Journal Article

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Recommended citation:

Kokubun, S., Ratcliffe, I. and Williams, P (2018) 'The interfacial, emulsification and encapsulation properties of hydrophobically modified inulin', *Carbohydrate Polymers*, vol 194, pp.18-23. doi: 10.1016/j.carbpol.2018.04.018.

The interfacial, emulsification and encapsulation properties of hydrophobically modified inulin

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Key words:
inulin, alkenyl succinic anhydrides, critical aggregation concentration, interfacial properties, emulsion stabilisation, encapsulation

ABSTRACT

Octenyl- and dodecenyl succinic anhydride derivatives (OSA- and DDSA-) of inulin have been synthesised and their solution and interfacial properties have been determined and compared to a commercially available alkylated inulin, Inutec SP1. All samples formed micellar aggregates in solution above a critical concentration (critical aggregation concentration) and were able to 'dissolve' a hydrophobic dye. They were also able to form stable oil-in-water (O/W) emulsions as assessed by measurements of their droplet size as a function of time. DDSA-inulin with a high degree of substitution was found to be effective at encapsulating beta carotene using the solvent evaporation method which yielded a solid which dissolved readily in simulated gastric fluid. The results confirm the potential application of these materials in a number of areas including, drug delivery, pharmaceuticals, neutraceuticals, cosmetics and personal care.

INTRODUCTION

Inulin is a polyfructan and is obtained commercially from chicory. It consists of β 2,1 fructose chains, with degrees of polymerisation ranging between 2 and 60, which terminate with a glucose residue. It is classed as a type of dietary fibre because it is not absorbed in the stomach or small intestine but is degraded by bacteria in the colon to form short-chain fatty acids which have health benefits. There has been considerable interest in recent years in the derivatisation of inulin to form a range of speciality chemicals (Stevens, Merigii & Booten 2001). Inutec SP1 is a hydrophobically modified inulin derivative which is produced commercially by reaction of inulin with dodecyl isocyanate in an aprotic solvent to yield inulin dodecyl carbamate (Stevens et al., 2001; Exerowa et al., 2007; 2009a, b; Gotchev et al., 2007; Nestor et al., 2007). It has a molar mass of about 5000 g/mol (Exerowa et al., 2009b; Nestor et al., 2005, 2007, 2008) and is used in a variety of industrial sectors for the stabilisation of emulsions and dispersions..

A number of other hydrophobic derivatives have been synthesised by reaction of inulin in organic solvents with fatty acid chlorides, methyl esters, alkyl epoxides, and alkyl isocyanates (Stevens, Merigii & Booten, 2001; Exerowa et al., 2009; Khristov & Czarnecki, 2010; Gochev et al., 2011). A 'green' approach to modification has been developed by Morros et al. (2010, 2011), Kokubun, Ratcliffe & Williams (2013; 2015) and Han, Ratcliffe and Williams (2015) who have recently reported the modification of inulin using alkenyl succinic anhydrides in water under mild alkaline conditions to produce inulin derivatives with varying alkenyl chain length and varying degrees of substitution. It was confirmed that these surfactants adsorbed at the air-water interface and that they formed micellar-like aggregates in solution above a critical concentration.

The ability of hydrophobically modified inulin derivatives to form micellar aggregates has attracted much interest in recent years. Muley et al. (2016), for example, used Inutec SP1 for the encapsulation and controlled release of the anti-cancer drug, paclitaxel. Encapsulation was achieved using both the 'thin film hydration' and 'solvent evaporation' methods and they demonstrated through dynamic light scattering and transmission electron microscopy studies that near spherical drug-loaded micellar aggregates of ~250nm were produced. Other groups have also used hydrophobic derivatives for encapsulation of active compounds within micellar-like structures. For example, Di Prima et al. (2017) synthesised an amine derivative which was further modified to incorporate retinoic acid to yield mucoadhesive micelles with enhanced transcorneal permeation properties while Mandracchia et al. (2017) produced derivatives containing both vitamin E and biotin capable of forming micelles for potential application as long-circulating carriers for receptor-mediated targeted drug delivery. In another approach,

Lopez-Molina et al. (2015) synthesised a cinnamoylated inulin derivative by reaction with cinnamic acid chloride in pyridine and produced microspheres for the targeted delivery of drugs to the colon.

The purpose of the present study was to synthesise octenyl and dodecenyl succinic anhydride derivatives of inulin and to investigate their solution and interfacial properties in comparison with Inutec SP1 and to evaluate their ability to encapsulate water insoluble beta carotene. It is our hypothesis that encapsulation using the anionic succinylated derivatives could have significant benefits in the controlled release of the beta carotene compared to the commercial non-ionic Inutec SP1.

