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RESEARCH PAPER

Insights into the Role of Polymer-Surfactant Complexes in Drug Solubilisation/Stabilisation During Drug Release from Solid Dispersions

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ABSTRACT

Purpose To evaluate the role of polymer-surfactant interactions in drug solubilisation/stabilisation during the dissolution of spray-dried solid dispersions and their potential impact on *in vivo* drug solubilisation and absorption.

Methods Dissolution/precipitation tests were performed on spray-dried HPMC-Etravirine solid dispersions to demonstrate the impact of different surfactants on the *in vitro* performance of the solid dispersions. Interactions between HPMC and bio-relevant and model anionic surfactants (bile salts and SDS respectively) were further characterised using surface tension measurements, fluorescence spectroscopy, DLS and SANS.

Results Fast and complete dissolution was observed in media containing anionic surfactants with no drug recrystallisation within 4 h. The CMCs of bile salts and SDS were dramatically reduced to lower CACs in the presence of HPMC and Etravirine. The maximum increases of the apparent solubility of Etravirine were with the presence of HPMC and SDS/bile salts. The SANS and DLS results indicated the formation of HPMC-SDS/bile salts complexes which encapsulated/solubilised the drug.

Conclusions This study has demonstrated the impact HPMC-anionic surfactant interactions have during the dissolution of non-ionic hydrophilic polymer based solid dispersions and has highlighted the potential relevance of this to a fuller understanding of drug solubilisation/stabilisation *in vivo*.

KEY WORDS bile salts · polymer-surfactant interaction · poorly water-soluble drugs · solid dispersions · solubilisation

INTRODUCTION

Solid dispersions, in particular water-soluble polymer-based dispersions, have been increasingly used for enhancing the oral absorption of poorly water-soluble drugs (1–3). It is believed that the formulation with best *in vitro* stability and *in vivo* performance should have the drug dispersed, ideally molecularly, in the polymer matrix (1–5). However, recently there has been an ongoing debate as to whether having a molecular dispersion is necessary for achieving the best dissolution outcomes (6). The improvement in drug release and absorption using such systems has been explained as being mainly associated with the fast dissolution of amorphous/molecularly dispersed drugs in the polymer matrix in comparison to those in the crystalline state. Improved absorption has also been attributed to the stabilisation effect of hydrophilic polymers on a supersaturated drug solution after dissolution (7,8). However, the recrystallisation of some drugs from the polymer dispersions after coming into contact with the dissolution media still often poses a barrier to

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realising dissolution enhancement for many solid dispersions. Non-ionic hydrophilic polymers, such as water-soluble cellulose derivatives (i.e. HPMC) and polyvinylpyrrolidone (PVP) are amongst the most studied matrix materials. Increased viscosity has been widely accepted as one of the key mechanisms involved in their ability to inhibit nucleation of drugs in supersaturated solution (9,10). However, for most orally administrated solid dispersions, the increase in the viscosity of the media by dissolving the amount of polymer in a single dose is trivial. This is particularly true for low viscosity grade polymers, such as HPMC E5 with 5 mPa.s viscosity for its 2% *w/v* solution. Therefore, other stabilisation mechanisms may exist and a fuller understanding of this behaviour can have an important impact on the development of solid dispersions and other related areas, such as the design of new pharmaceutical polymers. Although the drug release behaviour of these polymer based solid dispersions has been intensively studied, many of these studies were performed using *in vitro* dissolution conditions that have little relevance to the human gut environment. Therefore the true mechanisms of drug solubilisation and stabilisation of the supersaturated drug solution in the gut after oral administration of these solid dispersion formulations still remain poorly understood.

It is accepted that the human gut is a complex environment, which makes the mechanistic study on the formulation dissolution and absorption behaviour extremely challenging. Few studies have been conducted using *ex vivo* gastrointestinal model systems (11,12). In order to mimic human GI conditions, the testing fluids used in these models are often complex and contain multiple components. Mechanistic investigation of the interaction of each key component in the GI fluid with the formulation is thus very difficult to conduct. Therefore in order to simplify the system, in this study we have explored the effect of one of the key surfactant components in the gut, bile salts, and a model anionic surfactant sodium dodecyl sulphate (SDS) on the dissolution/solubilisation behaviour of HPMC E5 based solid dispersions. Bile salts are anionic surfactants with a CMC range from 2 to 20 mM (13,14). This range is attributed to the multi-component nature of bile salts. Depending on concentration, the formation of secondary micelles may occur and the shape of bile salts micelles can develop from spherical to rod shape micelles (13,14). The bile salts concentration in the intestinal region is higher than the stomach, both values are within the CMC range of bile salts (14), which leads to the presence of bile salts micelles in the GI tract. Interactions between anionic surfactants and non-ionic polymers are well documented (15–21), but there is limited knowledge of the interactions between bile salts and polymers in relation to drug formulation performance. In contrast to systems containing non-ionic surfactants and non-ionic polymers, where often no interactions or very weak interactions are considered to occur (22), anionic surfactants can actively interact with non-ionic polymers and form polymer-surfactant complexes (15–21).

Polymer-surfactant interactions have been extensively studied as a result of their wide application in the food, oil and pharmaceutical industries (15–21). The interaction is a cooperative process in which the surfactant culsters aggregate around the hydrophobic regions of the polymer chain *via* non-covalent binding/adsorption, by for example hydrophobic interaction. Many models have been proposed for describing the structure of polymer-surfactant complexes (15–21). One of the most widely accepted models is the 'pearl necklace' model which describes the adsorption of surfactant aggregates onto hydrophobic segments of the hydrophilic polymer (16,17). PVP/SDS complexes are a typical example of this model (23–26). The interactions between anionic surfactants and cellulose derivatives have also been intensively studied in non-biorelevant media. Similar aggregation behaviour of surfactant molecules around hydrophobic patches on the polymer chain have been hypothesised (19–21). Nilsson and co-workers conducted substantial studies on highly purified HPMC/SDS solution systems (19–21). They proposed the concentration (both HPMC and SDS) dependence of the interactions between HPMC and SDS in water occurs as illustrated in Fig. 1 (19). The HPMC-SDS interaction can only be initiated at a specific surfactant concentration (critical aggregation concentration, CAC). At and above the CAC, small SDS clusters adsorb onto the HPMC chain in a cooperative manner (19). The size of the adsorbed SDS clusters increase with SDS and HPMC concentration until a plateau value of the size is reached. Their results also suggested that at low polymer concentrations, the cluster adsorption is likely to

