Supplementary Information

Biphasic dissolving microneedles with cyclodextrin inclusion complexes for enhanced delivery of poorly soluble drugs

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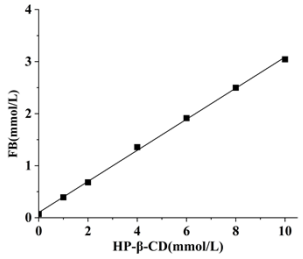
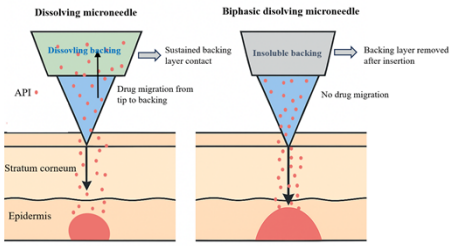
Supplementary Figure 1



Supplementary Figure S1. The phase solubility of flurbiprofen (FB)/HP-β-CD inclusion complex.

Supplementary Figure 2



Supplementary Figure S2. Schematic illustration comparing the structural design and drug delivery mechanisms between conventional dissolving microneedles and biphasic dissolving microneedles. In the conventional dissolving microneedle system (left), the drug may diffuse from the needle tips toward the water-soluble backing layer after skin insertion, resulting in partial drug loss and decreased transdermal delivery efficiency. In contrast, the biphasic dissolving microneedle system (right) incorporates an insoluble backing layer that is physically removed after insertion. This design minimizes drug back-diffusion and enables concentrated drug release within the intended skin layer.

Supplementary Table 1

Factor levels	Molar ratio	Temperature (℃)	Reaction Time (h)
1	1:1	20	4
2	1:2	40	6
3	1:3	60	8

Supplementary Table S1: Factor levels used in the orthogonal experimental design. This table presents the three-level settings for each factor investigated in the L9(3^3) orthogonal design. The experimental factors included the molar ratio of drug to cyclodextrin, reaction temperature, and reaction time, each tested at three defined levels.

Supplementary Table 2

No.	Molar ratio	Temperature (℃)	Reaction time (h)	S_1 (%)	S_2 (%)	S
1	1:1	20	4	91.33	72.2	73.85
2	1:1	40	8	92.72	77.8	77.47
3	1:1	60	6	94.32	80.48	83.33
4	1:2	20	8	94.08	62.5	67.40
5	1:2	40	6	96.45	53.67	78.23
6	1:2	60	4	96.07	66.42	63.02
7	1:3	20	6	96.19	45.64	63.03
8	1:3	40	4	92.03	32.03	61.91
9	1:3	60	8	91.49	56.66	56.66
K_1	220.48	170.34	160.65			
K_2	182.59	163.5	179.79			
K_3	134.33	203.56	196.96			
R	28.72	13.35	12.10			

Supplementary Table S2: Experimental results and range analysis of the L9(3^3) orthogonal design. S_1 and S_2 represent drug loading (%) and encapsulation efficiency (%), respectively. The evaluation index S was calculated as: $S = 0.3 \times S_1 + 0.7 \times S_2$. K_1-K_3 denote the sum of S values at levels 1, 2, and 3 for each factor, and R is the range ($R = \max_{(K)} - \min_{(K)}$), indicating the influence magnitude of each factor.

Supplementary Table 3

Materials	Proportion (v/v, %)
PUA-Cure 9110	54
HPMA	45
TPO	1

Supplementary Table S3: The formulation of insoluble backing layer used for biphasic dissolving microneedles, expressed as volume percentages (v/v).

Supplementary Table 4

Materials	Proportion (w/w, %)
HP-β-CD	30
HPMC E5	10
Water	60

Supplementary Table S4: The formulation of the soluble backing layer used for evaluating the effect of backing materials on drug delivery efficiency.

Supplementary Table 5

Source	SS	DF	MS	*F*	*P*
Molar ratio	1242.945	2	621.472	21.227	< 0.05
Temperature (℃)	306.129	2	153.064	5.228	> 0.05
Reaction time (h)	219.952	2	109.976	3.756	> 0.05
Error	58.556	2	29.278		

Supplementary Table S5. Results of one-way ANOVA evaluating the effects of molar ratio, temperature, and time on the preparation of inclusion complexes. Abbreviations: SS, sum of squares; DF, degrees of freedom; MS, mean square; F, F-value; P, probability level. Note: Differences were considered statistically significant when $P < 0.05$.

Supplementary Table 6

Model	Equation	R^2 (F4-SB)	R^2 (F4-IB)	k (F4-SB)	k (F4-IB)	n (F4-SB)	n (F4-IB)
Zero-order	$Q_t=k_0t$	0.962	0.913	4.27	2.53	–	–
First-order	$\ln(1-Q)=-k_1t$	0.945	0.880	0.0780	0.0650	–	–
Higuchi	$Q_t=k_Ht^{1/2}$	0.991	0.982	16.2	12.4	–	–
Korsmeyer–Peppas	$Q_t/Q_\infty=kt^n$	0.986	0.974	15.5	11.0	0.489	0.612

Supplementary Table S6. Kinetic model fitting parameters for drug release from F4-SB (F4-soluble backing) and F4-IB (F4- Insoluble backing) formulation.

Abbreviations:

Q_t, cumulative drug release at time t;

Q_∞, total amount of drug released at infinite time;

k_0, zero-order release constant;

k, release rate constant for first-order, Higuchi, and Korsmeyer–Peppas models;

n, release exponent in the Korsmeyer–Peppas model;

R^2, coefficient of determination.