

Supporting Information

Spherical agglomeration of high melting point drugs in water at low temperature by developing a two-step oiling-out mechanism and the design strategy

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1 General information

Table S1. Experimental conditions for the preparation of spherical particles based on a two-step oiling-out mechanism.

Serial number	Drug category	T_m (K)	m_{EVA} (g)	m_{drug} (g)	T_o (K)	m_{w1} (g)	m_{sc} (g)	m_{w2} (g)	t_c (min)	Stirring rate (rpm)	Yield (%)
1	ibuprofen	349.45	1.0	0.5	328.15	50	5.0	70	20	350	97.5
2	flurbiprofen	385.15	1.0	0.5	353.15	50	5.0	70	25	500	97.2
3	ipriflavone	393.15	1.0	0.5	353.15	50	5.0	70	10	500	95.8
4	aspirin	409.15	1.0	1.8	343.15	50	17.0	60	5	500	95.0
5	etodolac	421.15	1.0	0.5	353.15	50	5.0	70	20	600	97.4
6	naproxen	427.15	1.0	0.5	353.15	50	5.0	70	10	600	98.2
7	indometacin	435.15	1.0	0.2	333.15	50	5.0	70	10	650	95.3
8	indometacin	435.15	1.0	0.5	343.15	50	5.0	70	10	650	96.1
9	indometacin	435.15	1.0	1.0	353.15	50	5.0	70	20	650	95.7
10	celecoxib	437.45	1.0	1.0	353.15	50	5.0	70	5	600	96.9
11	benorilate	454.15	1.0	0.5	353.15	50	5.0	70	5	700	96.6
12	bezafibrate	457.15	1.0	0.3	353.15	50	5.0	70	4	600	96.5
13	probenecid	469.15	1.0	0.8	353.15	50	5.0	70	5	600	95.4
14	glimepiride	487.65	1.0	0.5	353.15	50	5.0	70	5	650	96.7
15	rivaroxaban	502.15	1.0	0.3	353.15	50	5.0	70	25	500	95.5
16	sulfadiazine	526.15	1.0	0.5	353.15	50	5.0	70	5	650	96.0

where T_m and T_o represent the melting point of drugs and operating temperature, respectively. The m_{EVA} and m_{drug} represent the masses of ethyl vanillin and drug added at the initial state, respectively. The m_{w1} and m_{sc} denote the masses of water and sodium chloride added at the initial state, respectively. The m_{w2} represents the mass of water re-added after co-oiling-out has occurred. The t_c indicates the time required from the onset of single-oiling-out to the formation of spherical particles. In the case of aspirin, a certain amount of aspirin needs to be pre-dissolved in the re-added water in order to ensure a high yield of the product.

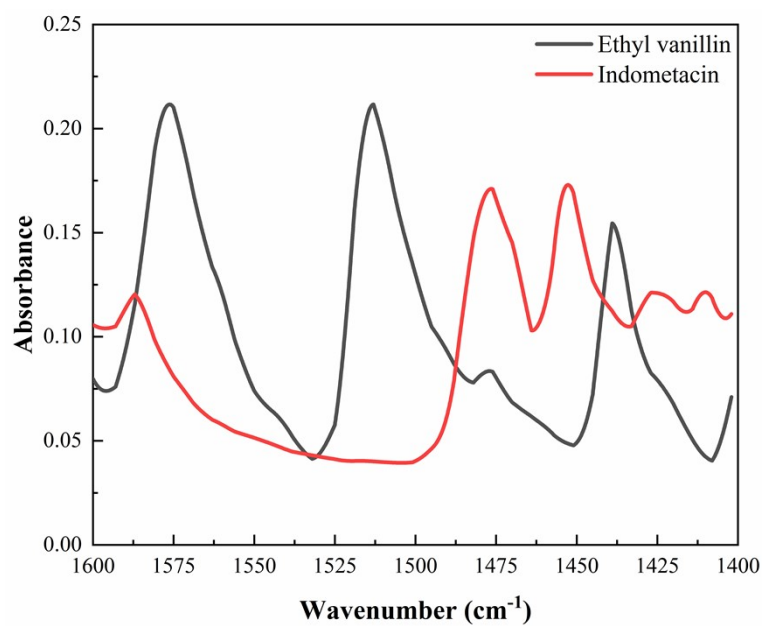


Fig. S1 IR spectra results of ethyl vanillin and indometacin solids.

