

Development of a Gelatin-free Soft Capsule

K. Meyer-Böhm [kathrin.meyer-boehm@basf.com], K. Kolter, BASF Aktiengesellschaft, Development Pharma Ingredients, 67056 Ludwigshafen, Germany

Purpose

Traditionally, bovine and porcine gelatins have been used for soft capsule shells. In recent years, soft gelatin capsule formulations have become very popular [1-2]. These formulations can mask odor and unpleasant tastes and are easy to swallow. They are suitable for encapsulation of lipid solutions and suspensions, making them a useful option when formulating poorly water soluble drugs. The development of a gelatin-free formulation for soft capsules reduces the fear of transmission of spongiform encephalopathy (TSE) caused by prions. Kosher products also benefit from a gelatin-free formulation. The intention of this paper is to compare the properties of gelatin based films with films based on Kollicoat® Protect, BASF Aktiengesellschaft.

Materials

Excipients

Film basis

- Gelatin 200 Bloom Type B, Gelita, Batch no. L622081

- Kollicoat® Protect, BASF Aktiengesellschaft, Batch no. 76773647G0

(mixture of polyvinyl-alcohol-polyethylene glycol graft copolymer + polyvinyl alcohol + silicon dioxide)

Softening agents

- Glycerin, Carl Roth GmbH, Lot. no. 05676446

Gelling agents

- Chitosan, low molecular weight, Sigma Aldrich, Batch no. 10124AB
- Gellan, Fluka, Batch no. 1212662
- Agar, Fluka, Batch no. 1141313
- Alginate, Knoll, Batch no. W68377
- Kappa carrageenan type I, Sigma Aldrich, Batch no. 073K0051

Film formulations

Formulation 1

Materials	Content [%]
Gelatin	33.3
Glycerin	33.3
Water	33.3
Total:	100

Table 1: Reference formulation for gelatin films

Formulation 2

Materials	Content [%]
Kollicoat Protect®	50
Glycerin	20
Water	30
Total:	100

Table 2: Formulation for Kollicoat Protect® films

Formulation 3

Materials	Content [%]
Kollicoat Protect®	50
Glycerin	20
Gelling agents	0.1–10
Water	20.0–29.9
Total:	100

Table 3: Formulation for Kollicoat Protect® films containing additives

Methods

The film formulations containing Kollicoat® Protect, glycerin, water and an additive optionally were prepared at 100 °C by using a reflux condenser (table 2, 3). As additives chitosan, gellan, agar, alginate and k-carrageenan were chosen. The gelatin formulation containing 33.3% gelatin, 33.3% glycerin and 33.3% water serves as a reference (table 1). Films of 200-300 µm thickness were drawn on an aluminum substrate using a film applicator (Erichsen, Coatmaster 509 MC, figure 1). The films tensile strength, elongation at break and the elastic modulus were characterized by using a tensile strength tester (figure 2). The tensile strength is the maximum tension with reference to the original cross-section of the sample, before the

film breaks (force per area). The elastic modulus of a film characterizes the tensile strengths at double lengths of the original material. Solubility in phosphate buffer at pH 6.8 as well as in 0.08 M HCl at pH 1 were determined. Sealing of the film was also tested, because production of soft capsules via the rotary-die-process demands dense sealing (figure 3).

