pH-independent immediate release polymethacrylate formulations – An observational study

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Abstract

Using Eudragit® E PO (EudrE) as polymethacrylate carrier, the aim of the study was to develop a pH-independent dosage form containing ibuprofen (IBP) as active compound via chemical modification of the polymer (i.e. quaternisation of amine function) or via the addition of dicarboxylic acids (succinic, glutaric and adipic acid) to create a pH micro-environment during dissolution. Biconvex tablets (diameter: 10mm; height: 5mm) were produced via hot melt extrusion (HME) and injection molding (IM). *In vitro* dissolution experiments revealed that a minimum of 25% of quaternization was sufficient to partially (up to pH 5) eliminate the pH-dependent effect of the EudrE/IBP formulation. The addition of dicarboxylic acids did not alter IBP release in a pH 1 and 3 medium as the dimethyl amino groups of EudrE are already fully protonated, while in a pH 5 solvent IBP release was significantly improved (cf. from 0 to 92% release after 1h dissolution experiments upon the addition of 20wt.% succinic acid). Hence, both approaches resulted in a pH-independent (up to pH 5) immediate release formulation. However, the presence of a positively charged polymer induced stability issues (recrystallization of API) and the formulations containing dicarboxylic acids were classified as mechanically unstable. Hence, further research is needed to obtain a pH-independent immediate release formulation while using EudrE as polmethacrylate carrier.

Introduction

Hot melt extrusion (HME) combined with injection molding (IM) is a versatile manufacturing technique which has generated significant interest in the pharmaceutical field based on the possibilities offered by this technique (Crowley et al., 2007, Repka et al., 2007, Follonier et al., 1994, Repka et al., 1999). It enables the production of tablets independent of the powders compactibility (Quinten et al., 2011). A homogeneous system can be created via a substantial energy input, provided by elevated temperature, high shear force and pressure. Different polymers are used as matrix drug delivery systems, wherein the drug is uniformly dispersed or dissolved (providing immediate or sustained drug release depending on the polymer properties) (Yang et al., 2008, Zhang and McGinity, 2000, Repka et al., 2003, Jijun et al., 2011, Zhu et al., 2006, Maniruzzaman et al., 2013). A well established drug delivery matrix which can be used for HME/IM applications is a methacrylate terpolymer based on n-butylmethacrylate (n-BMA), dimethylaminoethylmethacrylate (DMAEMA) and methylmethacrylate (MMA) in a 1/2/1.5-ratio (Eudragit® E PO) (Albers et al., 2009, Albers and Kleinebudde, 2008, Claeys et al., 2013, Qi et al., 2008, Six et al., 2003, Liu et al., 2010). It allows the development of stable glassy solid solutions, i.e. homogeneous one-phase systems with the drug molecularly dispersed in the matrix, ensuring immediate drug release (Albers et al., 2009, Claeys et al., 2013, Forster et al., 2001). However, the pH-dependent solubility of Eudragit E (i.e. insoluble at high pH, soluble at low pH) could possibly cause bioavailability problems when dealing with elderly (Russell et al., 1993, Riordan et al., 1997), upon food intake (Kararli, 1995) or diseases that tend to raise the stomach pH (Theisen et al., 2000, Williams and McColl, 2006).

In vitro dissolution studies of nimodipine, for instance, in a medium containing 0.1N hydrochloric acid and 0.05% (w/v) sodium dodecyl sulfate (SDS) showed that a solid dispersion with EudrE dissolved significantly faster than formulations with polyvinylpyrrolidone/vinyl acetate copolymer (PVPVA) and hydroxypropyl methylcellulose (HPMC) as polymer excipient. *In vivo* studies in male beagle dogs, on the other hand, revealed the fastest release for the formulation containing PVPVA as polymer excipient, followed by EudrE and HPMC (Zheng et al., 2007). This difference between in-vitro and in-vivo behavior could be due to the GI motility of a beagle dog which is among the fastest of all laboratory animal (fast stomach clearance), to the limited volume of gastric fluids (± 400mL) and most importantly to the gastric pH of the dogs which can reach pH 5 (Kararli, 1995). EudrE is also used as coating material for pH-controlled drug release in the treatment of inflammatory bowel disease (Leopold and

Eikeler, 1998). Lag times of drug release for EudrE-coated formulations were determined at 10min, 50min and 33h in media with pH values of 2, 5 and 6.8, respectively. The pH-dependent release profile of Eudragit E is due to its dimethylaminoethyl methacrylate (DMAEMA) moiety which becomes protonated at low pH values. Moreover, as shown in previous work (Claeys et al., 2013), the DMAEMA units are crucial with respect to API/polymer interaction (which are essential to create glassy solid solutions) and drug release characteristics.