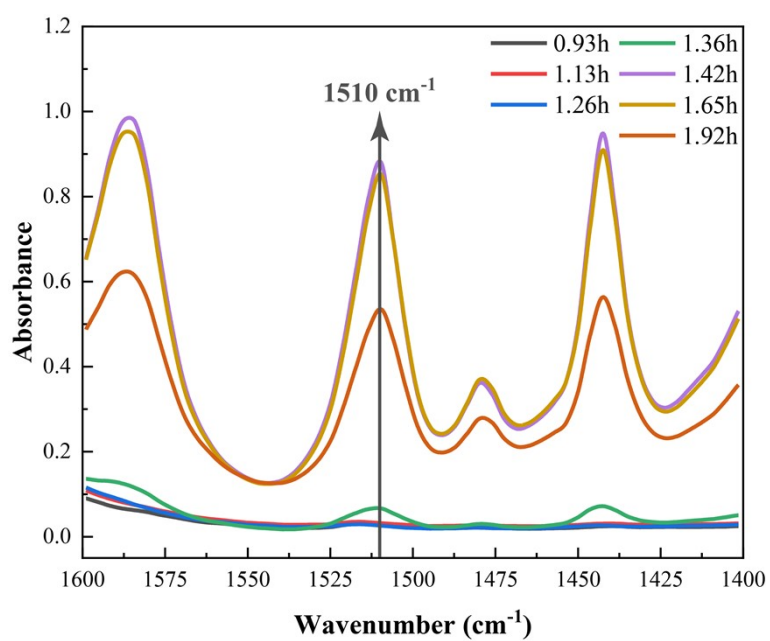


Fig. S2 Solvent-background-subtracted spectra of ethyl vanillin in aqueous solution.

Table S2. Comparison of solid properties of indomethacin products obtained by different methods.

Properties	Non-spherical commercial product	Spherical particles prepared by two-
	powders	step Oiling-out Mechanism ^α
Bulk density [g·cm ⁻³]	0.66	0.80
Angle of repose [°]	65.0	35.1

^α The spherical particles were prepared by the process serial number 4 in Table S1.

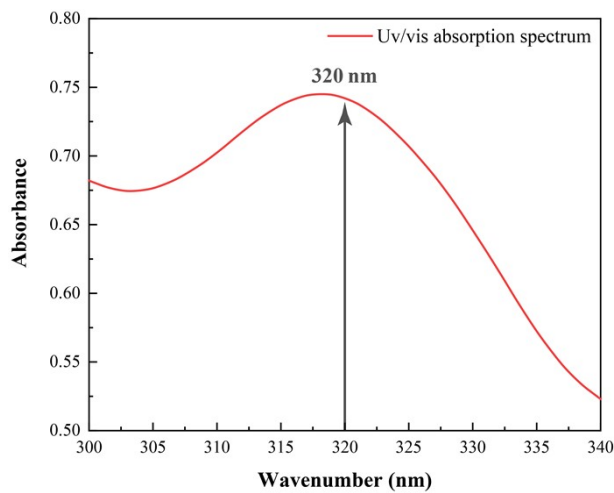


Fig. S3 UV/vis absorption spectrum of indometacin in ethanol.

