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# Enteric coated hard gelatin capsules

Professor Karl THOMA and Karoline BECHTOLD

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## Summary

During the early stages of pharmaceutical development an enteric coated hard gelatin capsule is often the only possibility to administer an acid labile drug or to protect the stomach from a potentially irritant drug substance. These and other therapeutic applications of enteric coated pharmaceutical dosage forms have been reviewed. The properties of the various enteric film forming agents are described along with plasticizers and other excipients and formulations with each polymer system are suggested.

General difficulties of enteric coating dosage forms and those specific to hard gelatin capsules are discussed as well as aspects of product stability. The coating processes most commonly used are described.

Over 100 references have been sited.

## About the authors

Karl Thoma is professor of pharmaceutical technology at the University of Munich. He graduated as a pharmacist in 1955 and received his doctorate in pharmaceutical technology in 1959. After lecturing at the University of Munich he became professor of pharmaceutical technology in Frankfurt in 1967 and was director of the Institute of Pharmaceutical Technology from 1970 to 1980 before returning to Munich. He is a member of the German Pharmacopoeia Commission and chairman of its Pharmaceutical Technology Section and an alternate member of the European Pharmacopoeia Commission. He is a member of one of the Commission of Experts for the Registration of New Drugs at the German Department of Health and Chairman of the Scientific Council of the German Association of Pharmacists. His research interests are in the area of drug stability and new dosage form design and he is the author of about 350 articles in scientific journals and books.

Karoline Bechtold is research assistant in the department of Pharmaceutical Technology at the University of Munich. She graduated as a pharmacist in 1988 from the University of Munich and continued as assistant to Prof. Thoma. Her research activities at present are in the area of the development and stability of enteric coated dosage forms.

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## I. Therapeutic applications of enteric coated films

### Field of application of enteric coated dosage forms

Enteric coated dosage forms, such as coated tablets, sugar-coated tablets, soft and hard gelatin capsules, granulates or pellets, have their firm place in the medical arsenal (1a, 2). An investigation of 181 ready-to-use enteric coated medicaments revealed that this sample comprised about 59 % sugar-coated tablets (106 preparations), about 27 % film-coated tablets (49 preparations) and about 14 % soft and hard gelatin capsules (25 preparations) (1). However, this group of investigated preparations covered only some of the preparations on the German market.

The preparations most commonly provided with enteric coatings contain pancreatin and other proteolytic enzymes, diclofenac, cardiac glycosides, electrolyte preparations with sodium, potassium and magnesium salts as well as calcium, iron and manganese preparations. Bisacodyl preparations, preparations containing valproic acid as well as formulations with plant extracts or terpenes are also common.

Nowadays, enteric coatings are in particular used to:

- protect active substances destroyed by the acidic gastric juice,
- improve tolerability of medicaments irritating the stomach by only releasing them in the small intestine,

- making active substances available after a time delay (sustained release),
- achieving targeted release and concentration in the small intestine.

## Enteric coating to stabilise acid-sensitive medicaments

Medicaments which could be destroyed by gastric juice include pancreatin and pancreatic lipase, which decompose at pH values of 4 and under. In artificial gastric juice, lipase activity decreases to about 10 % of the initial value within 15 minutes at pH 3.5. The majority of formulations containing pancreatin or other digestive enzymes are therefore processed to make them resistant to gastric juice (3, 4, 7).

In the case of enzyme preparations in particular, gastric-juice resistance often has to be associated with rapid degradation in the small intestine. Since food constituents are mainly absorbed in the duodenum or in the upper region of the jejunum (5, 6), where their enzymatic splitting must already have commenced here after passage through the stomach. An enteric coated dosage form should therefore degrade as quickly as possible in the small intestine. This is noticeably below the upper limiting value of degradation of not more than 60 minutes given in DAB 9.

In the case of cardiac glycosides there have also been reports of acid-associated hydrolysis and reduction in the efficacy of digitoxin has also been claimed (8, 11). In this case some findings do, however, dispute whether enteric coatings improve efficacy (9). Apart from digitoxin and digoxin, the possibility of hydrolytic degradation has also been reported in particular in connection with strophanthin (9) and proscillaridin (10), whereas the corresponding methyl ethers such as meproscillaridin are thought to be more stable (11).

With regard to antibiotics, penicillin G is known to be unstable in the presence of gastric acid (15). Nowadays, enteric coated penicillin formulations have, however, been superseded by the synthesis of stable penicillin derivatives.

The activity of antibiotic formulations containing erythromycin is significantly improved by enteric coating (12, 13, 14). The hydrochloric acid in the stomach transforms erythromycin as well as erythromycin stearate into the hydrochloride, which is 30 to 70 % less active (14). In this case erythromycin estolate, which is stable, could be used as an alternative to enteric coated formulations.

To improve stability, enteric coating is also recommended for bacterial preparations given when the intestinal flora is impaired (17). Other examples of medicinal substances which need to be protected against stomach acid are diethyl dithiocarbamate (18), the anti-tumour preparation N-ethylcarbamidomethylisoleucine (19) as well as tibenzonium iodide (16), an antimicrobial benzodiazepine derivative.

## Enteric coating to improve tolerance

Some active substances cause irritation of the gastric mucosa or are not tolerated for other reasons following their release in the stomach. Gastric disorders have, for example, been reported in connection with administration of diclofenac, phenylbutazone, oxyphenbutazone, salicylates, iron salts, bisacodyl, valproic acid, indomethacin, potassium chloride, tolbutamide, reserpine, nitrofurazone, anticoagulants, levodopa, ethionamide, thiazides and diphenhydramine (28, 30, 54-74, 76, 77).

Irritation of the gastric mucosa and gastrointestinal bleeding may occur after the peroral administration of certain analgesics. Disturbances of this type are, however, in part also connected with an influence of prostaglandin synthesis related to a systemic effect. Although it has been shown, for example in the case of acetylsalicylic acid and its derivatives, that side effects (20, 21, 24) are due to prostaglandin synthesis inhibition (23), some findings suggest that gastric lesions are markedly reduced when enteric coated dosage forms are given (22, 26).

