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TECHNOLOGICAL EVALUATION OF THREE ENTERIC COATING POLYMERS
II. WITH A SOLUBLE DRUG

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ABSTRACT

Three enteric coating polymers, cellulose acetate phthalate (CAP), hydroxy propylmethylcellulose phthalate (HP55) and cellulose acetate trimellitate (CAT) were evaluated on two different chemical substrates (soluble and insoluble). Gastric juice resistance was tested by dissolution using USP apparatus (paddle) in Britton buffer at different pH, under sink conditions over 5 hours. It can be said that the resistance of tablets depends on the coating formulation considered and the drug solubility. From our tests it results that CAP is more resistant than CAT for two drugs in intestinal medium and the resistance of HP55 depends on the solubility of the drugs. More, only CAT allows the release in the proximal small intestine for drugs whatever solubiliy.

INTRODUCTION

Cellulose esters are extensively used in the coating of solid forms to control and localize release of drugs in the intestine (1-5). A recent study (6) indicated that the efficiency of an enteric coated tablet is dependent on several parameters : the medium, the drug and the polymers properties. More, these authors report that the dissolution of polymer and the release rate of drug may be modified by interaction between film, drug and excipients.

In a former paper (7), the importance of the dissolution medium in the in vitro testing procedure has been shown. Three enteric coating polymers were studied : cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate (HP55) and cellulose acetate trimellitate (CAT) ; CAT has exhibited a dissolution pH lower than these of other cellulose derivate.

In another article (8), the gastric resistance properties and kinetics release of insoluble drug has been evaluated from coated tablets with three polymers to compare their coating properties.

The aims of the present work were to determine the influence of the drug solubility on the film coating properties and to investigate a possible interaction between drug and film. For this, the enteric properties of coated tablets of Sulfathiazole (8) were compared with these of coated tablets of Sulfathiazole Sodium, and the physico-chemical study of association drug-coating film was realized.

EXPERIMENTAL

Materials

The active substance is a water soluble drug : Sulfathiazole Sodium NF 11 (LEBUGLE and Cie, Vernouillet, France)

For the film coating, the polymers used were these studied in the precedent paper (8) : CAP*, HP55* and CAT*. The materials were obtained from commercial suppliers and used as received.

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* trademark

Methods

The core of tablet was prepared by the technique (8) used for the sulfathiazole tablets and its composition is the same. The composition of the coating system employed and the coating conditions were described in this paper.

Tests procedure

The tablets were subjected to the same tests that the Sulfathiazole tablets : average weight, hardness, friability, thickness and diameter, gastric resistance and intestinal disintegration test, drug release and stability.

Physico-chemical study

It has realized by spectral methods :

- **X-ray diffraction studies :** an X-ray powder diffractometer (C.G.R. O 80) with a selected cooper tube as a source of radiation was used to examine powdered samples of single substrates (SH and SNa), uncoated and coated tablets.

- **Infrared analysis :** Perkin Elmer infrared spectrophotometer was used to obtain I.R. spectra of pure drugs, uncoated and coated tablets.

RESULTS AND DISCUSSION

Differences between characteristics for the two types of tablets are displayed.

Disintegration and gastroresistance

The disintegration characteristics at pH 6.5 and the results of gastroresistance test at pH 1.2 of the coated tablets were listed in tables 1 and 2. For comparison the results obtained with insoluble sulfathiazole tablets were added (8). The gasric resistance of Sulfathiazole coated tablets was obtained with

TABLE 1

Tablets disintegration time at pH 6.5 (min).

coating solution (ml)	150	300	450	600	750	900	1050	1200	1350	1500
SH/CAT	-	11	11.3	12	12	13	-	-	-	-
SNa/CAT	-	-	-	-	-	-	-	-	-	13.5
SH/HP55	-	10	10	11.3	12	13	-	-	-	-
SNa/HP55	-	-	-	-	-	-	-	-	25	30
SH/CAP	-	10	11	13	14.5	15	-	-	-	-
SNa/CAP	-	-	-	-	-	-	-	30	34	37

