Toward an Improved Understanding of the Precipitation Behavior of Weakly Basic Drugs from Oral Lipid-Based Formulations

CORDULA STILLHART,[1,2] DÉSIRÉE DÜRR,[2] MARTIN KUENTZ[2]

[1]University of Basel, Department of Pharmaceutical Sciences, 4056 Basel, Switzerland
[2]University of Applied Sciences and Arts Northwestern Switzerland, School of Life Sciences, Institute of Pharma Technology, 4132 Muttenz, Switzerland

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ABSTRACT: The aim of the present study was to analyze the impact of lipid-based formulation (LBF) dispersion and digestion on the precipitation behavior of weakly basic drugs. Loratadine and carvedilol were formulated in a range of LBFs and drug solubilization was analyzed under simulated dispersive and digestive conditions (fasted state). The extent of supersaturation and drug precipitation as well as the solid-state properties and redissolution behavior of precipitated drugs were assessed. X-ray powder diffraction indicated that carvedilol precipitated in a crystalline form upon dispersion, but interestingly, this drug gave an amorphous precipitate during lipolysis. In contrast, loratadine precipitated as crystalline material during both formulation dispersion and digestion. No influence of the formulation composition on the type of precipitation was observed. These results suggested that *in vitro* conditions (dispersive *versus* digestive) largely influenced the solid-state properties of precipitating weak bases. Solid-state characterization of precipitated drugs under different experimental conditions should be routinely performed in formulation screening to better understand the biopharmaceutical behavior of LBFs. Hence, these findings are of high practical importance for the pharmaceutical development and *in vitro* assessment of LBFs using weakly basic drugs. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:1194–1203, 2014

Keywords: weak bases; formulation; lipid; precipitation; dispersion; lipolysis; solid-state; redissolution; *in vitro* models

INTRODUCTION

Poorly water-soluble drug candidates often show reduced and variable systemic bioavailability upon oral administration. The solubility issue is particularly complex in the case of ionizable drugs such as poorly water-soluble weak bases. These compounds are influenced by the pH gradient experienced during transition from the gastric to the intestinal environment. The gastric pH favors ionization of a basic drug, depending on pK_a, which generally results in adequate solubilization in the stomach. However, following transfer into the intestinal fluid, deprotonation to the free base can occur, leading to comparatively lower aqueous solubility. Depending on the administered dose, this decrease in drug solubility may cause drug supersaturation, with a risk of precipitation.

Drug precipitation is generally undesirable because redissolution is typically incomplete for poorly soluble compounds within the time span of intestinal transit. For this reason, the fraction of precipitated drug is frequently assumed not to be available for absorption. However, there is increasing evidence that the impact of drug precipitation on oral bioavailability does not only depend on the extent of precipitation. A significant determinant is the physical state of precipitated drug. Indeed, high-energy solids such as amorphous materials have higher apparent solubilities and might therefore redissolve faster compared with their crystalline counterparts.[1,2] The drug may have sufficient time to redissolve during intestinal transit and to become available for absorption. It is also important to consider the stability and extent of drug supersaturation, which is the driving force for drug precipitation. Although it is a metastable state, drug supersaturation defines the time span during which the drug is solubilized and becomes available for absorption.[3,4]

It has recently been shown that the stability toward intestinal precipitation of a weakly basic drug can be increased by a lipid-based formulation (LBF).[5] This is, however, only one mechanism by which LBFs possibly enhance oral drug bioavailability. The drug is already in a dissolved state when it is administered and thus the critical dissolution step is circumvented. Lipidic excipients also increase the apparent solubility of the drug in intestinal fluids, may reduce presystemic clearance, and can enhance drug permeation across the intestinal membrane.[6,7] Although LBFs offer a great potential for the oral administration of poorly water-soluble compounds, the improvement in oral bioavailability is ultimately governed by the fate of the formulation in the gut. Formulation dispersion and excipient digestion represent particularly critical steps because they change the microenvironment of a drug. Therefore, the capacity of a formulation to keep the drug in solution may be progressively reduced, developing an increased risk of drug precipitation.

There is considerable research interest in the factors that determine the precipitation of weakly basic compounds upon oral administration. Few studies have analyzed the features of intestinal drug precipitation *in vivo* by aspirating intestinal content.[8,9] However, as the *in vivo* evaluation of intraluminal content is inherently difficult, drug precipitation has generally been studied using *in vitro* assays. One- or two-compartment experimental setups were developed and simulated gastrointestinal media were usually employed to simulate the transfer

Correspondence to: Martin Kuentz (Telephone: +41-61-467-46 88; Fax: +41-61-467-47-01; E-mail: Martin.Kuentz@fhnw.ch)

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from the stomach into the small intestine.[10–15] These assays simulate dispersive conditions without digestive enzymes and can provide valuable information about the intrinsic pH-induced precipitation behavior of weakly basic compounds (in the presence of bile salts and phospholipids).

Other studies used digestive conditions to analyze the precipitation behavior of lipophilic weak bases in LBFs[16–18] and particular attention has been paid to the solid-state of precipitated drugs. The results of Sassene *et al.*[16], reporting the formation of an amorphous precipitate in the course of formulation digestion of the drug cinnarizine, are particularly interesting. Also important were the findings of the lipid formulation classification system consortium, which studied fenofibrate and tolfenamic acid in different LBFs.[19] While the precipitates of fenofibrate appeared to be of the same crystalline form as the reference drug, tolfenamic acid crystallized, at least partially, in a different polymorphic form. The latter work underlined the necessity to study the formulation behavior upon lipolysis, with a special emphasis on the solid-state characterization of potential precipitate.