MATERIALS AND METHODS

Materials

Inulin coded Fibruline® DS2 was supplied by Cosucra and was dried at 70 ˚C for 24 hours before use. It was found to have a weight average and number average molar mass of 3,760 and 3,000 g/mol respectively (Kokubun, Ratcliffe & Williams, 2013). Inutec SP1 was obtained by Beneo Biobased Chemicals and was used as supplied.

2-octen-1-yl-succinic anhydride (OSA) and 2-dodecen-1-yl-succinic anhydride (DDSA) were obtained from Aldrich Chemical Co. and were used as received. Medium Chain Triglyceride (MCT) gold oil was obtained from Trec Nutrition UK and was used as supplied. Sudan IV was obtained from the Eastman Kodak Company. Beta carotene Type I synthetic ≥ 93 % (UV) powder was obtained from Sigma-Aldrich Chemie GmbH., and was used as supplied.

Methods

Synthesis of hydrophobically modified inulin

Hydrophobically modified inulin samples were synthesised in aqueous solution under alkaline conditions using OSA and DDSA and were characterised by nuclear magnetic resonance (NMR) spectroscopy as previously reported (Kokubun, Ratcliffe & Williams, 2013). The samples obtained, namely OSA(1), OSA(2) and DDSA(1) had approximately 1 – 2 alkenyl chains per molecule and a further sample, DDSA(2), had ~5 alkenyl chains per molecule.

Critical aggregation concentration

The CAC was determined by the dye solubilisation technique using Sudan IV. 10mg of the dye was added to 10 mL of the OSA-, DDSA- inulins or Inutec SP1 at varying concentrations in deionised water. The samples were mixed at 40 °C overnight and filtered using a Millex-GP 0.22 µm filter (Millipore Ireland Ltd.) into disposable UV-grade 10 mm path length cuvettes (CXA-110-0053 from Fisher Scientific Ltd.). The absorbance of the solutions was measured at 510 nm using a Lambda 25 UV/vis Spectrometer PerkinElmer. The CAC was determined as the point at which the absorbance increased.

Surface and interfacial tension

The surface tension at the air / water interface and the interfacial tension at ASA-inulin or Inutec SP1 aqueous solution / MCT oil interface were measured at varying concentration at 25 ˚C ± 1 ˚C using the Du Nouy ring method with a Tensiometer K8 and a 4 cm circumference platinum ring RI 01 from Krüss GmbH. The equilibrium surface and interfacial tensions were plotted as a function of the sample concentration and the CAC was estimated from the change in slope of the plots.

Zeta potential

The zeta potential of inulin-coated emulsion droplets was determined at various pH at 25 ˚C using a Zetasizer Nano ZS (Malvem Instrument Lab, Malvern, UK) equipped with a 5 mw He-Ne laser (λ_0 633 nm) and a digital correlator. Measurements were carried out using a folded capillary cell DTS1060 (Malvern Instrument Lab, Malvern, UK). The cell was washed with ethanol and deionised water several times and dried before measurements. Oil-in-water (O/W) emulsions were prepared by mixing 1.5 g MCT oil with 8.5 g of 2.5% OSA-, DDSA- inulin or Inutec SP1 solution for 3 minutes at 24 000 rpm, using an IKA T25 digital Ultra-Turrax mixer. Two drops of the emulsion were added into 10mL 0.01M NaCl which was filtered with a type GN 0.2 µm filter (Millipore Ireland Ltd) before use. The system was mixed for 30 seconds and the pH was adjusted using 0.1M HCl and 0.1M NaOH. Ten runs were performed for each sample. The data was analysed using the Zetasizer Software 6.20 © 2002-2010 from Malvern Instruments Ltd and the zeta potential was determined from the electrophoretic mobility using the Smoluchowski equation.

Emulsification properties

O/W emulsions were prepared as above and droplet size measurements were made immediately after emulsion preparation and over a period of 21 days for samples stored at room temperature (25 ºC) and at 50 ºC using the Mastersizer 2000 (Malvern Panalytical Ltd Malvern, UK). Before measuring the samples, background readings for the instrument were

carried out to subtract the ambient light signals from the total scattering received from samples. Two or three drops of the sample were introduced into the dispersion unit containing distilled water. The dispersion unit pump speed was 2000 rpm. The obscuration was between 10% and 30%. The refractive index of the dispersing medium and the dispersed particles were 1.33 and 1.45 respectively. Measurements were performed in duplicate.

Encapsulation

Encapsulation of beta carotene using hydrophobically modified inulin was facilitated using the solvent evaporation method. Approximately 1.0 g of the beta carotene and 5.0 g of the ASA-inulin or Inutec SP1 were added to 70 mL of chloroform and the system was stirred with a magnetic stirrer and then left overnight at room temperature inside a fume cupboard to enable the chloroform to evaporate completely. The solubility of the beta carotene in the resulting solid matrix was determined by preparing a number of samples containing 0.02g of the solid in 10 ml deionised water or simulated gastric fluid and mixing at 37 °C. The simulated gastric fluid was prepared by adding 500 ml 1 M HCl and 10.22 g sodium chloride to 5 L deionised water and stirring with a magnetic stirrer overnight at room temperature to fully dissolve. 3ml of each of the dispersions was taken at various time intervals and filtered using a Millex-GP 0.22 μm filter (Millipore Ireland Ltd.) into disposable UV-grade 10 mm path length cuvettes (CXA-110-0053 from Fisher Scientific Ltd.). The absorbance of the solutions was measured at 455 nm using a Lambda 25 UV/vis Spectrometer PerkinElmer.

