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MOMENT ANALYSIS FOR THE EVALUATION OF IN VITRO DRUG RELEASE AND IN VIVO BIOAVAILABILITY OF THEOPHYLLINE MICROCAPSULES*

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ABSTRACT

Statistical moment analysis has been used to establish an in vitro-in vivo correlation for five types of theophylline ethylcellulose microcapsules prepared by using various concentrations of ethylene-vinyl acetate (EVA) copolymer as a coacervation-inducing agent. The concentration of EVA copolymer was found to be played an important function in the controlled release of theophylline microcapsules. Correlations were found between the in vitro dissolution behavior, e.g., $MDT_{0\rightarrow 7,\text{in vitro}}$, and the

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rate of bioavailability, e.g., Cmax, Tmax, $MDT_{in\ vivo}$ or $MRT_{0\to27}$, although there was no valid correlation with the extent of bioavailability, e.g., $AUC_{0\to27}$. Thus, moment analysis by studying the quantitative in vitro-in vivo correlations relating to drug release was validated.

INTRODUCTION

Statistical moment analysis has recently been developed and used as a noncompartmental approach to biopharmaceutical evaluations (1-4). The mean residence time (MRT) concept has been defined as a magnitude of the rate of bioavailability and also employed for the evaluation of the in vitro mean dissolution time (5). Recently, moment analysis has been suggested as a valuable method in studies of quantitative in vitro-in vivo correlations related to drug release (6).

We have previously determined that theophylline ethylcellulose microcapsules prepared by using ethylene-vinyl acetate (EVA) copolymer as a coacervation-inducing agent, showed a sustained release behavior in vitro and in vivo, but this was dependent on the concentrations of the coacervation-inducing agent used (7-9). The compression force and excipients

used significantly influenced the tablet properties and dissolution behavior of the compressed theophylline microcapsules, however, the particle size of microcapsules appeared less dependent (10).

The aim of this study is to investigate whether statistical moment analysis is applicable for in vitro-in vivo correlation of theophylline ethylcellulose microcapsules.

MATERIALS and METHODS

Materials:

Theophylline anhydrous powder was obtained from Wako Pure Chem. Co.(Tokyo, Japan). Ethylene-vinyl acetate (EVA, VA content: 28%) was obtained from Toyo Soda Manufacturing Co. (Tokyo, Japan). Ethylcellulose (100 cps) was purchased from Dow Chem. Co. (MI., USP). The remaining reagents were analytical reagent grade. The Sprague-Dawley rats were male rats purchased from the Animal Center of National Yangming Medical College, Taiwan, ROC and weighed 300-350 g.

Dosage forms:

Five different types of theophylline microcapsules were prepared by the phase separation method using five concentrations (0, 0.85, 1.7, 3.3 and 5 %) of EVA copolymer as a coacervation-inducing agent, as

described in previous studies (11-13). 250-450 um of particle size theophylline microcapsules were used for this experiment.

In vitro dissolution studies:

The in vitro dissolution rates for the theophylline microcapsules in 500 ml of pH 1.2 medium at 37 °C was determined by using the rotating basket method (100 rpm), according to USP XXI. Aliquots of the dissolution medium were assayed for theophylline by ultraviolet spectrophotometer at 270 nm (UVIKON 810, Kontron, Switzerland). Each test was carried out in triplicate.

In vivo bioavailability studies:

The SD rats were fasted from the night before and throughout the experiment. Each dosage form was tested in 6-8 male SD rats. Each rat was respectively administered a dose of 40 mg/kg of theophylline powder or an equivalent dose in microcapsules form. The test sample was given orally with 10 ml of water from a feeding tube. Blood samples were collected at prescribed time postdosing from a cannula in the arteria jugularis. The samples were centrifuged, the serum was removed and stored at -20 °C until analysis.

Theophylline concentrations in the serum were determined by EMIT method (Syva).

Data analysis:

In vitro:

If the dissolution process in vitro is regarded as statistically randomized variables, a moment analysis can be used for the description of the time course (5). The in vitro mean dissolution time ($MDT_{in\ vitro}$), describing the first moment of the dissolution rate-time curve, is defined as follows (14).

$$MDT_{in\ vitro} = \int_0^\infty t(dm/dt)dt / \int_0^\infty (dm/dt)dt \qquad (1)$$

where (dm/dt) is the time function of the dissolution rate. The second moment of the concentration time curve can be used to define the in vitro variance of dissolution time ($VDT_{in\ vitro}$).

$$VDT_{in\ vitro} = \int_0^\infty (t-MDT)^2 \frac{dAD(t)}{dt} dt / \int_0^\infty \frac{dAD(t)}{dt} dt \qquad (2)$$

In vivo:

The biopharmaceutical parameters (Cmax, Tmax and $AUC_{0\to27}$) were determined from the serum concentration of theophylline after a single dose administration. The Cmax was chosen as the highest observed serum theophylline concentration and Tmax was the time of the

maximum measured serum concentration. $AUC_{0\to27}$ was calculated by using the trapezoidal rule from zero to 27 hours.

