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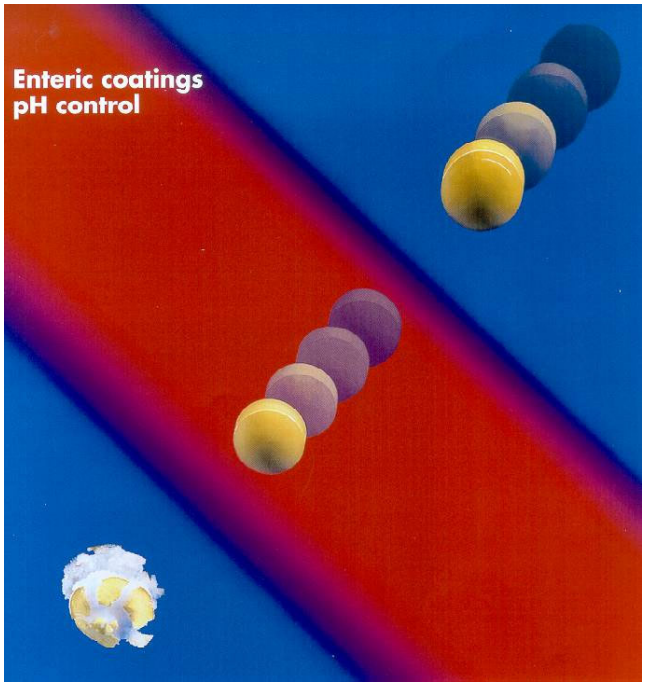
Röhm Pharma Polymers

Enteric Coatings-pH control with EUDRAGIT®



Introduction:

Many pharmaceutical dosage forms irritate the stomach due to their chemical properties. Others undergo chemical changes in gastric acid and through the action of enzymes.
Specific EUDRAGIT® acrylic polymers have been developed for peroral dosage forms with step-wise realease of active ingredients in the digestive tract. The pharmaceutical principle: reliable EUDRAGIT® coatings soluble as a function of environmental pH value.

Depending on the pharmaceutical or technical objective, different EUDRAGIT® polymers offer optimal solutions:

Coatings which dissolve at rising pH values:

- Release of active ingredients in the duodenum with EUDRAGIT® L 100-55 or the aqueous dispersion EUDRAGIT® L 30 D-55 at pH values over 5.5.
- Release of active ingredients in the jejunum to ileum with EUDRAGIT® L 100 at pH values over 6.0 or with mixtures of EUDRAGIT® L 100 and EUDRAGIT® S 100 in a pH range from 6.0 to 6.5.
- Release of active ingredients near the colon with EUDRAGIT® S 100 in a pH range fom 6.5 to 7.5.

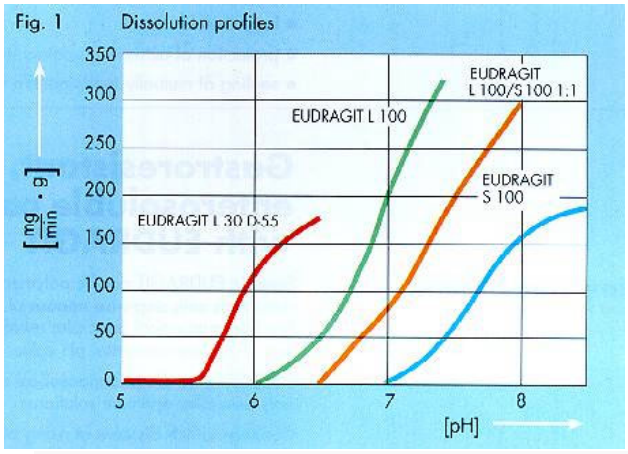
Products

EUDRAGIT® L and EUDRAGIT® S
grades are anionic polymers based on methacrylic acid esters. The films are insoluble below pH 5 and thus resistant to gastric fluid. By salt formation in the neutral to weakly alkaline medium of intestinal fluid, the films dissolve step-wise at pH values above 5.5.

Product properties

Of decisive importance for the controlled release of enteric-coated active ingredients is the dissolution profile of the EUDRAGIT® L/S film formers in the intestinal pH range from 5.5 to 7.0. The graph in Fig. 1 indicates how the film coatings dissolve in the intestine. In the duodenum, a pH range of 5.5 - 6.0 is to be expected; in the lower sections of the intestine, the pH value normally increases gradually to about pH 6.5 - 7.0 near the colon. However, the release of active ingredients also depends on the thickness of the film coatings and the solubility characteristics of the active ingredient under physiological conditions.

