DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 12(3), 265-287 (1986)

ACRYLIC LATICES FROM REDISPERSABLE POWDERS FOR PERORAL AND TRANSDERMAL DRUG FORMULATIONS*

Dr. K. Lehmann
Röhm GmbH
Central Research and Development Pharmaceuticals
Kirschenallee
D-6100 Darmstadt, Germany

ABSTRACT

Aqueous dispersions of acrylic resins may be converted to powders by spray or freeze drying. Such solids contain loose agglomerates of discrete latex particles, that disintegrate easily into the original latex particles of less than 2 µm in diameter. No film formation occurs, provided that the minimum film forming temperature of the latex is not exceeded during drying.

Such powders can be redispersed in water in the presence of 3-6 mol% of alkali or organic bases to obtain a stable latex system. This can be used for enteric film coating in the same way as the original latex dispersions.

---

* The Manuscript was presented previously in similar form at the 4th Pharmaceutical Technology Conference, April 10 - 12, 1984, Edinburgh

0363-9045/86/1203-0265$3.50/0

Redispersed methacrylic acid copolymers can be mixed with neutral, permeable emulsion polymers to adapt the release profile of drugs more specifically to match their pharmacokinetic properties. In this way the pH-dependent solubility of methacryic acid copolymers, which controls the release in the gut by dissolution or increasing permeability can be combined with the pH--independent permeability of neutral acrylic ester polymers, to give time controlled retardation. Similar formulations of acrylic resins can also be used to solve several problems of transdermal delivery systems.

The described redispersable polymer powders are stable under normal storage conditions, so their handling and use as redispersed aqueous coating formulations is much more easier and will open an extended field of application.

INTRODUCTION

1.Experiences with Aqueous Dispersions

Since our first publication in 1971 (1) until now, we have obtained extensive experience in the processing of aqueous dispersions, so called "latices", and have confirmed the advantages that we expected. The film formation proceeds at room temperature, when the polymeric particles are soft enough and is optimal within a few seconds under the usual working conditions of modern coating equipment with a temperature of drying air of 30 - 50°C (2). The first layer of dry polymer already gives a water insoluble isolating film, and the inclusion of water is prevented when the cores are prewarmed at the beginning of the coating process and the spray rate is carefully adapted. In only a very few cases and only with very sensitive drugs was an isolating layer of polymer applied in organic solvent necessary. Acrylic

latices were also found very useful for the coating of small drug particles as pellets, granules or crystals in a particle size range at or above 0.1 mm. They formed effective thin film layers of appr. 10 µm thickness, encapsulating also irregular structures to give isolating or sustained release coatings (3-6)

Owing to the higher content of solids in these low viscous aqueous dispersions, compared with solutions of polymers in water or organic solvents, it is possible to shorten process time at nearly the same or scarcely higher working temperatures. Therefore the energy consumption of both systems is comparable (7-8) so that all important advantages of the aqueous medium are valid such as elimination of the problems of inflammability, absence of toxic effects and avoidance of air pollution, without any remarkable disadvantages in processing.

PROCEDURES

2. Redispersable Solid Powders of Anionic Acrylic Resins

When emulsion polymers are dried below their minimum film forming temperature (MFT) the latex particles are not able to fuse to a film due to the low flexibility of the polymer chains. Down to the so called "white point" some adhesion of the particles is observed, but below this temperature a loose powder is formed. Thus it is very easy to obtain free flowing dry powders when polymers with a MFT above about 50°C are spray dried; in these products the larger beads are formed from droplets in the spray jet (Fig. 1) and the original latex particles can be seen at higher magnification (Fig. 2).

If the MFT is lower, so that film formation or fusion of some latex particles occurs during spray drying, then freeze drying

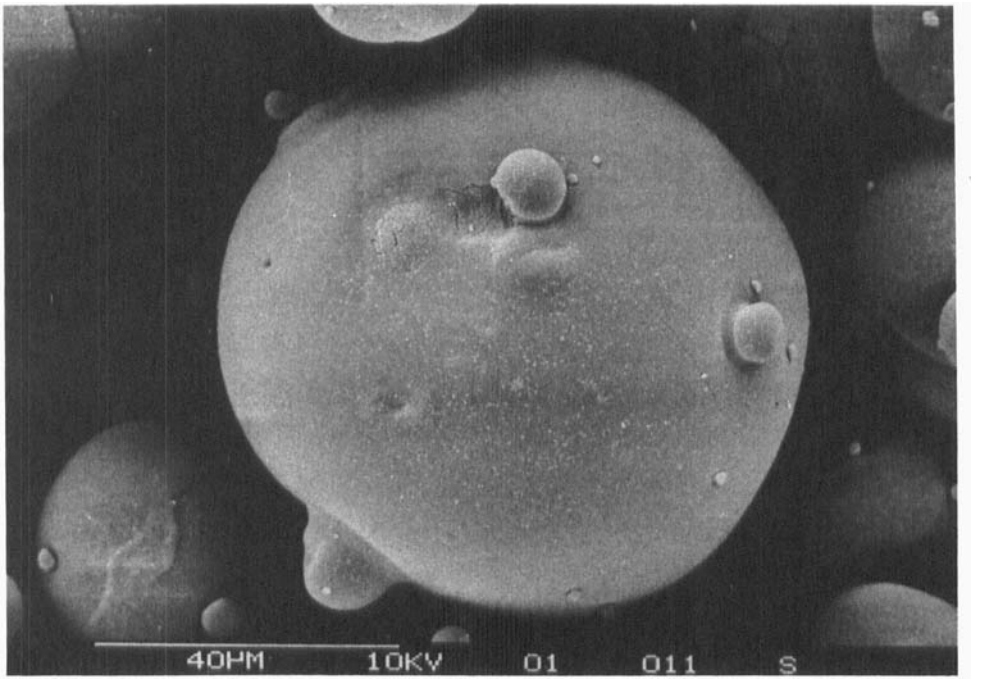


FIGURE 1

Sperical particles of Poly(MA_1-MMA_1) from spray dried latex. Particles size is in the range of 50 - 100 µm.

is used to prevent these effects. In this way loose agglomerates of singular latex particles can be obtained.

