

3.3. ZEIN – SHELLAC MIXED COATINGS

3.3.1. Compatibility of zein and shellac in mixed films

At organoleptic inspection zein and shellac were compatible with increasing shellac amount up to a ratio of zein:shellac 1:2, corresponding 66% shellac in the mixture (Table 17). Above this ratio, the films exhibited signs of separation with waxy drops distributed over the film. Therefore zein-shellac mixed coatings were investigated at the ratios 9:1, 4:1, 2:1, 1:1 and 1:2.

Table 17 Compatibility of zein-shellac mixed films cast from ethanolic solution

Zein-shellac ratio	Compatibility
9:1	+++
6:1	+++
4:1	++
2:1	+
1:1	+/-
1:2	+/-
1:4	-
1:6	-
1:9	-

+++ : clear film

++ : waxy drops on the edge

+ : waxy drops on 1/3 of the film

+/- : waxy drops on 2/3 of the film

--- : no clear film parts, overall signs of separation

3.3.2. Drug release from zein-shellac mixed coatings

In pH1.2 the fast drug release from pure zein coated pellets was decreased with increasing shellac ratio in the mixed films (Fig. 36A). However, an at least ratio of zein:shellac 2:1 was required, that a remarkable retardation of the drug release was possible. At the ratio

zein:shellac 1:2 already gastric resistance was achieved. However, even at this high shellac content the proteolytic enzyme pepsin still exerted an enhancing effect on the drug release, what can be attributed to the presence of zein in the films (Fig. 36B). Zein as a water-insoluble protein is sensitive to proteolytic degradation (Katayama and Kanke, 1992).

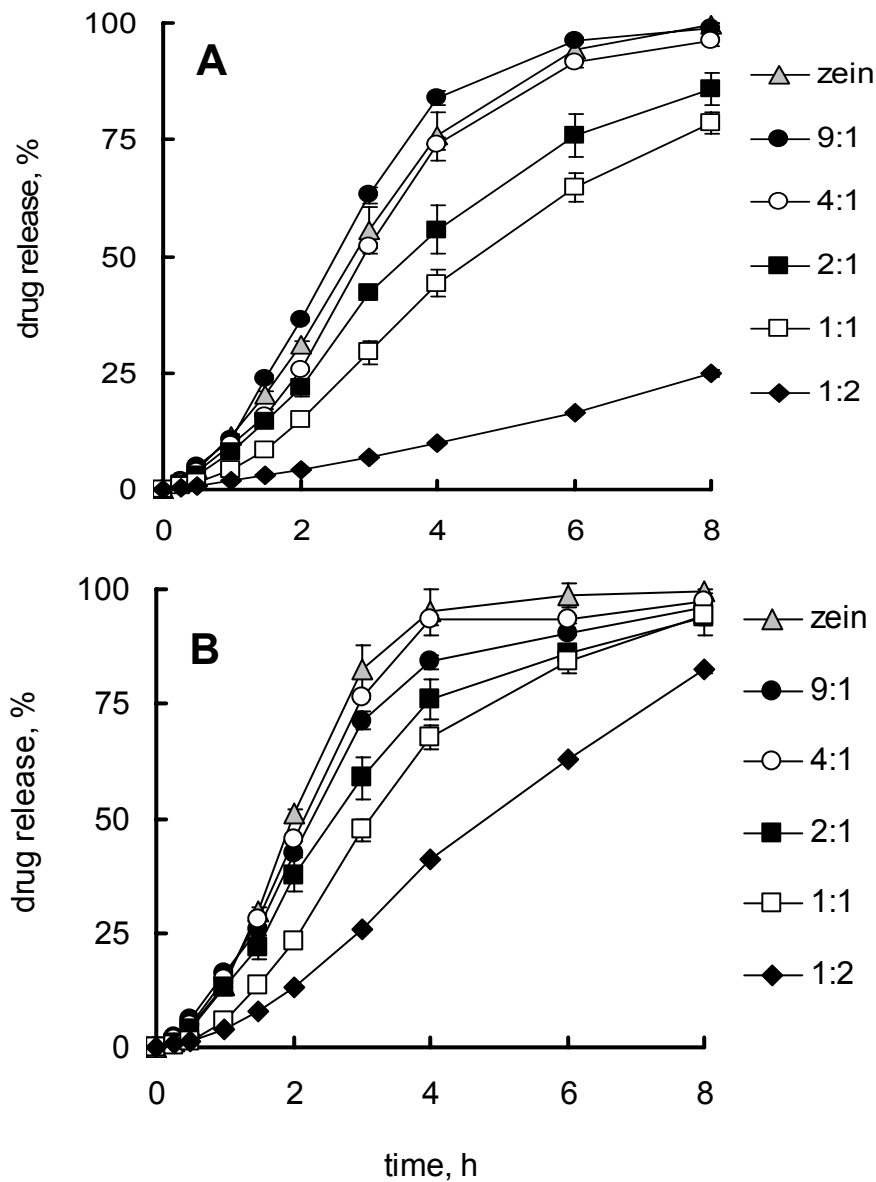


Figure 36 Drug release from coated pellets with pure zein vs. mixed films at different zein-shellac ratios: A: in pH 1.2, B: in pH 1.2+pepsin (model drug: theophylline; coating level: 20 %)

In pH6.8 the drug release from all formulations was similarly low (Fig. 37A). This can be attributed to the slow dissolution of shellac at this pH, due to the high pKa of shellac (6.9-7.5) (Hogan, 1995a). At pH7.4 the dissolution of shellac is improved and the drug release increases with increasing shellac ratio (Fig. 37B).

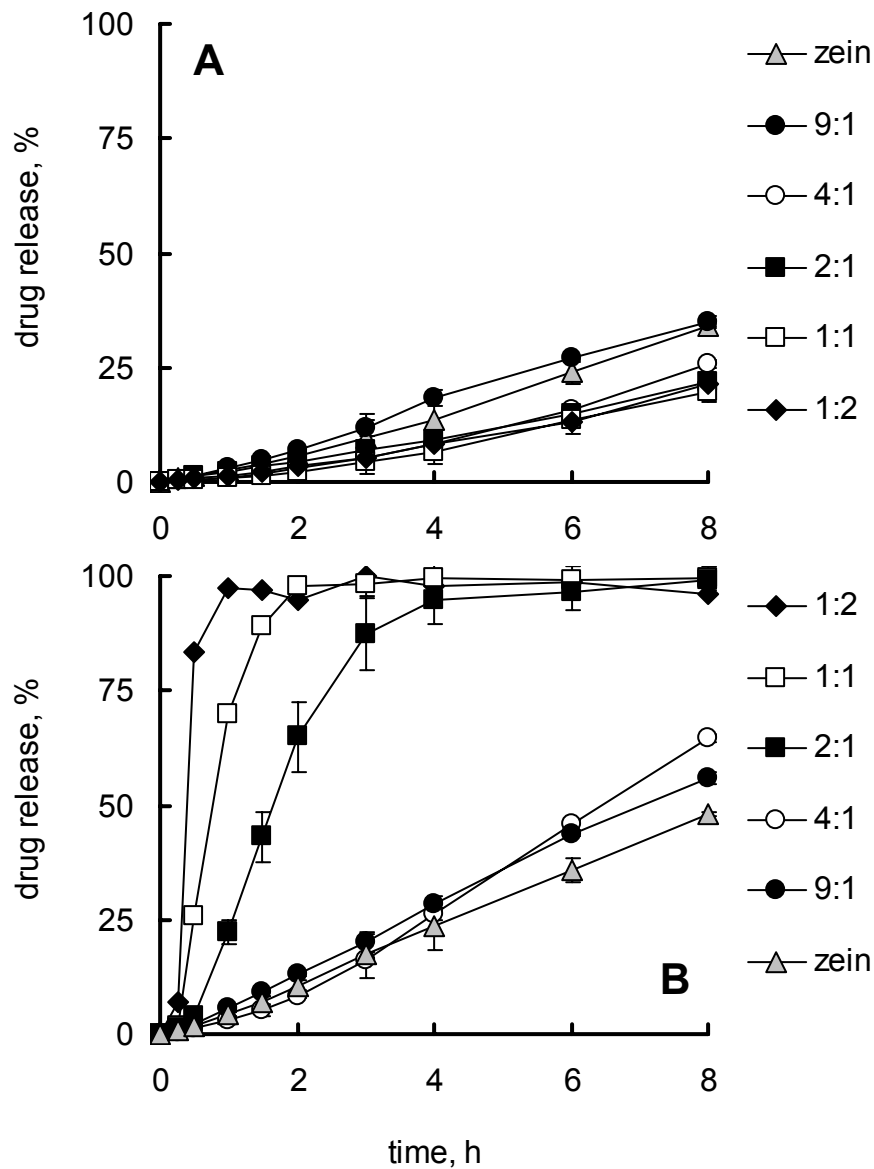


Figure 37 Drug release from coated pellets with pure zein vs. mixed films at different zein-shellac ratios: A: in pH 6.8, B: in pH 7.4 (model drug: theophylline; coating level: 20 %)

The best ratio for extended release over the entire pH-range of the slightly soluble model drug theophylline was zein:shellac 2:1 (Fig. 38). At 2 h in pH 1.2 followed by 6 h in pH 6.8 the drug release was controlled during the entire time.

However, the drug release with pH-change after 2 h from pH 1.2 to pH 6.8 followed the same profile as the release in only pH 1.2 during 8 h. The drug release was not slowed down or further retarded after the pH-change, as it could be expected, if compared to the release only in pH 6.8. The swelling of the film in pH 1.2 determined the drug release. The permeability of the film remained unaffected by the surrounding medium in the swollen state, and did not revert to a condition of lower swelling (Oh and Flanagan, 2003).

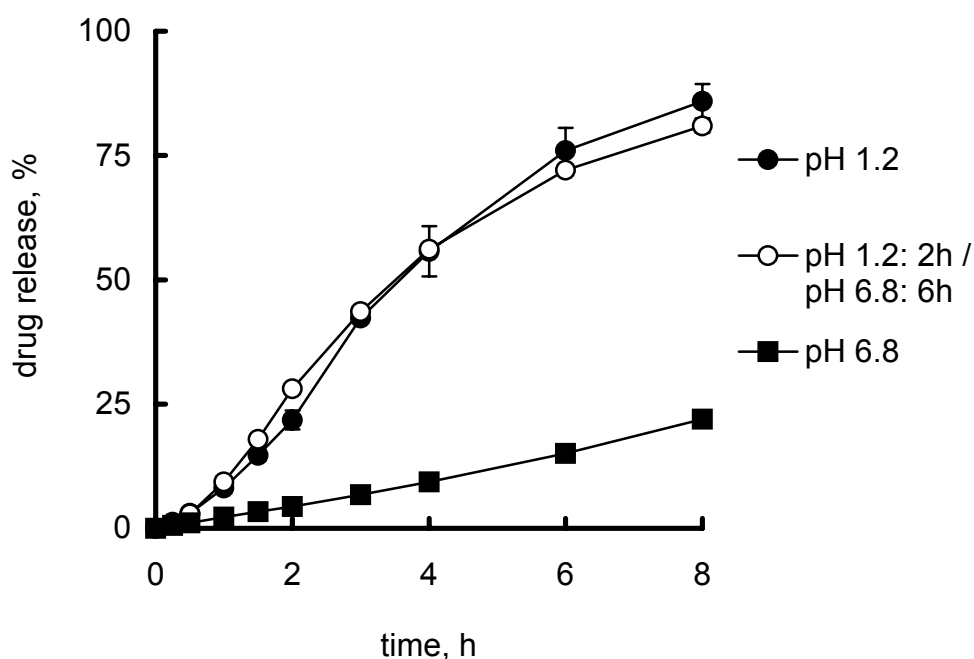


Figure 38 Drug release from zein-shellac mixed coated pellets with or without medium change (model drug: theophylline; zein-shellac ratio: 2:1; coating level: 20 %)

3.3.3. Effect of swelling on the mechanical properties and drug release

In pH 1.2, the increase in diameter of coated pellets decreased with increasing shellac content after incubation. Several hours were necessary to reach the plateau for pure zein films and zein-shellac 9:1, where no further swelling was observed. Films with higher shellac

content were not further swelling after 30 min incubation time (zein-shellac ratios 4:1, 1:1 and 1:2) (Fig. 39+40).

