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RESEARCH PAPER

# Study of Formulation Parameters by Factorial Design in Metoprolol Tartrate Matrix Systems

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## ABSTRACT

*The study of formulation parameters in hydrophilic matrices of metoprolol tartrate by $2^3$ factorial design was made. We compared the dissolution profiles of two hydrophilic polymers (hydroxypropylmethylcellulose and hydroxyethylcellulose) at high and low concentrations and in the presence or absence of an insoluble excipient (calcium hydrogen phosphate dihydrate). The results showed that the presence of an insoluble excipient influenced almost all of the dissolution parameters.*

***Key Words:*** *Dissolution parameters; Factorial design; Hydrophilic matrix; Metoprolol tartrate*

## INTRODUCTION

Matrix tablets made with hydrophilic polymers have applications in the development of controlled-release pharmaceutical dosage forms for water-soluble active ingredients (1).

Gel-forming agents have been used to modulate the release process of the active ingredient. One group of gel-forming agents is the hydrophilic cellulose ethers, which include hydroxypropylmethylcellulose and hydroxyethylcellulose (2). The physical properties of these polymers (viscosity, speed of gel formation, and compression behavior) can be used to balance the physical and chemical properties of the active ingredient to control its release characteristics. In addition, dosage forms can be prepared from these polymers such that physiologic parameters like pH, gastrointestinal motility, and ionic strength or enzymatic composition of the gastric fluid have little influence on the release from these matrices (3).

Theophylline, propanolol, vincamine, and acetaminophen are among the drugs that have been formulated in hydrophilic matrices of hydroxypropyl-

methylcellulose and hydroxyethylcellulose (4–7). One of the many advantages of using hydrophilic matrices for prolonged release is that the technology used in their manufacture is relatively simple and is similar to that used to prepare standard immediate-release tablets.

The target of this work was to use a factorial design to study the influence of several formulation factors on the in vitro release profile of metoprolol tartrate from hydrophilic polymer matrices. The variables examined were the type and concentration of polymer and the presence or absence of an insoluble excipient. The dissolution results were evaluated according to previously described parameters (8,9).

## EXPERIMENTAL

### Materials

Metoprolol (INN) tartrate (Esteve Química, S.A.); Polividone K-30 (GAF Chemicals); cellulose microcrystalline (FMC); lactose (Escuder, Barcelona, Spain); magnesium stearate (Escuder); and calcium hydrogen phosphate dihydrate (Escuder) were used. Hydroxypropylmethylcellulose (Methocel K100M, Dow Chemical Company, Midland, MI) and hydroxyethylcellulose (Natrosol 250 HHX, Hercules, Inc., Wilmington, DE) were used as received.

All the excipients complied with the third edition of the European Pharmacopoeia and USP 23 specifications.

### Methods

#### Manufacture of Hydrophilic Matrices

Hydrophilic matrices were prepared by wet granulation (hydroalcoholic solution) with 200 mg of active ingredient. The granulate was compressed into tablets using a Korsch tablet machine with biconcave 11-mm diameter punch.

The influence that differences in physical strength had on the release profile were not studied. All tablets had the same thickness. Batch size was 100 tablets.

#### Controls

The following controls were carried out after compression:

Resistance to crushing of tablets (European Pharmacopoeia, 3rd Ed., 2.9.8), Schleuniger Mod 3E/20S (specification limits 78.4–117.6 N)
Uniformity of mass (European Pharmacopoeia, 3rd Ed., 2.9.5)
Friability (European Pharmacopoeia, 3rd Ed., 2.9.7), Erweka friability apparatus (specification limits < 1%)
Active ingredient content by ultraviolet (UV) spectrophotometry (diode array Mod 8452 at 273 nm) (specification limits: 95%–105%)

#### Dissolution Studies

Studies showing the profiles of the dissolution of the active ingredient were carried out in an automated paddle apparatus (European Pharmacopoeia, 3rd Ed., 2.9.3) (Pharmatest type PTWS III) connected through a peristaltic pump to a spectrophotometer (Perkin Elmer Lambda 2 System) controlled by a personal computer.

The rotation speed was 100 rpm, and the dissolution medium was 900 ml of 0.1 N HCl at $37^{\circ}C \pm 0.5^{\circ}C$.

