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Research paper

Influence of aqueous coatings on the stability of enteric coated pellets and tablets

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Abstract

Pancreatin pellets, placebo pellets and tablets containing vitamin B_2 were coated with various aqueous and organic enteric polymers, HPMCAS, HP, Eudragit® L 100-55, Eudragit® L 30 D-55, CAP, CAT, CMEC and PVAP, comparatively investigated and tested for storage stability. With the exception of Eudragit® L 100-55 and Eudragit® L 30 D-55, higher amounts of coating material were needed to achieve gastro-resistance with aqueous coating than with organic coating. Film formation from aqueous dispersions of micronized HP 55 was affected by the degree of micronization and was improved by reducing the particle size of the polymer. Undercoating was another suitable measure to decrease the amount of coating material required. The choice of plasticizer was of special importance in the aqueous dispersions, and type and quantity must be appropriate for the polymer applied. Non-polymeric plasticizers such as triethyl citrate (TEC) evaporated along with water during the spraying or drying process and high temperatures promoted such losses. The moisture-sensitive pancreatic enzymes were damaged both by humidity and heat during aqueous coating. The extent of damage was dependent on the coating equipment used. Upon storage, coatings obtained from aqueous dispersions showed changes in enteric performance or release characteristics as a consequence of three chemical/physical mechanisms: hydrolysis of ester linkages in the polymer or plasticizer, evaporation of the plasticizer, delayed film formation. The active ingredient pancreatin induced hydrolysis of the ester based film-former hydroxypropyl methylcellulose acetate succinate (HPMCAS). However, even without the influence of enzymes, the phthalic ester groups of aqueous hydroxypropyl methylcellulose phthalate (HP) were partly cleaved after 11 months storage. In HPMCAS-coated pancreatin pellets, the plasticizer glyceryl triacetate was almost completely hydrolyzed by the enzymes, whilst triethyl citrate was lost by evaporation through permeable packaging material at elevated temperatures. Open storage at elevated temperatures and humidities caused changes in the surface structure of HPMCAS coatings, consisting of a smoothing of the originally somewhat porous film and sticking. When applied to vitamin B_2 tablets, Eudragit® L 100-55, Opadry® enteric (PVAP) and Aqoat® (HPMCAS) proved to be quite stable aqueous enteric coatings, whereas cellulose acetate phthalate CAP or cellulose acetate trimellitate CAT coatings as ammonia-neutralized aqueous solution or as water-based pseudolatex Aquateric® were unstable when stored under stress conditions.

Keywords: Aqueous coatings; Plasticizer; Film formation; Undercoating; Hydrolytic degradation; Pancreatic enzymes

1. Introduction

The use of organic solvents in the coating of pharmaceutical dosage forms has become problematic due to regulatory requirements, flammability and limits on solvent residues in the coated product [1,2].

The alternative aqueous coating systems can overcome these problems, but suffer from certain limitations [3,4]: they are susceptible to microbial contamination without the incorporation of preservatives, the comparatively higher

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energy of evaporation of water can increase process time; and moisture-sensitive cores (e.g. dry extracts, substances prone to hydrolysis, enzymes) can be damaged by the coating process [5–7]. In addition, substances readily soluble in water can be incorporated into the film and problems of long-term stability can arise due to the inclusion of water [8–10]. With dispersions, it is particularly important to avoid sedimentation or coagulation of the film-former and incomplete film formation [11–13]. The volatility of plasticizers in water vapor during the coating process can cause problems in film formation from aqueous dispersions [14].

In the present study, pancreatin pellets and film-coated tablets (containing riboflavine as indicator) have been used to illustrate the need for higher coating thicknesses in order to achieve gastro-resistance, the importance of choosing suitable plasticizers and the stability problems of the active ingredient pancreatin and various aqueous film coatings.

2. Materials and methods

2.1. Materials

Hydroxypropyl methylcellulose acetate succinate HPMCAS-MF (Aqoat®) and HPMCAS-MG, hydroxypropyl methylcellulose phthalate HP 55, HP 55-AF and -UF, hydroxypropyl methylcellulose (Pharmacoat® 606, all provided by Synthapharm, D-Mühlheim), carboxymethyl ethylcellulose (Duodcell® AQ), cellulose acetate phthalate (Aquateric®, Lehman and Voss, D-Hamburg, and Eastman CAP, Gustav Parmentier, D-Frankfurt), cellulose acetate trimellitate (CAT, Gustav Parmentier, D-Frankfurt), polyvinyl acetate phthalate (Opadry® OY-A, Colorcon, D-Königstein), Eudragit® L 100-55, Eudragit® L 30 D-55 (Röhm Pharma, D-Darmstadt), povidone (Kollidon® K25, BASF, D-Ludwigshafen), talc (Norwegian Talc Deutschland, D-Bad Soden-Salmünster and Erbslöh, D-Hamburg), silicone antifoam emulsion SE2 (Wacker Chemie, D-München), glyceryl triacetate (Riedel-de Haen, D-Seelze and Merck, D-Darmstadt), diethyl phthalate (Merck, D-Darmstadt), glyceryl monocaprylate (Imwitor® 908R, Hüls, D-Witten) and triethyl citrate (Citroflex® 2, Pfizer Chemie, D-Wiesbaden) were used as received.

The pancreatin pellet cores were manufactured at the pharmaceutical department of Solvay Pharma, D-Hannover, revealing a mean core size of 1.6 mm, an average density of 1.2 g/cm^3 and a specific surface area (BET-method) of about 1.2 m^2/g. Placebo pellets of the same size consisted of D + C Yellow 10, E 104, as indicator, PEG 4000, colloidal silicone dioxide (Aerosil 200), lactose (Pharmatose 200), microcrystalline cellulose (Avicel PH 101), crospovidone (Polyplasdone XL) and corn starch and were manufactured as the pancreatin pellets by wet granulation, extrusion and subsequent spheronization.

The tablet cores were manufactured by wet granulation technique and consisted of lactose, starch, microcrystalline cellulose (Avicel PH 101), povidone (Kollidon® 25), sucrose stearate and riboflavine sodium phosphate as indicator. The cores had a breaking force of 80–97 N, an average weight of 302 mg and a friability of $<0.3\%$ [15,17].

2.2. Coating procedure

Coating was performed using two types of lab scale fluidized bed coaters, STREA-1 and RotoProcessor, both Niro-Aeromatic, CH-Bubendorf, at inlet temperatures of 35°C, 55°C or 70°C for the pellets and 40–60°C for the tablets. The aqueous coating dispersions of HPMCAS and HP-55 were kept cool during manufacture at a temperature not exceeding 12°C. The weight of uncoated cores per batch ranged between 200 and 850 g for the STREA-1 and 400–1700 g for the RotoProcessor [15,17].

