Compartmental Absorption Modeling and Site of Absorption Studies to Determine Feasibility of an Extended-Release Formulation of an HIV-1 Attachment Inhibitor Phosphate Ester Prodrug

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ABSTRACT: BMS-663068 is a phosphonooxymethyl ester prodrug under development for the treatment of HIV/AIDS. The prodrug is designed to overcome the solubility-limited bioavailability of the active moiety, BMS-626529. BMS-663068 is not absorbed from the gastrointestinal (GI) tract and requires enzymatic conversion by alkaline phosphatase to BMS-626529 immediately before absorption. In the light of the known short *in vivo* half-life of BMS-626529, compartmental absorption modeling was used to predict the potential feasibility of extended-release (ER) delivery to achieve target C_{max}:C_{min} ratios. To further refine the model with respect to colonic absorption, the regional absorption of BMS-626529 following delivery of BMS-663068 to upper and lower GI sites was characterized through a site of absorption study in human subjects. A refined model was subsequently applied to guide the development of ER tablet formulations. Comparisons of results from the refined model to the *in vivo* human pharmacokinetic data for three selected ER formulations demonstrate the utility of the model in predicting feasibility of ER delivery and in directing formulation development. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:1742–1751, 2013

Keywords: dissolution; colonic drug delivery; site-specific absorption; *in silico* modeling; prodrugs

INTRODUCTION

There have been significant advances in antiretroviral drugs over the last three decades yielding over 30 drugs in use, and more in development, that are highly effective, convenient, and safe for newly diagnosed and treatment experienced patients.[1,2] The value of treatment is such that a 2006 analysis determined that treatment had yielded a total of at least 3 million years of patient survival benefit in the US alone over 20 years.[3]

However, the desire to improve on existing drugs, especially to deal with the development of resistance to existing agents, has spurred efforts to identify new approaches in interfering with the virus life cycle.[2] The prevention of viral entry into the host cells offers an attractive approach but existing approved treatments based on this principle, CCR5 antagonists (maraviroc) and fusion inhibitors (enfuvirtide), have limitations because of the need for tropism testing and a less-convenient administration route, respectively. Recently the identification of gp120 as a viable target for small molecule entry inhibitors was established[4] leading to the characterization of a series of potentially clinically useful candidates.[5,6] From this series, candidates for human clinical study

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were identified. Poor solubility led to drug delivery challenges, which for one candidate, BMS-488043, were mitigated by the creation of pharmaceutically stable amorphous dispersion of the drug in a hydrophilic polymer or by providing the crystalline drug size reduced to the nanometer range in a suitable formulation.[7,8] Prodrug approaches that might overcome solubility-limited oral absorption[9–11] have been suggested as useful drug delivery strategies in the case of HIV therapy[12] and are successfully utilized for an HIV treatment in the case of fosamprenavir.[13,14] Hence, it was rational to apply a phosphate ester prodrug approach to one of our candidates BMS-626529 and this candidate as its phosphate ester prodrug, BMS-663068 has recently been successfully explored in respect of clinical utility.[15] Structures of BMS-626529 and BMS-663068 are given in Figure 1. *In vivo* the highly soluble prodrug, BMS-663068, is converted to the highly permeable BMS-626529 by alkaline phosphatase in the gut. BMS-663068 has a very low Caco-2 permeability and because of this is very poorly absorbed.

Because of the very short apparent half-life of 1.5 h of BMS-626529[16] extended-release (ER) delivery of the prodrug, BMS-663068, was required to ensure acceptable C_{max} and C_{min} to minimize any plasma peak concentration adverse effects and assure viral inhibitory levels are sustained between doses. A maximum target C_{max}:C_{min} ratio of 20 was established and the minimum dosing period was defined as 12 h. Immediate-release delivery of BMS-663068 generated unacceptable C_{max}:C_{min} ratios in excess of 150 over the 12 h dosing period.

Extended-release delivery was initially considered a high-risk development strategy because of the very short half-life and uncertainty over the bioavailability of parent compound following prodrug delivery and around bioconversion in lower regions of gastrointestinal (GI) tract. The current paper describes how compartmental absorption modeling and site of absorption (SoA) studies were used to build a risk-based, progressive approach to enable ER formulation development.

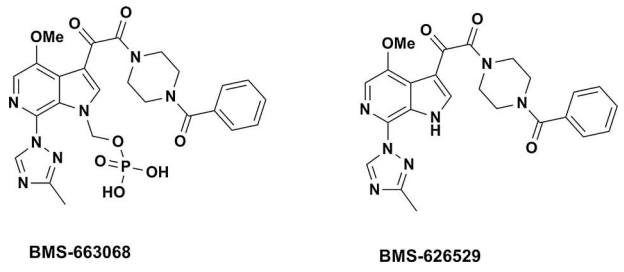

Figure 1. Chemical structures of BMS-663068 and BMS-626529.

EXPERIMENTAL SECTION

Initial Compartmental Absorption Modeling of Extended-Release Delivery

Commercially available software, GastroPlus, v 6.0 (Simulations Plus, Lancaster, California) was used to model the absorption in humans of the active parent compound BMS-626529 when the prodrug BMS-663068, as the 1:1 tromethamine salt, was administered orally for both immediate-release and theoretical ER delivery. Physicochemical parameters of BMS-663068 and BMS-626529 used in the model, for example, solubility, were experimental values measured at 25 °C. The difference between experimental temperature and physiological temperature is not expected to influence the simulation results because of the highly soluble nature of BMS-663068. The Caco-2 permeability of BMS-626529 was converted to a human jejunal permeability by reference to model compounds within the GastroPlus library. Estimates of volume of distribution and clearance were calculated using WinNonLin v5.0 (Pharsight Corporation, Mountain View, California) using data from the dosing of immediate-release capsules in human subjects.[16] The estimates were used as initial inputs for GastroPlus.

In the absence of knowledge on both the enzyme kinetics of dephosphorylation via alkaline phosphatase and enzyme expression in the lower GI tract, an empirical approach was taken towards the initial compartmental modeling. Simulations assumed that conversion of prodrug to parent was not rate-limiting and that all prodrug dissolved within each compartment of the GI model was available for absorption as the parent compound. In practice, the model employed those properties of the prodrug, BMS-663068, impacting dissolution related processes, for example, aqueous solubility of 250 mg/mL and those properties of the parent, BMS-626529, impacting permeability, distribution, metabolism, and elimination processes, for example, log P, effective permeability, volume of distribution, and clearance. As such, simulations were run using a theoretical molecule.

Within GastroPlus, the human-physiological-fasted condition and optimizable log D method for the calculation and scaling of absorption scale factor (ASF) were chosen to establish the compartmental method. The software's built-in multivariate, nonlinear optimization module was then used to adjust physiological parameters (ASF in the duodenal, jejunal, and ileal compartments) and the initial PK parameters to fit predicted plasma-concentration–time profiles to actual plasma concentration–time profiles measured in human subjects following the administration of BMS-663068 as immediate-release capsule formulation in a single ascending dose study.[16] ASF is a parameter used in GastroPlus software to