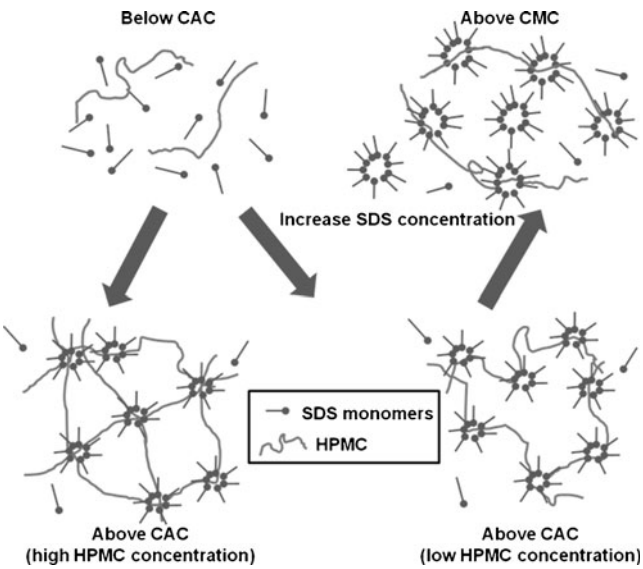

Fig. 1 Illustration of HPMC/SDS interaction in water reported in literature (re-produced based on Ref 19).

be an intramolecular (one SDS cluster adsorb on a single polymer chain) process which may cause polymer coil shrinkage. At high polymer concentrations, the adsorption of SDS clusters tends to switch from intramolecular to intermolecular (one SDS cluster shared by two or more polymer chains) in nature and leads to an increase in viscosity. After the saturation of SDS clusters on the HPMC chains, adding more SDS leads to the formation of normal SDS micelles and the loss of polymer network (19). However, little is known about the impact of these polymer-surfactant complexes on drug solubilisation or whether they can exert a stabilisation effect on supersaturated drug solutions. In the context of dissolution of solid dispersions in the presence of anionic surfactants, after the dissolution of polymer and drug, these polymer-surfactant complexes may have great potential for solubilising drug molecules *via* drug encapsulation in the complexes prior to the oral absorption process. The encapsulation can dramatically reduce the concentration of the free drug in the gut fluid and reduce the crystallisation/precipitation of the drug after it is released from the formulations, thus stabilising the dissolved drug in the GI fluid.

In this study, the effect of anionic surfactants on the drug release/precipitation of the formulations has been investigated in comparison to non-ionic surfactant (Tween 20) in order to gain insight into the impact of polymer-surfactant interactions on facilitating drug solubilisation in the gut environment. The multicomponent nature of bile salts often causes practical experimental difficulties in particular with characterisation techniques such as DLS and SANS (such as the formation of secondary micelles at high concentration). Therefore, the synthetic anionic surfactant, SDS, which has a CMC within the range of the CMC values of bile salts, at approximately 8 mM (27), was used as a simple anionic model surfactant in the mechanistic studies in order to obtain a preliminary structural understanding of the effect of HPMC E5-anionic surfactant interactions on drug solubilisation. A poorly water-soluble model drug Etravirine which has a solubility of <10 μg/ml in water/HCl/phosphate buffers and logP>5 at pH7.0 in octanol/buffer (28), was used in this study. Our previous work has confirmed the formation of a molecular dispersion of Etravirine in HPMC E5 with drug loadings at concentrations below 50% (*w*/*w*) (29). No drug release was observed in the media without anionic surfactant, and the addition of surfactant in the dissolution media allowed complete dissolution of the formulation within 30mins. No release was observed with the media containing non-ionic surfactant Tween 20 (30). Although improved surface wetting by adding surfactant can contribute to the fast dissolution, no release by adding Tween indicates the presence of other mechanisms. Significant absorption enhancement was achieved in the *in vivo* animal model studies of the HPMC solid dispersions in comparison to the nanocrystal suspension of the model drug (29). The main aim of this study is to reveal the underpinning mechanism behind the formulation behavior *in vitro* described above using a range of physical characterisation methods, including surface tension measurements, fluorescence spectroscopy, DLS, and SANS. In this study we report for the first time on the possible effect that polymer-anionic surfactant complexes may have on drug solubilisation from low viscosity grade HPMC based solid dispersion formulations during dissolution.

MATERIALS AND METHODS

Materials

Crystalline Etravirine was obtained from Johnson & Johnson, Beerse, Belgium. The hydroxypropylmethyl cellulose E5 (HPMC E5) 2910 grade (USP/EP substitution type) which has an apparent viscosity of 5 mPa.s as a 2% *w*/*v* polymer solution was provided by Johnson & Johnson. The HPMC used in this study has 7–12% hydroxypropyl and 28–30% methyl substitution. Sodium dodecyl sulfate (SDS) (≥99%, Fisher Bioreagents, UK), Pyrene (≥99.0%, GC, Fluka, 82648), Tween 20 and bile salts containing approximately 50% sodium cholic acid and 50% sodium deoxycholic acid (SigmaUltra, Sigma-Aldrich, Gillingham, UK) were used as received. Distilled water purified using a Millipore Milli-Q four-cartridge system (Millipore, Watford, UK) was used in all experiments.

Spray-Dried Etravirine-HPMC Solid Dispersions

Solid dispersions of various compositions were prepared by spray drying on a laboratory scale Mobile Minor spray drier (GEA Niro, Søborg, Denmark). Etravirine and HPMC were dissolved in an organic solvent mixture, after which the solvent was removed by spray drying. Powders with the following Etravirine:HPMC ratios (*w*/*w*) were prepared: 1:3 (TH 1:3), 1:1 (TH 1:1), and 1:0.5 (TH 1:0.5).

For the granulo-layered formulations, a solution of Etravirine:HPMC was sprayed onto lactose using a fluid bed with a Wurster insert. The carrier particles were bound together with the solid dispersion. After granulation, the powder was milled to the desired particle size.

Formulation Study—Precipitation Tests

The precipitation experiments were performed using 25 mg spray dried microspheres in 25 ml purified water/0.1 M HCl at room temperature. The suspensions were stirred intensively for different time periods (5 mins, 10 mins, 20 mins, 30 mins, 1 h, 2 h, and 3 h) at approximately 700 rpm using a magnetic stirring rod. For the vacuum filtration, a 12 μ 47mmØ Cyclopore™ polycarbonate

membrane filter was used. The nonionic surfactant, Tween 20 (2% *w/v*), and anionic surfactant, SDS (1% *w/v*), were added into the media separately and the precipitation tests were performed as described above. The residues were dried overnight at 40°C in a vacuum oven and were studied using ATR-FTIR spectroscopy (BioRad FTS 165 FTIR, Varian Limited, Oxford, UK).

Drug Solubilisation

First, the solubilisation effect of the surfactants, SDS and bile salts (biorelevant surfactant), on Etravirine was tested in the absence of polymer. An aqueous solution of 1% (*w/v*) surfactant (equivalent to 34 mM for SDS and 24 mM for bile salts) was stirred for 72 h at room temperature in the presence of excess drug. The resulting suspension was filtered through a 0.45 μm cellulose acetate filter (Millipore, Watford, UK) and the concentration of solubilised drug was determined in the filtrate (using λ_{max} of Etravirine at 312 nm) using UV-visible spectroscopy (Hewlett-Packard 8452A, Agilent Technologies, Stockport, UK). Second, an excess amount of the spray dried formulations with 1:3, 1:1, and 1:0.5 drug:polymer ratios were dispersed in the 1% surfactant solutions and stirred for 72 h at room temperature prior to filtration and the solubilised drug concentration analysis.