SNa = Sulfathiazole Sodium
SH = Sulfathiazole

TABLE 2
Gastric resistance of coated tablets at pH 1.2 (min)

coating solution (ml)	150	300	450	600	750	900	1050	1200	1350	1500
SH/CAT	80	>120	>120	>120	>120	>120	>120	>120	>120	>120
SNa/CAT	9.5	19.5	25	35	47.5	58.5	84	90	110	>120
SH/HP55	2	40	>120	>120	>120	>120	>120	>120	>120	>120
SNaHP55	11	19.2	21.5	34.6	38.6	55.6	87.5	92	>120	>120
SH/CAP	50	>120	>120	>120	>120	>120	>120	>120	>120	>120
SNa/CAP	6	9	20	40	45	75	100	>120	>120	>120

300 ml of coating solution for CAT and CAP and 450 ml for HP55 ; contrarly, the Sulfathiazole Sodium tablets require larger amounts of these solutions to reach the gastroresitance : 1200 ml with CAP, 1350 ml with HP55 and 1500 ml with CAT.

Then, it is difficult to obtain a coating film for Sulfathiazole Sodium tablets in contrast to insoluble Sulfathiazole tablets.

It can be said that the solibility of SNa in the solvent causes a light solubilization of the tablet and reduces adhesion to the tablet surface at the beginning of the coating process.

Physical characteristics

The physical properties of uncoated and coated tablets are presented in tables 3, 4 and 5 in termes of increasing application of coating solution. An analysis of variance and a Newman-Keuls' test had showed that the amount and the nature of coating solution had a marked effect on these properties. The evolution of these parameters is the same for the two drugs but, for the sulfathiazole sodium, it can be remark that :

- for any polymers, the hardness increases from the second application of the coating solution (300 ml)

- the thickness shows the same evolution from 450 ml with CAT, and CAP, and 300 ml with HP55

- the weight average is increased at the first application of the polymer solution (150 ml) with CAP and CAT and for a higher volume (750 ml) with HP55. These results show that the two batches of coated tablets (SH and SNa) are different from one another in adhesion of the film.

Physicochemical characteristics

The X-ray diffraction patterns of sulfathiazole sodium, tablet and film core interface are illustrated in figure 1.

The diffraction spectra of pure sulfathiazole sodium shows that the drug was highly crystalline in nature as indicated by numerous distinctive peaks in the X-ray diffractograms. In figures 1b and 1c representing the core and the film/core interface, the spectra possesse all the characteristics diffraction peaks of

TABLE 3

Hardness of uncoated tablets and coated tablets (kgp) : average and standard deviation (n = 10)

coating solution (ml)	SH/CAT	SNa/CAT	SH/HP55	SNa/HP55	SH/CAP	SNa/CAP
0	8.4 (0.8)	6.7 (0.6)	8.4 (0.8)	6.7 (0.6)	8.4 (0.8)	6.7 (0.6)
150	10.1 (0.7)	7.0 (0.9)	11.7 (0.6)	7.0 (0.3)	11.7 (0.8)	6.7 (0.5)
300	10.2 (0.4)	10.2 (1.0)	11.8 (0.7)	8.1 (0.5)	11.8 (0.7)	8.5 (0.6)
450	12.9 (0.8)	11.4 (1.1)	12.1 (0.8)	8.8 (0.6)	14.1 (1.0)	13.0 (0.4)
600	16.3 (0.8)	13.3 (0.7)	12.7 (0.6)	12.2 (0.4)	17.1 (0.6)	15.6 (0.7)
750	16.4 (0.8)	15.6 (0.8)	13.7 (0.7)	13.9 (0.5)	17.3 (1.4)	18.4 (0.8)
900	16.7 (0.9)	17.7 (0.5)	15.2 (1.0)	14.9 (0.5)	19.5 (0.6)	19.5 (0.5)
1050		19.1 (0.7)		17.4 (0.5)		
1200				18.1 (0.4)		
1350						
1500						

