DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(16), 2011-2020 (1993)

TECHNOLOGICAL EVALUATION OF THREE ENTERIC COATING POLYMERS
I. WITH AN INSOLUBLE DRUG

Y. Kané[1], J. Rambaud[2], H. Maillols[1], J. P. Laget[1], D. Gaudy[1], H. Delonca[1]

1. Institut Europeen des Sciences Pharmaceutiques Industrielles, Laboratoire de Technique Industrielle, Faculté de Pharmacie Université de Montpellier I. France
2. Chimie physique generale, Faculté de Pharmacie, Avenue Charles Flahaut, 34060 Montpellier Cedex, France

ABSTRACT

The enteric properties of a recent cellulose polymer, cellulose acetate trimellitate (CAT, EASTMAN KODAK) were evaluated on an insoluble substract for comparison , included in this paper are the properties of two other cellulose esters : cellulose acetate phthalate (CAP) and hydroxypropyl methylcellulose phthalate (HP55).

The physical properties and disintegration time at pH 1.2 and 6.5 were influenced by the level of coating solution. The gastroresistance was obtained more fastly with CAT and CAP than for HP55.

The influence of coating solution on drug release from tablet was investigated. The dissolution studies were made allowing the variation of pH in the dissolution medium during the kinetics.

Drug release from coated tablets was found to be dependent upon the type of polymers used to form film : higher release rates were obtained with CAT compared to CAP and HP55.

INTRODUCTION

In a previous paper (1), the authors have shown the interest of Cellulose Acetate Trimellitate used as enteric coating polymer for pharmaceutical tablets or granules. The main feature of this product revelated in this study is a dissolution pH at 4.8. This pH is lower than these of the others derivatives of cellulose used today as enteric coating materials.

Then it seemed interesting to take the investigation further in order to establish the pharmaceutical properties of this new film former.

The aim of this work is the comparative study of polymers enteric coating properties : Cellulose Acetate Phthalate (CAP), Hydroxypropylmethylcellulose Phthalate (HP55), Cellulose Acetate Trimellitate (CAT) applied on tablets. The selected drug is the Sulfathiazole. So the result could establish the behavior of CAT and help to discover eventual interaction between drug and film.

MATERIALS

Sulfathiazole anhydrous (Cooperation Pharmaceutique Française, Melun) was selected as the model drug entity.

Sulfathiazole tablet was prepared using : microcrystalline cellulose (Avicel pH 101 and Avicel pH 102), corn starch, polyvinylpyrrolidone (PVP K 30) and talc.

For the film coating, the materials used were cellulose polymers : cellulose acetate phthalate (CAP, EASTMAN KODAK), hydroxypropylmethylcellulose phthalate (HP 55, SHIN ETSU CHEMICAL) and cellulose trimellitate phthalate (CAT, EASTMAN KODAK).

MANUFACTURING PROCEDURE

Sulfathiazole tablets : 3,260 kg of sulfathiazole, 250 g of corn starch, 250 g of Avicel pH 101 and 300 g of PVP K 30 were granulated by wet granulation with water. Then the calibrated granules, 540 g of Avicel pH 102, 250 g of corn starch and 150 g of talc were mixed in Lodige blender for 15 minutes. Finally 5 kg of granules were compressed on a rotary tablet press (KILIAN) using 9 mm biconcave punches.

TABLE 1

Composition of sulfathiazole tablets (%w/w).

Materials	% (W/W)
Sulfathiazole	65.2
Corn starch	5 + 5
Avicel pH 101	5
Avicel pH 102	10.8
PVP K30	6.8
Talc	3

TABLE 2

Manufacturing procedure

Operations	Time (min)	Apparatus
Powder mixture	5	Lodigë M20 GRE
Granulation	15	Lodigë M20 GRE
Drying at 45°C	30	Glatt type TR5
Calibration		Frewitt Type MG 1mm/0,65
Lubrification (mixture of witth corn starch, avicel pH 102 and talc)	15	Lodigë M20 GRE
Compression		Kilian (Punch D9 biconcave)

The average surface of these tablets is 2.1 cm^2

The formulation of sulfathiazole tablets and the manufacturing procedure were summarized in table 1 and 2.

