Multi-fraction Absorption Model for Pharmacokinetic Analysis of Diltiazem Tablets

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Pharmacokinetic, parameters were evaluated using multi-fraction absorption model of diltiazem in mongrel dogs. A comparison was made between the conventional one compartment model (model A) and one compartment two-fraction absorption model (model B). It was found from this study that model 1 B could explain the concentration-time profile of diltiazem better compared to model 1 A.

PLASMA drug concentration data after oral administration of dosage forms were usually analyzed using compartment models with first-order absorption and elimination rate constants. In bioavailability assessment for dosage form development, details of absorption kinetics are important and approximation by an infinite first-order rate process is not always sufficient.[1] However, there are several cases which are not satisfactorily simulated by the conventional models due to dissolution characteristics of dosage forms or physiological factors in the gastrointestinal tract. Discontinuous absorption models[1,2] have been proposed for the analysis of plasma drug concentration data with irregular absorption profiles, in which the absorption rate constant is variable through out the process of absorption. However, these models are not always suitable.

In this report, we demonstrate the use of a multi-fraction absorption model applied to evaluate pharmacokinetics of diltiazem HCl in comparison to the conventional one compartment evaluation procedure. In this model, drug in the gastrointestinal tract is assumed to be divided into two fractions, each with its respective lag time and absorption rate constant.

Murata and Moda (1994)[3] used these models to investigate the pharmacokinetic absorption behavior of sustained release diltiazem preparation in dogs.

EXPERIMENTAL

Materials

Dilzem tablets 60 mg (Diltiazem HCl, Torrent Pharmaceuticals, India) were obtained from local market. HPLC grade Acentonitrile was purchased from Spectrochem Pvt. Ltd., Bombay. All other chemicals used are of analytical grade.

In vivo experiments

Mongrel dogs were fasted for 18th prior to drug administration. One tablet of diltiazem HCl was administered orally to each of three dogs by compulsive swallowing with 30 ml of water. Blood samples were taken at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 15 h. The plasma samples were frozen at -20°C until analysis.

Determination of diltiazem in Plasma :

Diltiazem was extracted from spiked or sample plasma by using disposable extraction cartridges containing C_{18} packing material.

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Table 1: Pharmacokinetic Parameter for Diltiazem in Dogs fitted to Model B

Parameter	Dog		
	1	2	3
X_{a1} mg	30.1	46.9	34.2
X_{a2} mg	29.9	13.8	25.8
K_{a1} h^{-1}	0.6010	0.5353	1.0811
K_{a2} h^{-1}	0.2437	1.2769	5.3506
K_{el} h^{-1}	0.7539	0.7294	0.8083
T_1 h	0	0	0
T_2 h	1.75	1.45	1.46
Vd/F L	0.0778	0.0911	0.1621

The plasma was passed through cartidges under negative pressure of 10 lb/sq in. Then the cartidges were washed with 2x2 ml of double distilled water and dried under a stream of nitrogen. After drying the drug was eluted from cartidges using 2x2 ml of dichloromethane. Then dichloromethane was evaporated under a stream of nitrogen and the residue was reconstituted with 0.01 M HCl. From this solution 50 ul was injected into the HPLC system.

The mobile phase consisted of acetonitrile:water (40:60) with a final pH 4.0 adjusted with 0-phosphoric acid. The flow rate was 1.5 ml/min. Samples were injected into column (Pecosil ODS 10 um, size 250 cm x 4.6 mm, Perkin Elmer, USA) and the absorptivity of the mobile phase was monitored at 238 nm using a variable wavelength UV detector (Perkin Elmer UV/Visible spectrophotometer detector LC 290). The output was recorded on an integrator (PE Nelson Model 1020, Perkin in Elmer, USA). The retention time of diltiazem was found to be 4.5 min.

Pharmacokinetic Analysis

Plasma diltiazem concentrations after oral administration of diltiazem HCl tablet to three dogs were analyzed with the conventional one compartment model (model A) and with the two- fraction

absorption model[4] (model B) shown appendix. In vivo release profiles of diltiazem were calculated by the Wagner-Nelson method.[5] A non-linear regression program was developed in our laboratory similar to the microcomputer program MFA-MULTI[6] that was developed for multi-fraction absorption models based on a simplex method[7] and used for the analysis of serum diltiazem concentration data using integrated equations:

$$C = C_i = \sum_{i=1,2} FX_{ai}/Vd\, K_{ai}/(K_{ai}-K_{el})\, (e^{-K_{el}\,(t-T)} - e^{-K_{ai}(t-T)})$$

$$C = C_1 \text{ for } (T_1 \le t < T_2)$$

$$C = C1 + C2 \text{ for } (t>T_2) \dots\dots\dots\dots\dots\dots 1$$

In eg. 1, X_{ai} is the amount of drug in the gastro-intestinal tract of ith fraction (i = 1,2), K_{ai} is the absorption rate constant of ith fraction (i = 1,2), K_{el} is the elimination rate constant, Vd is the volume of distribution, F is the fraction of absorption, and T_i is the lag time for the absorption of ith fraction (i=1,2).

