Prof. Dr. Roland Bodmeier

Name der Forschungsstelle(n)

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AiF-Vorhaben-Nr. / GAG

01.10.01 bis 29.02.04

Bewilligungszeitraum

Schlußbericht für den Zeitraum : 01.10.01 bis 29.02.04

zu dem aus Haushaltsmitteln des BMWi über die

AiF Otto von Guericke

geförderten Forschungsvorhaben

Forschungsthema : "Überziehen von festen Arzneiformen mit natürlichen Filmbildnern und phthalatfreien Überzügen"

Berlin, 25.05.2004

Ort, Datum

Unterschrift der/des Projektleiter(s)

Schlußbericht zum Projekt

„Überziehen von festen Arzneiformen mit natürlichen Filmbildnern und phthalatfreien Überzügen“

Forschungsstelle:
Prof. Dr. Roland Bodmeier
Institut für Pharmazie
Freie Universität Berlin

Mai, 2004

<u>Schlussbericht</u>

„Überziehen von festen Arzneiformen mit natürlichen Filmbildnern und phthalatfreien Überzügen“

Zusammenfassung (mit Gegenüberstellung der Ergebnisse mit den Zielsetzungen)

<u>Die Forschungsziele dieser Studie waren:</u>

a) die Entwicklung von Überzügen für feste Darreichungsformen basierend auf natürlichen Überzugsmaterialien (Schellack und Zein)

b) die Entwicklung phthalatfreier Überzüge

c) Anwendung des Trockencoatings auf Retardpolymere (Ethylcellulose, Eudragit RS und Schellack).

<u>Die Ergebnisse sind:</u>

- Schellack-Coatings wurden im Hinblick auf Formulierung und Prozeß optimiert, u.a. konnte das Problem des langsamen Zerfalls im Darmsaft durch Zusatz hydrophiler Substanzen gelöst werden [<u>Ziel (a) erreicht</u>].
- Zein, ein weiterer natürlicher Filmbildner, wurde erfolgreich als Retardüberzug eingesetzt, auch in Kombinationen mit Schellack [Ziel (a) erreicht].
- Toxikologisch eventuell bedenkliche phthalathaltige Weichmacher konnten durch phthalatfreie Weichmacher unter Beibehaltung der Freisetzungsprofile ersetzt werden [<u>Ziel (b) erreicht</u>].
- Das Trockencoating mit Polymerpulvern wurde erfolgreich auf Retardpolymere, wie Ethylcellulose, Eudragit RS und Schellack, ausgedehnt. Das Trockencoating hat viele Vorteile (z.B. keine Lösungsmittel, kurze Prozesszeiten) im Vergleich zum Coaten mit flüssigen Polymerformulierungen [<u>Ziel (c) erreicht</u>].

Das Ziel des Vorhabens wurde erreicht.

Darstellung der erzielten Ergebnisse, wirtschaftlicher Nutzen, innovativer Beitrag, industrielle Anwendungsmöglichkeiten

- wissenschaftliche Ergebnisse: siehe Anhang, der wie folgt gegliedert ist:
  - Schellack als magensaftresistenter Überzug
  - Zein als natürliches Überzugsmaterial
  - Coating mit Polymerpulvern
  - Phthalat-freie Überzüge

- Die Ergebnisse verkürzen die Entwicklungszeiten der pharmazeutischen Industrie und führen zu qualitativ „ausgereifteren“ und damit weniger problematischen Formulierungen.
- Innovativer Beitrag der Forschungsergebnisse zu neuen Produkten
  - Einsatz natürlicher Überzüge (Schellack und Zein) als Alternative zu synthetischen Überzüge/Zuckerdragierung bei Produktneuentwicklungen
  - Ersatz phthalat-haltiger Coating-Formulierungen mit phthalat-freien Formulierungen bei bestehenden Produkten, Empfehlungen für Neuentwicklungen.
  - Neues Trockenpulver-Coatingverfahren wurde auf bisher nicht verwendete Polymere erweitert.

Zusammenstellung der veröffentlichen Arbeiten

Die wissenschaftlichen Ergebnisse dieses Projektes wurden in folgenden wissenschaftlichen Zeitschriften und wissenschaftlichen Kongressen publiziert bzw. präsentiert:

<u>Publikationen:</u>

1. N. Pearnchob, A. Dashevsky, R. Bodmeier, Improvement in the disintegration of shellac-coated soft gelatin capsules in simulated intestinal fluid. J. Contr. Rel. 94 (2004) 313-321.
2. N. Pearnchob, R. Bodmeier, Coating of pellets with micronized ethylcellulose particles by a dry coating technique. Int. J. Pharm. 268 (2003) 1-11.
3. N. Pearnchob, R. Bodmeier, Dry powder coating with micronized Eudragit RS for extended drug release. Pharm. Research 20 (2003) 1970-1976.

2 weitere Publikationen zum Thema Zein werden noch geschreiben.

<u>Präsentationen:</u>

1. N. Pearnchob, A. Dashevsky, J. Siepmann R. Bodmeier, Effect of plasticizer and pore formers on physico-chemical properties of shellac. DPhG Tagung, Berlin. Arch. Pharm. Pharm. Med. Chem., Suppl. 1, 118 (2002).
2. I. Terebesi, R. Bodmeier, Extended drug release from Zein coated pellets: Effect of top-coatings on the protection against pepsin and on the drug release. 2003 AAPS Annual Meeting and Exposition, American Association of Pharmaceutical Scientists, Salt Lake City, USA, Vol. 5, Abstract W5166 (2003).
3. I. Terebesi, R. Bodmeier, Zein aqueous dispersions: methods of preparation and investigation of parameters affecting the particle size. International Meeting on

Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology 2004, Nuremberg, Germany, 625 - 626, (2004).

Gewerbliche Schutzrechte

Es wurden keine gewerblichen Schutzrechte beantragt, eine Beantragung ist nicht geplant.

Dieses Projekt wurde durch das BMWi über AiF gefördert.

Erklärung zur Weiterverwendung des beschafften Gerätes
(Texture Analyser S/N 1002):

Der Texture Analyser S/N 1002 wird weiterhin für Forschungszwecke im Rahmen der durch die industrielle Gemeinschaftsforschung (IGF) geförderten Projekte verwendet.

1. Shellac as a Natural Coating Material

Table of content:

Summary

With pharmaceutically accepted plasticizers, a small amount of plasticizer (5% w/w based on the polymer mass) is required to obtain optimal mechanical properties of the resulting film coatings (page 8).

TEC, triethyl citrate, is an appropriated plasticizer for shellac, because it is commonly used in pharmaceutical applications and showed the highest percentage of film elongation and the lowest modulus at puncture (page 8).

The coating level of 2-5% shellac showed a comparable release profile to those of synthetic coating (acrylic polymer, Eudragit L100-55 and cellulosic polymer, hydroxypropyl methylcellulose phthalate, HPMCP) (page 11).

The drug release in the intestine can additionally be prolonged at higher shellac coating levels (more than 10%) (pages 12-13).

Although sorbic acid is used as a pore-former, it significantly lowered the glass transition temperature of shellac, and thus acted as a plasticizer (pages 17-18).

Sorbic acid was very efficient leading to high dry weight loss rates of thin shellac films and short capsule disintegration times in phosphate buffer pH 6.8 (pages 20-21).

The addition of appropriate types and amounts of additives effectively decreased the observed disintegration times at high pH while the behaviour in 0.1N HCl remained unchanged (pages 20-21).

An ammoniated aqueous shellac solution is an acceptable enteric coating for solid dosage forms (e.g. pellets and soft gelatin capsules). In comparison to an ethanolic shellac solution, much higher coating levels are required (page 40).

By coating onto soft gelatin capsules, aqueous shellac coatings above 20mg/cm² were sufficient to provide gastric resistance, but the shellac-coated capsules showed undesirably poor disintegration in the intestinal medium (page 46).

The appropriate disintegration behaviour could be improved by adding hydrophilic additives.

Materials:

Polymers:

shellac:	Stroever Shellack Bremen
Eudragit L100-55:	poly-(methacrylic acid, ethyl acrylate) 1:1, Röhm Pharma
HPMCP:	hydroxypropyl methylcellulose phthalate, Shin-Etsu Chemical

Plasticizer:

TEC:	triethyl citrate, Morflex
Glycerin:	glycerol, Smith Kline Beecham
Propylene Glycol:	BASF
PEG 400:	Polyethylene glycol 400, BASF
Castor oil:	Sigma
AMG:	acetylated monoglycerides (Myvacet 9-45), Quest International

Additives:

Sorbic acid:	Sigma
Benzoic acid:	Sigma
Fumaric acid:	Sigma
Adipic acid:	Sigma
Citric acid:	Sigma

1.1 Physical-mechanical properties of ethanolic shellac films

PREPARATION OF SHELLAC FILMS

FORMULATION:

	Composition, % w/w		
	Formulation I	Formulation II	
Shellac	10.0	10.0	10 % w/w based on total solution
Plasticizer	0.5	1.0	5-10 % w/w based on the polymer mass
Ethanol (96 % v/v)	89.5	89.0	
Total	**100.0**	**100.0**	

Mechanical properties, film appearance and glass transition temperature of shellac films cast from ethanolic solutions with and without the addition of plasticizer (5 % w/w based on polymer)

Plasticizer	Film appearance	Puncture strength, MPa	Elongation, %	Modulus at puncture, kPa	Tg, °C
None	clear	1.73 (0.69)	0.99 (0.14)	67.50 (43.6)	39.7 (0.8)
TEC	clear	0.45 (0.11)	76.13 (18.6)	6.23 (1.40)	18.7 (0.8)
Glycerin	clear	0.73 (0.11)	71.26 (9.31)	14.04 (1.34)	17.2 (1.7)
PG	clear	1.00 (0.30)	78.63 (19.9)	35.18 (1.65)	14.1 (2.5)
PEG 400	clear	0.61 (0.43)	50.00 (13.1)	49.73 (11.3)	11.0 (0.0)
Castor oil	clear, oily	0.34 (0.24)	53.45 (6.90)	61.93 (9.53)	17.7 (0.3)
AMG	clear, oily	1.25 (0.43)	23.14 (1.76)	55.09 (2.19)	14.3 (0.5)

Effect of plasticizer (TEC) concentration on the mechanical properties, water content and weight loss of dry and wet shellac films (dissolution medium, 0.1 N HCl or phosphate buffer pH 6.8; exposure time, 2 h)

TEC, % w/w of polymer	Puncture strength, MPa	Elongation, %	Modulus at puncture, kPa	Water content, %	Weight loss, %
Before exposure					
None	1.73 (0.69)	0.99 (0.14)	67.50 (43.62)	-	-
5 %	0.45 (0.11)	76.13 (18.61)	6.23 (1.40)	-	-
10 %	0.45 (0.11)	120.84 (10.96)	5.90 (0.96)	-	-
Wet film (in 0.1 N HCl)					
None	1.93 (0.24)	10.08 (2.48)	19.78 (3.73)	4.77 (0.15)	1.72 (0.08)
5 %	1.48 (0.33)	37.40 (3.81)	56.63 (12.13)	6.31 (0.17)	2.12 (0.15)
10 %	1.14 (0.20)	40.22 (7.19)	61.93 (9.42)	8.58 (0.95)	3.98 (0.62)
Wet film (in phosphate buffer pH 6.8)					
None	1.73 (0.11)	26.03 (1.76)	9.23 (1.20)	55.05 (1.58)	9.73 (1.98)
5 %	1.13 (0.42)	26.19 (5.50)	122.00 (23.38)	62.11 (1.05)	17.84 (2.17)
10 %	0.83 (0.22)	32.28 (0.22)	131.23 (11.80)	68.61 (0.48)	18.85 (1.14)

1.2 Shellac-coated pellets

COATING OF DRUG-LOADED PELLETS

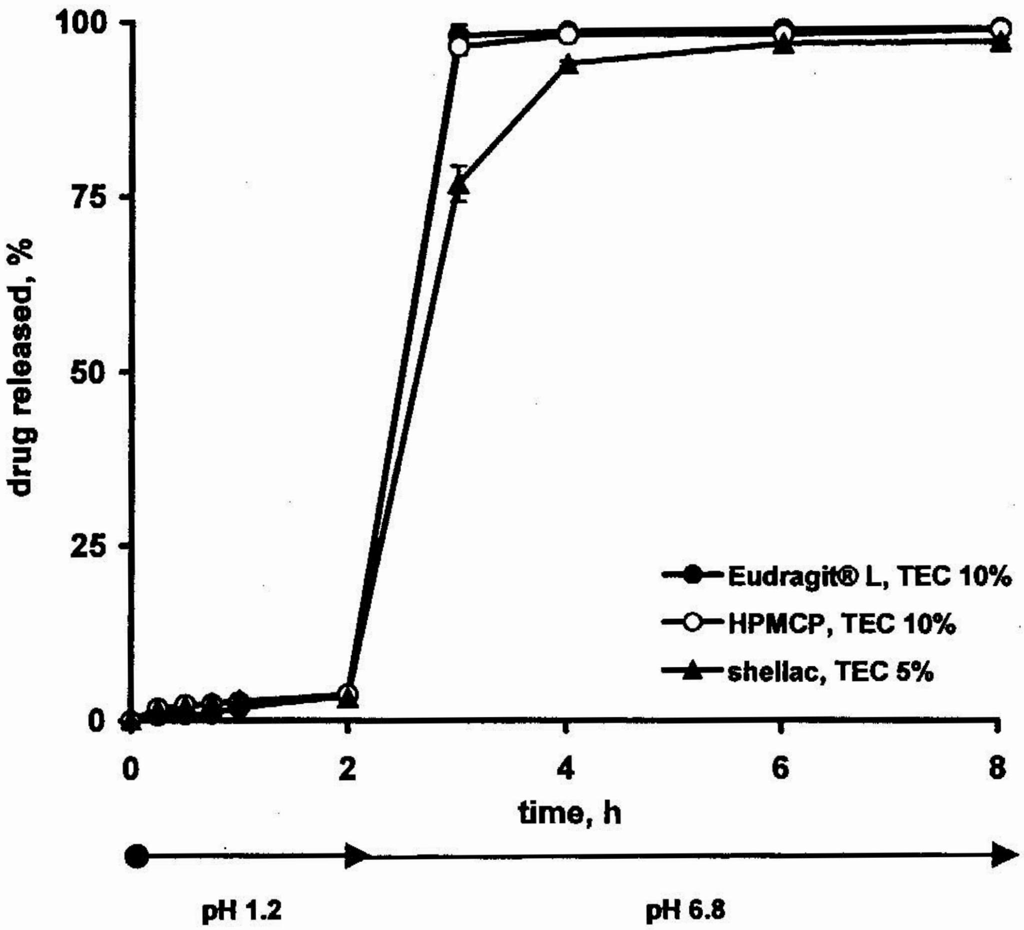
FORMULATION:

	Composition, % w/w	
Shellac	10.0	10 % w/w based on total solution
Triethyl citrate	0.5	5 % w/w based on the polymer mass
Talc	3.0	30 % w/w based on the polymer mass
Ethanol (96 % v/v)	86.5	
Total	**100.0**	

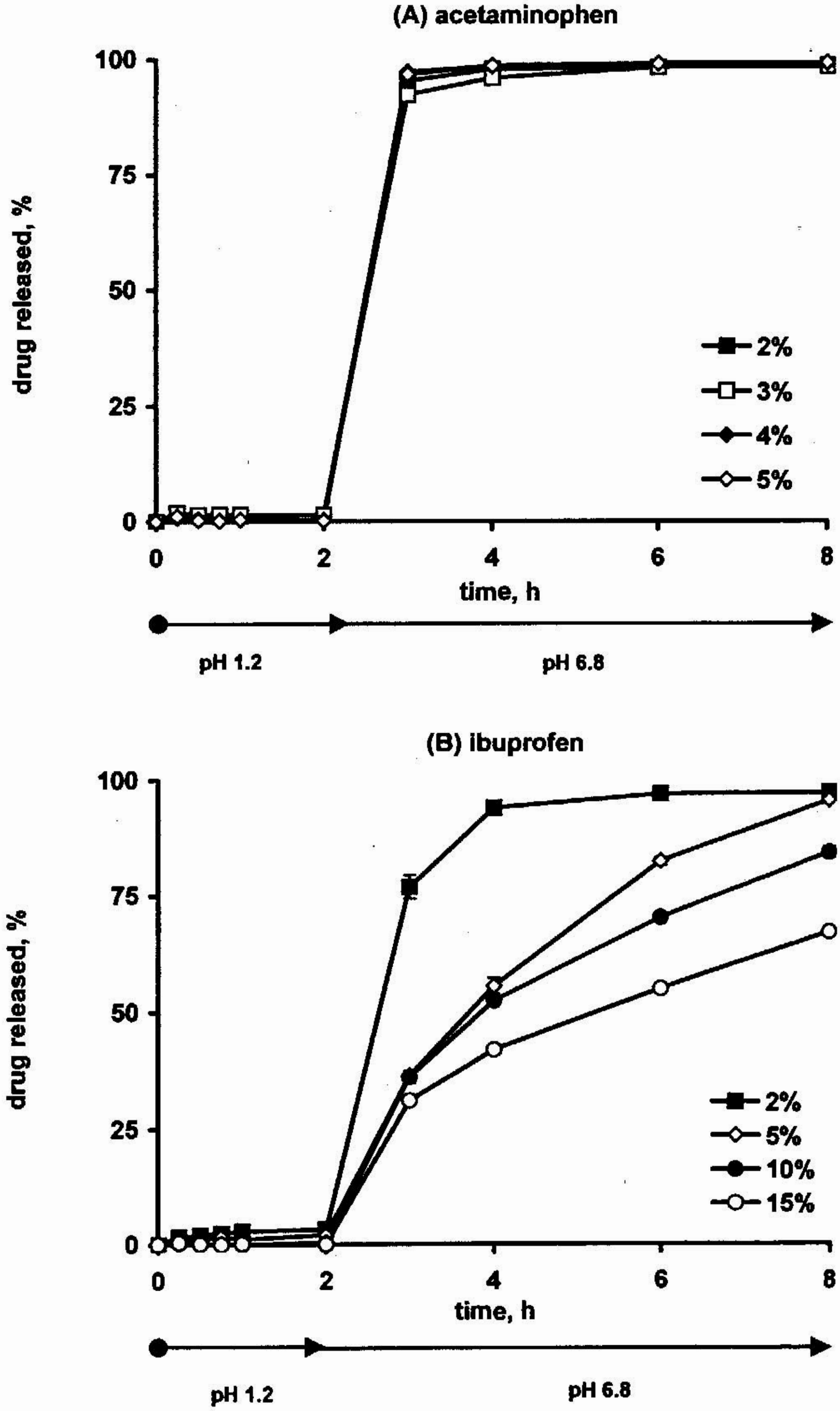
PROCESSING PARAMETER:

Fluidized bed coater	Glatt GPCG-1	Hüttlin Kugelcoater HKC 05 / UNILAB 05
Batch size	1.0 kg	0.5 kg
Inlet air temperature	23-25°C	23-25°C
Product temperature	22-24°C	22-24°C
Outlet air temperature	21-23°C	24-26°C
Air flow rate	90-100 m^3/h	25-50 %
Atomizing pressure	1.2 bar	0.4 bar
Microclimate pressure	-	0.2 bar
Spray rate	5-7 g/min	2-3 g/min
Spray nozzle diameter	1.2 mm	0.8 mm – 2 components
Secondary drying (23-25°C)	10-15 min	10-15 min

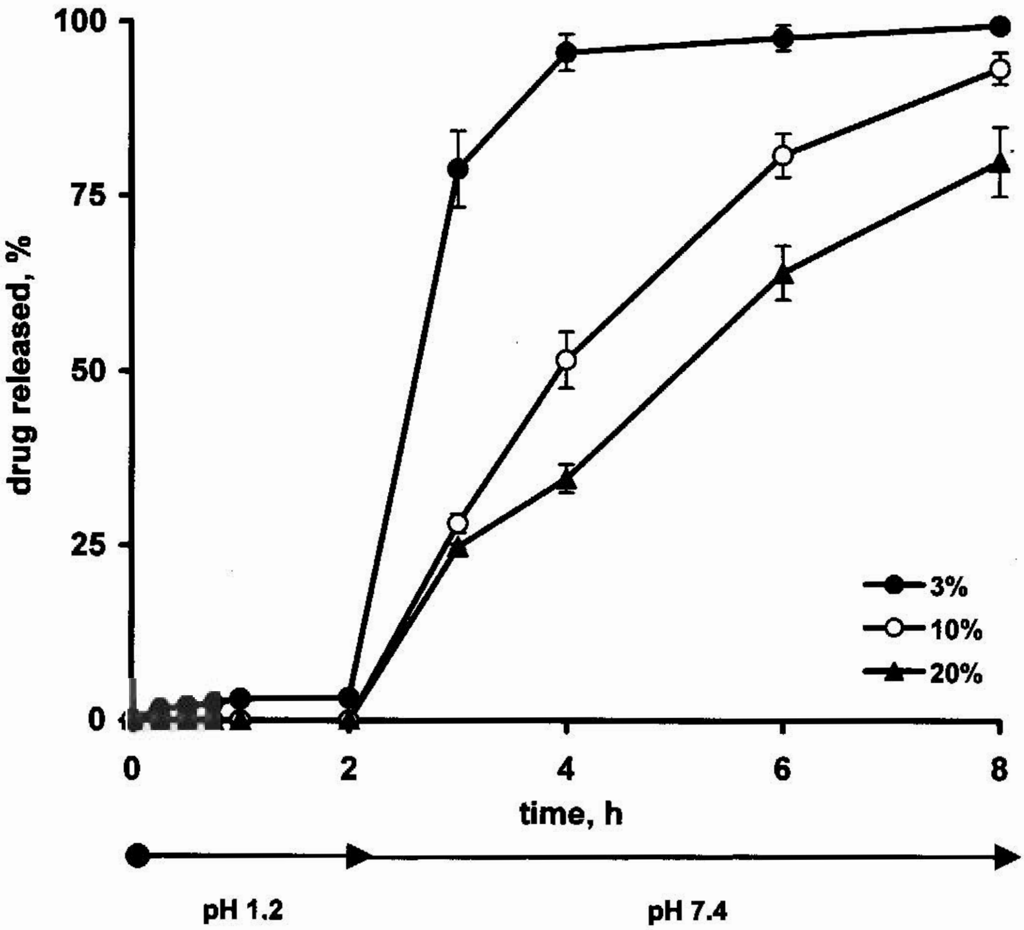
Comparison of shellac with commonly used synthetic polymers as enteric coating materials onto drug-loaded pellets (ibuprofen, release medium change after 2 h)



Effect of coating level on drug release from shellac-coated pellets: (A) acetaminophen and (B) ibuprofen (release medium change after 2 h)

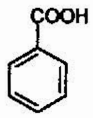
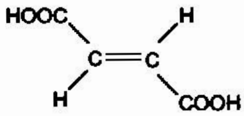
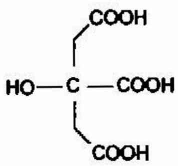


Effect of coating level on drug release from shellac-coated pellets in high-pH intestinal medium (propranolol hydrochloride, release medium change after 2 h)



1.3 Improvement of disintegration behavior of shellac-coated soft gelatin capsules

Chemical and physical properties of different organic acids

Organic acid	Molecular weight	pKa	Density, g/cm³	Melting point, °C	Solubility, mg/ml 0.1 N HCl	Solubility, mg/ml Buffer pH 6.8
Sorbic acid	112.13	4.76	1.20	135	1-2	15-16
$H_3C-CH=CH-CH=CH-COOH$						
Benzoic acid	122.12	4.19	1.32	122	3-4	22-23
						
Fumaric acid	116.07	pKa_1 3.03	1.64	287	4-5	20-21
		pKa_2 4.54				
Adipic acid	146.14	pKa_1 4.41	1.36	152	24-25	48-49
		pKa_2 5.28				
$HOOC-CH_2-CH_2-CH_2-CH_2-COOH$						
Citric acid	192.13	pKa_1 3.13	1.54	153	> 1000	> 1000
		pKa_2 4.76				
		pKa_3 6.40				

Physical properties and compatibility of ethanolic-based shellac films containing different acids

Additive, % w/w	Film appearance	Film flexibility
None	clear	very brittle
Sorbic acid		
5 %	clear	flexible
10 %	clear, crystal	very flexible
20 %	clear, crystal	very flexible
Benzoic acid		
5 %	clear	brittle
10 %	clear, crystal	flexible
20 %	clear, crystal	flexible
Fumaric acid		
5 %	cloudy, crystal	flexible
10 %	cloudy, crystal	flexible
20 %	cloudy, crystal	flexible
Adipic acid		
5 %	clear	flexible
10 %	clear, crystal	very flexible
20 %	clear, crystal	very flexible
Citric acid		
5 %	clear	very brittle
10 %	clear, crystal	very brittle
20 %	clear, crystal	very brittle

Glass transition temperature (Tg) of ethanolic-based shellac films containing different additives as plasticizer (% w/w based on the mass of the polymer)

Additive	Concentration, % w/w	Tg, °C
None	-	39.7 (0.8)
Citrate ester		
TEC	5	18.7 (0.8)
	10	14.0 (0.1)
Organic acid		
Sorbic acid	5	15.3 (1.0)
	10	9.0 (2.3)
Benzoic acid	5	11.6 (0.3)
	10	8.0 (0.6)
Adipic acid	5	10.8 (0.8)
	10	8.6 (0.5)

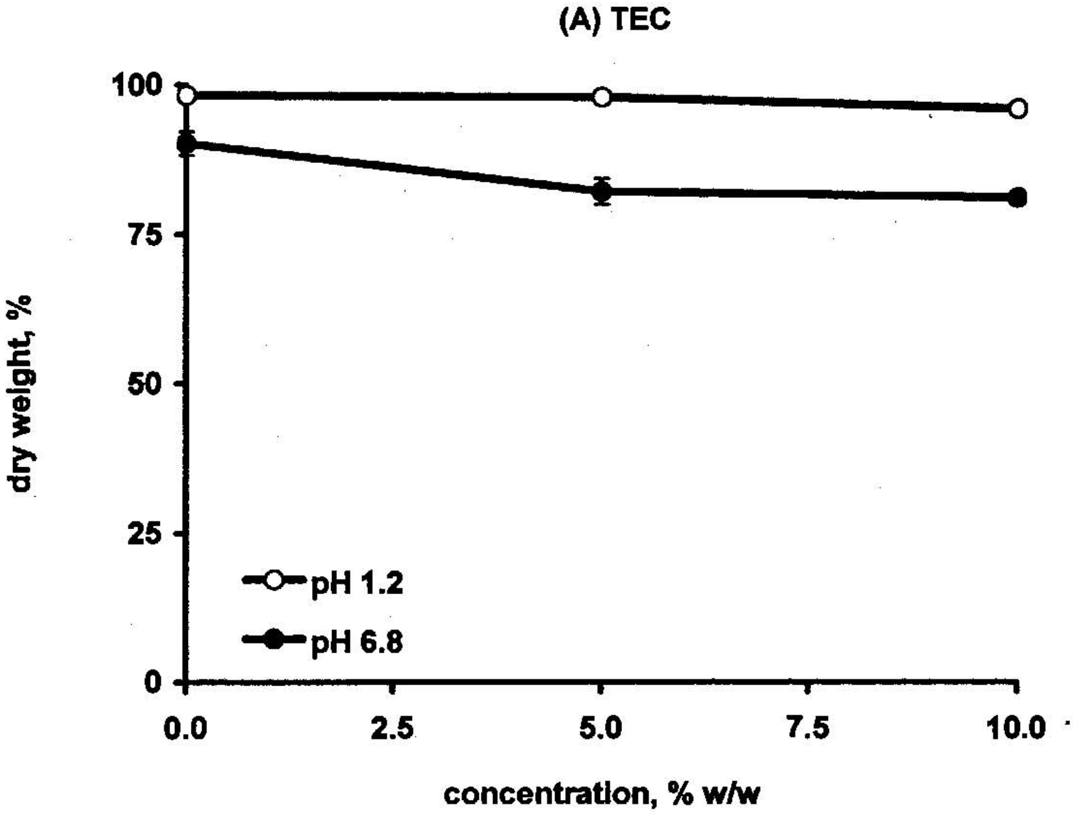
Mechanical properties of thin shellac films contained different organic acids (% w/w based on the mass of the polymer)

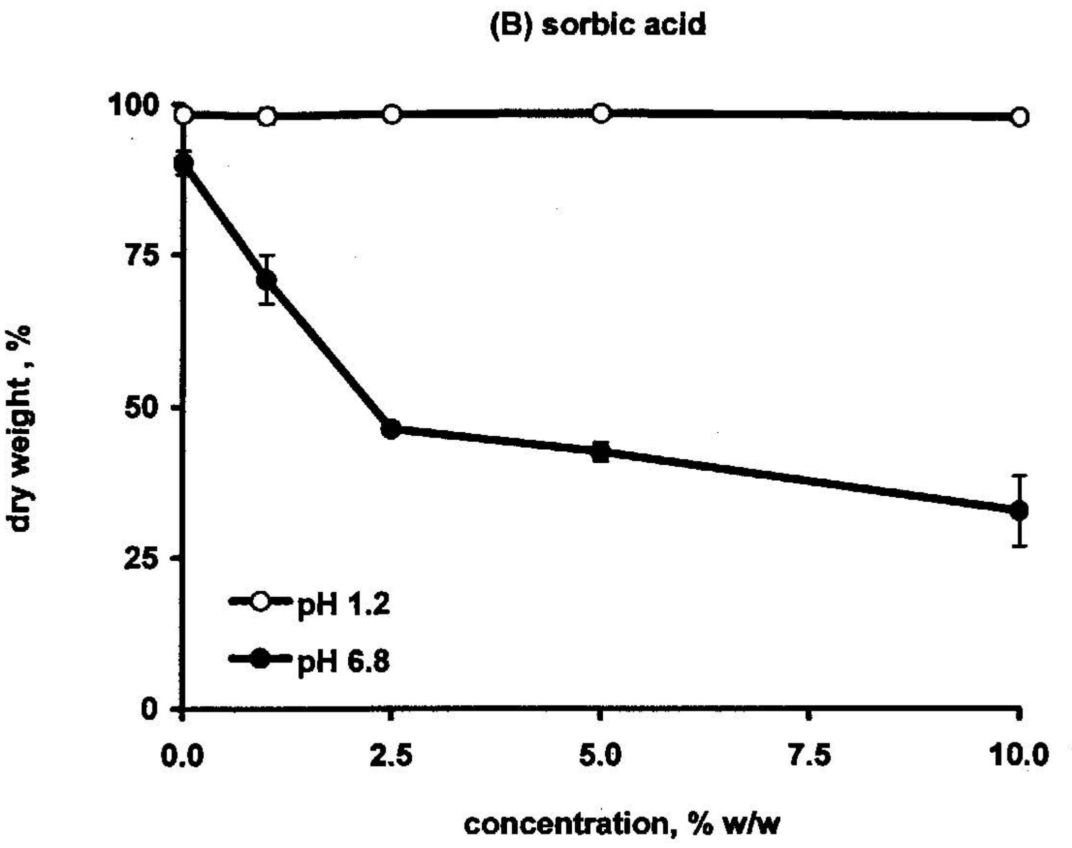
Additive	Concentration, % w/w	Elongation, %	Puncture strength, MPa	Modulus at puncture, kPa
None	-	1.0 (0.1)	1.7 (0.7)	67.5 (43.6)
Sorbic acid	5 %	35.6 (2.5)	1.9 (2.8)	53.3 (1.8)
Benzoic acid	5 %	52.0 (9.3)	1.7 (0.1)	22.7 (0.7)
Adipic acid	5 %	64.4 (5.2)	1.6 (0.3)	12.1 (0.8)

Mechanical properties of thin shellac films containing different additives as plasticizer and/or pore former in the dry and wet states (after exposure to 0.1 N HCl for 120 min)

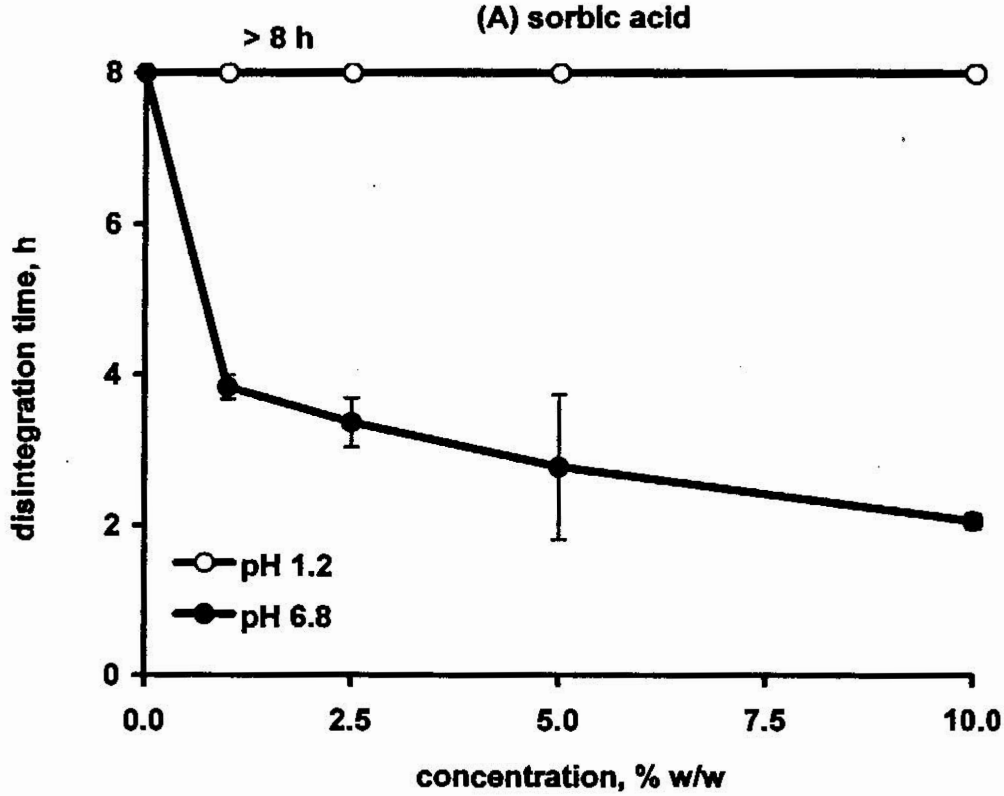
Additive, % w/w	Elongation, %		Puncture strength, MPa		Modulus at puncture, kPa	
	Dry film	Wet film	Dry film	Wet film	Dry film	Wet film
None	1.0 (0.1)	10.1 (2.5)	1.7 (0.7)	1.9 (0.2)	67.5 (43.6)	19.8 (3.7)
TEC						
5 %	76.1 (18.6)	37.4 (3.8)	0.5 (0.1)	1.5 (0.3)	6.2 (1.4)	66.6 (12.1)
10 %	120.8 (11.0)	40.2 (7.2)	0.5 (0.1)	1.1 (0.2)	5.9 (1.0)	61.9 (9.4)
Sorbic acid						
5 %	35.6 (2.5)	45.3 (0.6)	1.9 (2.8)	1.2 (0.1)	53.3 (1.8)	20.5 (5.6)
10 %	107. 6 (54.6)	54.6 (0.0)	1.6 (0.2)	1.3 (0.2)	19.37 (7.7)	21.0 (2.3)
HPMC E5 (plasticized with TEC 10 %)						
25 %	2.4 (0.5)	2.3 (0.5)	4.6 (1.4)	0.2 (0.1)	329.1 (55.2)	21.0 (0.0)

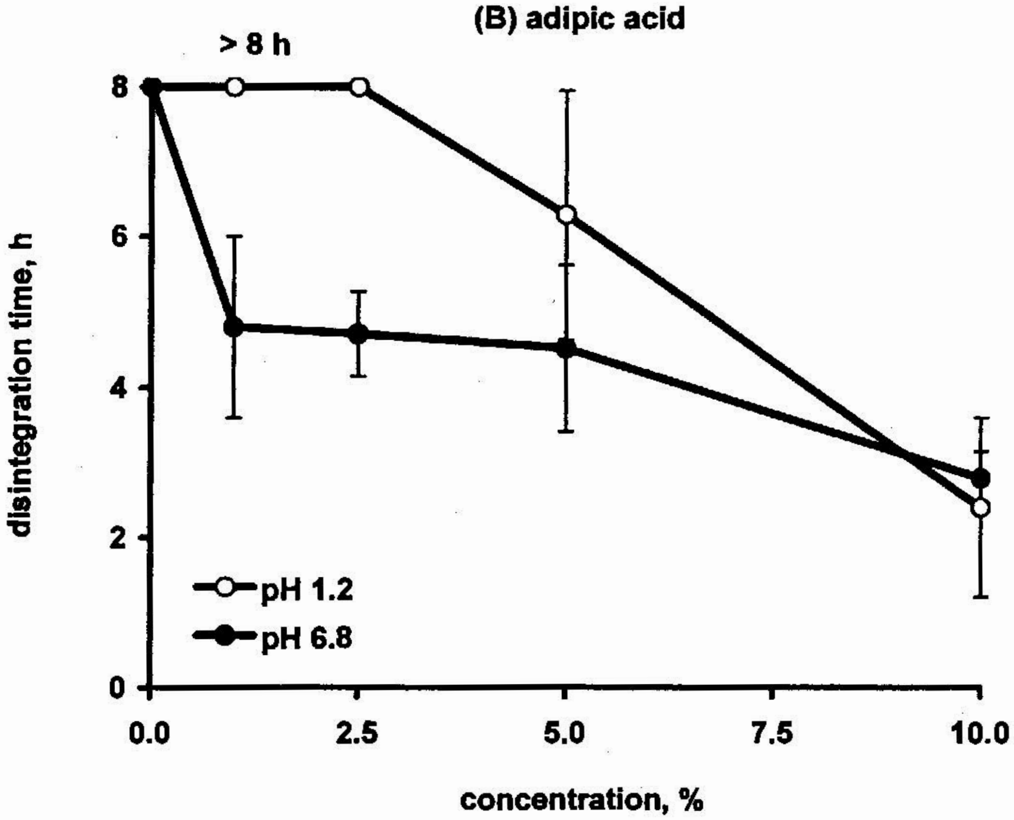
Effect of pH dissolution medium on dry weight (%) of thin shellac films containing different additives (%, w/w based on the polymer mass) after exposure to dissolution media for 120 min





Effect of pH dissolution medium on disintegration of thin shellac films containing different organic acids (%, w/w based on the polymer mass) (film thickness, 100-200 μm)





COATING OF SOFT GELATIN CAPSULES

FORMULATION I:

	Composition, % w/w	
Shellac	10.0	10 % w/w based on total solution
Triethyl citrate	0.5	5 % w/w based on the polymer mass
Talc	3.0	30 % w/w based on the polymer mass
Ethanol (96 % v/v)	86.5	
Total	**100.0**	

FORMULATIONS II-IV:

	Composition, % w/w			
	Formulation II	Formulation III	Formulation IV	
Shellac	10.0	10.00	10.0	10 % w/w based on total volume
Organic acid	0.5	0.75	1.0	5-10 % w/w based on the polymer mass
Talc	3.0	3.00	3.0	30 % w/w based on the polymer mass
Ethanol (96 % v/v)	86.5	86.25	86.0	
Total	**100.0**	**100.00**	**100.0**	

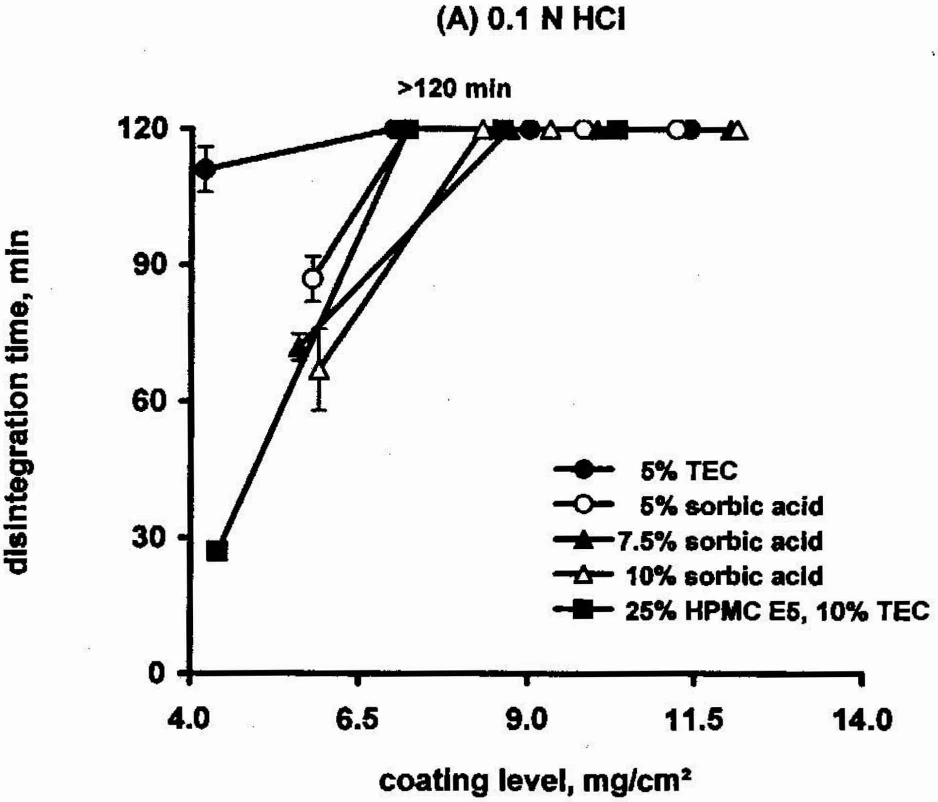
FORMULATION V:

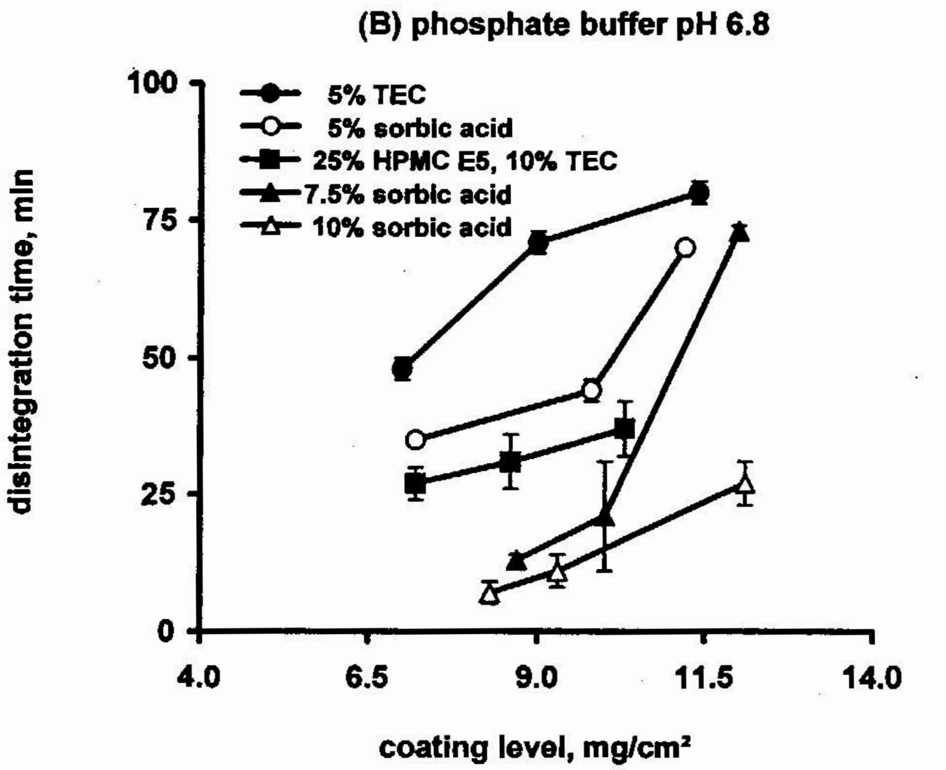
	Composition, % w/w	
Shellac	10.0	10 % w/w based on total solution
Triethyl citrate	1.0	10 % w/w based on the polymer mass
HPMC	2.5	25 % w/w based on the polymer mass
Water	17.3	water:ethanol (20:80)
Ethanol (96 % v/v)	69.2	
Total	**100.0**	

PROCESSING PARAMETER:

Glatt GC-300	Formulations I-IV	Formulation V
Batch size	1.2 kg	1.2 kg
Inlet air temperature	20-25°C	30-35°C
Product temperature	20-22°C	26-28°C
Outlet air temperature	21-23°C	27-30°C
Air flow rate	130 m^3/h	130 m^3/h
Atomizing pressure	1.2 bar	1.2 bar
Spray rate	5-7 g/min	5-7 g/min
Spray nozzle diameter	1.2 mm	1.2 mm
Rotational speed	15-21 rpm	15-21 rpm
Secondary drying (20-25°C)	10-15 min	10-15 min

Effect of pore-former on disintegration time of shellac-coated soft gelatin capsules in gastrointestinal fluids as a function of coating level (after exposure to 0.1 N HCl for 120 min, followed by phosphate buffer pH 6.8)





Coating level for gastric resistance and disintegration in intestine within 60 min of shellac-coated soft gelatin capsules containing different plasticizers and/or pore formers (after exposure to 0.1 N HCl for 120 min, followed by phosphate buffer pH 6.8)

		Coating level, mg/cm²	
Additive	Concentration, % w/w	Minimum for gastric resistance	Maximum for disintegration in intestine within 60 min
TEC	5 %	7.0	7.0
Sorbic acid	5 %	7.2	9.8
	7.5 %	8.7	10.0
	10 %	8.3	> 12.1
Shellac films plasticized with TEC (10 % w/w)			
HPMC E5	25 %	7.2	> 10.3

Disintegration behavior and mechanical properties of shellac-coated soft gelatin capsules contained different additives as plasticizer and/or pore former in gastrointestinal fluids (coating level, 9-10 mg/cm²; after exposure to 0.1 N HCl for 120 min, followed by phosphate buffer pH 6.8)

Additive, % w/w		Hardness, N				Disintegration time, min in buffer pH 6.8
		Dry state	0.1 N HCl (120 min)	Buffer pH 6.8 (10 min)	Buffer pH 6.8 (30 min)	
TEC	5 %	244.2 (37.3)	205.1 (21.6)	151.8 (19.6)	125.1 (16.1)	71 (2)
Sorbic acid	5 %	252.6 (44.4)	76.9 (23.5)	71.7 (18.5)	40.9 (19.0)	44 (2)
Shellac plasticized with TEC (10 % w/w)						
HPMC E5	25 %	230.9 (20.2)	89.1 (5.8)	63.7 (20.3)	44.6 (2.7)	37 (11)

Effect of adipic acid on the gastric resistance of shellac-coated soft gelatin capsules (exposure to 0.1 N HCl)

Additive	Concentration, % w/w	Coating level, mg/cm^2	Disintegration time, min in 0.1 N HCl
None	-	8.0	81 (28)
		9.7	90 (0)
		11.4	> 120
Adipic acid	5 %	7.6	11 (1)
		9.4	23 (0)
		11.5	43 (1)

1.4 Aqueous shellac coatings

PREPARATION OF AQUEOUS SHELLAC SOLUTION

FORMULATION:

	Composition, % w/w	
Shellac	10.00	10 % w/w based on total solution
Ammonium hydroxide solution (NH_4OH, 10 % v/v)	5.25	
Water	84.75	
Total	**100.00**	

COATING OF DRUG-LOADED PELLETS

FORMULATION:

	Composition, % w/w		
	Formulation I	Formulation II	
Aqueous shellac solution			10 % w/w polymer content
Shellac	9.95	9.80	
Water	89.55	88.24	
Plasticizer	0.50	1.96	5-20 % w/w based on the polymer mass
Total	**100.00**	**100.00**	

PROCESSING PARAMETER:

Fluidized bed coater	Glatt GPCG-1	Hüttlin Kugelcoater HKC 05 / UNILAB 05
Batch size	1.0 kg	0.5 kg
Inlet air temperature	60-65°C	60-65°C
Product temperature	50-51°C	48-52°C
Outlet air temperature	38-42°C	40-44°C
Air flow rate	90-100 m³/h	25-50 %
Atomizing pressure	1.2 bar	0.4 bar
Microclimate pressure	-	0.2 bar
Spray rate	5-7 g/min	2-4 g/min
Spray nozzle diameter	1.2 mm	0.8 mm – 2 components
Secondary drying (23-25°C)	10-15 min	10-15 min

COATING OF SOFT GELATIN CAPSULES

FORMULATION I:

	Composition, % w/w	
Aqueous shellac solution		10 % w/w polymer content
Shellac	9.95	
Water	89.55	
Plasticizer	0.50	5 % w/w based on the polymer mass
Total	**100.00**	

FORMULATION II:

	Composition, % w/w		
	Formulation I	Formulation II	
Aqueous shellac solution			10 % w/w polymer content
Shellac	9.85	9.70	
Water	88.67	87.38	
Plasticizer	0.49	0.49	5% w/w based on the polymer mass
Additive	0.99	2.43	10-25 % w/w based on the polymer mass
Total	**100.00**	**100.00**	

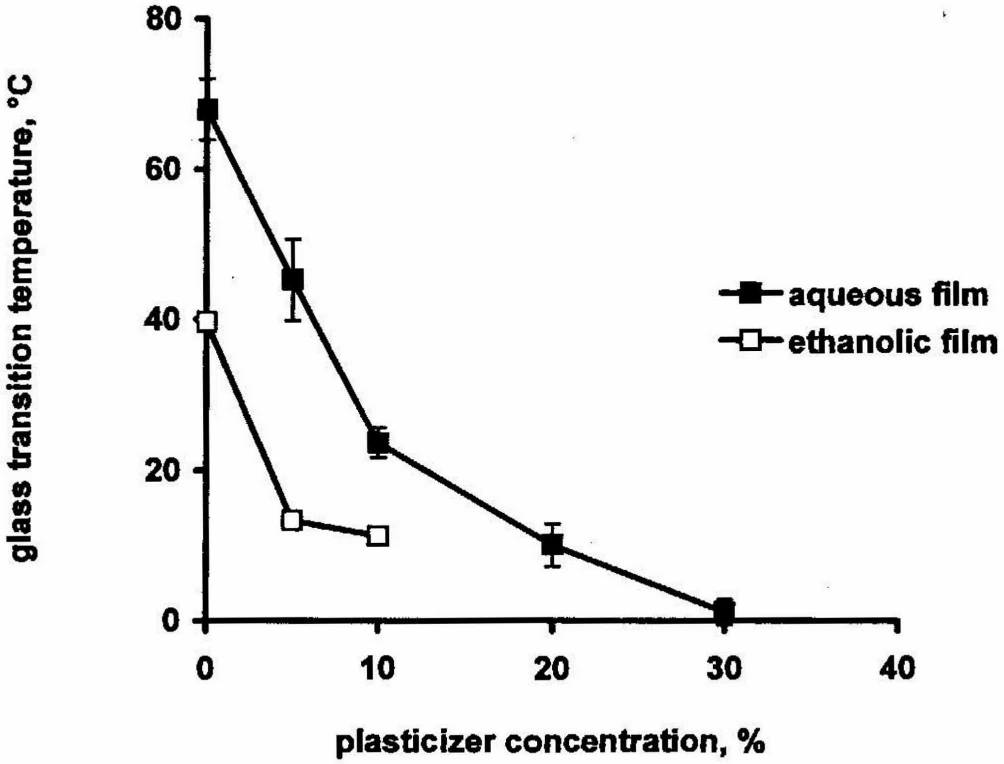
PROCESSING PARAMETER:

Glatt GC-300	
Batch size	1.2 kg
Inlet air temperature	60-65°C
Product temperature	50-52°C
Outlet air temperature	38-42°C
Air flow rate	130 m³/h
Atomizing pressure	1.2 bar
Spray rate	5-7 g/min
Spray nozzle diameter	1.2 mm
Rotational speed	15-21 rpm
Secondary drying (20-25°C)	10-15 min

Physical properties and compatibility of aqueous shellac films containing different plasticizers (ammoniated aqueous solution)

Plasticizer, % w/w	Film appearance	Film flexibility
None	clear	very brittle
PG		
10 %	clear	brittle
20 %	clear	flexible
30 %	clear	very flexible
Glycerin		
10 %	clear	brittle
20 %	clear	flexible
30 %	clear	very flexible
PEG 400		
10 %	clear	brittle
20 %	clear	flexible
30 %	clear	very flexible
TEC		
10 %	clear	very brittle
20 %	clear	brittle
30 %	cloudy	flexible
Castor oil		
10 %	clear, oily	very brittle
20 %	clear, oily	very brittle
30 %	clear, oily	very brittle
AMG		
10 %	cloudy, oily	very brittle
20 %	cloudy, oily	very brittle
30 %	cloudy, oily	very brittle

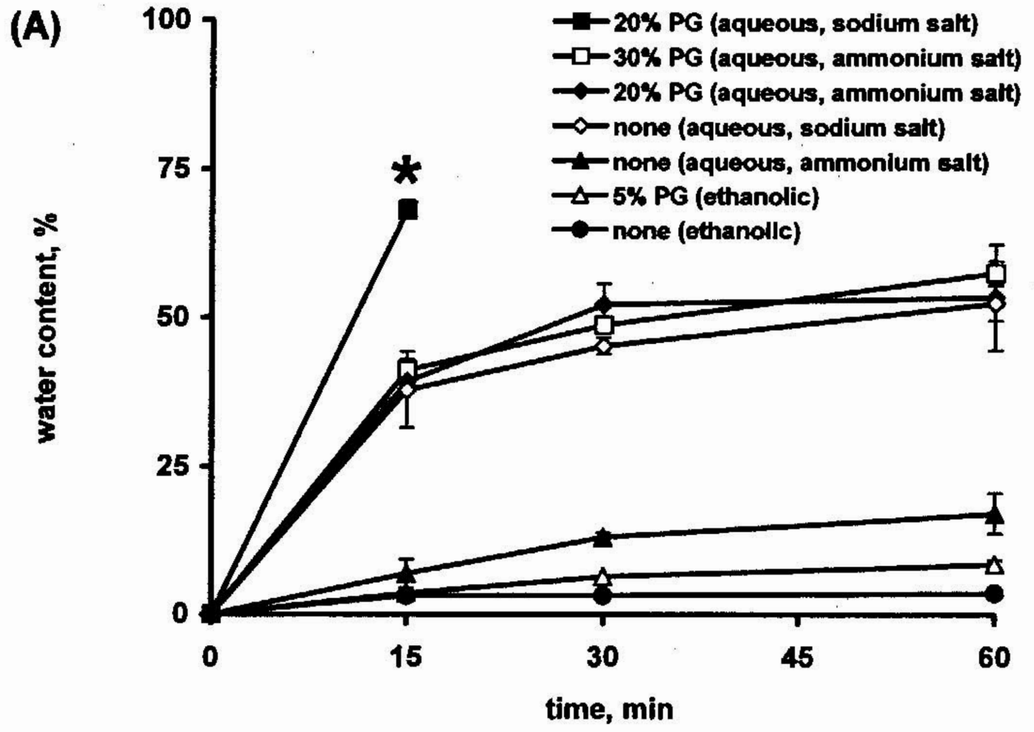
Glass transition temperature (Tg) of shellac films plasticized with propyleneglycol (%, w/w based on the mass of the polymer)

