Hydrodynamic Effects on Drug Dissolution and Deaggregation in the Small Intestine—A Study with Felodipine as a Model Drug

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ABSTRACT: The aim of this study was to understand and predict the influence of hydrodynamic effects in the small intestine on dissolution of primary and aggregated drug particles. Dissolution tests of suspensions with a low-solubility drug, felodipine, were performed in a Couette cell under hydrodynamic test conditions corresponding to the fed small intestine. Dissolution was also performed in the USP II apparatus at two paddle speeds of 25 and 200 rpm and at different surfactant concentrations below critical micelle concentration. The experimental dissolution rates were compared with theoretical calculations. The different levels of shear stress in the *in vitro* tests did not influence the dissolution of primary or aggregated particles and experimental dissolution rates corresponded very well to calculations. The dissolution rate for the aggregated drug particles increased after addition of surfactant because of deaggregation, but there were still no effect of hydrodynamics. In conclusion, hydrodynamics do not influence dissolution and deaggregation of micronized drug particles in the small intestine of this model drug. Surface tension has a strong effect on the deaggregation and subsequent dissolution. Addition of surfactants at *in vivo* relevant surface tension levels is thus critical for *in vivo* predictive *in vitro* dissolution testing. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:2969–2976, 2015

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INTRODUCTION

For orally administrated drugs in solid form, dissolution in the gastrointestinal fluids is a prerequisite for absorption. Bioavailability for oral administration of such drugs can thereby be deficient because of slow and incomplete dissolution from the dosage form.[1] This has become even more important as the majority of small organic drugs in modern drug development are highly hydrophobic and poorly soluble in water.[2] Dissolution is not only a consequence of the molecular properties such as hydrophobicity, but also strongly dependent on drug solid state form, excipients, and formulation manufacturing process. The understanding and prediction of the drug dissolution in the gastrointestinal (GI) tract are key aspects of pharmaceutical product development to design products with desired clinical performance and to ascertain consistent quality in commercial supply.

The drug dissolution rate is affected by composition of the GI fluids. The contents in the stomach and small intestine are well characterized, including factors such as pH, and bile salts. This has allowed development of various dissolution test fluids mimicking the content of GI fluids.[3] The dissolution is also potentially influenced by the hydrodynamic conditions in the GI tract. Fluid movements is created by the gut wall motility aimed to grind, mix, and transport material in the GI tract.[4] This creates convection and shear that may influence the rate of drug particle dissolution. Previously, it has been shown in *in vitro* experiments that the drug transport in the diffusion layer surrounding solid particles and consequently the dissolution rate indeed is affected by hydrodynamic conditions.[5–8] However, although these studies provided mechanistic insight in drug particle dissolution, the translation of those hydrodynamic effects observed *in vitro* to the conditions in the GI tract has been missing. Another sparsely investigated factor involved in the dissolution process is deaggregation of clusters of drug particles that can be formed during handling and pharmaceutical processing of adhesive materials. Aggregates have a smaller surface area than primary particles and are therefore a critical factor for the determination of the dissolution rate. Aggregates that are suspended in a fluid disintegrate when the hydrodynamic forces exceed the cohesive bonds between the particles primarily determined by the Brownian motion, electrostatic, and van der Waals interactions.[9]

The focus of the current study was therefore to evaluate the influence of hydrodynamics on drug particle dissolution at test conditions representative of the fed small intestine including the aspect of deaggregation. The fed state was selected as this represents a continuous state of mixing in the GI tract and thereby could potentially provide pronounced influence on drug dissolution. The present study combined *in vitro* drug particle dissolution experiments of a low-solubility model drug, felodipine, performed under well-controlled hydrodynamic conditions and previously performed computer simulations of hydrodynamics in the GI tract,[11,12] allowing to link *in vitro* and *in vivo* intestinal hydrodynamics. The simulations of the hydrodynamic conditions experienced by drug particles in the upper small intestine was performed by a unique computer simulation model based on the Lattice–Boltzmann algorithm describing gut wall motility patterns determined by *in vivo* magnetic resonance imaging (MRI) images.[4] The hydrodynamic conditions for the *in vitro* experiments were calculated

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allowing to define *in vitro* test conditions, by varying agitation, that mimicked the *in vivo* situation. Thereby, drug particle dissolution and deaggregation could for the first time be studied *in vitro* under *in vivo* relevant conditions. These *in vitro* experiments were performed in a Couette cell and thereafter repeated and further extended in the USP II paddle dissolution apparatus.

The aim of the present study was to investigate the effect of *in vivo* relevant hydrodynamics conditions on drug particle dissolution and deaggregation in order to allow definition of *in vivo*-predictive tools.