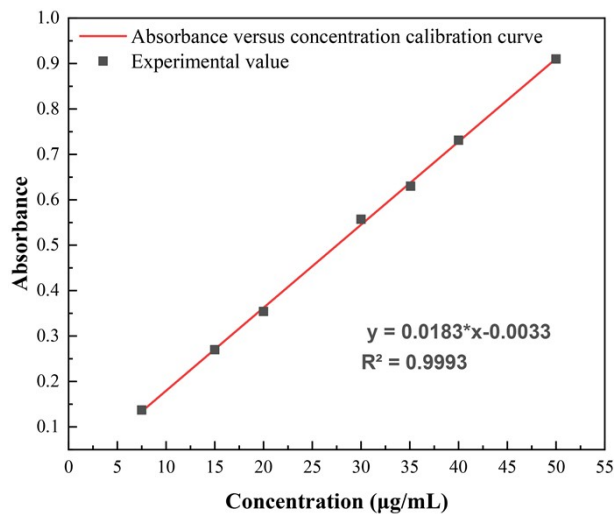


Fig. S4 Standard curve of UV/vis absorbance and concentration of indometacin.

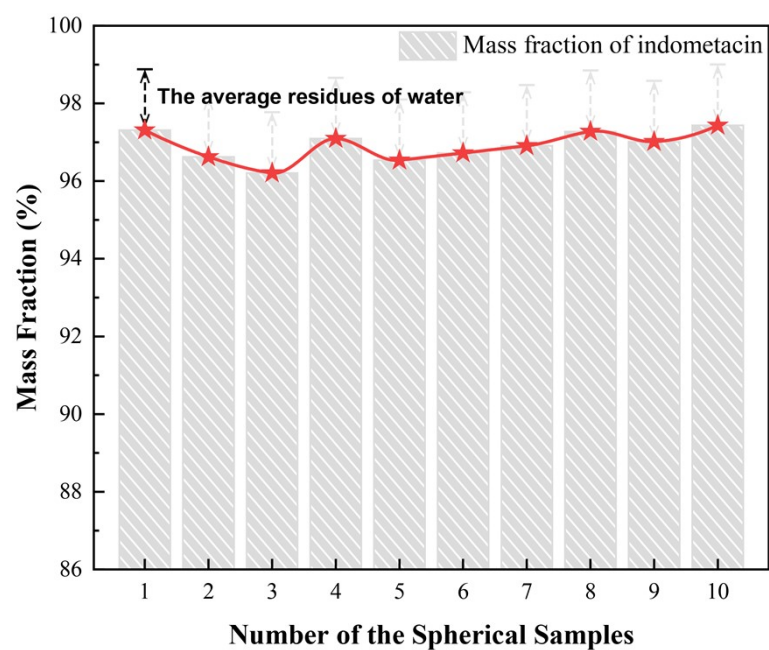


Fig. S5 The contents of indometacin in ten samples.

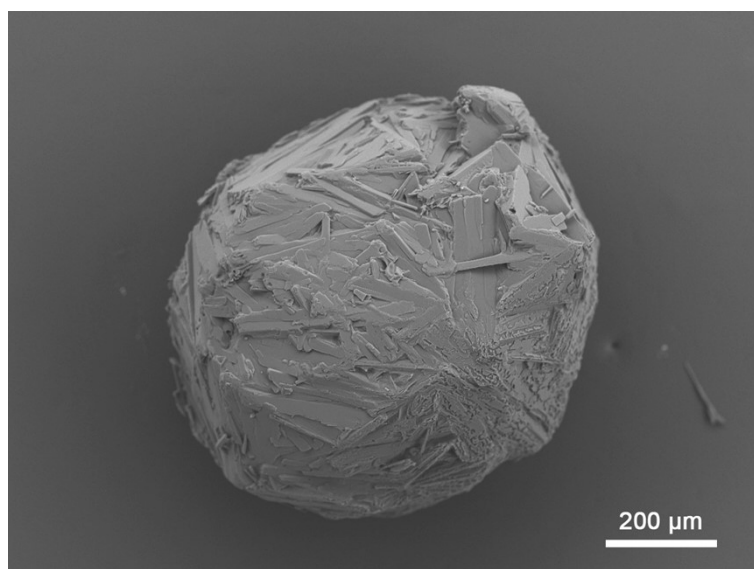


Fig. S6 Scanning electron microscope images of ibuprofen spherical particles prepared by a two-step oiling-out mechanism.

