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Toward pH-Responsive Coating Materials—High-Throughput Study of (Meth)acrylic Copolymers

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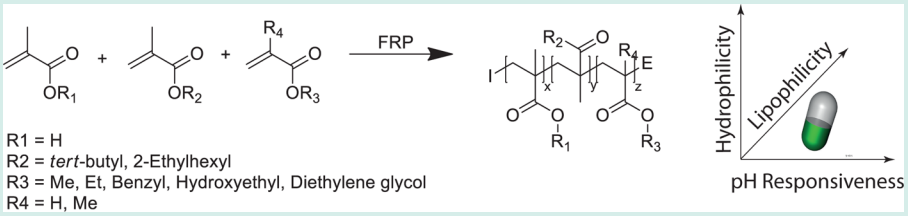

ABSTRACT: The release behavior of a model compound (β-naphthol orange) encapsulated in (meth)acrylate-based statistical copolymers under different environmental conditions was investigated. From monomers of varying polarity (methyl acrylate, ethyl acrylate, *tert*-butyl acrylate, 2-ethylhexyl methacrylate, and benzyl methacrylate) in combination with methacrylic acid, five polymer series were synthesized by free radical polymerization. The pH-dependent release kinetics were investigated via UV−vis spectroscopy at pH 1.2 and 6.8, simulating physiological conditions in the stomach and intestines. Furthermore, the influence of different ethanol contents (0 and 40 vol %) in the acidic medium was investigated. The whole approach was designed to meet the requirements of a high-throughput experimentation workflow.

KEYWORDS: *pH-responsive, high-throughput, poly(methacrylate), UV−vis spectroscopy*

INTRODUCTION

An extensively studied application field for polymers is their use in drug delivery devices.[1] In this context, the delivery of pharmaceuticals to a specific target area in the human body without harming healthy parts is the task of the polymeric carrying material. In recent studies, cell-specific targeting via small-scale delivery systems (e.g., polymeric micelles, vesicles, dendrimers, or stars) is associated with this topic.[2−4] Nevertheless, one should not forget that the peroral uptake of pharmaceuticals is one of the most common application forms.[5−7] Therein, polymers are mainly used as coating materials of tablets. The location of the release of a drug from a tablet can have a huge impact on the medical effect. In particular, protection from the harsh environment in the human stomach can be one important task for the tablet coating material if the drug is meant to be released in the intestines.[8−10]

The different pH values in the human digestive tract are often used as release triggers for encapsulated drugs.[11−13] Therefore, pH-responsive amphiphilic polymers are one method of choice to fulfill this task. Well-known and widely used commercially available examples are the Eudragit polymers from Evonik Industries.[14,15] The pH responsiveness of these statistical (meth)acrylic copolymers is based on the incorporated (meth)acrylic acid moieties, which are hydrophobic in the protonated state but hydrophilic when deprotonated. Different ratios between these acidic monomers and hydrophobic comonomers [e.g., aliphatic (meth)acrylates] lead to specific pH-dependent solubility behaviors of the obtained copolymers.

One serious issue is that the final drug release behavior is rather hard to predict because not only complete dissolution but also swelling of the polymer can lead to nearly complete release of the encapsulated medical component.[16,17] Because of that, structure−property relationships are difficult to elucidate, and the design of new materials requires extensive testing of multiple polymer compositions.

A problem in this special application is the potential uncertainty about the real chemical composition of the environment in the human digestive tract. Normally, to model the environment in the human body, the assumption of a rather pure aqueous solution with a certain pH value is sufficient in most cases. Nonetheless, some deviations are possible and can be very problematic, particularly for applications such as tablet coating.[18] For example, the ethanol

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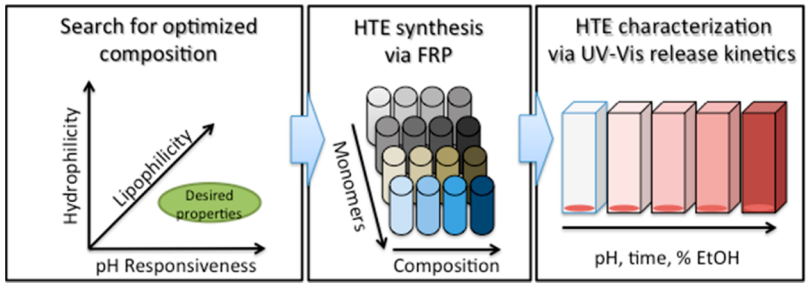

Figure 1. Workflow of the HTE study for pH-responsive coating materials.