Similarly, there is conflicting evidence in the case of phenylbutazone and its derivatives as to whether or not enteric coatings improve tolerance. Recent investigations suggest, however, that local tolerance of enteric coated phenylbutazone preparations is markedly superior to that of formulations which are not enteric coated (27, 28). A study involving 103 patients reacting to long-term phenylbutazone therapy with gastrointestinal disorders also yielded positive findings (28). It showed that these patients tolerated an enteric coated phenylbutazone preparation for six years without problems.

Enteric coating is also recommended for substances such as diclofenac, indomethacin, flufenamic acid and azapropazone, because of gastric intolerance (23, 25). According to the literature, enteric coated naproxen is not only better tolerated, but also displays superior biological availability (29).

Gastrointestinal disturbances, nausea and vomiting which may be associated with the ingestion of

iron salts (35), magnesium salts (34), cobalt chloride (32), sodium fluoride (33) and cobalt chloride (31) also often make enteric coatings desirable for medicaments containing them. In the case of potassium chloride, however, reports of irritation in the small intestine are more frequent in this connection (36).

In the case of theophylline and its derivatives, enteric coated formulations are believed to achieve a marked reduction in irritation (37). Very pronounced gastric side effects occur when valproic acid is ingested. Because of its liquid consistency, this anticonvulsant also presents pharmaceutical formulation problems and is generally processed in the form of enteric coated soft gelatin capsules (30). In the case of chloroquine phosphate (38), bisacodyl (41) and levodopa (39, 40) the desire, not only to prevent possible irritation, but also to achieve targeted release of the active substance or delayed activity, may necessitate enteric coating.

### Enteric coating to delay onset of action

To a certain extent, enteric coated formulations postpone onset of action via targeted release in the intestine (42, 43, 50, 52). Prolongation of effect is, for example, reported to occur with use of enteric coated and non-enteric coated granulates of antibiotics such as amoxycillin or cephalexin (44, 45). Similarly, in the case of sugar-coated preparations, the active substance content in a core with an enteric coating can be released about two to three hours later than the initial dosage coated thereon (75).

In some cases, delaying the onset of action is believed to improve the biological availability of medicaments. A longer duration of action and higher blood level values have, for example, been reported for enteric coated quinidine (48), theophylline (38), ephedrine (51), sodium fluoride (53) and enteric coated ergot alkaloids (49).

### Enteric coating for targeted release in the small intestine

Targeted release in the small intestine may be used to achieve higher local active substance concentrations. This may be desirable for laxatives containing bisacodyl and for sulphonamides used to treat intestinal disorders (46). It d also described for peppermint oil and terpene derivatives used in the treatment of colitis (47). In the case of vermicides, an enteric coating achieves targeted release of the active substance in the small intestine (41).

### Possibilities of enteric coated capsules in the product development phase

During the early stages of development of a new chemical entity availability of the active substance in sufficient quantities to develop a tablet or pellet can be a problem. In such cases on enteric coated capsule is often the only possibility to administer an acid labile drug.

Enteric coatings are thus used for numerous medicaments.

Critical appraisal is needed in those cases in which there are conflicting views on their use.

In principle and provided they display adequate resistance and disintegration properties, are pharmacokinetically appropriate and meet stability requirements, coatings of this type display important potential in:

- ensuring biological availability,
- controlling the effects of medicaments and,
- avoiding side effects.

## II. Film components

### a. General composition of film coating formulations*

Generally speaking, formulations for enteric film coating contain the following main components:

- enteric film formers,
- plasticizers,
- anti-adhesion agents,
- colourants or pigments,
- solubilizers or dispersion agents and
- other additives.

To these may be added viscosity-enhancing suspension stabilizers designed to retard the sedimentation of undissolved excipients or dispersed film formers.

Other additives that may be mentioned include surfactants used as wetting agents or to emulsify lipophilic plasticizers in aqueous formulations. Defoaming agents and hydrophobic substances are sometimes also added to formulations.

Whereas the majority of enteric coated films have hitherto been applied as solutions in organic solvents, there is a growing trend today to use neutralized aqueous solutions or aqueous polymer dispersions. On the one hand, the aqueous base relieves

(*) Data from the literature and the quoted film formulations are given without guarantee of correctness.

the user of certain disadvantages and problems of organic formulations such as (82):

- costs of exhaust air disposal or recovery for environmental protection reasons,
- removal of solvent residues in the film-coated product,
- need for explosion protection,
- protection of the workforce against the toxic effects of solvents,
- high cost of solvents,
- storage of substantial amounts of inflammable solvents.

Additional regulations regarding organic solvents cannot be ruled out.

Aqueous dispersions have the advantage that they can be sprayed in a higher percentage since viscosity is virtually independent of molecular weight. The greater heat of evaporation of water as compared to organic solvents can therefore be largely compensated.

On the other hand, transfer to aqueous systems raises numerous individual questions requiring clarification, and difficulties have to be solved when developing a medicinal form. In many cases, aqueous dispersions or solutions may present instability problems. Reference is made in this connection to the remarks made under point 4.3.

## b. Survey of enteric film formers

The disadvantage of the former practice of hardening hard gelatin capsules using formaldehyde, which brought about cross-linking of the gelatin and reduced gastric-juice solubility, is that post-hardening processes take place during storage which can cause the capsules to become increasingly insoluble, in intestinal juice too, over the entire physiological pH range (82, 83, 95, 92, 93).

Use of the following coating materials has largely been discontinued:

- esters of organic acids, fats, waxes, fatty acids, resins such as salol, colophonium, carnauba wax, carnauba wax mixed with n-butyl stearate, beeswax, acetylated fatty acid glycerides; these substances are decomposed by the digestive enzymes and the rise in pH in the intestine (88, 92, 93),

- proteins such as keratin, zein and gluten; these are resistant to pepsin in acid gastric juice, decomposition occurs in the intestine through the action of proteases (92, 93).