The data of the dissolution test were used to study the following parameters:

$t_{10\%}$, time for 10% active ingredient release
$t_{50\%}$, time for 50% active ingredient release
$Q_{max}$
Dissolution efficiency
MDT, mean dissolution time
AUC, area under curve

#### Factorial Design

The factorial design was carried out by the software Statgraph 8.0®. Response surface graphics were used to show the factor interaction between the considered variables. These graphics allow optimizing the formulation to obtain determined values.

The type and concentration of polymer and the presence or absence of insoluble excipient in the formulation were studied by factorial design of the dissolution parameters of the matrices for 12 h.

The factorial design was established as shown in Tables 1–3.

## RESULTS

Resistance to crushing, uniformity of mass, friability, and assay (percentage) are given for each formulation in Table 4. The graphic representation of the corresponding dissolution test is shown in Fig. 1. The kinetics of the process was determined as a function of the parameter that describes it (Table 5).

Table 6 shows the equations that describe each of the variables studied by factorial design.

***Table 1***

*Variables in the Factorial Design*

| + | − |
|---|---|
| Hydroxypropyl-methyllcellulose | Hydroxyethyl-cellulose |
| Polymer concentration 15%–20% | Polymer concentration 25%–30% |
| Presence of dicalcic phosphate | Absence of dicalcic phosphate |

***Table 2***

*Factorial Design Matrix*

| Assay | Polymer | Concentration | Excipient |
|---|---|---|---|
| 1 (2) | − | − | − |
| 2 (6) | + | − | − |
| 3 (3) | − | + | − |
| 4 (7) | + | + | − |
| 5 (4) | − | − | + |
| 6 (8) | + | − | + |
| 7 (5) | − | + | + |
| 8 (1) | + | + | + |

## DISCUSSION

### $t_{10\%}$, $t_{50\%}$, and $Q_{max}$

The data obtained from the study of equations for each variable and from the statistical analysis show that the factor with the biggest influence in the release time of the active ingredient was the type of polymer used. The use of hydroxypropylmethylcellulose increased the $t_{10\%}$ and $t_{50\%}$ values.

When the concentration of active ingredient at 12 h was studied, the factor of greatest importance was an increase of polymer concentration from 20% to 30% (statistically significant difference $P < .01$), which gave rise to an increase of approximately 9% in the quantity of active ingredient released.

The hydroxypropylmethylcellulose caused a 7% decrease of the metoprolol tartrate ($P < .01$) compared to the use of hydroxyethylcellulose. This phenomenon was due to the quicker hydration rate of hydroxypropylmethylcellulose compared to hydroxyethylcellulose. A gel layer outside the core was formed, which was dense and kept water from entering the inner layer and delayed active principle release.

However, the type of polymer cannot be taken into account by itself since the interaction between the type of polymer and the presence of insoluble excipient is observed. This interaction causes about a 5% decrease of the quantity of active ingredient released ($P < .01$) at 12 h with statistically significant differences.

The graphic of the response surface shows that the maximal active ingredient released at 12 h was obtained with insoluble excipient and hydroxyethylcellulose as a polymer ($P < .05$) (Fig. 2).

The presence or absence of insoluble excipient as an individual factor is the variable with less influence on $t_{10\%}$, $t_{50\%}$, and $Q_{max}$.

***Table 3***

*Formulations Studied*

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Active ingredient (%) | 39.25 | 39.25 | 39.25 | 39.25 | 39.25 | 39.25 | 39.25 | 39.25 |
| Polividone K-30 (%) | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 |
| Microcrystalline cellulose (%) | 20.00 | 20.00 | 12.50 | 12.50 | — | — | — | — |
| Lactose (%) | 20.00 | 20.00 | 12.50 | 12.50 | 17.50 | 17.50 | 12.50 | 12.50 |
| Magnesium stearate (%) | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 |
| Hydroxypropylmethylcellulose (%) | — | 20.00 | — | 30.00 | — | 20.00 | — | 30.00 |
| Hydroxyethylcellulose (%) | 20.00 | — | 30.00 | — | 20.00 | — | 30.00 | — |
| Calcum hydrogen phosphate dihydrate (%) | — | — | — | — | 17.50 | 17.50 | 12.50 | 12.50 |

