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RESEARCH PAPER THEME: PHYSICOCHEM INTERACTIONS

Electrolyte-Stimulated Biphasic Dissolution Profile and Stability Enhancement for Tablets Containing Drug-Polyelectrolyte Complexes

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ABSTRACT

Purpose Recently introduced drug-polyelectrolyte complexes prepared by hot-melt extrusion should be processed to solid dosage forms with tailor-made release properties. Their potential of stability enhancement should be investigated.

Methods Milled hot-melt extruded naproxen-EUDRAGIT® E PO polyelectrolyte complexes were subsequently processed to double-layer tablets with varying complex loadings on a rotary-die press. Physicochemical interactions were studied under ICH guideline conditions and using the Gordon-Taylor equation. Sorption and desorption were determined to investigate the influence of moisture and temperature on the complex and related to stability tests under accelerated conditions.

Results Naproxen release from the drug-polyelectrolyte complex is triggered by electrolyte concentration. Depending on the complex loading, phosphate buffer pH 6.8 stimulated a biphasic dissolution profile of the produced double-layer tablets: immediate release from the first layer with 65% loading and prolonged release from the second layer within 24 h (98.5% loading). XRPD patterns proved pseudopolymorphism for tablets containing the pure drug under common storage conditions whereas the drug-complex was stable in the amorphous state.

Conclusions Drug-polyelectrolyte complexes enable tailor-made dissolution profiles of solid dosage forms by electrolyte stimulation and increase stability under common storage conditions.

KEY WORDS biphasic drug release profiles · electrolyte-stimulated release · polyelectrolyte complex · physicochemical interactions · stability

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ABBREVIATIONS

BCS	Biopharmaceutical Classification System
DSC	differential scanning calorimetry
FT-IR	Fourier transform infrared spectroscopy
Ph. Eur.	European Pharmacopeia
RH	relative humidity
SMCC	high density silicified microcrystalline cellulose
Tg	glass transition temperature
XRPD	X-ray powder diffraction

INTRODUCTION

Numerous molecules have been synthesized by combinatorial chemistry and potential drug candidates have been identified by high-throughput screenings (1). More than 40% of these new chemical entities are estimated to be poorly water-soluble (2). They can be classified into classes II and IV of the Biopharmaceutical Classification System (BCS) (3). Water insolubility of the drug in the gastro-intestinal tract reduces bioavailability because drugs need to be dissolved at the absorption sites (4).

Leuner and Dressman (5) subdivided the approaches of improving drug solubility and/or the dissolution rate in physical and chemical modifications. One promising physical modification in order to enhance bioavailability of poorly soluble drugs is the formation of solid dispersions with suitable polymers. A solid dispersion is defined as a "dispersion of one or more active ingredients in an inert carrier or matrix at solid state" (6). Originally subdivided in six categories according to the number of phases and the molecular constitution, this scheme was expanded and adjusted by several researchers during the last decades (5,7,8).

In the context of solid dispersions, single-phase amorphous systems are of particular interest. With regard to Hancock and Zografi (9), Forster *et al.* described these systems as "ideal type of solid dispersions" (10), providing an amorphous compound with a low thermodynamic barrier and a maximal reduced particle size in a molecular dispersion (glassy solid solution). Complexes being a further subgroup of solid dispersions have to be differentiated from glassy solid solutions. They might also be characterized as single-phase amorphous systems, but the molecules are associated with each other stoichiometrically by electrostatic interactions.

A major disadvantage of single-phase amorphous systems is the tendency of the drug to recrystallize under storage, if the solubility in the carrier is exceeded. The drug is often stabilized only kinetically by the high viscosity of the carrier. Higher temperatures and relative humidities lead to a transition of the thermodynamically instable amorphous drug into the crystalline state. It is generally known that drug stability can be increased by intermolecular drug-polymer (7,11) and drug-drug interactions (12).

According to the classification system by Leuner and Dressman (5), salt formation of poorly soluble drugs is a reliable method to improve drug solubility and/or dissolution rate and thus bioavailability. The choice of a suitable salt form depends on several eligible salt characteristics, especially low hygroscopicity and stability during storage (13). Different crystal habits (modifications) of a molecule are called polymorphs. In case of different amounts of stoichiometrically included solvent molecules they are defined as pseudopolymorphs and specifically as hydrates if the solvent is water. A review of Zografi in 1988 (14) focuses on the influence of moisture on the physico-chemical properties of solids. Flowability, compactability and drug dissolution as significantly affected characteristics are evaluated in terms of polymorphism and pseudopolymorphism. Hydrate formation is considered crucial in classical pharmaceutical manufacturing processes like wet granulation and aqueous film coating by Khankari and Grant (15).

A previous study of our working group introduced the concept of electrolyte triggered drug release from polyelectrolyte complexes composed of poorly water soluble drugs and basic polymethacrylates (16). In general, polyelectrolyte complexes are formed mainly by electrostatic interactions which cause mutual binding (17,18). The original definition has been valid for polymer-polymer complexes and was later expanded to drug-polymer associates (19). Formation of hot-melt extruded drug-polyelectrolyte complexes was proved by solid-state analysis revealing a stable single-phase amorphous system and an acid–base reaction in the melt. Thus, poorly soluble model drugs were transferred to their ionic form. Despite low glass transition temperatures, the complex was stable under storage according to the ICH guideline Q1A (R2) (20). The sensitivity of different pH, ionic strength and particle size on the drug release of tablets containing solid complexes was investigated by Bonferoni *et al.* (21,22) and Aguzzi *et al.* (23). Their complexes were composed of the reverse electrostatic arrangement, namely of basic drugs (e.g. diltiazem, metoprolol) and acidic lambda carrageenan.

The objective of this study was to implement this new concept in the development of solid dosage forms. In the first approach, a solid dosage form should be developed with biphasic drug release profile, initiated and controlled by electrolytes (Fig. 1). The second approach focuses on the deeper understanding of the physico-chemical interactions which might serve for enhanced drug stability of the model drug substance in comparison to the pure drug.

