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APPLICATION OF ANALOGUE COMPUTATIONS TO DISSOLUTION MODEL DEVELOPMENT

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ABSTRACT

Analogue computations of the influence of variable experimental parameters on the dissolution kinetics of a drug have been applied to the development and programming of a flow-through type dissolution model. The investigations have been performed with non-formulated Phenylbutazone capsules. The analogue computations revealed definite values for a pH-time-profile and an in-vitro-absorption rate constant, if the simulations were related to in vivo-data. Thus, programming a dissolution device in this way the results meet both analogue computer simulation and in vivo-absorption kinetics.

INTRODUCTION

Dissolution models such as rotating basket or paddle are used in technological development and tes-

ting of oral drug preparations[1,2]. For these wellknown dissolution models the experimental parameters volume, pH of the medium, and agitation are fixed. This measure may cause differences between dissolution test results and in vivo-data. Flow-through type models are more adaptable to in vivo-properties because of variable experimental parameters such as flow rate and pH-time-profile which have to be programmed[3,4].

Analogue computations are a usual tool for pharmacokinetic work[5], but they have been unusual in the simulation of dissolution kinetics for the development of a dissolution test device. The present investigation deals with a new application of analogue computations to dissolution model development. Analogue computations are able to simulate in a very short time the influence of variable experimental parameters on the dissolution of a drug in a model. The aid of these simulations is in the evaluating of those experimental necessities which give a good correlation between dissolution test and in vivo-data. The purpose of this test was carried out with Phenylbutazone. Analogue computations were achieved with pH-time-profiles, which consider the pH- and pK_a-dependent solubility of Phenylbutazone. The effects of these pH-time-profiles on this solubility were made visible by solubility-time-profiles. The pseudo first-order absorption kinetics is also taken into consideration as in an organism after application of a drug an absorption process simultaneously takes place. Thus a dissolution profile with simultaneous absorption process results. With respect to the variation of resulting absorption kinetics compared to in vivo-data of a non-formulated capsule two important parameters have to be derived for the construction and programming of a dissolution test device:

the pH-time-profile,
and the absorption rate constant.

The results of analogue computations, of in vivo-data, and of dissolution model investigations will then be related to one another.

METHODS AND MATERIALS

Fig. 1 shows in detail the complete circuit for the analogue computations[6]. It consists of an integrator element at the top of the figure which construct the time axis (abscissa) with the aid of a time scaling factor β. All other computing elements of this circuit can be used alone or connected as shown. Each output of the computing elements was used to draw an ordinate function. The following functions were simulated:

pH-time-profile	pH (t)
solubility-pH-profile	L (pH)
solubility-pH-time-profile	L (pH,t)
dissolution-time-profile with simultaneous absorption	AL (t)
absorption kinetics	ABS (t)

The differentiation of L is necessary because of to avoid double integration. The variations of pH-time-profiles and of rates of absorption were achieved by two potentiometers "k" (pH-time-profile) and "k_a" (absorption rate constant).

in vivo-Data

Plasma level data of Phenylbutazone after application of a non-formulated capsule, which has been deter-

