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Research paper

Tailor-made release triggering from hot-melt extruded complexes of basic polyelectrolyte and poorly water-soluble drugs

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ABSTRACT

The aim of the study was the formulation of polyelectrolyte complexes composed of poorly water-soluble acid drugs and basic polymethacrylates by hot-melt extrusion enabling a tailor-made release pattern by the addition of inorganic salts. The influence of different electrolytes was analyzed at varying conditions in order to control drug delivery from the complexes. Poorly water-soluble model drugs naproxen and furosemide were applied in their non-ionic form.

After hot-melt extrusion of the naproxen-polymethacrylate powder blend, XRPD and DSC measurements indicated the formation of a single-phase amorphous system. Milled extrudates were stable under storage at long-term and intermediate conditions. Polyelectrolyte complex formation by an acid–base reaction during hot-melt extrusion could be proven by the lack of vibrations of dimethylamino and carboxylic groups by FT-IR and Raman spectroscopy. The complexes did not dissolve in demineralized water. Drug release could be immediately induced by addition of neutral electrolytes. Tailor-made dissolution profiles were realized by controlled electrolyte triggering. Maximal effects were achieved by concentrations of 0.05–0.15 M NaCl. Different anions of alkali halogenides revealed variant magnitudes of the effect depending on the anion radius. Polyelectrolyte complex formation and dissolution principles were also confirmed for furosemide.

1. Introduction

Processing poorly water-soluble drugs with polymers into solid dispersions is one of the most promising approaches in improving drug bioavailability. As a subcategory of solid dispersions, drug–polyelectrolyte complex formation is of high interest in this scientific work field [1].

Oppositely charged polyelectrolytes bound together by electrostatic interactions [2] are defined as polyelectrolyte complexes [3,4]. Interpolyelectrolyte complexes (IPEC) consisting of countercharged polymers were described as promising carriers for oral controlled drug delivery by Gallardo et al. [5] and Moustafine et al. [6]. More generally described as association complexes formed between oppositely charged molecules [7], furthermore, drug–polymer complexes can be included in the definition of polyelectrolyte complexes. Embedding of drugs in polymer–polymer matrices as well as polymer–drug associations is of major interest.

Polymer–drug polyelectrolyte complexes have been widely used in formulations for various purposes. Jimenez-Kairuz et al. [8] improved hydrolytic stability of procaine as basic drug by complexation with carbomer. Similarly, rapid diffusion of acid proteins out of hydrogel matrices could be prevented by complex formation with countercharged basic substances [9]. Complexes of DNA and cationic polymers like chitosan served as non-viral gene delivery vectors for gene therapy and oral vaccination [10]. Taste-masking of ionic drugs with high bitterness could be achieved by utilizing countercharged EUDRAGIT® E or L polymers [11–13].

Modulation of microenvironmental pH is a useful method for increasing the solubility of poorly soluble compounds or the drug release from solid dosage forms [14]. Some patents [15–18] claim the influence of salts on the pH-dependent solubility of poorly soluble acid and basic drugs. Acting as corresponding acid or base of the drug, electrolytes in the core of the solid dosage forms may influence pH microenvironment and thus increase drug solubility.

Contrary to the previous examples, this study focuses on neutral electrolytes that do not influence the pH value. It is well known from literature that polyelectrolyte complexes may be influenced by other electrolytes. Interactions between inorganic salts and polyelectrolyte complexes affect the formation and the stability of the complexes [19]. Dautzenberg [20] investigated the influence of sodium chloride (NaCl) on polyelectrolyte complex formation. He differentiated between low ionic strengths leading to aggregation and higher ionic strengths resulting in flocculation.

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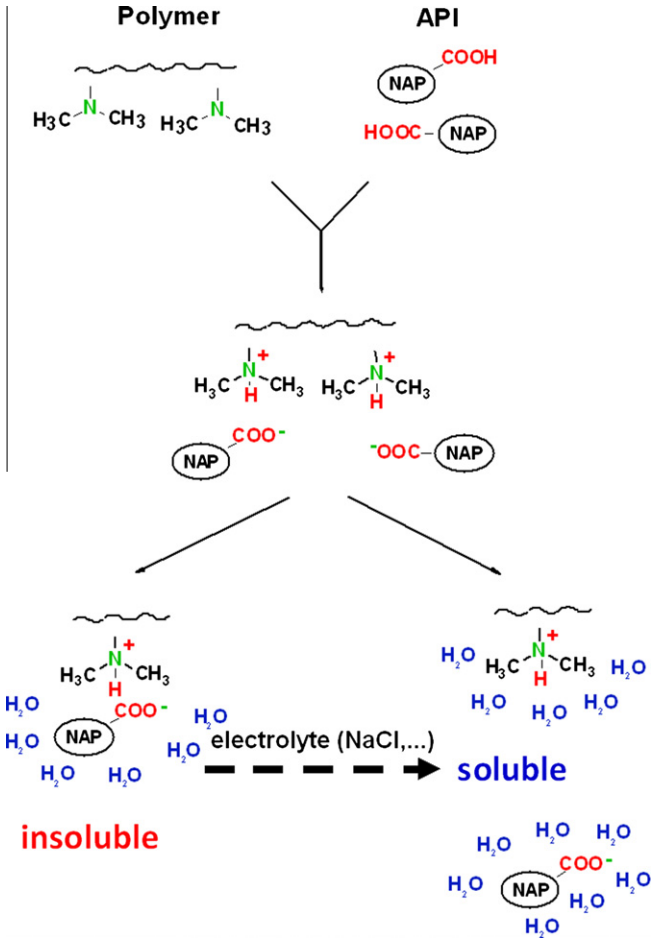

Fig. 1. Use of poorly water-soluble acids in their non-ionic form; acid–base reaction during pharmaceutical manufacturing process (→polyelectrolyte complex); drug release triggering by pH-neutral electrolytes. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Jimenez-Kairuz et al. [21,22] highlighted the drastic increase of release rates from carbomer–lidocaine and carbomer–metoclopramide hydrogels by using salts like NaCl. Titration experiments with NaCl revealed enhanced drug delivery from solid complexes of EUDRAGIT® E 100 and anionic drugs [23]. Different ionic strengths could control delay in dissolution of taste-masked countercharged compounds [11–13].