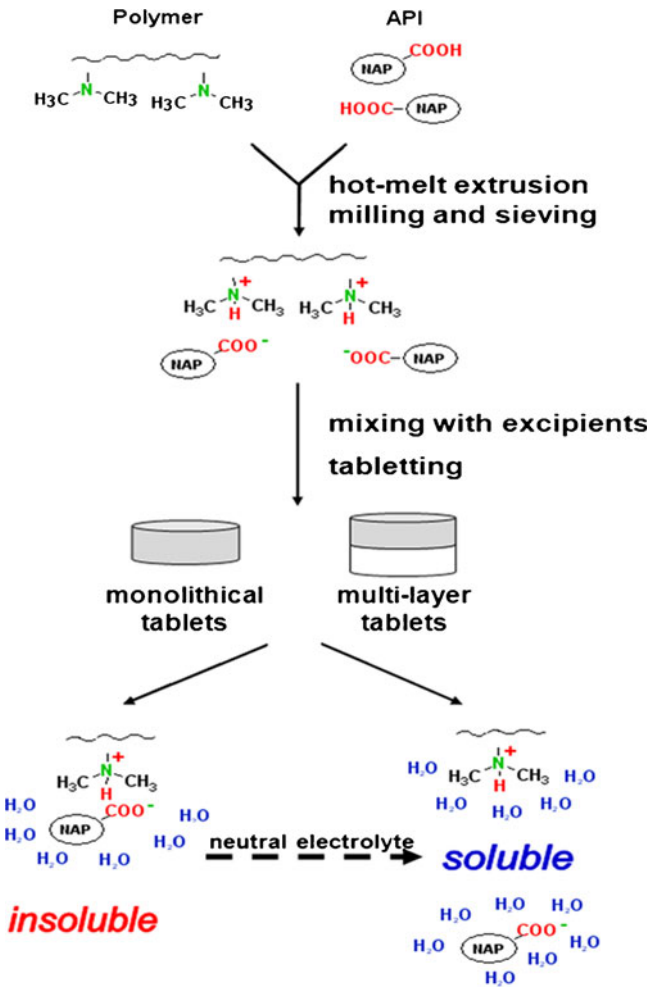

Fig. 1 General concept of electrolyte-stimulated, tailor-made release triggered from hot-melt extruded drug-polyelectrolyte complexes (16), modified for solid dosage form development.

MATERIALS AND METHODS

Materials

Naproxen (Divis Laboratories, Hyderabad, India) was used as model drug. Basic butylated methacrylate copolymer (EUDRAGIT® E PO) was kindly donated by Evonik industries (Darmstadt, Germany). Polysorbate 20 was obtained from Caesar and Loretz (Hilden, Germany). Potassium dihydrogen phosphate (analytical grade) was purchased from Grüssing (Filsum, Germany) and sodium hydroxide (analytical grade) from Sigma-Aldrich (Seelze, Germany). For tabletting high density silicified microcrystalline cellulose was acquired from JRettenmeier & Söhne (Prosolv® SMCC HD 90, Rosenberg, Germany), magnesium stearate from Welding (Hamburg, Germany) and colloidal anhydrous silica from Evonik (Aerosil® 200, Darmstadt, Germany).

Preparation of Extrudates and Milled Strands

Naproxen and EUDRAGIT® E PO were pre-blended in a LM20 mixer (Bohle, Enningerloh, Germany). Hot-melt extrusion was performed in a co-rotating twin-screw extruder (Leistritz Micro 27GL-28D, Nuremberg, Germany). A calibrated gravimetric powder feeder KCL KT20 (K-Tron Soder, Switzerland) was used to control the powder feed (22.5 g/min).

During its short residence time of about 1 min in the extruder barrel, the mixture was transported to the die plate of 2 mm by conveying elements and kneading blocks. The screw speed was set to 95 rpm. The temperatures of separately heated barrel segments were recorded during each process as well as the engine performance, die plate pressure and the temperature by sensors. The temperature setup was 90-90-90-125-125-90-25-25°C. The mixture could be processed about 30°C below the melting point of naproxen since the drug was dissolved in the molten polymer carrier during extrusion (cf. (16)).

On a band conveyer of 131 cm length extrudates were transported (Brabender, Duisburg, Germany) after passing the die plate. Milling was conducted in an ultra centrifugal mill (Retsch ZM 200, Haan, Germany) at 6000 rpm with an insert of 1.0 mm. By sieving (AS Control 200, Retsch, Haan, Germany), the 355–500 µm sieve fraction was obtained and used for characterization and subsequent processing.

Preparation of Tablets

The tabletting formulations were blended in a turbula mixer (W. Bachofen, Basel, Switzerland) with 42 rpm for 15 min. After the addition of the lubricant magnesium stearate, the mixtures were blended for further 2 min.

Processing of tablets and double-layer tablets was conducted using an instrumented rotary die press (IMA Pressima, Kilian, Cologne, Germany) at a tabletting speed of 10 rpm. The die press was equipped with a biplanar 12 mm tabletting tool. Mixtures were compressed to tablets with compaction forces of 10 kN. In order to obtain double-layer tablets, the mixture of the burst side was compressed at 7 kN at first. In a second step, the mixture of the prolonged side followed by the precompressed burst side were inserted in the matrice and subsequently compressed with a compaction force of 10 kN.

Characterization of Extrudates and Tablets

Differential Scanning Calorimetry (DSC)

Experimental glass transition temperatures of binary naproxen-EUDRAGIT® E PO mixtures were obtained by performing differential scanning microscopy measurements (DSC 821e, Mettler-Toledo, Gießen Germany). Samples of ~3 mg were sealed in pierced aluminum pan and heated twice in the range between 0 and 170°C with a heating rate of 10°C/min. Controlled cooling of the sample was conducted with a rate of 20°C/min.

Gordon-Taylor Equation

The Gordon-Taylor equation (24) allows the prediction of the glass transition temperature (Tg) of the binary mixture of naproxen and EUDRAGIT® E PO. In the simplified equation by Simha and Boyer (25), variables were the weight fractions of the substances (w), their glass transition temperatures (higher Tg with index 1) and the densities. Density of the polymer (1.11 g/cm^3) was taken from Albers *et al.* (26) and naproxen density (1.308 g/cm^3) from Allesø *et al.* (12).

$$Tg = \frac{w_1 Tg_1 + K w_2 Tg_2}{w_1 + K w_2} \quad K \approx \frac{\rho_1 Tg_1}{\rho_2 Tg_2}$$

X-Ray Powder Diffraction (XRPD)

By means of a powder X-ray diffractometer X'Pert MDP PW3040/00 (DY 653) from PANalytical (Almelo, Netherlands) XRPD patterns were recorded (Cu-anode radiation). Measurements were carried out with a 16 mm sample holder spinning at 60 rpm. In a range of 2 θ=5–60° measurements were

conducted in 0.0167° steps. Voltage and current were set to 40 kV and 40 mA respectively.