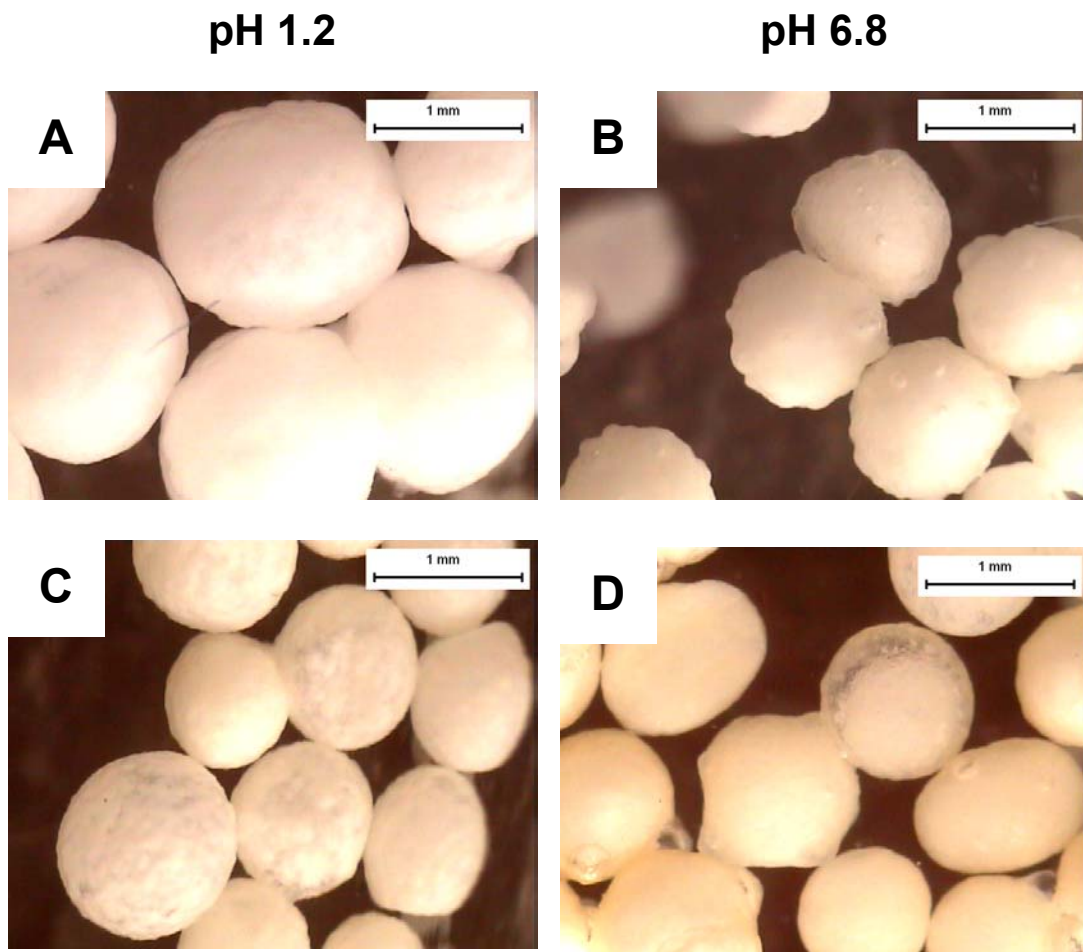


Figure 39 Macroscopic pictures of coated theophylline pellets after 6 h swelling in A: pH 1.2, pure zein; B: pH 1.2, zein-shellac 2:1; C: pH 6.8, pure zein and D: pH6.8, zein-shellac 2:1 (coating level: 20 %)

The increase in diameter of coated pellets depended on the swelling of the film coating itself as well as on the mechanical properties of the film. Osmotic pressure was built up inside the pellets during drug release, resulting in a size increase relative to the flexibility of the film. Both parameters were investigated on isolated films to explain the swelling behaviour of the coated pellets. The swelling of isolated zein-shellac mixed films was similar up to a ratio of 1:1. Remarkable decrease in the swelling of the pellets was observed at the ratio 1:2, which correlated to the biggest change in the drug release. (Fig. 36A vs. 40B).

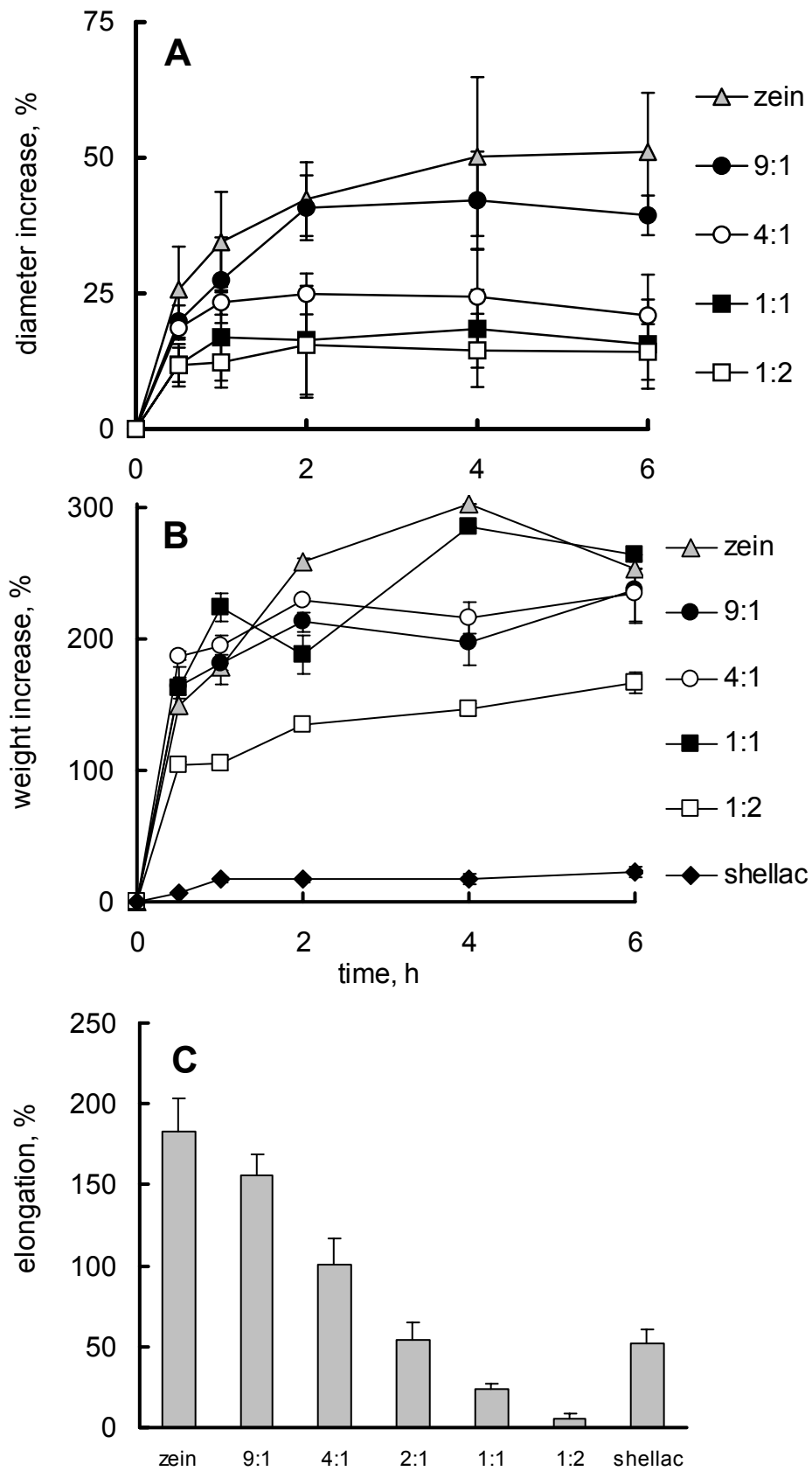


Figure 40 Effect of zein-shellac ratio on the swelling and mechanical properties: A: diameter increase of coated theophylline pellets, B: swelling of films in pH 1.2 and C: elongation of films after 2 h incubation in pH 1.2

The elongation of the films decreased with increasing shellac content due to a decrease in flexibility. The elongation for the zein-shellac ratios 1:1 and 1:2 was even less than for pure shellac films. This may be related to the starting incompatibility of the polymers at these compositions (Table 17).

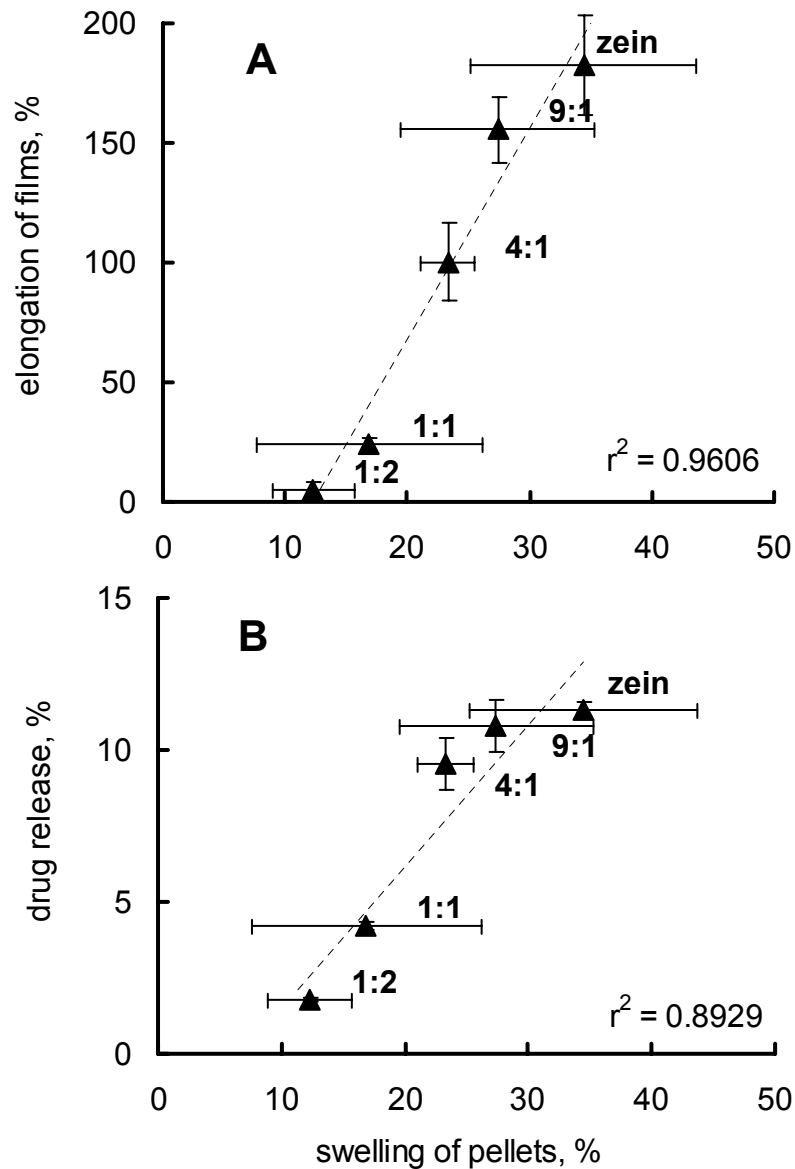


Figure 41 Correlation of the swelling of coated theophylline pellets to: A: elongation of isolated films after incubation and B: drug release after 1 h at different zein-shellac ratios (coating level: 20 %; medium: pH 1.2)

The elongation of the isolated films was linearly correlated to the swelling of the coated pellets ($r^2=0.9606$) (Fig. 41A). This proved the strong influence of the mechanical properties

of the films on the resulting swelling, while the extent of swelling showed linear relationship ($r^2=0.8929$) to the drug release from the coated pellets (Fig. 41B).

3.3.4. Influence of the drug solubility

To prove the concept of extended release by zein-shellac mixed coatings, the release of the freely soluble model drug CPM was investigated. As already found for theophylline, the drug release decreased with increasing shellac content (Fig. 42).

