Drug Development and Industrial Pharmacy, 2009; 35(10): 1210–1218

informa
healthcare

ORIGINAL ARTICLE

Citric acid as a pH-modifying additive in an extended release pellet formulation containing a weakly basic drug

Jan Ploen[1], Jens Andersch[1], Michael Heschel[1] and Claudia S. Leopold[2]

[1]*Business and Product Development, APOGEPHA Arzneimittel GmbH, Dresden, Germany and* [2]*Department of Pharmaceutical Technology, Institute of Pharmacy, University of Hamburg, Hamburg, Germany*

Abstract

Background: An extended release pellet formulation (ACES®) of the weakly basic drug propiverine was developed with spheronized citric acid crystals as starter cores. *Method*: Coated pellets, consisting of several layers of functional coatings, were manufactured by fluid bed coating. Different coating levels were examined with regard to their effect on drug release. Release profiles from the formulations with or without pH modifier and the free base as well as the hydrochloride salt of the active ingredient were compared. *Results*: The coated citric acid starter cores led to a controlled release of the drug and the pH modifier, resulting from modulation of the microenvironmental pH throughout the dissolution period of 17 hours. If microcrystalline cellulose pellets are used as starter cores drug release is strongly pH-dependent. Significant differences in the drug release profiles were observed between the formulations containing the free drug base and those with the hydrochloride salt as a result of an altered microenvironmental pH. *Conclusion*: The presented extended release pellet formulation is able to maintain a low pH within the pellet core and thus a sufficiently high drug solubility. By maintaining a low pH inside the pellets, a controlled drug release can be achieved.

Key words: *Coating; controlled release; microenvironmental pH; pellets; propiverine*

Introduction

Propiverine is an antimuscarinic drug used for the treatment of overactive bladder syndrome or neurogenic detrusor overactivity. Drugs with a comparable pharmacodynamic profile are tolterodine and oxybutynine.

An immediate release (IR) sugar-coated tablet containing 15 mg propiverine hydrochloride for twice-daily administration was first approved in 1981 in Germany (German Democratic Republic). In order to facilitate dosing and to improve patient compliance, an extended release (ER) pellet formulation containing 30 mg propiverine hydrochloride for once-daily administration was developed.

The clinical rationale of the development of an ER formulation of propiverine hydrochloride was to release the drug substance at a constant rate within 24 hours. This may result in a decrease of anticholinergic side effects due to the constant plasma levels. Clinical studies with the IR and the ER formulations showed that both dose regimens were highly effective in controlling detrusor overactivity and were well tolerated. The ER formulation provides the additional advantage of an easy once-daily administration as well as pharmacokinetic benefits[1].

Many drugs are weak acids or bases or salts thereof. Depending on their pK_a value and the pH of the dissolution medium or intestinal fluid, they are present in either their dissociated or nondissociated form.

The weakly basic drug propiverine is a tertiary amine with a pK_a value of 7.35. Its hydrochloride salt shows a distinct pH-dependent solubility. In the case of IR sugar-coated tablets, the drug is readily dissolved at the low pH of the fasting stomach.

However, the challenge of the development of the new propiverine ER formulation was the pH-dependent solubility of propiverine hydrochloride in media within

Address for correspondence: Claudia S. Leopold, Department of Pharmaceutical Technology, Institute of Pharmacy, University of Hamburg, Bundesstraße 45, 20146 Hamburg, Germany. Tel: +49 40 42838–3479, Fax: +49 40 42838–6519. E-mail: claudia.leopold@uni-hamburg.de

(Received 17 Apr 2008; accepted 10 Mar 2009)

ISSN 0363-9045 print/ISSN 1520-5762 online © Informa UK, Ltd.
DOI: 10.1080/03639040902882256

the pH range of the gastrointestinal lumen. At the pH found in the stomach the drug is readily soluble. In the small intestine and the colon, the solubility decreases dramatically and precipitation of the poorly soluble free base occurs. Precipitated drug cannot diffuse out of an ER dosage form. The higher intestinal pH results in incomplete drug release.

A pH-dependent drug release may result in variable plasma levels and thus bioavailability problems. A better control of drug release from such dosage forms is desirable to ensure a reliable drug therapy.

Several studies to overcome the problem of the pH-dependent solubility of weakly basic drugs have been published: One formulation approach involves the use of blends of enteric and sustained release polymers as film coating. In the gastric fluid, the enteric polymer is insoluble and contributes to the retardation of drug release. In the intestinal fluids, the enteric polymer dissolves and the permeability of the coating film is increased[2,3].

Another formulation strategy to improve the release of a weakly basic drug in the intestine is to incorporate organic acids as pH modifiers into the formulation[2–12]. These pH modifiers decrease the microenvironmental pH inside the solid dosage form. The microenvironmental pH can be described as the pH of the saturated solution in the immediate vicinity surrounding the drug particles[4]. With decreasing microenvironmental pH, drug solubility increases and drug release is enhanced.

If an organic acid is used as pH modifier, the extent and the duration of the pH-modifying effect strongly depend on the aqueous solubility, acidic strength and buffer capacity of the incorporated acid, and the solubility of the salt formed with the drug. The ratio of the amount of incorporated acid and that of the drug can influence drug release enhancement[5,6].

