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# Formulation and *in vitro* evaluation of theophylline-Eudragit® sustained-release tablets

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*Tablets containing theophylline (66.67%) based on a Eudragit® RS 30D and NE 30D matrices containing 10% to 30% of either of the polymer were produced by compression method. The influence of the different proportions of methacrylic esters, the use of lactose and tribasic calcium phosphate as diluents and also the effects of the addition of magnesium stearate as a hydrophobic agent lubricant on the theophylline release, were studied. Physicochemical analyses and drug content was evaluated.* In vitro *drug release studies were carried out in simulated gastric fluid without pepsin (pH1.2) and simulated intestinal fluid without pancreatin (pH7.5). A relatively prolonged release of theophylline from the polymer matrices for a 7 hr-release period was detected. Magnesium stearate at 0.5% and Eudragit® NE 30D at 10% was considered a better sustained-release matrix compressed theophylline tablets comparing with Eudragit® RS 30D in the same conditions (USP). Results from physicochemical analyses were in accordance with specifications. The release patterns were analyzed from the viewpoint of square-root of time and as a first-order, zero-order kinetics, and Higuchi. Additionally, half-life of release ($Td_{50\%}$) and dissolution rates (kd) were calculated. Higuchi was the model that better fitted theophylline kinetic, and diffusion controlled was involved.*

**Uniterms**
- Theophylline
- Matrices
- Sustained-release
- Dissolution
- Methacrylic acid esters

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## INTRODUCTION

In the last few years controlled release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. The objective of designing a controlled release system is to deliver drug at a rate necessary to achieve and maintain a constant drug blood level. Moreover these dosage forms have been specially designed to release the drug slowly over several hours, to protect the drug from the low pH of the stomach, and/or to protect the stomach from the irritating effects of the drug. Key advantages to the use of this technology are prolonged activity, fewer doses, fewer side effects and reduced toxicity. Too much of a medicinal ingested or injected all at once in order to have a maintenance concentration can mean wasted material or toxic side

effects. Decreasing the dose rate it is possible to avoid these problems and to find a better efficacy results. A major objective of the controlled release scientist is to determine the best speed of release to obtain optimal performance. The success of theophylline controlled release as a bronchodilator to treat bronchitis is due to its prolonged release rate (Acevez, Cruz, Hernandes, 2000; Chambin *et al.*, 2004; Myiagawa *et al*., 1996).

Theophylline, a bronchodilator, relaxes and opens the air passages to the lungs, making it easier to breathe. This drug is used mainly in solid oral dosage forms, particularly slow release forms, and has a narrow therapeutic index, requiring regular monitoring of serum theophylline concentrations to avoid adverse effects (Turner-Warwick 1988; Montplaisir, Walsh, Malo, 1982)

It is possible to design systems with continuous and uniform delivery of the drug, and the way to produce controlled release include micro-encapsulation, film coating, solid dispersions, and polymeric matrices. Usually specially designed polymers are used to make this control. Water insoluble materials like ethylcellulose have been used in matrices to achieve controlled release of drugs. Eudragit® RS 30D and Eudragit® NE 30D are able to slow down drug diffusion very noticeably since they are slightly swellable and slightly permeable. Their permeability is comparable, but Eudragit® NE 30D presents the advantage of being without any plasticizer addition, different from RS 30D that requires 20% in weight of triethylcitrate (Eudragit®, 2003) (Acevez, Cruz, Hernandez, 2000; Pather *et al.*, 1998, Salomon, Doelker, 1980).

The purpose of this work was to produce theophylline release matrix tablets using Eudragit® RS 30D and NE 30D and to evaluate the effect of these methacrylic acid esters polymers with respect to polymer type and concentration, diluent, magnesium stearate type intending to prevent the mixture to adhere to the punches formers as lubricant to control theophylline tablets release.

Theophylline was chosen as a model drug due to its efficiency to treat chronic obstructive pulmonary disease, and a narrow therapeutic index wich requires regular monitoring of serum theophylline concentrations. In this way slow release forms of theophylline can be used to avoid adverse effects and promote its more efficient use (Robinson, Eriksen, 1966; Hendeles, Weinberger, Johnson, 1978).

