European Journal of Pharmaceutical Sciences 77 (2015) 246–253

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

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

Controlled release of acidic drugs in compendial and physiological hydrogen carbonate buffer from polymer blend-coated oral solid dosage forms

R. Wulff [a], G.-M. Rappen [b], M. Koziolek [c], G. Garbacz [b], C.S. Leopold [a,*]

[a] University of Hamburg, Department of Chemistry, Division of Pharmaceutical Technology, Bundesstraße 45, 20146 Hamburg, Germany
[b] Physiolution GmbH, Walther-Rathenau-Straße 49 a, 17489 Greifswald, Germany
[c] University of Greifswald, Institute of Biopharmaceutics and Pharmaceutical Technology, Department of Pharmacy, Felix-Hausdorff-Straße 3, 17489 Greifswald, Germany

ARTICLE INFO

Article history:
Received 1 April 2015
Received in revised form 10 June 2015
Accepted 16 June 2015
Available online 17 June 2015

Keywords:
Quaternary polymethacrylate
Enteric polymethacrylate
Interpolyelectrolyte complex
Polymer blend
pH-independent drug release
Hydrogen carbonate buffer

ABSTRACT

The objective of this study was to investigate the suitability of "Eudragit® RL/Eudragit® L55" (RL/L55) blend coatings for a pH-independent release of acidic drugs. A coating for ketoprofen and naproxen mini tablets was developed showing constant drug release rate under pharmacopeial two-stage test conditions for at least 300 min. To simulate drug release from the mini tablets coated with RL/L55 blends in the gastrointestinal (GI) tract, drug release profiles in Hanks buffer pH 6.8 were recorded and compared with drug release profiles in compendial media. RL/L55 blend coatings showed increased drug permeability in Hanks buffer pH 6.8 compared to phosphate buffer pH 6.8 due to its higher ion concentration. However, drug release rates of acidic drugs were lower in Hanks buffer pH 6.8 because of the lower buffer capacity resulting in reduced drug solubility. Further dissolution tests were performed in Hanks buffer using pH sequences simulating the physiological pH conditions in the GI tract. Drug release from mini tablets coated with an RL/L55 blend (8:1) was insensitive to pH changes of the medium within the pH range of 5.8–7.5. It was concluded that coatings of RL/L55 blends show a high potential for application in coated oral drug delivery systems with a special focus on pH-independent release of acidic drugs.

1. Introduction

The success of an oral therapy performed with weakly acidic or basic drugs often suffers from the drug's pH-dependent solubility. Undesired blood drug level peaks or long lag times might result from the highly variable gastric emptying time and the changes of the pH within the gastrointestinal (GI) tract (Chan et al., 1990; Davis et al., 1986; Garbacz, 2010; Klein et al., 2013; Koziolek et al., in press). Therefore, a pH-independent release of weakly acidic and basic drugs from oral solid dosage forms has been investigated during the last decades (Gohel et al., 2003; Kohri et al., 1989, 1991; Kranz et al., 2005; Nie et al., 2004; Streubel et al., 2000; Tatavarti et al., 2004; Varma et al., 2005; Venkatesh, 1998). For oral coated dosage forms, two different approaches have been pursued. The first is the addition of pH-active excipients to adjust the micro-environmental pH to a suitable value. Thus, drug release becomes more or less independent of the pH of the surrounding medium. This approach has been used for acidic and basic drugs (Dashevsky et al., 2004; Doherty and York, 1989; Rao et al., 2003; Riis et al., 2007; Thoma and Ziegler, 1998). However, the addition of excipients to the core may cause problems such as additional manufacturing steps, a longer processing time, or increased (tablet) weight. The second approach is the use of pH-dependent permeable coatings to counteract the pH-dependent drug solubility. This approach was conducted successfully to obtain pH-independent drug release of the weakly basic verapamil-HCl (Dashevsky et al., 2004). In this study, an enteric coating polymer was added to a sustained release coating to achieve higher drug permeability after pore formation in basic/neutral media. Similar drug release rates were observed in hydrochloric acid and phosphate buffer. For a pH-independent release of acidic drugs, a coating with a high permeability in acidic media and low permeability in neutral/basic media is necessary. Most recently, this behavior has been described for coatings of the ammonio methacrylate copolymer "Eudragit® RL" (RL) containing small amounts of the poly(methacrylic acid-co-ethyl acrylate) "Eudragit® L-55" (L55) (Wulff and Leopold, 2014). Therefore, RL/L55 blend coatings are promising candidates for controlled release of acidic drugs.

