Self-emulsifying drug delivery systems (SEDDS): How organic solvent release governs the fate of their cargo

*Arne Matteo Jörgensen[1], Richard Wibel[1], Florina Veider[1], Barbara Hoyer[1], Joseph Chamieh[2], Hervé Cottet[2], Andreas Bernkop-Schnürch[1]**

[1]Department of Pharmaceutical Technology, University of Innsbruck, Institute of Pharmacy, Center for Chemistry and Biomedicine, 6020 Innsbruck, Austria

[2]IBMM, University of Montpellier, CNRS, ENSCM, 34095 Montpellier, France

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*Corresponding author
[1]Department of Pharmaceutical Technology, University of Innsbruck, Institute of Pharmacy, Center for Chemistry and Biomedicine, 6020 Innsbruck, Austria
Tel.: +43 512 507 58 600
Fax: +43 512 507-58699
Email: Andreas.Bernkop@uibk.ac.at

Abstract:

Organic solvents are commonly used in self-emulsifying drug delivery systems (SEDDS) to increase payloads of orally administered poorly soluble drugs. Since such solvents are released to a varying extent after emulsification, depending on their hydrophilic nature, they have a substantial impact on the cargo.

To investigate this impact in detail, quercetin and curcumin as model drugs were incorporated in SEDDS comprising organic solvents (SEDDS-solvent) of logP < 2 and > 2. SEDDS were characterized regarding size, payload, emulsification time and solvent release. The effect of solvent release on the solubility of these drugs was determined.

Preconcentrates of SEDDS-solvent$_{logP < 2}$ emulsified more rapidly (< 1.5 min) forming smaller droplets than SEDDS-solvent$_{logP > 2}$. Although, SEDDS-solvent$_{logP < 2}$ preconcentrates provided higher quercetin solubility than the latter, a more pronounced solvent release caused a more rapid quercetin precipitation after emulsification (1.5 versus 4 h). In contrast, the more lipophilic curcumin was not affected by solvent release at all. Particularly, SEDDS-solvent$_{logP < 2}$ preconcentrates provided high drug payloads without showing precipitation after emulsification.

According to these results, the fate of moderate lipophilic drugs such as quercetin is governed by the release of solvent, whereas more lipophilic drugs such as curcumin remain inside the oily phase of SEDDS even when the solvent is released.

Keywords: drug delivery, drug release, bioavailability, nanoemulsions, Taylor dispersion analysis (TDA), diffusion coefficient

Supporting information:

Table S-1:

Tabelle S-1: Solvent characteristics

Solvent	Characteristics
Benzyl alcohol	• Common preservative in peptide and protein products [1] • Acceptable daily intakes: 5 mg/kg (WHO) [2] • No adverse effects of chronic exposure in animal studies (rats and mice) [2] • Concentrations of 5% in adults are generally recognized as safe (Food and Drug Administration) [3] • Age, the ethnic polymorphism of alcohol dehydrogenase may influence toxicity [4][5] • Not recommended to be used in medicines for children < 3 [4][5] • Oral LD_{50} in rats = 3.12 $g \cdot kg^{-1}$ [6]
2-Phenoxy ethanol	• Broad antimicrobial activity • Preservative in various products including medicines (e.g. in vaccines), cosmetics and hand disinfecting up to a concentration of 5%, including products for infants [7] • Controversial safety reports trend from safe for human health [8] to adverse effects including topical allergic reactions and toxic effects on central nervous system [9][10] • Oral LD_{50} in rats = 1.26 – 2.58 $g \cdot kg^{-1}$ [8]
2-Phenyl ethanol	• Commonly used in cosmetics, pharmaceuticals as a preservative and in herbal products [11] • Approved flavoring agent by the Flavour and Extract Manufacturers Association (FEMA), the Food and Drug Administration (FDA), the Joint Expert Committee on Food Additives (JECFA), the Concil of Europe (COE) and other international organizations [12] • Oral LD_{50} in rats = 1.5 – 2.54 $g \cdot kg^{-1}$ [12]
Anisole/ Methoxybenzene	• Widely used as a food additive and in pharmaceutical preparations [13][14][15] • Harmless to the human body and the environment [13] • Found in a plant called “Tarragon”, a vegetable commonly used in French cuisine [16] • Oral LD_{50} in rats = 3.70 $g \cdot kg^{-1}$ [17]
Eugenol	• Functional ingredient of numerous products in the pharmaceutical, food and cosmetic industry [18] • Considered safe as food additive [19] • Limited and controversial studies on toxic effects [18][19] • Pharmacological properties include antimicrobial, anti-inflammatory, analgesic, anti-oxidant, anticancer, anti-ulcerogenic, effects on osteoporosis and especially on the central nervous system [19] ◦ increased potential of adverse effects • Similarities to paracetamol poisoning regarding hepatotoxic effects [20]

