International Journal of Pharmaceutics 526 (2017) 280–290

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Research article

Limited drug solubility can be decisive even for freely soluble drugs in highly swollen matrix tablets

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ARTICLE INFO

Article history:
Received 20 February 2017
Received in revised form 30 April 2017
Accepted 2 May 2017
Available online 6 May 2017

Keywords:
Drug release mechanism
HPMC tablet
Mathematical modeling
Diffusion
Solubility
Diprophylline

ABSTRACT

The aim of this study was to elucidate the importance of potential limited solubility effects for the control of drug release from hydrophilic matrix tablets loaded with a freely water-soluble drug. It is often assumed that the considerable amounts of water penetrating into this type of advanced drug delivery systems are sufficient to rapidly dissolve the entire drug loading, and that limited drug solubility is not playing a role for the control of drug release. Here, we show that this assumption can be erroneous. HPMC/lactose matrix tablets were loaded with 5 to 60% diprophylline (e.g. solubility in 0.1 M HCl at 37 °C: 235 mg/mL), and drug release was measured at low and neutral pH, respectively. A mechanistically realistic mathematical theory was applied, considering drug diffusion in axial and radial direction in the cylindrical matrices and the potential co-existence of dissolved and non-dissolved drug. Importantly, only dissolved drug is available for diffusion. It is demonstrated that during major parts of the release periods, non-dissolved drug excess exists within tablets containing 30% or more diprophylline, despite of the substantial water contents of the systems. This leads to partially almost linear drug concentration distance profiles within the tablets, and reveals a major contribution of limited drug solubility effects to the control of drug release, even in the case of freely water-soluble diprophylline. It can be expected that also in other types of drug delivery systems, e.g. microparticles and implants (containing much less water), limited drug solubility effects play a much more important role than currently recognized.

1. Introduction

Hydrophilic matrix tablets are commonly used to control drug release upon oral administration (Viridén et al., 2010; Siepmann et al., 2010; Viridén et al., 2011; Jain et al., 2014; Nep et al., 2015). They can provide major advantages, such as relatively easy and economic production at the industrial scale, the possibility to control drug release during variable periods of time, and the availability of different types of matrix formers on the market. Hydroxypropyl methylcellulose (HPMC) is such a frequently used matrix former for hydrophilic controlled release tablets. It is available in different polymer molecular weights and substitution patterns. In order to adjust desired drug release kinetics, further excipients (e.g. lactose or other types of polymers) might be added (Lamoudi et al., 2016; Van Snick et al., 2017). The presence of freely water-soluble excipients can increase the water content of the systems during drug release (and decrease the density of the HPMC network), leading to faster drug release, if desired. Recently, a ready-to-use, co-processed 50:50 HPMC:lactose blend (RetaLac, being mechanically inseparable) has been proposed for this purpose (Siepmann et al., 2013).

The underlying mass transport mechanisms controlling drug release from hydrophilic matrix tablets can be rather complex, because a variety of phenomena can be involved (Siepmann and Peppas, 2001; Bettini et al., 2001; Chirico et al., 2007; Williams et al., 2009; Pygall et al., 2009; Kaunisto et al., 2011). This includes for instance water penetration into the system upon contact with aqueous body fluids, polymer chain relaxation, drug dissolution, the diffusion of dissolved drug through the polymeric network and/or water filled pores out of the system, the dissolution of water-soluble matrix formers, system swelling, matrix erosion as well as the dissolution and diffusion of water-soluble excipients other than the matrix former (Barba et al., 2009; Viridén et al., 2009; Ghimire et al., 2010; Siepmann and Siepmann, 2013; Ghori et al., 2014). It has to be pointed out that not all of these phenomena necessarily play a major role for the control of drug release (Siepmann and Siepmann, 2008). Often, various processes

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http://dx.doi.org/10.1016/j.ijpharm.2017.05.001
0378-5173/

take place in a series (cascade of events). If one of the involved phenomena is much slower than the others, only this much slower process is really important for the overall control of drug release. The other, much faster phenomena occur, but do not have a noteworthy impact on the resulting drug release kinetics. For instance, very often the dissolution *rate* of drug particles in hydrophilic matrix tablets upon contact with water is much more rapid compared to subsequent drug diffusion through the swollen hydrogel (Siepmann and Siepmann, 2008).

To better understand which types of mass transport phenomena are of importance in a particular type of drug delivery system, the latter should be characterized before and after exposure to the release medium. This can include rather straightforward experimental techniques (e.g. in vitro drug release measurements, water uptake and dry mass loss studies), as well as more complex characterization techniques, such as magnetic resonance (micro) imaging (Rajabi-Siahboomi et al., 1994; Kaunisto et al., 2013), confocal laser scanning fluorescence microscopy (Michelle Mason et al., 2015), MALDI-TOF MS imaging techniques (Kreye et al., 2012), inverse gas chromatography (Baumgartner et al., 2006) or X-ray microtomography (Fahier et al., 2016). Furthermore, mechanistically realistic mathematical models can be used to quantify the occurring mass transport phenomena (Grassi et al., 2004; Krenzlin et al., 2012; Velghe et al., 2014; Caccavo et al., 2015). Such models can for instance take into account drug diffusion, system swelling and polymer dissolution (Siepmann et al., 2000, 2002; Kaunisto et al., 2010). Fitting this type of mechanistically realistic theories to sets of experimental data allows for the determination of system specific parameters (e.g. apparent drug diffusion coefficients). Based on this knowledge, deeper insight into the relative importance of the involved mass transport steps can be gained. The reliability of this type of mathematical analysis should be evaluated by comparing *theoretical predictions* (made by these models, e.g. predicting the effects of the tablet design on the resulting drug release kinetics) with *independent experimental data*. Caution should be paid, when only model fittings are shown (since in these cases, one or more model parameters have been intentionally adjusted to minimize differences between theory and experiment).

