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EDITORIAL

Physicochemical Interactions in Solid Dosage Forms

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ABSTRACT Complete characterization and mechanistic understanding of physicochemical interactions in solid dosage forms are not only important for consistent manufacturability, stability, and bioavailability of the drug product, but are also expected under the quality-by-design paradigm of drug development. Lack of this understanding can impact successful and timely development, scale-up, and commercial manufacture of dosage forms. This article highlights the stability and bioavailability implications of physicochemical interactions in dosage forms citing a couple of examples where such interactions necessitated the recall of commercial drug products.

KEY WORDS physicochemical interactions · product development · quality by design · solid dosage forms

INTRODUCTION

The need for complete characterization and better understanding of physiochemical interactions in solid dosage forms is at the forefront of drug product science and technology research. The physicochemical interactions in dosage forms can affect manufacturability, stability, and bioavailability of a drug product, thus often determining the developability and clinical viability of a drug. Proactive detailed characterization of physicochemical interactions and their mechanistic understanding are important not only for successful and robust product development, but also for patient safety and drug efficacy during the product life. In addition, an understanding of physicochemical interactions in dosage forms is expected under the quality by design (QbD) paradigm of drug development, encouraged by the United States Food and Drug Administration and other regulatory bodies worldwide. Under the QbD paradigm, mechanistic understanding of the degradation mechanism of the dosage form has become an integral part of the product development process. In most cases, the expectation regarding a thorough understanding of degradation mechanism in new drug applications has evolved from "nice to have" to "must have."

Physicochemical interactions that are not well understood and controlled can sometimes lead to adverse findings that even necessitate field alerts, batch recalls, or product withdrawal. For example, Viracept® (nelfinavir mesylate) tablets (250 mg) were recalled in 2007 due to the presence of high levels of ethyl methane sulfonate (EMS) in the drug product (1), and Norvir® (ritonavir) capsules were recalled in 1998 due to the formation of a less soluble crystal form in the capsules (2). Investigations into Viracept tablets were initiated by patient complaints of bad odor in the marketed product and adverse reactions such as nausea. Analysis of relevant tablet batches by headspace gas chromatography using dimethylsulfoxide as a solvent indicated the presence of acetaldehyde and dimethyl sulfide. The presence of these impurities was attributed to the reaction between dimethylsulfoxide used as solvent in the analysis and ethyl methane sulfonate (EMS) in tablets (Fig. 1a). The formation of EMS was attributed to the use of methane sulfonic acid (MSA) in the final manufacturing step of the drug substance. The storage of MSA under conditions that can lead to contamination with ethanol for prolonged periods of time could lead to the generation of EMS (Fig. 1b). This mechanistic understanding enabled the drug product manufacturer to implement several control strategies and process modifications that could ensure acceptably low levels of EMS in the drug product (1).

Several aspects of drug product stability and performance are linked to physicochemical interactions in the dosage form. These include the robustness of the formulation to the range of variability typically encountered in input materials and process parameters. In addition, the product is expected to remain stable with consistent bioavailability. Some of the aspects of stability and bioavailability are addressed in this theme issue through 11

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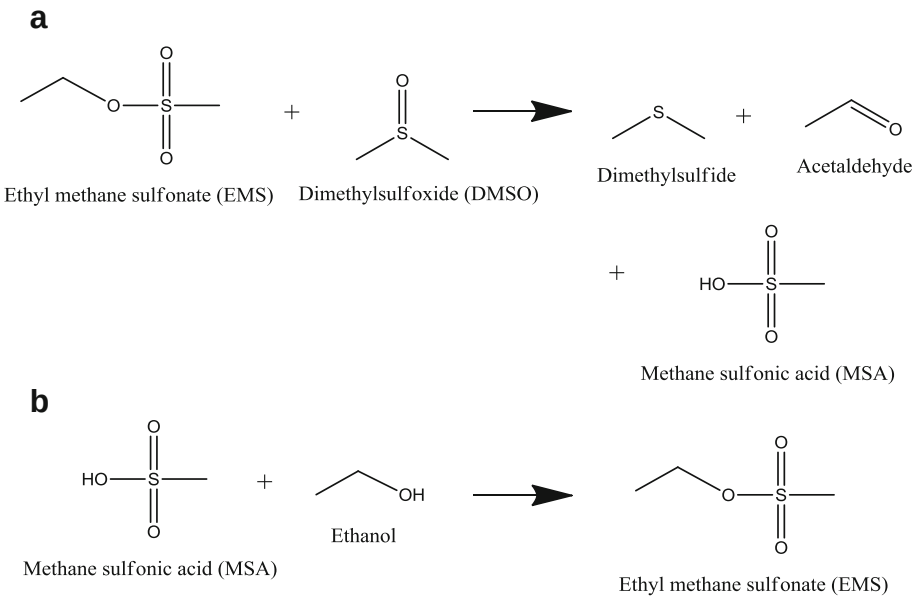

Fig. 1 Reaction pathway for (**a**) the generation of dimethylsulfide during headspace gas chromatography analysis of Viracept tablets and (**b**) the formation of ethyl methane sulfonate (EMS) in the tablets.

original research articles and 2 expert reviews. This theme issue brings forth emerging trends in pharmaceutical dosage form research through the latest work of international (Japan, Germany, Finland, France, and United States) leaders in respective areas from both academia and pharmaceutical industry.

