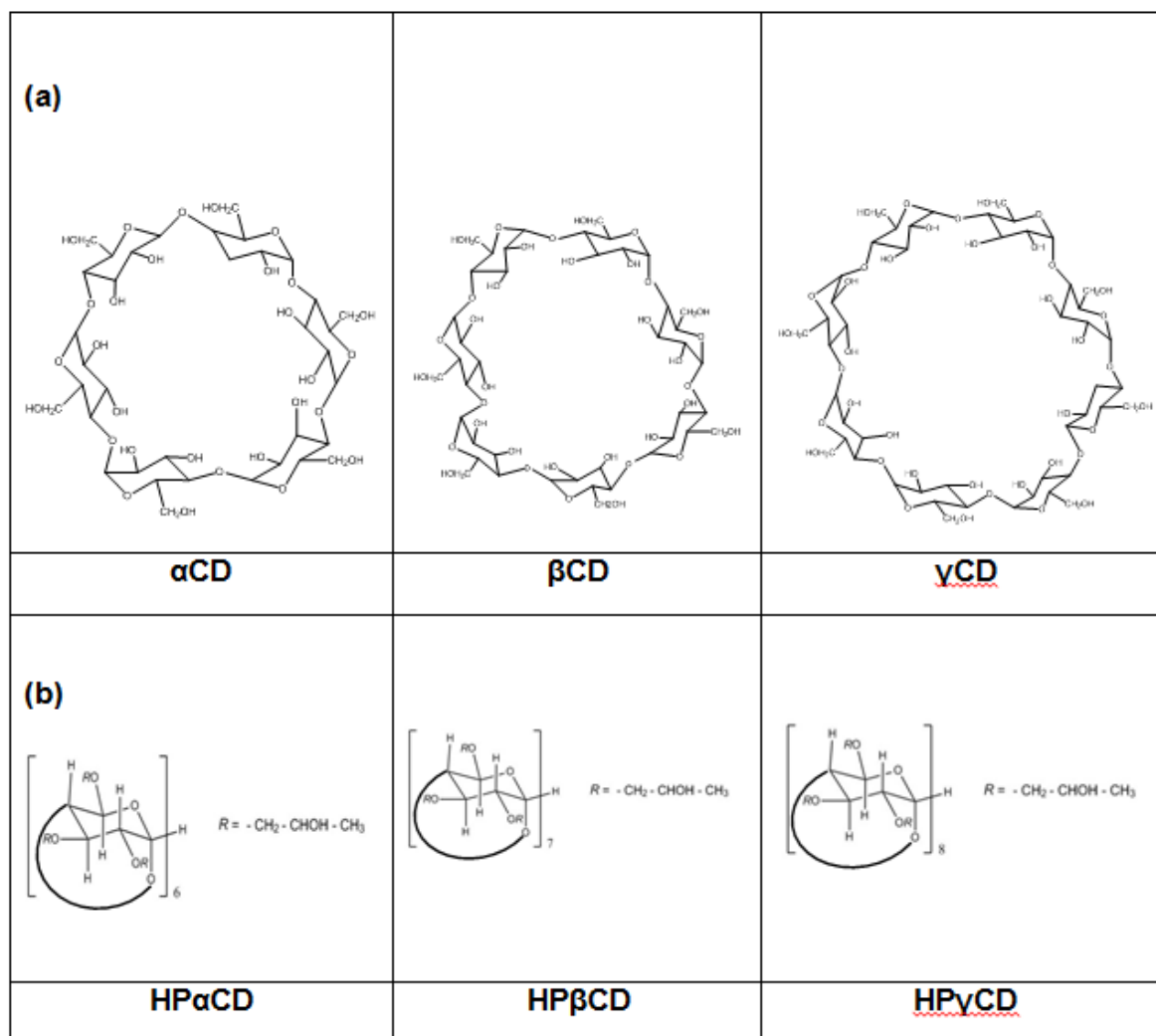
Supplementary Information

# Nepafenac-Loaded Cyclodextrin/Polymer Nanoaggregates: A New Approach to Eye Drop Formulation

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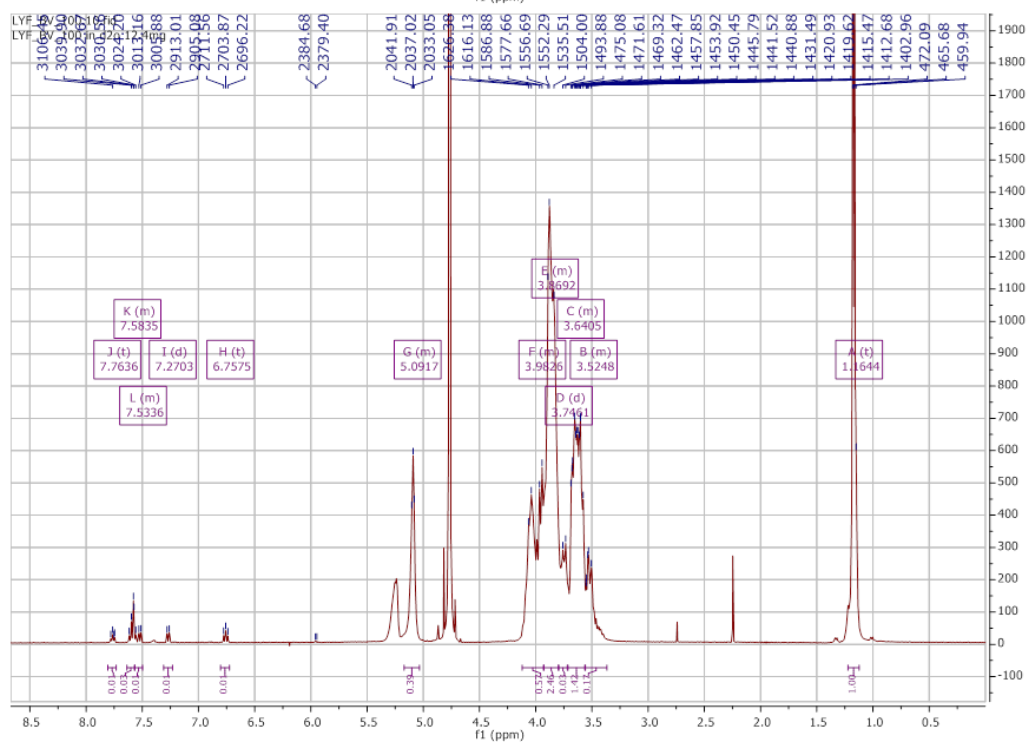