Laser Diffraction

Particle size distribution and median particle size were obtained by laser diffraction (Helos/KF-Magic, Sympatec, Clausthal-Zellerfeld, Germany). Powder samples were transported to a dry dispersion unit (RODOS, Sympatec) and measured in the laser beam with different lenses (0.25/0.45–87.5 µm; 0.5/1.8–350 µm; 0.5/4.5–875 µm) depending on the particle size. Data evaluation was conducted with the software Helos.

Flowability

Flowability measurements of the naproxen-EUDRAGIT® E PO polyelectrolyte complex in comparison to the corresponding physical mixture were performed with a ring shear tester (RST-01.pc, Schulze Schüttguttechnik, Wolfenbüttel, Germany). Data evaluation was conducted using the software RSTControl 95. During the automatic measuring routines different normal loads were applied for shearing the sample. Pre-shearing was conducted with 5 kPa. Four different normal loads (1 to 4 kPa with a repetition of 1 kPa) were applied in the measuring routine. The ff_c-value was calculated as the ratio of the consolidation stress to the unconfined yield strength

Tensile Strength

For the determination of the tensile strength, the crushing force of the tablets was determined with a hardness tester TBH 210 (Erweka, Heusenstamm, Germany) according to the Ph. Eur. monograph 2.9.8 ("Resistance to crushing of tablets") (27). Tensile strength was calculated using crushing force, tablet diameter and tablet thickness according to the equation of Fell and Newton (28). The equation enables a direct comparison of the mechanical stability of tablets with different thicknesses. The higher the tensile strength is, the higher the mechanical stability.

Disintegration

Disintegration of tablets was determined with a DT2 disintegration tester (Sotax, Basel, Switzerland). According to the Ph. Eur. monograph 2.9.1 ("Disintegration of tablets and capsules") six tablets were inserted in the cylindrical tubes and disks were added (27). With a frequency of 30 per minute the tubes were raised and lowered in demineralized water of 37±2°C. Tablets were defined as disintegrated if no residues remained in or stuck at the tubes.

Dissolution Studies

Drug release of milled extrudates (fraction 355–500 µm), tablets and double-layer tablets was investigated using Ph. Eur. apparatus II (Sotax AT7, Lörrach, Germany). Stirring speed was set to 100 rpm and phosphate buffer pH 6.8 (Ph. Eur.) was used as dissolution medium at 37±0.5°C (27). Quantification of drug release was carried out spectrophotometrically at 272 nm (Lambda 40, Perkin-Elmer, Rodgau-Juedesheim, Germany).

Scanning Electron Microscopy

Cross-sectional images of double-layer tablets were generated by a Leo 1430 VP scanning electron microscope (Leo Electron Microscopy, Cambridge, Great Britain). Samples were broken after cooling in liquid nitrogen in order to maintain a brittle fracture. This should guarantee an unchanged surface after preparation. All samples were sputtered with gold for 180 s (Agara Manual Sputter Coater B7340, Agar Scientific, Stansted, Great Britain) after drying to improve the conductivity of the surfaces. Measurements were carried out with a voltage of 20 kV at different operating distances.

Water Sorption System

Sorption and desorption curves of the starting materials, naproxen-EUDRAGIT® E PO extrudates and tablets were determined with the SPS 11 sorption analysis system (Projekt Messtechnik, Ulm, Germany). The temperature of the heatable system was set to 25°C. Relative humidity was adjusted with demineralized water. Measurements were conducted in 10% intervals of relative humidity and three cycles: 40 to 0%, 10 to 90% and 80 to 0%. After gravimetric balance of the samples (maximal 0.01% mass difference within 30 min), the system automatically moved to the next step of the cycles keeping each step for at least 120 min and 48 h maximum time.

Stability Testing

In order to observe if modification changes occur during storage, stability tests were carried out according to the ICH-guideline Q1A(R2) ("Stability testing of new drug substances and products"). Tablet formulations T1 and T2 were stored in HDPE bottles with and without drying aid for 2 months. Accelerated conditions were used in this study with 40±2°C and 75±5% relative humidity in the conditioning cabinet (KBF 240, Binder, Tuttlingen, Germany).

RESULTS

Transfer of the Drug-Polyelectrolyte Complex Concept to Solid Dosage Forms

Formulation Development

Hot-melt extrusion is a well-established method for processing drugs and polymers to solid dispersions (29–32). The continuous hot-melt extrusion process was used to prepare drug-polyelectrolyte complexes by a solvent-free method. As model substances naproxen and EUDRAGIT® E PO were used in equimolar ratio related to the acid carboxylic groups of the drug and the tertiary amine of the polymer (42–58% m/m). With a solubility of 65 mg/l in water at 37°C, naproxen is practically insoluble in water. The BCS class II drug reveals a pK_a of 4.1 (33) and a melting point of 156°C. EUDRAGIT® E PO is characterized by a pK_b of 7.7 (34) and a glass transition temperature (Tg) of about 50°C. A previous study (16) confirmed the formation of a drug-polyelectrolyte complex by an acid–base reaction during the hot-melt extrusion process. In DSC measurements, a single glass transition temperature for naproxen-EUDRAGIT® E PO extrudates was observed indicating the absence of crystals. These results were confirmed by detecting only halos in the XRPD pattern of the extrudates. The single-phase system was further investigated to highlight the acid–base reaction in the melt with Raman and FT-IR measurements.

With regard to the development of solid dosage forms, extrusion and subsequent milling offered further advantages in processing the complexes, especially in improving the flowability of the powder mixture. Free flowing powder mixtures are essential for a permanent flow into the cavity of a rotary die press and thus a prerequisite for the uniformity of produced dosage units. In general, flowability of a powder mixture can be improved by increasing the particle size. The starting materials naproxen and EUDRAGIT® E PO revealed d_{50}-values (median of size distribution) of 18.9 ±2.3 µm and 8.7±0.7 µm measured by laser diffraction. For the 355–500 µm sieve fraction of the milled naproxen-EUDRAGIT® E PO extrudates, a d_{50}-value of 416±3 µm was determined. The flowability of a physical mixture of naproxen and EUDRAGIT® E PO as well as the milled extrudate (355–500 µm sieve fraction) was investigated with a ring shear tester. The evaluation of ff_c-values was conducted according to Jenike (35). The equimolar physical mixture exhibited ff_c-values of 2.93 and 2.91 and was characterized as cohesive with poor flowability. In contrast, granules obtained from milled extrudates with the drug-polyelectrolyte complex exhibited free-flowing behavior with ff_c-values of 13.03 and 11.48. Thus, hot-melt extrusion and subsequent milling additionally led to a decisive improvement of flowability.

