Electronic Supplementary Material (ESI) for Green Chemistry.

Highly-efficient production of spherical co-agglomerates of drugs via an organic solvent-free process and a mechanism study

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Molecular structures of the drugs used in this work were shown in Chart S1.

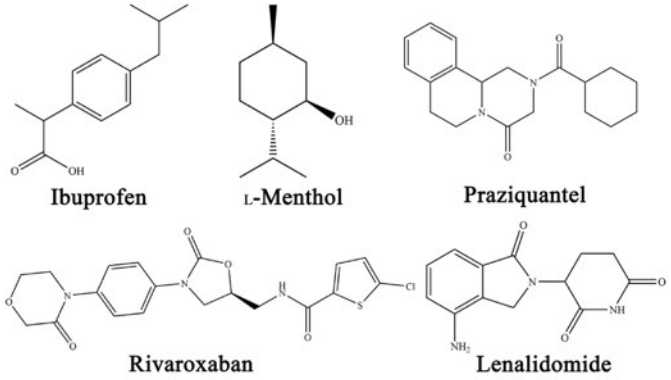

Chart S1 Molecular structures of ibuprofen, L-menthol, praziquantel, rivaroxaban and lenalidomide.

Specific operating conditions of OOCA for the four different co-agglomerates were described in Table S1.

Table S1 The operating temperatures for different co-agglomerates.

Co-agglomerate	Amount of APIs(/g)	Amount of water(/g)	SDS (/g)	Oiling-out T (/℃)	Quenching T (/℃)
IBU-MT	1.0-1.0	150.0	0.12	50.0	5.0
IBU-PZQ	2.0-0.5	150.0	0.12	80.0	5.0
IBU-RXB	1.0-0.5	150.0	0.12	80.0	5.0
IBU-LDM	1.0-1.0	150.0	0.12	80.0	5.0

At 5 ℃, supernatant sampled from the aqueous suspension of ibuprofen-L-menthol was analyzed by HPLC. The appearance time of the characteristic peak of ibuprofen (seen in Fig. S1(a)) is around 6.163 min. However, due to the insolubility of ibuprofen in water at 5 ℃, there was no signal observed at 6.163 in the test sample (Fig. S1 (b)).

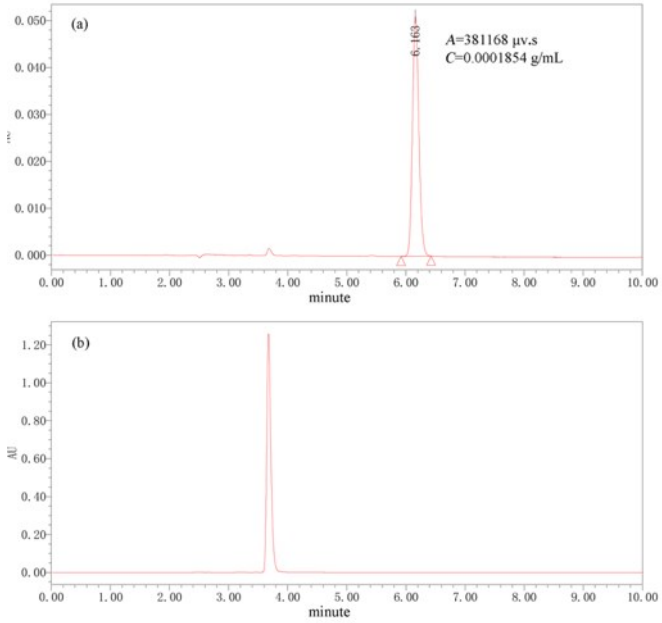

Figure S1 HPLC spectra of standard sample (a) and the supernatant sampled from the aqueous suspension of ibuprofen-L-menthol at 5 ℃ (b).

It can be predicted from the literature[1] (Fig. S2) that the solubility of L-menthol is expected to be lower than 10^{-4} g/g in water. Combining Fig. S1, at 5 ℃, the ternary phase diagram of ibuprofen-L-menthol-water can be simply considered as a $L+S_1+S_2$ region, where L is pure water.