- Oral LD_{50} in rats = 0.5 $g \cdot kg^{-1}$ [21]

Citronellol

- Compound used by food, cosmetic and pharmaceutical industry [22]
- Flavoring compound in citrus compositions [23]
- Practically no oral toxicity (European Chemicals Agency) [24]
- Oral LD_{50} in rats = 3.45 g kg^{-1}[25]

Benzyl benzoate

- Widely used in perfumes, pharmaceutical products and as food additive [26]
- Acceptable daily intake: 5 mg kg^{-1} body weight [2]
- After oral administration, renal excretion as hippuric acid (90% after 6 h) [27]
- Oral LD_{50} in rats = 0.50 – 2.80 $g \cdot kg^{-1}$ [27]

Figure S-1:

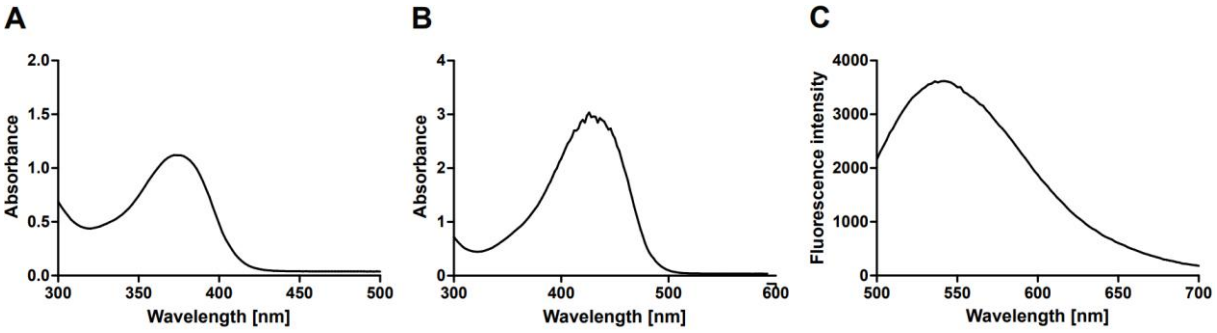


Figure S-1: Absorption spectra of quercetin **(A)** and curcumin **(B)**; **(C)** emission spectrum of curcumin (excitation: 435 nm).

Table S-2:

Table S-2: Composition of SEDDS preconcentrates in % (v/v).

Formulation	PEG35CO	Glyceryl caprylate	MCT	Cosolvent
SEDDS-A	45	15	20	
SEDDS-B	45	10	25	20*
$SEDDS_{benzyl\ alcohol}$-(A)	45	15	20	20
$SEDDS_{phenoxy\ ethanol}$-(A)	45	15	20	20
$SEDDS_{phenyl\ ethanol}$-(B)	45	10	25	20
$SEDDS_{anisole}$-(A)	45	15	20	20
$SEDDS_{eugenol}$-(B)	45	10	25	20
$SEDDS_{citronellol}$-(A)	45	15	20	20
$SEDDS_{benzyl\ benzoate}$-(B)	45	10	25	20

*replaced by demineralized water

Figure S-2:

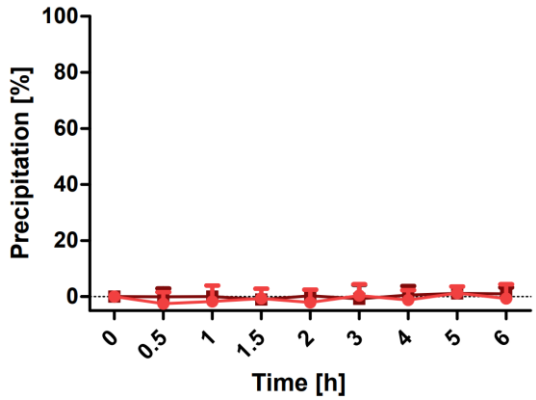


Figure S-2: Precipitation of quercetin from SEDDS-A (■) and -B (●) within 6 hours at 37 °C shaking at 550 rpm on a thermomixer.

Table S-3:

Table S-3: Quercetin and curcumin solubility in demineralized water with 2 µL of cosolvent after 6 h of incubation at 37 °C while shaking at 550 rpm.)