At least a portion of the pH modifier should be present inside the dosage form over the entire time period of drug release to maintain the pH-modifying effect[4]. To prevent rapid diffusion of the soluble organic acid out of the pellet, a coating barrier is recommended[7–10]. The desired drug release is only maintained if the acidic compound does not diffuse through this coating membrane or out of the pellets faster than the drug itself.

As acid modifiers differ with regard to their solubility and their pK_a value, the selection of a suitable organic acid is crucial in the development of a drug delivery system for a weakly basic drug.

The effect of the pH modifiers adipic acid, fumaric acid, succinic acid, and tartaric acid on the release of dipyridamole from extruded and spheronized pellets was investigated by Warren et al.[11] In general, the decrease of the microenvironmental pH led to an improved drug release. However, differences in drug release were found depending on the type of acid used. Only minimal drug release was observed as soon as the acid had left the pellet.

Fumaric acid was used by Munday et al.[3] to create an acidic environment within the core of verapamil hydrochloride containing pellets, coated with a blend of Eudragit® RS and hydroxypropyl methylcellulose acetate succinate (AQOAT®). Incorporation of 5% and 10% fumaric acid, respectively, into the pellet core led to enhanced drug release.

In a study by Guthmann et al.[12], different organic acids were incorporated into ER pellets, prepared by extrusion and spheronization followed by film coating with an aqueous polyvinylacetate/polyvinylpyrrolidone dispersion (Kollicoat® SR 30 D). The addition of fumaric acid caused a decrease of the pH within the core pellets during release of the weakly basic drug. Increased release rates even at higher pH values were observed leading to a pH-independent drug release. In contrast, drug release remained pH-dependent with pellets containing tartaric or adipic acid, which can be explained by the lower acidic strength and higher aqueous solubility of these acids.

Another approach is based on coated tartaric acid crystals as starter cores[7]. A blend of sustained release and enteric polymers was used as coating material for the tartaric acid crystals. The weakly basic drug was layered onto these coated cores. Subsequently, an overcoat consisting of sustained release and enteric polymers was applied. The use of polymer blends in both coating layers resulted in a significant retardation of tartaric acid release. However, tartaric acid release was faster than drug release. From these results, it was concluded that pH modifiers such as succinic or fumaric acid with a rather low aqueous solubility are required for maintaining the acidic microenvironmental pH within the dosage form.

In two patents, citric and tartaric acid were used in the form of coated starter cores for manufacture of drug delivery systems containing weakly basic drugs[8,9]. These readily soluble acids form a slowly depleting reservoir. Due to the enteric coating on the starter cores, a gradual increase in the organic acid release can be obtained. The suitability of this strategy has been demonstrated with diffusion pellets, consisting of coated citric acid cores and the drug dihydroergotamine methane sulfonate[10].

This study deals with the development of a propiverine ER pellet formulation containing coated citric acid pellets as starter cores[13]. A blend of enteric polymers was used as coating material for the citric acid starter cores. Pellets, comprising several coating layers, are manufactured by a fluid bed coating procedure. The formulation principle, based on membrane-coated multiple units, is illustrated in Figure 1.

The coated citric acid cores are able to create an acidic microenvironment leading to a high drug solubility inside the pellet formulation. Drug release, which is controlled

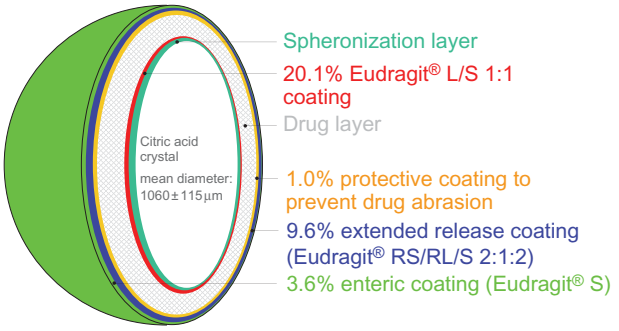

Figure 1. Propiverine hydrochloride ER pellets (ACES®—acid controlled extended release system).

by the microenvironmental pH and the functional polymer layers that surround each pellet, proceeds at an almost constant rate.

The aim of this study was to investigate a novel ER propiverine drug delivery system to confirm the effect of an acidic microenvironment on drug release and to correlate drug release with the release of the pH modifier. Another objective of this study was to evaluate and compare the effect of the form of the drug (i.e., free base or hydrochloride salt on drug release from ER pellets).

Materials and methods

Materials

The following chemicals were obtained from commercial suppliers and used as received: propiverine hydrochloride (APOGEPHA Arzneimittel GmbH, Dresden, Germany); anhydrous citric acid medium granular (Roche Citrique Belge N.V., Tienen, Belgium); Cellets® 700 (IPC Process Center GmbH, Dresden, Germany); Eudragit® RL 12.5 solution, Eudragit® RS 12.5 solution, Eudragit® S 12.5 solution, and Eudragit® L 12.5 solution (Röhm GmbH & Co. KG, Darmstadt, Germany); triethylcitrate (Merck KGaA, Darmstadt, Germany); Kollidon® 25 (BASF, Ludwigshafen, Germany); Sorbolac® 400 (Meggle GmbH, Wasserburg, Germany); 2-propanol (Merck KGaA); magnesium stearate (Merck KGaA); and talc (Merck KGaA). All other reagents were of analytical grade and were used without further purification.