A further benefit of reliable, mechanistically realistic mathematical theories describing drug release from pharmaceutical dosage forms is the possibility to avoid cost-intensive and time-consuming series of trial-and-error experiments. Instead, rapid computer simulations can be used to estimate the impact of the device design (e.g. geometry, dimensions, composition) on system performance. Such computer simulations are common practice in other research fields (e.g. automobile or aircraft industry), but not yet in pharmaceutics (Siepmann, 2013).

The aim of this study was to re-visit the general assumption that limited drug solubility effects are negligible for the control of drug release from hydrophilic matrix tablets loaded with freely water-soluble drugs. For this purpose different types of HPMC/lactose (RetaLac)-based matrix tablets were prepared by direct compression, loaded with 5 to 60% freely water-soluble diprophylline. Drug release was studied in 0.1 M HCl and phosphate buffer pH 7.4 (to simulate the contents of the stomach and small intestine) and mechanistically realistic mathematical theories were used to quantify the occurring mass transport processes.

2. Materials and methods

2.1. Materials

Diprophylline (Sigma-Aldrich, Lyon, France); RetaLac (a 50:50 w/w co-processed blend of HPMC and lactose; Meggle, Wasserburg, Germany); hydrophilic fumed silica (Aerosil 200 Pharma; Evonik, Darmstadt, Germany); magnesium stearate (Fagron, Waregem, Belgium).

2.2. Tablet preparation

Matrix tablets based on diprophylline and co-processed HPMC/lactose (RetaLac) were prepared by direct compression. The drug content was varied from 5 to 60% (w/w). Diprophylline was blended with the co-processed HPMC/lactose (RetaLac) and Aerosil (1% w/w) in a Turbula mixer (Bachoven, Basle, Switzerland) at 38 rpm for 5 min. Upon addition of magnesium stearate (0.5% w/w), the powder blend was mixed for another 5 min at 38 rpm. Cylindrical tablets were prepared with a single-punch tableting machine (EK-0; Korsch, Berlin, Germany), equipped with flat-faced punches 6.0, 11.3 or 16.0 mm in diameter (as indicated). The hardness of the tablets was kept constant at 60–70 N (Tablet Tester 8 M; Dr. Schleuniger Pharmatron, Solothurm, Switzerland). The height of the tablets was varied between 1.5 and 4.3 mm, as indicated. The tablet dimensions were measured using a micrometer gauge (Digimatic Micrometer; Mitutoyo, Tokyo, Japan).

2.3. Drug release measurements

Drug release from the tablets was measured in 900 mL 0.1 M HCl or phosphate buffer pH 7.4 (USP 35), using the USP 35 dissolution paddle apparatus (AT 7 Smart; Sotax, Basel, Switzerland) (80 rpm, 37 °C). At predetermined time points, 5 mL samples were withdrawn and analyzed spectrophotometrically (UV-1650 PC; Shimadzu, Champs-sur-Marne, France; $\lambda = 274$ nm) for their drug content. Each experiment was conducted in triplicate. Note that during all drug release studies, perfect sink conditions were provided in the surrounding bulk fluids.

2.4. Water uptake studies

The water content of the tablets upon exposure to phosphate buffer pH 7.4 (USP 35) or 0.1 M HCl was determined gravimetrically under the same conditions as used for the in vitro drug release measurements (described above). At predetermined time points, tablets were withdrawn, excess water carefully removed using Kimtech precision wipes (Kimberly-Clark, Rouen, France), accurately weighed [*wet mass (t)*], and dried in an oven (E28; Binder, Tuttlingen, Germany) at 45 °C to constant weight [*dry mass (t)*]. The *water content* (%) at time t was calculated as follows:

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

Each experiment was conducted in triplicate.

2.5. Determination of the drug solubility

The solubility of diprophylline (as received) in 0.1 M HCl and phosphate buffer pH 7.4 at 37 °C was determined in agitated flasks. An excess amount of diprophylline powder was exposed to 20 mL bulk fluid, kept at 37 °C under horizontal shaking (80 rpm; GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). Every 24 h, samples were withdrawn, filtered and analyzed spectrophotometrically for their drug content (as described above), until equilibrium was reached. Each experiment was conducted in triplicate.

2.6. Optical microscopy

Tablets were treated as for the *drug release measurements* (Section 2.3). At pre-determined time points, specimen were