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Review

Formulation and process considerations affecting the stability of solid dosage forms formulated with methacrylate copolymers

Hans-Ulrich Petereit*, Wolfgang Weisbrod

Röhm GmbH Chemische Fabrik, Kirschenallee, Darmstadt, Germany

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Abstract

General considerations concerning the stability of coated dosage forms are discussed, in order to avoid predictable interactions which may cause long-term stability problems. As polymers themselves maintain a high chemical stability and a low reactivity, instability phenomena mainly have to be explained by interactions of low molecular weight substances or physical changes. Possible interactions of functional groups can be predicted easily and insulating subcoates are proper countermeasures. Impurities, remaining in the polymeric material from the manufacturing process, may accelerate the hydrolysis of sensitive drugs. Instabilities of coated dosage forms are mainly based on physical interactions, caused by improper formulations of coating suspensions (i.e. plasticizers or pigments) or the film coating process. Residual moisture or solvents, probably enclosed in the core and migrating over time, may increase the permeability of coatings, due to plasticizing effects. The functionality of coatings from aqueous dispersions is linked to coalescence of latex particles. Thus any incomplete film formation, caused by too high or too low coating temperatures, may result in high permeable coatings. During storage, preferably under stress conditions this process will continue and thus change the release profile. Therefore bed temperatures of 10–20°C above MFT must ensure the formation of homogeneous polymer layers during the coating process. Stability test procedures and packaging materials also need to be adapted to the physicochemical properties of the dosage form, in order to get meaningful results in stability tests.

Keywords: Solid dosage forms; Methacrylate copolymers; Pharmaceutical technology

1. Introduction

Since coated dosage forms have been introduced in pharmaceutical technology, they maintained a challenge for formulators. High quality expectations had to be fulfilled which needed a great experience concerning formulations and processes. Furthermore,long term stability is a basic requirement for insuring the therapeutical effect.

Many active ingredients are unstable when exposed to influences such as light, air, heat and moisture (Fig. 1). For this reason, pharmaceutical dosage forms are often provided with protective coatings to prolong their shelf life. At the same time, these coatings based on polymethacrylates are designed to permit specific release profiles.

Very often stability testing needs longer time than the development of the dosage form and if the prototype fails, the development has to be restarted almost at time zero. Months or even years have been lost.

Therefore, a formulator needs to evaluate the properties of each substance he is going to use at the beginning of his work and to eliminate any possible reason for instability in order to succeed with a product development in a period of time as short as possible.

The aim of this paper is to summarise general considerations and experiences in order to identify possible reasons for instability as well as to give examples for successful formulations. The general aspects are valid for coated

* Corresponding author. Röhm GmbH Chemische Fabrik, Kirschenallee, 64293 Darmstadt, Germany. Fax: +49-6151-183188.

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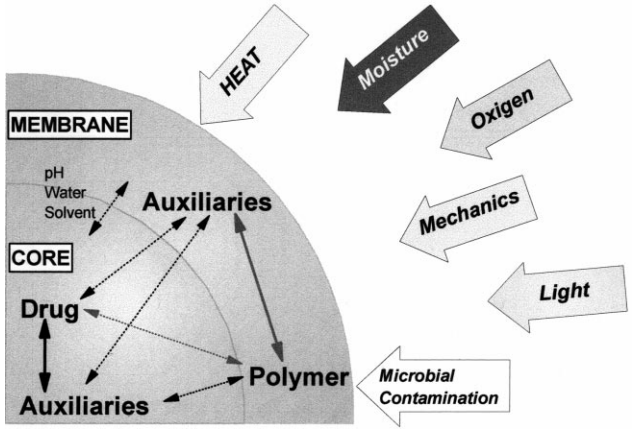

Fig. 1. Interactions in coated dosage forms.

dosages forms and matrix formulations. In some aspects, matrix systems have to be considered as more sensitive because the contact area is significantly larger.

2. Chemical reactions

As polymers maintain a lower reactivity than low molecular weight substances, this class of excipients is rarely involved in chemical degradation.

In contrast to cellulose ethers, whose glucose units are linked via an oxygen bond hydrolysable by acids and bases, polymethacrylates have a chemically very stable, coherent carbon skeleton [1]. This includes the ester groups in the side chain (Fig. 2).

Investigations of the chemical stability of the neutral polymer EUDRAGIT® NE 30 D in aqueous phase after storage for 10 years revealed that only 0.05% ethanol groups and less than 150 p.p.m. methanol groups were split off. The anionic polymer EUDRAGIT® L 30 D-55 was also found to be extremely stable in aqueous medium. After storage for 4 years at a pH around 3, only 0.3% of the ethyl ester groups had been hydrolysed, whereas the methyl ester groups remained largely intact over a period of 10 years, just as in the case of EUDRAGIT NE 30 D (Fig. 3). If the pure polymers, i.e. the commercial products in powder or granular form, are monitored over a period of 5 years, no change in the content of functional groups can be detected (Fig. 2).

Investigations of Lippold and Lippold [2] on free films resulted in a higher rate of hydrolysis of 1.5% in HPMCP films at 100% relative humidity over 90 days, even at 20°C. There was no significant difference between the casting from aqueous or organic media.

The hydrolysis of EUDRAGIT L 100 (cast from an organic solvent) or from EUDRAGIT L 30 D-55 was approximately 0.1% and thus negligible.

Even with modern and well validated manufacturing processes, the purity of excipients may affect the stability of dosage forms. In contrary to cellulose-based polymers, the initial content of free acid is lower and no further acid is released during storage (Fig. 4). Storage stability tests of an acid-labile macrolide combined with isothermal calorimetry indicated that the chemical purity and stability of methacrylates improved the stability of the coated dosage forms [3].