Methods

Solubility/pH profiles of propiverine hydrochloride and its corresponding base

The drug solubility was determined by adding propiverine hydrochloride or propiverine base with a magnetic stirrer to 50 mM buffer solutions over 2 hours at 37°C until equilibrium is reached. A sample volume of 5 mL of the saturated solution was filtered through a membrane filter, diluted to avoid crystallization, and filled in a high-performance liquid chromatography (HPLC) vial. Solubility of propiverine was determined with HPLC (DIONEX GmbH, Idstein, Germany; HPLC containing autosampler; pump HPG 680; column oven; detector UVD 340; column: RP-C8, 5 µm, 125 × 4 mm; UV detection at wavelengths 205, 210, and 220 nm; column oven TCC 100, 40°C; mobile phase: mixture of 560 mL 5 mmol potassium dihydrogenphosphate adjusted to pH 1.0 with phosphoric acid and 440 mL acetonitrile, flow rate 1.0 mL/min).

Manufacture of ER pellets

Multilayer coated pellets were prepared in a Hüttlin Unilab-05-TJ fluid bed coater (Hüttlin GmbH, Steinen, Germany) using 2-propanol and water as solvents. The real coating level (%, w/w) was calculated as follows[14]:

$$\text{Real coating level} = 100 \times \frac{(\text{weight of finished coated pellets (g)} - \text{weight of loaded pellets (g)})}{\text{weight of loaded pellets (g)}}.$$

The following manufacturing steps were performed.

Spheronization of citric acid crystals by fluid bed coating. In a first fluid bed coating step, a sieved fraction of 0.71–1.0 mm granular crystalline citric acid was coated with a suspension of dissolved povidone, citric acid, dispersed micronized lactose and talc. Povidone acts as binding agent, citric acid as pH modifier, lactose as filler, and talc as glidant. Through this manufacturing step, the roundness of the citric acid crystals is improved and sharp edges of the crystals are removed.
Eudragit® L/S coating of citric acid starter cores. In a second coating step the spheronized crystals were coated with a Eudragit® L/S (1:1) layer to control citric acid release. Other functional excipients of the coating suspension were triethylcitrate as plasticizer and talc as glidant. The coating level was 20.1% (w/w).
Drug layering onto the enteric coated pellets. For drug layering, a suspension containing the dissolved drug substance, povidone, citric acid, suspended talc, and magnesium stearate is sprayed onto the pellets. The drug content of the pellets after this manufacturing step is approximately 22% (w/w).
Protective coating to prevent drug abrasion. Mechanical abrasion is prevented by a thin protective layer consisting of povidone and talc, which was sprayed immediately onto the drug-layered pellets. The coating level was 1.0% (w/w).
Extended release coating. The ER coating layer consists of a polymer blend of two gastrointestinal tract-insoluble but permeable polymers (Eudragit® RS/RL) and a pH

dependent soluble polymer (Eudragit® S) in a ratio of 2:1:2. Eudragit® RS and Eudragit® RL represent the insoluble polymer portion, whereas Eudragit® S, which is soluble in the distal small intestine, makes the diffusion layer more permeable in the distal segments of the intestine by elution from the film. The composition of this coating layer was the result of preliminary experiments. Triethylcitrate was used as plasticizer and talc as glidant. The coating level was 9.6% (w/w).

Outer enteric coating. The outer enteric coating layer consists of Eudragit® S, which is soluble in intestinal fluids above pH 7. The role of this coating layer is to decrease the initial drug release during the first hours in order to achieve controlled release. The coating level was 3.6% (w/w).

To remove residual solvents, the multilayer coated pellets were dried for 50 hours at 70°C in a tray drier.

In vitro citric acid and drug release

Quantification of citric acid release from Eudragit® L/S-coated citric acid starter cores. Dissolution studies were performed at 37°C using the USP apparatus 1 (Erweka DT 800; Erweka GmbH, Heusenstamm, Germany; basket, 100 rpm). The dissolution medium was hydrochloric acid (0.1 mol/L) and the dissolution time period was 16 hours. The quantification of citric acid was carried out by potentiometric determination of the first equivalence point of citric acid with 0.1 mol/L sodium hydroxide solution (Mettler Titrator DL 58 with Solvotrode; Mettler-Toledo GmbH, Giessen, Germany). The calibration curve had a regression coefficient of 0.99.

Drug release from ER pellets. Dissolution studies were performed according to the FIP Guidelines for Dissolution Testing of Solid Oral Products[15] at 37°C using the USP apparatus 1 (Erweka DT 800). Drug release media were hydrochloric acid (0.1 mol/L) for 1 hour and then USP phosphate buffer (pH 5.8 and 6.8) for 16 hours. These pH values are close to the pK_a value of the drug substance. At both pH values sink conditions are retained. Phosphate buffer (pH 5.8) was used as dissolution medium for routine dissolution testing, because the drug substance shows a very low dissolution rate in phosphate buffer (pH 6.8).

