

## Comparison of bulk and microfluidic methods to monitor the phase behaviour of nanoparticles during digestion of lipid-based drug formulations using *in situ* X-ray scattering

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### Supplementary data

**Supplementary table 1.** Composition of formulations to construct the phase diagram of the 'digested' PHYT20TB emulsion. The formulation code contains the % w/w of TB and the % w/w of the digestion products (DP) in the formulation, where DP consists of BA and GLY.

Formulation	Buffer (g)	PHYT (g)	TB (g)	3BA+GLY (g)
20TB-0DP	2.700	0.240	0.012	0.057
18TB-2DG	2.700	0.240	0.011	0.058
16TB-4DP	2.700	0.240	0.010	0.059
14TB-6DP	2.700	0.240	0.008	0.061
12TB-8DP	2.700	0.240	0.007	0.062
10TB-10DP	2.700	0.240	0.006	0.064
0TB-20DP	2.700	0.240	0.000	0.071

**Supplementary table 2.** Composition of formulations to construct the phase diagram of the 'digested' PHYT20TB emulsion. The formulation code contains the % w/w of TB and the % w/w of the digestion products (DP) in the formulation, where DP consists of CA and MC.

Formulation	Buffer (g)	PHYT (g)	TC (g)	2CA+MC (g)
15TC-0DP	2.700	0.255	0.045	0.000
12TC-3DP	2.700	0.255	0.036	0.009
9TC-6DP	2.700	0.255	0.027	0.018
6TC-9DP	2.700	0.255	0.018	0.027
3TC-12DP	2.700	0.255	0.009	0.036
0TC-15DP	2.700	0.255	0.000	0.045

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To determine the position of complete diffusion along the microchannel, the time of complete mixing,  $t$ , was first calculated using equation (1). This equation takes into account the lateral distance the solute,  $x$ , in this case is lipase, must travel across, and its diffusion coefficient,  $D$ . For these calculations, the distance that the enzyme needed to diffuse across was 100  $\mu\text{m}$ , being half the width of the X-ray beam which was centred on the lipid-enzyme interface. The diffusion coefficient was also adjusted for Taylor-Aris diffusion using equation (3).

The complete mixing time was then converted to a position using equation (2). An example of these equations used for the total flow rate of 1200  $\mu\text{L/hr}$  can be found in Supplementary table 3. The distances of complete diffusion with adjusted diffusion coefficients for the pancreatic lipase is shown in Supplementary table 4 and Supplementary table 5.

$$t = x^2/2D \quad (1)$$

$$\text{Distance} = \text{Average velocity} \times t \quad (2)$$

$$\frac{K}{D} = 1 + \frac{1}{210} \left( \frac{Ud}{D} \right)^2 \quad (3)$$

**Supplementary table 3.** The variables used to calculate the position of complete diffusion of lipase from one stream to another during a digestion in the microfluidic device.

<b>Width of channel</b>	1.1	mm
<b>Enhanced diffusion coefficient of pancreatic lipase (for TFR 1200 <math>\mu\text{L/min}</math>)</b>	$7.09 \times 10^{-6}$	$\text{cm}^2/\text{sec}$
<b>x (travel distance, cm)</b>	0.01	cm
<b>Total flow rate</b>	1200.0	$\mu\text{L/hr}$
<b>Cross sectional area</b>	0.95	$\text{mm}^2$
<b>Flow rate (enzyme solution)</b>	10	$\mu\text{L/min}$
<b>Flow rate (lipid formulation)</b>	10	$\mu\text{L/min}$
<b>Flow Rate Ratio (enzyme:lipid)</b>	1	
<b>Width of recipient stream</b>	0.1	mm
<b>Time of complete mixing</b>	7.05	sec
<b>Distance of complete mixing</b>	2.47	mm

**Supplementary table 4.** Enhanced diffusion coefficients and the distance of complete mixing for each flow rate ratio for experiments conducted in the OTS-MF device.

<b>TFR (<math>\mu\text{L/hr}</math>)</b>	<b>120</b>	<b>300</b>	<b>600</b>	<b>1200</b>
<b>K</b>	0.1	1	3	11
<b>Enhanced D (<math>\text{cm}^2/\text{s}</math>)</b>	$7.10\text{E-}08$	$4.43\text{E-}07$	$1.77\text{E-}06$	$7.09\text{E-}06$
<b>Time of complete mixing (sec)</b>	704.40	112.76	28.19	7.05
<b>Distance of complete mixing (mm)</b>	24.71	9.89	4.94	2.47
<b>Distance of complete mixing (% of full channel length)</b>	24.71	9.89	4.94	2.47
<b>TFR (<math>\mu\text{L/hr}</math>)</b>	<b>2400</b>	<b>3600</b>	<b>6000</b>	<b>12000</b>
<b>K</b>	42	95	265	1059
<b>Enhanced D (<math>\text{cm}^2/\text{s}</math>)</b>	$2.84\text{E-}05$	$6.38\text{E-}05$	$1.77\text{E-}04$	$7.09\text{E-}04$
<b>Time of complete mixing (sec)</b>	1.76	0.78	0.28	0.07
<b>Distance of complete mixing (mm)</b>	1.24	0.82	0.49	0.25
<b>Distance of complete mixing (% of full channel length)</b>	1.24	0.82	0.49	0.25

**Supplementary table 5.** Enhanced diffusion coefficients and the distance of complete mixing for each flow rate ratio for experiments conducted in the S-MF device.

<b>TFR (<math>\mu\text{L/hr}</math>)</b>	<b>10</b>	<b>40</b>
<b>K</b>	1.55E-01	1.22E+00
<b>Enhanced D (<math>\text{cm}^2/\text{s}</math>)</b>	1.04E-07	1.67E-06
<b>Time of complete mixing (sec)</b>	119.98	7.50
<b>Distance of complete mixing (mm)</b>	28.05	7.02
<b>Distance of complete mixing (% of channel length)</b>	8.02	2.00