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Impact of sodium dodecyl sulphate on the dissolution of poorly soluble drug into biorelevant medium from drug-surfactant discs

Peter Madelung[a], Jesper Østergaard[a], Poul Bertelsen[b], Erik V. Jørgensen[b], Jette Jacobsen[a], Anette Müllertz[a,*]

[a] Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, Copenhagen, Denmark
[b] Takeda Pharma A/S, Langebjerg 1, Roskilde, Denmark

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ABSTRACT

The purpose was to elucidate the mechanism of action of sodium dodecyl sulphate (SDS) on drug dissolution from discs under physiologically relevant conditions. The effect of incorporating SDS (4–30%, w/w) and drug into discs on the dissolution constant and solubility were evaluated for the poorly soluble drugs griseofulvin and felodipine in a biorelevant dissolution medium (BDM). Dissolution constants from dissolution profiles of drug discs with and without SDS were measured using miniaturized rotating disc dissolution. Solid state changes were investigated by X-ray diffraction. Solubility was determined using HPLC-UV. The interaction between micelles in BDM and SDS was investigated by isothermal titration calorimetry and dynamic light scattering. Isothermal titration calorimetry showed that SDS formed mixed micelles with bile salt:phospholipid (BS:PC) micelles in BDM. Dynamic light scattering showed that the addition of SDS made the BS:PC micelles grow up to 2.5 times in volume. As a function of SDS addition, the dissolution constant showed an apparent exponential increase, while drug solubility showed a weak linear dependence. The pronounced effect on dissolution constant with SDS in the discs is not caused by an increased surface area as SDS dissolves, micelles in the bulk medium or changes in the solid state properties of the drugs. The proposed mechanism involves a high local concentration of SDS at the solid–liquid interface as SDS dissolves and this solubilizes the drug. The improved solubility at the solid–liquid interface provided a much steeper concentration gradient resulted in a faster dissolution. The total amount of SDS in the discs only gave a minor increase in total surfactant concentration in the dissolution medium and did therefore not to any large extent affect the drug solubility in the bulk.

1. Introduction

Poorly soluble drug (BCS class II) (Amidon et al., 1995) commonly have low and variable bioavailability (Schwebel et al., 2011), and for this reason strategies to improved dissolution rate or solubility of these drugs are of interest both in academia and industry.

Surfactants are widely used in tablets to improve the wetting and solubilization and thereby the bioavailability of poorly soluble drugs. The addition of surfactant to tablets appears largely to improve the dissolution rate since the amount of surfactant in a tablet is rarely sufficient to solubilize the dose entirely and once the tablet has disintegrated, the solubility of the drug within the intestinal fluid is increased to a minor degree only (de Waard et al., 2008; Heng et al., 1990; Ruddy et al., 1999; Schott et al., 1982). The surfactants SDS, Polysorbate 80 and Triton X-100 were used in range of 0.2 and 20% (w/w) (de Waard et al., 2008; Heng et al., 1990; Ruddy et al., 1999; Schott et al., 1982). The mechanisms behind the improved bioavailability obtained when surfactants are added to tablets, have been reported to be caused by the ability of the surfactants to induce faster disintegration and produce a finer dispersion of drug particles after disintegration of the tablet, which again will result in higher dissolution rates (Heng et al., 1990; Schott et al., 1982). The disintegration and dissolution in these studies were investigated using pharmacopoeial dissolution apparatus with either basket (Heng et al., 1990; Schott et al., 1982) or paddle stirring (de Waard et al., 2008). Relating the hydrodynamics of the USP I or II to the *in vivo* situation requires the use of the non-dimensional Reynolds number from fluid mechanics. The Reynolds

Abbreviations: BDM, biorelevant dissolution medium; BS, bile salt; CMC, critical micelle concentration; DLS, dynamic light scattering; FLP, felodipine; GRF, griseofulvin; IDR, intrinsic dissolution rate; ITC, isothermal titration calorimetry; PC, phosphatidyl choline; SDS, sodium dodecyl sulphate; XRD, X-ray diffraction.

* Corresponding author. Tel.: +45 353 36440; fax: +45 353 06031.
E-mail address: anette.mullertz@sund.ku.dk (A. Müllertz).

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number is the ratio of fluid inertia to viscous force around an object, in this case a tablet. The Reynolds number for the bulk flow in the USP I or II is much higher than what is estimated to occur *in vivo* and the Reynolds number at the interface between the tablet and the bulk medium is estimated to be even smaller than that of the bulk (Diebold, 2005). Disintegration is an intricate part of the currently suggested mechanism for increased bioavailability (de Waard et al., 2008; Heng et al., 1990; Schott et al., 1982), therefore it is important to be able to separate the effects of disintegration and dissolution from tablets, in order to understand the effects of surfactants in tablets.

The purpose of the present study was to elucidate the mechanism of action of surfactants added to drug discs under physiologically relevant conditions where the discs did not disintegrate. The effect of incorporating sodium dodecyl sulphate (SDS) into discs containing the poorly soluble drugs griseofulvin (GRF) and felodipine (FLP) were evaluated on the dissolution rate and solubility, under conditions where the discs did not disintegrate. GRF and FLP were selected as model drugs due to their similar molecular weights (352 and 384 g/mol, respectively) and different lipophilicities, since their solubility in medium chain triglycerides is 0.095% (w/w) (Kaukonen et al., 2004) and 3.1% (w/w) (von Corswant et al., 1998) for GRF and FLP, respectively. The discs in this study serve as miniaturized tablet analogues, enabling *in vitro* studies assumed to reflect the *in vivo* fasted state. The dissolution rate constant and solubility serve as a means to assess the effect of SDS incorporation in tablets, on the amount of these poorly soluble drugs available for absorption.