The concentration of propiverine in the dissolution media was measured spectrophotometrically with an online-coupled UV/VIS method at 239 nm at a background wavelength at 247 nm (Photometer Beckman DU 640i; Beckman Coulter, Inc., Fullerton, CA, USA).

Quantification of citric acid release from final coated propiverine hydrochloride ER pellets. In order to investigate the effect of the pH modifier citric acid on the ER of propiverine hydrochloride, the release of citric acid itself was determined. Dissolution studies were performed at 37°C using the USP apparatus 1 (Erweka DT 800). Dissolution media were hydrochloric acid (0.1 mol/L) for 1 hour, then USP phosphate buffer (pH 5.8) for 16 hours. Citric acid concentration was measured by HPLC [DIONEX GmbH, Idstein, Germany; RP-column: Ultrasep ES FS; Sepserv, 5 µm, 125 × 3 mm, mobile phase: 10 mM phosphoric acid (pH 2.9), pump HPG 680, flow rate: 0.55 mL/min, column oven TCC 100, 30°C, UV detection at 210 nm, Detector UVD 340U, degasser, autosampler Gina 50].

Preparation of the free base propiverine

Propiverine hydrochloride was dissolved in purified water. The drug containing solution was stirred while adding an aqueous ammonium hydroxide solution. The precipitated propiverine free base was washed with water and vacuum-dried. The propiverine base was used in powdered form for the drug-layering process.

Characterization of spheronized citric acid crystals by means of Automatic image analysis

Automatic image analysis is an appropriate tool for the characterization of size and shape of particles. The roundness (%) and aspect ratio values of spheronized citric acid crystals were determined by an Image Analyser (Leco IA 32; Leco Instrumente GmbH, Mönchengladbach, Germany; microscope MZ 12.5 with PixeLink digital camera, $n = 100$).

Results and discussion

Solubility of propiverine hydrochloride and its corresponding base

The drug is extremely poorly soluble in aqueous media with pH values above 6.5. At pH values below 5.51 the solubility exceeds 7.31 g/L, at pH 6.62 it decreases to about 0.57 g/L, and above pH 8 it is practically insoluble. Solubilities of propiverine hydrochloride and its corresponding base in buffer solutions at different pH values are shown in Figure 2.

The pH-dependent solubility can be explained by the weakly basic nature of propiverine. As demonstrated in Figure 3, a dissociation equilibrium of propiverine hydrochloride and its corresponding base exists.

Propiverine as a base will be protonated at lower pH values and turns soluble, whereas at higher pH values it is insoluble as an uncharged molecule. Therefore, the solubility of propiverine hydrochloride decreases with increasing pH values.

Eudragit® L/S-coated citric acid starter cores

In order to prevent a pH-dependent precipitation of the poorly soluble uncharged molecule form of propiverine inside the multiparticulate system, granular-shaped

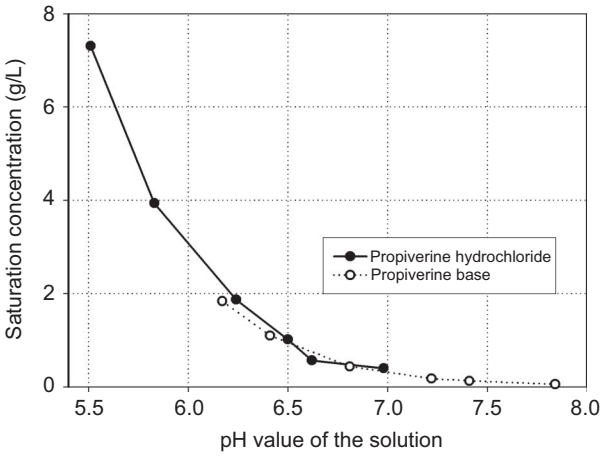

Figure 2. Solubility/pH profile of the drug in 0.05 M phosphate buffers at 37°C.

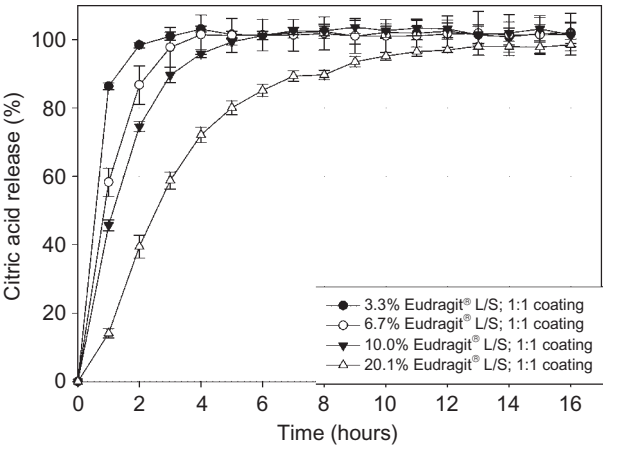

Figure 4. Effect of different Eudragit® L/S (1:1) coating levels on citric acid release from coated citric acid pellets (means ± SD, $n = 6$, dissolution medium: 0.1 mol/L hydrochloric acid).

citric acid crystals with a roundness of about 79% and aspect ratio values of about 1.26 are used as starter cores.