The objective of the study was to combine the ideas of polyelectrolyte complex formation and their potential instability toward electrolytes. Polyelectrolyte complexes consisting of poorly water-soluble acid drugs and basic polymer EUDRAGIT® E PO should be produced (Fig. 1).

Naproxen and furosemide (Fig. 2) were chosen as model drugs characterized by their poor aqueous solubility and acidic functional groups. Suitable analytical methods should be identified to reveal interactions at molecular level. The complex stability should be analyzed in the presence of different salts with varying ionic strength.

2. Materials and methods

2.1. Materials

Naproxen (Divis Laboratories, Hyderabad, India) and furosemide (BASF, Ludwigshafen, Germany) served as model drugs. "Basic butylated methacrylate copolymer" Ph.Eur. (EUDRAGIT® E PO) was kindly donated by Evonik industries (Darmstadt, Germany). Polysorbate 20 was purchased from Caesar and Loretz (Hilden, Germany). Sodium chloride (Ph.Eur. grade), sodium iodide (Ph.Eur. grade), potassium bromide (Ph.Eur. grade), and cesium chloride (analytical grade) were acquired from Sigma–Aldrich (Steinheim, Germany). Potassium chloride (analytical grade) was obtained from VWR Scientific Products (Darmstadt, Germany). Potassium iodide (analytical grade) was purchased by Acros Organics (Niddera, Germany). Sodium bromide (analytical grade) was obtained from Grüssing (Filsum, Germany).

2.2. Preparation of extrudates and milled strands

Naproxen and EUDRAGIT® E PO were pre-blended in a LM20 mixer (Bohle, Enningerloh, Germany) and subsequently hot-melt extruded using a co-rotating twin-screw extruder (Leistritz Micro 27GL-28D, Nuremberg, Germany). The powder feed (22.5 g/min) was controlled by the calibrated gravimetric powder feeder KCL KT20 (K-Tron Soder, Switzerland).

Screw speed conveying the mixture to the die plate of 2 mm diameter was set to 95 rpm. The screw configuration consisted of conveying elements and kneading blocks. This should provide intensive mixing of the melt during its short residence time (about 1 min). Barrel segments could be heated separately. A dynamic balance of constant pressure, engine performance, and die plate temperature was reached and recorded during each process by pressure and temperature sensors.

Extrudates passing the die plate were transported by a band conveyor (Brabender, Duisburg, Germany) with 131 cm length and cooled at room-temperature. Milling was performed in an ultra centrifugal mill (Retsch ZM 200, Haan, Germany) at 6000 rpm with an insert of 1.0 mm. 355–500 μm sieve fraction (355–500 μm) was gained by sieving (AS Control 200, Retsch, Haan, Germany).

2.3. Preparation of furosemide melt

The physical mixture of furosemide and EUDRAGIT® E PO was molten in a Heraeus vacutherm oven (VT 6025, Kendro Laboratory Products, Hanau, Germany); 180 °C was sufficient to prepare a transparent melt because of ionic interactions between both substances. Milling and sieving were carried out analogue to 2.2.

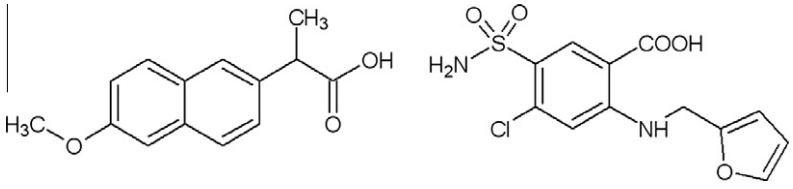

Fig. 2. Chemical structures of naproxen (left) and furosemide (right).

2.4. Analysis of solid-state

2.4.1. X-ray powder diffraction (XRPD)

XRPD patterns were recorded with the powder X-ray diffractometer X'Pert MDP PW3040/00 (DY653) from PANalytical (Almelo, Netherlands) using Cu-anode radiation. Starting materials, physical mixtures, extrudates, and melts were filled into a 16 mm sample holder spinning with 60 rpm. Measurements were performed for $2\theta = 5–60°$ in 0.0167° steps. Diffraction patterns were obtained at a voltage of 40 kV and a current of 40 mA.

2.4.2. Differential scanning calorimetry (DSC)

Differential scanning calorimetry was performed on physical mixtures, extrudates, and melts, using a DSC 821e (Mettler-Toledo, Gießen, Germany). About 3 mg of each sample was sealed in pierced aluminum pans.

Profiles were recorded with a heating rate of 10 °C/min in the range between 0 and 200 °C. After each measurement, DSC was heated up to 400 °C for cleaning. Indium, zinc, and cyclohexane were used for calibration of temperature and transition enthalpy.

2.5. Analysis of ionic interaction

2.5.1. FT-IR

FT-IR-measurements were conducted with a Spectrum One FT-IR Spectrometer (PerkinElmer, Waltham, USA). Powdered samples could be directly measured using the system's ATR-unit.

2.5.2. Raman

A Raman Rxn2 spectrometer (Kaiser Optical Systems, Ann Arbor, MI, USA) was used to obtain Raman spectra of drugs, polymers, physical mixtures, extrudates, and melts via an air-cooled CCD detector. The MR Probe System fiber-optic sampling device was equipped with an extruder compatible optic. A 785-nm NIR-laser was used for excitation. IC Raman software served for data collection and transfer. Data were further processed using SIMCA-P + v11.5 software (Umetrics AB, Umeå, Sweden).

2.6. Dissolution study

Dissolution of milled extrudates (fraction 355–500 μm) was performed using a Sotax AT6 (Sotax, Lörrach, Germany) equipped with paddles [24] at a stirring speed of 100 rpm. Different amounts of electrolytes were added to the dissolution medium (demineralized water and 0.001% polysorbate 20). Spectrophotometrical detection of naproxen was carried out at 272 nm (Lambda-2, Perkin-Elmer, Ueberlingen, Germany) specifically, since EUDRAGIT® E PO, polysorbate 20, and the electrolytes do not absorb radiation at this UV-wavelength.