(EtOH) content in the stomach has a significant impact on the solubility behavior of such coating materials.[19] Diverse coating materials for tablets that were created to resist an aqueous environment because of their hydrophobic nature may show far from optimal performance when an increased alcohol content leads to a more hydrophilic state. Thus, ideal materials should exhibit the desired features independently of the alcohol content. In this context, a maximum EtOH content of 40% can be seen as an absolute upper value. Though no official guidelines exist to date, this value is used in the pharmaceutical industry in test devices.

According to the materials on the market, (meth)acrylate-based copolymers were chosen for the present study.[14] Because of its versatility in terms of functionalities, this type of monomer is ideal for investigating the influence of different functional groups on its properties in a copolymer. On the basis of methacrylic acid as a pH-responsive moiety,[20] the aim was to achieve pH-responsive amphiphilic materials in combination with hydrophilic and hydrophobic comonomers, which should additionally show alcohol resistance. The desired ideal polymer would be insoluble under acidic conditions in water as well as in alcoholic solutions, while the encapsulated drug would be released in a neutral environment. To enable fast preparation of multiple copolymers, the polymerization method of choice was the free radical polymerization (FRP) technique.[21] The method enabled the fast and reliable synthesis of multiple polymer series with varying compositions.

The investigation of structure−property relationships is an absolute necessity if new properties are sought to be introduced into existing materials without losing the beneficial properties already incorporated in the polymer. While polymerization techniques for the preparation of large numbers of polymers with varying composition are available, this is not the case for simple testing methods for properties such as release behavior. Industrial testing methods, which are usually close to the real end application, require rather large amounts of material and are mostly limited in terms of parallel screening, meaning that real-life conditions for the coating material are mostly applied.[13] Therefore, an aqueous suspension of the investigated material with multiple additives is sprayed onto tablets to form a coating film.[13,15] Besides the necessity of large amounts of material, the technical equipment to perform spray coating experiments also represents an additional disadvantage. Both requirements limit the possibility of high-throughput experimentation (HTE). In order to develop a new product with improved properties, usually larger numbers of polymers with varying compositions have to be pretested. For this purpose, the requirements in terms of technical equipment and necessary material amounts should be relatively low, and the method itself has to be simple and fast to allow the testing of various polymer series up to extensive libraries. Consequently, small sample numbers and small composition ranges can be overcome by creating a test device suitable for multiple samples prepared by an HTE approach.

RESULTS AND DISCUSSION

To elucidate promising polymer candidates as tablet coating materials, a high-throughput approach was developed. The rather complex influence of the monomer structure and the chosen polymer composition are difficult to predict and therefore are best investigated experimentally. Figure 1 shows the workflow applied for the present study.

The most influential parameters for polymers in tablet coating applications are the ratio between hydrophilic and hydrophobic monomers on one hand and the amount of incorporated pH-responsive amphiphilic moieties on the other hand. A large number of combinations of different monomers and polymer compositions has to be tested in order to identify polymers with desired properties with respect to drug release behavior at specific sites under specific conditions. For this purpose, methacrylic acid-based statistical terpolymers were synthesized, characterized, and investigated in regard to their release properties. The monomer combinations used for the five different polymer series are schematically represented in Figure 2.

The synthesis of the polymeric materials was performed using FRP, which is a versatile technique for the polymerization of (meth)acrylic polymers. Although control over the polymer-

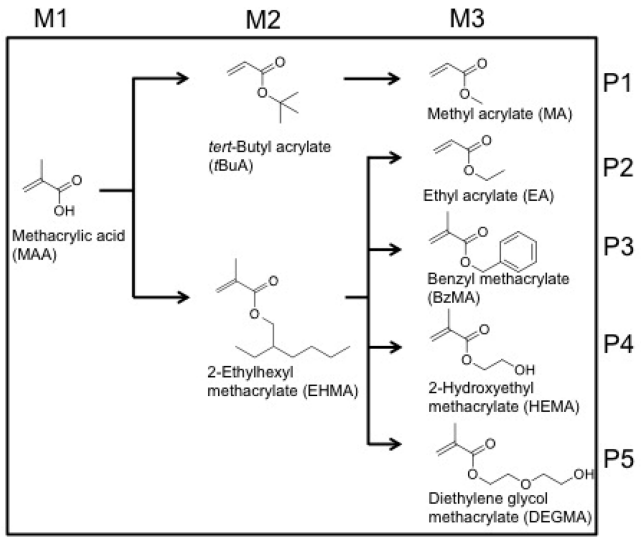

Figure 2. Schematic representation of the monomer combinations used.