Polymer-Surfactant Interactions

Critical Micellar Concentration (CMC) Measurements Using Surface Tension

The surface tensions of the surfactant and polymer-surfactant solutions were measured at 25°C and atmospheric pressure by the Wilhelmy plate method using a Langmuir trough (KSV Nima Technology, Coventry, UK) with supporting software to convert surface pressure readings into surface tension. Fresh filter paper plates (Whatman® Chromatography paper Grade 1Chr, Sigma-Aldrich, Gillingham, UK) were used in each measurement. At least 15–20 min equilibrating time was used for each measurement before the recording of the surface tension values of the solution. The pure surfactant (SDS and bile salts) solutions in water and in polymer solutions with HPMC E5 concentrations from 0.0125% to 0.05% (*w/v*) with and without Etravirine were tested. The rationale for the polymer concentrations selection was to cover a range of polymer concentrations expected after the complete *in vitro* dissolution of a commercialised tablet product with an Etravirine dose of 100 mg and 300 mg HPMC E5. All samples were prepared by serial dilution and those containing Etravirine were filtered prior to use. Six repeats were conducted for each measurement.

Critical Micellar Concentration (CMC) Measurements Using Pyrene Fluorescence

Aqueous solutions containing polymer, SDS, and a pyrene concentration less than 10^{-6} M were analysed using fluorescence spectroscopy. For all experiments, the steady-state fluorescence measurements were recorded on a spectrofluorimeter FluoroMax-2 (HORIBA Jobin Yvon Ltd, Middlesex, UK). Calibrations of determining the xenon lamp profile and water scan for emission sensitivity were made prior to running each set of experiments. The emission spectra of pyrene were obtained with an excitation wavelength of 334 nm. A one centimetre optical path quartz SUPRASIL cuvette (QS 111, Hellma GmbH & Co. KG) was used in all experiments. The ratios of vibronic peak intensities at 373 nm and 384 nm (I_1/I_3) in the emission spectra were measured for solutions containing different surfactant concetrations. The data were processed using computer program Origin following the calculation theories described by Aguiar *et al.* 2003 (31).

Dynamic Light Scattering (DLS) Analysis of Polymer-Surfactant Systems

The dynamic light scattering (DLS) measurements of the surfactant and surfactant-polymer solutions were carried out using a Zetasizer Nano ZS (Malvern, Worcestershire, UK) to measure the hydrodynamic particle size. The instrument was fitted with a 633 nm red laser. The detector position was fixed at 173° (backscattering detection). The samples were centrifuged at 5000 rpm for 10 min and equilibrated before the measurements for 5 min. For the formulations samples containing precipitates after dissolution, the supernatant was taken and centrifuged again for 5 min and filtered using 0.45 μm cellulose acetate filter (Millipore, Watford, UK) before measurements. All measurements were performed at 25°C. All final intensity-weighted hydrodynamic size distribution of the aggregates were derived by fitting intensity autocorrelation functions using the CONTIN algorithm. All the experiments performed in this study were repeated in triplicate.

Small Angle Neutron Scattering (SANS) Measurements on the Polymer-Surfactant-Drug Solutions

The SANS measurements were performed on the LOQ (32) at the ISIS facility of the Rutherford Appleton Laboratory (Oxfordshire, UK). Through all the measurements, a well-collimated incident neutron beam transmitted through the sample into the detector. The neutron beam was polychromatic, containing a range of neutron wavelengths from 0.5 to 6.5 Å. As ISIS is a pulsed source, the wavelengths of the transmitted neutrons are measured by their time-of-flight

(TOF) from the source to the detector. The magnitude of the scattering vector, Q ($Å^{-1}$), is calculated as described in Eq. (1).

$$Q \frac{4\pi}{\lambda} \sin 2\theta \quad (1)$$

The scattering intensity as a function of time-of-arrival were normalised for the sample transmission and converted to intensity *versus* Q using a standard data reduction routine (Colette) provided by the ISIS laboratory. Before the sample measurement, the instrument was calibrated with a copolymer standard to allow the data to be plotted on an absolute intensity scale. Backgrounds consisting of scattering from D_2O or 50% D_2O/50% H_2O were subtracted from the sample scattering. Data was taken for solutions of polymer (0.0125% *w/v*), model drug molecule (0.042% *w/v*) and surfactant (3.4 mM) using *d*-SDS in 50% D_2O/50% H_2O (partially deuterated water was used to reduce background), and *h*-SDS or Tween in D_2O. Data was fitted using models provided by the NIST Centre for Neutron Research, implemented in Igor Pro (Wavemetrics) (33).

RESULTS

Effect of Surfactant on Dissolution/Precipitation of Spray-Dried Solid Dispersions

The residues of the formulations dispersed in media with no surfactant were tested after certain time periods using ATR-FTIR spectroscopy. As seen in Fig. 2a, the residues of the spray dried TH 1:0.5 formulation show no significant changes in the IR spectra after exposure to media with no surfactant. No clear crystalline drug peaks were observed in the IR spectra of the residues. The drug/polymer peak ratios as well as the peak intensities also show no significant changes over the 3 h exposure period. This implies that no drug or polymer dissolution nor drug recrystallisation occurred over the 3 h testing period in the media. Similar behaviour was also found with TH 1:1 and TH 1:3 formulations. The reason behind this behaviour is not entirely clear. However, it is likely that the highly hydrophobic drug can lead to increased hydrophobicity of the surfaces of the spray dried Etravirine-HPMC particles hindering the dissolution of the water soluble polymer. The high interfacial tension of the spray-dried particles in the media can dramatically reduce the wettability therefore preventing the dissolution of the formulation. HPMC-Etravirine interactions may also contribute to the low level dissolution of HPMC into the media.

The spray-dried TH 1:3 formulation instantly dissolved and formed a clear solution in water/0.1MHCl containing 1% *w/v* SDS (equivalent to 34 mM) or bio-relevant surfactant (bile salts). No precipitation was observed after 4 h suggesting a good ability to solubilise the drug or potentially stabilise a supersaturated drug solution.