This research focuses on the development of a pH-independent Eudragit E-based formulation, using 2 approaches to achieve pH-independent ibuprofen release from an Eudragit E matrix processed via HME/IM: 1. chemical modification of the Eudragit polymer structure by quaternization of the amine function; 2. creation of a low pH microenvironment during dissolution via the addition of dicarboxylic acids (succinic, glutaric and adipic acid).

Experimental Section

Materials

Ibuprofen 25 (IBP), with a melting endotherm at 76°C and a Tg of -42°C, was purchased from Abbott (Ludwigshafen, Germany). Eudragit® E PO (EudrE), a methacrylate terpolymer based on n-butylmethacrylate (n-BMA), dimethylaminoethylmethacrylate (DMAEMA) and methylmethacrylate (MMA) in a 1/2/1.5-ratio, was supplied by Evonik (Darmstadt, Germany). Diethylether and acetic acid were purchased by Biosolve (Valkenswaard, Netherland), hydrochloric acid from VWR International (Leuven, Belgium). Iodomethane, silver nitrate and dicarboxylic acids (succinic, glutaric and adipic acid) were purchased from Sigma-Aldrich (St-Louis, USA) (Table 1).

Table 1: Chemical characteristics of dicarboxylic acids

Dicarboxylic acid	COOH -R- COOH	pKa_1	pKa_2	T_m (°C)	Solubility in H_2O (g/L) at 25°C	logP
Succinic	CH_2CH_2	4.2	5.6	184	60	-0.59
Glutaric	$(CH_2)_3$	4.3	5.4	95	430	-0.29
Adipic	$(CH_2)_4$	4.4	5.4	152	24	0.08

Quaternization of Eudragit® E PO

Eudragit® E PO (20g) was dissolved in 200mL methanol (final concentration: 100mg/mL), followed by the addition of 0.41, 1.02, 2.03 and 3.05mL iodomethane (methylating agent) to synthesize polymethacrylates with a quaternization degree of 10, 25, 50 and 75%, respectively. The reaction (addition of methylgroup to the polymer structure) was allowed to proceed for 2h at room temperature, followed by precipitation of the polymer via the addition of diethylether (1/20, v/v). Consequently, the iodide counter ion of the quaternary amine was replaced by chloride via dialysis (using a cellulose dialysis membrane with a Mw cut-off of 14 kDa) for 2 days against a 60g/L aqueous sodium chloride solution, which was refreshed multiple times. The removal of iodide ions was verified via the addition of a silver nitrate solution as described in previous research (Obermeier et al., 2010). Finally, the quaternized Eudragit® E polymer (EudrE-Q) was isolated as a dry powder by lyophilization (average yield: 70%).

^{1}H-Nuclear Magnetic Resonance (^{1}H-NMR) Spectroscopy

Polymer composition and degree of quaternization was determined through ^{1}H-NMR spectroscopy on a Varian Mercury 300 NMR Spectrometer (Vernon Hills, Illinois, USA). Samples were dissolved in deuterated methanol. ^{1}H-NMR (300 MHz, CD_3OD) δ = 4.12 (br, $COOC\underline{H}_2CH_2N(CH_3)_2$), 3.64 ($COOC\underline{H}_3$), 2.68 (br, $COOCH_2C\underline{H}_2N(CH_3)_2$), 2.35 (br, $COOCH_2CH_2N(C\underline{H}_3)_2$), 2.21-1.75 (br, $C\underline{H}_2$ backbone), 1.45 (br, $COOC(C\underline{H}_3)_3$, 1.30-0.8 (br, $C\underline{H}_3$). The degree of quaternization was verified according to Obermeier et al. (Obermeier et al., 2010).