2.3. Determination of lipase activity

The lipase activity of the pancreatin pellets was determined according to DAB 10 at 37.0 ± 0.5°C and pH 9.0 using an automatic titration apparatus (Dosimat 655, Impulsomat 614, pH meter 632, stirrer E649, automatical 5 ml burette, Deutsche Metrohm, D-Filderstadt). All reagents were of DAB 10 grade. Pancreatin reference and bile were received from Solvay Pharma, D-Hannover. The enzyme activity is expressed as F.I.P. units per gram.

2.4. Determination of the gastric resistance of enteric-coated pancreatin pellets

Coated pellets were placed into a 1000 ml beaker filled with 0.1 M hydrochloric acid of 37°C. A disintegration tester (Erweka disintegration tester ZT 24, Erweka, D-Heusenstamm) was run for 2 h. The pancreatin pellets were collected on a filter and the residual lipase activity was determined according to Section 2.3.

2.5. Determination of film thickness of coated tablets

Three tablets of each batch were halved by a scalpel and fixed to a glass slice. The smallest thickness at the band was measured under the microscope (Labophot, Nikon, J-Tokyo) by an ocular micrometer and defined to be the minimal coating thickness [15].

2.6. Determination of swelling of coated tablets during gastric resistance testing

Each tablet was exactly weighed before and immediately after the 2 h testing for gastric resistance in 0.1 N HCl. The weight gain (equal to water uptake) was expressed as a percentage of the initial weight [15].

2.7. Determination of disintegration of coated tablets

The tablets were tested in phosphate buffer pH 6.8 DAB 10 employing a disintegration tester PTZ 3E, Pharmatest Apparatebau, D-Hamburg. For visual inspection of the tablets during the run, the apparatus was equipped with a mirror and two fluorescent tubes [15].

2.8. Characterization of the film structure

The structure of the coated pellets was examined using scanning electron microscopy (SEM) on a Hitachi S-4100 microscope at 5 kV. Each sample was fixed to an Al sample holder either directly (surface) or after fracturing by a hammer (cross-section) and gold sputtered for 90 s.

2.9. Determination of plasticizer content

The amount of plasticizer in the film coatings was measured by GC using a Hewlett Packard 5890 gas chromatograph (with autosampler, 7673 injector, 35900 interface, 7673 controller) and flame ionization detection. A DB-1 capillary column (30 m length, 0.319 mm ID, 0.25 μm layer thickness, J & W Scientific, US-Folsom) was utilized. Diethylphthalate was employed as internal standard, triethyl citrate, glyceryl triacetate and diacetate as external stan-

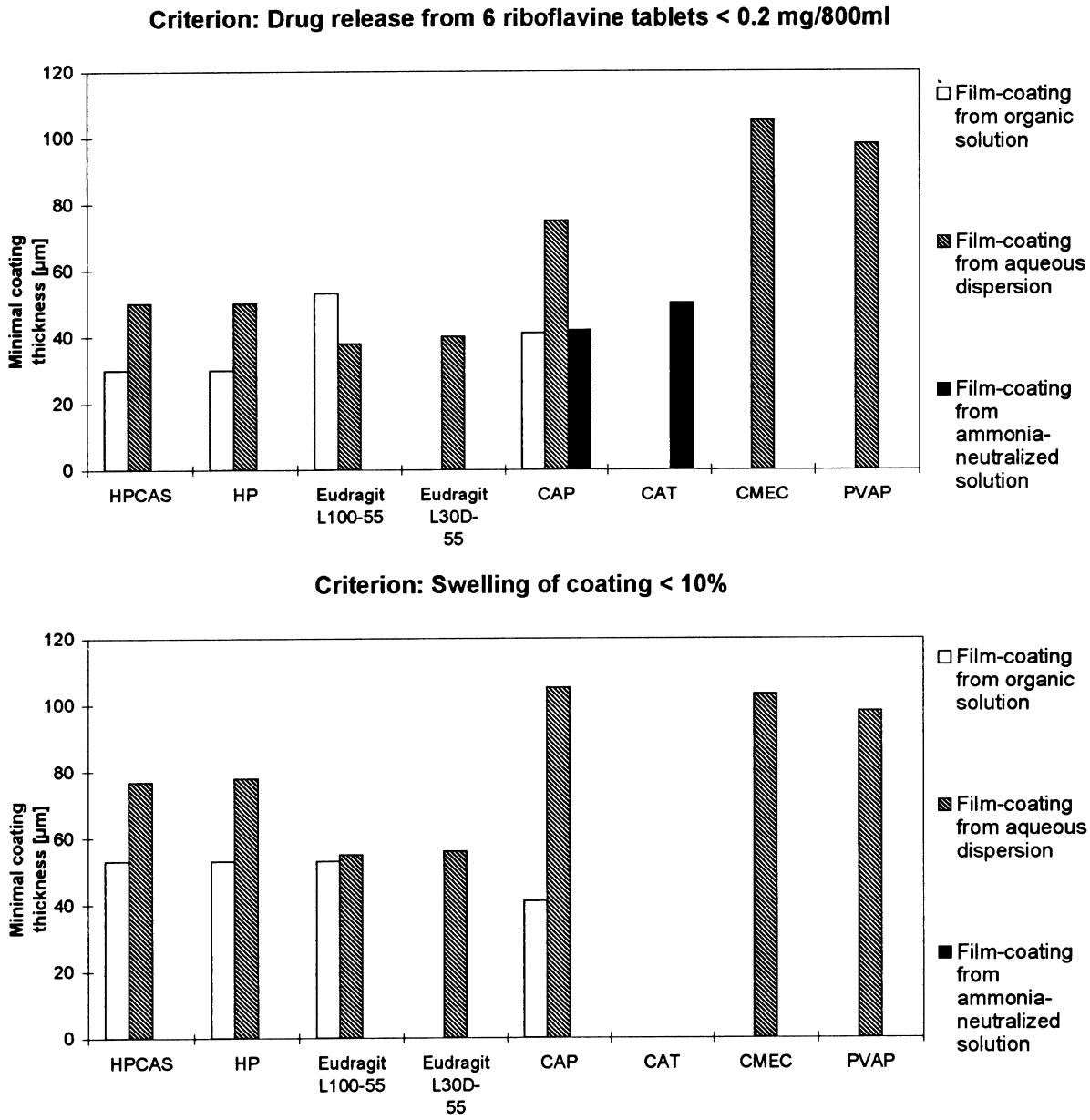


Fig. 1. Dependence of minimum coating thickness (μm) required for film-coated vitamin B_2 tablets to achieve gastro-resistance on the type of film and the film-former [15]. Resistance criterion (upper): drug release from six riboflavine tablets <0.2 mg/800 ml. Resistance criterion (lower): swelling <10%.

