Modeling in Frequency Domain Used for Assessment of In Vivo Dissolution Profile

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Purpose. To present a model-dependent approach for the assessment of the in vivo drug dissolution profile based on in vitro data for the multiple unit dosage form, as an alternative to the numerical method proposed in the study by Hayashi et al., Pharm. Res. 12:1333–1337 (1995).

Methods. The data for aspirin granules administered to healthy subjects obtained in the above mentioned study were re-evaluated. The subject dissolution system was considered to consist of two subsystems connected in series, i.e., the subsystem describing the gastric-emptying process and the subsystem describing the intestinal dissolution process. The frequency response method was used to model the subject dissolution system.

Results. The model in vivo dissolution profile of aspirin, assessed as the integral of the model weighting function of the subject dissolution system, was in agreement with the in vivo cumulative absorption profile calculated by the Wagner-Nelson method.

Conclusions. Comparison of dynamic properties of the subject dissolution system with the subsystem describing the gastric-emptying process yielded quantitative confirmation of the decisive role of the gastric-emptying process in the in vivo drug dissolution after administration in the multi unit dosage form.

KEY WORDS: aspirin; pharmokinetics; dissolution; weighting function; convolution; bioequivalence.

INTRODUCTION

Hayashi et al. (1) proposed a numerical convolution method for the assessment of drug dissolution profiles in the gastrointestinal (GI) tract based on in vitro data for the enteric-coated multiple unit. The goal of our study was to present an alternative model-dependent approach, utilizing the theory of linear dynamic systems and the system modeling in the frequency domain (2).

MATERIALS AND METHODS

Materials

In study (1), enteric-coated aspirin granules were administered to healthy subjects. The enteric-coated BaSO4 granules were administered concurrently to determine the gastric-emptying rate of the subject. The dissolution profile of aspirin in the GI and the absorption profile in the systemic circulation were assessed by the numerical convolution and by the Wagner-Nelson method (3), respectively. In our study, the data from Table II and Table III of study (1) were re-evaluated and the results for the representative subject Y.S. are presented.

System Definitions

In our study, the subject dissolution system \( H_{DIS,GE} \) was considered to be complex and consisting of two subsystems connected in serial, i.e., the subsystem \( H_{GE} \) describing the gastric-emptying process and the subsystem \( H_{DIS} \) describing the intestinal dissolution process (Figure 1). The system \( H_{DIS,GE} \), the subsystems \( H_{GE} \) and \( H_{DIS} \) were defined using their transfer functions (4) expressed by Eq. 1, Eq. 2, and Eq. 3, respectively

\[
H_{DIS,GE}(s) = \frac{D(s)}{I(s)}, \quad (1)
\]

\[
H_{GE}(s) = \frac{E(s)}{I(s)}, \quad (2)
\]

\[
H_{DIS}(s) = \frac{D(s)}{E(s)}, \quad (3)
\]

in the Laplace s-domain, where \( D \) was aspirin dissolution rate in the GI tract, \( I \) was the input of aspirin granules, and \( E \) was the gastric-emptying rate. Eq. 4 was written for the transfer function \( H_{DIS,GE}(s) \)

\[
H_{DIS,GE}(s) = H_{DIS}(s) H_{GE}(s). \quad (4)
\]

Assessment of In Vivo Dissolution Profile

Neither the subsystems \( H_{GE}, H_{DIS} \) for the system \( H_{DIS,GE} \) were available for measurement and thus the following procedure was used to obtain their model transfer functions:

- The model transfer function \( H_{GE,REF}(s) \) was estimated using the in vivo system \( H_{GE,REF} \) corresponding to the administration of BaSO4 granules to the subject, and defined by Eq. 5

\[
H_{GE,REF}(s) = \frac{E_{BaSO4,gran}(s)}{I_{BaSO4,gran}(s)}, \quad (5)
\]

where \( E_{BaSO4,gran} \) was the gastric-emptying rate of BaSO4 granules after administration in the form

\[
I_{BaSO4,gran}(t) = Dose_{BaSO4} \delta(t), \quad (6)
\]
using the point estimates of the parameters of the optimal model transfer functions (7), (9). To compare dynamic properties of the dissolution system $H_{DIS,GE}$ and the subsystem describing the gastric-emptying rate $H_{GE}$, the criterion $C_{dyn}$, expressed by Eq. 15

$$C_{dyn} = \frac{2 - \int_0^{\infty} \left[ \frac{W_{M,DIS}(t)}{G_{DIS}} - \frac{W_{M,GE}(t)}{G_{GE}} \right] dt}{2} \times 100\%,$$

was proposed and applied.

The arguments presented were based on the assumption that aspirin kinetics was linear. All calculations were performed using the program CXT-MAIN (http://www.cpb.ukhsd.edu/ pkfin/pkin.html) (6–10).

**RESULTS**

The calculated normalized frequency response (5) of the system $H_{GE,REF}$ and its optimal seventh-order model in the frequency band [0,3] rad h$^{-1}$ is shown in Figure 2a. The left part of Table I summarizes the values of the CC and AIC criteria corresponding to this model (the first row) and to some other model candidates. The point estimates of the parameters of the optimal model transfer function $H_{M,REF}(s)$, used to approximate the model transfer function $H_{M,GE}(s)$, are listed in the first column of Table II. Figure 3a illustrates the gastric-emptying

**Comparison of System Dynamic Properties**

The model parameter $MRT_M$ of the subsystems $H_{GE}$, $H_{DIS}$ and the system $H_{DIS,GE}$ were determined according to Eq. 14

$$MRT_M = b_1 - \frac{a_1}{a_0},$$

**Fig. 2a and 2b.** Polar plots of the calculated normalized frequency responses of the systems $H_{GE,REF}$ and $H_{DIS,DIS}$ (full circles) and their optimal models (full lines) in the complex plane.