However, the most common shape of individual starter cores for the development of controlled release multiparticulate formulations is a sphere, as a spheroid has a minimum surface to volume ratio, with a consistent and defined surface for drug release. Therefore, the citric acid crystals are spheronized in the fluid bed with a povidone containing suspension. Due to interparticular friction between the particles the roundness of the crystals is improved to about 83%. Citric acid crystals show a smooth surface and a spherical shape after spheronization in the fluid bed coating equipment.

Ideally, citric acid as pH modifier should dissolve slowly and remain within the pellet during the entire time period of drug release. Therefore, a release controlling coating layer is necessary. A blend of enteric coating polymers was used to control citric acid release. In Figure 4, the effect of the coating level on citric acid release is shown.

Due to the shape of the crystals with comparatively low roundness—and aspect ratio—values and thus an inhomogenous coating thickness, retardation of citric acid release through this coating film is not very effective.

The influence of different Eudragit® L/S (1:1) coating levels on coated citric acid pellets on drug release was also investigated. All four different batches of coated starter cores were used to manufacture the final coated pellets. Figure 5 shows the drug dissolution profiles from these formulations.

Citric acid cores coated with Eudragit® L/S (1:1) at 6.7%, 10.0%, and 20.1% coating levels increase drug release from final coated pellets. In contrast, a coating level of 3.3% resulted in a significant decrease in drug release, which can be explained by the too thin and thus

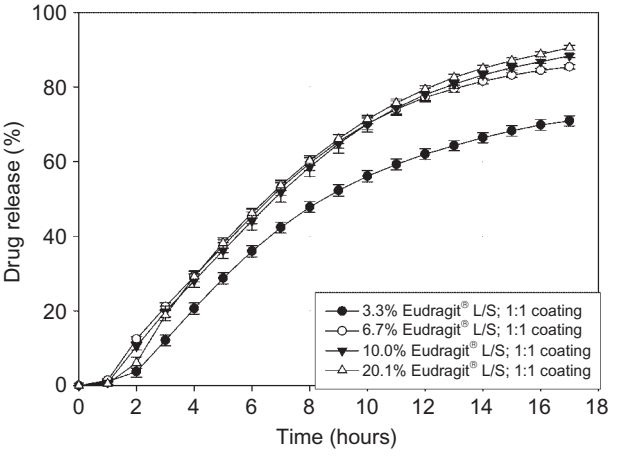

Figure 5. Effect of different coating levels of Eudragit® L/S (1:1) applied to the citric acid cores on drug release from the final coated pellets (9.6% ER and 1.8% final enteric coating) [means ± SD, $n = 6$, dissolution medium: phosphate buffer (pH 5.8)].

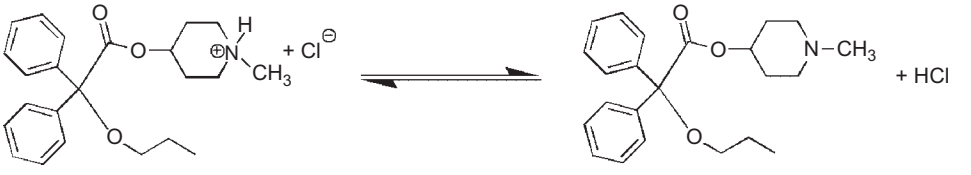

Figure 3. Dissociation equilibrium of propiverine hydrochloride and its corresponding base.

porous coating film. Therefore, the highest coating level was chosen for the formulation development of propiverine hydrochloride ER pellets.

Propiverine hydrochloride ER pellets

Drug release from coated multiparticulate dosage forms can occur by diffusion, osmosis, and polymer erosion[16]. A combination of these mechanisms usually occurs in every drug delivery system, with each mechanism contributing to a different extent[17,18].

In the case of propiverine hydrochloride ER pellets, gastrointestinal fluid will enter the core on contact with this aqueous environment. Subsequently, dissolution of the drug and the pH modifier within the pellet core starts. Due to the good solubility of the drug as well as of citric acid, an osmotic pressure builds up in the acidic microenvironment inside the pellet core. The osmotic pressure allows the drug and the citric acid to diffuse through the functional coating layers into the surrounding dissolution medium.

To study the effect of the coating level on the dissolution rate different coating levels of the outer functional coatings were examined (Figure 6).

As expected, the release of propiverine from ER pellets is reduced at higher coating levels. However, the drug diffuses out of the pellets even at high coating levels. This may be explained by its good solubility in the acidic microenvironment inside the pellet cores.

Release of the pH modifier citric acid was also determined at all coating levels to better understand the drug release mechanism. In Figure 7, the effect of the coating level on citric acid release from propiverine hydrochloride ER pellets is shown.

As observed with drug release, citric acid release from the pellets is reduced at higher coating levels. Interestingly, it is slower than drug release at all coating levels. This is in good agreement with the hypothesis of an acidic microenvironment inside the pellets. Obviously, citric acid indeed works as a pH modifier and remains in the pellet system during the entire period of drug release.

Generally, the overall goal in developing controlled release drug delivery systems containing weakly basic drugs is a pH-independent release system. However, drug release from the novel propiverine hydrochloride ER pellets still depends somewhat on the pH value of the dissolution medium.

In Figure 8, drug release profiles from the final coated propiverine hydrochloride ER pellets in buffer solutions of different pH values are shown.

