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TECHNOLOGICAL EVALUATION OF AQUEOUS ENTERIC COATING SYSTEMS WITH AND WITHOUT INSOLUBLE ADDITIVES

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ABSTRACT

The most recent dispersible enteric polymers such as AQUATERIC, HPMCP HP 55 F, EUDRAGIT L 100 55 and cellulose acetate phthalate (micronized in our laboratory), were evaluated on two different physical and chemical substrates (soluble and insoluble). Four standard formulations were used with and without the most common solid additives such as talc and titanium dioxide.

A good distribution of all coatings was obtained on the both substrates previously studied.

The mechanical properties and the dissolution profile of gastric resistance showed clearly that the methacrylic copolymer-based product is a good alternative to esther celluloses manufactured with the most modern technologies.

INTRODUCTION

Film coating of pharmaceutical solid dosage forms is being increasingly employed not only to improve product elegance and integrity, but also to achieve the required drug release characteristics.

Aqueous polymeric dispersions of water insoluble polymers have recently been introduced to coat pharmaceutical solid dosage forms. The advantages of these systems over organic solvent solutions are cleary evident with regard to ecology, toxicity and safety. Other advantages derived from the polymeric dispersion structure are the high solid content and their low viscosity.

These coating systems, defined by Vanderhoff as pseudolatex, are simple dispersions of polymer in water. The size of the particles dispersed is less than 1000 nm and the content of polymer can usually vary between 10 and 40% w/w (1,4).

Film formation by pseudolatex is more complex than by solvent solutions and occurs by means of the contact, penetration and coalescence of particles during gradual water evaporation. The mechanism of film formation is however complicated and for the best results a very small polymer particle size, an accurate choice of operative temperatures and the use of plasticizers to decrease the MFT (minimum film formation temperature) of polymer are essential (1,6).

The aim of this work was the technological evaluation of the most recent dispersible enteric polymers such as AQUATERIC, HPMCP HP 55 F, EUDRAGIT L 100 55, cellulose acetate phthalate (micronized in our laboratory), applied on substrates of different physical and chemical characteristics.

Several trials of enteric coatings were carried out in a perforated pan using four standard formulations containing the most common additives such as talc and titanium dioxide.
Therefore the gastric resistance properties by USP Test and kinetic release of drug at pH 6.8 were evaluated.
The initial technological tests and dissolution profiles were compared to those obtained after stability at different storage conditions.

MATERIALS

As tablet substrate two different drugs were used: Ketoprofen, an insoluble non-steroidal antiflammatory and Metiguanide, a soluble antidiabetic agent (the index of polarity, P_0, are 33.6 and 68,6 % respectively).
Ketoprofen tablets were prepared using: microcrystalline cellulose (AVICEL PH 101,FMC,USA), lactose (LACTOSE 200 mesh Die Milkindustrie Voghel, Neth.), sodium carboximethylcellulose (NYMCEL ZS B10, Nyma,Neth.) and magnesium stearate (Erba-Biochimica, Ital.).
On the other hand the Metiguanide tablets contained: colloidal silicon dioxide (GRACE, U.K.), povidone (KOLLIDON K25, BASF.,Ger.), microcrystalline cellulose (AVICEL/PH 101, FMC, USA) and stearic acid (Erba-Biochimica, Ital.).
For the film coating the materials used were redispersible cellulose acetate phthalate (AQUATERIC FMC, USA), hydroxypropyl methylcellulose phthalate (HPMCP HP55F, Shinetsu, Jap.), cellulose acetate phthalate (Eastman Kodak, USA), redispersible polymethacrylates (EUDRAGIT L 100 55, Rohm Pharma,

Ger.), triacetin (Erba-Biochimica, Ital.), polysorbate (TWEEN 80, Atlas, UK), talc (Talco e Grafite, Ital.) and titanium dioxide (Urai, Ital.).