Coating : Coating solution were prepared from 6% (w/w) of polymer in the selected solvant : acetone / alcohol 3 v : 1 V (2). These solution were obtained by

mixing and stirring of the polymer in the solvant until completely dissolution (RAINERI agitator with four blades).

The coating solution were applied in a classical coating pan of 28 cm in diameter, revolving at 20 rpm, using an air spray gun "type volumair".

The coating condition for a batch (900 g) were :

pan speed	20 rpm
spray rate	50 ml.min-1
spray time	10 s
pause	20 s
spray gun distance	17 cm

Increasing application of coating solution were made on the drug cores : 150 ml, 300 ml, 450 ml, 600 ml, 900 ml.

Finally all the freshly coated tablets were dried in the steamroom at 37 °C for 24 hours.

TESTS PROCEDURE

The tablets were subjected to the following tests :

-**Average weight** : on 20 tablets (Pharmacopée Française Xèm ed).

-**Hardness** : on 10 tablets (HERBELEIN).

-**Friability** : loss of weigth percentage of 10 tablets rotated at 25 rpm for 15 minutes in a ERWEKA TAP friabilator.

-**Thickness and diameter** : on 25 tablets using a micrometer to appreciate variation up to 5 micrometer. The thickness e was calculated from :

$$e = (de - dn) / 2$$

de and dn are respectively average diameter of coated and uncoated tablets.

-**Gastric resistance and intestinal disintegration test** : on 6 tablets in a buffer

solution during 2 hours at 37° C in a ERWEKA ZT3 without plastic discs (3). These tests help to evaluate the accurate moment of the onset of disintegration ; then the amount of drug diffused in 0.1 N HCl was determined for gastric resistant tablets.

For the intestinal disintegration test, the tablets showing resistance in the former tests were used. They were first rinsed with water and immediately immersed in Sorrensen buffer at pH 6.5 in the same apparatus but wih discs (3).

-**Drug release** : dissolution studies were carried out on the gastric resistant tablets using the USP paddle method (USP XXI ed). The volume of the dissolution medium was 500 ml and stirring rate of 50 rpm was used. The method proposed by Gaudy et al (4) was used, allowing the variation of pH in the dissolution medium during the kinetics of dissolution : pH 1.2 for 2 hours, pH 5 for 1 hour and pH 7,5 for 2 hours. Briton universal medium (5) ajusted to pH 1.2 with concentrated HCl and alkalinized with a 4N NaOH solution was selected.

-**Stability** : The coated tablets were stored in well-closed flasks at room temperature. The tests of gastric resistance at pH 1,2 and disintegration at pH 6,5 were made after a period of 6 and 12 months.

-**Macroscopic aspect** : the interest of this macroscopic exam was to observe the regularity and the homogenity of the coating (sticking and picking, asperity, orange peel).

RESULTS AND DISCUSSION

The physical properties of all tablets are listed in table 3 ; gastric resistance at pH 1.2 and disintegration time were added in this table ; average weight and diameter show a good distribution of film on the substrate ; for any polymer the results show the influence of coating solution on the physical properties. The influence was studied by analysis of variance (ANVA), the volume of the atomized liquid being the factor at six selected levels. Comparison multiple tests (DUNNET and NEWMAN - KEULS) was used respectively to compare at the uncoated tablet and to show the homogen groups.

TABLE 3

Physical properties and disintegration time at pH 1.2, 6.5 of Sulfathiazole tablets uncoated and coated by different enteric polymers.