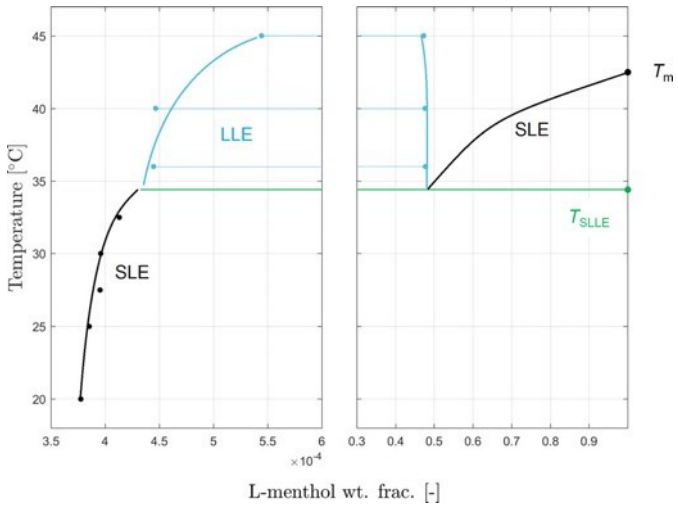

Figure S2 Binary phase diagram of L-menthol-water[1] (reproduced with permission).

From the analysis results of PXRD, FTIR, and DSC of the product, it can be concluded that praziquantel existed mostly in amorphous form. In Fig. S3(a), one can see the characteristic peaks of ibuprofen (5.9 and 13.8°) in the PXRD pattern of ibuprofen-praziquantel co-agglomerates, however, no characteristic peaks of praziquantel can be identified (Fig. S3(a)), showing praziquantel may exist as an amorphous phase in the co-agglomerate. This hypothesis was confirmed by the FTIR spectra (Fig. S3(b)), where one can see the amide carbonyl stretching vibration of the crystalline praziquantel exhibited a well-defined double peak at 1622 and 1647 cm^{-1}, however, at the similar frequency, the product showed overlapped peaks, revealing the amorphous praziquantel formed.[2] In the DSC result of the product (Fig. S3(c) and S3(d)), one can also see the glass transaction temperature of amorphous praziquantel around 39.2 ℃, which is approximate to the value (31.1 ± 2℃) reported by Shi et al.[3] Formation of amorphous praziquantel may improve the dissolution rate and bioavailability to some extent when compared with the crystalline form as demonstrated by Wang et al.[4]