NEWMAN-KEULS' test at level 5%

	SH/CAT		SNa/CAT		SH/HP55		SNa/HP55		SH/CAP		SNa/CAP	
vol	aver	gr	aver	gr	aver	gr	aver	gr	aver	gr	aver	gr
900	16.7	1	17.7	1	15.2	1	14.9	1	19.5	1	19.5	1
750	16.2	1	15.6	2	13.6	2	13.9	2	17.3	2	18.4	2
600	15.3	2	13.3	3	12.7	3	12.2	3	17.1	2	15.6	3
450	12.8	3	11.4	4	12.1	3/4	8.8	4	14.1	3	13.0	4
300	10.2	4	10.0	5	11.8	4	8.1	5	11.8	4	8.5	5
150	10.1	4	7.0	6	11.7	4	7.0	6	11.7	5	6.7	6
0	8.4	5	6.7	6	8.4	5	6.7	6	8.4	6	6.7	6

TABLE 4
Diameter of uncoated and coated tablets (mm) : average and standard deviation (n=25)

coating solution (ml)	SH/CAT	SNa/CAT	SH/HP55	SNa/HP55	SH/CAP	SNa/CAP
0	9.039 (0.003)	9.063 (0.004)	9.039 (0.003)	9.063 (0.004)	9.039 (0.003)	9.063 (0.004)
150	9.064 (0.006)	9.075 (0.006)	9.067 (0.005)	9.089 (0.007)	9.062 (0.006)	9.068 (0.007)
300	9.079 (0.005)	9.076 (0.006)	9.084 (0.005)	9.104 (0.010)	9.092 (0.006)	9.071 (0.008)
450	9.096 (0.006)	9.080 (0.008)	9.095 (0.005)	9.113 (0.010)	9.109 (0.006)	9.077 (0.008)
600	9.104 (0.005)	9.083 (0.01)	9.109 (0.006)	9.119 (0.006)	9.129 (0.010)	9.087 (0.007)
750	9.120 (0.007)	9.096 (0.007)	9.137 (0.006)	9.132 (0.010)	9.154 (0.010)	9.108 (0.008)
900	9.136 (0.009)	9.105 (0.007)	9.150 (0..009)	9.141 (0.010)	9.176 (0.009)	9.126 (0.008)
1050		9.111 (0.007)		9.159 (0.010)		9.147 (0.009)
1200		9.124 (0.008)		9.203 (0.010)		9.166 (0.009)
1350		9.156 (0.009)		9.207 (0.010)		9.182 (0.009)
1500		9.166 (0.011)		9.231 (0.010)		9.22 (0.009)

NEWMAN-KEULS'test at level 5%

vol	SH/CAT aver	gr	SNa/CAT aver	gr	SH/HP55 aver	gr	SNa/HP55 aver	gr	SH/CAP aver	gr	SNa/CAP aver	gr
1500			9.17	1			9.23	1			9.22	1
1350			9.17	2			9.21	2			9.18	2
1200			9.12	3			9.20	2			9.16	3
1050			9.1	4			9.16	3			9.14	4
900	9.14	1	9.10	5	9.15	1	9.14	4	9.18	1	9.12	5
750	9.12	2	9.10	6	9.14	2	9.13	5	9.15	2	9.11	6
600	9.11	3	9.08	7	9.11	3	9.11	6	9.15	2	9.11	6
450	9.10	4	9.08	7/8	9.10	4	9.11	6	9.11	4	9.08	8
300	9.08	5	9.08	8	9.08	5	9.10	7	9.09	5	9.07	9
150	9.06	6	9.08	8	9.07	6	9.09	8	9.08	6	9.07	9