Concerning compatibility, functional groups, which determine the properties of the polymer have to be considered as partners for reactions. Thus aminogroups of cationic methcrylates may form a salt with carboxylic functions of anionic drugs, such as non-steriodal antirheumatics like ibuprofen. As a consequence, the T_g of the polymer is decreased significantly and polymer layers become soft and sticky.

This type of interaction may be detected by a compatibil-

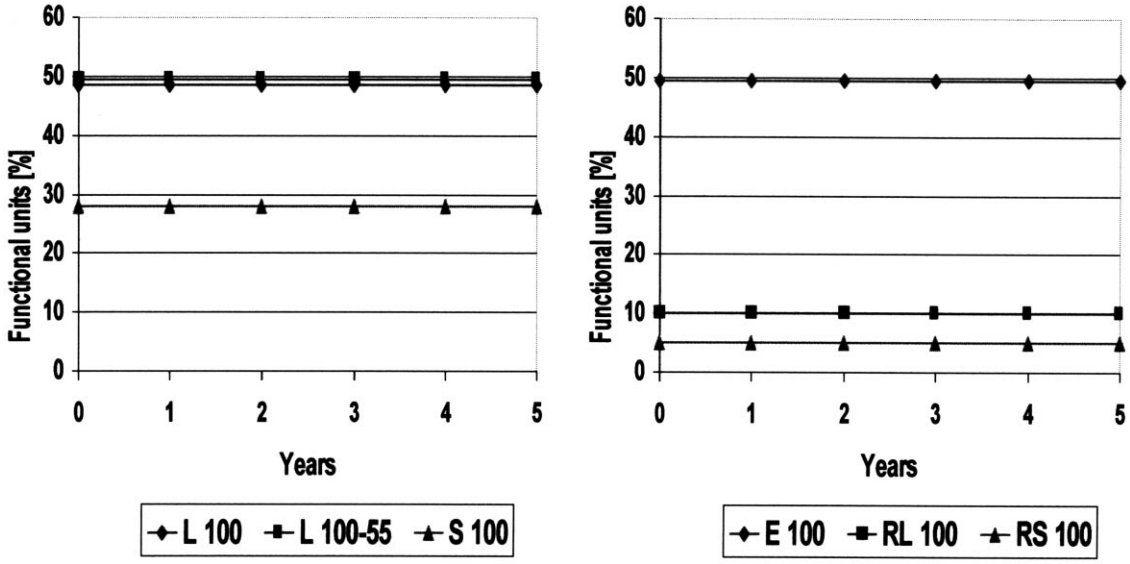

Fig. 2. Storage stability of solid EUDRAGIT polymers (Lit. 1).

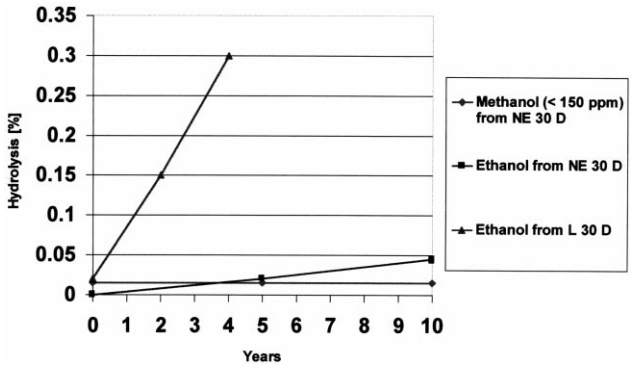

Fig. 3. Hydrolytic stability of EUDRAGIT dispersions (Lit. 1).

ity screening including all involved components based on differential scanning calorimetry (DSC). Repeated heating of a mixture of milled EUDRAGIT E 100 mixed with ibuprofen resulted in a loss of the thermal signal indicating the melting of the crystalline drug. Obviously this change indicates the interaction of the cationic polymer with the anionic drug. A mixture with anionic EUDRAGIT L 100 did not change after repeated heating (Fig. 5.)

Chemical reactions can largely be excluded by using the pH-independent polymers EUDRAGIT NE 30 D, RL and RS 100. On the other hand, pronounced hydrolysis of the active acetylsalicylic acid has been observed with dosage forms prepared with EUDRAGIT RL and RS 100.

When using the polymers EUDRAGIT E 100, L/S 100 and L 30 D-55, which carry reactive groups, it must be borne in mind that salt formation with acidic and basic excipients or actives may take place. Since such salts normally affect the physicochemical properties of the polymer, gastroresistant preparations and their special properties are particularly at risk. Moreover, changes in colour during storage cannot be ruled out and are accelerated by residual moisture in the core.

Multivitamin preparations are a problem of their own. Owing to the large number of different actives and excipients and the reactivity of the individual components, interactions are likely to occur. Therefore, it is sometimes advisable to cover the particles with a protective coating to prevent contact with other substances before the tabletting process is started. On many occasions, vitamin C is selected as the substance to be coated, because it is easy to obtain in an acceptable particle size range. In this case, talc should not be used as a glidant in the film coating, as it usually contains free magnesium ions which may cause discolouration of vitamin C during storage. Glycerol monostearate is generally more compatible as shown with enteric coated ASA tablets (Fig. 6).

3. Physical changes

The function of polymers in dosage forms is based on physical effects. Thus instability phenomena are mainly based on physical changes or physically induced effects.