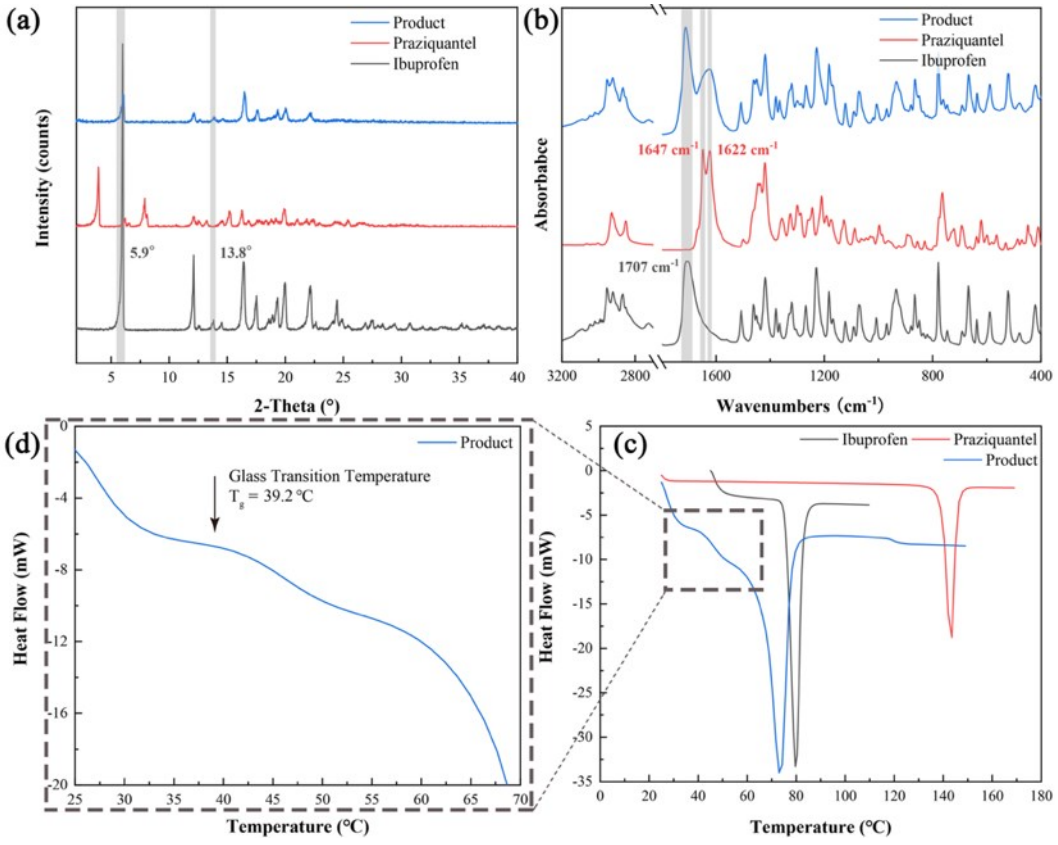

Figure S3. Solid state characterization of the starting materials and the product: (a) PXRD patterns of ibuprofen, praziquantel and the product; (b) IR spectra of ibuprofen, praziquantel, and

the product; (c) DSC curves of ibuprofen, praziquantel and the product; (d) magnification of the rectangular region in (c).

PXRD patterns and IR spectra of ibuprofen, rivaroxaban and the product were depicted in Fig. S4. Characteristic peaks of ibuprofen (5.9 and 12.0°) and rivaroxaban (22.4 and 26.5°) can be identified in the PXRD result of the product (Fig. S4(a)). In the IR spectra (Fig. S4(b)), the *ν*(C-H) around 2869~2957 cm^{-1} of ibuprofen,[5] and the secondary amide N-H stretching vibration band (3356 cm^{-1}) and the strong stretching frequencies of amide group (1668 and 1643 cm^{-1}) of rivaroxaban[6] can all be observed, demonstrating the product consists of the two starting materials.

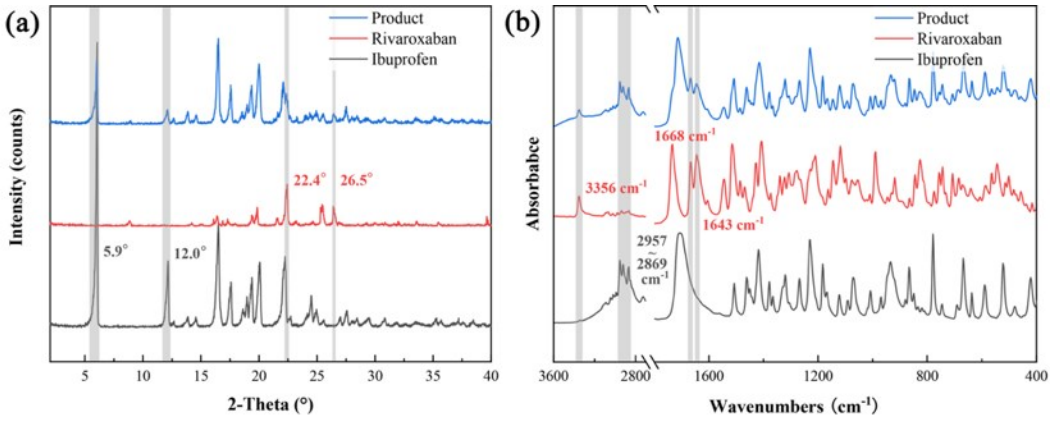

Figure S4 PXRD patterns and IR spectra of ibuprofen, rivaroxaban, and the product.