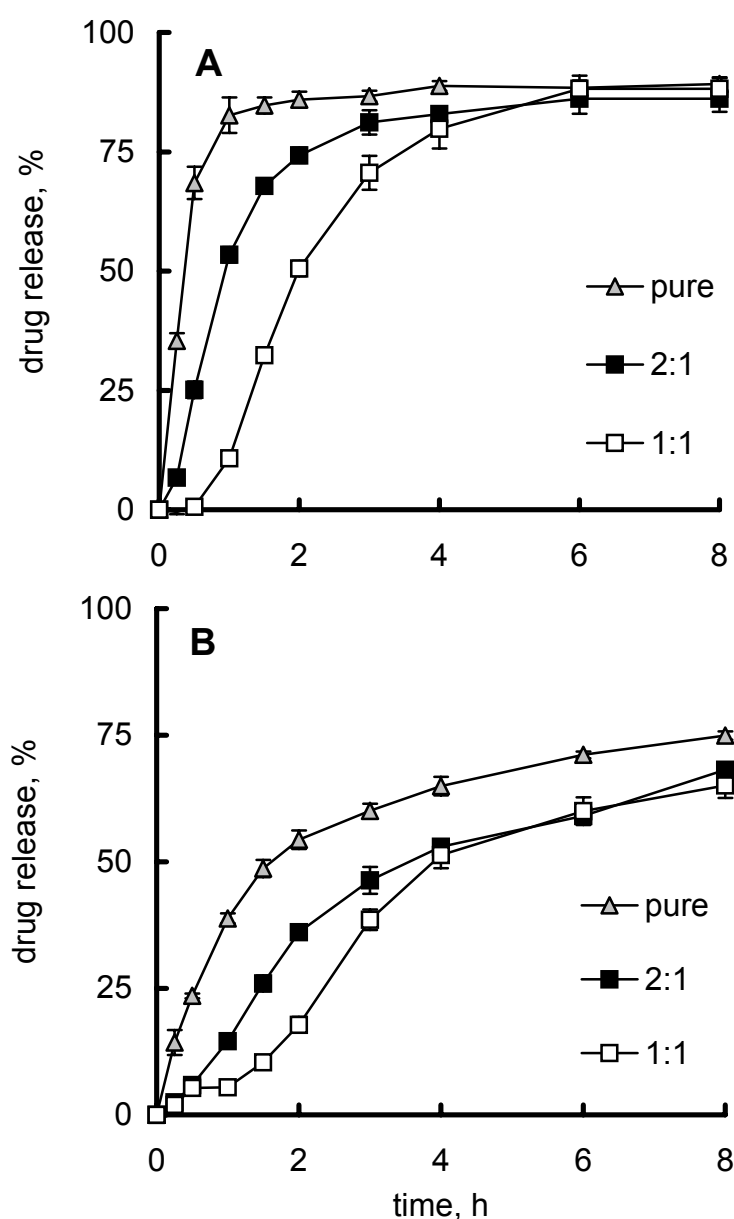


Figure 42 CPM release from coated pellets with pure vs. mixed coatings at different zein-shellac ratios in: A: pH 1.2; B: pH 6.8 (coating level: 20 %)

However, the ratio needs to be adjusted according the drug solubility to achieve extended drug release, as at the same zein-shellac ratio the retardation of the freely soluble CPM was less than of the slightly soluble theophylline. In pH6.8 the drug release was further decrease with increasing shellac ratio (Fig. 42B).

3.3.5. Stability on storage

Shellac is prone to self-polymerization on storage, leading to prolonged disintegration times and a slow down in drug release (Hogan, 1995b). This effect is more pronounced, if it is applied from ethanolic solution (Hogan, 1995b; Signorino, 1973; 2003; Specht et al., 1998). The drug release decreased on storage. The effects were stronger with increasing shellac amount in the coating and was observable in simulated gastric medium (pH 1.2) (Fig. 43) as well as simulated intestinal medium (pH 7.4) (Fig. 44).

However, the drug release was still determined by the swelling of the film in the initial release medium. The consecutive drug release with pH-change from pH 1.2 to pH 6.8 after 2 h followed the release as only in pH 1.2 (Fig. 45). The permeability of the film was still unchanged after reaching the swollen state, and did not revert to a condition of lower swelling (Oh and Flanagan, 2003).

Curing (thermal after-treatment) may induce the self-polymerization reaction, resulting in stable release profiles in a shorter time, which otherwise is achieved at storage after longer time periods (Johnston et al., 1966).

Pellets were cured at elevated temperature after the coating process and compared to the release profiles after 12 months storage at ambient temperature. The release profile was unchanged compared to the uncured pellets even after 7 days curing at 40 °C, whereas the drug release from pellets cured at 60 °C gradually decreased (Fig. 46). The drug release profile matched that of the uncured pellets after 12 m storage after 5 d curing at 60 °C. Longer curing times (7 d) did not alter the release profile further.

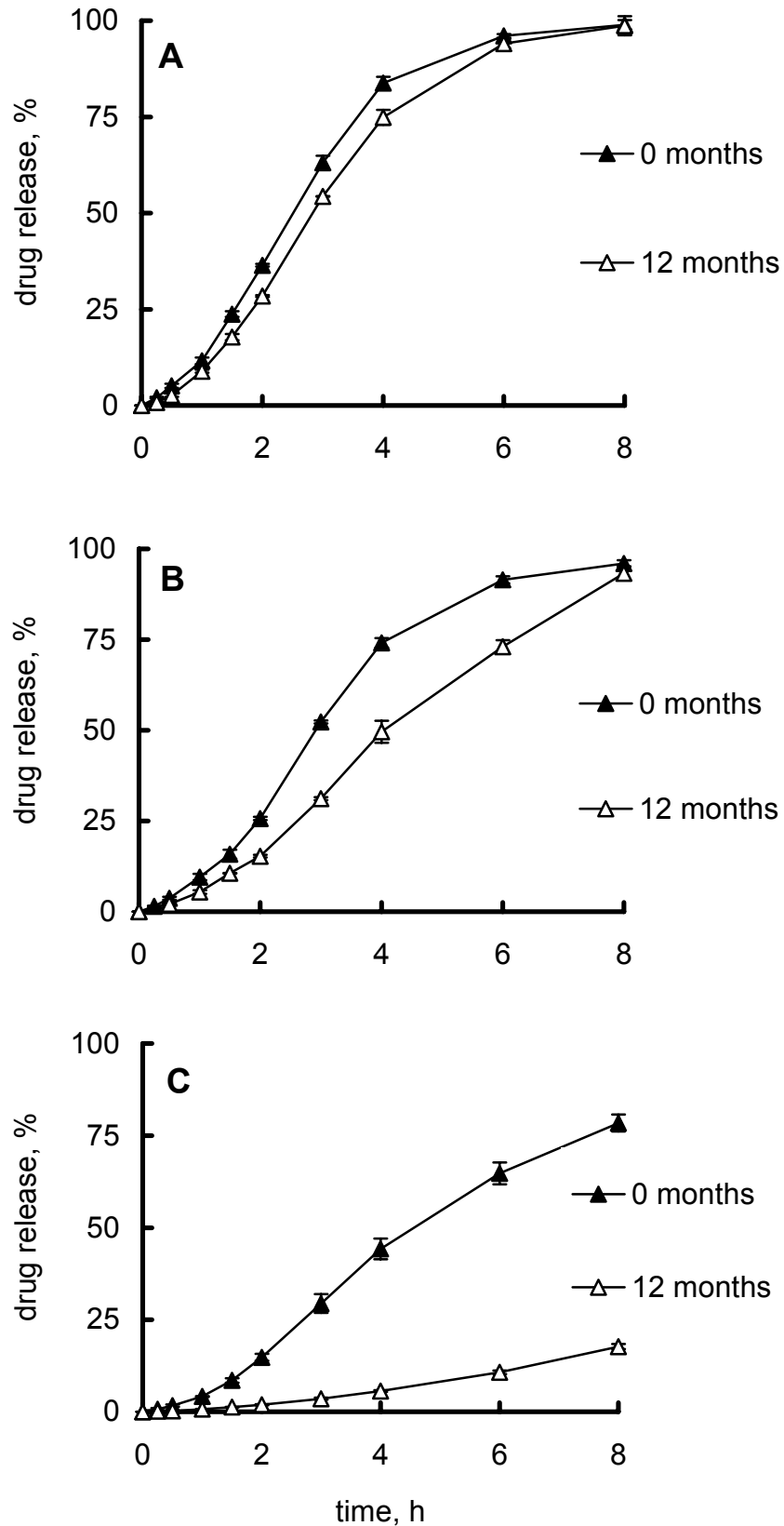


Figure 43 Drug release from zein-shellac mixed coated pellets after 12 months storage at the ratios: A: 9:1; B: 4:1; C: 1:1 (model drug: theophylline; coating level: 20 %; release medium: pH 1.2; storage at ambient conditions)

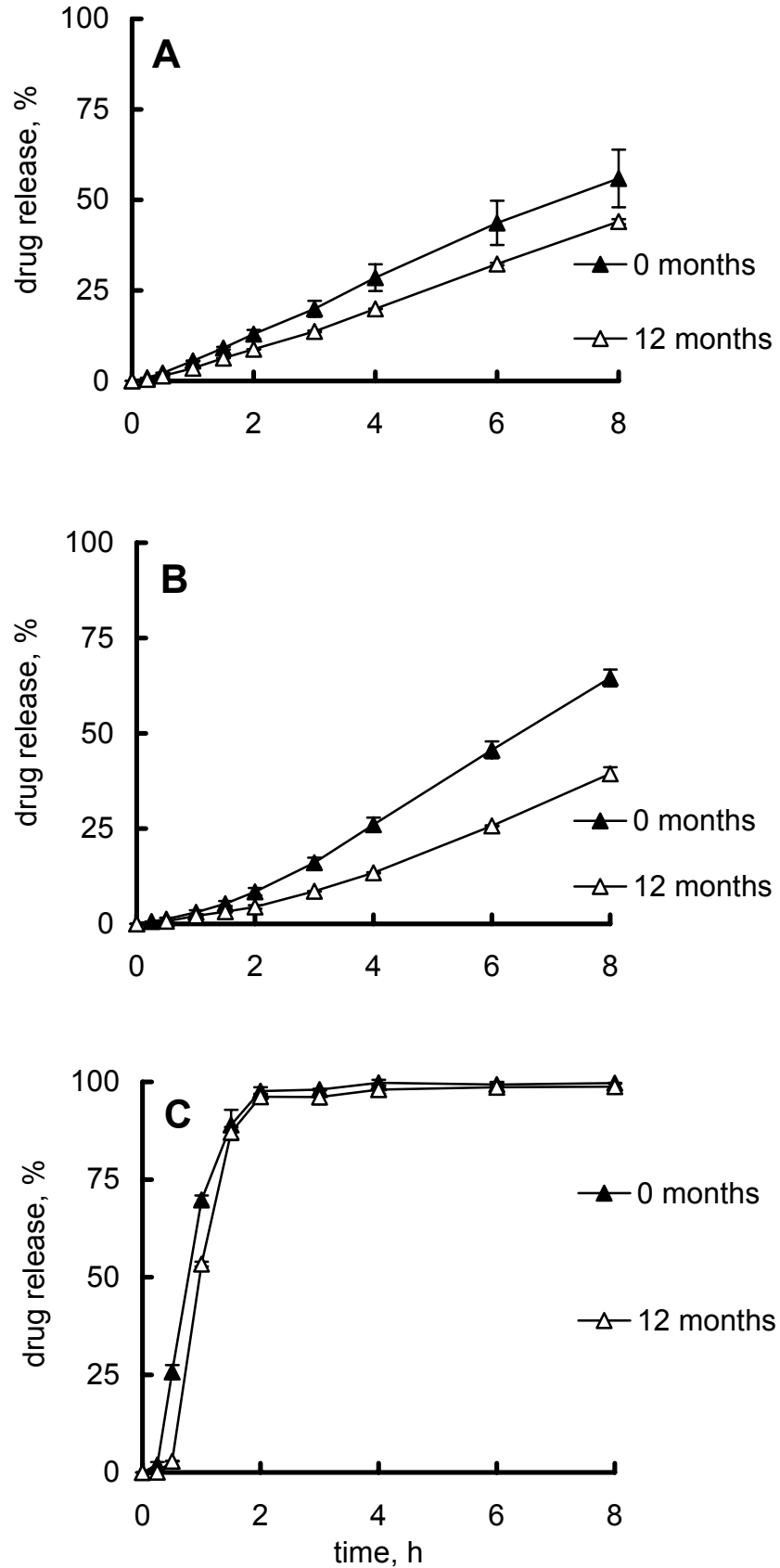


Figure 44 Drug release from zein-shellac mixed coated pellets after 12 months storage at the ratios: A: 9:1; B: 4:1; C: 1:1 (model drug: theophylline; coating level: 20 %; release medium: pH 7.4; storage at ambient conditions)