* Corresponding author.
E-mail address: Claudia.Leopold@chemie.uni-hamburg.de (C.S. Leopold).

http://dx.doi.org/10.1016/j.ejps.2015.06.015
0928-0987/

Drug release from RL coated drug pellets is predominantly depending on the ion exchange between the quaternary ammonium groups (QAGs) of the RL coating and the anions in the surrounding release medium. Thus, drug release from RL-coated pellets is sensitive to anions and their concentration but independent of the pH value of the release medium (Bodmeier et al., 1996; Jenquin et al., 1990; Wagner and Grützmann, 2005). In contrast, the drug release from drug pellets coated with RL/L55 blends is highly dependent on the pH value. Drug release studies with theophylline pellets coated with RL/L55 blends in phosphate buffers (pH 5.8–7.6) showed a drastic reduction of drug release compared to RL-coated pellets (Wulff and Leopold, 2014). The drug release in phosphate buffers depended on the RL/L55 blend ratio as well as on the pH value of the buffer. However, drug release at pH 5.8–7.6 was generally lower than in hydrochloric acid pH 1.2. Further studies confirmed the expected formation of interpolyelectrolyte complexes (IPEC) in neutral/basic media (Wulff and Leopold, 2014). IPECs were found to hinder ion exchange of the QAGs with the anions in the surrounding medium and are therefore associated with a decrease in drug release. However, the used buffers are fundamentally different from the gastrointestinal fluids in terms of ionic strength, surface tension, viscosity and the composition of the chyme. All parameters may be relevant in terms of drug release from coated dosage form (Garbacz and Klein, 2012; Hörter and Dressman, 2001). Thus, drug release tests simulating GI conditions are necessary to evaluate the suitability of RL/L55 blend coatings for providing pH-independent release of acidic drugs.

The simulation of the physiological conditions of the GI tract is a prerequisite for a good estimation of the drug delivery behavior of solid oral dosage forms. In the context of recent research, the overall buffer capacity of the dissolution medium plays an essential role for the intraluminal dissolution of ionizable compounds such as drugs and coating polymers and therefore hydrogen carbonate has been proven to be the most physiological buffer species (Fadda et al., 2009; Garbacz et al., 2013, 2014; Ibekwe et al., 2008; Liu et al., 2011).

Hydrogen carbonate buffers cover the physiological pH range of the luminal intestinal fluids from pH 5.0 to pH 8.4. However, their use for in vitro evaluation of the drug release performance of solid oral dosage forms is challenging. This is mostly due to their chemical instability resulting in an uncontrolled CO_2 loss followed by a pH increase (Fadda et al., 2009; Ibekwe et al., 2006, 2008; Liu et al., 2011; McConnell et al., 2008; Sheng et al., 2009). The pH value of a hydrogen carbonate buffer is the result of a complex and highly dynamic interplay of the concentration of hydrogen carbonate ions, carbonic acid, dissolved carbon dioxide and its partial pressure above the solution. This complex interplay results in instability of hydrogen carbonate solutions. In order to maintain the pH value, it is necessary to prevent the CO_2 loss which is hardly manageable under routine test conditions. However, the escaping CO_2 may be replaced by feeding equivalent gas volumes into the solution to re-acidify the buffer system (Garbacz et al., 2013, 2014).