	Quercetin	**Curcumin**
	Conc. [mg·mL^{-1}]	**Conc. [mg·mL^{-1}] ± SD**
H_2O	< 0.006	0.0014 ± 0.0000
Benzyl alcohol	< 0.006	0.0030 ± 0.0050
Phenoxy ethanol	< 0.006	0.0038 ± 0.0011
Phenyl ethanol	< 0.006	0.0016 ± 0.0014
Anisole	-	0.0038 ± 0.0012
Eugenol	< 0.006	-
Citronellol	< 0.006	-
Benzyl benzoate	< 0.006	0.0023 ± 0.0021

Figure S-3:

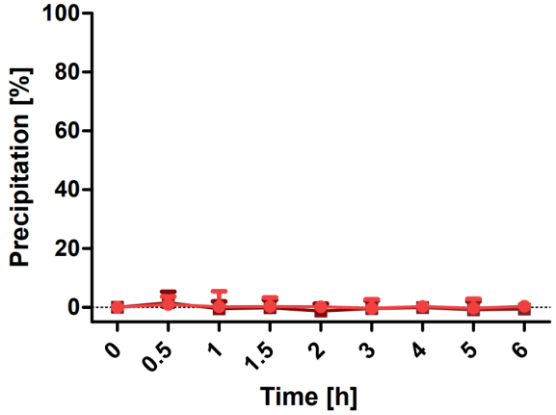
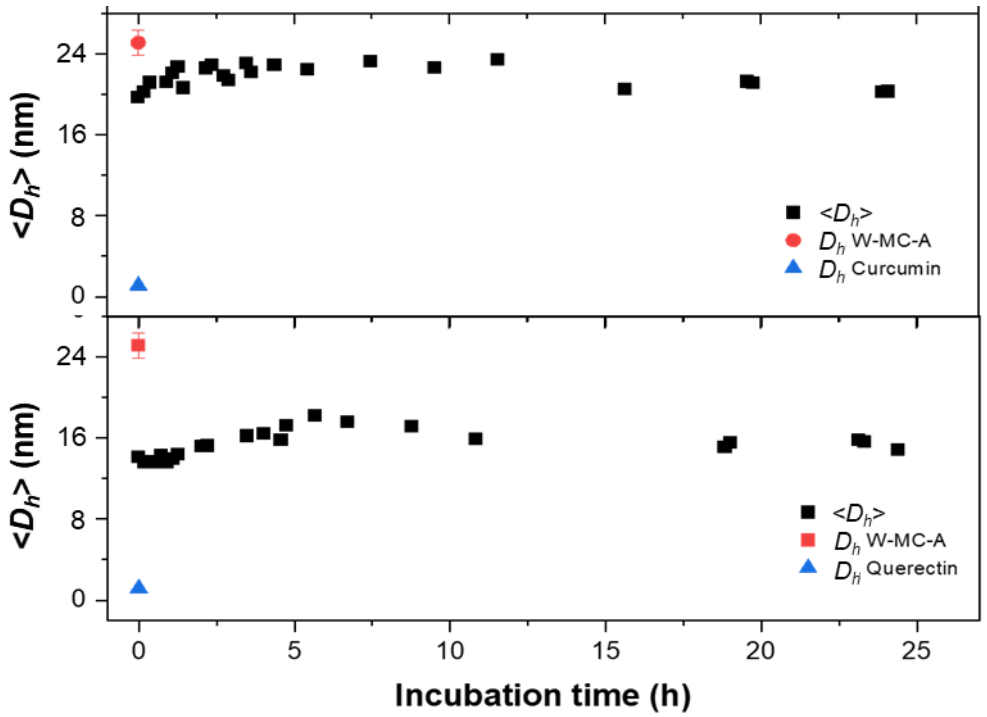


Figure S-3: Precipitation of curcumin from SEDDS-A (■) and -B (●) within 6 hours at 37 °C shaking at 550 rpm on a thermomixer.

