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# Application of Mixture Experimental Design in the Formulation and Optimization of Matrix Tablets Containing Carbomer and Hydroxypropylmethylcellulose

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Using mixture experimental design, the effect of carbomer (Carbopol® 971P NF) and hydroxypropylmethylcellulose (Methocel® K100M or Methocel® K4M) combination on the release profile and on the mechanism of drug liberation from matrix tablet was investigated. The numerical optimization procedure was also applied to establish and obtain formulation with desired drug release. The amount of TP released, release rate and mechanism varied with carbomer ratio in total matrix and HPMC viscosity. Increasing carbomer fractions led to a decrease in drug release. Anomalous diffusion was found in all matrices containing carbomer, while Case - II transport was predominant for tablet based on HPMC only. The predicted and obtained profiles for optimized formulations showed similarity. Those results indicate that Simplex Lattice Mixture experimental design and numerical optimization procedure can be applied during development to obtain sustained release matrix formulation with desired release profile.

**Key words:** Sustained release dosage form, Mixture experimental design, HPMC/carbomer matrices, *In vitro* tests, Dissolution

## INTRODUCTION

Polymeric materials have been widely used to modify and/or modulate the drug release from solid dosage forms such as sustained-release or controlled-release hydrophilic matrix tablets. However, a large number of factors (Furlanetto et al., 2006; Parojcic et al., 2004), including the physicochemical properties of the row materials (Khan and Zhu, 1999), the ratios in which ingredients are combined (Hayashi et al., 2005), as well as the processing conditions (Streubel et al., 2003; Kiortsis et al., 2005), can influence the drug release behavior from the final product. Molecular structure of the polymer, chain entanglement and crystallinity of the polymer matrix (Narasimhan, 2001) can be the most important factors influencing the differences in mechanisms of drug release from those systems (Siepman and Peppas, 2001).

Hydroxypropylmethylcellulose (HPMC) is frequently used hydrophilic polymer in the formulation of the solid dosage forms. It has linear structure without chemical crosslinking and water solubility therefore the release behavior is controlled by diffusing, swelling, dissolving and eroding the drug incorporated into the matrices (Zuleger et al., 2001, 2002).

Over the time there has been an increasing interest in developing and manufacturing formulations using other controlled released excipients, such as Carbopol® polymers. These polymers have been especially used for the formulations with mucoadhesive (Prudat-Christiaens et al., 1996; Khanna et al., 1997; Das et al., 2004) or floating properties (Li et al., 2003; Straubel et al., 2003), but also to control drug release from solid dosage forms (Perez-Markos et al., 1996). Unlike HPMC, Carbopol® polymers are high molecular

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weight crosslinked polymers, not soluble, but only high swellable in water in higher pH regions (Lubrizol, 2008a). The release mechanism from Carbopol® matrices is mainly controlled by the diffusion process (for water soluble drugs) but also polymer relaxation is present as predominant drug release mechanism for low soluble drugs. Some Lubrizol studies show, that at similar usage levels, Carbopol® polymers are very effective compared to cellulosic materials in sustaining the drug release. Significant reduction in the release rate of Theophylline (when Carbopol® 71G NF polymer was between 15-30% w/w of the tablet weight) is obtained (Lubrizol, 2008b).

Application of a combination of HPMC polymers of different types or viscosity grades for sustained release is not rare in the literature. However, there are only few examples of combination of polymers, such as HPMC and Carbopol®, based on different chemical structure and mechanisms of drug release. Some reports evaluate the drug release from a matrices contained a combination of HPMC (mainly K4M viscosity grade), and a Carbopol® 934 NF (Khanna et al., 1997; Li et al., 2003) or Carbopol® 974 NF (Perez-Marcos et al., 1994; Perez-Marcos et al., 1996; Streubel et al., 2003). However, there is only one publication relating to the drug release from the matrices based on Carbopol® 71G NF or 971P NF and the higher viscosity of HPMC, K100M or K4M, (Draganoiu et al., 2005).

The active material chosen for the study is aminophylline (AP), a complex of theophylline (TP) with ethylenediamine. AP is freely soluble in water, and in the body it liberates TP. Theophylline has narrow therapeutic index (Varshosaz et al., 2000) and is important to obtain uniform dosing (Hayashi et al., 2005). To overcome varying in drug release, as well as to maintain the drug concentration without fluctuations and inside the therapeutic range later in the body, in this study administration of TP as ethylenediamine complex with an extended release over 8 h is performed for *in vitro* evaluation.

Response surface methodology (RSM) is one of the well-known methods in the development and optimization of drug delivery systems. Based on the principles of design of experiments (DOE), the methodology involves the use of various types of experimental design, generation of mathematical relationships and mapping of the response over the experimental domain to select the optimal formulation. Box Behnken design, Factorial design (Li et al., 2003), Mixture design (Huang et al., 2004; Huang et al., 2005) are the different types of RSM designs available for statistical optimization of the formulation. Mixture experimental design as a part of RSM is recommended as the useful tool, when two or more components are varying, but the total amounts of those ingredients, are fixed and constant. Additionally, it requires fewer experimental runs and less time and thus provides a more cost-effective technique than the conventional process of formulating and optimization of dosage forms.