2. Materials and methods

NaH_2PO_4, SDS (≥98.5%) and Griseofulvin from *Penicillium griseofulvum* (97.0–102.0%) were purchased from Sigma–Aldrich (Copenhagen, Denmark). FLP was a gift from AstraZeneca in Sweden and phosphatidyl choline (PC) was purchased from Lipoid AG (Ludwigshafen, Germany). NaCl and NaOH were purchased from Merck (Darmstadt, Germany). Crude sodium taurocholate, from ox bile was used as bile salt (BS) (Sigma ID: T0750). The BS contains 90% conjugated cholic acids. The BS content was determined using a total bile acid assay from Diazyme Laboratories (Poway, CA, USA). Sodium taurocholate with a high purity, ≥95%, (Sigma ID: T4009) was used comparatively in dynamic light scattering (DLS).

2.1. Dissolution medium

The biorelevant dissolution medium (BDM) simulating the fasted state intestinal fluid consisted of 35 mM phosphate buffer (pH 6.5 and adjusted to an ionic strength of 154 mM with NaCl), 1.25 mM PC and 5 mM BS.

2.2. The effect of adding SDS on the micelles in BDM

Demicellization of SDS in buffer and in BDM was measured by isothermal titration calorimetry (ITC) on a VP-ITC (Microcal Inc., Piscataway, US), according to (Beyer et al., 2006; Taheri-Kafrani and Bordbar, 2009). The heating rate, required to maintain a constant temperature difference between the sample cell and a reference cell filled with deionized water, was measured and integration of the heat rate provides the total energy output of the injection. The particle size distribution of the micelles in BDM with the addition of SDS and concentration dependence of SDS on micellar size was determined by DLS. Using a Zetasizer nano ZS Model ZEN 3600 (Malvern Instruments Ltd., UK) equipped with a 532 nm laser and using a MPT-2 autotitrator (Malvern Instruments Ltd., UK). Samples were measured using default back scattering settings measuring at 173°, 5.55 mm from the cell wall, no laser attenuation and 10 min equilibration time for the sample cell to stabilize at 37 °C. The obtained data was processed using the Zetasizer Software, version 6.20 (Malvern Instruments Ltd., UK). By an autocorrelation function the software correlates the intensity fluctuations caused by scattered light from moving particles and transforms these fluctuations to diffusion coefficients and a particle size of the equivalent sphere using the Stokes-Einstein's equation. The mean particle size of the particles in BDM was calculated as a number distribution.

2.3. Solubility

The solubility of GRF and FLP in BDM with up to 1 mM SDS was determined by dispersing more than 1 mg/ml of drug for 21 h at 37 °C using end-over-end rotation. Samples ($n \geq 5$) were centrifuged for 15 min at 13,000 rpm and 37 °C. The supernatant was diluted 1:1 with acetonitrile (ACN) and centrifuged again. Standards were prepared by the same procedure. The amounts of drug dissolved were determined by HPLC.

2.4. Quantitative analysis

Samples for powder uniformity and drug solubility in BDM were analyzed on a Dionex Ultimate 3000 HPLC system. A Phenomenex Luna C18 column (125 μm × 4.00 μm × 5 μm), at 30 °C, a flow rate of 1.5 ml/min and a mobile phase of 70/30 ACN/water (v/v) were used. UV–vis detection was performed at 292 nm and 362 nm for GRF and FLP, respectively.

2.5. Disc characteristics before and after dissolution

In order to obtain similar particle sizes of the substances being mixed FLP, anhydrous lactose and SDS were ground in a mortar with a pestle for 10 min. GRF was already micronized and was used as received. Light microscopy of the ground powders showed particles sizes for GRF, FLP and SDS were less than 10 μm. Powder mixtures of 5–30% (w/w) SDS in GRF and 4–20% (w/w) SDS in FLP were produced by mixing drug and SDS, to give in total 0.5 g, in a mortar with a pestle for 2 min. Using the same approach, the powder mixtures of 30% (w/w) and 25% (w/w) lactose with GRF and FLP, respectively, were prepared. The uniformity of the powder mixtures with SDS were assessed by sampling 5 times from each mixture, dissolving each sample in ACN and quantifying the amount of GRF or FLP in the powder by using UV-HPLC. The composition of selected discs of FLP and SDS were analyzed after the dissolution experiments, by dissolving the remaining disc in ACN, measuring the FLP content and comparing it to the weight of the disc. Discs of powder mixtures were prepared using the mini-IDR compression system (Heath Scientific, Bletchley, UK). Approximately 10 mg of powder mixture were used and the discs of GRF and FLP with added SDS were compressed in the steel dies for 1 min at 30 and 25 bar, respectively. The prepared discs were examined under a light microscope before and after the dissolution experiments. X-ray diffraction (XRD) of the discs before and after dissolution were measured on a X'Pert PRO X-ray diffractometer (PANalytical, Almelo, The Netherlands; MPD PW3040/60 XRD; Cu KR anode; λ = 1.541 Å; 45 kV; 40 mA) using a custom made insert where the disc surface was levelled with the height of the aluminium plate ordinarily used for powder reflection measurements on this instrument. The intensity of the reflected x-rays was collected using X'Pert Data Collector software (PANalytical B.V.)

2.6. Dissolution

Dissolution profiles of discs in BDM were obtained using the μDISS Profiler (*p*ION Inc., Woburn, MA, USA), with Teflon disc stirrers and a fiber optic probe (1 cm path length). For each powder