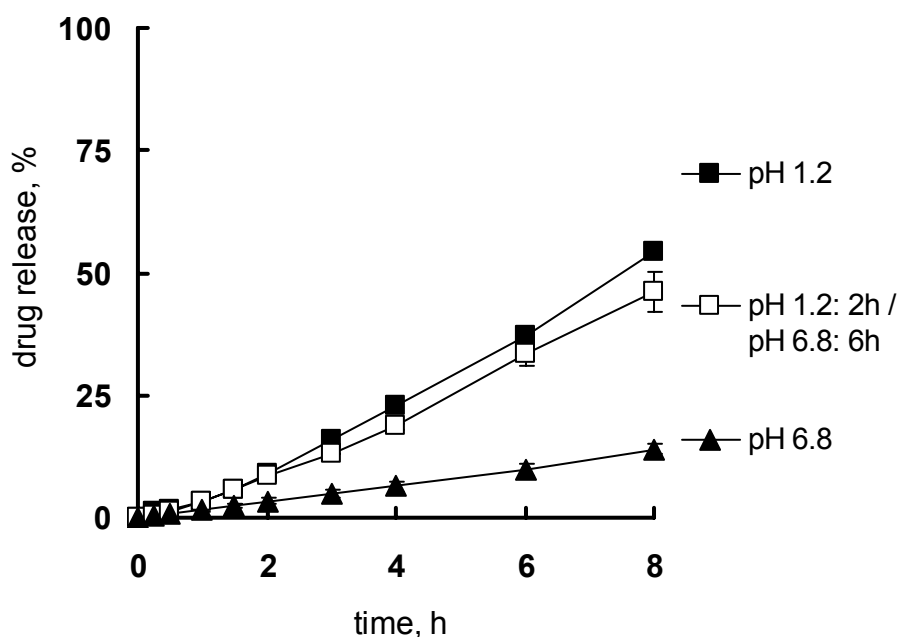


Figure 45 Drug release from zein-shellac mixed coated pellets after storage with or without medium change (model drug: theophylline; zein-shellac ratio: 2:1; coating level: 20 %; storage: 12 months at ambient conditions)

Curing at 80 °C resulted in sticking of the pellets, however after 2 h and 24 h a separation of the pellets was still possible. After 2 h the drug release was not affected while after 24 h the drug release was decreased as after storage (Fig. 46). The pellets could only be separated with strong mechanical impact after longer curing time and the drug release was enhanced as a result of the damage of the coat.

Aqueous solutions of shellac as alternative to ethanolic coating solutions are reported to prevent such instability on storage without necessitating a curing step after the coating process (Signorino, 2003; Specht et al., 1998).

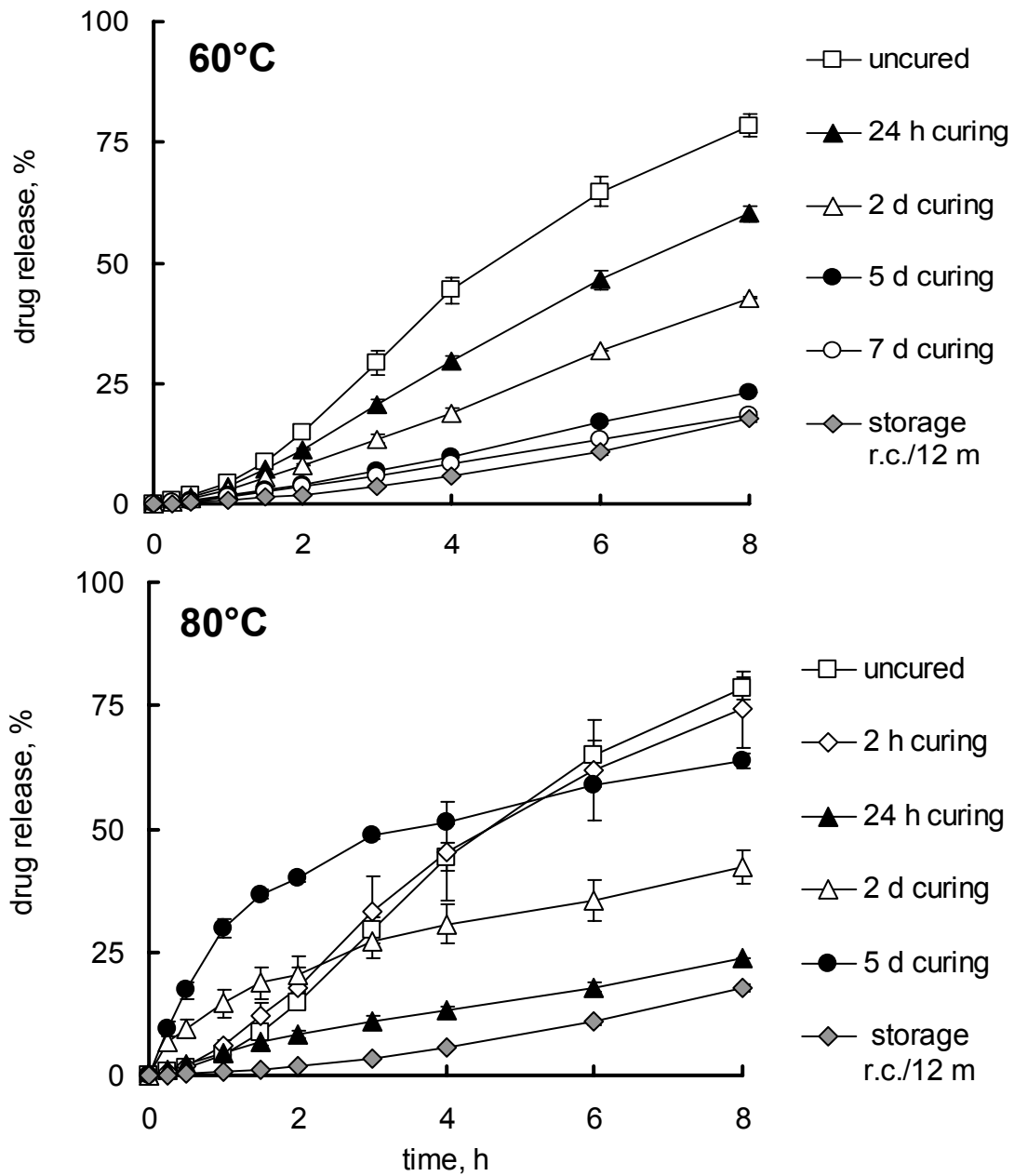


Figure 46 Effect of curing at 60 °C or 80 °C vs. storage at room conditions (r.c.) on the drug release from zein-shellac mixed coated pellets (model drug: theophylline; coating level: 20 %; release medium: pH 1.2)

3.4. SHELLAC TOPCOATS

Topcoats of enteric polymers over zein coatings were described to effectively reduce the fast drug release of pure zein coatings at low pH and sustain the action of the incorporated active over an extended period of time (Mazer et al., 1992). Shellac as a gastric resistant polymer seemed promising to reduce the rapid drug release of zein coatings in the gastric medium. Complete suppression of the drug release in pH 1.2 was achieved already at low coating levels of shellac (Pearnchob et al., 2003a). In a topcoat system shellac can form a continuous film, thus a strong decrease of the drug release of zein-coated pellets was expected.

3.4.1. Pure shellac topcoats

Topcoatings of shellac over zein coatings decreased the drug release in pH 1.2 (Fig. 47A). Gastric resistance was achieved at a topcoating level of only 2%. However, the drug release also decreased in pH 6.8, because of the slow dissolution of shellac (Fig. 47B). Shellac has a pKa of 6.9-7.5 (Hogan, 1995a) and thus dissolved more readily in pH 7.4 compared to pH 6.8 (Fig. 47C).

The decrease in drug release was related to a decrease in swelling, as could be observed on the coated pellets after incubation in pH 1.2 (Fig. 48 and 49). Shellac is a much tougher polymer than zein and thus resists higher puncture strengths (Fig. 50A). Zein, especially in the wet state is very soft (low puncture strength and modulus) and highly flexible (high elongation) (Fig. 50B), due to its higher extent of swelling in comparison to shellac, as quantitated by the medium uptake (Fig. 51). Therefore shellac is able to effectively inhibit the swelling of zein even at very low coating levels.

However, such a process is highly susceptible as small changes in the coating level will dramatically influence the resulting drug release profile. This makes an effective control of the product quality difficult.

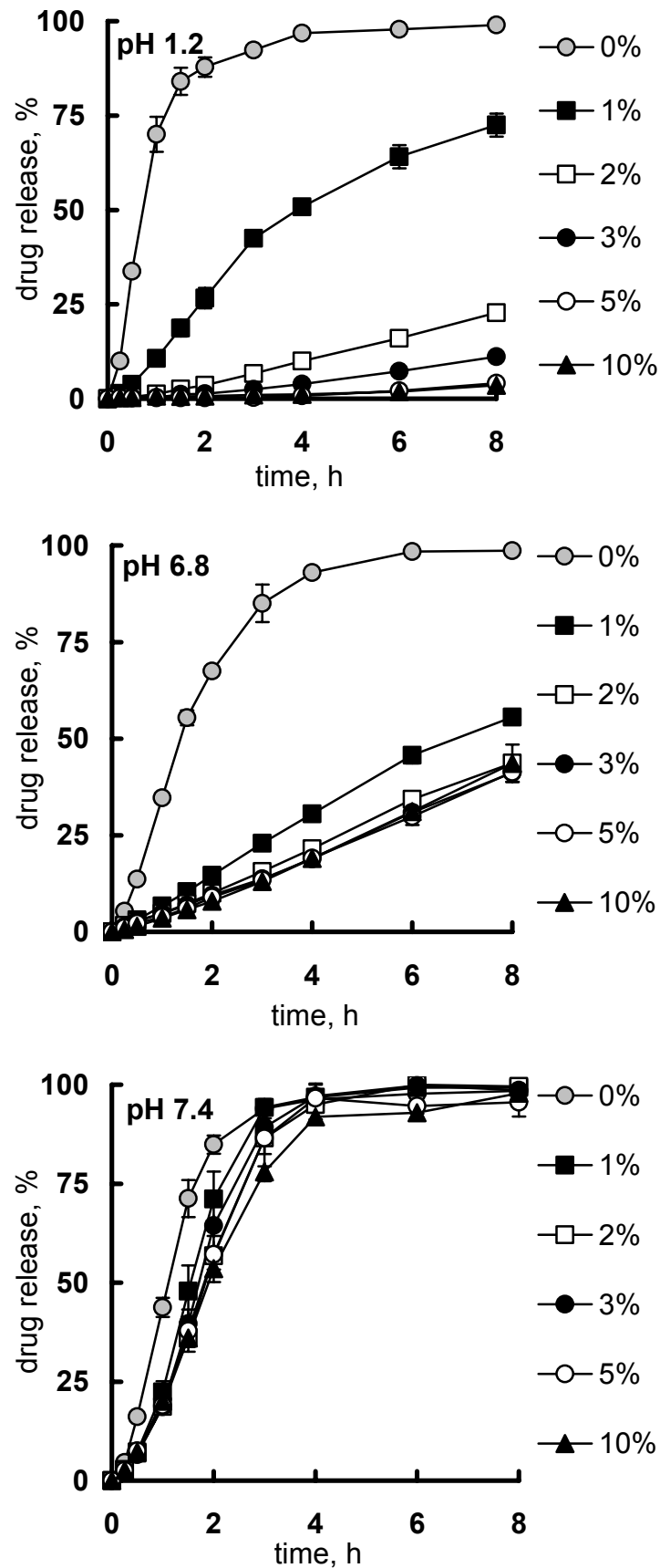


Figure 47 Drug release from zein-coated pellets with a shellac topcoat in pH 1.2, pH 6.8 and pH 7.4 (model drug: theophylline; zein coating level: 10%; topcoat level: 0-10%)