***Table 4***

*Study Results by Formulation*

| | Formulation | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| Resistance of crushing (N) | 87 | 92 | 95 | 85 | 109 | 107 | 99 | 112 |
| Uniformity of mass | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies |
| Assay (%) | 99.7 | 99.8 | 99.8 | 99.7 | 99.4 | 99.4 | 99.9 | 99.5 |
| Friability (%) | 0.2 | 0.1 | 0.2 | 0.1 | 0.1 | 0.2 | 0.2 | 0.1 |

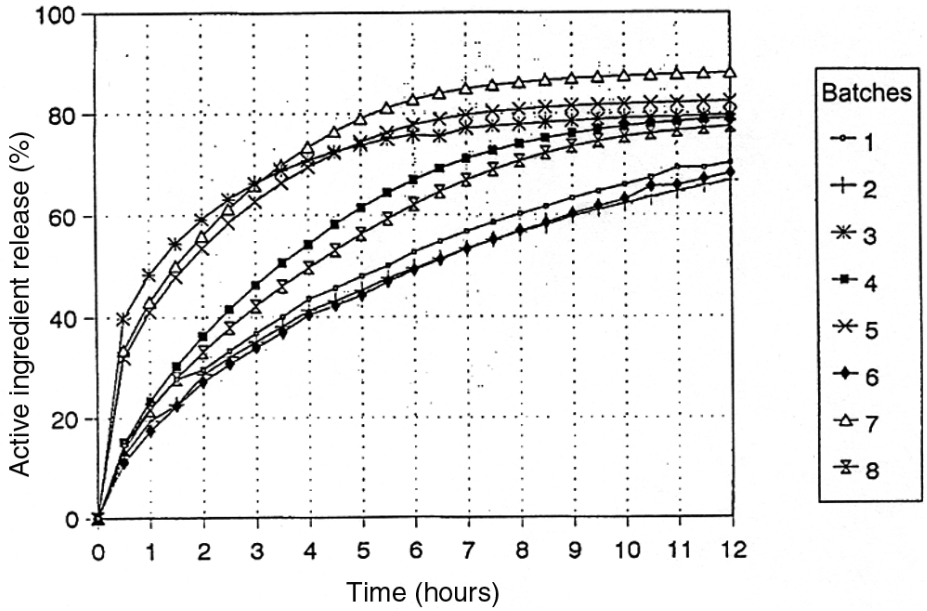


**Figure 1.** Dissolution test.

***Table 5***

*Experimental Results According to Parameters of the Dissolution Process*

| Assay | $t_{10\%}$ (h) | $t_{50\%}$ (h) | ED | MDT | AUC | $M_{final}$ (%) |
|---|---|---|---|---|---|---|
| 1 | 0.3132 | 5.26 | 48.77 | 2.5385 | 1170.6 | 70.24 |
| 2 | 0.5000 | 6.02 | 45.93 | 2.4600 | 1102.3 | 66.72 |
| 3 | 0.0055 | 0.96 | 68.89 | 2.2400 | 3355.2 | 79.61 |
| 4 | 0.2500 | 3.39 | 59.10 | 4.7600 | 2836.8 | 79.07 |
| 5 | 0.0350 | 1.49 | 69.63 | 2.9700 | 3342.6 | 82.31 |
| 6 | 0.4498 | 6.09 | 45.59 | 2.6800 | 1094.4 | 68.18 |
| 7 | 0.0470 | 1.33 | 73.91 | 3.2900 | 3547.9 | 87.94 |
| 8 | 0.3300 | 3.96 | 55.84 | 5.1600 | 2680.3 | 77.44 |

## Dissolution Efficiency

The *dissolution efficiency* is defined as the relation between the area under the curve of dissolved percentage as a time function at an observed time and the area of a rectangle that represents 100% dissolved at the same time (10).

$$DE = \frac{\int_0^t y \cdot dt}{y_{100} \cdot t} \times 100$$

Hydroxypropylmethylcellulose caused about a 15% decrease of dissolution efficiency ($P < .15$) in relation to hydroxyethylcellulose. On the other

