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Publication date	2025-02-01
Original Citation	Lange, J. J., Enzner, L., Kuentz, M., O'Dwyer, P. J., Saal, W., Griffin, B. T. and Wyttenbach, N. (2025) 'Exploration of solubilisation effects facilitated by the combination of Soluplus® with ionic surfactants', European Journal of Pharmaceutical Sciences, 205, 106957 (11pp). https://doi.org/10.1016/j.ejps.2024.106957
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1016/j.ejps.2024.106957
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Download date	2026-11-17 03:54:21
Item downloaded from	https://hdl.handle.net/10468/17020

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European Journal of Pharmaceutical Sciences 205 (2025) 106957

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Exploration of solubilisation effects facilitated by the combination of Soluplus® with ionic surfactants

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ARTICLE INFO

Keywords:
Soluplus®
Colloids
Surfactants
Preclinical formulations
Solubilisation
Micelles

ABSTRACT

Preclinical testing of new drug candidates frequently necessitates high-dose solution formulations to support robust testing in rodent models. This study aimed to expand the range of high solubilisation capacity formulations by exploring the solubilisation effects of the polymeric surfactant Soluplus® in combination with ionic surfactants. The interactions between Soluplus® and three ionic surfactants, sodium dodecyl sulphate, dioctyl sodium succinate, and sodium oleate, with a primary focus on solubility enhancement were investigated over a range of ionic surfactant concentrations. The solubilisation profiles for seven model drugs were obtained, and the vehicles were characterised by their visual characteristics, dynamic light scattering, and viscosity measurements. The solubilisation profiles were non-linear, indicating the formation of different colloidal species with individual solubilisation strengths depending on surfactant type and concentration, demonstrating substantial solubility enhancement. For certain drugs more than additive solubilisation, facilitated by synergistic interactions between Soluplus® and the ionic surfactants, was obtained. Overall, the solubility increase provided by the excipient combinations resulted in non-linear and drug specific solubilisation profiles. The non-linearities observed were reflected in visual observations of the vehicles appearance, DLS and viscosity measurements, which collectively indicated a change in polymer aggregation with increasing concentration of anionic surfactant. This investigation highlights that already low quantities of ionic surfactants introduced to Soluplus® may substantially enhance solubility, which offers a promising approach for further exploration in preclinical drug development where more conventional solubilising formulation strategies may fall short.

1. Introduction

Preclinical formulation scientists frequently face substantial challenges presented by drugs with poor aqueous solubility, which complicates achieving required exposure for effective testing of emerging drug candidates. Particularly in preclinical rodent studies, the volumes of administration are small, which necessitates high dose loaded enabling formulations to ensure sufficient in vivo exposure (Shah et al., 2014). Given sufficient solubilisation capacity, solution formulations are usually preferred over solid dosage forms or suspensions, as they are less susceptible to issues associated with dosing, dissolution, physical instability and non-uniformity (Neervannan, 2006). Formulating an aqueous solution of the drug candidate using surfactants is a well established method to improve the solubility of poorly water soluble drugs (Kuentz et al., 2007). However, the demand for novel solubility enhancing formulations during preclinical testing is continuously increasing to cope with the rise of poorly-water soluble drugs in drug discovery programs (O'Driscoll and Griffin, 2008; Holm et al., 2023).

Surfactants are amphiphilic molecules that, above their critical micelle concentration (CMC), assemble to colloidal species called micelles. This allows the micellar solubilisation of drugs to increase their apparent solubility (Maher et al., 2023). They represent a heterogeneous class of molecules which can be classified based on various aspects, including their state of ionisation, water-dispersibility, -solubility and by their hydrophilic–lipophilic balance (HLB) (Rangel-Yagui et al., 2005). Based on these attributes, they exert different properties of relevance to formulation scientist (Koehl et al., 2020; Saal et al., 2018).

One particularly noteworthy surfactant is the polymeric excipient Soluplus® (BASF), which has drawn significant interest for its

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https://doi.org/10.1016/j.ejps.2024.106957
Received 27 May 2024; Received in revised form 21 October 2024; Accepted 5 November 2024
Available online 17 November 2024
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potential use in the hot melt extrusion (HME) process of preparing amorphous solid dispersions (ASDs) (Hardung et al., 2010; Linn et al., 2012). Soluplus® is a graft copolymer composed of polyvinylcaprolactam and polyvinylacetate grafted to polyethylene glycol 6000, which confers bifunctional characteristics that make it amenable as both a hydrophilic matrix carrier for ASDs and a potent solubilizer due to its ability to form colloidal polymeric structures (Pignatello et al., 2022). Given its amphiphilic properties and notable solubilisation capacity for poorly water-soluble drugs, Soluplus® has been shown to be a viable preclinical solubiliser for drugs exhibiting high preclinical dose numbers (Tanida et al., 2016; Alopaeus et al., 2019).

It has been previously reported that the addition of other excipients to non-ionic polymers may alter their solution properties by influencing their supramolecular assembly (Shi et al., 2016; Liu et al., 2016). These changes in aggregation behaviour can affect clouding, viscosity, and most importantly, solubilisation of the system by adsorption and redistribution of the ionic surfactant between polymer and bulk phase (Hansson and Lindman, 1996; Holmberg et al., 1997). Thus far, research has primarily concentrated on poloxamers and non-ionic cellulose derivatives (Clulow et al., 2020; Qi et al., 2012). Interactions for the latter have been described through the 'pearl-necklace' model. This model illustrates the cooperative, non-covalent interactions between the hydrophobic elements of a polymer and the surfactant's tailgroup, resulting in the formation of clusters of surfactant molecules around the hydrophobic parts of polymer coils (Qi et al., 2012; Persson et al., 1996; Nilsson, 1995). Notably, these interactions have recently demonstrated their relevance in poly(vinylpyrrolidone-vinyl acetate) 64 (PVP-VA 64) systems as well, as reported by Liu et al. (2016).

The effect of combining a polymeric surfactant with an additive on solubility has been categorised as either additive, synergistic, or non-synergistic (Clulow et al., 2020; Feng et al., 2018; Nishikido, 2020). Additive behaviour is observed when the drug's solubility in the excipient combination matches the solubilisation provided by the micelles formed by the excipients independently (Clulow et al., 2020). If the behaviour is synergistic, the solubilisation is greater than the sum of the individually determined solubility values, which indicates that the interactions between the polymer and the additive result in the formation of assemblies with a higher affinity for the drug. If colloids of lower affinity assemble, a decrease in solubility over the separately measured solubility values would be expected (Clulow et al., 2020).

Another method for analysing a drug's affinity for solubilisation is to consider the slope derived from plotting the solubilised drug concentration against the concentration range of the introduced co-excipient. If the mode of association as a function of added excipient is concentration independent, a constant slope would be expected across the concentration gradient. Any apparent non-linearity would indicate that the mode of association between the excipients is subject to change as a function of co-excipient introduced (Clulow et al., 2020).

Attempts to incorporate ionic surfactants into polymers may reveal challenges in adapting to solution formulations due to the restricted solubilisation ability of prevalent non-ionic polymers. Moreover, studies thus far typically concentrated on diluted systems (Liu et al., 2016; Qi et al., 2012). The influence of mixed non-ionic surfactant systems and sodium dodecyl sulphate (SDS)-non-ionic surfactant systems was investigated by Feng et al. (2018), and it was concluded for a set of eight compounds that mixed non-ionic surfactants in aqueous solutions follow additive behaviour, whereas the combination of non-ionic surfactants with SDS negatively influenced solubility, albeit forming mixed micellar systems. Notably, the non-ionic surfactants investigated encompassed different chemical characteristics, spanning from ethoxylated fatty acids, to ethoxylated polysorbates and higher molecular weight polymers such as Lutrol® F 127.