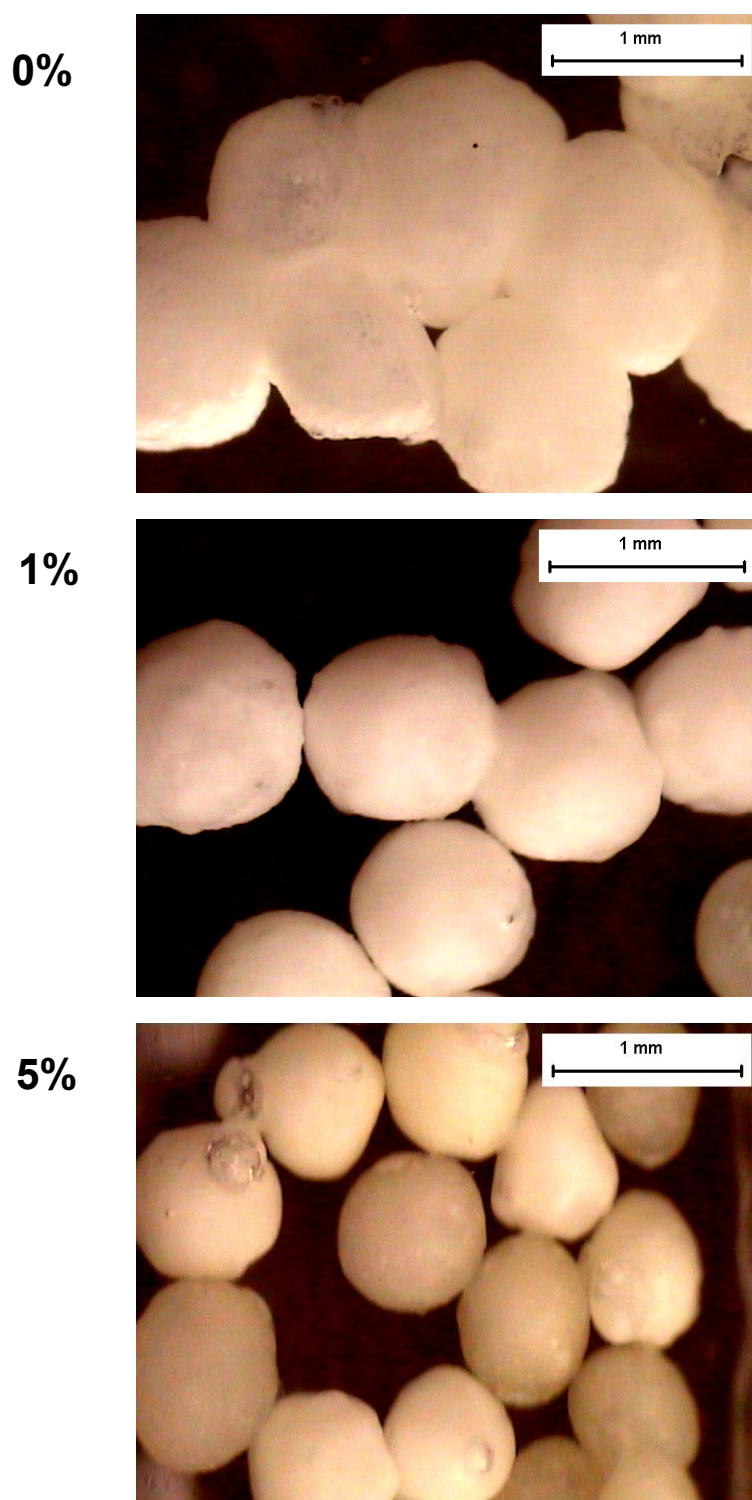


Figure 48 Microscopic pictures of zein coated pellets with 0 %, 1 % and 5 % shellac topcoat after incubation (zein coating level: 20 %; medium: pH 1.2; incubation time: 6 h)

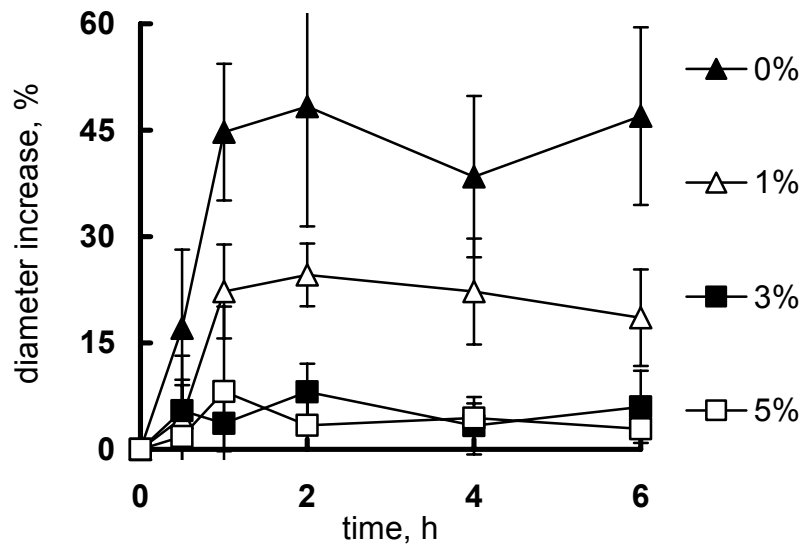


Figure 49 Effect of a shellac topcoat on the increase in diameter after swelling of zein coated pellets in pH 1.2 (zein coating level: 10 %; topcoat level: 0-5 %)

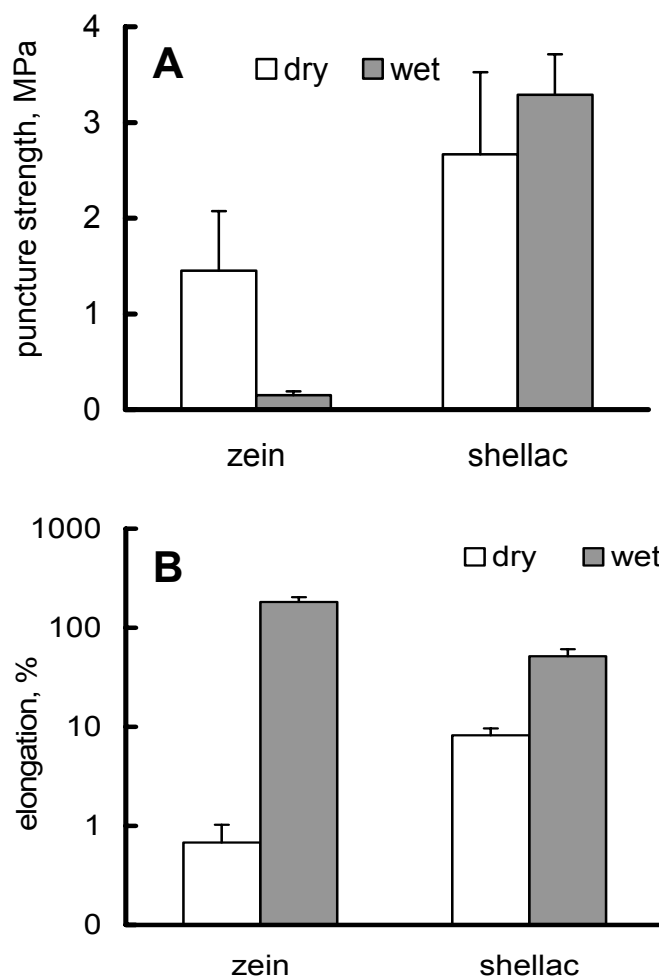


Figure 50 Mechanical properties of thin isolated films of zein and shellac in the dry and wet state: A: puncture strength; B: elongation (wet state: 2 h incubation in pH 1.2)

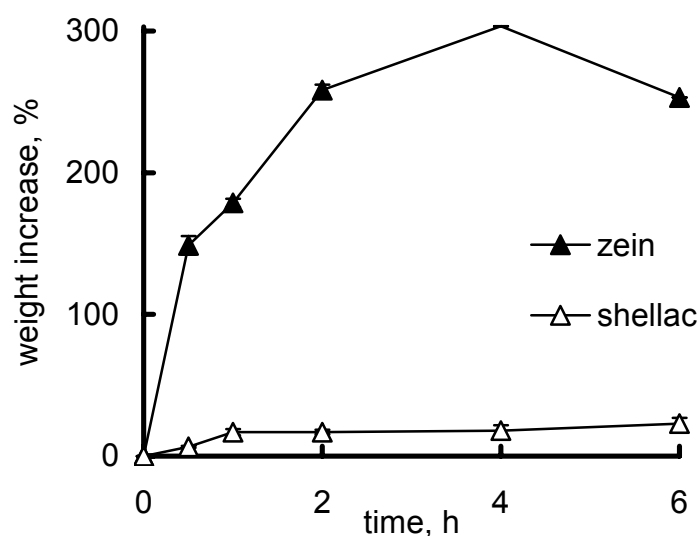


Figure 51 Medium uptake over time of thin films of zein and shellac (medium: pH 1.2)

3.4.2. Shellac topcoats of higher permeability

A coating process with improved control of the drug release can be achieved by altering the composition of the shellac topcoat. The idea was to develop a formulation with gradually decreasing drug release related to the coating level resulting in better predictable product properties. This can be accomplished by a more permeable coating, where the drug release is decreased stepwise with increasing coating level.

a. Shellac-HPMC topcoats

Water soluble HPMC was added to the topcoat to increase its permeability. The drug release was slightly increased with 25 % HPMC in the topcoat compared to the pure shellac (Fig. 52). Nevertheless, 5 % coating level of the topcoat was again sufficient to obtain gastric resistance in pH 1.2 with still strong retardation in pH 6.8 compared to pH 7.4.

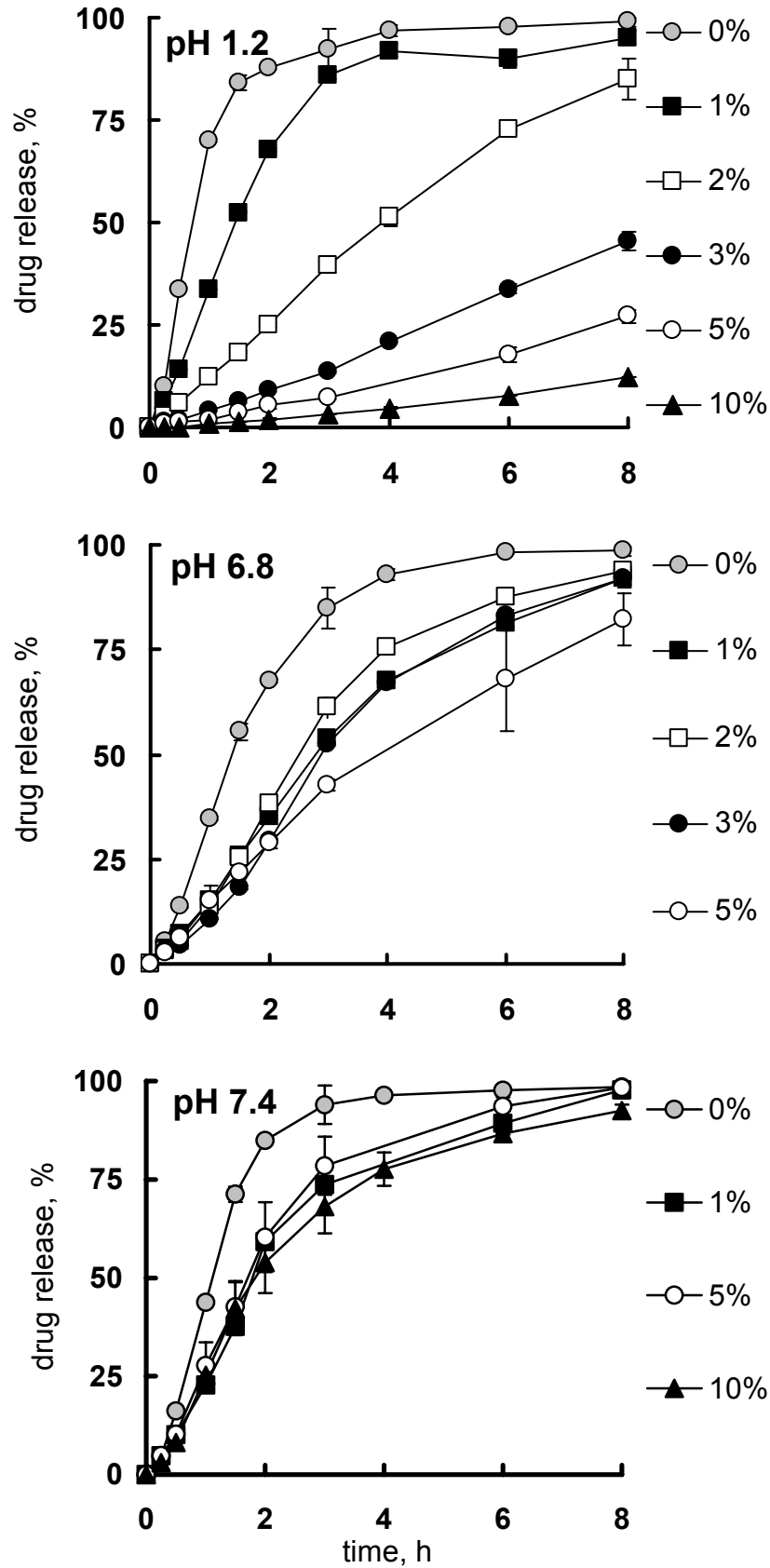


Figure 52 Drug release from zein-coated pellets with a shellac topcoat containing 25 % HPMC in pH 1.2, pH 6.8 and 7.4 (zein coating level: 10 %; topcoat level: 0-10 %)