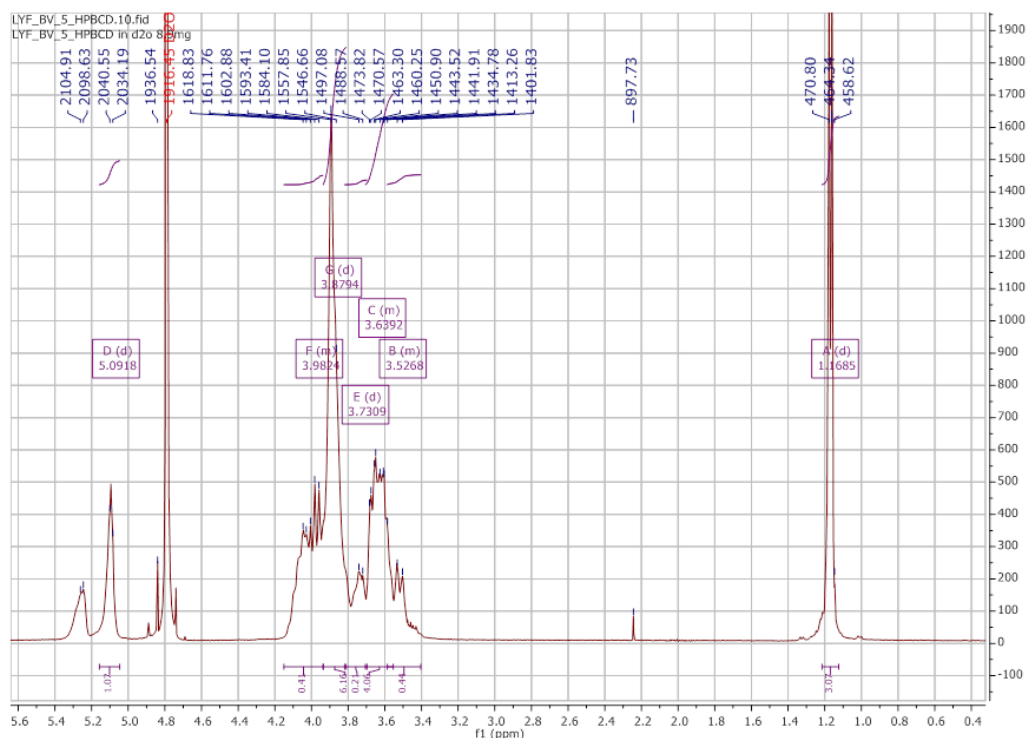
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**Figure S1.** Chemical structure of (a) natural cyclodextrins ( $\alpha$ -,  $\beta$ - and  $\gamma$ -CDs) and (b) their hydroxyl-propyl derivatives (HP $\alpha$ -, HP $\beta$ - and HP $\gamma$ -CDs).