The quality of natural substances such as shellac is liable to vary (81, 107).

Shellac is also used mixed with other enteric coating polymers and to isolate sensitive cores (107).

The film formers mainly in use today are polymers with carboxyl groups, which are water insoluble in the protonized state and pass into solution in the weakly acid to neutral range between pH 5 and 6,5 through formation of salts.

Manufacturers of film polymers offer products displaying a variety of release profiles since the release characteristics can be directed in certain ranges through the number of carboxyl groups and the nature of the acids in the molecule (99). It is therefore possible to choose a lower or higher dissolution pH as required to influence the onset of degradation and release in the small intestine.

Film formers may be subdivided into:

- polymethacrylates:
  – methacrylic acid ethacrylate poly ($MA_1$ - $EA_1$),
  – methacrylic acid methyl methacrylate poly ($MA_1$ - $IMMA_1$) and poly ($MA_1$ - $MMA_2$),
- cellulose-based polymers:
  – cellulose acetate phthalate CAP,
  – cellulose acetate trimellitate CAT,
  – cellulose acetate succinate CAS,
  – hydroxypropylmethylcellulose phthalate HPMCP,
  – hydroxypropylmethylcellulose acetate succinate HPMCAS,
- polyvinyl derivatives:
  – polyvinyl acetate phthalate PVAP,
- other copolymers:
  – half esters of the copolymerisate of styrene and maleic acid,
  – half esters of the copolymerisate of vinyl ether and maleic acid,
  – copolymerisate of vinyl acetate and crotonic acid.

Their acid groups are either firm constituents of the molecular skeleton or are secondarily introduced through esterification of alcohol groups with di- and poly-basic acids such as phthalic acid, trimellitic acid or succinic acid. The principle of manufacture therefore has consequences for the stability of the resultant films (sensitivity to hydrolysis).

## c. Characterization of enteric film formers

### Polymethacrylate

Trade names:

– for aqueous film coating
  Eudragit L 30 D (30 % aqueous dispersion),

– for aqueous and organic film coating
  Eudragit L 100-55 (redispersable powder),
  Eudragit L 100 and S 100 (dry powder),
– for organic film coating
  Eudragit L 12.5 and S 12.5 (12.5 % solutions in isopropanol),
  Eudragit L 12.5 P and S 12.5 P (12.5 % solutions in isopropanol with 1.25 % dibutyl phthalate as plasticizer).

Manufacturer: Röhm Pharma, Weiterstadt, Germany.
Solubility: Eudragit L from pH 6.0,
Eudragit S from pH 7.0,
Eudragit L 30 D / L 100-55 from pH 5.5.

Eudragit L and S are copolymerisates based on methacrylic acid and methyl methacrylate. The ratio of the free carboxyl groups to the esters is about 1 : 1 for Eudragit L and ca. 1:2 for Eudragit S (101), resulting in enteric coatings with varying dissolution pH values (L = easily soluble, S = sparingly soluble). Preferred solvents are isopropanol, acetone and ethanol, as well as mixtures thereof. Delivery is either in isopropanolic solution with or without added plasticizers or as solvent-free powder under the trade name Eudragit L 100 or S 100 respectively. The latter product types can be dissolved in organic solvents and mixtures or redispersed in water.

Eudragit L 30 D and L 10-055: acrylic resins for use in aqueous coating formulations consisting of a copolymerisate of methacrylic acid and ethyl acrylate, the carboxyl ester group ratio being 1 : 1. Eudragit L 10-055 is only the lyophilized adjunct to Eudragit L 30 D dispersion (100). On partial neutralization with sodium hydroxide solution or organic bases the powder can be reprocessed into a redispersion latex (degree of neutralization 3-6 %). In contrast, Eudragit L 30 D only needs to be diluted to appropriate concentrations.

Since aqueous dispersions of Eudragit L 100 or S 100 have high film-forming temperatures (> 85°C), mixing with the softer Eudragit L 30 D or L 100-55 makes it possible to reduce the film-forming temperature to < 40°C, thus reaching the conventional processing range (100, 103). Mixing makes it possible to achieve fine differentiation in the active substance release profile (pH 5.5-7.0), further modulations in release profile can also be achieved by mixing in Eudragit NE 30 D (polyethylacrylate- methylmethacrylate) (99, 103).

Organic Eudragit lacquers are often applied as 6 to 10 % spray solutions (101), 10 to 20 % plasticizer being recommended. Suitable plasticizers are, for example, triacetin (91), PEG 6000 (81), dibutyl phthalate (85) and diethyl phthalate (94).

Aqueous Eudragit dispersions are processed in more concentrated form, generally between 15 and 30 % (101), although the upper concentration range tends to be used for porous dosage forms. It should be noted with regard to the spectrum of excipients that there is incompatibility between Eudragit L 30 D / L 100-55 and magnesium stearate (coagulation). The added plasticizer in these MA-EA dispersions should be at least 10 % based on the dry polymer substance content and may if necessary, be raised to 20-25 % without impairing the specific solubility characteristics of the film (101). It is possible to use various polyethylene glycols, citric acid esters (Citroflex®), triacetin, dibutyl phthalate, 1,2-propylene glycol (101) and clibutyl sebacate (84). Eudragit acrylic resins have such a high pigment binding capacity that twice to three times the amount of pigments or other excipients can be added relative to the dry polymer substance (101).

Reference: FDA Drug Master File for Eudragit, USP XXII / NF XVII "Methacrylic Acid Copolymer, Type A, B, C" ;

**Cellulose derivatives**
**Cellulose acetate phthalate**

– for aqueous film coating:
  Aquateric (FMC Corporation, USA),
  CAP as ammonium salt (Eastman Kodak, USA),
– for organic film coating
  CAP (Eastman Kodak, USA).

Solubility: above pH 6.2-6.5.

Aquateric: a dry powder that must be dispersed in water before use (redispersion latex). Other constituents apart from 63-70 % cellulose acetate phthalate (98) are polyoxypropylene-polyoxyethylene block copolymer and acetylated monoglycerides intended to improve the physical stability and formulation of the product and necessary for technical manufacturing reasons.