***Table 6***

*Coefficients of Regression Line*

| | |
|---|---|
| $t_{10\%}$ | $Y = 14.47 + 8.46X_1 - 4.99X_2 - 1.55X_3 - 0.55X_1X_2 + 1.99X_1X_3 + 3.37X_2X_3$ |
| $t_{50\%}$ | $Y = 1.56 + 1.30X_1 - 1.15X_2 - 0.34X_3 - 0.03X_1X_2 + 0.50X_1X_3 + 0.58X_2X_3$ |
| $M_{\text{final}}$ | $Y = 76.43 - 3.58X_1 + 4.57X_2 + 2.52X_3 + 0.82X_1X_2 - 2.57X_1X_3 - 0.85X_2X_3$ |
| AUC | $Y = 2391.26 - 462.81X_1 + 713.78X_2 + 275.03X_3 + 116.31X_1X_2 - 316.14\ X_1X_3 - 265.98X_2X_3$ |
| MDT | $Y = 3.26 + 0.50X_1 + 0.59X_2 + 0.26X_3 + 0.59X_1X_2 - 0.10X_1X_3 + 0.09X_2X_3$ |
| ED | $Y = 58.58 - 6.96X_1 + 6.10X_2 + 2.66X_3 - 0.24X_1X_2 - 3.56X_1X_3 - 2.47X_2X_3$ |