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RESULTS AND DISCUSSION

Critical aggregation concentration and interfacial properties

The results obtained for the dye solubilisation studies are presented in Figure 1. It is seen that the absorbance increased at values of 0.70% +/-0.1%, 0.02% +/-005% and 0.002% +/-0.001% for the OSA(1)-inulin, DDSA(1)-inulin and Inutec SP1 respectively.

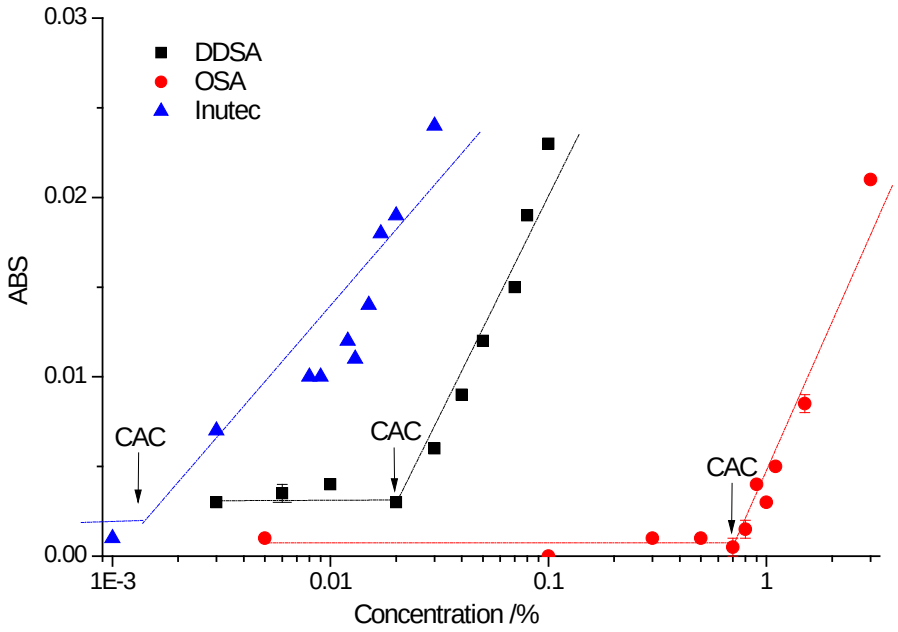


Figure 1. Absorbance of OSA(1), DDSA(1)-inulin and Inutec SP1 at varying concentrations in the presence of Sudan IV.

The increase is attributed to the formation of micellar-like aggregates through hydrophobic association of the inulin molecules and the dissolution of the dye in the hydrophobic core as discussed previously (Kokubun, Ratcliffe & Williams, 2013). The CAC values for the succinylated samples are expected to be higher than those for Inutec SP1 since the former have an anionic carboxylate group in the linkage between the alkenyl chains and the inulin molecule which will tend to inhibit molecular aggregation due to intermolecular electrostatic repulsions. The CAC is significantly higher for OSA-inulin compared to DDSA-inulin which is consistent with our previous studies (Kokubun, Ratcliffe and Williams, 2013; 2015; Han, Ratcliffe and Williams (2015)) and the work of van Kempen et al. (2013a; 2013b; 2014) who studied the CAC of a series of inulin fatty acid esters with alkyl chain lengths ranging from C8-C16.

The surface tension of OSA-inulin, DDSA-inulin and Inutec SP1 samples are plotted as a function of concentration in Figure 2. The surface tension was found to decrease with increasing concentration and an inflexion was observed at 0.70% +/-0.08%, 0.020% +/-0.0025% and 0.005% +/-0.001% respectively for the OSA-inulin, DDSA-inulin and Inutec SP1 and these values closely correspond to the CAC values reported above obtained by dye solubilisation.