(a)



(b)

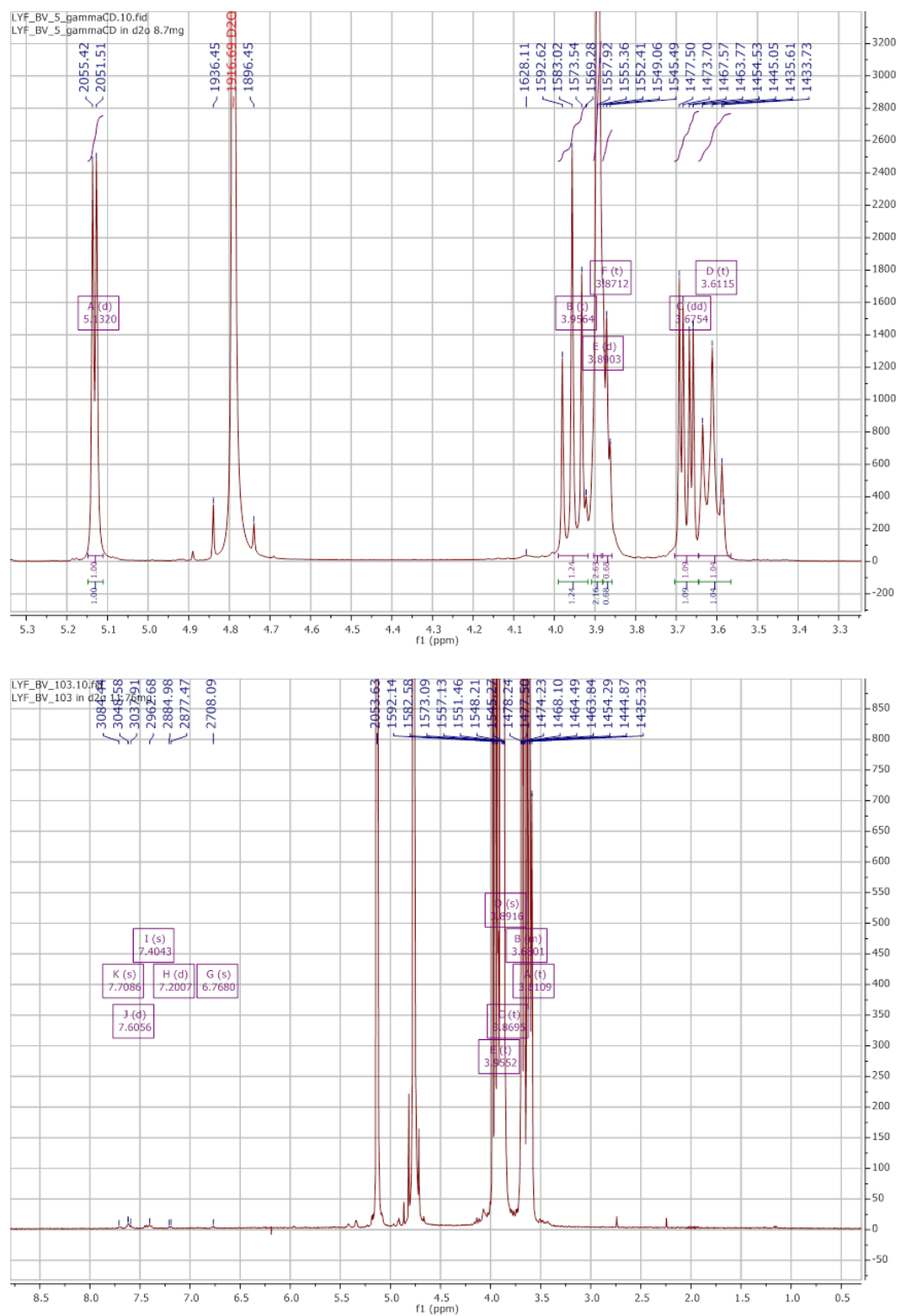
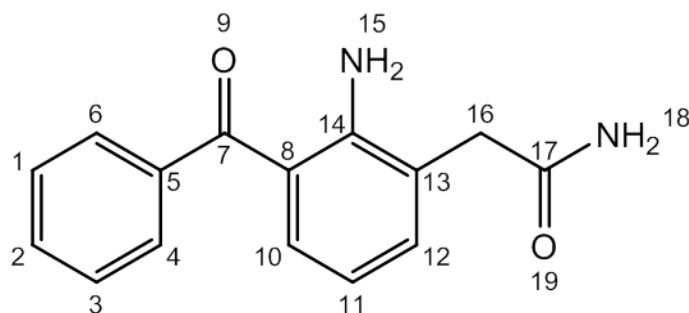