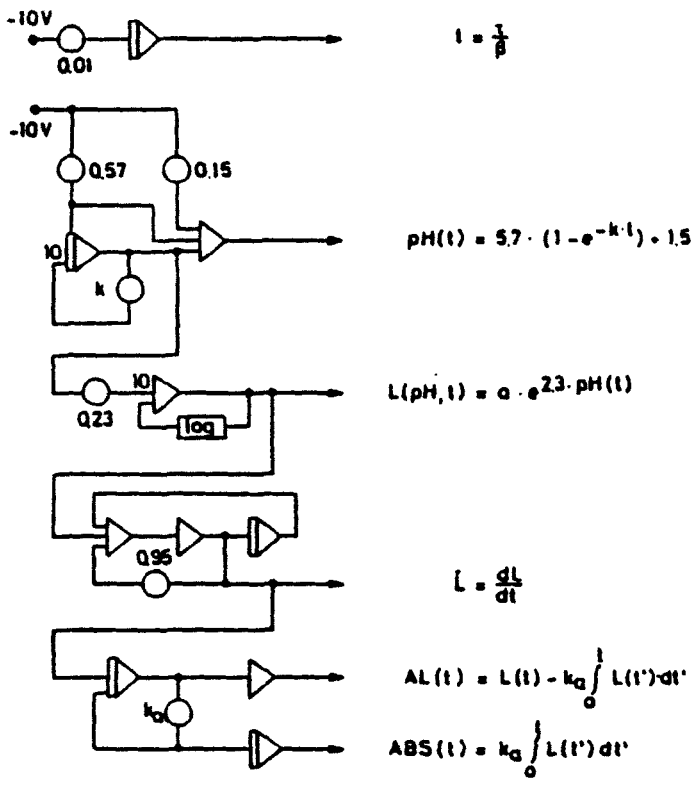

FIGURE 1

Analogue Computer Circuit for the Simulation of Dissolution and in vitro-Absorption Kinetics of Phenylbutazone

mined by LEESON et al.[7] has been used to evaluate the rate constant of absorption[8].

Dissolution Model Investigations

The device of a flow-through type dissolution model and results of investigations has been published elsewhere[4].

RESULTS

pH-Time-Profiles

The simulations of pH-time-profiles were made for the range of pH 1.5 to 7.2 according to a possible normal pH-profile in the human gastrointestinal tract. The pH-time-profiles were constructed by an exponential equation. The results of these simulations are shown in fig. 2. The analogue computer circuit with its dimensions is shown inside the figure.

The variation of the first-order rate constant k ranges from 0.3 to 0.02 [min^{-1}]. These variations re-

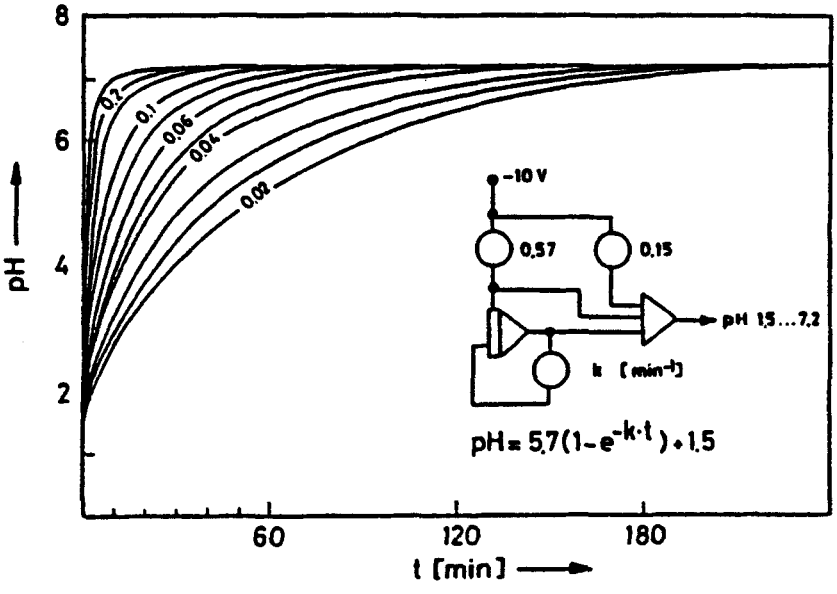

FIGURE 2

Analogue Computer Simulation of pH-Time-Profiles

sults in time values of 20 minutes to 240 minutes reaching a pH of 7.2.

pH-pK_a-dependent Solubility of Phenylbutazone

The solubility of Phenylbutazone depends on its pK_a-value (4.5) and the pH of the medium. Solubility data of Phenylbutazone are used to apply a simplified solubility function according to that of KREBS and SPEAKMAN[9]. This solubility-pH-function (fig. 3) is simulated by a zero-order pH-profile for the abscissa as it is used for time axis construction and by a positive exponential device as shown in detail in fig. 1.