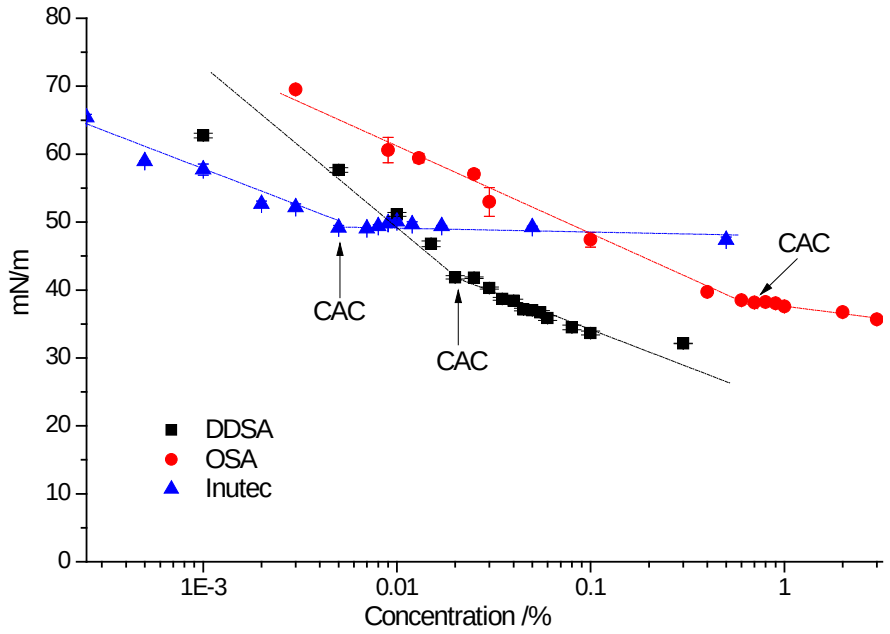


Figure 2. Surface tension of OSA(1), DDSA(1) -inulins and Inutec SP1 as a function of concentration.

Our studies have shown that the surface tension was 38 mN/m, 42 mN/m and 49 mN/m at the CAC for the OSA-inulin, DDSA-inulin and Inutec samples respectively. Nestor et al. (2005) have also determined the surface tension of Inutec SP1 and found that it decreased from ~ 68 to ~45 mN/m with increasing concentration and observed an inflexion at $7x10^{-7}$ mol·dm^{-3} which is equivalent to 0.00035% assuming an Mw of 5000g/mol. These workers also determined the CAC by static light scattering and observed an inflexion in the light scattering intensity at a concentration of $5x10^{-6}$ mol·dm^{-3} (equivalent to 0.0025%) which is in agreement with our findings. Srinarong et al (2010) also determined the CAC of Inutec SP1 by surface tension measurements and showed that the surface tension decreased to ~55 mN/m at a concentration of 0.009% which corresponded to the CAC.

The surface excess, Γ / molm^{-2}, was calculated from the gradient of the plot of surface tension as a function of the logarithm of the concentration determined at a concentration just below the CAC.

The area/molecule, A, was calculated using equation (1)

$$\Gamma = -\frac{c}{2RT}\frac{d\gamma}{dc} = -\frac{1}{2RT}\frac{d\gamma}{d\ln c} \qquad (1)$$

The surface excess and the area per molecule for OSA-, DDSA-inulins and Inutec SP1 are presented in Table 1.

Table 1. The surface excess and the area/molecule for OSA-, DDSA- inulins and Inutec SP1

Sample name	dγ/dlnc/Nm^{-1}	Γ/molm^{-2}	Γ^{-1}/ m^{2}molecule^{-1}	Γ^{-1}/ nm^{2}molecule^{-1}
Surface tension				
OSA-inulin	-0.0132	1.16 x10^{-6}	1.44x10^{-18}	1.44
DDSA-inulin	-0.0255	2.23x10^{-6}	7.43x10^{-19}	0.74
Inutec SP1	-0.0108	1.89x10^{-6}	8.78x10^{-6}	0.87

The value of A from surface tension measurements at the air-water interface was found to be 1.44, 0.74 and 0.87nm^2 for OSA-inulin, DDSA-inulin and Inutec SP1 respectively. Stevens et al. (2001) have reported values of 0.9 nm^2 for octyl inulin carbamate at the air-water interface. The values for A are significantly larger than those reported for simple sugar-based surfactants based on one or two sugar residues as might be expected due to the higher molar mass of inulin. Soultani et al. (2003) reported values of 0.05 – 0.2 nm^2 for hydrophobically modified fructose and sucrose surfactants while Garofalakis et al. (2000) reported values of 0.29 – 0.68 nm^2 for surfactants based on xylose, galactose, sucrose and lactose. It is evident that A for the modified inulins will depend on the number of the hydrophobic groups attached to the inulin molecules and to their location along the chain.