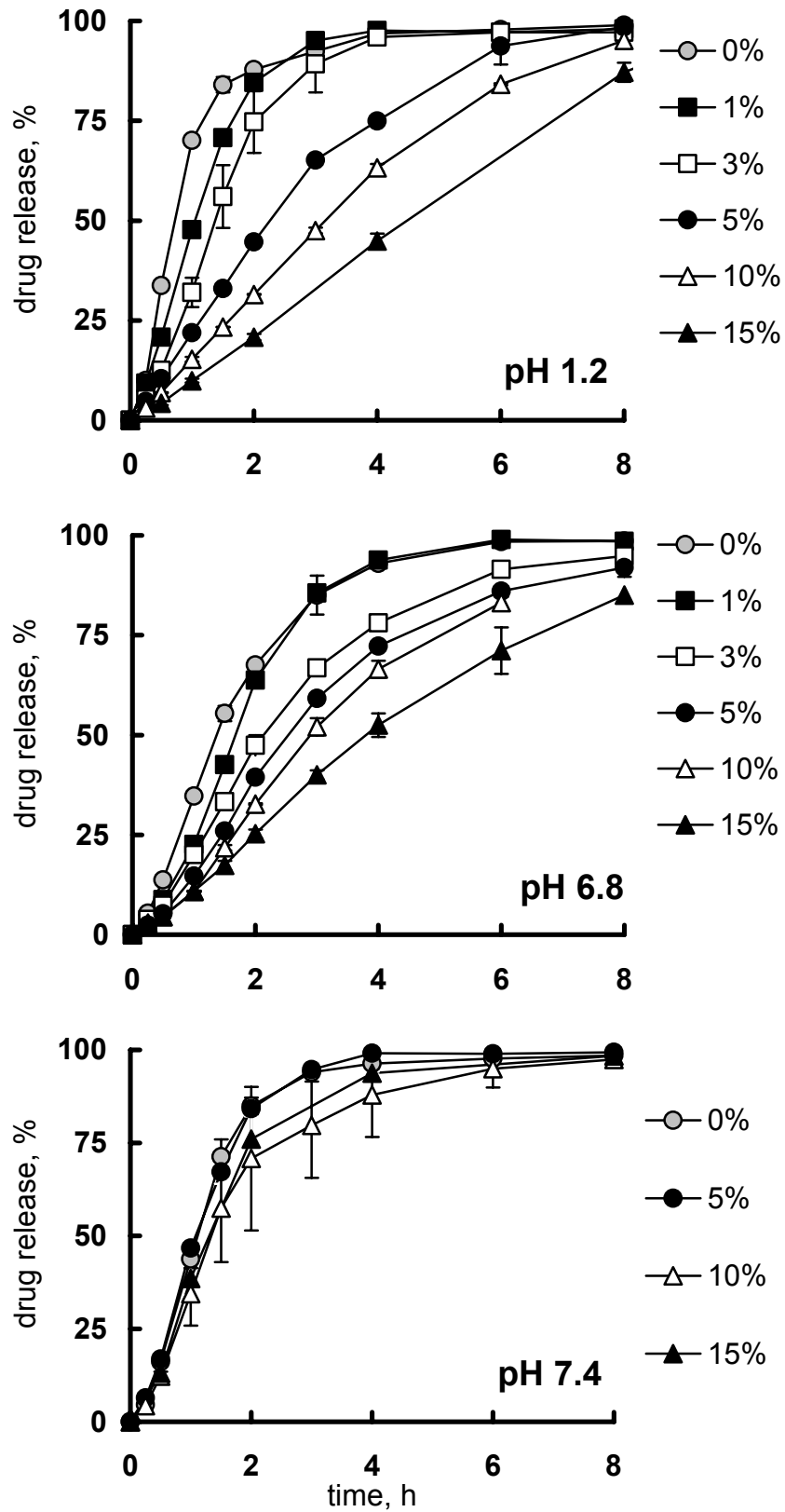


Figure 53 Drug release from zein-coated pellets with a shellac topcoat containing 50 % HPMC in pH 1.2, pH 6.8 and pH 7.4 (zein coating level: 10 %; topcoat level: 0-15 %)

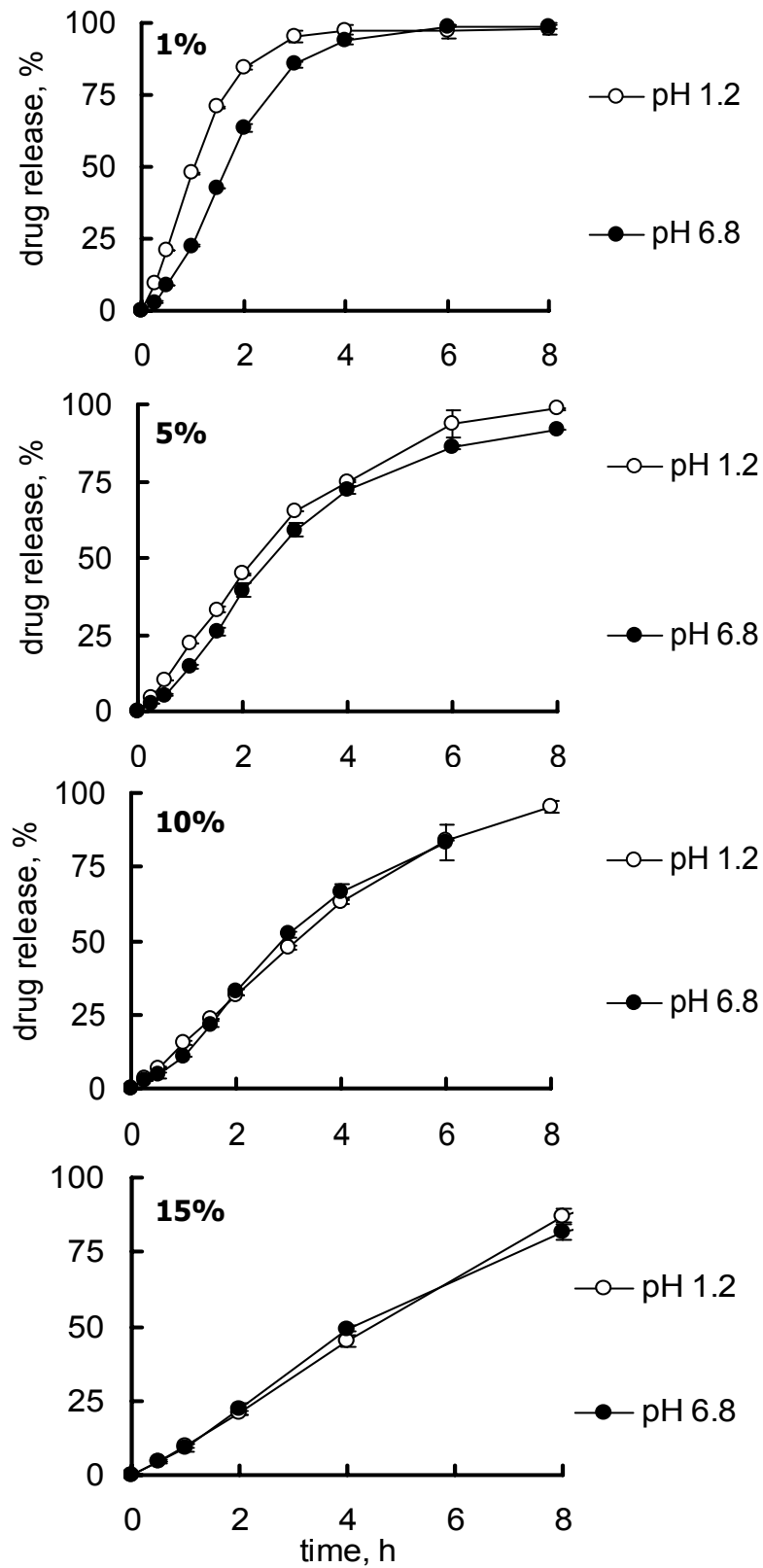


Figure 54 Comparison of the drug release in pH 1.2 vs. pH 6.8 from zein-coated pellets with a shellac topcoat containing 50% HPMC (zein coating level: 10%; topcoat level: 0-15%)

3. Results and Discussion

A 50 % ratio of HPMC in the topcoat formulation decreased gradually the drug release with increasing coating level, both in pH 1.2 and pH 6.8 (Fig. 53).

The release profile of the drug in the two media was identical above a coating level of 5 % (Fig. 54). The retardation of the drug release in pH 6.8 was still observed in contrast to the release in pH 7.4, where no significant retardation occurred (Fig. 53).

Shellac dissolves only slowly at pH 6.8, because of its pKa value of 6.9 (Hogan, 1995a), and leads to a retardation of the drug release at this pH (Fig. 47, 52, 53). HPMC in the mixture with shellac even at a ratio of 50 % was not able to render the topcoat such permeable, that the drug release was not further affected by the undissolved shellac in pH 6.8 (Fig. 53).

The hydration of the HPMC in pH 6.8 seems to be inhibited by the shellac in the mixed topcoat, as confirmed by microscopic pictures (Fig. 55). No gelation or swelling was observed in pH 6.8, whereas the gelation of HPMC in pH 7.4 is not inhibited and leads to a fast dissolution of the topcoat, not affecting the drug release in this medium (Fig. 53 vs. 55).

To investigate the effect of the drug solubility, the release of CPM was compared to theophylline. CPM was shown to be released faster from zein coated pellets in comparison to theophylline, due to the higher solubility of the drug (CPM: freely soluble; theophylline: slightly soluble; Fig. 15).

Pure shellac topcoats were able to decrease the CPM-release in pH 1.2 at low coating levels, but slightly retarded the release in pH 6.8, too (Fig. 56).

Shellac-HPMC mixed topcoats however were not able to significantly retard the fast drug release in pH 1.2 of CPM-loaded pellets, even at a ratio of shellac-HPMC 4:1 (Fig. 57), whereas a pure shellac topcoat suppressed the drug release in pH 1.2 for 6 h at a coating level of only 5 %.