TABLE 5
weight of uncoated and coated tablets (mg) : average and standard deviation (n=20)

coating solution (ml)	SH/CAT	SNa/CAT	SH/HP55	SNa/HP55	SH/CAP	SNa/CAP
0	304.9 (2.0)	307.6 (6.1)	304.9 (2.0)	307.6 (6.1)	304.9 (2.0)	307.6 (6.1)
150	305.3 (2.1)	311.0 (7.9)	305.2 (2.1)	308.3 (4.5)	305.0 (2.5)	309.2 (8.1)
300	307.8 (1.5)	311.5 (7.9)	308.4 (2.5)	311.4 (7.5)	309.9 (1.9)	311.2 (6.3)
450	309.3 (2.8)	312.8 (3.7)	308.9 (2.8)	311.8 (8.5)	310.6 (2.5)	313.8 (7.7)
600	312.0 (1.8)	313.4 (5.4)	311.7 (1.9)	313.0 (7.2)	314.5 (2.4)	315.8 (8.9)
750	313.7 (1.8)	314.1 (1.3)	314.0 (2.5)	313.3 (3.2)	317.1 (3.0)	319.9 (9.3)
900	314.4 (1.4)	317.1 (7.3)	316.0 (2.7)	318.8 (6.6)	321.0 (2.9)	320.8 (8.3)
1050		320.0 (7.3)		320.3 (6.4)		326.6 (6.9)
1200		325.9 (7.3)		323.1 (4.0)		330.8 (4.5)
1350		328.9 (9.4)		324.1 (3.7)		333.1 (6.3)
1500		329.7 (5.3)		330.4 (4.7)		342.3 (7.3)

NEWMAN-KEULS' test at level 5%

	SH/CAT		SNa/CAT		SH/HP55		SNa/HP55		SH/CAP		SNa/CAP	
vol	aver	gr	aver	gr	aver	gr	aver	gr	aver	gr	aver	gr
1500			329.7	1			330.4	1			342.3	1
1350			329.1	1			334.1	2			333.1	2
1200			325.9	1			324.1	2			330.8	3
1050			320.0	2			320.2	3/4			326.6	4
900	321.0	1	317.0	2/3	316.0	1	318.7	4	315.4	1	320.8	4
750	317.1	2	313.9	3/4	314.0	2	313.8	4	313.7	2	319.9	5
600	314.5	3	313.4	3/4	311.7	3	313.0	5	312.0	3	315.8	5
450	310.6	4	312.8	3/4	308.9	4	311.7	5	309.3	4	313.8	5/6
300	309.9	4	311.5	3/4	308.4	4	311.3	5	307.8	5	311.2	6
150	305.5	5	311.0	3/4	305.2	5	308.2	5	305.3	6	309.2	7
0	304.9	5	308.1	5	304.8	5	307.6	5	304.9	6	307.6	8