Tablets with Modified Drug Release

In a former study, drug release of drug-polyelectrolyte complexes was tailor-made in demineralized water as model medium by the addition of pH-neutral electrolytes. These salts served as a stimulus or pulse, of which the strength depended on concentration and on the radius of the anion (16). In this work, solid dosage forms should be developed with electrolyte-stimulated biphasic drug release profile. For *in-vitro in-vivo* correlations, naturally occurring electrolytes in biological fluids have to be considered (36,37). Consequently, drug release can be either modified by the electrolytes of the external fluids or by the incorporation of electrolytes in the dosage form. This study focuses on the second approach, using the electrolytes of the buffer medium pH 6.8 (Ph. Eur.) to control drug release.

Therefore, in order to investigate the influence of drug-polyelectrolyte complex loading on the drug release, tabletting mixtures with 98.5% and 70% complex loading were compressed to 12 mm tablets (Table I). Dissolution experiments of tablets with 98.5% complex loading exhibited a release of 73% after 12 h (Fig. 2) and complete naproxen release within 24 h. Tablets exhibited neither disintegration nor swelling tendencies. The erosion of the tablet matrix was observed after more than 24 h.

To elucidate the mechanism of drug release, dissolution profile up to 60% dissolved naproxen was investigated in detail. With a coefficient of determination (R^2) of 0.996, a zero order drug release kinetic was derived from the experimental release profile.

In order to enable an immediate naproxen release of the polyelectrolyte complex, besides reducing the tablet loading

Table I Tabletting Mixtures of Formulations T0, T1, T2 and T3; in %

	naproxen	EUDRAGIT E PO	naproxen sodium	SMCC	colloidal anhydrous silica	crospovidone	magnesium stearate
T0	98.5 as polyelectrolyte complex				0.5		1
T1	70 as polyelectrolyte complex			24.5	0.5	4	1
T2		39.06	30.94	24.5	0.5	4	1
T3			30.94	63.56	0.5	4	1

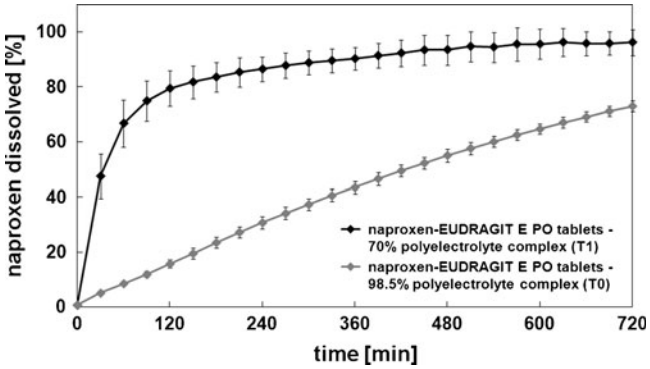

Fig. 2 Drug release of naproxen-EUDRAGIT® E PO tablets with 98.5% and 70% polyelectrolyte complex loading respectively; 100 mg drug; 1000 ml phosphate buffer pH 6.8 (Ph. Eur.); 37 ± 0.5°C; 100 rpm; 272 nm; mean ± SD, n=5.

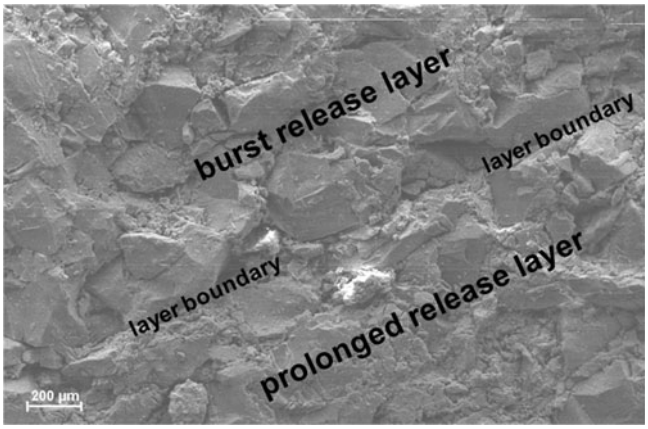

Fig. 3 SEM cross-section image of naproxen-EUDRAGIT® E PO polyelectrolyte complex double-layer tablets; high voltage 20 kV.

to 70%, as further tabletting aids, silicified microcrystalline cellulose (SMCC) as filler and binder and crospovidone for enhanced disintegration were added to the formulation (Table I). SMCC is known to reduce sticking tendencies of powder mixtures during tablet compression. Its ability of plastic deformation leads to tablets of high mechanical stability (38). The tablets showed an immediate naproxen release after fast disintegration (Fig. 2). After 2 h of test time, about 80% of the drug was dissolved.

Consequently, depending on the polyelectrolyte complex loading of the tablets, immediate as well as prolonged drug release profiles were generated. With the objective to generate biphasic drug release profiles both approaches were combined in the development of double layer tablets. The part of the double-layer tablets with a drug load of 98.5% was defined as "prolonged side". For a further enhanced drug release the "burst side" formulation contained 65% polyelectrolyte complex. Both sides were correlated in a 1:1 mass ratio of naproxen resulting in a heavier "burst side" (Table II).

In Fig. 3, SEM cross-sections of a double-layer tablet show the distinct parts of both tablet sides. Table III lists the properties of the tabletting performance and the resulting double-layer tablets.

Drug release behavior was subdivided into two phases, each determined by the dissolution of one tablet side (Fig. 4). During the first 120 min, the "burst side" disintegrated resulting in an immediate drug release. Subsequent drug release can be referred to the surface erosion of the "prolonged side".

Uniformity of dosage units was determined for the double-layer tablets according to the Ph. Eur. monograph 2.9.40 (27). Therefore, drug content of 10 double-layer tablets was determined after dissolution. The acceptance value (AV) of 6.6 complied with the specifications in Ph. Eur. 2.9.40 (AV ≤15).

Stability of Drug-Polyelectrolyte Complexes

In the second approach of solid dosage form development, it should be verified whether drug-polyelectrolyte complexes offer advantages in storage stability compared to the salt form of the model drug naproxen.