The residues of the formulations in the media containing Tween 20 with a concentration of 16 mM show different results. The concentration of 16 mM was chosen because that it is well above the CMC of Tween 20 (the CMC of Tween 20 is below 0.1 mM), and recreates the concentration of Tween in solution after the complete dissolution of the granulo-layered formulations (the formulations containing Tween 20). As seen in Fig. 2b, the formulation with the highest drug loading (TH 1:0.5) as well as the formulation with the lowest drug loading (TH 1:3) show a clear reduction in the peak intensity of the polymer associated peak (broad peak at 1113 cm^{-1}) indicating the loss of polymer from the spray dried microparticles. The obvious increases in the crystalline drug peaks intensities (within the finger print region) indicate the drug recrystallization in the residues. Thus the presence of Tween 20 promotes the escape of HPMC from the spray dried solid dispersions that seems to outweigh its contribution to drug solubilisation. One possible explanation is that the dissolution of HPMC could be accelerated by the presence of Tween 20 which reduces the interfacial tension between the spray dried particles and the release media. As HPMC is hydrophilic, it can be rapidly removed from the solid dispersion into the media by dissolution with much faster kinetics than the drug solubilisation by Tween 20. In comparison to SDS/bile salt, the solubilisation capacity of a non-ionic surfactant alone is often weaker than a ionic type surfactant. This could lead to the ratio of Etravirine to HPMC being higher than the solid solubility of the drug in polymer. The supersaturation of drug in the dispersion eventually causes drug crystallisation.

Similar results were also observed in the granulo-layered material (with drug to polymer ratio of 1:3), containing Tween 20. As seen in Fig. 2c, over the 3 h test period, the intensity of the polymer associated peak gradually reduced with time; whereas the crystalline drug peak intensities increase. This further confirms that the presence of Tween 20 facilitates the fast dissolution of HPMC, but has no significant solubilisation effect on the drug. The dissolution of polymer from the solid dispersions resulted the recrystallisation of Etravirine during immersion. Further investigation on the mechanism of the interaction between Tween and HPMC will be discussed elsewhere. As the presence of SDS showed a clear solubilisation effect on the formulations, the key focus of the following section in this paper is to facilitate a better understanding of the underlying mechanism behind the effect of anionic surfactants (SDS and bile salts) on the drug solubilisation of HPMC E5 based solid dispersions.

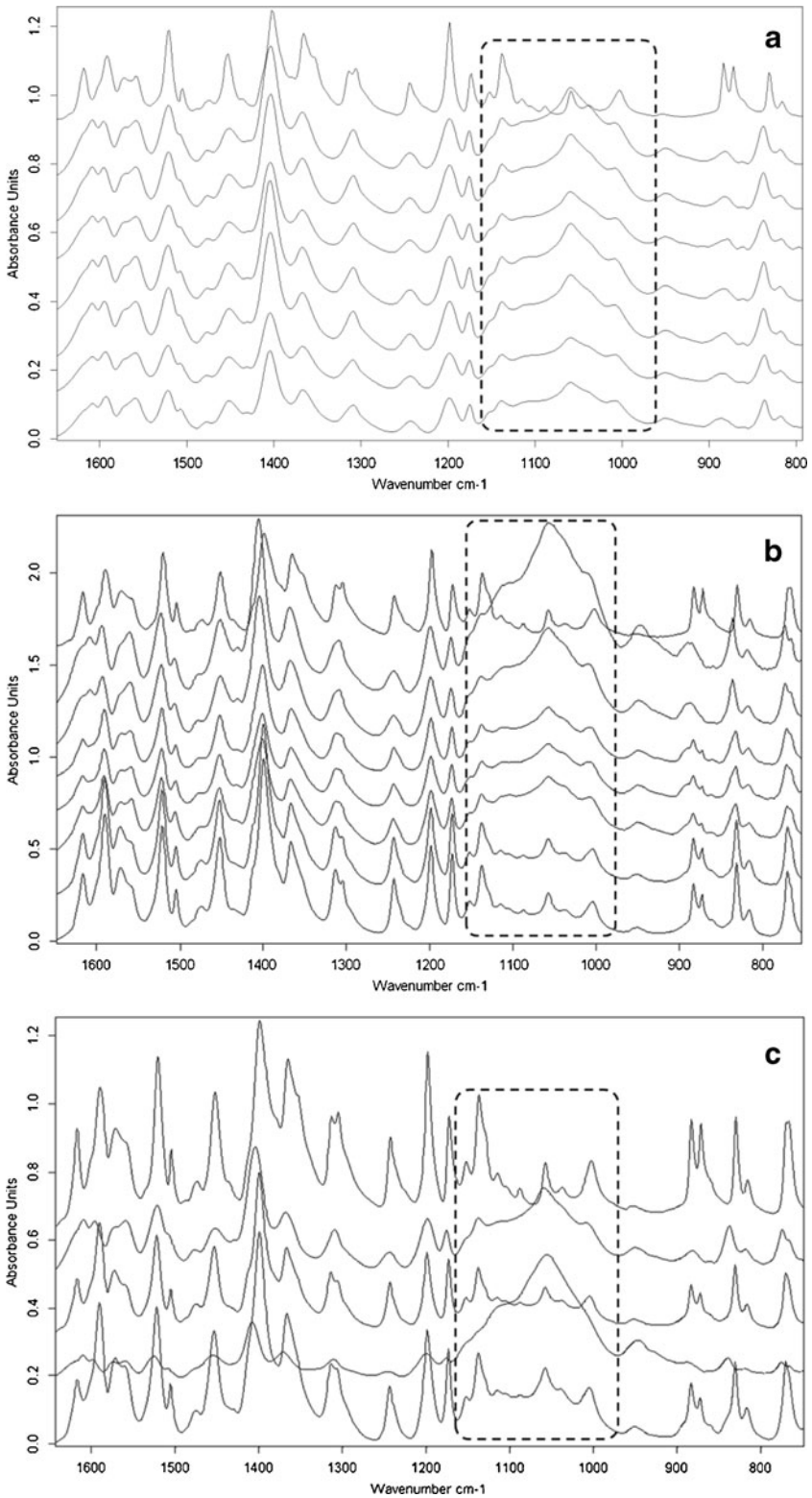

Fig. 2 FT-IR spectra (from top to bottom) of (**a**) the crystalline Etravirine prior to exposure, TH 1:0.5 before exposure, TH 1:0.5 after exposure to 0.1 M HCl for 5 min, 10 min, 30 min, 1 h, 2 h, 3 h followed by drying; (**b**) the crystalline Etravirine prior to exposure, TH 1:0.5 before and after exposure to 0.1 M HCl containing Tween20 for 3 h, and TH 1:3 before and after exposure to 0.1 M HCl containing Tween20 for 3 h followed by drying; (**c**) the crystalline Etravirine prior to exposure, layered granules containing Tween20 before exposure, after exposure to 0.1NHCl for 5 min, 10 min, 30 min, 1 h, 2 h, and 3 h followed by drying.