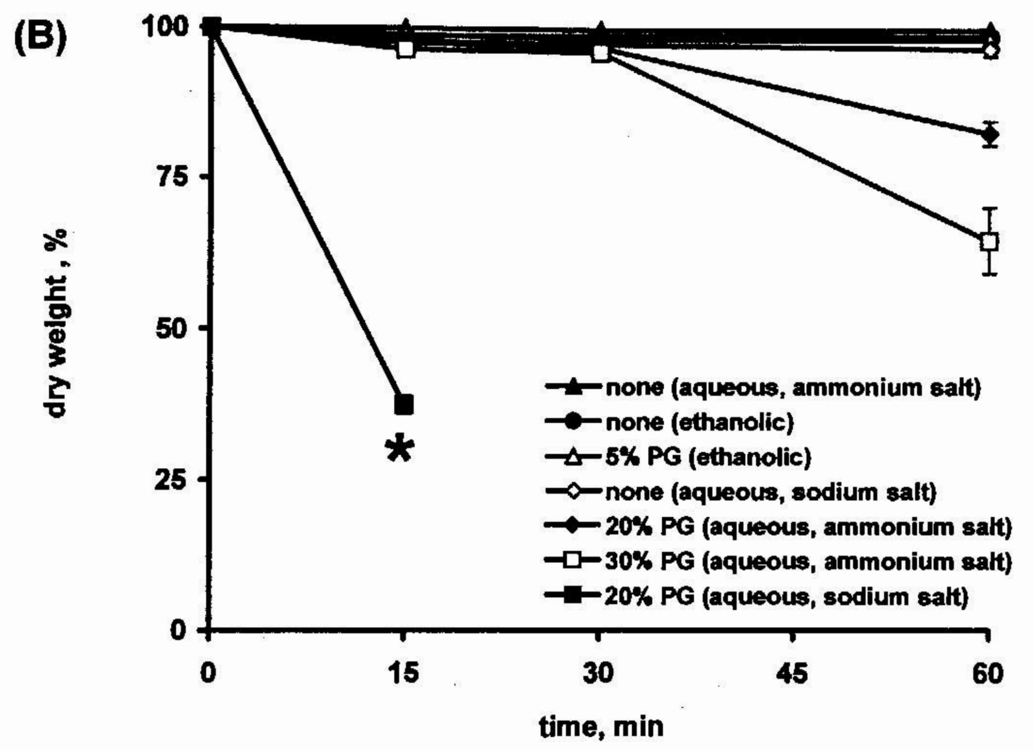


Effect of neutralization on mechanical properties of thin shellac films plasticized with propylene glycol in dry and wet states after exposure to the dissolution media for 120 min (0.1 N HCl and phosphate buffer pH 6.8, respectively)

PG, % w/w of polymer	Elongation, %			Modulus at puncture, kPa		
	Dry film	0.1 N HCl	Buffer pH 6.8	Dry film	0.1 N HCl	Buffer pH 6.8
ETHANOLIC SYSTEM						
None	1.0 (0.1)	10.1 (2.5)	26.0 (1.8)	67.5 (43.6)	19.8 (3.7)	9.2 (1.2)
AQUEOUS SYSTEM						
Ammonium salt						
None	0.1 (0.0)	40.4 (4.4)	26.8 (4.2)	673.9 (129.8)	92.4 (15.3)	84.4 (30.4)
20 %	60.0 (6.2)	21.5 (3.7)	7.2 (0.8)	106.8 (9.8)	71.9 (5.4)	124.1 (24.0)
30 %	81.5 (21.3)	23.2 (9.3)	10.1 (4.4)	46.2 (2.5)	117.8 (28.3)	137.4 (35.3)
Sodium salt						
None	0.0 (0.0)			1585.9 (602.4)		
20 %	42.5 (7.3)	Films dissolved		121.1 (24.5)	Films dissolved	
30 %	69.2 (12.8)			52.4 (4.3)		

Effect of neutralization on relationship between water content (%) and dry weight (%) versus time (min) of thin shellac films (in 0.1 N HCl; plasticizer, propyleneglycol)
* films dissolved in the dissolution medium after 15 min





Physical and mechanical properties of thin shellac films in the dry and wet states (ammoniated aqueous solution; after exposure to 0.1 N HCl for 120 min)

Pore former, % w/w	Visual appearance (dry film)	Puncture strength, MPa		Elongation, %	
		Dry film	Wet film	Dry film	Wet film
None	clear	3.71 (1.80)	11.3 (1.51)	0.12 (0.01)	26.74 (2.31)
TEC 5 %	clear	3.62 (0.32)	9.10 (2.00)	0.21 (0.04)	29.95 (1.14)
Ammonium sorbate 5 %	clear	3.75 (0.14)	9.22 (5.11)	0.10 (0.00)	27.73 (0.80)
Shellac-based films plasticized with TEC (5 % w/w)					
Gelatin 10 %	clear	3.55 (1.93)	7.33 (1.08)	0.45 (0.02)	31.92 (0.15)
Alginic acid 10 %	cloudy	3.42 (2.83)	8.14 (3.22)	0.51 (1.00)	32.65 (1.12)
HPMC E5 25 %	clear	4.12 (1.11)	8.76 (2.43)	0.23 (0.01)	30.12 (1.44)

Mechanical properties and disintegration behavior of aqueous shellac-coated soft gelatin capsules contained different additives as pore former in gastrointestinal tract (ammoniated aqueous solution; coating level, 19-23 mg/cm²; after exposure in 0.1 N HCl for 120 min, followed by phosphate buffer pH 6.8)

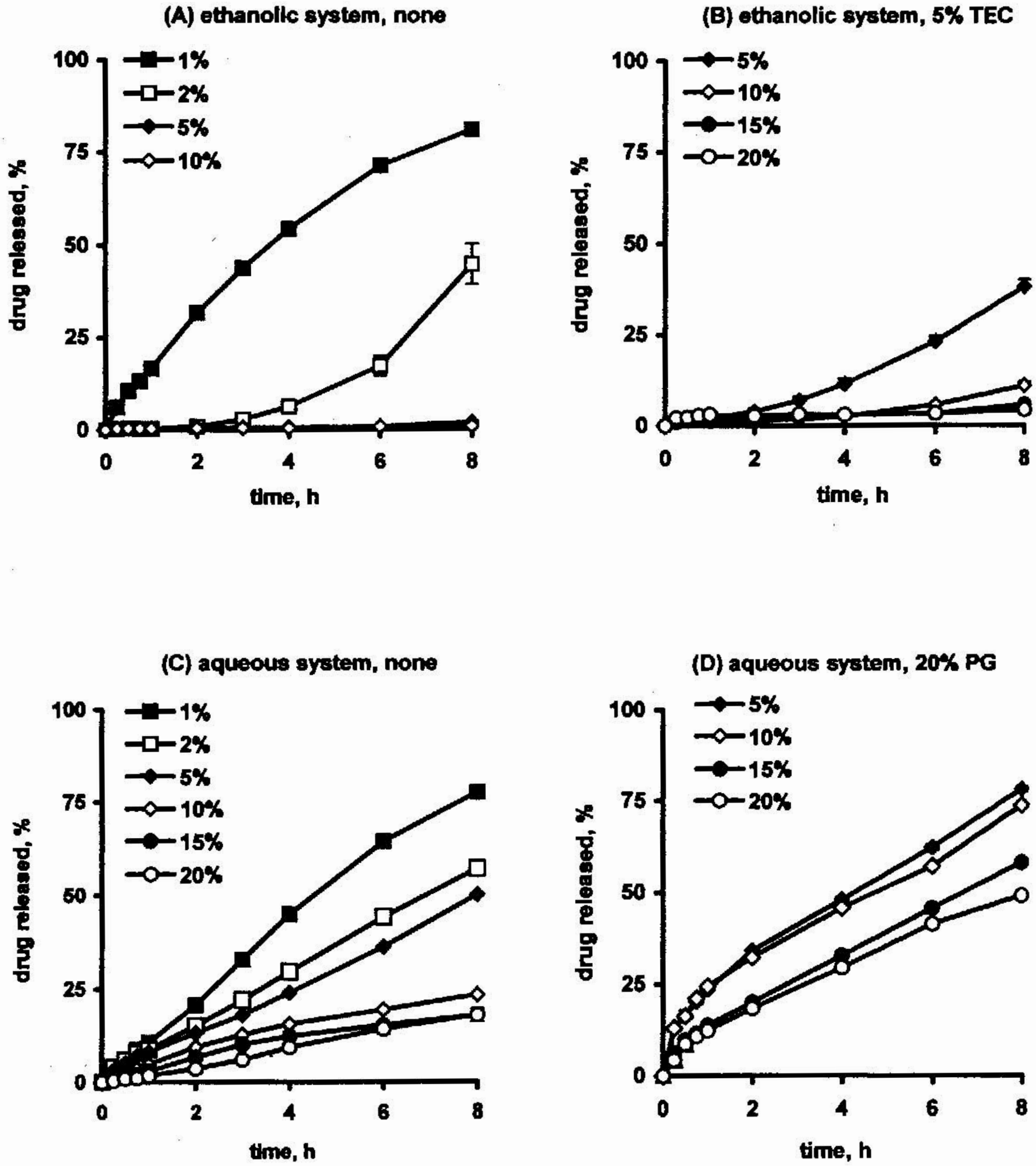
Pore former, % w/w	Hardness, N				Disintegration time, min in buffer pH 6.8
	Dry state	0.1 N HCl (120 min)	Buffer pH 6.8 (30 min)	Buffer pH 6.8 (60 min)	
None	185.8 (28.0)	85.5 (20.6)	17.9 (2.0)	9.3 (3.3)	60*
TEC 5 %	200.9 (32.9)	67.0 (15.5)	14.5 (2.0)	5.4 (1.8)	60*
Ammonium sorbate 5 %	145.0 (23.6)	75.5 (3.9)	15.5 (3.9)	9.6 (3.0)	25-30*
Shellac-based films plasticized with TEC (5 % w/w)					
Gelatin 10 %	200.9 (32.9)	84.7 (13.9)	29.3 (6.0)	4.8 (9.3)	25-30*
Alginic acid 10 %	159.9 (21.3)	55.0 (15.9)	14.6 (7.1)	6.8 (5.5)	25-30*
HPMC E5 25 %	174.5 (27.5)	capsules disintegrated in 0.1 N HCl after 20 min			

* capsule cores softened and swelled, but film coating were remained intact

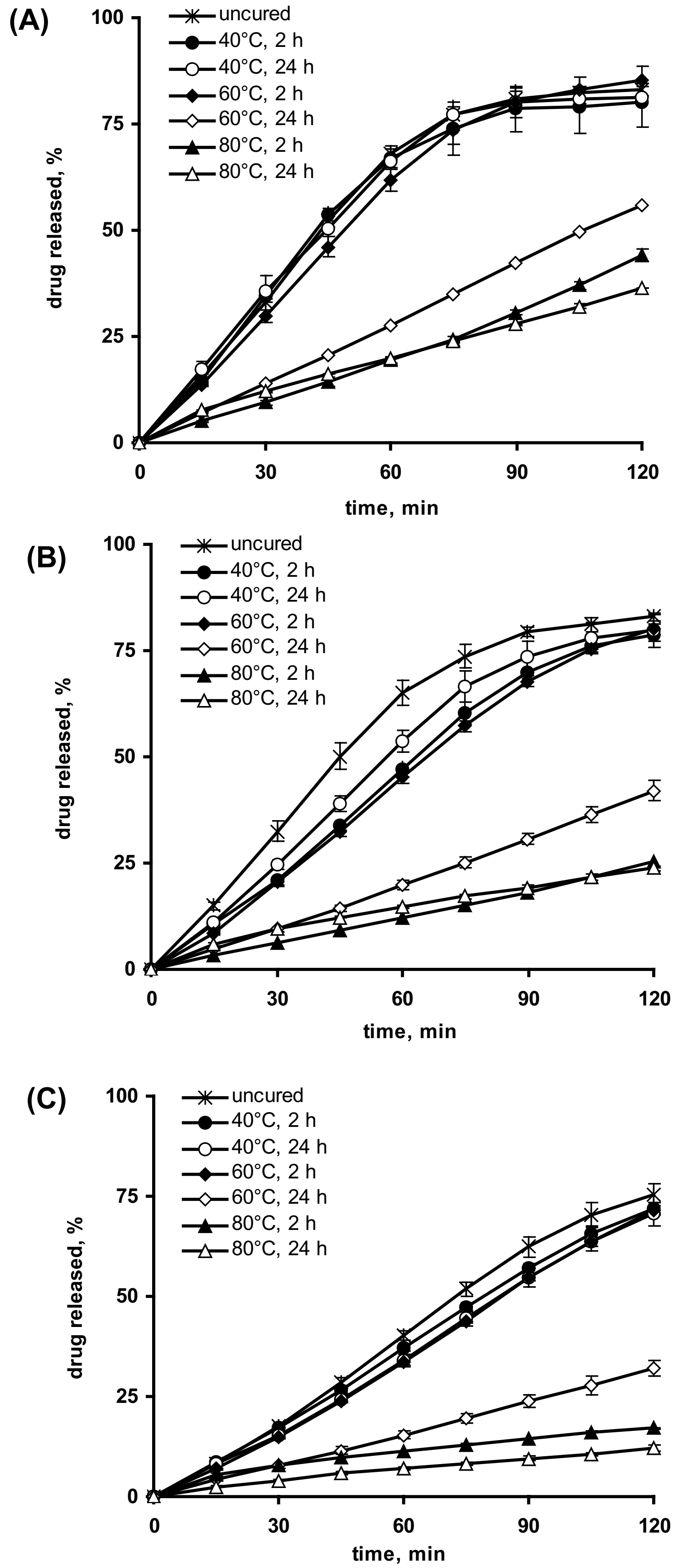
Effect of type of additive as pore former on relationship between dry weight (%) and water content (%) of thin shellac films (ammoniated aqueous solution; after exposure to 0.1 N HCl for 120 min, followed by phosphate buffer pH 6.8 for 60 min)

Pore former,	Dry weight, %		Water content, %	
% w/w	0.1 N HCl	Buffer pH 6.8	0.1 N HCl	Buffer pH 6.8
None	99.62 (0.03)	98.52 (0.59)	23.80 (1.69)	54.43 (1.70)
TEC 5 %	99.15 (0.69)	98.35 (0.58)	27.57 (2.90)	51.06 (0.18)
Ammonium sorbate 5 %	99.47 (0.24)	99.68 (0.01)	17.77 (0.27)	65.91 (0.10)
Shellac-based films plasticized with TEC (5 % w/w)				
Gelatin 10 %	99.45 (0.17)	72.55 (3.26)	37.86 (0.37)	68.85 (1.93)
Alginic acid 10 %	99.42 (0.55)	70.21 (0.72)	37.23 (2.97)	66.50 (6.33)
HPMC E5 25 %	94.42 (1.28)	62.75 (3.13)	40.34 (1.10)	67.16 (2.68)

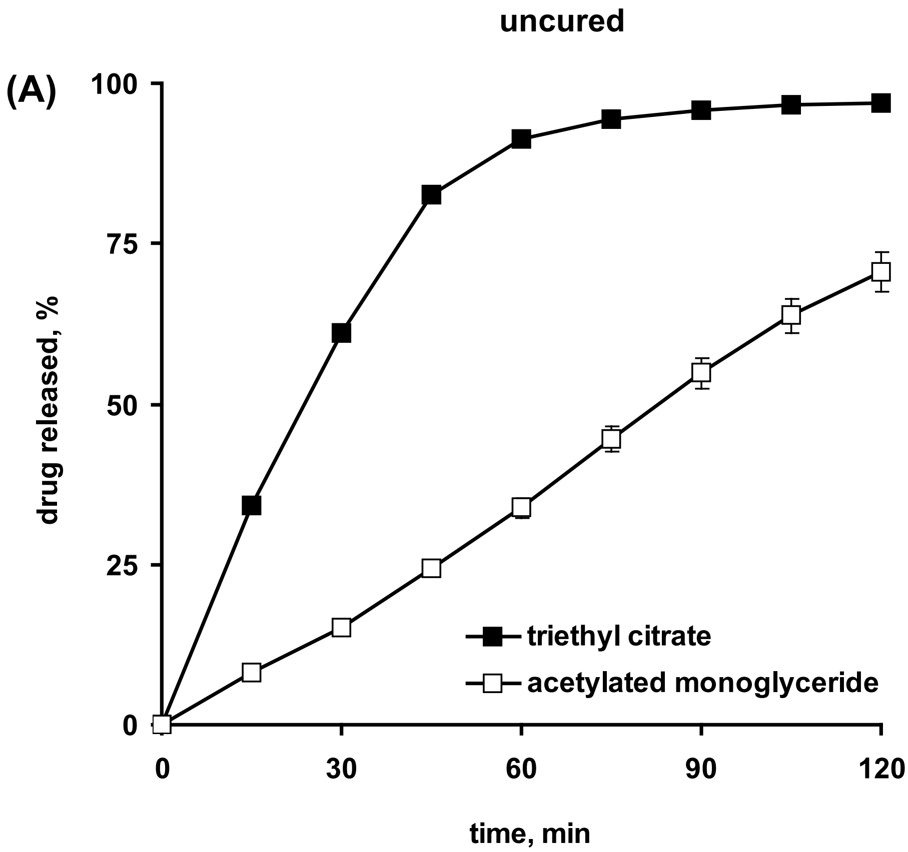
Effect of neutralization on the drug release in 0.1 N HCl from pellets coated with shellac as a function of coating level (acetaminophen)

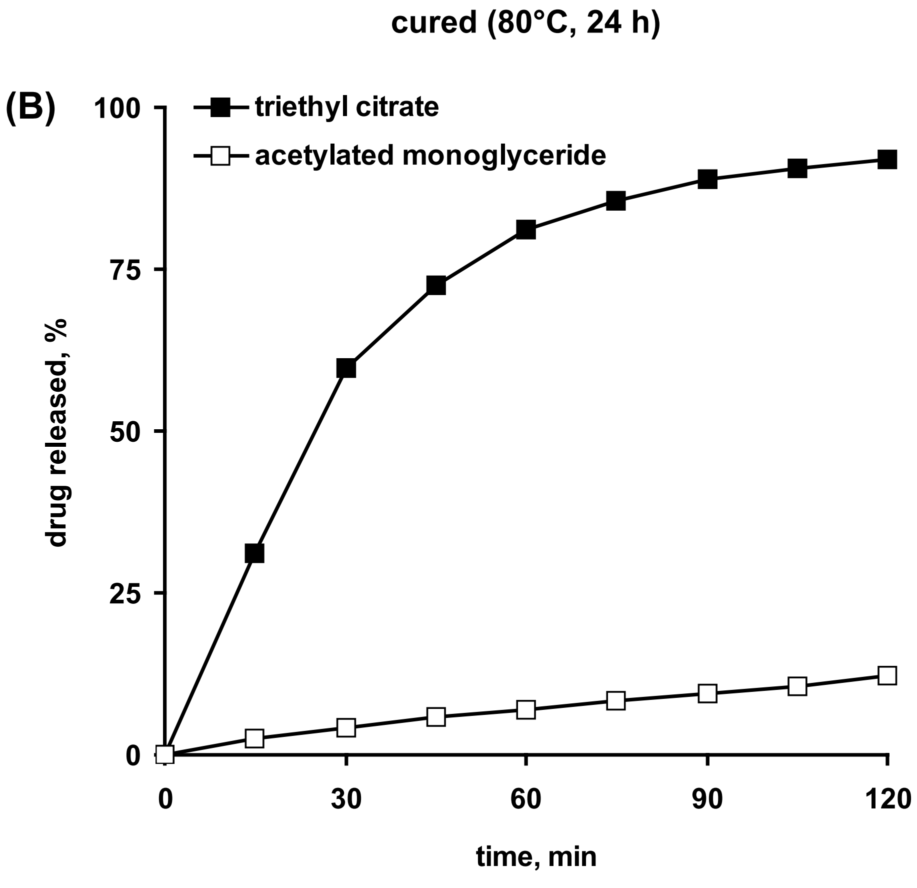


Effect of curing conditions on the acetaminophen release in 0.1 N HCl from shellac-coated pellets containing 40 % acetylated monoglyceride: at different coating levels (A) 18.1 %; (B) 22.0 %; and (C) 25.2 %.

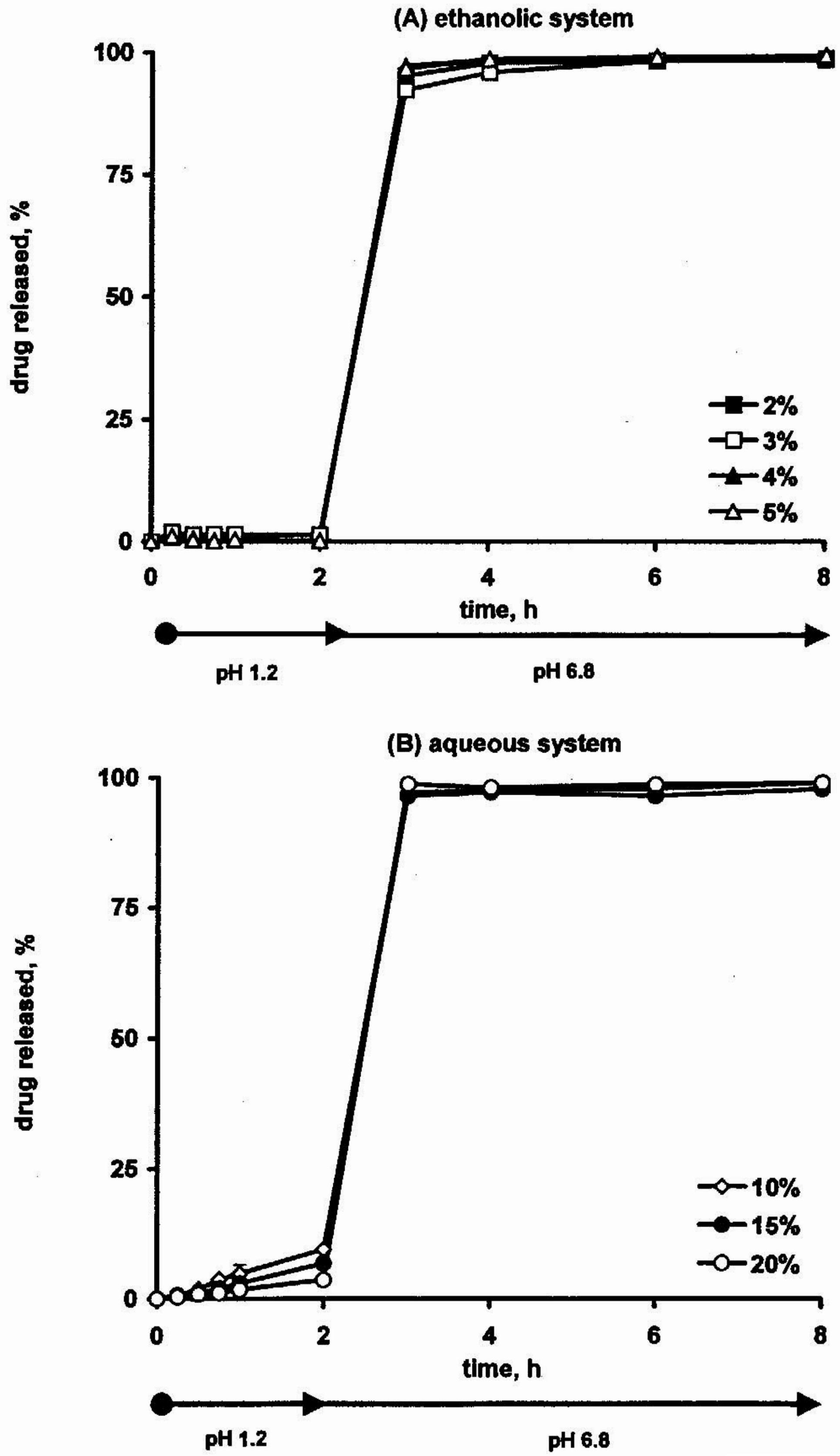


Effect of plasticizer (40 % w/w, based on the polymer) on acetaminophen release in 0.1 N HCl from shellac-coated pellets at coating levels of 23.9-25.2 %: (A) uncured pellets; and (B) cured pellets (80°C, 24 h).

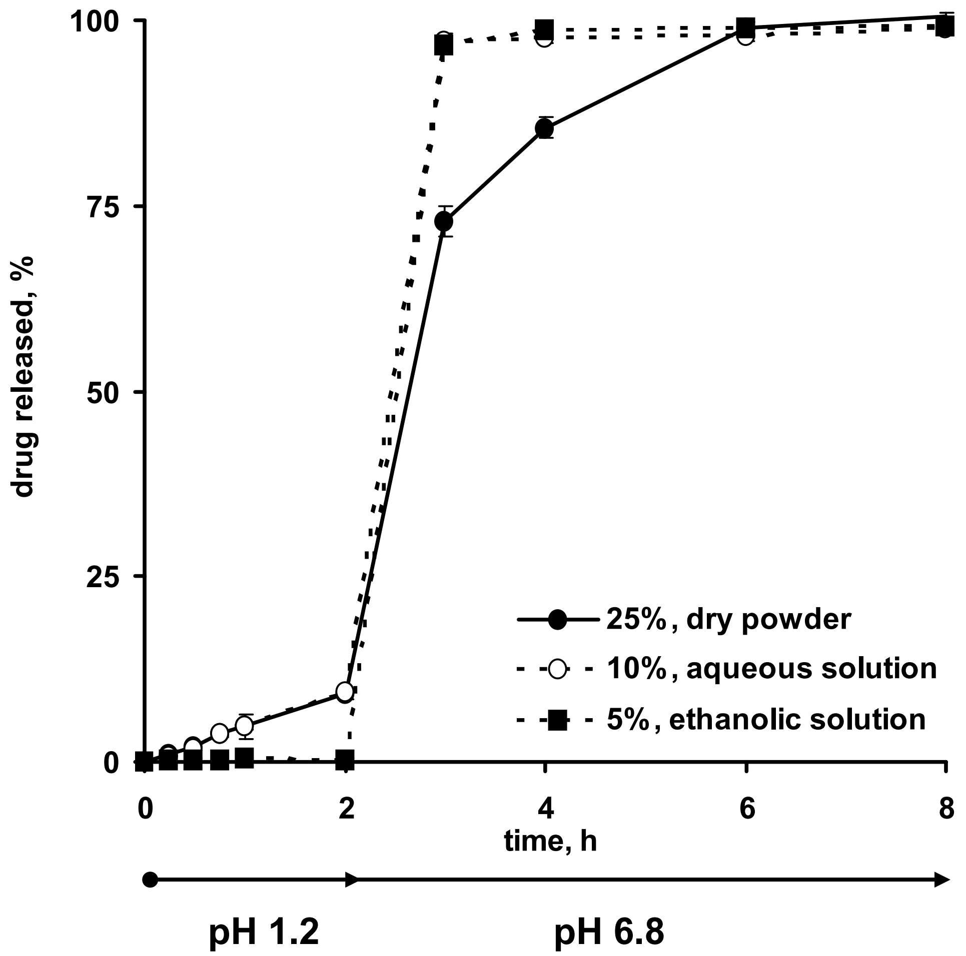




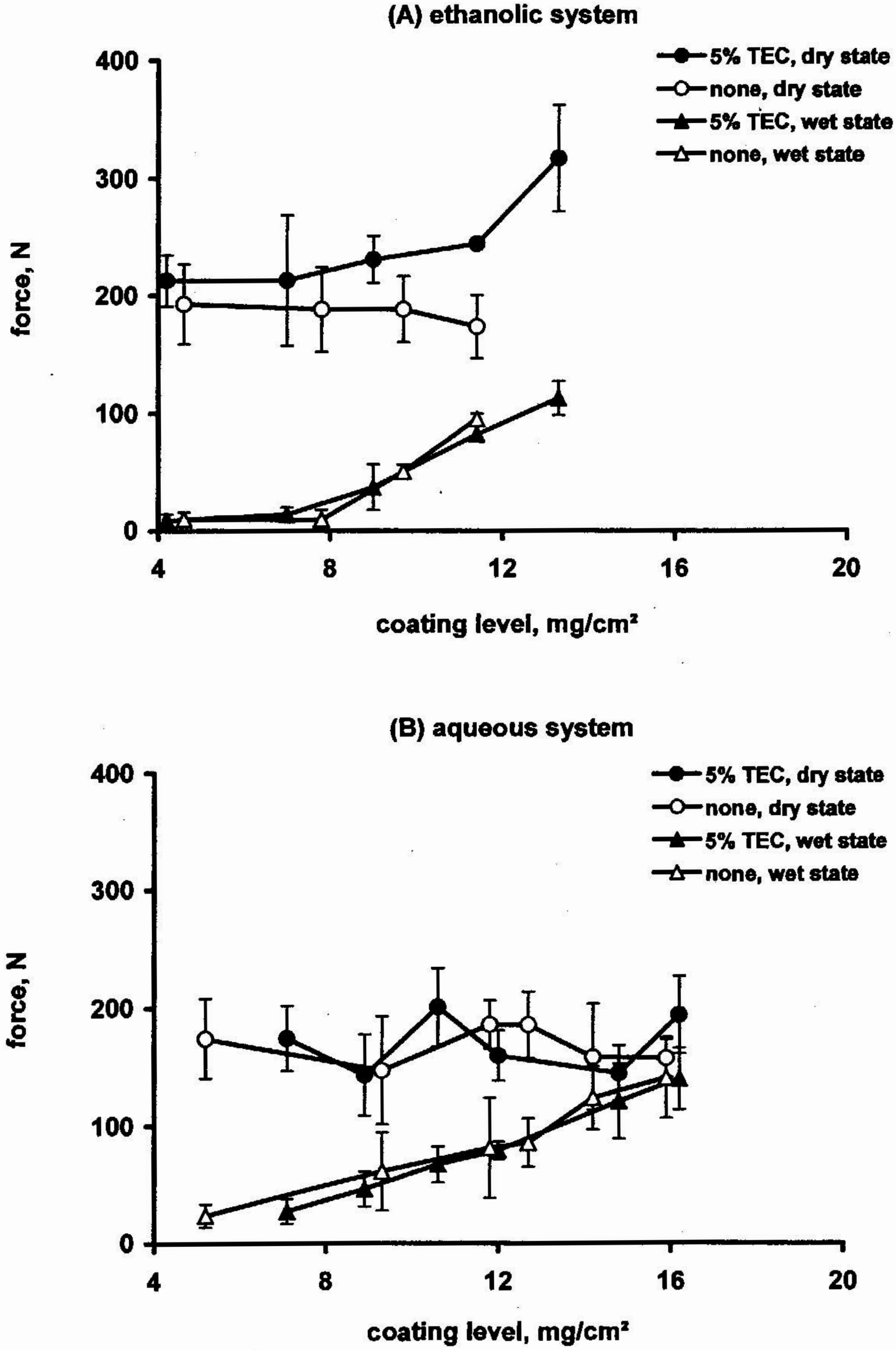
Effect of neutralization on the drug release in gastrointestinal fluids from pellets coated with shellac as a function of coating level (A) ethanolic solution and (B) ammoniated aqueous solution (model drug, acetaminophen; without plasticizer; medium change after 2 h)



Drug release from pellets coated with different shellac-coated formulations (%, coating level): ethanolic shellac solution, 5 % triethyl citrate; ammoniated aqueous shellac solution, none; shellac powder, 40 % acetylated monoglyceride, curing at 80°C for 24 h (release medium change after 2 h).



Effect of coating level on hardness of shellac-coated soft gelatin capsules in dry and wet states (after exposure to 0.1 N HCl for 120 min)



Effect of coating level on disintegration behavior of enterically coated soft gelatin capsules with shellac prepared from ethanolic- and aqueous-based systems (after exposure to gastric medium for 120 min, followed by intestinal medium)

TEC, % w/w of polymer	Coating level, mg/cm^2	Disintegration time, min	
		0.1 N HCl	Buffer pH 6.8
ETHANOLIC SYSTEM			
None	4.6	90 ± 0	
	7.8	> 120	28 ± 15
	9.7	> 120	> 60
	11.4	> 120	> 60
5 %	4.2	111 ± 5	
	7.0	> 120	48 ± 2
	9.0	> 120	> 60
	11.4	> 120	> 60
AQUEOUS SYSTEM			
None	9.3	30 ± 1	
	11.8	78 ± 9	
	15.4	113 ± 2	
	19.2	> 120	51 ± 16
	21.2	> 120	> 60
5 %	9.7	> 120	> 60
	13.3	> 120	> 60
	15.5	> 120	> 60
	18.2	> 120	> 60
	20.9	> 120	> 60

2. Zein as a Natural Coating Material

Table of content:

Summary

Organic solutions

In general hydrophilic plasticizer exerted a stronger plasticizing effect than the hydrophobic ones (page 6).

For zein films casted from ethanolic solutions 10% plasticizer based on the polymer amount were sufficient (page 7).

Pellets coated with ethanolic zein solutions showed in pH 1.2 medium a fast drug release while exhibiting in pH 6.8 extended drug release profiles. This release behaviour could be explained with the results of swelling studies on isolated zein films in media of varying composition (pages 11-16).

Zein coated pellets revealed excellent storage stability of drug release within 6 months at ambient conditions as well as under accelerated conditions (40°C / 75% r.h.) (pages 18-22).

The drug release from pellets, coated with different zein batches were compared. The effect of a purification step with petrolether was investigated, where lipophilic components were extracted, resulting in coatings with higher permeability and enhanced drug release (pages 24, 25).

Zein batches with varying xanthophyll-content were also investigated. From the results it can be concluded, that the drug release profile at high and low xanthophyll content is comparable (page 26).

Zein-shellac mix coatings were investigated in terms of reducing the influence of the proteolytic enzymes as well as the fast drug release in pH 1.2 (pages 30, 31).

At shellac contents ≥50% in the mix coating an increasing retardation of the drug release in the acidic pH could be achieved. The drug release was retarded even in the presence of the proteolytic enzyme pepsin, however faster, if compared to the drug release in the enzyme free medium (page 31).

In pH 6.8 the drug release from all mix coatings was retarded, while in pH 7.4 the formulations with a shellac content ≥50% revealed a fast drug release. This is related to the improved dissolution of shellac at higher pH (page 32).

At a zein-shellac ratio of 2:1 an extended drug release of theophylline over an 8h period could be achieved over the entire pH-range of the GIT (page 33).

With zein-shellac mixtures as coating material the drug release even of freely soluble drugs could be retarded. This was shown with the freely soluble model drug chlorpheniramine maleate (page 34).

Shellac topcoats over zein-coated pellets could effectively retard the drug release already at very low topcoat levels (~1% for slightly soluble drugs, ~5% for freely soluble drugs). Moreover the drug release in pH6.8 could be further retarded (pages 38-40).

The extended drug release profile could be explained by swelling studies on the coated pellets, where a restriction in swelling of the top coated pellets could be found, compared to the pure zein-coated pellets (page 41).

Aqueous dispersions

Different methods for the preparation of aqueous zein dispersions were investigated. Stable dispersions with mean particle size below 400nm could be achieved at low polymer concentrations (page 43).

A reduction of the surface tension of the water phase during the preparation did not yield in a decreased particle size. Some surface-active additives even lead to a destabilization of the system, expressed by an increase of the particle size (page 45).

Different solvents suitable as organic phase for the preparation of the aqueous dispersions were evaluated. Dispersions prepared from methanolic solutions yielded in dispersions with smaller particle size compared to the standard system prepared from ethanolic solution (page 46).

The preparation of aqueous dispersions from different zein batches was compared. Hereby there was obvious, that the stability of the resulting aqueous dispersion correlated to the intensity of the colour of the respective batch of zein. By measurements of the glass transition temperature the plasticizing effect of xanthophyll could be shown (pages 47, 48).

The key role of water as a plasticizer for the preparation of zein films from aqueous dispersions could be shown (page 50).

In general, zein films prepared from aqueous dispersions required higher plasticizer concentrations than films cast from ethanolic solutions (page 51).

Pellets, coated with an aqueous zein dispersion (3% w/v polymer content) up to a coating level of 20 % exhibited an extended drug release over 6h in pH 6.8 (page 52).

Aqueous dispersions with high polymer contents (> 8% w/v) lead to increased instability in particle size and agglomeration (page 54).

Different methods for the preparation of redispersible powder formulations were evaluated: milling, spay drying and lyophilization. The strong increase in particle size during lyophilization was caused by the freezing step. The effect of different additives as lyo-protectors was investigated (page 57-66).

Moisture protection

The potential of zein coatings to protect moisture-sensitive drugs was investigated. The hydrolysis of the moisture-sensitive model drug acetylic salicylic acid was hereby comparably well suppressed as with HPMC, the standard polymer used for such tasks (pages 71, 72).

Taste masking

The superior efficacy of zein compared to HPMC as coating material to retard the perception of the bitter taste of the model drug paracetamol was revealed. The dissolution profile at the used low coating levels (≤ 3%) was not affected (pages 73, 74).

Materials:

Polymers:

Zein:	Kaul GmbH, Elmshorn, Deutschland
Shellac:	Stroever Shellack Bremen

Plasticizer:

TEC:	Triethylcitrat, Morflex
TBC:	Tributhylcitrat, Morflex
ATEC:	Acetyltriethylcitrat, Morflex
ATBC:	Acetyltributylcitrat, Morflex
MCT:	medium chain triglycerides (Mygliol 812), Synopharm
Castor Oil:	Sigma
AMG:	acetylated monoglycerides (Myvacet 9-45), Quest International
Tartaric acid:	Jungbrunzlauer, Ladenburg, Deutschland
Glycerol:	Smith Kline Beecham
PEG 400:	Polyethylenglycol 400, BASF
Propylene glycol:	BASF

Additives:

Pepsin:	Sigma
Pancreatin:	Sigma
Tween 20:	Polysorbate 20, Roth
Tween 80:	Polysorbate 80, Unigema
Span 80:	Sigma
PEG 1500:	Polyethylenglycol 1500, BASF
Pluronic F 68:	Poloxamer 188, BASF
Pluronic F127:	Poloxamer 407, BASF

2.1 Zein from organic solutions

Physical properties, film appearance, compatibility, flexibility and other observations on zein films cast from ethanolic solutions with and without the addition of plasticizers (20% w/w based on polymer)

Plasticizer	Appearance	Compatibility	Flexibility	Shrinkage	Liftage	Stickyness
None	clear	-	-	-	-	-
TEC	clear	+	+++	+	-	-
TBC	opaque	+	+	+	+	-
ATEC	opaque	+	+	-	+	-
ATBC	opaque	+	+	+	+	-
MCT (812)	opaque	±	-	+	+++	-
Castor oil	clear	±	-	+	++	++
AMG	opaque	+	++++	-	-	+
Tartaric acid	slightly opaque	+	++++	-	-	±
Saccharose	clear	+	++++	-	-	+
Glycerol	clear	+	++++	++	-	-
PEG	clear	+	+++	+	-	-
Propylene Glycol	clear	+	++++	-	-	±

Effect of plasticizer concentration on the physical properties, film appearance, compatibility, flexibility and other observable film characteristics (plasticizer content is given w/w based on polymer content)

Plasticizer	**Plasticizer content**	Appearance	Compatibility	Flexibility	Shrinkage	Liftage	Stickyness
None	-	clear	-	-	-	-	-
Tartaric acid	10	clear	+	++++	-	-	+
	20	slightly opaque	+	++++	-	-	±
	40	clear	+	++++	-	-	+++
Propylene Glycol	10	clear	+	++++	-	-	+
	20	clear	+	++++	-	-	±
	40	clear	+	++++	-	-	++

Effect of different plasticizers on the plass transition temperature of zein films (plasticizer concentration: 20% w/w based on polymer)

Plasticizer	Tg [°C]
None	166.9 (0.97)
Tartaric acid	127.1 (1.65)
Sorbic Acid	93.8 (0.41)
Glycerol	77.1 (0.13)
Propylene Glycol	81.4 (1.08)

Effect of the plasticizer concentration on the glass transition temperature of zein films

Plasticizer	Plasticizer Conc. [% w/w]	Tg [°C]
None	-	166.9 (0.97)
Tartaric acid	20	127.1 (1.65)
	40	57.8 (0.44)

Formulation:

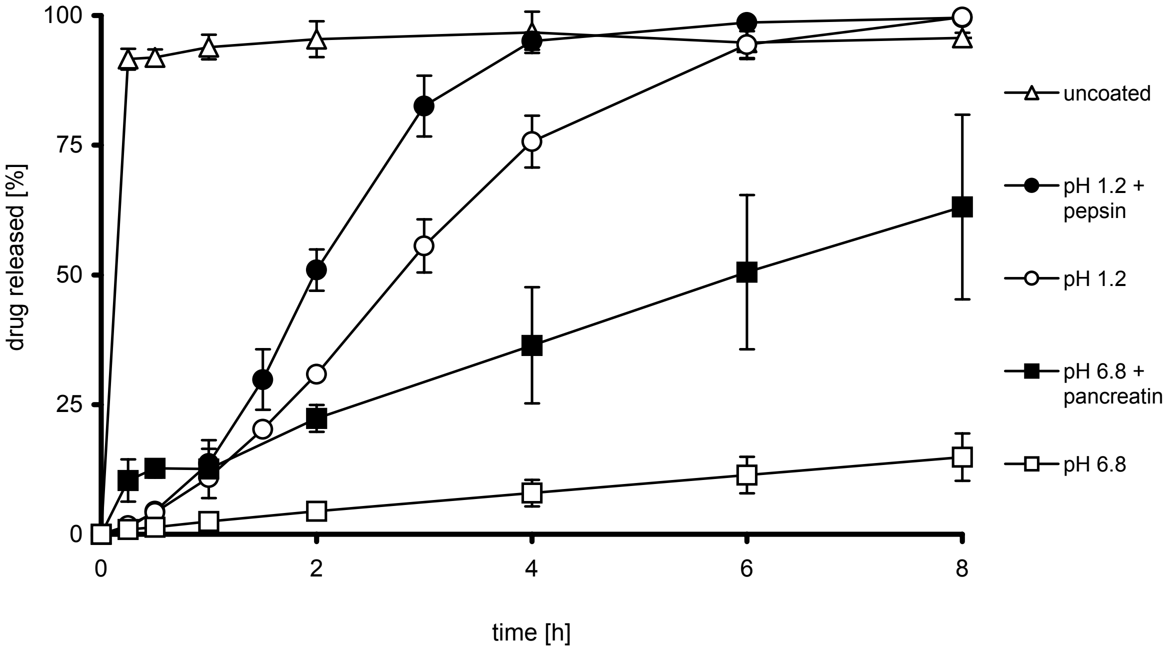
	Composition, % w/w	
Zein	10	10% w/w based on total solution
Propylenglycol	1	10% w/w based on polymer mass
Talc	3	30% w/w based on polymer mass
Ethanol (70% v/v)	86	
Total	**100**	

Process Parameters:

Coater: Hüttlin Kugelcoater HKC 05 / Unilab 05

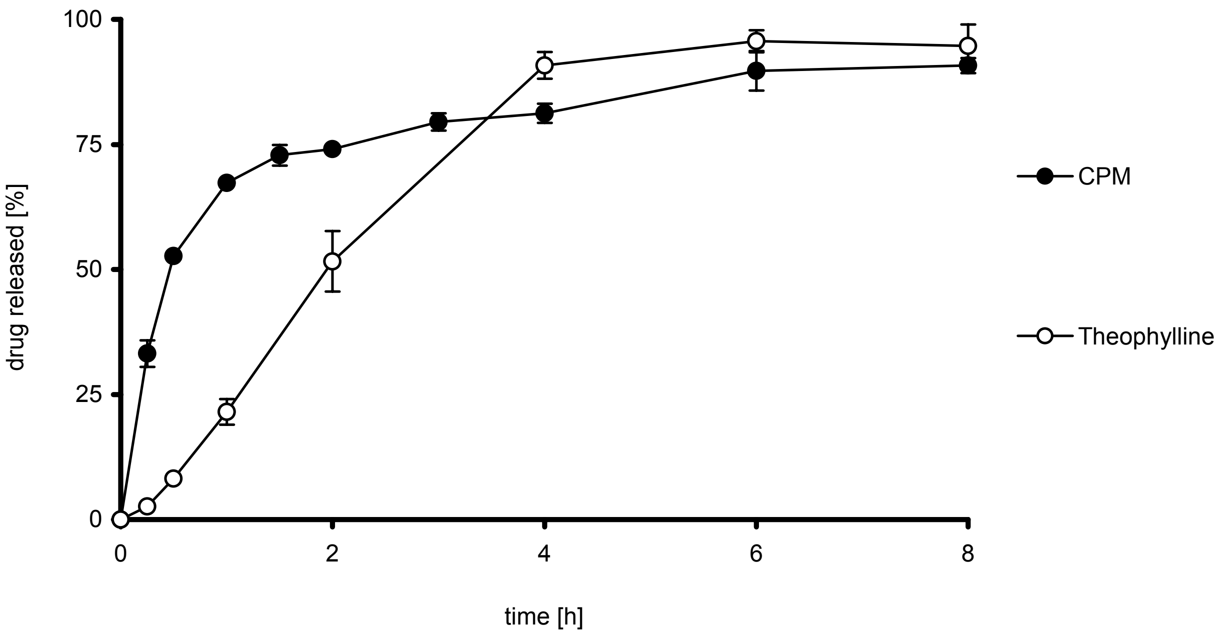
Parameters	Values
Batch size	0.4 kg
Inlet air temperature	30-32°C
Product temperature	27-30°C
Outlet air temperature	29-31°C
Air flow rate	50%
Atomizing pressure	0.4 bar
Microclimate pressure	0.2 bar
Spray rate	1.7–2.7 g/min
Spray nozzle diameter	0.8 mm – 2 nozzles
Secondary drying	15-20 min

Drug release from zein-coated pellets at 20% coating level in different media with and without proteolytic enzymes (model drug: theophylline)

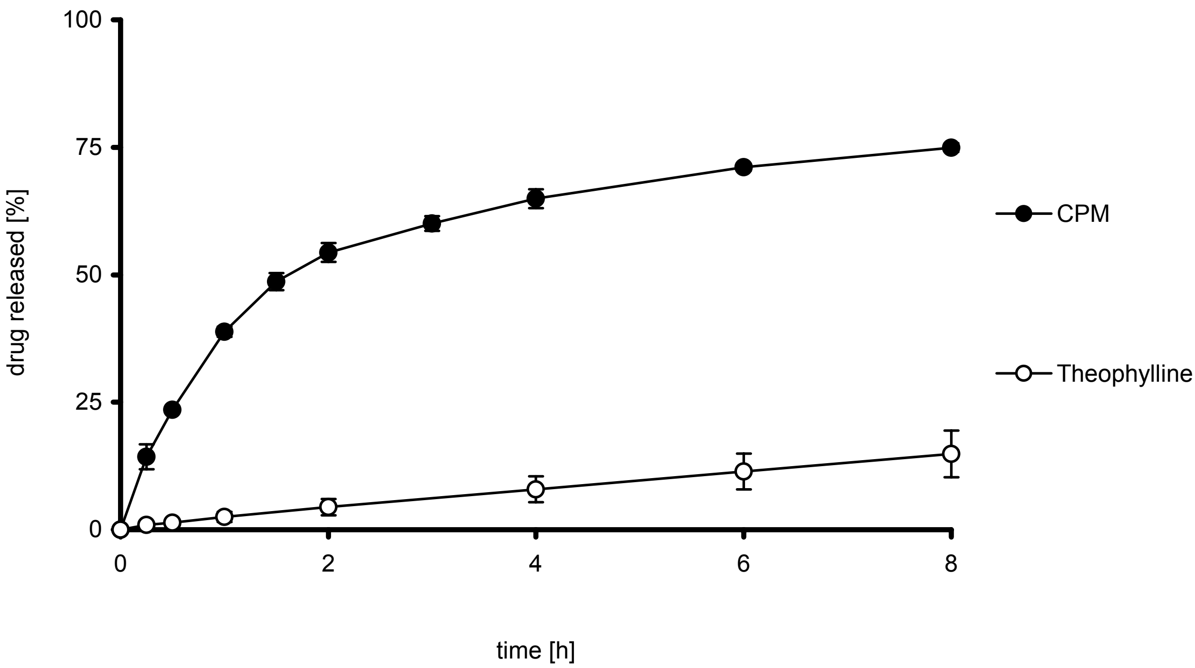


Drug release of different model drugs from zein coated pellets:
chlorpheniramine maleate (CPM; freely soluble) vs theophylline (slightly soluble)

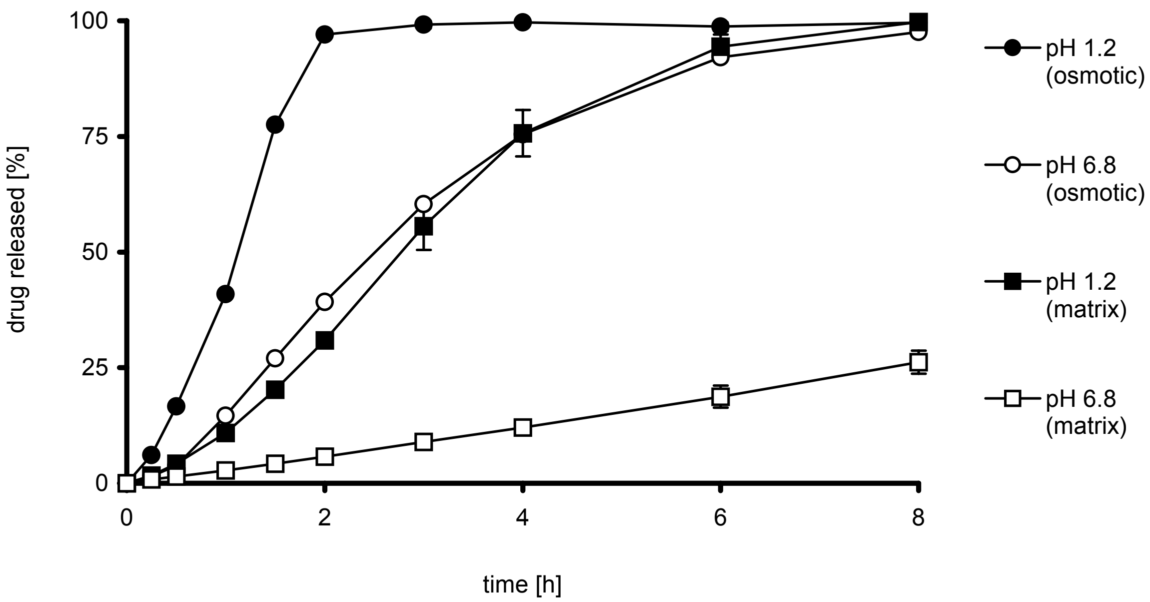
pH 1.2 + pepsin



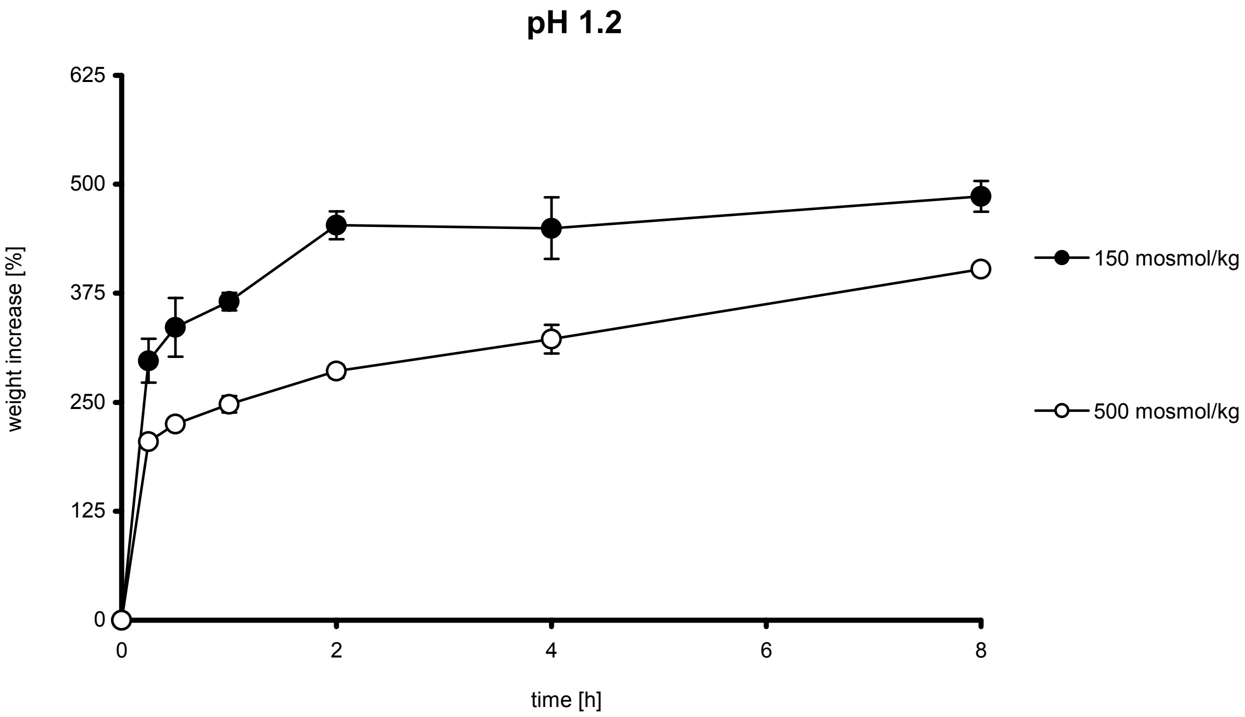
pH 6.8



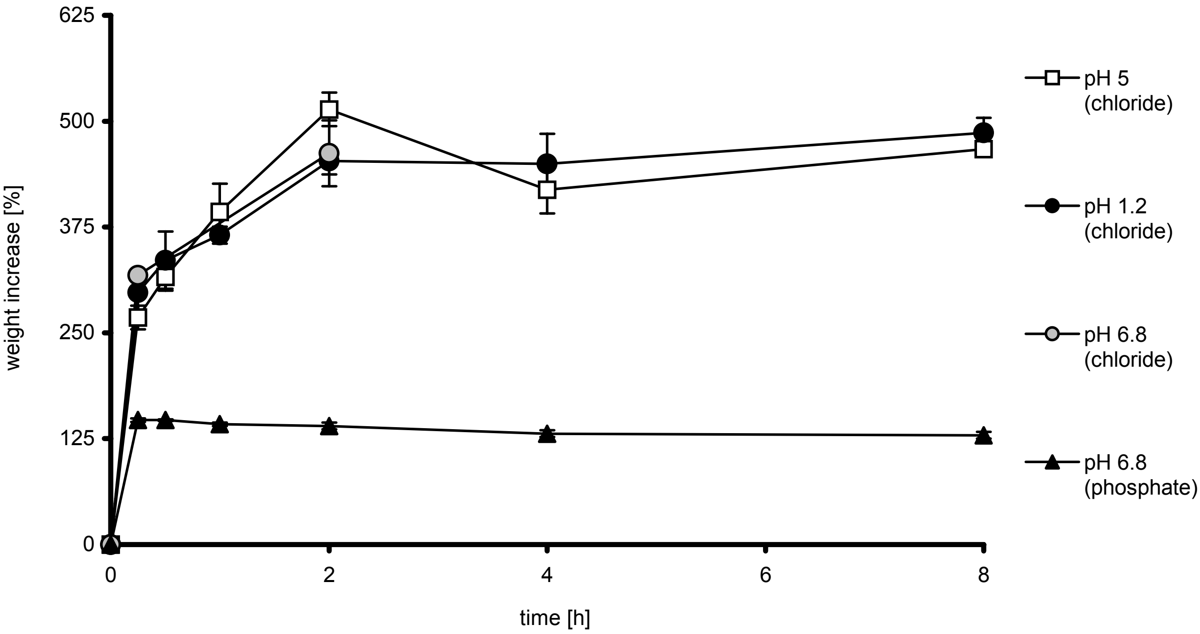
Influence of an osmotically active vs matrix core on drug release (model drug: theophylline; osmotically active core: 6% drug, 86.5% saccharose, 7.5% starch; matrix core: 94% drug; coating level: 20%)