Amorphous systems tend to crystallize if the solubility of the drug in the polymer is exceeded. The Tg of a single-phase amorphous system is a crucial parameter for the prediction of its storage stability. According to Hancock and Zografi (9) these systems should be stored 50°C under the Tg to avoid recrystallization. Forster *et al.* used the Gordon-Taylor equation to analyze the potential of drug-polymer mixtures for the production of single-phase amorphous systems by hot-melt extrusion (39). The equation enables the prediction of the Tg of a miscible, binary mixture (24).

A variable of the Gordon-Taylor equation is the Tg of the drug. In this study, Tg of naproxen could not be determined due to its rapid recrystallization. Some scientific researchers used the empirical rule, that the ratio of the glass transition temperature and the melting point of a substance is ~0.7 (40), resulting in a Tg prediction of about

Table II Tabletting Mixtures of the Two Sides of the Double-Layer Tablets; in %

	polyelectrolyte complex	SMCC	colloidal anhydrous silica	crospovidone	magnesium stearate
burst side	65	31.5	0.5	2	1
prolonged side	98.5		0.5		1

Table III Compaction Force for the Double-Layer Tablet Production and their Mechanical Properties

	compaction force [kN]	mass [mg]	tensile strength [N/mm^2]	thickness [mm]	diameter [mm]
double-layer tablets	9.96 ± 0.21	607.36 ± 1.13	0.67 ± 0.09	5.22 ± 0.01	12.07 ± 0.01

24°C for naproxen. Recently, Allesø *et al.* (12) determined an experimental Tg of 6°C for naproxen experimentally via quench-cooling. Calculations in this study were conducted with this value.

Figure 5 compares the Tg's of different naproxen-EUDRAGIT® E PO mixtures predicted by the Gordon-Taylor equation with experimental DSC data, determined from the second heating curve of the corresponding physical mixtures. By reducing the interactions between polymer chains, drug substances often reveal a plasticizing effect (41). The experimental results show maximum Tg values at amounts of 42 and 50% naproxen in the mixture. These values were higher than those predicted by the Gordon-Taylor equation.

In order to evaluate the stability of ionic naproxen within the complex, experiments were conducted in comparison to the naproxen sodium salt. Several pseudopolymorphic forms of naproxen sodium are known as well as their instability towards moisture has been studied. Di Martino *et al.* (42) and Kim and Rousseau (43) investigated the sorption mechanisms of hydration and dehydration of naproxen sodium at different relative humidities. The influence of different hydrates of naproxen sodium on subsequent manufacturing processes was highlighted. Depending on the drying procedure, pseudopolymorphs exhibited differing tabletability after wet granulation with a high-shear mixer (44). Another study showed the impact of the polymorphism of naproxen salts on several mechanical properties like the compressibility and compactibility (45).

In order to highlight the stability of the ionic naproxen as a part of the polyelectrolyte complex in comparison to naproxen sodium, water sorption measurements of the substances were carried out at 25°C. Sorption (0–90% RH) and desorption (90–0% RH) isotherms of naproxen, EUDRAGIT® E PO and the naproxen-EUDRAGIT® E PO polyelectrolyte complex as well as naproxen sodium are shown in Fig. 6. According to the ICH-Guideline Q1A (R2) (20), relative humidities of 40–75% relative humidity were of particular interest.

XRPD measurements at several points of the sorption curve were conducted and compared to literature (44) to follow up modification changes at different humidities. Characteristic reflections of naproxen sodium pseudopolymorphs are listed in Table IV.

Naproxen showed almost indifferent behavior at different relative humidities (Fig. 6). At 90% RH water uptake was less than 0.1% compared to the initial mass at 0% RH. In XRPD measurements, similar reflection patterns with similar intensities confirmed that no change of modification occurred (Fig. 8). Contrary to the non-ionic form, naproxen sodium revealed a water uptake of 14% at 60% RH and of 32% at 90% RH (Fig. 6). Furthermore, the sorption and desorption curves built a hysteresis area. Samples at 40 and 50% RH exhibited similar XRPD patterns which could be assigned to the naproxen sodium anhydrate (Fig. 7). Despite low intensity, characteristic reflections of the dihydrate were apparent. A complete conversion to the dihydrate at 60% RH could be proved by sorption as well as XRPD. The mass increase of about 14% corresponds to a water uptake of two mol water, and the dihydrate reflection pattern was detected in XRPD measurements. A comparable mass uptake of two mol water occurred at 70 and 80% RH. This

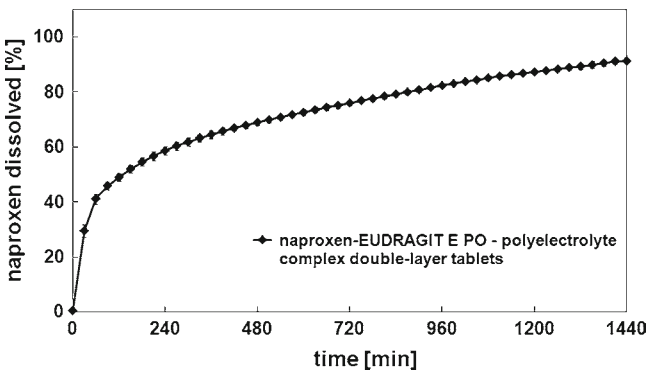

Fig. 4 Drug release of naproxen-EUDRAGIT® E PO polyelectrolyte complex double-layer tablets; 200 mg drug; 1000 ml phosphate buffer pH 6.8 (Ph. Eur.); 37 ± 0.5°C; 100 rpm; 272 nm; mean ± SD, n=5.

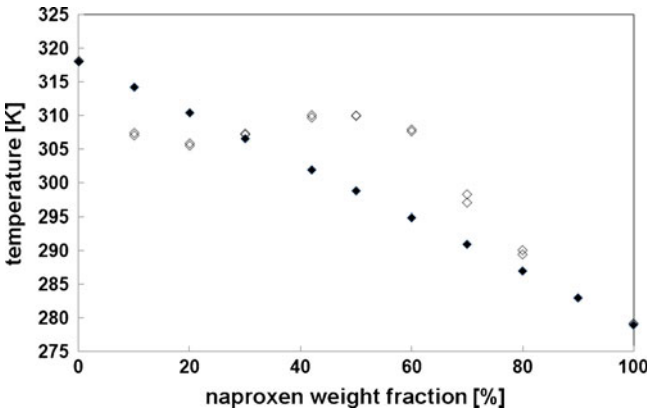

Fig. 5 Glass transition temperature of EUDRAGIT® E PO at different naproxen drug loads; open symbols - experimental Tg, filled symbols - prediction according to the Gordon-Taylor equation.