We have recently found that by adding small amounts of alkali to such latex powders to adjust the pH to around 5 a complete redispersion of anionic acrylic resins i.e. Poly(MA_1-EA_1)*) is possible. The addition of alkali necessary for redispersion is

*) MA = Methacrylic acid
EA = Ethylacrylate
MMA = Methylmethacrylate

The index numbers indicate the molar proportions of monomer units in the copolymer

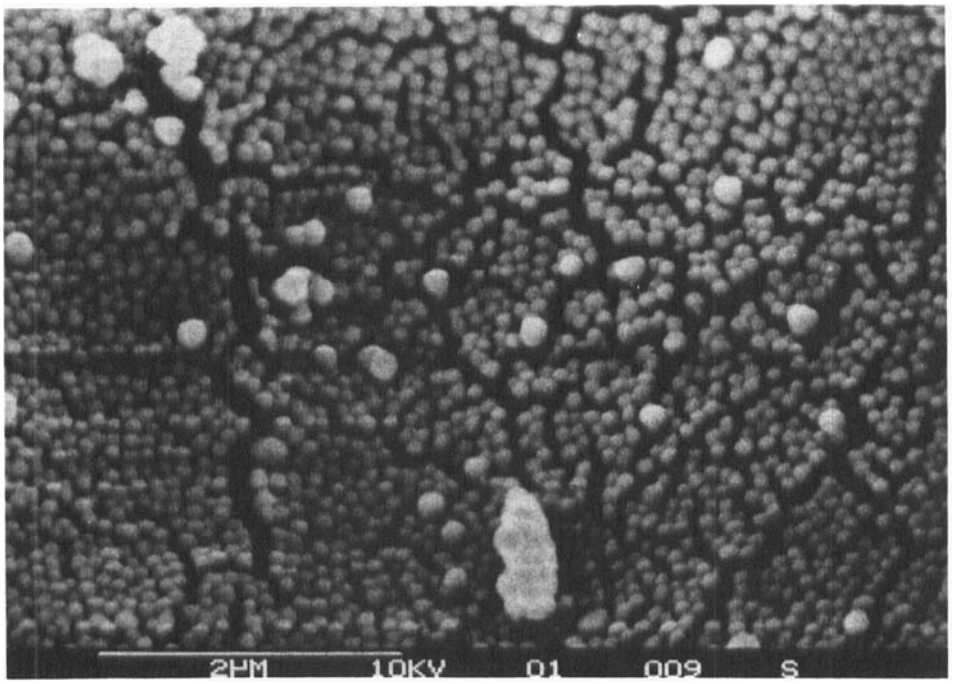


FIGURE 2

Higher magnification shows that the powder particles of Figure 1 contain numerous latex particles only 0.1 μm in diameter forming loose aggregates without any film formation.

equivalent to a degree of neutralisation of 3-6 mol% of the carboxylic groups in the polymer, which depends to some extent on the particle size of the latex, but this does not lower the gastroresistant properties of film coatings made with such redispersed systems. Methacrylic acid copolymers of the composition used here become water soluble at a degree of neutralisation of approx. 20-30 %. For redispersion only a limited number of carboxylic acid groups, presumably mainly at the surface of the latex particles and exposed parts of the polymer chains, are required to be neutralized. So we believe that the negative charges of the anionic groups produce a mutual repulsion of the latex particles that overcomes the weak cohesive forces between

them, and leads to a reformation of the original latex dispersion.

Several basic substances are effective for redispersion and added as appr. molar solutions while stirring to the suspension of the polymer powder in water. Table 1 gives a selection of examples. The reproducible process of redispersion can be followed by observation of the particle size of the suspension. Initially the suspended particles are just visible but disappear successively while the suspension obtains a milk-like appearance Concurrently the viscosity decrease below 50 mPa sec during stirring within 30-60 min. The resulting latex shows no or very little sedimentation of particles (less than 1 % after 24 hours) The particle size distribution of the original latex is essentially reattained. In many experiments we found a mean value, measured in a nanosizer, of only 5-15 % higher than before, sometimes both determinations were within the error of the measurement. More detailed testing of the particle size distribution in the ultra centrifuge showed a very similar position and shape of the peak (Fig. 3) and we calculated an increase of particle diameter R_w from 103 to 115 µm (+ 11.6 %). Some increase of the very small peak in the range of 2-3 µm is without practical importance provided it is below 1 %. Altogether an excellent reconstruction of the latex system from unfilmed drug polymer powders was achieved in a very simple way.

Instead of sodium hydroxide other basic substances are useful in equivalent amounts as shown in Tab. 1. For redispersion in production batch size for coating of appr. 250 kg of tablets or appr. 100 kg of pellets the simple equipment of Fig. 4 can be used. The vessel of about 45 cm in diameter has a volume of about 80 l so that it is possible to suspend about 15 kg of polymer powder in a volume of appr. 50 l.