The aim of the current study was developing and optimizing an oral aminophylline (AP) dosage form for sustained release of theophylline (TP) using optimization technique i.e. Simplex Lattice Mixture Experimental design. The effect of Carbopol® 971P NF and HPMC (Methocel® K100M or Methocel® K4M) mixture on the theophylline (TP) release profile and on the mechanisms of drug liberation from AP matrix tablets was examined. Formulation with the desired release profile was obtained using appropriate optimization procedure.

## MATERIALS AND METHODS

### Materials

Aminophylline hydrous (BASF), Hydroxypropylmethylcellulose (HPMC 2208, Methocel® K 100M PremiumEP and Methocel® K4M PremiumEP, Colorcon Ltd), carbomer (Carbopol® 971P NF, Lubrizol), microcrystalline cellulose (Avicel® PH 101, FMC Biopolymer), polyvinylpyrrolidon (Kollidon® K-30, BASF), talc (Merck) and magnesium stearate (Galenika a.d.) were used as received. All other reagents were analytical grade.

### Experimental design

In order to evaluate the influence of HPMC/carbomer mixture in matrices the mixture experimental design was used to prepare model formulations with two independent variables. According to mixture experimental design, 8 model formulations including 3 replicate formulations were randomly arranged by Design-Expert® software (Version 7.0, Stat-Ease Inc.).

Selected dependent and independent variables are shown in Table I, as well as their low and high levels, which were selected based on the results from preliminary investigations (Petrovic at al., 2006). The fraction of HPMC ($X_1$) of K100M or K4M viscosity type in a range from 0.75 to 1.00, and the fraction of carbomer ($X_2$) from 0.00 to 0.25, in the total amount of polymers were independent variables. The dependent variables were: the percent of drug dissolved in 2h ($Y_{2h}$), in 4 h ($Y_{4h}$), in 6 h ($Y_{6h}$) and in 8 h ($Y_{8h}$) of drug release study.

The amount of total polymers was fixed at 80 mg per tablet, the amount of AP at 380 mg and tablet weight at 510 mg.

**Table I**. Variables in the Mixture design

| Factor | Level | |
|---|---|---|
| | Low | High |
| $X_1$ = fraction of HPMC in total polymer | 0.75 | 1.00 |
| $X_2$ = fraction of carbomer in total polymer | 0.00 | 0.25 |
| Respons variables | Constrains | |
| $Y_{2h}$ = percent dissolved in 2 h | $15\% \leq Y_{2h} \leq 30\%$ | |
| $Y_{4h}$ = percent dissolved in 4 h | $30\% \leq Y_{2h} \leq 50\%$ | |
| $Y_{6h}$ = percent dissolved in 6 h | $40\% \leq Y_{2h} \leq 65\%$ | |
| $Y_{8h}$ = percent dissolved in 8 h | $60\% \leq Y_{2h} \leq 80\%$ | |

The amount of total polymers was fixed at 80 mg.
$X_1 + X_2 = 1$.
All amounts were calculated with respect to total tablet weight of 510 mg.

### Preparation of matrix tablets

All tablets contained: 380 mg aminophylline hydrous, 80 mg of total polymer mixture according to mixture experimental design, 50mg of excipients (40% Avicel PH 101, 30% Povidon® K-30 and 30% of talc and magnesium stearate) and were prepared by wet non-aqueous granulation. The amounts of HPMC K100M or K4M ($X_1$) and Carbopol® 971P NF ($X_2$), used to prepare each of the total 16 formulations are given in Table II. The drug, HPMC and microcrystalline cellulose were mixed and granulated with 10% w/w ethanol solution of Kollidon K-30. The wet mass was forced through 4 mm US sieve and dried at 45°C in fluid bed drier. The dried, sieved granules were mixed with carbomer, talc and magnesium stearate. Tablets (510 mg) were compressed using a 12 mm circular, biconcave punch on single punch tablet machine (Erweka type EKO). The upper punch compaction pressure used was about 1.6 MPa, while the resistance to crushing of the tablets was kept between 150 and 200 N.

### Drug release study

The dissolution study was performed using USP paddle method at 37°C, at stirring speed of 50 rpm, using 900 mL of pH 1.2 simulated gastric fluid without pepsin USP 30 (SGF) for 1h, and pH 7.5 simulated intestinal fluid USP 30 (SIF) from 2-8 h of the study, as the dissolution media. The concentration of TP was determined by UV-VIS spectrophotometric method at 271 nm (spectrophotometer Cary 3, Varian Mulgrave). Cumulative percentage of drug release was calculated and the mean of three determinations was used in data analysis.

### Data analyses

Dissimilarity (*f1)* and similarity (*f2)* factors according to actual equations (Yuksel, 2000; Costa and Sousa-Lobo, 2001) were used for dissolution profiles comparison. For the calculation purpose, Run 1 profile, matrices based on HPMC K100M or K4M polymer only, was used as a reference.