In this context, Soluplus® remains relatively unexplored and given it confers both, micellar and polymeric characteristics, it may exhibit advantages over other conventional polymeric excipients. Thus far, most studies primarily focused on its use as a hydrophilic matrix carrier for ASDs. Special attention has been given to the effects of incorporating ionic surfactants on solid-state physical stability, and supersaturation–precipitation kinetics (Baghel et al., 2018; Xia et al., 2016). Recent studies focusing on liquid state by Xia et al. (2016) highlighted the effect of adding SDS to Soluplus® in the context of supersaturation maintenance of cyclosporin A, where a higher degree of apparent supersaturation was maintained by the introduction of SDS due to the formation of Soluplus®-SDS complexes. Simultaneously, the complexities arising from this combination were noted by Thiry et al. (2016) during dissolution testing of Soluplus® - itraconazole extrudates. It was found that SDS increased the hydrophobicity of Soluplus®, which prevented the material from eroding and releasing from the ASD matrix.

SDS, dioctyl sodium sulfosuccinate (DOSS) and sodium oleate (NaOleate) represent frequently utilised excipients in oral formulation development. In addition, NaOleate is considered a highly biocompatible dietary substrate (Maher et al., 2023). This study aimed to investigate a systematically narrowed range of ionic surfactant concentrations added to Soluplus® to enhance the solubilisation of poorly water-soluble drugs. Additionally, the aim was to explore the formation of various colloidal assemblies as a function of the incorporated ionic surfactant.

2. Materials & methods

2.1. Materials

Soluplus® was provided by BASF (Ludwigshafen, Germany). SDS and DOSS were sourced by Sigma-Aldrich (VT, USA) with a purity of ≥ 99.9%, respectively. NaOleate exhibited a purity of > 97.0% and was purchased from Tokyo Chemical Industry Co. LTD. (Tokyo, Japan). Acetonitrile was obtained from Sigma-Aldrich (LiChrosolv; Supelco; gradient grade for liquid chromatography, VT, USA). To investigate solubilisation by Soluplus®-ionic surfactant systems, seven model drugs exhibiting poor aqueous solubility were investigated. Apart from RO1, all drugs were commercially obtained as specified in Table 1. A representative chemical diversity was targeted with the selected drugs regarding their physicochemical properties, focusing on lipophilicity expressed as calculated logP, melting point, and molecular weight.

2.2. Methods

2.2.1. Solubility determination using a miniaturized assay for Solubility and Residual Solid Screening (SORESOS)

To probe the additive effect of combining ionic surfactants with Soluplus®, the solubility of seven model drugs was determined in composite systems and in their sole constituents. Soluplus® was consistently maintained at a concentration of 10% [w/v], either as the sole surfactant or in conjunction with the ionic surfactants SDS, DOSS, or NaOleate. Vehicles were prepared by dispensing the ionic surfactants in volumetric flasks and dissolving them in water MilliQ or vehicles containing 10% [w/v] Soluplus® in water MilliQ. The solubility of the model drugs in the composite system containing SDS and DOSS was investigated in vehicles possessing concentrations of up to 2.5% [w/v]. Soluplus® solutions including NaOleate contained a maximum of 10% [w/v] NaOleate. These concentrations were rationalised by changes in visual appearance of these solutions during preliminary studies. Sole surfactant systems containing DOSS were investigated up to a concentration of 1% [w/v], as limited by DOSS's solubility in water. Drug solubilisation by NaOleate only was examined up to a concentration of 4% [w/v] NaOleate, also constrained by its aqueous solubility.

Solubility measurements were conducted at room temperature according to a previously published solubility assay (Wyttenbach et al., 2007). Parylene coated stirring bars (VP 711D, 1.98 μm diameter, 4.80 μm length, VP&P Scientific Inc., CA, USA) and drug substance were

Table 1
Physicochemical properties of the investigated APIs.

INN	M_w [g mol^{-1}]	Aqueous solubility [µg/mL]	clogP[a]	T_m [°C]	pKa[b]	Supplier	Purity [%]
Bicalutamide	430.37	1.98 (± 0.06)	2.88	193.99	9.45	Combi-Blocks	98
Cilostazol	369.46	2.61 (± 0.05)	3.46	159.41	–	TCI	> 98
Felodipine	384.25	1.19[d]	3.96	144.34	2.73	Melrob-Eurolabs	> 99
Fenofibrate	360.83	0.06 (± 0.01)	4.68	81.18	–	Sigma Aldrich	≥ 99
RO1	543.46	2.40 (± 0.18)	3.94	139.94	–	F. Hoffmann-La Roche	> 98
Sorafenib	464.82	9.86×10^{-3} ($\pm$ 1.39×10^{-3})[c]	5.55	208.54	11.37, 11.99, 3.03	Combi-Blocks	98
Tadalafil	389.40	1.87 (± 0.04)	2.21	302.51	–	Combi-Blocks	98

[a] Calculated crippen logP via RDKit (Landrum, 2016).
[b] predicted pKa by MoKa (Molecular Discovery).
[c] e Sousa et al. (2014).
[d] Fagerberg et al. (2014).

dispensed into a 96-well plate (Microplate 96/F-PP; white border; Eppendorf AG, Hamburg, Germany) through a manual powder dispenser for 96-well plates. By volumetrically dispensing, each well contained approximately 10–15 mg of drug substance subject to the density of the powder. Pipetting 200 µL of vehicle into each well was followed by head-over-head rotation (Heidolph Reax 2, Heidolph Instruments GmbH & Co. KG, Germany) for at least 24 h under ambient conditions. Each well was sealed with a pre-split seal (SepraSeal™; Thermo Fisher Scientific Inc, MA, USA). After equilibration, the suspension was transferred to a 96-well filter plate (MultiScreen®, MSSLBPC10; polycarbonate, 0.40 µm, Merck Millipore, Bedford, MA, USA). By centrifugation into a 96-well plate (twin.tec PCR plate 96; skirted; Eppendorf AG, Hamburg, Germany), the liquid was separated from the solid. Filtrates were diluted appropriately with acetonitrile:water mixture (50:50) by using Gilson positive displacement pipettes (Mettmenstetten, Switzerland) to enable quantification via Ultra Performance Liquid Chromatography (UPLC). Samples were separated on an Acquity UPLC BEH C18 column (2.1 *x* 50 mm, 1.7 µm particle size) by Waters™ at 30 °C (Milford, CT, USA). The parameters and detection wavelengths were adapted to the given drug in accordance with previous SORESOS work (Wyttenbach et al., 2007). Drug detection was enabled by a 2996 photodiode array detector. The mobile phase A consisted of MilliQ purified water/formic acid (0.1% [v/v]) and mobile phase B of acetonitrile/formic acid (0.1% [v/v]). The residual solid remained in the filter plate and was analysed by X-ray powder diffraction (XRPD) to detect potential residual solid form changes manifested during equilibration. A STOE STADI P Combi diffractometer, fitted with a primary Ge monochromator (Cu Kα radiation, 1.5406 Å) was used. Obtained X-ray patterns were compared against the pattern of the as received drug substance. The final pH after equilibration was monitored.

2.2.2. Solid state analysis

Differential Scanning Calorimetry (DSC) was used to determine the melting point of each drug. The onset of the melting endotherm was recorded with a DSC 1 instrument (Mettler-Toledo AG, Greifensee, Switzerland). The inclusion of solvates or hydrates among the model drugs was excluded based on the absence of characteristic weight losses during thermo-gravimetric analysis (TGA/DSC 1 STARe system, Mettler-Toledo AG, Greifensee, Switzerland). The experimental protocols were executed as outlined previously (Wyttenbach et al., 2015).

