Fitting drug dissolution measurements of immediate release solid dosage forms by numerical solution of differential equations.

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Abstract

Dissolution profiles of ketoprofen are measured from immediate release powder mixtures, granules, and tablets with different compositions. Fast data sampling is performed by means of a paddle dissolution tester connected to an optimized pumping system including a photometer- PC combination quantifying the drug concentration with time. The observed data are fitted by means of a computer program for parameter estimation in systems of ordinary differential equations. The mathematical model is derived from the Noyes-Whitney equation into which distribution functions reflecting the alterations of the „effective“ surface in dependence on time are inserted. The combination with the lognormal distribution corresponds best with dissolution data and shows to be best adaptable to different curve shapes. Dissolution rate factors f_{rate} are calculated from the estimated parameters. The maximum $f_{rate,max}$ and the time t_{max} at which the maximum appears are used to characterize the drug liberation. Comparing these values by t-tests indicates the influences of excipients and manufacturing processes. $f_{rate,max}$, therefore, can be an effective aid for optimizing formulations and controlling manufacturing.

Keywords: Dissolution from solid preparations, Immediate release preparations, Dissolution kinetics, Data fitting, Parameter estimation, Differential equations, Wetting and „effective“ surface, Influence of excipients, Ketoprofen.

1. Introduction

Drug liberation from solid dosage forms (tablets, granules, capsules etc.) results from a series of simultaneous and successive, primary and secondary processes (wetting, capillary penetration, swelling, disintegration, diffusion, dissolution etc.) which strongly depend on type, quantity, and properties of the ingredients (drugs and additives) as well as on the results of unit operations of the manufacturing procedures (Hersey and Krycer, 1980). Furthermore, the rate controlling steps vary in dependence on the mentioned parameters. Consequently, the drug liberation-time curves show very different shapes, and it is extremely difficult to create mathematical equations describing the liberation process based on the partial mechanisms. In consequence, the literature of dissolution mathematics is extensive.

Inserting the parameters (mean and standard deviation) obtained from lognormal particle size distribution of the dissolved powder into the Hixson-Crowell equation, Carstensen and Musa (1972) describe the weight decrease of undissolved particles. In order to expand the application limits of the mathematical models, Brooke (1973, 1974) and Veng Pedersen et al. (1977, 1978) develop approximations to dissolution profiles which were based on the integral of the particle weights of lognormally distributed powders combined with the cube-root law. Sunada et al. (1989) and Yonezawa et al. (1990) experimentally correlate the dissolution curves to the changes in the particle surface area. There is, however, the problem that the particle surface may not be evenly involved into the dissolution process. This is especially relevant if solid drug preparations are subjected to dissolution. Thus, kinetics of drug dissolution from dosage forms have to take into account that the particle surface is only partly in contact with the solvens at the beginning of the process when the drug preparation is immersed in the dissolution medium. In the initial stage, which can be of great importance to the course of drug release, the water has to penetrate the dosage form, and wetting is often restricted by hydrophobic surfaces. These processes delay the dissolving, but they are not sufficiently described by the above-mentioned equations in all cases. For this reason, Leary and Ross (1983) as well as Kervinen and Yliruusi (1993) derived mathematical functions with S-shaped curves.

In the present paper we develop new mathematical models consisting of differential equations based on the Noyes-Whitney function that reflect the change in the actually involved surface area during the dissolution process. Experimental observations of drug dissolution from several solid preparations with different

immediate release characteristics are fitted to these equations and the estimated parameters are statistically tested for significant differences.

2. Materials and Methods

2.1. Materials

Ketoprofen (Bayer AG, D-Leverkusen), Fp. 95°C (Literatur: 93-96°C; Liversidge, 1981), saturation in water: c_s = 0.2422 g/l (37°C) (Schreiner, 1995).

Lactose D 20, Tablettose, Microtose, and Cellactose (spray dried mixture of 75% α-lactose and 25% cellulose): Meggle GmbH, D-Wasserburg.

Avicel PH 200: Lehmann & Voss & Co, D-Hamburg.