MANUFACTURING PROCEDURE

Ketoprofen tablets:50 Kg of Ketoprofen, 30 Kg of microcrystalline cellulose and 20 Kg of lactose were granulated by lab unit solid processor PK (Patterson Kelley) preparing three batches. Then 100 Kg of calibrated granulate, 13.4 Kg of microcrystalline cellulose, 0.7 Kg of sodium carboxymethylcellulose and 0.9 Kg of magnesium stearate were blended in a Ribon blender (Viani) for 20 minutes. Approximately 100,000 tablets were compressed on a rotary tablet press (Ronchi AM 13/8) using 0.7 cm bevelled edge punches.

Metiguanide tablets:20 Kg of Metiguanide, 0.2 Kg of colloidal silicon dioxide and 0.72 Kg of povidone K 25 were granulated in the same granulator as that used for Ketoprofen.

20 Kg of calibrated granulate, 1.031 Kg of microcrystalline cellulose, 0.382 Kg of colloidal silicon dioxide and 0.382 Kg of stearic acid were mixed in a ribbon blender (Viani) for 20 minutes.

Approximately 4000 tablets were compressed on the same tablet press Ronchi using 1.2 cm bevelled edge punches.

The formulation of coating dispersions are given in table 1 and the properties of the coating agents are included in the same table.

The polysorbate 80 was dissolved in a small quantity of hot water and then added to the remaining water under vigorous agitation at constant temperature (not higher than 20°C).

TABLE 1
Formulations of enteric dispersions.

Cellulose derivatives	10.0			Film former
Polymethacrylates (*)			10.0	Film former
Glyceryl triacetate	3.5		1.0	Plasticizer
Polysorbate 80		0.1		Emulsifier
Talc (**)		2.0		Antiadherent
Titanium dioxide (**)		1.0		Opaquant
Purified water to reach 100 parts				Vehicle

(*) Small amounts of alkali (NaOH) were added to reach a final pH of 5.0.

(**) Dispersed solid additives were employed singly and in mixture (talc/titanium dioxide).

Then triacetine was put into the surfactant solution, still under vigorous agitation until the solution turned clear. Then the solid polymers (or aqueous dispersion and talc or titanium dioxide) were gently and cautiously poured on the dispersion, with further slight agitation for 15 minutes. The resulting pseudolatex was then homogenized by a suitable homogenizer.

Tablet batches of 10 Kg were coated in a 24" Accela Cota pan. The operative coating conditions are shown in Table 2.

For Ketoprofen tablets the weight increases after coating (due to the polymeric materials deposited on tablets) were 7 mg, 10 mg and 13 mg with respect to the

TABLE 2

Coating conditions for Ketoprofen and Metiguanide tablets using enteric coating formulation.

Tablet load, Kg	10
Air inlet temperature, °C	80
Air outlet temperature, °C	43
Product temperature, °C	33
Pumping rate, rpm	30
Preheating, min	5
Pan speed, rpm	12
Atomizing Air Pressure, Kg/cm^2	1

uncoated tablet weights (corresponding to 4.82, 6.89 and 8.96 mg of coating on 1 cm^2 of tablet surface). For Metiguanide tablets the weight increases after coating were 26 mg and 52 mg with respect to the uncoated tablet weights (corresponding to 6.26 and 12.53 mg of coating on 1 cm^2 of tablet surface).
Finally all the freshly coated tablets were dried in the same pan at 60°C for 60 minutes.

TEST PROCEDURE

The tablets were subjected to the following tests:

- Weight uniformity: on 100 dusted tablets, the individual and average weights, the standard deviation and the coefficient of variation were calculated.

- Crushing strength: 20 tablets were individually subjected to diametral compression on a Schleuninger Tester Models.

- Friability: loss of weight percentage of 20 tablets rotated at 24 rpm for 5 minutes in a Roche friabilator.

- Thickness and diameter: on 10 tablets using a vernier caliper.

- Drug release and gastric resistence: the tests were performed according to U.S.P. XXI, pg. 1245 with Apparatus 2.