2.2.3. Colloidal size determination

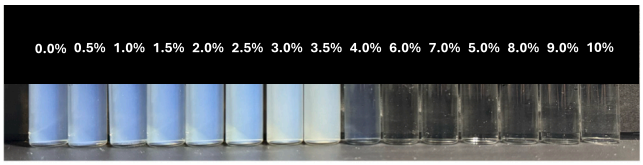
The colloidal size of the aggregates of each vehicle was analysed by dynamic light scattering (DLS) using a ZetaSizer Ultra (Malvern Pananalytical Limited, Malvern, UK). Each vehicle was filtered through an Ultrafree® - MC-HV Centrifugal filter device containing a Durapore® PVDF – 0.45 µm filter membrane (MilliPore Sigma, Bedford, MA, USA) prior to analysing the sample. DLS measurements were performed in triplicate using disposable polystyrene cuvettes and undiluted vehicle. Each sample was equilibrated for 180 s before quantifying the sample. To account for the impact of viscosity on calculating the hydrodynamic diameter and the polydispersity index (PDI) via the autocorrelation function and the Stokes–Einstein equation, the viscosity of each sample was measured and set for dispersant viscosity in the instrument. The refractive index (RI) of the dispersant was set to 1.33 and for the material to 1.45. The size of the aggregates was determined for the non-drug loaded samples.

2.2.4. Viscosity determination

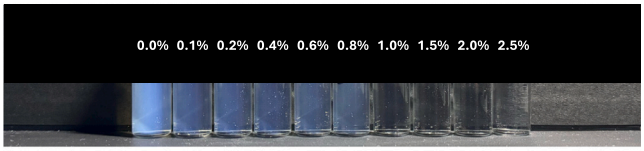
The viscosity of each sample was determined using a viscosimeter/rheometer-on-a-chip (m-VROC) (RheoSense INC., CA, USA) making use of microfluidics and micro-electro-mechanical systems (MEMS). In brief, the dynamic viscosity of the sample is measured by detecting the pressure drop, which is proportionate to shear stress, as a function of the applied shear rate across four sensors embedded in a rectangular slit. The shear rate is controlled by applying shear stress via a positive displacement pump incorporated into a 250 µL sample syringe. Prior to each measurement, the syringe and the unit cell, which was fitted with Chip A for low viscous sample, was cleaned with ethanol to remove the vehicle residues from the device before starting the next measurement. Solvent was infused repeatedly, until the measured viscosity corresponded to the solution's viscosity. Vehicle viscosity was determined by filling the syringe and dislodging air bubbles before initiating the measurement. After mounting the sample syringe onto the instrument, the vehicle was dispensed until no further viscosity fluctuations were observed. Depending on the sample viscosity, appropriate shear rates were applied automatically. The data is reported as apparent viscosity in mPa s. During the experiment, the temperature was controlled at 22 °C. The viscosity was measured of the vehicles without any drug incorporated.

2.2.5. Data analysis and visualisation

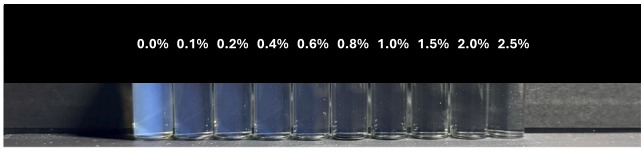
As both vehicle constituents represent surfactants with the ability to solubilise drugs above their CMC, the solubility in the composite system over the sum of the solubility values in both constituents was evaluated to distinguish the cooperative solubilising gain from the solubilisation by the sole counterparts. This was termed the solubility additive factor (SAF) (Eq. (1)), and the corresponding standard error was calculated using error propagation principles. Where C_x denotes the concentration of the drug in the composite vehicle, C_y in 10% [w/v] Soluplus®, and C_z the solubility of the drug in neat ionic surfactant solutions.



(a) Effect of increasing NaOleate concentration in 10% [w/v] Soluplus® solution. Up to 10% [w/v] NaOleate was added. The addition of NaOleate to Soluplus® led to increased opalescence, followed by a transition to clear solutions.



(b) Increasing concentration of SDS added to 10% [w/v] Soluplus®. A maximum of 2.5% [w/v] SDS was incorporated.



(c) Increasing concentration of DOSS added to 10% [w/v] Soluplus®. A maximum of 2.5% [w/v] DOSS was incorporated.

Fig. 1. Visual appearance of 10% [w/v] Soluplus® upon incorporating ionic surfactants at room temperature.

The amount of ionic surfactant concentration utilised is denoted by subscripted (i).

$$SAF = \frac{C_{x_{(i)}}}{C_y + C_{z_{(i)}}} \quad (1)$$

While this metric is a useful way of quantifying synergistic aspects of solubilisation it should be noted that it does not express the systems' overall solubilisation capacity.

To determine inflection points of viscosity and dynamic light scattering results, the data was interpolated with 'scipy' and 'numpy' modules in Python (Virtanen et al., 2020; Harris et al., 2020) First, the data was interpolated based on an appropriate datapoint range. Subsequently, the first and second derivative were calculated based on a function that calculates a gradient. Prior to the calculation of the inflection points based on the derivatives, the curve resulting from the obtained function was smoothed by a Gaussian filter.

3. Results

3.1. Visual characteristics of 10% [w/v] Soluplus® as a function of ionic surfactant added

Fig. 1 presents the visual characteristics of 10% [w/v] Soluplus® in the presence and absence of incorporated ionic surfactants at room temperature.

The incorporation of NaOleate considerably influenced the visual characteristics of a 10% [w/v] Soluplus® solution (Fig. 1(a)). Initially, the opalescence of the solution increased, which was most notable for concentrations of 2.5–3.5% [w/v] NaOleate incorporated. Further increases in NaOleate led to a loss of opalescence. The samples containing SDS and 10% [w/v] Soluplus® demonstrated a steady decline in opalescence. The solutions became transparent once more than 0.8% [w/v] SDS was incorporated and remained clear upon incorporating higher concentrations of up to 2.5% [w/v] (Fig. 1(b)). Similarly, the incorporation of DOSS resulted in a steady decline in opalescence (Fig. 1(c)). The solutions containing DOSS turned clear above concentrations of 0.6% [w/v].