TABLE 1

Dispersing of ®EUDRAGIT Methacrylic Acid Copolymers by Partial Neutralisation

Polymer	Base	Mol %	w/w %	Dry Substance (%)	Viscosity mPa·sec	Sediment in 24 h(%)	MFT (°C)	Particle Size R (nm)	
L 100-55	NaOH	5.0	1.1	30	--	--			
Poly(MA_1-EA_1)	NaOH	3.0	0.7	40	28	--	18	130	
	NH_3	3.0	0.3	30	11	1	3	124	a
	TRIS	3.2	2.2	30	--	1	3	117	b
	TEA								
	$(NH_4)_2CO_3$	3.0	0.8	30	<50	1	--	---	a
L 100	NaOH	5.0	1.1	34	--	0	78	124	b
Poly(MA_1-MMA_2)	NH_3	5.0	0.5	30	--	0	77	---	a
S 100	NaOH	5.2	0.7	30	--	2	>95	139	
Poly(MA_1-MMA_2)	NH_3	8.0	0.5	30	--	1	74	---	a/b
	TRIS	5.0	2.0	30	--	<1	88	---	b
	TEA	5.0	0.8	30	--	0	84	---	b

a = 5 % Tween 80 b = 10 % PEG

TRIS = tris(hydroxymethyl)aminomethane TEA = triethanolamine

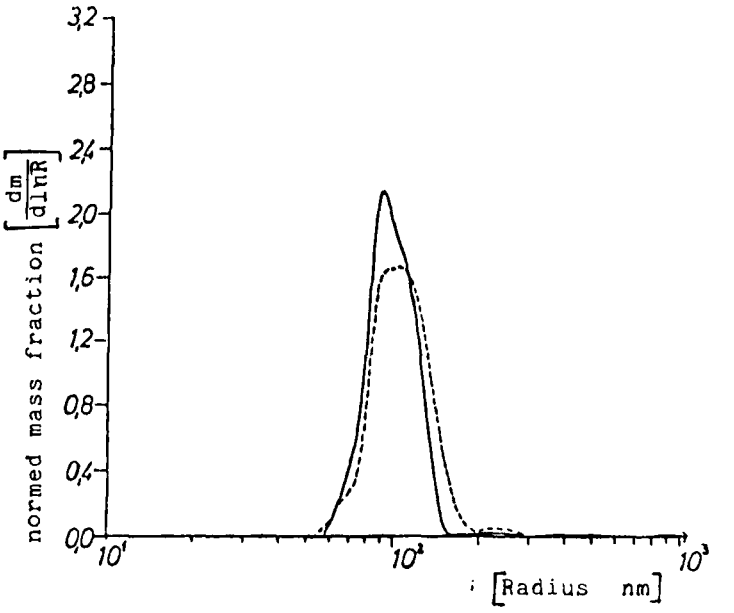


FIGURE 3

Particle size distribution of latex particles of Poly(MA -EA) measured in a ultracentrifuge. The scale of the ordinate is the mass fraction, normed that the area under the curve is 1 for any peak.
Key: ——— ®EUDRAGIT L 30 D original latex
------ ®EUDRAGIT L 100-55 freeze dried poweder, redispersed

In Table 2 some experiments for the preparation of enteric coated tablets are summarized. In a normal coating pan and in an accela cota a Walther air gun with a 1 mm nozzle and air pressure of 1 bar was used. Warm air of 55-75°C was introduced analogue to the process described in (9) trial No. 1.5. page 27 ff.

In a Glatt fluid bed granulator WSG 5 with Wurster insert and a similar air gun with 1 mm nozzle, air pressure of 1.5 bar and air inlet temperature of 45-50°C, air outlet 45°C were used; overall spray time was 120-150 min in each batch.

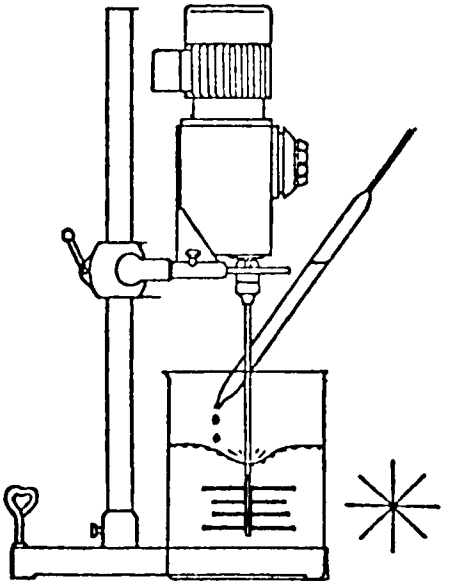


FIGURE 4

Apparatus for redispersion of polymer powders to an aqueous latex in the laboratory or pilot plant. It is important that the stirrer is able to mix even at low rotation rate of appr. 100 rpm the suspension, which is relatively thick in the beginning of the redispersion process. The alkali solution is added dropwise within appr. 5 min and stirring is continued for appr. 30 min.

In Table 2 results of testing for resistance in simulated gastric fluid and disintegration time in simulated intestinal fluid are described. Acceptable values were obtained with 4-6 mg/cm^2 very similar to the analogous experiment with the original emulsion polymer Poly(MA_1-EA_1) = ®EUDRAGIT L 30 D.