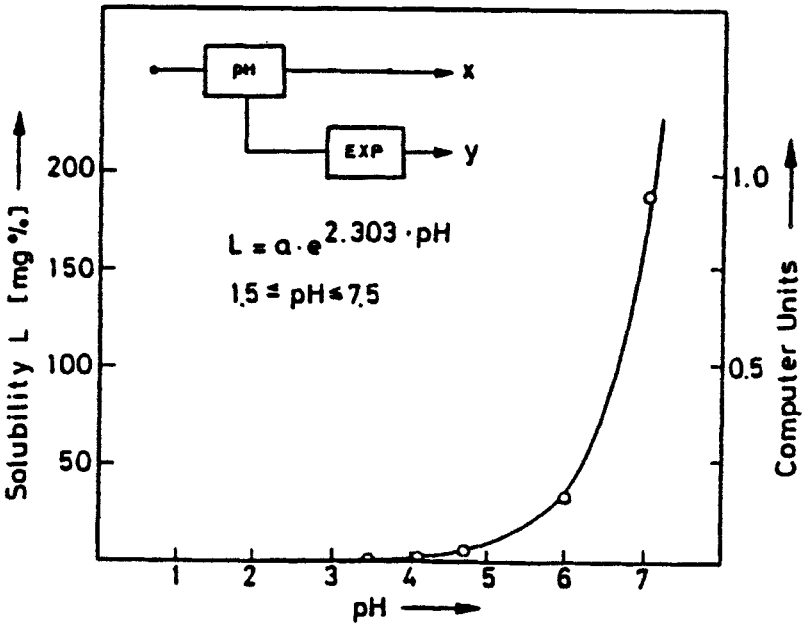

FIGURE 3

Analogue Computer Simulation of the pH-dependent Solubility of Phenylbutazone

The resulting function for simulating solubility data of Phenylbutazone is

$$L = a \cdot e^{2.303 \cdot pH} \quad \text{for } 1.5 \leq pH \leq 7.2.$$

The origin of the computing constant "a" is miscellaneous. It includes the maximum solubility value of 200 mg% at pH 7.2, depends on the pK_a-value of Phenylbutazone, and is related to the minimum solubility at pH 1.5. As can be seen from fig. 3 all solubility data can be described by this function.

Influence of pH-Time-Profiles on Solubility-Time-Profiles

The solubility-time-profiles of Phenylbutazone are simulated under the influence of various pH-time-profiles, which have been described above. These simulations are shown in fig. 4. Maximum solubility of 1.0 computer units is defined by 200 mg% according to a pH of 7.2.

A fast pH-time-profile with a rate constant of 0.2 [min^{-1}] requires 45 minutes to reach a maximum solubility. A smaller rate constant e.g. of 0.06 [min^{-1}] results in 180 minutes for maximum solubility.

Differentiation of the Solubility-Time-Profiles

The solubility-time-profiles have to be differentiated for further simulations in order to avoid double integration. This differentiation is performed by the circuit inside fig. 5. The curve dL/dt is generated from the solubility-time-profile L, the general form of which is illustrated in fig. 5.