RESULTS AND DISCUSSION

The dissolution profile of the tablets used in this study is shown in **Fig. 1**. Typical mean serum con-
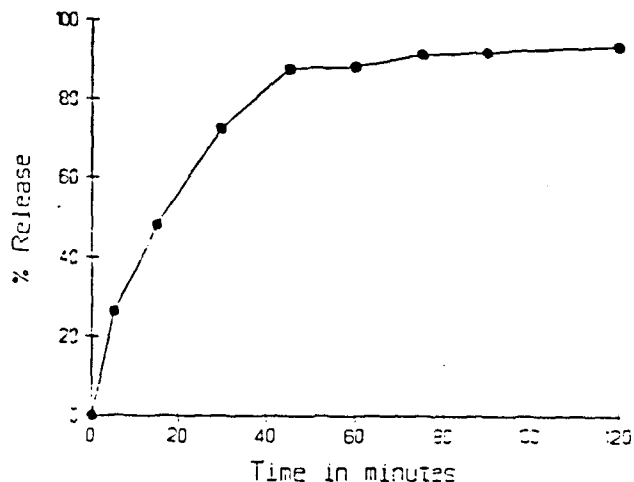
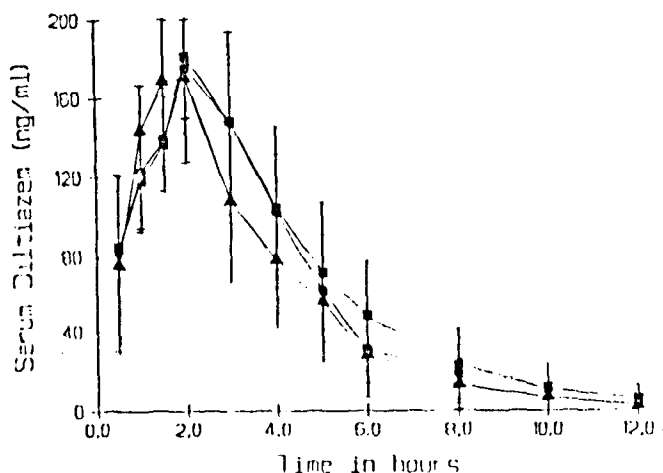**Fig.1. Dissolution profile of diltiazem HCl tablet used in this study.**

Fig 2. Mean (± S.D) serum concentration of diltiazem In dogs. Key:(O) actual concentration, (▲) curve fitted using model A, (□) curve fitted using model B.

Table 2: Curve fitting to serum diltiazem concentration in dogs by using model A.

Dog	Equation
1.	$C = -821.1\ e^{-0.4760(t-0)} + 924.9e^{-0.3198(t-0)}$
2.	$C = -2639.4\ e^{-0.7235(t-0.14)} + 2527.1\ e^{-0.5504(t-0.14)}$
3.	$C = -1303.9\ e^{-0.9639(t-0.24)} + 1280.5\ e^{-0.7269(t-0.24)}$

centration data from 3 male mongrel dogs after oral administration of a 60 mg tablet of diltiazem HCl are shown in **Fig.2**. The figures also depict the curve fitted lines using conventional one compartment
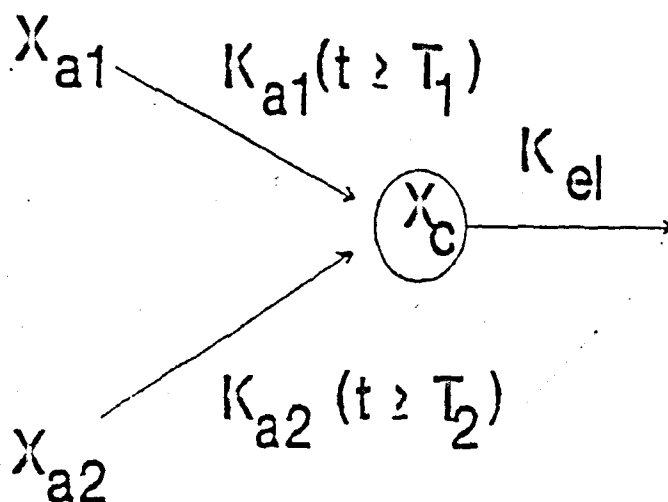
APPENDIX

Model A

One compartment model with one first-order absorption process and one elimination process.

$$X_a \xrightarrow{\ K_a(t \geq T)\ } X_c \xrightarrow{\ K_{el}\ }$$
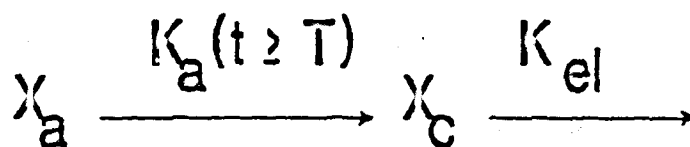
Model B

One compartment model with first-order absorption process from two fractions and one first-order elimination process.

where,

X_a = the amount of drug in the gastrointestinal tract

X_{ai} = the amount of drug in the gastrointestinal tract of the ith fraction (i = 1,2)

X_c = the amount of drug in the central compartment

K_a = absorption rate constant

K_{ai} = absorption rate constant of the ith fraction (i = 1,2).

F = fraction of absorption

T = lag time for absorption

T_i = lag time for absorption of the ith fraction (i = 1,2)

model (model A) and multi-fraction absorption model (model B). The serum diltiazem concentration data could not be fitted to model A, but could be well fitted to model B. As shown in figures 2, the observed and calculated plasma concentrations were in good agreement with each other, supporting the validity of the multifraction absorption model (model B). AICs for the model A and model B were 38.6 ± 4.5 and 29.4 ± 9.2, respectively. **Table 1** shows the pharmacokinetic parameters estimated using the model B. Table 2 shows the equations used for the fitting of diltiazem serum data by model A in 3 dogs. In model B diltiazem seemed to be divided into two fractions in the gastrointestinal tract with respective absorption rate constants. It is concluded that multi-fraction absorption models are applicable for the analysis of plasma drug concentration data with irregular absorption profiles.

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