The time course of plasma concentration (Cp) following a single dose is usually regarded as a statistical distribution curve (1). The in vivo mean residence time (MRT) is defined as the mean time for drug molecules to transit through the body, which involves the in vivo release kinetic from the dosage form, absorption into the body and all disposition processes. The MRT is calculated from the ratio between the area under the first moment of the plasma concentration curve and the area under the zero moment:

$$MRT = \int_0^\infty tCp\ dt / \int_0^\infty Cp\ dt \qquad (3)$$

The variance of residence of a drug in the body (VRT) is defined as followed.

$$VRT = \int_0^\infty (t-MRT)^2\ Cp\ dt / \int_0^\infty Cp\ dt \qquad (4)$$

The in vivo mean dissolution time ($MDT_{in\ vivo}$) from the microcapsules in the body is calculated according to Eq. 5:

$$MDT_{in\ vivo} = MRT_{microcapsules} - MRT_{solution} \qquad (5)$$

Where $MRT_{microcapsules}$ and $MRT_{solution}$ are the mean

residence time for the microcapsules and the aqueous solution, respectively.

In using the above equations, the moments were calculated by means of the trapezoidal integration of the time course curve. The moments obtained from the experimental data were carried out on a personal computer with programming in BASIC. Data are expressed as the mean and standard error (S.E.). The paired Student's t-test was used for statistical analysis.

RESULTS and DISCUSSION

The biopharmaceutical parameters (Cmax, Tmax, $AUC_{0\to27}$) were determined from the serum theophylline concentration time profiles after single oral administration of theophylline microcapsules. The in vitro mean dissolution time, $MDT_{0\to7,\ in\ vitro}$ describing the first moment of the dissolution rate time curve is also calculated from Eq. 1. Fig. 1 shows the relationship between the biopharmaceutical parameters and $MDT_{0\to7,\ in\ vitro}$. It is obvious that there were statistically significant correlations between Cmax and $MDT_{0\to7,\ in\ vitro}$ (r=0.9426), and Tmax and $MDT_{0\to7,\ in\ vitro}$ (r=0.9647); whereas $AUC_{0\to27}$ and $MDT_{0\to7,in\ vitro}$ (r=0.0863) showed no correlation. This implies that in vitro mean dissolution time correlated

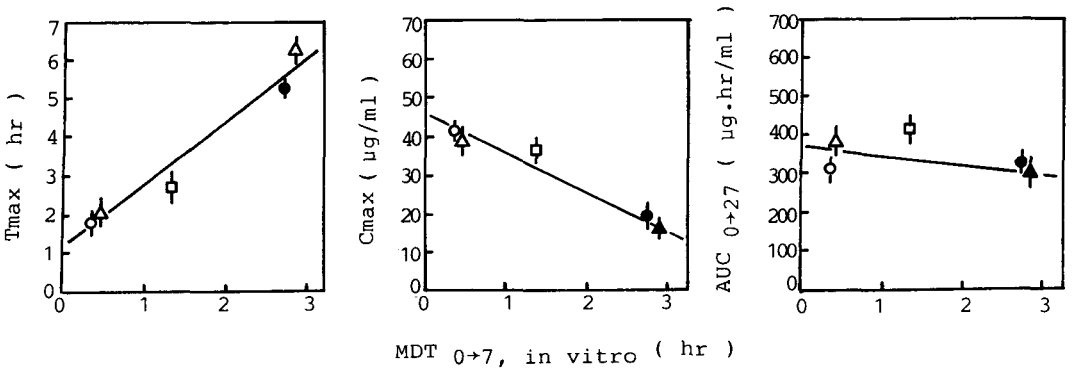
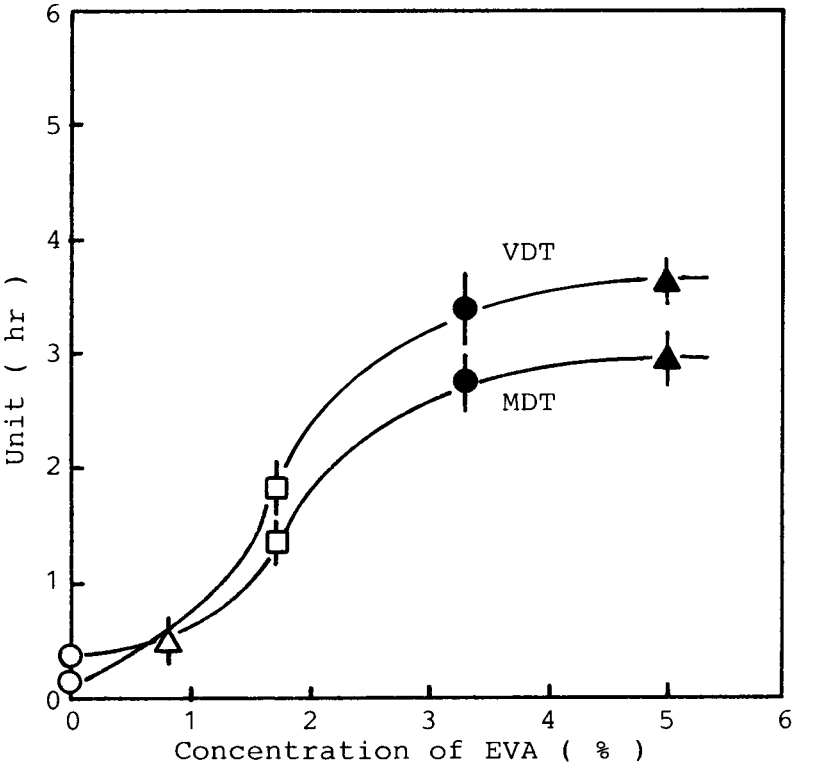