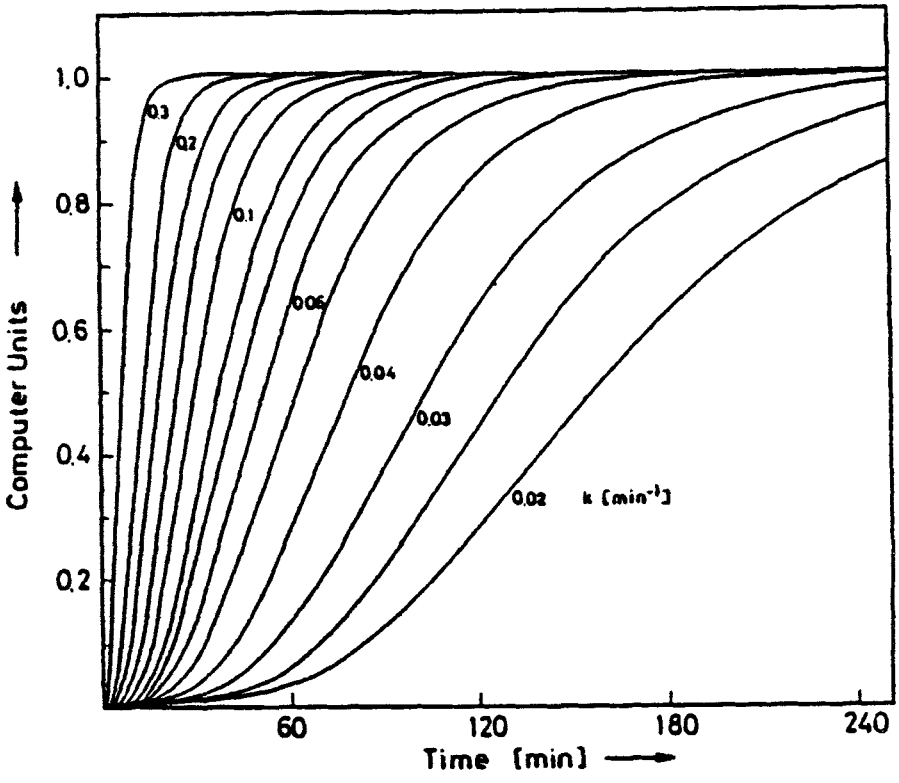

FIGURE 4

Analogue Computer Simulation of Solubility-Time-Profiles of Phenylbutazone; Variation of pH-Time-Profiles

Dissolution Kinetics with Simultaneous Absorption

An absorption process with a first-order rate constant is simultaneously connected to the differentiated solubility-time-profile. This measure results in the solubility-time-profile by integration with simultaneous absorption, which indicates possible dissolution kinetics in a flow-through type model.

Dissolution profiles were obtained under the influence of different rate constants of pH-time-profiles

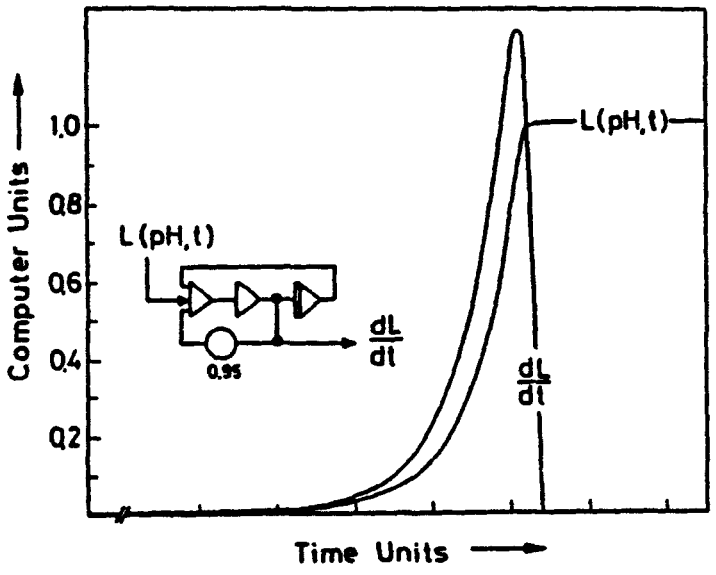

FIGURE 5
Differentiation of a Solubility-Time-Profile

and absorption kinetics. Fig. 6 shows an example of a constant rate of absorption with k_a = 0.828 [h^{-1}] with various rates of pH-time-profiles.

The continuous processes of increasing dissolved drug amounts by pH- and time-dependent solubility and of simultaneous decreasing by absorption characterize dissolution profiles with a maximum. This maximum rises to 0.78 computer units at 30 minutes with a rate constant of pH-time-profile of 0.2 [min^{-1}]. The maximum decreases to lower values with decreasing rate constants of pH-time-profile and the time for reaching this maximum increases simultaneously.

A constant rate of pH-time-profile has been used to demonstrate the influence of different absorption rate constants (fig. 7). The maximum amounts of dis-