- Stability: enteric tablets in PVDC/AL blisters were stored at R.T., 35°C, 35°C+80% R.H. and 500 F.C.. The gastric resistance and the drug release in buffer phase were tested after 12 weeks storage.

RESULTS

The physical properties of all tablets are listed in Tables 3,4,5. Weight uniformity, thickness and diameter clearly show a good distribution of film on the substrate. The most important parameter is the crushing strength which defines the mechanical resistence of film and represents the hardness of the tablet. It can be said that the mechanical resistance of enteric tablets is not influenced by the thickness of the film coating, but depends only on the coating formulations considered. From our tests it results that EUDRAGIT L 100 55 is more resistant than HPMCP-HP 55 F, CAP UF and AQUATERIC confirming the results obtained in the mechanical characterization study (7). The presence of inorganic pigments, such as talc and titanium dioxide, in films slightly decreased the mechanical performances of the tablets when coated with HPMCP HP 55 F and CAP

TABLE 3

Physical properties of the Ketoprofen tablets uncoated and coated by different aqueous-based enteric polymers with and without solid additives mixture.

Batch	Average weight (mg±SD)	Thickness(*) (mm)	Diameter(*) (mm)	Crushing Strength (Kg±SD)
KT(**)	115.7±0.4	3.02	7.00	2.4±0.2
AT1	122.5±1.7	3.15	7.11	5.2±0.2
	126.3±1.8	3.16	7.16	5.8±0.4
	129.8±1.6	3.23	7.20	6.3±0.3
CT1	122.1±1.4	3.14	7.15	5.4±0.3
	125.6±1.9	3.18	7.20	7.6±0.5
	128.3±1.9	3.21	7.25	7.5±0.3
HT1	122.4±1.6	3.16	7.18	6.9±0.5
	126.0±2.2	3.23	7.25	8.5±0.3
	127.9±2.0	3.26	7.28	8.9±0.3
ET1	122.7±1.5	3.17	7.14	7.7±0.5
	124.4±1.6	3.18	7.15	8.4±0.7
	127.0±1.6	3.21	7.18	8.8±0.6
AT5	123.1±1.8	3.14	7.10	5.7±0.3
	127.4±1.5	3.16	7.15	5.6±0.2
	131.6±1.6	3.23	7.20	6.2±0.3
CT5	123.6±1.8	3.13	7.12	3.9±0.2
	125.9±1.7	3.15	7.20	4.5±0.3
	130.8±1.7	3.20	7.30	4.2±0.2
HT5	122.7±1.5	3.14	7.17	6.4±0.3
	126.3±2.2	3.20	7.23	7.8±0.6
	128.8±1.6	3.22	7.28	7.5±0.4
ET5	122.5±2.0	3.15	7.14	8.8±0.5
	125.8±1.6	3.18	7.15	10.3±0.7
	129.3±1.8	3.21	7.20	12.9±0.5

Where: KT=Uncoated Ketoprofen tablets, A=AQUATERIC, C=CAP UF, H=HPMCP HP 55 F, E=EUDRAGIT L 100 55, T=triacetin, 1=without solids, 5=talc/titanium dioxide.
(*) The standard deviations of tablet thickness and diameter are below ± 0.03mm.
(**) Friability index is 0.43%.

TABLE 4

Physical properties of the Ketoprofen tablets uncoated and coated by different aqueous-based enteric polymers with single solid additives.