Fig. 1 Dissolution profiles



All polymer types in Fig. 1 can be mixed with each other in any desired ratio, thus making it possible to adjust intermediate values. The release values established in vitro must be confirmed in pharmacological and clinical tests.

Application

EUDRAGIT® polymers can be applied as coatings to all conventional, solid oral dosage forms such as tablets, capsules, small particles. These polymers can also be used to manufacture pellets, granules and sustained-release tablets.

Polymers processed form

- Solution in organic solvents (alcohols, acetone)
- Mixtures of organic solutions with water
- Purely aqueous latex dispersions

The coatings can also be processed with ease in all film-coating or fluidized-bed equipment that is commonly used worldwide.

Further possible applications

EUDRAGIT® L/S coatings show an excellent sealing effect even at very thin layers. This enables the following technical effects to be obtained:

- Protection against atmospheric humidity
- Isolating mutually incompatible particles in combination products
- Masking of cores with an unpleaseant odour or taste
- Granulation of active ingredients in powder form

The sealing effect of the film coatings naturally increases in proportion to the film thickness. In that case however, the release of active ingredients in digestive fluids with a pH of less than 5 is also delayed. Compromises can, however, be found.

Basic formulations for organic polymer solutions

EUDRAGIT® L/S solid substances can be dissolved with ease in alcohols and acetone, providing solutions of about 10 - 15%.
The addition of plasticizers and glidants is a must in order to ensure sufficient elasticity of the films and to reduce as much as possible the tendency of the cores to stick together during the processing.
When manufacturing EUDRAGIT® solutions, the regulations for handling flammable solvents must be observed. All processing equipment must be observed. All processing equipment must be explosion-proof. To avoid the risk of toxicity, workplaces must be properly ventilated and contamined air extracted. The working equipment must be earthed.

I. Basic formulation for a colorless enteric coating
Sufficient for opprox. 12 kg cores of average size. (Ø 8 mm, 200 mg in weight or
approx. 3 - 5 kg pellets (Ø 0.5 - 1.2 mm)

EUDRAGIT® L/S 100	600 g
Triethyl citrate	60 g
Talc	300 g
Water	500.g
Isopropyl alcohol	8,540 g
	10,000 g
Solids content:	9.6%
Polymer content:	6.0%

Pigments can be incorporated in the formulation. Suitable pigments are titanium dioxide as a white pigment and food colour lakes based on aluminium oxide or iron oxide pigments. It contains 20% polyethylene glycol on polymer. To obtain a plasticizing effect, 10% is usually sufficient. The higher concentration given here additionally provides a gloss-enhancing effect.

II. Formulation for colored final coats on enteric coated preparations
Sufficient for approx. 25 kg cores of average size. (Ø 8 mm, 200 mg in weight) or
opprox. 10 - 20 kg pellets (Ø 0.5 -1.2 mm)

Polymer solution	
EUDRAGIT® L/S 100	250 g
Solvent	7,250 g
Pigment suspension	
Polyethylene glycoi 6000	50 g
Talc	400 g
Titanium dioxide / pigments	300 g
Water	100 g
Isopropyl alcohol	1,650 g
	10,000 g
Solids content:	10.0%
Polymer content:	2.5%

III. Formulation for full-colored enteric coatings
Sufficient for approx. 12 kg cores of average size. (Ø 8 mm, 200 mg in weight) or approx. 3 - 5 kg pellets (Ø 0,5 - 1,2 mm)

Polymer solution	
EUDRAGIT L/S 100	625 g
Solvent	8,125 g
Pigment suspension	
Polyethylene glycol 6000	65 g
Talc	190 g
Titanium dioxide / pigments	125 g
Water	130 g
Isopropyl alcohol	740 g
	10,000 g
Solids content:	10.1%
Polymer content:	6.3%

Aqueous dispersions
Aqueous coating formulations can be prepared by stirring the EUDRAGIT® powder into water and adding alkali.

IV. Basic formulation for colorless enteric coatings.
Sufficient for opprox. 35 kg cores of average size (Ø 8 mm, 200 mg in weight) or approx. 10 - 15 kg pellets (Ø 0.5 - 1.2 mm)

Redispersion	
EUDRAGIT L 100-55	1,755 g
4% NAOH (1 N) solution	585 g
Water	3,510 g
Pigment suspension	
Triethyl citrate	175 g
Glycerol monostearate	35.9
Water	3,940 g
	10,000 g
Solids content:	19.9%
Polymer content:	17.6%

When manufacturing full-colored enteric film coatings, the ratio of pigments to titanium dioxide can be varied as a function of the disered intensity of colour. The quantities given in formulation VI provide a uniform colour coat on white tablet cores.