Suitable plasticizers: diethyl phthalate (98), triacetin (81). Triethyl citrate, on the other hand, is incompatible with Aquateric (82).

CAP: suitable organic solvents are acetone (85, 91), mixtures of acetone and ethanol (81, 83), of isopropanol or ethanol and methylene chloride, or ethyl acetate (81, 93, 95), of acetone and methylene chloride (90), of isopropanol methylene chloride water (81).

Suitable plasticizers: triacetin 20-30 % related to the polymer (81, 91), diethyl phthalate 25-60 % (111, 85), propylene glycol 133 % (90).

Eastman Kodak also offers a possibility of using CAP as a neutralized aqueous solution. The polymer powder is not marketed in micronized form, with the result that it is not possible to prepare a dispersion in water by analogy with Aqoat® (HPMCAS). Instead, CAP is dissolved in a dilute ammonia solution, the time to produce the clear spray solution depending on the amount of neutralization agent, excess ammonia accelerating the dissolution process. A disadvantage of this form of enteric film coating is the presence of ammonium salts in the dry film, causing the coat to be highly hydrophilized. In addition, the unpleasant smell of ammonia causes problems during formulation.

Reference: DAB 9, USP XXII-NF XVII, Drug Master File No. 8 (105).

**Cellullose acetate trimellitate**

– for organic and ammoniacal-aqueous film coating: CAT (Eastman Koeak, USA).

Solubility: above pH 5.2.

Since CAT already begins to pass into solution at ph 5.2, the polymer is a necessary addition to CAP. What is more, the two film formers can be mixed in any ratio, making it possible to achieve a release profile between CAT and CAP.

Solvent: e.g. acetone-water, methylene chlorideethanol, acetone -ethanol, ethyl acetate-ethanol.

Plasticizers: triacetin, acetylated fatty acid glycerides, diethyl phthalate.

Reference: Drug Master File No. 6703, USFDA (105).

**Hydroxypropyimethylcellulose phthalate**

– for organic film coating
  HP 50, HP 55, HP 55 S (Shin Etsu, Japan),
– for aqueous film coating
  HP 50 F and HP 55 F S (Shin Etsu, Japan, micronized powder),
– HPMCP 50 and HPMCP 55 made by Eastman Kodak may be applied as aqueous solution, both in organic solution and neutralized with ammonia to yield an aqueous solution.

Solubility: HPMCP 50 above pH 5.0,
HPMCP 55 above pH 5.5.

The two types of film former have different substitution patterns and hence different solubility profiles. HP-50 has a lower proportion of phthalic acid groups (21-27 %) than HP-55 (27-35 %) and therefore passes into solution at lower pH values than its analog.

Suitable plasticizers: PEG 400 to 6000 (80, 86), films containing the higher molecular weight PEG being mechanically more stable and less sticky, triacetin (81).

Solvents: e.g. ethanol-water (79), acetone-water, acetone- isopropanol or ethanol (86, 81), ethyl acetate-ethanol, methylene chloride-ethanol (81), isopropanol-ethylene glycol monoethyl ether-water (81).

Reference DAB 9, USP XXII-NF X11 type 220824 and 200731 (105).

**Hydroxypropyimethylcellulose acetate succinate**

Aqoat LF, MF, HF (Shin Etsu, Japan), micronized powder specially for the aqueous film coating using dispersions.

Solubility: HPMCAS LF above pH 5.0,
HPMCAS MF above pH 5.5,
HPMCAS HF above pH 7.0.

The polymer is supplied in three types in each case with a different release profile determined by different proportions of succinic acid,

Suitable plasticizers: triethyl citrate, triacetin.

Reference: Drug Master File No. 7507 (106).

**Carboxymethylethyl cellulose**

Duodcell (Freund ind. Co. Ltd.)
Solubility: above pH 5.0.

Carboxymethylethyl cellulose is manufactured by ethylation of carboxymethyl cellulose and, in contrast to the cellulose derivatives described above, the hydroxyl groups of which have been partially reacted with di- or poly-basic acids, contain no ester groups, but only ether groups. The mode of manufacture is intended to ensure an absence of sensitivity to hydrolysis and special storage stability (110):

CMEC may be dissolved to about 8 % in 70 % propanol, ethanol-water mixtures, methylene chlorideethanol and processed to ca. 8-12 % in water as redispersible powder (8 1, 110).

Suitable plasticizers for organic or organica-queous solutions are myvacet 9-40, silicone oil, triacetin, diethyl phthalate, triethyl citrate and acety[tributyi citrate; glycerin monocaprylate being used for aqueous dispersions (Imwitor 908 R) (110),

Reference: Standards for ingredients of drugs not in the Japanese Pharmacopeia (110).

**Polyvinyl derivatives**
**Polyvinyl acetate phthalate**

Coateric (Colorcon, UK).
Opadry (Aqueous) Enteric (Colorcon, UK).
Solubility: > pH 5.0.

This enteric coated film former is characterized by a low dissolution pH of 5.0.

Suitable plasticizers for PVAP are diethyl phthalate, triethyl citrate (82), acetyltriethyl citrate, triacetin, PEG 400.

Suitable solvents are ethanolacetone-water 21:12 (83), methanol, methanolmethylene chloride mixtures.

The dry commercial product Coateric is a film concentrate containing a suitable plasticizer in addition to the film former PVAP.

Opadry (Aqueous) Enteric contains all formulation constituents already premixed: film formers, plasticizers, anti-adhesion agents, pigments. The spray formulation no longer needs to be reconstituted by adding water or solvent, a little ammonia solution being added to aqueous dispersions to achieve partial neutralization. 15 parts by weight of Opadry are recommended for aqueous systems; 5 parts by weight for organic systems.

Reference: USP XXII / NF XVII.