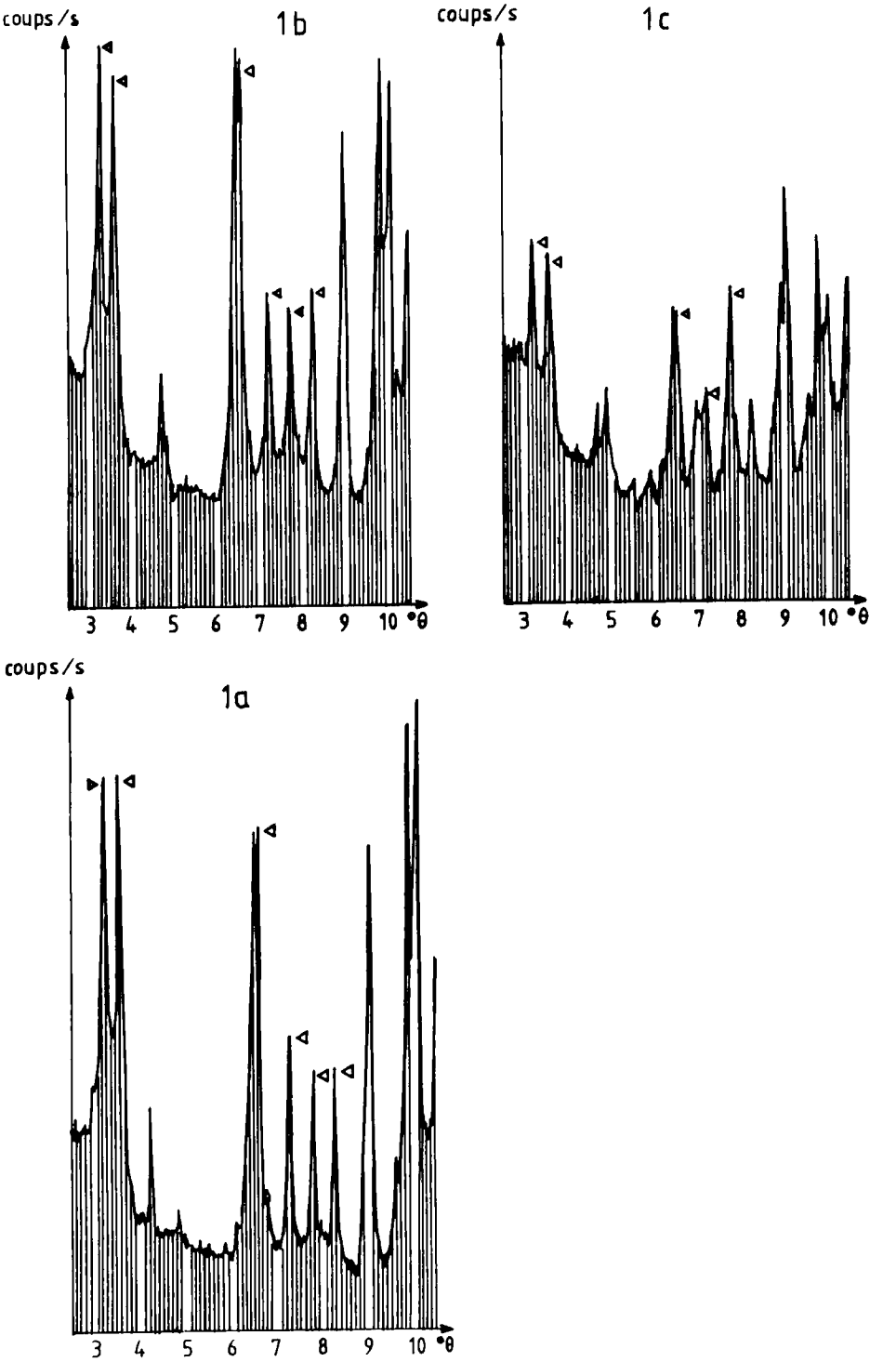

FIGURE 1

X-ray diffractograms of : 1a pure sulfathiazole sodium, 1b sulfathiazole sodium tablet, 1c cuticule sulfathiazole sodium coated with CAT