Drug Solubilisation in the Presence of Polymer and Surfactants

In order to further establish that the co-presence of HPMC and anionic surfactant is essential for the enhanced solubilisation effect, the static state equilibrium solubility of the drug in the solution containing HPMC and SDS/bile salts were tested. Table I shows the maximum apparent solubility results of Etravirine in bile salts and SDS aqueous solutions. The apparent solubilities of Etravirine increased in both anionic

Table I Apparent Solubility of Etravirine in Different Media Containing Either 1% *w/v* SDS (34 mM) or 1% *w/v* Bile Salts (24 mM)

Solution systems	Maximum Drug Solubility (mg/ml)
Etravirine	<0.01
Etravirine + HPMC	<0.01
SDS + Etravirine	0.175
SDS + Etravirine/HPMC 1:0.5*	0.245
SDS + Etravirine/HPMC 1:1*	0.251
SDS + Etravirine/HPMC 1:3*	0.275
Bile Salts + Etravirine	0.136
Bile Salts + Etravirine/HPMC 1:0.5*	0.275
Bile Salts + Etravirine/HPMC 1:1*	0.310
Bile Salts + Etravirine/HPMC 1:3*	0.325

*Spray dried Etravirine-HPMC E5 solid dispersions

surfactants solutions after being formulated into spray dried amorphous dispersion with HPMC. Slight increases in the apparent solubility of Etravirine were observed with decreasing the ratio of drug to HPMC. No improved solubilisation effect was found for the systems with the non-ionic surfactant, Tween 20 (16 mM). The maximum apparent solubility of Etravirine is higher in bile salts than in SDS. For both surfactants the apparent solubilities of the drug are much higher in the HPMC-surfactant solutions than the surfactant solution alone. This again indicates that the presence of both of HPMC E5 and the anionic surfactants is essential for the fast dissolution and stable supersaturated Etravirine solution after dissolution.

Mechanistic Study 1: Effect of Polymer and Drug on Surfactant Aggregation Behaviour

Many studies have demonstrated that the addition of a hydrophilic polymer to the media can have significant impact on the critical micellar concentration (CMC) of an ionic surfactant *via* the adsorption of surfactant molecules onto the hydrophobic segments of the polymer chain (15–26). The concentration at which the surfactant molecules start to interact with the hydrophobic regions of the polymer chain is known as critical aggregation concentration (CAC). The thermodynamic driving force for the adsorption of surfactant molecules onto the hydrophobic segments of the polymer and forming micelles-like structures with a lower aggregation number is more energetically favourable than the formation of free surfactant micelles in water with a higher aggregation number. Therefore a decrease of the original CMC of the surfactant with the presence of the polymer to a lower value, the CAC, is often observed (15–26).

The CMCs of the bile salts and the model anionic surfactant, SDS, were measured using Wihelmy plate surface tension and confirmed by fluorescence spectroscopy (involving the use of pyrene as the fluorescent probe) and pendand drop (see Supplementary Material) methods in water. In the literature, the surfactant tension of polymer-surfactant system has been preferably measured using pendant drop method. This is mainly because that pendant drop measurements are less disruptive during the long equilibrium period of the surface tension of the solutions (20,21). However, it has also been confirmed that the kinetics of equilibrium is highly polymer concentration dependent (20,21). At polymer concentrations above 0.001% (*w/w*), the surface tension equilibrium of the solutions containing different grades of cellulose derivatives and SDS can be reached within the time timeframe of 10–15 min (20,21). This suggests that at high polymer concentration the surface tension measured by pendant drop method should be similar to the results obtained from classic Wihelmy plate method. As all polymer concentrations used in this study were significantly higher than 0.001% (*w/w*), the Wihelmy plate method was used to test the effect of HPMC E5 on the micellisation behaviour of the surfactants.

As seen in Figure 3a, the CMC value for bile salts alone was measured at 5.9 mM. When HPMC was added at concentrations between 0.0125 and 0.05% (*w/v*) the CAC value is reduced to approximately 1.3 mM. The CAC was also reduced to approximately 1.2 mM on addition of Etravirine. Similar results were found in the case of SDS, as seen in Fig. 3b. The CMC value of SDS alone was found to be 7.6 mM which is in agreement with literature values (15–26). HPMC alone reduced the CAC of SDS to 3.4 mM. The addition of Etravirine reduces the CAC of SDS (with and without HPMC E5) to 3.4 mM. The mechanism of how Etravirine reduces the CAC of the surfactants is not yet clear. We speculate that the Etravirine may act as nuclei for the formation of surfactant aggregates as it is highly hydrophobic. In turn the surfactant aggregates solubilise the drug. From these data it can be concluded that HPMC and Etravirine had a greater effect on the aggregation behaviour of bile salts than that of SDS. This is likely to be associated with the multi-component nature and unique micellisation behaviour reported in the literature (13,14). As a result of the complex bile salts behaviour, this study focuses on understanding the basic interactive principle between HPMC E5 and anionic surfactants using SDS as the model in water in the first instance in order to gain insights into the nature of the interaction and any practical impacts.

In order to confirm the effect of HPMC on the aggregation behaviour of SDS and further probe the nano-structure of the complexes, the CMC of SDS was measured using pyrene as a fluorescent probe in water with and without HPMC (0.033% *w/v* which is equivalent to a finishing tablet of TH 1:3 formulation of the spray dried microspheres

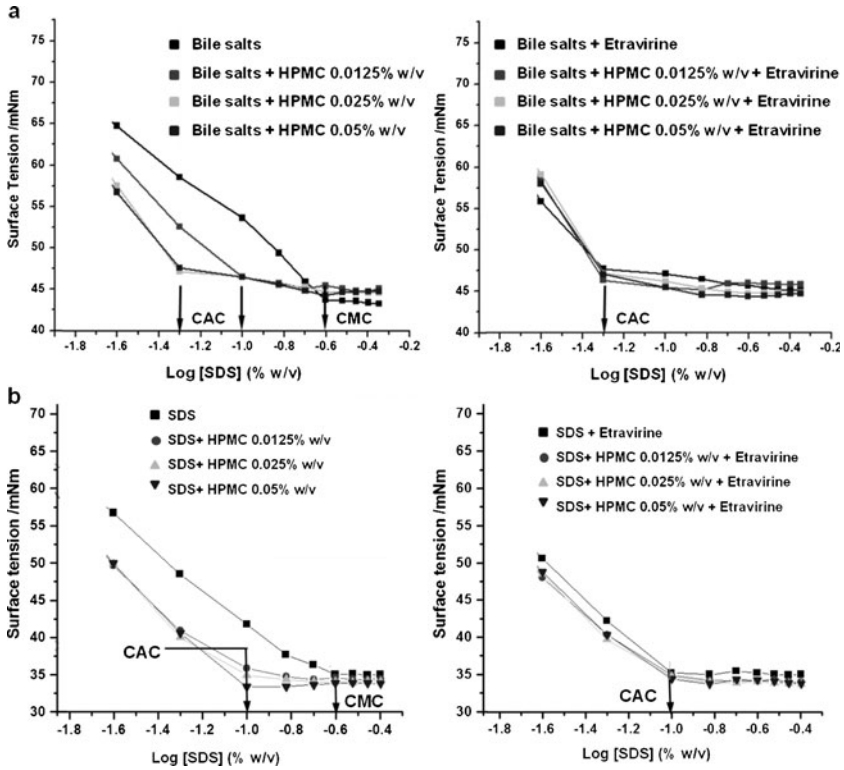

Fig. 3 The effect of HPMC E5 and Etravirine (0.136 mg/ml) in water at 25°C on the aggregation behaviour of (**a**) bile salts and (**b**) SDS studied using surface tension measurements.