Determination of pKa

A polymer sample (200mg) was dissolved in 5mL 0.1M HCl solution, followed by the addition of 45mL demineralized water. While continuously measuring the pH, small amounts of 0.1M NaOH were added to the polymer solution up to pH 12. Consequently, the pKa was determined as a minimum of the first derivative of the titration cruve.

Thermal analysis

Thermogravimetric analysis (TGA 2950, TA instruments, Leatherhead, UK) was used to investigate the thermal stability of the polymers. The samples were equilibrated at 30°C and heated (10°C/min) to 500°C under an N_2 atmosphere.

Tg and melting point (T_m) of pure components, physical mixtures (homogenized using mortar and pestle) and injection molded tablets were analyzed by modulated differential scanning calorimetry (MDSC Q2000, TA Instruments, Leatherhead, UK) using a heating rate of 2°C/min. The modulation period and amplitude were set at 1min and ±0.318°C, respectively. Dry nitrogen at a flow rate of 50ml/min was used to purge the MDSC cell. A heating/cool/heat cycle was run between -70 and 120°C. All results were analyzed using the TA Instruments Universal Analysis 2000 software.

X-ray diffraction (XRD)

The crystallinity of the samples was determined via X-ray diffraction using a D5000 Cu Kα diffractor (λ = 0.154 nm) (Siemens, Karlsruhe, Germany) with a voltage of 40 kV and a current of 40 mA in the angular range of $10° < 2\theta < 60°$ using a step scan mode (step width = 0.02°, counting time = 1 s/step).

Production of injection molded tablets

Physical mixtures of IBP and polymer (30/70, wt.%) were extruded at 90°C using a co-rotating twin-screw extruder at 90rpm (Haake MiniLab II Micro Compounder, Thermo Electron, Karslruhe, Germany). Biconvex tablets (mass: 349 ± 2.1mg; diameter: 10mm; height: 5mm) were produced via injection molding (Haake MiniJet System, Thermo Electron). The injection pressure was 800bar during 10s, in combination with a post-pressure of 400bar for 5s. Formulations containing dicarboxylic acids were processed via HME/IM at a constant drug load (30%), but varying ratios of Eudragit E to dicarboxylic acid: 60/10, 55/15 and 50/20 (wt.%).

***In vitro* drug release**

Drug release from the injection molded tablets was determined using the paddle method on a VK 7010 dissolution system (VanKel Industies, New Jersey, USA) with a paddle speed of 100rpm. Hydrochloric acid (pH 1), citric buffer (pH 3 and 5) and phosphate buffer (pH 7) were used as dissolution media (900mL) at 37 ± 0.5°C. Samples were withdrawn at 5, 10, 15, 20, 30, 45 and 60min, and spectrophotometrically analyzed for API concentration at 221nm.

Results and Discussion

Ibuprofen (IBP) is a weak acid with a pKa of 4.4. The carboxylic group in the chemical structure is responsible for its pH-dependent solubility. At pH 7, IBP is completely dissolved after 15 min, whereas, the release at pH 5, 3 and 1 is limited to 57, 40 and 29%, respectively, after 60min of dissolution testing. The tertiairy amine function in the chemical structure of Eudragit® E (EudrE) causes its pH-dependent release profiles. In contrast to IBP, a higher pH reduces the dissolution rate of EudrE. It was therefore appropriate to combine both components (IBP and EudrE) in one formulation.

The processing of an EudrE mixture containing 30wt.% ibuprofen (IBP) via hot melt extrusion (HME), followed by injection molding (IM) yielded a transparent formulation, classified as a glassy solid solution. Thermal analysis revealed a single Tg, located between the Tg values of the individual components, indicating complete miscibility and compatibility between drug and polymer (Claeys et al., 2013). Spectroscopic analysis indicated that electrostatic interactions between the ammonium group of the polymer and the carboxyl group of IBP (i.e. salt formulation) were responsible for the solubilization of IBP (Claeys et al., 2013). EudrE is a fast dissolving polymer in acidic media (pH 1 and 3) due to the hydration of the dimethylamino groups that are fully protonated at this lower pH range, yet it is insoluble in media with a pH above 5. Chemical modification of the tertiary ammonium group of the polymer to its quaternized form should allow to determine the minimum amount of positive charges needed to eliminate this pH-dependent effect, quaternisation of 10, 25, 50 and 75% were tested.