Furosemide dissolution samples (2 ml) were collected after 6, 12, 30, 45, 60, 66, 72, 90, 105, and 120 min and filtered (0.45 μm filter, VWR International, Radnor, USA) into HPLC vials.

2.7. High-performance liquid chromatography (HPLC)

Quantification of furosemide was conducted using the La Chrom Elite HPLC system (Hitachi, Tampa, USA) equipped with pump (L-2300), auto sampler (L-2200), column oven (L-2300), and UV-detector (L-2400). The column (Zorbax Extend C-18; 150 × 3.00 mm; 3.5 μm) was purchased from Agilent (Waldbronn, Germany). The column oven was tempered at 40 °C. Measurements were performed for 10 min with an injection volume of 50 μl. Flow rate was set constant to 0.7 ml/min resulting in a column pressure of about 205 bar. A 10 mM KH_2PO_4-buffer pH 3.5 served as mobile phase pumped isocratically through the column. UV-detection was carried out at 339 nm specific for furosemide.

2.8. Stability testing

Stability tests were performed according to the ICH guideline "Stability testing of new drug substances and products Q1A(R2)". Milled extrudates were stored at long-term (25 °C, 60% RH) and intermediate conditions (30 °C, 65% RH) in HDPE-bottles with and without (for long-term conditions) drying aid. Storage was conducted in conditioning cabinets (KBF 240, Binder, Tuttlingen, Germany).

Recrystallizing tendency of samples stored at 25 °C and 60% relative humidity was tested by DSC and XRPD after 3, 6, and 12 months. Materials under intermediate conditions were analyzed after 3 and 6 months.

2.9. Saturation solubility

In order to determine saturation, a surplus of naproxen and furosemide were dissolved in 1000 ml demineralized water at 37 °C and shaken (SM 25, Edmund Buehler, Tuebingen, Germany). After 24 h, saturated suspensions were filtered and measured immediately as described under 2.6 and 2.7.

3. Results and discussion

3.1. Preparation of polyelectrolyte–drug-complexes

Hot-melt extrusion was chosen as the process technology for the preparation of polyelectrolyte complexes consisting of drug substance and polymer. The continuous process offers the opportunity to work solvent-freely. Aqueous media might interfere in complex formation or destruction. Residuals of organic solvents could be avoided.

During hot-melt extrusion, the substances should fulfill certain preconditions for complex formation. The components should be mutually soluble or miscible under process conditions in order to interact. The choice of substances was made by the potential of acid–base complexation.

The model drug naproxen is characterized by poor aqueous solubility (~65 mg/l at 37 °C), a pK_a of 4.1 [25] and a melting point of 154 °C. It is categorized into BSC class II. As corresponding basic compound, EUDRAGIT® E PO was applied revealing a pK_b of about 7.7 [26]. It has a glass transition temperature (T_g) of about 50 °C. The content of basic dimethylaminoethyl groups of the copolymer is set from 20.8% to 25.5% according to the Ph.Eur.

The quantities of dimethylaminoethyl groups of EUDRAGIT® E PO were correlated in a 1:1 molar ratio to the carboxylic functions of naproxen resulting in a 42% naproxen and 58% EUDRAGIT® E PO mixture (m/m).

Many approaches have been introduced in order to predict drug–polymer solubility and miscibility in solid dispersions. They can be categorized to theoretical and practical approaches. Three-dimensional solubility parameters indicating dispersion forces, polar interactions, and hydrogen bond formation have been introduced and modified by various researchers [27–30]. However, the solubility parameters do not consider drug solubility in the polymer matrices at different temperatures but solubility in different organic solvents at room temperature. Furthermore, group attributions are limited to non-ionic molecules restraining the utility of these methods.

Common experimental techniques for predicting drug–polymer miscibility are hot-stage microscopy and DSC [31]. Fig. 3 displays DSC patterns of EUDRAGIT® E PO as first heat scans of a naproxen–EUDRAGIT® E PO physical mixture and a milled extrudate. Glass transition temperature of EUDRAGIT® E PO was followed by an endothermic peak which reflects a time-dependent

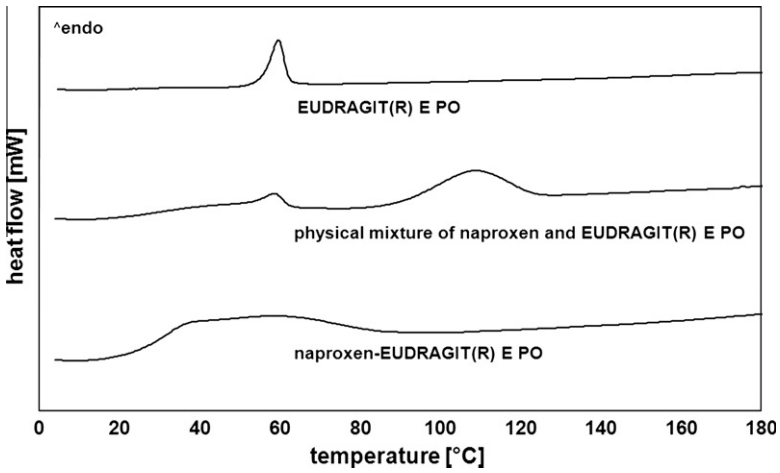

Fig. 3. DSC patterns of EUDRAGIT® E PO, physical mixture of naproxen and EUDRAGIT® E PO and naproxen–EUDRAGIT® E PO extrudate; heating rate 10 °C/min.