FIG. 1
Correlation of MDT with Tmax, Cmax and AUC of theophylline microcapsules
Key: ○, 0%; △, 0.83%; □, 1.7%; ●, 3.3%; ▲, 5%; the bars indicate SEM

better with Cmax and Tmax, which corresponds to the rate of absorption, than with $AUC_{0\rightarrow27}$ which reflects the extents of absorption. The no valid correlation between in vitro mean dissolution time and extent of absorption may be due to the fact that the extent of absorption was significantly affected by the various physiological factors in the GI tract, compared to the rate of absorption (9,15).

The effect of EVA concentrations on the moment of dissolution curves ($MDT_{0\rightarrow7,\ in\ vitro}$, $VDT_{0\rightarrow7,\ in\ vitro}$), and moment of serum concentration profiles ($MRT_{0\rightarrow27}$ and $VRT_{0\rightarrow27}$) are shown in Figs. 2 and 3, respectively. A sigmoid curve is found in Fig. 2, whereas a good linear relation is found in Fig. 3. The more the



Key: see FIG. 1

FIG. 2

The effect of EVA copolymer concentration used on the MDT and VDT of theophylline microcapsules

concentration of EVA copolymer, the higher the value of moment parameters. The result suggests that MRT and MDT significantly depend on the concentration of EVA copolymer used. This implies that the concentration of EVA copolymer plays an important function in the controlled release of theophylline microcapsules in vitro and in vivo.