Release rates and Lag times ($k_0$ for zero order, $k_2$ for the square root and $k_p$ for the power model) were calculated according to zero order model, square root model and power low model (Siepman and Peppas, 2001; Kiortsis et al., 2005).

Diffusion exponent $n$ for the predicting of the possible drug transport mechanism was calculated according to model proposed by Ritger and Peppas (1987). The received $n$ values were used for evaluation of the contributions of diffusion and/or erosion process, on drug release, influenced by different carbomer fractions in the total amount of polymers. The correlation coefficient value closer to 1.0 as the lag time value closer to zero was the preferred values for good correlation with the treated model.

The computer program Origin version 6.0 (OriginLab Corp.) was used for data analysis.

### Statistical analyses

The influence of variables on drug release was evaluated by experimental design analyses. In the first step, the responses (percent of drug released after 2, 4, 6 and 8 h of examination for model formulations) were treated by three mathematical models: linear, quadratic and cubic model. Several statistical parameters: the predicted residual sum of square/PRESS/, adjusted multiple correlation coefficient/Adjusted $R^2$/ and predicted multiple correlation coefficient/Predicted $R^2$/were analyzed. The chosen model had the smallest PRESS value.

The values of the coefficients $b_1$, $b_2$ and $b_{12}$ were calculated to find out if the variables ($X_1$ and $X_2$) had some effects on the responses.

Thereafter, numerical optimization procedure was applied to define and obtain formulation with desired drug release profile.

## RESULTS AND DISCUSSION

Dissolution profiles of TP from matrix formulations based on different HPMC/carbomer ratios are presented in Fig. 1-2.

The dissimilarity of dissolution profiles was found i.e., $f1$ values higher than 15 and the $f2$ lower than 50 (Table II.) was obtained. The exception (in both sets of experiments) is: Run 7 that is a replicate of Run

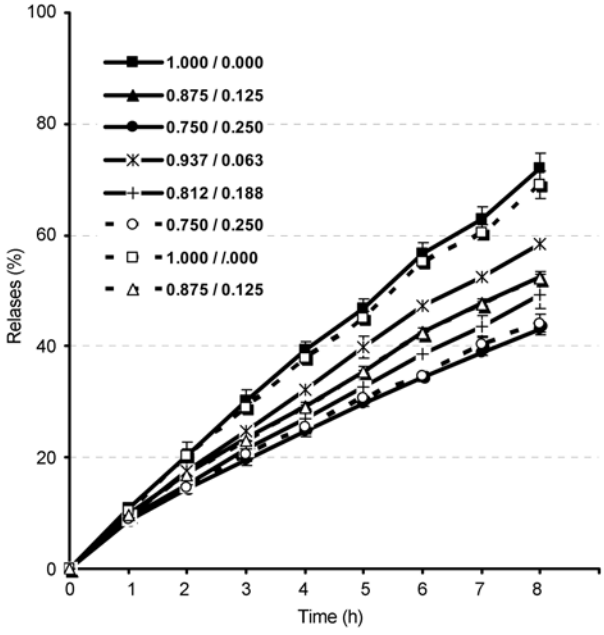


**Fig. 1.** TP release from matrix tablets based on different HPMC K100M/Carbomer ratios in total polymer matrices. Each point represents the mean of three replicates ± S.D.

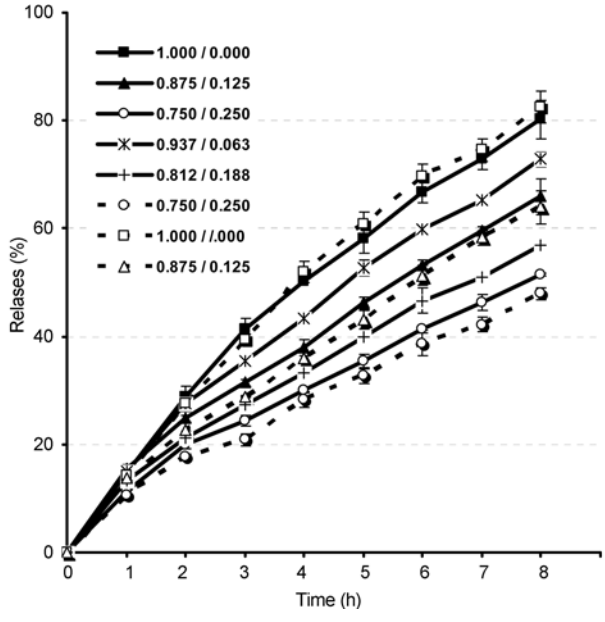


**Fig. 2.** TP release from matrix tablets based on different HPMC K4M /Carbomer ratios in total polymer matrices. Each point represents the mean of three replicates ± S.D.