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ization is relatively poor compared with "living/controlled" polymerization techniques, it represents an ideal technique if the value of the polydispersity index (PDI) or the architecture of the copolymers is secondary to price and time. The radical reaction mechanism allows a fast and efficient synthesis of polymers. Additionally, no further reactants besides low amounts of a radical-forming species are required, thereby minimizing the price of the synthesized polymers. Furthermore, although inert reaction conditions are a necessity, the method is much less demanding in terms of purity compared with other techniques.

To ensure pH responsiveness, an acidic moiety is required. For this purpose, methacrylic acid was incorporated in different amounts into each copolymer. The polymers should be water-insoluble under neutral conditions but soluble in an acidic environment, which can be tuned by the amounts of additional hydrophobic and hydrophilic comonomers. The use of multiple combinations of monomer types and ratios allowed a systematic investigation of the way in which the polymer composition influences the final solubility behavior.

To increase the hydrophobicity of the polymers, varying methacrylic and acrylic monomers with different nonpolar side groups were used: methacrylic acid (MAA), ethyl acrylate (EA), *tert*-butyl acrylate (*t*BuA), 2-ethylhexyl methacrylate (EHMA), and benzyl methacrylate (BzMA). More hydrophilic moieties were introduced by polymerization with 2-hydroxyethyl methacrylate (HEMA) and diethylene glycol methacrylate (DEGMA). The amphiphilic MAA groups can contribute to both properties depending on the pH, as MAA is either hydrophilic in its deprotonated state or hydrophobic under acidic conditions. Thus, a polymer consisting of, for example, EHMA and MAA should be insoluble under acidic conditions, whereas the partially deprotonated MAA should act as water-soluble moiety under neutral conditions. Therefore, the two monomers would compete in terms of solubility in the latter case. The final adjustment of the ratio between the two monomers would then allow the tuning of the final overall solubility behavior of the copolymer. A schematic plot of the ternary composition is shown in Figure 3.

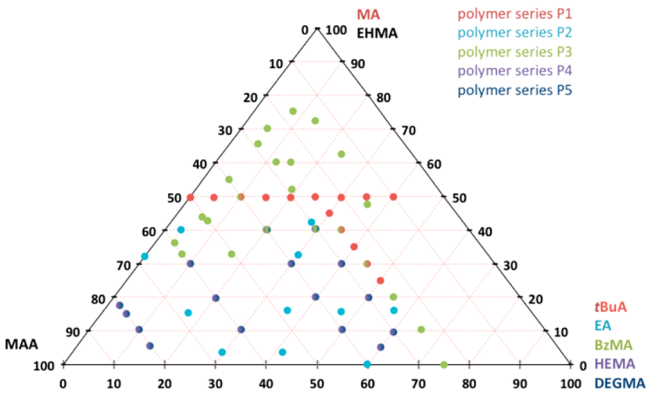

Figure 3. Ternary compositions of polymer series **P1** to **P5**.

Multiple batches of polymers were prepared. Each polymer was designed to have a distinctive composition in terms of monomers as well as feed ratios applied. A constant necessity for all polymers was the incorporation of the acidic moiety to ensure pH responsiveness. On the other hand, the comonomers were varied to cover a wide range of overall hydrophilicity properties of the obtained polymers. The feed ratios as well as the characterization data are summarized in Tables 1 to 5. As expected for polymers prepared via FRP, the