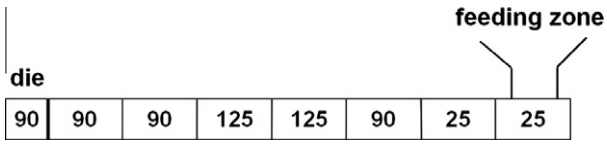

Fig. 4. Temperature profile of the extruder barrels and die – production of naproxen–EUDRAGIT® E PO extrudates.

relaxation [32]. The melting peak of pure crystalline naproxen was broadened and shifted to lower temperature (~120 °C) in the physical mixture.

Extrusion setup could be deduced from DSC patterns. Heating barrels 4 and 5 were set to 125 °C, about 30 °C below naproxen melting point. To obtain a sufficient viscosity of the melt, temperature of the heating barrels 6 and 7 as well of the die plate heating ring was adjusted to 90 °C (Fig. 4).

3.2. Characterization of extrudates

3.2.1. Solid-state

Chiou and Riegelman [33] classified solid dispersions into six categories, namely simple eutectic mixtures, solid solutions, glass solutions/suspensions, amorphous precipitations in a crystalline carrier, compound or complex formations as well as combination and miscellaneous mechanisms. XRPD and DSC measurements should generate data to evaluate solid-state properties of drug and carrier and the number of system phases.

In XRPD measurements, naproxen revealed characteristic reflections, whereas EUDRAGIT® E PO showed halo patterns that are typical of amorphous substances (Fig. 5). A homogenous mixture of an equimolar amount of both substances led to a mixed pattern representing the sum of both signals. The absence of reflections in extrudate measurements proved the conversion to an entirely amorphous system with a limit of sensitivity of 5% crystallinity.

DSC measurements should determine whether both components formed a single-phase amorphous system. Since only one glass transition temperature was observed, two different types of solid dispersion systems according to Chiou and Riegelman might be obtained, a glassy solid solution or a compound/complex formation.

3.2.2. Drug–polyelectrolyte interaction

Investigating solid-state interactions should elucidate whether the drug was molecularly dispersed in the amorphous polymer matrix or complexes bound together by electrostatic interactions were built. FT-IR-measurements are well established in revealing

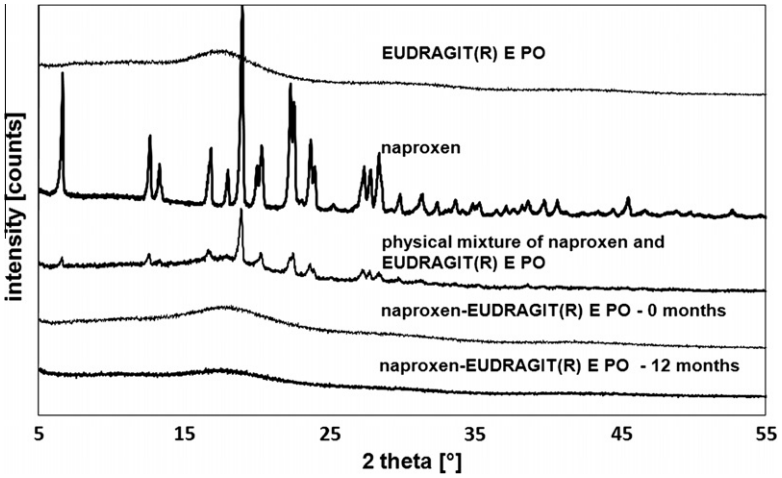

Fig. 5. XRPD patterns of EUDRAGIT® E PO, naproxen, physical mixture of naproxen and EUDRAGIT® E PO, naproxen–EUDRAGIT® E PO (355–500 μm) after 0 months and naproxen–EUDRAGIT® E PO (355–500 μm) after 12 months storage (long-term conditions).

protonation of EUDRAGIT® E PO dimethylamino groups (e.g. [23,34–36]). Non-protonated tertiary amine exhibited two characteristic stretching vibrations of the vicinal CH_2 group at 2771 and 2823 cm^{-1}. The intensities of these bands were significantly lowered in the comparison of physical mixture and extrudate. This indicates a decrease of non-protonated amine at the expense of its ionic form (Fig. 6). Corresponding to these results, carboxylate absorption bands appearing at 1606 cm^{-1} increased in favor of asymmetric stretching vibrations at 1727 cm^{-1} which can be assigned to carboxylic acid group.

Raman measurements were conducted to underline the proof of an acid–base-reaction and complex formation in the melt. They were highlighted to be a "new approach for the analytical assessment of solid dispersions" [37] by Breitenbach et al. in 1999. Recently, it has been successfully used to observe solid-state behavior during hot-melt extrusion as Process Analytical Tool (PAT) [38,39].

Fig. 7 displays a characteristic region which illustrates significant differences between physical mixture and extrudate. At a Raman shift of 1684 cm^{-1}, symmetric stretching vibrations of carbonyl group were located. They appeared for the pure drug substance as well as for the naproxen fraction of the physical mixture. The stretching vibrations disappeared when measuring the extrudate.

To conclude the spectroscopic investigations via FT-IR and Raman, polyelectrolyte complex formation of the acid drug naproxen and basic polymer EUDRAGIT® E PO could be proven. Thus, according to the categories of solid dispersions, these extrudates should rather be classified as complexes than as glassy solid solution.

3.2.3. Stability on storage

One phase systems of amorphous drug and carrier are metastable if the solubility of the drug in the polymer is exceeded. In this case, the system is supersaturated and only kinetically stabilized by high viscosity. Lowering temperature causes an increase of viscosity but a higher probability of nucleation simultaneously. Hancock and Zografi [40] proposed that glassy solid solutions should be stored 50 °C below T_g to avoid recrystallization. In addition, drug–polymer complexes are known to have a stabilizing effect on drug stability [41].

Revealing a T_g of 33 °C, the naproxen–EUDRAGIT® E PO milled extrudate raised suspicion to recrystallize under storage. XRPD patterns showed typical amorphous halos for all samples indicating no recrystallization after storage of 3, 6, and 12 months (Fig. 5).