## MATERIAL AND METHODS

### Reagents and Materials

The material used, in accordance with pharmaceutical grade of purity, were: anhydrous theophylline (Ariston), Eudragit® RS 30D (Rhöm Pharma), Eudragit® NE 30D (Rhöm Pharma), triethylcitrate (Rhöm Pharma), lactose M200 (Henrifarma), tribasic calcium phosphate (Merck) and magnesium stearate (Quimibrás Brasil). The reagents of analytical grade were: potassium phosphate monobasic (Merck), sodium hydroxide (Merck), sodium chloride (Merck), and hydrochloric acid 37% (Merck). Anhydrous theophylline 99.80%, donated by Ariston, was used as reference standard in quantitative determinations.

### Tablet Preparation

Formulations of controlled release tablets were prepared with different proportions of Eudragit® NE 30D or RS 30D as polymers, using soluble and insoluble diluents, and varying magnesium stearate percentages. Tables I and II show matrices compositions, with Eudragit® NE 30D and Eudragit® RS 30D, respectively.

Theophylline and diluents, either lactose or tribasic calcium phosphate, were passed through a 60-mesh sieve and thoroughly mixed in a conical blender Multipex (Apex CO) for 15 minutes. Next, the mixture was transferred to a Mullinex processor and either the polymer (RS 30D) or the aqueous-based polymeric suspension (NE 30D) was added. For formulations with Eudragit® RS 30D, 20% in weight of triethylcitrate, used as plasticizer, was added. The mixtures were ground and simultaneously dried by hot air. The granu-

**TABLE I** - Composition of theophylline tablets formulated with Eudragit® NE 30D

| Components (%) | EUD NE 1 | EUD NE 2 | EUD NE 3 | EUD NE 4 | EUD NE 5 | EUD NE 6 | EUD NE 7 |
|---|---|---|---|---|---|---|---|
| Anhydrous theophylline | 66.67 | 66.67 | 66.67 | 66.67 | 66.67 | 66.67 | 66.67 |
| Eudragit® NE 30D | 10.00 | 20.00 | 30.00 | 10.00 | 20.00 | 30.00 | 10.00 |
| Magnesium stearate | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 | 0.50 |
| Lactose | 20.33 | 10.33 | 0.33 | - | - | - | 22.83 |
| Tribasic calcium phosphate | - | - | - | 20.33 | 10.33 | 0.33 | - |

**TABLE II -** Composition of theophylline tablets formulated with Eudragit® RS 30 D

| Components (%) | EUD RS 1 | EUD RS 2 | EUD RS 3 | EUD RS 4 | EUD RS 5 | EUD RS 6 | EUD RS 7 |
|---|---|---|---|---|---|---|---|
| Anhydrous theophylline | 66.67 | 66.67 | 66.67 | 66.67 | 66.67 | 66.67 | 66.67 |
| Eudragit® RS 30D | 10.00 | 15.00 | 20.00 | 10.00 | 15.00 | 20.00 | 10.00 |
| Trietylcitrate | 2.00 | 3.00 | 4.00 | 2.00 | 3.00 | 4.00 | 2.00 |
| Magnesium stearate | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 | 0.50 |
| Lactose | 18.33 | 12.33 | 6.33 | - | - | - | 20.83 |
| Tribasic calcium phosphate | - | - | - | 18.33 | 12.33 | 6.33 | - |

les formed were sieved using a sieve of 35 mesh and dried at 50 ºC for 24 h. Magnesium stearate was added and mixed for 10 minutes. The granules were compressed in a single punch tablet machine (Fabbe), with 10 mm diameter (Ojoe *et al*, 2003).

### Granulometric distribution

Granules produced before formulation compression were submitted to granulometric analyses. The material was sieved through several sieves progressively more fine-meshed, aperture of 115-mesh sieve and shaken in a mechanical shaker for 30 minutes followed by the calculation in percentage of the amount of mass retained on each sieve.