Table 1. Composition (Feed Ratio) and Characterization Data for Polymer Series P1

polymer	MA:*t*BuA:MAA [mol %]	M_n [g mol^{-1}]^a	M_w [g mol^{-1}]^a	PDI^a
P1-1	50:25:25	50 600	125 100	2.47
P1-2	45:30:25	45 700	118 000	2.43
P1-3	40:35:25	46 600	126 300	2.70
P1-4	35:40:25	43 200	120 000	2.78
P1-5	30:45:25	47 200	122 700	2.58
P1-6	25:50:25	43 200	128 200	3.00
P1-7	50:40:10	31 000	109 300	3.86
P1-8	50:35:15	37 000	113 800	3.10
P1-9	50:30:20	42 200	124 600	2.94
P1-10	50:25:25	45 800	132 600	2.97
P1-11	50:20:30	49 600	144 300	2.98
P1-12	50:15:35	51 400	132 400	2.57
P1-13	50:10:40	60 400	148 000	2.46
P1-14	50:5:45	58 800	153 600	2.59
P1-15	50:0:50	50 800	144 200	2.80

^{a}Determined by SEC.

Table 2. Composition (Feed Ratio) and Characterization Data for Polymer Series P2

polymer	EHMA:EA:MAA [mol %]	M_n [g mol^{-1}]^a	M_w [g mol^{-1}]^a	PDI^a
P2-1	0:60:40	232 200	620 000	2.67
P2-2	17:36:47	212 400	582 000	2.74
P2-3	31:0:68	262 000	678 000	2.59
P2-4	33:30:37	222 500	687 700	3.09
P2-5	40:4:56	203 200	845 700	4,20
P2-6	17:56:26	94 000	490 300	5.20
P2-7	4:66:29	86 600	429 700	4.95
P2-8	17:36:47	179 200	758 400	4.23
P2-9	16:17:66	164 700	672 600	4.08
P2-10	4:41:55	166 800	604 300	3.60
P2-11	41:30:29	377 900	907 900	2.41

^{a}Determined by SEC.

PDI values are larger than 2 in most cases. The molar masses [obtained by size-exclusion chromatography (SEC)] alone can provide only a hint for the masses of the polymers because of the difference between the prepared macromolecules and the used calibration standards. In particular, MAA significantly influences the hydrodynamic volume and therefore the observed molar mass. With increasing amounts of incorporated MAA, the errors between the calculated molar masses and the values determined by SEC become progressively larger. Further characterization of the whole polymer series regarding final composition would be too time-consuming for a primary screening approach. Moreover, theoretical assumptions are not simply performed because of the complex terpolymer structure. Only advanced NMR investigations would provide an indication of the monomer composition.

To purify the prepared polymers, precipitation into non-solvents was the method of choice. The wide range of solubility properties of the materials caused by the varied compositions and used monomer combinations proved to be rather demanding in terms of optimizing the precipitation conditions. The more hydrophilic polymers were easily precipitated into

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Table 3. Composition (Feed Ratio) and Characterization Data for Polymer Series P3

polymer	EHMA:BzMA:MAA [mol %]	M_n [g mol^{-1}][a]	M_w [g mol^{-1}][a]	PDI[a]
P3-1	70:5:25	93 100	149 900	1.61
P3-2	60:15:25	105 500	164 600	1.56
P3-3	40:35:25	113 800	176 400	1.55
P3-4	30:45:25	96 000	156 500	1.63
P3-5	20:55:25	69 200	118 300	1.71
P3-6	10:65:25	75 900	147 200	1.94
P3-7	0:75:25	80 900	151 300	1.87
P3-8	76:8:16	114 400	205 920	1.80
P3-9	66:6:28	90 900	203 600	2.24
P3-10	72:14:14	98 200	203 300	2.07
P3-11	60:11:28	98 100	191 300	1.95
P3-12	62:23:15	121 000	216 600	1.79
P3-13	52:19:29	110 000	200 200	1.82
P3-14	48:36:16	110 100	215 800	1.96
P3-15	40:30:30	82 500	193 900	2.35
P3-16	54.5:5.5:40	106 300	203 033	1.91
P3-17	50:10:40	104 900	222 400	2.12
P3-18	40:20:40	111 800	210 200	1.88
P3-19	45.5:4.5:50	104 300	200 300	1.92
P3-20	42:8:50	111 200	201 300	1.81
P3-21	33:17:50	100 400	193 800	1.93
P3-22	36.3:3.6:60	101 400	200 800	1.98
P3-23	33.3:6.7:60	96 900	217 100	2.24

[a]Determined by SEC.