MATERIAL AND METHODS

Overall Study Design

The fluid shear rates at drug particles in the small intestine at fed-state motility were calculated by a previously developed computer model.[11,12] The simulations used motility patterns from *in vivo* MRI images obtained in rats under fed conditions. Physiological parameters such as dimensions and motility frequencies were transposed from the rat to the human situation. The simulations applied a modified Lattice–Boltzmann algorithm with a three-dimensional geometric model used to set boundaries conditions.

Dissolution experiments using felodipine as a model substance was performed on drug suspensions containing micronized primary particles or aggregated clusters of the same micronized particles. These experiments were performed under very well-controlled hydrodynamic conditions allowing to calculate and subsequently match the shear rate on the particles to magnitudes relevant for the *in vivo* situation, as determined by above-described computer model. To obtain controls and predictable hydrodynamics, dissolution testing was performed in a Couette cell, which is a cylindrical beaker with an inner rotating cylinder. The density of the dissolution medium was increased to make the drug particles neutrally buoyant. The different shear rates were obtained by varying the rotation rate of the inner cylinder.

As the Coutte cell is not a practically useful method for product dissolution testing, additional experiments with felodipine suspensions were performed in the standard USP II paddle apparatus. In order to bridge the *in vivo* relevant results obtained in the Coutte cell, testing in the same medium was performed in USP II at different paddle speeds. Furthermore, the influence of surfactants on the deaggregation of particle clusters was studied in the USP II apparatus.

All *in vitro* dissolution data were compared with theoretical dissolution calculations by Eq. (1) to support interpretation of dissolution results. Particle size distributions in the test suspensions were determined as well as drug solubility in the test media and zeta potential for suspensions mixed with dissolution test media further underpinning mechanistic interpretations of results.

Test Formulations

A low solubility, BCS class II drug, felodipine (AstraZeneca, Södertälje, Sweden) was used in the present study. Suspensions with micronized drug as primary and aggregated particles were manufactured as described below.

Manufacturing

For both the primary and the aggregated particle suspensions, the total drug concentration was 2 mM. The same batch of micronized drug was used to obtain both the aggregated and primary particle suspensions. To stabilize the suspensions, 0.2% and 2% (w/w) polyvinylpyrrolidone (PVP) (Kollidon 30™; BASF, Geismar, LA, USA) were added for the primary and aggregated particles suspensions, respectively. The PVP concentration of 2% (w/w) has no influence on the drug solubility.[12] The aggregated suspensions were prepared using a previously developed method where drug particles are added to half the suspending fluid and than the other half is added followed by gentle mixing.[13] The primary particle suspensions were obtained by deaggregating drug particles in an ultrasonic bath (S2; Covaris, Woburn, MA, USA).

Felodipine suspensions with additional CsCl (ICN Biomedicals Inc., Irvine, CA, USA) were also manufactured for dissolution tests where this salt was included in the dissolution medium. CsCl was used to density match the dissolution medium with the drug particles to avoid sedimentation of the particles during the dissolution experiments. Because of the lower solubility for felodipine in the density-matched media, the suspensions with CsCl had a lower drug concentration of 1 mM compared with the 2-mM used for the suspensions without this salt.

The homogeneity of drug content in suspension samples added to the dissolution experiments was verified by measuring total drug concentration in such samples in triplicates for each batch prior to dissolution testing. The variation in drug concentration was less than 10% allowing accurate dose administrations to the dissolution experiments.

Drug Particle Size Distribution Measurements

The particle size distribution for the suspensions used in the dissolution experiments was determined by laser diffraction using the Mastersizer 2000 (Malvern Instruments, Worcestershire, UK).

Zeta Potential Measurements

The zeta potential representing electrostatic repulsion is a key indicator of electrostatic attraction or repulsion between particles. For particles that are small enough, a low zeta potential will favor aggregation. Zeta potential was measured for felodipine by a Zetasizer (Malvern Instruments, Worcestershire, UK) for 25 μM felodipine suspensions in 0.05% N,N-dimethylacetamide (DMA) (Scharlau Chemie S.A, Sentmenat, Spain) as a reference and with addition of different concentrations the surfactants sodium dodecyl sulfate (SDS) (0.01–1 mM) or 2.6 mM sodium taurocholate (Sigma–Aldrich, Saint Louis, MO, USA). All samples were prepared by using the primary particle suspension.

Dissolution Experiments

in the Couette Cell

The Couette cell used was a modified UL-adapter connected to a digital Viscometer model LVDV-II+ (Brookfield Engineering Laboratories, Inc., Middleboro, MA, USA).[14] The UL-adapter was modified by introducing a valve at the base for sampling (Fig. 1). The internal cylinder was connected to the viscometer that was used to rotate the internal cylinder at a constant

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