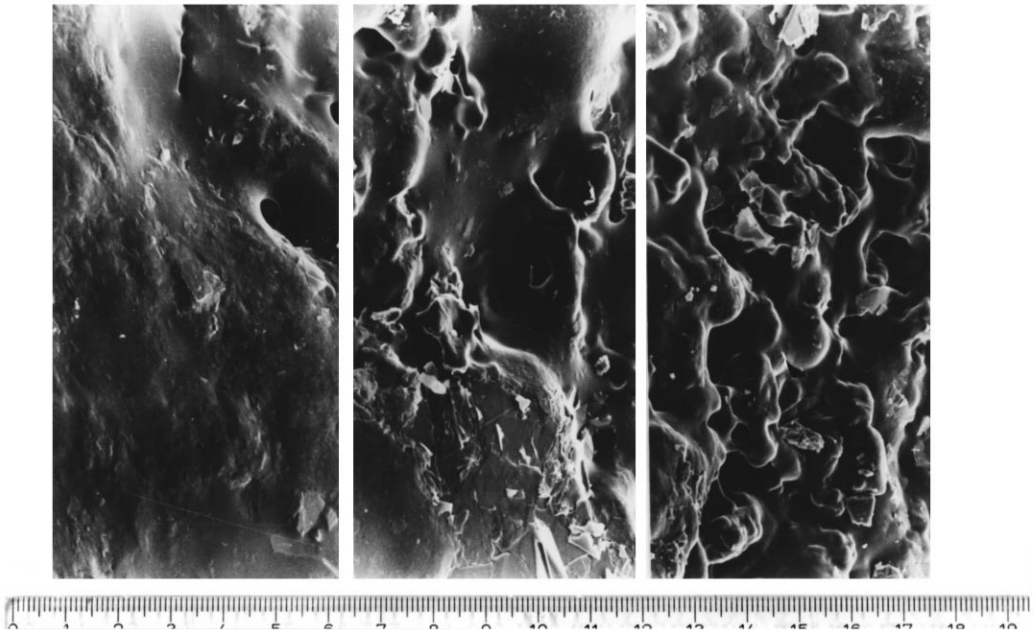


Fig. 2. Effects of plasticizer concentration on the improvement in film formation from micronized HP 55 on pancreatin pellets (TEC concentration, from top to bottom, 40, 50, 65%, magnified 1000 times) [17].

dards. The analysis was performed raising the temperature from 100 to 300°C at a heating rate of 10°C/min. The coated pellets were extracted overnight by diethyl ether, centrifuged and the clear solution examined for the plasticizer content.

2.10. Determination of the ester content of the film formers

The coatings were removed from the pellets by a mixture of acetone and dichloromethane 1:1, the organic solvent evaporated and the residue dissolved in phosphate buffer pH 7.0. The film former was again precipitated by addition of 1-molar hydrochloric acid. The precipitate was carefully washed by demineralized water and dried at 40°C under vacuum. The succinyl and phthalyl esters were titrimetrically determined in neutralized acetone/ethanol/water 2:2:1 by 0.1-molar sodium hydroxide solution after addition of phenolphthalein as indicator. The results were to be corrected for the water content of the samples.

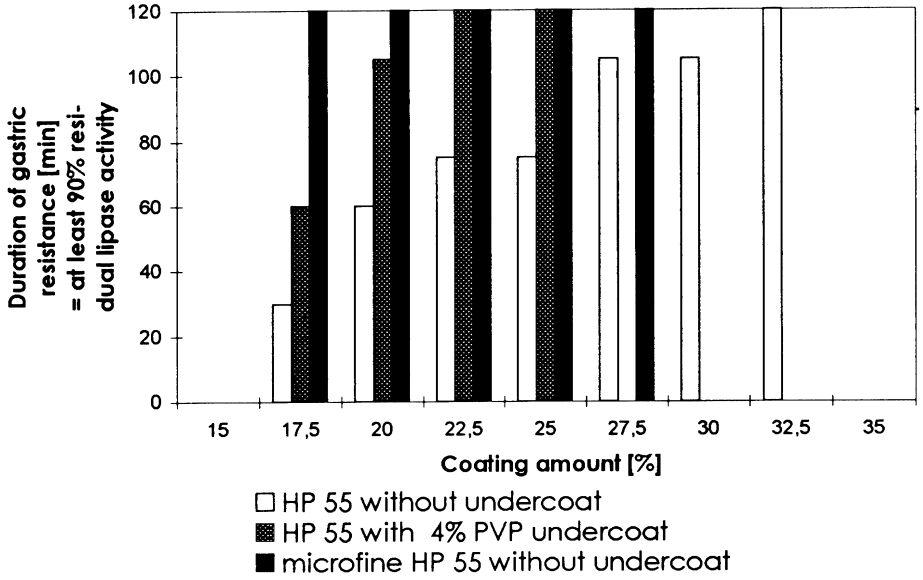


Fig. 3. Effects of particle size of the film-former and application of an undercoat of 4% PVP on the gastro-resistance properties of pancreatin pellets coated with aqueous HP 55-dispersions [17]. Theoretical TEC concentration 40% relative to the polymer. Resistance criterion: at least 90% residual lipase activity after 2 h in 0.1 N HCl.

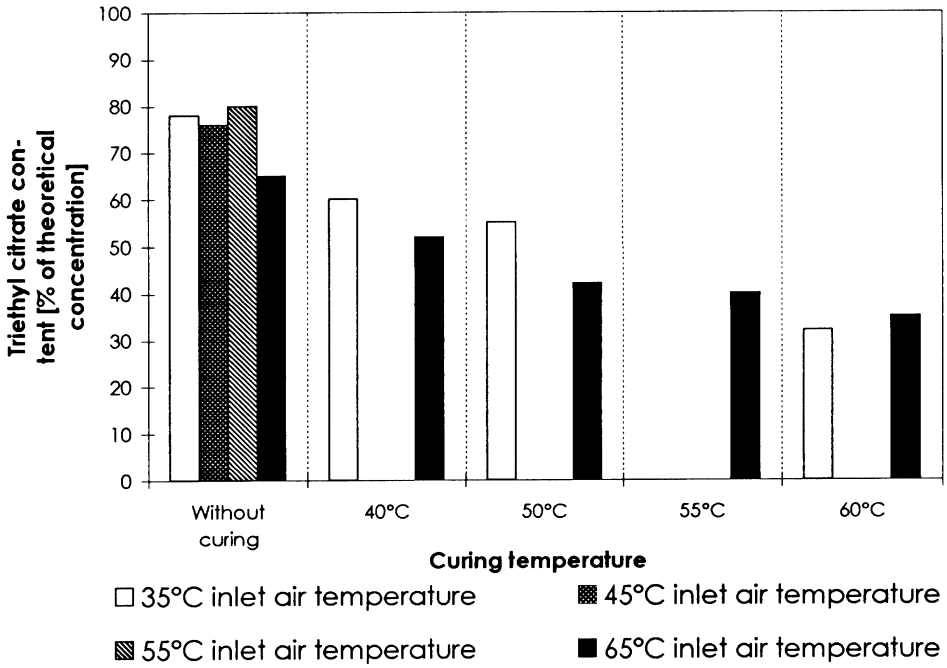


Fig. 4. Effects of the coating and curing conditions (48 h drying) on the triethyl citrate content of aqueous HPMCAS-MF coatings of pancreatin pellets after coating in a laboratory fluidized bed apparatus (MF, micronized film-former) [17].