All polymer samples were analyzed via ^{1}H-nuclear magnetic resonance spectroscopy to verify the degree of quaternization. Figure 1 illustrates that the decrease of the signal of the tertiary ammonium group R-N$(CH_3)_2$ at ~2.7 ppm is correlated with larger signals of the quaternary ammonium group R-N$^{+}(CH_3)_3$ at ~3.15 ppm. The deviation between the theoretical calculated and experimental degree of quaternization was 5, 7, 5 and 8% for EudrE-Q10, -Q25, -Q50 and -Q75, respectively. As the objective was to determine the relative influence of the degree of quaternization on drug release, these differences were regarded as negligible.

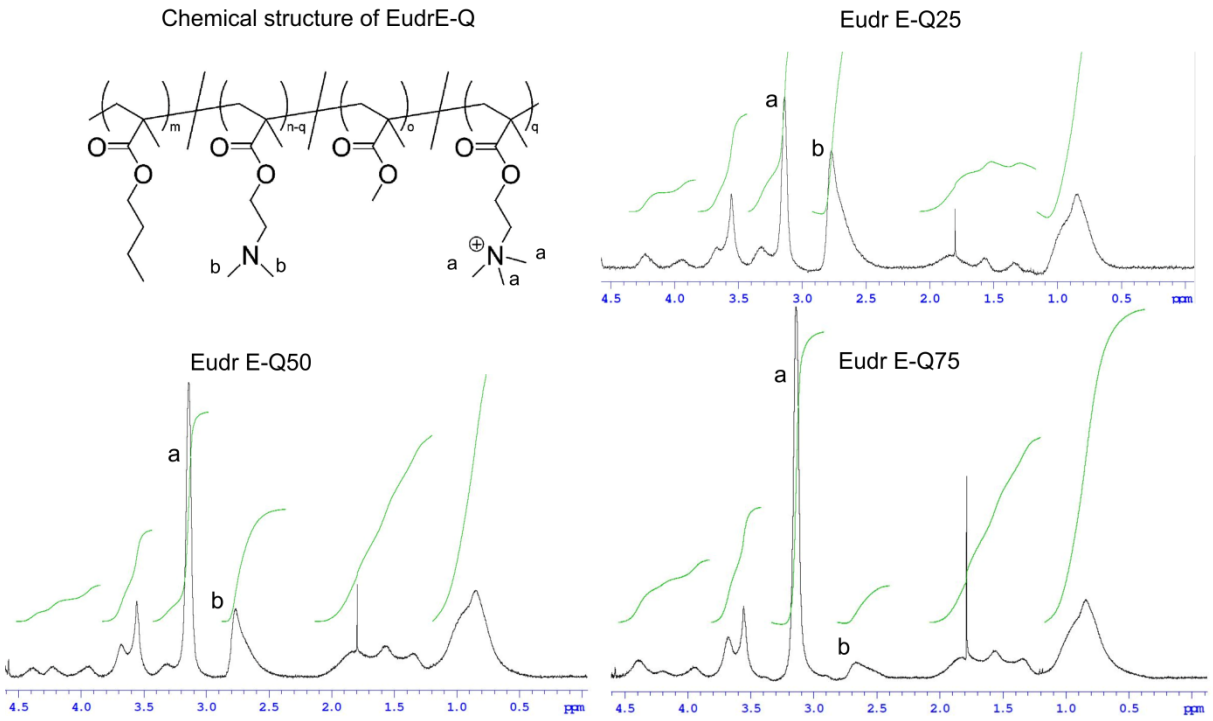


Figure 1. ^{1}H-NMR (300 MHz, CD_3OD) of EudrE-Quaternized (EudrE-Q) to verify the degree of quaternization via integration of the signals a and b, representing the signals of the quaternary and tertiary ammonium groups, respectively.