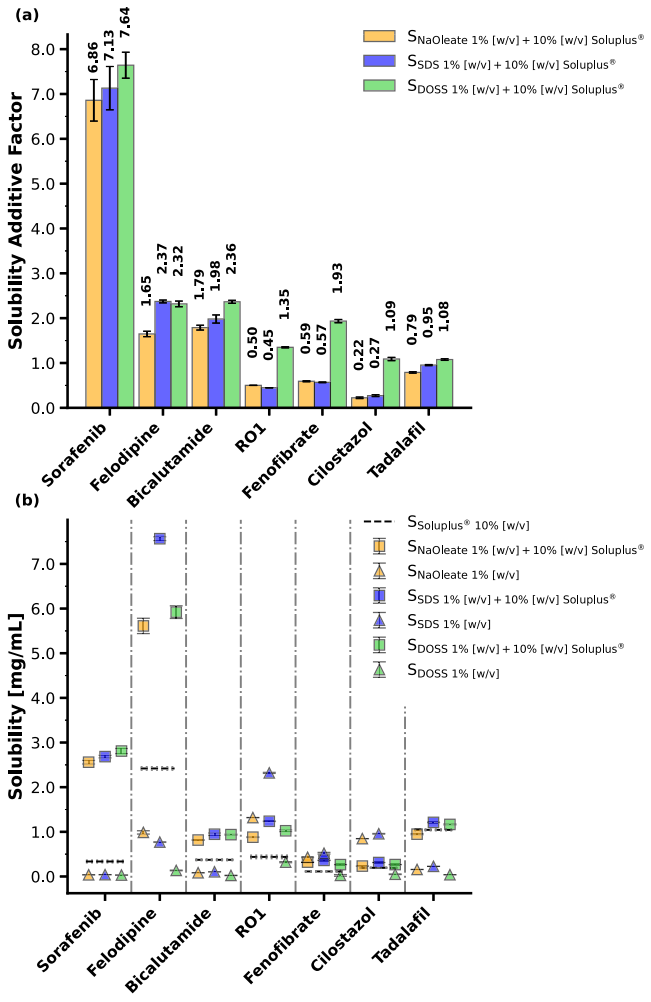


Fig. 2. Quantitative evaluation of solubility results obtained by combining 1% [w/v] ionic surfactant with 10% [w/v] Soluplus®. Figure (a) depicts calculated SAF factors at 1% [w/v] (n=3 ± SE) ionic surfactant incorporated. This concentration was chosen to enable comparison across different systems. Figure (b) displays the measured solubility values of each API in the composite system and in its counterparts (n=3 ± SD). The solubility in 10% Soluplus® is displayed as a line and the standard deviation is reported as dotted upper and lower boundaries.

3.2. Impact of increasing concentration of ionic surfactant in 10% [w/v] Soluplus® aqueous solutions: Effect on drug solubilisation

An overview on how the addition of 1% [w/v] ionic surfactant to 10% [w/v] Soluplus® impacted solubilisation is provided in Fig. 2. For six out of seven drugs, the inclusion of ionic surfactant increased the solubilisation capacity, with tadalafil-NaOleate-Soluplus® combinations being the only exception to this trend. Figs. 3–5 present drug concentration as a function of incorporated ionic surfactant concentration. It was demonstrated that the increase was non-linear and drug specific over a broad range of incorporated ionic surfactant concentrations.

3.2.1. Quantitative assessment of synergistic solubilisation

The introduction of SDS, DOSS, and NaOleate to 10% [w/v] Soluplus® solutions resulted in more than additive solubilisation behaviour at any concentration investigated for the model drugs sorafenib, felodipine and bicalutamide. This is expressed by SAF values > 1, corresponding to a higher net solubility in the composite system over the sum of the solubility values measured in the system's constituents. A 10% [w/v] Soluplus® solution alone already resulted in substantial solubility enhancement, reflected by 34078-, 2025- and 188-fold

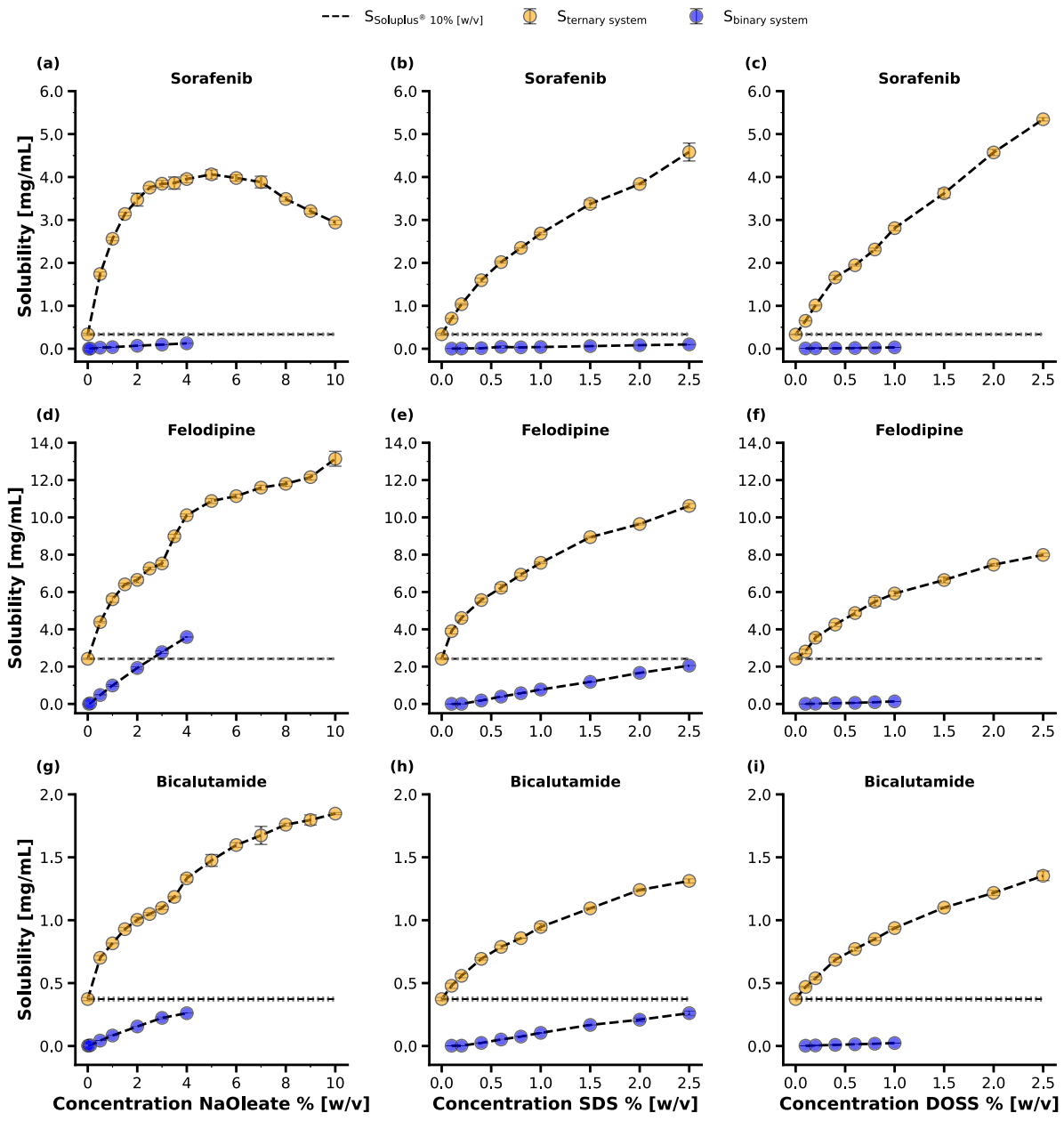


Fig. 3. Solubilisation profiles for sorafenib (a, b, c), felodipine (d, e, f), and bicalutamide (g, h, i) in 10% [w/v] Soluplus® as a function of ionic surfactant incorporated (n=3; mean ± SD). The orange markers represent the solubility in the ternary formulation. The blue markers visualise the solubility of the drug in aqueous solution containing ionic surfactant only (binary system). Solubility experiments in solutions containing only ionic surfactant were carried out in a concentration range up to the solubility limit of each ionic surfactant. The grey dashed line corresponds to the solubility of each drug in 10% [w/v] Soluplus®. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

increase for sorafenib, felodipine, and bicalutamide, respectively over their aqueous solubility (Table 1).