$$\%\ \text{Phthalyl content} = \frac{149 \times 0.1\ \text{molar NaOH (ml)}}{(100 - \text{water content (\%)}) \times \text{weight (g)}}$$

$$\%\ \text{Succinyl content} = \frac{101 \times 0.1\ \text{molar NaOH (ml)}}{(100 - \text{water content (\%)}) \times \text{weight (g)}}$$

The acetyl groups in the polymer HPMCAS had to be hydrolyzed before titration. After addition of 0.1-molar sodium hydroxide solution, exactly measured, the film former was refluxed for 30 min. The amount of base not consumed was determined by titration with 0.1-molar hydrochloric acid solution using phenolphthalein as indicator.

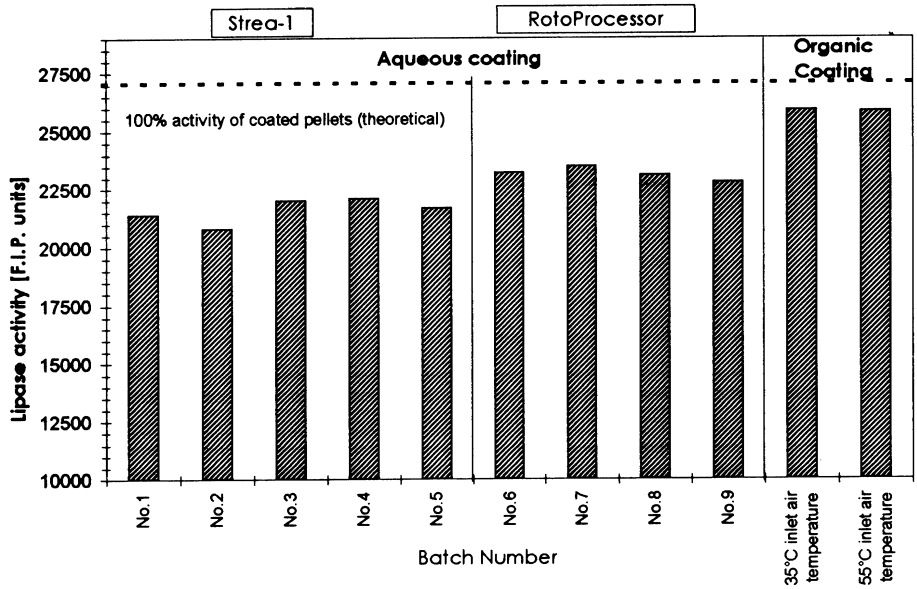


Fig. 5. Influence of the coating apparatus (Strea-1, RotoProzessor) and the coating system (aqueous suspension or organic solution) on the decrease in lipase activity on aqueous coating with HPMCAS [17]. Organic coating performed in the Strea-1.

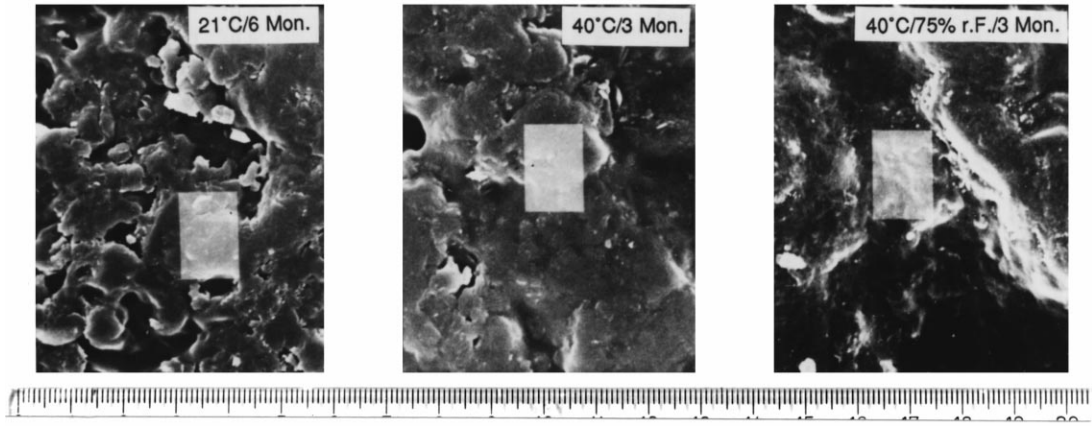


Fig. 6. Surfaces of aqueous-coated pancreatin pellets after 6 months storage at 21°C (left), after 3 months storage at 40°C (middle) in both cases in tightly closed glass containers, and after 3 months open storage at 40°C/75% RH (right). HPMCAS-MF coating with 30% TEC, 4% PVP undercoat, magnified 1200 times [17].

$$\%\ \text{acetyl content} = \frac{43 \times (0.1\ \text{molar HCl}_{\text{blank}}\ (\text{ml}) - 0.1\ \text{molar HCl}_{\text{sample [ml]}}(0.851 \times \text{succinyl [\%]})}{(100 - \text{water content[\%]}) \times \text{weight[g]}}$$

3. Results and discussion

3.1. Investigation of the minimum film thickness for gastro-resistant coatings

When aqueous coatings are used, it is often necessary to apply more coating material to achieve the desired function such as resistance to gastric juice or delay in release, than with comparable organic coatings [16].

Fig. 1 shows the minimum thicknesses of coating needed to produce gastro-resistant film-coated tablets using the polymers hydroxypropyl methylcellulose acetate succinate (HPMCAS), hydroxypropyl methylcellulose phthalate (HP MCP), the methacrylic acid copolymers Eudragit L100-55 and Eudragit L30D-55, cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), carboxymethyl ethylcellulose (CMEC) and polyvinyl acetate phthalate (PVAP). The aqueous film was superior to the organic only with the latex systems based on the polyacrylate Eudragit, whereas almost double the film thicknesses were needed with HP MCAS, HP and the CAP-pseudolatex Aquateric.