Figure S-4: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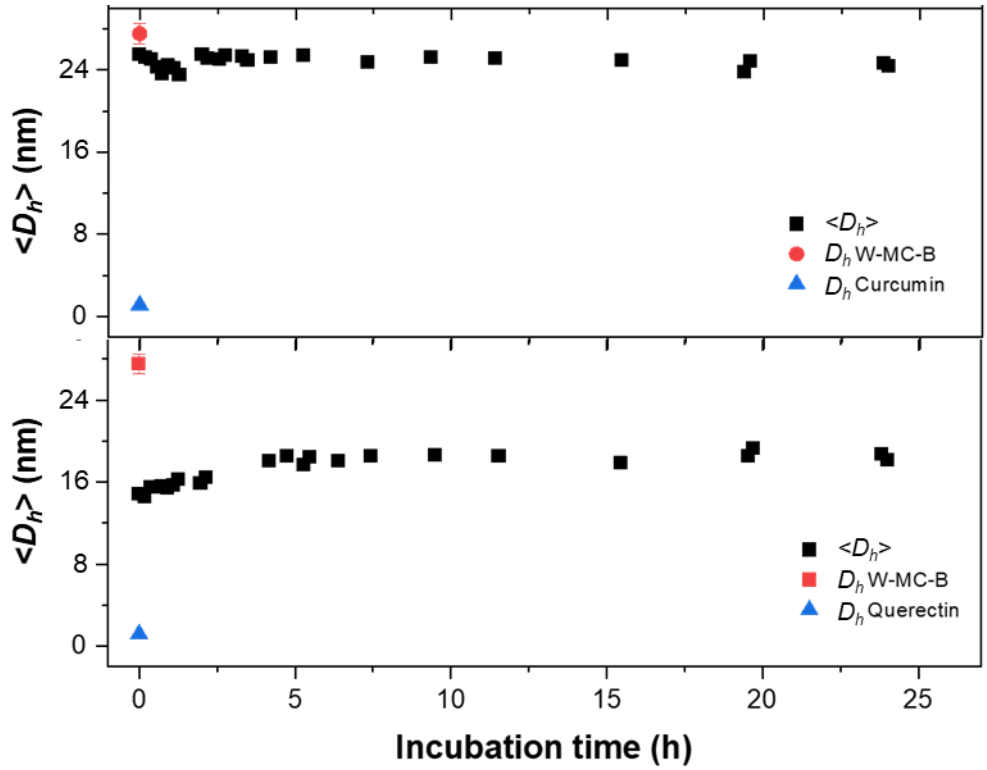
Incubation time (h)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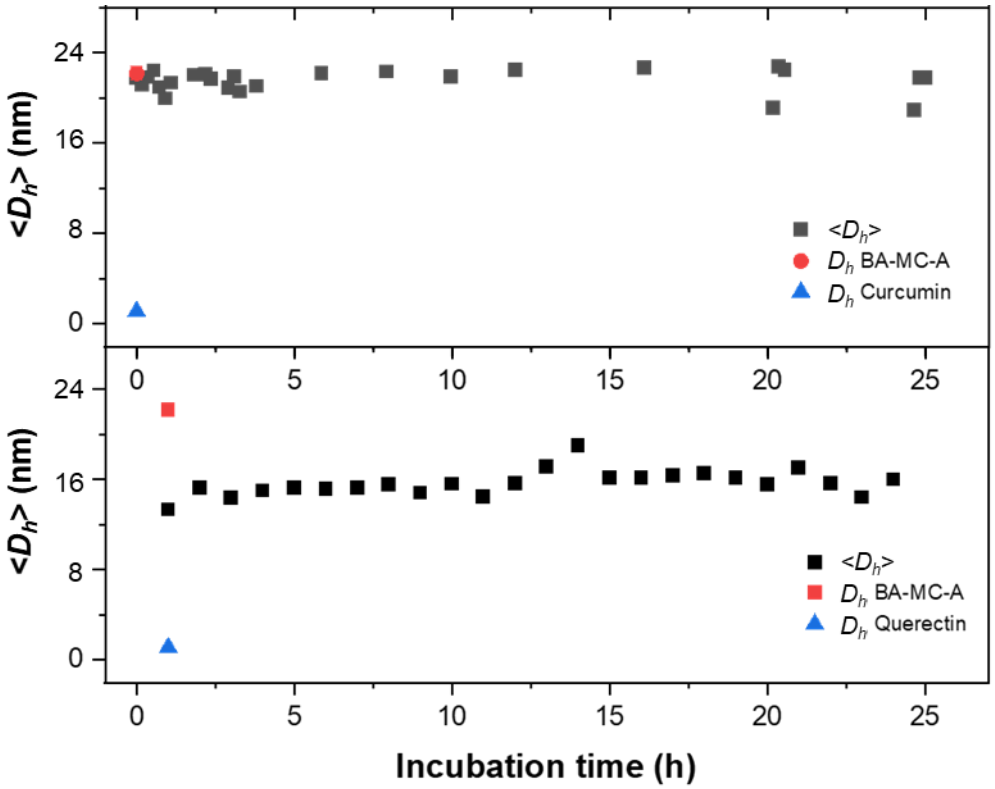