**Other copolymers**

Coating CE 5142 (BASF AG, Ludwigshafen)

The copolymerisate of vinyl acetate and crotonic acid is converted into the salt with ammonia and is applied as an aqueous solution (108). Since the hydrophilized ammonium salts do not decompose under the conditions of spray application and drying, and the added amounts of ammonia are removed, the film has a marked tendency to swelling and softening, making it necessary to apply very high minimum thicknesses (107).

As far as we know, the film polymer is no longer commercially available.

## d. Plasticizers

Plasticizers are generally liquids or solids with a high boiling point which are intended to distribute themselves evenly in film polymers and improve their mechanical properties through interaction with the polymer film.

By using the appropriate plasticizer it is possible to reduce the tendency of a film to become brittle and to increase its resilience. Spray formulations containing plasticizers often spread better over the surface of the material and in the case of aqueous dispersions, addition of a plasticizer is generally needed to encourage film formation by means of thermosetting or coalescence. Plasticizers increase the motility of the polymer chains by interposing themselves between the molecule chains and thus restricting the ability of the film-forming chains to interact or bringing about conformative changes. A dynamic equilibrium is assumed (81) to develop between plasticizer and polymer segments. Use of a plasticizer reduces the glass transition temperature $T_g$.

Because of its consistency, a coated gelatin capsule is more susceptible to deformation, for example when being removed from a blister pack, and slightly more plasticizer may be needed to prevent damage to the film.

Plasticizers that have been named are (104):

– alkyl esters of citric, tartaric and sebacic acids; examples: diethyl sebacate, triethyl citrate, tributyl citrate, acetyitriethyl citrate, acetyltributyl citrate, dibutyl tartrate,
– esters of phthalic acid, such as dimethyl phthalate, diethyl phthalate, clibutyl phthalate, dioctyl phthalate, ethylphthaloyl- and butylphthaloyl ethyl glycolate,
– glycerol esters such as castor oil, sesame oil, acetylated fatty acid glycerides, glycerol diacetate, glycerol triacetate,
– higher alcohols such as glycerol, 1,2-propylene glycol,
– polyethers such as polyethylene glycols and polyoxyethyiene-polyoxypropylene block copolymers; PEG also enhances gloss effects,
– surfactants such as PEG-400 stearate, PEG sorbitane monooleate, sorbitane monooleate.

## e. Anti-adhesion agents, pigments, colourants

Adhesion of coating substances during film coating gives rise to unwanted aggregates. In addition, the freshly applied coats may be damaged in the attempt to separate the adhered parts. This effect may be counteracted by anti-adhesion additives in

the formulation or by applying the substances directly into the coating chamber. Useful separating agents include talcum, magnesium stearate, Syloid® (micronized amorphous silicic acid), Aerosil® and kaolin.

Film coatings can be coloured with titanium dioxide and pigments (foodstuff colouring lakes, iron oxide pigments). Undissolved excipients should be finely distributed in appropriate dispersion agents separately from the film formers, preferably using a ball mill, a toothed colloid mill or an Ultraturrax machine and only subsequently mixed with the remaining constituents. When adding finely distributed pigments it is desirable to add additional nonionic emulsifiers, stabilizers, wetting agents such as PVP, Tween 60/80 and PEG, to the pigment suspensions (101). Spray suspensions generally need to be stirred during the spray application. Many instructions recommend use of the smallest possible pigment particle sizes (< 15 µm) to obtain smooth films. Care must be taken when adding pigments to ensure that the upper limit for the particular film is not exceeded since the films increasingly lose their compactness and resilience beyond this value.

In the case of capsules, anti-adhesion agents or added pigments may cause difficulties since the opaque coatings formed cause the originally often brightly coloured and glossy gelatin capsules to become matt. It is therefore advisable either to work without adding insoluble substances or else to select pastel coloured hard gelatin capsules from the outset.

### f. Other additives

Since aqueous dispersions can coagulate as a reaction to foaming, foam can form in bubbles in the finished film and pronounced foaming can impair processing, it is advisable, when using large batches, to add an antifoaming agent, e.g. various silicon emulsions or sorbitan sesquioleate (109). To prevent suspended pigments or polymer particles seclimenting too quickly in the spray formulation it is possible to use suspension stabilizers such as PVP (in the form of Kollidon 25). Emulsifiers or wetting agents such as polyethylene glycol sorbitan fatty acid ester are added to formulations to moisten pigments or to distribute fat soluble substances (plasticizers, silicon oils) in aqueous spray formulations.

## III. Formulations for the enteric coating of hard gelatin capsules

The amount of polymer needed must be calculated before starting the film coating process. In the case of hard gelatin capsules, the surface area of the product to be coated is calculated (82, 101) and the amount of coating required is then given in mg of dry polymer substance per $cm^2$ . The surface may either be calculated using the formula $A = \pi \times d \times h$ ($mm^2$) or any of the available tables (84, 101):

| Capsule size | 5 | 4 | 3 | 2 | 1 | 0 | 00 | 000 |
|---|---|---|---|---|---|---|---|---|
| Surface area $mm^2$ | 175 | 235 | 290 | 350 | 410 | 500 | 616 | 800 |

There are five basic types of application system, each of which has quite specific properties.

The film can be applied:
- as an organic solution,
- as an aqueous-organic coating emulsion,
- as an aqueous alcoholic coating solution,
- as an aqueous dispersion,
- as a neutralized aqueous solution.

In the case of neutralized aqueous solutions, the acids are only released from the salts of the film polymers under the influence of the gastric acid.

Formulations for the film coating of hard gelatin capsules quoted in the literature are set out below to provide a summary of the practical application of the film formers presented. These formulations should only be regarded as indications and should be adapted to the appropriate requirements and modified to suit the product and process in each individual case.