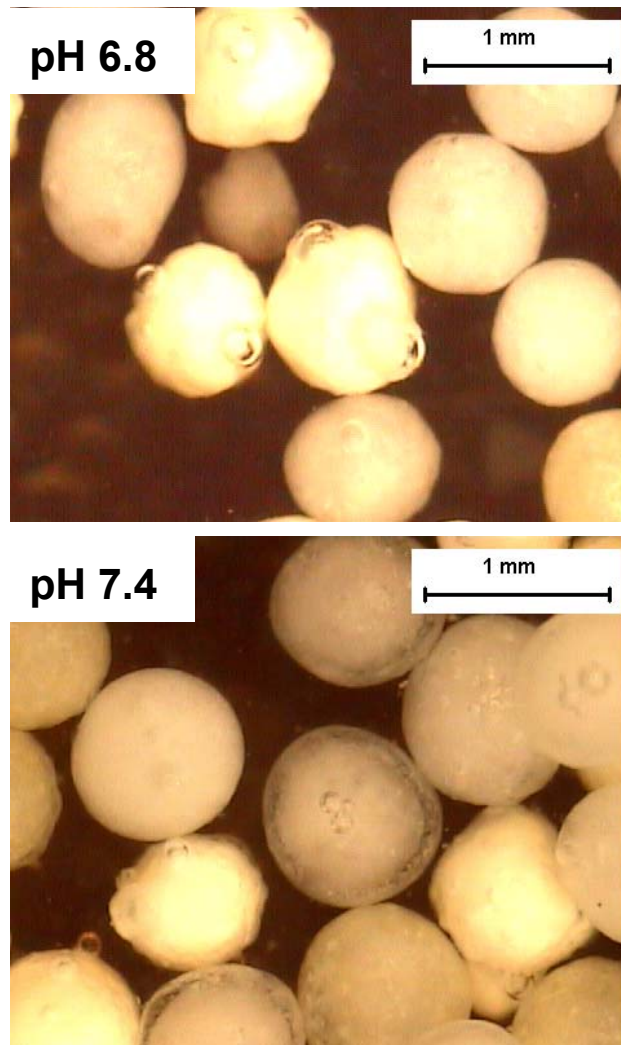


Figure 55 Macroscopic pictures of zein-coated pellets with a shellac topcoat containing 50 % HPMC in pH 6.8 and pH 7.4 after 30 min incubation at 37 °C (zein coating level: 10 %; topcoat level: 10 %)

With increasing shellac ratio the drug release could be decreased in the first 30 min. However, thereafter the drug was release in a pulsatile manner. Thus it could be assumed, that the topcoats failed, irrespective of the permeability due to the composition.

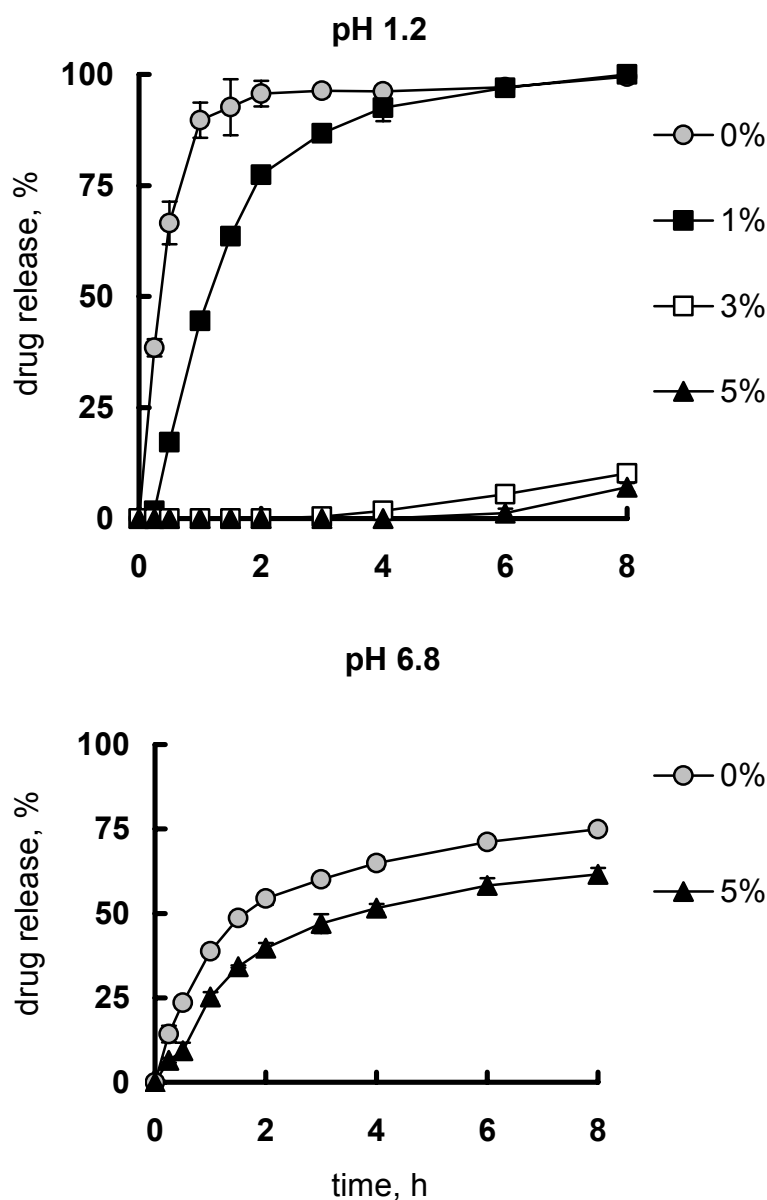


Figure 56 Drug release from zein-coated pellets with pure shellac topcoats in pH 1.2 and pH 6.8 (zein coating level: 20 %; topcoat level: 0-5 %; model drug: CPM)

CPM-loaded pellets have an osmotically active core, as the drug was layered on sugar pellets. Thus, during drug release osmotic pressure is built up. Exceeding a certain value, the topcoats rupture and the drug is release without further retardation.

To prove this assumption, theophylline was used to prepare pellets with osmotically active cores. The drug was released comparable to CPM with no retarding effect of the topcoat (Fig. 58). Thus, the osmotic activity inside the cores plays is more decisive than the drug solubility for pellets coated with shellac-HPMC topcoats.

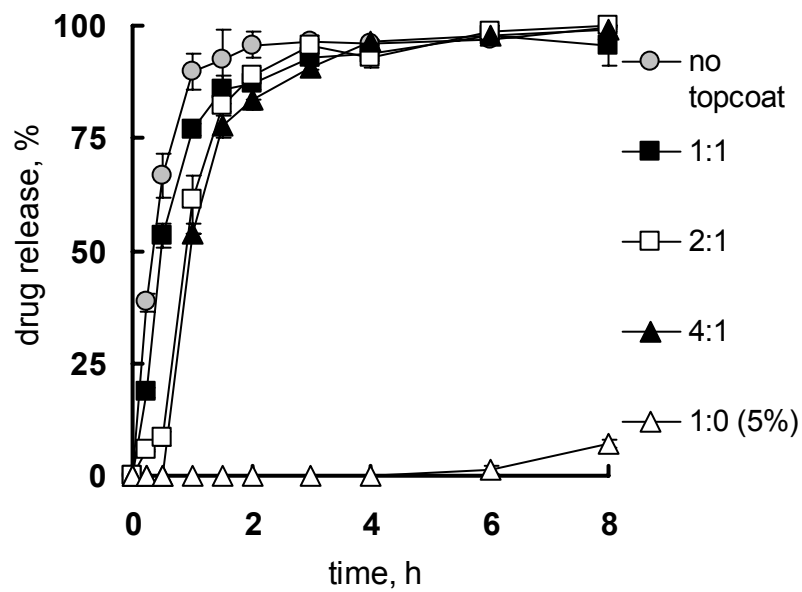


Figure 57 Drug release from zein-coated pellets with shellac-HPMC topcoats of different ratio vs. pure shellac (1:0) in pH 1.2 (zein coating level: 20 %; topcoat level: 15 %; model drug: CPM)

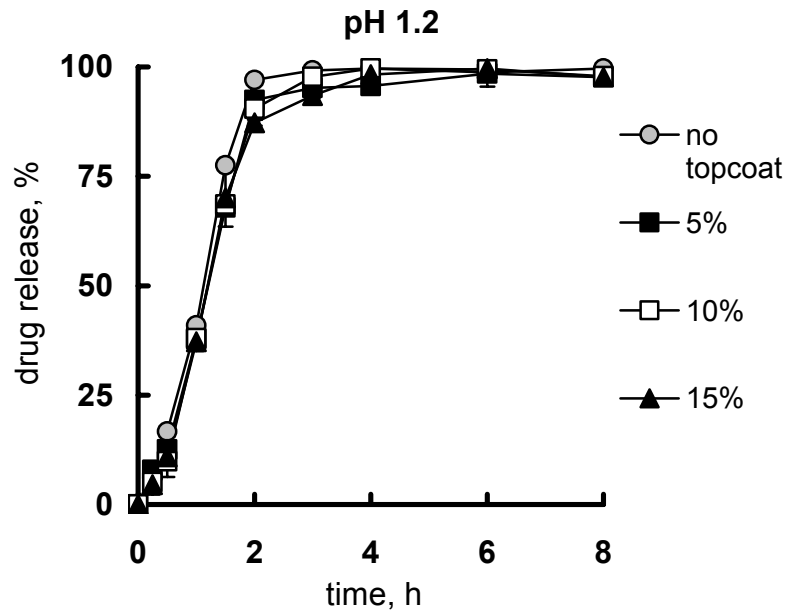


Figure 58 Drug release from zein-coated pellets with a shellac-HPMC 1:1 topcoat at different coating level in pH 1.2 (zein coating level: 20 %; topcoat level: 0-15 %; model drug: theophylline, osmotically active cores)

b. Shellac-organic acid topcoats

Organic acids were reported to reduce the disintegration time of shellac-coated soft gelatine capsules (Pearnchob et al., 2004b). They enhance the dissolution of shellac at elevated pH due to their pH-dependent solubility and seemed therefore a promising alternative to improve the drug release from shellac topcoat systems at pH 6.8.

The physical properties required are a low solubility in pH 1.2 to ensure a retarding effect of the topcoat in this medium, and a high solubility in pH 6.8 to increase the permeability of the topcoat at this pH (Table 18).

Table 18 Physical properties and solubility of organic acids

Organic acid	Mw *	pKa *	Solubility (mg/ml) *	
			0.1N HCl	pH 6.8
Sorbic acid	112.1	4.76	1-2	15-16
Fumaric acid	116.7	pKa ₁ : 3.03 pKa ₂ : 4.54	4-5	20-21
Aspartic acid	133.1	pKa ₁ : 1.88 pKa ₂ : 3.65 pKa ₃ : 9.60	n.d.	n.d.
Alginic acid	~240 000	-	insoluble at pH<3	soluble

* from Merck Index, 1989

n.d.: not determined

The drug release with 10 % (w/w) sorbic acid content in the shellac topcoat was comparable to the release of pellets with pure shellac topcoats in pH 1.2, whereas in pH 6.8 the release was slightly enhanced (Fig. 59). However, there was still a pronounced retardation by the topcoat in pH 6.8 as well as pH 7.4, revealing, that the solubility of shellac in the respective medium still governs the drug release.