V. Formulation for colored final coats on enteric-coated preparations
Sufficient for approx. 50 kg cores of average size (Ø 8 mm, 200 mg in weight) or approx. 25 kg pellets (Ø 0.5 -1.2 mm)

Polymer dispersion	
EUDRAGIT® L 30 D-55	1,670 g
Water	3,335 g
Pigment suspension	
Triethyl citrate	50 g
Talc	830 g
Titanium dioxide / pigments	500 g
Sodium carboxymethyl-cellulose	35 g
Polyethylene glycol 6000	80 g
Water	3,500 g
	10,000 g
Solids content:	20.0%
Polymer content:	5.0%

VI: Formulation for full-colored enteric coatings
Sufficient for approx. 30 kg cores of average size (Ø 8 mm, 200 mg in weight) or approx. 10 - 15 kg pellets (Ø 0.5 -1.2 mm)

Polymer dispersion	
EUDRAGIT® L 30 D-55	4,710 g
Water	1,755 g
Pigment suspension	
Triethyl citrate	140 g
Talc	640 g
Titanium dioxide / pigments	175 g
Sodium carboxymethyl-cellulose	55 g
Polyethylene glycol 6000	55 g
Water	2,470 g
	10,000 g
Solids content:	24.8%
Polymer content:	14.1%

If more intensive colour is required and tablets of perhaps uneven colour are to be entirely covered, the quantity of white and coloured pigments must be increased. In that case, it may be advisable to first apply a colourless enteric base coat and then intensively coloured polymer layer.

VII: Formulation for enteric coatings with delayed dissolution in intestinal fluid

Sufficient for approx. 30 kg cores of average size (Ø 8 mm, 200 mg in weight) or approx. 10 - 15 kg pellets (Ø 0.5 - 1.2 mm)

Recommended post stirring time after the addition of the plasticiser: 1 hours

Redispersion	
EUDRAGT® S 1 00	1,440 g
1.7% ammonia solution	731 g
Triethyl citrate	720 g
Water	4,306 g
Pigment suspension	
Glycerol monostearate	43 g
Water	2,760 g
	10,000 g
Solids content:	22.2%
Polymer content:	14.4%

VIII: Formulation for enteric coatings with delayed dissolution in intestinal fluid

Sufficient for approx. 30 kg cores of average size (Ø 8 mm, 200 mg in weight) or approx. 10 - 15 kg pellets (Ø 0.5 - 1.2 mm)

Recommended post stirring time after the addition of the plasticiser: 16 hours

Redispersion	
EUDRAGT® S 100	1,440 g
KOH, 1N solution	734 g
Triethyl citrate	720 g
Water	4,306 g
Pigment suspension	
Glycerol monostearate	43 g
Water	2,757 g
	10,000 g
Solids content:	22.4%
Polymer content:	14.4%

Excipients

Plasticizer
Films of EUDRAGIT® tend to become brittle (cracking) below 10%. To improve the elasticity up to 25% can be added. EUDRAGIT® L 100 and EUDRAGIT® S 100 in aqueous formulations require a much higher proportion of plasticizer (40 - 50%). In all formulations, triethyl citrate has proved its worth as a plasticizer.

Solvents
Acetone and alcohols are preferentially used for manufacturing polymer solutions. An overview of the average dissolution time in minutes for the most common solvents or solvent / water mixture shows the following table.

Solvent	EUDRAGIT® L 100-55	EUDRAGIT® L 100	EUDRAGIT® S 100
Methanol	10	15	30
Methanol / water 97:3	10	15	25
Ethanol	20	10	10
Ethanol/water 97:3	20	10	25
Ethanol/water 6:4	20	20	40
Isopropyl alcohol	30	40	35
Isopropyl alcohol / water 97:3	20	15	20
Isopropyl alcohol / water 6:4	20	25	45
n-Butanol	30	70	swelled
Acetone	35	15	10
Acetone / water 97:3	15	25	10
Acetone / water 6:4	15	15	swelled
Acetone / isopropyl alcohol 4:6	-	30	5

Glidants
Polymer solutions and dispersions go through a tacky phase during drying. To avoid agglomeration of the cores, glidants are added to the spray suspensions. At critical points of manufactures, these can also be added in the form of a powder.