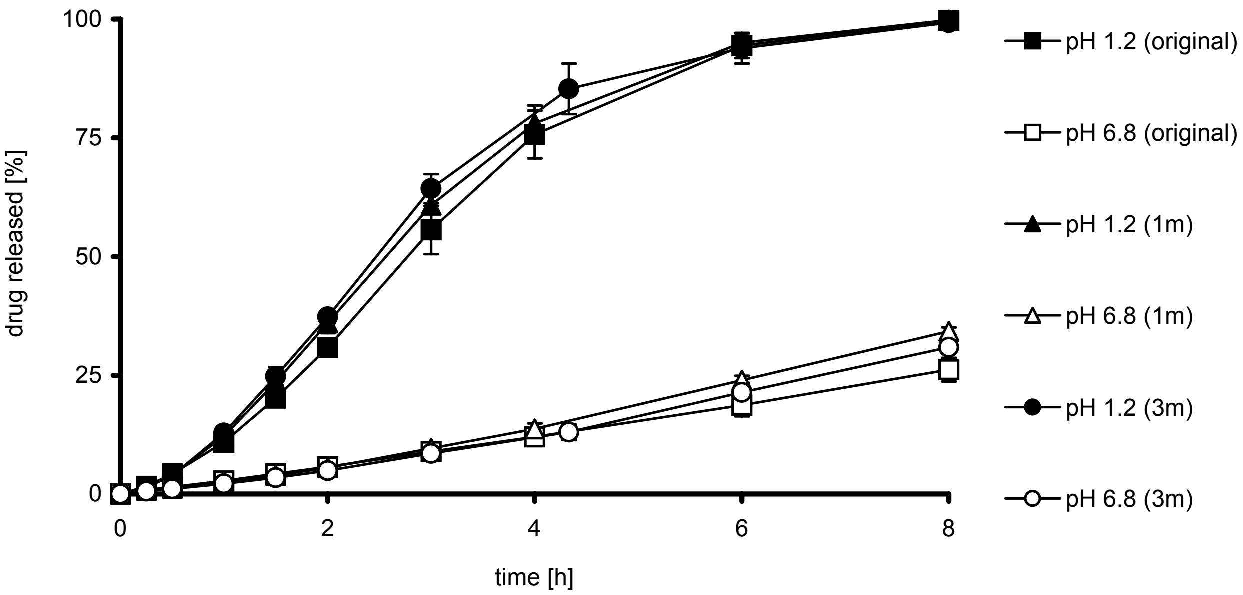
Effect of osmolarity on the swelling of zein films (films casted from ethanolic solution; media: 0.1N HCl (pH 1.2); osmolarity adjusted by NaCl)



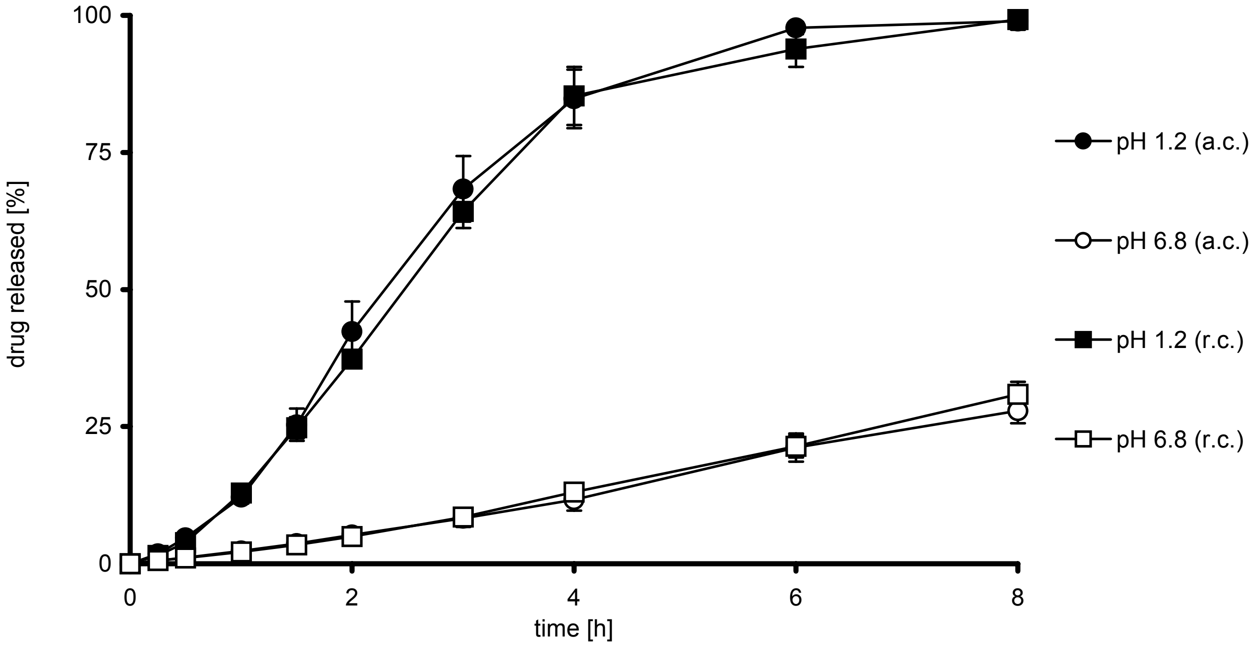
Effect of pH and buffer ion species on the swelling of Zein films (films casted from ethanolic solution; media: pH 1.2 – 0.1 N HCl; pH 5: water adjusted by HCl, pH 6.8 (chloride): water + NaCl, pH 6.8 (phosphate): phosphate buffer Ph.Eur)



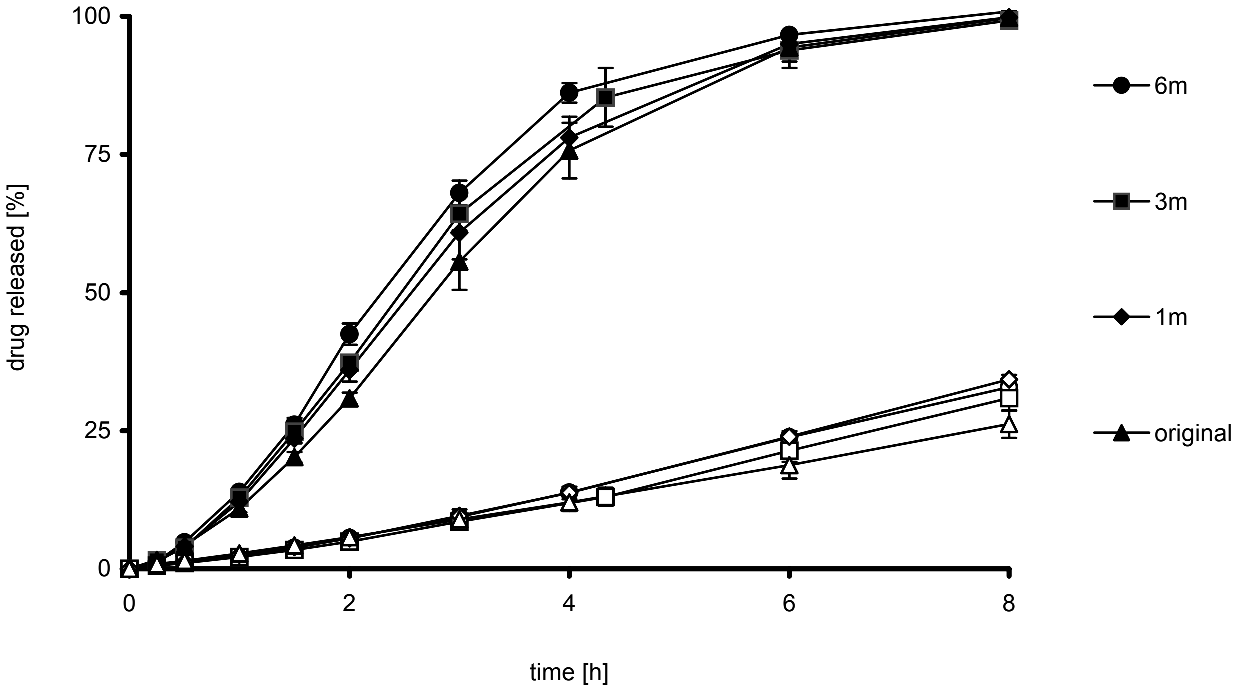
Stability of drug release from zein-coated pellets after different storage times (coating level: 20%; model drug: theophylline; storage times: 0 / 1 / 3 months; storage condition: *room conditions*)



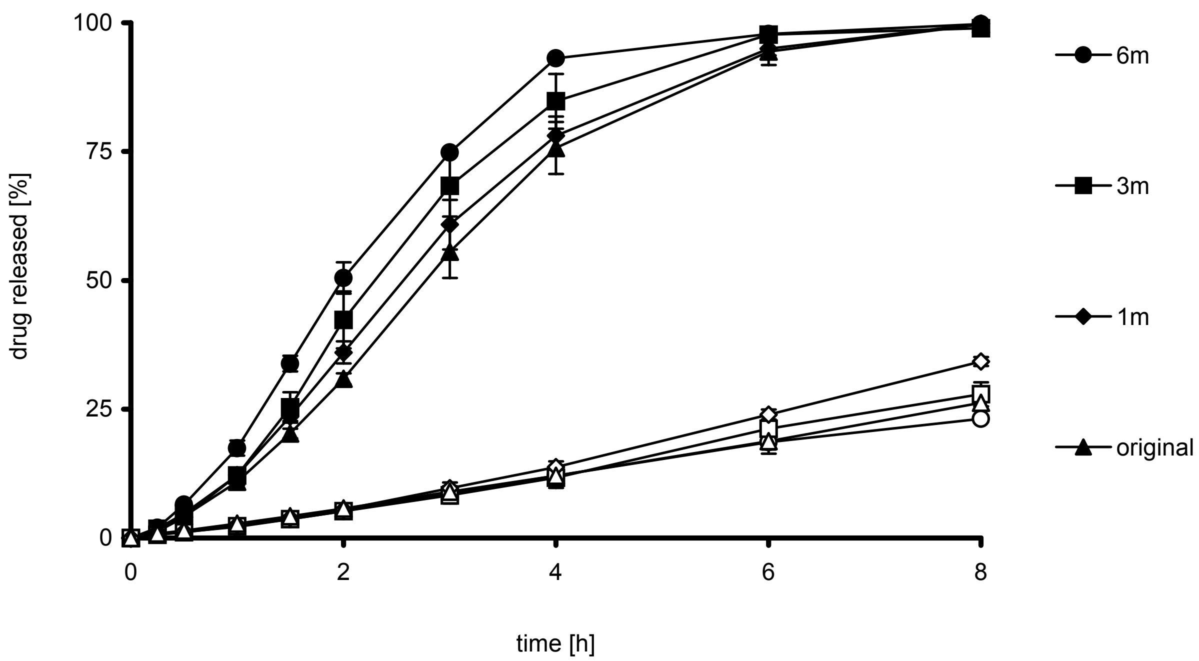
Stability of drug release from zein-coated pellets after storage at different conditons (coating level: 20%; model drug: theophylline; storage: r.c.: 3 months room condition; a.c.: 1month room condition + 2 months accelerated conditions (40°C / 75% r.H.))



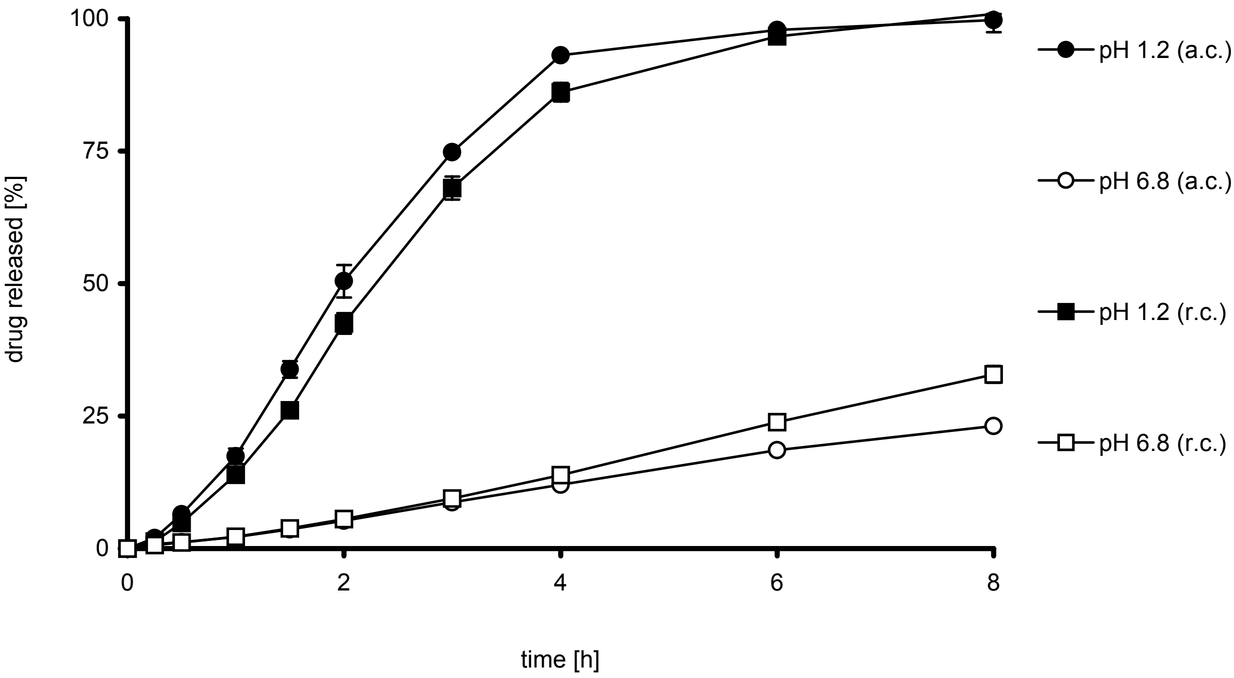
Stability of drug release from zein-coated pellets after different storage times (coating level: 20%; model drug: theophylline; storage times: 0 / 1 / 3 / 6 months; storage condition: *room conditions*; closed symbols: pH 1.2 / open symbols: pH 6.8)



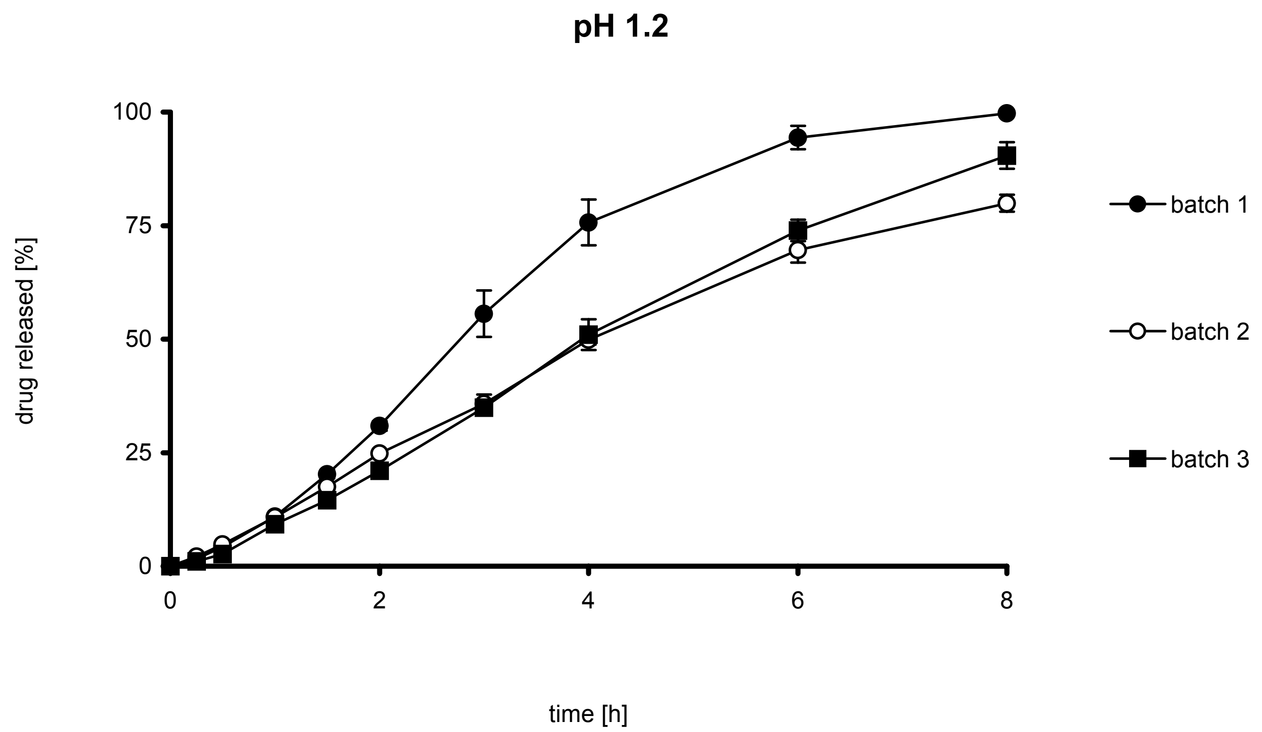
Stability of drug release from zein-coated pellets after different storage times (coating level: 20%; model drug: theophylline; storage times: 0 / 1 / 3 / 6 months; storage condition: accelerated conditions; closed symbols: pH 1.2 / open symbols: pH 6.8)

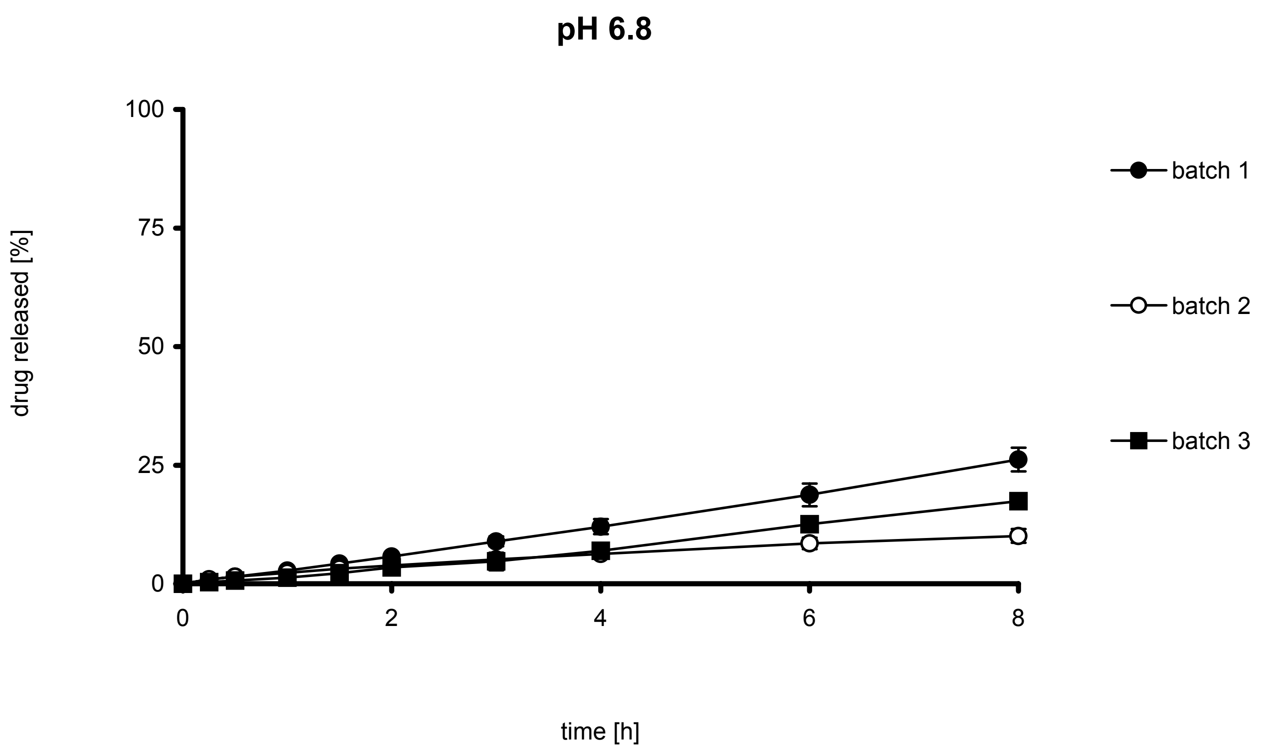


Stability of drug release from zein-coated pellets after storage at different conditions (coating level: 20%; model drug: theophylline; storage: r.c.: 6 months room condition; a.c.: 1month room condition + 5 months accelerated conditions (40°C / 75% r.H.))

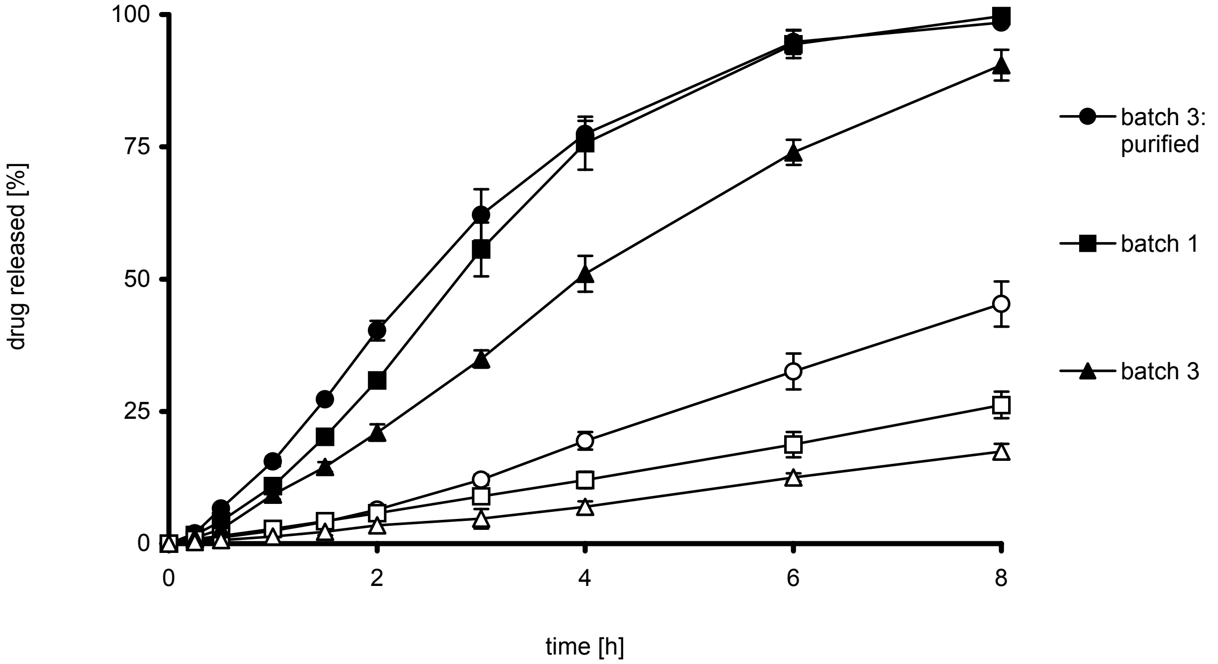


Batch-to-batch variability in drug release of pellets coated with different zein batches (coating level: 20%; model drug: theophylline)

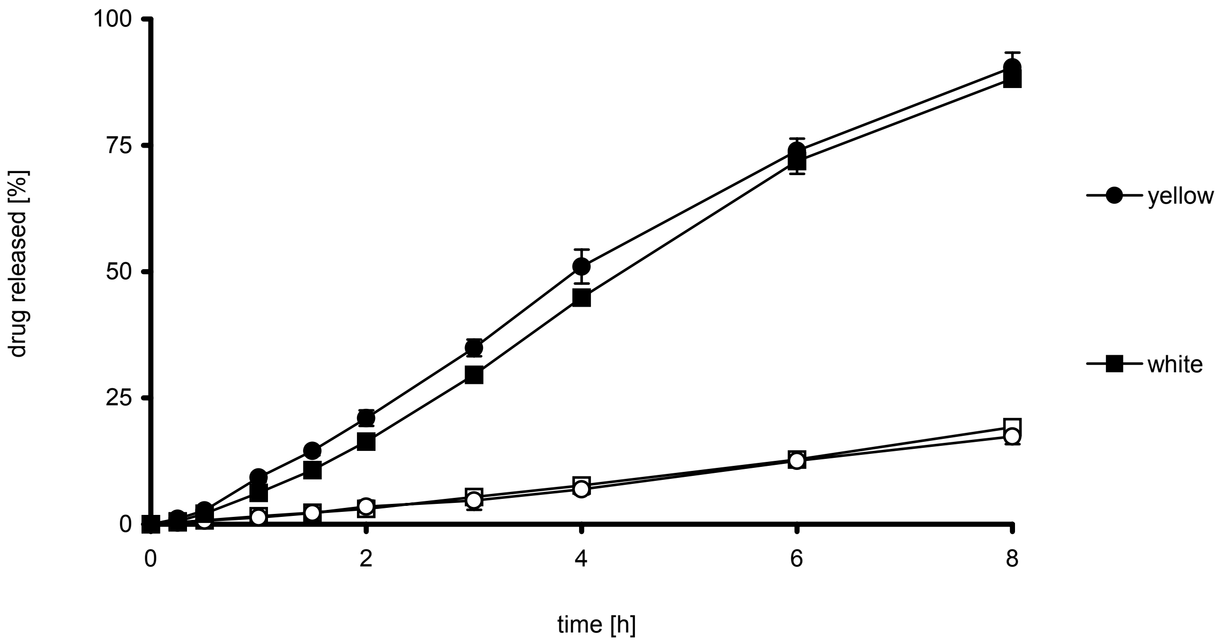




Influence of a purification step on zein prior coating on drug release of coated pellets (purification: by petrolether; coating level: 20%; model drug: theophylline; closed symbols: pH 1.2, open symbols: pH 6.8)



Influence of the colour of zein on drug release from coated pellets (coating level: 20%; model drug: theophylline; zein yellow: grade F4000, batch 3; zein white: grade F6000, batch 5; closed symbols: pH 1.2, open symbols: pH 6.8)



Investigation of the compatibility of zein-shellac *mixtures* in films cast from ethanolic solutions

Zein- Shellac Ratio	Compatibility	Zein- Shellac Ratio	Compatibility
10:1	+++	1:10	-
8:1	+++	1:8	-
6:1	+++	1:6	-
4:1	++	1:4	---
2:1	+	1:2	+/-
1:1	+/-	1:1	+/-

Zein-shellac mixtures as coating formulations

Investigated ratios of zein - shellac:

Ratio	~ shellac content [w/w]
9:1	10%
4:1	20%
1:1	50%
1:2	66.6%

Formulation:

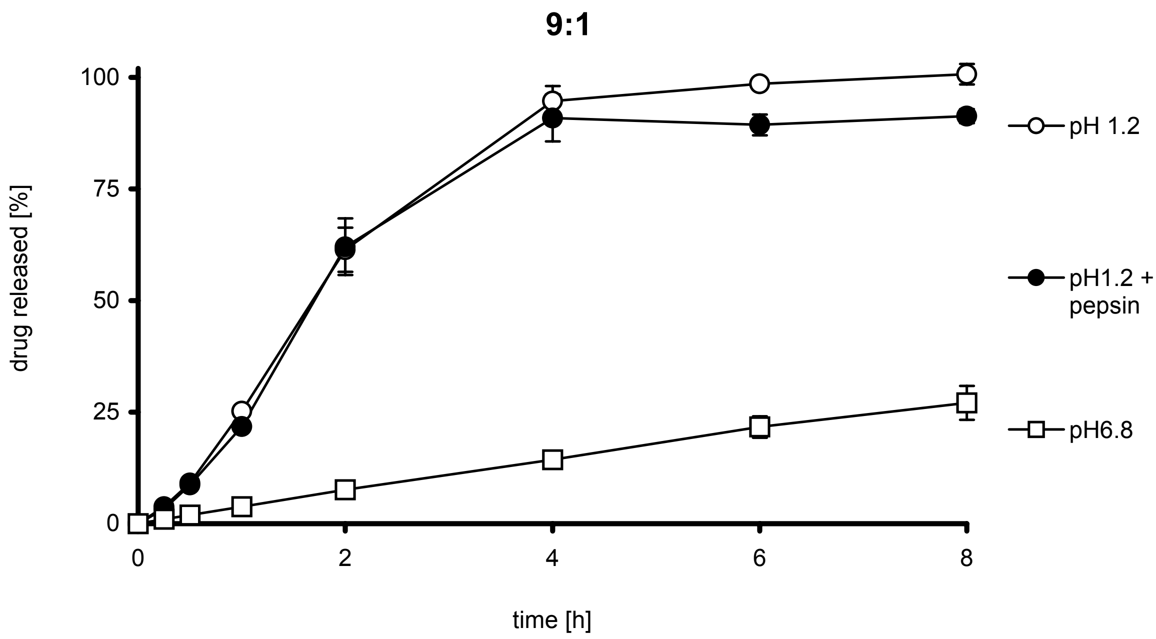
	Composition [% w/w]	
Polymer mixture	15.0	15% w/w based on total solution
Propylenglycol	1.5	10% w/w based on polymer mass
Talc	4.5	30% w/w based on polymer mass
Ethanol (70% v/v)	79.0	
Total	**100.0**	

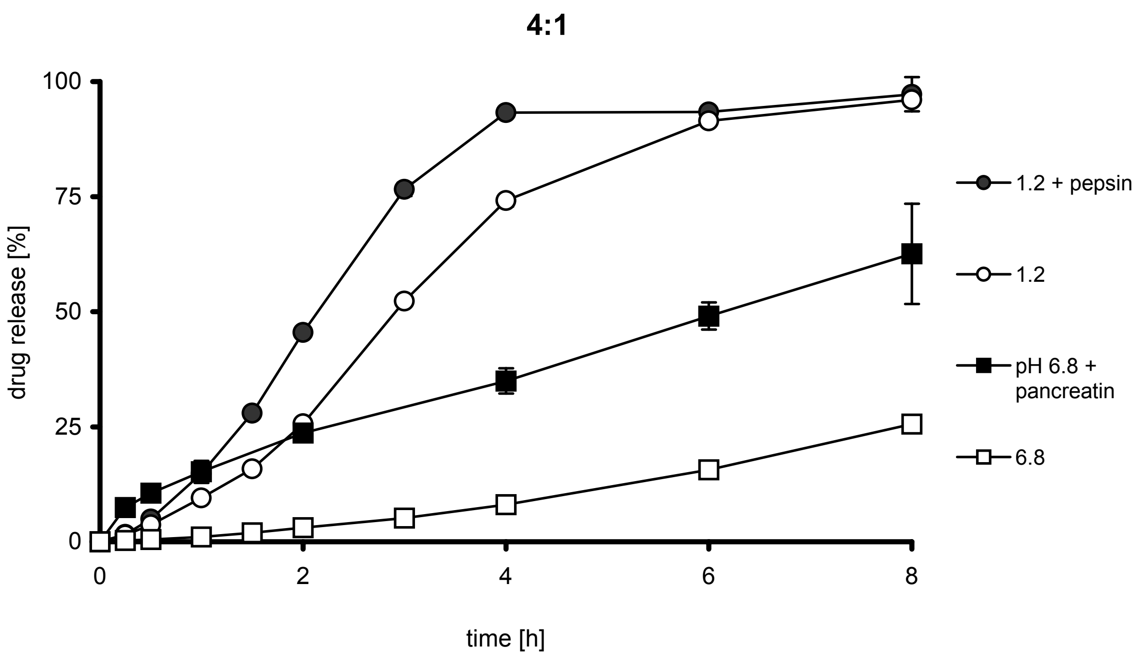
Process Parameters:

Coater: Hüttlin Kugelcoater HKC 05 / Unilab 05

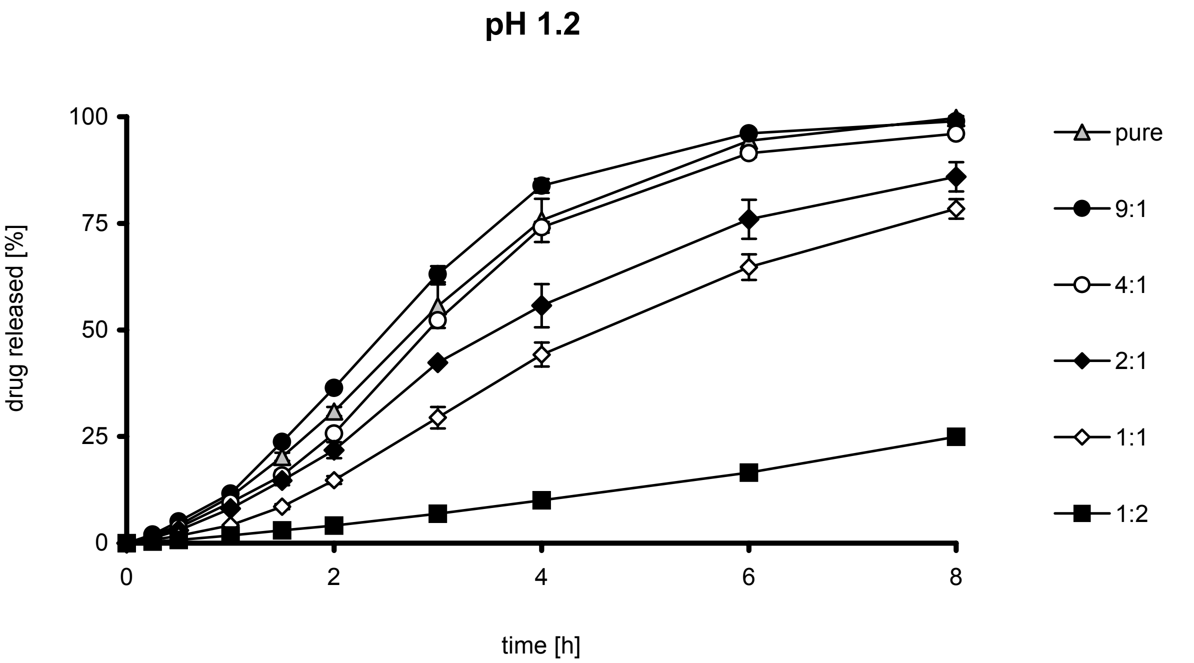
Parameters: same as for the pure zein coating process

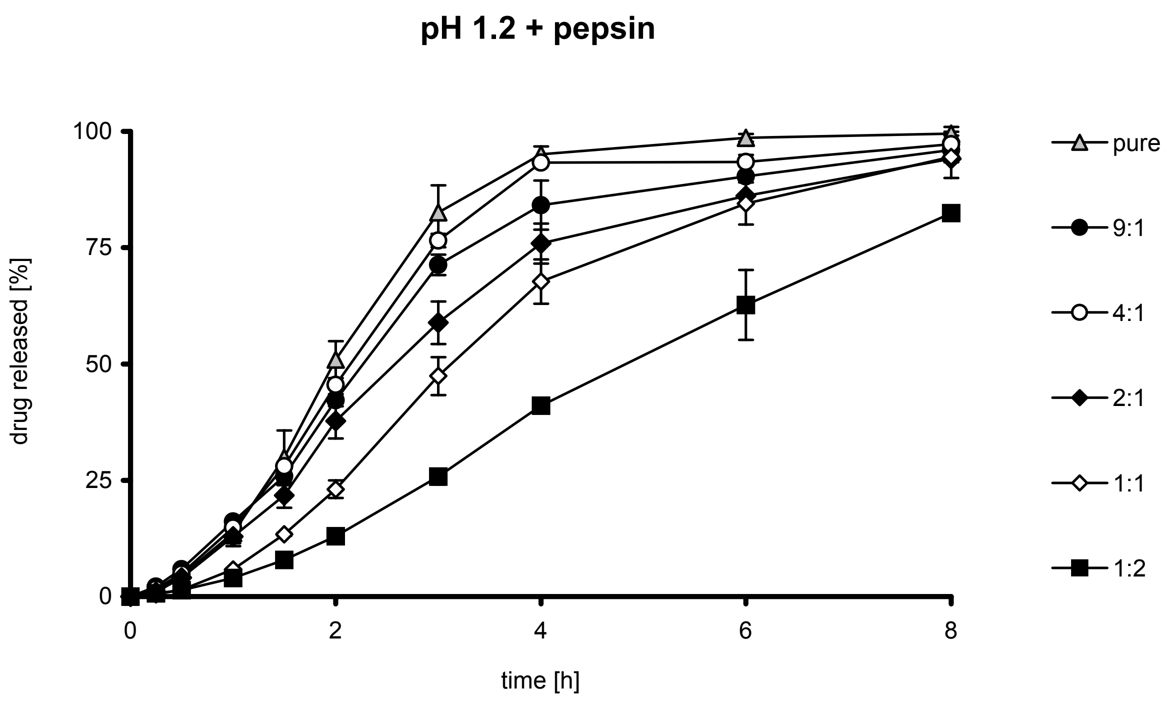
Drug release in different media of coated pellets with zein-shellac mixtures of different ratios (coating level: 20%; model drug: theophylline)





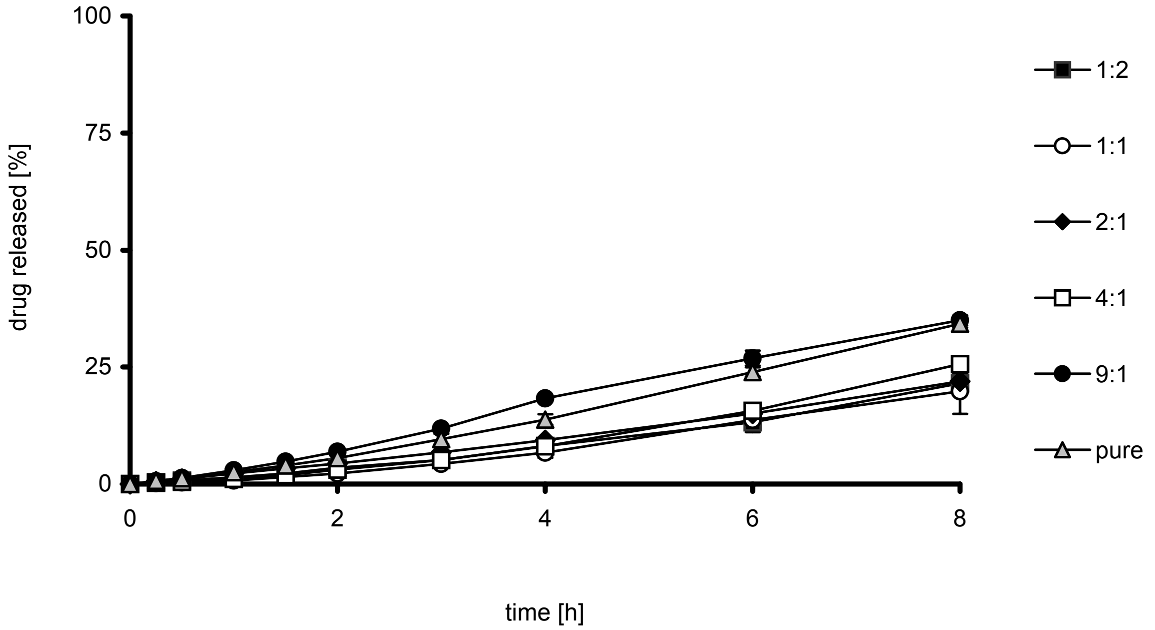
Comparison of drug release of coated pellets with different zein-shellac mixtures of different ratios (coating level: 20%; model drug: theophylline)



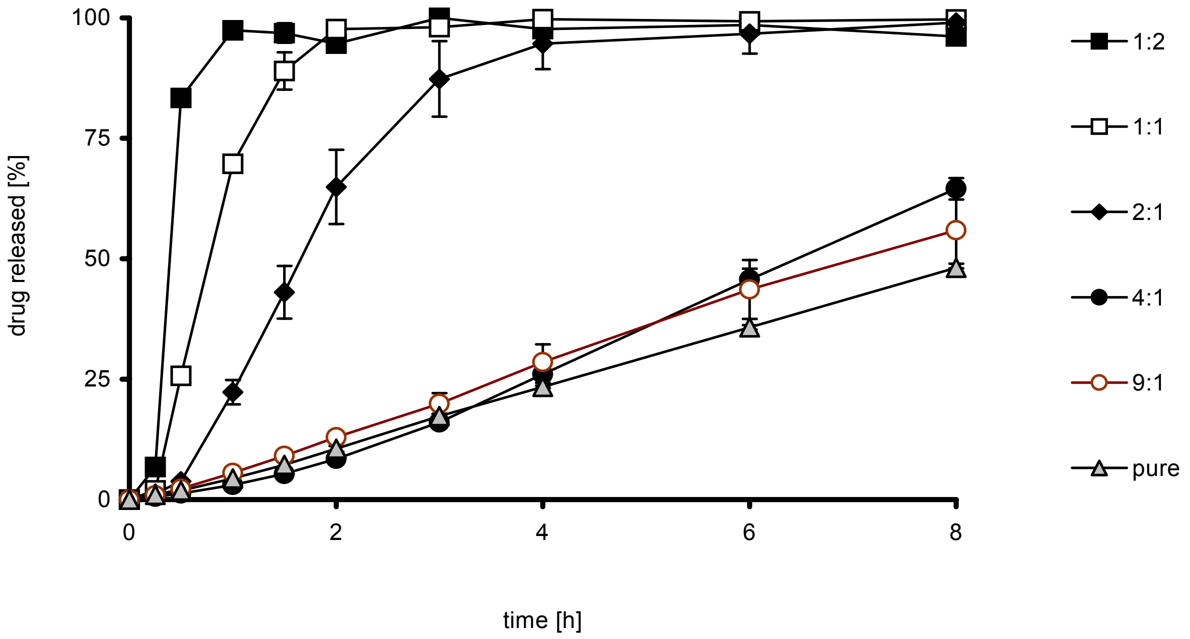


Comparison of drug release of coated pellets with different zein-shellac mixtures of different ratios (coating level: 20%; model drug: theophylline)

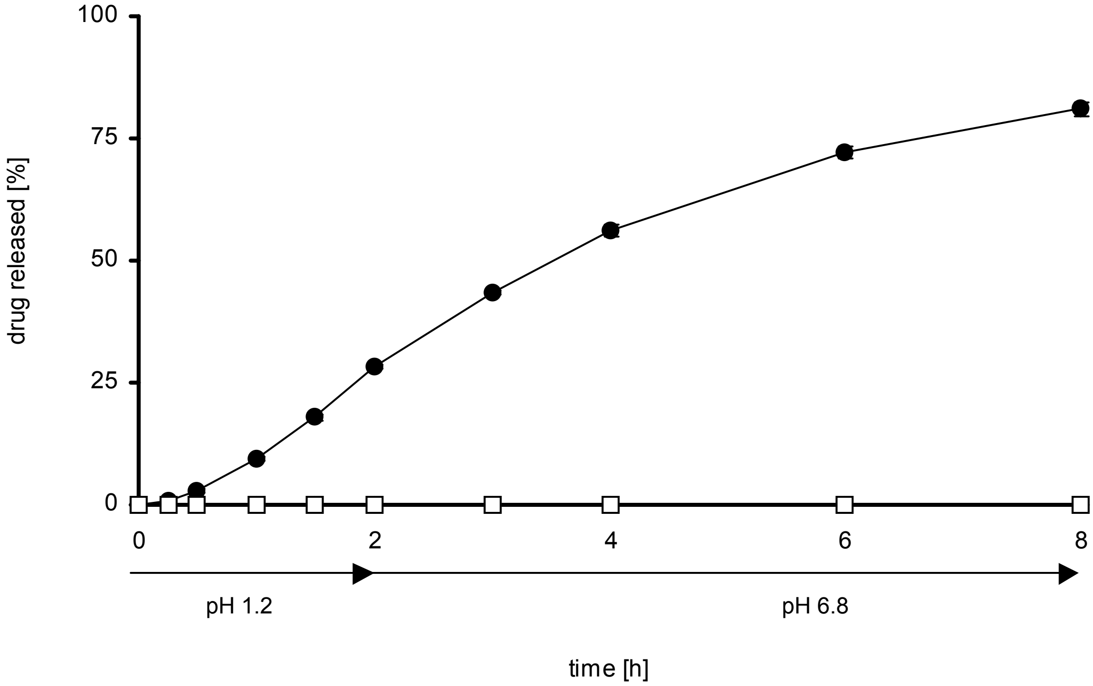
pH 6.8



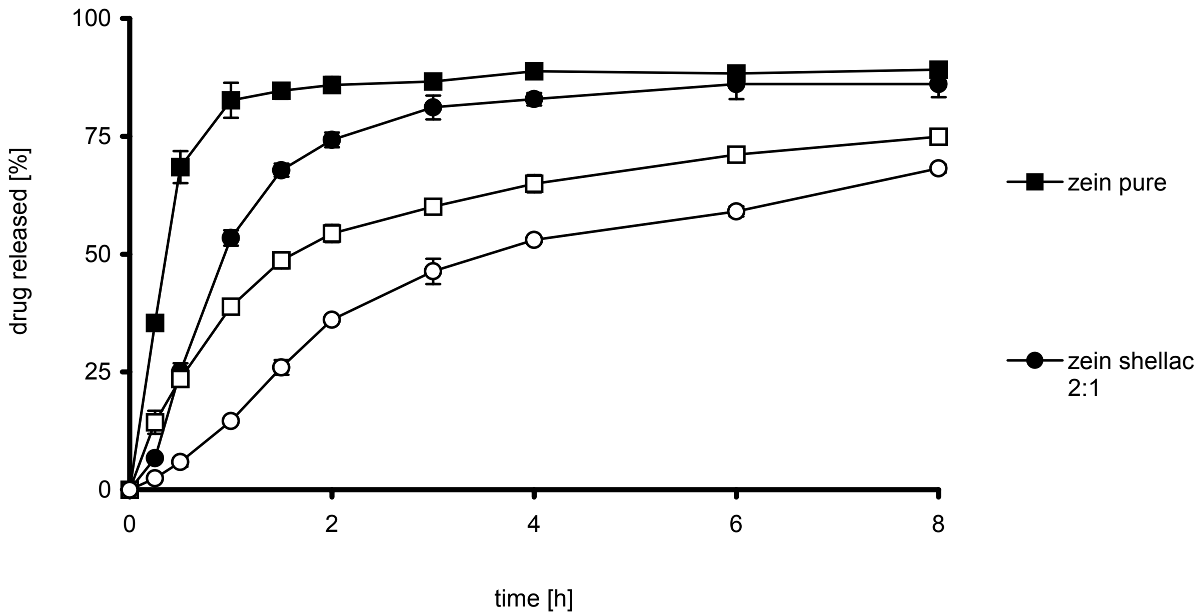
pH 7.4



Drug release from coated pellets with a zein-shellac ratio of 2:1 consecutively released (coating level: 20%; model drug: theophylline; pH 1.2: 2h, pH 6.8 :6h)



Drug release of a freely soluble drug from coated pellets with a zein-shellac ratio 2:1 in different release media (coating level: 20%; model drug: chlorpheniramine maleate; closed symbols: pH 1.2, open symbols: pH 6.8)

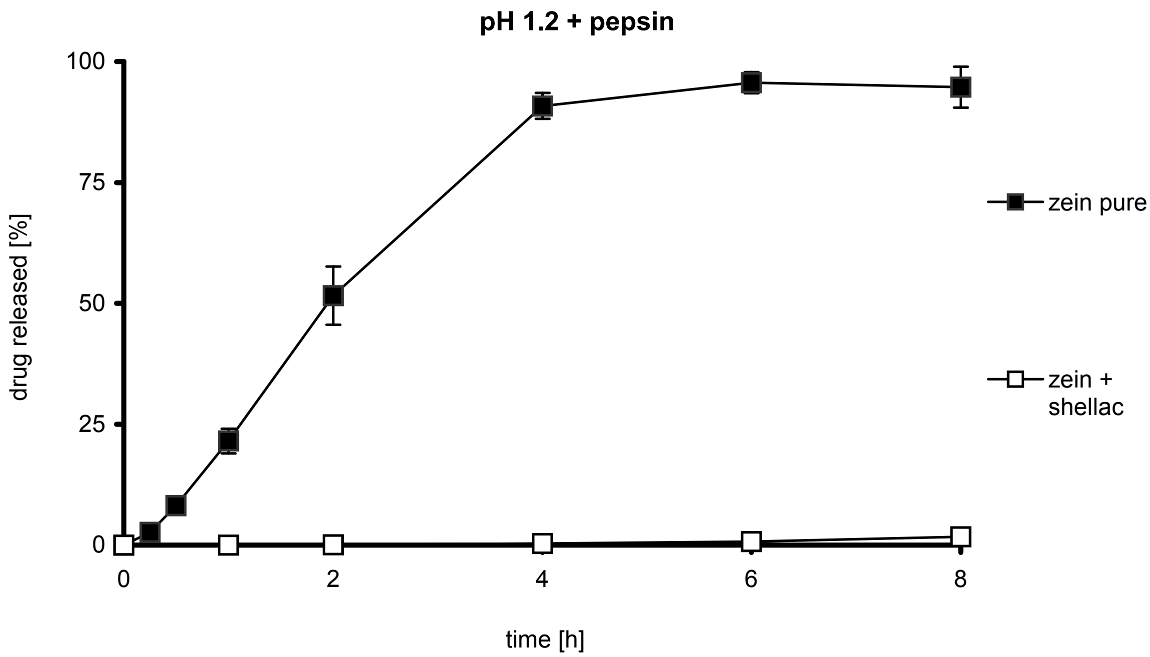


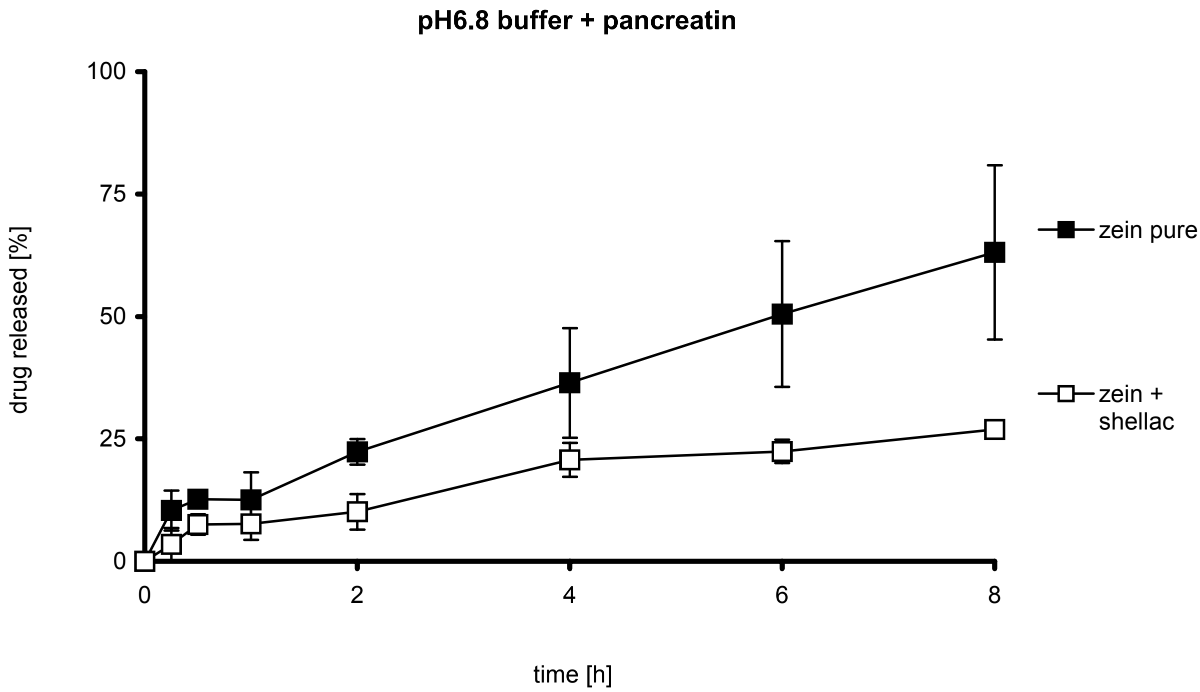
Shellac as an overcoat on zein-coated pellets

Formulation:

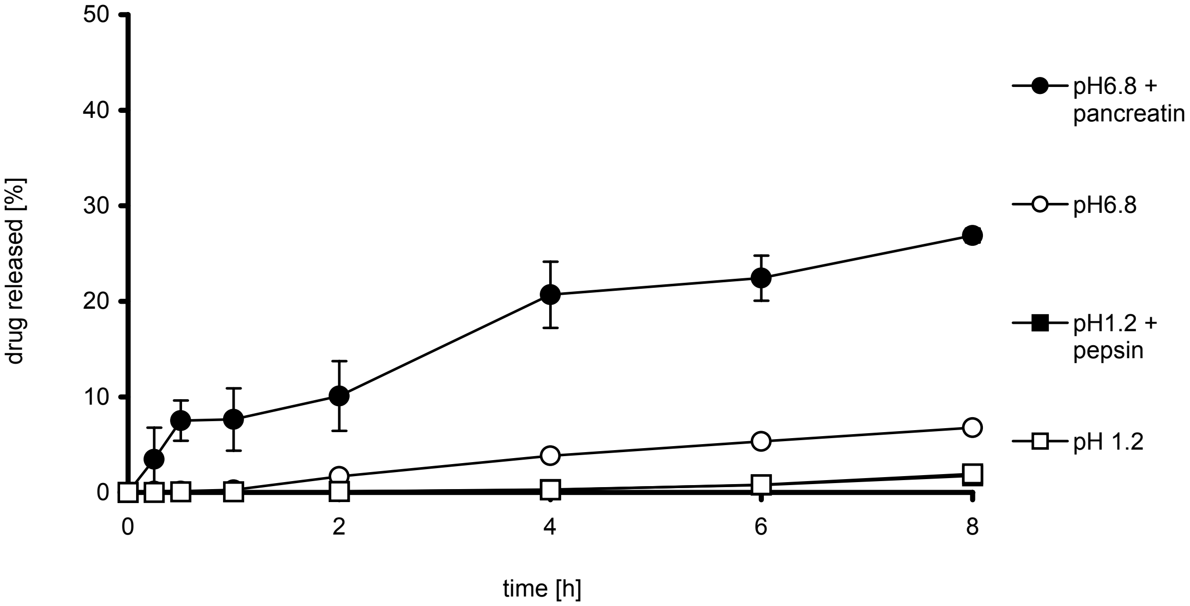
	Composition, % w/w	
Polymer mixture	20	20% w/w based on total solution
Propylenglycol	1	5% w/w based on polymer mass
Talc	6	30% w/w based on polymer mass
Ethanol (70% v/v)	73	
Total	**100**	

Effect of a shellac overcoat in comparison to pure zein coatings (model drug: theophylline; basic coating: zein; coating level: 20% / shellac overcoat; coating level:12.5%)

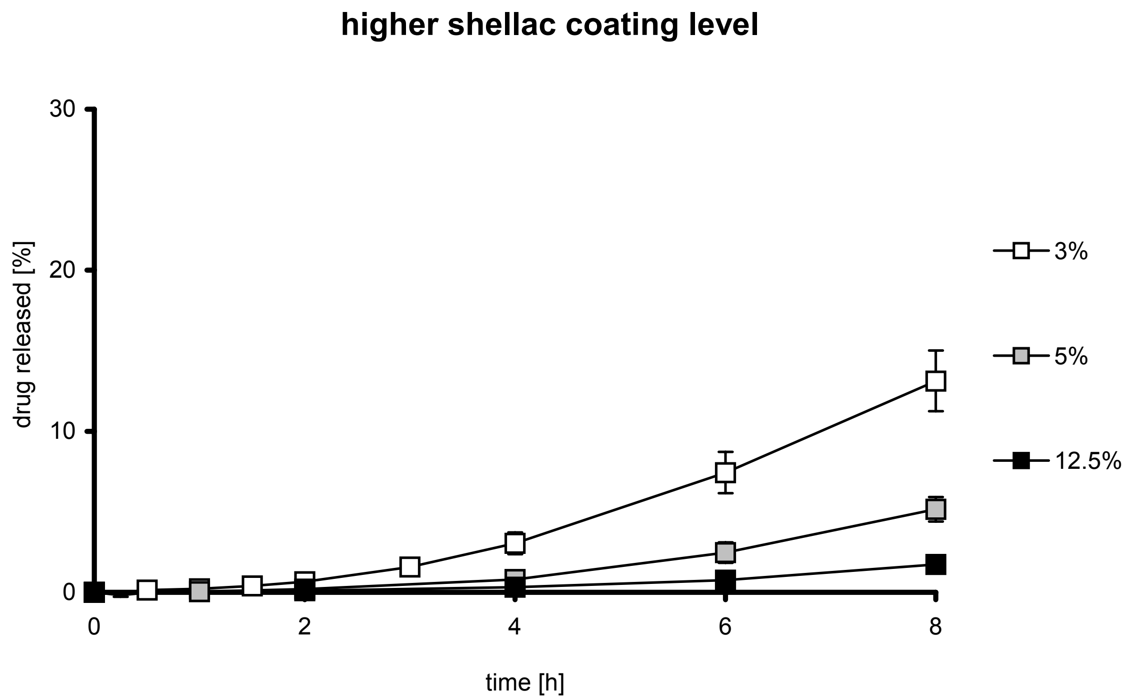


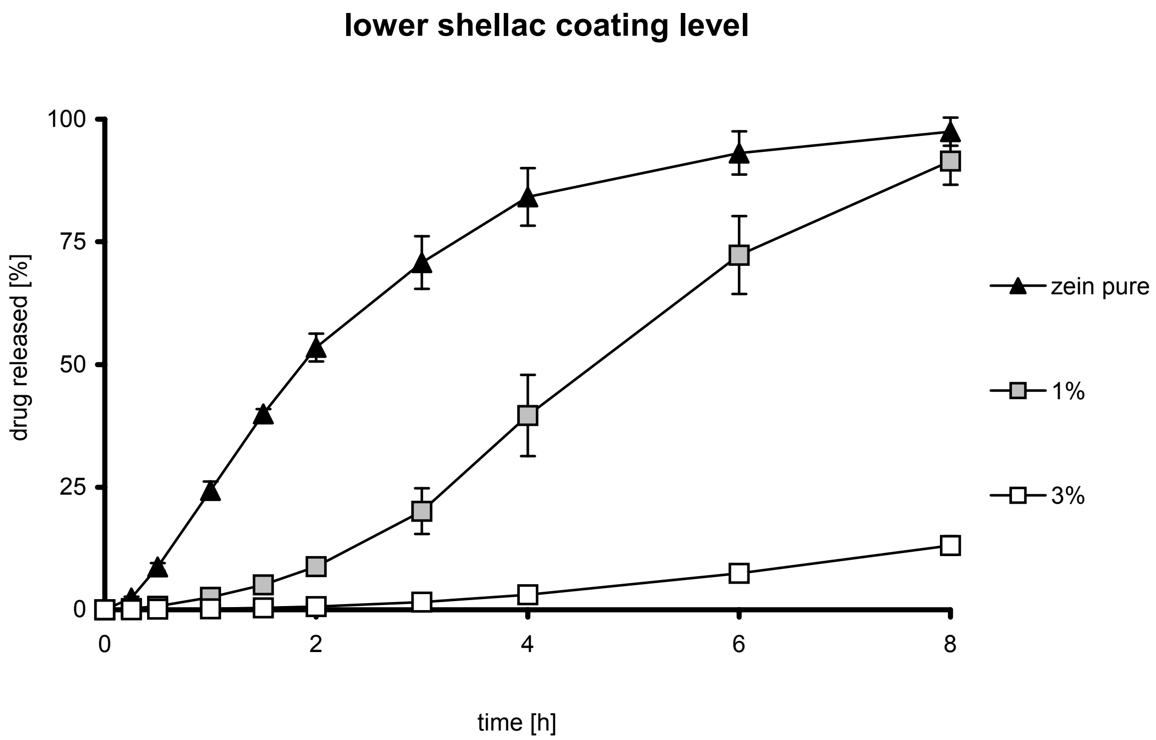


Effect of a shellac overcoat on zein coated pellets: comparison of different release media (model drug: theophylline; basic coating: zein; coating level: 20% / shellac overcoat; coating level:12.5%)

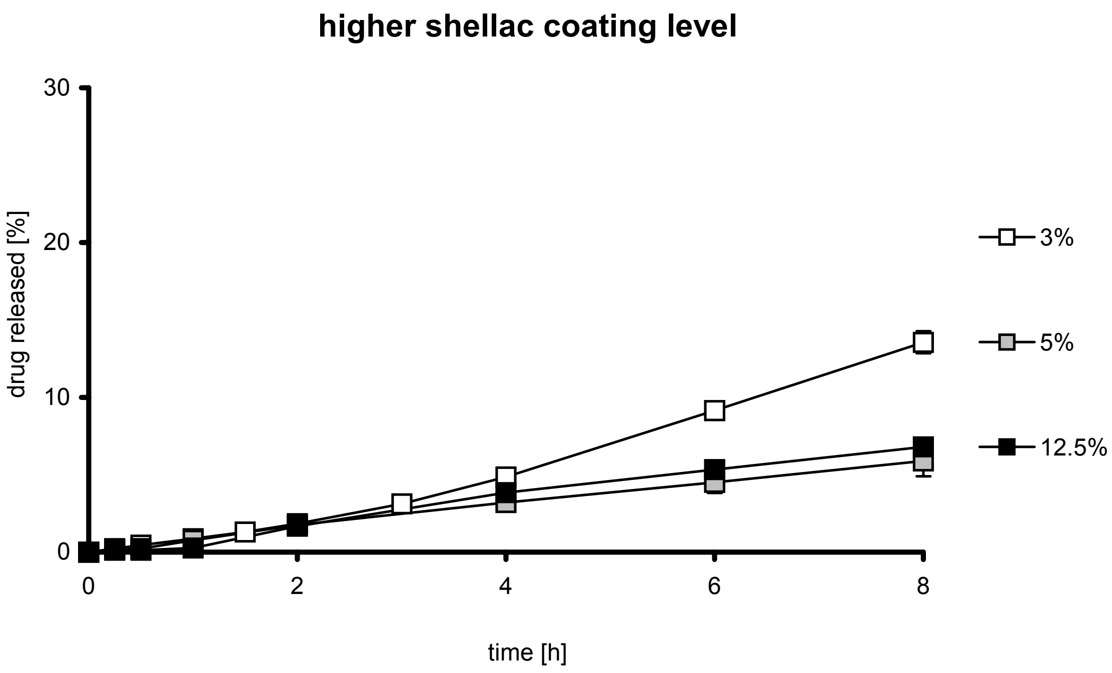


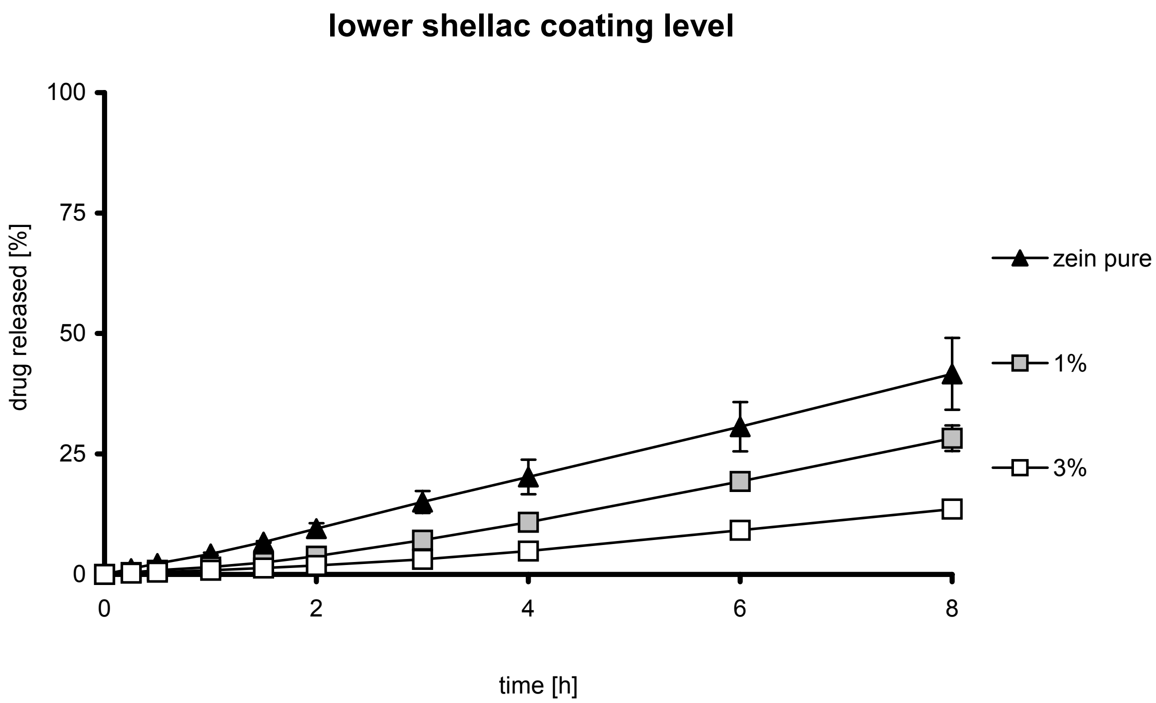
Effect of a shellac overcoat on drug release from zein coated pellets: comparison of different amount of shellac overcoat (model drug: theophylline (slightly soluble); first coat: zein; coating level 20% / overcoat: shellac; release media: ***pH 1.2 + pepsin***)





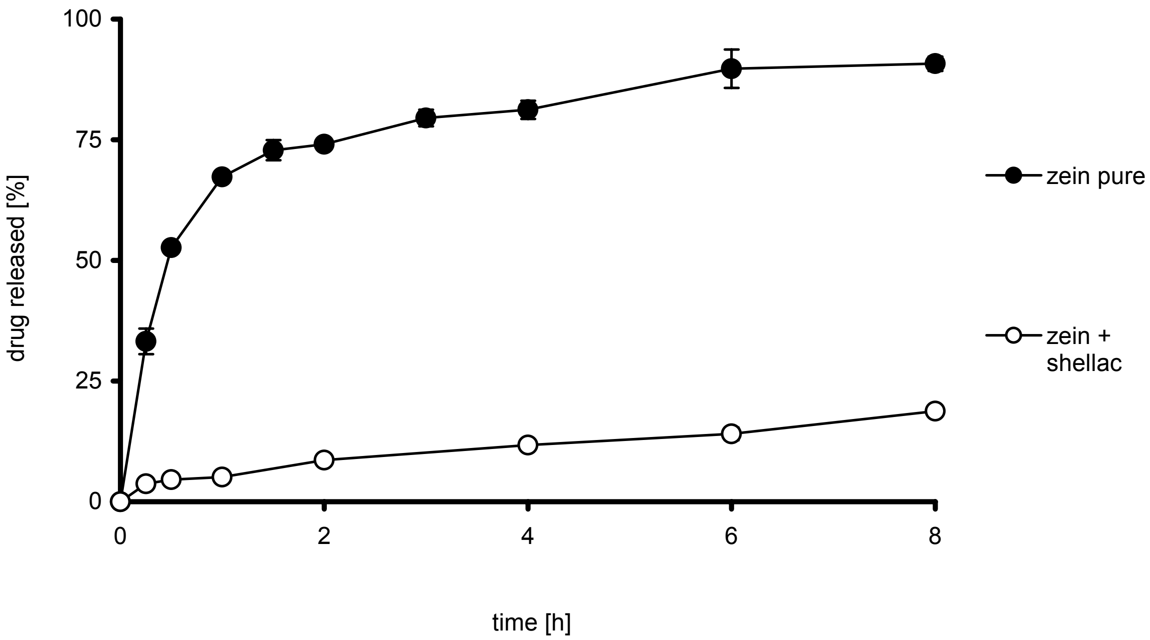
Effect of a shellac overcoat on drug release from zein coated pellets: comparison of different amount of shellac overcoat (model drug: Theophylline (slightly soluble); first coat: zein; coating level 20% / overcoat: shellac; release media: ***pH 6.8***)



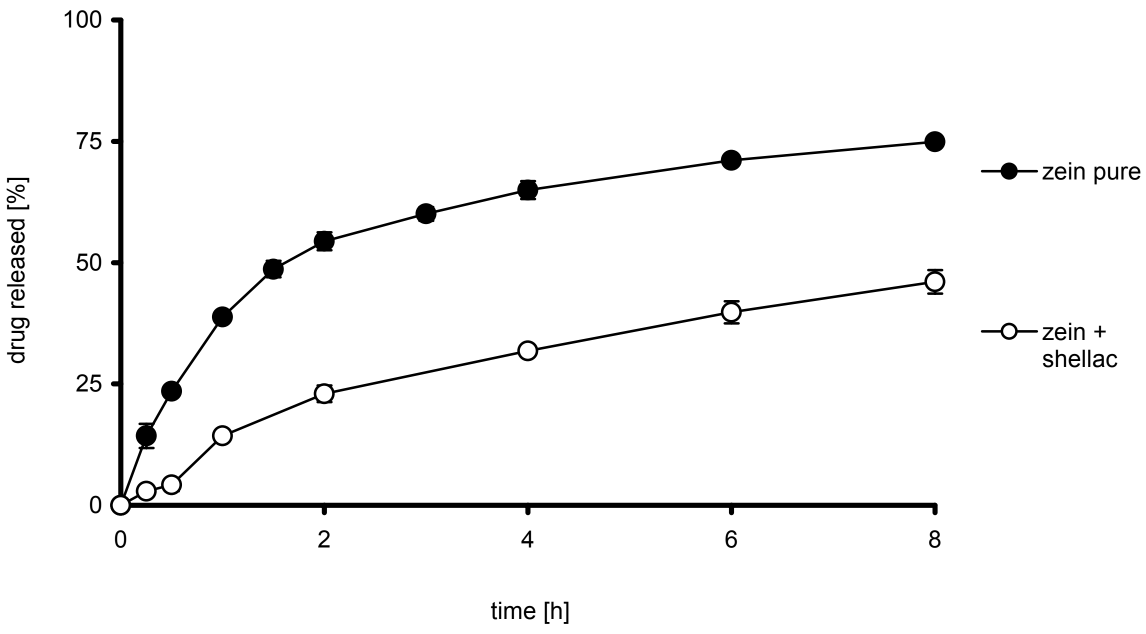


Effect of a shellac overcoat on the release of an easily soluble drug from zein coated pellets (model drug: Chlorpheniraminmaleate; first coating: zein; coating level: 20% / shellac overcoat: coating level: 5%)

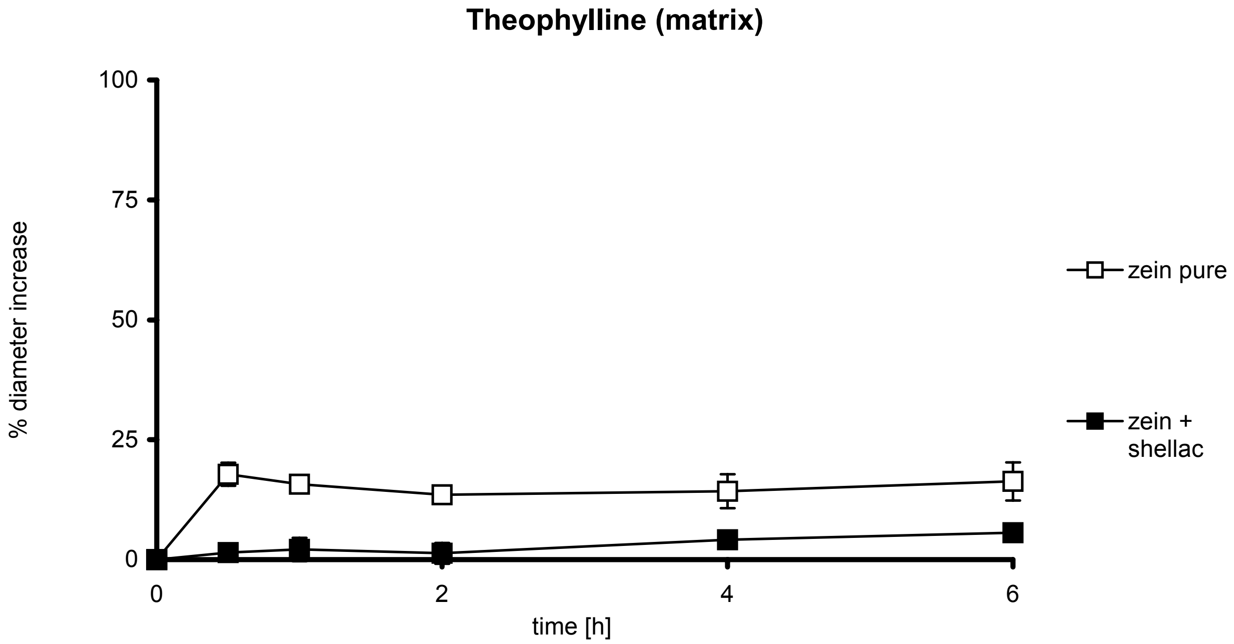
pH 1.2 + pepsin

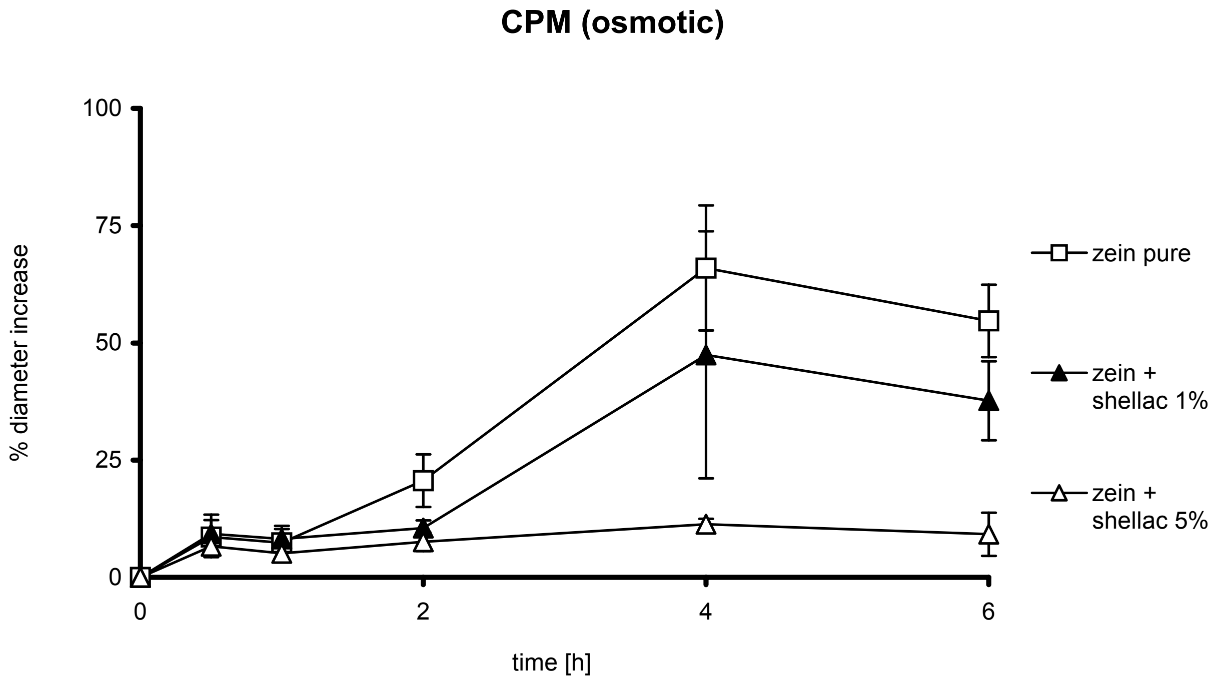


pH 6.8



Influence of a shellac overcoat on the size increase by swelling of zein-coated pellets upon exposure to 0.1 N HCl pH 1.2 (model drug: *theophylline*: first coating: zein 20%; shellac overcoat: 5%, *chlorpheniramine maleate (CPM)*: first coating: zein 20%; shellac overcoat: 1% / 5%)





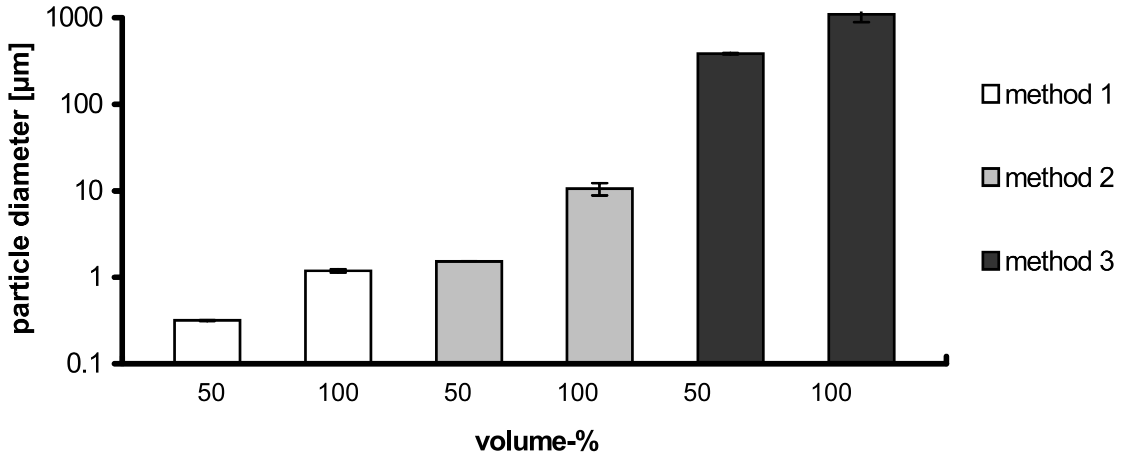
2.2 Zein from aqueous dispersions

Methods:

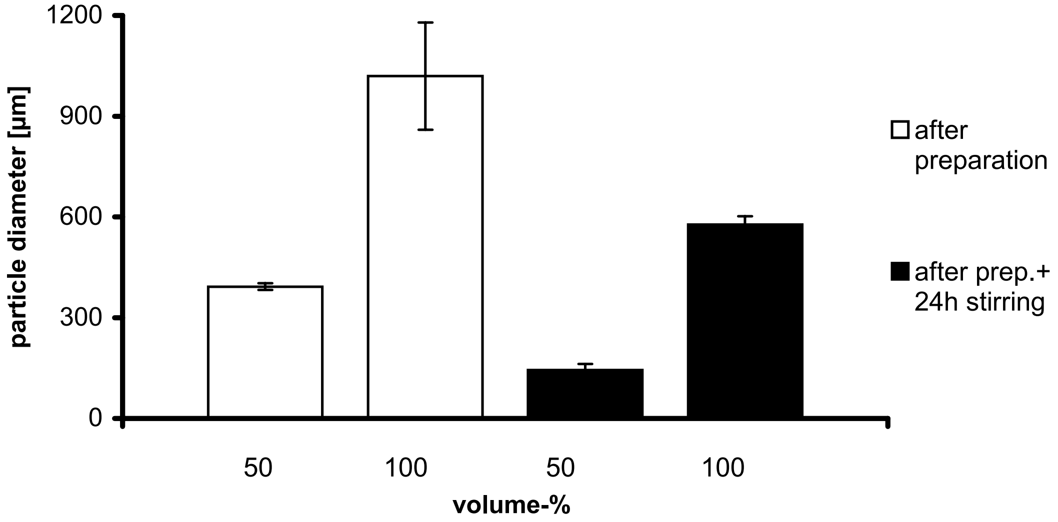
Investigated preparation procedures:

Method	Preparation	Resulting particle size [µm]	
		50% volume	100% volume
1	organic zein solution injected into the water phase by a syringe + needle (∅ 0.45mm)	0.317 (0.004)	1.2 (0.05)
2	organic zein solution injected into the water phase without needle	1.5 (0.008)	10.6 (1.7)
3	Immersion of zein powder into the water → stirring → treatment with Ultra Turrax (5 min.)	383 (6.6)	1091 (202)

Influence of the preparation procedure on the particle size of the resulting dispersion



Influence of the stirring time after preparation: comparison of the particle size after 24h stirring (preparation method 3):



Aqueous Phase:

Influence of the surface tension of the aqueous phase on the particle size of zein aqueous dispersions prepared by preparation method 1 (organic phase: 80% ethanol; polymer concentration:5% (w/v))

Additive	Surface tension [mN / m]	Particle size [µm]
none	78.2 ± 0.3	0.3
PEG 400	74.3 ± 0.9	0.4
Tween 20	-	9.3
Tween 80	43.0 ± 1.4	8.2
Pluronic F68	51.0 ± 1.5	0.4
Pluronic F127	40.6 ± 1.0	0.9

Organic Phase:

Influence of solvent used for the organic phase during preparation on the particle size of zein aqueous dispersions (polymer concentration in the organic solvent: 5% (w/v))

Solvent	**Dispersion properties**	**Particle size [µm]**
Ethanol	pale yellow	0.317
Acetone	pale yellow; similar as from Ethanol	0.427
Isopropanol	deep yellow; immediate precipitation	-
Methanol	pale yellow; shiny	0.118

Batch-to-batch comparison:

Comparison of the particle size of aqueous zein dispersions related to the physical appearance of different batches (organic phase: 80% ethanol, polymer concentration: 5%)

Batch	Colour	Odour	Particle size [µm]
1	pale yellow	weak	0.317
2	deep yellow	strong	preparation not possible (lump formation)
3	deep yellow	weak	0.406 (main fraction) 1.2 (small fraction)
4	pale yellow	weak	0.358
5	white	weak	0.422

Influence of the colour of different zein batches on the glass transition temperature (Tg) measured by differential scanning microscopy

Batch	Tg [°C]	s.d.
1	166.9	1.0
2	165.2	2.1
3	167.1	1.2
4	163.7	1.9
5	171.5	0.2

Physical properties, film appearance, compatibility, flexibility and other observable film characterisitcs of zein films cast from aqueous dispersions with following drying at different conditions (plasticizer content: 40% based on polymer)

Room temperature (~25°C)

Plasticizer	Appearance	Compatibility	Flexibility	Shrinkage	Liftage	Stickiness
None	white	-	-	-	++	-
Tartaric acid	yellow transparent	+	++++	-	-	-
Glycerol	white	+	-	-	+++	-
Propylenglycol	yellow transparent	+	++++	-	-	+

40°C

Plasticizer	Appearance	Compatibility	Flexibility	Shrinkage	Liftage	Stickiness
None	yellow-white	-	-	-	++	-
Tartaric acid	yellow transparent	+	++++	-	-	±
Glycerol	yellow-white	+	-	-	+	-
Propylenglycol	yellow transparent	+	++++	-	-	+

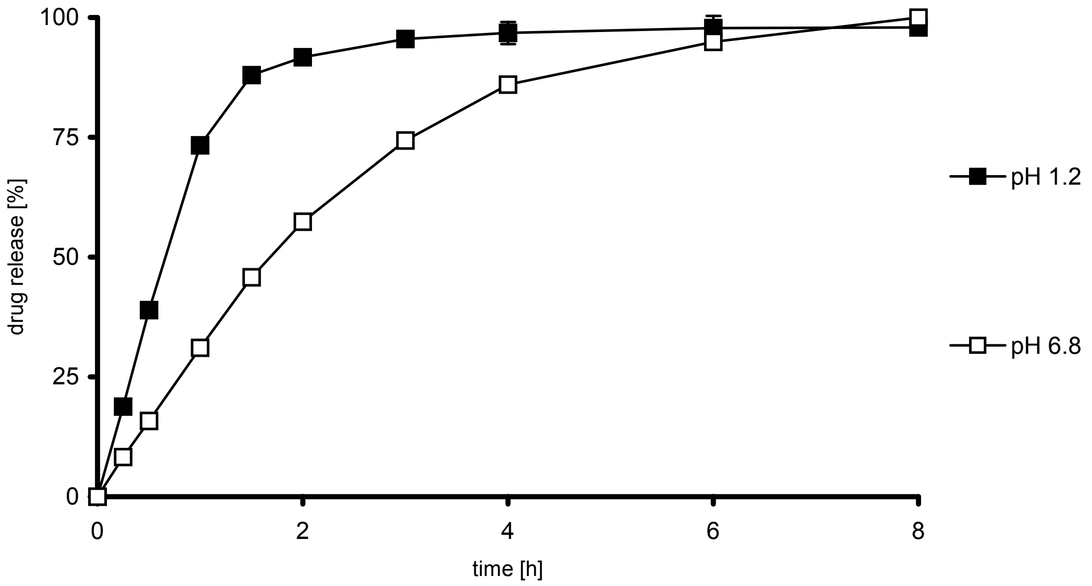
60°C

Plasticizer	Appearance	Compatibility	Flexibility	Shrinkage	Liftage	Stickiness
None	yellow + white spots	-	-	-	+	-
Tartaric acid	yellow transparent	+	-	-	-	-
Glycerol	opaque	+	-	-	-	-
Propylenglycol	yellow transparent	+	++	-	-	-

Effect of the plasticizer concentration on the physical properties, film appearance, compatibility, flexibility and other observable film characteristics of zein films casted from aqueous dispersions (plasticizer: tartaric acid; drying a 40°C)

Plasticizer conc. (w / w)	Appearance	Compatibility	Flexibility	Shrinkage	Liftage	Stickiness
20	yellow transparent	+	-	-	-	-
30	yellow transparent	+	-	-	-	-
40	yellow transparent	+	++++	-	-	±

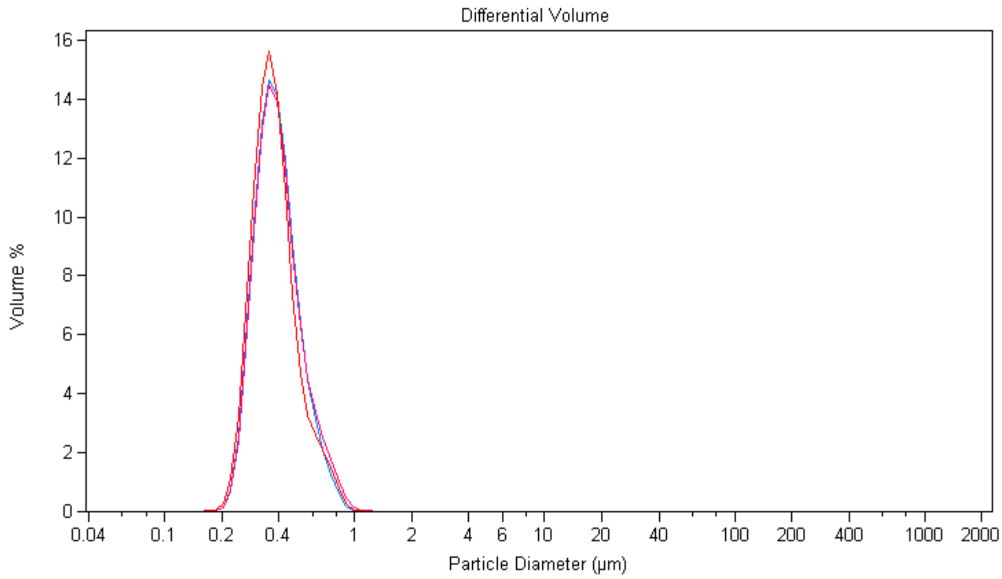
Drug release from zein coated pellets prepared from an aqueous zein dispersion (aqueous dispersion: preparation method 1; polymer content: 3%; plasticizer: tartaric acid: 30% based on polymer; coating level: 20%)



Particle size distribution of a zein aqueous dispersion measured by laser diffractometry (preparation method 1)

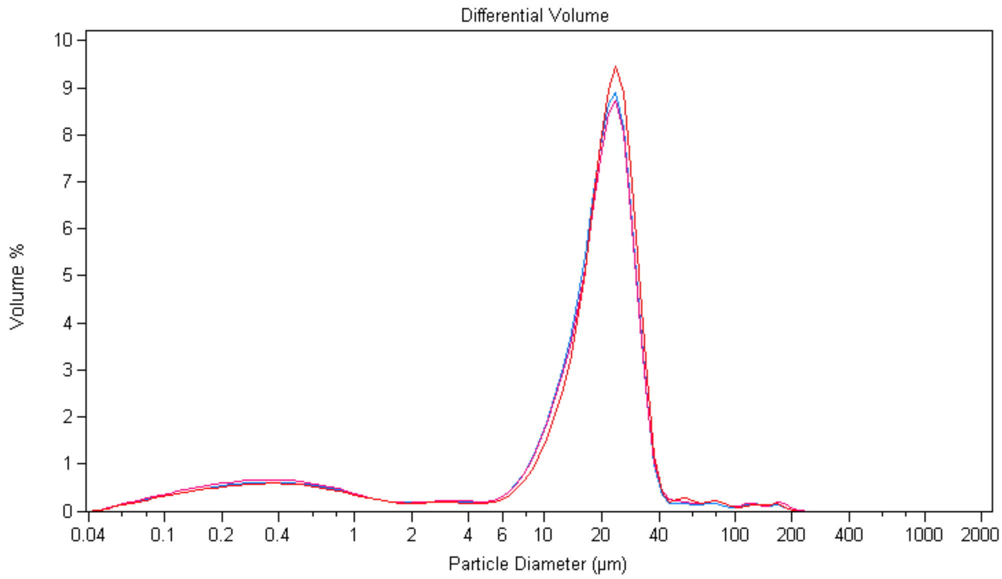
after preparation

polymer content: 2.5% (w/v)



concentrated dispersion

polymer content: 8.4% (w/v)

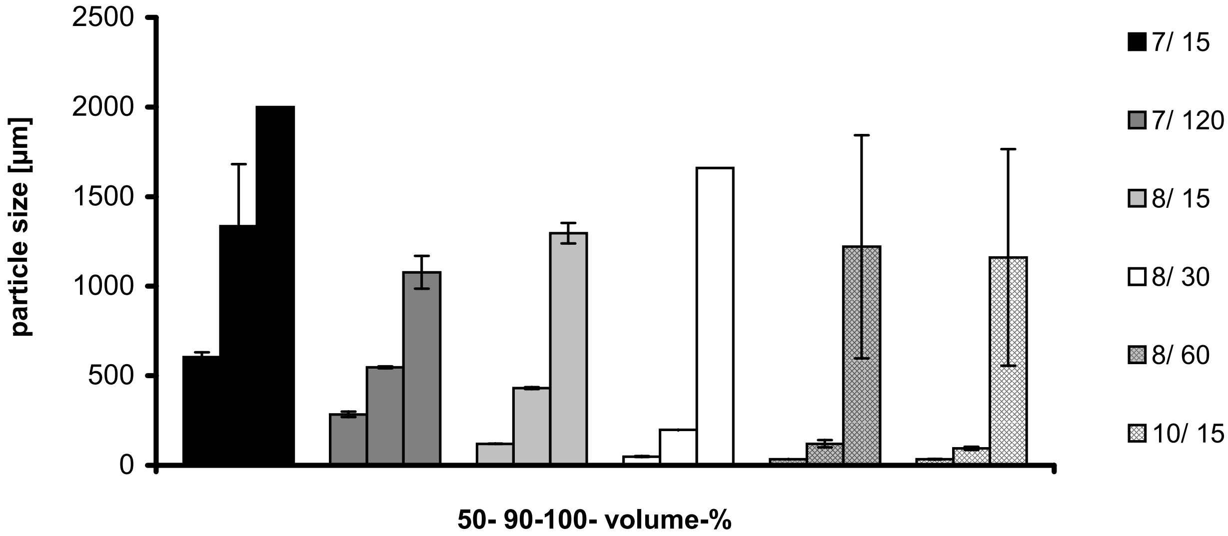


Stabilizing efficiency of different additives on the particle size distribution of concentrated aqueous zein dispersions (preparation method 1; highest polymer concentration with unchanged particle size distribution given)

Additive	Conc. [% (w/w)] based on polymer	Polymer conc. [% (w/v)]
SDS	~	immediate flocculation
Tween 80	6.6	11.1
Span 80	9.8	7.6
PEG 400	30.9	12.6
PEG 1500	30.9	8.2
AMG	30.3	8.7

Milling

Effect of different milling conditions on resulting zein powders (milling conditions: mill-speed / time [min])



milling condition (mill speed / time [min])	**volume-%**	**mean [µm]**	**s.d. [µm]**
7 / 15	50	605	27
	90	1336	347
	100	2000	0.0
7 / 120	50	285	14
	90	547	5.7
	100	1077	91
8 / 15	50	121	0.8
	90	430	5.4
	100	1295	57
8 / 30	50	49	0.3
	90	198	2.1
	100	1660	0.0
8 / 60	50	34	2.1
	90	120	21
	100	1220	622
10 / 15	50	34	2.4
	90	95	8.4
	100	1161	605

Particle size by swelling of milled zein powders after redispersion in water

milling condition (mill speed / time [min])	**volume-%**	**mean [µm]**	**s.d. [µm]**	**volume-%**	**mean [µm]**	**s.d. [µm]**
	dry; after milling			after 60 min. in water		
10 / 15	50	34	2	50	60	2
	90	95	8	90	143	6
	100	1161	605	100	1054	430
8 / 60	50	34	2	50	59	2
	90	120	21	90	208	19
	100	1220	622	100	1660	0
8 / 30	50	49	0.25	50	74	2
	90	198	2	90	315	31
	100	1660	0	100	1887	160

Spray-drying

Particle size of zein powders after spray-drying (aqueous or ethanolic system) and redispersion in water

condition	volume-%	mean [µm]	s.d. [µm]	volume-%	mean [µm]	s.d. [µm]
original dispersion	50	0.37	0.0	-	-	-
	90	0.50	0.0	-	-	-
	100	0.77	0.1	-	-	-
spraydried powders				*redispersed powders*		
aqueous dispersion	50	2.8	0.1	50	5.4	0.3
	90	8.3	0.3	90	58	38
	100	27	0.0	100	331	118
organic solution	50	3.2	0.4	50	27	5.6
	90	6.6	2.0	90	339	112
	100	12	5.2	100	1143	0.0

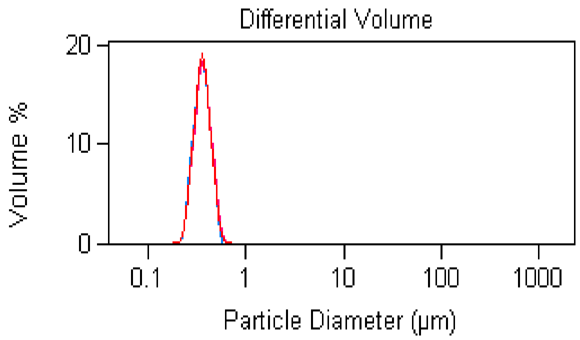
Lyophilization

Particle size of zein powders after lyophilization of aqueous zein dispersions, milling and redispersion in water

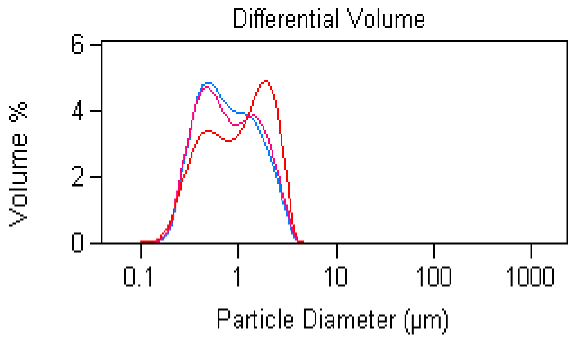
condition	volume-%	mean [µm]	s.d. [µm]	volume-%	mean [µm]	s.d. [µm]
original dispersion	50	0.4	0.0	-	-	-
	90	0.5	0.0	-	-	-
	100	0.8	0.1	-	-	-
dry powders				*redispersed powders*		
lyophylized powder	50	58	0.7	50	266	0.3
	90	220	1.4	90	673	3.6
	100	1143	0.0	100	1768	76
lyophylized + milled powder	50	36	0.3	50	50	1.0
	90	106	0.5	90	344	22
	100	436	19	100	1660	0.0

Effect of freezing / thawing on the particle size of zein aqueous dispersions

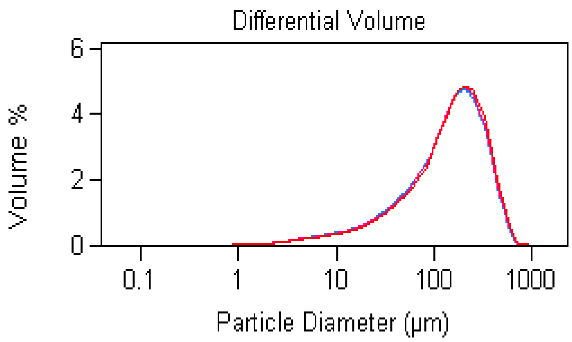
after preparation (***no freezing***)



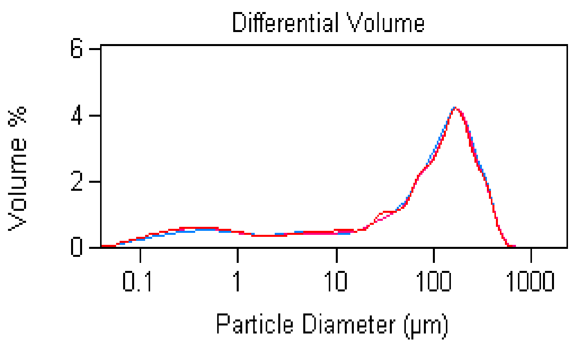
2.4% polymer conc.



3.4% polymer conc.

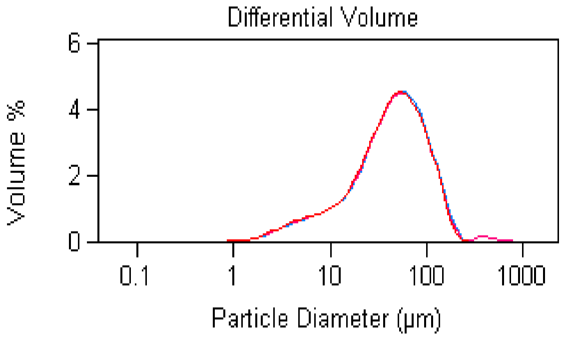


9.0% polymer conc.

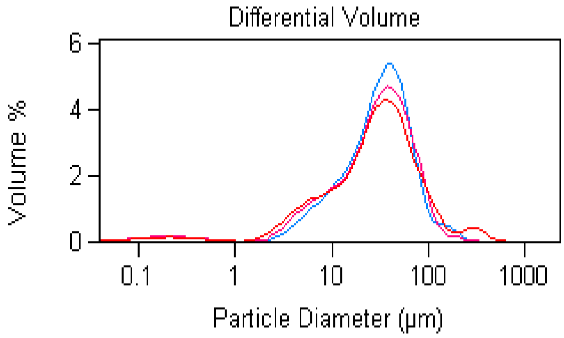


Stabilizing efficiency of propylene glycol on the particle size distribution of concentrated aqueous zein dispersions on freezing / thawing (3.4% polymer content)

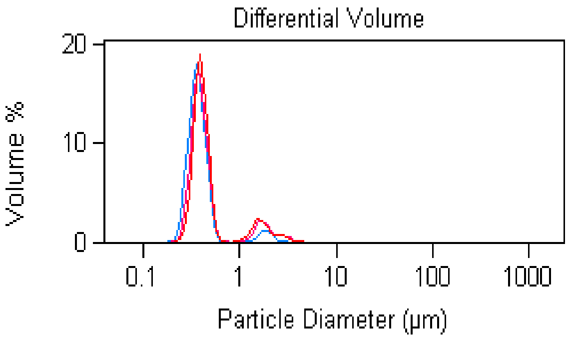
5% based on polymer



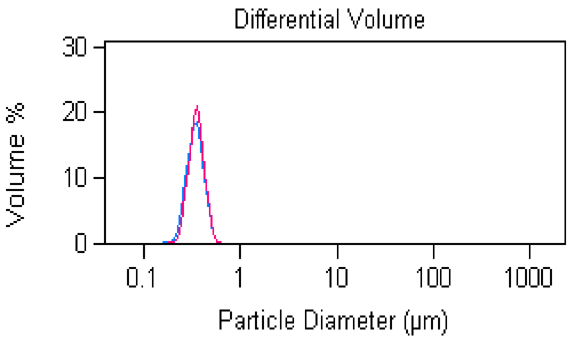
10% based on polymer



20% based on polymer

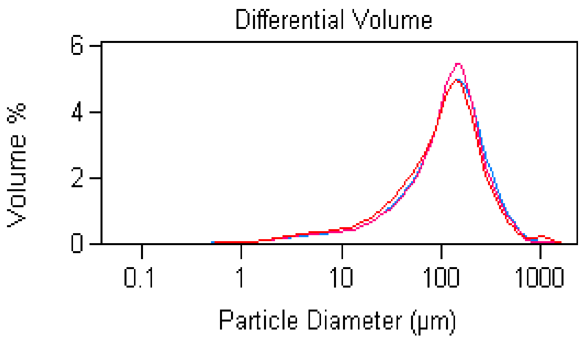


30% based on polymer

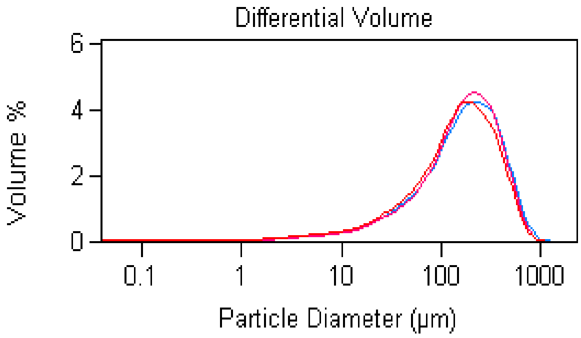


Stabilizing efficiency of propylene glycol on the particle size distribution of concentrated aqueous zein dispersions on freezing / thawing (9.0% polymer content)

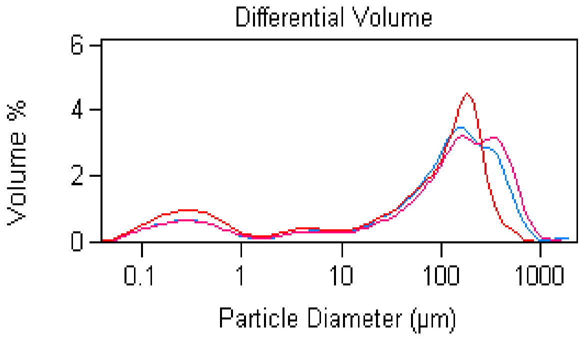
10% based on polymer



20% based on polymer

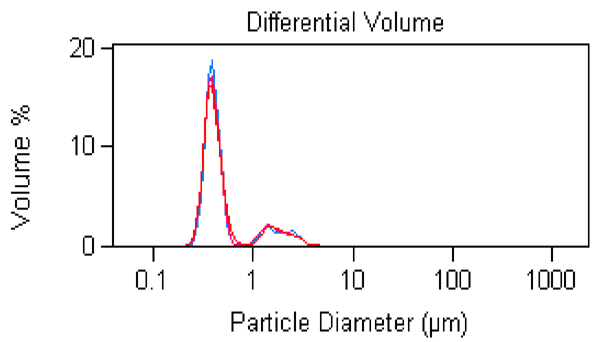


30% based on polymer

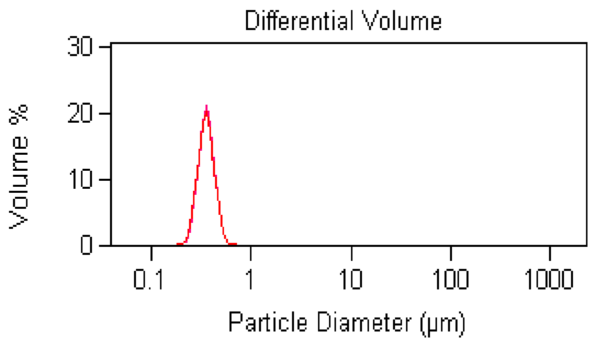


Stabilizing efficiency of tartaric acid on the particle size distribution of concentrated aqueous zein dispersions on freezing / thawing (3.4% polymer content)

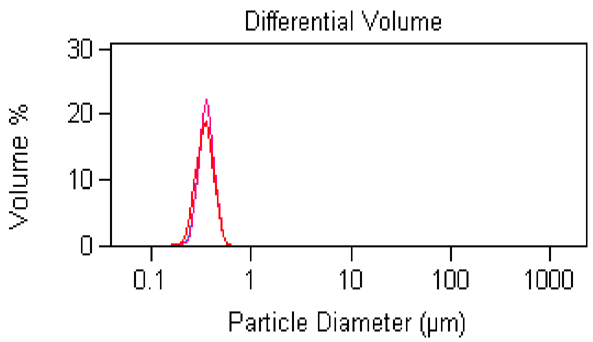
5% based on polymer



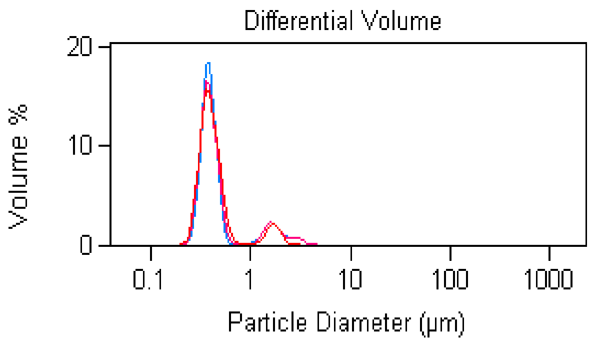
10% based on polymer



20% based on polymer

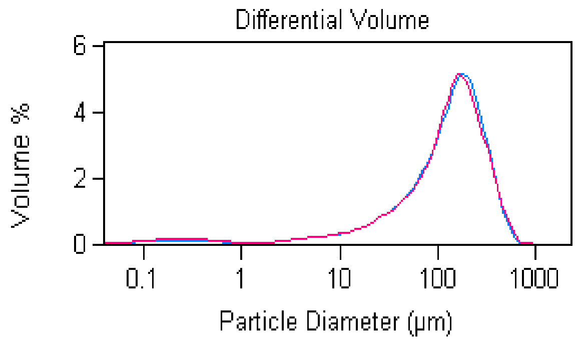


30% based on polymer

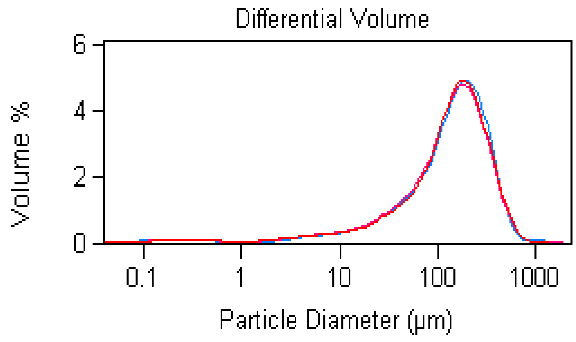


Stabilizing efficiency of tartaric acid on the particle size distribution of concentrated aqueous zein dispersions on freezing / thawing (9.0% polymer content)