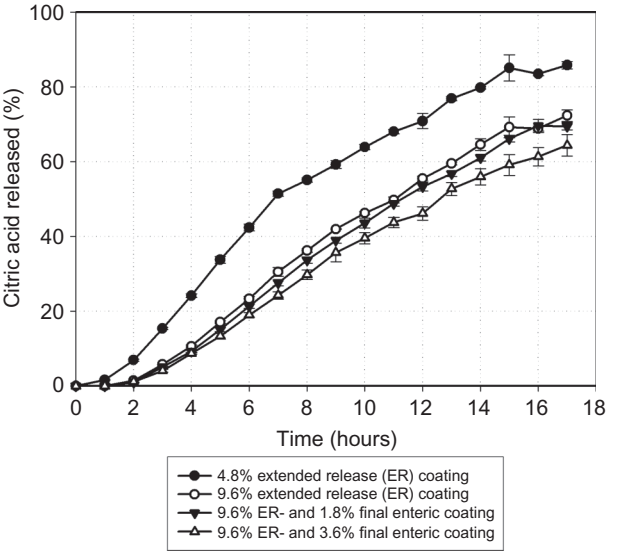

Figure 7. Effect of different coating levels on citric acid release from coated pellets [means ± SD, n = 6, dissolution medium: phosphate buffer (pH 5.8)].

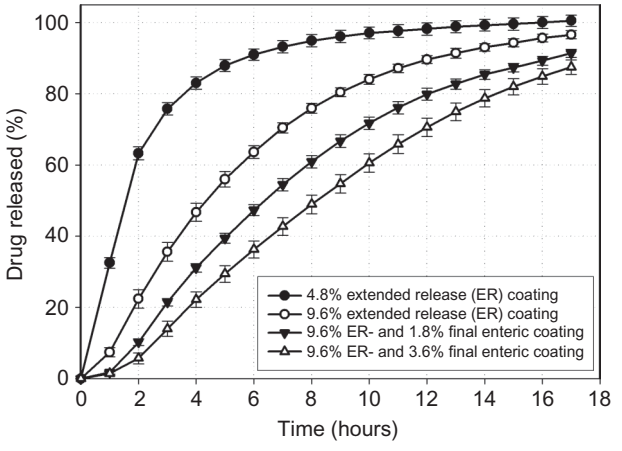

Figure 6. Effects of different coating levels on drug release from coated pellets [means ± SD, n = 6, dissolution medium: phosphate buffer (pH 5.8)].

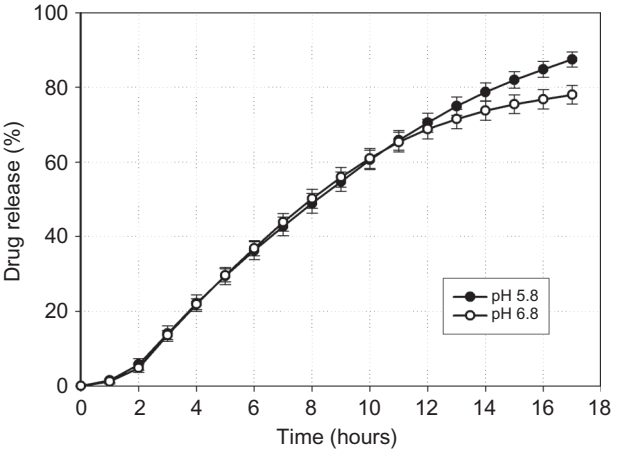

Figure 8. Effect of the pH on drug release from final coated pellets (9.6% ER and 3.6% final enteric coating) containing coated citric acid pellets as pH modifier (means ± SD, n = 6).

As illustrated in Figure 8, drug release profiles are superimposed during the first 11 hours. Citric acid works as a pH modifier and remains in the pellets during the entire period of drug release. Obviously, at pH 6.8, citric acid is unable to modify the pH value inside the pellet effectively longer than 11 hours, and propiverine starts to precipitate out. If the pH is close to the pK_a value of the drug, even minimal changes in the pH can considerably alter ionization and hence affect solubility. Under dissolution conditions of pH 5.8, which is far below the pK_a value of the drug, precipitation does not take place.

Propiverine hydrochloride ER pellets without pH modifier

To evaluate and compare the effect of microcrystalline cellulose pellets (Cellets®) as starter cores on drug release from final coated propiverine hydrochloride ER pellets, dissolution studies were performed in the same buffer media of different pH values.

Figure 9 illustrates that drug release profiles are significantly different if no acid modifier is incorporated into the pellet formulation. This is in agreement with the above-mentioned hypothesis of the formation of an acidic microenvironment by citric acid inside the pellets.

Propiverine ER pellets

In order to investigate the effect of the uncharged form of the drug, propiverine ER pellets were manufactured using equimolar quantities of its corresponding free base. Coated pellets with and without outer enteric coating layer (Eudragit® S) were investigated.