### Dissolution Studies

*In vitro* studies of theophylline release from the prepared matrix tablets were conducted according to USP 25 , II apparatus at 37 ± 0.5 ºC and padle speed of 50 rpm. The dissolution studies were carried out for 7 hours; initial 1 hour with 900 mL of simulated gastric fluid without pepsin (pH 1.2) and rest 6 hours in 900 mL of simulated intestinal fluid without pancreatin (pH 7.5) under sink condition, performed in a Hansson Research SRII 6-flask tester. At predetermined intervals samples of 10 mL were withdrawn from the dissolution medium and replaced with fresh medium to maintain a constant volume. After centrifugation and appropriate dilution, the sample solution was analyzed at 270 nm (pH 1.2) and 277 nm (pH 7.5) by a UV spectrophotometer (Shimadzu, UV-1601). The amounts of drug present in the samples were calculated with the help of appropriate calibration curves constructed from reference standards. Drug dissolved at specified time periods was plotted as percent release versus time (hours) curve.

Different kinetic equations (zero-order, first-order and Higuchi's equation) were applied to interpret the release rate from matrix system using linear regression. The dissolution rate (kd), correlation coefficients (r), and half-life of release ($Td_{50\%}$) were also determined.

### Additional Tests

Tablet hardness was measured with a Pharma Test PTB 311 tester. The hardness (kgf) of 10 tablets was measured, and the mean hardness was calculated and reported.

The tablet friability was determined on a Coel HX-4 friabilator. The weight of 20 tablets was measured on an analytical balance (Mettler H15) and then loaded into the friabilator. After 100 revolutions, the tablets were removed, dedusted, and reweighed. The difference of the weight was calculated as a percent loss.

Diameter and thickness were measured using Paquimetre Mitutoyo for 10 tablets.

To study weight variation, 20 tablets were weighed individually using an electronic balance (Mettler H15), and the test was performed according to the official method.

The drug content was determined as described above; five tablets were weighed and crushed. The amount of powder equivalent to the mean of these five tablets was weighed in 100 mL of water and the volume adjusted to 200 mL. After 20 minutes of centrifugation, aliquots of 1 mL were taken from this solution and diluted to 100 mL with simulated gastric fluid without pepsin (pH 1.2) and simulated intestinal fluid without pancreatin (pH 7.5). Absorbancies of resulting solutions were measured in a spectrophotometer at 270 nm for pH 1.2 and 271 nm for pH 7.5. Simultaneously, a 10 µg/mL theophylline standard solution prepared in the same medium (pH 1.2 and 7.5) was recorded. Content of theophylline was calculated. The drug content test was carried in duplicate.

## RESULTS AND DISCUSSION

The granulation process to obtain matrices showed difficulties with the increasing percentages of Eudragit®. The hard homogeneous mass formed during this process in some lots of tablets seemed to pass through the mesh 35 sieve with difficulty. Consequently, resulted in less

efficiency and low productivity. Considering the polymer Eudragit® RS 30D, there was a limitation when amounts of the polymer, higher than 20%, were applied. Even when Eudragit® NE 30D was used, the amounts of 20% and 30% also showed difficulties. During granulometric analyses, the granules obtained in lots EUD NE 2, EUD NE 3, EUD NE 5, and EUD NE 6 presented less than 10% of fine powder, when passed through sieve aperture of 115 mesh. According to Salomon and Doelker (1980), these quantity of fine powder is considered ideal, once large quantities can lead to an elastic characteristic in pharmaceutical dosage forms, increasing the volume of tablet during the compression process. This volumetric increase makes hydration and diffusion easy, thus resulting in high amount of drug released. This phenomenon probably contributed to increase the amount of drug released from lots EUD NE 1, EUD NE 4, and EUD NE 7 (Figure 1 and 2), which granules presented high percentages of fine powder (Table III). The granules produced with Eudragit® RS 30 D polymer, with high percentage of fine powder were in lots EUD RS 4, EUD RS 5, EUD RS 6 and EUD RS 7 (Table IV).

In accordance with pharmacopoeia specifications (United States Pharmacopoeia, 2002; Farmacopéia Brasileira, 1988), tablets between 200 and 300 mg, may have a variation around 7.5% of the labeled weight. The weights of the formulations EUD NE 6, EUD RS 1, and EUD RS 2 (Table V) were in accordance with the pharmacopoeia limits but the coefficients of variation showed that they could be out of the tolerance limits. Friability is an important parameter related to mechanical resistance of tablets.