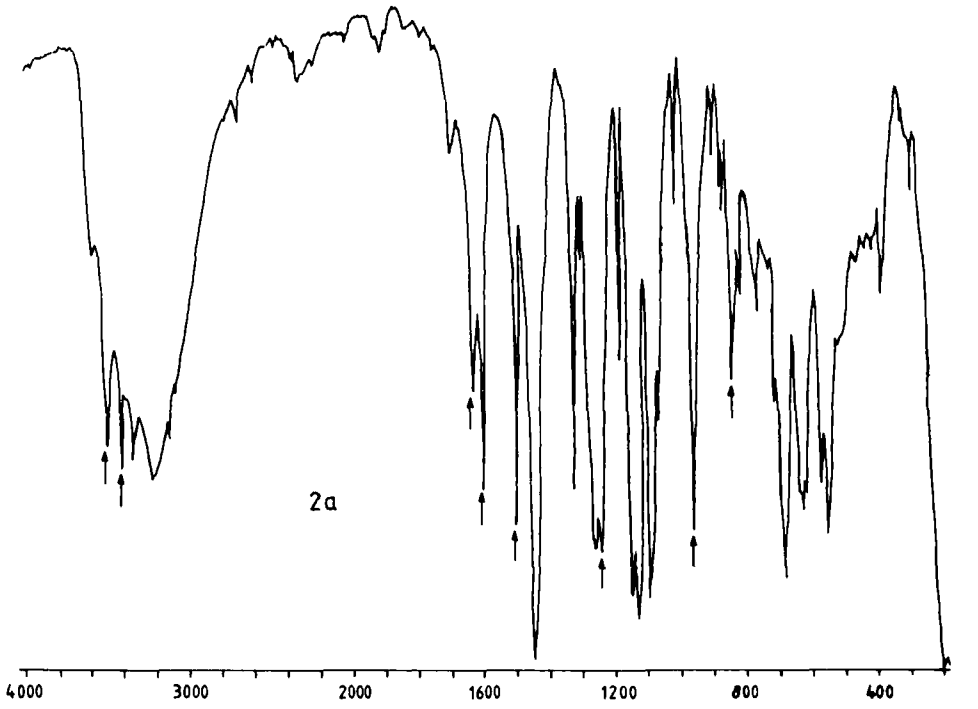

FIGURE 2a
I.R analysis of pure sulfathiazole sodium

sulfathiazole sodium. This reveals that sulfathiazole sodium appears in initial state, in the core and in the coated tablet.

This study was made for the three polymers and the X-ray diffractograms give the same results.

It can be conclude in favour of absence of interaction between sulfathiazole sodium and ingredient or film. These results are confirmed by I.R analysis (fig. 2).

It can be said that the experimental procedure and the core formulation used in this study prevent the formation of an interaction drug / excipent or drug / film found by N. BENHALIMA and al (9).

Drug release

All tablets checked for their capacity to stay intact in gastric juice passed the USP test. This test was realised on coated tablets on which it was sprayed 900 ml of coating solution for SH and 1500 ml of solution for SNa drug.

