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Dissolution enhancement of griseofulvin from griseofulvin-sodium dodecyl sulfate discs investigated by UV imaging

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ABSTRACT

The purpose of study was to investigate the dissolution rate enhancement obtained when sodium dodecyl sulfate (SDS) is co-compressed with griseofulvin into discs using a UV imaging-based flow-through dissolution testing setup. Griseofulvin dissolution rates obtained from discs containing 5.92 and 10.6% (w/w) SDS in phosphate buffer (pH 6.5) were similar to dissolution rates from pure griseofulvin discs when applying 20 and 100 mM SDS as dissolution medium, respectively. Dynamic light scattering of effluent samples revealed nanosized particles (approximately 135 nm in diameter) escaping the discs during dissolution. Scanning electron microscopy of co-compressed griseofulvin-SDS discs prior to dissolution testing showed surfaces apparently consisting of granules (100 and 200 nm in diameter) as well as particles present on the disc surfaces possibly related to the high initial dissolution rates. Material swelling or precipitation was observed for discs containing 10.6 or 15.8% (w/w) SDS. UV imaging revealed increased griseofulvin concentrations near the solid-liquid interface of griseofulvin-SDS discs, e.g., a 45-fold increase in concentration was observed for discs containing 10.6% (w/w) SDS as compared to discs without SDS, which is the likely cause of the enhanced dissolution rates found for the co-compressed griseofulvin-SDS discs.

1. Introduction

Surfactants, such as sodium dodecyl sulfate (SDS), are used in tablets to increase the bioavailability of poorly soluble drugs [1]. FDA's inactive ingredients database has 54 approved drug products containing SDS, with loads as high as 96 mg per tablet or capsule [2]. The function of surfactants in tablets is to facilitate dissolution since the dose can rarely be solubilized entirely by the amount of surfactant in a tablet [3–6]. Upon tablet disintegration and surfactant dissolution, the solubility of the drug in the intestinal fluid is only increased to a minor degree by the inclusion of surfactants [3–6]. Surfactants have previously been reported to produce a faster disintegration of the tablet and dispersion of smaller drug particles, which results in a higher dissolution rate that may lead to improved bioavailability [3,4].

The dissolution of griseofulvin and felodipine from drug-SDS discs has been studied using a miniaturized rotating disc setup [7]. The drug dissolution rate was observed to increase several orders of magnitude when 30% (w/w) SDS was present in the discs as compared to discs without SDS. The pronounced effect of SDS on drug dissolution rate was not caused by 1) an increased surface area as SDS dissolved from the discs; 2) increased solubility of the drug due to the surfactants in the bulk medium; nor 3) changes in solid state properties of the drug by co-compression with SDS. It was suggested that a high local concentration of SDS near the solid-liquid interface would increase drug solubility locally. The improved local solubility would provide a steeper concentration gradient resulting in faster dissolution [7].

UV imaging, also termed dissolution imaging, has been introduced as a method for studying various drug dissolution and release processes [8–17]. UV imaging allows 2D concentration

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maps of a flow cell to be constructed based on absorbance images of UV light at a specific wavelength. Thus, the images provide for spatially separated or local drug concentrations to be measured as a function of time. This feature can be used to monitor dissolution events as they occur at the interface between the solid drug and the dissolution medium in the flow cell [10,11,13–17].

The purpose of this study was to further investigate the role of SDS in relation to dissolution rate enhancement when SDS is co-compressed with a drug substance into discs. Using griseofulvin as model drug, the effect of SDS in co-compressed SDS and griseofulvin discs on drug dissolution as a function of SDS content was evaluated by UV imaging, scanning electron microscopy with energy dispersive X-ray spectroscopy (SEM-EDX) and dynamic light scattering (DLS).

Griseofulvin is a poorly water soluble class II compound according to the Biopharmaceutical Classification System [18]. A previous study showed that the dissolution rate of griseofulvin is significantly increased upon co-compression with SDS [7]. In the present study, the role of SDS on griseofulvin dissolution rate from co-compressed griseofulvin-SDS discs was evaluated based on the griseofulvin concentrations near the solid-liquid interface and from griseofulvin dissolution rates, both determined using UV imaging. The dissolution rate from of griseofulvin from pure griseofulvin discs was furthermore investigated in SDS solutions in order to compare the effect on dissolution rate of SDS in the discs and in the dissolution medium.

2. Materials and methods

Ammonium acetate, D-lactose, dimethyl sulfoxide (>99,8%), formic acid (>98%), NaCl (99.5%) and NaOH pellets were purchased from Merck (Darmstadt, Germany). Griseofulvin from *Penicillium griseofulvum* (97.0–102.0%), NaH_2PO_4, NH_4OH solution (28–30% w/v) and SDS (>98.5%) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Acetonitrile (ACN) (99.9%) was purchased from VWR (International S.A.S., Fontenay-sous-Bois, France). Purified water was obtained from an SG Ultra Clear water system (SG Water USA, LLC, Nashua, NH, USA).