Figure S2. H-NMR spectra of (a) HP $\beta$ CD alone (top) and their complex (bottom), and (b)  $\gamma$ CD alone (top) and their complex (bottom).

**Table S1.** Effect of cyclodextrins and excipients on osmolality, viscosity and size of binary and ternary systems with nepafenac.

Cyclodextrin	Excipient	Osmolality (mOsm/kg)	Viscosity (cP)	Size (nm)*
15% $\gamma$ CD	No additive	120 $\pm$ 0	1.89 $\pm$ 0.38	220.3
	PVA	140 $\pm$ 1	3.20 $\pm$ 0.02	296.1
	PVP	161 $\pm$ 1	3.22 $\pm$ 0.04	163.6
	Tyloxapol	117 $\pm$ 2	2.22 $\pm$ 0.02	230.7
	CMC	166 $\pm$ 1	4.34 $\pm$ 0.23	322
15% $\gamma$ CD/2.5%H P $\beta$ CD	No additive	71 $\pm$ 1	1.40 $\pm$ 0.06	277.8
	PVA	117 $\pm$ 1	2.89 $\pm$ 0.06	279.2
	PVP	125 $\pm$ 2	1.93 $\pm$ 0.02	281.7
	Tyloxapol	102 $\pm$ 2	1.69 $\pm$ 0.02	317
	CMC	133 $\pm$ 3	6.92 $\pm$ 0.1	317
15% $\gamma$ CD/ 5%HP $\beta$ CD	No additive	88 $\pm$ 2	1.54 $\pm$ 0.02	180.8
	PVA	158 $\pm$ 1	3.16 $\pm$ 0.01	547
	PVP	149 $\pm$ 0	2.02 $\pm$ 0.10	306
	Tyloxapol	130 $\pm$ 2	1.83 $\pm$ 0.02	1466
	CMC	166 $\pm$ 2	11.00 $\pm$ 0.10	459
15% $\gamma$ CD/ 8%HP $\beta$ CD	No additive	101 $\pm$ 2	1.53 $\pm$ 0.02	161.2
	PVA	219 $\pm$ 1	4.37 $\pm$ 0.05	246.5
	PVP	220 $\pm$ 2	2.37 $\pm$ 0.06	1524
	Tyloxapol	204 $\pm$ 2	2.37 $\pm$ 0.02	730
	CMC	238 $\pm$ 2	16.00 $\pm$ 0	319

\* The diameter of the mean population (nm) is displayed.

**Table S2.** Chemical shift corresponding to free nepafenac alone and in the presence of  $\gamma$ CD or HP $\beta$ CD.

Protons	Nepafenac	Nepafenac/HP $\beta$ CD	$\Delta\delta^*$	Nepafenac	Nepafenac/ $\gamma$ CD	$\Delta\delta^*$
H-4	7.6301	7.7301	0.1	7.6301	7.7856	0.1555
H-6	7.6301	7.7316	0.1015	7.6301	7.7856	0.1555
H-2	7.5236	7.6286	0.105	7.5236	7.6055	0.0819
H-3	7.4513	7.4273	-0.024	7.4513	7.5556	0.1043
H-1	7.4513	7.4273	-0.024	7.4513	7.5556	0.1043
H-12	7.2373	7.2237	-0.0136	7.2373	7.2973	0.06
H-11	6.8189	6.7910	-0.0279	6.8189	6.7793	-0.0396
H-16	3.5635	*	*	3.5635	*	*

\* Due to the overlapping of CD protons, it is not possible to access the resonance of proton.