3.3. Dissolution tests

3.3.1. Polyelectrolyte complex in aqueous media

A single-phase amorphous system could be confirmed by XRPD- and DSC-measurements, whereas FT-IR- and Raman-analysis revealed the formation of a polyelectrolyte–drug-complex. A complex consisting of countercharged naproxen anion and EUDRAGIT® E PO cation should be uncharged. Insolubility of uncharged complex in polar dissolution medium should cause slower drug release.

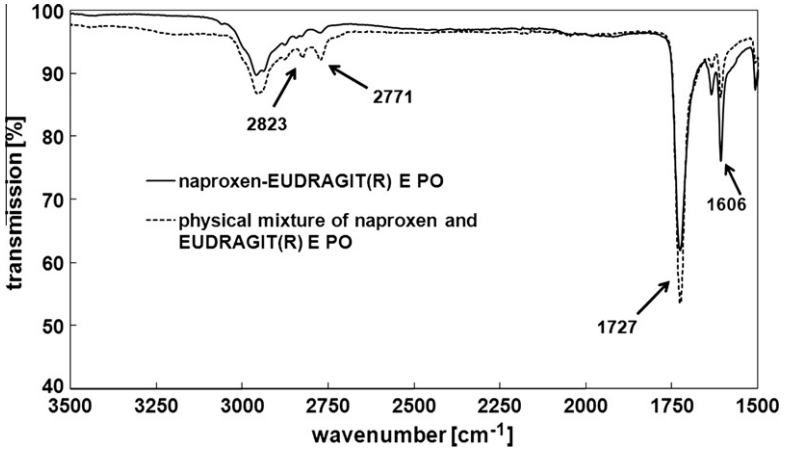

Fig. 6. FT-IR spectra of naproxen–EUDRAGIT® E PO and the physical mixture of naproxen and EUDRAGIT® E PO.

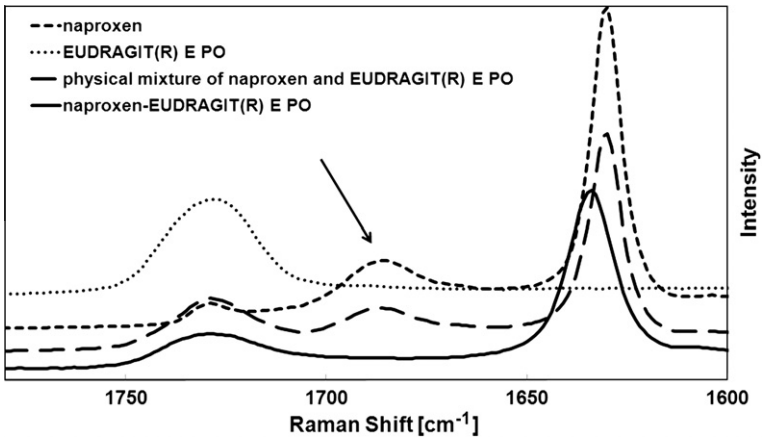

Fig. 7. Raman spectra of naproxen, EUDRAGIT® E PO, naproxen–EUDRAGIT® E PO, and the physical mixture of naproxen and EUDRAGIT® E PO.

To evaluate the stability of the electrostatic interaction, dissolution experiments in aqueous media of different electrolyte concentrations were carried out.

To obtain discriminating dissolution experiments, non-sink conditions with 50 mg naproxen (saturation solubility of naproxen in demineralized water: 65 mg/l) were chosen. Fig. 8 shows dissolution profiles of the pure drug substance naproxen, the 355–500 μm sieved fraction of milled extrudates and the physical mixture of naproxen and EUDRAGIT® E PO (42–58%) in demineralized water. Naproxen was dissolved almost completely after 60 min. In contrast, only 10% naproxen was released from milled extrudates after 1 h and 18% after 2 h of dissolution testing. Electrostatic attraction between the counterions of the complex was superior to solvation tendencies. The addition of sodium chloride (NaCl) corresponding to a 0.15 M solution after 60 min led to an abrupt increase of drug release. A pronounced destabilizing effect on complex stability could be observed. Hence, drug release pulse could be triggered by the addition of NaCl.

Surprisingly, the physical mixture of acid drug and basic polyelectrolyte showed the reaction to electrolyte triggering as well. The effect of complex formation seemed to take place at the interfaces of polymer particles. However, the effect was less pronounced, and higher standard deviations were observed in comparison to the milled extrudate.

To underline the formation of ionic naproxen stabilized in a complex during hot-melt extrusion, further dissolution experiments were carried out with a ten times higher drug amount. As expected, dissolution of 500 mg naproxen stopped in its saturation solubility of about 65 mg/l (Fig. 9). An equimolar amount of soluble naproxen sodium was dissolved immediately under these conditions. The polyelectrolyte complex, uncharged in total, proved to be insoluble and stable in demineralized water, whereas after electrolyte addition drug release was triggered. Maximum solubility of naproxen was exceeded and corresponded to the naproxen sodium salt. Again, the same effect could also be observed by the physical mixture.

Thus, two main effects can be deduced. On the one hand, drug release of the polyelectrolyte complex was even lowered compared to the poorly soluble naproxen in demineralized water. Electrostatic interaction forces between acid drug and basic polymer in the complex reduced solvation processes. On the other hand, although naproxen was used as starting material, acid–base reaction during hot-melt extrusion led to enhanced solubility corresponding to naproxen salt after electrolyte addition.

