Journal of Controlled Release 141 (2010) 216–222

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Modeling drug release from PVAc/PVP matrix tablets

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ARTICLE INFO

Article history:
Received 11 May 2009
Accepted 31 August 2009
Available online 6 September 2009

Keywords:
Matrix tablet
Diffusion
Release mechanism
Modeling

ABSTRACT

Kollidon® SR-based matrix tablets containing various amounts of diprophylline were prepared and thoroughly characterized in vitro. This includes drug release measurements in 0.1 M HCl and phosphate buffer pH 7.4, monitoring of changes in the tablet's height and diameter, morphology as well as dry mass upon exposure to the release media. Based on these experimental results, a mechanistic realistic mathematical theory is proposed, taking into account the given initial and boundary conditions as well as radial and axial mass transport in cylinders. Importantly, good agreement between theory and experiment was obtained in all cases, indicating that drug diffusion with constant diffusivity is the dominant mass transport mechanism in these systems. Furthermore, the proposed theory was used to quantitatively predict the effects of the initial tablet height and diameter on the resulting drug release patterns. These theoretical predictions were compared with independently measured drug release kinetics. Good agreement was observed in all cases, proving the validity of the mathematical theory and illustrating the latter's practical benefit: The model can help to significantly facilitate the recipe optimization of this type of advanced drug delivery systems in order to achieve a desired release profile.

1. Introduction

Polymeric matrix tablets offer a great potential as oral controlled drug delivery systems [1,2]. Often, hydroxypropyl methylcellulose (HPMC) is used as a matrix former [3–6]. However, also other types of polymers can be used for this purpose [7–9]. Kollidon® SR is a formulation consisting of 80% poly(vinyl acetate) (PVAc), 19% poly (vinyl pyrrolidone) (PVP), sodium lauryl sulfate and colloidal silicon dioxide in powder form. It has been shown to be a highly suitable matrix former in controlled release tablets [9–13]. The latter can for instance be prepared by direct compression. However, yet the underlying mass transport mechanisms controlling drug release out of these dosage forms are not fully understood and device optimization is generally based on time-consuming series of experiments. So far, no mechanistic realistic mathematical model has been reported allowing for a quantitative description of the mass transport phenomena in PVAc/PVP-based matrix tablets.

The use of mechanistic realistic mathematical theories for the quantitative description of drug release from a pharmaceutical dosage form can provide two major benefits [14]: (i) such theories can be applied to determine system-specific parameters, which allow for the identification of the *dominant* mass transport phenomena in a particular device. Thus, the underlying drug release mechanisms can be elucidated [15–17]. (ii) This type of models can be used to quantitatively predict the effects of formulation and processing parameters on the resulting drug release kinetics. For instance, the impact of varying the composition and geometry of the device on drug release can be simulated in silico [18,19]. Thus, the optimization of the respective drug delivery systems can be significantly facilitated: The required formulation to achieve a desired drug release profile can be theoretically predicted. Furthermore, the controlled drug delivery system is not treated as a "black box". Thus, challenges encountered during formulation optimization, up-scale and production can be more easily addressed [14].

In order to develop a mechanistic realistic mathematical theory for a particular type of drug delivery system, the latter should first be characterized as thoroughly as possible using a broad spectrum of techniques, such as water uptake and dry mass loss studies, monitoring of potential changes in the morphology of the device upon exposure to different release media and of course drug release measurements. It has to be pointed out that not only one formulation should be prepared and characterized, but different types of systems, differing for example in the drug loading. Based on the obtained experimental results, a mathematical theory can be developed, which can be more or less complex. It is decisive to consider all major mass transport phenomena. In contrast, negligible ones should not be taken into account, otherwise the model becomes too cumbersome to be used.

The most important physicochemical phenomena which can be involved in the control of drug release from polymeric dosage forms include water and drug diffusion, polymer swelling, drug and polymer dissolution, erosion and polymer degradation as well as osmotic effects and onset of crack formation in film coatings. The mechanisms

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doi:10.1016/j.jconrel.2009.08.027

controlling drug release from matrix tablets can be rather complex. For instance, in case of HPMC-based tablets generally diffusional mass transport as well as polymer swelling and polymer dissolution need to be taken into account simultaneously [5]. Significant polymer swelling can lead to fundamental changes in drug mobility. In these cases, the diffusion coefficient of the drug might strongly depend on time and on position, resulting in rather complex mathematical theories, which can only be solved numerically. Ideally, a mathematical model should be easy to apply and system-specific parameters required for model predictions should be straightforward to determine.

The major objectives of this study were: (i) to better understand the underlying drug release mechanisms in Kollidon® SR-based matrix tablets, and (ii) to develop a mechanistic realistic mathematical theory allowing for the quantitative description of drug release from this type of advanced drug delivery systems.

2. Materials and methods

2.1. Materials

Diprophylline (BASF, Ludwigshafen, Germany), Kollidon® SR [80% poly(vinyl acetate) (PVAc), 19% poly(vinyl pyrrolidone) (PVP), sodium lauryl sulfate and colloidal silicon dioxide; BASF], magnesium stearate (Coopération pharmaceutique francaise, Melun, France), colloidal silicon dioxide (Aerosil R972®; Schering Plough, Hérouville Saint-Clair, France) and methylene blue (Sigma-Aldrich, Saint Quentin Fallavier, France) were used as received.