Batch	Average weight (mg±SD)	Thickness(*) (mm)	Diameter(*) (mm)	Crushing Strength (Kg±SD)
KT(**)	115.7±0.4	3.02	7.00	2.4±0.2
AT2	122.6±1.9	3.11	7.10	5.5±0.2
	127.1±1.7	3.18	7.15	5.7±0.3
	131.1±1.7	3.21	7.20	5.8±0.2
CT2	122.8±2.1	3.14	7.18	5.2±0.4
	126.4±1.9	3.15	7.22	5.1±0.4
	130.1±2.5	3.18	7.33	5.0±0.3
HT2	122.1±2.2	3.17	7.18	6.0±0.5
	124.7±1.9	3.19	7.22	6.8±0.3
	127.5±2.4	3.21	7.25	7.8±0.5
ET2	122.1±1.9	3.17	7.18	8.6±0.5
	125.1±1.5	3.16	7.15	9.9±0.8
	128.6±1.8	3.22	7.19	12.2±0.4
AT3	121.7±1.6	3.13	7.10	5.9±0.4
	126.9±1.4	3.17	7.16	6.0±0.3
	130.7±1.7	3.25	7.20	6.7±0.2
CT3	122.6±2.1	3.12	7.14	5.7±0.5
	126.3±1.8	3.17	7.10	6.7±0.3
	129.1±1.6	3.20	7.25	6.5±0.3
HT3	123.1±1.7	3.15	7.18	6.7±0.6
	126.5±1.6	3.20	7.25	8.2±0.6
	128.4±1.2	3.23	7.28	8.6±0.5
ET3	121.8±1.8	3.15	7.13	7.3±0.6
	125.2±1.7	3.18	7.16	8.7±0.6
	127.7±1.8	3.21	7.19	9.3±0.7

Where: KT=Uncoated Ketoprofen tablets, A=AQUATERIC, C=CAP UF, H=HPMCP HP 55 F, E=EUDRAGIT L100 55, T=triacetin, 2=talc, 3=titanium dioxide.
(*) The standard deviations of tablet thickness and diameter are below ± 0.03mm.
(**) Friability index is 0.43%.

TABLE 5

Physical properties of the Metiguanide tablets uncoated and coated by different aqueous-based enteric polymers with solid additive mixture.

Batch	Average weight (mg±SD)	Thickness(*) (mm)	Diameter(*) (mm)	Crushing Strength (Kg±SD)
MT(***)	568.0±7.2	5.30	12.00	11.9±2.1
AT5	589.9±8.4	5.38	12.12	15.2±1.7
	605.9±9.7	5.48	12.24	15.2±2.1
	617.9±3.2	5.51	12.28	17.2±1.5
CT5	593.1±8.3	5.42	12.25	15.2±2.0
	609.2±9.5	5.46	12.29	16.7±1.4
	621.3±7.8	5.50	12.36	16.9±2.2
HT5	591.4±13.1	5.40	12.21	15.1±1.4
	612.0±12.5	5.52	12.38	18.4±1.7
	624.3±10.8	5.60	12.40	18.4±0.9
ET5	592.5±8.3	5.40	12.19	18.0±2.5
	609.5±7.8	5.47	12.23	> 20.0
	620.7±5.3	5.51	12.30	> 20.0
MT/S	578.0±8.9	5.34	12.20	15.9±2.2
AT5/S	615.0±10.8	5.52	12.25	18.0±2.0
(**)	643.5±7.4	5.58	12.40	19.0±1.3
AT5(**)	660.5±15.5	5.63	12.45	19.1±0.8

Where: MT=Uncoated Metiguanide tablets, S=Subcoated Metiguanide tablets, A=AQUATERIC, C=CAP UF, H=HPMCP HP 55 F, E=EUDRAGIT L100 55, T=triacetin, 5=talc and titanium dioxide.
(*) The standard deviations of tablet thickness and diameter are below ± 0.05mm.
(**) Tablets obtained with double amount of coating or after the subcoat processing (standard cellulose aqueous formula).
(***) Friability index is 0.21%.