1 as well as Run 4 that contains the lowest carbomer share of 0.063. Those results indicate that the application of carbomer (0.125 parts or more) in HPMC matrices affects the dissolution profiles. Significant retardation in drug release (less then 43% i.e. 48% of the drug) after 8h was obtained for matrices contained 0.250 parts of carbomer and HPMC K100M or K4M in combination. Only matrices contained HPMC showed higher release of the drug; i.e., with K100M 69-72% of the drug and with HPMC K4M 80-82%. These results were similar to earlier studies which were explained by the difference in drug molecular structure and the polymer-drug interaction. In the case of propranolol hydrochloride, the retardation in drug release (Perez-Marcos et al., 1996) was explained through the formation of drug-Carbopol® insoluble complex in a base medium; for theophylline anhydrous synergistic interaction between the Carbopol® and HPMC at higher pH values, contributed to matrix integrity and to the higher control of drug release (Draganoiu et al., 2005).

**Table II.** Experimental plan and obtained similarity/ dissimilarity factor results

| Run | $X_1$ HPMC | $X_2$ Carbomer | K100M/ carbomer | | K4M/ carbomer | |
|---|---|---|---|---|---|---|
| | | | f1 | f2 | f1 | f2 |
| 1 | 1.000 | 0.000 | - | - | - | - |
| 2 | 0.875 | 0.125 | 32 | 46 | 19 | 48 |
| 3 | 0.750 | 0.250 | 59 | 37 | 36 | 34 |
| 4 | 0.937 | 0.063 | 20 | 55 | 10 | 61 |
| 5 | 0.812 | 0.188 | 43 | 42 | 30 | 38 |
| 6 | 0.750 | 0.250 | 55 | 38 | 41 | 31 |
| 7 | 1.000 | 0.000 | 3 | 85 | 4 | 83 |
| 8 | 0.875 | 0.125 | 32 | 46 | 23 | 44 |

Ionic interactions in solution, or solid state have been reported (Lubrizol, 2008b) for ionized carbomers with cationic drugs (propranolol, metoclopramide, procaine, clarithromycin, dextrometorphan, etc.), so insoluble complex formation can be expected to be retardation factor during the release of these drugs from HPMC-carbomer matrices.

Since AP is not of a cationic nature but a complex (of TP with ethyllenediamine), obtained significant retardation in drug release from AP matrix tablets can be attributed to synergistic interaction of the two polymers. Furthermore, a strong gel structure formed, decrease drug diffusion and consequently prolong drug liberation.

Considering the similar release of TP obtained for Run 6 (in both sets of experiments), it could be assumed that Carbopol® had very strong influence on drug release delay, compared to the HPMC.

According to Design-Expert® software for HPMC K4M matrices the best fit was obtained for linear mathematical model (Eq. (1)), while in case of HPMC K100M matrices quadratic model (Eq. (2)) showed better results.

$$Y = b_1 X_1 + b_2 X_2 \quad (1)$$

$$Y = b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 \quad (2)$$

The values of the coefficients $b_1$, $b_2$ and $b_{12}$ are related to the effect of variables ($X_1$ and $X_2$) on the responses (Table III). A positive sign of coefficient indicates synergistic effects upon responses as well as the larger coefficient value indicate the higher influence of the factor on the response.

For the HPMC K100M/carbomer matrices the values for coefficients of $b_1$ were smaller than that of $b_2$, indicating that the influence of K100M ($X_1$) on drug liberation during the time was less than that of carbomer ($X_2$). Also, the influence of K100M ($X_1$) fraction on the amount of drug released, was higher ($b_1$ value 55.79 and 70.10) at later stages (6 h, 8 h) than at the earlier stages of drug release (after 2 h and 4 h). Obtained results can be attributed to the swelling and hydration ability of HPMC. Higher polymer grade as K100M requires more time for water penetration, swelling and formation of gel layer, so the impact of $X_1$ - K100M ratio on drug liberation at the early stages of examination is smaller.

The coefficient of $b_{12}$ was largest showing that the effect of HPMC and carbomer combination ($X_1 X_2$) was the main factor influencing the drug release from matrix tablets throughout the dissolution test. Also, the degree of influence of those two factor combinations was higher and more significant at the later stages of examination. This could be explained by the proposed powerful synergistic interactions between two strong gel layers formed by HPMC and Carbopol®. Significant influence of interaction factors (*X1X2*) at the later stages can be connected with the slower gelling of higher viscosity of HPMC at the beginning and rapid gelling of Carbopol® only in higher pH regions of the dissolution media (later phase of examination).

The ratio of polymers in matrix had an opposite effect on drug release (negative sign for $b_{12}$).The slowest drug release was obtained for the combination of lower ratio of HPMC and higher amount of Carbopol® in total polymer matrix.