### Eudragit films

*a. Organic solution of Eudragit L 100 (8 1)*

| Constituents | % parts by weight in finished formulation |
|---|---|
| Eudragit L 100 | 5.0 |
| Polyethylene glycol 6000 (14 % based on the film former) | 0.7 |
| Talcum | 6.0 |
| Pigments | 3.3 |
| Isopropanol | 41.0 |
| Acetone | 41.0 |
| Water | 3.0 |

Solid content of spray suspension: 15,0 %
Content of dry polymer substance: 5.0 %
Coating of dry polymer substance: 2-4 $mg/cm^2$

*b. Aqueous dispersion of Eudragit L 30 D (78)*

| Constituents | % parts by weight in finished formulation |
|---|---|
| Eudragit L 30 D | 54.85 |
| Triethyl citrate (20 % based on the film former) | 3.30 |
| Tween 80 as 33 % solution (i.e. 0.24 % surfactant in the formulation) | 0.72 |
| Water | 41.13 |
| Solid content of spray suspension: 20.0 % | |
| Content of dry polymer substance: 16.5 % | |
| Coating of dry polymer substance: 10.0 mg/cm² or 9.1 % | |
| Total dry substance coating: 12.1 mg/cm² or 11.1 % | |
| Coating machine: coating drum 35 em cliarn. with air atomization (1 mm bore) | |
| Machine loading: 1.5 kg size 0 capsules | |
| Drying temperature: 45°C | |
| Product temperature: 27°C | |
| Spraying pressure: 0.8 bar | |
| Srapying rate: 4.32 g/min/kg | |
| Spraying time: 128 min | |

The already precoated capsules were sprayed with this dispersion. The precoat was composed of 46.51 parts Eudragit L 30 D, 4.65 parts glycerol (33 % related to the DPS), 4.65 parts Tween 80 (as 33 % solution, i.e. the formulation contains 1.40 % surfactant) and 44.19 parts water. A precoat was needed to improve adhesion of the film to the smooth surface of the capsule. 0.22 mg/cm² or 0.20 % polymer or 0.32 mg/cm² or 0.29 % solid substance was applied. Alternatively it is possible to use an HPC precoat (78), applied as a 5 % solution to obtain a coating of 4.0 to 6.0 mg dry polymer substance per cm² (84).

*c. Aqueous dispersion of Eudragit L 100-55 (81)*

| Constituents | % parts by weight in finished formulation |
|---|---|
| Eudragit L 100-55 | 12.5 |
| PEG 6000 | 1.0 |
| Triethyl citrate (17.6 % based on the film former) | 1.2 |
| Talcum | 3.1 |
| Pigments | 2.1 |
| Water | 79.9 |
| NaOH | 0.2 |
| Solid content of spray suspension: 20.1 % | |
| Content of dry polymer substance: 12.5 % | |
| Coating of dry polymer substance: 3-5 mg/cm² | |

## Celluloseacetate phthalate films

*a. Organic CAP formulation (111)*

| Constituents | % parts by weight in finished formulation |
|---|---|
| Cellulose acetate phthalate | 5.56 |
| Diethyl phthalate (60 % based on the film former) | 3.34 |
| Isopropanol | 22.78 |
| Methylene chloride | 68.32 |
| Solid content of spray suspension: 8.9 % | |
| Content of dry polymer substance: 5.56 % | |
| Amount applied: 32.5 mg film per capsule | |
| Coating machine: coating pan | |
| Product: size 2 capsules | |

Using acetone as solvent, Jones (85) obtained capsule coatings of even smoothness. Application of 4-6 mg/cm² CAP, corresponding to 25 to 35 jum film thickness, a 5 % solution with 1.25 % diethyl phthalate as plasticizer produced an enteric coating of uniform appearance.

*b. Aqueous formulation of Aquateric (98)*

| Constituents | % parts by weight in finished formulation |
|---|---|
| Aquateric | 10.66 |
| Diethyl phthalate | 3.73 |
| Tween 80 | 0,32 |
| Water | 85.29 |
| Solid content of spray suspension: 14.71 % | |
| Amount applied: 5.75 to 15 mg/cm², depending on filler | |
| Coating machine: fluidized air bed | |
| Spray pressure: 1 bar | |
| Drying temperature: 40°C | |
| Coating speed: 3.5 ml/min | |

A precoat of 7.2 parts Eudragit RS 100 and 0.8 parts dibutyl phthalate in methanol (0.4 mg/cm²) was needed to obtain gastric-juice resistance for hard gelatin capsules filled with sodium salicylate since this active substance adjusts to a pH of 6 in the diffusion layer and thus causes partial solubility of the acid polymer.

## Carboxymethylethyl cellulose films

*Aqueous formulation of Duodcell (81)*

| Constituents | % parts by weight in finished formulation |
|---|---|
| Duodcell | 8.0 |
| Trisodium citrate | 0.70 |
| Tween 80 | 0.04 |
| Glycerol monocaprylate | 2.40 |
| Water | 88.86 |
| Amount applied: 7 mg/cm$^2$ | |

## Hydroxypropyimethyl cellulose phthalate films

*a. Organic HPMCP solutions (79)*

| Constituents | % parts by weight in finished formulation |
|---|---|
| HP-55S | 6.0 |
| Triethyi citrate | 0.9 |
| Ethanol | 79.1 |
| Water | 14.0 |
| Coating machine: Aeromatic Strea-1 with 1.2 mm jet diam. | |
| Loading: 250 g size 1 capsules | |
| Coating amount: 47 mg polymer per capsule (750 g spray soln.) | |
| Spray pressure: 0.8 bar | |
| Drying air temperature: 36-38 OC | |
| Product temperature: 31-33 'C | |
| Coating speed: 6.3 g/ min | |

The gastric-juice resistance and appearance of capsules film coated in a laterally ventilated drum instead of in a fluidized air bed were inferior (somewhat cloudy, overlap between body and cap insufficiently covered).