The thermal stability of polymers is important if melt processes are applied. High temperatures up to 150°C may be necessary to reduce the melt viscosity for casting or spraying processes. The method of thermogravimetry, linked with mass spectroscopy, allows to identity the mechanism of thermal degradation. Methacrylates generally start degradation at the side chain above 150°C. The stability of the polymer after a process with thermal stress can be checked with a simple titration of the functional groups. Reactions of the main chain, i.e. depolymerisation or cross-linking starts above 180°C. EUDRAGIT NE30 D and the anionic types tend to be more stable than the cationic copolymers (Fig. 7).

Thermal degradation can be excluded as a reason for instability in long term stability test even under stress conditions.

4. Interactions as sources for instability

The effect of macromolecules in dosage forms is very

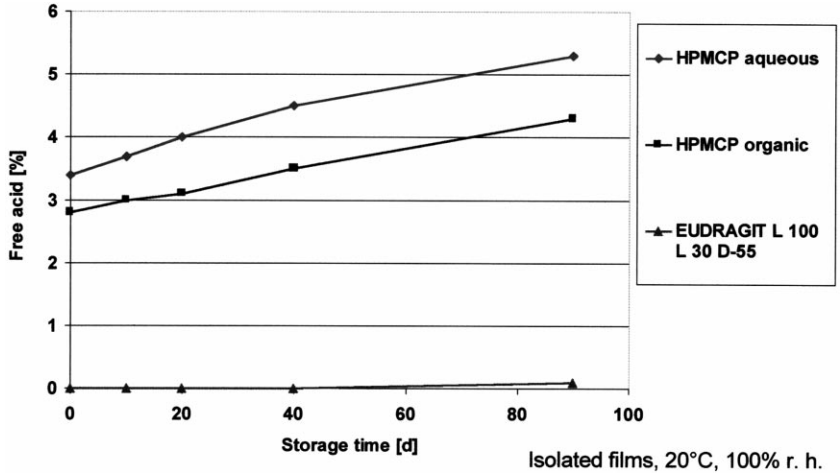

Fig. 4. Hydrolysis of ester groups in enteric coatings (Lit. 2).

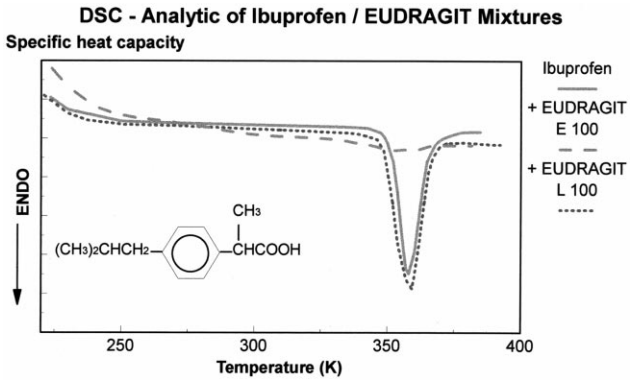

Fig. 5. Thermograms of ibuprofen mixture with EUDRAGIT E 100 and EUDRAGIT L 100 (drug/polymer ratio 1:1 mol/mol, Perkin Elmer DSC 2C, sample 10 mg, closed Al-pans, 20 deg./min, N2-atmosphere).

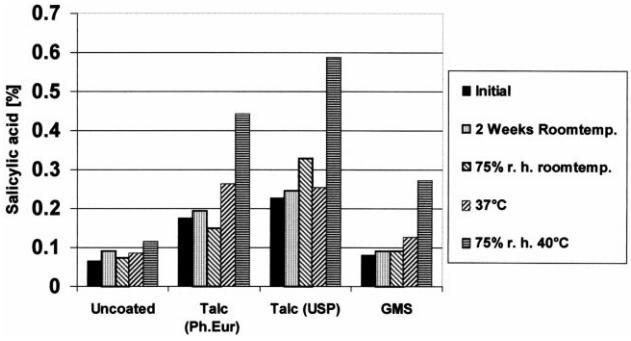

Fig. 6. Stability of enteric coated ASA tablets with different glidants.

often based on interactions with auxiliaries. Plasticizers are of most importance in this context. They improve the coalescence of latex particles by decreasing the T_g and thus ensure reproducible film formation in aqueous coating processes. Migration of plasticizers have not been reported, if the recommended quantities of 10–20%, calculated on the polymer was added.

During long term storage the concentration of tritethyl citrate is more stable in coatings than triacetin [4], which is subject to hydrolysis (Fig. 8).

Even high quantities of 50% triethyl citrate maintain stable colon delivery systems with redispersed EUDRAGIT S 100 [5], coated with an aqueous suspension (Fig. 9).

In contrast to interactions within the coating, interactions with components of different parts of the dosage form may influence the stability of a dosage form. Drugs and excipients may migrate in the coating or may be entrapped during the coating process as abrasion from weak cores caused by mechanical forces. This effect usually causes an increased permeability of the polymer layer. A proper countermeasure are insulating layers of soluble polymers, which stabilise the core surface and avoid migration of substance from one compartment into another.

5. Coating process

In aqueous coating processes, the conditions determine both the functionality and the stability of the films. Not only the quantity of the polymer is important, but also the conditions of application. The macromolecules must form a homogenous film.

Based on the recommended formulations of spray suspensions including aqueous methacrylate dispersions, the bed temperature during the spraying process is the most important parameter. It is linked with the minimum film-forming temperature (MFT) which is adjusted to 10°C or lower. Homogenous film forming is ensured if the bed temperature is kept approximately 20°C higher.

As the amount of process air usually has to be adjusted according to the equipment or to the properties of the cores, spray rate and inlet air temperature may be used to adjust the bed temperature.