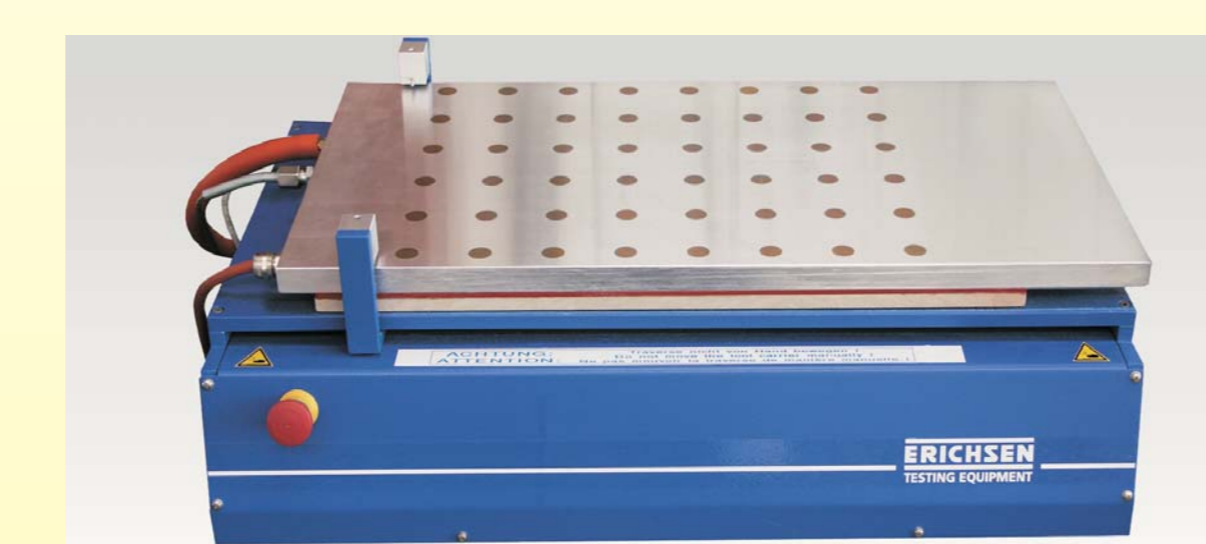


Figure 1: Film applicator (Coatmaster 509MC, Erichsen)



Figure 3: Sealing gripper (Kopp HZ)



Figure 2: Tensile strength tester (Texture Analyser TA XT2i, Stable Micro Systems)

Results

The gelatin film showed a tensile strength of 6.95 N/mm². Its elongation at break was 171% (table 4). The film dissolved quickly at pH 6.8 as well as at pH 1, < 2 min (table 5). Films based on Kollicoat® Protect even without any additives are smooth, clear and flexible. They show comparable results regarding tensile strength (6.68 N/mm²) and elongation at break (195%, table 4). It dissolves slightly slower than the gelatin film (table 5).

Comparison of properties of Gelatin and Kollicoat® Protect films

Type of film	Film appearance	Tensile strength	Elongation at break [%]	E-Modulus [N/mm ²]	Assessment of results and film handling
Gelatin film	Clear and smooth	6.95	171	3	+++
Protect film without additives	Clear and smooth	5.41	181	27	++

Table 4

Solubilities of Gelatin and Kollicoat® Protect films at different pHs

Type of film	Solubility pH 6.8 [min:s]	Solubility pH 1.0 [s:min]
Gelatin film	1:53	1:37
Protect film without additives	6:26	5:33

Table 5

The following tests were carried out to identify the impact of different additives on Kollicoat® Protect film properties. Because of its insolubility in water the low molecular weight chitosan does not influence the film properties in a positive way (table 6). The addition of gellan causes a rough film surface. The additive agar leads to turbid films. After 3 days of storage they get mouldy. Alginate generates brownish coloured films. Adding 0.1% k-carrageenan shows best results. Its addition results in clear, smooth and flexible films. Elongation at break increases up to 195%.

Influence of different additives on film properties

Gelling agent	Film appearance	Tensile strength [N/mm ²]	Elongation at break [%]	E-Modulus [N/mm ²]	Assessment of results and film handling
without	–	5.41	181	27	++
Chitosan	insoluble	–	–	–	–
Gellan	rough surface	–	–	–	–
Agar	turbid, mouldy after 3 days	–	–	–	–
Alginate	brown	5.51	109	31	+
k-carrageenan	clear	6.68	195	28	+++

Table 6

To find out the concentration of carrageenan for most flexible films 10-0.1% of carrageenan were added (table 3). Figure 4 shows that the only addition of 0.1% of carrageenan leads to more flexible films than without or with higher concentrations of carrageenan.