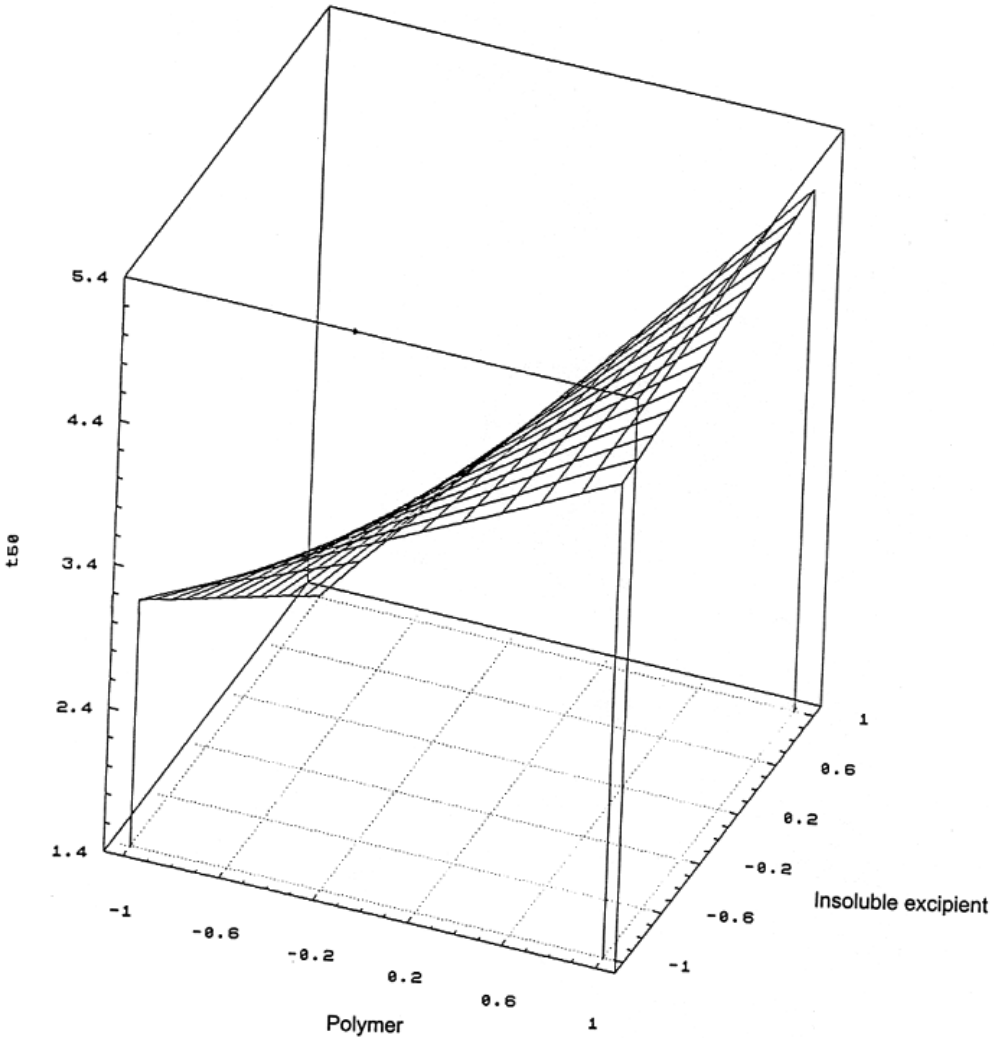


**Figure 2.** Maximal active ingredient released at 12 h.

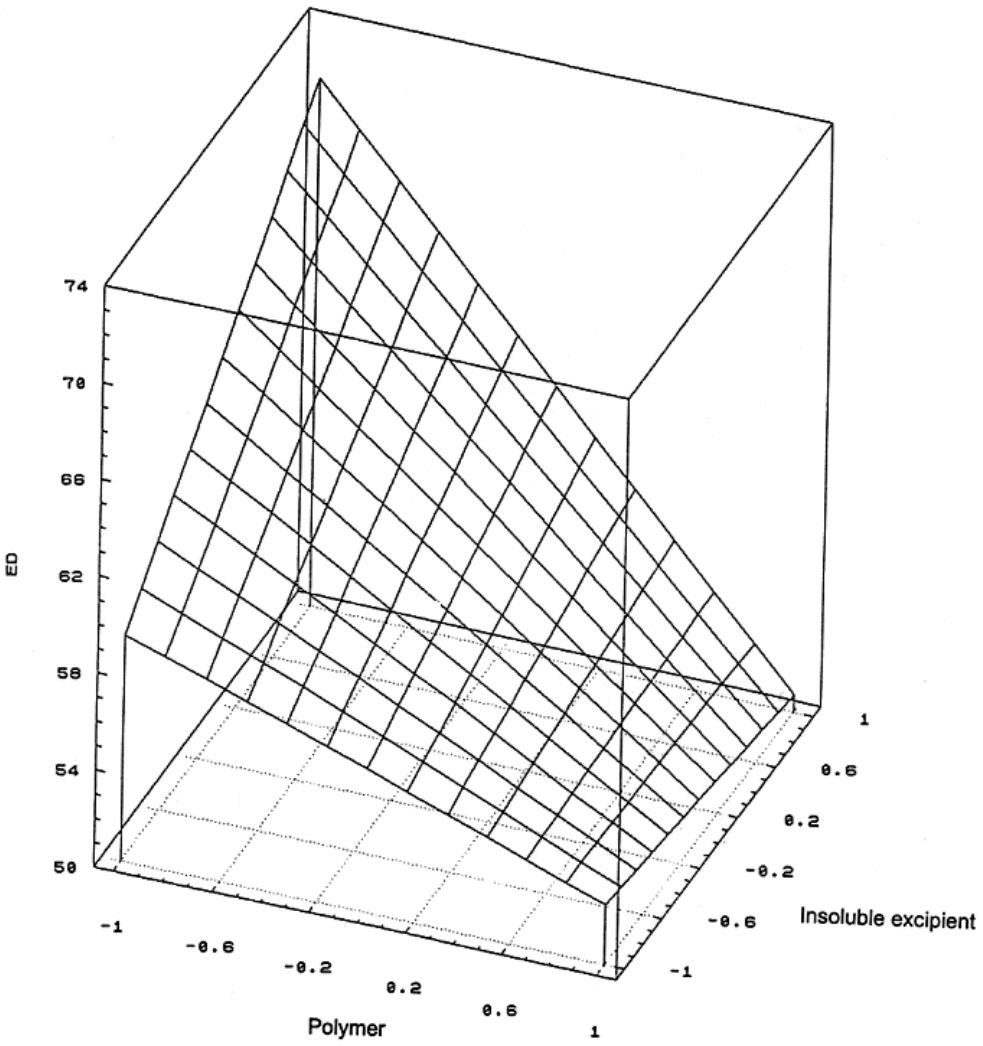


**Figure 3.** Maximal dissolution efficiency.

hand, the use of high concentrations (30%) of any of the two polymers increased dissolution efficiency to 12%.