6. Water content

Residual water present in the dosage forms may affect the

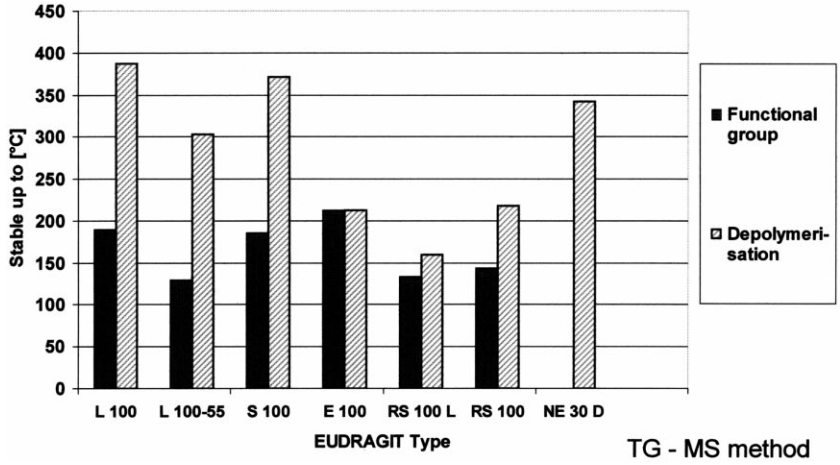

Fig. 7. Thermal stability of methacrylate copolymers (thermogravimetry-mass spectroscopy).

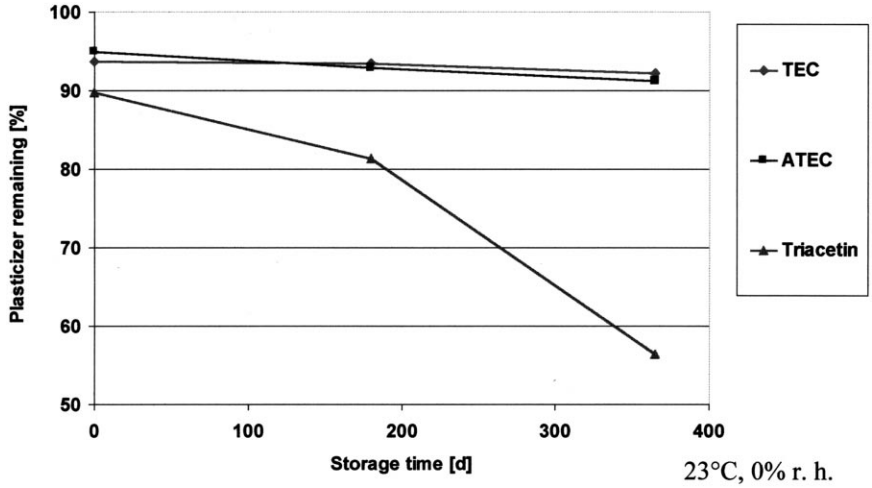

Fig. 8. Stability of plasticizers in EUDRAGIT L 30 D-55 films (Lit. 4).

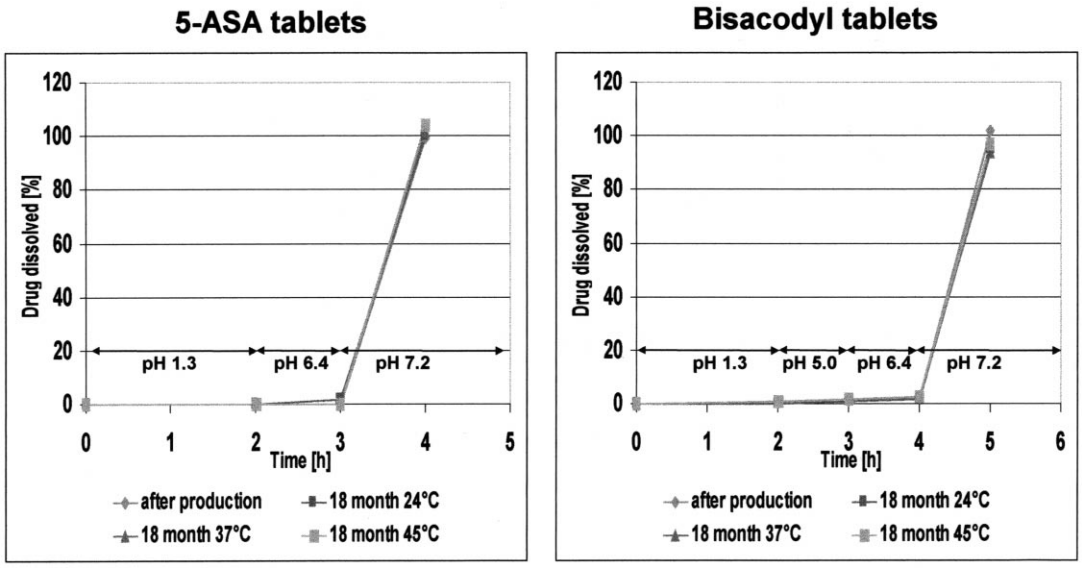

Fig. 9. Stability of tablets coated with an aqueous dispersion of EUDRAGIT S 100 (Lit. 5).