STABILITY

Excipients influence formulation stability not only by direct interaction with the drug, but also by modifying drug product characteristics such as microenvironmental pH, unbound water, and plasticity/mobility of reactive components (3). Additionally, trace amounts of impurities present in excipients can react with the drug or other functional excipients (4).

In this theme issue, Narang, Desai, and Badawy review the impact of excipient interactions on solid dosage form stability. The authors describe common mechanistic themes that often underlie degradation in the solid dosage forms, such as the role of water and pH on solid-state reactions. This is followed by a discussion of common pathways of physical and chemical instability, and prospective stability modeling and assessment during drug development. Several original articles in this theme issue highlight the recent research in these areas. Heljo *et al.* discuss the role of water in the crystallization tendency of amorphous materials. Qian *et al.* discuss the impact of plasticization by water on the stability of amorphous systems. Qian, Wurster, and Bogner describe on the role of water in crystalline to amorphous phase transformation of compounds in the presence of porous media. Kindermann *et al.* describe the role of temperature and moisture on form and dissolution stability of drug-polyelectrolyte complexes in tablets. DeHart and Anderson report the kinetics and mechanism of chemical instability of a model asparagine-containing peptide in amorphous lyophiles.

BIOAVAILABILITY

Physicochemical interactions in dosage forms can significantly influence drug bioavailability by affecting its dissolution or by interacting with physiologic processes involved in drug absorption. At a simplistic level, these effects can be directly related to the functionality of excipients, such as the use of binder and disintegrant in tablets or direct drug–excipient interactions (5). However, recent research highlights the role of indirect mechanisms and possible interplay of more than one mechanism. In this theme issue, Panakanti and Narang discuss case studies and the mechanistic basis of excipients affecting drug bioavailability through interactions with physiologic processes and drug product characteristics.

A commonly utilized modality of dissolution rate enhancement in solid dosage forms is milling of the active pharmaceutical ingredient (API) to reduce its particle size, thereby increasing the surface area. This process, however, can lead to generation of high-energy surface, leading to processability concerns such as sticking during roller compaction and tablet compression. Ho *et al.* discuss the importance of particle shape, attachment energy, and crystal slip systems in understanding fracture behavior of crystalline drugs.

Supersaturation of a drug in an aqueous medium with the change of pH, such as that of a basic drug transitioning from the acidic gastric environment to the basic intestinal milieu, can increase the bioavailability of certain poorly soluble drugs. The supersaturation behavior can be inherent to a drug molecule (*e.g.*, a drug with surfactant properties) or induced by the dosage form, such as the use of amorphous solid dispersions or self-emulsifying drug delivery systems (SEDDS). In this theme issue, Hsieh *et al.* report the precipitation and supersaturation behavior of 10 weak base compounds by studying the pH-concentration-time profiles and the properties of

the precipitated material. Shah and Serajuddin describe the development of solid SEDDS and a method of incorporation of the drug in these systems by first dissolving the drug in the lipid in liquid state. Qian *et al.* report the correlation between solution behavior of amorphous solid dispersions made with two different polymers to the oral bioavailability of a model compound. Kojima *et al.* explore the stabilization mechanism of a supersaturated solution of mefanamic acid from its solid dispersion in Eudragit® EPO.

Physical stability of amorphous drug–polymer solid dispersions to crystallization during shelf-life storage is often linked to drug–polymer miscibility through molecular interactions. In this theme issue, Eerdenbrugh and Taylor report the effect of molecular weight on the miscibility behavior of a low molecular weight compound in a polymer, and Greco *et al.* propose a method to predict the time to crystallization of amorphous solid dispersions by studying the crystallization behavior at different temperature and humidity conditions.

This theme issue on the physicochemical interactions in formulations and their impact on the stability and bioavailability of drugs from solid dosage forms brings forth several original articles of current research in this area. In the landscape of commercial formulations, there are about 15 commonly used excipients in the oral and parenteral dosage forms. However, stability-related issues keep surfacing during the product development, sometimes delaying product launch or during commercialization triggering batch and/or product recalls. These observations emphasize the need for better mechanistic understanding of the physicochemical interactions. More scientific advances are needed to comprehend many of the physicochemical interactions brought forth in this theme issue. We hope this theme issue draws attention of the pharmaceutical scientists toward knowledge gaps in these areas and helps foster more research in this field.

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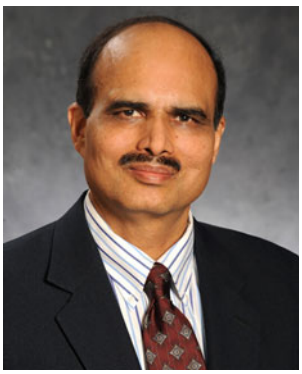

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