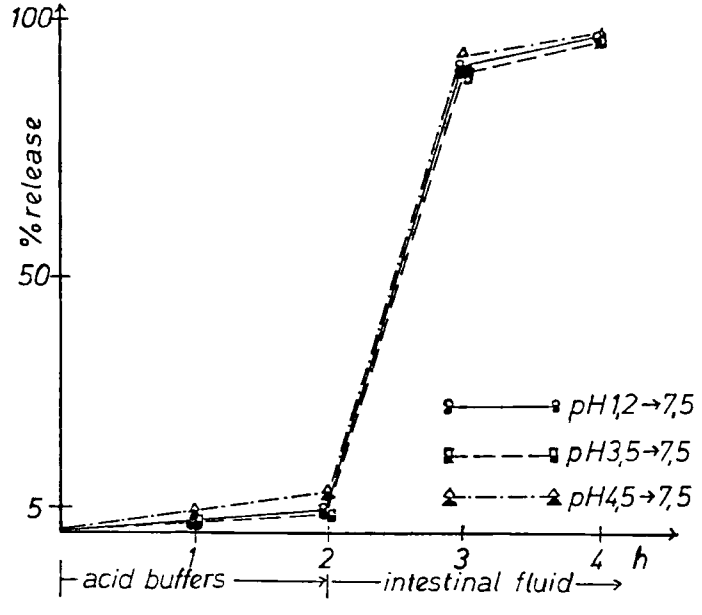
Fig. 5 shows with enteric coated acetylsalicylic acid crystals that here also the same results were obtained with original and redispersed latices of this polymer. In particular no difference in the permeability of both coatings was found in the pH-range

TABLE 2

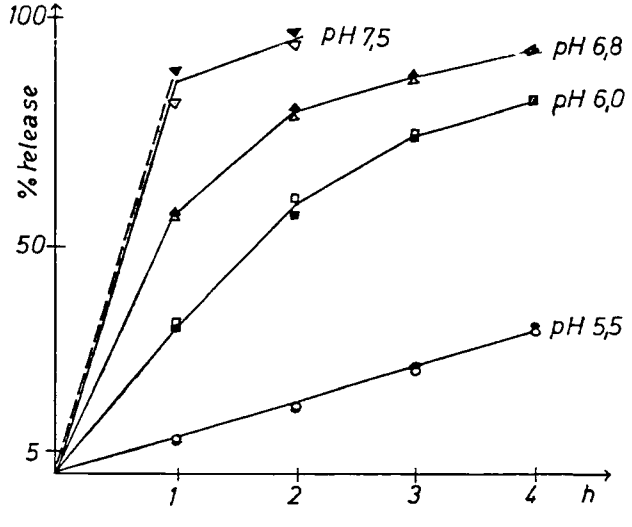
Coating of Tablets with Redispersed Methacrylic Acid Copolymer Poly(MA_1-EA_1) ®EUDRAGIT L 100-55

Process	Tablets per batch Diameter	Base	Applied Amount of Redispersion with 30 % solids	Applied Additives	Disintegration time (min) in Gastric fluid	in BP intestinal fluid pH 6.8 4 mg/cm²	5 mg/cm²	6 mg/cm² *
Coating pan	3 kg 7 mm Ø	NaOH 3 Mol%	730 g	Pigments 90 g	> 120	4	7	10
Coating pan	3 kg 7 mm Ø	NaOH 6 Mol%	740 g	Talkum 67 g	> 120	3	3	6
Coating pan	3 kg 10 mm Ø	NH_3 3 Mol%	600 g	Talkum 17 g	> 60	2	3	4
Accela Cota	12 kg 10 mm Ø	TRIS 3 Mol%	2800 g	Talkum 72 g	> 120	-	-	9
WSG 5 / Wurster	8 kg 7 mm Ø	NaOH 3 Mol%	2000 g	Pigments 240 g	> 120	6	8	11
WSG 5 / Wurster	8 kg 7 mm Ø	TRIS 3 Mol%	2000 g	Pigments 240 g	> 120	5	8	10
Coating pan (Comparison with original L 30 D)	3 kg 7 mm Ø	-	510 g	Talkum 15 g	> 120	6	8	--

* applied amount of coating in mg dry polymer substance per square cm of tablet surface



A



B

FIGURE 5

Release of Acetylsalicylic acid from enteric coated particles (USP-paddle method, 50 rpm).
A: Testing of resistance to acid buffers followed by release test at pH 7.5. Buffer solutions: simulated gastric juice USP XX, ammonium acetate buffer BP 80 pH 3.5; phosphate buffer BP 80 pH 4.5.
B: Testing of release rate at pH 5.5 - 7.5. Buffer solutions: isotonic phosphate buffer pH 5.5 and pH 6.5 (11), simulated intestinal fluid BP 80 pH 6.8 and USP XX pH 7.5. The dotted line represents the release rate at pH 7.5 measured in A to demonstrate identical release rate with or without pretreatment with acidic buffers.
Key: open symbols = original latex EUDRAGIT L 30 D/black symbols = redispersion from EUDRAGIT L 100-55

of 1.2-4.5 and also the release rate was the same at and above pH 5.5.

2.1. Redispersion of Freeze Dried Powders from Acrylic Emulsion Polymers

A useful formulation is:

®EUDRAGIT L 100-55 = Poly(MA_1-EA_1)	300.0 g
NaOH (106 ml 1N)	4.2 g
Polyethylene glycol 6000	30.0 g
Water	ad 1100.0 g

The equipment is shown in Fig. 4. The stirrer should guarantee an effective mixing of the suspended particles from the beginning without stressing the material with high sheering forces which may endanger good redispersion by causing coagulation of just redispersed latex particles. Also the incorporation of air bubbles should be prevented.

2.2. Redispersion of Spray Dried Powders from Acrylic Emulsion Polymers

Aqueous emulsion polymers, which besides methacrylic acid contain methyl methacrylate as comonomer show MFT values above 70°C. They are easily spray dried to give free flowing powders that consist of spherical agglomerates with a particle size around 50 µm. Such products are commercially available as EUDRAGIT L 100 = Poly(MA_1-MMA_1) and EUDRAGIT S 100 = Poly(MA_1-MMA_2). Scanning electron micrographs of these powders show the above described spherical particles (Fig. 1) and, at higher magnification, that they consist of loose agglomerates of the original single latex particles (Fig. 2). Aqueous suspensions of these agglomerates can be transformed to films in a so called thermogelation process by using 50-60 % of plasticizer (polyethylen-

glycol and Tween) as described by Bauer and Osterwald (10) so that gastroresistant coatings were obtained.