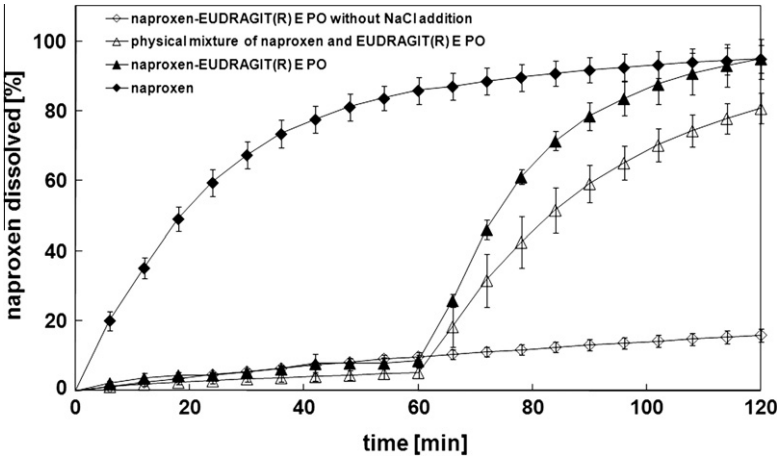

Fig. 8. Drug release of naproxen, naproxen–EUDRAGIT® E PO (355–500 μm fraction), and the physical mixture of naproxen and EUDRAGIT® E PO; paddle apparatus; 50 mg drug; 1000 ml demineralized water + 0.001% polysorbate 20; addition of 8.77 g NaCl after 60 min (according to 0.15 M electrolyte solution); 37 °C; 100 rpm; 272 nm; mean ± SD, $n = 5$.

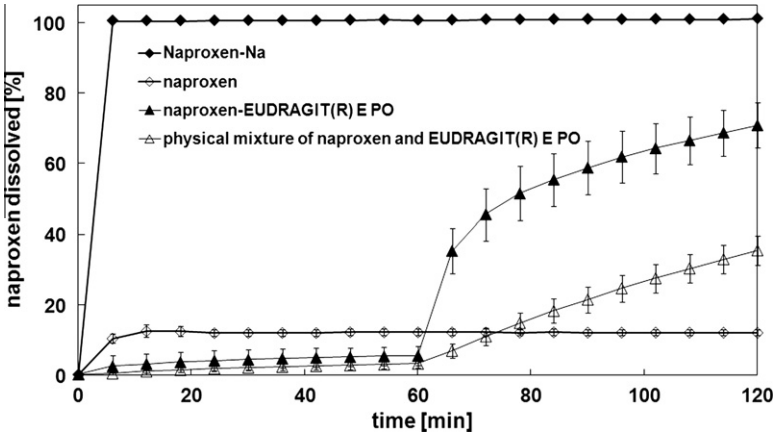

Fig. 9. Drug release of naproxen sodium, naproxen, naproxen–EUDRAGIT® E PO (355–500 μm fraction), and the physical mixture of naproxen and EUDRAGIT® E PO; paddle apparatus; 500 mg drug; 1000 ml demineralized water + 0.001% polysorbate 20; addition of 8.77 g NaCl after 60 min (according to 0.15 M electrolyte solution); 37 °C; 100 rpm; 272 nm; mean ± SD, $n = 5$.

3.3.2. Influence of ionic strength on complex stability

To elucidate the influence of ionic strength on the stability of the polyelectrolyte complex, dissolution studies were performed in media of different electrolyte concentrations. Fig. 10 illustrates the amount of naproxen dissolved after 30 min as a function of NaCl concentration in the dissolution medium. NaCl concentrations up to 0.1 mol/l led to an enhanced drug release. This was expected because more electrolyte molecules can serve as polyelectrolyte complex breaking agents. Surprisingly, further increase of electrolyte concentration led to a reduction of drug release. Mobility of the polymer chains might be constrained by the rising number of dissolved molecules. Therefore, complex stability is increased in a medium of high ionic strength until a certain limit.

3.3.3. Tailor-made dissolution profiles

Different electrolyte concentrations affected complex stability in different manner. Tailor-made dissolution profiles should be realized by using the versatile opportunities of ionic strength modulation. It was intended to design different drug release profiles according to the European Pharmacopeia definition of modified-release dosage forms.

A release profile imitating a conventional release (immediate release) dosage form was observed by adding NaCl (according to a 0.15 M solution) at the dissolution start resulting in complete drug release within 30 min (Fig. 11).

Modified-release dosage forms can be subdivided in prolonged-release, delayed-release, and pulsatile-release dosage forms. Different amounts of NaCl were added at different time points to the dissolution medium. Delayed-release profile was induced by adding NaCl (according to a 0.15 M solution) after 60 min. Prolonged-release was achieved using a 0.002 M NaCl-solution. By combining both measures, pulsatile-release was obtained by adding different amounts of NaCl at two different time points (0.002 M after 30 min; 0.15 M after 60 min).

3.3.4. Effect of different electrolytes on drug release

Naproxen reveals pH-dependent solubility. In a strong acidic milieu, the non-ionic drug is almost insoluble in water. According to the Henderson–Hasselbalch equation, about 90% naproxen is present as highly soluble carboxylate in aqueous media of pH 5.1. A pH modulation by basic salts would create a microenvironment increasing drug solubility.

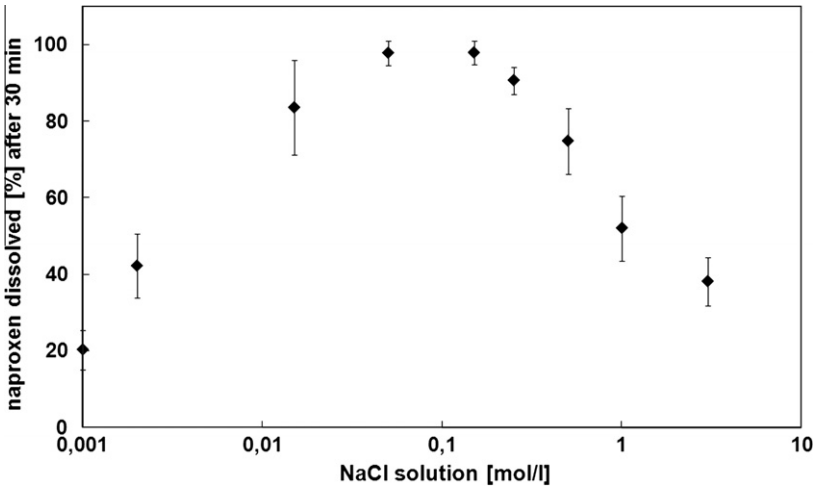

Fig. 10. Drug release of naproxen–EUDRAGIT® E PO (355–500 μm fraction); paddle apparatus; 50 mg drug; 1000 ml demineralized water + 0.001% polysorbate 20; concentration of NaCl according to *x*-axis; 37 °C; 100 rpm; 272 nm; mean ± SD, *n* = 5.