For the matrices with lower viscosity grade of HPMC (K4M) and carbomer the $b_1$ *and* $b_2$ coefficient values indicated that both factors had significant effect on the drug release. The influence of HPMC K4M fraction ($X_1$) was higher ($b_1$ value 67.5 and 80.8) at later stages (6h, 8h) while the influence of carbomer fraction ($X_2$) on the drug release, was high during all period of examination (-44.8 and -45.0). The ratio of carbomer ($X_2$) in matrix had an opposite effect on drug release (negative sign for $b_2$). HPMC K4M, as a lower viscosity grade polymer, requires less time for water penetration, swelling and gel formation so the influence of this polymer on the drug release should be seen even in the first phase of testing, but is more evident at later stages. The similar behavior was noticed with higher type HPMC K100M. However, the gel barrier of K4M has viscosity smaller then K100M, and has less impact on the amount of the drug released at the later stage. The main effect on drug retardation from K4M/Carbopol® matrices has Carbopol® gel layer. As the amount of the Carbopol® increases in matrix, stronger and more uniform gel layer is performed influencing higher decrease in drug release.

Calculated kinetic parameters: release rate constants $k_0$, $k_2$, $k_p$ exponent $n$, the correlation coefficients $r$, and the Lag times values are shown in Table IV. For both two sets of experimental Runs, zero order or square root drug release rates decrease with the increasing carbomer fraction in the HPMC matrix. The slowest release rate was observed for matrices consisting of 25% of carbomer (Run 3 and 6), with the slower rate obtained with the lower carbomer content (Run 5, and there after Run 2, 8 and 4) and the highest rate observed for tablets based on HPMC only (Run 1 and 7). Matrices based on higher viscosity grade of HPMC in combination with carbomer gave slower release rates than that of K4M and carbomer prepared in the

**Table III.** Optimal regression equation for each response variable for HPMC / carbomer matrices

| Matrices: | HPMC K100M/carbomer | | | | HPMC K4M/carbomer | | | |
|---|---|---|---|---|---|---|---|---|
| Model: | Quadratic | | | | Linear | | | |
| Coefficient | $Y_{2h}$ | $Y_{4h}$ | $Y_{6h}$ | $Y_{8h}$ | $Y_{2h}$ | $Y_{4h}$ | $Y_{6h}$ | $Y_{8h}$ |
| Sd | 0.34 | 0.66 | 0.69 | 1.59 | 1.05 | 1.82 | 1.56 | 1.48 |
| Adjusted $R^2$ | 0.979 | 0.985 | 0.993 | 0.978 | 0.998 | 0.957 | 0.981 | 0.986 |
| Predicted $R^2$ | 0.971 | 0.968 | 0.987 | 0.960 | 0.887 | 0.933 | 0.967 | 0.975 |
| PRESS | 1.1 | 6.5 | 6.7 | 32.1 | 12.8 | 36.3 | 29.2 | 27.3 |
| $B_1$ (X1) | 20.2 | 38.4 | 55.7 | 70.1 | 28.6 | 49.6 | 67.5 | 80.8 |
| $B_2$ (X2) | 32.7 | 111.4 | 103.9 | 181.9 | -10.3 | -37.1 | -44.8 | -45.0 |
| $B_{12}$ ($X_1$ $X_2$) | -47.5 | -167.9 | -176.8 | -288.2 | - | - | - | - |

**Table IV.** Calculated kinetic parameters for HPMC K100M or K4M/carbomer matrices: release rate constants $k_0$, $k_2$, $k_p$ exponent $n$, the correlation coefficients $r$, and the Lag times values

| Run | Zero order | | | Square root | | | Power low | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | r | $k_0$ ($min^{-1}$) | Lag/Burst (min) | r | $k_2$ ($min^{-0.5}$) | Lag/Burst (min) | r | $k_p$ ($min^{-n}$) | Lag/Burst (min) | n |
| HPMC K100M/carbomer matrices | | | | | | | | | | |
| 1 | 0.998 | 0.14 | -23.5 | 0.995 | 4.34 | 6.0 | 0.999 | 0.27 | 1.6 | 0.91 |
| 2 | 0.997 | 0.10 | -45.0 | 0.995 | 3.07 | 5.3 | 0.999 | 0.36 | 1.2 | 0.81 |
| 3 | 0.998 | 0.08 | -55.9 | 0.995 | 2.46 | 5.0 | 0.999 | 0.35 | 1.5 | 0.78 |
| 4 | 0.998 | 0.12 | -30.1 | 0.995 | 3.54 | 5.8 | 0.999 | 0.26 | 0.0 | 0.88 |
| 5 | 0.999 | 0.09 | -40.9 | 0.993 | 2.86 | 5.4 | 0.999 | 0.31 | 1.8 | 0.82 |
| 6 | 0.997 | 0.08 | -57.4 | 0.996 | 2.52 | 4.9 | 0.999 | 0.36 | 1.0 | 0.78 |
| 7 | 0.998 | 0.14 | -25.6 | 0.995 | 4.16 | 5.9 | 0.999 | 0.27 | 0.8 | 0.90 |
| 8 | 0.998 | 0.10 | -42.2 | 0.994 | 3.08 | 5.4 | 0.999 | 0.33 | 0.7 | 0.82 |
| HPMC K4M/carbomer matrices | | | | | | | | | | |
| 1 | 0.988 | 0.15 | -70.8 | 0.999 | 4.62 | 4.6 | 0.998 | 0.56 | -4.9 | 0.80 |
| 2 | 0.991 | 0.12 | -81.0 | 0.994 | 3.58 | 4.1 | 0.999 | 0.90 | 1.2 | 0.69 |
| 3 | 0.989 | 0.09 | -92.5 | 0.991 | 2.71 | 3.7 | 0.998 | 0.93 | 1.7 | 0.65 |
| 4 | 0.990 | 0.13 | -77.5 | 0.998 | 4.06 | 4.3 | 0.999 | 0.73 | -1.0 | 0.74 |
| 5 | 0.991 | 0.10 | -82.0 | 0.995 | 3.09 | 4.1 | 0.999 | 0.76 | 1.0 | 0.70 |
| 6 | 0.989 | 0.08 | -91.6 | 0.984 | 2.49 | 3.6 | 0.994 | 1.00 | 2.3 | 0.63 |
| 7 | 0.989 | 0.16 | -56.9 | 0.999 | 4.90 | 5.0 | 0.997 | 0.45 | 6.0 | 0.84 |
| 8 | 0.995 | 0.12 | -61.8 | 0.992 | 3.59 | 4.7 | 0.998 | 0.66 | 1.8 | 0.74 |