Although the coatings made from fully neutralized CAP and CAT solutions prevented escape of the active ingredient when enteric integrity was tested in 0.1 N HCl, the film-coated tablets swelled markedly due to penetration of testing medium into the core. An acid-sensitive product such as pancreatin is damaged by the influx of hydrochloric acid, despite fulfilling the criteria for gastro-resistance according to the disintegration test [17,18].

With aqueous dispersions, the process conditions such as spraying rate, drying temperature, amount of drying air and spraying pressure must be carefully chosen because if, as a result of the process conditions, the product bed temperatures are too low, they will be insufficient to achieve the desired filming above the minimum film-forming temperature. On the other hand, excessively high product bed temperatures allow the dispersion agent to evaporate so rapidly that the film-former is spray dried. The dispersion medium water also has a plasticizing effect [19]. Unfavourable process conditions are often reflected by low coating yields.

3.2. Influence of the plasticizer and the polymer particle size

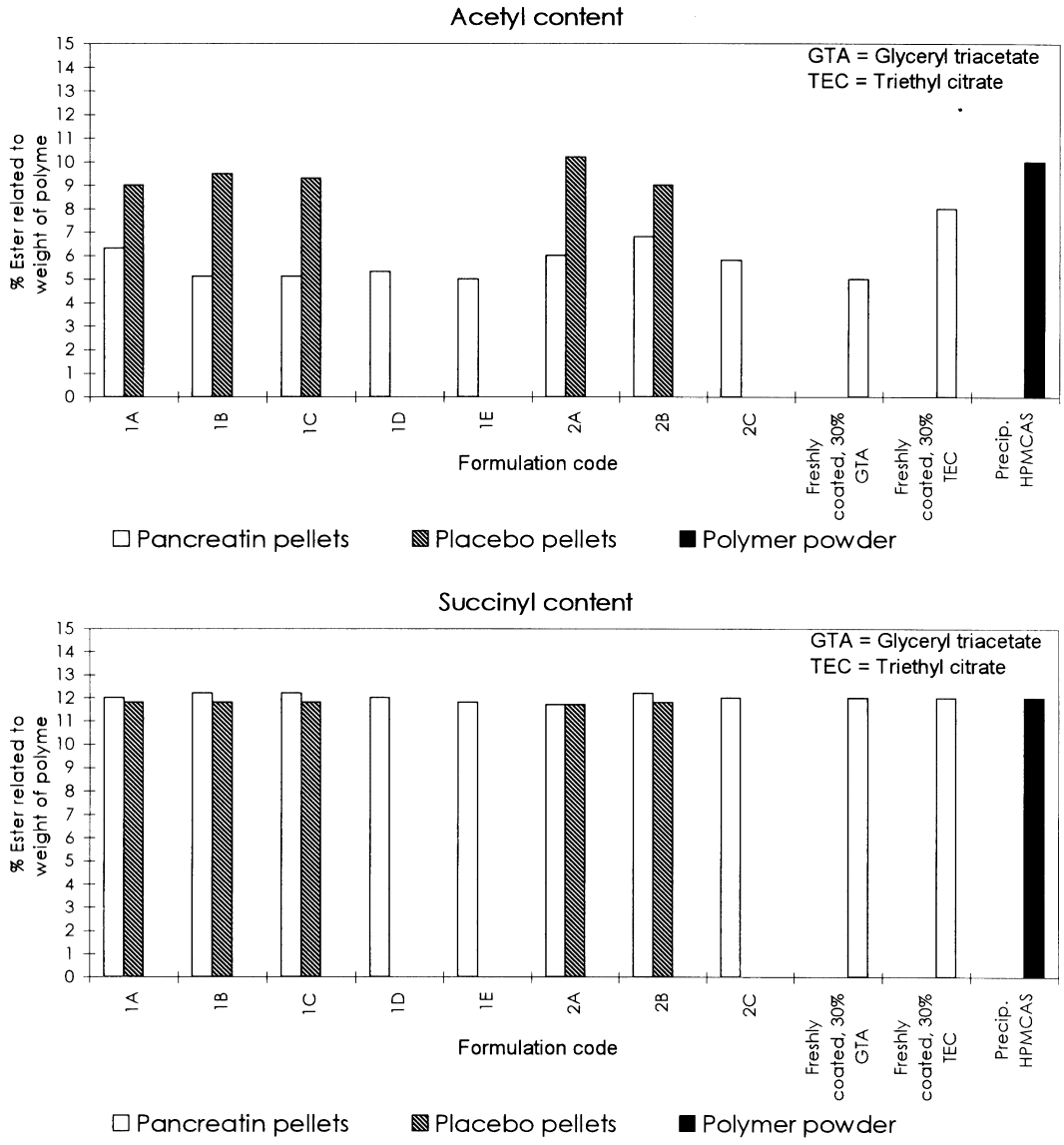
The plasticizer, which must be suitable for the polymer both in terms of nature and quantity, has a key role in aqueous dispersions [20–22]. Plasticizers generally need to be added to film-former dispersions in order to reduce the resistance of the film-former particles to deformation [23]. Plasticizers must be active and increase the mobility of the chain molecules, at least at the surface of the dispersed particles. The filming effect produced by the sliding network of polymer threads is facilitated by plasticizers or is made possible even at lower processing temperatures. Fig. 2 shows the surface of pancreatin pellets with an aqueous HP 55 coating containing differing proportions of the plasticizer triethyl citrate (TEC), ranging from 40 to 65% relative to the polymer. A 40% proportion of plasticizer merely produced a coating with a highly porous surface, whereas by increasing the proportion to 65%, the craters disappeared and a smooth film was formed.

Film formation from aqueous dispersions can be improved by reducing the size of the polymer particles [24]. Experiments with powdered HP 55 having a mean particle size of 10 mm produced gastro-resistant pancreatin pellets only if the amount of polymer was at least 33%, whereas after halving the particle size to 5 mm through more intensive micronization, the required 2 h resistance to gastric juice could be achieved with only 20% film-former.

The application of an undercoat, which smoothes the core

surface and reduces the removal of the 'plasticizer' water through absorption by the cores during the coating process, decreased the amount of gastro-resistant dispersion polymer required (Fig. 3).

Non-polymeric plasticizers such as the frequently used triethyl citrate (TEC) can show a certain degree of volatility in water vapor during aqueous coating [14,17]. Higher coating or drying temperatures promote such loss of plasticizer. For example, at an inlet air temperature of 35°C, only 20% TEC escaped during the coating process, at 65°C some 35% and after 48 h curing on racks at 60°C, the loss of plasticizer in the film coating was 65% (Fig. 4).