Table 4. Composition (Feed Ratio) and Characterization Data for Polymer Series P4

polymer	EHMA:HEMA:MAA [mol %]	M_n [g mol^{-1}][a]	M_w [g mol^{-1}][a]	PDI[a]
P4-1	10:60:30	136 500	377 500	2.76
P4-2	20:50:30	151 000	395 000	2.61
P4-3	30:40:30	122 000	346 000	2.83
P4-4	40:30:30	122 000	300 000	2.46
P4-5	10:50:40	122 000	367 000	3.00
P4-6	20:40:40	114 000	293 000	2.57
P4-7	30:30:40	144 000	417 000	2.9
P4-8	40:20:40	133 000	315 000	2.37
P4-9	5:35:60	137 000	269 000	1.96
P4-10	10:30:60	119 000	265 000	2.23
P4-11	20:20:60	136 000	250 000	1.84
P4-12	30:10:60	132 000	235 000	1.79
P4-13	5:15:80	108 000	204 000	1.90
P4-14	10:10:80	97 000	191 000	1.96
P4-15	15:5:80	90 000	186 000	2.05
P4-16	18:2:80	82 500	171 000	2.08

[a]Determined by SEC.

nonpolar solvents such as hexane, while the more hydrophobic materials were purified by precipitation into ethyl acetate.

The purified polymers were finally characterized by SEC to determine the molar masses and to ensure their monomodal distribution. Nevertheless, it has to be stated again that molar masses determined by SEC are only relative values calculated in correlation to a polymer standard, in this case poly(methyl methacrylate). The measured parameter represents the hydrodynamic volume of the dissolved polymer coils. Thus, the changing compositions prohibited a determination of reliable molar masses by SEC. However, the method allows a more or less accurate characterization of the polymers in a fast way and visualizes unexpected and undesired flaws in the molar mass distribution, such as shoulders due to chain coupling or tailing caused by termination.

Table 5. Composition (Feed Ratio) and Characterization Data for Polymer Series P5

polymer	EHMA:DEGMA:MAA [mol %]	M_n [g mol^{-1}][a]	M_w [g mol^{-1}][a]	PDI[a]
P5-1	10:60:30	125 500	750 500	6.00
P5-2	20:50:30	115 000	600 000	5.26
P5-3	30:40:30	168 000	497 000	2.96
P5-4	40:30:30	151 000	380 000	2.51
P5-5	10:50:40	151 000	503 000	3.33
P5-6	20:40:40	158 000	437 000	2.76
P5-7	30:30:40	150 000	381 000	2.55
P5-8	40:20:40	131 000	317 000	2.42
P5-9	5:35:60	115 000	363 000	3.16
P5-10	10:30:60	106 000	258 000	2.43
P5-11	20:20:60	144 000	330 000	2.28
P5-12	30:10:60	92 000	199 000	1.99
P5-13	5:15:80	87 000	188 000	2.14
P5-14	10:10:80	76 000	197 000	2.22
P5-15	15:5:80	79 000	151 000	1.91
P5-16	18:2:80	92 000	170 000	1.85

[a]Determined by SEC.

When the general solubility behavior of the prepared polymers is compared with the performance in the final application, an interesting issue can be observed. While one polymer can be insoluble in a chosen medium, the release of an encapsulated drug can take place anyhow. A reason for such an unexpected behavior can be the swelling of the coated film. Therefore, an application-inspired method has to be used to gain information about the release behavior. The present study makes use of parallel temperature-controlled UV−vis investigations to determine the pH-dependent release of a water-soluble test compound from a polymer film. Because of the desired application of such polymers as tablet coatings, the method for investigating the solubility properties was designed to mirror partially the application parameters. For this purpose, a UV−vis-detectable compound, β-naphthol orange, was encapsulated into the polymer film and exposed to aqueous media with varying pH values at 37 °C. An important advantage of this method is the small amount of polymer required. β-Naphthol orange has a similar solubility behavior as water-soluble drugs.