The interfacial tension at the interface between aqueous solutions of OSA-inulin, DDSA-inulin or Inutec SP1 and MCT oil are plotted as a function of concentration in Figure 3 and was found

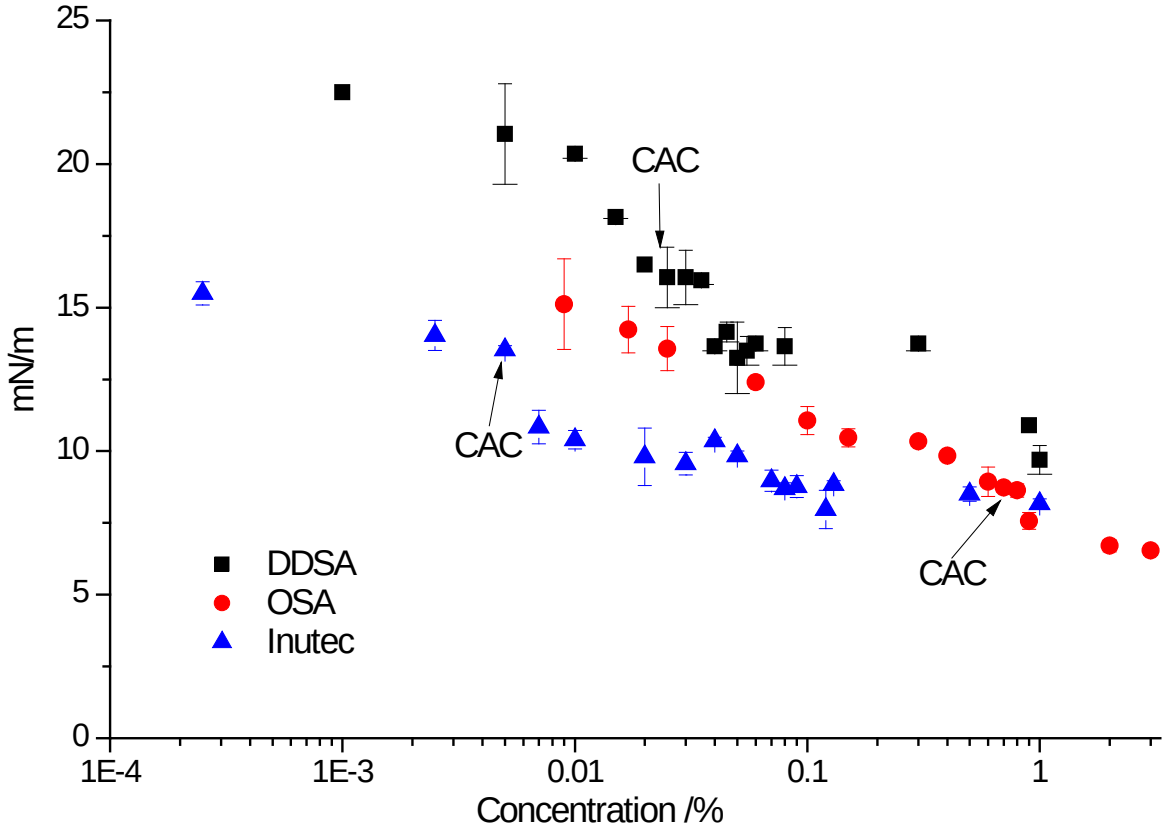


Figure 3. Interfacial tension of OSA(1), DDSA(1) -inulins and Inutec SP1 at the oil / water interface as a function of concentration.

to decrease as the concentration increased but there was no clear inflexion corresponding to the CAC values noted above. This is likely to be due to the very heterogeneous nature of the modified inulin samples. The interfacial tension was found to be 8 mN/m, 16 mN/m and 13 mN/m at the CAC for the OSA-inulin, DDSA-inulin and Inutec SP1 respectively. Stevens et al. (2001) measured the interfacial tension for octyl inulin carbamate at the IsoparM oil / water interface and reported an interfacial tension of 6.8mN/m at the CAC.

Emulsification properties

The zeta potential of droplets for O/W emulsions prepared using OSA- and, DDSA -inulins and Inutec SP1 are plotted as a function of pH in Figure 4. It is noted that the zeta potential increased with increasing pH from -4.8 mV at pH 1.9 to -60.8 mV at pH 9.7 for OSA-inulin and from -2.2 mV at pH 1.8 to -55.5 mV at pH 10.2 for DDSA-inulin.