Elcema P 100: Degussa, D-Frankfurt.

Potato starch: Roquette GmbH, D-Frankfurt.

Corn starch: Cerestar Deutschland GmbH, D-Krefeld.

Polyvinylpyrrolidone (PVP): Kollidon 25, BASF, D-Ludwigshafen.

Tween 80 and Myrj 45: Atlas Chemie, D-Essen.

Propanol-2, magnesium stearate: Merck, D-Darmstadt.

Some characteristics of the excipients are given in Table 1.

2.2. Methods

2.2.1. Manufacturing drug preparations

The formulations used for dissolution experiments are summarized in Table 1.

Powder mixtures: The components (total quantity 200 g) are mixed in a Turbula mixer (type T2C, Bachofen, CH-Basel) at 42 rpm for 20 min totally subdivided in two steps of ten min, whereas microtose containing formulations are processed in a Stephan mixer (type UMC5 electronic, Stephan GmbH, D-Hameln) at 3000 rpm five times for 1 min. The mixing times are validated by preliminary tests controlling the homogeneity of substance distribution.

Granulations: The powder mixture (50 g) is blended with propanol-2 or 10% PVP solution in water to a pastry, passed through a sieve (900 µm) and dried for 24 hours (binder granulation at (40±1)°C, propanol granulation at room temperature (22±3)°C). The used amount of the liquids varies with the solid components and is optimized by preliminary productions. The particle fractions 710-1000 µm obtained by sieving are used for the further work. The homogeneity of the drug content is controlled.

Tablets: Powder mixtures and the above-mentioned granulations (single dose containing (20±1) mg ketoprofen) are separately compressed to tablets (diameter: 6.5 mm) using a hydraulic press (Perkin-Elmer, D-Überlingen) equipped with a

pressure measuring device (pressure measuring cell type C 2 with amplifier type M6 3120A-S 32, HBM Hottinger Baldwin Meßtechnik GmbH, D-Darmstadt, and recorder Servogor 310, Brown Boveri BBC Metrawatt, D- Nürnberg). The filled material is compressed at 59 or 296 MPa for 20 s.

Tablets containing magnesium stearate: 1% Magnesium stearate is added to the mixture of the other components, then the material is mixed for further 3 min in a Turbula mixer and compressed at 296 MPa as described above.

2.2.2. Dissolution measuring

(20±1) mg ketoprofen or a preparation containing this dose, are subjected to dissolution in a paddle device (European Pharmacopoeia, USP; Erweka, D-Heusenstamm; paddle rotation: 100 rpm), which is combined with a system pumping the solvent through a circulation unit. This unit contains a HPLC-filter (diameter 7 mm, pore diameter 20 µm, Nr. 32173, Alltech GmbH, D-Unterhaching) at the inlet side positioned 3 mm above the paddle, a gear pump (type MC-Z + Z P186/15, Ismatec, D-Wertheim; performance: 13.5 ml/min), and a spectrophotometer (Lambda 3, Perkin-Elmer, D-Überlingen) equipped with a flow-through cell having a small volume (type 176.003 QS, d=10 mm; Hellma GmbH, D-Müllheim/Baden). The volume of the circulation system is minimized and amounts totally to 5.3 ml with 1.8 ml from the filter to the photometer cell. Result is an experimentally verified lag-time of 8 s. The solvent (1000 g water) is degassed by ultrasound for 15 min at 45°C, then cooled down to (37.0±0.1)°C and kept at this temperature by a thermostat during the experiment. Tablets are directly dropped into the beaker. Powder mixtures and granulations are weighed out in a glass cap (diameter 20 mm, height 12 mm). The cap having a little hole is supplied with a nylon thread that holds it in a position between water surface and paddle and the opening directed to the side so that the content trickles out. All the experimental parameters described above are validated.

The photometer is connected on line by an interface (RS-232-C/V 24) with a PC programmed to save up to one measured value every second. The dissolution data are fitted by means of the program EASY-FIT (Schittkowski, 2001).