From a theoretical point of view, drug release from ER pellets containing propiverine should be slower than that from propiverine hydrochloride ER pellets,

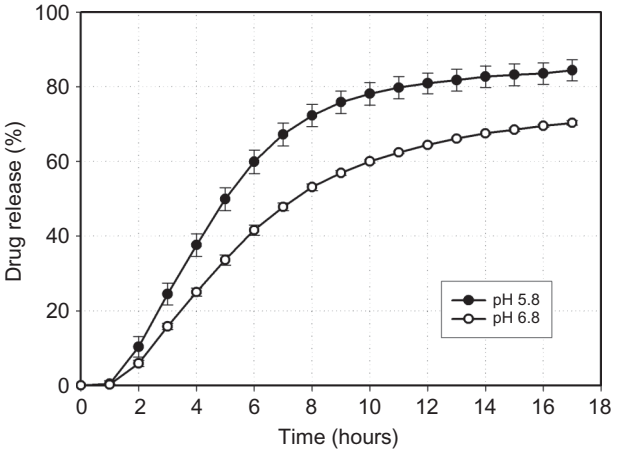

Figure 9. Effect of the pH on drug release from final coated pellets (9.6% ER and 3.6% final enteric coating) containing no acid modifier (means ± SD, $n = 6$).

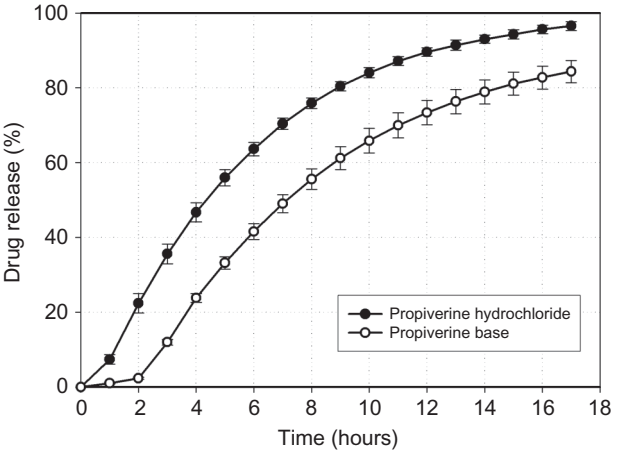

Figure 10. Effect of the free base and the hydrochloride salt form of active ingredient on drug release from 9.6% ER coated pellets [means ± SD, $n = 6$, dissolution medium phosphate buffer (pH 5.8)].

because the uncharged form of the drug has to be transformed into the readily soluble salt form before diffusing out of the pellet formulation. This transformation can only take place, if citric acid diffuses out from the inner core of the pellet into the drug layer. Because of the Eudragit® L/S coating of the citric acid starter cores, a steady citric acid release controls the microenvironmental pH inside the pellet ultimately leading to an ER of the drug substance.

Dissolution profiles of propiverine ER pellets without enteric coating

A significant difference in drug release was observed between the formulations with propiverine and those with the hydrochloride salt.

In Figure 10, the effect of the different drug forms of active ingredient on drug release from ER coated pellets is shown. As illustrated in this figure, drug release from the hydrochloride ER pellets is faster compared to that from propiverine ER pellets. The slower drug release from propiverine ER pellets may be explained by the time-consuming transformation of propiverine into the soluble salt form, caused by a comparatively higher microenvironmental pH inside the pellets. Whereas the readily soluble propiverine hydrochloride dissolves fast (pH of an aqueous solution is about 3.0), citric acid is necessary for the dissolution of propiverine base, which is released from the coated starter cores. As a result of this transformation process due to the considerably higher microenvironmental pH, the onset of drug release is delayed.

Dissolution profiles of propiverine ER pellets with enteric coating

The effect of the free base and the hydrochloride salt form of active ingredient on drug release from the final enteric coated pellets is illustrated in Figure 11.

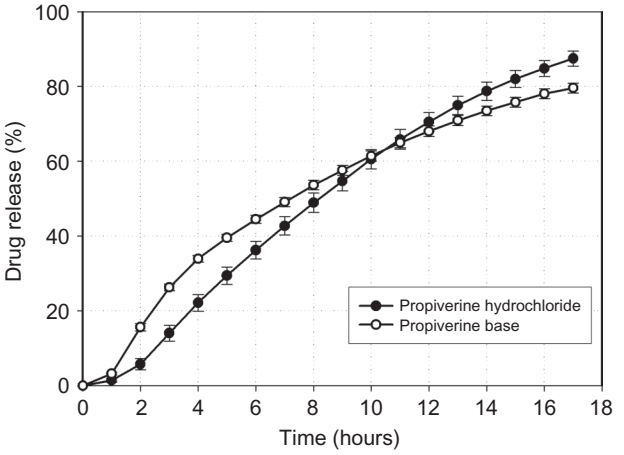

Figure 11. Effect of the free base and the hydrochloride salt form of active ingredient on drug release from 9.6% ER and 3.6% final enteric coated (ER) pellets [means ± SD, n = 6, dissolution medium: phosphate buffer (pH 5.8)].

Surprisingly, drug release from propiverine ER pellets was comparatively faster during the first 8–10 hours. This effect can also be attributed to the higher microenvironmental pH inside the pellets containing the free base.

Apparently, in the case of propiverine hydrochloride ER pellets, the outer enteric coating layer is stabilized by citric acid diffusing out from the inner cores. The outer enteric coating layer dissolves faster at a comparatively higher microenvironmental pH inside the pellets, which may be observed with the propiverine ER pellets within the first 8–10 hours as well as with the propiverine hydrochloride ER pellets at a later time.