All formulations were compliant with official friability specifications (Table V), which allow not more than 1% of mass lost on 20 tablets weight. Hardness can affect the disintegration rate of tablets and consequently, drug dissolution. Hardness of the tablets were in conformity with pharmacopeial tolerance limits except formulations EUD NE 6 and EUD RS 2, in which hardness for values were lower than the limit of 4.6 kgf. However, this fact did not affect theophylline release in tablets, but can facilitate drug release by encreasing permeability of the drug in solution. The content of the drug in the tablets were determined following USP 25 specifications which stated that the quantity of drug in

**TABLE III -** Granulometric analyses of formulations prepared with Eudragit® NE 30D

| | Mass retained on the sieve (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Tyler (Mesh)** | **EUD NE 1** | **EUD NE 2** | **EUD NE 3** | **EUD NE 4** | **EUD NE 5** | **EUD NE 6** | **EUD NE 7** |
| 35 | 0,15 | 0,07 | 59,37 | 51,32 | 64,02 | 55,43 | 13,83 |
| 48 | 10,22 | 33,25 | 39,22 | 9,28 | 17,27 | 13,68 | 6,49 |
| 60 | 3,30 | 31,29 | 1,41 | 10,49 | 5,61 | 12,68 | 1,37 |
| 65 | 32,64 | 25,70 | 0,08 | 5,45 | 3,62 | 13,18 | 28,11 |
| 80 | 0,11 | 0,29 | 0,04 | 5,98 | 2,97 | 0,41 | 15,73 |
| 100 | 0,04 | 0,07 | 0,04 | 0,98 | 1,83 | 0,16 | 0,00 |
| 115 | 0,07 | 0,25 | 0,03 | 0,64 | 0,12 | 0,04 | 4,15 |
| >115 | 53,48 | 8,96 | 0,67 | 15,26 | 0,08 | 1,33 | 28,49 |

**TABLE IV -** Granulometric analyses of formulations prepared with Eudragit® RS 30D

| | Mass retained on the sieve (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Tyler (Mesh)** | **EUD RS 1** | **EUD RS 2** | **EUD RS 3** | **EUD RS 4** | **EUD RS 5** | **EUD RS 6** | **EUD RS 7** |
| 35 | 7,16 | 25,68 | 47,91 | 1,42 | 4,69 | 18,94 | 3,33 |
| 48 | 37,05 | 25,30 | 10,01 | 8,53 | 9,67 | 12,09 | 4,17 |
| 60 | 4,77 | 1,79 | 2,05 | 8,79 | 8,05 | 4,84 | 11,87 |
| 65 | 17,11 | 18,66 | 8,11 | 26,14 | 19,94 | 8,43 | 8,46 |
| 80 | 35,48 | 22,89 | 0,29 | 42,01 | 18,25 | 8,00 | 4,33 |
| 100 | 0,27 | 0,79 | 0,14 | 0,54 | 1,31 | 6,17 | 10,07 |
| 115 | 0,07 | 0,16 | 0,07 | 0,15 | 5,51 | 5,34 | 1,76 |
| >115 | 0,00 | 0,05 | 0,00 | 12,45 | 32,58 | 32,03 | 56,43 |