3. Results

3.1. Dissolution kinetics and mathematical model

The basic equation describing the dissolution rate is created by Noyes and Whitney (1897) and completed by Nernst (1904) and Brunner (1904). If the receptor reveals perfect sink characteristics $(c(t) << c_s)$, we get

$$\dot{c}(t) = \frac{D}{h \cdot V} \cdot S^* \cdot c_s \qquad (1)$$

where *c(t)* is the actual concentration of the solute in the solvens at time *t*, c_s the saturation concentration, *D* the diffusion coefficient, *S** the effective surface of the solid actually involved in the dissolution process, *h* the distance passed by diffusion, and *V* the volume of the solvens. The dot denotes the derivative with respect to the time variable *t*. The parameters *D*, *h*, and *V* depending on the defined experimental conditions, can be joined to the rate constant $k_{NW} = D/(h \cdot V)$ simplifying (1) to

$$\dot{c}(t) = k_{NW} \cdot S^* \cdot c_s \qquad (2)$$

It is not possible, however, to use Eq. (2) with a constant effective surface *S*.* Regarding the dissolution from a powder preparation, the effective drug particle surface is permanently changes by surface wetting and molecule escape. These processes with opposite effects force *S** to depend on the time *t* and also on the concentration *c*, expressed by replacing *S** in Eq. (2) by *S*(t,c),*

$$\dot{c}(t) = k_{NW} S^*(t,c(t)) \cdot c_s \qquad (3)$$

The value *S*(t,c)* is not known and cannot be measured directly, but it can be expected that the S* curve over time shows a maximum, if wetting is faster than dissolution after a startup period. With regard to the particle size distribution, it seems to be reasonable to describe the change of the effective surface area with time by modified statistical functions, for example a lognormal or χ^2-distribution. Inserting a function *y(t,c)* with these characteristics into Eq. (3) requires to compensate for the effective surface area immediately at the start when the solid preparation and the solvens come into contact. This is adjusted by adding the constant a_0 to the distribution function. Depending on the properties of the substances and the manufacturing processes, a_0 can considerably vary. Furthermore, the end of the dissolution process is marked by $1 - \frac{t}{t_e} = 1 - \frac{c(t)}{c_e}$, which is derived from a zero order kinetic. Steady-state is obtained when $c=c_e$ or $(1–c/c_e)=0$, respectively. We obtain

$$S^*(t,c) = (a_0 + y(t))(1 - c/c_e) \qquad (4)$$

Inserting these transformations into Eq. (3) gives

$$\dot{c}(t) = k_{NW}\,(a_0 + y(t))(1 - c(t)/c_e)\cdot c_s \qquad (5)$$

where *y(t)* stands for a modified distribution function or any other suitable function. $c_e = m_d/V$ is the concentration which is obtained after complete dissolution, with total drug quantity m_d and the volume V of the solvens. The following distribution functions are investigated, see also Table 2:

- normal distribution
- lognormal distribution
- χ^2- distribution
- Weibull distribution
- Bateman function

For instance, Eq. (6) is the combination of Eq. (5) with the modified lognormal distribution function

$$\dot{c}(t) = \left(a_0 + a_1 \Big/ t\, \exp(-a_2(\ln(t) - a_3)^2\right)\left(1 - c(t) \Big/ c_e\right)\cdot c_s \qquad (6)$$

Since k_{NW} cannot be estimated by our approach, we suppose for simplicity that the parameter is included in a_0 and a_1, respectively. a_0 , a_1, and a_2 are the variables to be estimated, and c and t are the dependent and independent model parameters for which measurements are available from the dissolution process. c_e and c_s are separately determined. In more general terms, the dynamical model is described by a rate function $f_{rate}(t,c)$ and the differential equation

$$\dot{c}(t) = f_{rate}(t, c(t))\cdot c_s \qquad (7)$$

with initial value $c(0)=0$. The time and concentration dependent rate factor $f_{rate}(t,c)$ is a function of the surface actually involved in the dissolution process at time t and concentration c, and includes the Noyes-Whitney rate constant k_{NW}.

