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# Comparative Study of Aqueous and Organic Enteric Coatings of Chlorpheniramine Maleate Tablets

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## ABSTRACT

*Two acrylic polymers (Eudragit® L 12.5 P and L 30 D) and a cellulosic polymer (cellulose acetate trimellitate, CAT) in organic and aqueous formulations were used in order to obtain an enteric coating on tablets containing clorpheniramine maleate as a water-soluble model drug. The coating of tablets was executed in a coating pan in similar conditions for each kind of solvent. The coated tablets were tested according to the delayed-release test of USP 23 (Method A). In our experimental conditions different amounts of polymers were needed to obtain an enteric coating. The lowest amount was in the case of Eudragit L 30 D (aqueous), after which appeared Eudragit L 12.5 P (organic), CAT (organic), and finally, CAT (aqueous) as the polymer that needed to be of the highest amount. During the dissolution test differences in the size and aspect of the tablets were observed according to the polymers. Acrylic polymers did not show changes in size and aspect, but CAT polymers showed a notable increase in size. The different behavior of the tablets during the dissolution test can explain the differences observed in the adjustment of the release data. The release data were tested assuming common kinetic models. In the present study it was observed that Eudragit L polymers release the drug in a first-order kinetic and that CAT releases it according to a zero-order kinetic.*

## INTRODUCTION

Enteric coatings are frequently used in the pharmaceutical industry for different purposes. In order to obtain enteric coatings, different polymers can be used. The most frequently employed are cellulosic or acrylic polymers (1). These polymers can be classified according to their pH/dissolution behavior. In our work we have chosen Eudragit® L 30 D, Eudragit L 12.5 P and cellulose acetate trimellitate (CAT) because all of them dissolve at pH 5.5. This dissolution profile is very convenient in order to obtain good bioavailability in the first portion of proximal intestine (2). Our objective is to study possible drug release differences between polymers (acrylic or cellulosic) and solution media (aqueous or organic). We have chosen chlorpheniramine maleate as a water-soluble model drug.

## MATERIALS

The soluble drug is chlorpheniramine maleate (CID, Spain). Avicel PH 102 (FMC International) and L-HPC LH/21 (Shin Etsu Chemical Co., Ltd.) were the core excipients. For the enteric coating, the polymers used were Eudragit L 12.5 P, Eudragit L 30 D (Hüls Española SA), and CAT (Eastman Kodak). The plasticizers employed were triacetin PR (Panreac) and dibutylphthalate (Griffin & George Limited). The solvents were purified water, isopropanol QP (Panreac), and acetone QP (Panreac). The media of the enteric assay were prepared with: hydrochloridic acid 37% (Panreac), sodium hydroxide 97% (Panreac), and tribasic sodium phosphate $12H_2O$ (Panreac). Ammonium hydroxide (Probus) was used for CAT dissolution.

## METHODS

### Tablet Manufacturing

The core of the tablet was prepared with the following composition: chlorpheniramine maleate, 24 mg (12%); L-HPC LH/21, 7 mg (3.5%), and Avicel PH 102, 169 mg (84.5%). Tablets of 200 mg were manufactured in an eccentric machine, model B type 40, BONALS® (Spain).

### Characterization of Tablets

The tablets were subjected to the following tests: uniformity of content, disintegration, uniformity of weight and dissolution according to the British Pharmacopoeia (3); resistance of crushing of tablets and friability in a multiblade apparatus as described in Pharmaeuropa (4). Aspect and tablet size were also characterized.

### Coating Process

Chlorpheniramine maleate tablets were coated with different polymers in a conventional coating pan. The formulations are shown in Table 1. During the coating process the inlet temperature was kept within 40° and 50°C when using organic solvents, and within 60° and 70°C for aqueous formulations.

These formulations are composed of an enteric polymer, the correspondent solvent, and the plasticizer. This plasticizer was, when possible for its miscibility, dibutyl phthalate. Table 1 shows the compositions of the different formulations.

### Dissolution Test of Enteric Coated Tablets

The enteric coated tablets were tested according to the delayed-release test of USP 23 (Method A) (5). At least three samples of each formulation were evaluated. Samples were taken at different times, filtered and assayed by spectrophotometry, at 262 for the acid solutions and 265 nm for the neutral solutions.

