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Research paper

Predictability of drug release from water-insoluble polymeric matrix tablets

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ABSTRACT

The purpose of this study was to extend the predictability of an established solution of Fick's second law of diffusion with formulation-relevant parameters and including percolation theory.

Kollidon SR (polyvinyl acetate/polyvinylpyrrolidone, 80/20 w/w) matrix tablets with various porosities (10–30% v/v) containing model drugs with different solubilities (C_s = 10–170 mg/ml) and in different amounts (A = 10–90% w/w) were prepared by direct compression and characterized by drug release and mass loss studies. Drug release was fitted to Fick's second law to obtain the apparent diffusion coefficient. Its changes were correlated with the total porosity of the matrix and the solubility of the drug.

The apparent diffusion coefficient was best described by a cumulative normal distribution over the range of total porosities. The mean of the distribution coincided with the polymer percolation threshold, and the minimum and maximum of the distribution were represented by the diffusion coefficient in pore-free polymer and in aqueous medium, respectively. The derived model was verified, and the applicability further extended to a drug solubility range of 10–1000 mg/ml.

The developed mathematical model accurately describes and predicts drug release from Kollidon SR matrix tablets. It can efficiently reduce experimental trials during formulation development.

1. Introduction

Mathematical modeling of drug release has two major aims: the elucidation of underlying mechanisms and the simulation of drug release and therefore the reduction in the number of experiments required during formulation development [1].

Mechanistic models for matrix systems with diffusion-controlled drug release are based on Fick's second law of diffusion [2].

$$\frac{\partial c}{\partial t} = \frac{1}{r} \cdot \left\{ \frac{\partial}{\partial r}\left(rD\frac{\partial c}{\partial r}\right) + \frac{\partial}{\partial \theta}\left(\frac{D}{r}\cdot\frac{\partial c}{\partial \theta}\right) + \frac{\partial}{\partial z}\left(rD\frac{\partial c}{\partial z}\right) \right\} \quad (1)$$

where c is the concentration of the diffusing compound with diffusion coefficient D, t represents the time, and r, θ, and z are the three spatial directions.

For its solution, two special cases have to be distinguished [3]: dissolution or diffusion is the release rate limiting step.

If dissolution of the drug is slower compared to its diffusion, dissolved and dispersed drug coexist in the wetted areas of the system. Drug release from this type of matrix can be described by the Higuchi model, initially developed for homogeneous systems (Eq. (2)) [4]:

$$Q = \sqrt{D(2A - C_s)C_s t} \quad (2)$$

where Q is the release rate per unit surface area, D is the diffusion coefficient of the drug in the homogeneous matrix media, A is the amount of drug per unit volume, C_s is the solubility of the drug in the permeating fluid, and t is the time.

The model was extended to heterogeneous systems where diffusion occurs through water-filled pores within the granular matrices (Eq. (3)) [5]:

$$Q = \sqrt{\frac{D\varepsilon}{\tau}(2A - \varepsilon C_s)C_s t} \quad (3)$$

The diffusion coefficient (D) describes the diffusion of the drug through the permeating fluid and the restricted volume, and the winding of the pores is expressed in the model by the porosity (ε) and the tortuosity (τ) of the matrix.

Its simplicity often tempted researchers to apply Eq. (3) to matrix tablets. However, two key conditions have to be met: First, drug diffusion is restricted to one direction only; valid systems comprise ointment films, transdermal patches, or films for oral delivery [6]. A cylindrical geometry is only covered if all surfaces

Abbreviations: KSR, Kollidon SR; PVAc, polyvinyl acetate; PVP, polyvinylpyrrolidone.

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but one are impermeable for the active. And second, the drug loading has to exceed the solubility in the medium filled matrix. As long as solid drug is present and sink conditions are maintained, the concentration gradient and therefore the diffusion rate remain constant.

If dissolution is faster than diffusion in the wetted matrix, Eq. (3) cannot be applied. A modification has been proposed to extend the Higuchi model to this case [7]. An error of 0.5% compared to a numeric solution of Fick's second law of diffusion has been postulated. However, the restriction to one-dimensional diffusion remained.

Drug release from cylindrical bodies is described by another solution of Fick's second law, valid for matrices with drug loadings that are rapidly dissolved in the wetted matrix [8]:

$$\frac{M_t}{M_\infty} = 1 - \frac{32}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{q_n^2} \cdot \exp\left(-\frac{q_n^2}{R^2} \cdot D_{app} t\right) \cdot \sum_{p=0}^{\infty} \frac{1}{(2p+1)^2} \cdot \exp\left(-\frac{(2p+1)^2 \cdot \pi^2}{H^2} \cdot D_{app} t\right) \quad (4)$$

where M_t/M_∞ is the cumulative drug release, n and p are real numbers, q_n are the roots of the Bessel function of the first kind of zero order ($J_0(q_n) = 0$), D is the apparent diffusion coefficient of the drug in the matrix, t is the time, and R and H represent the radius and the height of the tablet, respectively.