Formulation Code

1A 30% GTA, no undercoating

1B 30% GTA, 4% HPMC undercoating

1C 30% GTA, 4% povidone undercoating

1D 30% GTA, no undercoating

1E 30% GTA, no undercoating

2A 30% TEC, no undercoating

2B 30% TEC, 4% HPMC undercoating

2C 30% TEC, 4% povidone undercoating

Fig. 7. Acetyl and succinyl contents of aqueous HPMCAS-MF coatings after 28 months storage of coated pancreatin and placebo pellets at 26°C in closed packaging compared to freshly coated product or freshly precipitated film-former [17].

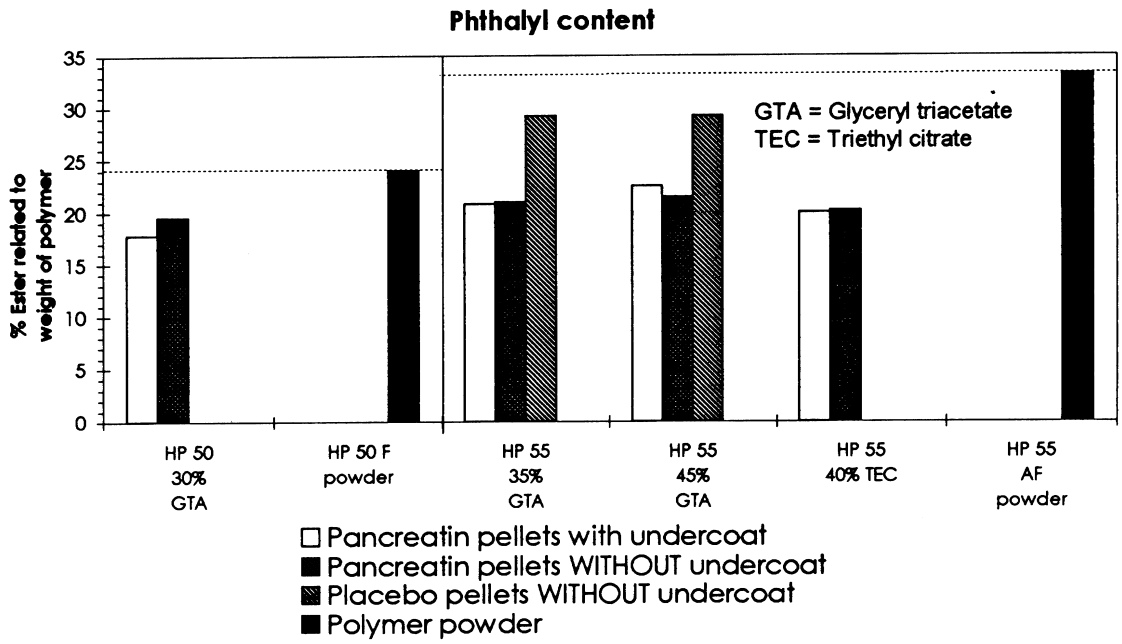
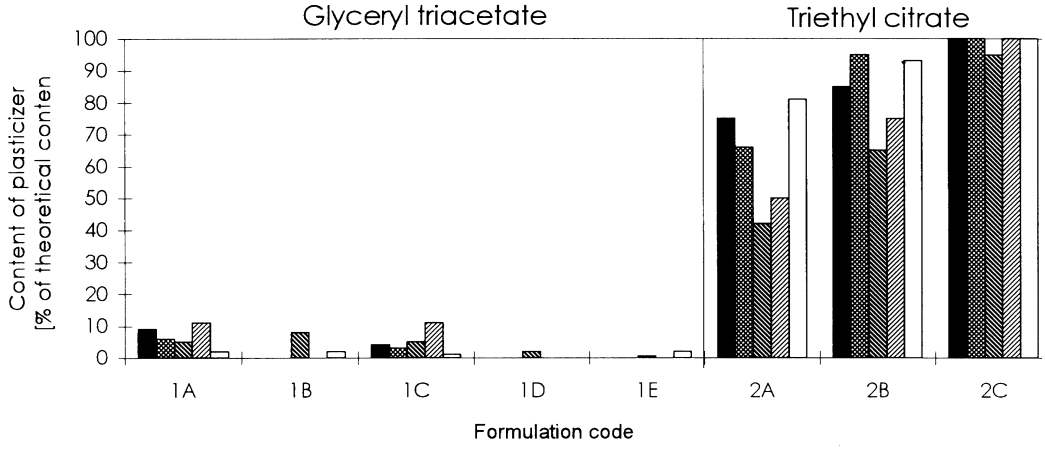


Fig. 8. Phthalyl content of aqueous HP coatings after 11 months storage of coated pancreatin and placebo pellets at 26°C in closed packaging in comparison with powdered film-former [17]. Original ester content in film-former HP 50 or HP 55.



Formulation Code

1A	30% GTA, no undercoating	**1E**	30% GTA, no undercoating
1B	30% GTA, 4% HPMC undercoating	**2A**	30% TEC, no undercoating
1C	30% GTA, 4% povidone undercoating	**2B**	30% TEC, 4% HPMC undercoating
1D	30% GTA, no undercoating	**2C**	30% TEC, 4% povidone undercoating

Fig. 9. Effects of coating composition, storage temperature, relative humidity and packaging on plasticizer content of pancreatin pellets coated with HPMCAS after 24 months storage under various conditions [17].