*b. Aqueous HPMCP dispersions (81)*

| Constituents | % parts by weight in finished formulation |
|---|---|
| HP-50F | 10.0 |
| Triacetin | 3.0 |
| Water | 87.0 |
| Coating of dry polymer substance: 8 mg/cm$^2$ | |

*c. Low solvent content emulsion coating of HP-55 (87*)

| Constituents | % parts by weight in finished formulation |
|---|---|
| HP-55 | 9.00 |
| Plasticizer (triacetin, PEG 6000, polyethylenegiycol-400-monostearate or dibutyl phthalate) | 1.50 |
| Ethyl acetate | 32.00 |
| Sec-butanol | 8.00 |
| Ethyl glycol | 12.50 |
| Water | 37.00 |

Although emulsion coatings still contain solvent, they are no longer inflammable due to the amount of water present. The addition of water causes the gelatin to swell slightly when the formulation is applied ' polymer penetrates the capsule shell and the film adheres well. Tendency to brittleness is also counteracted (87, 88).

*d. Aqueous-alcoholic solutions of HP-55 (87)*

| Constituents | % parts by weight in finished formulation |
|---|---|
| HP-55 | 9.00 |
| Plasticizer (see above) | 1.50 |
| Isopropanol | 36.00 |
| Ethyl glycol | 17.50 |
| Water | 36.00 |

A clear film is formed since ethyl glycol, which has a high boiling point, is.a good solvent for the film constituents (87).

## Hydroxypropyl cellulose acetate succinate films

No published formulations for the film coating of hard gelatin capsules were found.

## Polyvinyl acetate phthalate films

*a. Organic formulation of PVAP (81)*

| Constituents | % parts by weight in finished formulation |
|---|---|
| PVAP | 11.0 |
| PEG 400 | 1.0 |
| Ethanol | 66.0 |
| Water | 22.0 |

*b. Aqueous formulation using Opadry Enteric (81)*

| Constituents | % parts by weight in finished formulation |
|---|---|
| Opadry Enteric | 15.0 |
| Water | 85.0 |
| Added ammonia | |

### Protective coatings

A special problem when film coating capsules with organic polymer solutions is imperfect adhesion of the enteric coating onto the smooth surface of the capsule, the so-called orange peel effect.

A precoat can be applied to prevent this. For example, a 5 % aqueous solution of HPC (Klucel EF, Hercules) or HPMC (Pharmacoat, Shin Etsu) is suitable (83,84) with a coating of 3 to 6 mg/cm$^2$ dry polymer substance. A solution of PVP or HPMC in an ethanol-mthylene chloride mixture has also been described as a precoat (87) (coating 5 to 10 % of the total coating weight).

The main difficulty with aqueous formulations is that the gelatin shell softens. This can be prevented by applying an intermediate layer of gastric-juice soluble Eudragit E in aqueous-alcoholic solution in an amount of about 10 % of the total coating (87).

Since the film polymers presented are only insoluble in water in the protonized state, basic capsule fill materials which form a diffusion layer with neutral to alkaline pH value may reduce gastric-juice resistance. Diffusion barriers in the form of precoats such as Eudragit RS should then be used (98).

During storage of the film coated capsules, adhesion which sometimes occurs can be prevented by an overcoat also composed of HPC or HPMC (83.84). Use of an overcoat also improves the appearance of the capsules and can have a positive effect on the stability of the product.

## IV. Technological aspects and problems in enteric coating capsules

### a. General film coating problems

Aqueous dispersions are to a greater or lesser extent sensitive to electrolytes, pH shifts, foam formation, higher temperatures and frost, the effects of shearing force in high speed stirrers, partly also to the presence of organic solvents and finely distributed pigments. Coagulation may then occur (101, 102). Coagulated dispersions are not reclispersible and can consequently not be used.

In view of their sensitivity, ready-to-use aqueous Eudragit dispersions should be processed within 1 to 2 days. Cooling is necessary in the case of some dispersions, such as HPMCAS.

Aggregates of polymer can block the spray jets To prevent this, aqueous dispersions are passed through a fine sieve before the coating is applied (0.1 - 0.25 mm mesh size).

Dosage forms can stick together during film coating, thereby damaging films layers already applied. Very soft films have also been found to stick together during storage. The addition of anti-adhesion agents can lead to a loss of desired film transparency in the case of hard gelatin capsules.

Spraying losses due to the spray drying of the polymer have been observed in the case of aqueous dispersions. The distance between the jet and the product should be carefully adjusted, suitable plasticizers should be selected and optimum process parameters (drying temperature, amount of air, spraying pressure, spraying speed, batch loading, etc.) should be determined so that the spray yield is acceptable.

### b. Special problems relating to capsules

Problems occuring during the coating of capsules are generally due to the characteristics of the capsule wall - gelatin. This is illustrated by the following list of problems and their remedies:

- During coating with aqueous spray formulations the gelatin shell softens and becomes sticky due to solubilization.
  Remedy: precoating.
- The gelatin shell becomes brittle due to water evaporation and drying, especially when coating begins.
  This may also occur during long term storage. The brittleness causes the capsules to lose their mechanical stability and they break under slight pressure (87).
  Remedy: precoating.
- Insufficient adhesion of the film with splintering and peeling of the coat (orange peel effect), especially with organic spray formulations.

The capsule shell is very smooth and gives little anchorage (81, 86, 87, 88).
The influence of moisture causes film coats and the gelatin wall to swell to a varying extent, which also causes the coat to become detached.

Remedy: higher plasticizer content (81), a precoat in the form of a two-layer film coating (PVP, HPMC, Eudragit E) or the use of an aqueous-alcoholic solution or a hydrated coating emulsion with low solvent content (81, 87). Addition of PEG 400 or PEG 6000 should also improve contact (86).

- Increased cracking on handling the medicament.

Remedy: a higher proportion of plasticizer makes films more ductile (90).

- Separation of the capsule halves due to movement in the coating machine (85).

Remedy: use of hard gelatin capsules having patent closures or banding the capsules.

- Problem zone: contact zone between upper and lower capsule parts (94),

Remedy: to prevent any liquid penetrating the space between the cap and body when spraying begins, 0.2 to 0.3 % Aerosil 200 may be added to the spray formulation to achieve rapid filling of the intermediate space (95).

More plasticizer and the choice of a suitable coating machine also improve coverage at the join (79). Cracks may form at the contact site.

Another possibility to prevent such effects is to apply a gelatin band to the capsule at the point of overlap between the cap and body.