Batch	Average weigth (mg)	Hardness (kp)	Diameter (mm)	Gastroresitance time at pH 1.2	Disintegration time at pH 6.5
SH	304.9 (2.0)	8.4 (0.8)	9.039 (0.003)	7.5	--
SH/CAT1	305.3 (2.1)	10.1 (0.7)	9.064 (0.006)	80	--
SH/CAT2	307.8 (1.5)	10.2 (0.4)	9.079 (0.005)	>120	11
SH/CAT3	309.3 (2.8)	12.9 (0.8)	9.096 (0.006)	>120	11.30
SH/CAT4	312.0 (1.8)	16.3 (0.8)	9.104 (0.005)	>120	12
SH/CAT5	313.7 (1.8)	16.2 (0.8)	9.120 (0.007)	>120	12
SH/CAT6	315.4 (1.4)	16.7 (0.9)	9.136 (0.009)	>120	13
SH/HP1	305.2 (2.1)	11.7 (0.6)	9.067 (0.005)	2	--
SH/HP2	308.4 (2.5)	11.8 (0.7)	9.084 (0.005)	40	--
SH/HP3	308.9 (2.8)	12.1 (0.8)	9.095 (0.005)	>120	10
SH/HP4	311.7 (1.9)	12.7 (0.6)	9.109 (0.006)	>120	11.3
SH/HP5	314.0 (2.5)	13.7 (0.7)	9.137 (0.006)	>120	12
SH/HP6	316.0 (2.7)	15.2 (1.0)	9.150 (0.009)	>120	13
SH/CAP1	305.0 (2.5)	11.7 (0.8)	9.062 (0.006)	50	--
SH/CAP2	309.9 (1.9)	11.8 (0.7)	9.092 (0.006)	>120	10
SH/CAP3	310.6 (2.5)	14.1 (1.0)	9.109 (0.006)	>120	11
SH/CAP4	314.5 (2.4)	17.1 (0.6)	9.129 (0.010)	>120	13
SH/CAP5	317.1 (3.0)	17.3 (1.4)	9.154 (0.010)	>120	14.3
SH/CAP6	312.0 (2.9)	19.5 (0.6)	9.176 (0.009)	>120	15

*Standard deviations in parenthese. SH = Sulfathiazol tablets. 1= 150ml of atomized liquide 2=300ml, 4= 600ml, 5= 750ml, 6=900ml

TABLE 4
NEWMAN-KEULS test at level 5%

	SHCAT		SHHP55		SHCAP	
Volum	means	groups	means	groups	means	groups
900	321.09	1	316.07	1	315.49	1
750	317.17	2	314.00	2	313.71	2
600	314.53	3	311.77	3	312.00	3
450	310.68	4	308.96	4	309.38	4
300	309.99	4	308.43	4	307.89	5
150	305.95	5	305.29	5	305.30	6
0	304.98	5	304.88	5	304.98	6

Average weigth

The result of ANVA shows global influence of the coating solution on the tablet weight ($p < 1‰$), for any polymer. DUNNET's test (P= 95%) shows that for all the three polymers, 150 ml of the solution leads to tablets the same weight as the uncoated tablets. One can flatly notice an increase of this parameter compared to the reference tablets. The NEWMAN-KEULS test lies to detect difference between any means with sample volume larger than 150 ml (table 4).

Hardness

There is a global influence of the volume of the atomized liquid on the hardness of the tablets ($p<1‰$). DUNNET' s test (P=95%) confirms that all the coated tablets are harder than the specimen. Finally NEWMAN-KEULS' test enables to differenciate between the six volumes of the atomized liquid of the various homogeneous groups according to the polymer which has been used (table 5).

Thickness

For any coating polymer which has been used the thickness increases according to the amount of the atomized liquid ($p < 1‰$) every volume defining a particular group (table 6)

The hardness of the tablet is influenced by the thickness of the film coating and by the coating formulation. It results that CAP is the most resistant for volume coating solution larger than 300 ml.