Incubation time (h)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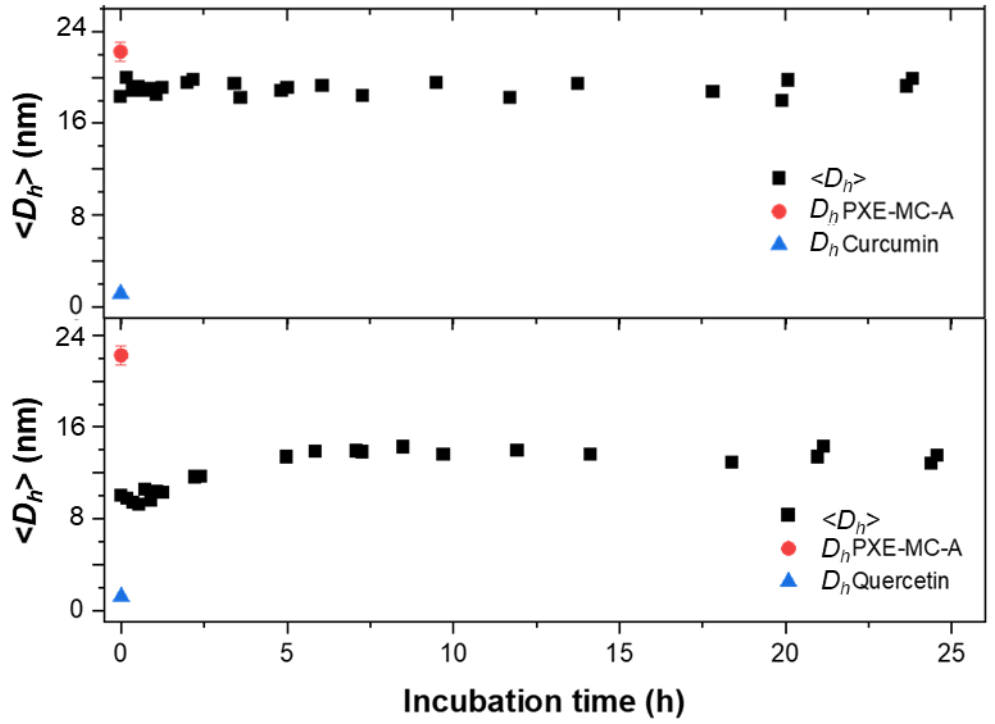
Incubation time (h)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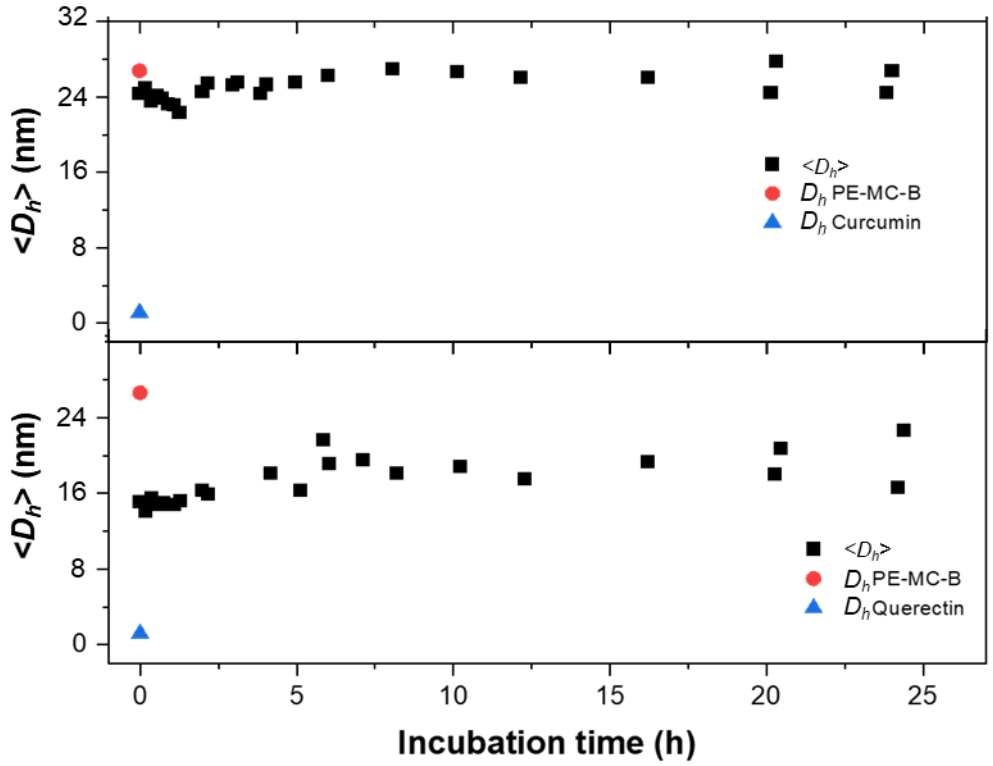