The in vitro dissolution data obtained in the enteric dissolution tests were adjusted to four common drug release kinetic models: zero-order, first-order, square-root law and cube-root law. According to Banakar (6), these are the most useful algebraic functions to define the dissolution kinetic of both conventional fast-release dosage forms and nonconventional modified-release dosage forms.

During the dissolution test, differences in the dimension of the tablets were evaluated. The evaluated dimensions were maximum height ($H$), minimum height ($h$), and diameter ($d$).

## RESULTS AND DISCUSSION

The pharmacotechnical characteristics of the chlorpheniramina maleate tablets are shown in Table 2. The tablet size is described in Table 3.

The results obtained for Eudragit L 30 D, Eudragit L 12.5 P, aqueous CAT, and organic CAT in enteric dissolution tests are summarized in Figs. 1–4.

In coatings of Eudragit L 30 D, enteric properties with amounts of coating higher than 2.39 mg/cm$^2$ were

***Table 1***

*Enteric Coating Formulations*

| | |
|---|---|
| Eudragit L 30 D formulation | |
| Eudragit L 30 D | 200 ml (60 g dry polymer) |
| Water | 400 ml |
| Dibutyl phthalate (DBP) | 15 ml (25% on dry polymer weight) |
| Eudragit L 12.5 P formulation | |
| Eudragit 12.5 P | 160 ml (20 g dry polymer, 2.5 g DBP) |
| Isopropanol | 200 ml |
| Acetone | 200 ml |
| Dibutyl phthalate | 2.5 ml (25% on dry polymer) |
| Cellulose acetate trimellitate, aqueous formulation | |
| CAT | 20 g |
| Water | 1000 ml |
| Ammonia hydroxide | 15 ml |
| Triacetin | 4 ml (25% on dry polymer) |
| Celullose acetate trimellitate, organic formulation | |
| CAT | 20 g |
| Isopropanol | 500 ml |
| Acetone | 500 ml |
| Dibutyl phthalate | 4 ml (25% on dry polymer) |

***Table 2***

*Pharmacotechnical Characteristics of the Chlorpheniramine Maleate Cores*

| | |
|---|---|
| Uniformity of content | 99.82% ± 0.97 |
| Disintegration | $t_d$ = 5 min 50 s |
| Uniformity of weight | 199.74 ± 0.98 |
| Dissolution | $t_{80}$ < 10 min |
| Resistance to crushing | > 15 UE |
| Friability | 3.28 $10^{-5}$% |

***Table 3***

*Tablet Size*

| | |
|---|---|
| Maximum height ($H$) | 4.80 mm |
| *SD* | 0.00 |
| Minimum height ($h$) | 2.52 mm |
| *SD* | 0.00 |
| Diameter ($d$) | 7.50 mm |
| *SD* | 0.00 |
| Surface area ($A_s$) | 4.21 $cm^2$ |

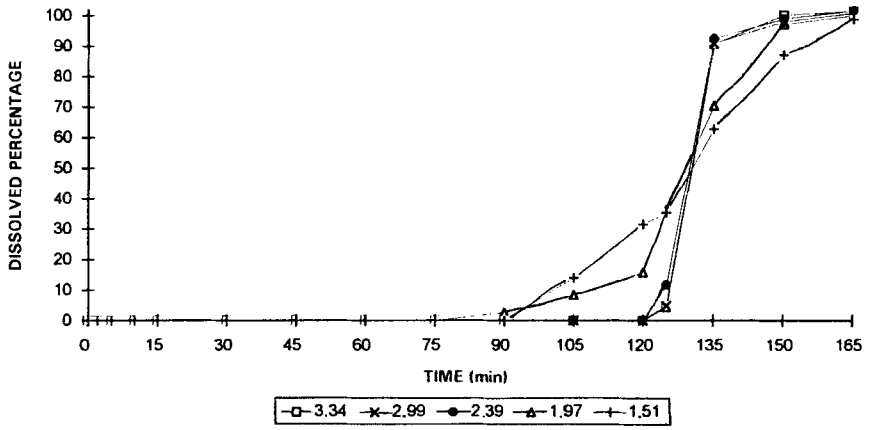


**Figure 1.** Cumulative amounts of chlorpheniramine maleate released from tablets coated with Eudragit L 30 D ($mg/cm^2$).