same polymer ratios. These results confirmed the previous assumption based on different gelling ability of HPMC K100M or K4M as well as synergistic interaction between those two polymers (HPMC and Carbopol®).

The evaluated mechanism of TP release showed that $n$ values were equal or less than 0.88 (for HPMC K100M/carbomer matrices) i.e. less than 0.74 (HPMC K4M/carbomer combination) and that both diffusion and erosion processes influenced the drug release, indicating that Anomalous (non-Fickian) diffusion was present. The increase in carbomer loading in matrices decreased the $n$ value from 0.88 to 0.78, i.e. from 0.74 to 0.63 (HPMC K4M/carbomer).The highest $n$ values (more than 0.90) for Runs based only on HPMC K100M matrices indicated Case-II transport. For evaluated matrices based on HPMC only, obtained $n$ values show that the erosion is the predominant mechanism of TP release. In contrast, when Carbopol® is placed in contact with dissolution media, the external surface of the matrix becomes hydrated, swells and forms a gel layer (hydrogel) that further controls the release of the drug from the tablet. Since the carbomer is not water soluble, it does not dissolve, and erosion in the manner of linear polymers does not occur. When the hydrogel is fully hydrated, osmotic pressure from within may break up the structure, essentially by sloughing off discrete pieces of the hydrogel (polymer relaxation). For matrices that represent a combination of HPMC and carbomer, diffusion mechanism, which originates from the presence of Carbopol® shows greater impact on drug release and therefore the decrease in factor $n$ value is obtained, aiming to Anomalous transport. Similar result was obtained by Lubrizol, 2008b, for the theophylline release from Carbopol matrices®.

Based on linear model regarding the ANOVA results for exponent, $n$, the significant effect on the release mechanism is that of carbomer fraction in the linear mixture with HPMC K100M ($p < 0.002$) i.e. with HPMC K4M ($p < 0.0003$).

The sustained-release matrices should have specific profile and be released in specific time period. Therefore, for optimization procedure the range of four responses was chosen and established as follows:

$Y_{2h}$ : 15%-30%, the goal value 25%;
$Y_{4h}$ : 30%-50%, the goal value 40%;
$Y_{6h}$ : 40%-65%, the goal value 55%;
$Y_{8h}$ : 60%-80%, the goal value 70%;

The predicted profiles for the HPMC/Carbopol® combination were obtained through the numerical optimization procedure and the independent variables

**Table V.** Predicted and obtained responses (amount of drug release %) of optimized sustained release formulations

| | $Y_{2h}$ | $Y_{4h}$ | $Y_{6h}$ | $Y_{8h}$ | f2 |
|---|---|---|---|---|---|
| HPMC K100M / carbomer (1.000/0.000) | | | | | |
| Predicted ***($P_1$)*** | 20.25% | 38.37% | 55.72% | 70.00% | - |
| Obtained ***($O_1$)*** | 22.10% | 41.03% | 60.64% | 72.90% | 74 |
| Predicted error | 9.1 % | 6.9 % | 8.8 % | 4.1 % | |
| HPMC K4M / carbomer (0.899 / 0.101) | | | | | |
| Predicted ***($P_2$)*** | 24.48% | 40.42% | 55.58% | 67.47% | - |
| Obtained ***($O_2$)*** | 24.80% | 37.91% | 53.22% | 65.96% | 84 |
| Predicted error (%) | 1.3 % | -6.2 % | -4.2 % | -3.0 % | |