Redispersion of the same spray dried powders to the particle size of the original latices was easily achieved by adding 3-5 Mol% of alkali or other basic substances calculated on the molar basis of the contained carboxylic acid groups. The resulting latices showed the original particle size but also high MFT in the range of 75-80°C as before.

To achieve film formation under the usual mild conditions for film coating of drugs below 40°C mixing with relatively soft, neutral acrylic emulsion polymers was found to be very useful. The MFT of these polymers was in the range of 0-30°C. Table 3 shows a selection of mixtures from hard and soft emulsion polymers and the resulting MFT's. Films from these mixtures show a dispersed phase of the hard particles in a homogeneous phase of the soft polymer which has formed the film (Fig. 6). These heterogeneous films were clear in acid buffers and became turbid when the dissolution-pH of the methacrylic acid copolymer component was reached. By pH-stat titration a consumption of alkali was measured that was equivalent to the content of carboxylic acid groups in the film, and the carboxylic acid group containing polymer was leached out of the film (Fig. 7). It could be precipitated from the solution by acidification and identified by IR-spectrum.

RESULTS

3. Enteric and Sustained Release Coatings

Freeze dried methacrylic acid copolymer is easily redispersed in water (Table 1) and gives excellent enteric coatings on tablets

TABLE 3

Mixtures of Aqueous ®EUDRAGIT Dispersions as Enteric Coatings

Hard Component	Soft Component	Mixing ratio w/w	MFT(°C)	+ 10% PEG	Gastro resistance
Poly(MA_1-MMA_1) EUDRAGIT L 100	Poly(MA_1-EA_1)	50:50	32	16	
	EUDRAGIT L 30 D	75:25	66	36	
		90:10	79	59	
" "	Poly(EA_2-MMA_1)	30:70	13	--	+
	EUDRAGIT E 30 D	40:60	15	--	+ (PEG)
		50:50	20	--	
Poly(MA_1-MMA_1) EUDRAGIT S 100	Poly(MA_1-EA_1)	50:50	17	3	+
	EUDRAGIT L 30 D	75:25	>94	74	+
		90:10	>94	83	
" "	Poly(EA_2-MMA_1)	30:70	11	--	+
	EUDRAGIT E 30 D	40:60	13	--	
		50:50	15	--	
Poly(MA_1-EA_1) EUDRAGIT L 30 D	Poly(EA_2-MMA_1)	30:70	<25	--	+
	EUDRAGIT E 30 D	40:60	<25	--	+
		50:50	<25	--	+

MA = Methacrylic acid. MMA = Methylmethacrylate EA = Ethylacrylate

MFT = Minimum Film Forming Temperature PEG = Polyethyleneglycol 6000

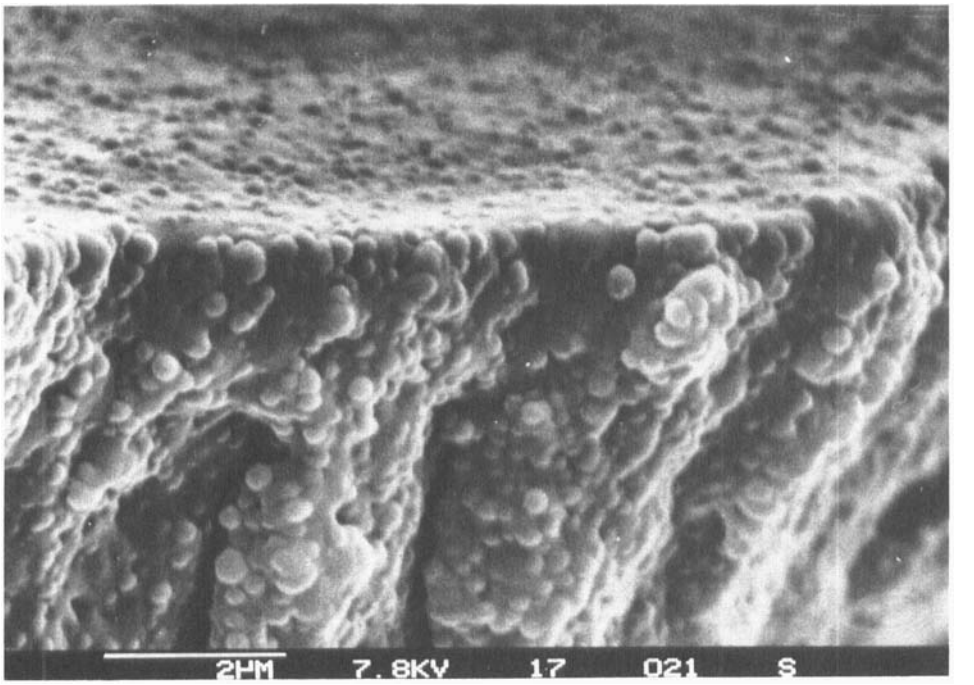


FIGURE 6

Heterogeneous film structure formed from a mixed latex of soft, neutral Poly(EA_2-MMA_1) and hard, anionic Poly(MA_1-MMA_1) in a ratio of 6:4. Obviously the hard, unfilmed latex particles of the anionic polymer are embedded in a continious phase of the soft polymer. This film was gastroresistant.

(Table 2) and on small particles (Fig. 5) with identical release pattern compared to original latex. We have also used latex mixtures and found pH-dependent release pattern (Fig. 8) controlled by the content of carboxylic groups in the polymers comparable to analogeous organic coatings (11).