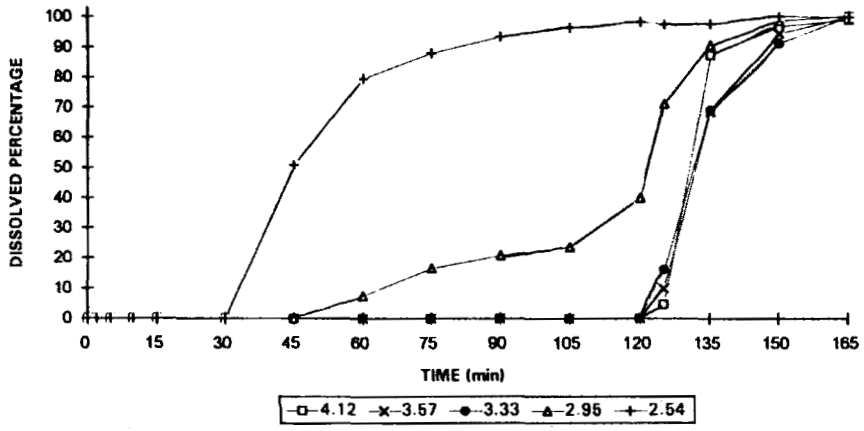


**Figure 2.** Cumulative amounts of chlorpheniramine maleate released from tablets coated with Eudragit L 12.5 P (mg/cm²).

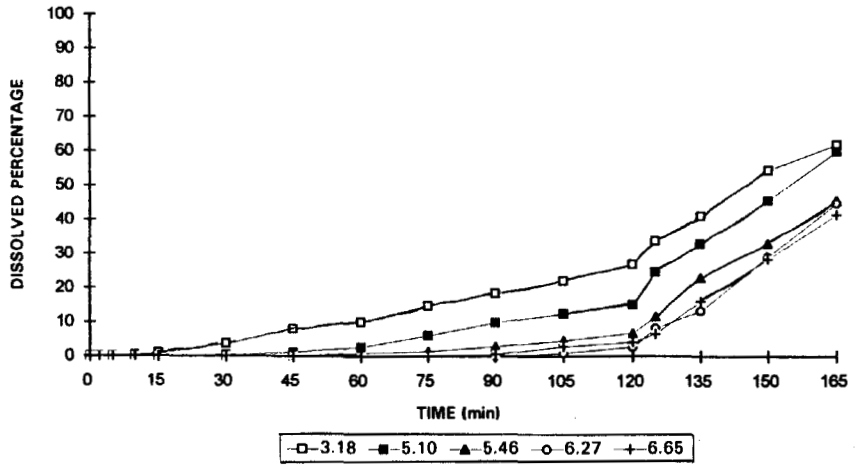


**Figure 3.** Cumulative amounts of chlorpheniramine maleate released from tablets coated with CAT (aqueous base) (mg/cm²).

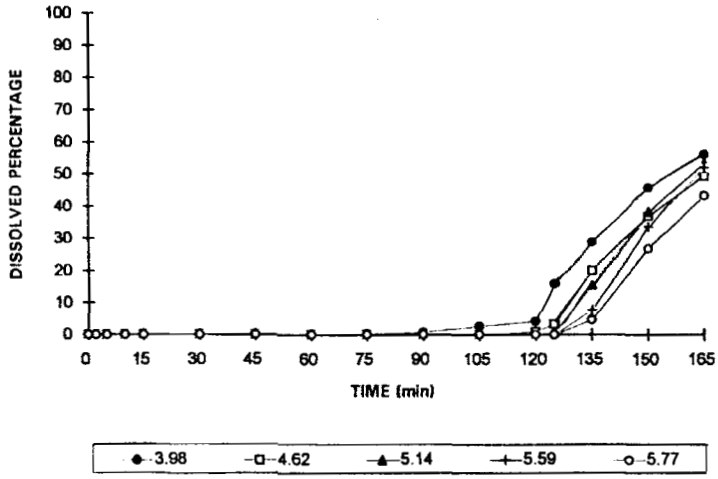


**Figure 4.** Cumulative amounts of chlorpheniramine maleate released from tablets coated with CAT (organic base) (mg/cm²).