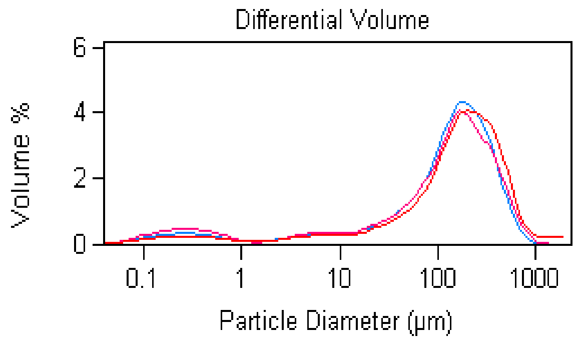
10% based on polymer



20% based on polymer



30% based on polymer

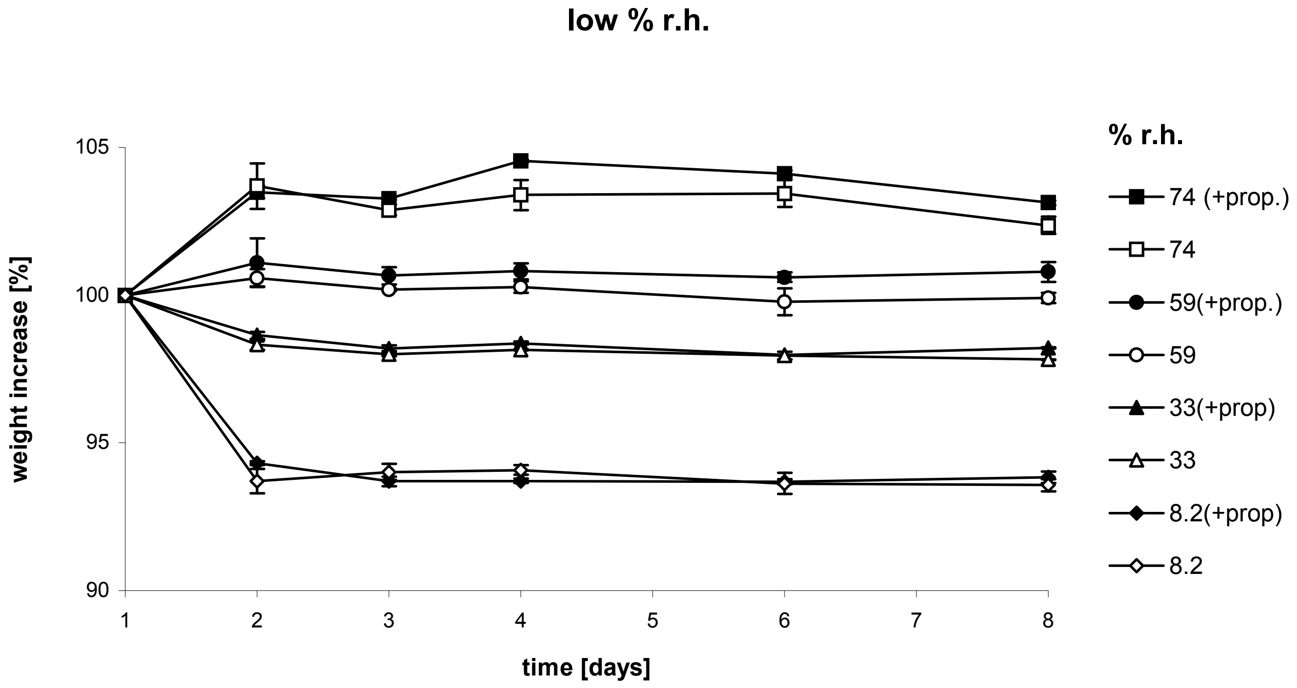


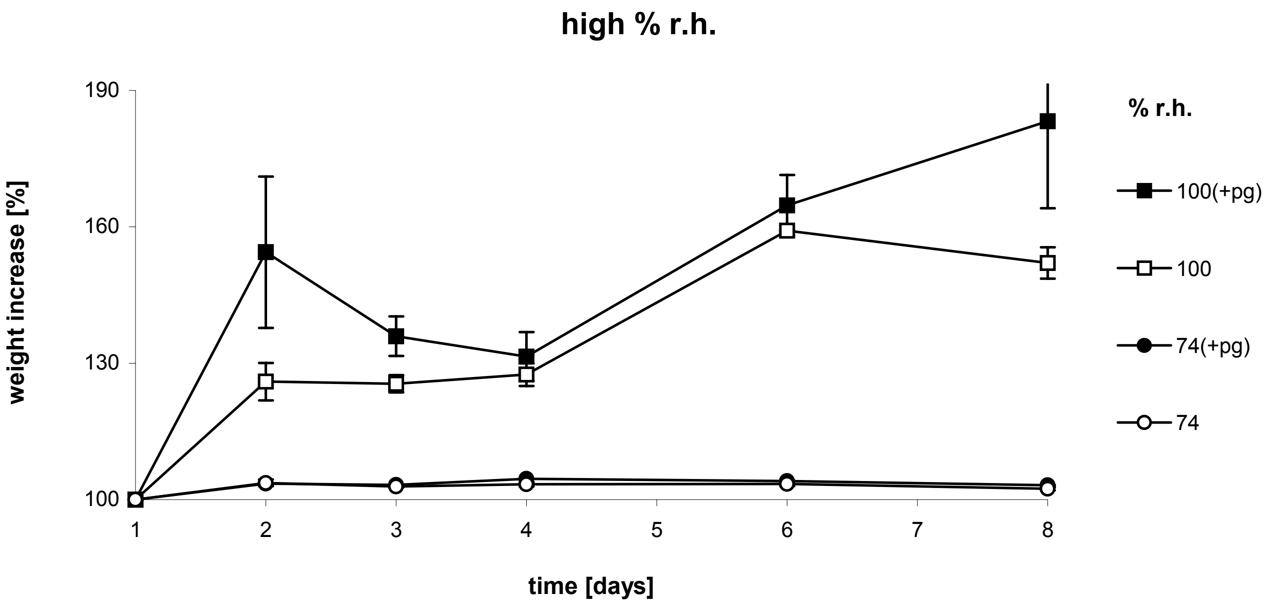
Stabilizing efficiency of different additives on the particle size distribution of concentrated aqueous zein dispersions *after freezing / thawing* (preparation method 1; highest polymer concentration with unchanged particle size distribution given)

Additive	**Conc. [% (w/w)] based on polymer**	**Polymer conc. [% (w/v)]**
Tween 80	6.6	6.8
Span 80	9.8	no effect
PEG 400	30.9	7.0
PEG 1500	30.9	no effect
AMG	30.3	no effect

2.3 Moisture Protection

Moisture uptake of zein films at different relative humidities (pure vs plasticized films; plasticizer: propylene glycol 40% (w/w))





Change in appearance and flexibility in dependence of differentrelative humidities (pure vs plasticized films; plasticizer: propylene glycol 40% (w/w))

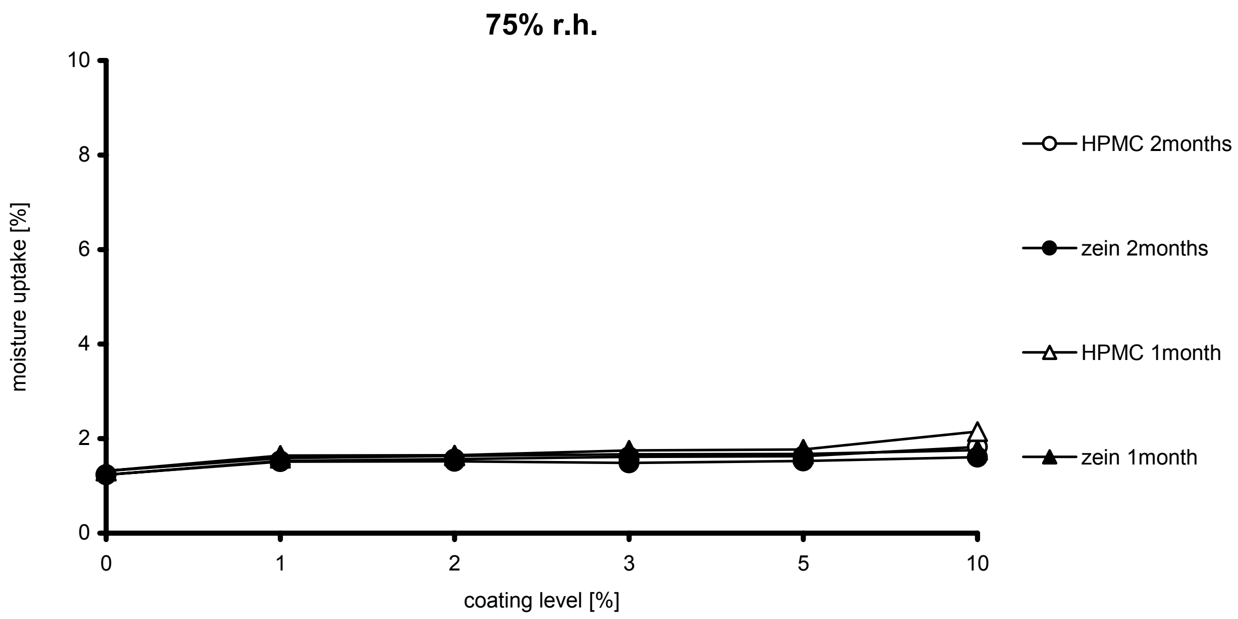
Pure Zein

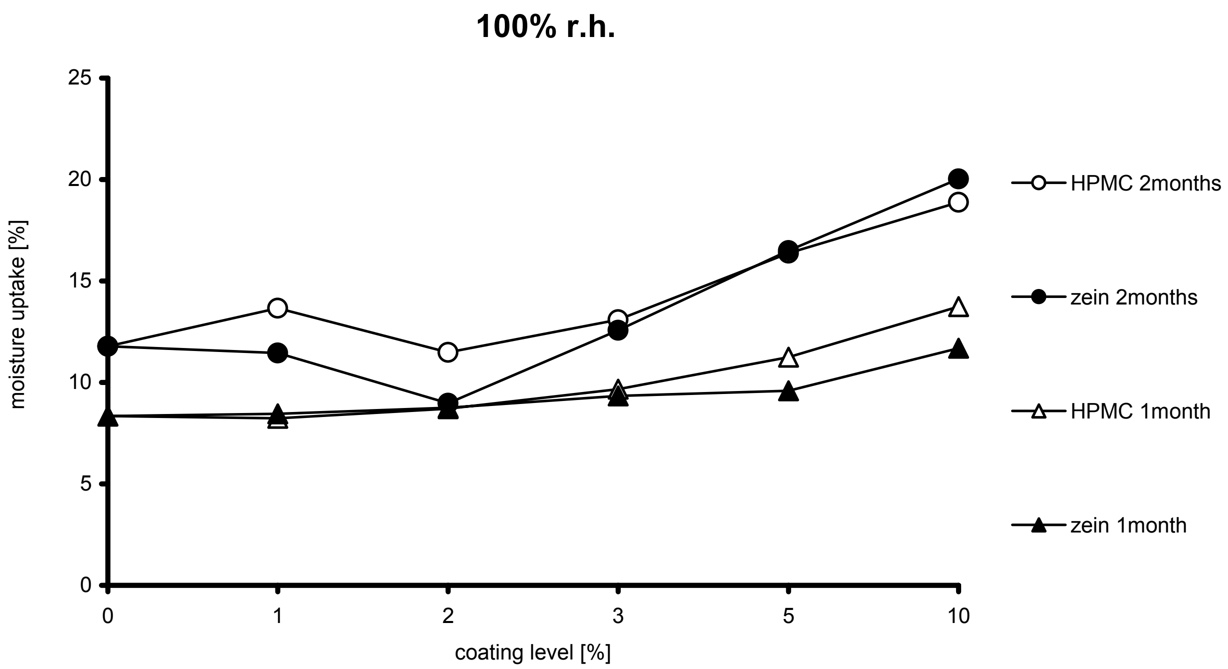
day / r.h. [%]	2	4	8	2	4	8
100.0	++++	++++	++++	opaque, wet	opaque, wet	opaque, wet
74.4	+	+	+++	clear	clear	clear
59.1	+/-	-	+/-	clear	clear	clear
33.0	-	-	-	clear	clear	clear
8.2	-	-	-	clear	clear	clear

Zein + Propylene Glycol 40% (w/w)

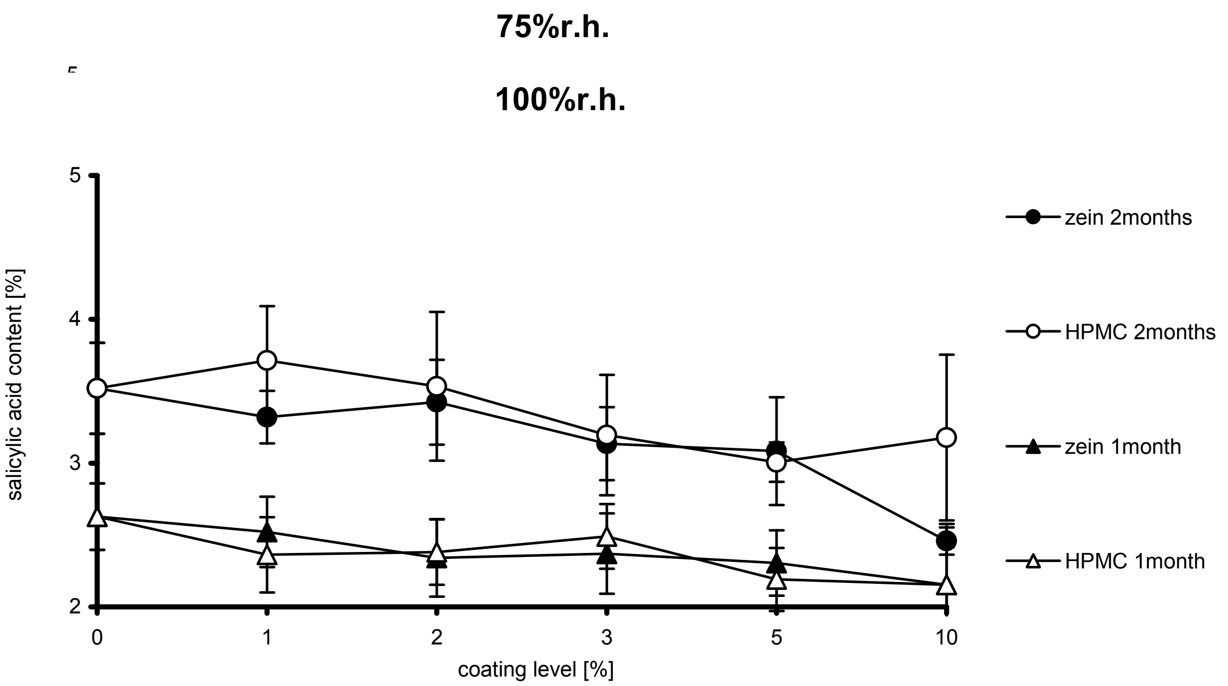
day / r.h. [%]	2	4	8	2	4	8
100.0	++++	++++	++++	opaque, wet	opaque, wet	opaque, wet
74.4	+++	+++	+++	clear	clear	clear
59.1	+	++	+++	clear	clear	clear
33.0	-	-	-	clear	clear	clear
8.2	-	-	-	clear	clear	clear

Moisture uptake of coated acetylic salicylic acid tablets in dependence of the coated polymer, coating level and storage condition (polymers: zein vs HPMC; coating levels: 1-10%; storage conditions: 75 / 100% r.h.; degradation product: salicylic acid)



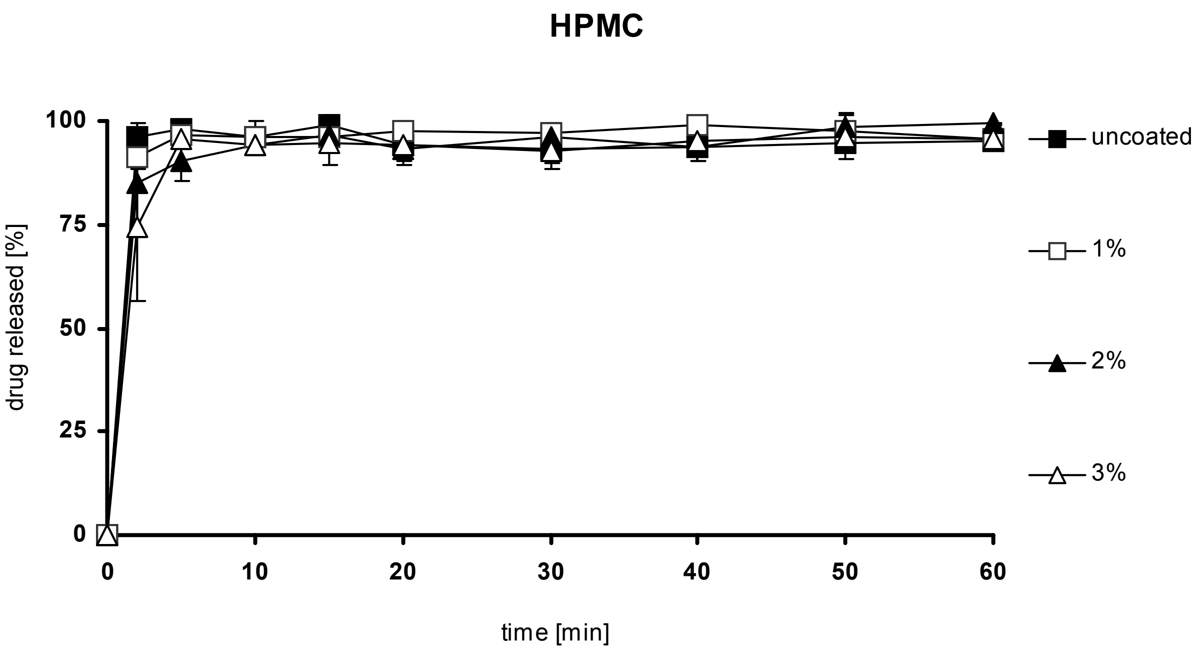


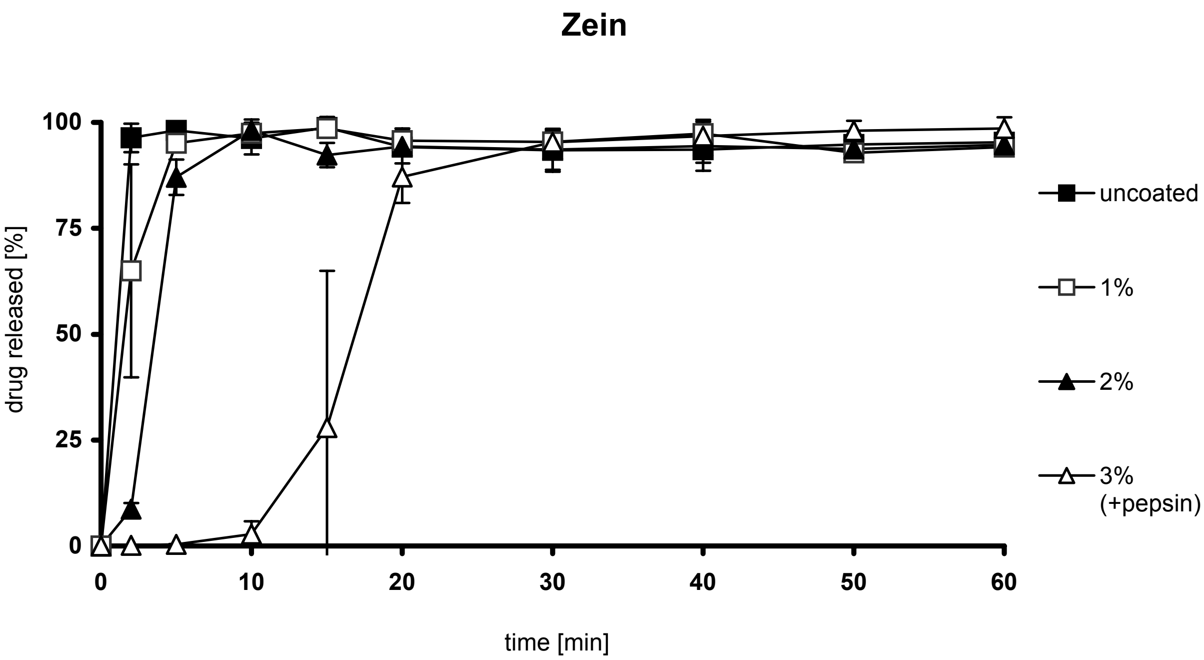
Degradation of the moisture sensitive drug acetylic salicylic acid in dependence of the coated polymer, coating level and storage condition (polymers: zein vs HPMC; coating levels: 1-10%; storage conditions: 75 / 100% r.h.; degradation product: salicylic acid)



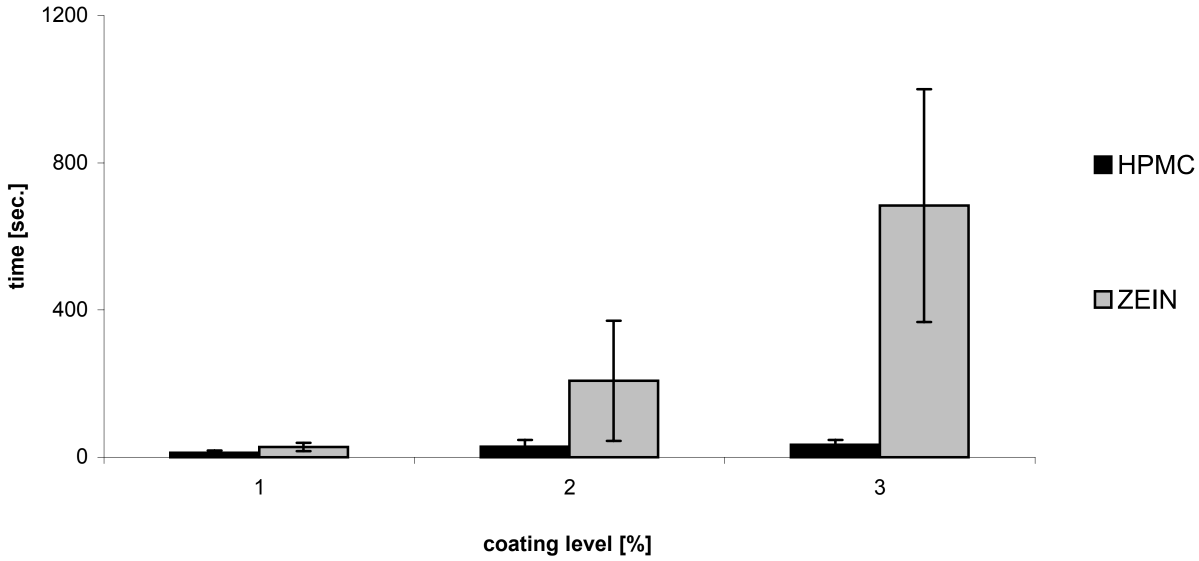
2.4 Taste masking study

Drug release from coated tablets: effect of the coating polymer (polymers: zein vs HPMC; dissolution media: pH 1.2)





Time until bitter taste perception of coated tablets: Zein vs HPMC- coatings (n = 7)



coating level [%]	mean	s.d.
uncoated	8	8
HPMC		
1	12	6
2	29	18
3	34	14
ZEIN		
1	28	11
2	208	163
3	684	316

3. Dry Coating Technology

Table of content:

Summary

Micronised ethylcellulose, shellac, Eudragit RS powders can be used for dry powder coating.

Controlled drug release was achieved with coating levels of 15 - 20 % (w/w polymer basis) for ethylcellulose (page 11) and 10-15 % for Eudragit RS (pages 29-31) and for enteric resistance 25 % of shellac (page 50).

High plasticizer concentrations (40%) and a thermal after-treatment (curing) were necessary for the coalescence of the polymer particles and good film formation (pages 7-10, 33, 35-37, 47-49).

Ethylcellulose required a higher curing temperature (pages 7-10) and time than Eudragit® RS (page 34) because of its higher glass transition temperature (133°C vs. 58°C).

A smaller polymer particle size also promoted film formation. In general, pellets coated with polymer powders required higher coating levels to obtain similar drug release patterns as pellets coated with organic polymer solutions and aqueous polymer dispersions.

The major advantages of this technique compared to conventional coating methods include:

The avoidance of organic solvents
The avoidance of large amount of water
A substantial reduction of the required processing time

1.1 Ethylcellulose

COATING OF DRUG-LOADED PELLETS

MATERIALS:

Polymer	Ethylcellulose (EC; Ethocel® 10FP)
Plasticizers	Acetylated monoglyceride (AMG; Myvacet® 9-45) Acetyltributyl citrate (ATBC) Triethyl citrate (TEC)
Binder material	Hydroxypropyl methylcellulose (HPMC E5; Methocel® E5)

FORMULATION: Ethylcellulose powder coatings

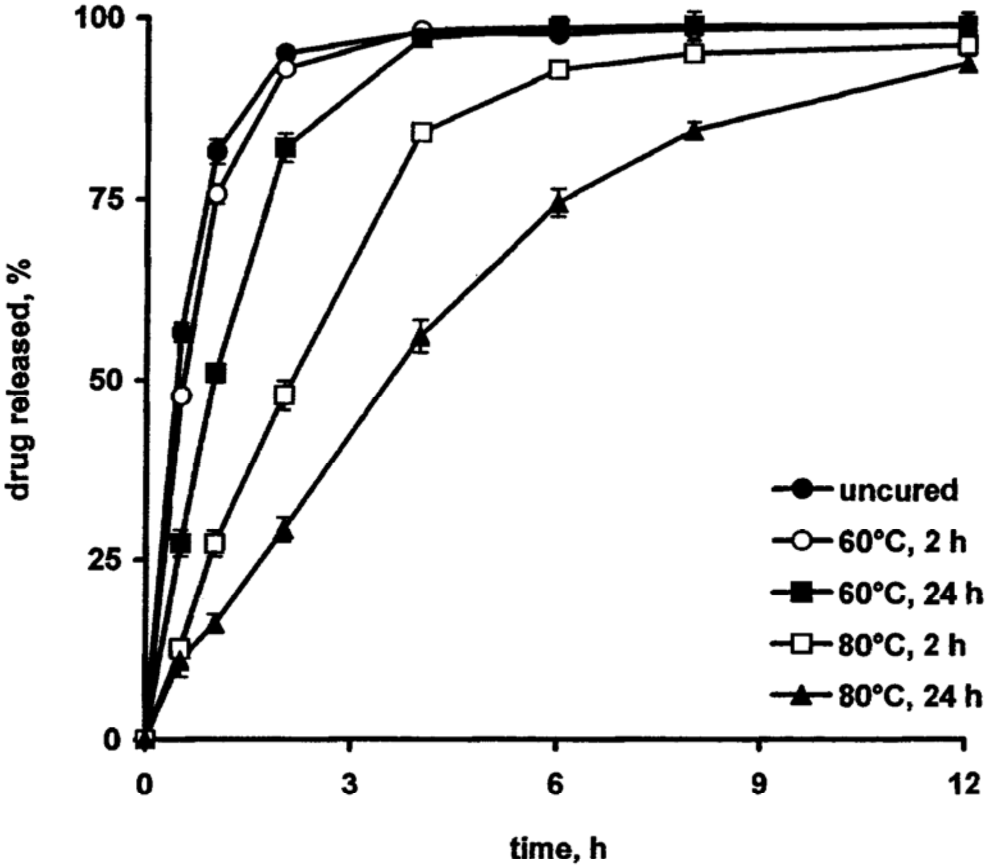
	Composition, % w/w	
POWDERS		
Ethylcellulose	76.9	
Talc	23.1	
Total	**100.0**	

LIQUIDS		
Plasticizer	50.0-75.0	30-40 % w/w based on the polymer mass
HPMC E5 solution (10 % w/w in water)	25.0-50.0	
Total	**100.0**	

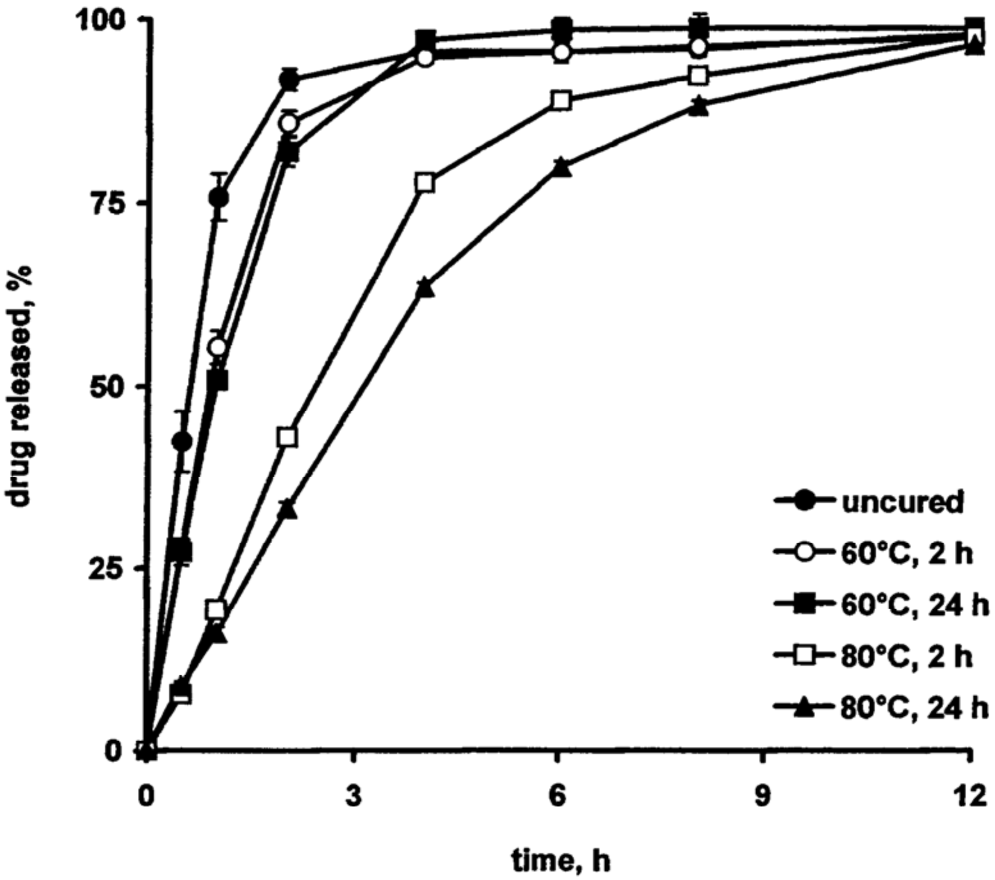
PROCESSING PARAMETER:

Fluidized bed coater	Glatt GPCG-1, Wurster insert
Batch size	1.2 kg
Inlet air temperature	55-57°C
Product temperature	45-47°C
Outlet air temperature	40-41°C
Air flow rate	60-80 m^3/h
Atomizing pressure	1.2 bar
Spray nozzle diameter	1.2 mm
Spray rate	3-5 g/min
Powder-feeding rate	10-14 g/min
Drying temperature, °C	45-65
Drying period, min	10-15
THERMAL TREATMENT	
Curing condition, in oven	80°C, 24 h

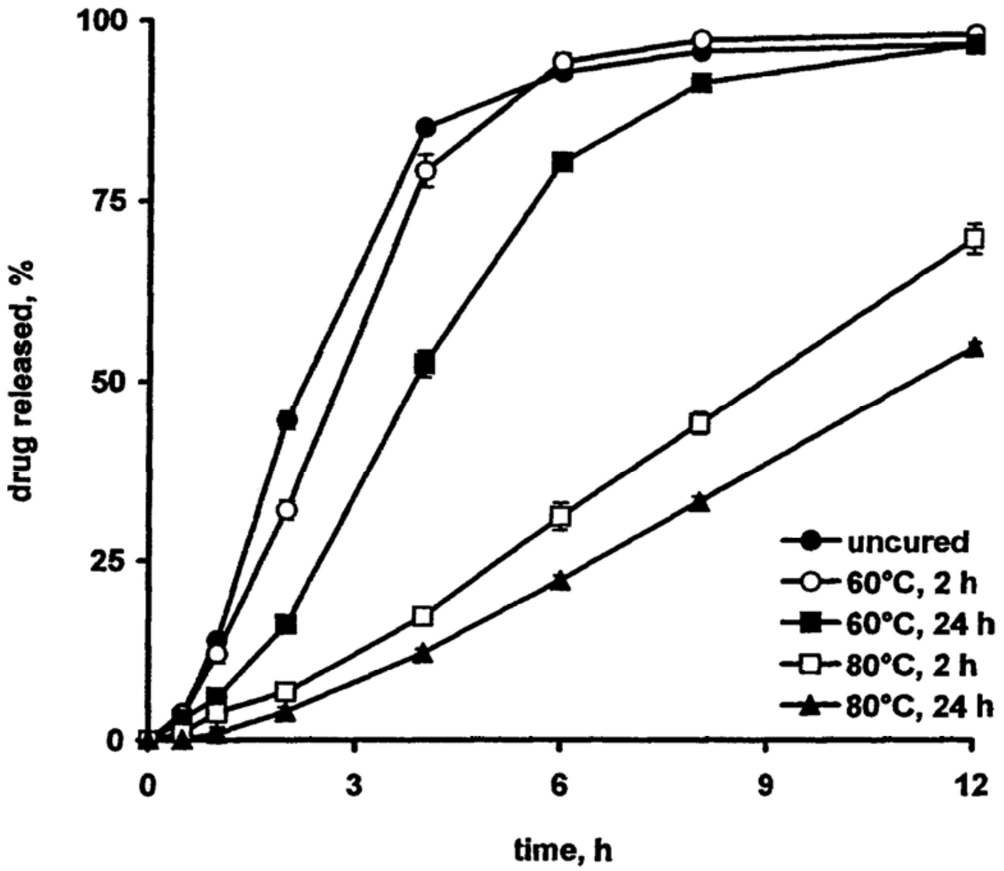
Effect of curing condition on drug release from ethylcellulose-coated pellets plasticized with <u>ATBC</u> (propranolol HCl-loaded pellets; coating level, 18.1 %; plasticizer concentration, 40 % w/w; dissolution medium, 0.1 N HCl)



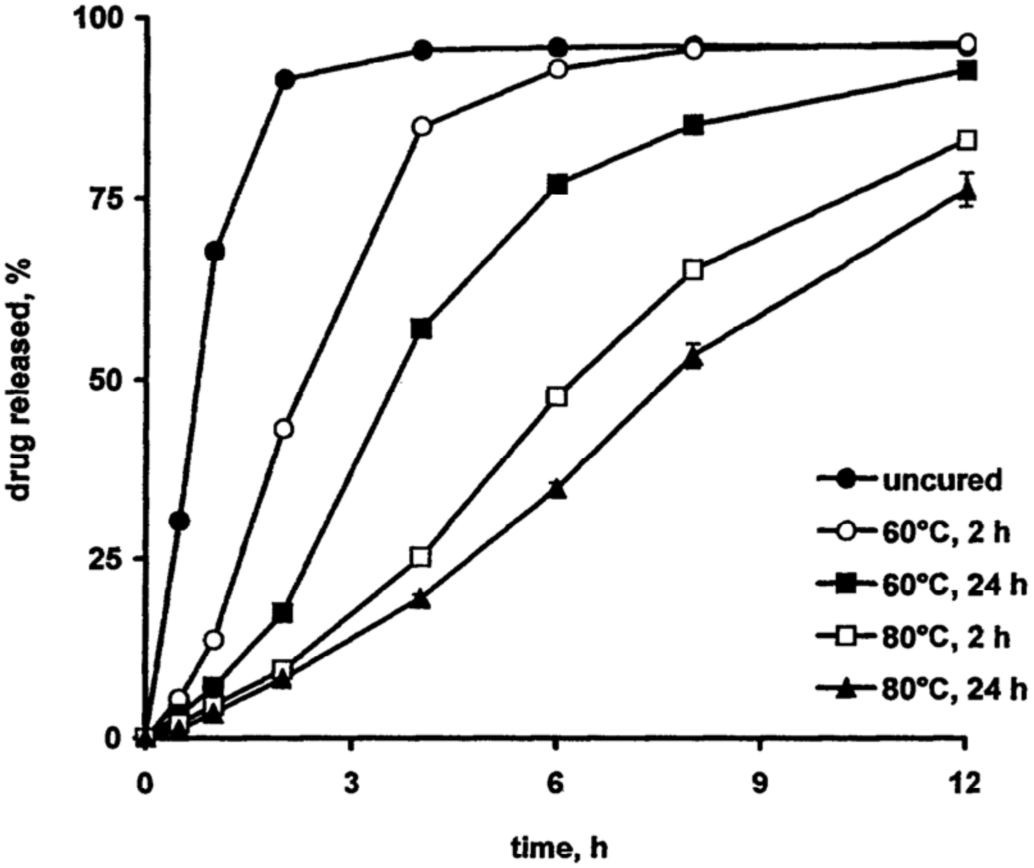
Effect of curing condition on drug release from ethylcellulose-coated pellets plasticized with <u>TEC</u> (propranolol HCl-loaded pellets; coating level, 18.9 %; plasticizer concentration, 40 % w/w; dissolution medium, 0.1 N HCl)



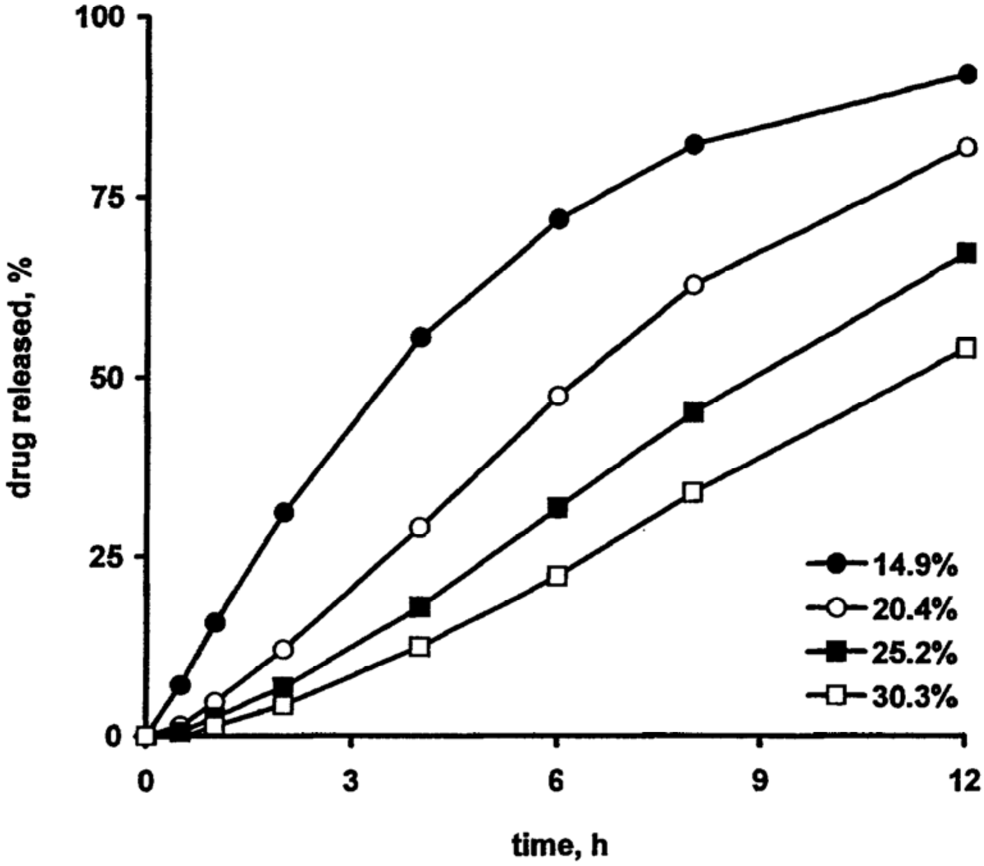
Effect of curing condition on drug release from ethylcellulose-coated pellets plasticized with **AMG** (propranolol HCl-loaded pellets; coating level, 30.3 %; plasticizer concentration, 40 % w/w; dissolution medium, 0.1 N HCl)



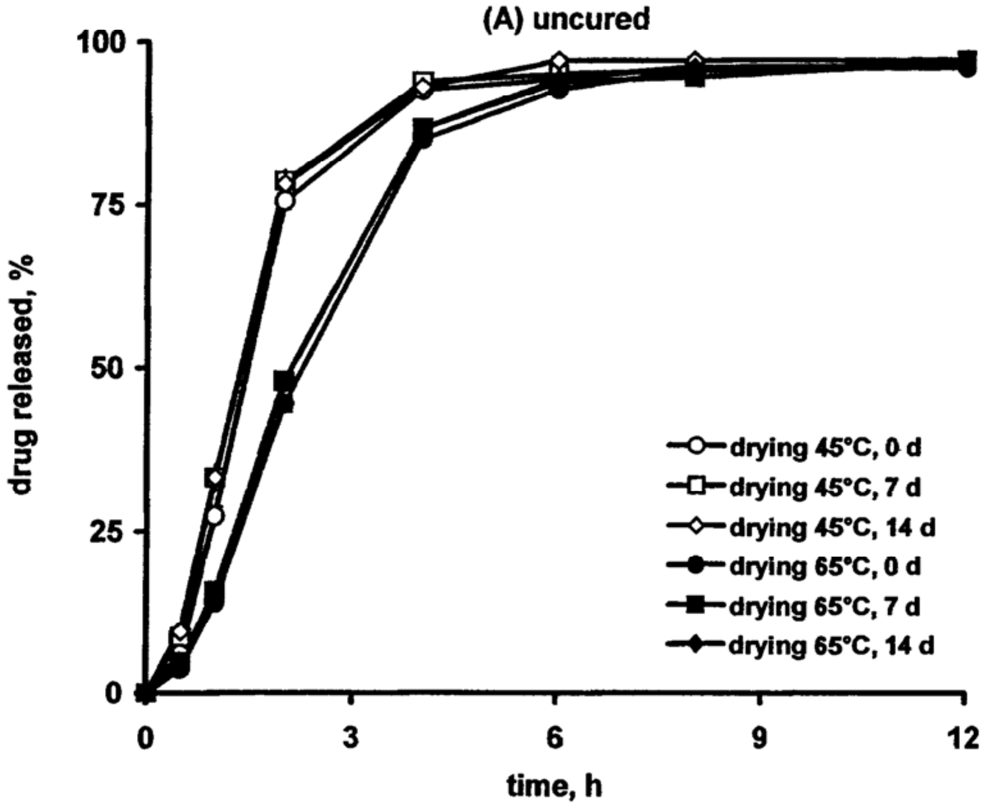
Effect of curing condition on drug release from ethylcellulose-coated pellets plasticized with AMG by using ethylcellulose powders soaking with TEC (30 % w/w) (propranolol HCl-loaded pellets; coating level, 14.3 %; plasticizer concentration, 40 % w/w; dissolution medium, 0.1 N HCl)

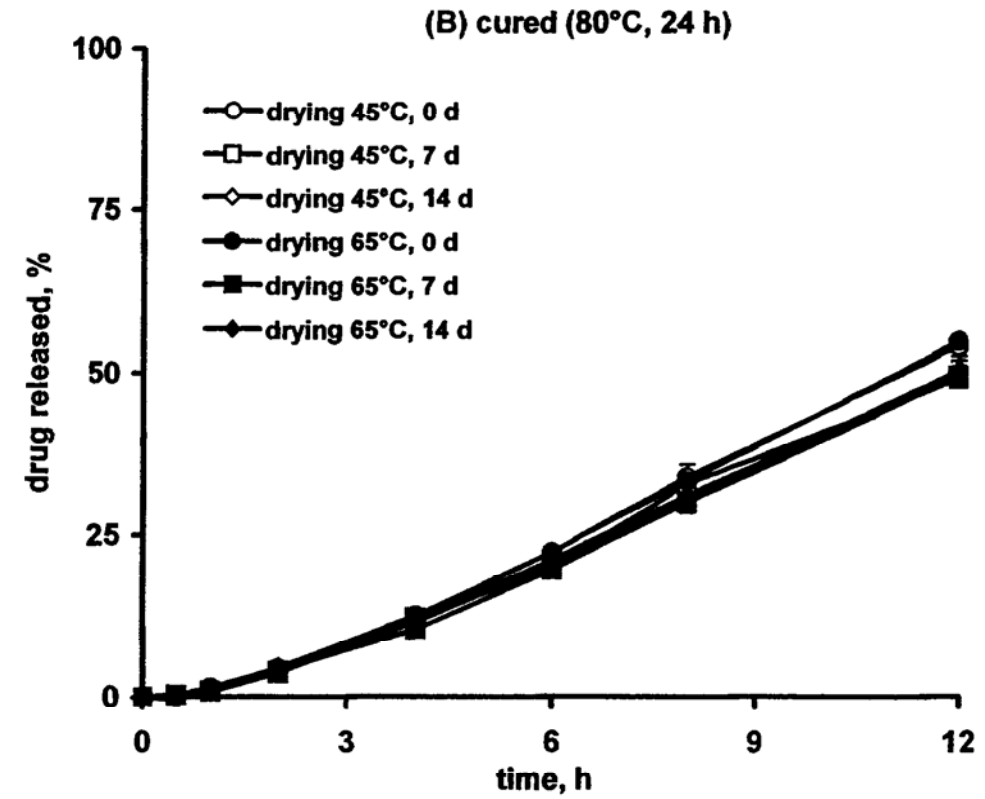


Effect of **coating level** on drug release from ethylcellulose-coated pellets plasticized with AMG (propranolol HCl-loaded pellets; plasticizer concentration, 40 % w/w; curing condition, 80°C for 24 h; dissolution medium, 0.1 N HCl)

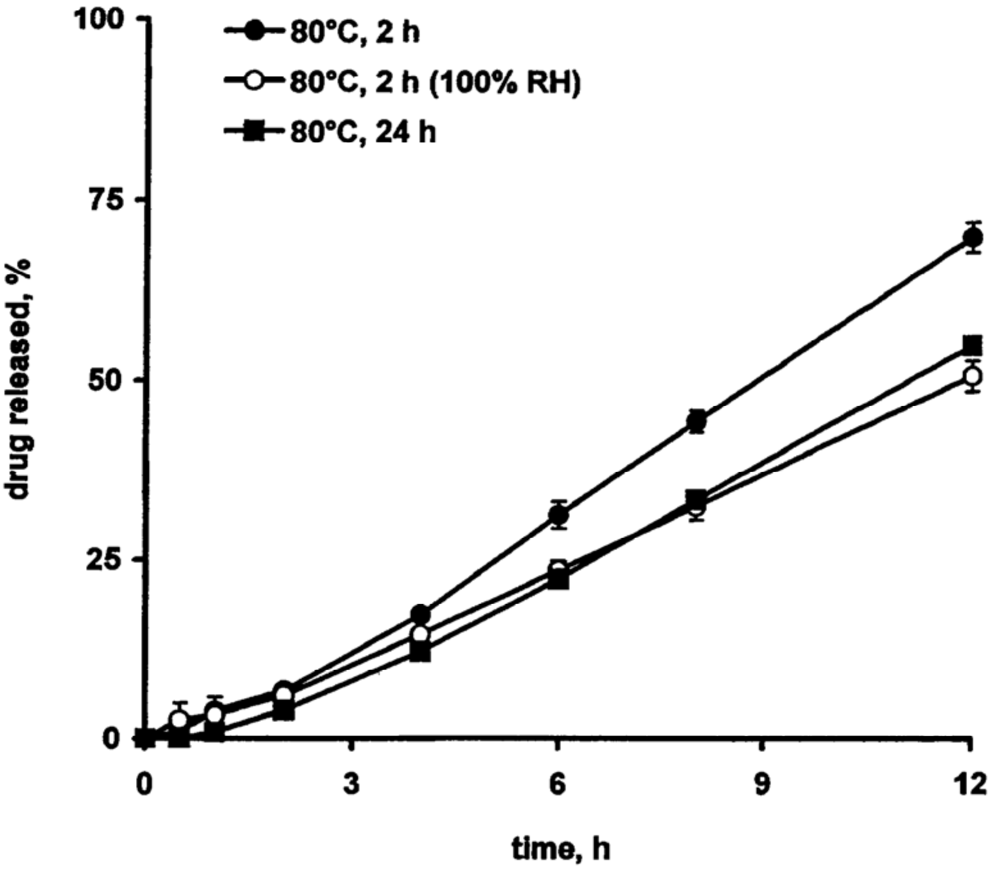


Effect of <u>**drying temperature and storage time**</u> on film-formation of ethylcellulose-coated pellets after storage at room temperature: (A) uncured pellets and (B) cured pellets (coating level, 30.3 %; plasticizer concentration, AMG 40 % w/w; drying period, 10 min; dissolution medium, 0.1 N HCl)





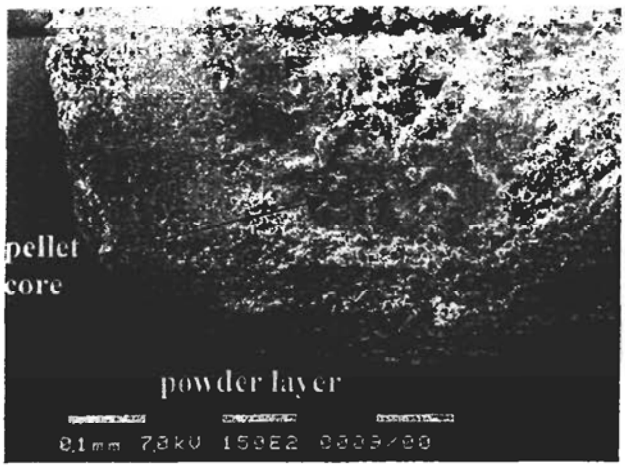
Effect of **curing condition** on film-formation of ethylcellulose-coated pellets after storage at elevated temperature and humidity (propranolol HCl-loaded pellets; coating level, 30.3 %; plasticizer concentration, 40 % w/w; dissolution medium, 0.1 N HCl)



<u>Curing effect</u> on film-formation of ethylcellulose-coated pellets by using dry powder coating system (coating level, 20.4 %; plasticizer type, acetylated monoglyceride; plasticizer concentration, 40 % w/w)

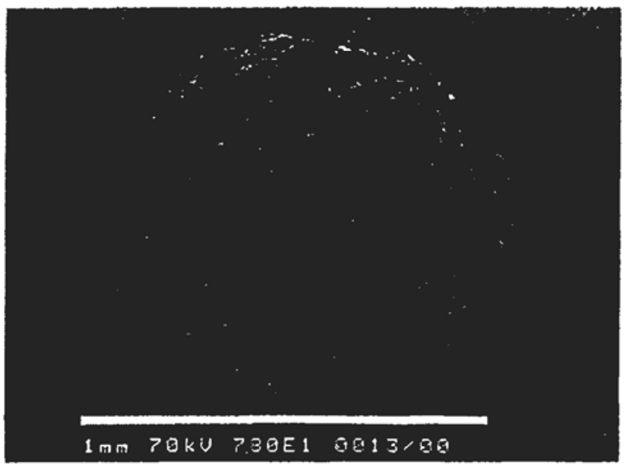
Uncured	**Cured (80°C, 24 h)**

(A) cross-section of pellet



(B) cross-section of pellet

(C) pellet surface



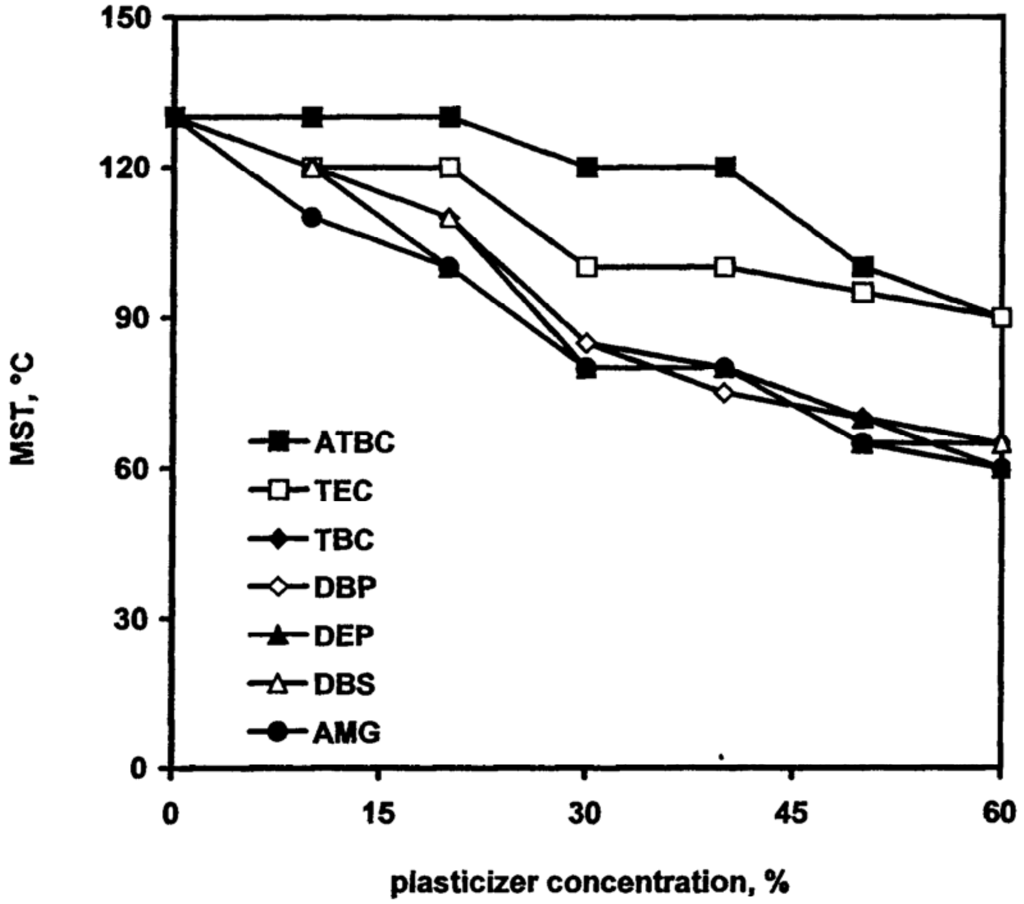
(D) pellet surface

Effect of **plasticizer concentration** on film-formation of ethylcellulose coated-pellets by using dry powder coating system (plasticizer type, acetylated monoglyceride; curing condition, 80°C for 24 h)

