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Original Article

Development and validation of an *in vitro–in vivo* correlation (IVIVC) model for propranolol hydrochloride extended-release matrix formulations

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ABSTRACT

The objective of this study was to develop an *in vitro–in vivo* correlation (IVIVC) model for hydrophilic matrix extended-release (ER) propranolol dosage formulations. The *in vitro* release characteristics of the drug were determined using USP apparatus I at 100 rpm, in a medium of varying pH (from pH 1.2 to pH 6.8). *In vivo* plasma concentrations and pharmacokinetic parameters in male beagle dogs were obtained after administering oral, ER formulations and immediate-release (IR) commercial products. The similarity factor f_2 was used to compare the dissolution data. The IVIVC model was developed using pooled fraction dissolved and fraction absorbed of propranolol ER formulations, ER-F and ER-S, with different release rates. An additional formulation ER-V, with a different release rate of propranolol, was prepared for evaluating the external predictability. The results showed that the percentage prediction error (%PE) values of C_{max} and $AUC_{0-\infty}$ were 0.86% and 5.95%, respectively, for the external validation study. The observed low prediction errors for C_{max} and $AUC_{0-\infty}$ demonstrated that the propranolol IVIVC model was valid.

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1. Introduction

In vitro–in vivo correlation (IVIVC) plays a key role in the pharmaceutical development of dosage forms. IVIVC can serve as a surrogate for *in vivo* bioavailability and to support biowaivers. It also allows setting of the dissolution specification and methods [1,2]. In order to prove the validity of a new formulation, a bioequivalence study may be needed, taking a considerable amount of time and money. Thus, the application of IVIVC attracts the attention of the pharmaceutical industry.

Development and validation are two critical stages in the evaluation of an IVIVC model. In the first stage, the development of a level A IVIVC model is usually estimated by a two-stage process [1]. At the first stage, the observed fraction of the drug absorbed is estimated using the numerical

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deconvolution method. The IVIVC model is developed by using the observed fraction of the drug absorbed and that of the drug dissolved. Based on the IVIVC model, the predicted fraction of the drug absorbed is calculated from the observed fraction of the drug dissolved. The predicted fraction of the drug absorbed is then convolved to the predicted plasma concentrations by using the convolution method. In the second stage, the predictability evaluation of the IVIVC model should focus on estimating the percent prediction error (%PE) between the observed and predicted plasma concentration profiles, such as the difference in pharmacokinetic parameters [C_{max} and the area under the curve from time zero to infinity ($AUC_{0-\infty}$)]. The internal and/or external evaluation of the %PE may also be appropriate. The internal predictability is based on the initial data used to define the IVIVC model, and the external predictability is based on the additional data [1].

Propranolol is a non-selective beta adrenergic blocking agent and is widely used for the treatment of angina pectoris, hypertension, and many other cardiovascular disorders. After oral administration, propranolol is almost completely absorbed. However, the bioavailability of propranolol is extremely limited (30%), due to the hepatic first-pass effect, and its elimination half-life is also relatively short (approximately 2–6 hours) [3]. For hypertension treatment, the usual dose is 120–240 mg divided in 2–3 doses/day; the maximum daily dose is 640 mg. Therefore, propranolol was a good candidate for the preparation of the once-daily extended-release (ER) dosage formulation. Many IVIVC studies have been reported regarding controlled-release formulations [4–10], but there are none regarding propranolol matrix ER formulations. Thus, developing an IVIVC model of propranolol ER tablets is beneficial for obtaining biowaivers for scale-up and certain pre- or post-approval changes. The objective of this study was to develop an IVIVC model for propranolol ER dosage formulations. The validation of the internal and external predictabilities was completed for a wide range of formulations. In addition, IVIVC of the drug in the animal models provides the feasibility of the drug delivery system for a given drug candidate. The objective of this study was to use propranolol as a model drug, using hydroxypropyl methylcellulose (HPMC), Avicel, and lactose to develop formulations with different release rates, and also to set up the IVIVC animal model to evaluate the feasibility of the drug delivery system. Such an approach may also be applied to the development of other drug candidates in the future.

2. Methods

2.1. Materials and equipment

Propranolol hydrochloride and p-hydroxybenzoate-butyl ester were purchased from TCI Co. (Tokyo, Japan), hydroxypropyl methylcellulose (HPMC) was from Shin Etsu, (Tokyo, Japan), microcrystalline cellulose (Avicel) was from Asahi Co. (Tokyo, Japan), and lactose was from New Zealand Lactose Co (Hawera, New Zealand). All chemicals and solvents used were of analytical reagent grade.

Six Beagles dogs used in this study were supplied from the animal center of National Pingtung University of Science and Technology (NPUST) (Pingtung, Taiwan). Each adult beagle dog weighed between 8 and 14 kg.

2.2. Formulations

ER tablets of propranolol hydrochloride formulated using HPMC, Avicel, and lactose for modifying the release rates have been discussed previously [11]. Two ER tablets were designed to release propranolol at two different rates referred to as: slow (ER-S) and fast (ER-F) for the development of the IVIVC model. The compositions of these ER tablets are shown in Table 1. For evaluating the external predictability of the IVIVC model, an additional formulation, ER-V, with a release rate between those of formulation ER-S and ER-F, was prepared; it underwent dissolution test and *in vivo* absorption studies.

2.3. Dissolution test

The release characteristics of the propranolol ER tablets were determined using USP apparatus I, the basket method. The rotation speed was set at 100 rpm. The propranolol tablets were placed in 900 mL of gastric fluid and maintained at 37°C. Samples (5 mL) were collected, each at an appropriate interval. After 1.5 hours, the pH of the dissolution medium was varied from 1.2 to 6.8 by adding 80 mL of concentrated phosphate buffer to simulate the intestinal fluid, and then the experiment was run for the specified time. The dissolution samples were collected at the following time intervals: 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours. The amount of drug released was analyzed by ultraviolet/visible spectrophotometry at 290 nm wavelength. At least six tablets of each formulation were accomplished. The mean and standard deviation (SD) of dissolved percentages were calculated.

2.4. In vivo absorption studies

The animal experimental protocol was approved by the Institutional Animal Care and Use Committee of Kaohsiung Medical University. The committee confirmed that the animal experiment had followed the guidelines as set forth by the Guide for Laboratory Fact lines and Care. All of the dogs were fasted 12 hours prior to the experiment, but water drinking was not limited. Their legs were pre-shaved, and a forefoot vein was cannulated using an 18-gauge cannula. Blood samples (3 mL) were collected in a heparin tube at the

Table 1 – Propranolol extended-release tablets used in the development and validations of *in vitro–in vivo* correlation IVIVC.

	Formulations		
	ER-F	ER-S	ER-V
BioStudy	Internal	Internal	External
Ingredients (%) of tablets			
HPMC	28.0	60.0	38.4
Avicel	26.2	15.0	5.8
Lactose	20.8	0.0	27.3

Each tablet contains propranolol 100 mg.
HPMC = hydroxypropyl methylcellulose.

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