**TABLE V -** Results of weight, friability, diameter, thickness, hardness, and drug content of theophylline

| Formulations | Weight (mg) | Friability (%) | Diameter (mm) | Thickness (mm) | Hardness (kgf) | Drug content (%) |
|---|---|---|---|---|---|---|
| EUD NE 1 | 303.19 (4.56) | 0.28 | 10.01 (0.02) | 4.00 (0.38) | 6.73 (0.22) | 98.14 |
| EUD NE 2 | 301.49 (3.38) | 0.22 | 10.00 (0.01) | 4.37 (0.08) | 5.56 (0.15) | 99.38 |
| EUD NE 3 | 302.33 (5.50) | 0.12 | 10.00 (0.01) | 4.31 (0.02) | 5.31 (0.10) | 92.74 |
| EUD NE 4 | 298.85 (3.19) | 0.37 | 10.03 (0.02) | 4.14 (0.08) | 5.05 (0.09) | 99.18 |
| EUD NE 5 | 301.90 (2.21) | 0.11 | 10.02 (0.02) | 4.11 (0.06) | 7.10 (0.11) | 95.20 |
| EUD NE 6 | 289.47 (7.54) | 0.15 | 10.01 (0.01) | 4.21 (0.17) | 4.39 (0.08) | 97.97 |
| EUD NE 7 | 320.64 (6.84) | 0.42 | 10.01 (0.04) | 3.98 (0.35) | 9.59 (0.46) | 93.70 |
| EUD RS 1 | 305.15 (10.13) | 0.55 | 10.04 (0.03) | 4.00 (0.07) | 5.46 (35.4) | 95.44 |
| EUD RS 2 | 291.35 (7.92) | 0.36 | 10.04 (0.02) | 3.77 (0.03) | 3.47 (7.5) | 99.33 |
| EUD RS 3 | 303.15 (4.36) | 0.23 | 10.02 (0.02) | 3.89 (0.07) | 5.56 (11.5) | 96.67 |
| EUD RS 4 | 300.99 (5.17) | 0.51 | 10.04 (0.03) | 4.02 (0.12) | 9.39 (3.10) | 99.48 |
| EUD RS 5 | 306.96 (4.79) | 0.63 | 10.05 (0.03) | 3.86 (0.11) | 6.84 (16.1) | 91.36 |
| EUD RS 6 | 305.26 (6.53) | 0.40 | 10.02 (0.02) | 5.10 (0.05) | 5.20 (4.50) | 96.02 |
| EUD RS 7 | 301.40 (1.45) | 0.09 | 10.06 (0.03) | 3.81 (0.31) | 10.97 (4.20) | 96.28 |

Coefficients of variation (%) in parenthesis.

tablets should not be less than 90.0% or more than 110.0%. All drug contents in formulations were between these limits.

## Dissolution Studies

*In vitro* dissolution studies are valuable tools to judge quality and stability of sustained release dosage forms and are often used to predict *in vivo* performance.

As can be observed in Figures 1 and 2, both polymeric materials (Eudragit® RS 30D and NE 30D) were able, in first instance to produce true matrices, influencing the release profile of theophylline. Therefore in polymer NE 30D, an increase in its content, more than 10% of the polymer and tribasic calcium phosphate used as diluent, did not result in a different profile of theophylline release in formulations (Figure 1).

Some of the reasons that led to the stabilization of theophylline profile when different amounts of Eudragit® NE 30D were used, could be related to the large quantity of polymer applied, theophylline solubility or the utilization of 3% of magnesium stearate, an hydrophobic lubricant that decreases theophylline release in formulations. Moreover, the use of an insoluble excipient like tribasic calcium phosphate could also decrease drug release, diminishing the matrix hydration.

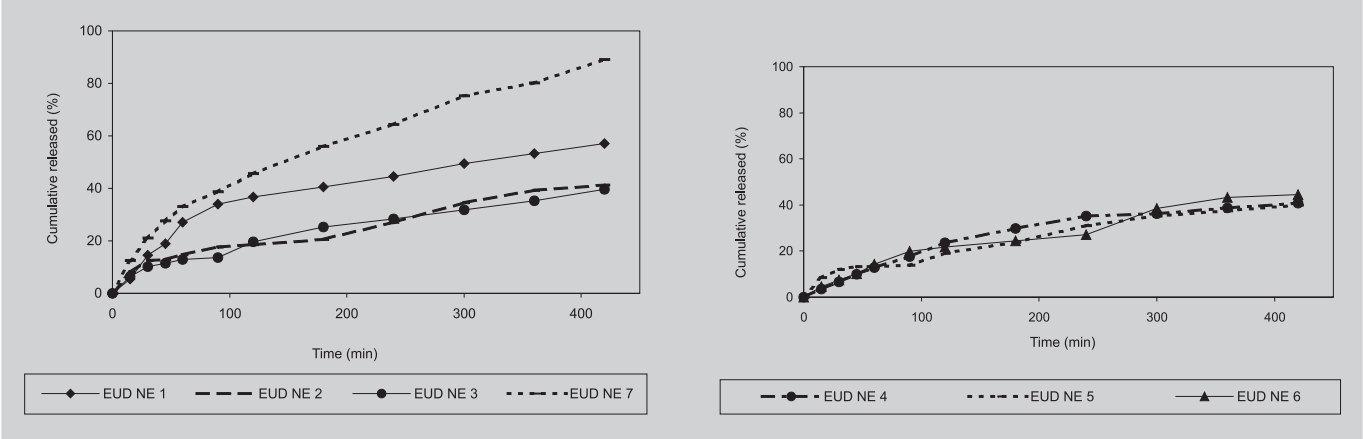


**FIGURE 1** - Release profiles of theophylline tablets with Eudragit® NE 30D with lactose and tribasic calcium phosphate respectively, applying USP 25 ed. dissolution test (Test 10).