- Talc and Kaolin are often used in combination with pigments.
- Glycerol monostearate e. g. Imwitor® 900 is a good alternative to talc as a glidant in all the aqueous formulations mentioned.
- Micronised silic acid can be used in quantities of 10-30% on polymer and does have a matting effect and increases the permeability of film coatings.
- Magnesium stearate is somewhat more effective than talc and often provides good sealing of the film coatings and low permeability. However, it can only be used in organic polymer solutions, since coagulation or thickening may occur in aqueous dispersions.
- Pigments for film coating processes, both socalled aluminium colour lakes and iron oxides are suitable. Watersoluble dyes usually lead to inhomogeneous colouring of the coatings, which moreover rub off during handling.
- Titanium dioxide, apart from adjusting the intensity of the coatings, which moreover rub off during handling.

The Process

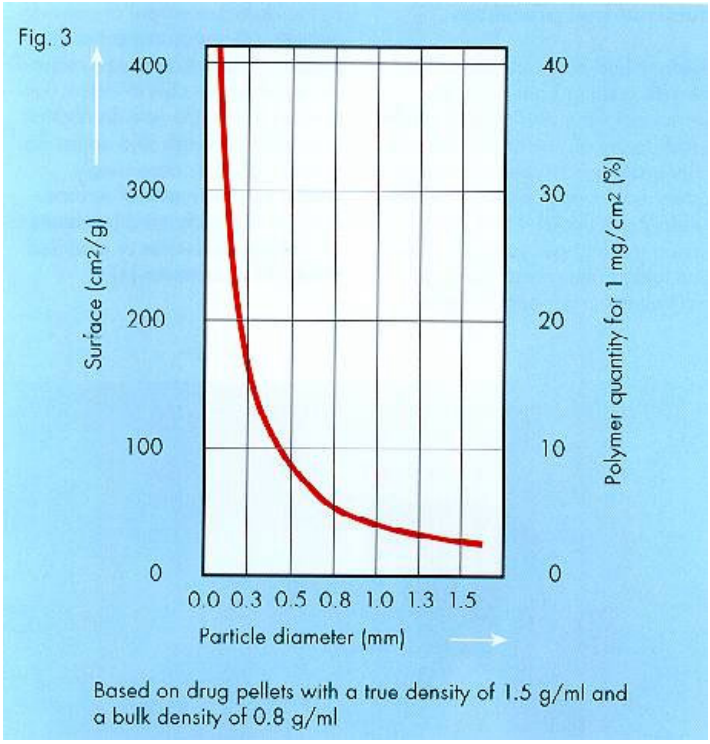
EUDRAGIT® polymethacrylates can be processed in all conventional types of coating equipments, by all coating operation commonly performed in the pharmaceutical industry.
Coating pans with spraying devices and high drying air capacity are particularly suitable for tablets. Fluid-bed coaters are preferred for small particles, which show a more pronouced tendency to agglomeration.

Suggestions for processing

Quantities to be applied

For enteric coatings, 4 to 6 mg polymer are applied per cm^2 of tablet surface, or 10 to 30 per cent by weight on particles such as pellets, granules or crystals with sizes in the range of about 0.5 to 1.5 mm. The required polymer quantity may vary according to surface structure, mechanical stability or solubility of the dosage form to be coated.

Fig. 3



Based on drug pellets with a true density of 1.5 g/ml and a bulk density of 0.8 g/ml

Pan process

A maximum of air should be introduced to ensure rapid drying of the sprayed solution. In order to reduce attrition during rotation or fluidisation to a minimum, cores of adequate stability have to be used. Inclusion of a substancial amount of fines increases the permeability of the film coats and may result in loss of enteric properties.

Abrasion of the applied films, espacially along tablet bands, is also to be avoided. It can damage the film coatings.
The spray rate has to be adjusted in such a way that spraying is performed more or less continuously and simultaneously with adequate drying.
Because of the high atomization pressure to which spray suspensions are exposed in airless spray systems, a certain minimum spray rate is required, which permits continuous spraying only from batch sizes of 80- 100 kg onwards.

Fluidized-bed processes

Fluidized-bed processes are mainly used for the coating of small particles. Because of the much higher throughput of drying air in comparison with other coating operations, spraying is faster and the agglomeration tendency less pronounced. Since particles have a much larger specific surface than tablets, the overall coating requirement in per cent is higher.

To facilitate assessment of polymer requirement, measurement of the product surface area is recommended. Simple measurements of surface area can be performed by means of a Blaine apparatus or modified Friedrichs manometer.