To perform these measurements with the least possible disturbance of the polymer material by the sample preparation, the films were applied directly to the bottom of the UV−vis cuvettes. This was done in a sandwichlike manner to avoid the influence of film detachment from the cuvette material. First, a polymer film was applied via drop-casting. This was followed by addition of the dye, which was subsequently covered by another polymer layer. A schematic description is provided in Figure 4. The layer-by-layer application of the polymer was chosen to avoid undesired dye release due to a possible simple detachment of the polymer film from the cuvette. Redissolution of the second polymer layer with the drug could not be avoided, but all of the samples were prepared in the same way and thus exhibited the same systematic error.

The exposure of coated tablets to environments with changing pH values, meaning first the acidic stomach followed

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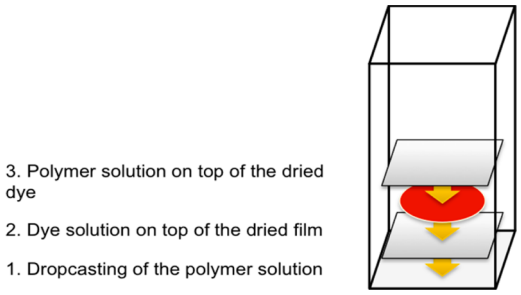

Figure 4. Schematic visualization of the sample preparation.

by the nearly neutral intestines, was simulated by applying aqueous buffer solutions with different pH values (1.2 and 6.8) for a certain amount of time. In addition to a pure aqueous environment, an alcohol-containing medium with 40% EtOH was tested. Upon exposure to this acidic or neutral medium, the changing dye concentration in the aqueous environment was followed by online UV−vis measurements. In this way, the time- and pH-dependent release kinetics for each material could be obtained, as shown for all polymer series in Figure 5. For polymer series **P1**, the pH responsiveness in the release behavior is clearly visible for most of the polymers in the nonalcoholic aqueous environment. The MAA moiety was found to be too hydrophilic for the given task, even in the protonated state, as can be observed by the loss of pH responsiveness for the samples **P1-11** to **P1-14**. The MAA content of these samples surpasses 35%, thereby changing the overall release behavior of the polymer to a state that is too hydrophilic. Therefore, the solubility of the polymer has to be tuned with much more nonpolar comonomers. In an alcohol-containing environment (40% EtOH), the pH-dependent release of the encapsulated dye is nearly lost for all polymers of this series. Nevertheless, the possibility to observe the influence of the polymer composition on the release performance with the chosen method is obvious. The increasing resistance against an alcohol-containing environment is correlated with the loss of pH-responsive release behavior. By comparison of the different release patterns of the different polymer series, a general correlation between the two properties is revealed. The slower the encapsulated dye is released from the film, the worse the performance under alcohol-free conditions.

The release performance of **P2** is similar to that of **P1**. Under alcoholic conditions, the encapsulated dye is released much faster. Most importantly, the pH responsiveness shown under alcohol-free conditions is nearly not observable anymore. Nevertheless, the influence of the two aliphatic monomers is as expected. The less nonpolar EA usually leads to decreased alcohol resistance (compare **P2-1**, **P2-7**, and **P2-10**). In comparison, samples with high contents of EHMA (e.g., **P2-3**, **P2-4**, and **P2-5**) show a relatively good resistance against EtOH. However, the pH responsiveness becomes insufficient for all samples with increasing EtOH content.

Polymer series **P3** shows the importance of sufficient amounts of MAA units in the polymer to ensure a pH-responsive behavior at all. Besides some exceptions, the general MAA content is too low in nearly all cases, as shown by the fact that the release behavior is nearly indifferent to the pH of the environment. Similarly to **P2**, a high EHMA content goes hand in hand with increased alcohol resistance due to the decreased overall polarity of the polymer.

The polymer samples of series **P4**, with MAA contents ranging from 30% up to 80%, show again the desired pH-responsive behavior, at least in alcohol-free media. Similar to the previous polymer series, in alcohol-containing media an increased release of the encapsulated dye is observed. This observation can also be made for the last series, **P5**, which is shown to have some pH responsiveness in alcohol-free media while losing that property in an EtOH-containing environment.

Although the alcohol resistance can be influenced and increased by choosing the right comonomers and compositions, no combination showing the desired properties at an EtOH content of 40% was found until now. Nevertheless, the developed workflow provides a promising method to investigate further combinations in a fast and efficient way in the future.