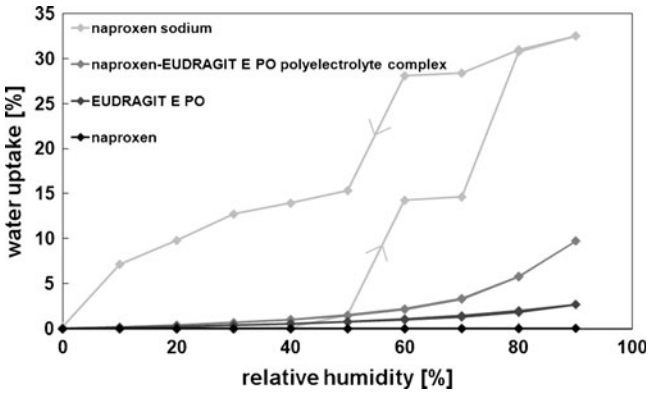

Fig. 6 Sorption and desorption isotherms of naproxen sodium (with hysteresis curve), the naproxen-EUDRAGIT® E PO polyelectrolyte complex, EUDRAGIT® E PO and naproxen at 25°C.

indicates the formation of naproxen sodium tetrahydrate which was recently described by Di Martino *et al.* (46). Modification changes proved not to be directly reversible because the desorption isotherm was not congruent with the sorption isotherm.

The amorphous polymer EUDRAGIT® E PO showed maximal water absorption of less than 3% at 90% RH (Figs. 6 and 8).

In contrast to the single component naproxen, at 40 and 90% RH typical amorphous halos were observed for the naproxen-EUDRAGIT® E PO polyelectrolyte complex (Fig. 8). Corresponding to the relative humidity used for long-term storage conditions of 60%, the polyelectrolyte complex revealed a water uptake of 2.2% (Fig. 6). Taking the minor content of 42% naproxen into account, the water uptake of the extrudate was considerably lower compared to the sodium salt at 60% RH (14.2%).

Further investigations were performed to elucidate whether ionic naproxen in the polyelectrolyte complex showed also superior stability against moisture to naproxen sodium in tablets. For this, tablet formulations T1 and T3 (Table I) were subjected to water sorption measurements analogous to the starting materials and milled extrudate (Fig. 9). Due to the high amount of SMCC in the formulations, the SMCC sorption curve was included into the characterization. SMCC showed a sigmoidal curve with a maximum water uptake of 10.6% at 90% RH.

Table IV Pseudopolymorphic Forms of Naproxen Sodium with Three Reflections of Highest Intensity

	reflections with highest intensity - 2 theta [°]
naproxen sodium anhydrate	13.0–17.4–22.4
naproxen sodium dihydrate	11.8–17.4–21.6
naproxen sodium tetrahydrate	19.4–26.5–29.6

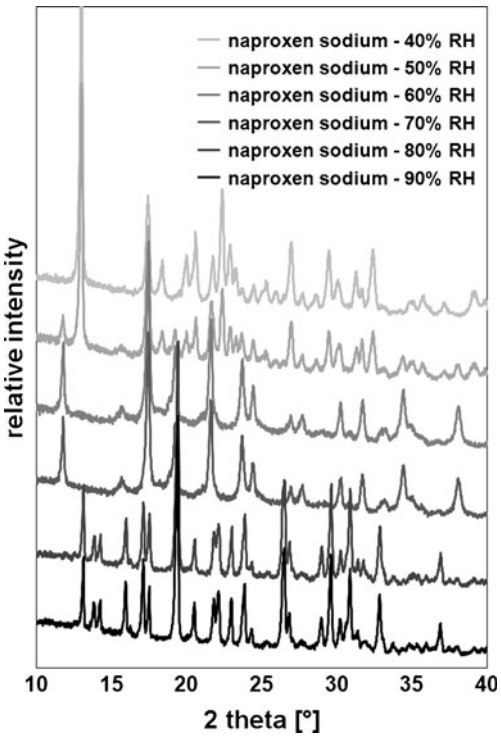

Fig. 7 XRPD patterns of naproxen sodium at different relative humidities.

The same tendencies observed for the pure substance naproxen sodium recurred for the tablets. Referring to the decreased drug load of 30.9%, the steps of mass uptake were

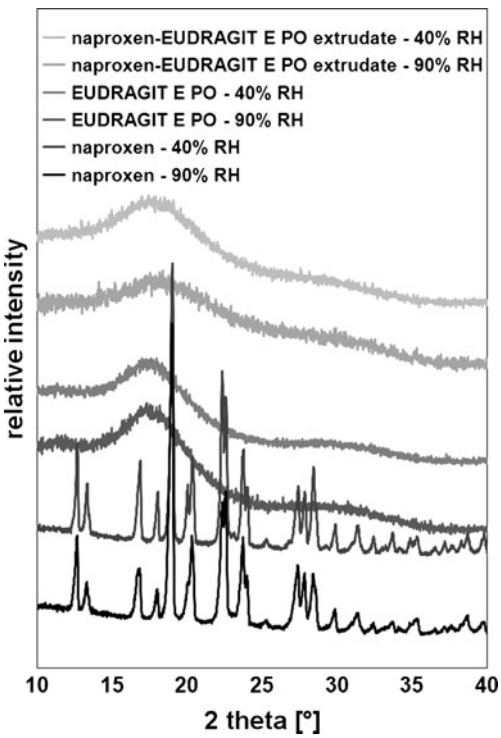

Fig. 8 XRPD patterns of naproxen-EUDRAGIT® E PO polyelectrolyte complex, EUDRAGIT® E PO and naproxen at different relative humidities.

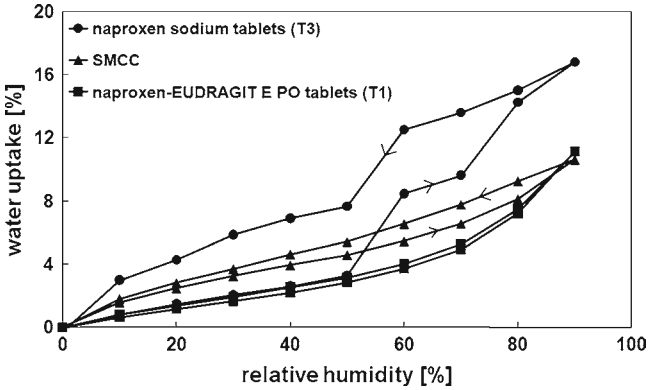

Fig. 9 Sorption and desorption isotherms of naproxen sodium tablets (T3), SMCC and naproxen-EUDRAGIT® E PO tablets (T1) at 25°C.

less pronounced. Water uptake of 4.5% again corresponds to two mol of water in this case. The change from anhydrate to dihydrate was proved by XRPD measurements between 50 to 60% RH and to the tetrahydrate between 70 and 80% RH (Fig. 10).