The stability of a moisture sensitive active filled into the capsule can be affected by aqueous coating.

This also applies to the use of not totally anhydrous solvents (95). The hard gelatin capsule does not provide a complete barrier since the contact point of the two halves of the capsule and the thin gelatin film at the transition between the cylindrical and the curved part of the capsule represent possible moisture penetration zones.

Remedy: if this occurs, anhydrous solvents should be used (95), at least for the sealing coating.

- Loss of the desired glossy, attractive appearance of the capsule due to a non transparent film.

Remedy: no pigment with a matt effect should be added if the bright capsule colour is to be retained. The uniformity of the film (81), choice of plasticizer and solvent also determine the transparency of the film coat (79).

### c. Stability of coated hard gelatin capsules

Regardless of which enteric coated dosage form is used, instability does occur when films are applied. Investigations involving 181 preparations, predominantly tablets, revealed a number of stability problems depending on duration of storage, temperature, coated active substance and other factors (96, 97).

Particularly in the case of hard gelatin capsules stability problems are encountered above all in enteric coats applied in the form of aqueous dispersion systems. A report by Murthy** (82), who has published investigations in this field of aqueous coat-> ings, showed that hard gelatin capsules coated with Aquateric displayed noticeably slower release after three-months' storage at room temperature due to reaction of the gelatin coat with CAP or with its hydrolysis products phthalic acid and acetic acid which makes the gelatin insoluble.

Delayed dissolution, which may be due to changes in the polymer, has been reported for Coateric films 9 months after manufacture.

Good stability was reported for Eudragit L 30 D. Film characteristics and release performance remained constant, even after somewhat more stringent storage conditions. Enteric film formers with an ester structure are liable to hydrolyse under the influence of moisture; in the case of cellulose derivatives, HPMCAS is considered more stable than HPMCP and this, in turn, more stable than CAT and CAP.

A stability study (83) compared organically applied films of polymethacrylic acid-methyl methacrylate Eudragit L 100, polyvinyl acetate phthalate and cellulose acetate phthalate with films obtained from aqueous dispersions of Eudragit L 30 D, Coateric and Aquateric. The authors used diethyl phthalate as plasticizer. Aqueous dispersions of Eudragit were nonetheless somewhat superior to organic polyacrylate solutions whereas Aquateric only matched up to organic CAP systems when an overcoat was used. Capsules film-coated with Coateric displayed signs of instability in the form of lost gastric-juice re-

sistance. PVAP organic system coaJts needed a protective coating to prevent adhesion of the product.

In this context, reference is made to special investigatory methods for testing acid permeability (88) or release kinetics in vivo (89).

## V. Processes for coating hard gelatin capsules

Developments in machinery over the last few years in the field of coating methods have led to further refinements, which are described briefy below:

**Dipping processes,** used only occasionally and on a small scale or in formulations made up by pharmacists (80, 86, 91), call for rather more viscous dipping media. Using tweezers or capsule halves fixed to a rotating plexiglass disc (91), each capsule half is dipped into the film solution. The process is repeated until the layer has the desired thickness.

### Use of horizontal drums

The Acela Cota (Manesty Machines Limited, UK) is an example of a machine with a perforated drum. It works on the principle of a horizontally mounted, rotating cylinder to which drying air is fed through a lateral lymounted shoe and then withdrawn from another location after passing through the bed of product to be coated. The spray device is inside the drum and sprays the rotating capsules from above.

The Diacoater, Hi-Coater and Glatt-Coater are similar machines of this type.

### Use of fluidized air bed processes

In fluidized air bed processes, air flowing through a screen in the base of the equipment keeps the material moving and is then sprayed with the film formulation either in a counterflow principle from above (top spraying) or in a parallel flow principle from below.

Movement of the material can be controlled more accurately by use of guide cylinders (Wurster inserts). The capsules are propelled upwards in an almost laminar flow through the central guide tube by a powerful air flow, sprayed with the coating formulation and simultaneously dried by the stream of air. On discharge from the tube, the material flows freely downwards outside of the cylinder towards the screen in the base the equipment under gravity against a less powerful air flow and passes back into circulation.

Examples of this type of machine include Strea-1 (laboratory model) and Aerocoater (Niro, Bubendorf, Switzerland) optionally with Wurster insert and Uni-Glatt (laboratory model) and Glatt-WSG (Glatt, Binzen, Germany) also optionally with Wurster insert.

### More recent combined processes

In the drum process the material is mainly moved by rotation of the container and in the fluidized air bed process it is moved by the stream of air. Combination of both principles yields new possibilities of handling the material and optimizing the stream of air as a means of drying. In this combined process the stream of drying air does not have to move the material on its own and consequently less air is needed. The interaction of centrifugal force, stream of air and gravitation causes circular movement of the material.

A report by Osterwald on the coating of gelatin capsules (87) compared the Driacoater, Wurster-WSG and Rotor-WSG with respect to HPMCP-55 film coatings. It was found on the basis of the process parameters that the fluidized air bed permitted a larger batch volume but needed more energy because of the larger amount of inlet and exhaust air. There was, however, a comparative saving in energy due to the rotor technology which optimizes the air input.

Application of HP-55 emulsion in classic fluidized air bed processing in the WSG produced relatively rough coatings since drying occurred very quickly in the strong flow of air, moreover the spraying losses were higher than when other machines were used.

The rotor model produced a comparatively faster film coating: capsules film-coated in this manner with an aqueous- alcoh oli c HP-55 formulation quickly became gastric-juice resistant and had glossy, transparent coats.

Other exarnples of more recent combined processes are the Roto-Processor (Niro, Bubendorf, Switzerland), the Ultracoater (also Niro) and the CF-Granulator (Freund Industrial Co. Ltd., Japan).

Finally, a machine of a different type is the HüttlinKugelcoater (Hüttlin Entwicklung und Verfahrenstechnik, Steinen).

Practical trials are needed in each individual case to determine the best coating equipment and best film coating formulation.

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