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Supplementary Materials: Enhancement of Skin Delivery of Drugs using Proposome Depends on Drug Lipophilicity

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Supplementary Material S1. Consideration of Drug Concentration and Sink Condition

In this study, the concentration for all drugs was set at 5.6 mM, which is an arbitrary value. During the preparation of proposome, the total amount of drug was mixed with pure PG first. Each drug was easily soluble and formed clear solution at 5.6 mM. Also, the concentration was selected to ensure sink condition in the receptor compartment for skin permeation study.

The calculation of sink condition for each drug is shown in Table S1. For example, the solubility of ibuprofen is 3.4 mg/mL at 37 °C [1]. If 20% of the drug solubility is regarded as the sink condition, the concentration at sink condition is 3400/5 = 680 μg/mL. On the other hand, the amount of ibuprofen added to the donor compartment is 58.17 μg and the maximum possible drug concentration in the receptor compartment (containing 4 mL of PBS pH 7.4) is 58.17/4 = 14.5 μg/mL, which is lower than the sink condition concentration (28 μg/mL). Moreover, 1 mL sample solution was replaced with fresh medium at collection time, further ensuring the sink conditions.

Table S1. Drug solubility and sink condition calculation.

Drug	Solubility in Aqueous Solution (mg/mL)	Amount (μg) in 50 μL of Proposomes	Max. Drug Concentration in Receptor Cell (μg/mL)	Sink Conditions (μg/mL)
Ibuprofen	3.4 (pH 7.4) [1]	58.17	14.5	680
Ibuprofen Na	8.7 (pH 6.8) [1]	64.37	16.1	1740
Tofacitinib Citrate	0.15 (basic) [2]	142.27	35.6	30
Rhodamine B	15 [3]	135.08	33.8	3000
Lidocaine	44.5 (pH 7.4) [4]	66.08	16.5	8900

Supplementary Material S2. High Performance Liquid Chromatography (HPLC) Conditions for Ibuprofen, Tofacitinib Citrate, Rhodamine B and Lidocaine

Table S2. HPLC conditions for the test drugs.

Drugs	Ibuprofen and Ibuprofen Na [5]	Tofacitinib Citrate [6]	Rhodamine B [7]	Lidocaine [8]
Column	ACE 5 C18 column (Advanced Chromatography Technologies, 5 µm, 4.6 × 250 mm)	Zorbax Eclipse XDB C18 column (Agilent, 5 µm, 4.6 × 150 mm)	Zorbax Eclipse XDB C18 column (Agilent, 5 µm, 4.6 × 150 mm)	ACE 5 C18 column (Advanced Chromatography Technologies, 5 µm, 4.6 × 250 mm)
Mobile Phase & Composition	Isocratic Mode 0.05M Sodium Acetate buffer	Gradient Mode A: 0.01 M Ammonium Acetate buffer, pH 5.0 adjusted with Acetic acid. B: Acetonitrile. The gradient is: 0–4.3 min: 75% A and 25% B; 4.31–4.9 min: 5% A and 95% B; and 5.0–10.0 min: 75% A and 25% B)	Isocratic Mode Methonal (75%) Water (25%)	Isocratic Mode 5% Acetic Acid pH=3.4, adjusted with 1.5M NaOH (80%) Acetonitrile (20%)
Detector	UV	UV	Fluorescence	UV
Detection wavelength (nm)	264	287	Excitation: 550 Emission: 580	254
Flow rate (mL/min)	0.8	1	1.1	1.5
Retention time (min)	9.2	4.8	5.2	4.9
Calibration range (µg/mL)	1–200	0.5–500	0.1–25	1–500
Calibration equation and R^2	y = 1990.3x R^2 = 0.9981	y = 39703x − 2618.6 R^2 = 1	y = 2E+07x − 722617 R^2 = 0.9987	y = 1269.4x − 91.271 R^2 = 1

Supplementary Material S3. Drug pKa and Formulation pH

During the process of the proposome preparation, the pH of the solution was not buffered. The final pH of each formulation, i.e., drug laden proposome in 30% PG, has been measured using a glass pH meter and shown in Table S3. PG is a co-solvent, which should be uniformly distributed throughout the continuous aqueous phase of the colloidal system, not particularly localized to lipid bilayer or core of the proposome.

Table S3. The pH of the final proposome formulation and pKa of each drug.

Drug	pH of Final Formulation	pKa	Source
Blank	4.5 ± 0.2	-	-
Ibuprofen	4.3 ± 0.2	4.4	[9]
Ibuprofen Na	6.7 ± 0.1	4.4	[9]
Tofacitinib	4.1 ± 0.2	5.2	[2]
Rhodamine B	3.4 ± 0.2	4.2	[10]
Lidocaine	7.5 ± 0.4	7.9	[4]

Supplementary Material S4. Intensity of Confocal Laser Light at Different Skin Depth

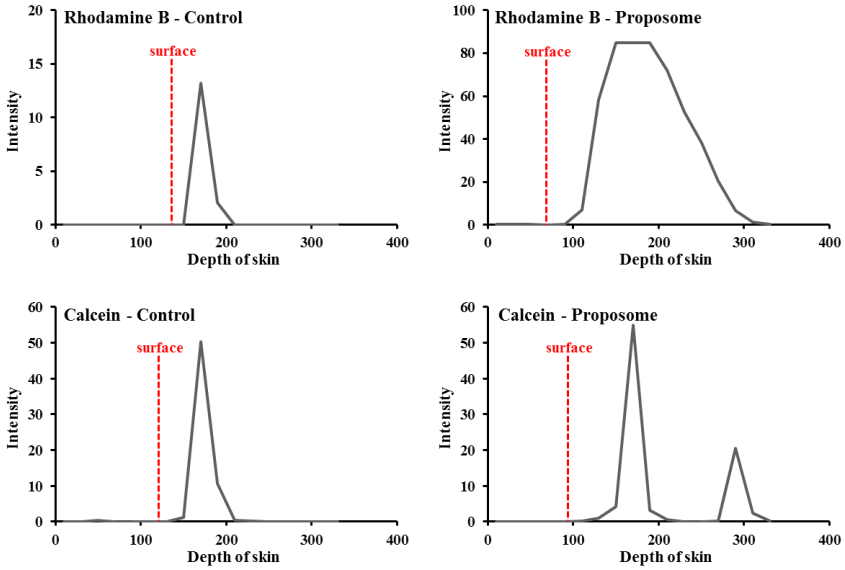

Figure S1. The fluorescent intensity of rhodamine B and calcein inside skin.

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