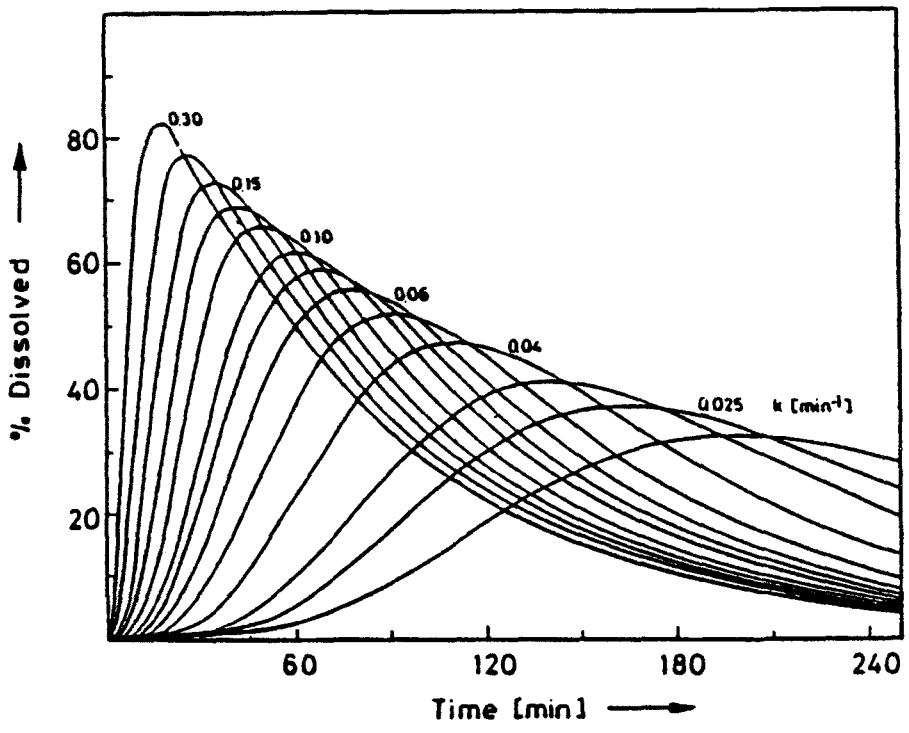

FIGURE 6

Analogue Computer Simulation of Dissolution Kinetics with Simultaneous Absorption (k_a=0.828 h^{-1}; Variation of pH(t))

solved drug do not change with this variation, but the time to reach this maximum decreases with decreasing rate constants of absorption.

Absorption Kinetics

The former programming has been used to draw the various resulting absorption curves. These absorption curves should be related to in vivo-absorption data in order to get parameters for the dissolution model development. Firstly, the absorption kinetics are generated

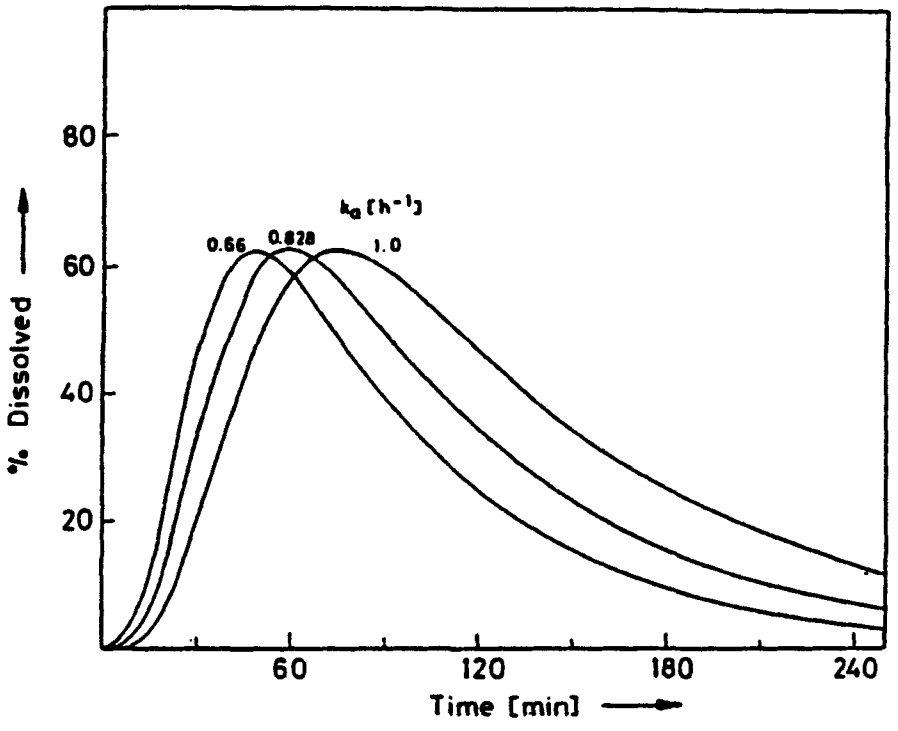

FIGURE 7

Analogue Computer Simulation of Dissolution Kinetics with Simultaneous Absorption (pH(t) by k=0.08 min^{-1}; Variation of k_a)

by various pH-time-profiles with a constant rate of absorption, and secondly, by a constant pH-time-profile with different rates of absorption (fig. 8 and 9).