Ibuprofen, lenalidomide, and the product were all analyzed using PXRD and FTIR, with the results shown in Fig. S5. One can see the PXRD characteristic peaks of the product contain peaks of ibuprofen (5.9 and 16.4°) and lenalidomide (15.6 and 23.7°). The *v*(C-H) (around 2957~2869 cm^{-1}) in ibuprofen and the characteristic peaks for lattice water round 3561~3343 cm^{-1} in lenalidomide (Form 2, hemihydrate)[7] can all be observed in the IR spectrum of the product, indicating the products obtained were co-agglomerates of ibuprofen and lenalidomide.

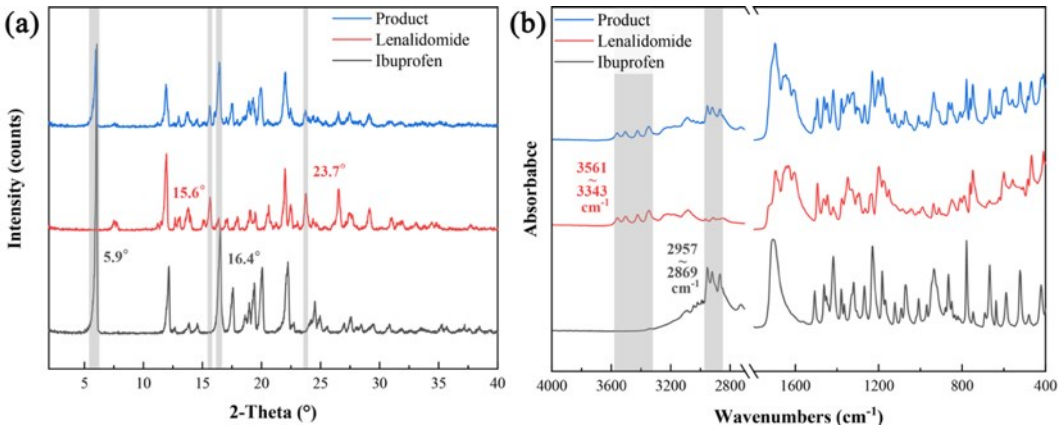

Figure S5 PXRD patterns and IR spectra of ibuprofen, lenalidomide, and the product.

The calculated isosteric adsorption heats between the surfaces of L-menthol, (1, -1, 1), (-1, 1, 1), (-1, 1, 0) and (-1, 1, -1), and water molecules were shown in Fig. S6. They all possess a minimum value at 35 ℃.

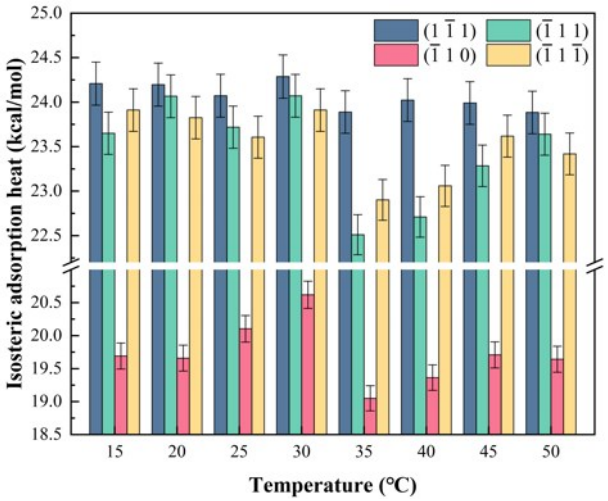

Figure S6 Isosteric adsorption heats between the MI crystal surfaces of L-menthol and the water molecules at different temperatures.