Incubation time (h)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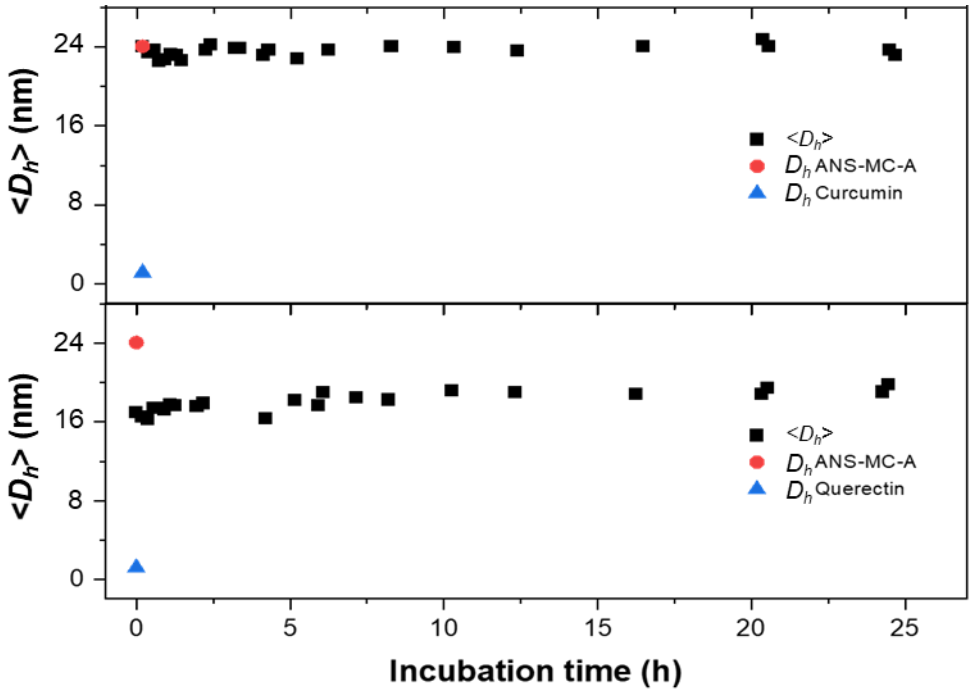
Incubation time (h)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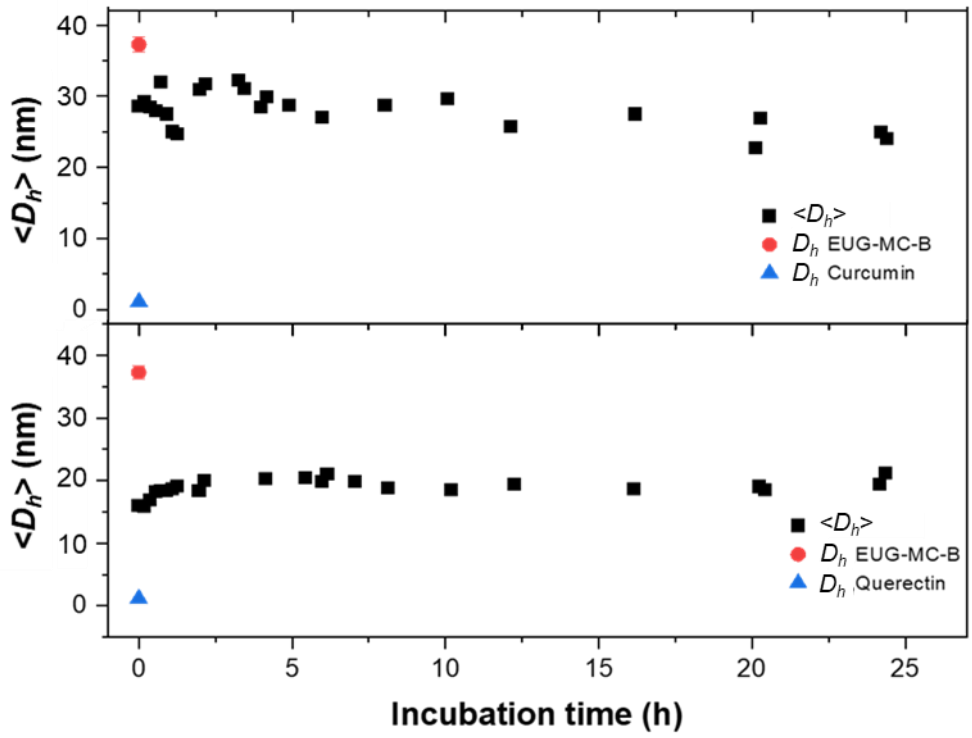