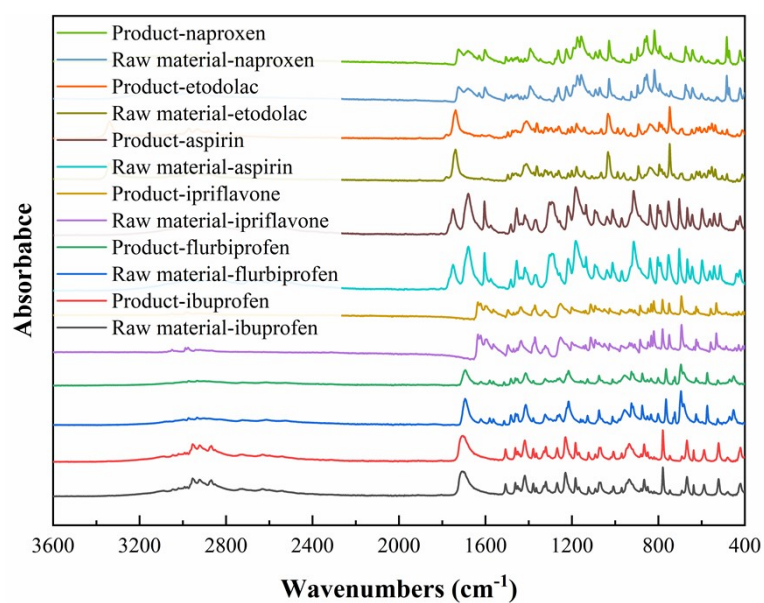


Fig. S7 IR spectrum of pharmaceutical spherical products and raw materials (part 1).

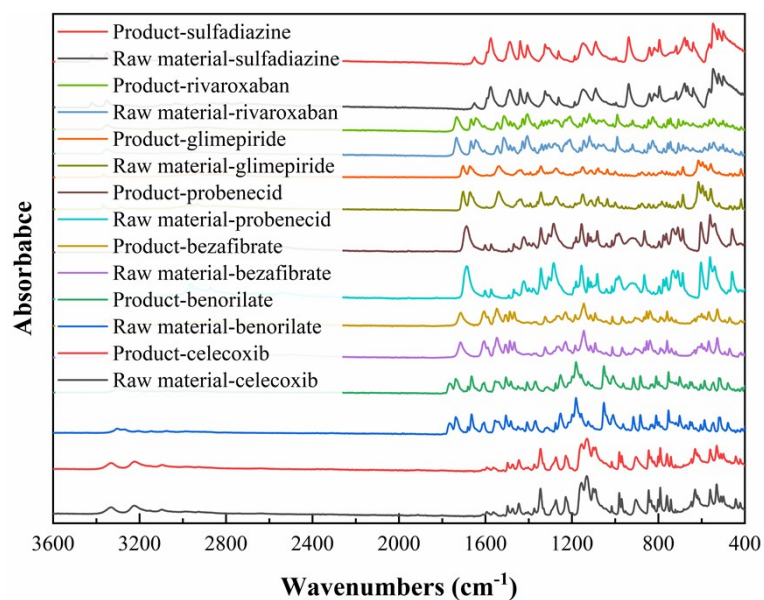


Fig. S8 IR spectrum of pharmaceutical spherical products and raw materials (part 2).