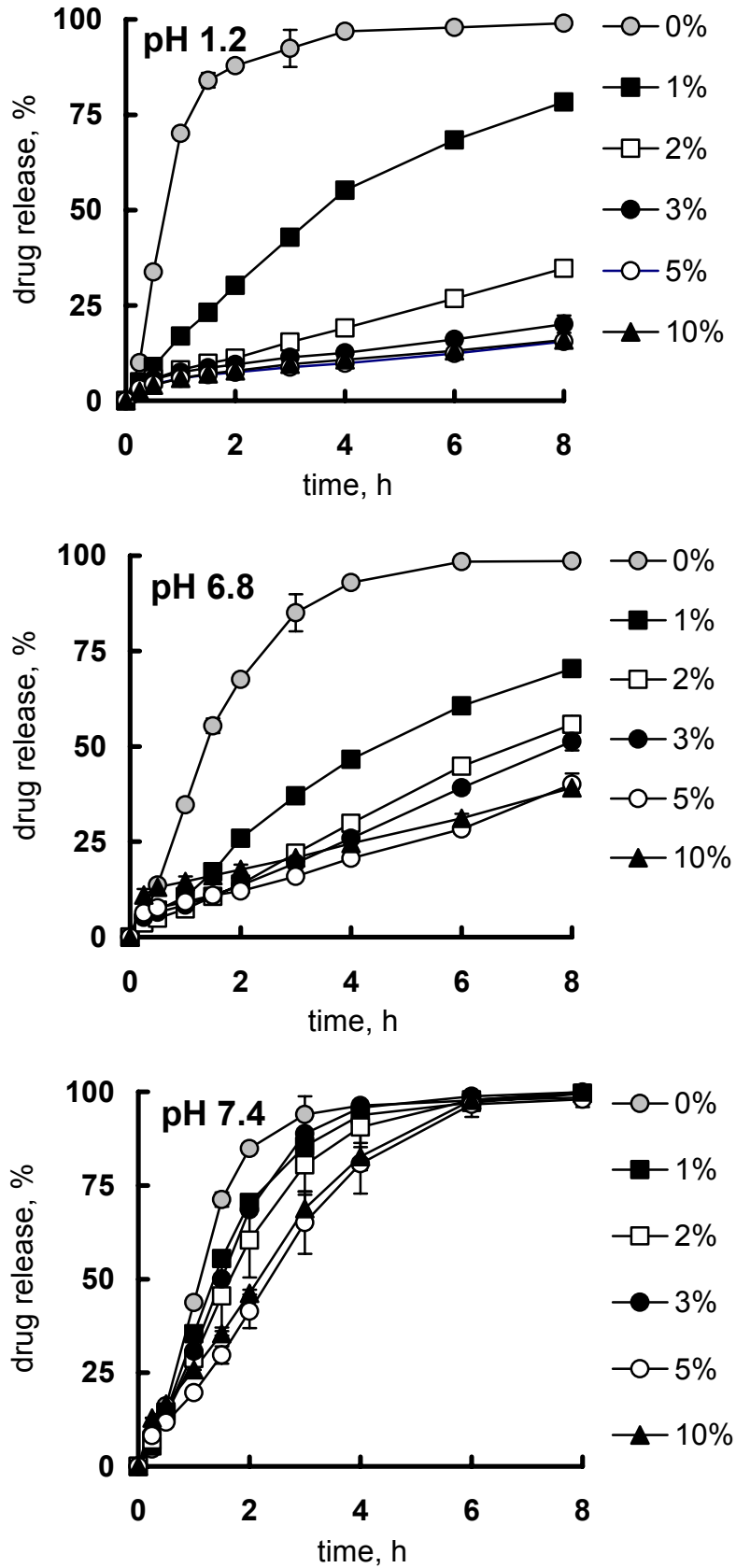


Figure 59 Drug release from zein-coated pellets with shellac topcoats containing 10 % sorbic acid in pH 1.2, pH 6.8 and pH 7.4 (zein coating level: 10 %; topcoat level: 0-10 %; model drug: theophylline)

3. Results and Discussion

Organic acids were soluble in the ethanolic polymer solution up to 30 % (w/w) as used for the preparation of isolated films. The formulations resulted in very sticky films or even no film formation, due to the strong plasticising effect of the organic acid for the polymer at these concentrations (Table 19).

Table 19 Appearance and physical properties of shellac films containing organic acids

Plasticizer (% w/w based on formulation)	Properties	Appearance
None	brittle	clear
Sorbic acid		
10	flexible	clear
20	flexible	turbid (milky)
30	-	no film formation, crystals
Fumaric acid		
10	flexible	clear
20	flexible	small crystals
30	flexible, sticky	turbid, small crystals

The organic acids were not dissolved completely at 50 % (w/w) content. At this concentration the organic acid is present as a solid in the coating solution and thus can perform as an antitacking agent during coating. Micronised aspartic acid at a ratio of 1:1 in the shellac topcoat was coated without sticking of the pellets during the process. The drug release was steadily decreased with increasing coating level in pH 1.2 (Fig. 60). Finally, in pH 6.8 as well as pH 7.4 no further retardation of the drug release was observed even at higher coating level.

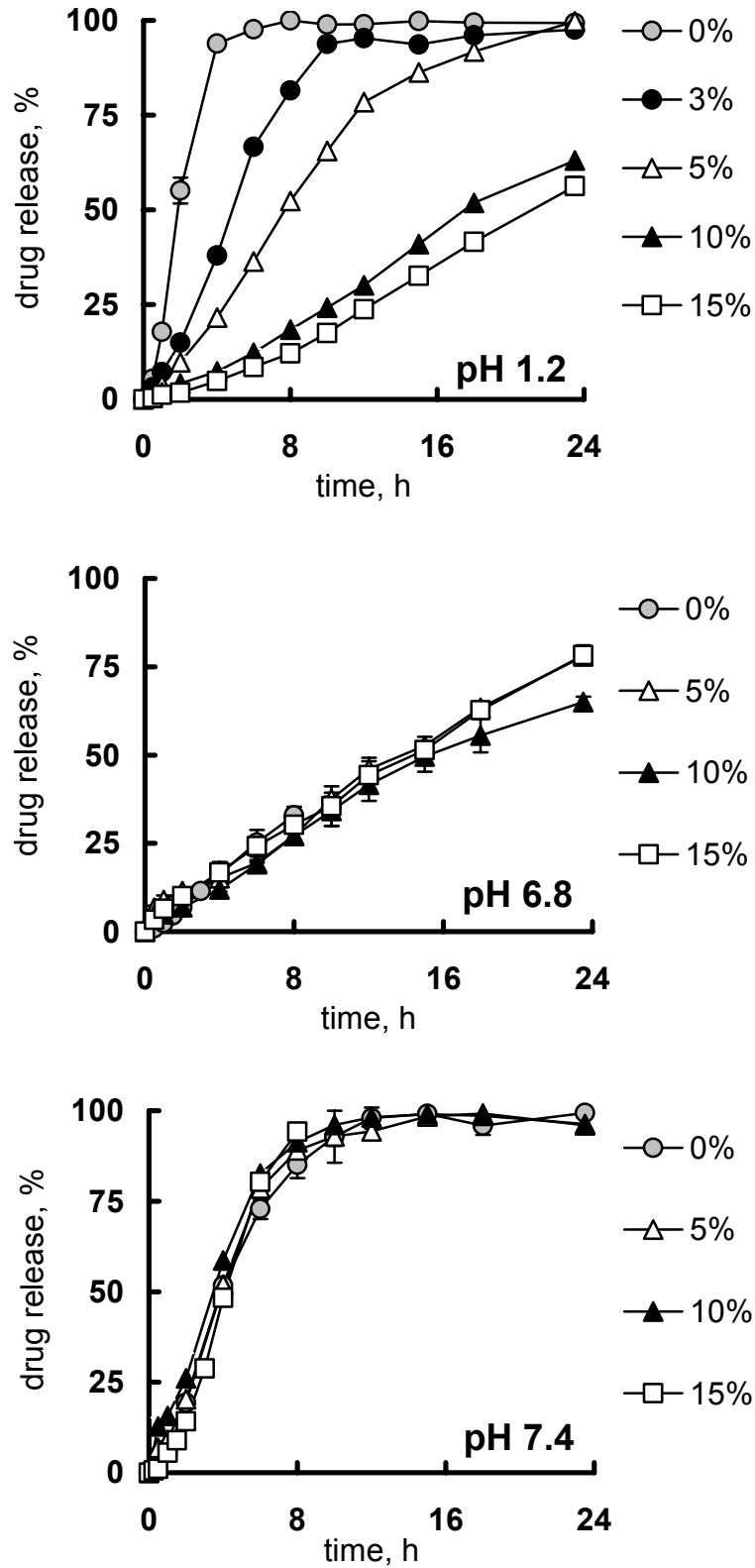


Figure 60 Drug release from zein-coated pellets with a topcoat of shellac-aspartic acid 1:1 in pH 1.2, pH 6.8 and pH 7.4 (zein coating level: 20 %; topcoat level: 0-15%; model drug: theophylline)

3. Results and Discussion

No retardation of the drug release could be achieved any more, if the organic acid content was further increased up to 80 % in the formulation (Fig. 61). The mechanical resistance of the topcoat with such a high amount of solid content may be not sufficient to inhibit effectively the swelling of the zein-coated pellets.

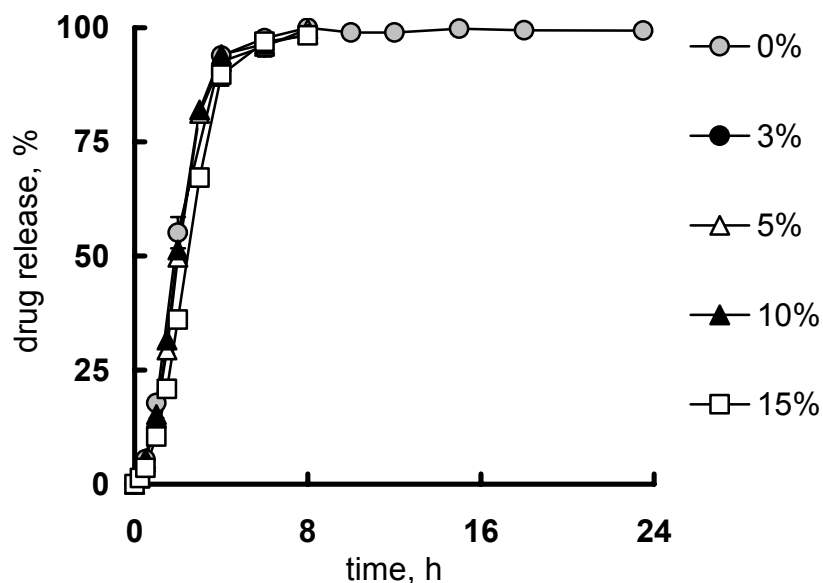


Figure 61 Drug release from zein-coated pellets with a topcoat of shellac:aspartic acid 1:4 in pH 1.2 (zein coating level: 20 %; topcoat level: 0-15%; model drug: theophylline)

Organic acids with film forming properties may be an alternative to small molecular weight organic acids as additives to shellac topcoats. Sodium alginate was thus investigated as a topcoat for zein coated pellets. Alginate is a film forming polymer containing carboxylic groups, having a pH-dependent solubility (Table 18).

Sodium alginate is a water soluble salt of alginic acid, which precipitates in pH 1.2 as alginic acid and renders insoluble. Only at higher pH it can dissolve again. The fast drug release of the zein-coated pellets in pH1.2 was decreased by a 10 % topcoat level. In pH 6.8, the drug release was not further retarded, but rather slightly enhanced (Fig. 62). Sodium alginate was coated from an aqueous solution and may have caused a pre-hydration of the zein coat during the coating process. However, the coating solution of sodium alginate was of high

viscosity already at a polymer content of only 10 %. The coating process was therefore very time consuming, making the shellac topcoats to be the preferred formulations.

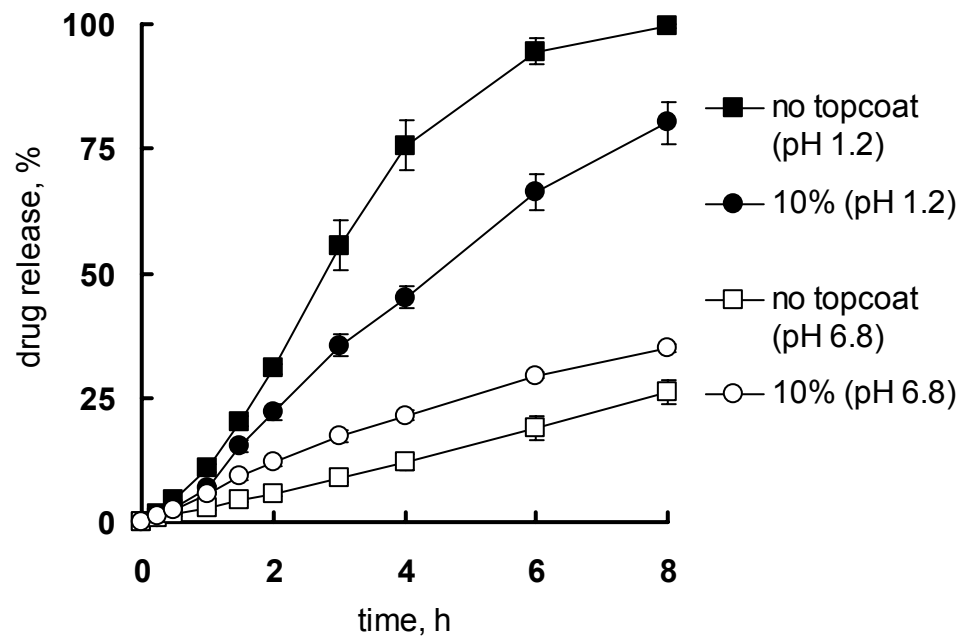


Figure 62 Influence of alginate topcoats on the drug release of zein coated pellets (zein coating level: 20 %; alginate coating level: 10 %; model drug: theophylline)