3.2. Numerical implementation

Numerical tests are performed on a PC. We apply the software system EASY-FIT (Schittkowski, 2001) and to fit the experimental dissolution data to the distribution functions of Table 2. A particular advantage is that after fixing and verifying the model equations, the underlying numerical code can be executed independently from the user interface for performing large bulks of production runs. The differential equations are solved be the implicit Runge-Kutta method RADAU5 for stiff equations (Hairer and Wanner, 1991). The code DFNLP is executed to compute an optimal least

squares fit. The mathematical method is a combination of the Gauss-Newton and a quasi-Newton method (Schittkowski, 1988).

3.3. Test for suitability of the distribution functions

Fitting the ketoprofen dissolution data of an exemplary drug preparation (ketoprofen-microtose mixture, formulation f3 in Table 1, intermediately processed with propanol-2 to granulation and compressed with 296 MPa to tablets) leads to the curves of Fig. 1. Eq. (5) is combined with all of the distribution functions of Table 2. The lognormal distribution, cf. Eq. (6), coincides with the measured values to a considerably higher accuracy than all other ones, as shown in Table 3. It is used, therefore, for data fitting in all subsequent evaluations.

The adaptability of Eq. (6) is exemplarily demonstrated by the fitted dissolution curves of different drug preparations (Fig. 2). Fig. 3 is derived from dissolution data, which were obtained from ketoprofen mixed with elcema and processed into different dosage forms. It illustrates the dependence of the release rate factor on time, which reflects the changes in the effective surface during the dissolution process. The height of the maximum $f_{rate,max}$ and the time t_{max} after which the maximum appears indicate the maximum of the effective drug particle surface. In agreement with theory, the integrals of the areas under the curves correspond with each other within a standard deviation of $\pm$1.2%. The curves $f_{rate}(t)$ can be used for comparisons of several drug formulations, if the experimental dissolution conditions are constant. The values $f_{rate,max}$ and t_{max} determined for different preparations can be statistically differentiated, for example by t-tests, and used as in-vitro drug release characteristics of certain dosage forms which mark the processes preceding drug absorption.

3.4. Comparison of several drug formulations by dissolution measurements

The contact angle of ketoprofen to water is measured by Schreiner (1995) with sessile drop method θ (54 $\pm$2)°, h-ε method θ=(53 $\pm$3)°. The particle surface, therefore, shows hydrophobic properties, which influence the dissolution process by reducing the „effective surface“ (Lippold and Ohm, 1986). Several authors working with different hydrophobic substances reported that this effect is diminished by mixing with hydrophilic excipients (e.g. Lerk and Bolhuis, 1977, Loth and Schäfer, 1985, Hemgesberg, 1986, Ishizaka et al., 1988, and Te Wierik et al., 1992). In order to test the suitability of Eq. (7) and the maximal rate factor to indicate the influences of additives and manufacturing processes on drug dissolution, Ketoprofen is mixed

with several kinds of lactose, starches, and/ or celluloses (Table 1). The powder mixtures, granulations, and tablets are subjected to dissolution measurements. Two batches of each formulation are separately produced, and six samples of each batch ($n=n_1+n_2=12$) are measured, exceptions are indicated. The $f_{rate,max}$ and t_{max} values of the preparations tested are summarized in Table 4, and are compared by the t-test of the means with unequal variances (Sachs, 1997).

According to the above-mentioned surface properties, pure crystalline ketoprofen powder significantly shows the lowest dissolution rate factor of all the powder mixtures investigated. The probability that the mean of the rate factor is different to those of all the other formulations is greater than 0.99. The dissolution rate is considerably increased by adding a small amount of a diluted tenside solution to the ketoprofen powder (0.1 ml 0.1% between 80 or myrj 45 in water to 20 mg drug, 30 min incubation before starting dissolution). But, admixing of excipients to the drug can have about the same effect (e.g. cellactose, potato and corn starch) or may even exceed it (elcema and the powder mixtures l1+cs, l3+c1, and l3+c2; $p \geq 0.95$).