The possible interactions to take into account are the polymer type together with the presence of insoluble excipient in the formulation, which produces a decrease of approximately 7% in the dissolution efficiency.

The graphic of the surface response shows that the maximal dissolution efficiency value was obtained with hydroxyethylcellulose as a polymer in the presence of insoluble excipient (Fig. 3).

When hydroxypropylmethylcellulose was used as a polymer, the lower value of dissolution efficiency was obtained. There was no statistically significant difference between the data obtained in the presence or absence of insoluble excipient.

## Mean Dissolution Time

The polymer type and its concentration influenced MDT values as individual variables ($P < .05$ and $P < .06$, respectively). The two factors produced an increase in the result.

However, the type of polymer/concentration of polymer should be considered jointly in the MDT values obtained. When 30% hydroxypropylmethylcellulose was used, the value of MDT increased around 1.19 h ($P < .05$).

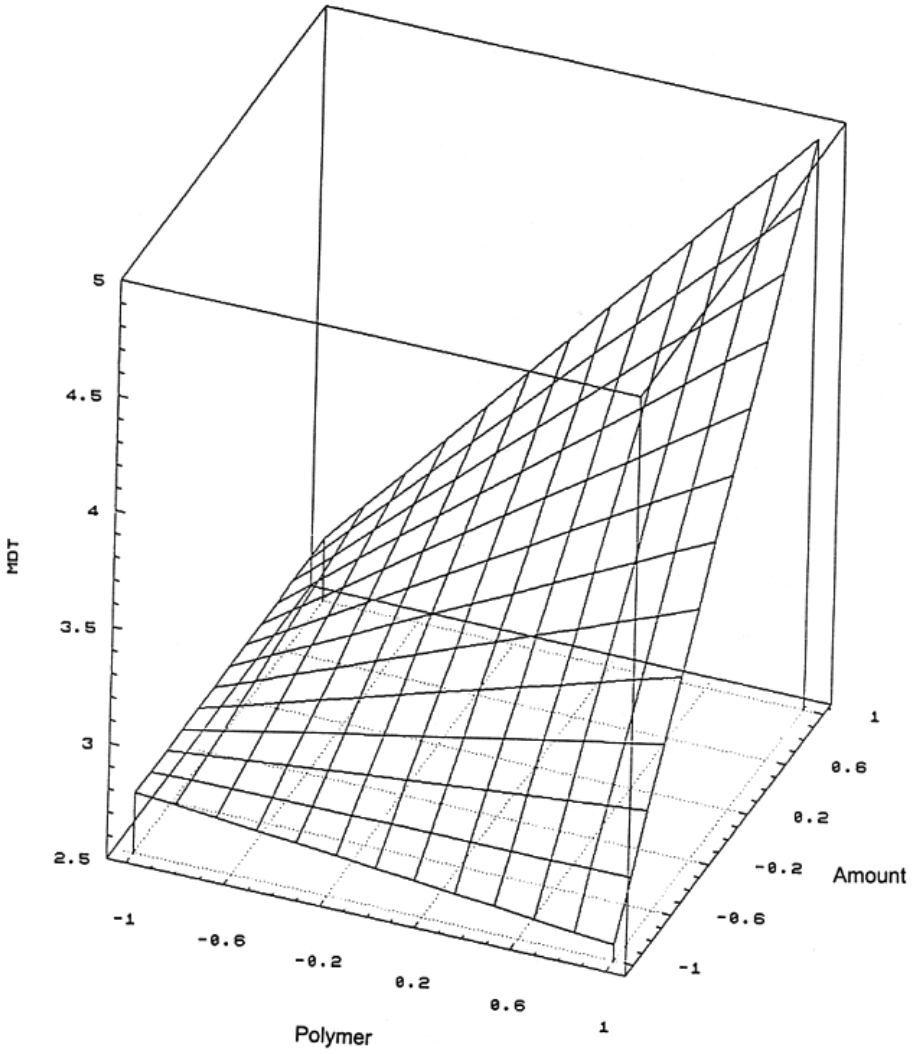


**Figure 4.** Maximal MDT values.

The graphic of the surface response shows that the maximal values of MDT were obtained when hydroxypropylmethylcellulose was used at high concentrations (Fig. 4).