completely dissolved in 900 ml dissolution media) by fluorescence spectroscopy. The tendency towards the formation of the excimers of pyrene is a measure of the viscosity of the microenvironment of the probe molecule during the formation of the micelles. Since pyrene is extremely poorly water-soluble it partitions into micelles or other hydrophobic regions present in the solution. The formation of excimers requires at least two pyrene monomers to be present in a surfactant micelle during the excited state lifetime. The CMC and CAC values with the presence of HPMC measured using pyrene florescence show that the CMC is reduced from 7.7 mM to 3.6 mM as seen in Fig. 4. This is in good agreement with the values obtained by the surface tension measurements. There is no excimer formation for the tested SDS concentrations in the presence of HPMC. This may be due to the reduced aggregation number, therefore increased overall number of SDS aggregates in the presence of polymer (19). This indicates that the number of SDS micelles is greater than the dissolved pyrene molecules leading to no formation of excimer. The formation of surfactant aggregates/micelles can facilitate the solubilisation of poorly water-soluble compounds. No significant excimer formation occurred in the SDS/HPMC solutions (Fig. 4 inserted graph) indicating high solubilisation capacity of the SDS/HPMC solution. This also may explain that the addition of SDS in the dissolution media triggers dissolution of Etravirine from the formulations (30). In order to further probe the solubilisation mechanism of SDS with the presence of HPMC, the HPMC-SDS interactions were characterised by dynamic light scattering (DLS) and small angle neutron scattering (SANS).

Mechanistic Study 2: Evidence of Formation of Polymer-Surfactant Complexes

The surface tension and pyrene florescence spectroscopic methods both confirmed that the CMC of SDS (in water) is

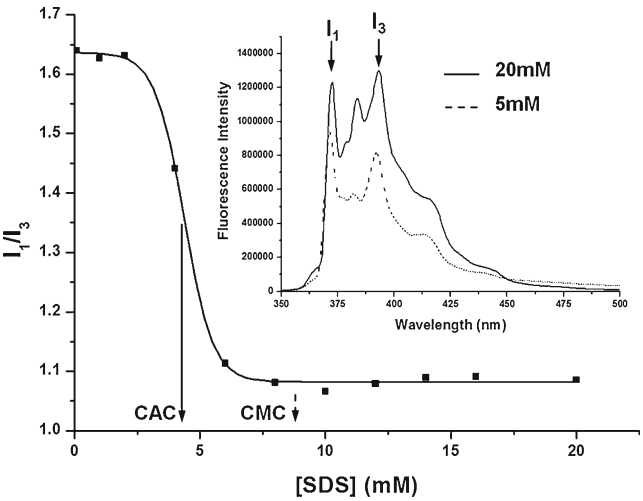

Fig. 4 The effect of HPMC E5 on the aggregation behaviour of SDS in water measured using pyrene fluorescence at 25°C. (The CMC of SDS without the presence of HPMC is indicated on the graph, and the inserted graph of the fluorescence emission spectra of HPMC solution containing 0.5 mM (below CMC) and 20 mM (above CMC) of SDS in water).

decreased from 8 mM to a CAC of 3.4–3.6 mM with the addition of HPMC. In order to obtain more direct evidence of the presence of polymer-surfactant aggregates/complexes, DLS measurements were performed. The DLS results of the HPMC E5 alone in water (with concentrations from 0.0125 to 0.05% *w/v*) indicated that at a concentration of 0.0125% (*w/v*), polymer aggregation already occurs. The hydrodynamic particle sizes of the HPMC E5 aggregates with concentration of 0.025% *w/v* show bimodal distribution (approximately 18 nm and 260 nm) in water, as seen in Fig 5a. The DLS results of the SDS (34 mM) micelles alone in water indicate a micelle size of around 1.2 nm (data not shown). From the surface tension measurement, it is known that the CAC of SDS can be reduced to 3.4 mM with the addition of HPMC E5. As seen in Fig. 5a, with the presence of HPMC E5 at SDS concentration of 3.4 mM, a bimodal distribution occurs with two populations of colloidal particles with hydrodynamic sizes of 15 and 230 nm. With increasing the SDS concentration to 34 mM, no significant change in the size of the two populations is observed (Table II). These values are slightly smaller than the ones in the polymer solutions without SDS. The SDS clustering on the HPMC chains (the formation of complexes) leading to the shrinkage of HPMC coil may be responsible to the slight reduction on the sizes (19). The dissolution of the spray dried Etravirine-HPMC formulations leads to a significant increase in the hydrodynamic sizes of the complexes. The TH 1:3 formulations containing highest proportion of HPMC E5 and lowest concentration of drug showed rapid and complete dissolution in the SDS solutions. As seen in Fig. 5a, all formulations show dramatic increase in the size of the complexes. The significant increases in complexes hydrodynamic sizes can be contributed to the drug encapsulation/solubilisation which leads to the swelling of the complexes. The TH 1:3 formulations gives the largest size of the aggregates in comparison to TH 1:1 and TH 1:0.5. This trend correlates well with the results of the drug solubilisation study (Table I). This indicates that the drug encapsulation/solubilisation capacities of the HPMC-SDS complexes are concentration dependent.