Intermolecular interaction energy, an effective indicator to assess the solute-solvent interaction, between L-menthol and water molecules were calculated at different temperatures via molecular dynamics (MD) simulation using Material Studio (Fig. S7). The computational process included three steps: (1) an amorphous cell (AC) composed of 500 solvent molecules and one solute molecule was constructed and optimized; (2) MD simulation with an NVT ensemble at different temperatures was performed (500 ps with a time step of 1 fs, controlled by an Andersen thermostat[8]); (3) energies of the isolated solute, isolated solvent, and the amorphous cell model containing solute and solvent molecules were calculated by Forcite module, respectively.

The intermolecular interaction energy of the solute-solvent (E_{int}) was defined as Eq. 1:[9]

$$E_{int} = E_{tot} - (E_{solu} + E_{sol}) \quad (1)$$

where E_{tot} represents the total energy of the AC model of the solute-solvent; E_{sol} and E_{solu} stand for the energies of the isolated solute molecule and solvent molecule, respectively.

The result (Fig. S7) shows a similar trend with the calculation of isosteric adsorption heats where a considerable decrease was observed at 30~35℃.

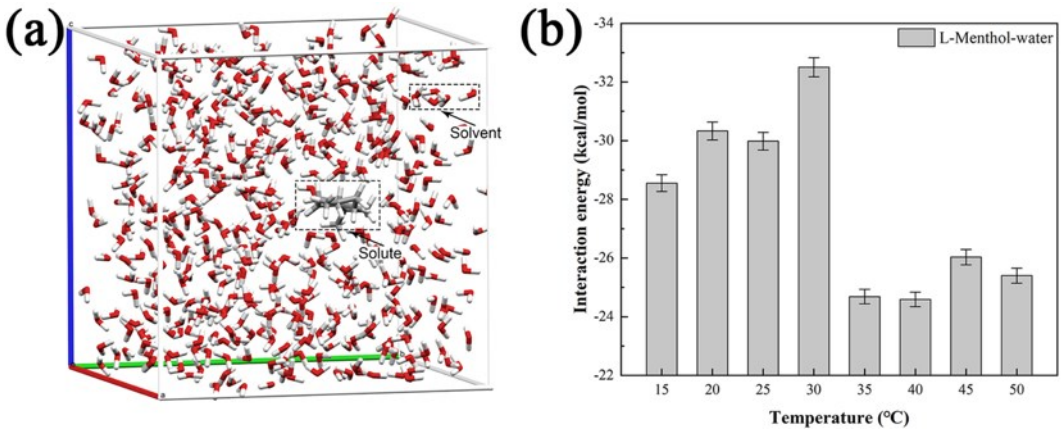

Figure S7 Intermolecular interaction energies between L-menthol-water molecules at different temperatures.

The calculated isosteric adsorption heats between the MI surfaces of ibuprofen and water molecules were shown in Fig. S8(a), and the intermolecular interaction energy of ibuprofen-water at different temperatures were depicted in Fig. S8(b). The minimum values of isosteric adsorption heats for all surfaces were observed at 75 ℃, and the result of intermolecular interaction energy calculation show the same trend.