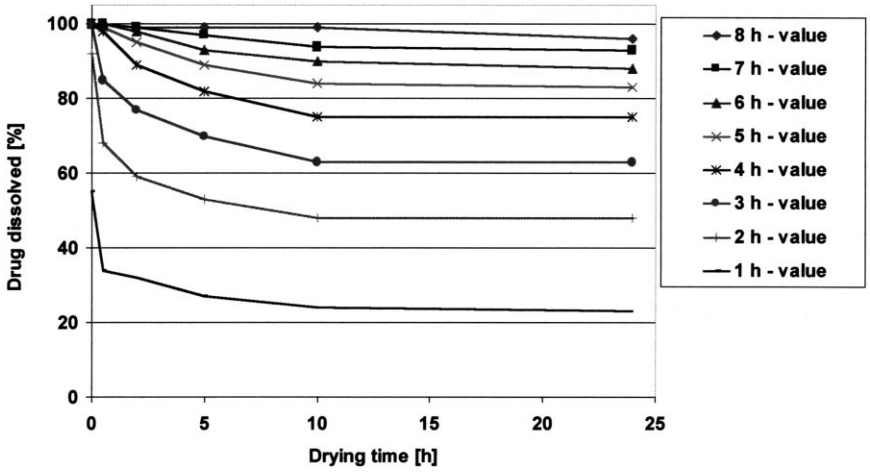

Fig. 10. The effect of coalescence on the permeability of EUDRAGIT RL/RS 30 D coatings (curing at 40°C) (Lit. 6).

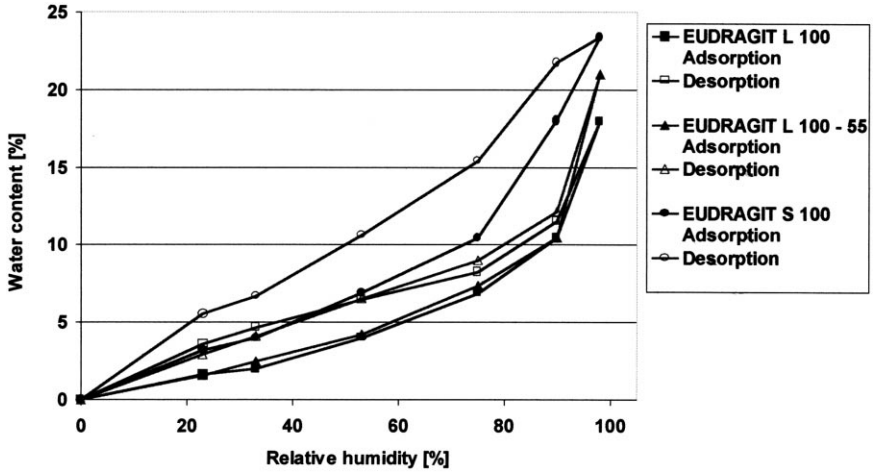

Fig. 11. Sorptionisotherms of anionic methacrylate copolymers (Lit. 7).

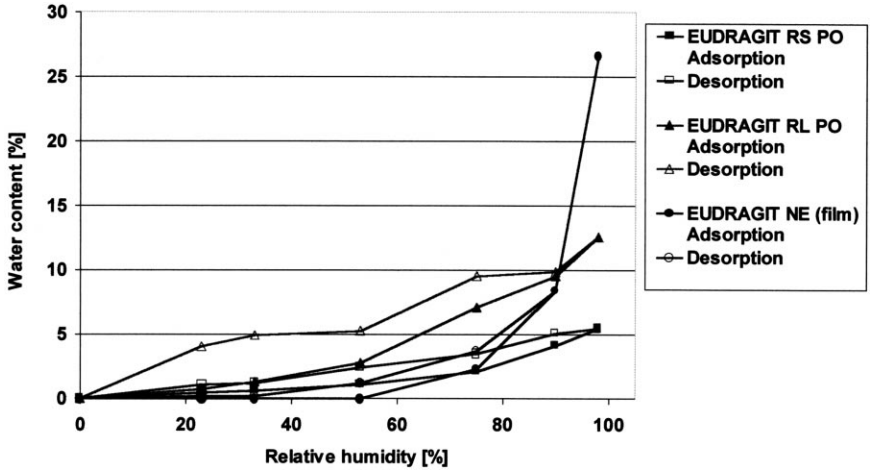

Fig. 12. Sorptionisotherms of cationic and neutral methacrylate copolymers (Lit. 7).

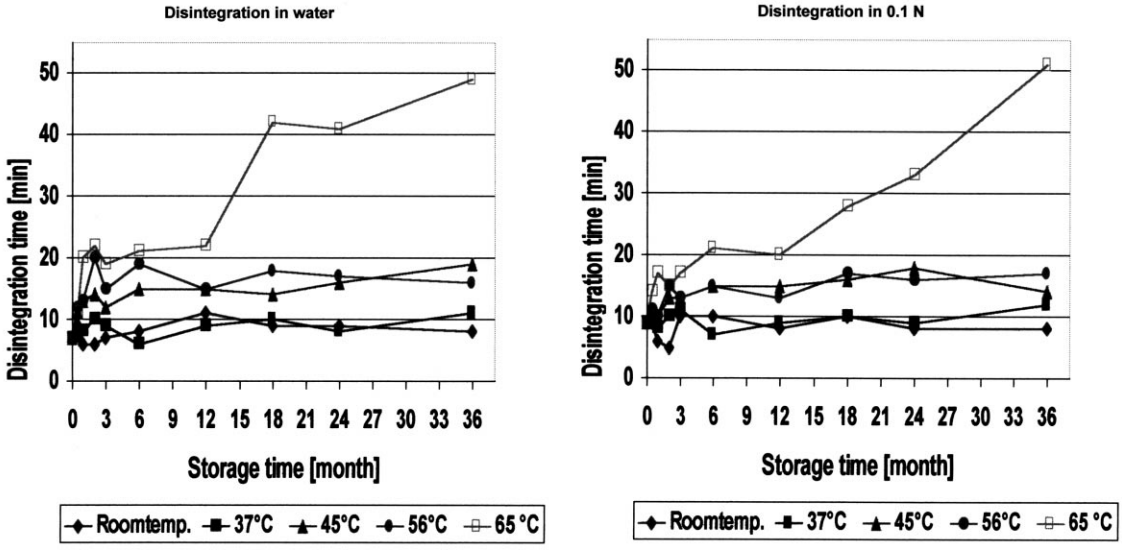

Fig. 13. Storage stability of film coated placebo tablets (Lit. 8) (polymer weight gain: 1 mg/cm^2 from EUDRAGIT RL 30 D).