CONCLUSION

To study potential polymer candidates for tablet coating applications, the high-throughput synthesis of (meth)acrylate-based terpolymers was performed via free radical polymerization. Thus, minimal price (compared with controlled radical polymerizations), high reaction velocity, and decreased needs in terms of purity could be ensured, all of which are necessary requirements for HTE investigations. An appropriate HTE workflow to investigate the performance of the synthesized polymers as pH-responsive encapsulation materials was developed and applied. Parallel temperature-controlled UV−vis spectroscopy was used to reveal time-dependent dye release kinetics for multiple environments with different pH values and alcohol contents. Thus, the synthesized materials can be studied for potential application as materials for tablet coatings, which then enables fine-tuning of the drug release in specific regions of the human digestive tract. From the prepared materials, a perfect fit to the desired properties was not yet discovered. Nonetheless, certain samples can be seen as promising starting points for further investigations. The samples **P2-7** and **P2-8** still showed pH responsiveness even under increased contents of alcohol in the surrounding medium, while most other samples lost this property. In the **P4** and **P5** series, the samples **P4-1** and **P5-10** were the most promising candidates. Here, again the pH responsiveness was not lost when the alcohol content was raised. The mentioned polymers could still be triggered in their release behavior by changes in the pH value while providing a certain resistance against alcohol. In future investigations, also other alcohol concentrations (e.g., 10%, 20%, and 30%) will be investigated to find more promising candidates that can then be modified to work also at 40% ethanol. In addition, a more detailed polymer characterization will provide additional insights into structure−property relationships that are essential for the development of optimized products.

EXPERIMENTAL PROCEDURES

Materials. Unless specified otherwise, solvents were obtained from standard suppliers and used without further purification. BzMA, MAA, EHMA, and HEMA were provided by Evonik Industries. MA, EA, *t*BuA, and DEGMA were purchased from Aldrich. All monomers were passed over a column filled with Inhibitor Remover from Aldrich prior to use. Azobis(isobutyronitrile) (AIBN) was purchased from Aldrich and recrystallized from methanol.

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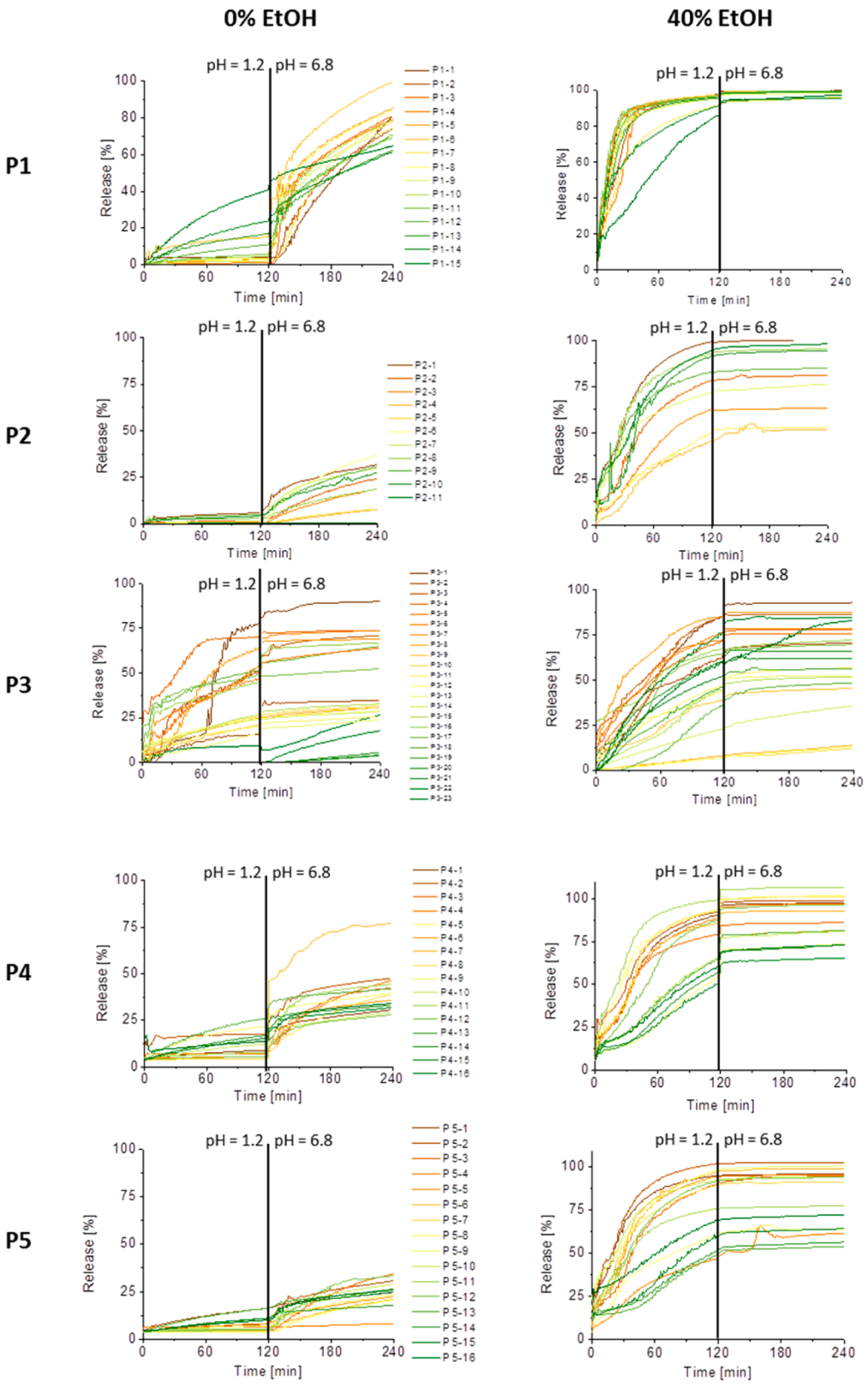