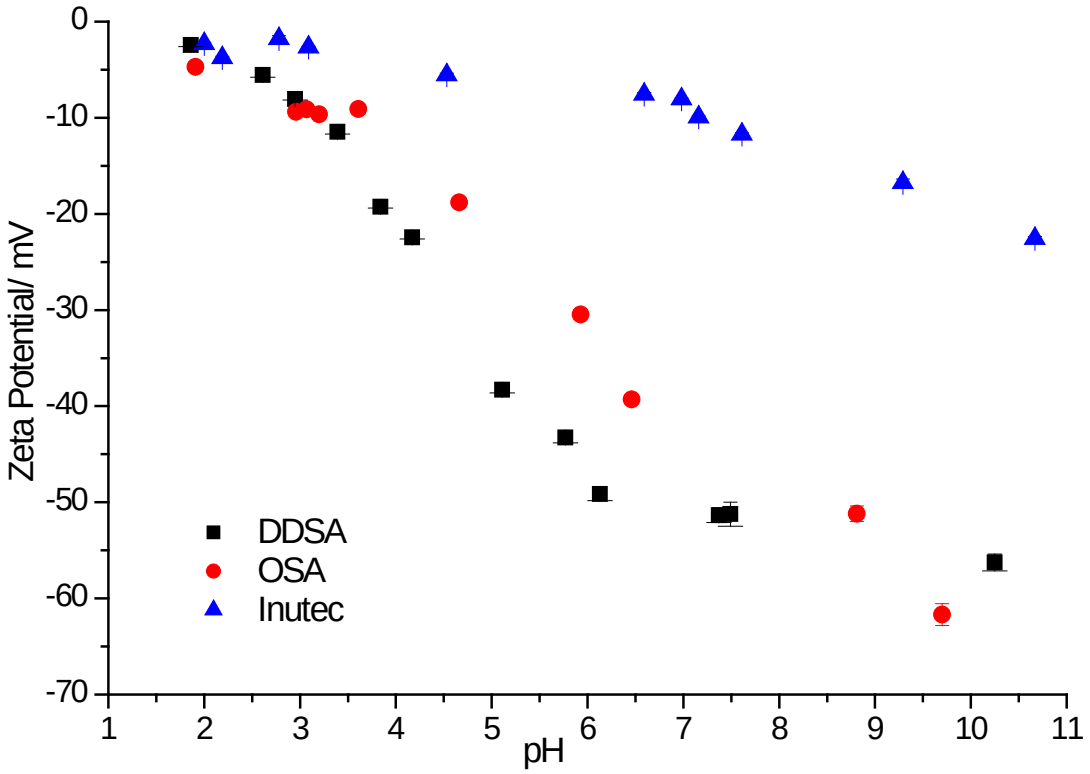


Figure 4. Zeta potential of OSA(1), DDSA(1) -inulins and Inutec SP1 as a function of pH.

The increase in zeta potential is due to the fact that OSA-, DDSA- inulins have a carboxylic acid group present in the linkage between the inulin and alkenyl moieties arising from the alkylene succinic anhydride and this dissociates as the pH increases to form the carboxylate ion. Inutec SP1 does not contain ionic groups (Nestor et al., 2005) and hence does not show this trend. The slight increase in the zeta potential observed for Inutec SP1 is likely to be due the adsorption of hydroxide ions at the O/W interface and/or ionisation of hydroxyl ions of the inulin and/or MCT oil (Xin et al., 2013; Liu et al., 2006).

The droplet sizes for emulsions prepared using 2.5% OSA- and DDSA -inulins and Inutec SP1 over time at room temperature and 50 ˚C are presented in Figures 5.