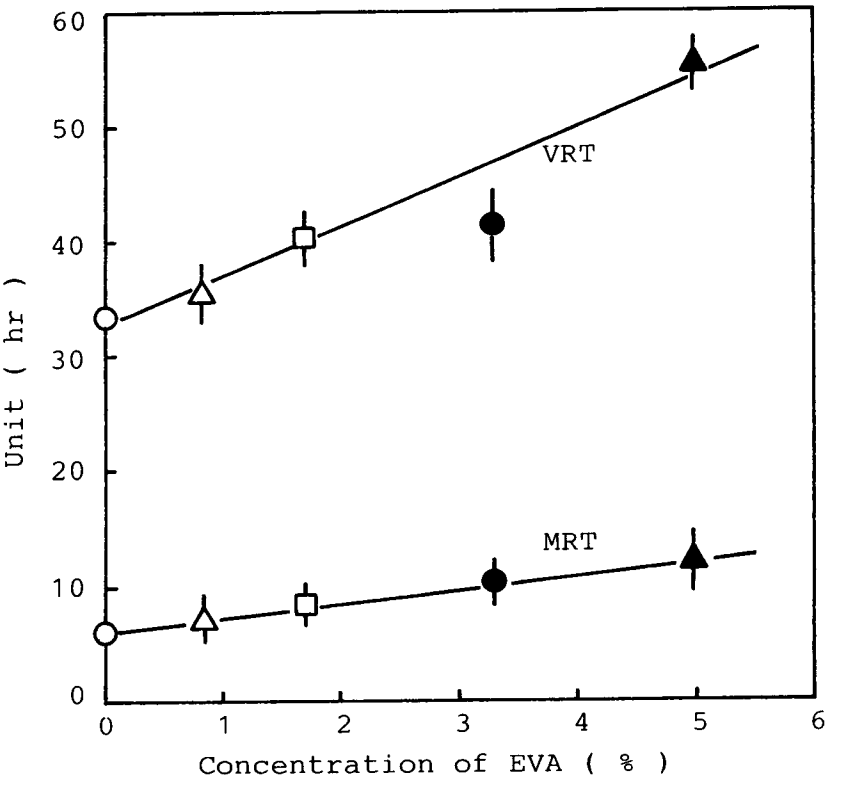


FIG. 3

The effect of EVA copolymer concentration used on the MRT and VRT of theophylline microcapsules
Key: see FIG. 1

The relationship between $MRT_{0\rightarrow27}$ and $MDT_{0\rightarrow7,\ in\ vitro}$ of the different types of microcapsules is shown in Fig. 4. The mean regression line was found to be $MRT_{0\rightarrow27} = 1.937\ MDT_{0\rightarrow7,\ in\ vitro} + 5.889$, the correlation coefficient (r) was 0.9474. This result indicates that there is a quantitative in vitro-in vivo correlation for theophylline which is

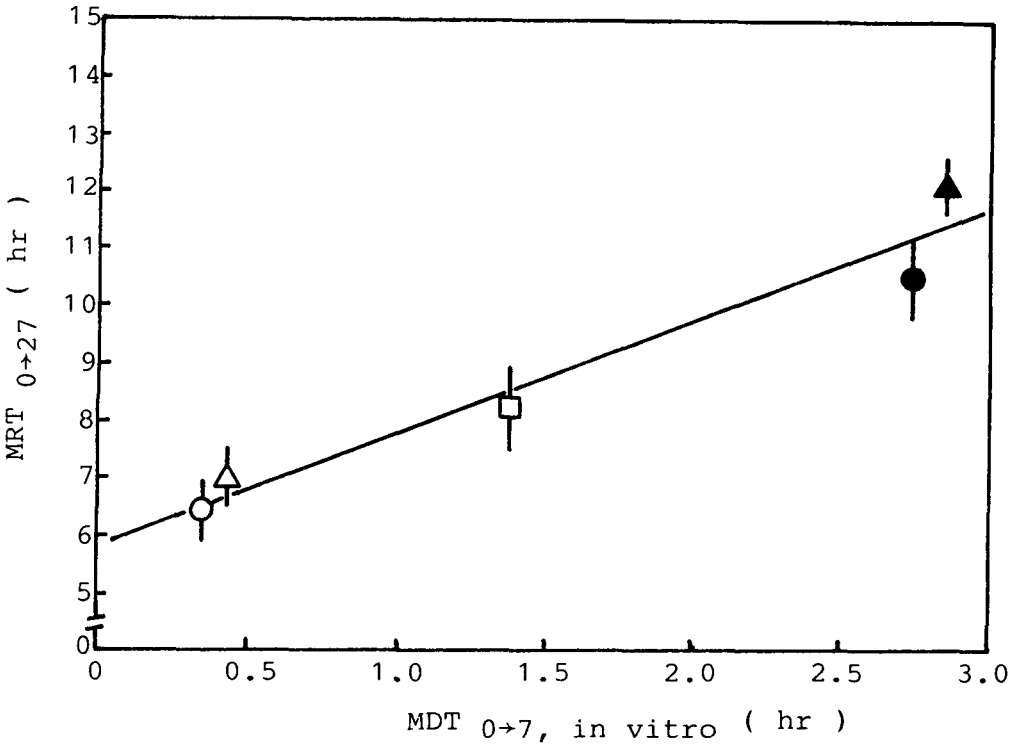


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FIG. 4

Correlation between MRT and MDT for theophylline microcapsules

encapsulated into microcapsule dosage form. The intercept on the y-axis, 5.88, can be interpreted as the mean in vivo residence time for an oral aqueous solution, $MRT_{solution}$. The value of $MRT_{solution}$ was substitued into Eq. 5 and the data of $MDT_{in\ vivo}$ was obtained. A linear relationship was also obtained

for theophylline microcapsules between mean dissolution time in vivo and in vitro when applying statistical moment analysis.

From the above results, it is obvious that moment analysis can easily help to establish correlation between the in vitro dissolution behavior and in vivo bioavailability of sustained release theophylline microcapsules.

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