Second, it was determined whether quaternized Eudragit® E (q-EudrE) samples were suitable as polymers to solubilize ibuprofen (IBP) upon processing via hot melt extrusion (HME) and injection molding (IM). As the quaternization of EudrE did not significantly alter the polymers' glass transition temperature and a similar drug load (30wt.%) was used, the processing conditions were chosen similar to the EudrE/IBP 70/30 mixture (Claeys et al., 2013). All processed formulations with quaternized EudrE (EudrE-Q) as carrier were transparent with smooth surfaces. Figure 2 illustrates their dissolution behavior in function of pH. At pH 1, all formulations had similar release characteristics. At pH 3, the protonation rate of the tertiary ammonium group of EudrE is reduced, resulting in a slower hydration of the polymer and a lower IBP release rate compared to pH 1. In contrast, all quaternized EudrE (EudrE-Q) formulations were not affected by this lower acidic character of the dissolution medium. As a positive charge is intrinsically present in the chemically modified polymers, the lag phase for polymer protonation and hydration is avoided, yielding faster release profiles for EudrE-Q formulations. At pH 5, no IBP was released from the EudrE formulation, while the EudrE-Q10 formulation resulted in a release of 40% after 1h. At pH 5, not all ammonium groups of the polymer are protonated by the solvent based on their pKa value of 6.1, resulting in insufficient or no release from the EudrE-Q10- and EudrE-formulations, respectively. Eudr-Q25, -Q50 and

-Q75 formulations, on the other hand, still resulted in fast IBP release profiles as they already carried sufficient positive charges (due to the high degree of quaternization) and do not rely on protonation by the solvent to obtain fast drug release. At pH 7, release from all formulations (EudrE as well as EudrE-Q grades) was slow, indicating that at this pH even a high degree of quaternisation could not ensure fast hydration of the chemically modified polymethacrylate. Possibly, the formation of a complex between the positively charged polymer and the negatively charged IBP also contributed to the incomplete release under these conditions (Kislalioglu et al., 1991, Jiang et al., 2005). Overall, *in vitro* dissolution experiments revealed that a minimum of 25% of quaternization was sufficient to partially (up to pH 5) eliminate the pH-dependent effect of the EudrE/IBP formulation.

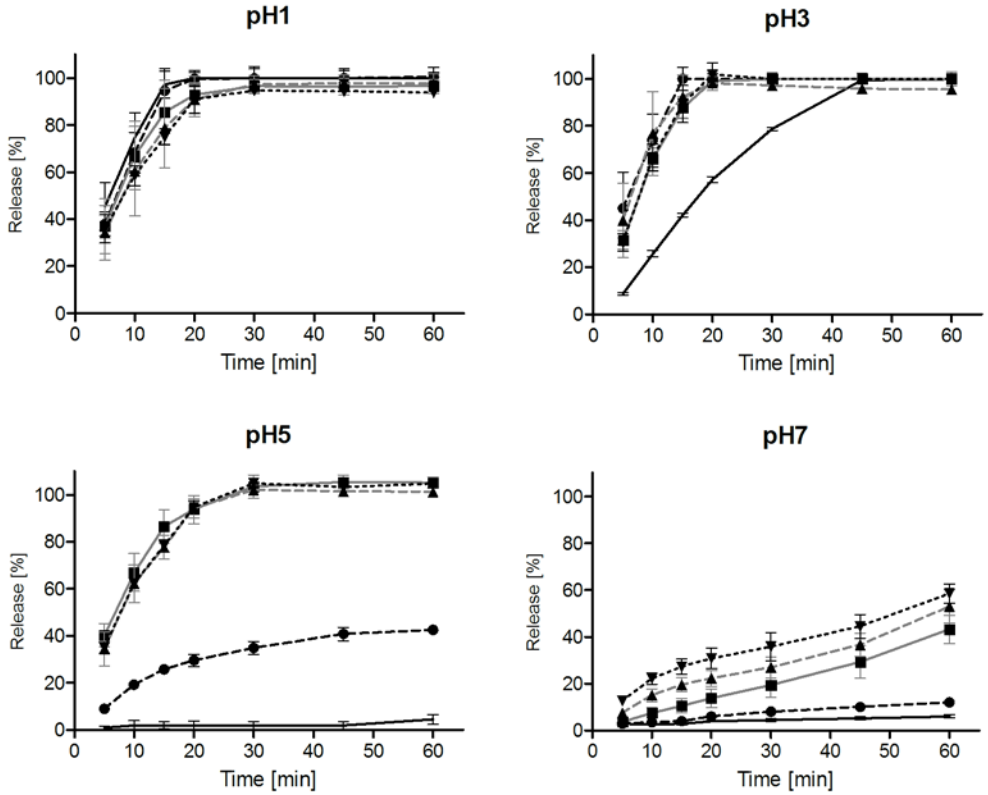


Figure 2. Release characteristics at different pH-values (1, 3, 5 and 7) of formulations containing 30wt.% ibuprofen and different polymethacrylate carriers: EudrE (no symbol), EudrE-Q10 (●), EudrE-Q25 (■), EudrE-Q50 (▲), EudrE-Q75 (▼).