Influence of different concentrations of carrageenan on film flexibility

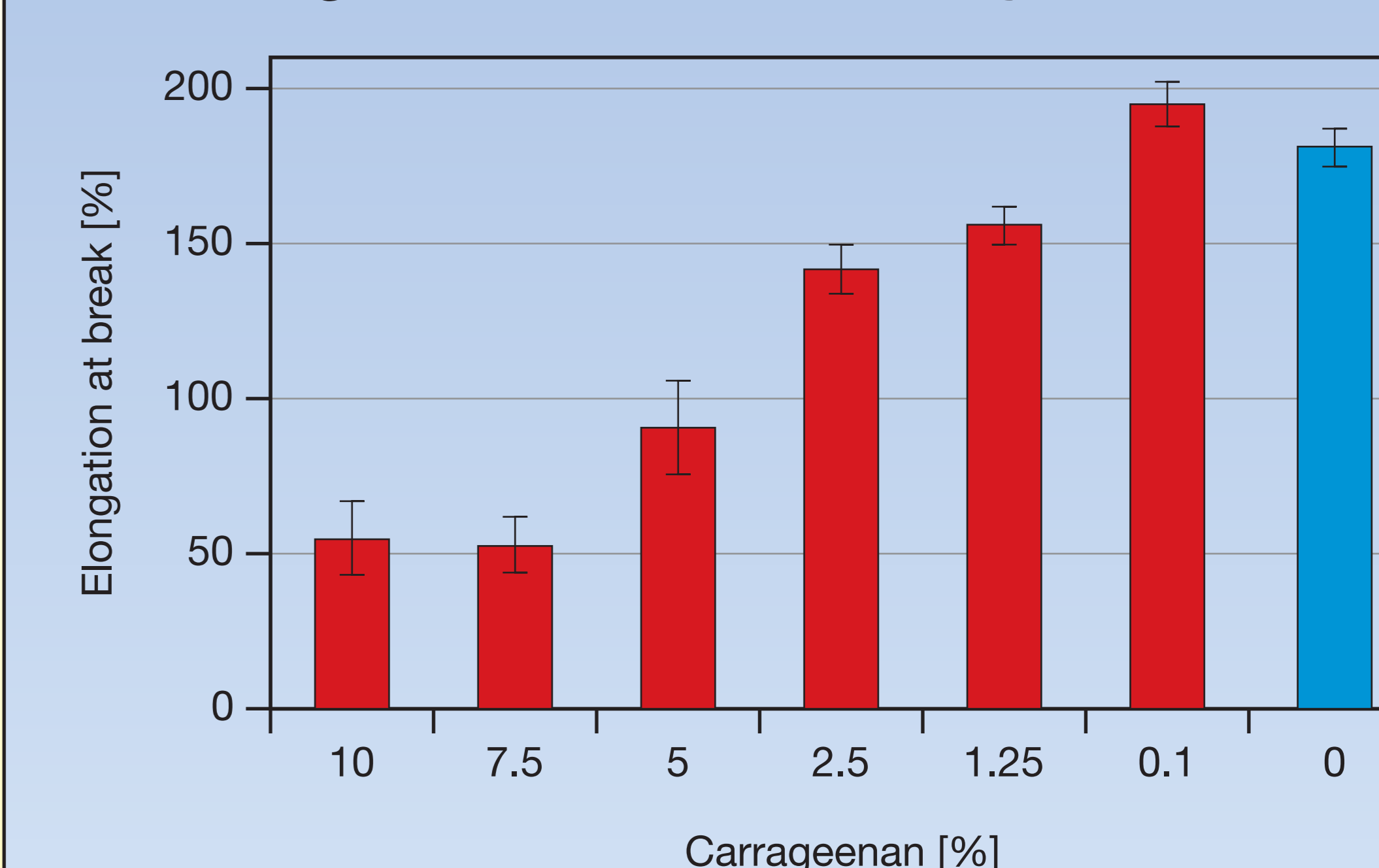


Figure 4

For close sealing of Kollicoat® Protect films – independent of additives – by using a sealing gripper shown in figure 3 – a defined residual moisture of 12% and a temperature of 125 °C seem to be ideal. Under these defined conditions gelatin films cannot be sealed; sealing is only possible via drying.

Conclusions

- As a gelatin-free material for soft capsules, a Kollicoat® Protect formulation can be recommended.
- 50% Kollicoat® Protect and 20% glycerin lead to ideal film properties.
- Adding 0.1% k-carrageenan improves flexibility and stability of the film.
- Optimal sealing conditions for Kollicoat® Protect films were defined.

References

- [1] Review article: Mechanisms of drug release from tablets and capsules. I: Disintegration, C. D. Melia, S. S. Davis, Alimentary Pharmacology & Therapeutics, 3 (3):223-232, 1989
- [2] Buccal Mucosa As A Route For Systemic Drug Delivery: A Review, A. H. Shojaei, J. Pharm. Pharmaceutical Science, 1 (1):15-30, 1998