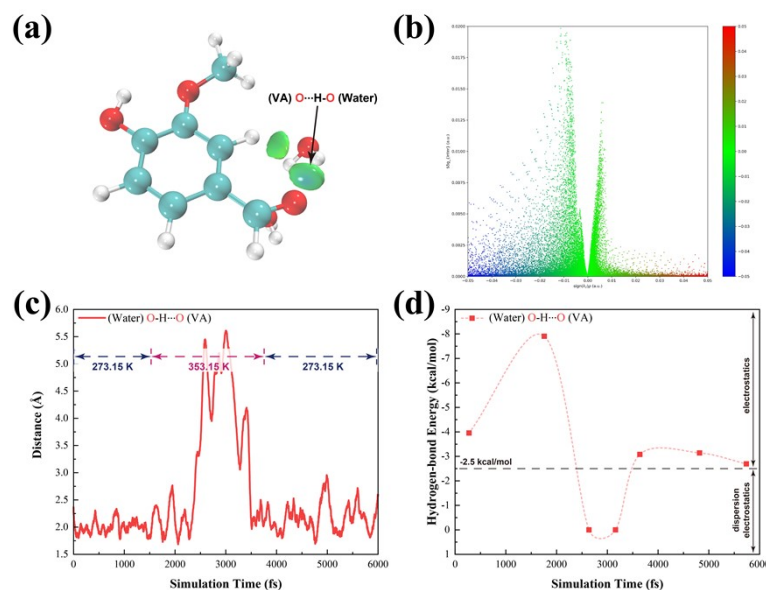


Fig. S9 Noncovalent interaction gradient isosurface (a) and scatter plot (b) produced by IGM analysis. (c) Curves of hydrogen bond length between water and vanillin (VA) molecules with change in temperature. (d) The curve of hydrogen bonding energy between molecules with temperature.

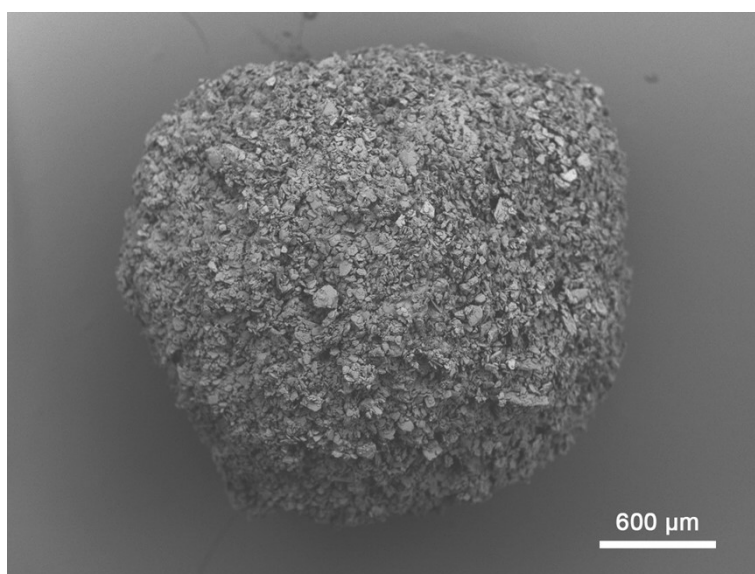


Fig. S10 Scanning electron microscopy images of spherical particles of indomethacin prepared by two-step oiling-out mechanism using sodium chloride as inhibitor and vanillin as oiling-out mate.

Table S3. Process parameters and energy consumption for the preparation of celecoxib spherical particles by different processes.^a

Category	Value	Unit
general information		
production capacity	200	t/a
melt granulation process ^b		
operating temperature	443.15	K
steam consumption (0.1 MPa)	26.668	t/a
steam consumption (1.3 MPa)	24.687	t/a
cooling water consumption	1277.460	t/a
instrumentation air	19.346	Nm ³ /a
nitrogen	2.901	Nm ³ /a
the energy consumption per unit product	17.598	kgoe/t
two-step oiling-out spherical agglomeration process ^c		
operating temperature	353.15	K
heat exchange of hot water	173085	MJ/a
instrumentation air	19.346	Nm ³ /a
nitrogen	2.901	Nm ³ /a
the energy consumption per unit product	10.341	kgoe/t

^a The data for utilities are derived from process simulation software (Aspen Plus), and the energy consumption calculation method reference GB/T50441-2016.