As glassy solid solutions are inherently thermodynamically metastable, recrystallization is inevitable. However, a previous study indicated that the tertiary ammonium group of the polymer is of high importance as an interaction with the carboxylgroup of IBP (i.e. salt

formation) stabilizes the glassy solid solution for at least 6 months of storage at 25°C and 60% relative humidity (Claeys et al., 2013). Performing a stability study in similar conditions revealed the recrystallization of IBP in all formulations containing quaternized EudrE polymers (EudrE-Q) upon 3 months of storage, irrespective of the amount of quaternization. The transparent formulations became opaque, an IBP melting endotherm was observed via thermal analysis and XRD-spectra evidenced clear signs of crystallinity (data not shown). Hence, quaternization of EudrE, even at a low percentage (i.e. 10%), limits the interactions between drug and polymers, and reduces the stability of IBP solid solutions upon storage. Possibly the positive charges of EudrE-Q polymers are obstructing the ability of IBP to release its hydrogen atom, limiting the possibility for electrostatic interaction with the polymer which is essential for the stabilization of molecularly dispersed ibuprofen in an Eudragit E matrix. It is also possible that EudrE-Q polymers, obtained after quaternization in methanol, precipitation in diethylether, dialysis and lyophilization, still contained some residual solvents. These can alter the molecular mobility of IBP and increase its tendency to recrystallize.

As protonation of EudrE is responsible for the fast hydration/dissolution of the polymer and as this protonation is evidently reduced at higher pH values, a second approach to achieve pH-independent release was to create a low pH micro environment around the tablet during dissolution via the addition of acids to the HME/IM processed formulations. High concentrations of acids in the diffusion layer during dissolution could lower the pH, leading to accelerate protonation of EudrE and enhance the drug release rate. To this end, several dicarboxylic acids (succinic, glutaric and adipic acid) were added to the formulation (Table 1).

The addition of dicarboxylic acids to the IBP/EudrE 30/70 mixture did not influence the formulation's ability to form transparent tablets. Dissolution experiments illustrated that the addition of dicarboyxlic acids did not alter IBP release in a pH 1 and 3 medium (data not shown), as the dimethyl amino groups of EudrE are already fully protonated. Moreover, the ability of dicarboxylic acids to release hydrogen atoms is lower at this pH given pKa values of succinic, glutaric and adipic acid of 4.2, 4.3 and 4.4, respectively. At pH 5, IBP release was significantly improved (Figure 3) upon the addition of dicarboxylic acids, as the low pH environment in the diffusion layer around the tablet enhances IBP release rate. This improvement was concentration driven as higher concentrations of dicarboxylic acids induced faster drug release. IBP release depended also on the type of dicarboxylic acid: the fastest release was observed in combination with succinic acid, while adipic acid had less impact. This

could be related to the polarity of the dicarboxylic acids, as succinic acid was the most polar compound (log P -0.59, vs. -0.29 and 0.08 for glutaric and adipic acid, respectively) (Table 1).