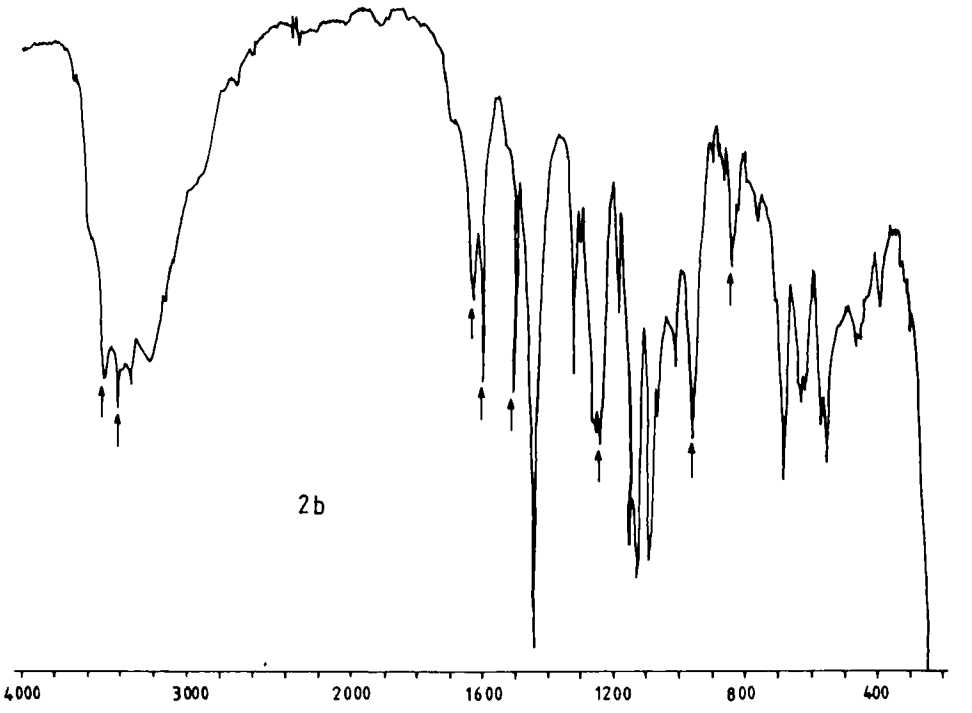

FIGURE 2b
I.R analysis of sulfathiazole sodium tablet

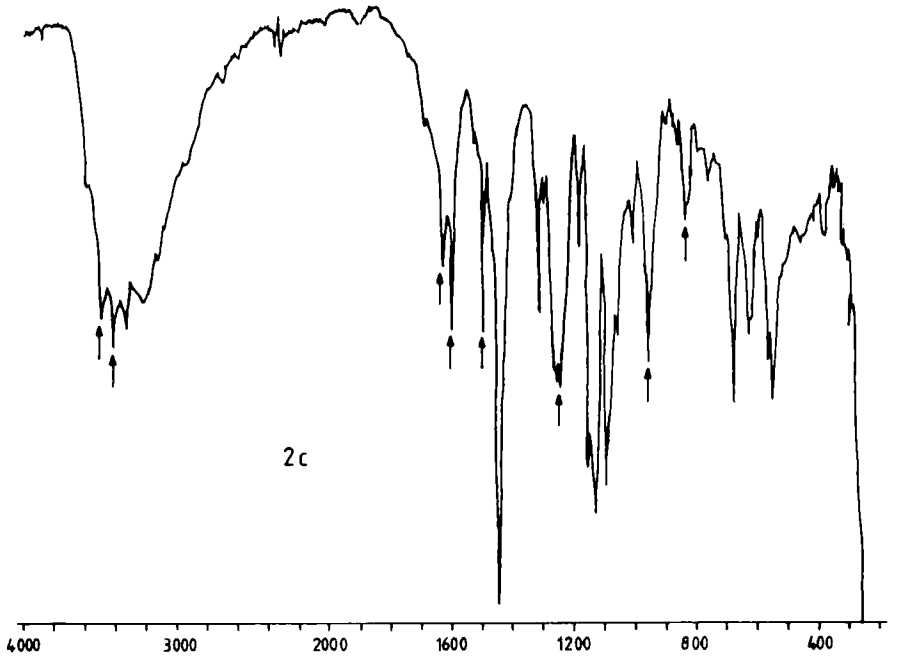

FIGURE 2c
I.R analysis of cuticule sulfathiazole sodium tablet coated with CAT

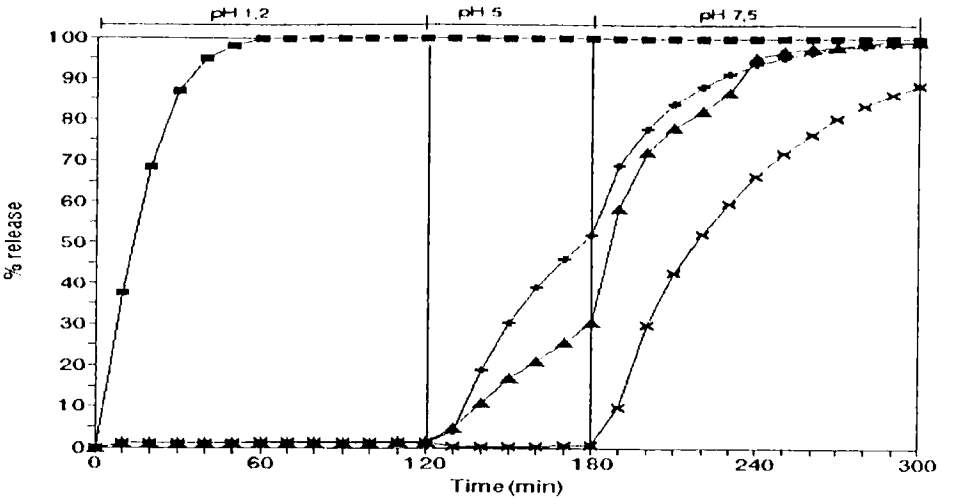

FIGURE 3

Release of sulfathiazole from uncoated and coated tablets : ▬ uncoated tablet SH + coated with CAT ▲ with HP55 X with CAP