3.5. Implication of processing methods on drug dissolution

Comparisons of ketoprofen dissolution rate factors $f_{rate,max}$ of different preparations with identical compositions by t-tests of the means mostly result in significant differences at significance levels $p \geq 0.99$ (some at $p \geq 0.95$). For this reason, Table 5 gives only the pairs with insignificant differences ($p < 0.95$). The great majority of significantly differentiated cases show the important influences of manufacturing methods and operations on the dosage form properties, which control drug liberation. In general, the drug mostly dissolves quicker from powder mixtures than from binder granulations and from binder granulations quicker than from propanol granulations. But, significantly verified exceptions ($p \geq 0.99$) indicate that the systems can show specific behavior, e.g. ketoprofen dissolution rate from

microtose:	powder < binder granulation,
microtose+elcema:	powder < binder granulation,
corn starch:	powder < propanol granulation,
potato starch:	binder granulation < propanol granulation,
corn starch:	binder granulation < propanol granulation,
lactose D20+corn starch:	binder granulation < propanol granulation.

The different abilities of the liquids to dissolve ketoprofen and excipients during the granulation process lead to different structures, drug distributions, and properties of

the compacted products. This situation may be altered furthermore after compression of these preparations to tablets in dependence on the compression force. Correspondingly, Schreiner (1995) observes that the tablets produced from powder mixtures, binder and propanol granulations with identical composition and used in this investigation show different porosities, drug „surface concentrations“ (drug distribution at the surface region measured by IR-ATR), contact angles to water, and water uptake rates. In consequence of the presented results, the manufacturing operations have to be controlled with regard to the implication in drug dissolution.

3.6. Influence of composition on drug release

However, the rate factors very considerably vary not only in dependence on the manufacturing processes but on the composition of the preparations as well. Table 6 summarizes the highest $f_{rate,max}$ values of each type of preparation and the significance of the differences of the highest to the succeeding values. Regarding the tablets compressed with the stronger pressure, the composition avicel + corn starch shows the fastest liberation rate independently whether they are produced from powder mixtures or granulations. This, however, is not generally the „best“ formulation. Powder mixtures and granulations show the quickest ketoprofen release of all the dosage forms. The „best“ formulation of each type has another composition but never avicel + corn starch. Finally, the tablets compressed with 59 MPa (which cannot be used as tablets because of lack in hardness, but as filling of gelatine capsules) have the greatest differences in the $f_{rate,max}$ values, when the products from powder mixtures and granulations are compared. The tablets with the highest release rate result from the microtose-elcema binder granulation. Furthermore, the effects of lubricants, e.g. magnesium stearate, on the release rates do not depend only on the added amounts and the mixing process (Lerk and Bolhuis, 1977) but also on the composition of the respective preparations (Table 4).

3.7. Conclusions

We summarize factors influence drug dissolution from immediate release dosage forms, which have, therefore, to be recognized and controlled. For this reason, the Food and Drug Administration (1997) provided recommendations for dissolution testing and statistical comparison of dissolution profiles with the aim to determine, when dissolution testing is sufficient instead of in vivo bioequivalence studies. The presented dissolution equations in combination with the described fitting method are shown to be well adaptable to different release profiles. Hence, the effects of

composition and processing are sensitively detectable, and formulations and manufacturing can be optimized in this way. Furthermore, the dissolution profiles of the products can be statistically compared with respect to the drug release rates required to reach special pharmacodynamic or pharmacokinetic properties. This can be performed, for example, by means of confidence intervals or curve similarity factors according to the FDA Guidance or by t-tests of the fitted parameters.

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Legends

Fig. 1.

Dissolution of ketoprofen tablets containing microtose as exipient, granulated with propanol-2 and compressed with 296 MPa. The data have been fitted using Eq. (5) combined with the indicated functions. Every 3rd measured value is shown in the figure.

Fig. 2.

Fitting curves of ketoprofen dissolution from the indicated preparations calculated with Eq. (6a). Every 2nd measured value is shown in the figure.

Fig. 3.

Dissolution rate factors of ketoprofen (mixed with elcema and processed to the indicated preparations) in dependence on time and drug preparation. The dissolution rate factors f_{rate} were calculated from the fitted parameters.