Table 1
Stability data of plain coated dosage forms with methacrylate copolymers

EUDRAGIT	Auxiliaries	Applied polymer (mg/cm^2)	Dosage form	Drug	Storage condition (°C/% r.F.)	Storage time (month)	Disintegration time (min)	
							0.1 N HCl	H_2O
E 100	Talc	0.5	Coated tablets	Minerals	23/ambient	0	<2	<3
						46	<1	<12
E 100	Talc	2.0	Coated tablets	Hormons	23/ambient	0	<2	<5
RL 30 D	Talc/TEC	0.7	Coated tablets	Spyramycin	23/ambient	0	<3	<3
						23	<3	<3
RL 30 D	Talc/TEC	1.0	Coated tablets	Acetaminophen	23/ambient	0	<2	<2
						11	<2	<2
RL 30 D	Talc/TEC	1.0	Coated tablets	Ethambutol	23/ambient	0	18–30	16–20
						22	23–47	14–29
RL 30 D	Talc/TEC	1.2	Coated tablets	Garlic	23/ambient	0	–	47
						15	–	<42
RL 30 D	Talc/TEC	1.0	Coated tablets	Aminophylline	23/ambient	0	21	9
						65	16	19
RS 30 D	Syloid/TEC	15	Coated tablets	Aminophylline	23/ambient	0	5 min: 49	15 min: 73
						53	5 min: 53	15 min: 96
L 30 D-55	Syloid/TEC	15	Particles	Aminophylline	23/ambient	0	5 min: 78	15 min: 85
						53	5 min: 9	15 min: 100
E 100	Citric acid, Talc	1.0	Coated tablets	Placebo	23/ambient	0	<2	<2
						24	<2	<2
E 100	Citric acid, Talc	1.0	Coated tablets	Placebo	45/ambient	0	<2	<2
						24	<2	<2

GMS, mono- and diglycerides NF (glycerol monostearate).

Table 2
Stability data of enteric coated dosage forms with methacrylate copolymers

EUDRAGIT	Auxiliaries	Applied polymer (mg/cm^2)	Dosage form	Drug	Storage conditions (°C/% r.F.)	Storage time (month)	Disintegration time (min)[a]	
							0.1 N HCl	Buffer pH 6.8
L 100	None	22% w/w	Gelatine capsules	ASA	23/ambient	0	>120	<42
						96	>120	<42
L 30 D-55	Talc	6.0	Tablets	Garlic	23/ambient	0	>120	<12
						32	>120	<9
L 30 D-55	Talc	11.0	Tablets	Na-valporate	23/ambient	0	>120	<24
						37	>120	<21
L 30 D-55	Talc	4.3	Tablets	Erythromycine	23/ambient	0	>120	<16
						39	>120	<14
L 30 D-55	Talc	3.6	Tablets	Na-diclofenac	23/ambient	0	>120	<3
						48	>120	<3
L 30 D-55	Talc	6.0	Tablets	Placebos	23/ambient	0	>120	<6
						24	>120	<5
L 30 D-55	Talc	4.0	Tablets	Methylene blue	23/ambient	0	>120	<3
						24	>120	<5
L 100-55	Talc	4.8	Tablets	Quinidine sulphate	23/ambient	0	>120	<6
						50	>120	<7
S 100	Talc	9.2	Tablets	Trimebutine	23/ambient	0	>120	<31
						33	>120	<38
L 100	Talc	4.0	Tablets	Acetylsalicylic acid	23/ambient	51	>120	<30
							>120	<20
L 30 D-55		5.0	Tablets	Acetylsalicylic acid	23/ambient	0	120/0.4%[b]	60/24, 120/51
						55	120/0.3%	60/32, 120/62

GMS, mono- and diglycerides NF (glycerol monostearate).
[a]Pharm. Eur.
[b]Drug release, USP method 2, paddle (min/% drug released).

Table 3
Stability data of coated sustained release dosage forms with methacrylate copolymers

►EUDRAGIT	Auxiliaries[a]	Applied polymer (mg/cm^2)	Dosage form	Drug	Conditions (°C/% r.F.)	Time (month)	Drug dissolved (%)[b]				
							1 h	2 h	3 h	4 h	6 h
NE 30 D	Talc	10	Particles	Aminophylline		0	55	66	70	74	79
					23/ambient	39	48	61	68	75	80
NE 30 D	Talc	13.8	Pellets	Quinidine sulphate		0	31	57	71	79	90
					23/ambient	50	30	56	73	82	92
NE 30 D	Talc	13	Pellets	Chlorphen-amine maleate		0	19	40	58	71	86
					23/ambient	30	16	39	59	70	81
NE 30 D	Talc	8	Crystals	KCl		0	17	38	54	67	
					23/ambient	44	18	38	53	70	
NE 30 D	Talc	20	Pellets	Phenylpropanol amine-HCl		0	5	37	55	66	80
					23/ambient	36	5	33	56	70	85
NE 30 D	Talc	3.5	Pellets	Propranolol-HCl		0	1	7	15	27	45
					23/ambient	36	1	6	15	25	47
RS 30 D	Talc/DBS	10	Pellets	Phenylpropanol amine-HCl		0	21	37	51	59	72
					23/ambient	30	22	27	46	56	66
RS 30 D	Syloid/ATEC	2.5	Crystals	Acetaminophen		0	58	79			
					23/ambient	12	60	87			
NE 30 D	Talc	14	Crystals	KCl		0	16[c]	37[c]	53[c]	67[c]	
					23/ambient	12	12	33	47	61	
					37/ambient	12	12	34	48	63	
RL/RS 30 D 1:9	Syloid/TEC	7	Granules	Theophylline		0	30	54	68	78	92
					23/ambient	36	19	42	61	76	93
RL/RS 30 D 1:9	Syloid/TEC	9	Granules	Theophylline		0	18	33	45	54	69
					23/ambient	36	16	31	44	54	72
					23/ambient	58	18	36	49	59	73
RL/RS 30 D 1:1	Talc/TEC	5	Pellets	Diclofenac-Na		0	1	1	46	63	74
					23/ambient	17	2	3	49	68	82
NE 30 D	-	14	Disintegration tablets	KCl		0	13	31	51	74	98
					23/ambient	25	13	30	47	61	87
NE 30 D	GMS	14	Crystals	KCl		0	20	54	76	87	97
					23/ambient	5	20	56	83	90	96
					37/ambient	8	23	60	75	90	93
					37/75	8	18	53	78	89	95