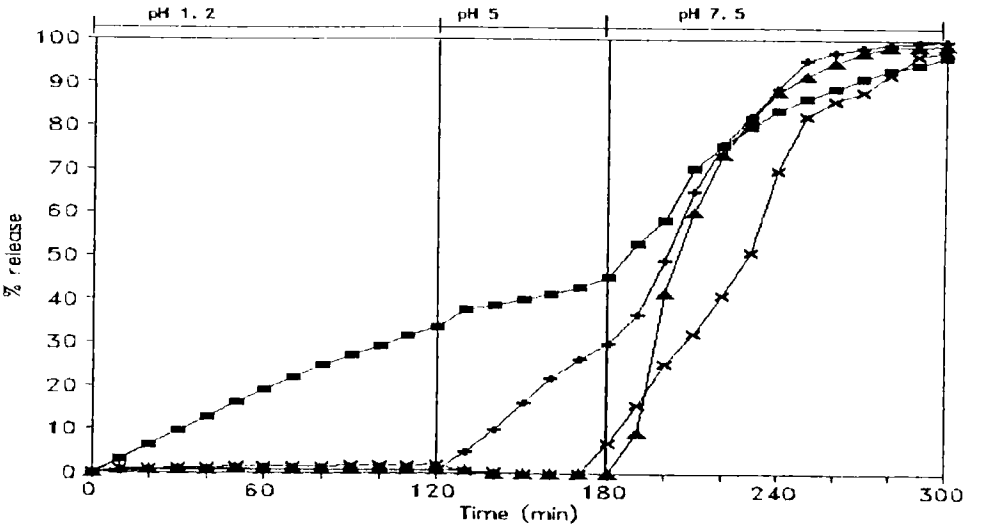

FIGURE 4

Release of sulfathiazole sodium from uncoated and coated tablets : ▬ uncoated tablet SH + coated with CAT ▲ with HP55 X with CAP

Figures 3 and 4 show drug release profiles from uncoated and coated tablets in Britton buffer of different pH.

The uncoated preparation containing the two drugs show significant differences of chemical properties on both drugs substrates. SH show faster dissolution rate than SNa : SH is completely released in gastric medium within an hour, even though SNa release is complete after 5 hours in simulated intestinal fluid (pH = 7.5). All tablets being the same composition and hardness, this result is probably related to the drug solubility.

No release was noted from coated tablets at pH 1.2 : all polymers maintened their gastric resistant performance.

It appears clearly that CAP and HP55 are more resistant than CAT at pH 5 ; in fact, the results obtained show the drug (SH or SNa) is released from coated tablets with CAT. At this pH, it can be observed a difference in the coated tablets with HP55 for the two drugs : the amount of dissolved SH in this dissolution medium is 30 % after 3 hours and it is noticed no release of the active soluble ingredient. This result is related to the great solubility of SH in acid medium. In fact OZTURK and al (6) has studied the great dependence of coating dissolution on the bulk pH when aciding or non ionizing compounds form the core tablet. Then, for on acid drug as SH, the core pH generated is much greater than the polymer pKa (for HP55 pKa = 5.26) (7) and it can be polymer dissolution throughout the coating layer and drug release.

In intestinal fluid, the drug release is increased for all polymers and for two drugs since the films dissolve at this pH. But it can be noticed that drug release is less prononced with CAP. It can be said that this result is related to a greater hardness of tablets coated with this polymer and to its
dissolution pH higher than CAT and HP55.

CONCLUSION

An important factor in the design of enteric coated dosage forms include the choice of an appropriated polymer. This choice will depend on the tablet substract and localized desired release of drugs.

The results obtained show that for an absorption in the proximal small intestine (pH = 5), CAT is the coating polymer which guaranted best results for drugs whatever solubility may be because a low dissolution pH. For a drug

absorption in intestinal medium (pH = 7.5), CAP exhibited the best performance for the two drugs. Even though the resistance of HP55 film was found to be dependent on the solubility of the drugs : for this polymer, the buffer capacity plays a leading part.

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