Despite the importance of this research field, little information is currently available regarding the impact of specific formulation processing, that is, dispersion *versus* digestion, on the precipitation behavior of weak bases. Moreover, there is a lack of understanding about the influence of formulation composition on the solid-state properties of a precipitate. Such understanding is fundamental for more rational development of pharmaceutical LBFs and for selecting appropriate *in vitro* assays for formulation screening.

The present study focused on the precipitation behavior of lipophilic, weakly basic drugs from LBFs. A major aim was to investigate the influence of dispersion and digestion on the precipitation behavior of model bases. Therefore, the effect of pure dispersion was analyzed separately from the dispersion in a digestive environment. Particular attention was directed to the extent of drug supersaturation and precipitation, as well as to the solid-state properties and redissolution behavior of evolving precipitates. A further aim was to evaluate the influence of the LBF composition on dispersion- and lipolysis-triggered drug precipitation. The present study offers an improved understanding of the fate of LBFs with poorly soluble weak bases in the intestinal lumen.

MATERIALS AND METHODS

Materials

We obtained loratadine, carvedilol, and 4-bromophenylboronic acid (4-BPBA, ≥95.0%) from AK Scientific (Union City, California). Trizma® maleate, calcium chloride dihydrate (≥99%), pancreatin (from porcine pancreas, 8× United States Pharmacopeia specifications), sodium chloride (≥99%), ammonium acetate (≥99%), chloroform, and acetonitrile were from Sigma–Aldrich Chemie GmbH (Buchs, Switzerland). Lipoid E PC S [phosphatidylcholine (PC) from egg yolk] was supplied by Lipoid GmbH (Ludwigshafen, Germany), sodium taurodeoxycholate (NaTDC) by Prodotti Chimici e Alimentari S.p.A. (Basaluzzo, Italy), and sodium hydroxide 1 M by Scharlab S.L. (Sentmenat, Spain). Imwitor® 988 was purchased from Sasol Germany GmbH (Witten, Germany), Miglyol® 812 N from Hänseler AG (Herisau, Switzerland), and Cremophor® EL from BASF AG (Ludwigshafen, Germany). Ethanol was obtained from Baker (Deventer, Netherlands). Transcutol® HP and Capryol® 90 were kindly donated by Gattefossé (Saint-Priest, France). Purified water was prepared with an Arium® 61215 water-purification system from Sartorius Stedim Biotech GmbH (Göttingen, Germany).

Table 1. Composition of Drug-Free Lipid-Based Formulations

Excipient	Formulation F1 (%, w/w)	Formulation F2 (%, w/w)	Formulation F3 (%, w/w)
Miglyol® 812	30.0	12.5	–
Imwitor® 988	30.0	12.5	–
Cremophor® EL	30.0	65.0	44.6
Ethanol	10.0	10.0	–
Capryol® 90	–	–	33.0
Transcutol® HP	–	–	22.4

Imwitor® 988 was a blend of medium-chain glycerides (54.6% monoglycerides, 38.0% diglycerides, and 7.1% triglycerides) with average molecular weights of 197, 340, and 483 g/mol, respectively (according to the certificate of analysis; Cremer Oleo GmbH, Hamburg, Germany). Miglyol® 812 N was a medium-chain triglyceride consisting of 57.9% (w/w) caprylic acid (C8), 41.2% (w/w) capric acid (C10), 0.5% w/w (lauric) acid (C12), and 0.1% (w/w) caproic acid (C6) with an average molecular weight of 517 g/mol (according to the certificate of analysis, Hänseler AG). Capryol® 90 was composed from propylene glycol monocaprylate (99.9% caprylic acid (C8), certificate of analysis, Gattefossé AG) and the surfactant Cremophor® EL consisted of polyoxyl 35 castor oil.

Preparation of Formulations

Three LBFs were selected as model formulations and the compositions are detailed in Table 1. The lipidic components were mixed on a magnetic stirrer at 40°C until a clear solution was obtained. The mixtures were then slowly cooled to room temperature and finally the cosolvent (ethanol or Transcutol® HP) was added.

Loratadine and carvedilol were selected as lipophilic, weakly basic model compounds (Fig. 1). The formulations were loaded with the free bases at 80% of their saturation solubility in the corresponding formulation. All formulations were visually assessed for absence of undissolved drug particles prior to use.

Preparation of Simulated Intestinal Medium and Pancreatic Extract

The simulated intestinal medium was composed of an aqueous buffer, 1.25 mM PC, and 5 mM NaTDC at concentrations simulating fasted-state intestinal conditions. PC was dissolved

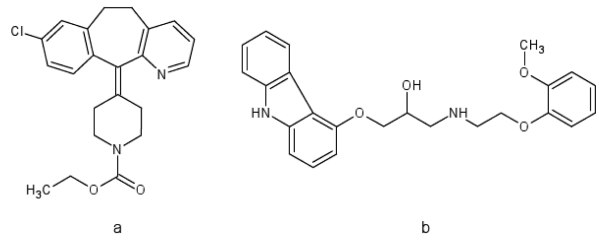

Figure 1. Chemical structures of the model drugs (a) loratadine (pK_a = 5.3,[20] log P = 3.9) and (b) carvedilol (pK_a = 7.8,[20] log P = 4.1).