The in vivo-absorption process of a non-formulated capsule was best described by a pH-time-profile with a rate constant k = 0.08 [min^{-1}] and an absorption rate constant k_a = 0.828 [h^{-1}]. The analogue computation of absorption kinetics with these data meets all in vivo-data past 45 minutes. The first three in vivo-values up to 45 minutes are higher than the simulated values within an absolute deviation of 6%.

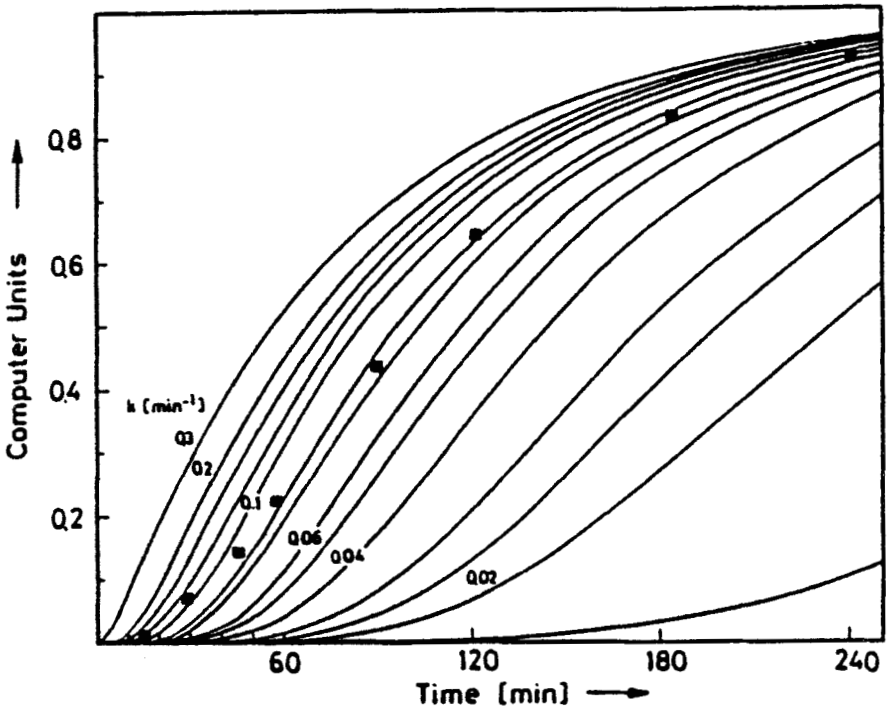

FIGURE 8

Analogue Computer Simulation of Absorbed Drug Amounts (k_a=0.828 h^{-1}; Variation of pH(t); ■ : in vivo-Data after LEESON, 1975)

Dissolution Model Programming

The analogue computations of the influences of various pH-time-profiles and absorption rates result in two important values:

1. pH-time-profile with k = 0.08 [min^{-1}]
2. rate constant of absorption k_a = 0.828 [h^{-1}],

which meet the in vivo-data after application of a non-formulated capsule. These values are the programming parameters for a flow-through type dissolution model[4]. The absorption rate of k_a = 0.828 [h^{-1}] is maintained