obtained. These results are similar to the results obtained by Plaizer-Vercammen et al., who used hard gelatin capsules of ASA, where it was necessary to use from 2.57 to 7.09 mg/cm$^2$ depending on the polymer (7). However, some authors have obtained enteric properties only with 1.37 mg/cm$^2$ (8). This difference could be due to the different drug solubility.

According to Lehmann et al. (9), 1 mg/cm$^2$ produces a coating 10 μm thick. Our results are within the limits of 10 and 30 μm (10).

In case of Eudragit L 12.5 P, the minimum amount necessary for obtaining enteric properties is 3.33 mg/cm$^2$. This value is slightly higher than that obtained for Eudragit L 30 D and the theoretical values that have been indicated in the literature (10). This difference can be due to the different formulation of the coating solution or the coating conditions, which could affect the film-forming process.

The minimum amounts of CAT coating for obtaining enteric properties were 5.46 mg/cm$^2$ for aqueous solution and 3.98 mg/cm$^2$ for organic solution, as can be seen in Figs. 3 and 4. These values are higher than that obtained with acrylic polymers. Similar results were obtained by Paizer-Vercammen et al., in an aqueous coating of CAT, with values between 4.80 and 5.50 mg/cm$^2$ (7). However, other authors have obtained better results (8).

The amount of CAT in organic solution is similar to the amount of Eudragit L 12.5 P. It is important to notice that CAT in organic solution is needed in lower amounts than CAT in aqueous solution (in our experimental conditions), while the acrylic dispersion Eudragit L 30 D is needed in lower amount than Eudragit L 12.5 P.

The difference observed in CAT formulations could be due to the different plasticizer employed. However, some authors (11) did not observe a great influence of plasticizer. So, this different behavior must be attributed to the nature of the coating solution or to the process conditions.

During the enteric dissolution test of coated tablets, it was observed that the tablets experimented different behaviors depending on the nature of the polymer. All the tested acrylic polymers behave in a similar way without any significant effect of the solution medium (organic or aqueous). A similar effect was observed with the CAT formulations. Table 4 shows variations in maximum height, minimum height, diameter, and aspect of two formulations of coated tablets that can be considered as a model of our tested formulations.

When testing the tablets coated with the acrylic polymers, it was observed that there was no change in tablet dimensions during the period in acid medium. That indicates that water intake is negligible. When the medium is neutralized, it was observed that the coating dissolves rapidly and the tablets disintegrate after its dissolution.

Tablets coated with CAT experienced an increase in size due to the water intake. This process is due to the permeability of this type of coatings (7,8). After the

***Table 4***

*Coated Tablet Characteristics During Enteric Test*

| Polymer | Time (min) | Max. Height, *H* (mm) | Diameter, *d* (mm) | Min. Height, *h* (mm) | Aspect, Color/Gloss |
|---|---|---|---|---|---|
| Eudragit L 30 D | 0 | 5.00 | 7.60 | 2.83 | White/+ |
| 7.03% | 5 | 5.00 | 7.60 | 2.83 | White/+ |
| 3.34 mg/cm$^2$ | 10 | 5.00 | 7.60 | 2.83 | White/+ |
| | 15 | 5.00 | 7.62 | 2.87 | White/+ |
| | 60 | 5.00 | 7.67 | 2.85 | White/+ |
| | 120 | 5.06 | 7.68 | 2.85 | White/+ |
| | 165 | — | — | — | — |
| CAT (aqueous solution) | 0 | 5.20 | 7.68 | 3.02 | Brown/– |
| 14.00% | 5 | 6.27 | 7.83 | 3.38 | Brown/+ |
| 6.65 mg/cm$^2$ | 10 | 7.06 | 8.13 | 3.38 | Brown/+ |
| | 15 | 7.15 | 8.27 | 4.17 | Brown/+ |
| | 60 | 7.20 | 8.45 | 4.25 | Brown/+ |
| | 120 | 7.20 | 8.50 | 4.37 | Brown/+ |
| | 165 | 7.20 | 8.58 | 4.40 | Brown/+ |