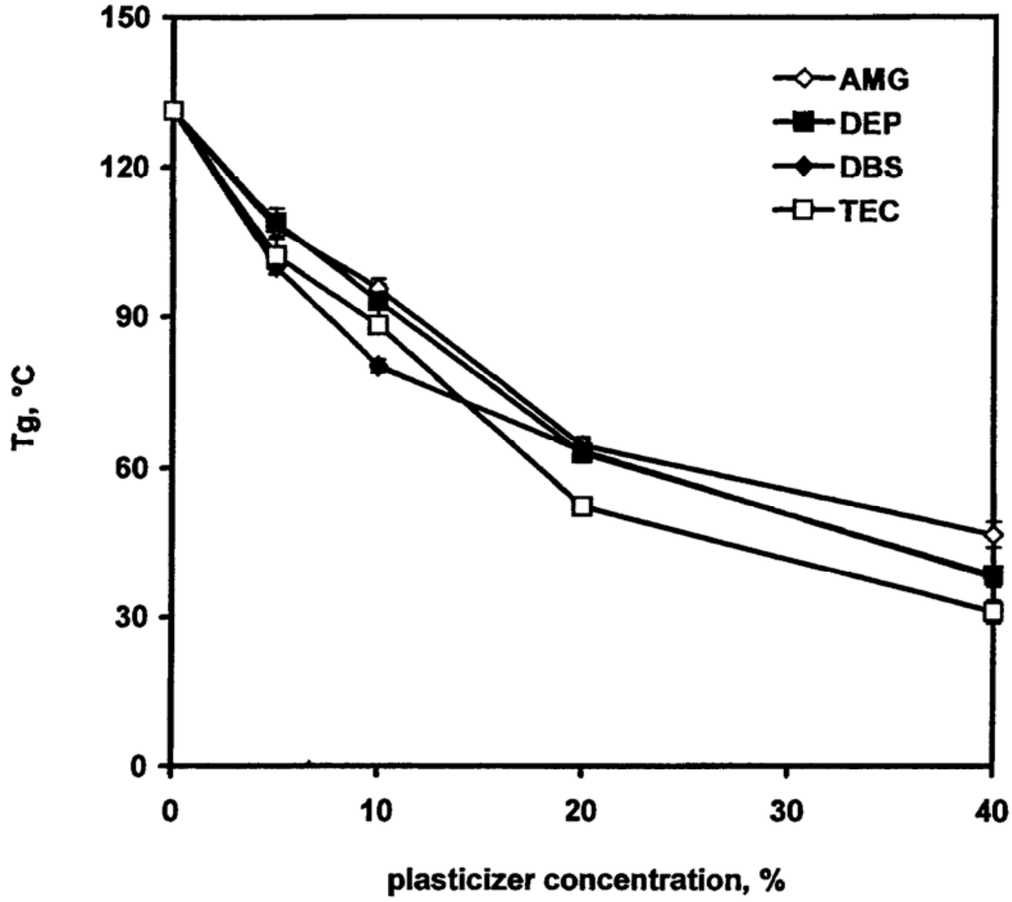
(A) 23.1 % EC, AMG 30 %

(B) 20.4 % EC, AMG 40 %

Effect of **plasticizer concentration** on the minimum polymer-softening temperature (MST) of ethylcellulose powders

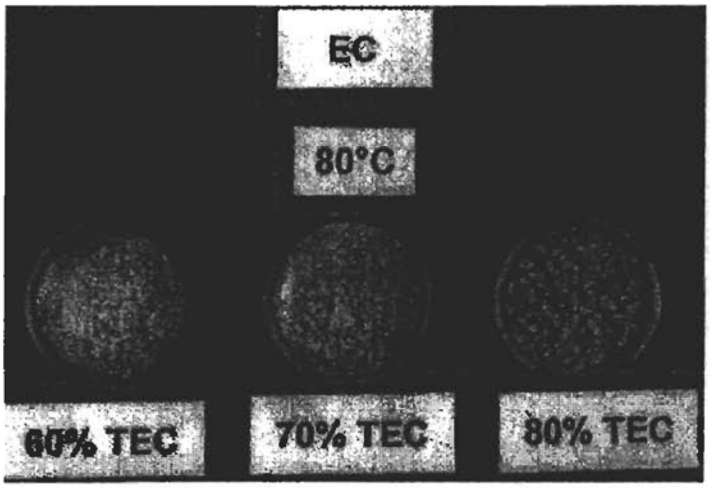


Effect of **plasticizer concentration** on the glass transition temperature (Tg) of ethylcellulose films (organic-based solution)

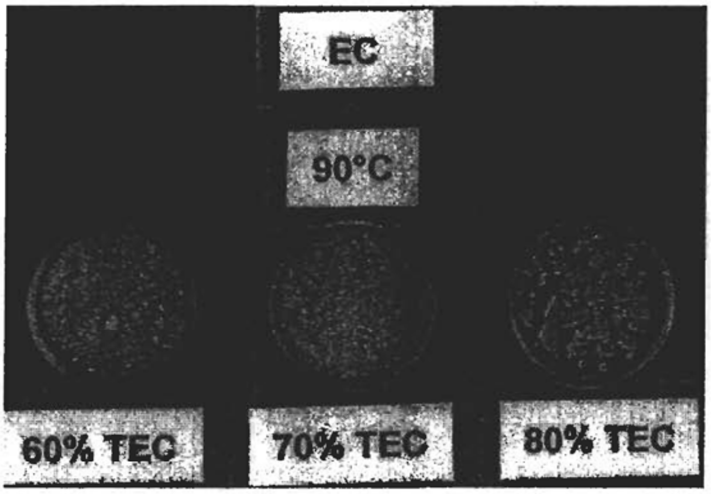


Effect of **plasticizer and temperature** on the film-forming ability of ethylcellulose powders (% w/w based on the mass of the polymer; after 24 h in an oven)

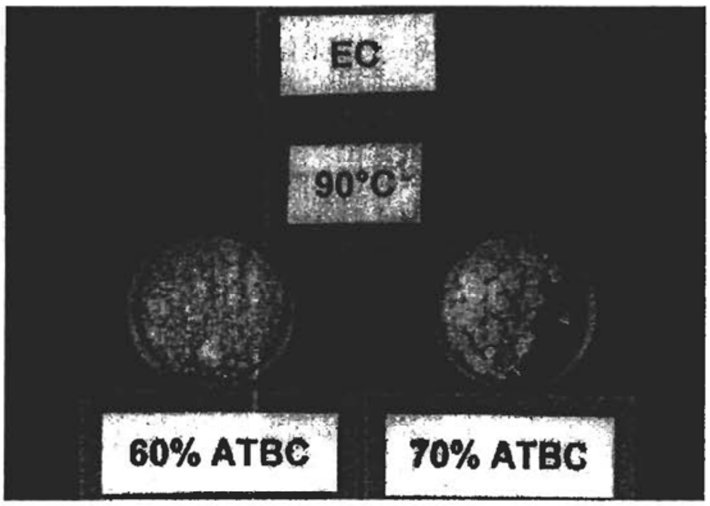
(A)



(B)



(C)

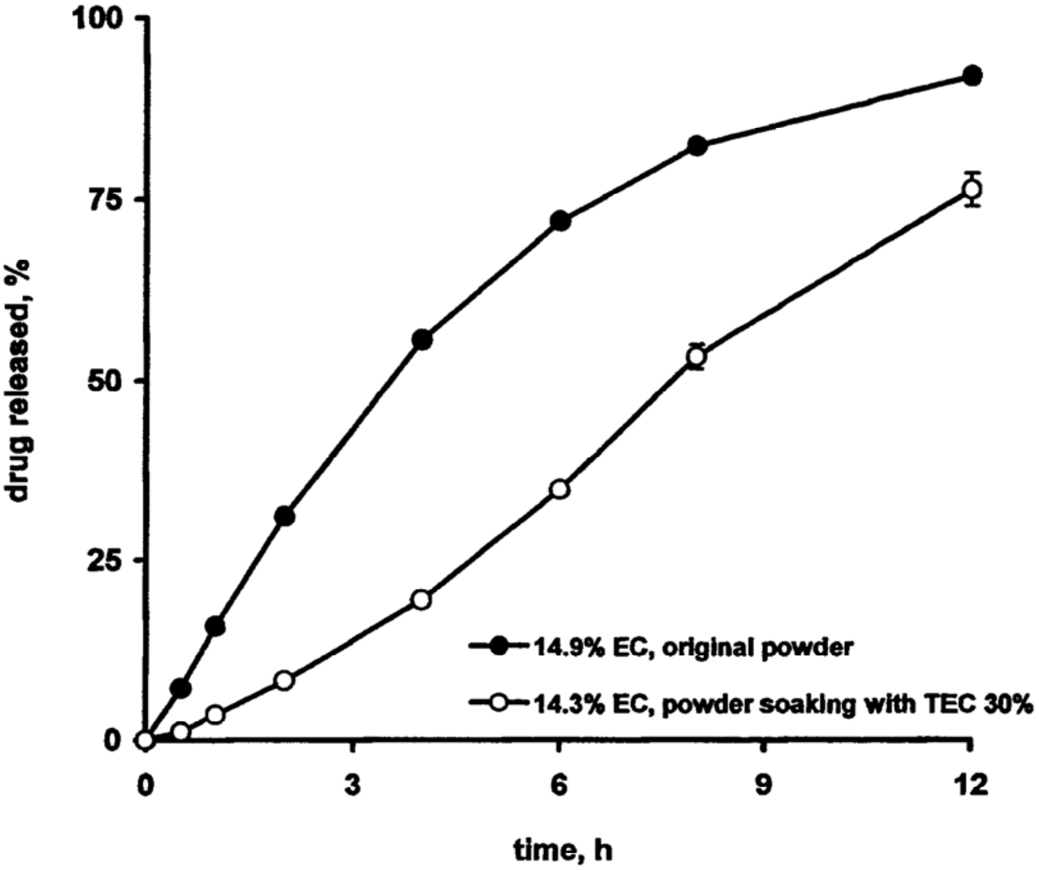


The minimum polymer-softening temperature (MST) of ethylcellulose powders soaking with different plasticizers (plasticization time, 24 h)

Plasticizer	% w/w	MST, °C
None	-	130
AMG*	10	130
	15	120
	20	110
ATBC*	10	130
	15	120
	20	110
DBS*	10	100
	15	95
	20	90
DEP*	10	95
	15	90
	20	80
TEC	10	130
	15	120
	20	110
	30	95

* the ethylcellulose dispersion containing more than 20% plasticizer exhibited a sticky mass

Comparison of drug release from ethylcellulose-coated pellets by using polymer powders with and without plasticizer-soaking (propranolol HCl-loaded pellets; plasticizer type, acetylated monoglyceride; plasticizer concentration, 40 % w/w; curing condition, 80°C for 24 h; dissolution medium, 0.1 N HCl)

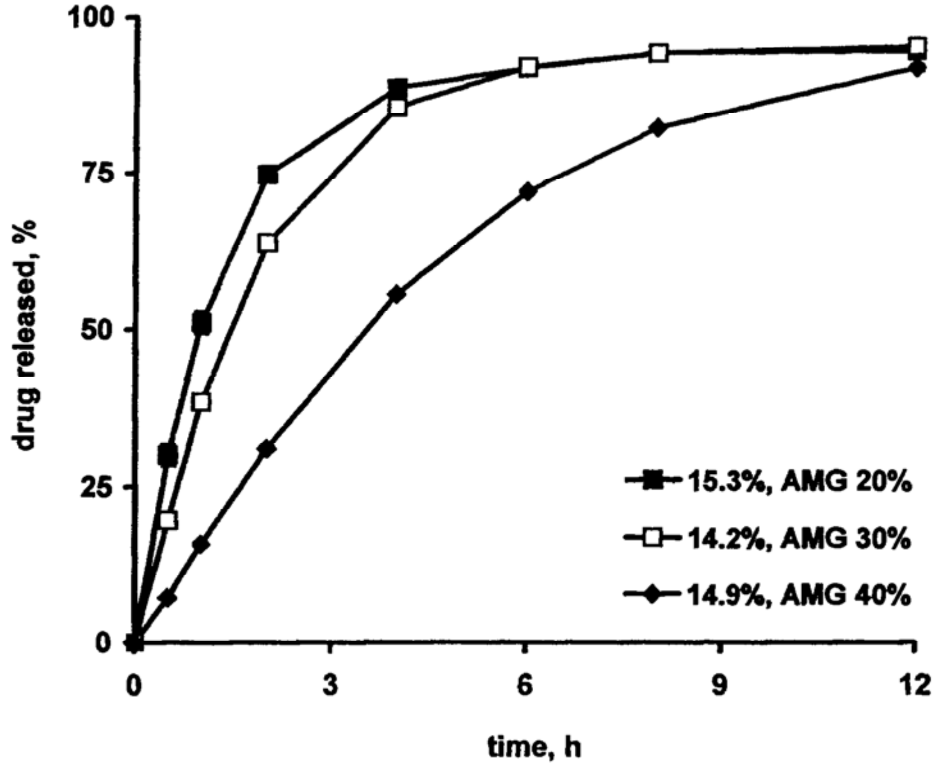


The minimum polymer-softening temperature (MST) of freeze-dried ethylcellulose powders soaking with different plasticizers (ethylcellulose pseudolatex, Aquacoat® ECD; plasticization time, 24 h; particle size, >70 μm)

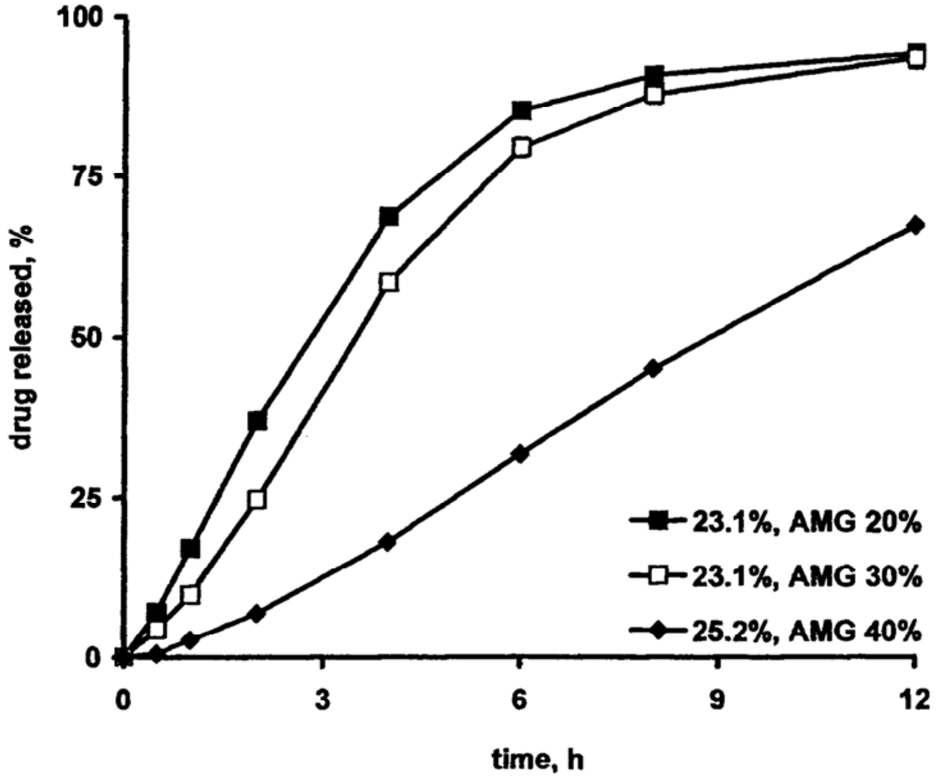
Plasticizer	% w/w	MST, °C
None	-	70
AMG	5	70
	10	60
	15	50
	20	50
TEC	5	70
	10	60
	15	50
	20	50

Effect of **plasticizer content and coating level** on drug release from ethylcellulose-coated pellets plasticized with AMG at different coating levels (propranolol HCl-loaded pellets; curing condition, 80°C for 24 h; dissolution medium, 0.1 N HCl)

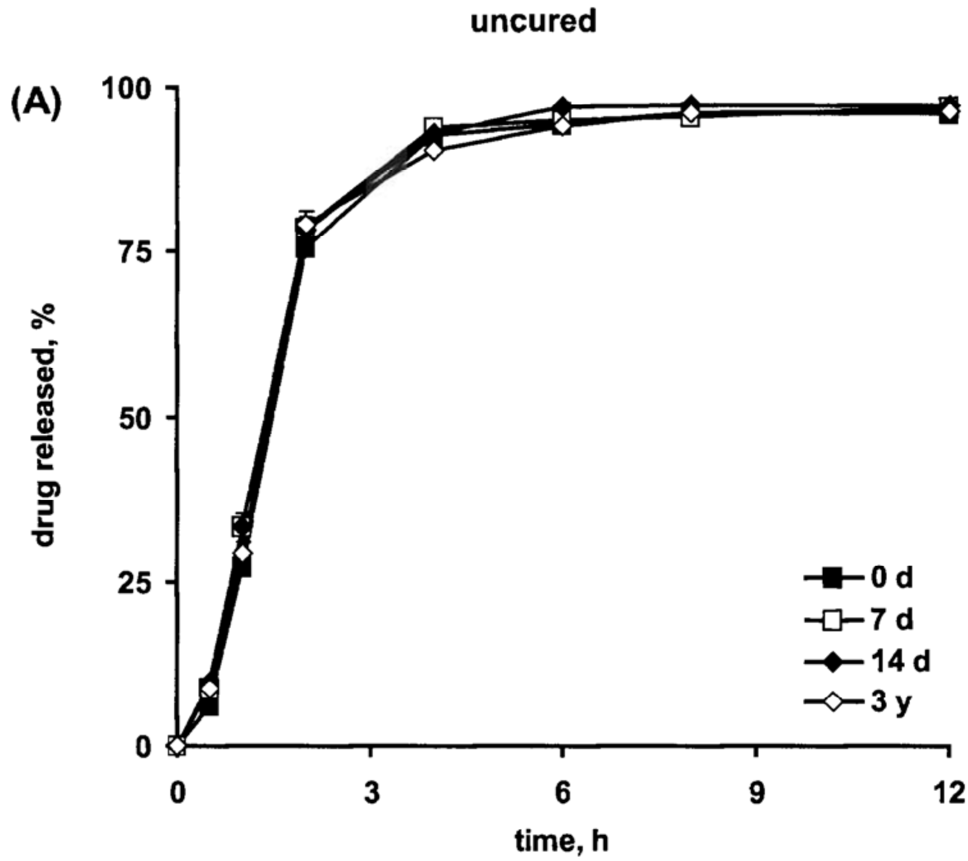
(A)

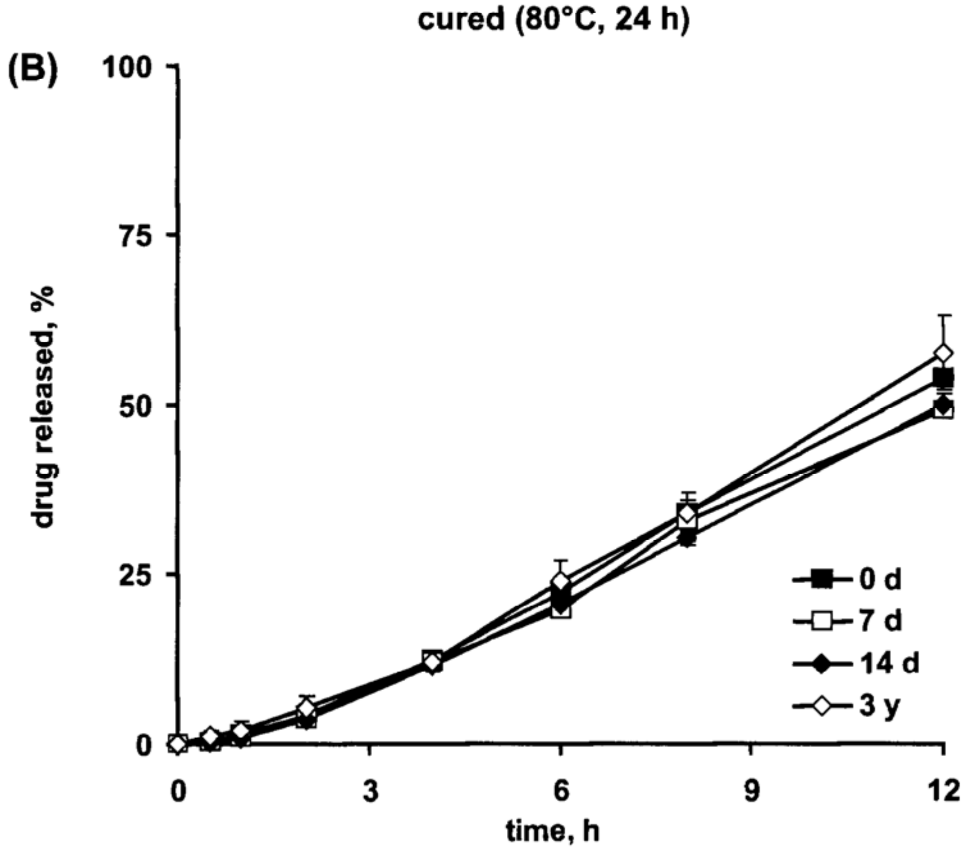


(B)

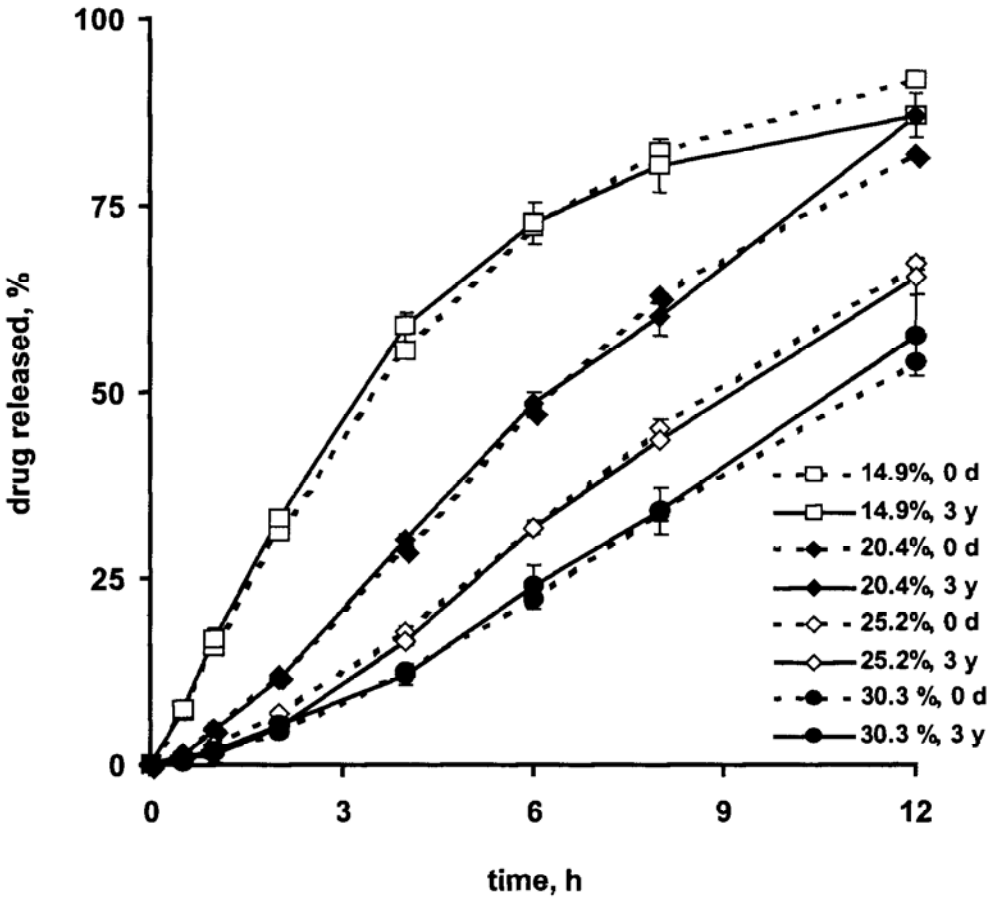


Effect of short- and long-term storage at room temperature on propranolol hydrochloride release from ethylcellulose powder-coated pellets: (A) uncured pellets; and (B) cured pellets at 80°C for 24 h (coating level, 30.3 %; 40 % acetylated monoglyceride).

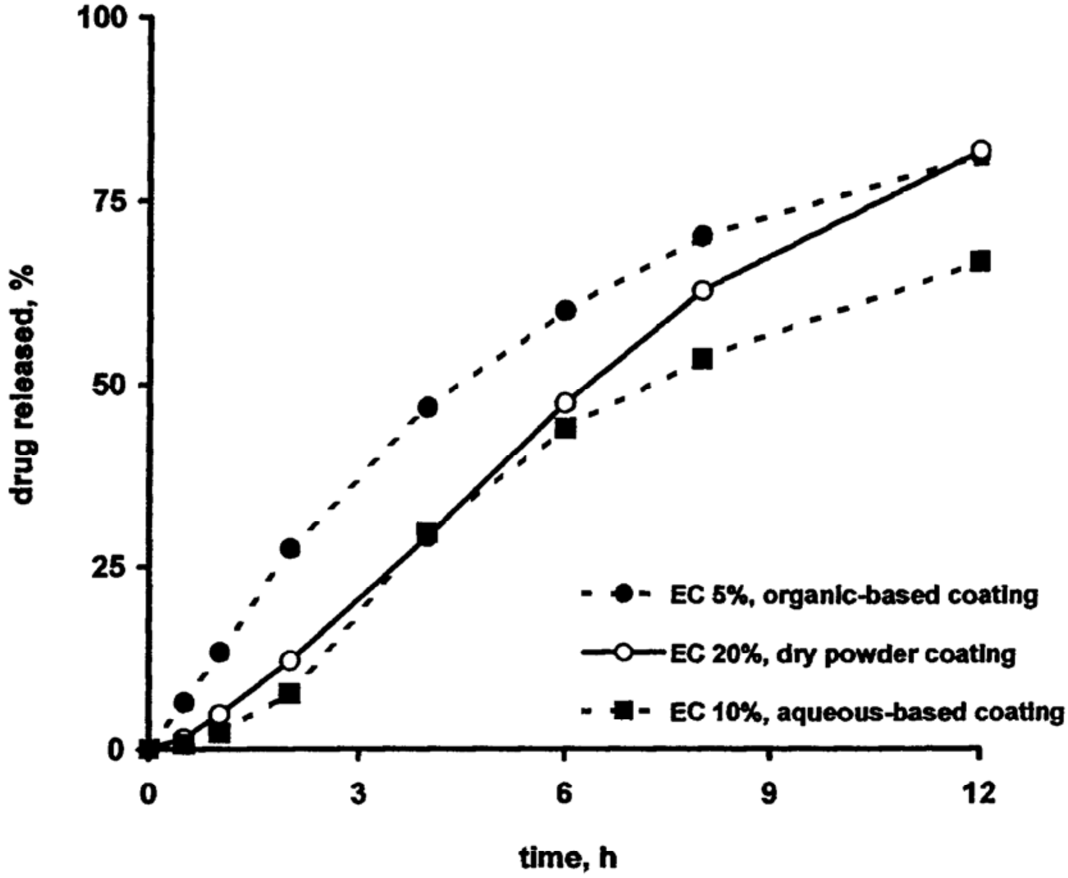




Propranolol hydrochloride release from ethylcellulose powder-coated pellets at different coating levels after storage at room temperature for 3 years (40 acetylated monoglyceride, cured at 80°C for 24 h).



Comparison of ethylcellulose-coated pellets in different coating systems (propranolol HCl-loaded pellets plasticizer type, acetylated monoglyceride; dissolution medium, 0.1 N HCl)
Organic-based coating: plasticizer concentration, 20 % w/w
Aqueous-based coating: plasticizer concentration, 20 % w/w; curing condition, 60°C for 24 h
Powder coating: plasticizer concentration, 40 % w/w; curing condition, 80°C for 24 h



Processing time of polymer-coated pellets by using dry powder coating with comparison to organic- and aqueous-based coatings (Wurster insert, Glatt GPCG-1)

Coating system	Ethylcellulose	Processing time, min
Dry powder coating	20 %	30
Aqueous-based coating	10 %	113
Organic-based coating	5 %	141

1.2 Eudragit RS

COATING OF DRUG-LOADED PELLETS

FORMULATION: Eudragit® RS powder coatings

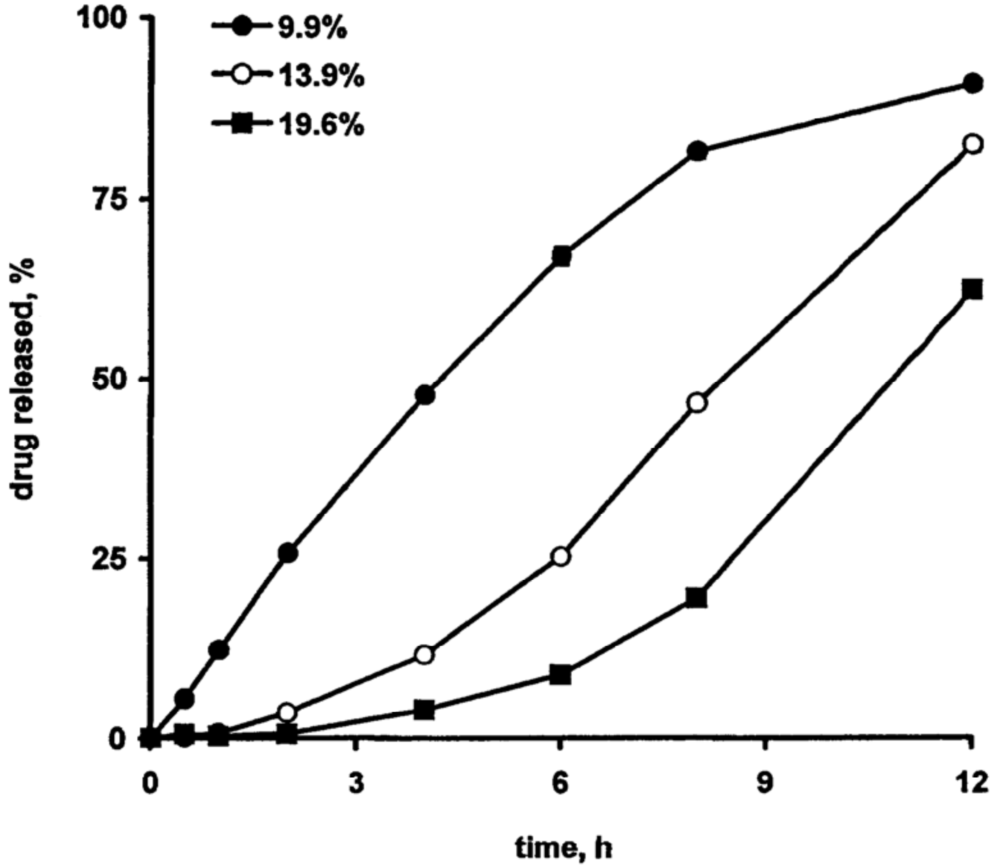
	Composition, % w/w	
POWDERS		
Eudragit® RS micronized powders	50.0	
Talc	50.0	
Total	**100.0**	

LIQUIDS		
Plasticizer	75.0	30-40 % w/w based on the polymer mass
HPMC solution (10 % w/w in water)	25.0	
Total	**100.0**	

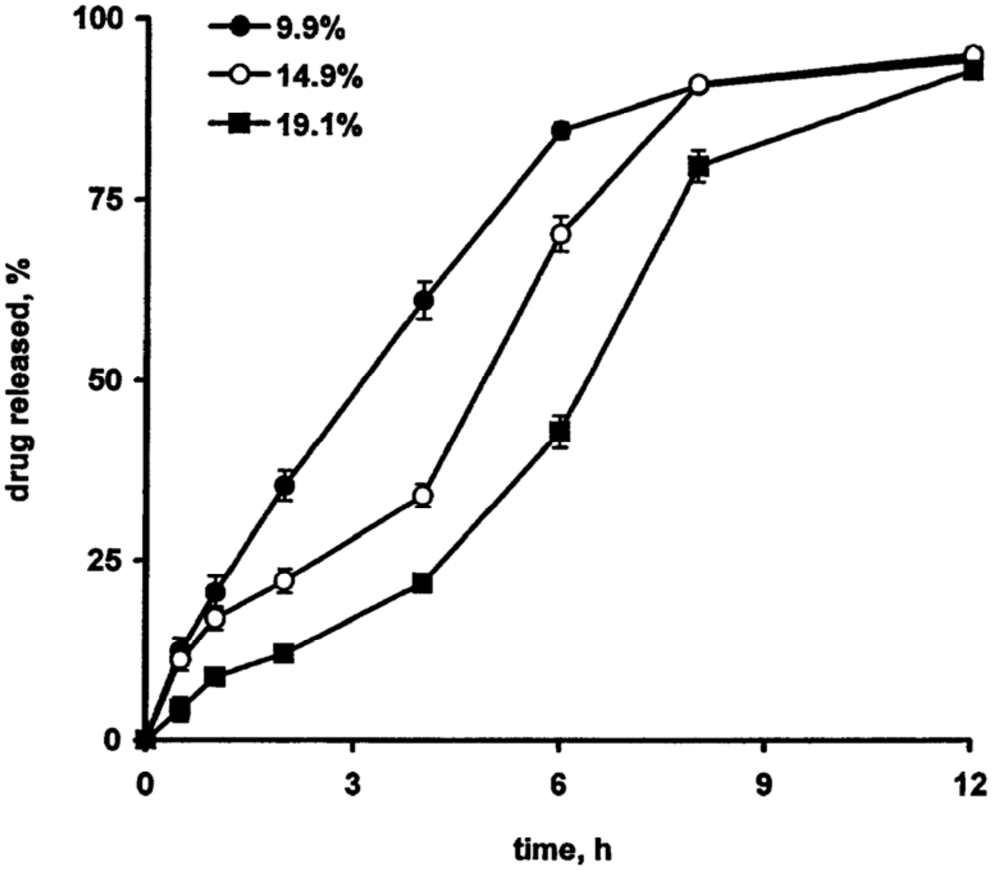
PROCESSING PARAMETER:

Fluidized bed coater	Glatt GPCG-1, Wurster insert
Batch size	1.2 kg
Inlet air temperature	45-47°C
Product temperature	35-38°C
Outlet air temperature	32-34°C
Air flow rate	60-80 m³/h
Atomizing pressure	1.2 bar
Spray rate	3-5 g/min
Spray nozzle diameter	1.2 mm
Secondary drying (35-40°C)	10-15 min

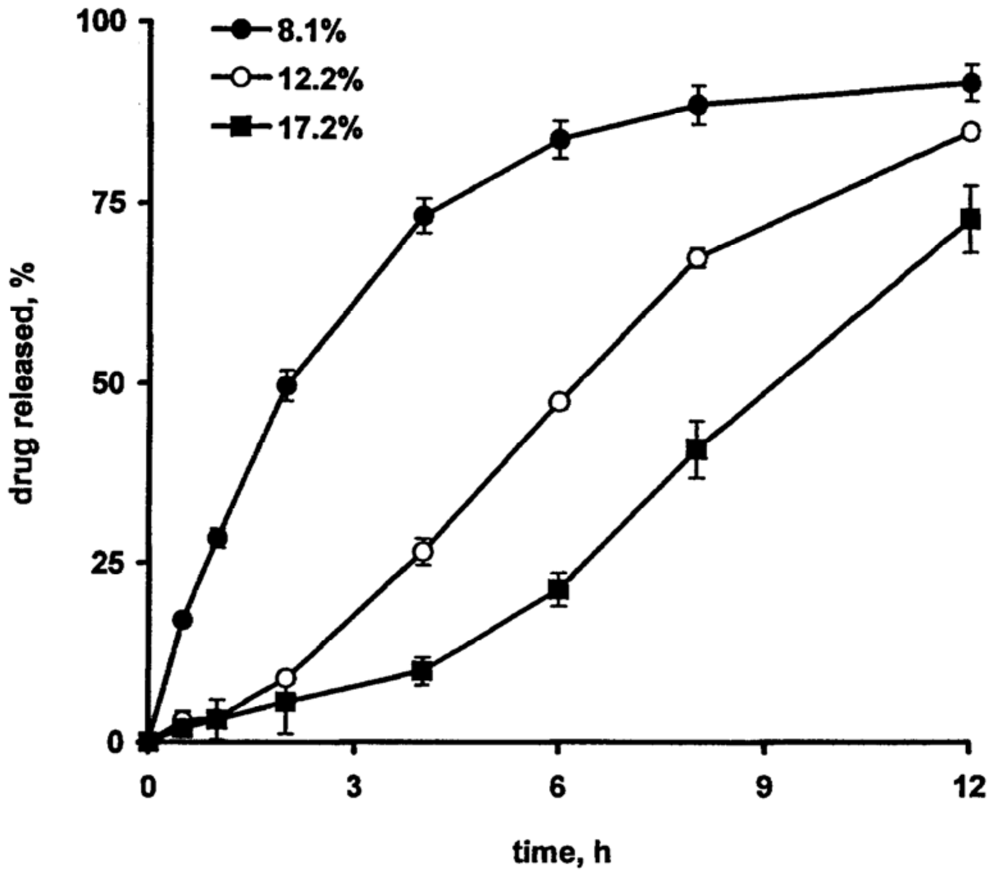
Effect of coating level on drug release from Eudragit® RS-coated pellets plasticized with AMG (propranolol HCl-loaded pellets; plasticizer concentration, 40 % w/w; curing condition, 60°C for 2 h; dissolution medium, 0.1 N HCl)



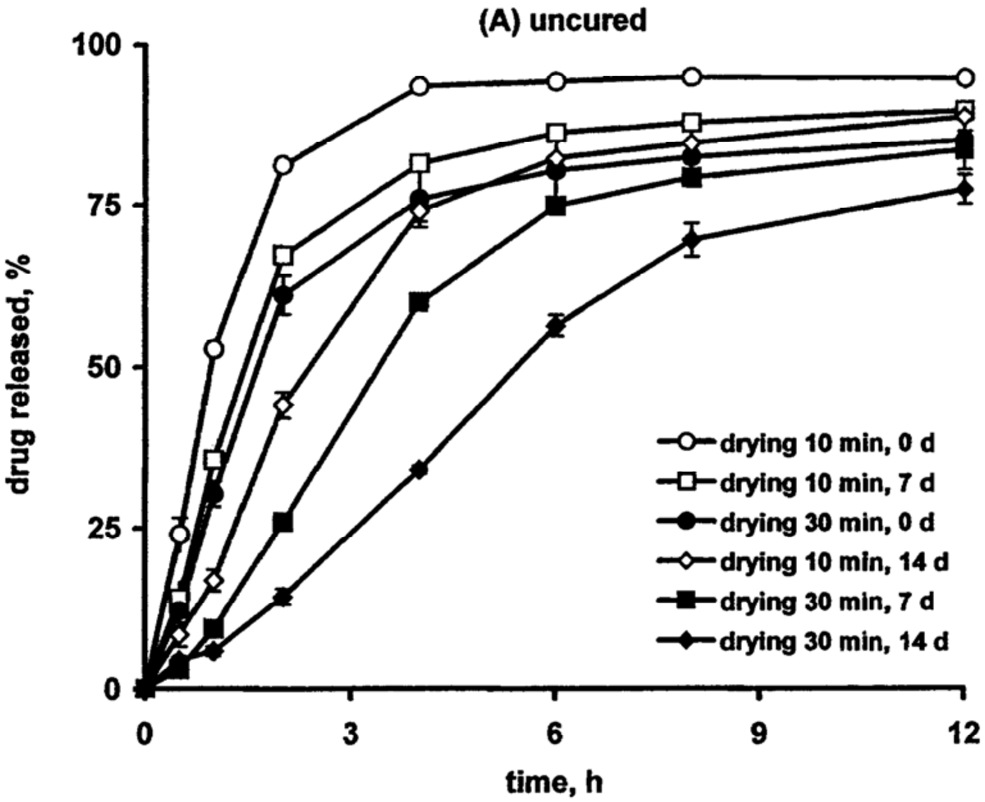
Effect of coating level on drug release from Eudragit® RS-coated pellets plasticized with TEC (propranolol HCl-loaded pellets; plasticizer concentration, 40 % w/w; curing condition, 60°C for 2 h; dissolution medium, 0.1 N HCl)

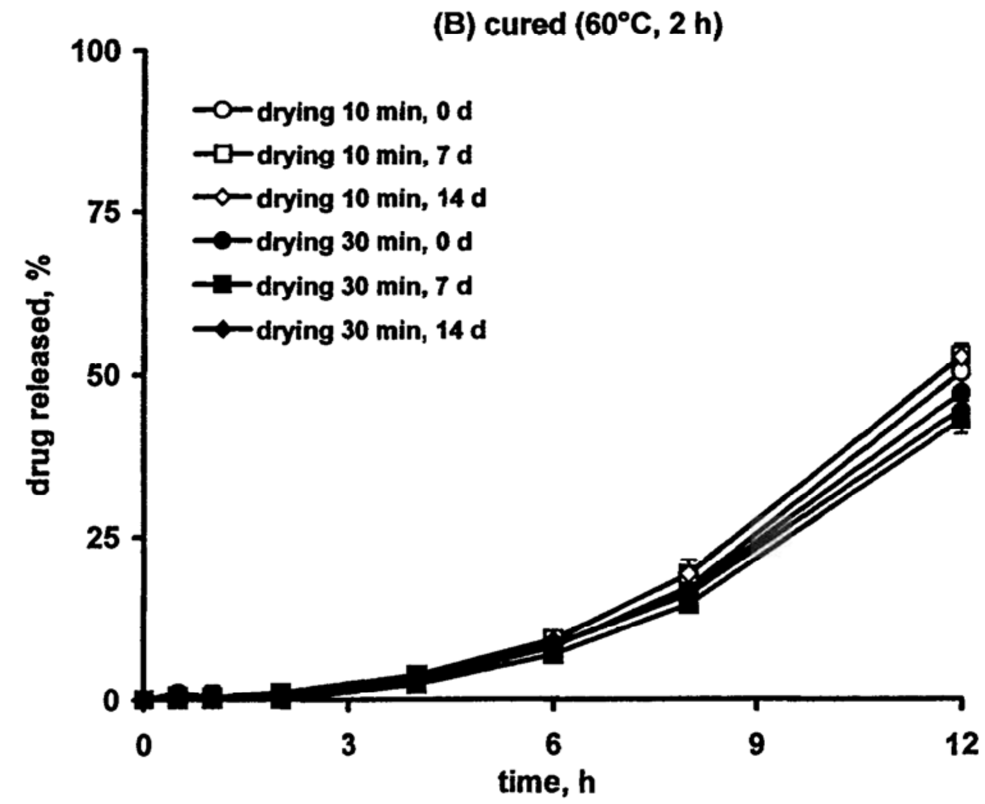


Effect of coating level on drug release from Eudragit® RS-coated pellets plasticized with ATBC (propranolol HCl-loaded pellets; plasticizer concentration, 40 % w/w; curing condition, 60°C for 2 h; dissolution medium, 0.1 N HCl)

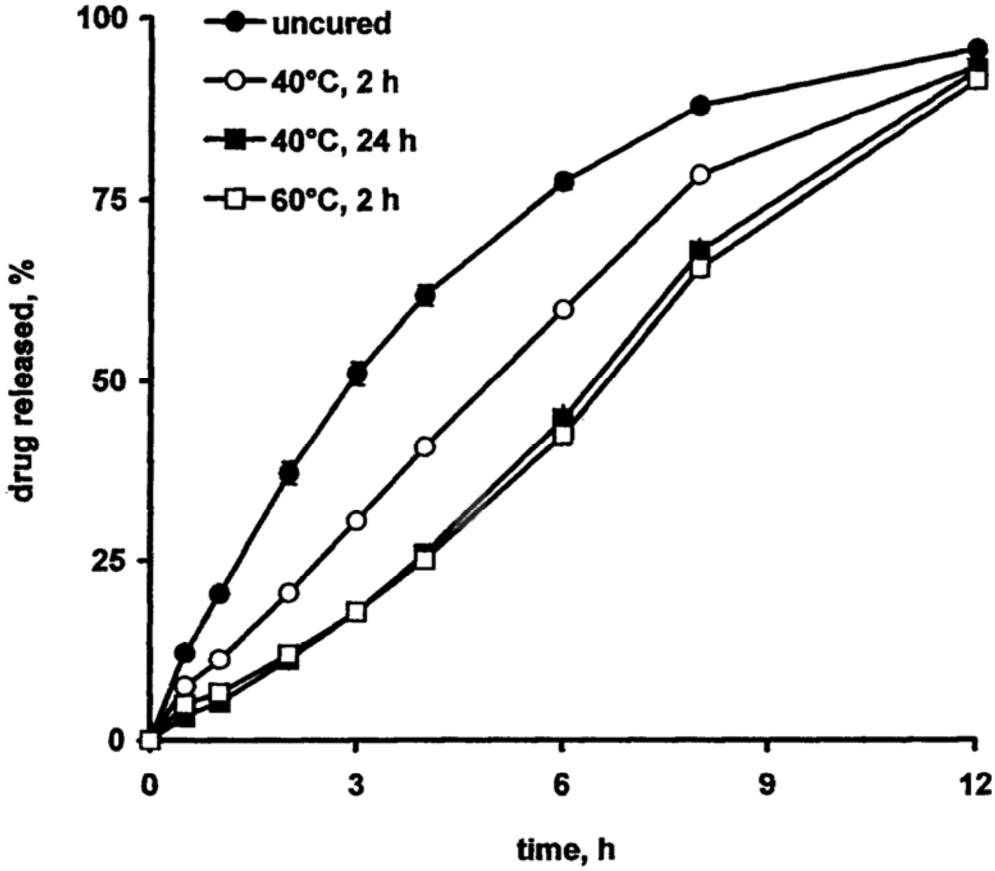


Effect of drying period in coating chamber (at 35°C) on film-formation of Eudragit® RS-coated pellets after storage at room temperature: (A) uncured pellets and (B) cured pellets (coating level, 25.3 %; plasticizer concentration, AMG 50 % w/w; dissolution medium, 0.1 N HCl)

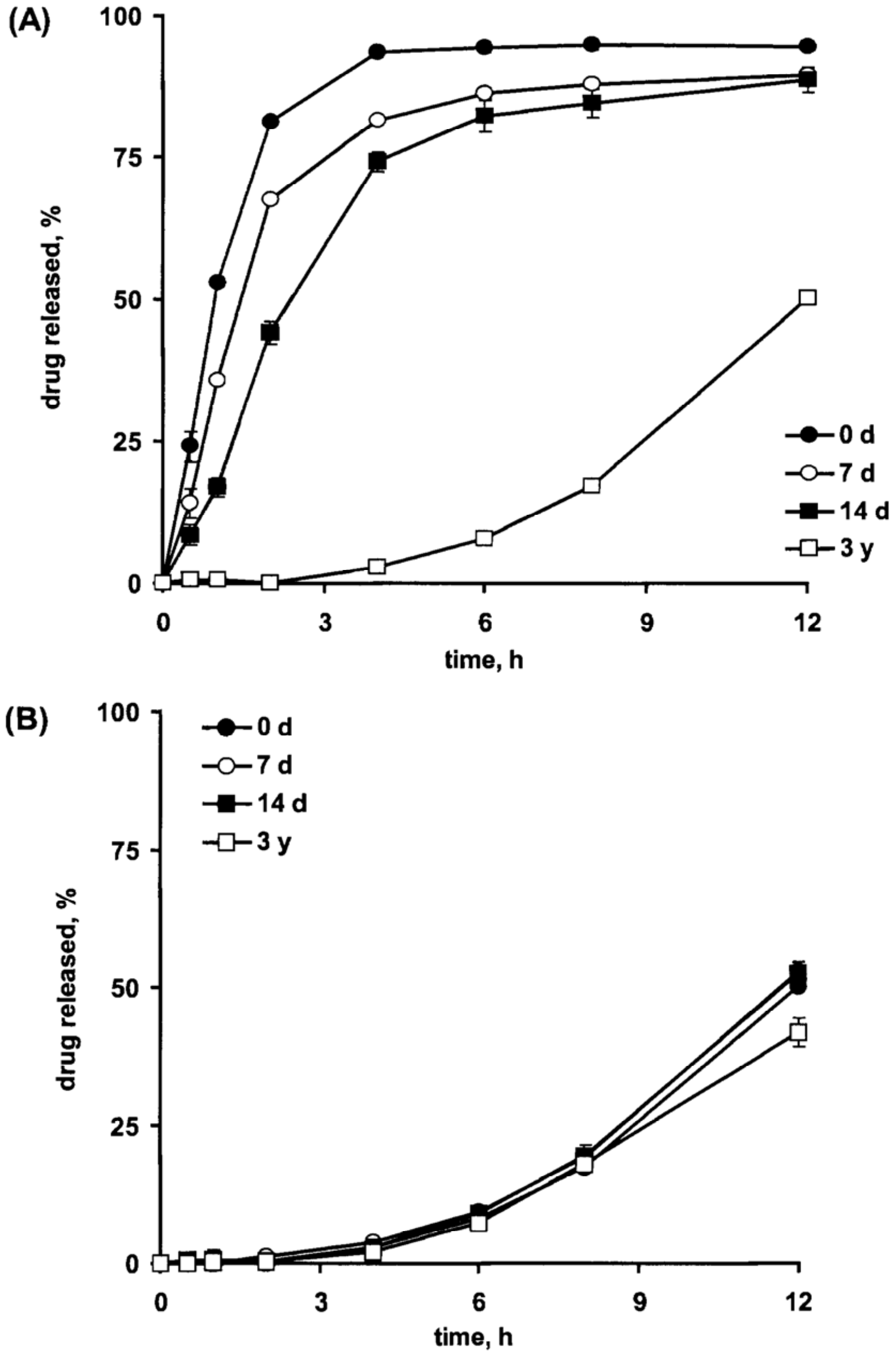




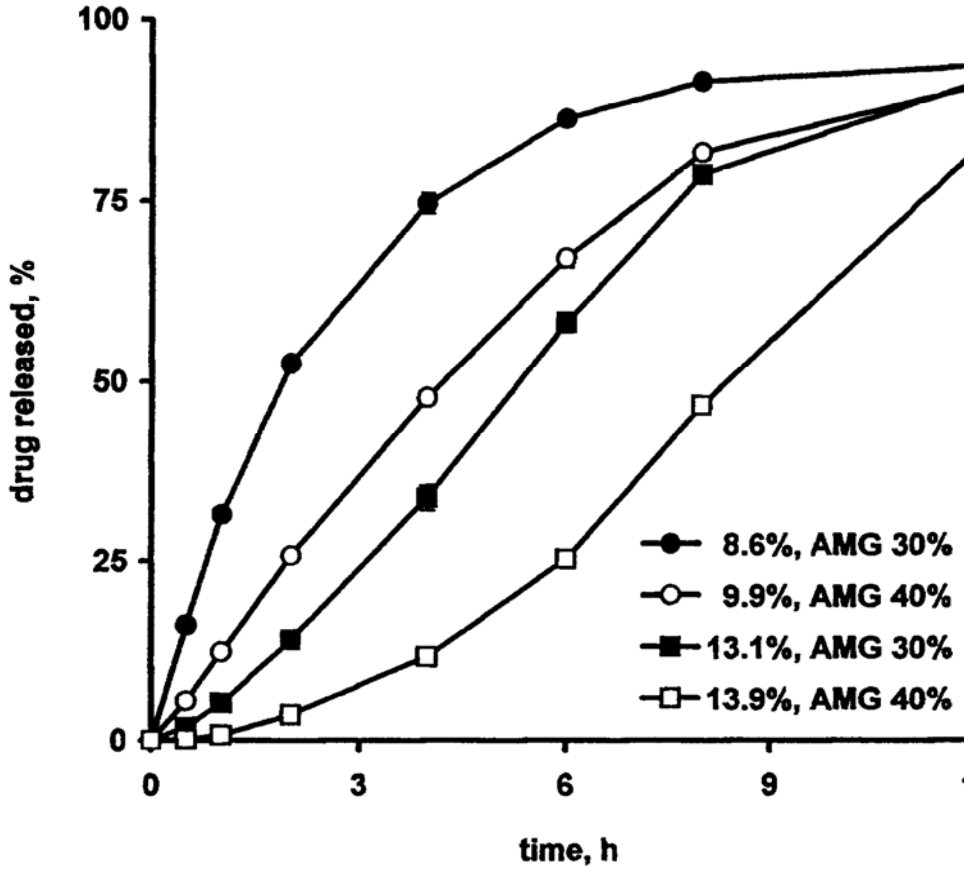
Effect of curing condition on drug release from Eudragit® RS coated-pellets plasticized with AMG (propranolol HCl-loaded pellets; coating level, 14.5 %; plasticizer concentration, 40 % w/w; dissolution medium, 0.1 N HCl)



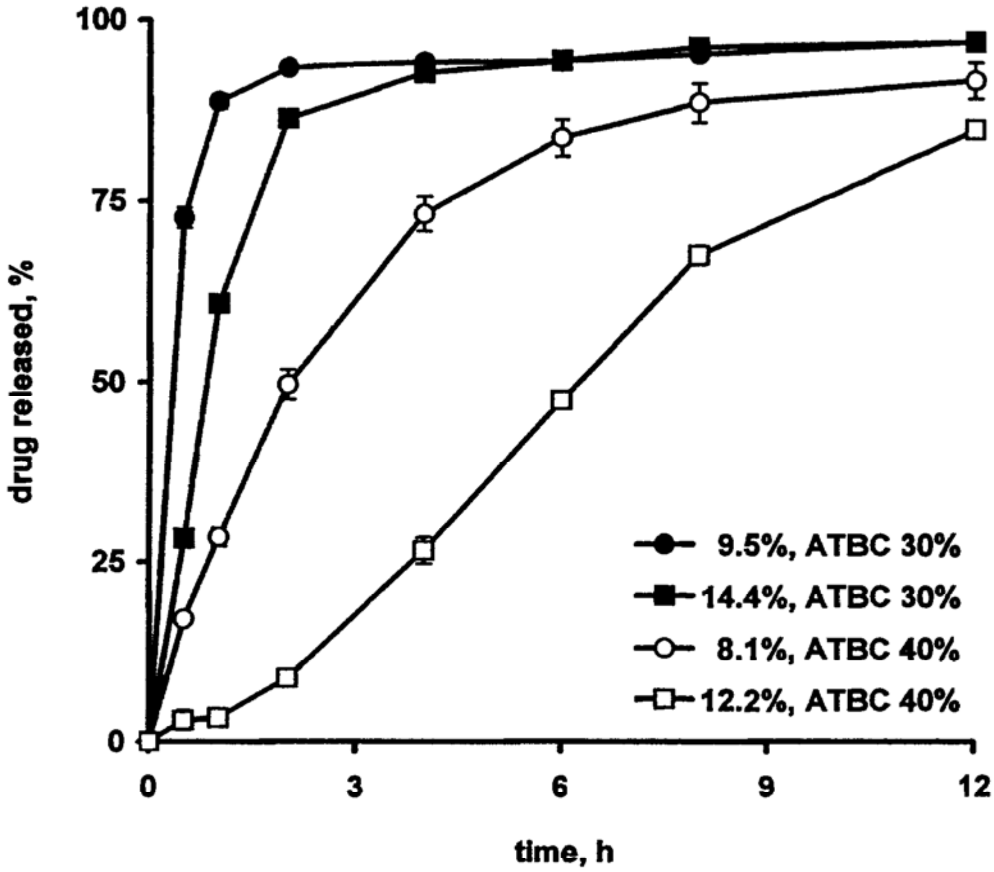
Effect of storage time on the propranolol hydrochloride release from Eudragit® RS-coated pellets after storage at room temperature: (A) uncured pellets; and (B) cured pellets (coating level, 22.4 %; 40 % acetylated monoglyceride; curing at 60°C for 2 h).