Figure 5. pH-dependent dye release of **P1** to **P5** in 0% and 40% EtOH.

Methods. SEC was performed on a Shimadzu system equipped with an SCL-10A system controller, an LC-10AD pump, and an RID-10A refractive index detector using a solvent mixture containing chloroform, triethylamine, and isopropanol (94:4:2) at a flow rate of 1 mL min^{-1} on a PSS-SDV-linear M 5 μm column at 40 °C. For polymers that were not soluble in chlorofrom, a second Shimadzu system was equipped with an SCL-10A system controller, an LC-10AD pump, an RID-10A refractive index detector, and both a PSS Gram30 and a PSS Gram1000 column in series, and *N*,*N*-dimethylacetamide with 5

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mmol of LiCl was used as an eluent at a flow rate of 1 mL min^{-1}. The system was calibrated with PMMA standards (2000 to 88 000 g mol^{-1}). The column oven was set to 60 °C. Dye release studies were performed via UV−vis spectroscopy with an Analytik Jena Specord 250 spectrometer with a heatable eight-cell changer at 37 °C at a wavelength of 485 nm.

General Procedure for the Free Radical Polymerization. In a representative example for **P3-23**, with [M]/[I] = 1000, EHMA (545 mg, 2.7 mmol), BzMA (55 mg, 0.31 mmol), MAA (400 mg, 4.6 mmol), and anisole (2.8 mL) were mixed in a microwave vial. AIBN (1.3 mg, 7.7×10^{-3} mmol) was added, and the vial was capped. The reaction mixture was flushed with argon for 30 min, placed in an oil bath, and heated to 80 °C for 3 h. Afterward, the solution was cooled to room temperature, and the polymer was obtained by precipitation into hexane.

Procedure for Dye Release Tests. In a representative example, the polymer was diluted in methanol (1 mg mL^{-1}), and β-napthol orange was diluted in water (2.5 mg mL^{-1}). The polymer solution (50 μL) was applied to the bottom of a UV−vis cuvette. After complete drying, 25 μL of the dye solution was distributed homogeneously on top of the formed polymer film and left to dry. Subsequently, the dried dye was covered with a second layer of the polymer solution (50 μL). Again, the sample was allowed to dry at room temperature. Afterward, 2 mL of HCl (0.1 mol L^{-1}) was added to the cuvette. The UV−vis measurement started immediately and was performed for 120 min at 37 °C. Subsequently the acidic medium was removed and replaced by 2 mL of phosphate-buffered saline (pH 6.8), followed by a second UV−vis measurement period of 2 h. The same experiment was equally performed in an acidic medium containing 40 vol % ethanol.

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Notes

The authors declare no competing financial interest.

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