TABLE 5
NEWMAN-KEULS test at level 5%

	SHCAT		SHHP55		SHCAP	
Volum	means	groups	means	groups	means	groups
900	16.71	1	15.21	1	19.50	1
750	16.29	1	13.68	2	17.36	2
600	15.31	2	12.75	3	17.16	2
450	12.89	3	12.12	3/4	14.18	3
300	10.23	4	11.85	4	11.82	4
150	10.10	4	11.72	4	11.71	5
0	8.43	5	8.43	5	8.43	6

TABLE 6
NEWMAN-KEULS test at level 6%

	SHCAT		SHHP55		SHCAP	
Volum	means	groups	means	groups	means	groups
900	9.14	1	9.15	1	9.18	1
750	9.12	2	9.14	2	9.15	2
600	9.11	3	9.11	3	9.13	3
450	9.10	4	9.09	4	9.11	4
300	9.08	5	9.08	5	9.09	5
150	9.06	6	9.07	6	9.08	6

The influence of coating solution on gastric resistance and disintegration time is pointed out : the CAT and the CAP showed a gastric resitance for an atomized volume of 300 ml whereas 450 ml is needed for the HP 55 ; for this last polymer the disintegration times are faster than these obtained with CAP and CAT.

Somme differences in the release of the sulfathiazole uncoated and coated tablets at pH 5 after 120 min were observed (fig 1) : in this domaine the drug release is much faster for CAT coating, there is not release with CAP. It should be noted that drug release increased for three polymers at pH 7.5 after 180 min.

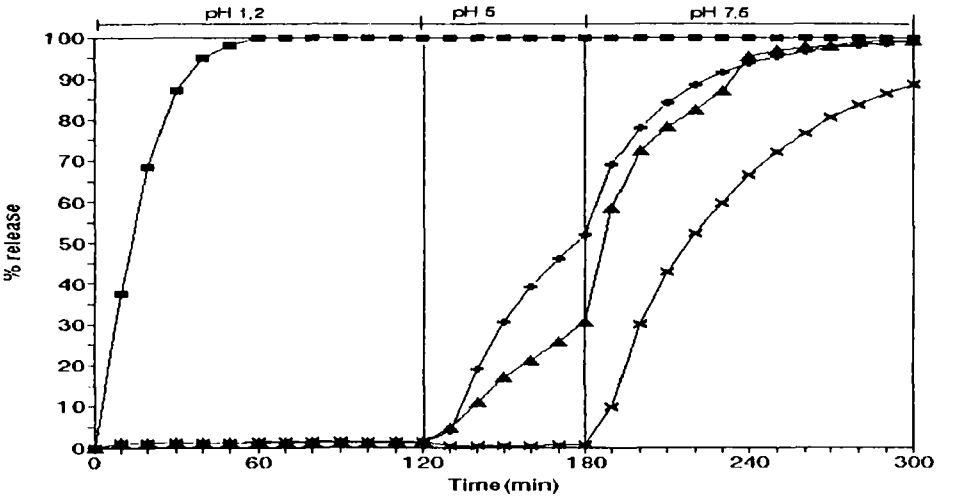

FIGURE. 1
: Dissolution profile of Sulfathiazole from uncoated and coated tablets.
■ Uncoated tablet
+ Coated with CAT(900 ml)
▲ " HP55(900 ml)
× " CAP(900 ml)

CONCLUSION

The coating tablets show different physical and chemical characteristics. A small amount of polymer is required to get a good gastric resistance with the cellulose acetate phthalate (CAP) and the cellulose trimellitate phthalate (CAT).

The drug release profile shows that all film forming agent play their role of protection at pH 1.2 for 2 hours : the percentage of drug release is 0%.

At pH 5, very close to the upper part of intestine, drug release from coated tablets was found to be dependent upon the type of polymer used in this study : tablets coated with CAT show a faster drug release (50%), than with HP55 (33%) and CAP (0%).

At high pH condition (7.5) we notice no difference between the dissolution profile of coated tablet with CAT and HP55.

REFERENCES

1. Y. Kané, J. Rambaud, H. Maillols, J. P. Laget, H. Delonca, Pharm. Acta. Helv., in press.

2. Al Salloum. I. Thèse Pharmaceutical Sciences. Montpellier University, (1984).

3. USP XXI-NF XVI, U. S. Pharmacopeia Convention, Inc., Rockville, MD, pg 1578 (1990).

4. D. Gaudy, M. Muniz De Albuquerque, G. Baylac, A. Puech et M. Jacob, Sci. Techn. Pharm., 5, (11), 750 (1989).

5. D. D. Perrin, Aust. J. Chem., 16, 572 (1963).