### Area Under Curve

The factors with the main influence on the AUC were the concentration of polymer and the interaction presence or absence of insoluble excipient/type of polymer. The high values of AUC were obtained with hydroxyethylcellulose as a polymer and in the presence of insoluble excipient (Fig. 5).

## CONCLUSION

The presence of an insoluble excipient in the formulation exerted an influence on almost all the parameters of the dissolution profile of hydrophilic matrices of metoprolol tartrate; the effect was greater when hydroxyethylcellulose polymer was used.

The mechanism of principle active release from hydrophilic matrices was by a diffusion phenomenon through the gel layer of the core. The insoluble excipients can delay the dissolution rate by decreasing the surface available to wetting. This type of excipient can induce uniform swelling of tablets.

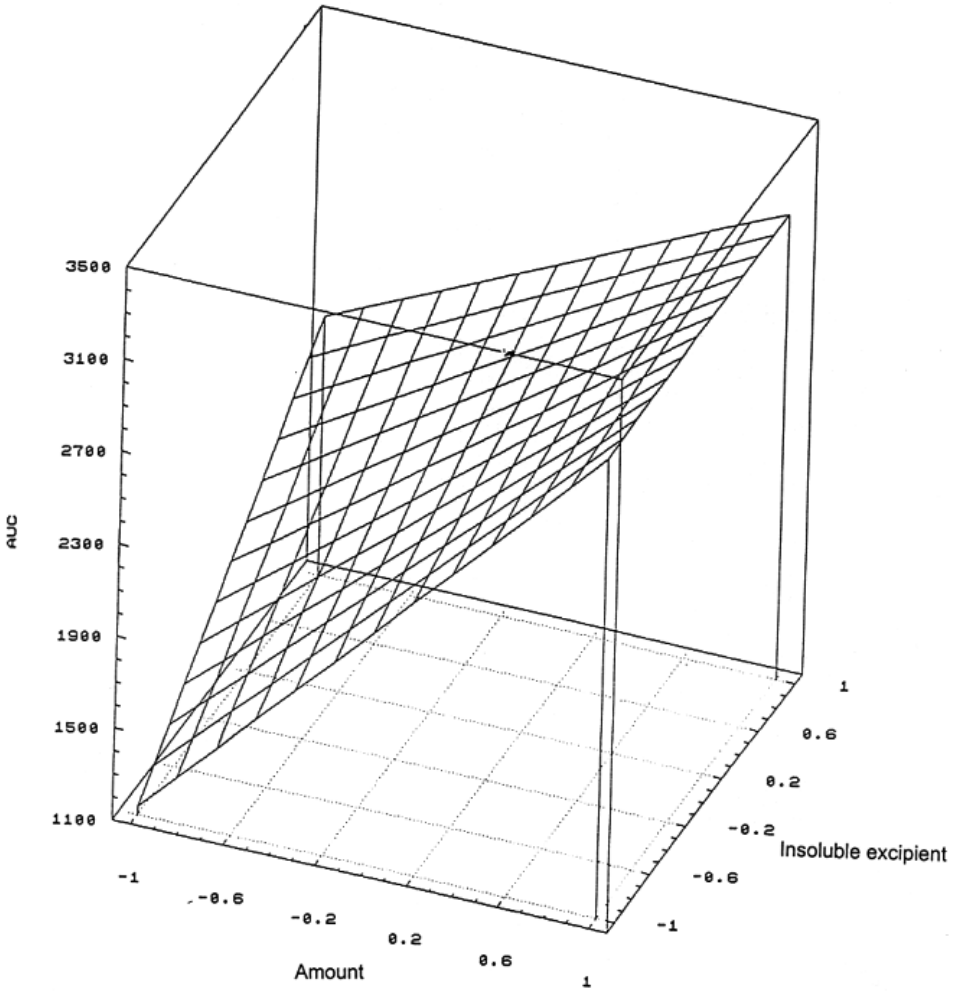


**Figure 5.** Maximal AUC values.

Hydroxypropylmethylcellulose does not significantly modify the values of the parameters. Nevertheless, slower release of the active ingredient throughout the dissolution process was achieved when hydroxypropylmethylcellulose was used in the presence of insoluble excipients.

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