Predicted error (%) = (observed value – predicted value)/predicted value × 100%

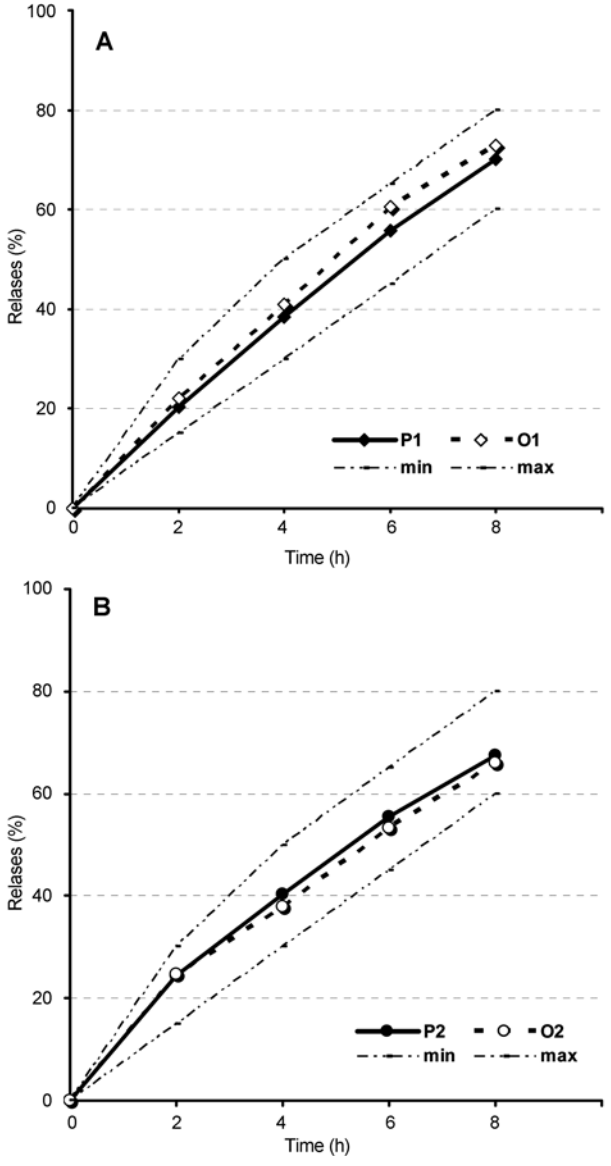


**Fig. 3.** Predicted and obtained dissolution profiles of optimized formulation based on HPMC K100M/carbomer (1.000/0.000) matrice (**3a**) and HPMC K4M/carbomer (0.899/0.101) matrice (**3b**)

($X_1$ and $X_2$) values as showed in Table V. Recommended ratio for K100M of 0.999 parts was very close to the combination given by Run 1, therefore matrice according to this composition was prepared and examined. In the case of HPMC K4M/carbopol matrices the proposed combination of 0.899/0.101 was investigated. Dissolution profiles for the optimized sustained release tablets, as well as the predicted values, are shown in Table V and in Fig. 3. The predicted and observed values of responses showed no significant difference, the predicted errors of $Y_{2h}$, $Y_{4h}$, $Y_{6h}$ and $Y_{8h}$, were below 9.1% for HPMC K100M and 5.3% for K4M combination, and the similarity of dissolution profiles were obtained.

## CONCLUSION

In summary, it was shown that Simplex Lattice Mixture Experimental Design can be applied in the evaluation of the influence of carbomer (Carbopol® 971P NF) and HPMC (Methocel® K100M and Methocel® K4M) combination on the release properties of TP from AP matrix tablets. Furthermore, numerical optimization procedure was useful for establishing tablet formulation with desired drug release profile.

Extended release of TP from AP matrix tablets, during almost 8 hour examination was obtained for all prepared experimental runs based on approximately 75% of the drug and 15% of total polymer matrix (carbomer and HPMC in combination). Higher retardation in drug release was found for matrices with carbomer compared with that prepared on HPMC only. The higher the carbomer fraction, the slower release rate and lower n value were found. For HPMC matrices erosion was predominant mechanism (i.e. Case II transport), while incorporation of carbomer led to Anomalous transport where both erosion and diffusion were present.

## REFERENCES


Costa, P. and Sousa-Lobo, J. M., Modeling and comparison of dissolution profiles. *Eur. J. Pharm. Sci*., 13, 123-133 (2001).

Das, N. G. and Das S. K., Development of mucoadhesive dosage forms of buprenophine for sublingual drug delivery. *Drug Dev*., 11, 89-95 (2004).

Draganoiu, E., Muca, B., Stansbrey, A., Luo, H., Wilber, W., and Guo, H., Effect of Carbomer and hydroxypropyl methylcellulose combination on drug release from matrix tablets. *Eur. J. Pharm. Sci*., 25S1, S222-S223 (2005).

Furlanetto, S., Cirri, M., Maestrelli, F., Corti, G., and Mura, P., Study of formulation variables influencing the drug release rate from matrix tablets by experimental design. *Eur. J. Pharm. Biopharm*., 62, 77-84 (2006).

Hayashi, T., Kanbe, H., Okada, M., Suzuki, M., Ikeda, Y., Onuki, Y., Kaneko, T., and Sonobe, T., Formulation study and drug release mechanism of a new theophylline sustained-release preparation. *Int. J. Pharm.,* 304, 91-101 (2005).