To quantitatively assess synergistic effects, SAF values were calculated for a subset of the data at an ionic surfactant concentration of 1% [w/v]. Fig. 2 illustrates the SAF values and the corresponding drug concentration measured. For comparative reasons, an ionic surfactant concentration of 1% [w/v] was chosen due to the constrained solubility of DOSS in aqueous solutions, which limits the highest feasible concentration for SAF value calculation in these systems. For the model drug sorafenib, SAF values of 7.64 (± 0.25) were achieved upon incorporating DOSS as an ionic surfactant, which is also reflected by the highest solubility of 2.81 mg mL^{-1} (± 0.06 mg mL^{-1}). For the model drug felodipine, concentrations of 7.56 mg mL^{-1} (± 0.03 mg mL^{-1}) were achieved, reflected by a SAF of 2.37 (± 0.04) for SDS. A similar SAF value was obtained for bicalutamide upon incorporation of DOSS, which reflected a solubility of 0.94 mg mL^{-1}(± 0.01 mg mL^{-1}). For the model drugs RO1, fenofibrate, cilostazol, and tadalafil, synergistic solubilisation was only noted when DOSS was used as the ionic surfactant at a concentration of 1% [w/v]. For SDS and NaOleate, the interaction resulted in non-synergistic solubilisation, reflected by SAF values ≤ 1 (Fig. 2(a)).

For six out of seven drugs the solubilisation was still enhanced over Soluplus® with tadalafil in NaOleate-Soluplus® being the only exception to this general trend (Fig. 2(b)). The SAF values presented in Fig. 2(a) demonstrate that especially for the surfactants SDS and NaOleate values below one were obtained. Since the SAF value calculation involves the drug concentrations in the binary systems, the high solubilisation facilitated by the ionic surfactants reduced the SAF value. Throughout this study, DOSS displayed the lowest solubilisation

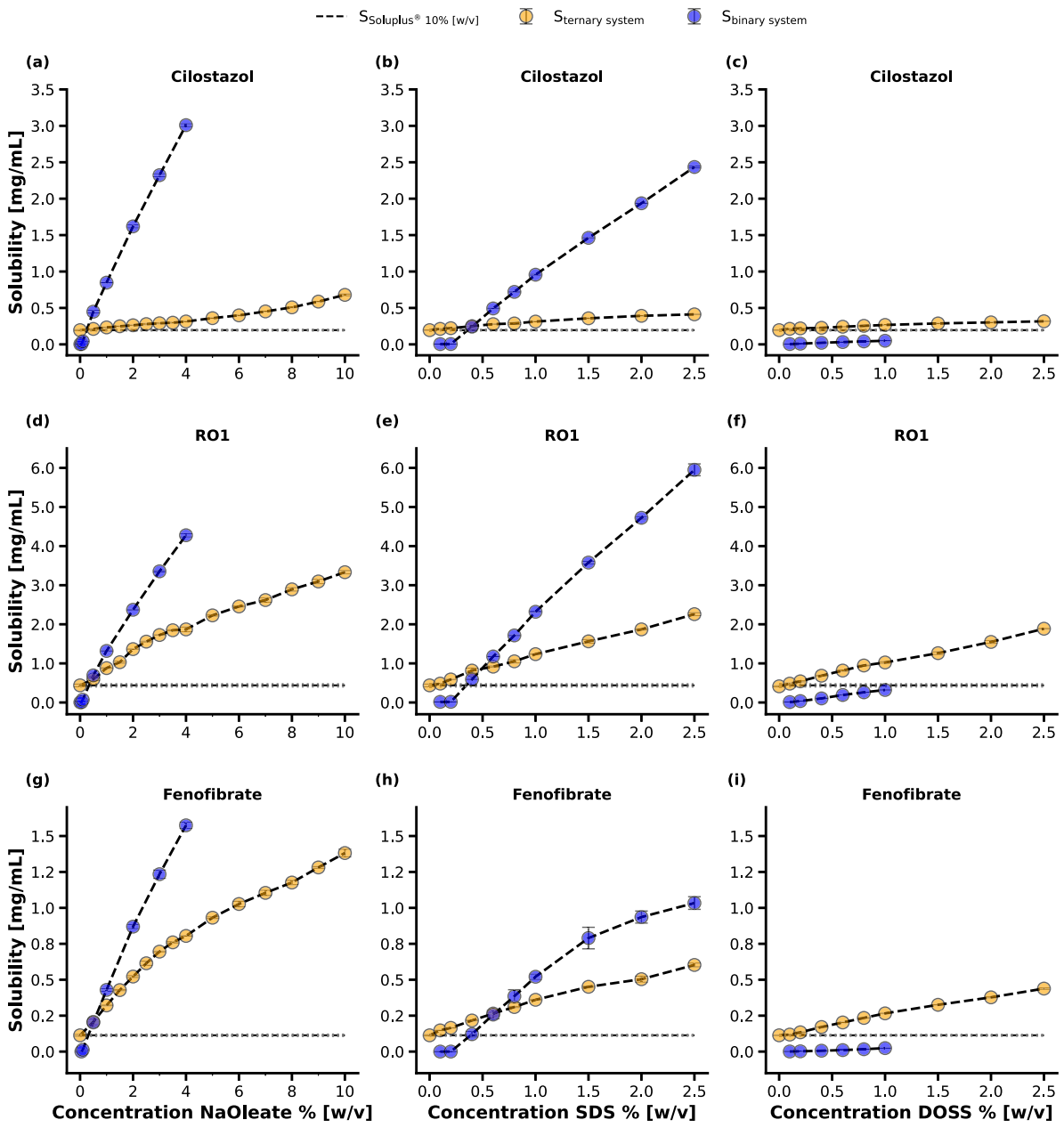


Fig. 4. Solubilisation profiles for cilostazol (a, b, c), RO1 (d, e, f), and fenofibrate (g, h, i) in 10% [w/v] Soluplus® as a function of ionic surfactant incorporated (n=3; mean ± SD). The orange markers represent the solubility in the ternary formulation. The blue markers visualise the solubility of the drug in aqueous solution containing ionic surfactant only (binary system). Solubility experiments in solutions containing only ionic surfactant were carried out in a concentration range up to the solubility limit of each ionic surfactant. The grey dashed line corresponds to the solubility of each drug in 10% [w/v] Soluplus®. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

capacity, which in this case explained the high SAF values obtained irrespective of the DOSS concentration.

Since these SAF values provide only an overview on the synergistic aspects for a small subset of the data, the solubility for each drug in systems containing the maximum concentration of SDS and DOSS (2.5% [w/v]) for all systems and for systems containing NaOleate (10% [w/v]) are illustrated in the supporting information (SI) (Figure S1).

In order to relate the solubility gain by ionic surfactant incorporation to solubilisation provided by Soluplus® alone, such ratios are illustrated in Figure S2 (SI). It is notable that, although being non-synergistic, the solubility over 10% [w/v] Soluplus® was enhanced in all but one case upon use of the NaOleate-Soluplus® vehicle. For fenofibrate and cilostazol, the solubility enhancement was more than twice as high as the solubility enhancement facilitated by 10% [w/v] Soluplus®.