Latex mixtures described above are also useful for the manufacture of sustained release drug formulations not only in the form of tablets but also as pellets, granules or crystals. If the content of gastroresistant-enterosoluble methacrylic acid co-

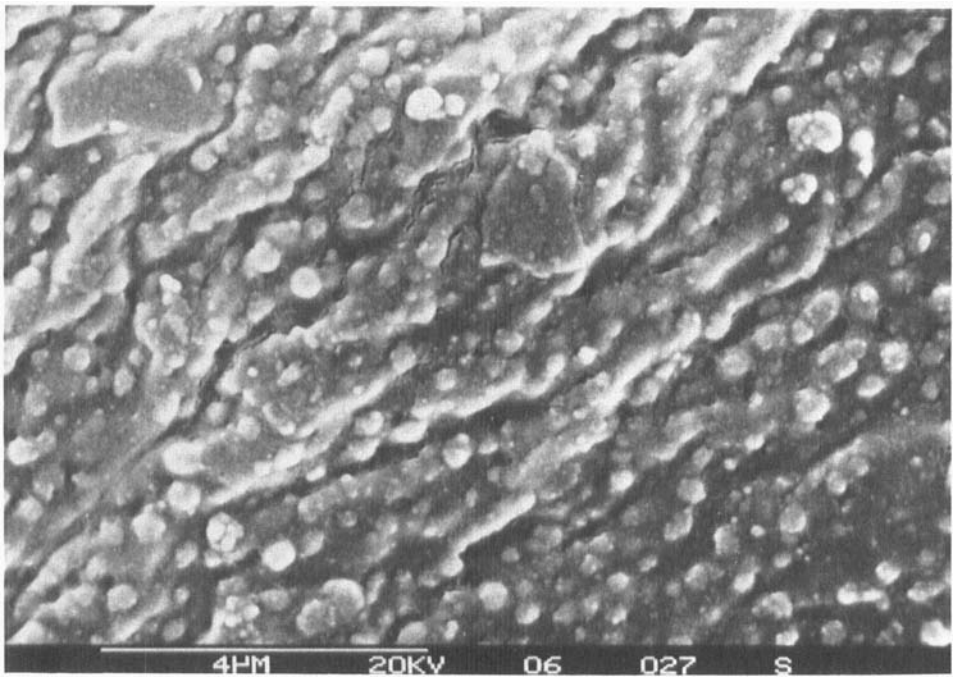


FIGURE 7

Structure of the film of Figure 6 after agitation in simulated intestinal fluid BP 80 pH 6.8, 2 hr at 37°C. The dissolution tendency of the anionic latex particles leading to a porous film can be seen.

polymer in the mixture is low, as shown in Fig. 9, with a mixing ratio of neutral Poly(EA_2-MMA_1) to anionic Poly(MA_1-EA_1) of 10 : 1 the release rate through thin film layers (5 % coating) is similar to a first order reaction.

With more coating (7.5 %) a more linear release pattern, especially above pH 6, was observed. With more coating, up to 15 %, only the release rate in the first three hours was reduced but after this time when the pH was increased to pH 6.5 the release rate also increased owing to leaching out of the enterosoluble portion of the mixed film, increasing the permeability.

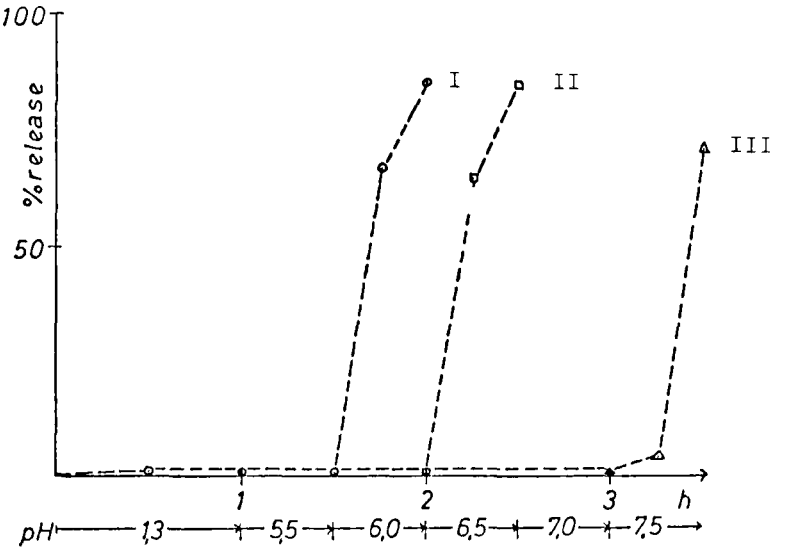


FIGURE 8

Disintegration and drug release of gastroresistant-enterosoluble coated tablets in a BP-disintegration apparatus without discs. After agitation in simulated gastric fluid for 1 hr, buffer solutions of increasing pH as indicated were added for 30 min each until disintegration was observed and the released drug measured photometically.

Key: I Poly(EA_2-MMA_1): Poly(MA_1-EA_1) = 7:3
II Poly(EA_2-MMA_1): Poly(MA_1-MMA_1) = 7:3
III Poly(EA_2-MMA_1): Poly(MA_1-MMA_2) = 7:3

With a mixing ratio of 1:1 a more pH-dependent release pattern was obtained (Fig. 10).

By redispersion of enterosoluble acrylic polymer powders to microfine latices and mixing with soft neutral emulsion polymers a new system of aqueous coating formulations was developed which showed adaptable release patterns for controlled release drugs.