2.2. Tablet preparation

Drug-free and drug-loaded Kollidon® SR-based tablets were prepared by direct compression. Table 1 shows the compositions of the investigated systems. The diprophylline and Kollidon® SR contents were varied between 0 and 60% and between 38.5 and 98.5%, respectively. The relative colloidal silicon dioxide and magnesium stearate contents were kept constant at 1.0 and 0.5%, respectively. Diprophylline, Kollidon® SR, colloidal silicon dioxide and magnesium stearate were passed through a 180 μm sieve (Saulas, Paris, France) and blended thoroughly with a pestle and mortar. Cylindrical tablets were prepared with a single-punch tabletting machine (Frogerais, Vitry sur Seine, France) using flat-faces punches (5.0, 11.3 or 16 mm in diameter). The hardness of the tablets was kept constant (175–180 N; Tablet Tester 8M; Dr. Schleuniger Pharmatron, Solothurm, Switzerland), if not otherwise stated. The height of the tablets was varied between 1.3 and 4.1 mm, as indicated. The tablet weight varied between 60 and 600 mg (depending on the system's diameter and height).

2.3. In vitro drug release studies

Diprophylline release from the tablets was measured using the USP 30 dissolution apparatus (paddle method, 80 rpm, 37 °C) in 900 mL 0.1 M HCl or phosphate buffer pH 7.4 (USP 30) (VK 700; Varian, Palo Alto, CA). At predetermined time points, 5 mL samples were withdrawn and analyzed spectrophotometrically (UV-1650 PC; Shimadzu, Champs-sur-Marne, France) for their drug content ($\lambda = 274$ nm). All experiments were conducted in triplicate.

Table 1
Composition (%) of the investigated tablets.

Drug content	0%	10%	20%	40%	60%
Diprophylline	0.0	10.0	20.0	40.0	60.0
Kollidon® SR	98.5	88.5	78.5	58.5	38.5
Colloidal silicon dioxide	1.0	1.0	1.0	1.0	1.0
Magnesium stearate	0.5	0.5	0.5	0.5	0.5

2.4. Water uptake and dry mass loss studies

The water uptake and dry mass loss kinetics of the tablets were determined gravimetrically under the same conditions as used for the in vitro drug release measurements described above. The tablets were weighed before exposure to the release media [0.1 M HCl and phosphate buffer pH 7.4 (USP 30), respectively] at time $t = 0$. At predetermined time points, samples were withdrawn, accurately weighed (upon removal of excess water) [wet mass (t)], and dried in an oven (Binder, Tuttlingen, Germany) at 45 °C to constant mass [dry mass (t)]. The water content (%) and dry tablet mass (%) at time t were calculated as follows:

$$water\,content(\%)(t) = \frac{wet\,mass(t) - dry\,mass(t)}{wet\,mass(t)} \cdot 100\% \quad (1)$$

$$dry\,tablet\,mass(\%)(t) = \frac{dry\,mass(t)}{dry\,mass(t=0)} \cdot 100\% \quad (2)$$

All experiments were conducted in triplicate.

2.5. Monitoring of changes in the tablet dimensions

Dynamic changes in the tablet dimensions (radius and height) upon exposure to 0.1 M HCl and phosphate buffer pH 7.4 (USP 30) were monitored with an optical imaging system (SMZ-U; Nikon, Tokyo, Japan). Tablets were treated as described above for the in vitro drug release measurements. At predetermined time points, samples were withdrawn and their radius and height were measured in the wet state. All experiments were conducted in triplicate.

2.6. Monitoring of changes in the internal morphology

Dynamic changes in the internal morphology of the tablets upon exposure to 0.1 M HCl containing methylene blue (0.35% w/w) were monitored using an optical imaging system. Tablets were placed into 250 mL glass flasks filled with 200 mL of preheated medium in a horizontal shaker (37 °C, 80 rpm; GFL 3033, Gesellschaft fuer Labortechnik, Burgwedel, Germany). At predetermined time points, samples were withdrawn, cut with a razor blade in axial direction and analyzed with an optical imaging system (Stemi 2000-C; Carl Zeiss Jena, Jena, Germany) equipped with a digital camera (DXm 1200C; Nikon, Tokyo, Japan) and the NIS-Elements software (NIS-Elements; Nikon corporation, Kanagawa, Japan).

3. Results and discussion

3.1. Effects of the tablet hardness

Fig. 1 shows the effects of the tablet hardness on diprophylline release from Kollidon® SR-based tablets in 0.1 M HCl. The drug loading was 10%, the initial tablet diameter and height were equal to 11.3 and 2.7 mm. Clearly, the resulting drug release rate was almost unaffected in the range of 150–180 N by the tablet hardness. At much lower/higher values (80 and 340 N, respectively), the release rate was slightly increased/decreased due to the decreased/increased tablet density. Based on these results, the hardness of all further tablets investigated in this study was kept in the range of 175–180 N.

Importantly, the observed relative release rates monotonically decreased in all cases with time. Thus, diffusional mass transport might play a major role in the control of drug release. To better understand the underlying mass transport mechanisms, the water uptake and dry mass loss kinetics as well as changes in the tablets'