Incubation time (h)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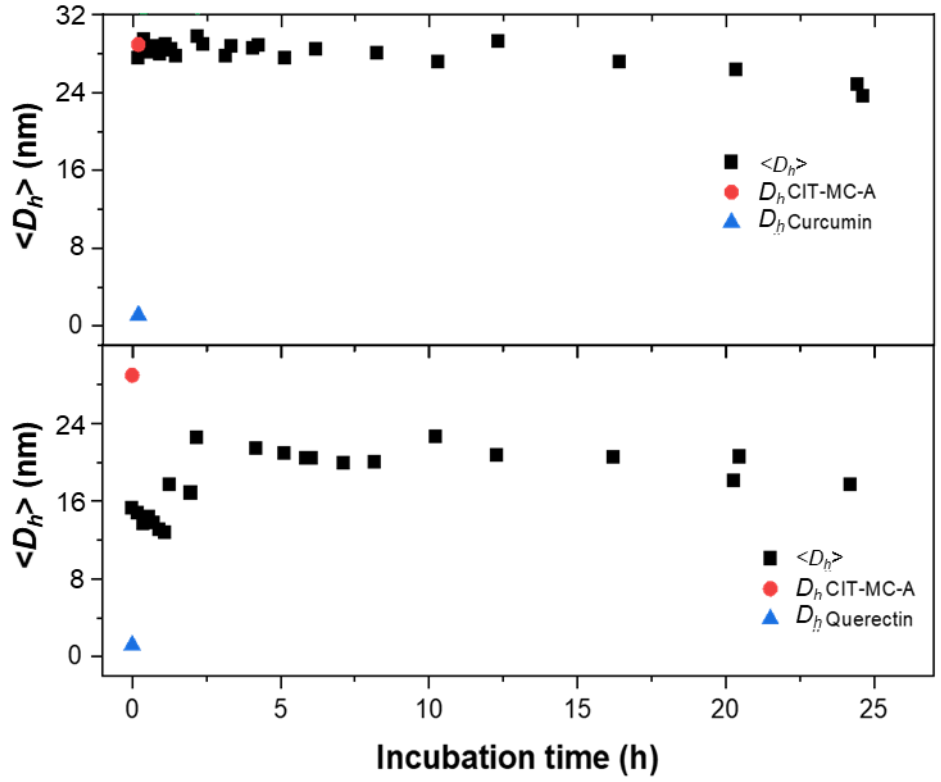
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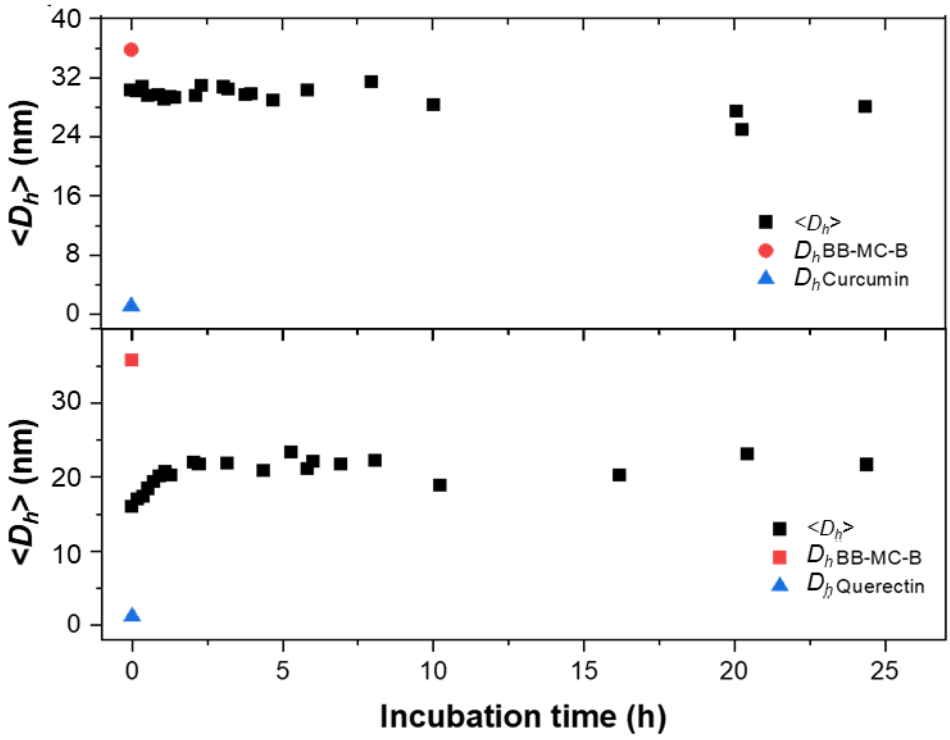