4. Formulation of Transdermal Delivery Systems

Several types of EUDRAGIT acrylic resins can be used in the formulation of transdermal delivery systems since these polymers

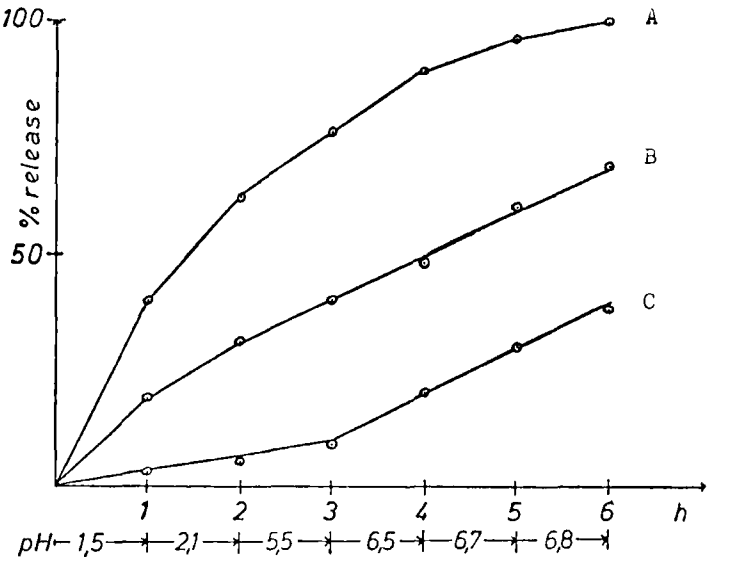


FIGURE 9

Release of Theophylline from granules coated in a fluid bed process with a latex mixture of neutral Poly(EA_2-MMA_1) and anionic Poly(MA_1-MMA_1) in a ratio of 10:1. Release tests in a USP-Paddle apparatus and half change method (12) with simulated gastric juice and intestinal fluid BP 73.
With increasing thickness of the coating more retardation was observed but above pH 5.5 the release rate was enhanced by dissolution of the anionic component of the mixed film.

Key: A = 5 % coating
B = 7.5 % coating
C = 15 % coating.

are well tolerated by the skin and have a high binding capacity for incorporating drug substances.

The permeable types RS 100 and RL 100 are used in organic solutions or extrusion processes to form the desired drug reservoir layers or diffusion controlling membranes. The aqueous dispersions E 30 D and L 30 D as well as redispersed L 100/S 100 can be used when the drug is not sensitive to water during the production process.

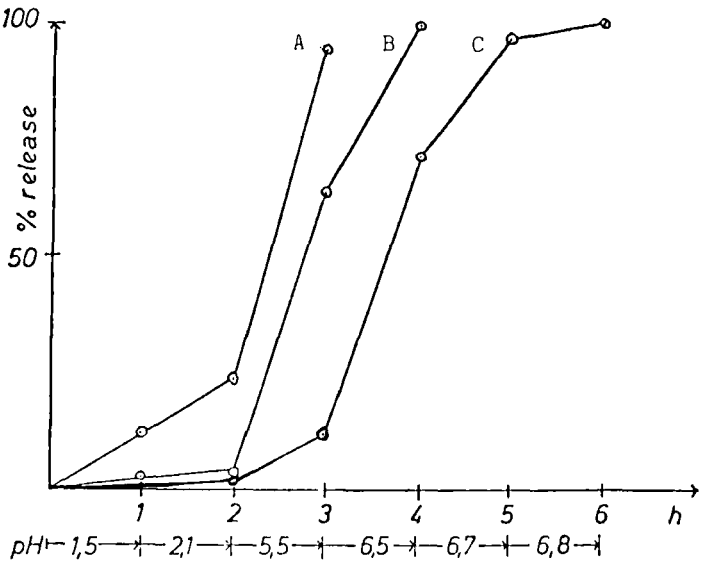


FIGURE 10

Release of Theophylline from granules coated is a fluid bed process with a latex mixture of neutral Poly(EA_2-MMA_1) and anionic Poly(MA_1-EA_1) in a ratio of 1:1. Release tests as described in Figure 11. With 15 % or more coating, the particles are resistant to gastric juice. Above pH 5.5 the release rate increases due to the dissolution of the anionic polymer in the mixed film.

Key: A = 10 % coating
B = 15 % coating
C = 20 % coating

If a molecular dispersion of the drug in the polymer layer is formed, good retardation is normally obtained with concentrations of approx. 10-20 % w/w calculated as solid drug in solid polymer. If the drug is insoluble or only partly soluble in the polymeric phase the release rate can be influenced or even controlled by the particle size of the drug.

The permeability of the polymer films can be adapted to the desired release rate by mixing RS 100 of low permeability with the

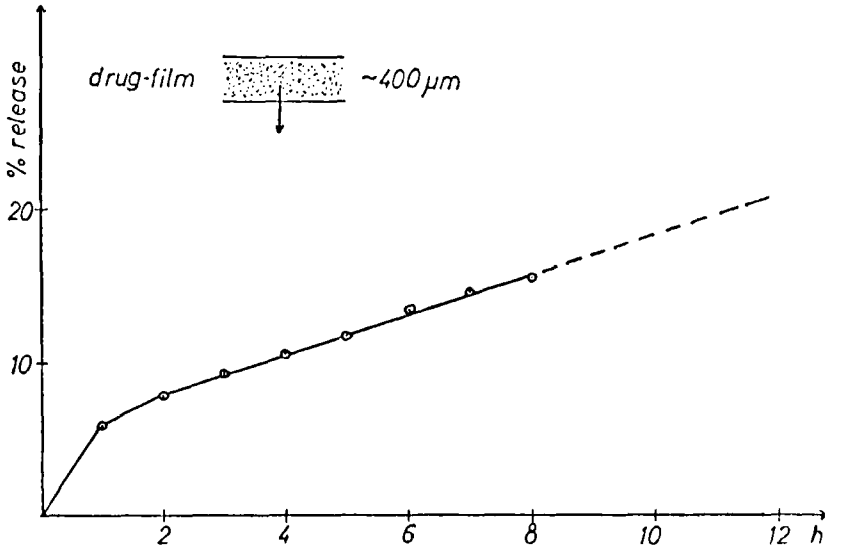


FIGURE 11

Release of Norephedrine (5 mg/cm^2) from ®EUDRAGIT E 30 D films at pH 6.8

more permeable type RL 100, these may be mixed in all proportions. The E 30 D emulsion polymer can be modified in its retarding effect by adding more or less hydrophilic additives such as Polyethylenglykol, Cellulose ethers or esters etc.