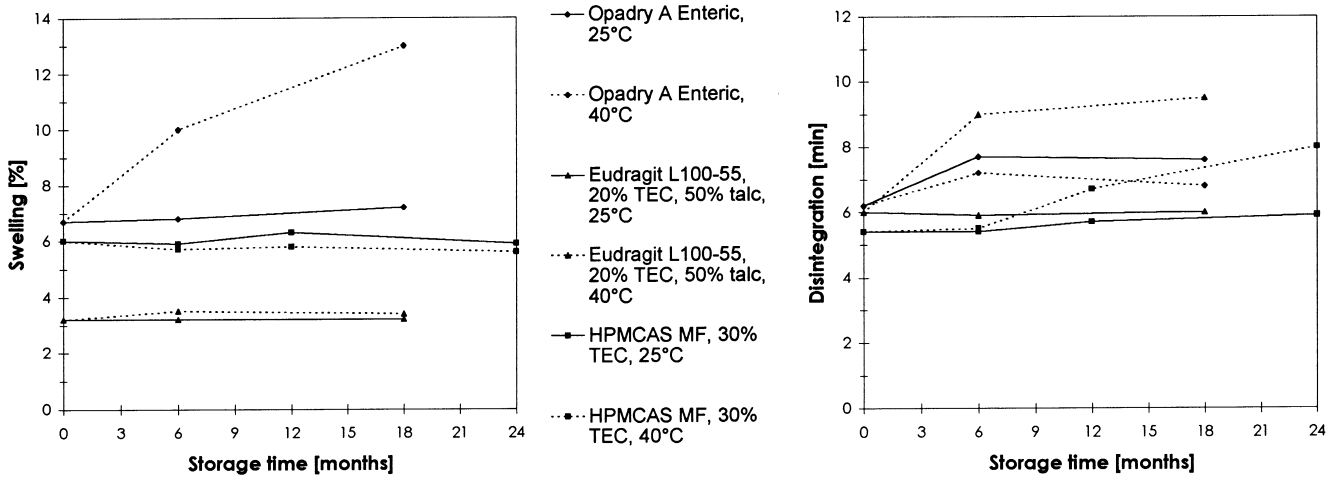


Fig. 10. Effects of temperature and duration of storage on the swelling and disintegration behavior of Eudragit L 100-55, HPMCAS-MF and Opadry coatings on vitamin B_2 tablets made from aqueous dispersions [15].

3.3. Stability problems encountered with aqueous coated pancreatin pellets

Hydrolytic decomposition reactions of active ingredients and excipients can be promoted by the inclusion of moisture during the coating process.

3.3.1. Stability of the pancreatin

Sensitive products such as pancreatic enzymes can be damaged by the simultaneous effects of moisture and heat. The lipase activity of pancreatin pellets remaining after fluidized bed coating from an aqueous dispersion of HPMCAS is compared with that of the same pellets after coating with an organic solution in Fig. 5. The aqueous coating technique, with a 13 to 23% loss of activity, was clearly inferior to the organic film coating where the average enzyme loss was only 5%. Separation of spraying and drying zones in the rotor fluidized bed apparatus RotoProzessor protected the product, since the enzymes pellets were kept suspended in the warm air for a shorter time than in a normal fluidized bed coater (Strea-1).

3.3.2. Stability of the film coating

Apart from loss of plasticizer and reduced protection against moisture, dispersion coatings are particularly likely to show a more porous film structure or cracks along remaining particle borders [25]. The release characteristics of the dosage form can be altered and sticking can occur along with a reduction in the functional properties of the film. Sticking can be avoided by applying an additional overcoat of water-soluble material such as HPMC or HPC [26].

Storage-induced changes in aqueous HPMCAS-MF coatings (MF, micronized film-formers) on pancreatin pellets are shown in Fig. 6. After 6 months in Climatic Zone I, the surface structure of the film remained highly porous,

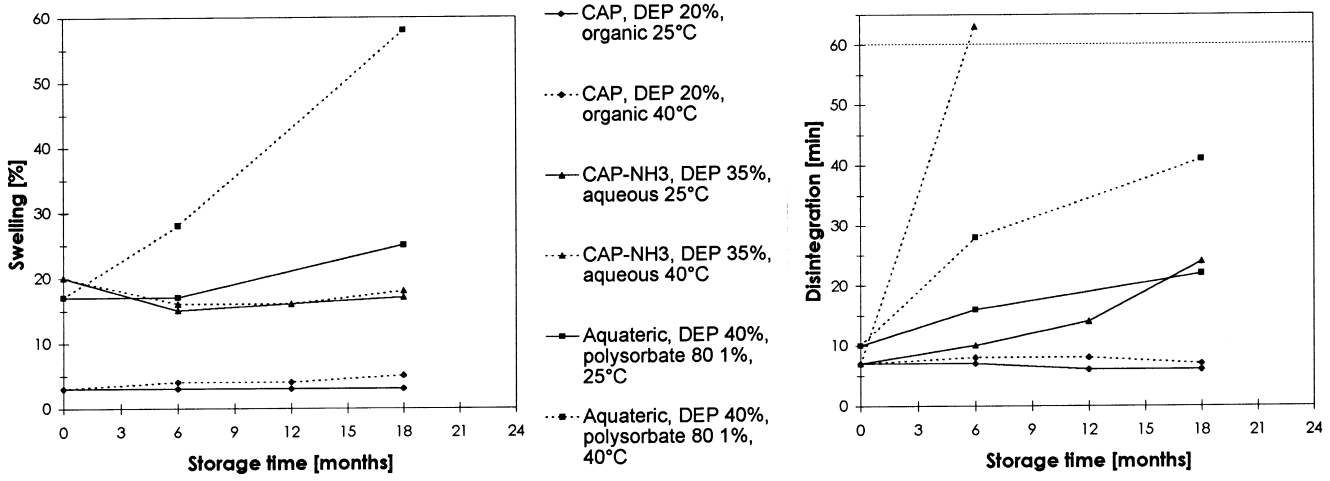


Fig. 11. Effects of temperature and duration of storage on the swelling and the disintegration behavior of aqueous CAP coatings on vitamin B_2 tablets prepared from organic and aqueous ammoniated solutions and from an aqueous dispersion [15].

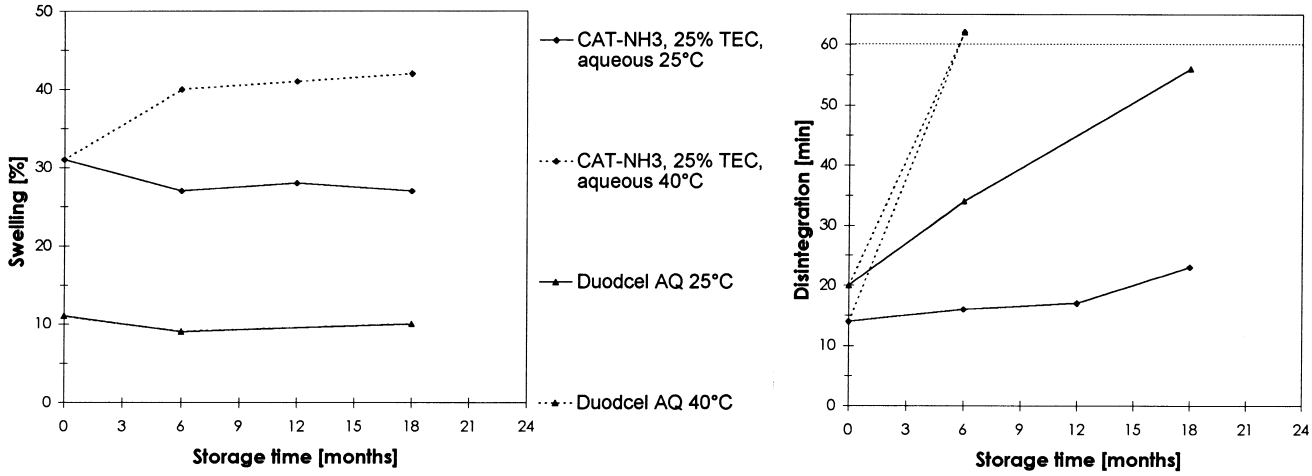


Fig. 12. Effects of temperature and duration of storage on the swelling and disintegration behavior of coatings of CAT from ammoniated aqueous solution and Duodcell AQ from an aqueous dispersion applied to vitamin B_2 tablets [15].

whereas after 3 months storage at the elevated temperature of 40°C, the originally discrete film-former particles had already fused together to a considerable degree. Moist storage at 40°C eventually led to a closure of all pores, associated with a sticking together of the pellets [17].