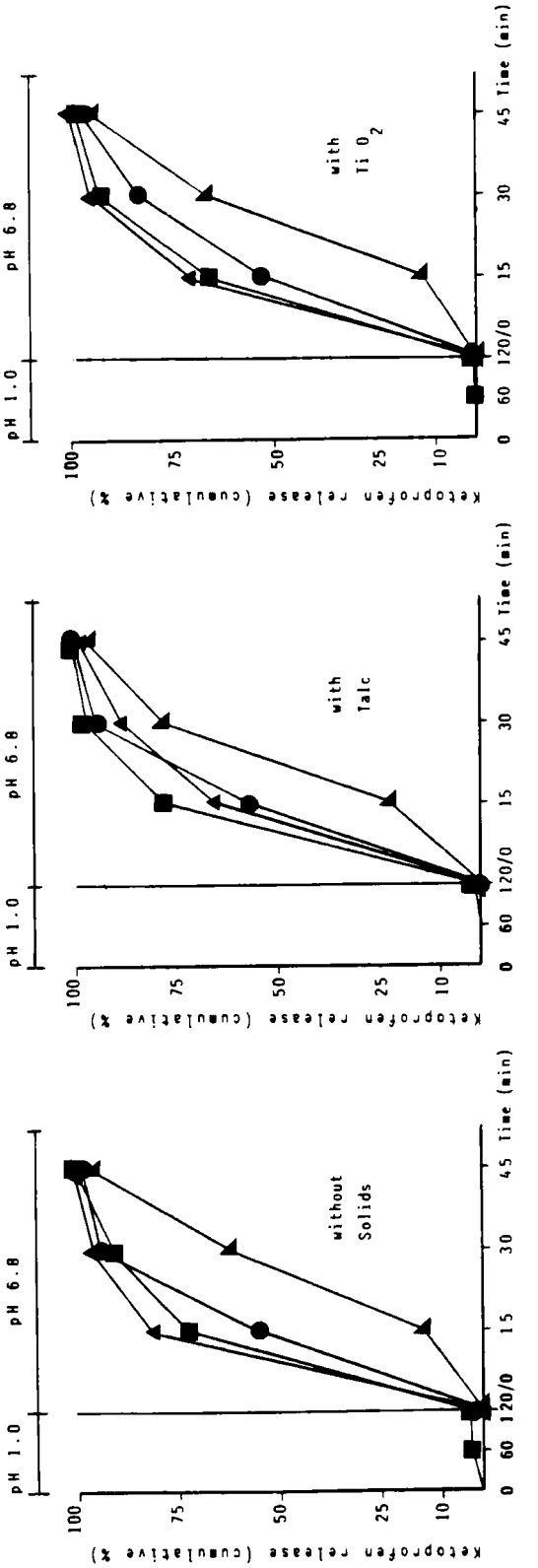

FIGURE 1

Effect of coatings with different polymer systems on gastro-resistance and entero-solubility of Ketoprofen tablets; the vertical line indicates USP threshold for minimal acceptable resistance (USP XXI method A, Enteric-coated articles at 37°C and 60 rpm).
(■) = AQUATERIC, (▲) = CAF UF, (◆) = HPMCP HP 55 F and (●) = EUDRAGIT L 100 55 S.