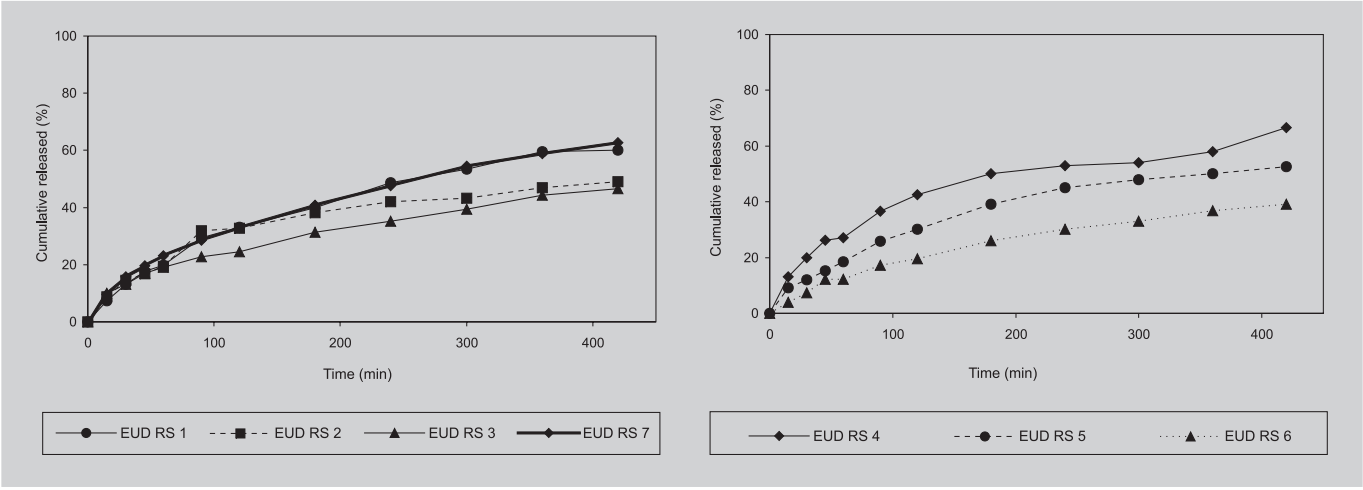


**FIGURE 2 -** Release profiles of theophylline tablets with Eudragit® RS 30D with lactose and tribasic calcium phosphate respectively applying USP 25 ed. dissolution test (Test 10).

In formulations such as EUD RS 1, EUD RS 2, and EUD RS 3, where the diluent content was lactose, different release of the drug was evident when the medium was changed from pH 1.2 to pH 7.5 (Figure 2) probably related with the characteristics of polymer solubility. In formulations with 10% of polymer, the decrease in lubricant content from 3% in EUD RS 1, to 0.5% in EUD RS 7, had no influence on theophylline release in tablets.

An ideal matrix system is that in which the drug released constantly, from the beginning to the end, in a zero order kinetic model (Pather *et al.*, 1998; Ishikawa *et al.*, 2000; Robinson, Eriksen, 1966). Drug release from matrix tablets, in general, becomes progressively slower with time, like Higuchi's model, in which the amount of drug released is proportional to the square root of time (Higuchi, 1963).