The model is valid for drug release from matrix tablets since it considers axial as well as radial diffusion and has been successfully applied to Gelucire matrices [9] and Kollidon SR tablets [10]. With known apparent diffusion coefficient, drug release from tablets of different initial dimensions can be predicted due to the low degree of swelling and hence the constant dimensions of the systems [11]. However, the apparent diffusion coefficient has not been evaluated in detail, which limits the predictability of this approach. A distinction between homogeneous and heterogeneous matrices is not provided since all formulation parameters except for the matrix dimensions merge into the apparent diffusion coefficient of the drug.

The objective of this study was to evaluate parameters influencing the apparent diffusion coefficient of the diffusion model (Eq. (4)), to develop a mathematical model with high predictive power, and to better understand the processes governing drug diffusion from water-insoluble polymeric matrix tablets. For this purpose, Kollidon SR, a co-processed blend of polyvinyl acetate (PVAc) and polyvinylpyrrolidone (PVP) in a ratio of 8:2, was chosen as matrix carrier due to its excellent flow and compression behavior and its drug release retarding effect [12–14].

2. Materials and methods

2.1. Materials

Metoprolol tartrate (Moehs, Barcelona, Spain), propranolol hydrochloride, Kollidon SR (spray dried PVAc 80%, PVP 19%, 0.8% sodium lauryl sulfate and 0.6% fumed silica, lot No. 81969968E0), PVP (Kollidon 30) and micronized theophylline, caffeine, and diprophylline (BASF SE, Ludwigshafen, Germany), pentoxifylline (Sigma Aldrich Chemie GmbH, Taufkirchen, Germany), fumed silica (Aerosil 200, Evonik Industries AG, Darmstadt, Germany), and magnesium stearate (Baerlocher GmbH, Unterschleissheim, Germany) were used as received.

2.2. Tablet formulation and preparation

Kollidon SR and drug powders were physically mixed in a mortar with a pestle and 1% w/w Aerosil and Mg stearate each were blended to the powder mixtures as glidant and lubricant.

Tablets were prepared by compressing the powder mixture with an instrumented single punch tabletting machine (EK0, Korsch AG, Berlin, Germany) recording compression force during the compaction process (MGCplus, catman, HBM, Darmstadt, Germany). The tablets were characterized with regard to their dimension and hardness (Multicheck, Erweka GmbH, Heusenstamm, Germany). The porosity was calculated from the ratio of apparent density and true density of the tablets.

2.3. Drug release

Drug release tests were performed using a USP paddle apparatus (VK 7010, Agilent Technologies Deutschland GmbH, Böblingen, Germany), 900 ml phosphate buffer pH 6.8 at 50 rpm and 37 °C. Filtered samples were taken at predetermined time points and analyzed spectrophotometrically (at 272, 290, and or 295 nm, $n = 3$).

2.4. Mass loss studies

The mass loss of Kollidon SR matrices after drug release was determined gravimetrically. Dry tablets were weighed to determine the initial dry mass (m_{ini}). The wet tablets were dried in an oven after the drug release testing (Heraeus T6060, Thermo Fischer Scientific GmbH, Dreieich, Germany) at 105 °C overnight and weighed again (m_{final}). The mass loss was calculated as follows:

$$\text{Mass loss}\% = \frac{m_{ini} - m_{final}}{m_{final}} \cdot 100 \quad (5)$$

2.5. Solubility determination

An excess of drug powder was added to PVP solutions in phosphate buffer pH 6.8 (0%, 10% and 20% w/w PVP) in a glass vial and shaken at 37 °C and 80 rpm (incubation shaker GFL 3033, GFL Gesellschaft für Labortechnik mbH, Burgwedel, Germany) for 48 h. The concentration of the drug in the supernatant was measured spectrophotometrically (at 272 nm, $n = 3$).

3. Results and discussion

Kollidon SR matrix tablets containing water-soluble drugs release the drug in a diffusion-controlled manner. The drug release kinetics obeyed Fick's second law of diffusion (Eq. (4)), which facilitated modeling the effect of matrix dimensions on drug release [10]. Formulation parameters affecting the apparent diffusion coefficient of the drug (D), however, were not considered.

In the present study, the matrix dimensions were kept constant in order to facilitate the evaluation of factors influencing the apparent diffusion coefficient. Previous work [5,7,11,15] indicated the importance of parameters such as porosity, tortuosity, drug loading, and drug solubility for the drug release from water-insoluble matrices. Therefore, the correlations of these parameters with the apparent diffusion coefficient were investigated in this study. The aim is a mathematical description of drug release extending the existing model and thereby increasing its predictive power.

3.1. Initial porosity

The porosity of a solid body describes its pore volume in relation to its total volume. Tablets are solid dosage forms that contain considerable amounts of air depending on the degree of compaction. Generally, the porosity decreases with increasing compression force.