Figure S-4: Average hydrodynamic diameter obtained by TDA as function of incubation time, for quercetin and curcumin loaded SEDDS with varying cosolvent (black squares), W: water; BA: Benzyl alcohol; PXE: 2-Phenoxy ethanol; PE: 2-Phenylethanol; ANS: Anisol; EUG: Eugenol; CIT: Citronellol; BB: Benzyl benzoate. The size of the droplet determined using lumogen red is shown as a red circle while the size of the free drug in the release media is shown as a blue triangle.

Figure S-5:

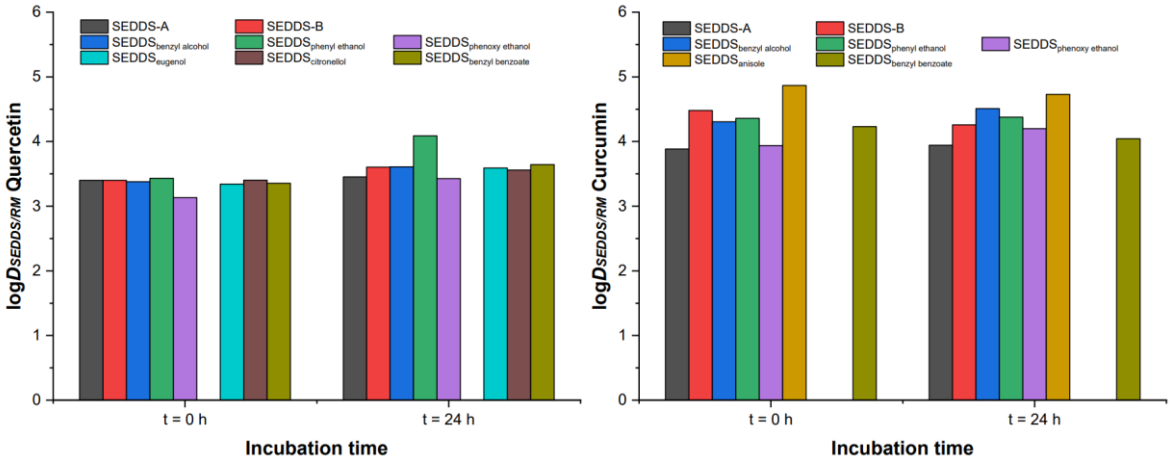

Figure S-5: Calculated $logD_{SEDDS/RM}$ from TDA data for quercetin and curcumin at 0 (the first TDA run immediately after dispersion) and 24h of incubation.)

Figure S-6:

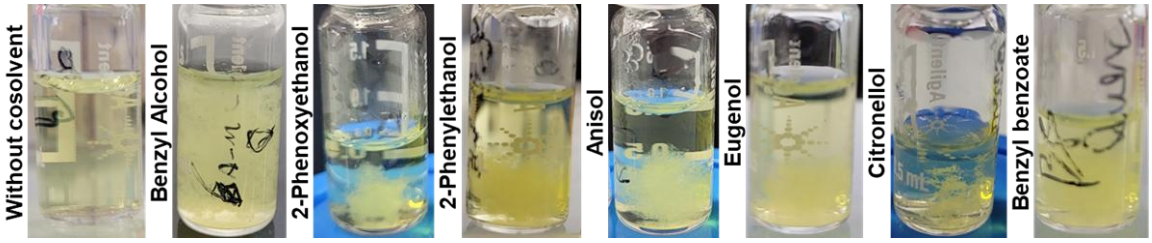

Figure S-6: Pictures of the different 1:100 diluted quercetin saturated SEDDS after 24 h of incubation.

Notice the precipitation in all formulations except the one without a (co)solvent.

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