3.2.2. *Qualitative interpretation of solubilisation profiles*

To further explore the interactions between Soluplus® and the ionic surfactants, obtained solubilisation profiles as a function of concentration of incorporated surfactant were evaluated. Fig. 3 illustrates the obtained results for the drugs demonstrating synergistic solubilisation behaviour. Clearly, the solubilisation profiles obtained for the composite systems show non-linear behaviour. A substantial increase in solubility was observed for all three drugs upon the introduction of lower quantities of ionic surfactants. When focusing on ionic surfactant concentrations ≤ 2.5% [w/v], regardless of the type of ionic surfactant, there was a noticeable decrease in the slope of the solubilisation curve as the ionic surfactant concentration increased. The incorporation of concentrations > 2.5% [w/v] NaOleate, which were rationalised based on the differing opalescence–concentration relationship (Fig. 1(a)),

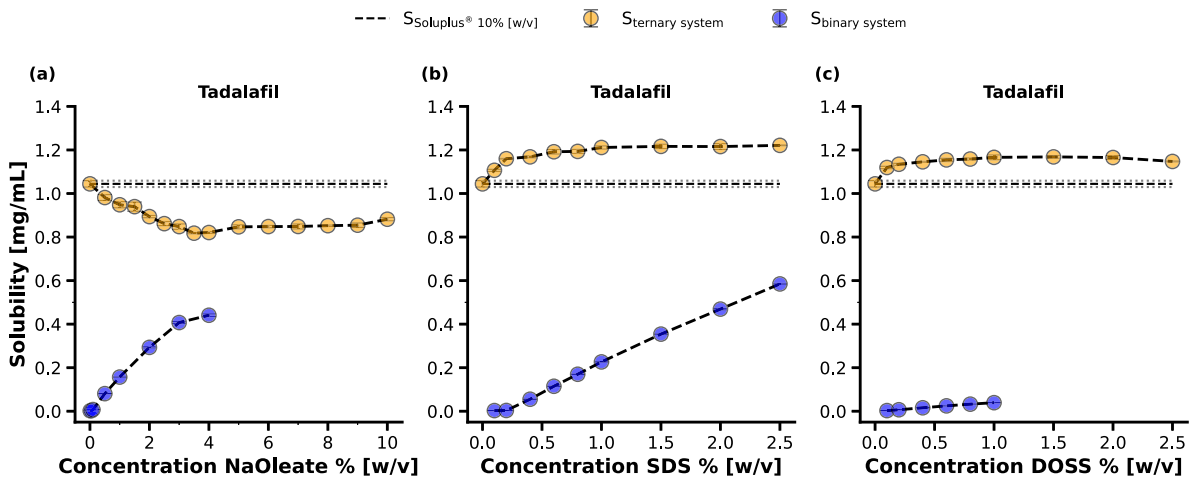


Fig. 5. Solubilisation profiles for tadalafil in 10% [w/v] Soluplus® as a function of ionic surfactant incorporated (n=3; mean ± SD). The orange markers represent the solubility in the ternary formulation. The blue markers visualise the solubility of the drug in aqueous solution containing ionic surfactant only (binary system). Solubility experiments in solutions containing only ionic surfactant were carried out in a concentration range up to the solubility limit of each ionic surfactant. The grey dashed line corresponds to the solubility of each drug in 10% [w/v] Soluplus®. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

presents further slope changes. Specifically, as the concentration increased further, the solubilisation curve for felodipine and bicalutamide exhibits an increase in slope (Figs. 3(d), 3(g)). Overall, for concentrations of ≥ 4% [w/v] NaOleate, the slope of the solubilisation curve remained consistently lower when compared to the initial segments of the curve. Comparable to the model drugs felodipine and bicalutamide, the solubilisation slope for sorafenib declined when concentrations were elevated to 3% [w/v] NaOleate (Fig. 3(a)). However, at concentration ≥ 3% [w/v], drug solubility decreased upon incorporating higher quantities of NaOleate. A plateau in solubilisation was observed at 5% [w/v] NaOleate, which corresponded to $4.06\,mg\,mL^{-1}$ ($\pm\ 0.11\,mg\,mL^{-1}$) sorafenib. At a concentration of 10% [w/v] NaOleate incorporated, the solubility of sorafenib was measured to be $2.94\,mg\,mL^{-1}$ ($\pm\ 0.05\,mg\,mL^{-1}$). For each of the presented model drugs, distinct breakpoints in the solubilisation curve became evident, consistently at concentrations between 3–3.5% [w/v] and 4%–5% [w/v] NaOleate incorporated.

For four of the seven drugs, solubilisation was not synergistic. However, it was noticed that the solubilisation patterns for the systems containing 10% [w/v] Soluplus® and ionic surfactant exhibited similar slope segments if compared to the previously described solubilisation patterns, where synergistic solubilisation was obtained (Fig. 4). For example the solubilisation profile obtained for cilostazol demonstrates a breakpoint at approximately 3.5% [w/v] NaOleate incorporated (Fig. 4(a)). The same applies to the other model drugs, e.g. tadalafil solubilisation approaches zero slope at this concentration ionic surfactant incorporated (Fig. 5(a)). However, in terms of solubilisation gain, atypical behaviour was observed for tadalafil being the only case where a minor decrease in solubilisation was observed upon incorporating ionic surfactant, i.e., NaOleate to 10% [w/v] Soluplus®. Additionally, it was also the only case were drug solubility consistently approached zero slope upon incorporation of higher quantities of any surfactant.

Throughout this study no solid form changes after equilibration were observed via XRPD. While the addition of NaOleate increased the pH of the vehicle, the addition of SDS and DOSS negligibly decreased the pH.

3.3. Particle size analysis of composite systems

NaOleate-Soluplus® systems were further characterised by DLS measurements. To elucidate how the aggregation behaviour of Soluplus® is influenced by adding NaOleate, the aggregate size was measured as a function of NaOleate added (Fig. 6(a)). While 10% [w/v] Soluplus® solutions without the addition of NaOleate formed micelles with a hydrodynamic diameter of 21.4 nm (± 0.09 nm), the particle size rapidly increased when small quantities of NaOleate were added. The low polydispersity indices indicated a uniform size distribution. Increasing the NaOleate concentration further led to a substantial size increase of the colloidal species, which results in a maximum of 140.57 nm (± 2.73 nm) (PDI=0.07) at 3.5% [w/v] NaOleate incorporated. At concentrations above 4% [w/v] NaOleate incorporation, high polydispersity with PDI values consistently around one were obtained.

3.4. Viscosity analysis of composite systems

Viscosity measurements serve as a valuable tool to explain intra- and interpolymer, as well as ionic surfactant and polymer interactions, providing insights on the influence of ionic surfactant on the aggregation behaviour of the polymer. The rheology of the composite system of NaOleate and 10% [w/v] Soluplus® was analysed by viscometry to detect potential changes in the aggregation behaviour of Soluplus®. Fig. 6(b) displays the increase in viscosity observed by adding NaOleate to 10% [w/v] Soluplus®. The viscosity of 10% [w/v] Soluplus® in its unaltered state, without the inclusion of NaOleate, was measured to be 4.92 mPa s (± 0.03 mPa s). Upon incorporation of NaOleate, the viscosity increased considerably, notably, in a non-linear way. A breakpoint in the obtained curve can be observed between 3.5 and 4% [w/v] NaOleate incorporated. After surpassing this concentration, the viscosity increased further with a less steep slope. A maximum in viscosity was observed upon incorporation of 10% [w/v] NaOleate at 29.71 mPa s (± 0.26 mPa s). Inflection points were calculated to interpret changes in curvature as the initiation of a change in polymer aggregation, i.e. to determine the spontaneous assembly of a new colloidal assembly. Calculating the inflection points based on the derivatives resulted in two inflection points after higher quantities of NaOleate were added. Two main inflection points calculated at concentrations of 2.7% [w/v] and 4.5% [w/v] NaOleate added to 10% [w/v] Soluplus® respectively.