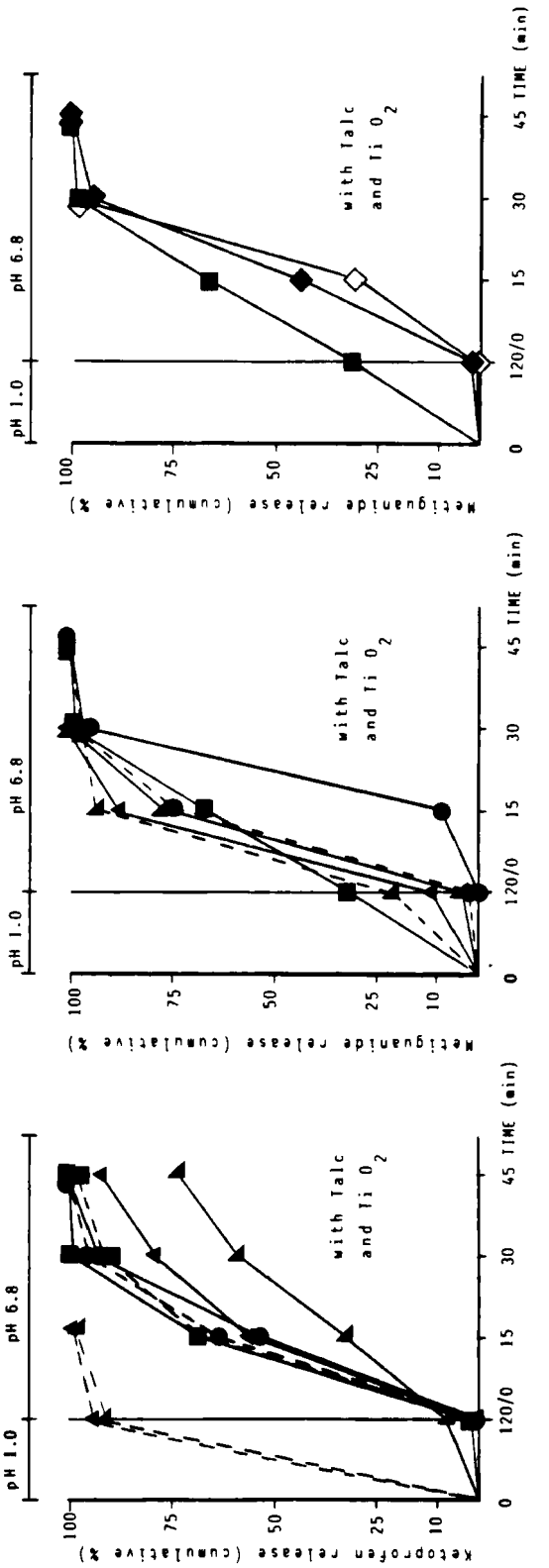

FIGURE 2

Effect of coatings with different polymer systems on gastro-resistance and entero-solubility of Ketoprofen and Metiguanide tablets; the vertical line indicates USP threshold for minimal acceptable resistance (USP XXI, method A, Enteric articles, at 37°C and 60 rpm). Broken line is the lowest coating and continuous line is the highest coating.
(■) = AQUATERIC, (▲) = CAP UF, (●) = HPMCP HP 55 F, (●) = EUDRAGIT L 100 55, (◆) = AQUATERIC with sub-coating and (◇) = AQUATERIC with double coat.