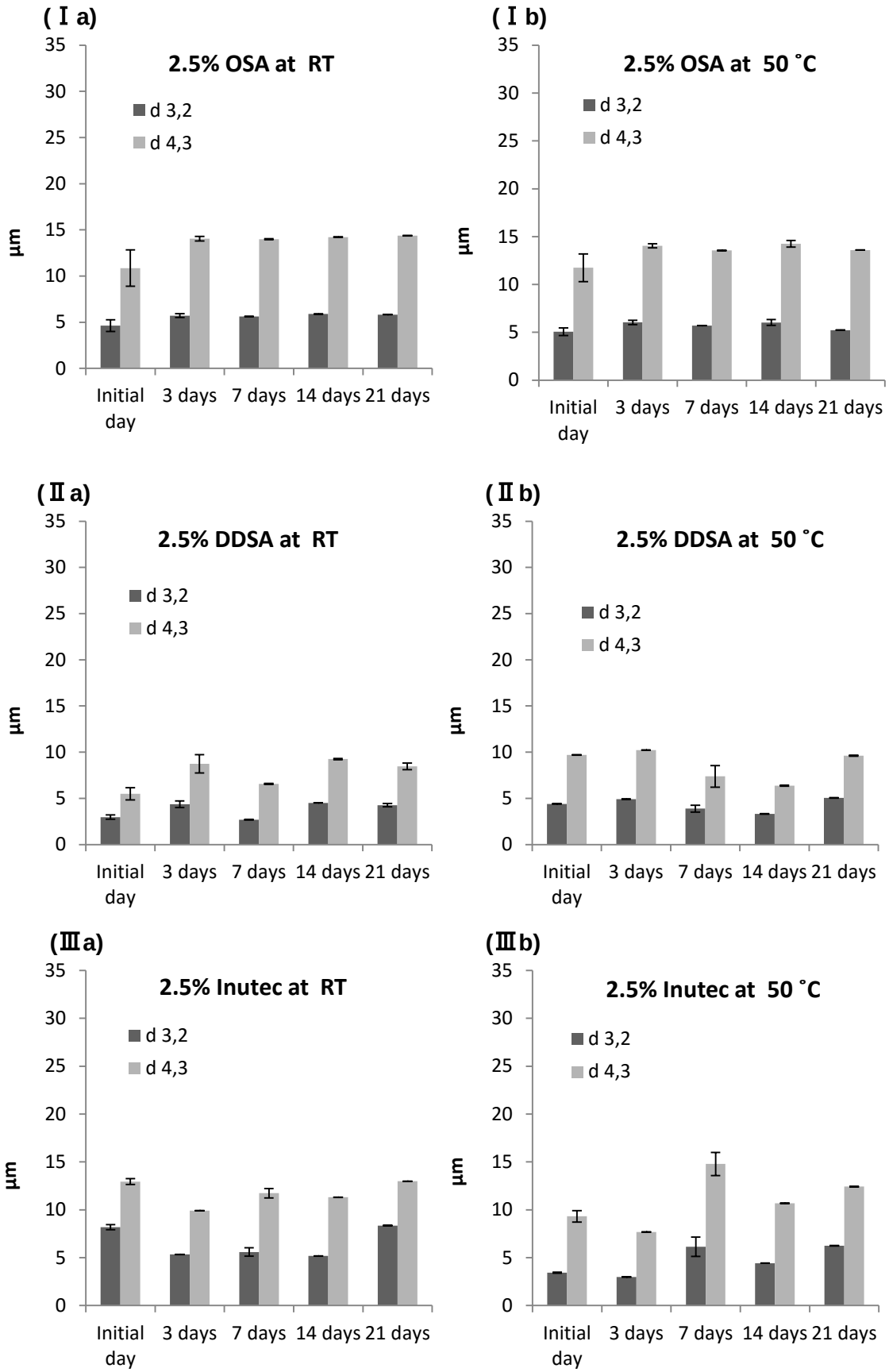


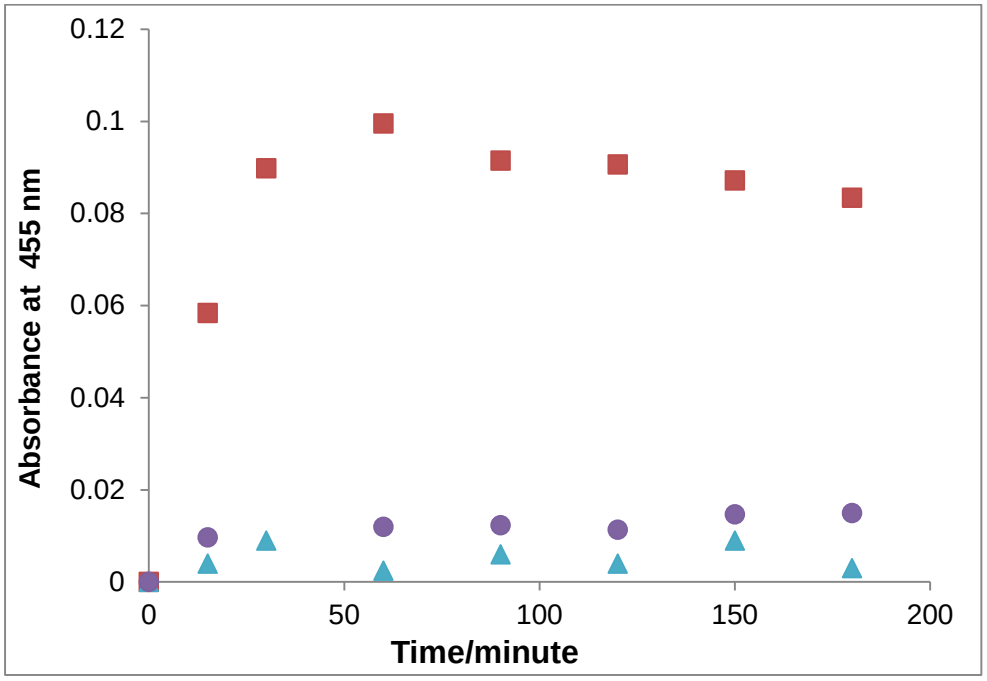
Figure 5. Surface weighted mean ($d_{3,2}$) and volume weighted mean ($d_{4,3}$) diameters of O/W emulsions using 2.5% OSA (9%)-(Ⅰ), DDSA (12%)-inulin(Ⅱ) and Inutec (Ⅲ) over 21 days (a) at room temperature and (b) 50 ˚C.