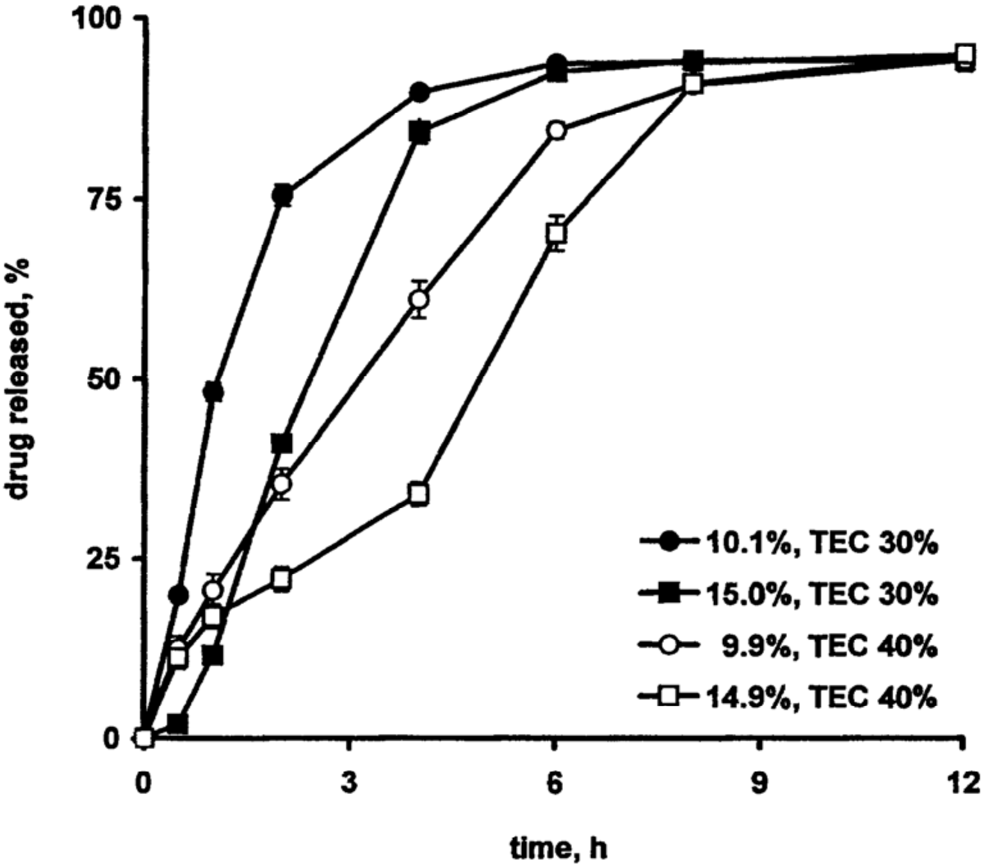
Effect of plasticizer content on drug release from Eudragit® RS-coated pellets plasticized with AMG (propranolol HCl-loaded pellets; curing condition, 60°C for 2 h; dissolution medium, 0.1 N HCl)



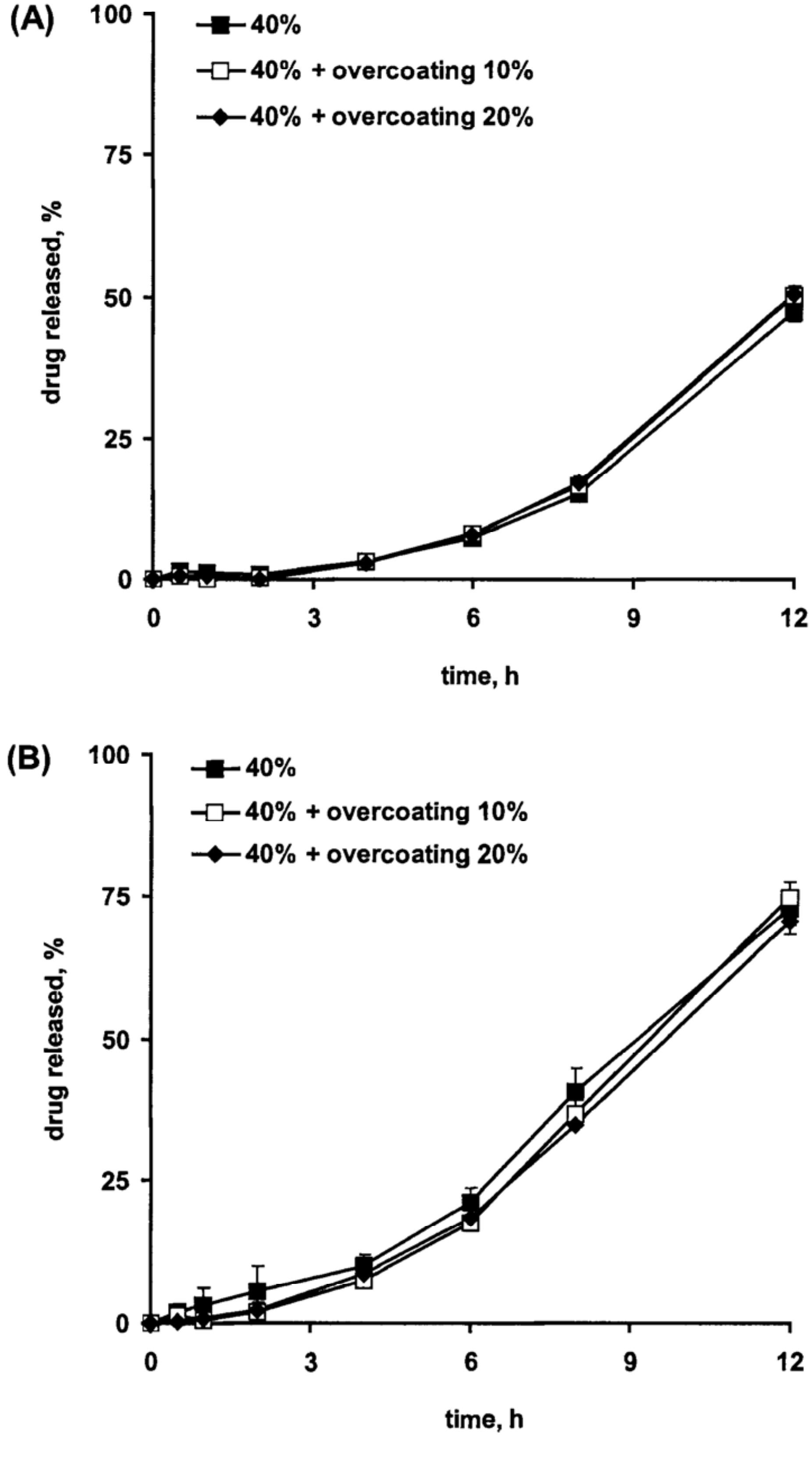
Effect of plasticizer content on drug release from Eudragit® RS-coated pellets plasticized with ATBC (propranolol HCl-loaded pellets; curing condition, 60°C for 2 h; dissolution medium, 0.1 N HCl)



Effect of plasticizer content on drug release from Eudragit® RS-coated pellets plasticized with TEC (propranolol HCl-loaded pellets; curing condition, 60°C for 2 h; dissolution medium, 0.1 N HCl)



Effect of plasticizer/HPMC - overcoating on the propranolol hydrochloride release from Eudragit® RS-coated pellets (curing at 60°C for 2 h): (A) acetylated monoglyceride (coating level, 22.4 %); and (B) acetyltributyl citrate (coating level, 17.2 %).

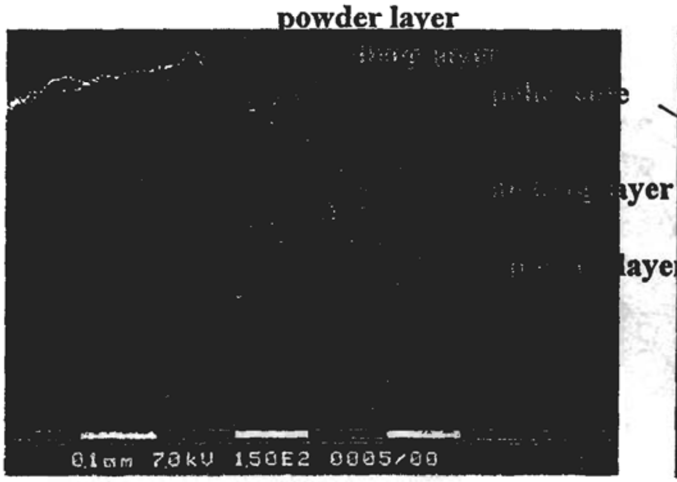


Curing effect

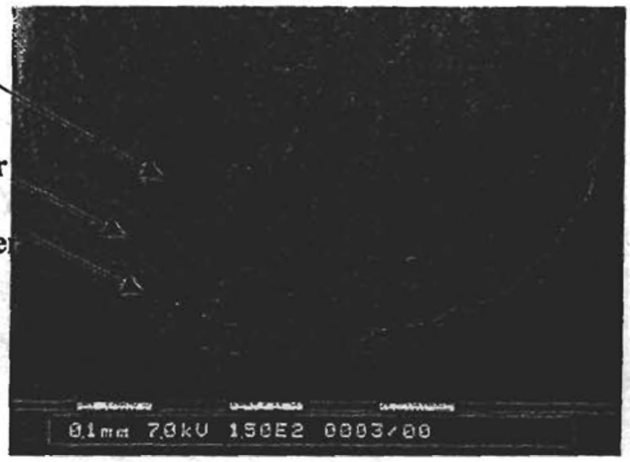
Eudragit® RS 9.87% plasticized with AMG 40.89%

Uncured | **Curing 60°C, 2 h**

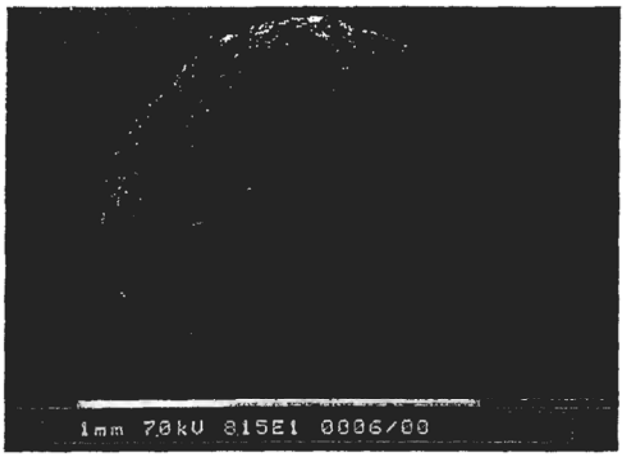
A cross-section of pellet



B cross-section of pellet



C pellet surface



D pellet surface

<u>Effect of plasticizer content on film formation</u>

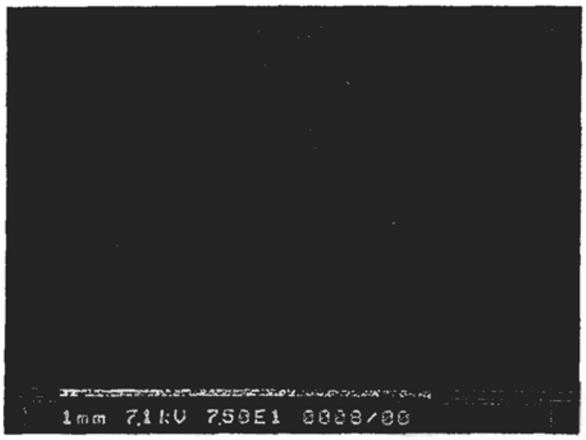
1. Eudragit® RS 9.87% plasticized with AMG 40.89% (based on polymer)

A uncured pellet

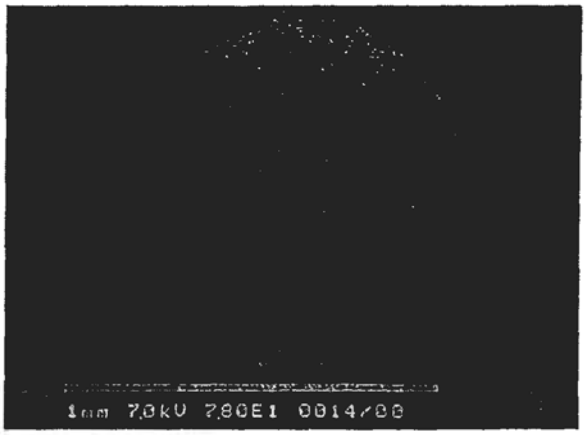
B curing at 60°C, 2 h

2. Eudragit® RS 8.58% plasticized with AMG 30.29% (based on polymer)

C uncured pellet



D curing at 60°C, 2 h



film-thickness.doc

<u>Effect of polymer content on film thickness</u>

(curing at 60°C, 2 h)

A Eudragit® RS 9.87% (polymer content)

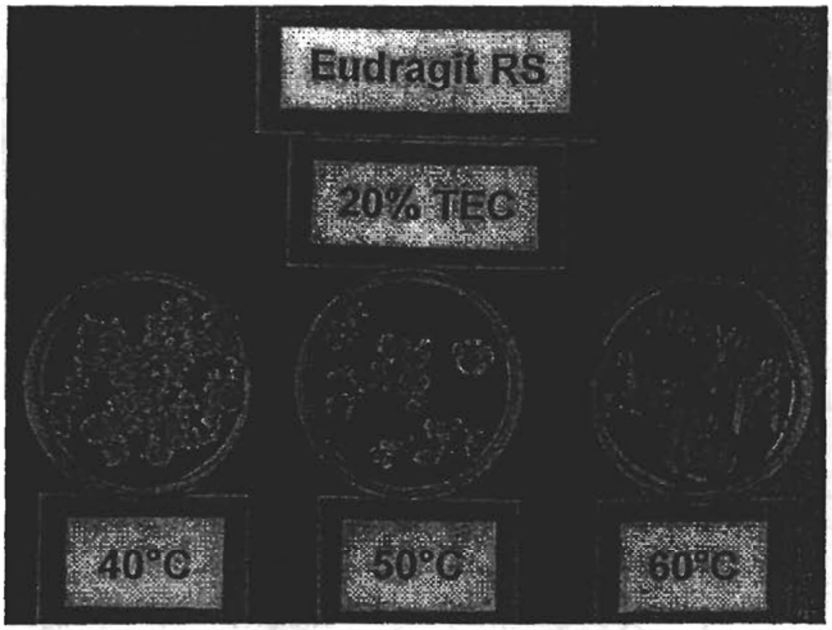
with AMG 40.89%

B Eudragit® RS 19.56% (polymer content)

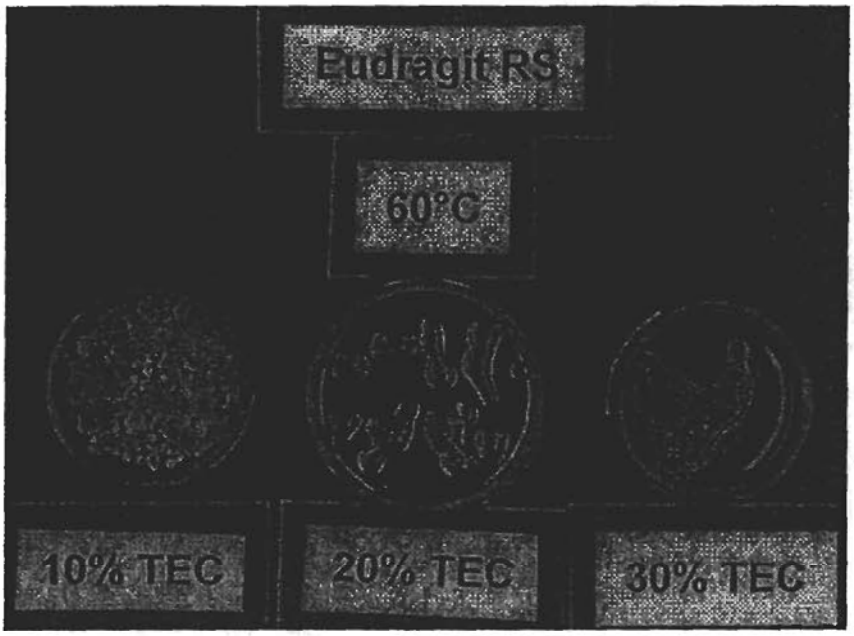
with AMG 40.85%

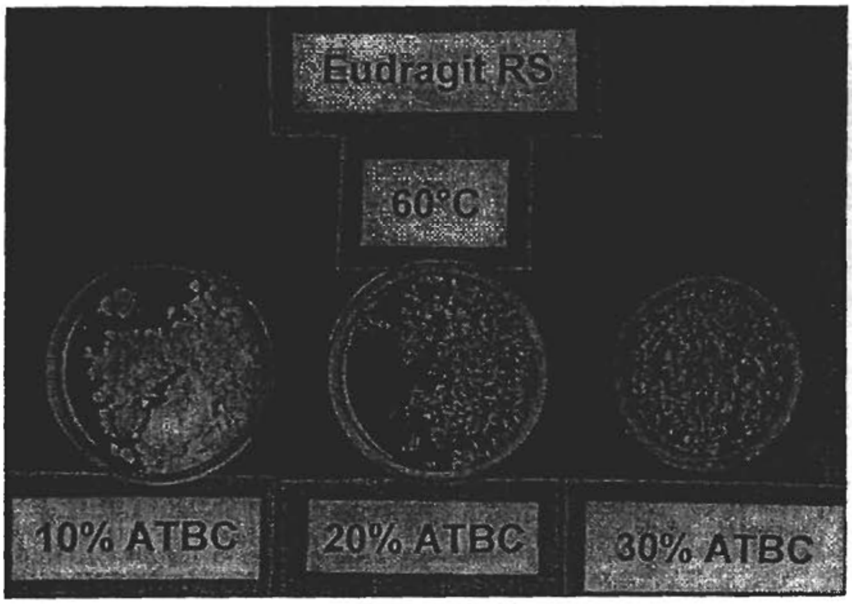
*cross-section of pellets

Effect of temperatures on film-forming morphology of the mixture of Eudragit® RS and plasticizer (% w/w based on the mass of the polymer)



Effect of types of plasticizer and plasticizer contents on film-forming morphology of the mixture of Eudragit® RS and plasticizer (% w/w based on the mass of the polymer)





1.3 Shellac

COATING OF DRUG-LOADED PELLETS

MATERIALS:

Polymer	Shellac (SSB® Pharma)
Plasticizers	Acetylated monoglyceride (AMG; Myvacet® 9-45) Triethyl citrate (TEC)
Binder material	Hydroxypropyl methylcellulose (HPMC E5; Methocel® E5)

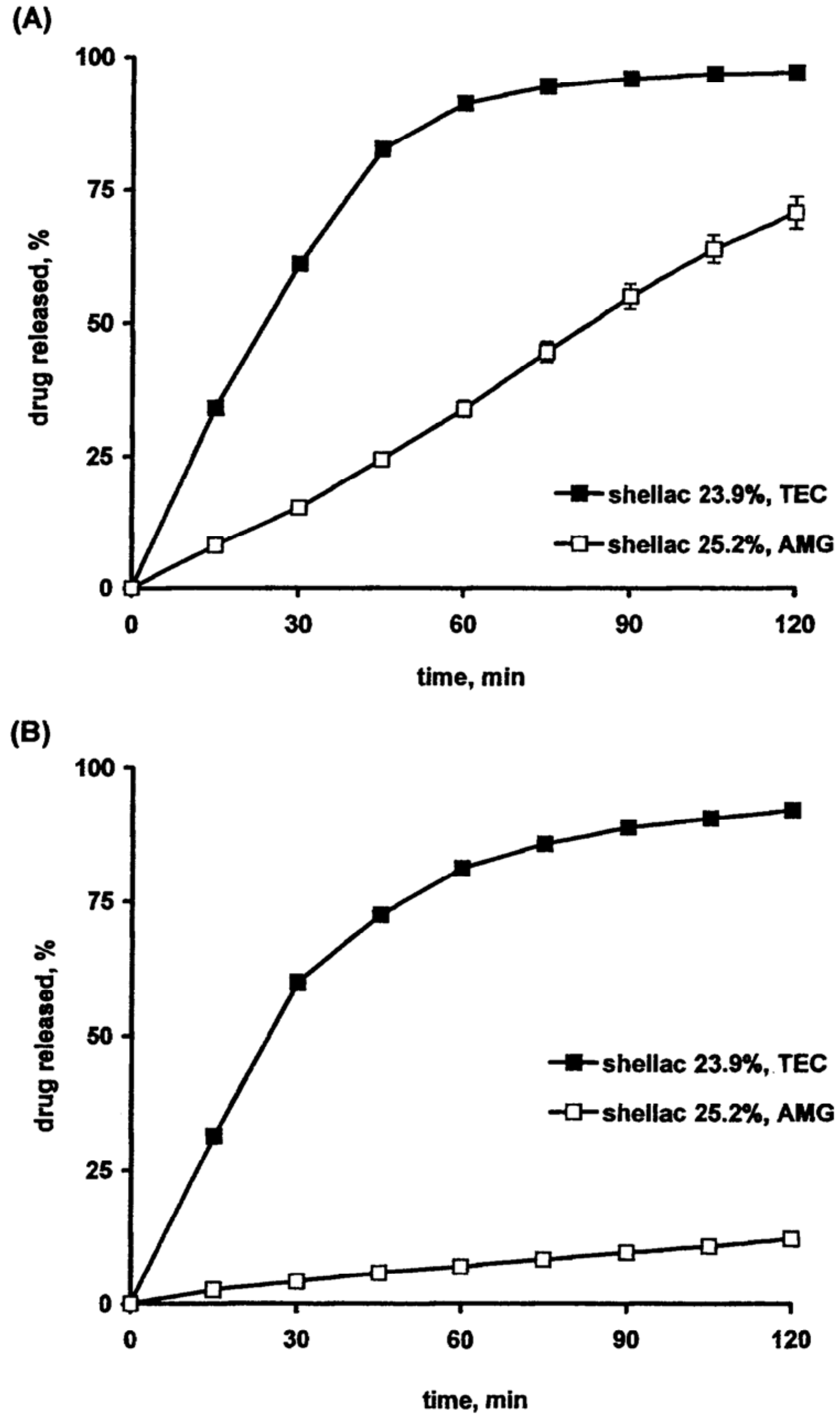
FORMULATION: Shellac powder coatings

	Composition, % w/w	
POWDERS		
Shellac	50.0	
Talc	50.0	
Total	**100.0**	
LIQUIDS		
Plasticizer	50.0-75.0	30-40 % w/w based on the polymer mass
HPMC E5 solution (10 % w/w in water)	25.0-50.0	
Total	**100.0**	

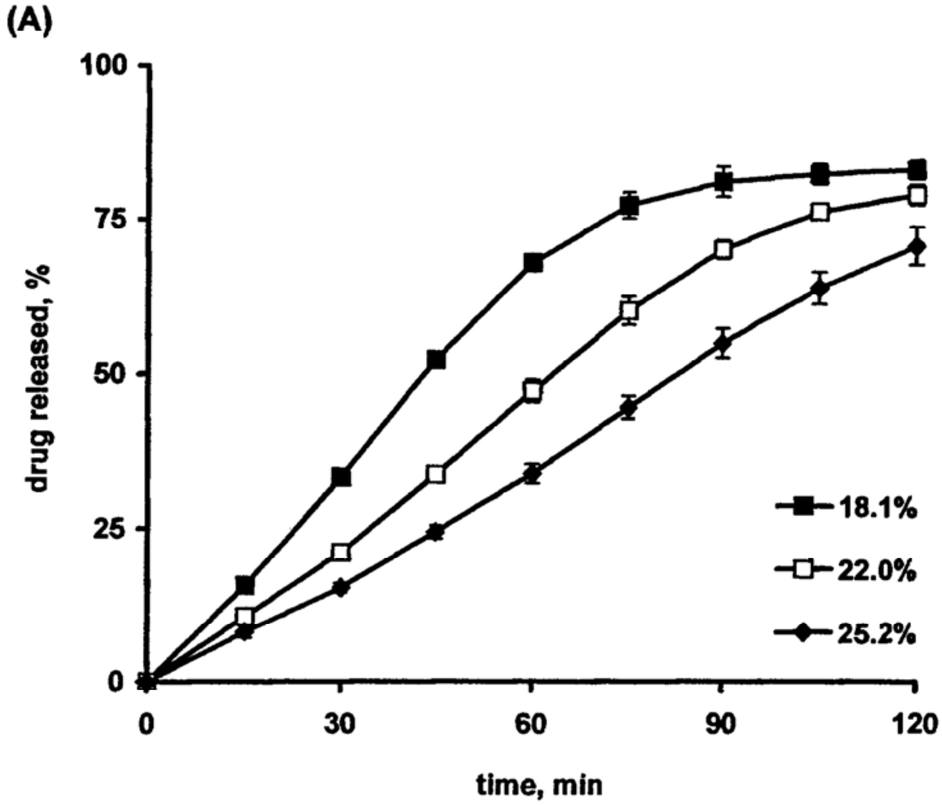
PROCESSING PARAMETER:

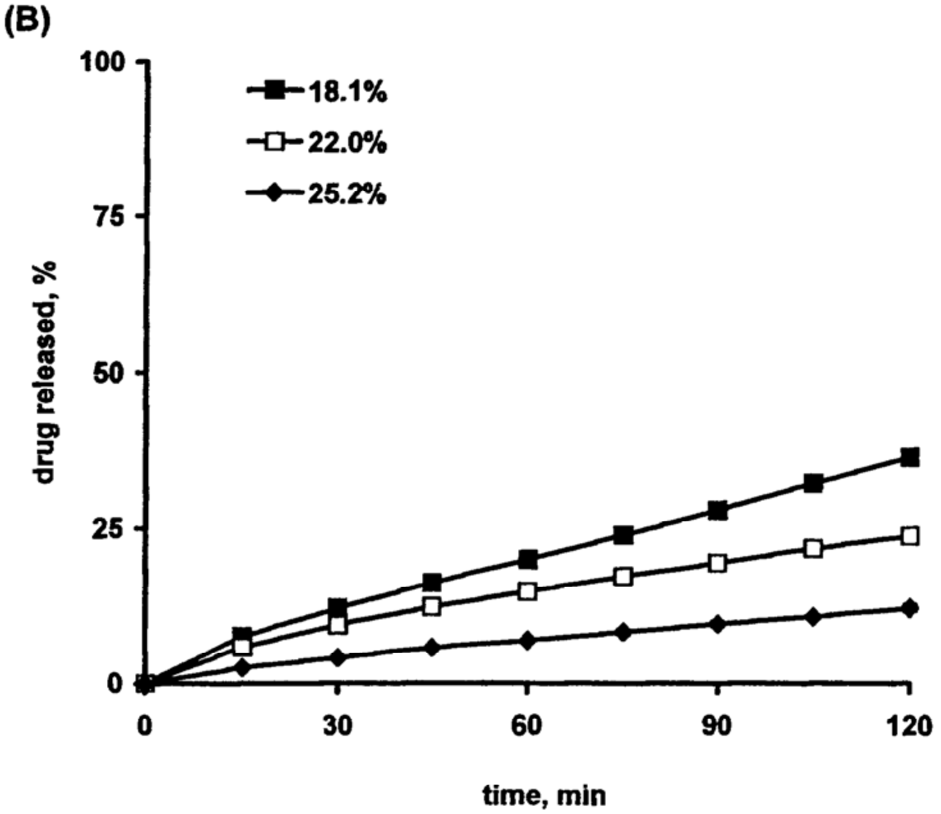
Fluidized bed coater	Glatt GPCG-1, Wurster insert
Batch size	1.2 kg
Inlet air temperature	60-62°C
Product temperature	50-52°C
Outlet air temperature	40-45°C
Air flow rate	60-80 m^3/h
Atomizing pressure	1.2 bar
Spray nozzle diameter	1.2 mm
Spray rate	3-5 g/min
Powder-feeding rate	11-12 g/min
Drying temperature, °C	50-55
Drying period, min	10-15
THERMAL TREATMENT	
Curing condition, in oven	80°C, 24 h

Effect of **plasticizer content and curing condition** on drug release from shellac-coated pellets plasticized with triethyl citrate or acetylated monoglyceride: (A) uncured pellets and (B) cured pellets (propranolol HCl-loaded pellets; plasticizer concentration, 40 % w/w; curing condition, 80°C for 24 h; dissolution medium, 0.1 N HCl)

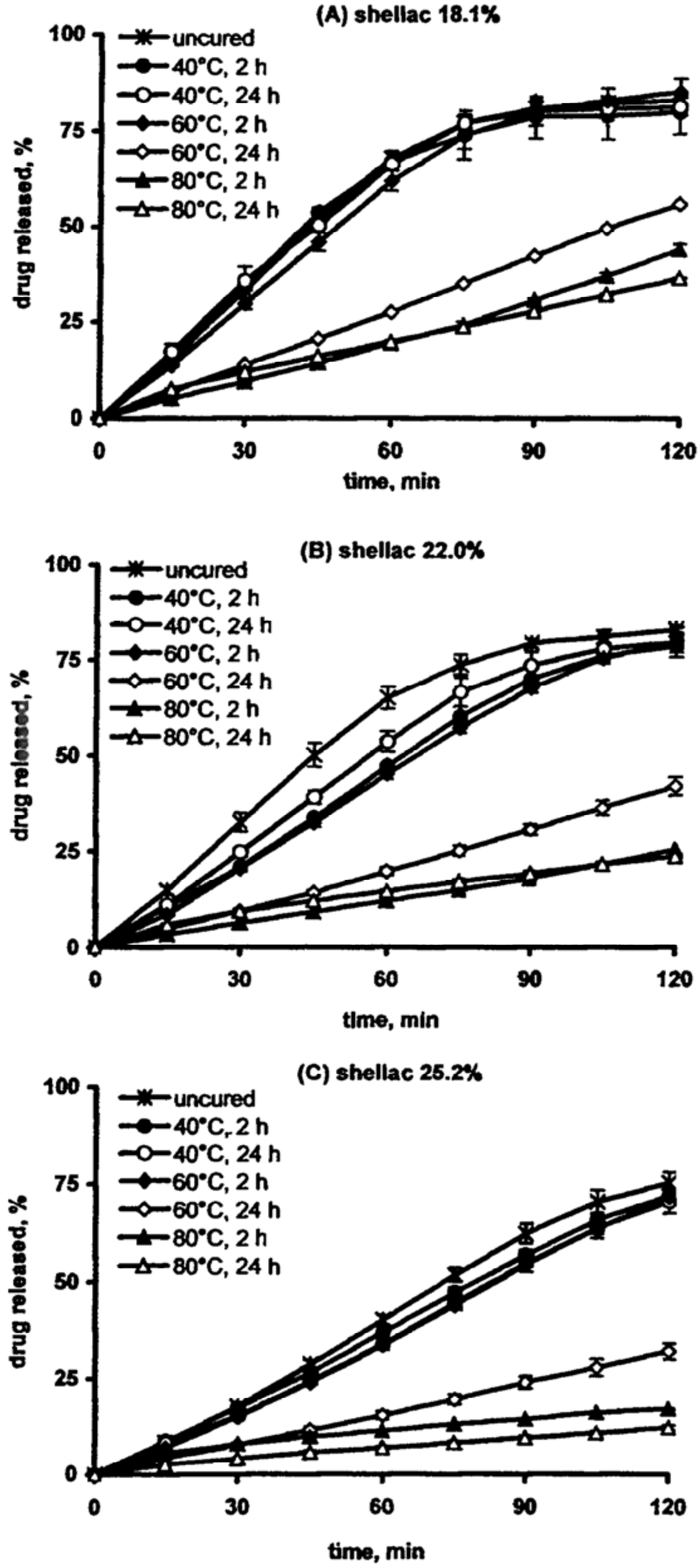


Effect of **coating level and curing condition** on drug release from shellac-coated pellets plasticized with triethyl citrate or acetylated monoglyceride: (A) uncured pellets and (B) cured pellets (propranolol HCl-loaded pellets; plasticizer concentration, 40 % w/w; curing condition, 80°C for 24 h; dissolution medium, 0.1 N HCl)

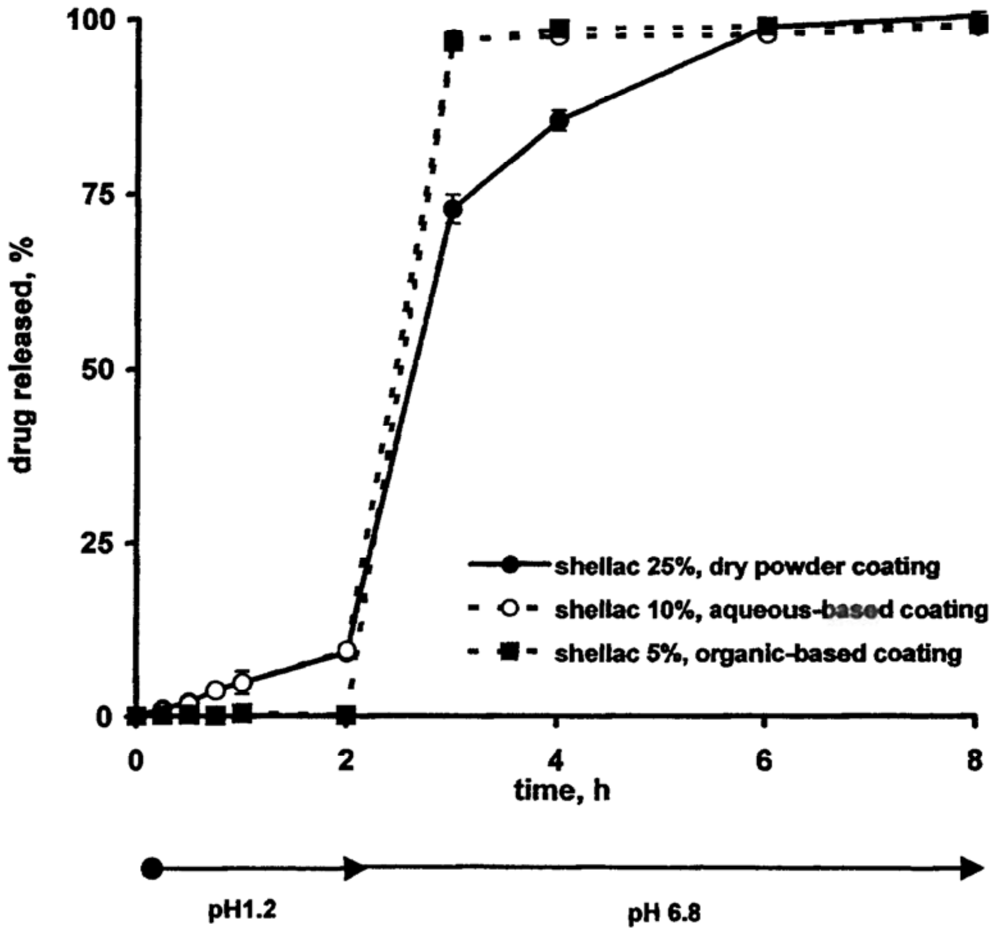




Effect of **curing condition** on drug release from shellac-coated pellets plasticized with acetylated monoglyceride at different coating levels (acetamoniphen-loaded pellets; plasticizer concentration, 45 % w/w; dissolution medium, 0.1 N HCl)



Comparison of shellac-coated pellets in different coating systems (acetaminophen-loaded pellets; dissolution medium, 0.1 N HCl)
Organic-based coating: plasticizer type, triethyl citrate; plasticizer concentration, 5 % w/w
Aqueous-based coating: no plasticizer
Powder coating: plasticizer type, acetylated monoglyceride; plasticizer concentration, 45 % w/w; curing condition, 80°C for 24 h



Processing time of polymer-coated pellets by using dry powder coating with comparison to organic- and aqueous-based coatings (Wurster insert, Glatt GPCG-1)

Coating system	Shellac	Processing time, min
Dry powder coating	25 %	70
Organic-based coating	5 %	72
Aqueous-based coating	10 %	161

4. Phthalate-Free Coating Materials

Table of content:

Summary

The use if solubility parameters is helpful in determining the physicochemical properties of ethylcellulose (EC) and facilities the preparation of EC films.

Since H-bonding potential of plasticizer is important for polymer-plasticizer interaction, plasicizers with very low H bonding potential (i. g. phthalate esters and sebacate esters) are located far from EC point. Interestingly, citrate esters and oils are located close to the EC point (pages 10-13).

By coating onto drug-loaded pellets, EC plasticizing with all pharmaceutically accepted plasticizers exhibited the drug release profiles within the window profile of phthalate esters (pages 25-27).

All pharmaceutically accepted plasticizers are appropriate for EC as good as phthalate esters.

Similarities in:

Polymer-plasticizer compatibility
Effectiveness of plasticizer
Plasticizer permanence
Plasticizer processability
Drug release characteristic (hydrophilic and lipophilic drugs)

FORMULATION: Ethanolic solutions

	Composition, % w/w	
Ethylcellulose	4.65	5 ~~10~~ % w/w based on total solution
Plasticizer	0.93	20 % w/w based on the polymer mass
Talc	1.40	30 % w/w based on the polymer mass
Ethanol (96 % v/v)	93.02	
Total	**100.00**	

PROCESSING PARAMETER:

Fluidized bed coater	Hüttlin Kugelcoater HKC 05 / UNILAB 05
Batch size	0.5 kg
Inlet air temperature	33-35°C
Product temperature	32-34°C
Outlet air temperature	36-38°C
Air flow rate	50-75 %
Atomizing pressure	0.4 bar
Microclimate pressure	0.2 bar
Spray rate	3-4 g/min
Spray nozzle diameter	0.8 mm – 2 components
Drying temperature	23-25°C
Drying period	10-15 min

FORMULATION: Aqueous dispersions (Aquacoat® ECD)

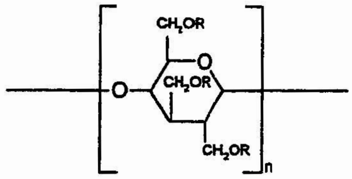
	Part by weight, g	Composition, % w/w	
Aquacoat® ECD	200.0		
Ethylcellulose	54.0	13.06	15 % w/w based on total dispersion
Plasticizer	13.5	3.27	25 % w/w based on the polymer mass
Water	200.0	83.67	
Total	**413.5**	**100.0**	

PROCESSING PARAMETER:

Fluidized bed coater	Hüttlin Kugelcoater HKC 05 / UNILAB 05
Batch size	0.5 kg
Inlet air temperature	48-50°C
Product temperature	40-42°C
Outlet air temperature	44-47°C
Air flow rate	50-75 %
Atomizing pressure	0.4 bar
Microclimate pressure	0.2 bar
Spray rate	3-4 g/min
Spray nozzle diameter	0.8 mm – 2 components
Drying temperature	40-45°C
Drying period	10-15 min
THERMAL TREATMENT	
Curing condition, in oven	60°C for 24 h

1.1 Physical-chemical properties of ethylcellulose and plasticizers

Physical and chemical properties of the studied ethylcellulose

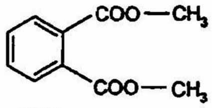
Property	Value
Chemical structure	
Substituent group -R	$-CH_2CH_3$
Degree of substitution	2.2-2.6
Ethoxyl content, % w/w	44.0-51.0
Bulk density, g/ml	0.4
Specific gravity	1.12-1.15

Physical constant data of plasticizers

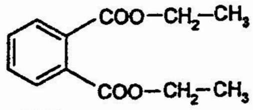
Plasticizer		Molecular Weight	Boiling Point, °C (at 1 mm Hg)	Specific gravity (at 25°C)	Water Solubility, mg/ml
Phthalate esters					
DMP	$C_{10}H_{10}O_4$	194.2	280	1.19	<1.00
DEP	$C_{12}H_{14}O_4$	222.2	295	1.12	0.90
DBP	$C_{16}H_{22}O_4$	278.4	340	1.05	0.01
Citrate esters					
TEC	$C_{12}H_{20}O_7$	276.3	288	1.14	55.35
ATEC	$C_{14}H_{22}O_8$	318.4	294	1.14	3.56
TBC	$C_{18}H_{32}O_7$	360.4	322	1.05	0.05
ATBC	$C_{20}H_{34}O_8$	402.5	326	1.05	<1.00
Sebacate esters					
DBS	$C_{18}H_{34}O_4$	314.5	349	0.94	11.97
Glycerides/Oils					
AMG	-	-	>500	0.94	negligible
Castor oil	$C_{57}H_{110}O_9$	939.50	313	0.96	negligible

Chemical structures of different plasticizers

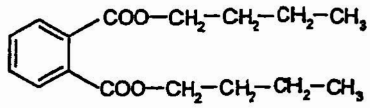
Phthalate esters



DMP

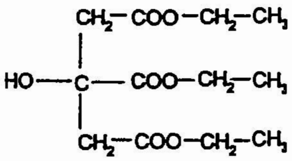


DEP

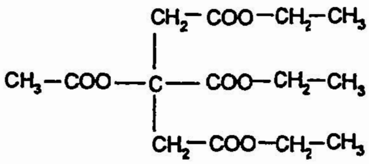


DBP

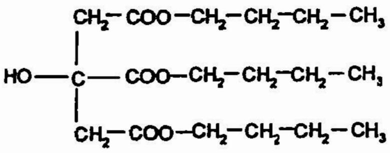
Citrate esters



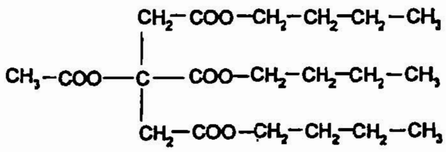
TEC



ATEC



TBC



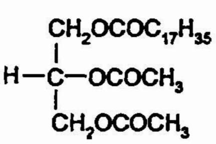
ATBC

Sebacate esters

$$CH_3-(CH_2)_3-COO-(CH_2)_8-COO-(CH_2)_3-CH_3$$

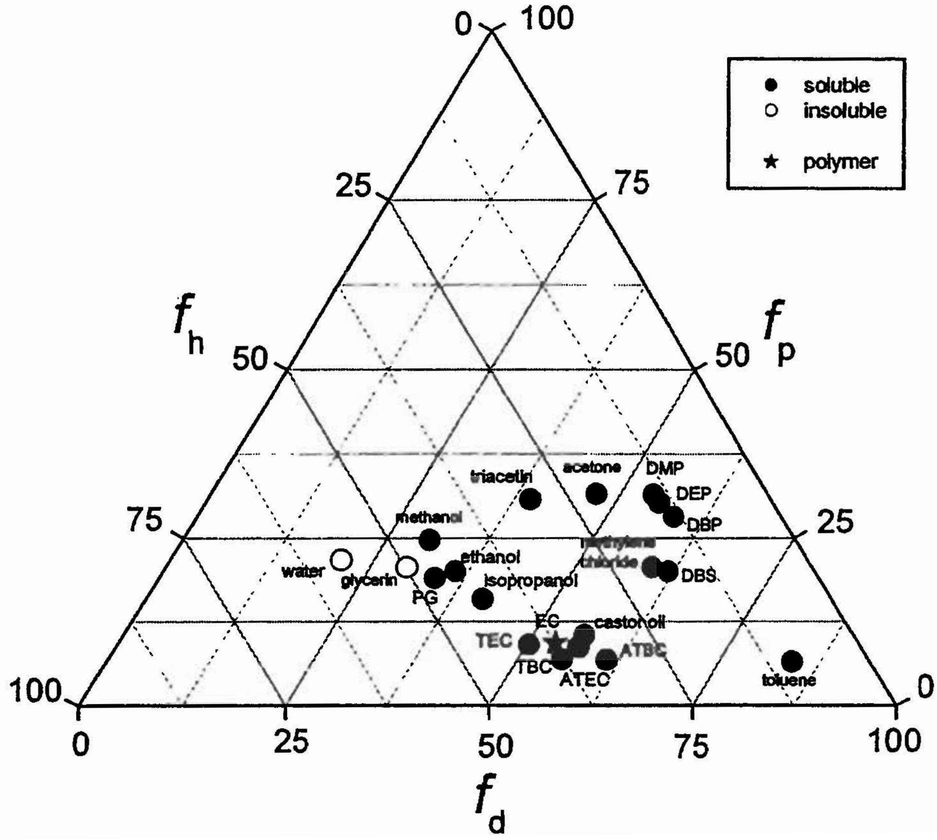
DBS

Glycerides/Oils

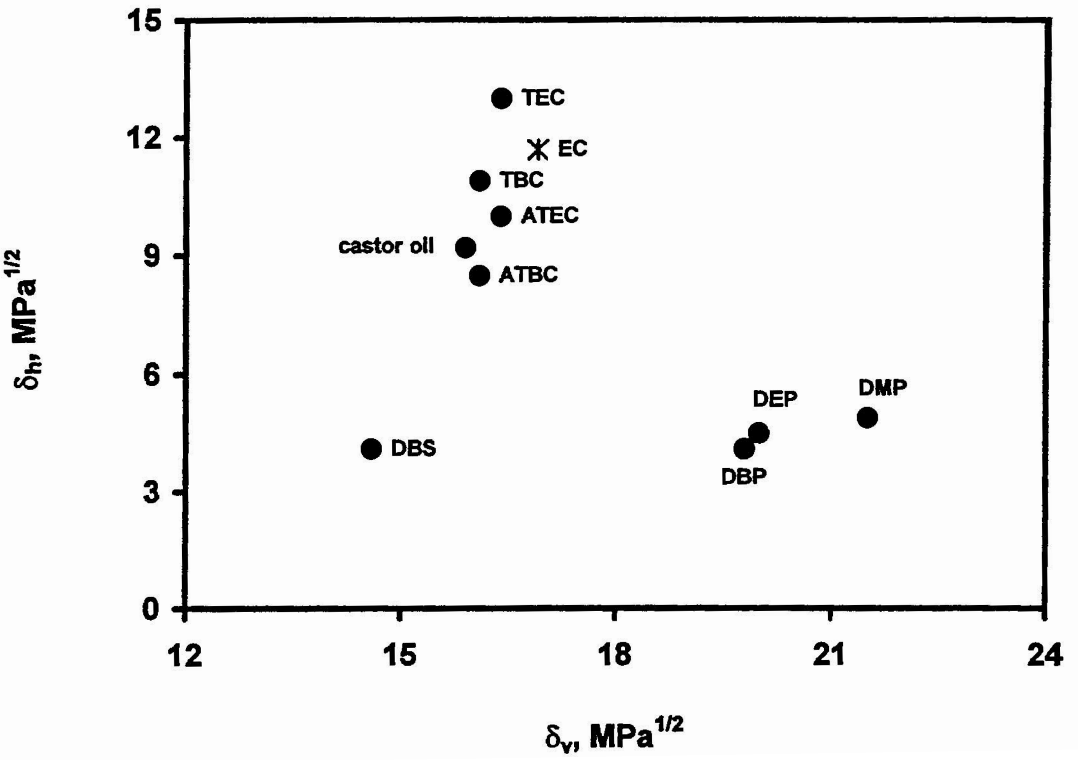


AMG

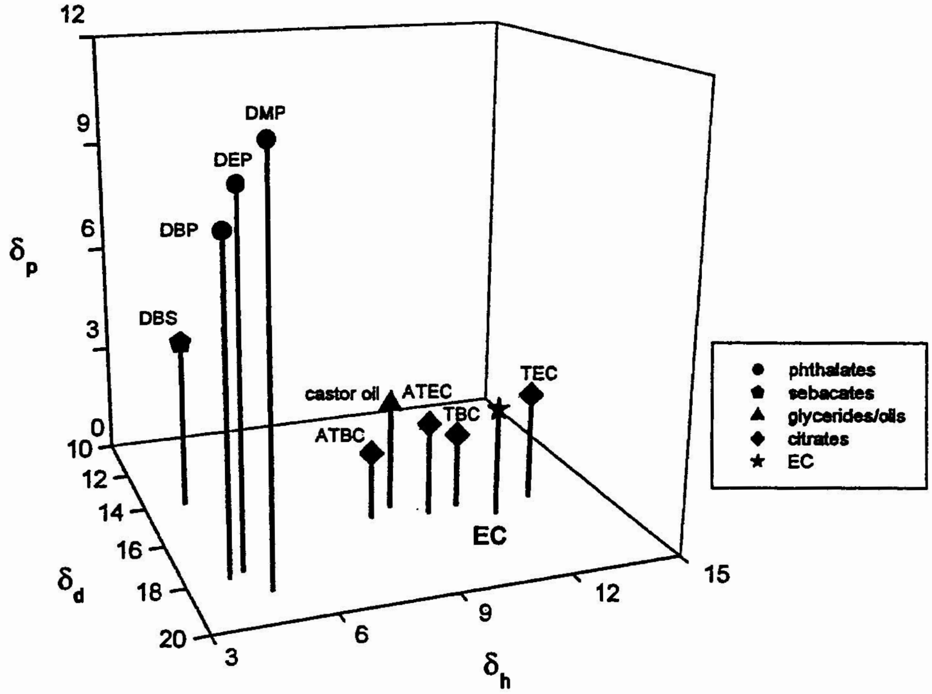
Teas graph on polymer solubility areas by using a set of fractional parameters



Solubility parameter map, Bagley diagram, for ethylcellulose showing the positions of different plasticizers



Three-dimensional solubility parameter diagram of ethylcellulose and different plasticizers



Solubility of ethylcellulose and Hansen cohesion parameter data

Plasticizer	δ, MPa$^{1/2}$			
	$^{i}\delta_d$	$^{i}\delta_p$	$^{i}\delta_h$	^{ij}R, MPa$^{1/2}$
TEC	16.1	2.9	13.0	1.8
TBC	16.0	2.0	10.9	1.8
ATEC	16.2	2.5	10.0	2.0
castor oil	15.6	2.9	9.2	3.3
ATBC	16.0	1.8	8.5	3.7
DBS	13.9	4.5	4.1	9.6
DBP	17.8	8.6	4.1	9.8
DEP	17.6	9.6	4.5	10.0
DMP	18.6	10.8	4.9	11.1
	$^{j}\delta_d$	$^{j}\delta_p$	$^{j}\delta_h$	^{j}R
EC	16.7	2.9	11.7	19.2

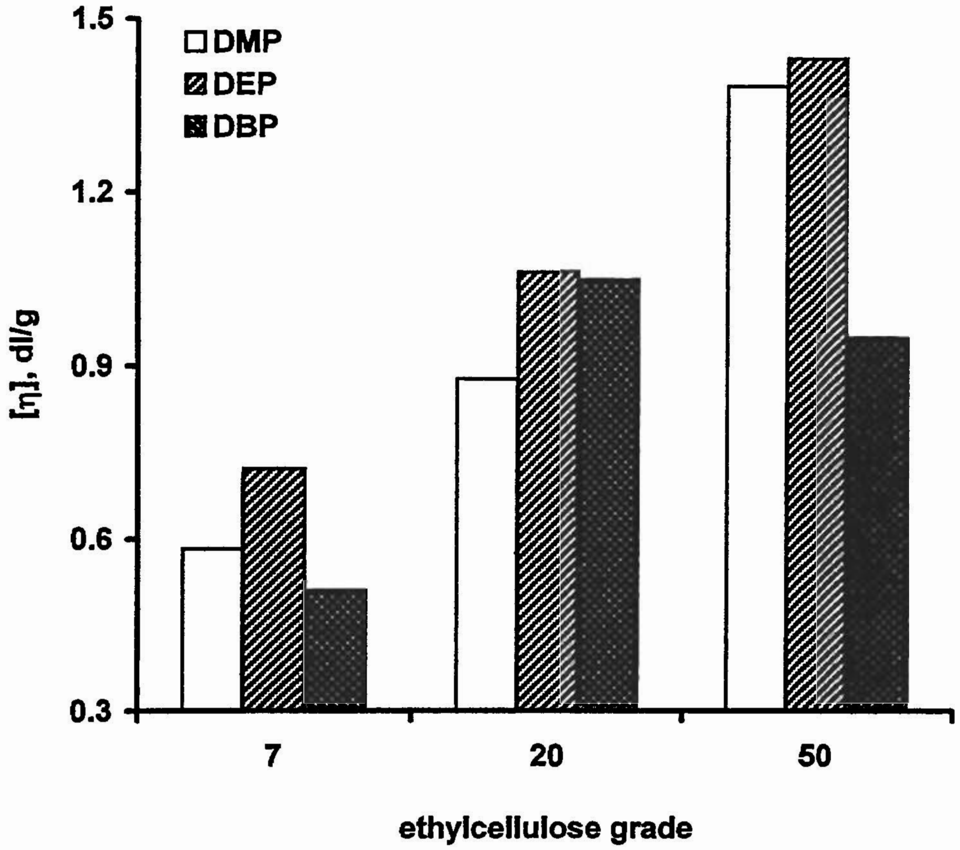
^{ij}R is the distance of the plasticizer coordinates from the center point of the polymer sphere of solubility.