4. Discussion

The need for high-dose loadings in preclinical testing, such as toxicological trials, combined with the growing challenge of poor aqueous solubility of drug candidates, underscores the necessity to expand the range of preclinical oral formulations. Exploring combinations of excipients opens an extensive formulation landscape that thus far has

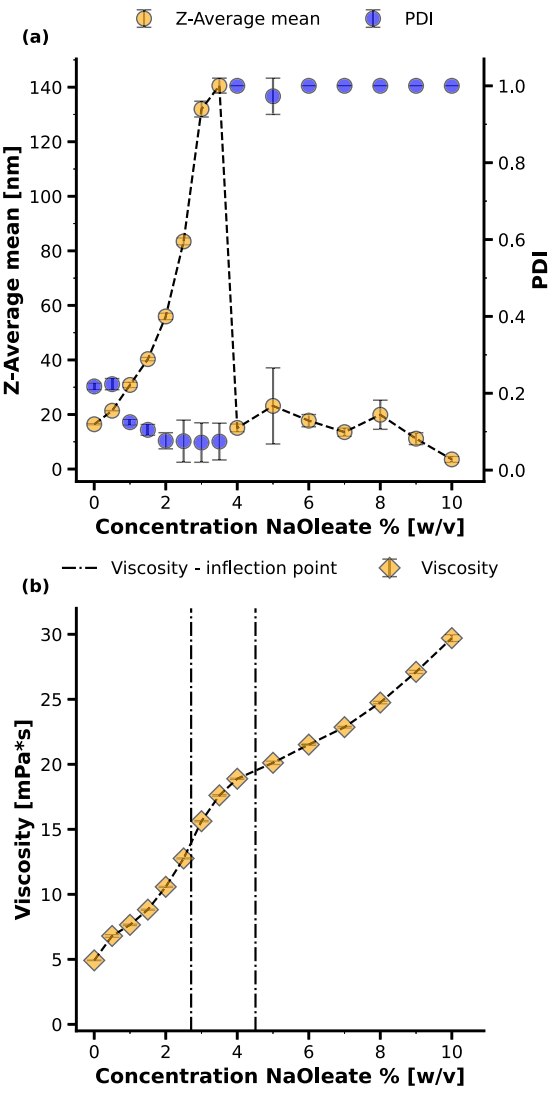


Fig. 6. (a) Particle size measurements as a function of concentration of NaOleate incorporated into 10% [w/v] Soluplus® (n=3 ± SD). (b) Viscosity measurements of the samples containing 10% Soluplus® as a function of NaOleate incorporated (n=5; ± SD).

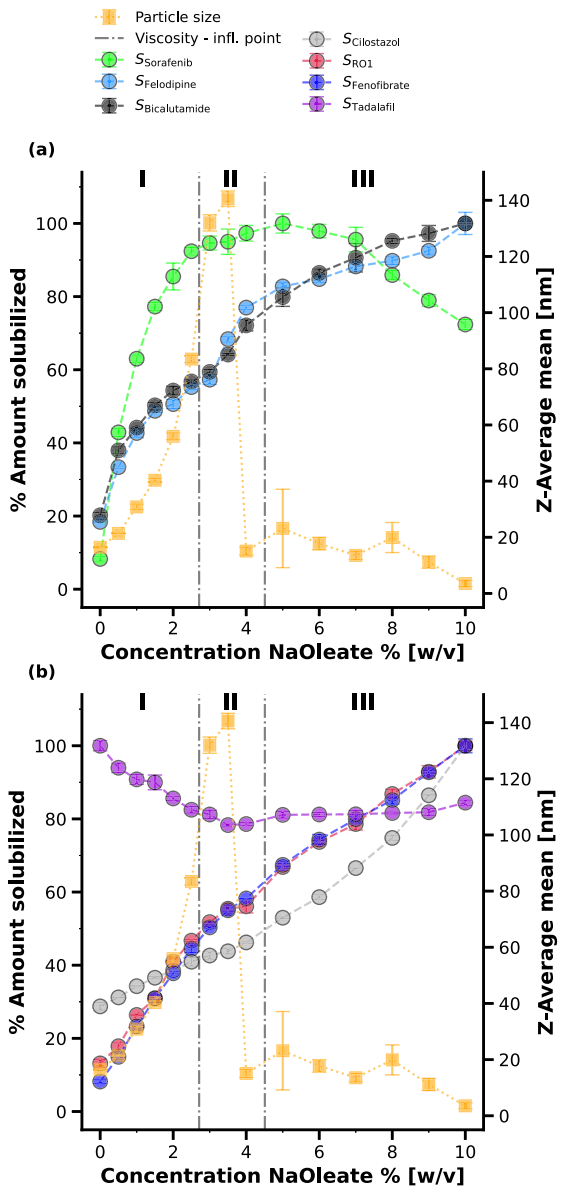


Fig. 7. Normalised solubilisation profiles as a function of % [w/v] NaOleate incorporated, including particle size measurements as well as inflection points in viscosity profiles. three segments were identified based on different analytical techniques. Figure (a) Normalised solubilisation profiles for the model drugs demonstrating synergistic solubilisation upon incorporating NaOleate in 10% [w/v] Soluplus® and particle size measurements. Figure (b) Normalised solubility values for the model drugs demonstrating non-synergistic solubilisation behaviour.

remained relatively unexplored. Previous studies have explored combinations of ionic surfactants and polymers for supersaturating delivery systems. However, in many cases, these polymers demonstrate limited intrinsic solubilisation capacities, which restricts their use in preclinical studies (Liu et al., 2016; Qi et al., 2012). Soluplus® is unique in that it offers both, micellar and polymeric characteristics, making it particularly suited to achieve required dose loadings for preclinical solution formulations. The inherent solubilisation strength and polymeric structure open the interesting possibility to probe whether its solubilisation strength in aqueous solutions can be further amplified by the addition of ionic surfactants to move closer to a universal vehicle for preclinical testing.

This study demonstrated that the addition of ionic surfactants to Soluplus® in six out of seven cases increased solubilisation of Soluplus®. When any of the ionic surfactants were introduced, an alteration in the solution's properties was observed by complementary analytical techniques, which suggests a modification of the aggregation behaviour of Soluplus®, thereby leading to a concentration dependent change in solubilisation performance.

The synergistic solubilisation observed for sorafenib, bicalutamide and felodipine upon incorporation of ionic surfactant suggests a greater affinity of these drugs for the present colloidal assemblies (Figs. 2 and 3). This observation strengthens the assumption of a mixed colloidal system, since a mere additive behaviour (SAF = 1) would be expected if separate micelles were forming (Feng et al., 2018). Conversely, when SDS and NaOleate were introduced, cilostazol, RO1, fenofibrate, and tadalafil did not demonstrate synergistic solubilisation, but still, solubility over 10% [w/v] Soluplus® was enhanced. Although a non-synergistic solubilisation interaction was noted in this case, it reinforces the hypothesis of a mixed colloidal system, but with a lower attraction for these model drugs. However, for the ionic surfactant DOSS, SAF values > 1 were obtained for cilostazol, RO1 and fenofibrate. The reason for this can be linked to the limited solubility-enhancing capabilities of DOSS-only aqueous solutions for all the model drugs, a factor that plays a role in the denominator of Eq. (1). It should be noted that it is expected that DOSS assembles into micelles within the

investigated concentration range, as the CMC of DOSS was previously reported to be 0.17% [w/w] in deionised water (Steffy et al., 2011). Furthermore, it was recently observed that DOSS may form vesicles, exhibiting solubilisation potential, depending on surfactant and salt concentration in the media (Vinarov et al., 2018). The rather limited solubilisation strength of DOSS was also noted by Saal et al. (2018) and this finding was attributed to the branched and therefore bulky hydrophobic tail groups of the surfactant molecule that may impede drug solubilisation (Maher et al., 2023).