[a]TEC, triethyl citrate; ATEC, acetyl triethyl citrate; DBP, dibutyl phthalate; DBS, dibutyl sebacate; GMS, mono- and diglycerides NF.
[b]Method USP method 2, paddle, 2 h pH 1.2 followed by phosphate buffer pH 6.8.
[c]Method USP method 2, paddle, test in water.

storage stability more or less noticeably. Since water is a fairly reactive substance, hydrolysis reactions with corresponding actives, such as acetylsalicylic acid, for example, cannot be ruled out. This aspect is particularly important since more and more aqueous acrylic dispersions are being used for coating and granulation purposes. Inadequate process control and/or insufficient drying can cause water to be entrapped in the dosage form, which may prompt chemical decomposition reactions.

Increased water contents also have an influence on film coatings. Thus, small amounts of water may exert a plasticizing effect, thereby affecting permeability. This becomes immediately obvious in the disintegration or release behaviour of the dosage form. If residual moisture escapes by evaporation during storage or if the films pick up moisture from the cores, this is bound to change the disintegration behaviour of coated tablets or the release profile of coated particles.

Similar effects are produced in the manufacture of matrix tablets by wet granulation. Good batch-to-batch uniformity of the release profile is achieved as long as the water content can be kept below 2%. If the residual moisture content is higher, the release profile will vary in an unforeseeable manner.

7. Process parameters

Above the so-called MFT, aqueous latex dispersions form films by coalescence of their latex particles. Reliable for-

Table 4
Stability data of coated enteric dosage forms with methacrylate copolymers

EUDRAGIT	Auxiliaries	Applied polymer (mg/cm^2)	Dosage form	Drug	Storage conditions (°C/% r.F.)	Storage time (months)	Drug dissolved[a]			
							1 h	2 h	3 h	4 h
L 30 D-55	Kaolin ATEC	9	Crystals	Acetylsalicylic acid		0	1	2	98	
					23/ambient	24	2	3	97	
L 30 D-55	Talc/TEC	11	Crystals	Acetylsalicylic acid		0	2	3	102	
					23/ambient	24	2	3	99	
L 30 D-55 Redispersed	Kaolin ATEC	8	Crystals	Acetylsalicylic acid		0	3	5	106	
					23/ambient	24	3	5	101	
L 30 D-55	Kaolin ATEC	8	Crystals	Acetylsalicylic acid		0	1	2	96	
					23/ambient	24	2	3	108	
L 30 D-55 Redispersed	Talc/ATEC	8	Crystals	Acetylsalicylic acid		0	2	4	98	
					23/ambient	24	3	4	93	
L 30 D-55 NE 30 D 1:1	GMS/TEC	12	Crystals	Acetylsalicylic acid		0	3	5	99	100
					23/ambient	57	–	6	87	98
L 30 D-55 NE 30 D 1:1	GMS/TEC	12	Disintegration tablets	Acetylsalicylic acid		0	4	7	96	100
					23/ambient	57	–	11	71	95
L 30 D-55	Talc/ATEC	30	Pellets	Isoniazid		0	0	3	96	
					23/ambient	27	0	3	99	
L 30 D-55	GMS/TEC	12	Crystals	Acetylsalicylic acid		0	3	4	100	
					23/ambient	3	3	4	100	
					37/ambient	3	3	4	100	
					45/ambient	3	3	5	100	

[a]USP method 2, Paddle, 2 h pH 1.2 followed by phosphate buffer pH 6.8.

mulations of coating suspensions contain plasticizers, which adjust the MFT to 5–15°C. If the product temperatures during processing are only close to the MFT, film formation remains incomplete. This process may, however, progress slowly during storage (Fig. 10), so that the coatings are eventually better filmed and less permeable [6]. This normally slows down disintegration or lowers release rates. Similar effects are produced when an insufficient amount of plasticizer is added to latex systems, especially to EUDRAGIT RL/RS 30 D, so that a desired MFT of $<$10°C is exceeded. Very high processing temperatures, on the other hand, may cause solvent or water to dry too quickly, so that the polymer chains lack time to settle homogeneously. Moreover, spray-dried particles may be included in and exert a negative influence on the film structure. Depending on the storage temperature, this may eventually result in rearrangement of the polymer chains and impaired permeability, preferably if polymers with a low T_g are used.