Film-formers and plasticizers of an ester structure can undergo hydrolysis during storage [8]. The gastro-resistant film-formers HPMCAS and HP possess varyingly sensitive ester components, especially when the ester-cleaving pancreatin is the core material. The acetyl functions of HPMCAS were already attacked during the aqueous coating of the pancreatin pellets, whereas the succinic acid ester groups responsible for the gastro-resistance properties of the polymer remained intact even after storage. In coated placebo pellets, the acetyl functions of the HPMCAS were stable (Fig. 7).

The hydrolysis-promoting effect of pancreatin on the film former HP was demonstrated by the comparison with coated placebo pellets. However, even without the enzymic effect about 1/3 of the phthalic acid ester groups responsible for gastro-resistance underwent cleavage after storage for 1 year (Fig. 8). This led to a release of active ingredient even at higher pH [17].

3.3.3. Volatility, migration and degradation of plasticizer

Losses through volatility or through migration into the core can occur when coatings containing non-polymer plasticizers are stored, as well as hydrolytic cleavage reactions [14]. The plasticizer glyceryl triacetate (GTA) is subject to very rapid cleavage, whilst triethyl citrate (TEC) is chemically more stable. However, the latter plasticizer undergoes considerable evaporation at higher storage temperatures and with less dense packaging materials such as plastic blisters.

As shown in Fig. 9, under the influence of pancreatic enzymes, the plasticizer glyceryl triacetate in HPMCAS-coated pancreatin pellets was subject to practically quanti-

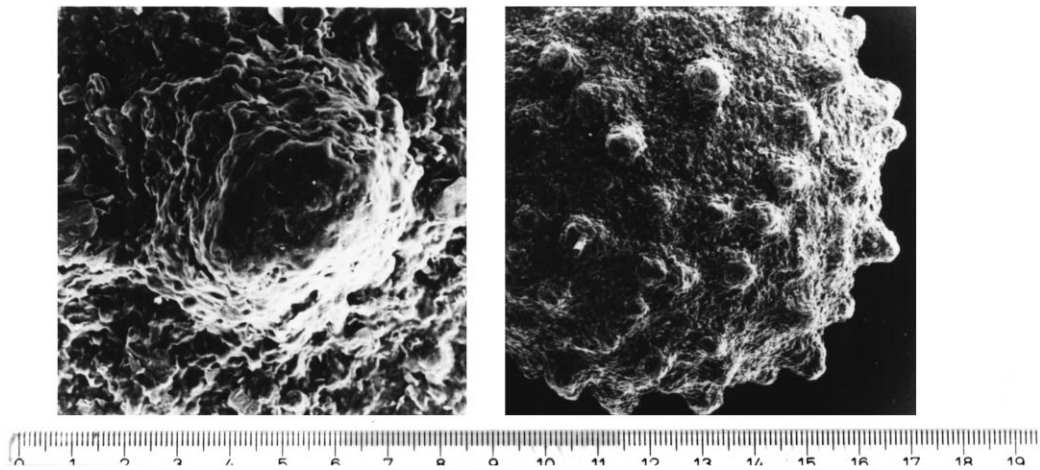


Fig. 13. HPMCAS-coated pancreatin pellets (30% glyceryl triacetate as plasticizer) with coagulate inclusions after 24 months storage at 26°C in tightly closed glass containers. Magnification: ×40 and ×250 [17].

tative cleavage and acetic acid, mono- and diacetate were found as degradation products. If triethyl citrate was used as plasticizer in films applied to pancreatin pellets, no degradation products were found, so that loss must have been exclusively due to evaporation. At a storage temperature of 26°C, far more triethyl citrate evaporated than at 21°C, especially in the packaging material PVC-PVDC blisters instead of screw-capped glass bottles.

3.4. Storage-induced changes in swelling behavior and disintegration time

Instability during storage may also lead to alterations in the properties of the film. Eudragit® L 100-55, Opadry® enteric (PVAP) and Aqoat® (HPMCAS) proved to be very stable gastro-resistant aqueous coatings that underwent little swelling during the test for gastro-resistance and showed virtually no changes in disintegration time with storage (Fig. 10).

In contrast, aqueous CAP coatings were less stable. Ammoniated aqueous films showed higher swelling rates in the test for gastro-resistance due to the hydrophilicity of the polymer salts. Especially at an elevated storage temperature of 40°C, the disintegration time of the coated tablets rose to >60 min after only 6 months due to hydrolysis of the phthalic ester groups and formation of insoluble cellulose acetate.

The coatings prepared from organic solutions were stable under the same conditions. Coatings made from the CAP-pseudolatex Aquateric showed marked swelling in the resistance test and an increase in disintegration time when stored at 40°C (Fig. 11). Probably, this can be attributed to late film formation, since film-coated tablets made from Aquateric® tended to stick together during storage.

Ammoniated aqueous CAT coatings behaved in the same way as neutralized CAP films (marked swelling, significant rise in disintegration time at 40°C), CAT being also susceptible to ester hydrolysis. Duodcell® films, i.e. an aqueous dispersion of micronized carboxymethyl ethylcellulose (CMEC), showed a rise in disintegration time even after only a few months storage at 20°C, possibly due to late film formation, since the polymer is chemically stable (Fig. 12).

During the production of coatings from dispersions of micronized film-formers, there is a risk of coagulation at elevated temperatures, for example in the drying zone of the coating apparatus, especially if the formulation contains sufficient plasticizer. If through coating not fused polymer particles sinter during storage, coagulate inclusions can become apparent as unevenness in the coating. This is how the spikes shown in Fig. 13 (that were identified by IR spectroscopy as film-formers) could have occurred in aged HPMCAS coatings [17].

These findings demonstrate that the switch from organic to aqueous coatings is also possible with water-insoluble film-formers such as gastro-resistant polymers, and the resulting coated dosage forms show good stability. However, not all coating systems are equally suitable for the particular case. For example, ammoniated aqueous coatings are problematic. With dispersions of water-insoluble film-formers, the degree of fusion of the film-former particles is particularly important, both during preparation and in stability testing.

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