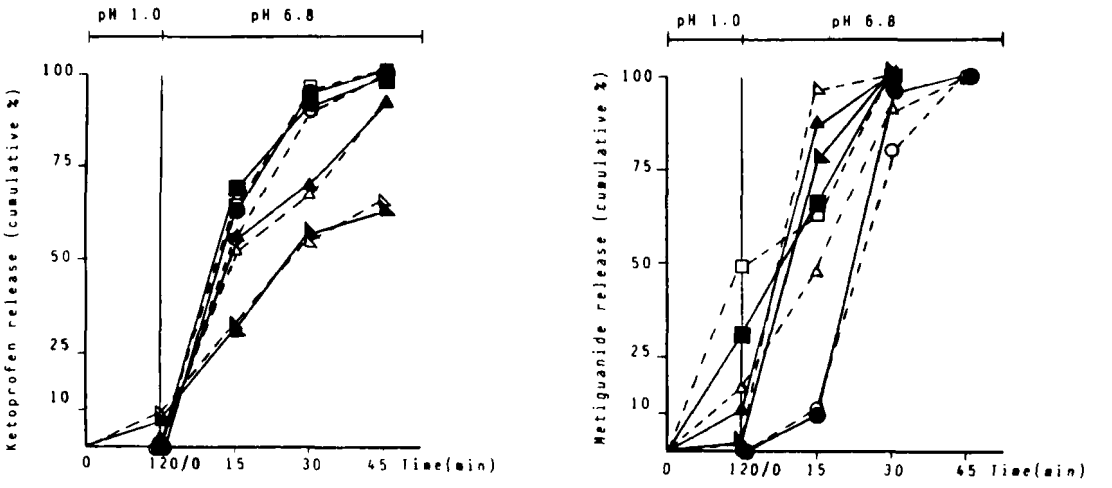

FIGURE 3
Drug dissolution profiles of Ketoprofen and Metiguanide tablets coated by different enteric polymer systems after different storage conditions; the vertical line indicates USP threshold for minimal acceptable resistance (USP XXI, method A, Enteric articles, at 37°C and 60 rpm).
(■) (□) = AQUATERIC, (▲) (△) = CAP UF, (◣) (◺) = HPMCP HP 55 F, (●) (○) = EUDRAGIT L 100 55.
Continuous lines are the initial control and broken lines are the controls: after three months at 35°C + 80% RH for Ketoprofen and 1 year at 25°C for Metiguanide.

UF, while it did not affect AQUATERIC and EUDRAGIT L 100 55 (the latter improved with talc). All tablets checked for their capacity to stay intact in gastric juice passed the USP test.

Some differences in the release of the Ketoprofen tablets at pH 6.8 after 15 min were pointed out, but after 30 min all coatings exhibited similar dissolution profiles (Fig. 1). On the contrary the coated preparations containing the two solid additives, showed significant differences of physico-chemical properties on both drug substrates (Fig. 2).