2.1. Dissolution medium

An isotonic buffer consisting of 35 mM phosphate was adjusted to pH 6.5 with NaOH and to an ionic strength of 154 mM with NaCl. Solutions of 5, 20 and 100 mM SDS were produced by dissolving SDS in the buffer.

2.2. Solubility of griseofulvin

The solubility of griseofulvin in buffer was determined by dispersing 1 mg/ml griseofulvin in 15 ml buffer for 21 h at 23 ± 1 °C using end-over-end rotation. Samples ($n \geq 5$) were filtered (0.22 μm syringe filter), centrifuged for 15 min at 15000 rpm and 23 °C, followed by the 1:1 dilution of the supernatant with ACN [7]. Standards were prepared by the same procedure. The amounts of griseofulvin dissolved were determined using HPLC-UV measured on a Dionex Ultimate 3000 HPLC system (Dionex Corporation, Sunnyvale, California, USA), equipped with a Phenomenex Luna C18 column at 30 °C (125 mm × 4 mm, 5 μm; Phenomenex, Torrance, CA, USA). The mobile phase consisted of 70% (v/v) ACN and 30% (v/v) 10 mM ammonium acetate in purified water. A flow rate of 1.5 ml/min was applied and UV detection was performed at 292 nm.

2.3. UV imaging

An Actipix SDI300 dissolution imaging system (Paraytec Ltd., York, UK) monitored the dissolution and a syringe pump infused or withdrew the dissolution medium through the flow cell. Details on the instrumentation is described elsewhere [9]. Dissolution UV imaging was performed at a wavelength of 297, 365 or 510 nm. The images were acquired at a rate of 0.55 frames/s using Actipix software version 1.3 (Paraytec Ltd., York, UK). Dissolution experiments were conducted by first collecting a background of the dissolution medium, then inserting the disc and monitoring the dissolution. A flow of 1 ml/min was applied for 2 min to remove air bubbles; afterwards the flow was reduced to 0.1 ml/min for 60 min. Absorbance images acquired during the first 2 min at 1 ml/min were not used. In selected experiments, effluent samples were collected over 3 min intervals. Absorbance values were converted into concentrations using a standard curve based on images of griseofulvin standard solutions drawn through the flow cell at 1 ml/min for 4.5 min. Griseofulvin standards in buffer solution at 5 concentration levels were prepared from stock solutions in ACN, 20 mM or 100 mM SDS. The concentration of ACN did not exceed 1% (v/v). Absorbance depended linearly on griseofulvin concentration ($R^2 > 0.997$) in the ranges tabulated in Table 1. All dissolution imaging experiments and construction of standard curves were conducted at 23 ± 1 °C. Data analysis and graphical presentations were conducted using Actipix software version 1.5 (Paraytec Ltd., York, UK) or SDI software version 2.0 (Sirius-Analytical, Forest Row, UK), respectively.

2.4. Quantification of griseofulvin in effluent and dissolution rate

Quantification of griseofulvin in effluent samples from the dissolution imaging experiments was determined using a Dionex HPLC system (Dionex Corporation, Sunnyvale, California, USA), consisting of a P680 HPLC pump, an ASI-100 automated sample injector and a PDA-100 photodiode array detector, equipped with a Phenomenex Luna C18 column at room temperature (125 mm × 4 mm, 5 μm; Phenomenex, Torrance, CA, USA). The mobile phase consisted of 70% (v/v) ACN and 30% (v/v) 10 mM ammonium acetate in purified water, the flow rate was 1.0 ml/min and detection was performed at 292 nm. The dissolution rate (R) was calculated by multiplying the effluent concentration ($C_{effluent}$; mean over 3 min) with the dissolution flow rate (Q) and dividing with the surface area of the disc (A):

Table 1
Griseofulvin standard curves in buffer and SDS solutions.

Media	Wavelength filter (nm)	Absorbance range (mAU)	Griseofulvin concentration range (mM)	Molar absorption coefficient (m^2/mol ± SD)	R^2
Buffer	297	0–750	0–0.085	$2.24 \cdot 10^3 \pm 12$	0.9971
5 mM SDS	297	0–710	0–0.087	$2.06 \cdot 10^3 \pm 21$	0.9996
0, 4, 8, 12, 16 and 20 mM SDS	365	0–300	0–1.1	71.3 ± 1.1	0.9976
20 mM SDS	365	0–300	0–1.1	69.8 ± 0.9	0.9986
100 mM SDS	365	0–350	0–2.0	49.1 ± 0.7	0.9967