Polyelectrolyte complex tablets exhibited no recrystallization tendencies at 90% RH. Intensities in the reflection pattern could be referred to partly crystalline SMCC (Fig. 11) as well as a small hysteresis area between sorption and desorption curve (Fig. 9).

In order to ascertain whether the results obtained by water sorption measurements can be transferred to the conditions described in the ICH-guideline (20), samples of

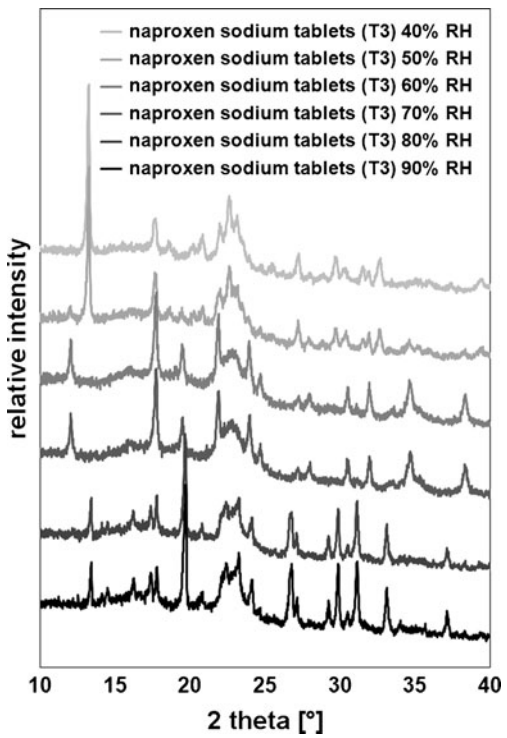

Fig. 10 XRPD patterns of naproxen sodium tablets (T3) at different relative humidities.

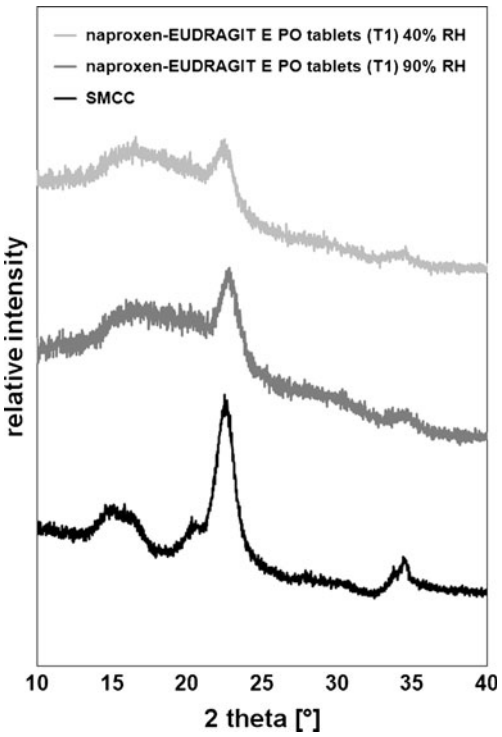

Fig. 11 XRPD patterns of naproxen-EUDRAGIT® E PO tablets (T1) at different relative humidities and of SMCC.

T1 and T2 were stored under accelerated conditions exemplarily. XRPD measurements for samples with and without drying aids in HDPE bottles were performed before and after 2 months storage. Although 40°C storage temperature was higher than the Tg of the naproxen-EUDRAGIT® E PO polyelectrolyte complex, the absence of naproxen reflections in the XRPD pattern revealed no signs of recrystallization of the single-phase amorphous system (Fig. 12).

Depending on the storage conditions, changes in the modification of naproxen sodium occurred (Fig. 13). The samples taken after tabletting and those after two month storage with a drying aid could be assigned to the anhydrous form of naproxen sodium. Without drying aid at 40°C and 75% RH the dihydrate pseudopolymorph was generated. These results correspond to the observations in the water sorption system.

DISCUSSION

The formation of drug-polyelectrolyte complexes of poorly soluble acid drug and basic polymers via hot-melt extrusion has already been discussed in our previous paper (16). The proton-transfer of model drug naproxen to the tertiary amine groups of EUDRAGIT® E PO generated two counter-charged molecules. During hot-melt extrusion no further substances like solvents were needed for the process; therefore both substances were attracted by electrostatic

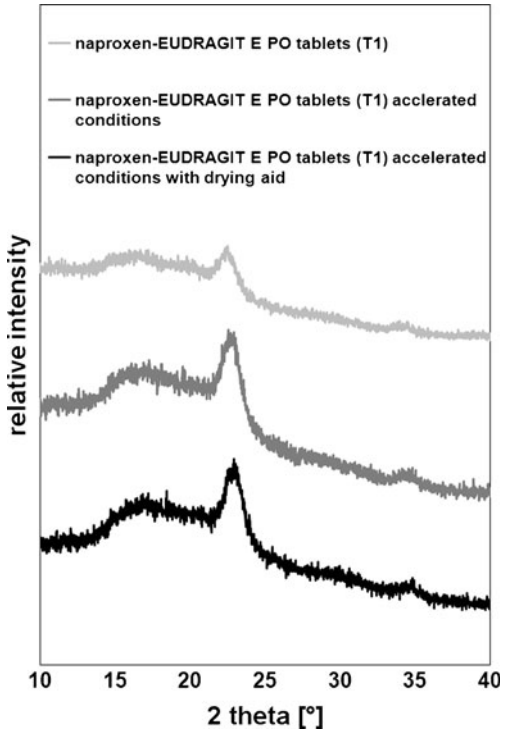

Fig. 12 XRPD patterns of naproxen-EUDRAGIT® E PO tablets (T1) after 2 months of storage under accelerated conditions (40°C/75% RH) with and without drying aid; for comparison: XRPD patterns of tablets before storage tests.

interactions. The drug release of polyelectrolyte complexes was tailor-made by pH-neutral electrolytes in demineralized water.