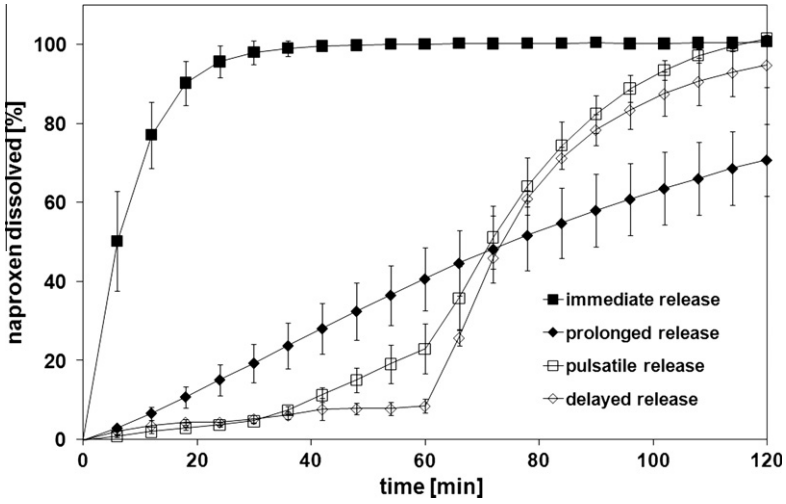

Fig. 11. Drug release of naproxen–EUDRAGIT® E PO (355–500 μm fraction); paddle apparatus; 50 mg drug; 1000 ml demineralized water + 0.001% polysorbate 20 + NaCl cf. 3.3.2; 37 °C; 100 rpm; 272 nm; mean ± SD, *n* = 5.

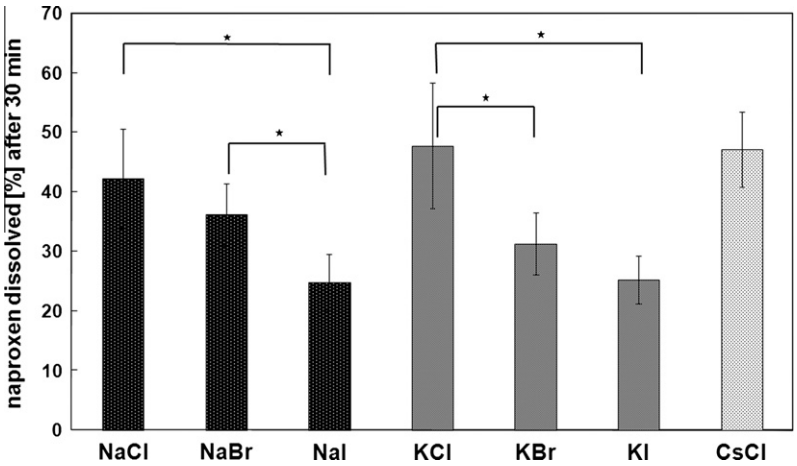

Fig. 12. Drug release of naproxen–EUDRAGIT® E PO (355–500 μm fraction); paddle apparatus; 50 mg drug; 1000 ml demineralized water + 0.001% polysorbate 20; addition of neutral electrolyte according to an 0.002 M solution; 37 °C; 100 rpm; 272 nm; mean ± SD, $n = 5$; level of significance $\alpha = 5\%$.

This study focuses on neutral electrolytes that do not influence pH by themselves during solvation processes. Different alkali-halogen-electrolytes were investigated regarding their influence on polyelectrolyte complex stability. Electrolytes of different charges were not investigated in this study to exclude the influence of further interactions (e.g. complexation) and pH modifying effects on the electrolyte triggering effect.

In order to reveal a discriminating effect of different electrolytes and to warrant equal ionic strengths, dissolution was performed in media of each 0.002 M concentration. Fig. 12 illustrates the amount of naproxen dissolved after 30 min of dissolution assigned to the electrolyte used.

Jimenez-Kairuz et al. [22] determined electrokinetic potentials of polyelectrolyte complexes from metoclopramide/carbomer hydrogels with a particle microelectrophoresis apparatus. In the polyelectrolyte microenvironment, negative electrokinetic potentials induced by carboxylate groups could be revealed leading to high affinity for cations. Surrounding aqueous bulk medium showed positive electrokinetic potentials.

The present study highlights the reverse arrangement of ionic drug and polymer from milled extrudates. Thus, positive electrokinetic potentials of naproxen–EUDRAGIT® E PO complex surface can be deduced. Ideally complete reaction of naproxen and EUDRAGIT® E PO in equimolar ratio should cause an uncharged complex to the surrounding medium. Nevertheless, known from ion exchangers, in reality, some contact points (dimethylamino groups) do not take part in the complexing procedure.

Two main possible influences were investigated – the effect of different alkali ions as well as halogenide ions. NaCl, KCl, and CsCl revealed no significant changes of drug release after 30 min. Thus, cationic influence was considered as negligible for polyelectrolyte-complex stability.

Dissolution experiments with alkali-chloride, -bromide and -iodide ions showed significant correlations for halogens. Drug release was reduced almost half comparing chloride and iodide alkali ions. Hence, anions were proved to be one determining variable triggering the splitting of naproxen–EUDRAGIT® E PO complex.

The series of chloride, bromide to iodide ion is characterized by an increasing ion radius, decreasing electronegativity as well as minor tendency of hydration. Smaller ionic radius of chloride-ion and higher charge density led to increasing affinity with naproxen–EUDRAGIT® E PO complex in exchanging ionic naproxen. These results are coherent with the assumption of a positively charged complex mentioned above.

In summary, complex stability and therewith drug release were dependent on different alkali halogenides used in this study. Anionic halogenides proved to be a decisive variable in controlling drug release, whereas alkali-cations did not influence dissolution kinetics.

3.4. Development of dosage forms – outlook

In this study, the system of polyelectrolyte complex formation as well as their characterization and potential of modified release were highlighted. Further ongoing studies deal with the formulation development based on this concept.