Conclusion

The presented ER pellet formulation containing citric acid (ACES®) is able to maintain a low pH within the pellet core and thus a sufficiently high drug solubility. Therefore, the precipitation tendency of the poorly soluble propiverine base is reduced. By maintaining a low pH inside the pellets, a controlled drug release can be achieved.

The advantage of this formulation design as compared to other drug delivery systems with pH modifiers is the high proportion of readily soluble citric acid, ensuring a low microenvironmental pH throughout the entire time course of drug release. Due to the Eudragit® L/S (1:1) coating on the spheronized citric acid crystals, the release of the pH modifier proceeds gradually from a slowly depleting reservoir.

The incorporation of coated citric acid starter cores in propiverine hydrochloride ER pellets decreases the pH dependency of the drug solubility. If no acid modifier is incorporated into the pellet formulation, drug release is strongly pH-dependent. Furthermore, drug release depends on the film thickness of both outer functional coatings, which can be used to modify the drug release rate. Citric acid release from propiverine hydrochloride ER pellets is slower than drug release at all coating levels.

These results confirm the hypothesis of an acidic microenvironment inside the pellets of this novel drug delivery system. If the uncharged form of the drug was used, significant differences in the drug release profiles were observed between the ER formulations of the free base and those of the hydrochloride salt. This is caused by an altered microenvironmental pH inside the pellets.

Declaration of interest: The authors report no conflicts of interest.

References

1. Jünemann K-P, Hessdorfer E, Unamba-Oparah I, Berse M, Brünjes R, Madersbacher H, et al. (2006). Propiverine hydrochloride immediate and extended release: Comparison of efficacy and tolerability in patients with overactive bladder. Urol Int, 77:334–9.
2. Dashevsky A, Kolter K, Bodmeier R. (2004). pH-independent release of a basic drug from pellets coated with the extended release polymer dispersion Kollicoat SR 30 D and the enteric polymer dispersion Kollicoat MAE 30 DP. Eur J Pharm Biopharm, 58:45–9.
3. Munday DL. (2003). Film coated pellets containing verapamil hydrochloride: Enhanced dissolution into neutral medium. Drug Dev Ind Pharm, 29:575–83.
4. Siepe S. (2005). Strategies to improve oral absorption of weakly basic drug substances by modulating the microenvironmental pH. Doctoral Thesis, University of Genf, Switzerland.
5. Thoma K, Zimmer T. (1990). Retardation of weakly basic drugs with diffusion tablets. Int J Pharm, 58:197–202.
6. Thoma K, Ziegler I. (1998). The pH-independent release of fenoldopam from pellets with insoluble film coats. Eur J Pharm Biopharm, 46:105–13.
7. Venkatesh GM. (1998). Development of controlled release SK&F 82526-J buffer bead formulations with tartaric acid as the buffer. Pharm Dev Tech, 3:477–85.
8. Gruber P, Brickl R, Bozler G, Stricker H. (1980). Neue Dipyridamol-Retardformen und Verfahren zu ihrer Herstellung. EP Patent 0032562, December 17, 1980.
9. Gruber P, Schmid J, Lechner H, Bauer E. (1982). Bromhexin-Retardform und Verfahren zu ihrer Herstellung. EP Patent 0069259, June 18.
10. Thoma K, Knott F. (1991). Retardierung schwach basischer Arzneistoffe. Pharm Ind, 53:778–85.
11. Warren SJ, MacRae RJ, Melia CD. (1999). Investigation into the effect of weak acid modifiers on improving the release of dipyridamole from extruded spheronised pellets. Proc Intern Symp Control Rel Bioact Mater, 26: 6370.
12. Guthmann C, Lipp R, Wagner T, Kranz H. (2007). Development of a multiple unit pellet formulation for a weakly basic drug. Drug Dev Ind Pharm, 33:341–9.
13. Gramatté T, Gruber P, Güldner P, Heschel M, Pamperin D, Ploen J, et al. (2003). Oral dosage form for propiverine or its pharmaceutically acceptable salts with an extended release of the active ingredient. W.O. Patent 03/030869, October 8, 2003.
14. Kumpugdee M. (2002). Überziehen von pellets mit wässrigen, magensaftresistenten polymerdispersionen in

der Wirbelschichtanlage. Doctoral Thesis, University of Hamburg, Germany.
15. Siewert M. (1997). FIP Guidelines for dissolution testing of solid oral products. Pharm Ind, 59:760–6.
16. Hogan J. (2001). Coating of tablets and multiparticulates. In: Aulton ME, ed. Pharmaceutics: The science of dosage form design. New York: Churchill Livingstone, 441–8.
17. Ozturk AG, Ozturk SS, Palsson BO, Wheatley TA, Dressman JB. (1990). Mechanism of release from pellets coated with an ethylcellulose-based film. J Control Release, 14:203–13.
18. Dressman JB, Palsson BO, Ozturk A, Ozturk S. (1994). Mechanisms of release from coated pellets. In: Ghebre-Sellasie I, ed. Multiparticulate oral drug delivery. New York: Marcel Dekker, 285–306.