Influence of Drug Property and Product Design on *In Vitro–In Vivo* Correlation of Complex Modified-Release Dosage Forms

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ABSTRACT: The present study examines how drug's inherent properties and product design influence the evaluation and applications of *in vitro–in vivo* correlation (IVIVC) for modified-release (MR) dosage forms consisting of extended-release (ER) and immediate-release (IR) components with bimodal drug release. Three analgesic drugs were used as model compounds, and simulations of *in vivo* pharmacokinetic profiles were conducted using different release rates of the ER component and various IR percentages. Plasma concentration–time profiles exhibiting a wide range of t_{max} and maximum observed plasma concentration (C_{max}) were obtained from superposition of the simulated IR and ER profiles based on a linear IVIVC. It was found that depending on the drug and dosage form design, direct use of the superposed IR and ER data for IVIVC modeling and prediction may (1) be acceptable within errors, (2) become unreliable and less meaningful because of the confounding effect from the non-negligible IR contribution to C_{max}, or (3) be meaningless because of the insensitivity of C_{max} to release rate change of the ER component. Therefore, understanding the drug, design and drug release characteristics of the product is essential for assessing the validity, accuracy, and reliability of IVIVC of complex MR products obtained via directly modeling of *in vivo* data. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:507–516, 2014

Keywords: modified release; bimodal release; dissolution; kinetics; absorption; disposition; pharmacokinetics; IVIVC; simulation; superposition

INTRODUCTION

Modified-release (MR) drug products are designed and developed to achieve possible therapeutic benefits, such as improved efficacy and reduced adverse events, increased convenience and patient compliance, optimized performance, a greater selectivity of activity, or new indications.[1] In general, the product design objective for modifying oral drug release is to alter the rate and/or timing of drug input (dissolution/absorption) in the intestinal lumen to obtain a predetermined plasma profile. Common modes of oral MR delivery include (1) delayed release (DR); (2) extended release (ER); (3) multiphasic release via combining immediate release (IR) with ER or DR components, enabling unique drug release characteristics, for example, pulsatile, bimodal, site-specific or timed release. In addition, these drug release features are often incorporated into fixed dosage combination (FDC) products. These types of dosage forms are more complex than their IR or ER counterparts. Figure 1 illustrates some examples of MR delivery profiles.[2] Among the various drug release pattern designs, bimodal (or biphasic) delivery profiles are most commonly utilized. The usual rationales for such designs include (1) providing rapid onset of action by adding an IR component to an ER dosage form, (2) optimizing dosing schedules for chronotherapeutic drugs by incorporating a DR component in an ER dosage form, (3) generating fluctuations of plasma levels to avoid or attenuate the development of acute tolerance because of constant drug exposure at the receptor site, or (4) overcoming the problems associated with nonlinear pharmacokinetics, extensive first-pass metabolism, idiosyncratic pharmacokinetics, or pharmacodynamics resulting in reduced bioavailability or altered drug/metabolite ratios.[3–6] Since the 1980s, many marketed products with bimodal drug release have been developed for various classes of therapeutic drugs, such as acetaminophen, verapamil, diltiazem, nifedipine, methylphenidate, zolpidem, and so on.

For MR dosage forms, *in vitro–in vivo* correlations (IVIVC) is highly desirable in that it provides a critical linkage between product quality and clinical performance. With an established IVIVC, an *in vitro* test, such as dissolution test, can serve as a critical tool for product and process understanding, aid product/process development, manufacturing and control, provide significantly increased assurance for consistent product performance, and predict *in vivo* performance throughout the life cycle of a MR product. The existing regulatory guidance on *IVIVC* for MR products[7–9] primarily focuses on concepts/approaches applicable to ER products with monolithic release mechanism and characteristics (e.g., zero-order, square-root-of-time, first-order kinetics). Specifically, two key bioequivalence parameters used in the evaluation, validation, and application of IVIVC are the area under the plasma concentration–time curve (AUC) and maximum observed plasma concentration (C_{max}). The basic principle of the regulatory guidelines is to assess accurately and reliably how changes in the *in vitro* drug release rate may affect bioavailability characteristics of an ER dosage form. Problems or challenges can arise when the *in vivo* data of many of the above-mentioned complex dosage forms involving more than one release components and mechanisms are directly utilized to build and evaluate an IVIVC model using methodologies described in the guidance. In general, AUC and C_{max} of a