At first sight, the instability of hydrogen carbonate buffers can be considered as a substantial disadvantage. At a closer look, these buffers offer the possibility to simulate the dynamic intraluminal pH changes within the human small and large intestine. However, this requires a continuous and dynamic pH adjustment of the buffer system by acidification and alkalization. It is well known that the acidification of the commonly used hydrogen carbonate buffers is a rather fast process in comparison to the relatively slow CO_2 loss. Under drug release test conditions simulating the intraluminal pH profile of the GI tract the degassing process can be accelerated and controlled by purging the solution with a neutral gas such as N_2 or compressed air. If neutral gas is introduced into the release medium, it enlarges the surface available for gas exchange and increases the CO_2 evacuation rate, which results in a rapid increase of the pH value. Acidification as well as alkalization can be performed with high accuracy and resolution using automated controllers such as the pHysio-grad® device (Garbacz et al., 2014).

It should be mentioned that the main problem with the simulation of in vivo pH changes along the intestinal tract is the substantial lack of data with regard to individual intraluminal pH profiles of sufficiently high accuracy. To date, several techniques are available for the determination of gastrointestinal pH values. However, only telemetric capsules such as IntelliCap® allow a real-time pH and temperature monitoring along the whole GI tract. The profiles obtained in such studies may be used as an input function for the simulation of the intraluminal conditions (Koziolek et al., in press).

The aim of this study was to investigate the ability of RL/L55 blend coatings to provide a pH-independent drug release of acidic drugs from coated mini tablets. Further objectives were to estimate drug release from RL/L55 coated mini tablets in different release media mimicking the physiological conditions of the gastrointestinal passage and to investigate the influence of various factors on drug release, including buffer capacity and composition of the release medium as well as pH changes.

2. Materials and methods

2.1. Materials

Eudragit® RL PO, Eudragit® L 100-55 and Aerosil® 200 were donated by Evonik (Germany). Ketoprofen was obtained from Kreussler Pharma (Germany), naproxen from Roche (Switzerland), theophylline and talc from Caelo (Germany). Prosolv® SMCC 90 was donated by JRS Pharma (Germany), Avicel® PH-200 from FMC BioPolymer (Ireland), and Kollicoat® IR Red from BASF (Germany). Hydrochloric acid 1.0 mol l^{-1}, sodium hydroxide 1.0 mol l^{-1}, trisodium phosphate and potassium chloride were all purchased from Carl Roth (Germany). Sodium chloride, potassium dihydrogen phosphate, and disodium hydrogen phosphate were provided by Grüssing (Germany). Calcium chloride and magnesium sulfate heptahydrate were purchased from Merck (Germany). Sodium hydrogen carbonate and magnesium stearate were obtained from Fagron (Germany), disodium hydrogen phosphate from Riedel-de Haën (Germany). All reactants were of analytical grade. Carbon dioxide from Linde AG (Germany) and compressed air were of technical grade.

2.2. Production of mini tablets

Ketoprofen, naproxen, and theophylline were mixed with Prosolv® SMCC 90 in a Turbula® blender (T2F equipped with a 2 l container, Willy A. Bachofen, Switzerland) for 60 min at 72 rpm, respectively. Subsequently, talc and Aerosil® 200 were added and mixing was continued for 2 min. The final powder mass was 300 g and contained 10% drug, 88.5% Prosolv® SMCC, 1% talc, and 0.5% Aerosil®. The powder blend was compacted with a rotary tablet press (Fette 102i, Fette Compacting, Germany) equipped with a Fill-o-Matic fill shoe and Euro-B 19-tip punches at a compression speed of 5 rpm and a medium compaction force of 2.2 kN. The mass of the obtained biconvex mini tablets was approximately 6 mg, the diameter and the band height were both 2 mm. The resulting mini tablets were tested to ensure a similar performance in the subsequent coating step and to verify an uniform drug content. The tablets were accurately weighed on an analytical balance, subsequently the content uniformity of the mini tablets was tested by dissolving randomly selected tablets in phosphate buffer pH 6.8 and determining the content spectrophotometrically at compound specific wavelengths ($n = 5$; Agilent 8453, Agilent, USA). The