DOSS and SDS yielded similar solubilisation patterns, which may be attributed to the sulphate headgroup that both surfactants share. It appears that the different hydrophobic tailgroups of the surfactants did not have a substantial impact on the ionic surfactant's interaction with Soluplus®. This was not only reflected by the comparable solubilisation pattern, but also by the steady reduction in opalescence of these solutions, which can be attributed to the clouding behaviour of Soluplus® (Figs. 1(b), 1(c)). The cloud point of Soluplus® was previously determined to be 35.8 °C in water (Shi et al., 2016), but early signs of clouding, reflected by opalescence, can already be observed at room temperature (Fig. 1). Such behaviour is related to the hydration of the polymer in solution (Sarkar, 1979). It appears that the introduction of SDS and DOSS influenced the clouding behaviour of Soluplus® which may be explained by an interaction between polymer moieties and the ionic surfactants that may have led to increased solvation of the polymer. An interaction between the hydrophobic motifs of Soluplus® and SDS was previously described by Xia et al. (2016) and termed as Soluplus®-SDS complex formation, which led to higher apparent supersaturation maintenance of cyclosporine A during solvent shift experiments.

The solubilisation curves, which were non-linear, showed a decreasing slope as the concentrations of SDS and DOSS increase. This observation implies that at low concentrations, there are initial alterations in polymer aggregation leading to increased solubilisation, but these changes do not continue to intensify, resulting in a reduction in the slope, potentially due to saturation of hydrophobic domains of Soluplus® or the formation of a colloidal assembly that is less potent in solubilisation.

Upon visual inspection of the vehicles containing NaOleate, a noticeable variation in the opalescence–concentration relationship was observed (Fig. 1(a)). This prompted an investigation into a wider concentration range by complementary DLS and viscosity measurements. Interactions between ionic surfactants and polymer can have a significant impact on viscosity. Previous studies have shown that if surfactant-promoted interpolymer interactions are formed, a pronounced increase in viscosity may be observed for cellulose polymer derivatives in the semidilute region upon combination with SDS due to the formation of junctions or strengthening of existing interpolymer interactions (Nystroem et al., 1995; Holmberg et al., 1997). It can be expected that Soluplus® may have a higher tendency to exhibit interpolymer interactions due to its amphiphilic character and due to the fact that elevated concentrations of the polymer were used in this study. The steep rise in viscosity upon NaOleate incorporation is accompanied by an increase in particle size of the colloidal species in solution (Fig. 6). This suggests that NaOleate interacts with the polymer and may give rise to an increased amount of interpolymer interactions, which were previously described to have a strong impact on the viscosity of polymer-ionic surfactant systems.

Conceptually, if the mode of association between ionic surfactant and polymer starts to change, a change in curvature of the obtained profiles can be expected. To explore this, inflection points were calculated based on the viscosity and DLS data. The inflection point observed in the interpolated viscosity function coincided with an inflection point in the interpolated DLS data at a NaOleate concentration of 2.7% [w/v]. Another inflection point was obtained for the viscosity data, which coincided with the onset of a high degree of polydispersity in the DLS data, suggesting the formation of a separate colloidal species. Fig. 7 illustrates these inflection points, and their alignment with the solubilisation profiles, which were standardised to enable comparison. The three identified segments match with the visual characteristics illustrated in Fig. 1(a) as well as the solubilisation profile.

For the three model drugs exhibiting synergistic solubilisation a steep increase in solubility can be noted upon incorporation of NaOleate (Fig. 7(a)). As felodipine and bicalutamide continue to increase in solubility after surpassing the first inflection point, sorafenib's solubility plateaus in segment II. This observation suggests that felodipine and bicalutamide exhibit a stronger affinity for this colloidal species, whereas sorafenib solubilisation is unaffected. At a NaOleate concentration of 3.5% [w/v], the vehicle shifts from increasing opalescence to turbidity. The second inflection point, calculated based on the viscosity function, coincided with substantial polydispersity and a transition from turbidity to clear solutions. While felodipine and bicalutamide's solubility consistently increased, sorafenib's solubility decreased at approximately 7% [w/v] NaOleate added. This decrease may indicate the formation of another colloidal species less favourable for sorafenib solubilisation, or it could be due to additional NaOleate molecules competing with solubilised sorafenib molecules for hydrophobic pockets of Soluplus®, resulting in lower drug solubilisation.

Since no further pronounced inflection points were observed in neither the DLS nor the viscosity data, the latter hypothesis is considered more plausible. This is further supported by the fact that any further changes in aggregation would likely manifest as slope changes for bicalutamide and felodipine solubilisation as well. For all the remaining drugs a breakpoint was observed within segment II. It appears that the change in aggregation behaviour led to decreased affinity of tadalafil, fenofibrate, and RO1 towards the colloidal species, as indicated by the decreasing solubilisation slope. However, the increase in slope observed for cilostazol indicates a higher affinity for the drug towards the terminal colloidal species. Based on Fig. 4, it is evident that the drugs not exhibiting more than additive solubilisation behaviour display high affinities for micelles consisting of ionic surfactants alone.

Interaction between non-ionic polymers and ionic surfactants have been previously reported in the literature, especially in the context of interactions between cellulose derivatives and SDS (Nilsson, 1995; Persson et al., 1996). Interactions between SDS and Soluplus® were reported by Thiry et al. (2016) and investigated as a supersaturating drug delivery system by Xia et al. (2016). It was hypothesised that the swelling of Soluplus® micelles occurred due to the adsorption of SDS onto the hydrophobic segments of Soluplus®, resulting in increased hydrophobicity of the system. This study observed a similar trend but relates it to the enhancement of equilibrium solubility, considering a diverse set of molecules and different ionic surfactants. Hansson and Lindman (1996) suggested that the addition of ionic surfactant influences the balance between intra- and interpolymer interactions. The charged nature of ionic surfactants introduces cooperative, non-cooperative, and anticooperative regions, and it was hypothesised that any favourable interaction between both constituents would reflect a dramatic change in solution properties around a characteristic critical aggregation concentration (Hansson and Lindman, 1996). The high degree of cooperativity is especially complex in the case of Soluplus® due to its amphiphilic character, which leads to micelle formation on its own. Nevertheless, the observed changes in solution properties, as tested by viscosity, DLS, and solubility measurements, suggest a critical aggregation concentration within segment 2 of Fig. 7.

5. Conclusion

This study demonstrated how the combination of ionic surfactants with 10% [w/v] Soluplus® can enhance solubilisation for a diverse set of poorly water-soluble drugs. The solubility enhancement was non-linear and drug specific. Of particular relevance is the occurrence of synergistic solubilisation. Mechanistically, this synergistic solubilisation phenomenon can be attributed to interactions between the

ionic surfactant and Soluplus®, leading to alterations in aggregation behaviour that may ultimately result in the creation of environments of preferential solubilisation. For a subset of compounds, less than additive solubilisation was observed, highlighting the drug specific effects on solubilisation by mixed colloidal systems. Alterations in visual appearance, viscosity, and DLS data further substantiated these changes in aggregation behaviour in the NaOleate system. The investigation of further model drugs as well as broader Soluplus® concentrations is merited to understand how physicochemical attributes of drugs are related to synergistic solubilisation. These findings hold great significance for the development of preclinical solution formulations, especially when high dose loadings are required.

CRediT authorship contribution statement

Justus Johann Lange: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lukas Enzner:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Martin Kuentz:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Patrick J. O'Dwyer:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Wiebke Saal:** Writing – review & editing, Supervision, Project administration. **Brendan T. Griffin:** Writing – review & editing, Project administration, Funding acquisition. **Nicole Wyttenbach:** Writing – review & editing, Supervision, Project administration.

Acknowledgements

This project has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No 955756. The authors thank BASF (Ludwigshafen, Germany) for providing a sample of Soluplus®.

Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.ejps.2024.106957.

Data availability

Data will be made available on request.

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