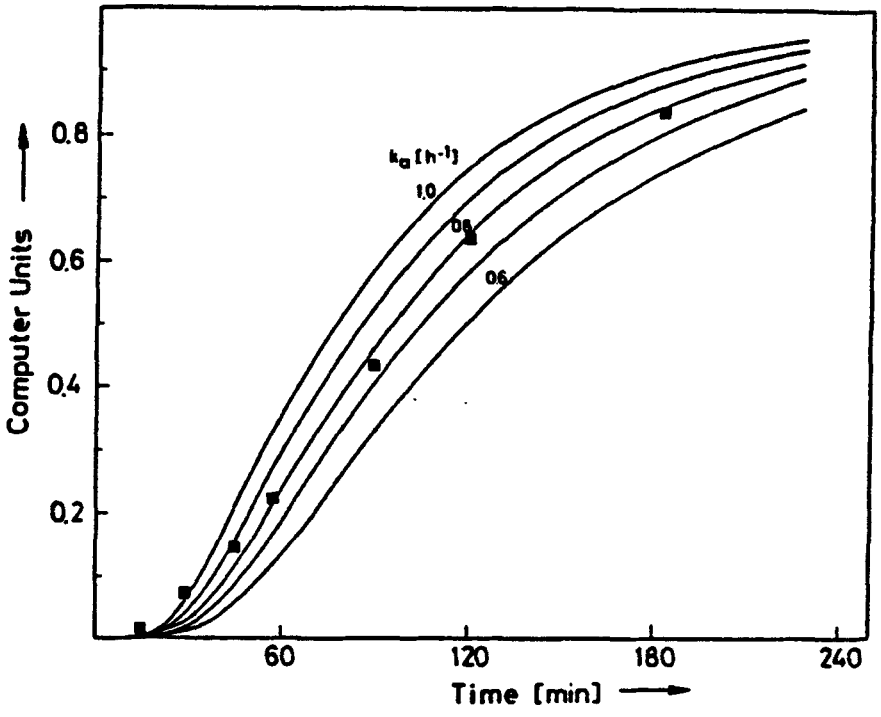

FIGURE 9

Analogue Computer Simulation of Absorbed Drug Amounts (pH(t) by k=0.08 min^{-1}; Variation of k_a; ● : in vivo-Data after LEESON, 1975)

by a flow rate of 0.86 ml/min and a dissolution volume of 62.3 ml. To meet the requirements of the pH-time-profile with k = 0.08 [min^{-1}] an acidic medium with decreased capacity has to be used, which is continuously neutralized by artificial intestinal buffer solution with the flow rate mentioned above.

Relation between Analogue Computations and Dissolution Model Investigations

Two examples of dissolution model investigations with different acidic capacity of the medium meet the

analogue computation curves for Phenylbutazone with pH-time-profiles described by rate constants of k = 0.10 [min^{-1}] and k = 0.08 [min^{-1}] respectively. The analogue computer rate of absorption is k_a = 0.828 [h^{-1}]. The absorption rate in the dissolution model has been increased to 0.88 [h^{-1}] to give a correlation (fig. 10).

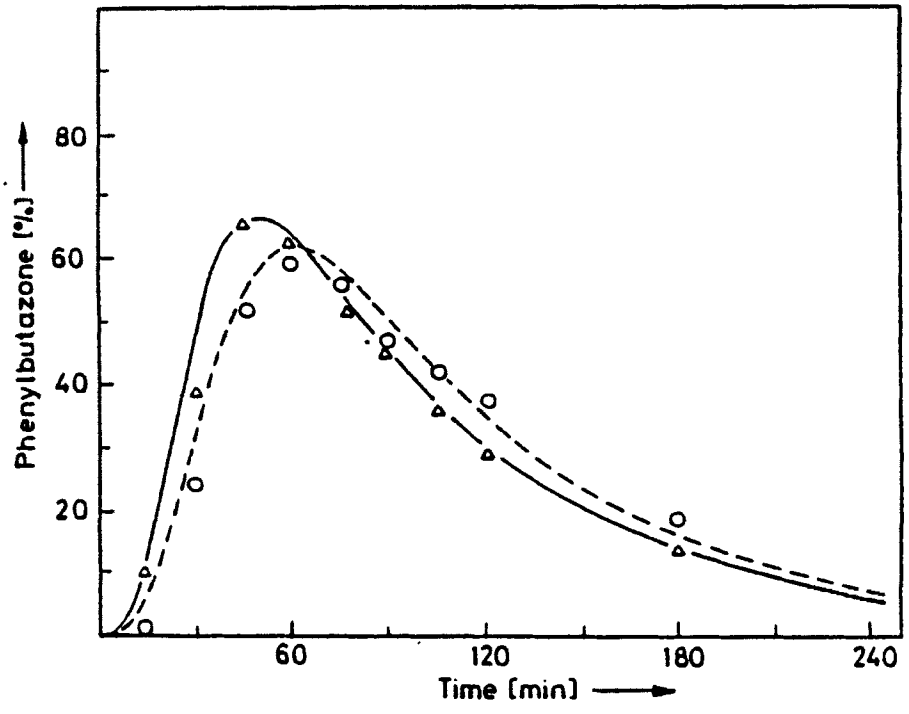

FIGURE 10

Relation beetween Analogue Computations and Dissolution Model Investigations of Phenylbutazone

Analogue Computations:

—— pH(t) by k=0.10 min^{-1}

--- pH(t) by k=0.08 min^{-1}

k_a=0.828 h^{-1}

Dissolution Model Investigations (nonform. Capsule):

▲ pH(t) by 0.2 rel. acid.