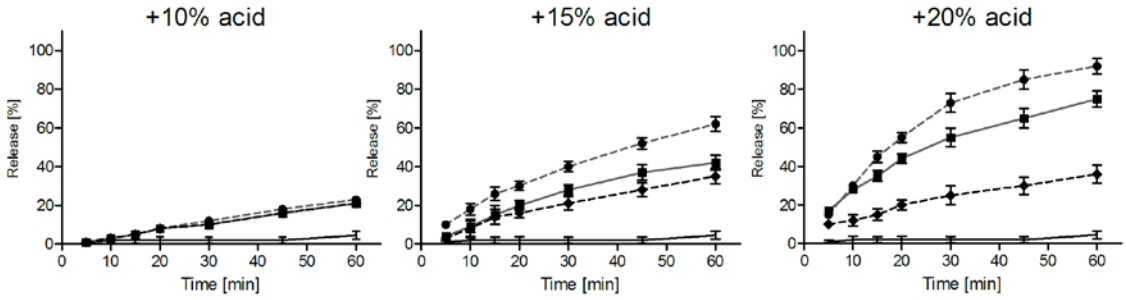


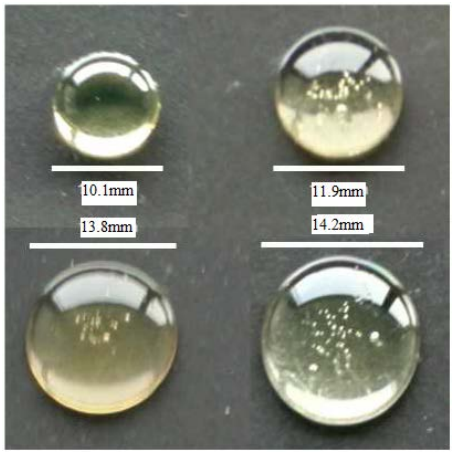
Figure 3. Release profiles of IBP/EudrE 30/70 mixtures (no symbol) at pH 5 with the addition of 10, 15 and 20% of adipic (♦), glutaric (■) and succinic acid (●), respectively.

The importance of low pH in the diffusion layer was illustrated by the addition of 20% disodium succinate to the formulation: IBP release was limited to 10% after 60 min, vs. 92% in combination with 20% succinic acid (cf: a solution containing 0.1N of succinic acid and disodium succinate has a pH value of 2.7 and 7, respectively).

Figure 4 illustrates the formulation's stability at room temperature. The glassy solid solution tablets containing dicarboxylic acids were mechanical unstable (unable to maintain their structure). Two underlying reasons were identified: 1. The plasticizing effect of IBP on EudrE (Claeys et al., 2013). Increasing the dicarboxylic acid concentration also increased the IBP/EudrE ratio thereby inducing more molecular mobility; and 2. The molecular mobility of the dicarboxylic acids. Figure 4 and Table 2 illustrates that the formulation's mechanical stability was dependent on the length of the dicarboxylic acid (stability of formulation with succinic > glutaric > adipic). It is known from previous research (Claeys et al., 2013) that the change of a t-butyl group in the polymer structure to a n-butyl group increases the molecular mobility of the polymer as a result of an increase in free volume and a less denser polymer structure. As adipic acid had the highest amount of carbons between its 2 carboxylic groups, the polymer's free volume and its molecular mobility were increased to a higher extent compared to succinic and glutaric acid containing formulations, resulting in a lower mechanical stability (Table 2).

Table 2. Tablet diameter upon 1 month of storage at 25°C, 60% relative humidity of EudrE/IBP 70/30 with the addition of 10, 15 and 20% of dicarboxylic acid, respectively.

Dicarboxylic acid	IBP/EudrE/Acid 30/70/0	30/60/10	30/55/15	30/50/20
Succinic	10.0mm	10.2mm	10.4mm	11.9mm
Glutaric	10.0mm	10.4mm	11.1mm	13.8mm
Adipic	10.0mm	10.4mm	11.4	14.2mm



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298 **Figure 4.** Tablet diameter upon 1 month of storage at 25°C, 60% relative humidity of EudrE/IBP 70/30 (upper
299 left) with the addition of 20% succinic acid (upper right), glutaric acid (lower left) and adipic acid (lower right),
300 respectively.

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Conclusion

A pH-independent immediate release polymethacrylate formulation was created via a chemical modification of the polymer (i.e. quaternisation of amine function) and via the addition of dicarboxylic acids (succinic, glutaric and adipic acid). The presence of a positively charged polymer and the low pH micro-environment during dissolution allowed the release of IBP independent of the solvent pH (up to pH 5). However, the quaternization of the polymer induced stability issues (recrystallization of API) and the formulations containing dicarboxylic acids were classified as mechanically unstable. Hence, further research is needed to obtain a pH-independent immediate release formulation containing EudrE and IBP.

Declaration of Conflicts of interest

The authors have no declaration of conflicts of interest

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