medium neutralization an unexpected behavior was observed because the coating did not dissolve as quickly as the acrylic coatings. This phenomenon produced an extended release where 60% of the drug was released in 45 min. This effect has not been mentioned before in literature. For this reason we think that it must be a modification of film properties. Recently, Obara et al. affirmed that film formation was not obtained from spraying CAP dispersion (12). This effect could have happened in our tablets coated with CAT and could explain the behavior observed.

Data from the enteric dissolution test were adjusted by linear regression to four equations. Table 5 shows the determination coefficients ($r^2$) obtained from the different formulations when adjusted to different kinetic models.

As an example, we show the adjustment of two formulations that comply with USP 23 specifications (kinetic adjustment in neutral medium) and two formulations which do not comply (kinetic adjustment in acid medium). In the formulations that comply with specifications, we considered the data obtained during the later 45 min when the tablets are in a neutral medium. During the first part of the test there is no release to be considered. For this reason, we took data from faultily coated tablets in order to obtain release data in acid medium.

Tablets coated with acrylic polymers release their content as conventional forms, according to a first-order kinetic, after the film dissolution. Tablets coated with CAT are able to keep their structure, and the drug must diffuse through the coating. These tablets release their content according to a zero-order kinetic; this release profile is very convenient for sustained-release forms (13).

## CONCLUSIONS

It is necessary to use lower amount of the polymer Eudragit L than CAT in order to obtain enteric coatings. Polymeric coating of Eudragit L 30 D and Eudragit L 12.5 P give an enteric coating to our tablets from 2.39 and 3.33 mg/cm$^2$, respectively. It is necessary to have more than 5.46 and 3.98 mg/cm$^2$ of CAT in aqueous solution and organic solution, respectively, for obtaining similar results.

Tablet behavior during enteric dissolution test depends on the type of polymer. Tablets coated with acrylic polymers (Eudragit L 30 D and L 12.5 P) do not have any modification in their dimensions during the dissolution test, while tablets coated with CAT present a size increase during this test. This change is due to the water intake through the permeable coating. This fact provokes the tablet disintegration because of the excipient swelling. The CAT coatings keep their integrity but not the form under the action of the pressure caused by the excipient swelling.

It has been observed that the release kinetic depends on the type of polymeric coating. On one hand, tablets coated with acrylic polymers release their drug according to a first-order kinetic, after the coating dissolution. On the other hand, tablets coated with CAT present a better adjustment to zero-order kinetic, the more common of sustained-release forms, as a consequence of the nondissolution of their coating.

***Table 5***

*Kinetic Adjustment*

| Coating | Neutral Medium Eud. L 30 D 3.34mg/cm$^2$ | Neutral Medium CAT (aq.) 6.65 mg/cm$^2$ | Acid Medium Eud. L 12.5 P 2.54 mg/cm$^2$ | Acid Medium CAT (aq.) 3.18 mg/cm$^2$ |
|---|---|---|---|---|
| Equations | | | | |
| zero-order | | | | |
| $Q = Kt + a$ | 0.808 | 0.998 | 0.778 | 0.993 |
| First-order | | | | |
| $\text{Ln}(Q_\infty - Q) = \text{Ln}\ Q_\infty - Kt$ | 0.999 | 0.991 | 0.996 | 0.986 |
| Cubic-root law | | | | |
| $(Q_\infty - Q)^{1/3} = Q_\infty^{1/3} - Kt$ | 0.969 | 0.995 | 0.959 | 0.989 |
| Square-root law | | | | |
| $Q = K\sqrt{t}$ | 0.814 | 0.997 | 0.831 | 0.951 |

The aqueous dispersion Eudragit L 30 D presents the best characteristic for the enteric coating due to its nontoxicity, safety, low viscosity, and quick application. On the other hand, CAT aqueous solutions allow the preparation of coatings with sustained-release profile.

## ACKNOWLEDGMENTS

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