**Smart Phase Transformation System Based on Lyotropic Liquid Crystalline@Hard Capsules for Sustained Release of Hydrophilic and Hydrophobic Drugs**

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**Supporting information**

**1 Differential scanning calorimetry**

DSC thermograms were displayed in **Fig. S1**.



Figure S1 DSC thermgrams of precursor capsule contents (A:GMO, Gelucire 39/01, PEG 1000; B: GMO-Gelucire 39/01mixture; C: GMO-PEG 1000 mixtures; D:GMO-PEG 1000-Tween 80 mixtures)

**2 Polarizing microscope photos**

 Polarizing microscope photos were displayed in **Fig. S2**

Figure S2 Polarizing microscope photos of GMO-drug-additive-water systems (A: a 45/2.5/15/7.5/30 wt ratio GMO-drug-PEG 1000-Tween 80-water system; B: a 50/5/15/30 wt ratio GMO-drug- Gelucire 39/01-water system)

The isotropic homogeneity of the two systems was indicated by the dark view with on polarized texture in both Figure S2 A and Figure S2 B [[1](#_ENREF_1" \o "Li,  #49)]. A preliminary conclusion that both systems were cubic phase was speculated, which should be further confirmed by Small Angle X-ray diffractograms.

**3 Small Angle X-ray diffractograms**

 Small Angle X-ray diffractograms were displayed in **Fig. S3**.



Figure S3 Small Angle X-ray diffractograms of GMO-drug-water systems and GMO-drug-additive-water systems (A: 62.5/7.5/30 wt ratio GMO-DOXY-water system; B: 50/5/15/30 wt ratio GMO-DOXY-Gelucire 39/01-water system; C: 67.5/2.5/30 GMO-MLX-water system; D: 45/2.5/15/7.5/30 wt ratio GMO-MLX-PEG 1000-Tween 80-water system)

The SAXS diffractogram of DOXY LLC systems without gelucire 39/01 showed single Bragg diffraction peak (**Figure S3 A**). With the addition of gelucire, three Bragg diffraction peaks (*q*1 = 0.1263, *q*2 = 0.1541, *q*3 = 0.1771) (**Figure S3 B**) was in accordance with Pn3m cubic phase (*q*1: *q*2: *q*3 = √2: √3 : √4).

The SAXS diffractogram of MLX LLC systems without PEG1000 showed four Bragg diffraction peaks (*q*1 = 0.1041, *q*2 = 0.1263, *q*3 = 0.1462, *q*4 =0.1803) (**Figure S3 C**), indicating Pn3m cubic phase (*q*1: *q*2: *q*3: *q*4 = √2: √3 : √4: √6 ). With the addition of PEG 1000, three Bragg diffraction peaks (*q*1 = 0.1136, *q*2 = 0.1390, *q*3 =0.1605) (**Figure S3 D**) was in accordance with Pn3m cubic phase (*q*1: *q*2: *q*3 = √2: √3 : √4) [[2](#_ENREF_2)].

The SAXS results reflected that the addition of gelucire 39/01 changed the GMO-DOXY-water system from lamellar phase to cubic phase. However, the addition of PEG1000 could not reverse GMO-MLX-water system back to lamellar phase. A tendency from lamellar phase to cubic phase or hexagonal phase will spontaneously happen for the LLC systems. Only with the help of extra energies, such as heat and light, the phase transition of LLC systems could be reversible [[3-5](#_ENREF_3)].

The authors put forward a hypothesis that the disparity in the drug release rate might be due to the different viscosities of the systems. GMO-MLX-water system with PEG1000 with lower viscosity might show a higher drug release rate [[6](#_ENREF_6)]. We will perform further studies to confirm such a hypothesis.

###### 4 Accelerated stability of SPTS@hard capsules

An accelerated stability investigation was performed on the SPTS@hard capsules. The optimized formulation was stored at high humidity (75% RH and 95% RH) conditions. Under the corresponding conditions, the weight gain of samples was recorded at time intervals of 0, 5 and 10 days.

Generally, there is about 14~16% water in the shell of hard capsules acting as plasticizer. SPTSs in the capsules could absorb the water from capsule shells and storage environment, leading to a change in drug release. Therefore, the water gains of blank capsules, excipients and SPTSs in hard capsules were recorded in high humidity (75% RH and 95% RH) conditions for the accelerated stability tests.

After 10-day storage, the weight gains under 90 ± 5% RH were obviously higher than those under 75 ± 5% RH for all the samples except the hydrophobic gelucire39/01 and MLX. The weight gains of blank capsules were 1.15 ± 0.25% and 3.47 ± 0.99% in 75 ± 5% RH and 90 ± 5% RH respectively. The capsules became soft and sticky, indicating the high humidity conditions should be avoided for hard capsules. For DOXY SPTS capsules, the weight gain was equal to the sum of the weight gains of each of them. However, the weight gain of MLX SPTS@hard capsules was much lower than the sum of single component. It is worth noting that PEG 1000 showed strong absorption capacity, the weight gains were 5.91 ± 0.84% and 6.70 ± 1.33% in 75 ± 5% RH and 90 ± 5% RH respectively. When mixed with GMO, the weight gains substantially decreased to 0.83 ± 1.08% and 1.07 ± 1.22%. The incorporation of hydrophobic materials into the hydrophilic could reduce the water absorption. The weight gain after 10-day storage under 75 ± 5% RH of DOXY-SPTS@hard capsules and MLX-SPTS@hard capsules were lower than 2%, indicating an acceptable accelerated stability.

Tab. 1 Weight gain after exposing to high humidity (%, *n* = 3)

|  |  |  |
| --- | --- | --- |
| Samples | 75 ± 5% RH | 90 ± 5% RH |
| Blank capsule | 1.15 ± 0.25 | 3.47 ± 0.99 |
| GMO | 0.51 ± 0.72 |  0.71 ± 1.73 |
| DOXY  | 0.03 ± 1.12 | 1.52 ± 0.98 |
| Gelucire39/01 | 0.05 ± 1.07 | 0.05 ± 2.02 |
| GMO-DOXY-Gelucire39/01  | 0.58 ± 1.55 | 1.76 ± 0.81 |
| DOXY-SPTS@hard capsules | 0.96 ± 1.01 | 1.91 ± 1.60 |
| MLX | 0.02 ± 1.81 | 0.01 ± 0.54 |
| PEG1000 | 5.91 ± 0.84 | 6.70 ± 1.33 |
| GMO-PEG1000 | 0.83 ± 1.08 | 1.07 ± 1.22  |
| GMO-MLX-PEG 1000-Tween 80 | 0.17 ± 1.54 | 1.51 ± 0.45 |
| MLX-SPTS@hard capsules | 1.17 ± 0.74 | 2.42 ± 0.71 |

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