Kinetic models which fit zero order and Higuchi are more suitable for controlled release formulations, while first order model is more appropriate for conventional tablets (Higuchi, 1963). The best fit with higher correlation ($r^2 > 0.98$) was found with the Higuchi's equation for the majority of formulations (Table VI). This fact was expected considering that difusion is the preferential mechanism of drug release from this kind of matrices. On the other hand,

**TABLE VI -** Kinetic assessment: correlation coefficient (r) of kinetic model, dissolution rate (k) and half-life of release ($t_{50\%}$)

| Formulations | Correlation coefficients (r) | | | k ($min^{-1}$) | $t_{50\%}$ (min) |
|---|---|---|---|---|---|
| | Zero Order | First Order | Higuchi | | |
| EUD NE 1 | 0.8465 | 0.9188 | 0.9652 | 0.0287 | 294.47 |
| EUD NE 2 | 0.9485 | 0.9655 | 0.9666 | 0.0194 | 675.19 |
| EUD NE 3 | 0.9522 | 0.9747 | 0.9901 | 0.0192 | 711.39 |
| EUD NE 4 | 0.9068 | 0.9361 | 0.9755 | 0.0226 | 555.37 |
| EUD NE 5 | 0.9475 | 0.9693 | 0.9788 | 0.0197 | 662.60 |
| EUD NE 6 | 0.9526 | 0.9699 | 0.9720 | 0.0230 | 542.08 |
| EUD NE 7 | 0.9398 | 0.9812 | 0.9977 | 0.0438 | 141.81 |
| EUD RS 1 | 0.9275 | 0.9743 | 0.9915 | 0.0321 | 271.38 |
| EUD RS 2 | 0.8355 | 0.8909 | 0.9635 | 0.0249 | 375.95 |
| EUD RS 3 | 0.9216 | 0.9641 | 0.9979 | 0.0224 | 478.91 |
| EUD RS 4 | 0.8496 | 0.9274 | 0.9743 | 0.0312 | 222.03 |
| EUD RS 5 | 0.9046 | 0.9481 | 0.9866 | 0.0278 | 340.79 |
| EUD RS 6 | 0.9387 | 0.9661 | 0.9924 | 0.0198 | 691.85 |
| EUD RS 7 | 0.9405 | 0.9875 | 0.9985 | 0.0326 | 252.77 |

theophylline although being a slight soluble drug, released from Eudragit® matrices by diffusion and not by erosion, considering that the matrices maintained their original shape from the start to end of dissolution tests.

## CONCLUSION

At present, the polymers studied in this work are used extensively in pharmaceuticals to control the release of drug. The approach of the present study was to make a comparative evaluation among these methacrylic esters polymers and to find out factors involved on drug release profile. The type of polymers used imparts a conspicuous effect on release mechanism. The lubricant, magnesium stearate, at low concentration improved theophylline release in tablets prepared with Eudragit® NE 30D. The correlation values obtained when mathematical models were applied to release data suggested that the releases of drug from these tablets were preferentially a diffusion-controlled process. According to USP 25, formulation EUD NE 7 showed amount of dissolved theophylline close to specifications in Test 10.


## RESUMO

**Desenvolvimento e avaliação *in vitro* de comprimidos de liberação prolongada de teofilina preparados com Eudragit®**

*Comprimidos contendo teofilina (66.67%) e polímeros de Eudragit® NE 30D e RS 30D entre 10 e 30% foram produzidos por compressão. A influência das diferentes proporções de ésteres do ácido metacrílico, uso da lactose e fosfato de cálcio tribásico como diluente, bem como os efeitos da adição de estearato de magnésio como agente lubrificante hidrofóbico na liberação da teofilina foram estudados. Análises físico-químicas e teor de fármaco foram avaliados. Estudos da liberação do fármaco* in vitro *foram conduzidos em fluido gástrico simulado (pH 1,2) e fluido intestinal simulado sem pancreatina (pH 7,5). Observou-se liberação prolongada relativa de teofilina partindo de polímeros matriciais, em 7 horas de dissolução. Estearato de magnésio a 0,5% e de Eudragit® NE 30D a 10% foi considerado o sistema de liberação adequado para comprimidos matriciais comparado com de Eudragit® RS 30D nas mesmas condições (USP). Os resultados das análises físico-químicas apresentaram-se dentro das especificações. Modelos matemáticos de ordem zero, primeira ordem e Higuchi foram aplicados para estudar a liberação de teofilina nos comprimidos. Adicionalmente, foram calculadas a meia-vida ($Td_{50\%}$) e a velocidade de dissolução (kd). O modelo de liberação de Higuchi foi o que melhor representou a liberação do fármaco nos comprimidos, sendo demonstrado que o principal mecanismo de liberação foi a difusão.*


*UNITERMOS: Teofilina. Matrizes. Liberação prolongada. Ésteres do ácido metacrílico.*


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