This study challenged the transfer of electrolyte-triggered drug dissolution in phosphate buffer pH 6.8 (Ph. Eur.). The electrolytes of the buffer medium induced drug dissolution and were used to stimulate biphasic drug release profiles. The tablet layer with 65% complex loading disintegrated into single particles showing an immediate release profile. The other tablet layer with 98.5% loading did not disintegrate during dissolution. After contact with the dissolution medium a non-swelling matrix was built. The matrix eroded during the dissolution and revealed a continuous prolonged drug release. Dissolution behavior of the tablets of the naproxen-EUDRAGIT® E PO polyelectrolyte complex corresponded to a "surface erosion" as described by Siepmann and Göpferich (47). Thus, it was possible to release the soluble ionic naproxen stimulated by electrolytes of the medium, depending on the relative amount of polyelectrolyte complex in the formulation.

Experimentally produced tablets in the range between 75 and 90% complex loading exhibited dissolution profiles with high standard deviations. The tablets showed differing disintegration behavior leading to tablet fragments with irregular shape and size. Hence, these tablets showed non-reproducible drug dissolution comparing different tablets of the same batch. Thus, 70% complex loading was deduced to be the highest complex loading which guarantees a complete disintegration into extrudate particles for an immediate drug release.

The use of phosphate buffer pH 6.8 revealed valuable insights into the polyelectrolyte complex behavior in pharmaceutical relevant media of high electrolyte concentrations. Nevertheless, further studies have to elucidate the transferability of the concept to *in-vivo* conditions in detail. This includes the analysis of the tablets at different pH values typical of the gastro-intestinal passage comparable to measurements performed by Bonferoni *et al.* (21) and Aguzzi *et al.* (23). Biorelevance of the electrolyte-stimulated drug-release triggering should be investigated and differentiated by the impact of pH and electrolyte concentrations on complex stability determining drug release kinetics.

The comparison of theoretical glass transition temperatures (Gordon-Taylor equation) and experimental results of differently composed binary mixtures of naproxen and EUDRAGIT® E PO revealed a maximum Tg at 42 (equimolar) and 50% drug amount. This indicated a stabilization of the single-phase amorphous system in a stoichiometrically ratio of naproxen carboxylic groups and tertiary amins of the polymer. The electrostatic interactions of the counter-charged molecules seem to immobilize the drug molecules

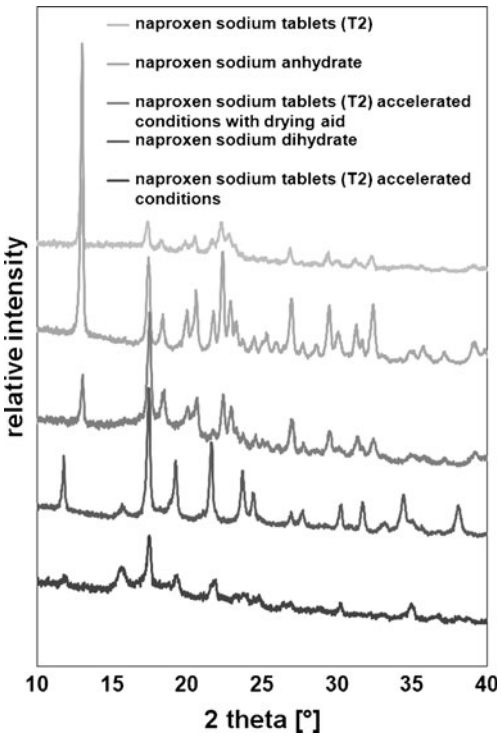

Fig. 13 XRPD patterns of naproxen sodium tablets (T2) after 2 months of storage under accelerated conditions (40°C/75% RH) with and without drying aid; for comparison: XRPD patterns of tablets before storage tests and naproxen sodium dihydrate/anhydrate.

at the binding sites of the polymer. Consequently, recrystallization of the drug is prevented.

Salt formation is a common way to circumvent bioavailability problems of poorly soluble non-ionic substances. Nevertheless, the formation of a salt is often accompanied by pseudopolymorphism which leads to stability problems. Therefore, the behavior towards moisture on the ionic naproxen of the polyelectrolyte complex and the sodium salt of naproxen were compared. Both substances were analyzed in the pure state and in compressed tablet formulations. In both cases, the polyelectrolyte complex showed superior results, revealing a stable amorphous system. In XRPD patterns, no reflections of recrystallizing naproxen were detected. Hydration was observed for naproxen sodium as pure substance and in tablets with high water uptakes. The changes occurring in XRPD measurements were referred to the formation of dihydrate and tetrahydrate pseudopolymorphs. In order to underline the instability of the sodium salt, stability tests according to the ICH-guideline were carried out. This examination revealed corresponding results comparing sorption isotherms and storage tests. Again, pseudopolymorphic dihydrate was formed in naproxen sodium tablets whereas the polyelectrolyte complex was stable, although the storage conditions were set above the Tg of the complex. This was not expected since the rule of thumb according to Hancock and Zografi (9) proposes storage 50°C under the Tg of an amorphous system.

CONCLUSIONS

The concept of electrolyte-stimulated drug release from drug-polyelectrolyte complexes was successfully transferred to solid dosage forms. The poorly soluble model drug naproxen was processed together with the basic polymethacrylate EUDRAGIT® E PO. Via an acid–base reaction during the extrusion process the naproxen-EUDRAGIT® E PO polyelectrolyte complex was formed *in situ* in equimolar ratio. Advanced flowability of the milled extrudates in comparison to the physical mixture of the components was proved.

Tablets with 98.5% naproxen-EUDRAGIT® E PO complex loading provided a prolonged release profile in drug release studies. Electrolytes of the buffer medium triggered splitting of the complex. A constant drug release over 24 h corresponded to a zero order kinetic due to surface erosion. Reducing the complex load to 70% enhanced the disintegration of tablets and led to an immediate drug release during dissolution. The versatility of modified release was transferred to the production of double-layer tablets on a rotary-die press. Biphasic drug release profiles were obtained by a "burst" and a "prolonged" layer.

By means of DSC measurements a maximum glass transition temperature was determined for the equimolar ratio of acidic drug and basic polymer groups contrary to the Gordon-Taylor equation. Stability studies showed that naproxen sodium revealed pseudopolymorphism with high water uptake, whereas the amorphous single-phase system of the complex remained stable. The results were confirmed for all tablet formulations and by stability tests according to the ICH requirements.

To conclude, the concept offers a biopharmaceutical platform technology for electrolyte-stimulated modified drug-release profiles. The electrostatic interactions within the complex stabilize naproxen, but enable good water solubility and rapid dissolution. Moreover, tablets containing the complex are considerably less sensitive towards moisture under common storage conditions.

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