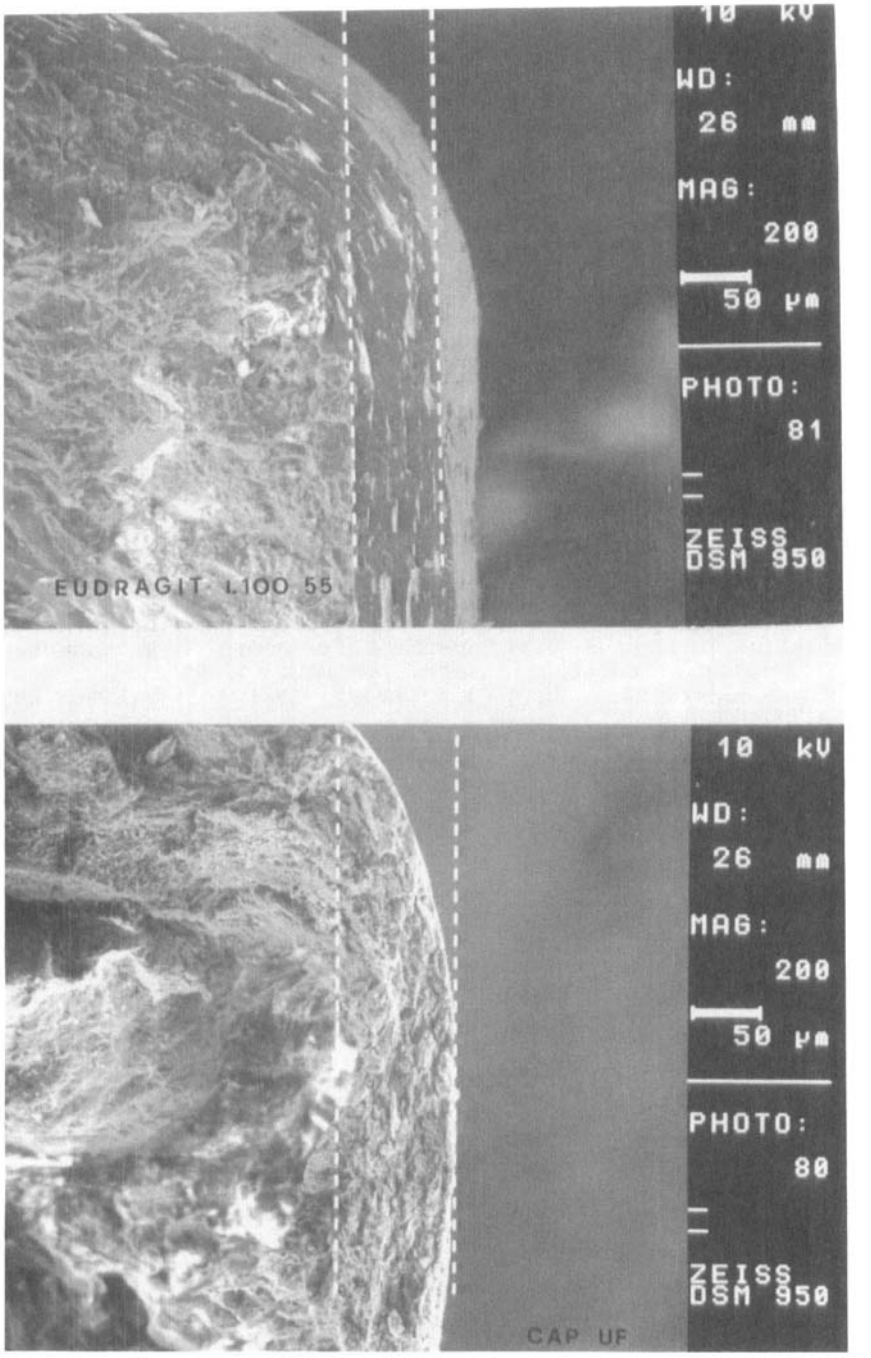

FIGURE 4

Scanning electron microscope: cross section of Ketoprofen tablets coated by CAP-UF and EUDRAGIT L 100 55 systems with talc and titanium dioxide mixture.

Ketoprofen tablets, coated with CAP UF and HPMCP HP 55 F, disintegrated easily in gastric environment when the lowest coating amounts were applied. But the AQUATERIC and EUDRAGIT L 100 55 films exhibited the best performance in the USP test for the various thicknesses of the coated tablets.

Metiguanide coated tablets did not pass the USP test using AQUATERIC and CAP UF, as with HPMCP HP 55 F at the lowest coat. By using EUDRAGIT L 100 55 the dissolution profiles were excellent, but also the AQUATERIC film guaranteed good results when the uncoated tablets were insulated by subcoating barriers or were coated with double amounts of the coat (Fig.2).

After 12 weeks of stability at 45°C and a 35°C/80% RH Ketoprofen coated tablets mantained their gastric-resistant performance and showed no significant differences of release at pH 6.8 in comparison with the initial control (Fig. 3). Moreover after 1 year of stability at 25°C Metiguanide coated tablets proved gastroresistant only with EUDRAGIT L 100 55 and HPMCP HP 55 F films.

These results guarantee the reliability of these enteric coatings. It therefore appears clearly that EUDRAGIT L 100 55 is the polymer that suffer the least from the stiffness caused by talc and titanium dioxide and hence best fulfil the different formulative requisites (Fig.4).

CONCLUSIONS

The small amount of plasticizer required to get a good mechanical enteric coating, the adaptability to different formulations, the possibility of coating tablets with different physical and chemical characteristics even without previous sealing and the

unchanged drug release profiles after stability test are all factors which have enhance the EUDRAGIT L 100 55 performance.

The metacrylic copolymer-based product is a good alternative to esther celluloses manufactured with the most modern technologies.

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REFERENCES

1. G. S. Banker, E. Peck, Pharm. Technol., 5 (4) 54 (1981).
2. M. Mehta, M. J. Valazza, S. E. Abele, Pharm. Technol., 10 (4) 46 (1986).
3. R. Gurny, F. Gumowsky, E. Doelker, "Proceedings of 4th International Conference on Pharmaceutical Technology", Paris, 5, 117-122 (1986).
4. K. Lehman, Drug Dev. Ind. Pharm., 12 (3), 265-287 (1986).
5. M. B. Davis, G. E. Peck, G. S. Banker, Drug Dev. Ind. Pharm., 12 (10), 1419-1448 (1986).
6. L. Lachman, H. A. Liberman, J. L. Kanig, "Theory and practice of Industrial Pharmacy", eds Lea and Febiger, Philadelphia, 346 (1986).
7. R. Bianchini and C. Vecchio, "Proceeding of 5th International Conference on Pharmaceutical Technology", Paris, 1, 416-425 (1989).