1.2 Ethylcellulose and phthalate esters interaction

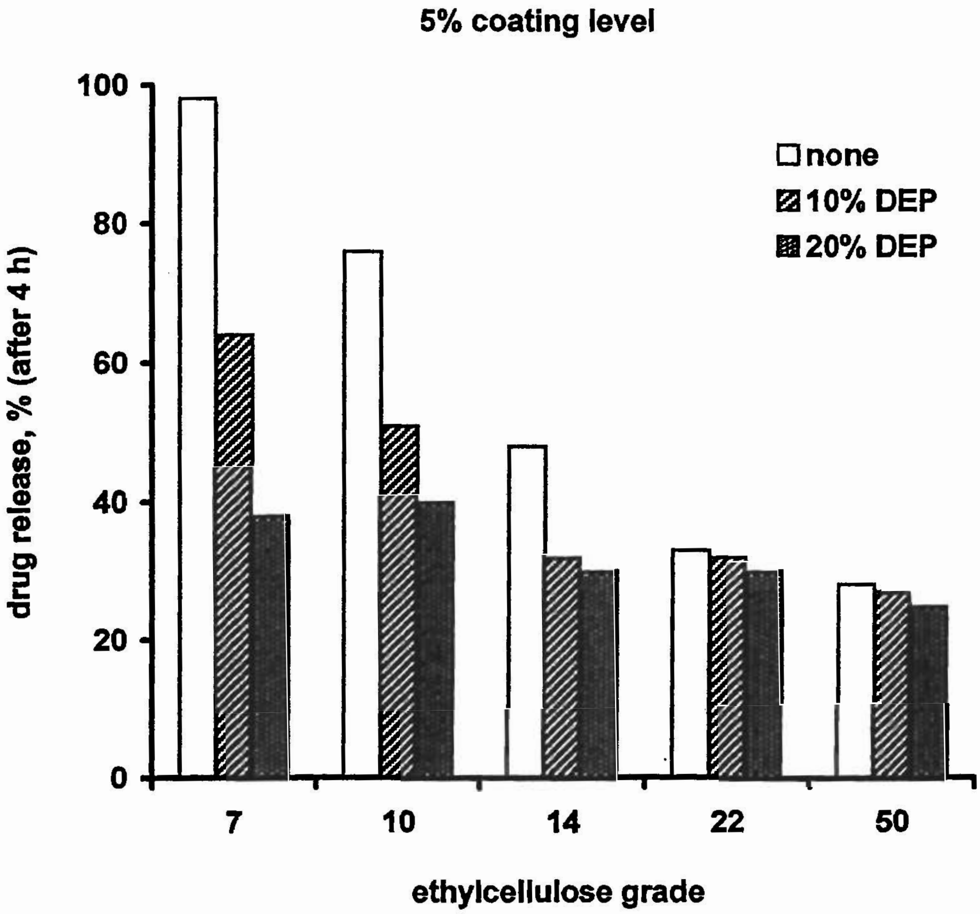
Physicochemical properties of ethylcellulose and dialkyl phthalates

EC/Phthalates	Molecular weight	δ, $(cal/cm^3)^{1/2}$	Tg, °C (20% w/w plasticizer)
None	22 920	10.3	131.3 ± 1.2
DMP	194.2	10.7	64.1 ± 2.2
DEP	222.2	10.0	62.9 ± 1.6
DBP	278.4	9.3	66.1 ± 0.2

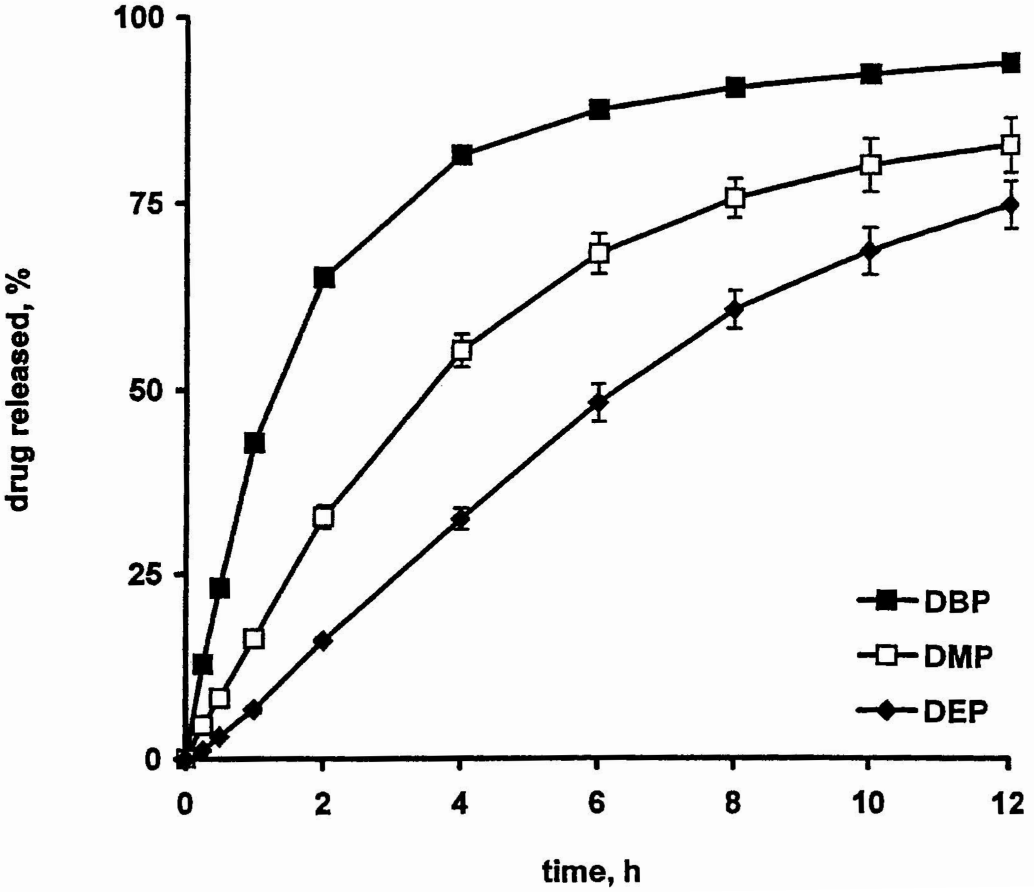
Intrinsic viscosity for different grades of ethylclellulose dissolved in the dialkyl phthalates (Kent and Rowe, 1978; Entwistle and Rowe, 1979; Rowe et al, 1984)



Effect of molecular weight of ethylcellulose and plasticizer concentration on propanolamine release in simulated gastric fluid (plasticizer, diethyl phthalate: DEP) (Rowe, 1986)

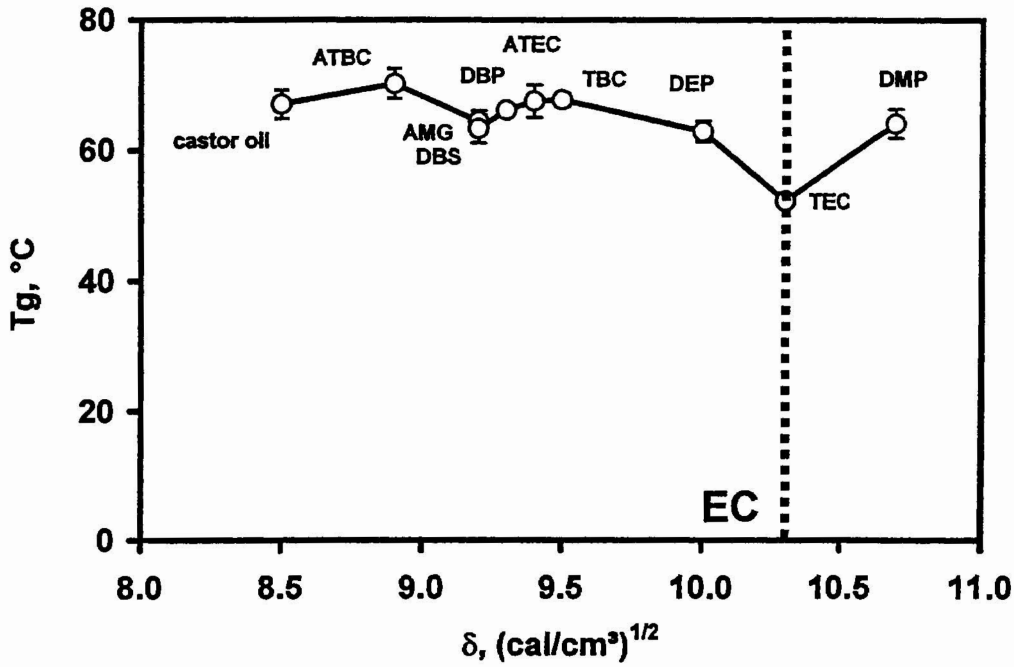


Effect of dialkyl phthalates on drug release from ethylcellulose-coated pellets in acidic medium (model drug, propranolol hydrochloride; plasticizer concentration, 20%; coating level, 5%)

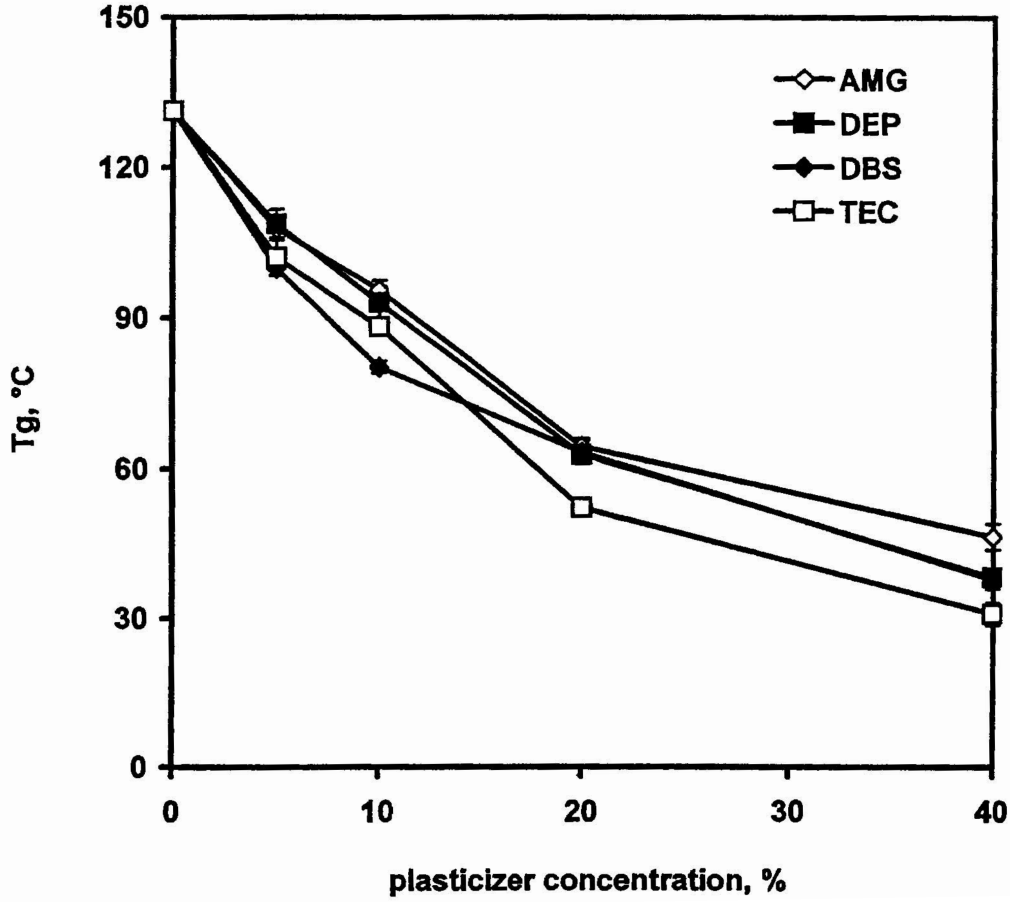


1.3 Ethylcellulose and phthalate-free plasticizers interaction

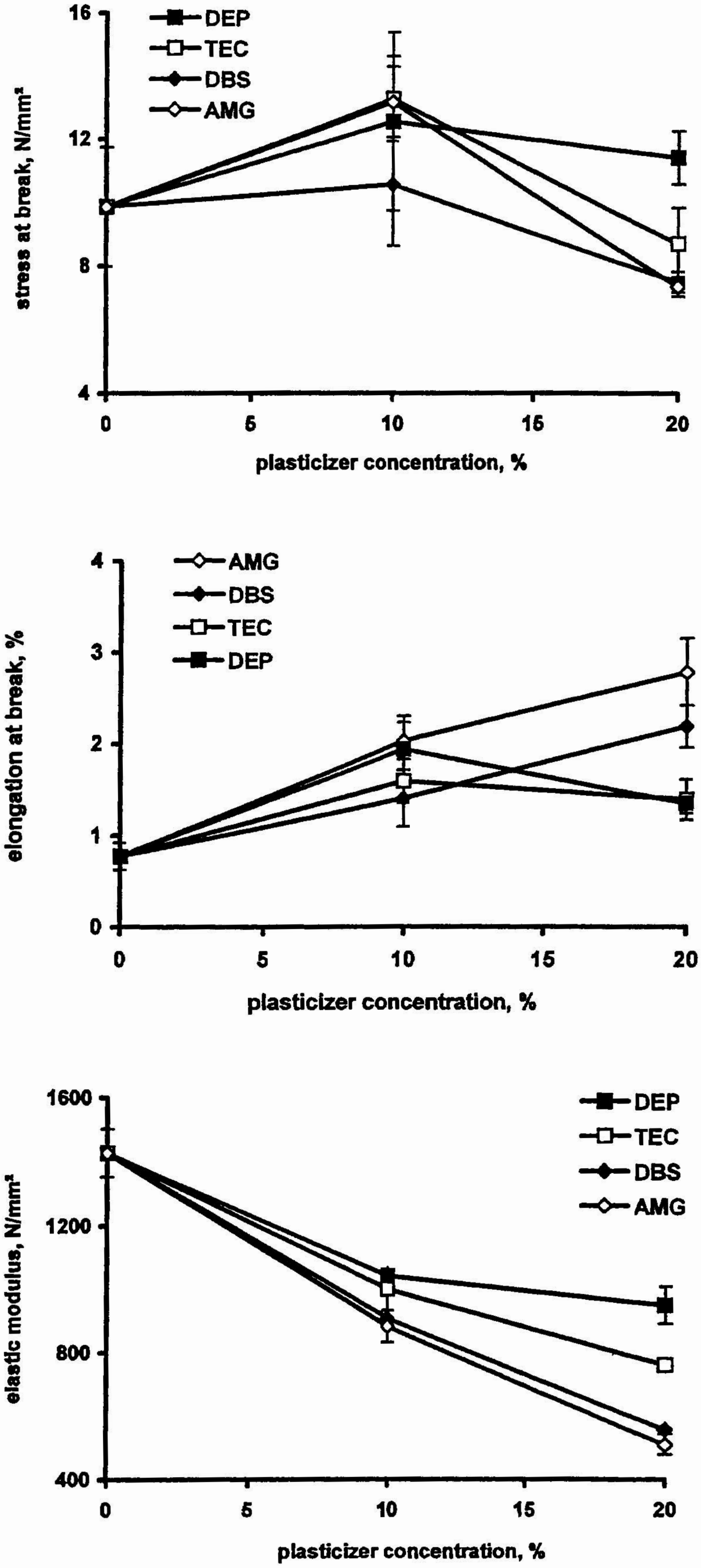
Effect of plasticizers type on glass transition temperatures (Tg) of ethylcellulose as a function of solubility parameters (plasticizer concentration, 20%)



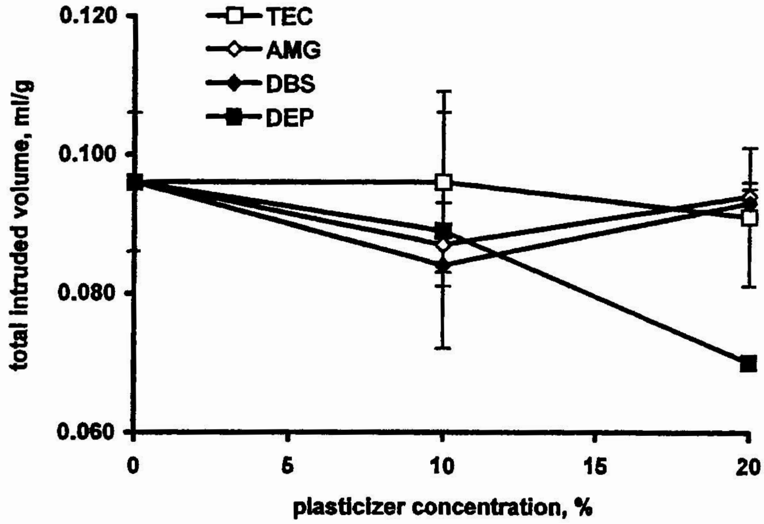
Effect of plasticizer concentration on glass transition temperature (Tg) of ethylcellulose films

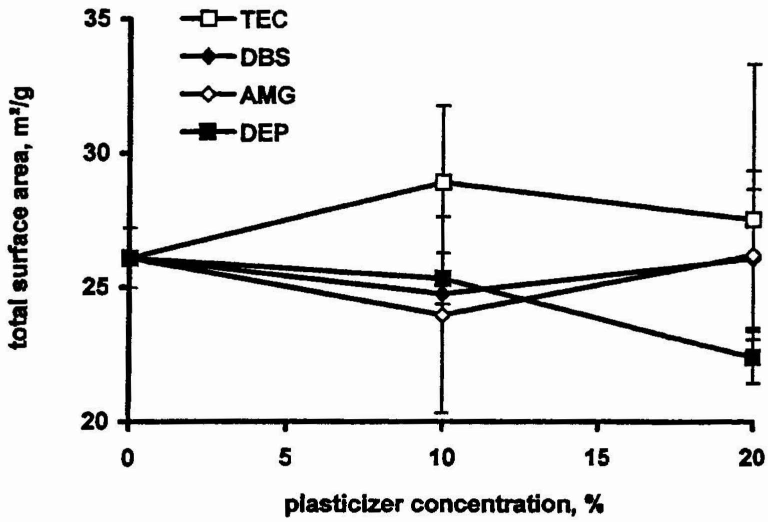


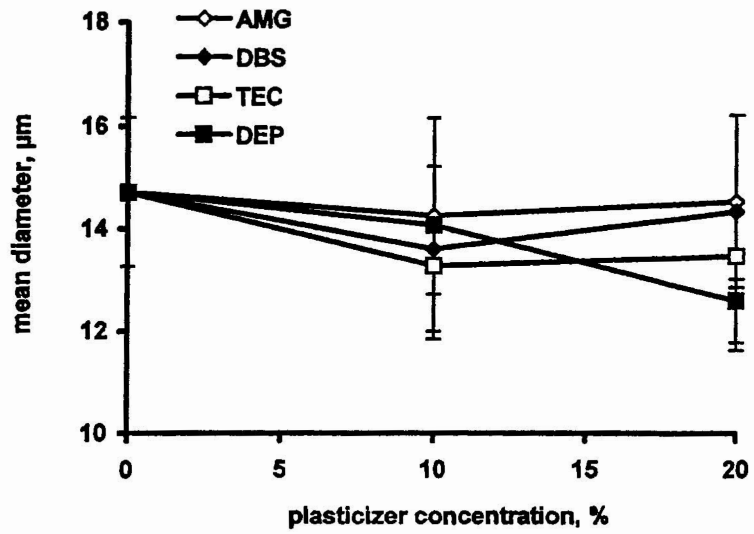
Mechanical properties of ethylcellulose films plasticized with different plasticizers (ethylcellulose 22 grade) (Hyppölä et al, 1996)



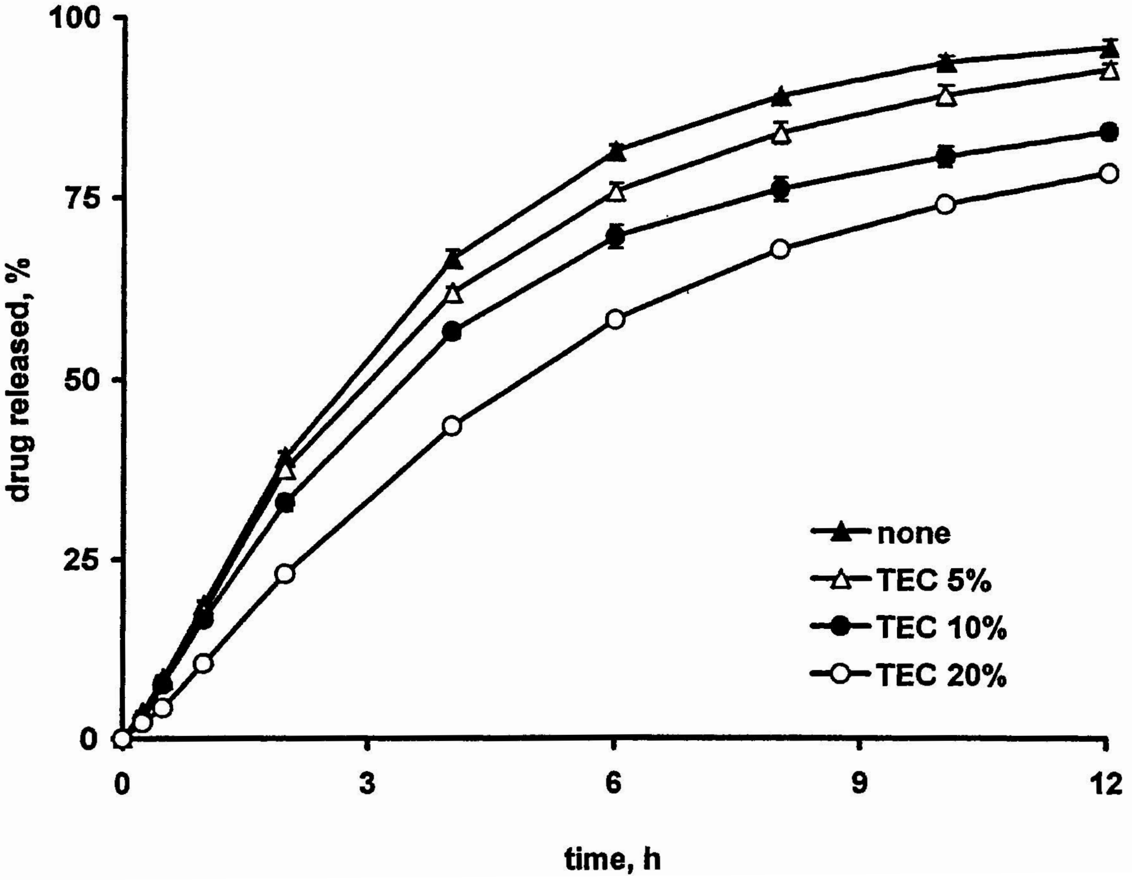
Porosity results of ethylcellulose films plasticized with different plasticizers (ethylcellulose 22 grade) (Hyppölä et al, 1996)



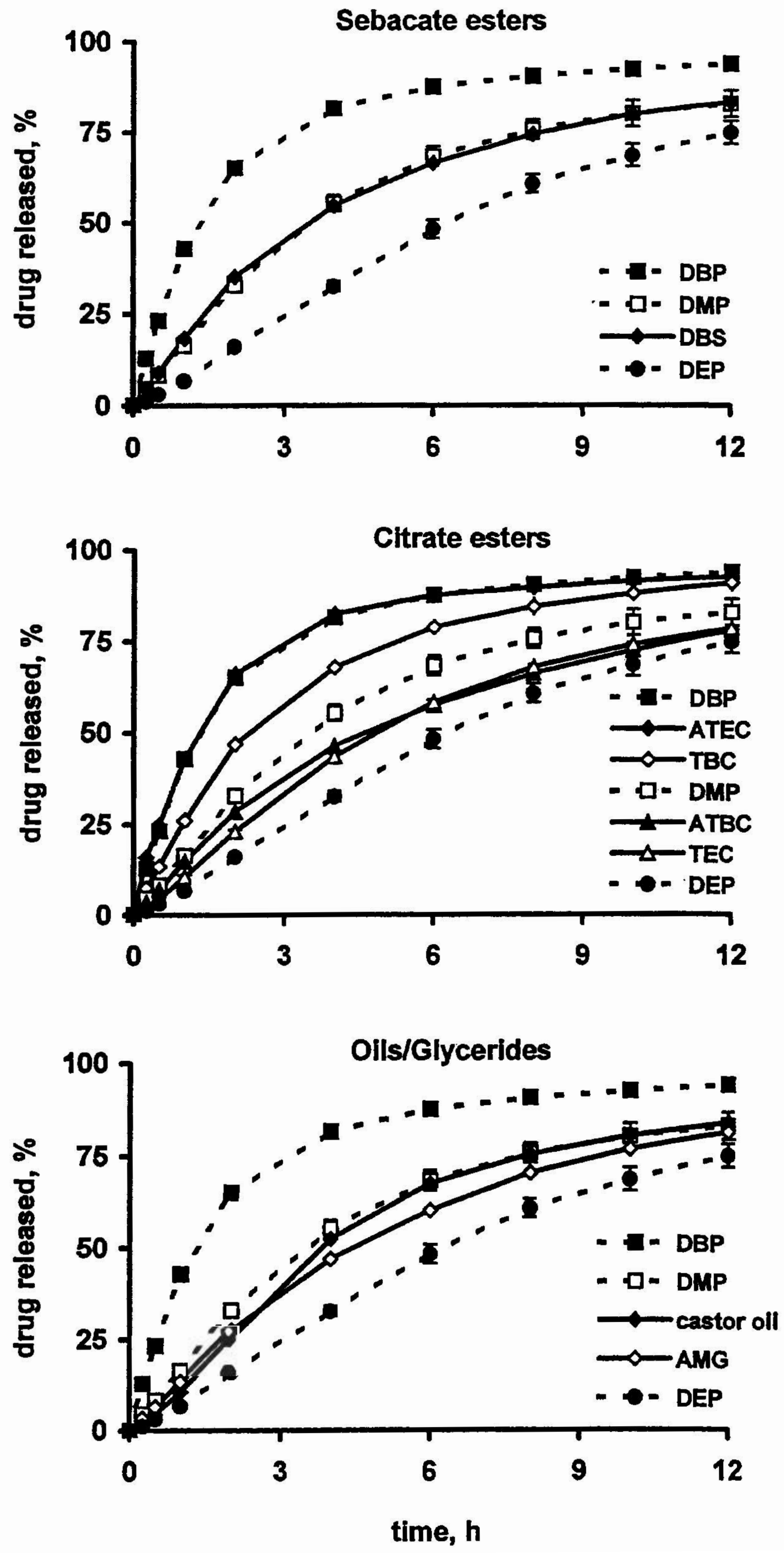




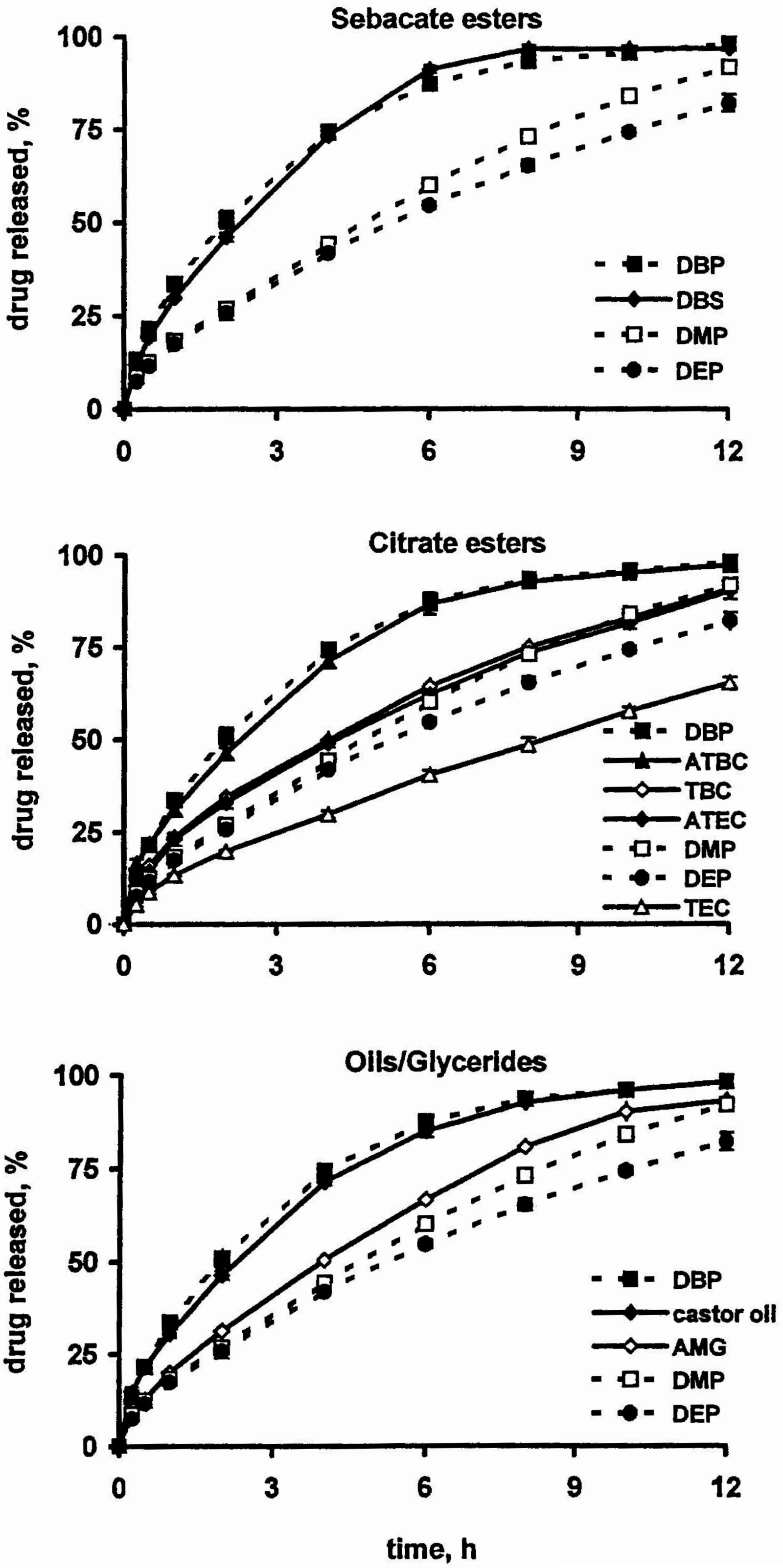
Effect of plasticizer concentration on drug release in 0.1 N HCl from ethylcellulose coated-pellets (propranolol hydrochloride-loaded pellets; ethanolic solution; coating level, 5%; plasticizer, triethyl citrate:TEC)



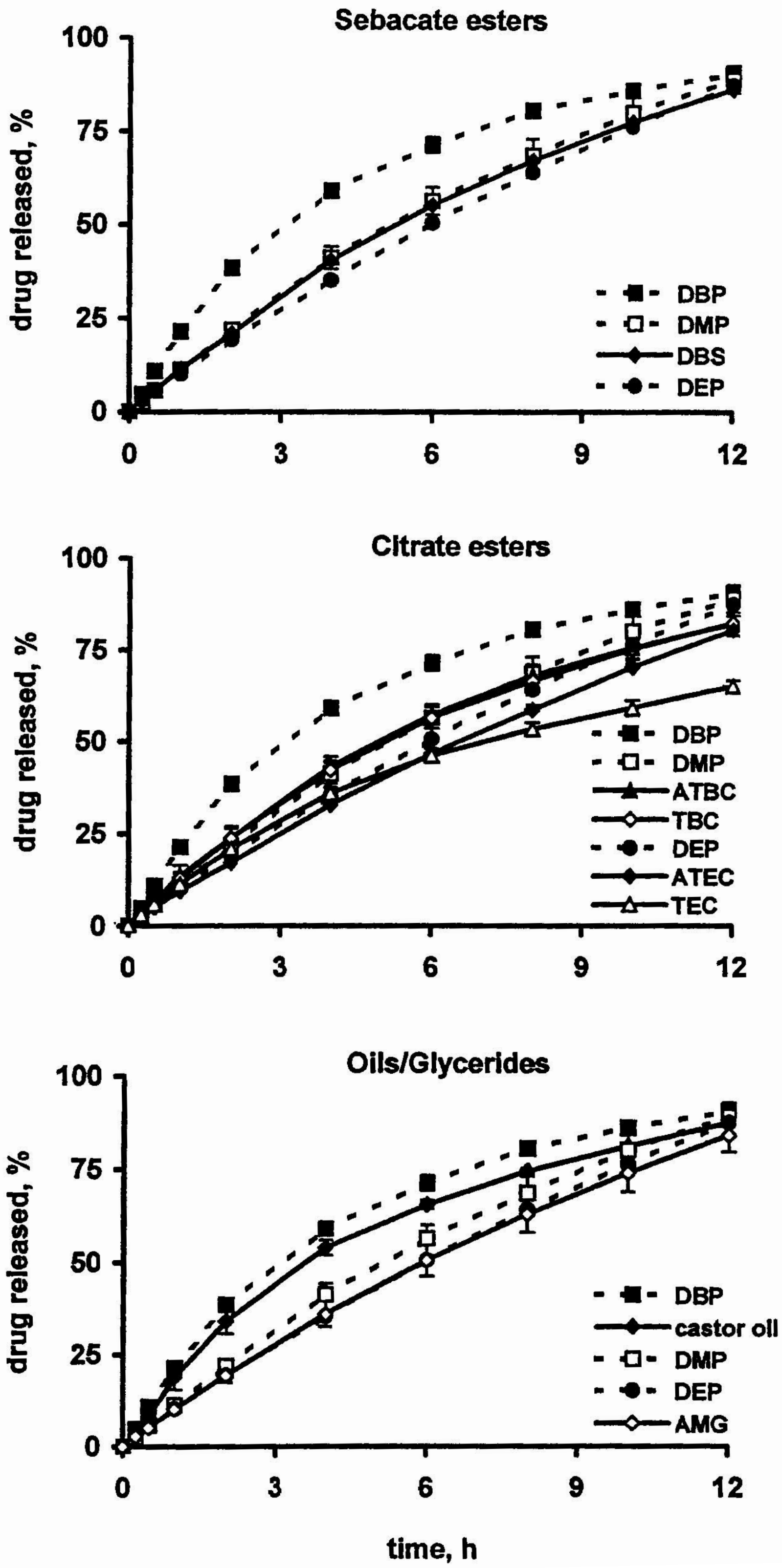
Effect of plasticizer type on drug release in 0.1 N HCl from ethylcellulose coated-pellets (propranolol hydrochloride-loaded pellets; ethanolic solution; plasticizer concentration, 20%; coating level, 5%)



Effect of plasticizer type on drug release in phosphate buffer pH 7.4 from ethylcellulose coated-pellets (ibuprofen-loaded pellets; ethanolic solution; plasticizer concentration, 20%; coating level, 5%)



Effect of plasticizer type on drug release in 0.1 N HCl from ethylcellulose coated-pellets (theophylline-matrix pellets; ethanolic solution; plasticizer concentration, 20%; coating level, 5%)



1.4 Ethylcellulose – Aquacoat ECD coatings

Film formation properties of ethylcellulose – pseudolatex Aquacoat® ECD (Paeratakul, 1993; Guo, 1996)

Plasticizer	Association coefficient	Rate constant, h^{-1}	Absorbed plasticizer, %	Starting film formation	Tg, °C (Plasticizer 30 % w/w)
None	-	-	-	-	92
Phthalate esters					
DEP	37.96	1.35	14.2	15 min	38
DBP	34.51	0.38	16.4	2 h	n.d.
Citrate esters					
TEC	5.69	-	-	-	32
ATEC	32.26	1.26	15.9	30 min	38
TBC	47.30	0.80	15.5	1 h	38
ATBC	38.75	0.29	18.2	8 h	41
Sebacate esters					
DBS	40.35	-	-	-	36
Glycerides/Oils					
AMG	-	-	-	-	39

n.d., not determined

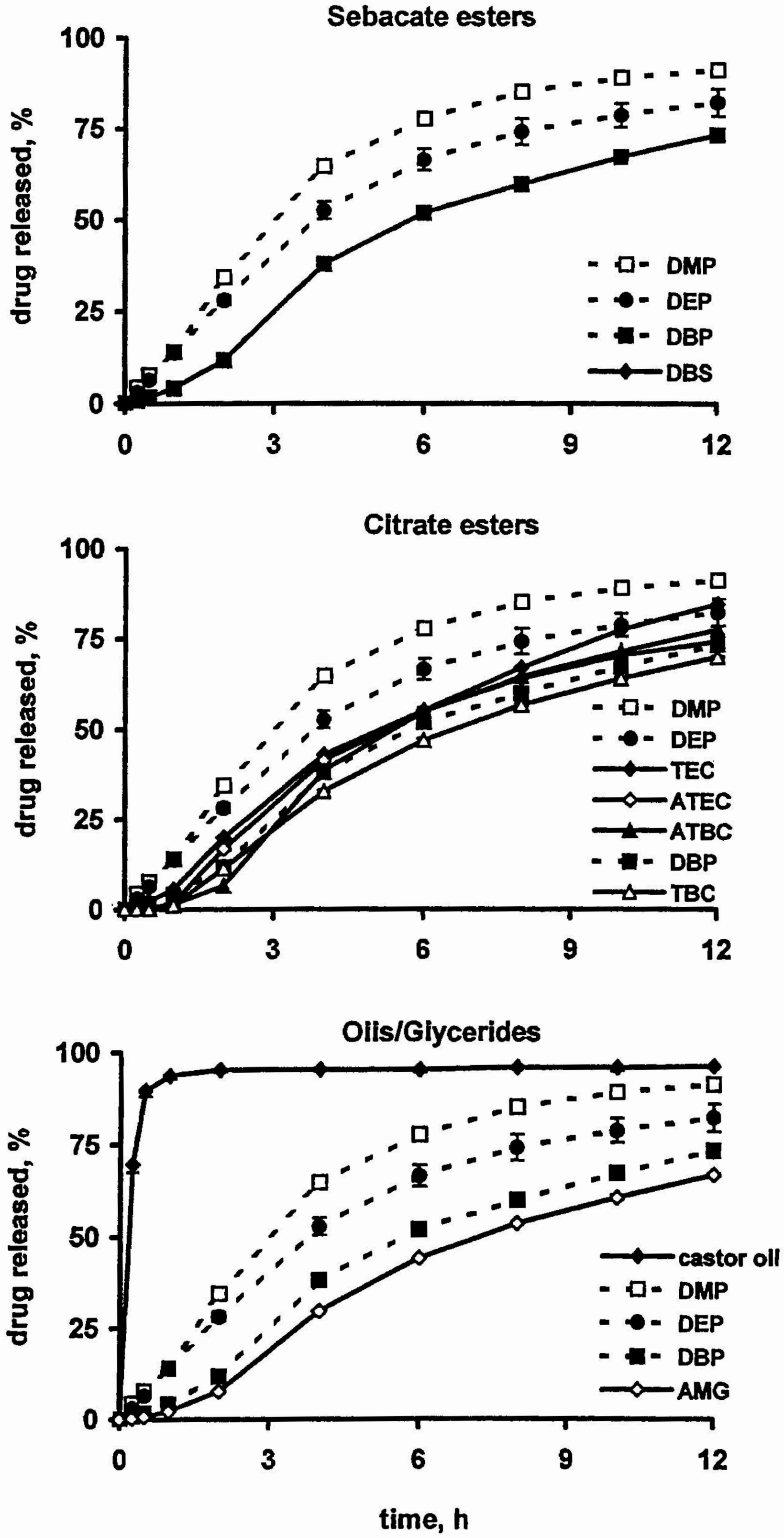
Mechanical properties of dry and wet Aquacoat® ECD films plasticized with different plasticizers (30 % w/w) (dissolution medium, 0.1 M NaCl; exposure time, 24 h) (Paeratakul, 1993)

Plasticizer	Puncture strength, MPa		Elongation, %	
	Dry film	Wet film	Dry film	Wet film
Phthalate esters				
DEP	0.18 (0.02)	0.11 (0.02)	0.21 (0.12)	0.28 (0.12)
DBP	0.60 (0.02)	0.22 (0.02)	1.21 (0.07)	2.28 (0.09)
Citrate esters				
TEC	0.34 (0.11)	0.10 (0.02)	1.34 (0.18)	0.13 (0.02)
ATEC	0.18 (0.05)	0.06 (0.00)	0.38 (0.15)	0.31 (0.05)
TBC	0.50 (0.06)	0.16 (0.01)	2.25 (0.45)	1.79 (0.66)
ATBC	0.16 (0.05)	0.19 (0.02)	0.18 (0.09)	1.69 (0.21)
Sebacate esters				
DBS	0.19 (0.04)	0.09 (0.01)	0.25 (0.09)	0.30 (0.06)

Water uptake and weight loss of Aquacoat® ECD films plasticized with different plasticizers (30 % w/w) (dissolution medium, distilled water; exposure time, 10 h)
(Guo, 1996)

Plasticizer	Water uptake, mg/g film	Weight loss, %
None	100 (4)	6.28 (1.23)
Phthalate esters		
DEP	291 (13)	23.17 (1.33)
Citrate esters		
TEC	684 (23)	25.54 (2.07)
ATEC	308 (17)	20.18 (1.24)
TBC	80 (13)	10.74 (0.67)
ATBC	68 (3)	8.45 (0.54)
Sebacate esters		
DBS	83 (11)	8.50 (0.67)

Effect of plasticizer type on drug release in 0.1 N HCl from ethylcellulose coated-pellets (propranolol hydrochloride-loaded pellets; aqueous dispersion; plasticizer concentration, 25%; coating level, 10%; curing condition, 60°C for 24 h)



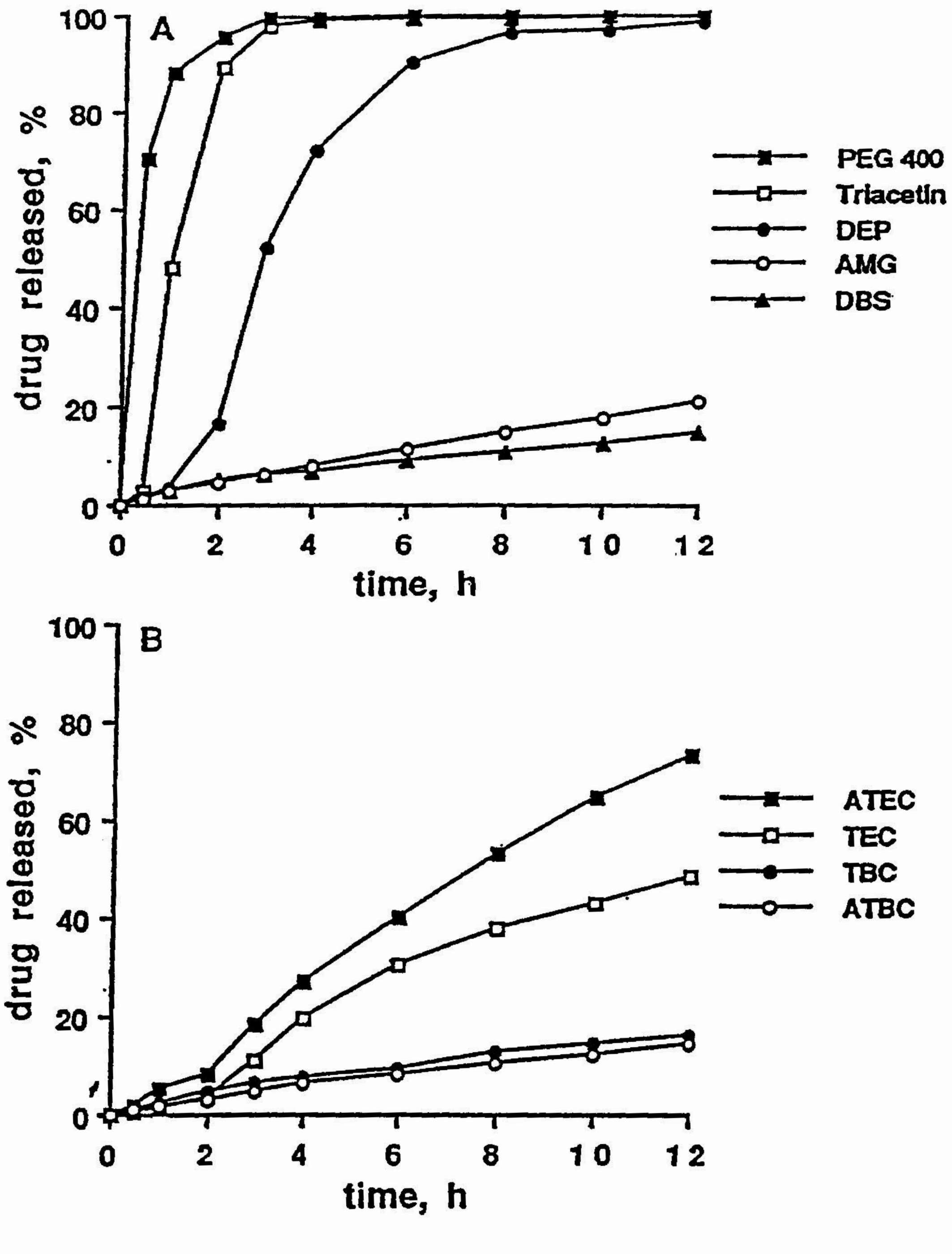
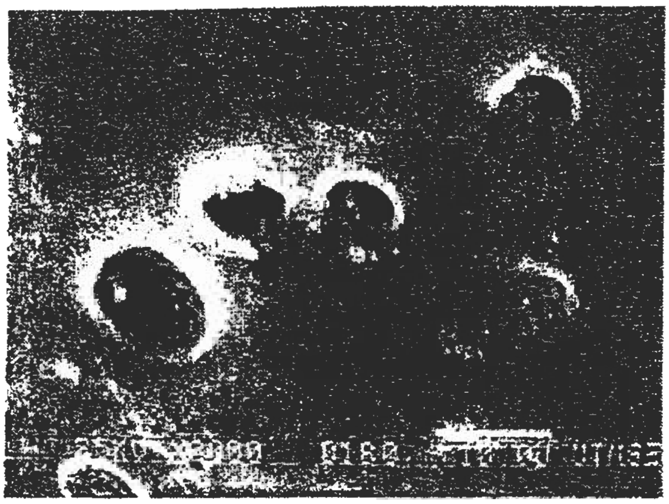
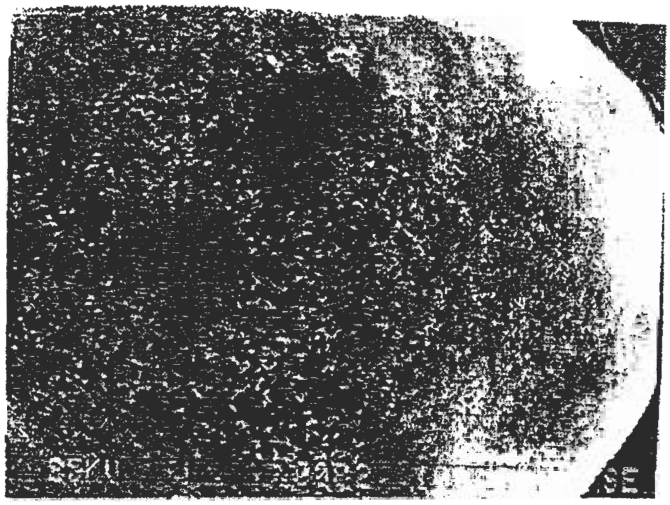


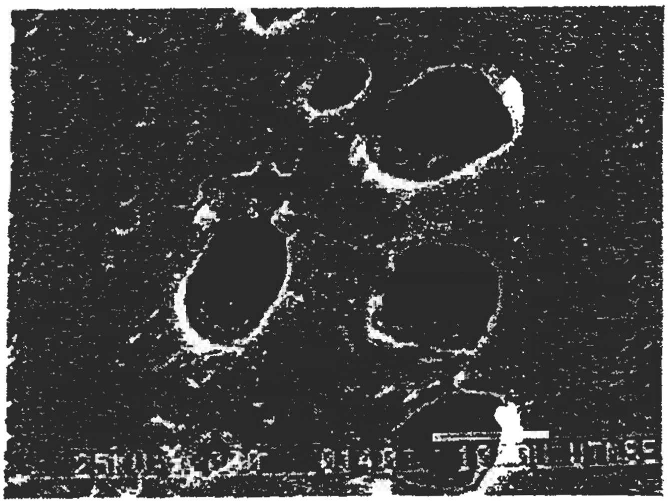
Figure 3.101 Effect of plasticizers on theophylline release from pellets coated with 15% Aquacoat in 0.1M HCl.



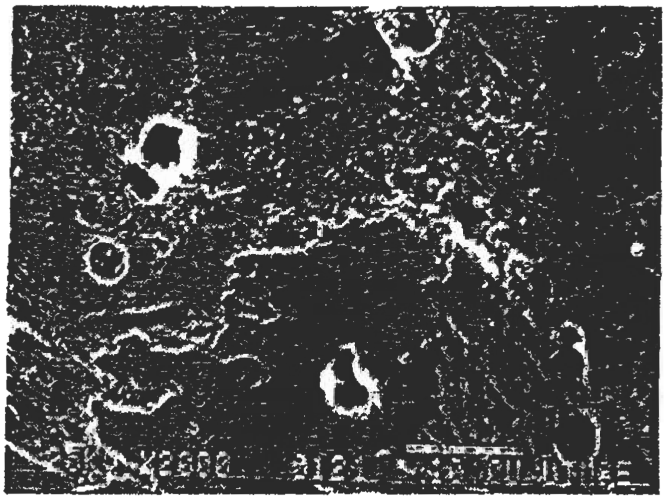
Aquacoat-coated bead (30% ATEC), after 10 hours dissolution (x2000)



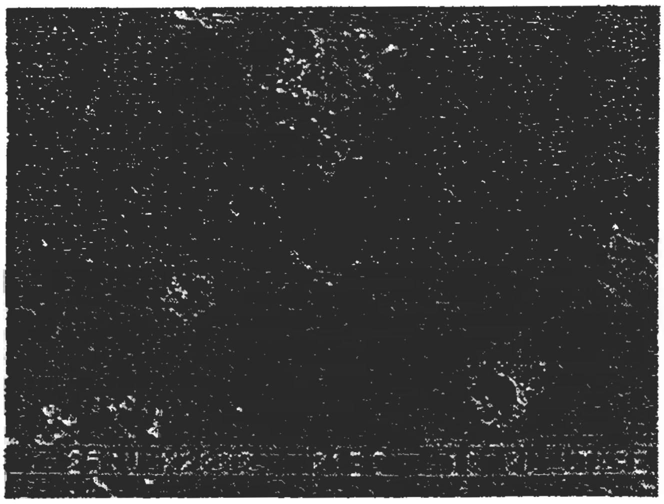
Aquacoat-coated bead (30% ATEC), before dissolution (x100)



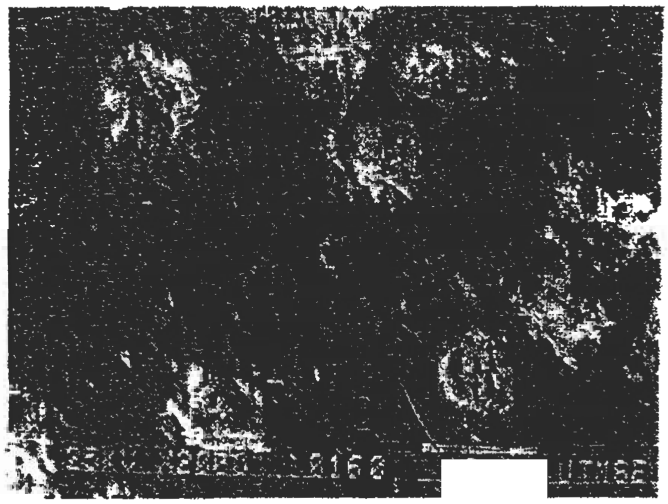
Aquacoat-coated bead (30% DEP), after 10 hours dissolution (x2000)



Aquacoat-coated bead (30% Triacetin), after 2 hours dissolution (x2000)



Aquacoat-coated bead (30% TEC), after 10 hours dissolution (x2000)



Aquacoat-coated bead (30% TBC), after 10 h[illegible]lution (x2000)

Figure 3. Scanning electron micrographs of Aquacoat® coated beads, before and after dissolution in purified water.

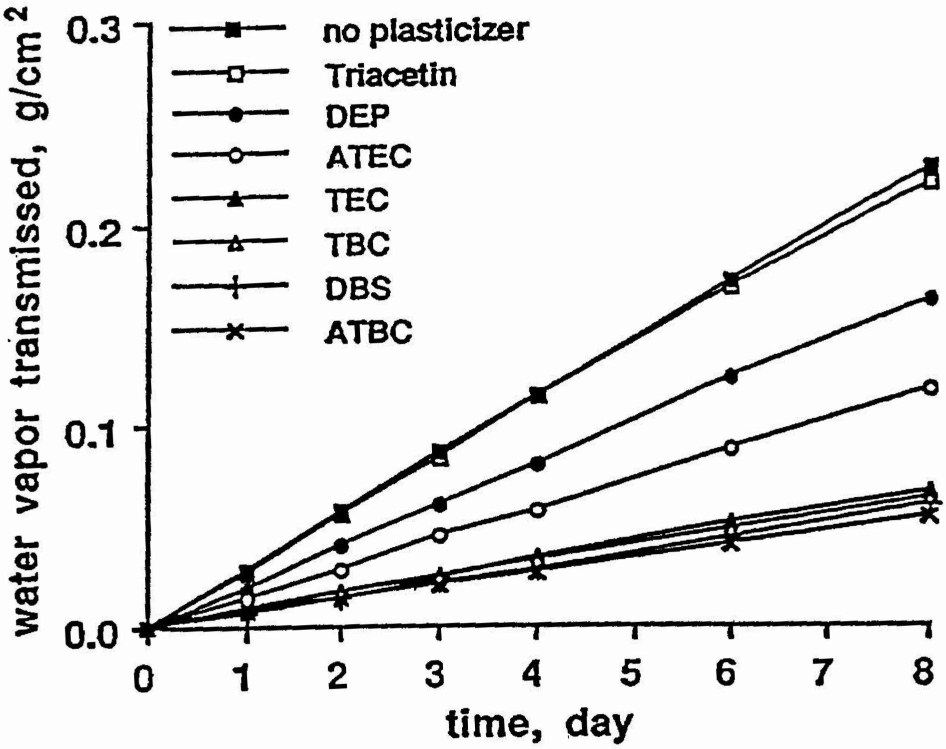


Figure 3.100 Effect of plasticizers on water vapor transmission at room temperature through Aquacoat films (70 μm) with 30% plasticizers at 100% relative humidity.