Huang, Y. B., Tsai, Y. H., Yang, W. C., Chang, J. S., and Wu, P. C., Once-daily propranolol extended-release tablet dosage form: formulation design and *in vitro*/*in vivo* investigation. *Eur. J. Pharm. Biopharm*., 58, 607-614 (2004).

Huang, Y. B., Tsai, Y. H., Lee, S. H., Chang, J. S., and Wu, P. C., Optimization of pH-independent release of nicardipine hydrochloride extended-release matrix tablets using response surface methodology. *Int. J. Pharm*., 289, 87-95 (2005).

Khan, G. M. and Zhu, J. B., Studies on Drug Release Kinetics from Ibuprofen-carbomer hydrophilic matrix tablets: Influence of co-excipients on release rate of the drug. *J. Control Release,* 57, 197-203 (1999).

Khanna, R., Agarwal, S. P., and Ahuja, A., Muco-adhesive buccal tablets of clotrimazole for oral candidiasis. *Drug Dev. Ind. Pharm.,* 23, 831-837 (1997).

Kiortsis, S., Kachrimanis, K., Broussali, T., and Malamataris, S., Drug release from tableted wet granulations comprising cellulosic (HPMC or HPC) and hydrophobic component. *Eur. J. Pharm. Biopharm*., 59, 73-83 (2005).

Li, S., Lin, S., Daggy, B. P., Mirchandani, H. L., and Chien, Y. W., Effect of HPMC and Carbopol on the release and floating properties of Gastric floating Drug Delivery System using factorial design. *Int. J. Pharm*., 253, 13-22 (2003).

Lubrizol, Pharmaceutical Polymers for Controlled Release Tablets and Capsules, *Pharmaceutical Bulletin 30,* Oct (2008a).

Lubrizol, Formulating Controlled Release Tablets and Capsules with Carbopol® Polymers, *Pharm. Bull.,* 31 (2008b).

Narasimhan, B., Mathematical models describing polymer dissolution: Consequences for drug delivery. *Adv. Drug. Del. Rev.*, 48, 195-210 (2001).

Parojcic, J., Duric, Z., Jovanovic, M., and Ibric, S., An investigation into the factors influencing drug release from hydrophilic matrix tablets based on novel carbomer polymers. *Drug Dev.,* 11, 59-65 (2004).

Perez-Marcos, B., Ford, J. L., Armstrong, D. J., Elliot, P. N. C., Rostron, C., and Hogan, J. E., Release of propranolol hydrochloride from matrix tablets containing hydroxypropyl methylcellulose K4M and Carbopol 974. *Int. J. Pharm.,* 111, 251-259 (1994).

Perez-Marcos, B., Ford, J. L., Armstrong, D. J., Elliot, P. N. C., Rostron, C., and Hogan, J. E., Influence of the pH on the release of propranolol hydrochloride from matrices containing hydroxypropyl methylcellulose K4M and Carbopol 974. *J. Pharm. Sci.*, 85, 330-334 (1996).

Petrovic, A., Trajkovic, S., Ibric, S., Popadic, D., Cvetkovic, N., and Djuric, Z., Theophylline release from aminophylline matrix tablets containing HPMC and Carbopol®. *Proc. 5th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Geneva March 2006,* Abstract book, kxksv-~1 (2006).

Prudat-Christiaens, C., Arnaud, P., Allain, P., and Chaumeil, J. C., Aminophylline bioadhesive tablets attempted by wet granulation. *Int. J. Pharm.,* 141, 109-116 (1996).

Ritger, P. L. and Peppas, N. S., A simple equation for disposition of solute release II: Fickian and anomalous release from swellable devices. *J. Control. Release,* 5, 37-42 (1987).

Siepman, J. and Peppas, N. A., Modeling of drug release from delivery systems based on hydroxypropylmethylcellulose (HPMC). *Adv. Drug. Del. Rev*., 48, 139-157 (2001).

Streubel, A., Siepmann, J., and Bodmeier, R., Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. *Eur. J. Pharm. Sci*., 18, 37-45 (2003).

Varshosaz, J., Ghafghazi, T., Raisi, A., and Falamarzian, M., Biopharmaceutical characterization of oral theophylline and aminophylline tablets. Quantitative correlation between dissolution and bioavailability studies. *Eur. J. Pharm. Biopharm*., 50, 301-306 (2000).

Yuksel, A., Comparison of in vitro dissolution profiles by Anova based model dependent and independent methods. *Int. J. Pharm.*, 209, 57-67 (2000).

Zuleger, S. and Lippold, B. C., Polymer particle erosion controlling drug release. I. Factors influencing drug release and characterization of the release mechanism. *Int. J. Pharm.,* 217, 139-152 (2001).

Zuleger, S., Fassihi, R., and Lippold, B. C., Polymer particle erosion controlling drug release. II. Swelling investigations to clarify the release mechanism. *Int. J. Pharm.,* 247, 23-37 (2002).