As shown in Fig. 10, small amounts of NaCl caused an abrupt destabilizing effect on polyelectrolyte complex stability. This is advantageous since for a dosage form, only small amounts of electrolytes are needed to obtain drug release triggering. However, biological fluids contain high amounts of ionic substances inducing drug release.

Basically, we therefore use the triggering effect in two different ways. Either drug release should be modified by electrolytes incorporated in the dosage form or by the external fluids. In ongoing studies, tablets have been produced based on the same principle enabling immediate as well as modified release.

3.5. Transfer of the concept to furosemide

It should be investigated whether the phenomena presented in this study are specific for the model drug naproxen or whether general principles can be deduced. Characterized by similar properties concerning aqueous solubility, acid strength, and partition coefficient compared to naproxen, furosemide was chosen for verification. Again, an equimolar amount of carboxylic groups of furosemide and dimethylamino functions was calculated resulting in a ratio of 50.6–49.4 which was molten.

Analysis of solid-state performed with DSC and XRPD revealed the formation of a single-phase amorphous system. The formation of a furosemide–EUDRAGIT® E PO polyelectrolyte complex by an acid–base reaction in the melt was confirmed by FT-IR and Raman measurements. The FT-IR pattern is presented in Fig. 13 revealing a decrease of CH_2 stretching vibrations neighbored by the non-ionic amino-group (2770 and 2823 cm^{-1}).

Drug release by the drug–polymer-complex was significantly decreased in comparison to FUR pure substance in demineralized water, analogous to the naproxen results. Addition of NaCl after

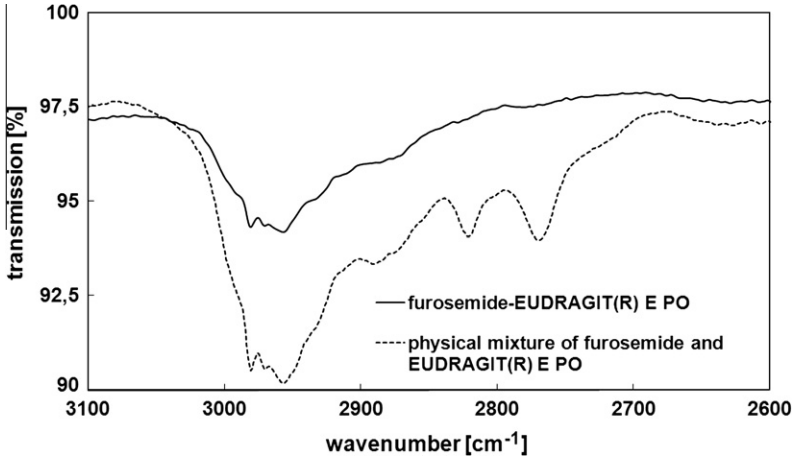

Fig. 13. FT-IR spectra of furosemide–EUDRAGIT® E PO and the physical mixture of furosemide and EUDRAGIT® E PO.

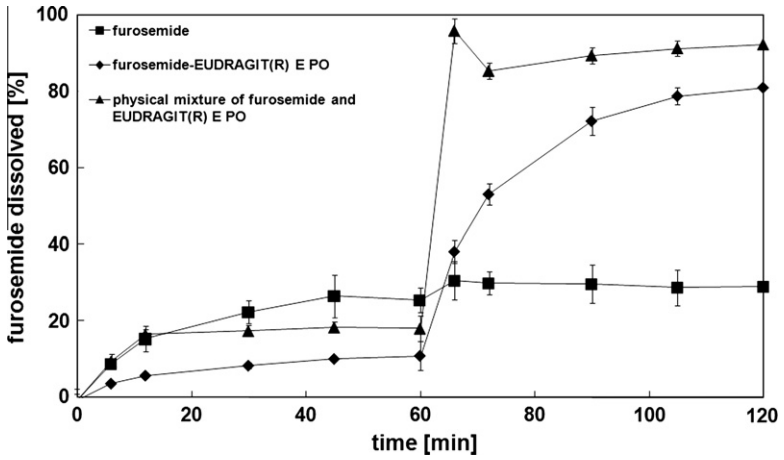

Fig. 14. Drug release of furosemide, furosemide–EUDRAGIT® E PO (355–500 μm fraction) and the physical mixture of furosemide and EUDRAGIT® E PO; paddle apparatus; 40 mg drug; 1000 ml demineralized water + 0.001% polysorbate 20; addition of 8.77 g NaCl after 60 min (according to 0.15 M electrolyte solution); 37 °C; 100 rpm; 339 nm; mean ± SD, $n = 6$.

60 min again triggered complex splitting and thus drug release (Fig. 14).

4. Conclusions

Polyelectrolyte complexes of poorly soluble acid drug naproxen and basic polymer EUDRAGIT® E PO were successfully produced via hot-melt extrusion. Solid-state behavior was investigated by XRPD and DSC measurements revealing an amorphous one phase system. Further analysis with molecular spectroscopy methods (FT-IR and Raman) exposed ionic interactions in the melt. Ionic form of naproxen was generated in the melt forming a polyelectrolyte complex.

The complex was composed of counter-charged drug anion and EUDRAGIT® E PO cation and uncharged in total. Dissolution experiments showed complex stability in aqueous media of low ionic strengths. Drug release could be instantaneously triggered by addition of pH neutral alkali-halogen electrolytes. Although the drug was used in its poorly soluble non-ionic form, dissolution behavior correlated to the soluble ionic salt. The amount of electrolytes reflected in the ionic strength of the dissolution medium played a decisive role in controlling drug delivery. This knowledge was used to create tailor-made dissolution profiles typical for immediate and modified release.

Deeper analysis of the release triggering effect revealed significant differences using various alkali-halogen electrolytes. The use of anionic halogenides with small ionic radii proved to be relevant for the acceleration of drug release kinetics.

Polyelectrolyte complex formation and dissolution principles were confirmed for the second model drug furosemide.

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