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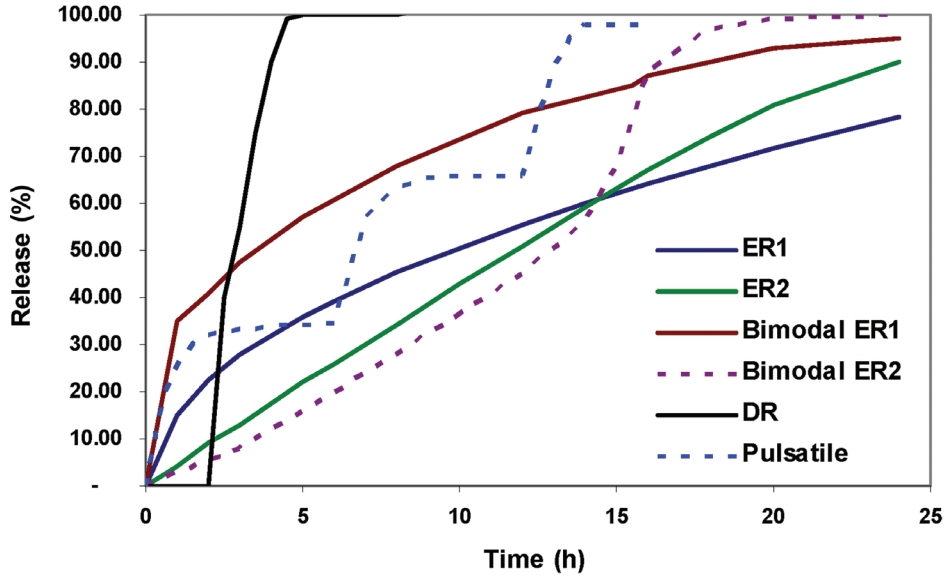

Figure 1. Illustrative examples of MR profiles (with permission).

complex MR product are not only dependent on the input rate and extent, but also on drug properties and product design characteristics. In addition, the *in vitro* and *in vivo* relationships (IVIVR) are often different between the underlying ER and IR or DR components. Furthermore, quantitative IVIVR is, in most cases, absent for IR or DR components. For example, for a MR dosage form consisting IR and ER components exhibiting bimodal drug release, AUC usually does not change with release rate or pattern if the drug substance is soluble and has favorable apparent regional absorption properties throughout the intestinal tract. However, the C_{max} may be dictated by drug release rate and/or kinetics from the underlying IR or ER component depending on (1) the designed dose ratio of the IR to ER component and (2) the elimination rate of drug. If the drug has a short half-life ($t_{1/2}$), C_{max} may be determined by the IR component while AUC may be insensitive to the release rate of the ER component. Hence, rate changes of the ER component will have no impact on either C_{max} or AUC, making IVIVC assessment meaningless. For bimodal drug release consisting of two ER components (second one delayed), C_{max} or presence of double peaks is determined by both ER components depending on (1) dose ratio and rate of the two ER components, (2) onset of the second ER, and (3) the elimination rate constant of individual drugs. In addition, accuracy and meaning of the average plasma profiles will also be affected by the intersubject variability of the lag time of the second ER. Therefore, the objective of this study is to examine how drug properties, product design, and release characteristics influence evaluation and applications of IVIVC for MR dosage forms that consist of IR and ER component and exhibit bimodal drug release.

MATERIALS AND METHODS

Model Drugs and Drug Release Pattern of MR Dosage Form

Three analgesic drugs, acetaminophen, tramadol, and naproxen, were used as model compounds to evaluate the effect of drug property and product design on IVIVC. These model drugs were selected from the consideration of their physicochemical, biopharmaceutical and pharmacokinetic properties, technical feasibility, and clinical needs for MR delivery (Table 1).[10–12] A bimodal drug release pattern was chosen based on the corresponding dosage form design of the available marketed MR products of each model drug, that is, IR followed by ER designed to provide prolonged pain relief with fast onset.

Simulation

To assess the effect of drug property and release pattern on error and reliability of IVIVC modeling and prediction for MR dosage forms consisting of an IR and an ER component, simulations of *in vivo* pharmacokinetic profiles were conducted using data and/or parameters derived from the pharmacokinetic studies of the model drugs available in the literature. More specifically, the simulated *in vivo* plasma concentration–time profiles of the MR dosage form with bimodal release were compared with those of the underlying IR and ER components to examine (1) how changes in dosage form design, such as IR percentage and release characteristics, may lead to failing IVIVC modeling and prediction because of the insensitivity of C_{max} to rate change of the ER component or confounding effect of IR contribution to plasma levels and (2) the influence of

Table 1. Model Drugs, Properties, and Drug Release Design of the Corresponding Marketed Products

Drug	BCS	Intestinal Absorption	Marketed MR Product with Bimodal Release	IR Dose (%)
Acetaminophen	Class I	Passive transport	Tylenol® 8Hour	50
Tramadol HCl		Wide absorption window	Ryzolt®	25
Naproxen			Naprelan®	30

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