The DDSA - inulin sample was found to have the greatest emulsification capacity producing droplets with a smaller size compared to OSA-inulin and Inutec SP1 stabilised emulsions. The surface weighted mean ($d_{3,2}$) and the volume weighted mean ($d_{4,3}$) diameters for all samples remained relatively constant over 21 days at room temperature and 50 ˚C. This is consistent with the work of Tadros et al. (2004) who prepared 50/50 (v/v) Isopar/water emulsions containing 2% Inutec SP1 (w/v). They demonstrated that emulsion droplets were stable and there was no oil separation over a one year period. It is assumed that the hydrophobic chains covalently attached to the modified inulins facilitate the adsorption of the molecules onto the surface of the oil droplets and that the carbohydrate residues protrude into the aqueous phase. According to Gochev et al.(2011) and Khristov et al. (2010) the inulin molecules form loops at the interface and that the size of the loops will depend on the number of alkyl chains attached. It is evident for Inutec SP1 that droplet aggregation is prevented through steric repulsive forces arising from the interaction of the carbohydrate moieties (Nestor et al., 2005; Stevens et al., 2001). For the OSA- and DDSA -inulin samples, which have a significantly shorter inulin chain compared to Inutec, stabilisation will be achieved by electrostatic repulsive forces due to the presence of the carboxylate ions in the head-group (Kokubun, Ratcliffe & Williams (2015)). This is supported by the zeta potential measurements reported above which show that the droplets acquire a significant negative charge as the pH is increased.

Encapsulation

OSA-, DDSA- inulin and Inutec SP1 solid dispersions were formed by the solvent evaporation method and their ability to disperse in water and in simulated gastric fluid was determined by measuring the absorbance of the solution as a function of time. The results are reported in Figures 6a and 6b. The absorbance of the filtered solutions for the DDSA(2) sample was found to increase to a maximum value of 0.1 after ~30 minutes in water but increased to significantly higher values in the gastric fluid. The increase in absorbance is evidence of the presence of micellar aggregates in which the beta carotene is dissolved in the hydrophobic core. Only very small increases in absorbance were observed for Inutec SP1 and the other less substituted OSA-, DDSA- inulin samples.

(a)



(b)

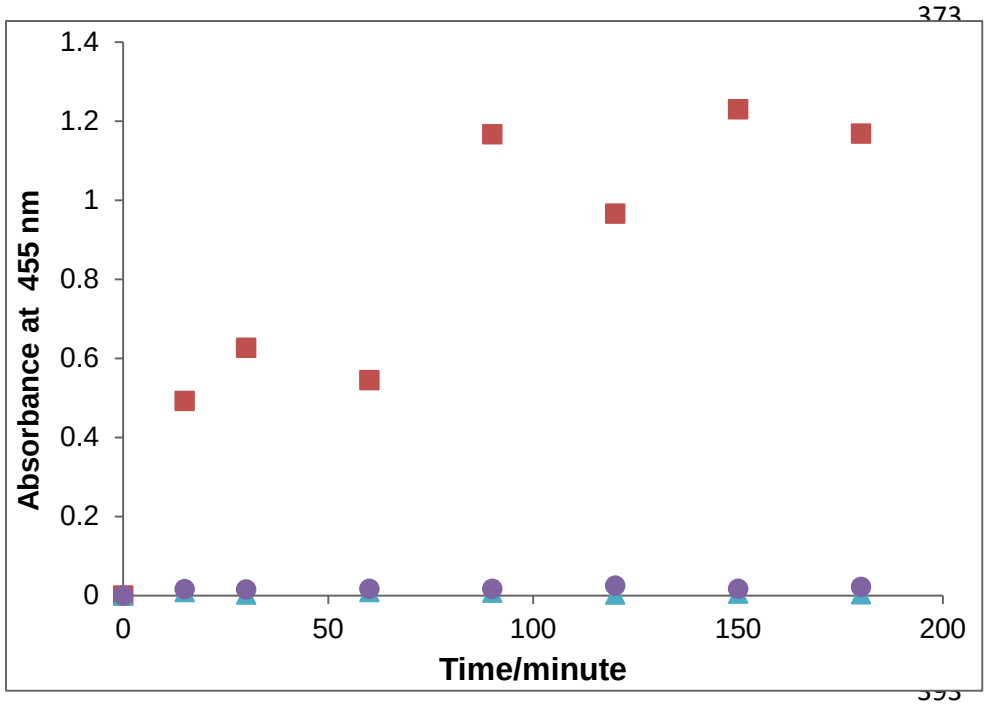


Figure 6 Absorbance of dispersions of beta carotene and OSA(2) [triangles], DDSA(2)-inulin [squares] and Inutec SP1 [circles] as a function of time dispersed in (a) water (b) simulated gastric fluid.

Conclusions

This study has shown that OSA-, DDSA- inulin and Inutec SP1 form micellar aggregates in solution above a critical concentration which are able to dissolve hydrophobic compounds. In addition, they are effective at reducing the interfacial tension at the air-water and oil-water interface and can stabilise O/W emulsions. The DDSA(2) sample with a higher degree of modification proved more effective than the OSA-inulin and Inutec SP1 to encapsulate and release beta carotene when the solid dispersion was dispersed in water and simulated gastric fluid. These materials have considerable potential for application in the encapsulation of active compounds, such as drugs, vitamins, antimicrobials and aromas for use in, for example, pharmaceutical, neutraceutical, personal care and cosmetic products.

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