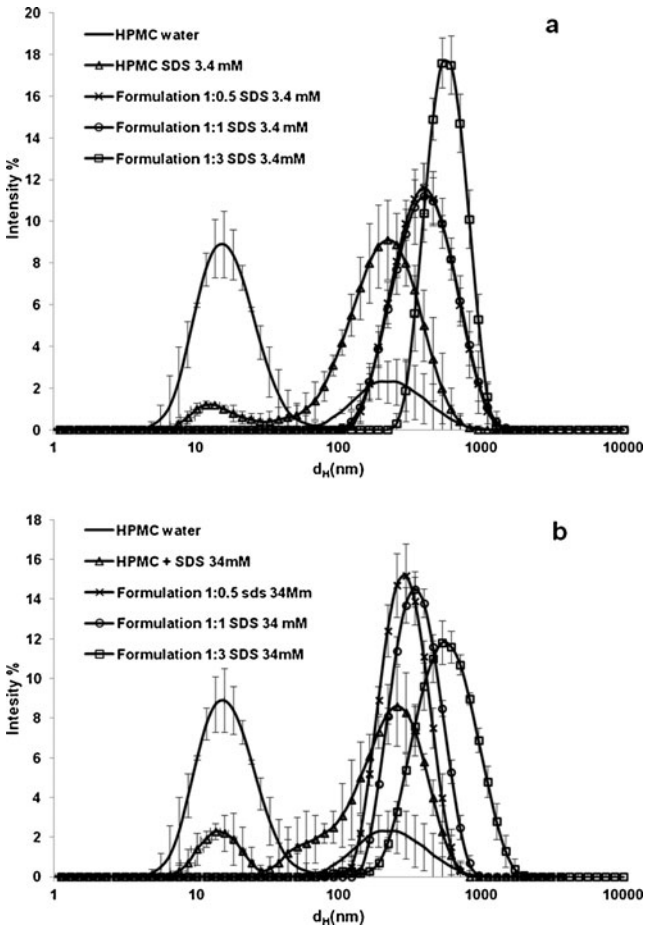

Fig. 5 DLS profiles of SDS solutions containing dissolved spray dried HPMC-Etravirine formulations with drug:polymer ratios from 1:3 to 1:0.5; (**a**) the solutions with SDS concentration of 3.4 mM; and (**b**) the solutions with SDS concentration of 34 mM.

In order to further confirm the structure of the polymer-anionic surfactant complexes and their solubilisation mechanism, the polymer-surfactant with and without model drug were studied using SANS. The *h*-SDS/100% D_2O and *d*-SDS 50% D_2O solutions were examined. Without HPMC, at SDS concentrations 3 mM (below the CMC), no scattering was detected implying that no micelles are present in solution. The SANS results of the solution with high SDS concentration (70 mM) in water (well above the CMC) showed good fit to a slightly ellipsoid shape with a structure factor indicating the presence of micelle-micelle interaction, as seen in Fig. 6a. The fitted charge data suggested that the aggregation number of each SDS micelle is approximately 60 with 30% of SDS molecules being charged. This data is in good agreement with the reported aggregation number of SDS in water (34).

With the addition of HPMC (*h*-SDS/HPMC in D_2O), the scattering intensity slightly increased for the high SDS concentration solution (70 mM). However, at this high concentration the polymer chains have been saturated with SDS micelles resulting in a large number of free SDS micelles in the solution. Therefore, the scattering is dominated by the intensity contributed from the free SDS micelles, and little information on the polymer-SDS complexes can be obtained. Reducing the SDS concentration to 3 mM, which is below the CMC of SDS but close to the CAC of SDS in the presence of HPMC, can help to enhance the scattering of the HPMC-SDS complexes. The SANS results of the sample with 3 mM *h*-SDS/HPMC in D_2O show an increase in the scattering intensity. However, the scattering density is still proportionally lower than 1/20th of the density of the 70 mM *h*-SDS/HPMC samples in D_2O, indicating that the SDS aggregates (may not be perfect micelles as the concentration is slightly below the CAC in

Table II Summary of the Hydrodynamic Size Changes of the Aggregated with the Addition of Etravirine

Sample	Hydrodynamic size(diameter) nm	
HPMC in water	Population 1: 18 ± 0.96	Population 2: 260 ± 0.83
HPMC + SDS 3.4 Mm	Population 1: 15 ± 0.23	Population 2: 230 ± 1.4
Etravirine/HPMC 1:0.5* + SDS 3.4 mM	438 ± 6.8	
Etravirine/HPMC 1:1* + SDS 3.4 mM	445 ± 1.2	
Etravirine/HPMC 1:3* + SDS 3.4 mM	594 ± 9.6	
HPMC + SDS 34 mM	Population 1: 15 ± 0.8	Population 2: 239 ± 1.3
Etravirine/HPMC 1:0.5* + SDS 34 mM	308 ± 1.2	
Etravirine/HPMC 1:1* + SDS 34 mM	370 ± 0.6	
Etravirine/HPMC 1:3* + SDS 34 mM	612 ± 0.8	

*Spray dried Etravirine-HPMC E5 solid dispersions

the presence of HPMC) are likely to be penetrated by the HPMC polymer chains. The data fitting suggested a more ellipsoid shape of the micelles than the SDS micelles without the presence of HPMC.

The scattering intensity of the SDS/HPMC/Etravirine solution with high SDS concentration (70 mM) is very similar to the pure SDS and HPMC-SDS results. This can be explained by the high concentration of SDS micelles in the solution, which dominate the scattering pattern. At low SDS concentration (3 mM), the scattering of the solution containing HPMC and Etravirine changed dramatically in comparison to the solution without the drug. The contrast for the *h*-SDS has reduced from 5.7×10^{-6} to 0.6×10^{-6} and the size/shape of the micelles changed from largely spherical to long and thin ellipsoid by the addition of the drug as suggested in Fig. 6b. This can be an indication of the encapsulation of the highly hydrophobic drug molecules in the SDS aggregates particularly in the near head-group region. As the data suggested that the head-groups are increased relative to the tail groups in volume, which may partially contribute to the conversion of spherical micelles into cylinder-shaped aggregates. The comparison of the nano-structures of polymer-surfactant complex before and after drug addition indicates the main mechanism being drug encapsulation into the surfactant aggregates which are adsorbed on the hydrophobic patches of the polymer chain.

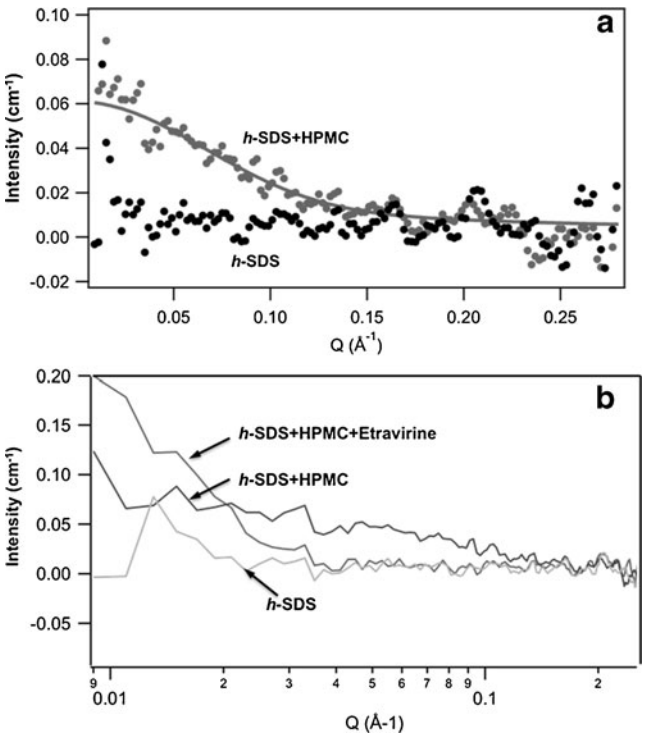

Fig. 6 SANS patterns of (**a**) *h*-SDS (3.4 mM)/HPMC (0.0125% *w/v*) solutions in 100% D_2O. The smooth line is a fit to the data using a model of charged ellipsoids; (**b**) *h*-SDS (3.4 mM)/HPMC (0.0125% *w/v*)/Etravirine (0.0042% *w/v*) solutions in 100% D_2O showing the increase in scattered intensity due to the formation of aggregates as HPMC E5 and HPMC/drug are added to the SDS solution.