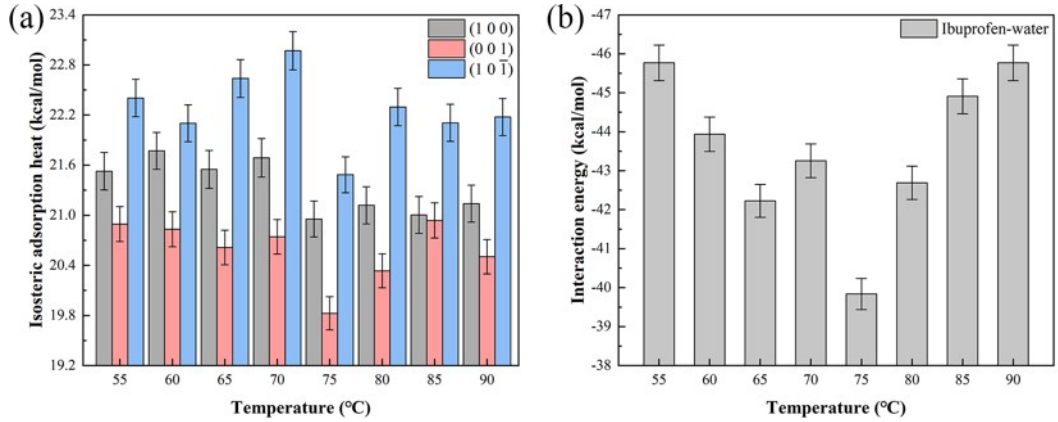

Figure S8 The result of molecular dynamics simulation. (a) The isosteric adsorption heats results of ibuprofen. (b) The intermolecular interaction energy results of ibuprofen.

In order to investigate the reason of selective aggregation of ibuprofen and L-menthol in aqueous solution as shown in the stability calculation, Radial distribution function (RDF) analysis was performed by Material Studio. RDF is a helpful tool to show the interaction of atoms at a distance from a specified atom[10,11]. Generally speaking, dominant energy varies with radial distances.[12] The time step and the calculation period were set at 1 fs and 500 ps, respectively, controlled by an Andersen thermostat method.[13,14] RDFs were analysed with the oxygen atom in the solute molecule serving as a reference substance, and then the interactions between the oxygen atoms reflected the actual intermolecular effects. The peak in a distance range of 2.4~3.0 Å on the RDF curve reveals hydrogen bond formed between the selected atomic pairs.[15] Therefore, the peak at 2.7 Å in the RDF curve of ibuprofen-L-menthol in Fig. S9(b) indicates strong hydrogen bonds were formed between oxygen atom in -OH of L-menthol and hydrogen atom in acid -OH of ibuprofen, accounting for the spontaneous aggregation of the two APIs. No peak was found around 2.4~3.0 Å in RDF analyses of L-menthol-water and ibuprofen-water, showing no hydrogen bond was formed between the APIs and the water molecules.

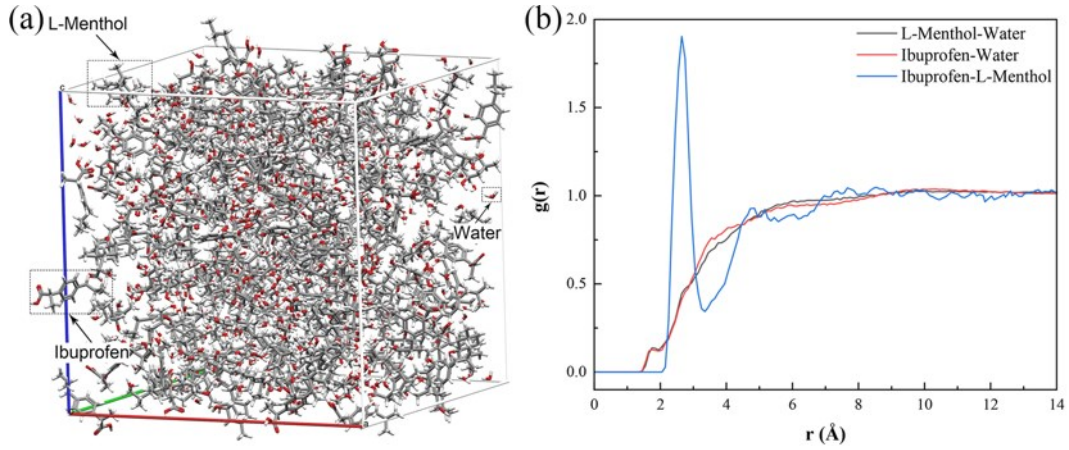

Figure S9 RDF analysis of the system of L-menthol-ibuprofen-water.

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