In Fig. 11 the release rate of Norephedrine HCl, embedded in a monolayer of Poly(EA_2-MMA_1) is shown. The drug was dissolved directly in the 30 % aqueous dispersion of the polymer and dried to a film layer of 400 µm at room temperature so that approx. 10 % of drug substance was incorporated as a solution in the polymer. No crystallisation was observed. After a fast release of some 10 % of the drug in the first two hours a nearly linear rate was observed during at least 8 hours. In the experiment shown in Fig. 12 the release from the reservoir was modified by

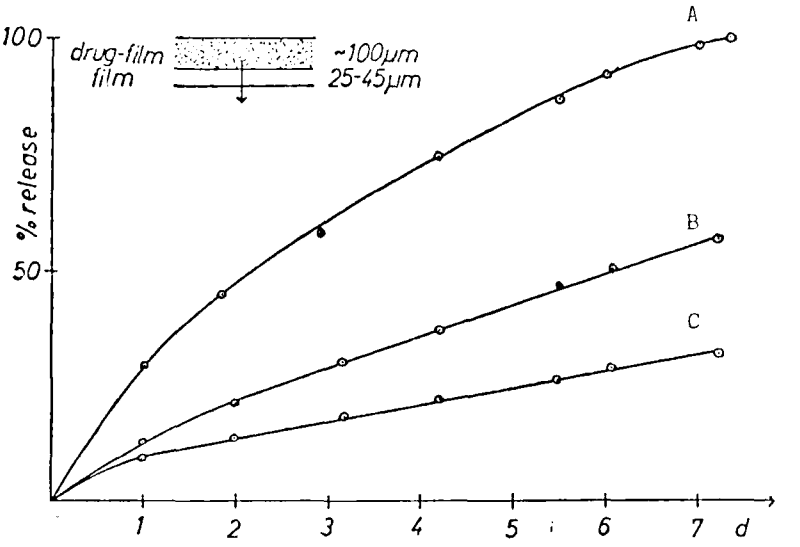


Figure 12

Release of Idoxuridine (10 mg/cm^2) from EUDRAGIT E 30 D films at pH 7.2.

Key: A = 25 µm film thickness
B = 35 µm film thickness
C = 45 µm film thickness

an additional diffusion controlling membrane on top of the drug reservoir, which contained the drug in crystalline form. Depending on the thickness of this membrane, in the range of 25-45 µm, the release could be controlled, for up to seven days.

Apart from extrusion processes and film casting from organic solutions the water based formulations of emulsion polymers or redispersed latex systems described are very useful, since they do not require the use of explosion proof machinery and do not cause any toxic hazards or air pollution problems during production. Owing to the low film forming temperature of EUDRAGIT-latices drug formulations can be processed under very mild conditions.

CONCLUSIONS

Emulsion copolymers of methacrylic acid can be freeze or spray dried to redispersable powders. Redispersion proceeds spontaneously under mild agitation of the aqueous suspension at a pH around 5 and the original latex system is reconstituted with a very similar particle size distribution in the range of 50 - 150 nm.

Redispersed latex emulsions can be used for enteric coating of tablets and small drug particles and film properties regarding resistance to gastric juice, permeability and dissolution rate in intestinal fluid didn't show any difference compared with the original latex.

Emulsion copolymers of high film forming temperature can be mixed with soft, neutral acrylic latex for sustained release drug formulations with a more or less pH-dependent release pattern in the pH-range of 6-8. Similar films are also useful in the formulation of transdermal delivery systems.

Redispersable powders of methacrylic acid copolymers facilitate the handling of aqueous latex systems for enteric coating of drugs and open a more convenient and more flexible technology for controlled release formulations.

ACKNOWLEDGEMENTS

I thank Mr. Dieter Dreher and Mr. Harry Götz for the redispersion experiments, Dr. Krämer and Mag.pharm. Petereit for the transdermal preparations and Dr. Panke for ultracentrifuge measurements.

REFERENCES

(1) K. Lehmann, D. Dreher: Pharm. Ind. 34, 894-99 (1972)
(2) K. Lehmann: Acta Pharm. Techn., 21(4), 255-60 (1975)
(3) K. Lehmann, D. Dreher: Int.J.Pharm.Tech.&Prod.Mfr., 2(4), 31-43 (1981)
(4) K. Lehmann, H. Bössler, D. Dreher: Acta Pharm. Suecica, Vol. 13, Supp. 1976, 37
(5) K. Lehmann, H. Bössler, D. Dreher: Midland Macromolecular Monograph Series, Symposium "Polymeric Delivery Systems", August 1976, 111-19
(6) K. Lehmann, Dr. Dreher: Pharm. Techn.March 1979, 53-56, 99
(7) W. Rothe, G. Groppenbächer: Pharm.Ind. 34, 892,94 (1972)
(8) K. Lehmann: Acta Pharm. Fenn. 91, 225-238 (1982)
(9) Praktikum des Lackdragierens, Röhm Pharma GmbH, 1983
(10) H. Osterwald, Bauer, K.H.: FIP-Kongress Wien 1981, S. 152
(11) K. Lehmann: Drugs Made in Germany Vol. XI, 34-41 (1968)