DISCUSSION

This study has investigated the behaviour of HPMC E5 in solution in the presence of anionic (bile salts and SDS) and compared with the behaviour in media containing non-ionic (Tween 20) surfactants. The dissolution/precipitation tests of the spray dried solid dispersions were performed in the presence of both non-ionic (non-interacting model) and anionic (complex formation model) surfactants. With anionic surfactants fast dissolution and stable supersaturated drug solutions were obtained (in which drug crystallisation can be prevented for a reasonable period of time during which the drug absorption can take place). Studies on the interaction of polymer and surfactants were carried out in order to reveal the underlying mechanisms of these experimental observations. The presence of Tween 20 in the media induces rapid removal of HPMC from the solid dispersion and leads to drug recrystallisation in solution. Without any surfactant in the media, although no dissolution occurred, the molecular dispersion of HPMC-Etravirine surprisingly showed high integrity in solution without obvious drug recrystallisation or polymer escaping/dissolution from the

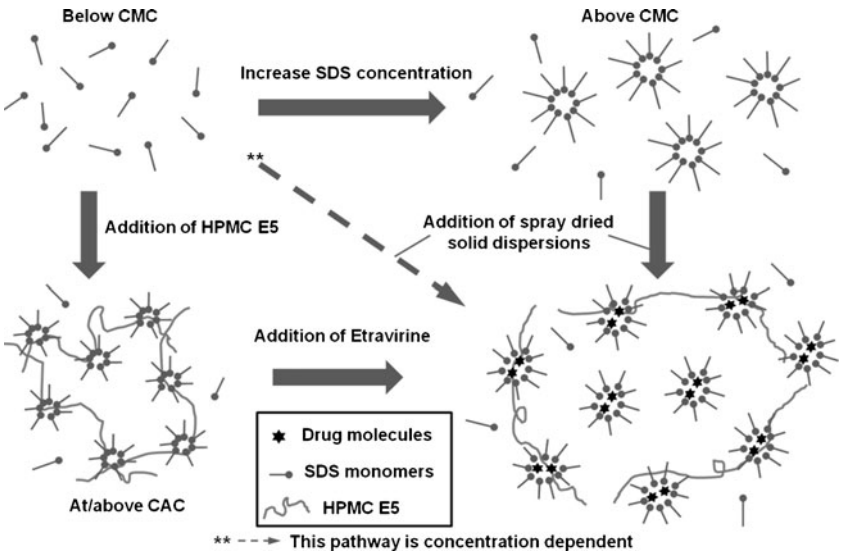

Fig. 7 Illustration of the possible solublidation/stabilisation mechanisms of poorly water-soluble drugs *via* polymer-surfactant interactions.

formulations. The dissolution/precipitation results provide strong experimental evidence of the role anionic surfactants, such as bile salts in human gut, may play during the dissolution of solid dispersions of hydrophilic non-ionic polymers, such as HPMC. These results are experimental evidence for the hypothesis of polymer-surfactant interaction and correlate well with mechanisitic studies such that the polymer-surfactant complexes act as a solubilisation carrier for the drug during dissolution from the solid dispersions.

The nature of the interaction was investigated using surface tension measurements, fluorescence spectroscopy, DLS, and SANS. The investigation of the mechanism of interaction and solubilisation contains three main stages, the indication of interactions (effects on micellisation behaviour), understanding the interaction between HPMC E5 and SDS alone, and the structural understanding of HPMC-SDS-Etravirine complexes. The anionic surfactants, bile salts and SDS, both demonstrated a strong binding affinity towards the polymer chain in solution as evidenced by the significant changes of CMC to lower CAC values. This is associated with the fact that thermodynamically, adsorption of surfactant molecules onto polymer chains is more energetically favourable than forming free micelles at higher concentration (15–21). Bile salts showed stronger responses to the addition of HPMC and Etravirine than SDS. The DLS and SANS results support the 'pearl necklace' model of the polymer-surfactant complex structure. The hydrodynamic particle size of the polymer aggregates showed slight decrease with the presence of SDS at and above the CAC due to the shrinkage of the polymer coil after the adsorption of SDS clusters. The hydrodynamic sizes of the polymer-surfactant complexes only significantly increase once the complexes solubilize the drug. The SANS data confirmed the model and suggested the shallow penetration of the polymer chain into the surfactant micelles. The SANS data also suggested that the encapsulation of the drug molecules in the SDS clusters (at low surfactant concentration) or SDS micelles (at high surfactant concentration) adsorbed onto the HPMC chain (forming the polymer-surfactant complexes) leads to the evolution of spherical shaped micelles to a more cylinder shape. These experimental data supported the hypothesis of the formation of HPMC-anionic surfactant complexes which may play an important role in drug solubilisation and stabilisation (from drug recrystallisation under supersaturated conditions) during dissolution. In the gut environment, the presence of bile salts, in particular in the small intestine region where there is a high concentration of bile salts, the HPMC-bile salts complexes could be one a key mechanisms involved in the dissolution and subsequent absorption of poorly water-soluble drugs *via* solubilisation of drug molecules in the complexes as illustrated in Figure 7. Investigations on the effect of media properties (i.e. pH, ionic strength) and polymer structure/properties on the polymer-bile salts interactions are ongoing in order to gain better understanding of the behaviour of other pharmaceutical polymers in the gut fluid.

CONCLUSION

This study has reported for the first time the potentially vital role that polymer-surfactant complexes may play in facilitating fast dissolution of poorly water-soluble drugs and prevention of drug precipitation. This study focused on the interaction between a nonionic hydrophilic polymer (HPMC E5) and surfactants including anionic (bile salts and SDS) and a non-ionic surfactant (Tween 20). The results indicated that the formation of polymer-anionic surfactant complexes had a high encapsulation capacity for a

poorly water-soluble model drug; whereas the non-ionic surfactant promoted polymer dissolution and rapid drug recrystallization during dissolution. This is an important finding, suggesting that for solid dispersions containing HPMC the use of non-ionic surfactant such as Tween should be avoided to prevent any drug recrystallization during dissolution. The results suggested that the formation of nonionic polymer-anionic surfactant complexes *via* the adsorption of surfactant clusters on the polymer chain contributes significantly to the solubilisation and stabilisation of supersaturated solution of poorly water-soluble drug.

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