^b The melt granulation process of celecoxib consists of two parts: crystallization and granulation. In the crystallization part, celecoxib crystals were prepared by cooling crystallization using an ethanol system (high temperature: 343.15 K, low temperature: 303.15 K). In the granulation part, the operating temperature was 443.15 K. The thermodynamic data involved were obtained from the literature.^{1,2}

^c Hot water at 373.15K was used as the heat source.

The energy consumption of the energy-consuming system is calculated according to the following formula.

$$E = \sum (G_i C_i) + \sum Q_i \quad (1)$$

where E denotes the energy consumption of the energy-consuming system. G_i and C_i represent the consumption and equivalent coefficient of primary energy consumption of utilities, respectively. Q_i denotes the amount of standard energy consumption equivalent to the heat exchanged between the energy-consuming system and the environment.

The energy consumption per unit of product is calculated according to the following formula.

$$e = E/G \quad (2)$$

Where e denotes energy consumption per unit of product (kgoe/t), E and G represent the energy consumption (kgoe/a) and product production (t/a) of the energy-consuming system, respectively. According to the energy consumption calculation standards (GB/T50441-2016), the equivalent coefficient of primary energy consumption of the utilities involved in this work are determined: 0.1 MPa steam (55 kgoe/t), 1.3 MPa steam (80 kgoe/t), cooling water (0.06 kgoe/t), instrumentation air (0.038 kgoe/Nm³), nitrogen (0.15 kgoe/Nm³). In addition, the heat input or output through heat exchange (333.15-393.15 K) between energy-consuming systems is discounted by half to calculate the standard energy consumption. In the case of celecoxib, the energy consumption required for the melt granulation process and the two-step oiling-out spherical agglomeration process can be calculated respectively based on the utilities data in Table S3.

$$\begin{aligned} e_{melt\ granulation} &= \frac{26.668 \times 55 + 24.687 \times 80 + 1277.460 \times 0.06}{200} \quad (3) \\ &= 17.598\ kgoe/t \end{aligned}$$

$$e_{TSOO} = \frac{173085 \div 2 \div 41.8675 + 19.346 \times 0.038 + 2.901 \times 0.15}{200} = 10.341\ kgoe/t \quad (4)$$

After calculating the energy consumption per unit of product, the annual CO₂ emission reduction R can be calculated.

$$R = \frac{(17.598 - 10.341) \times 1.4286 \times 2.5 \times 200}{1000} = 5.2\ t \quad (5)$$

Table S4. Comparison of solvent systems employed for the preparation of spherical particles of high melting point drugs.

Drug category	two-step oiling-out mechanism		Classical spherical agglomeration technology				authors
		good solvent	anti-solvent	bridging liquid	m_{os} (g/g)		
indomethacin	water	acetone	water	dichloromethane	/		Kamble et al. ³
celecoxib	water	ethanol	water	cyclohexane	63.8		Yu et al. ⁴
etodolac	water	acetone	water	dichloromethane	5.3		Jitkar et al. ⁵
naproxen	water	acetone	water	dichloromethane	7.3		Saritha et al. ⁶
glimepiride	water	dimethyl formamide	water	carbon tetrachloride	22.3		Makar et al. ⁷

where m_{os} indicates the mass of organic solvent consumed to prepare a unit mass of spherical product. The specific parameters for the preparation of spherical particles of indomethacin by classical spherical agglomeration technology are not given in the literature and thus the value of m_{os} could not be calculated.

Using etodolac as an example, the organic solvent consumption is calculated. According to the description "For a batch of 1 g of drug, the agglomeration zone at 45 mL of water, 5 mL of acetone, and 1 mL of dichloromethane gave best results and was taken forward for further trials" in the literature, the amount of organic solvent consumed per 1 g of spherical product prepared can be calculated after querying the density data.

$$m_{os} = \frac{5 \times 0.8 + 1 \times 1.3}{1} = 5.3 \text{ g/g} \quad (6)$$

2 References

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