○ pH(t) by 0.3 capacity

k_a=0.88 h^{-1}

Correlation Test

The basis for a correlation is absorption kinetics, which has been obtained by analogue computations, in vivo-data, and dissolution model investigation. This correlation test is shown in detail in fig. 11: open

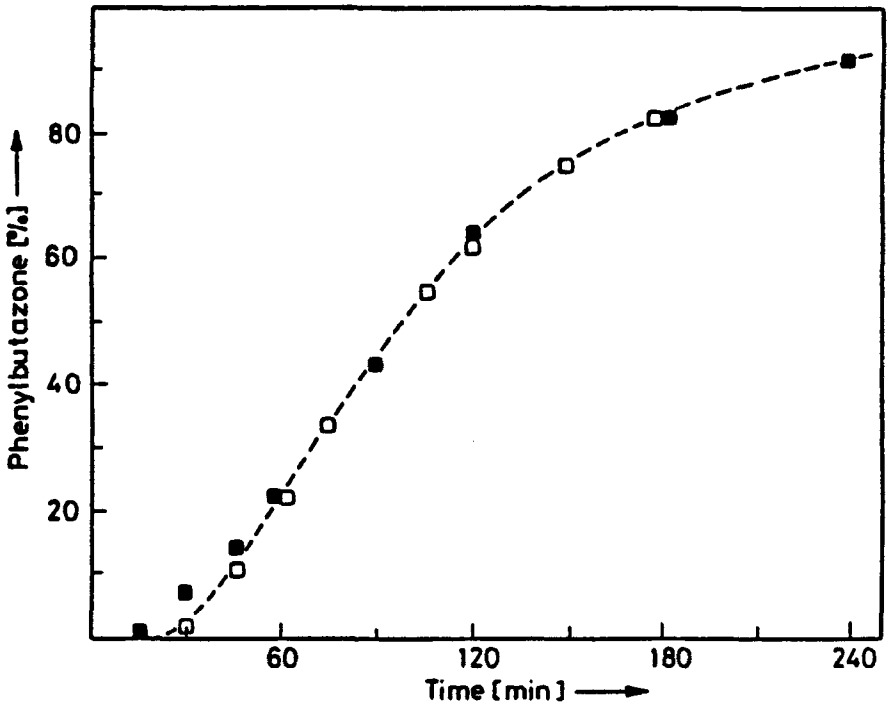

FIGURE 11

Correlation between Analogue Computations, in vivo-Data, and Dissolution Model Investigations

--- Analogue Computer Simulation
k_a=0.828 h^{-1}; pH(t) by k=0.08 min^{-1}

● in vivo-Data after LEESON, 1975
nonformulated Capsule

□ Dissolution Model Investigation
nonformulated Capsule
k_a=0.88 h^{-1}; pH(t) by 0.3 rel.acid.cap.

squares indicate dissolution model results, filled squares are in vivo-absorption data, and the broken line shows the analogue computation.

As can be seen from fig. 11 these three kinetic processes are going together on nearly one line.

DISCUSSION

The application of analogue computation to dissolution model development leads to an integrated system of kinetic functions. These kinetic functions depend on the behaviour of a drug in the organism and on properties of the drug itself. In the case of Phenylbutazone there is a pH-dependent solubility, which rapidly increases at pH 5.5 and higher (fig. 3). Therefore, the pH-time-profile below pH 5.5 is less important for solubility. The interesting part of this profile is above pH 5.5. The pH-time-profiles shown in fig. 2 are simplified with no respect to physiological properties. If the pH-time-profile and the solubility function is connected, solubility-time-profiles result. The simultaneous absorption leads to dissolution kinetics in an open system. The registration of absorption kinetics is the tool for the possible relation of analogue computations to in vivo-data (figs. 8, 9). Two important parameters will be obtained for the device and program of a flow-through type dissolution model. The result of such a dissolution test is the possibility to relate its overall kinetics with those of in vivo-data. This method seems to be more convenient than the relation of a dissolution point (e.g. time for % dissolved) to height of blood level or area under curve. The application of analogue computations helps to develop and program a

dissolution model in order to forecast bioavailability of drug forms in a better way than contemporary models do.

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