8. Drying

Freshly coated dosage forms usually contain some residual solvent or water in the coating, which affects permeability and thus disintegration or release. The resultant effects are described above. For this reason, coated dosage forms must be adequately post-dried before conducting release and disintegration tests, especially if the measured values are to serve as zero values of storage stability. Post-drying of enteric-coated dosage forms is difficult if residual solvent or water needs to be extracted from the core. Because of the increased film thickness in comparison with rapidly disintegrating or sustained-release coatings, enteric coatings are only sparingly permeable and even residual solvent cannot be eliminated from the coating at the usual post-drying temperatures between 40°C and 50°C within a reasonable period of time [9].

Therefore, the process parameters have to be selected so that solvent uptake by the core is avoided at the start of the process and effective subsequent drying is guaranteed.

9. Storage tests

There are no prospective aspects. Another problem is based on the fact that there is a lack of general test procedures. Although artificial gastric and intestinal fluids are characterised sufficiently nowadays, health authorities require in vitro release data at pH-values of 3 to 4 more frequently. As no distinguished medium is described in the Pharmacopoeia, different buffer solutions, such as citrate, acetate, phosphate or other systems are used. As most of them do not correspond to the physiological situa-

Table 5
Stability data of enteric dosage forms with colonic drug release, coated with methacrylate copolymers

EUDRAGIT	Auxiliaries[a]	Applied polymer (% w/w)	Dosage form	Drug	Storage temperature (°C)	Storage time (months)	Drug dissolved (%)[b]				
							1 h	2 h	3 h	4 h	5 h
S 100	GMS/TEC	8	Pellets	Bisacodyl		0		0.4	0.8	2.2	102
redispersed					23	12		0.4	0.7	3.0	80
					37	12		0.0	0.4	1.4	96
					45	12		0.2	0.9	2.1	98
S 100	Talc/TEC	12	Granules	5 Amino-salicylic acid		0		0.1	0.1[c]	103[d]	
redispersed					23	12		0.1	0.1	101	
					37	12		0.1	0.1	98	
					45	12		0.1	0.1	98	
S 100	Talc/TEC	10	Pellets	Prednisolone		0	0	0.1	0.2	0.2	110
redispersed					23	12	0	1.3	1.8	2.8	90
					37	12	1	1.0	1.3	0.9	106
					45	12	1	1.0	1.3	1.1	106
S 100	GMS/TEC	10	Pellets	Prednisolone		0	0	0.1	0.2	0.4	114
redispersed					23	12	0	1.5	1.3	1.5	105
					37	12	0	1.1	0.6	1.1	106
					45	12	0	1.2	0.5	1.1	98

[a]TEC, triethyl citrate; ATEC, acetyl triethyl citrate; GMS, mono- and diglycerides NF (glycerol monostearate).
[b]USP method 2, paddle: 2 h pH 1.2, 3 h pH 5.0, 4 h pH 6.8, 5 h pH 7.5.
[c]Phosphate buffer pH 6.4.
[d]Phosphate buffer pH 7.2.

tion in the human GI-tract, the results may be misleading, if ionic polymers f-e-with quaternary ammonium groups are incorporated in the coating. Usually an addition of chloride ions, which are present in the digestive environment lead to more reliable results.

On many occasions, coated dosage forms or matrix systems are subjected to stability tests at elevated temperatures and higher relative humidity in order to quickly obtain information on their stability at room temperature. The USP XXIII requires stability data at 40°C and 75% relative humidity. This preliminary piece of harmonisation helps to agree upon standard testing methods but it only identifies problems after a formulation is finished.

Methacrylate copolymers only absorb up to 10% of water up to 75% relative humidity at room temperature. The more hygroscopic anionic methacrylates absorb more than 5% of water (Fig. 11), while neutral polymers absorb less than 5% (w/w) [7]. Among those, EUDRAGIT RS PO is the less hygroscopic type because of the lower content of quaternary ammonium groups (Fig. 12).

As humidity contributes to possible instability reactions, a protective packaging improves the stability of dosage forms significantly.

The problem involved in such stress tests is that the kinetics of possible chemical reactions increase drastically at temperatures just above 40°C, while the same reactions are not observed at room temperature. Furthermore, the meaning of these data very often do not indicate the properties of the dosage forms at ambient conditions, because Arrhenius' law is not applicable. At the glass transition temperature (T_g), the properties of incorporated polymers change significantly and not gradually as assumed in predictions which are based on stress tests. Often stress tests do not allow a reliable forecast of long term stability behaviour of new dosage forms.

The disintegration of placebo tablets in purified water and artificial gastric fluid is stable over 36 months at room temperature and 37°C while an initial delay of disintegration from 7–9 min to 15–20 min during the first 2 months was observed at 45°C and 56°C [8]. This level remains constant until 36 months. A continuous increase up to 50 min occurred at 65°C (Fig. 13).

Another example is based on ASA as an active ingredient. It shows a tendency towards pronounced hydrolysis when the storage temperature is only slightly increased. Even changes in the disintegration and release behaviour cannot necessarily be attributed to the polymer used. When the product is stored above 40°C, the storage temperature may well exceed the glass temperature of the polymer, so that the latter becomes "soft'. This is caused by Brownian motion of the chain segments, possibly leading to changes in the coating structure and thus to impaired permeability.

Tables 1–5 summarise stability data of coated dosage forms with methacrylate copolymers. Different auxiliaries are used in order to obtain reliable functionality of the pharmaceutical product.

10. Summary

The stability of coated dosage forms is very often predetermined by the concept, designed in early phases of a development. DSC investigations are a useful tool in order to identify possible interactions with active ingredients.

If methacrylate copolymers are used, the reasons for instability phenomena are mainly based on physical changes, which may be caused by the formulation or the coating process.

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