# FORMULATION OF BIOADHESIVE MATRIX TABLETS WITH DIFFERENT CONCENTRATIONS OF CARBOPOL AND SODIUM CARBOXYMETHYL CELLULOSE USING AN EXPERIMENTAL DESIGN

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**Abstract**

***Aims.*** *The aim of this work was to study the effect of different combinations of three widely used bioadhesive polymers on the properies of bioadhesive matrix tablets with famotidine.*

***Materials and methods.*** *To perform the study an experimental design with two factors and three levels was used. The formulation factors studied were: the percentage of Carbopol and the percentage of sodium carboxymethyl cellulose. The tablets were studied regarding their in vitro dissolution behavior, the bioadhesion, the water uptake and the erosion profile.*

***Results.*** *According to the obtained results, despite the big difference between total polymer content in the tablets, the dissolution and water uptake profiles were similar between the tested formulations. Regarding the erosion profiles, the formulation with the higher amounts of polymer, in particular with higher amount of Carbopol showed a marked erosion. In terms of bioadhesiveness the combination of Carbopol and sodium carboxymethyl cellulose showed a synergic effect of bioadhesive properties with increasing concentration. Over the range of 35% to 65% of total polymer concentration the formulation factors did not have a massive impact on the properties of bioadhesive maxtrix tablets.*

***Conclusions.*** *The higher the concentration of Carbopol (30%) and sodium carboxymethyl cellulose (30%) used in the formulation, the slower the release rate which is governed by diffusion through the gel layer and erosion of the matrix. The combination of Carbopol and sodium carboxymethyl cellulose used in higher concentrations also favors the bioadhesive forces of the formulations.*

**Keywords:** bioadhesive tablets, bioadhesive polymers, experimental design, famotidine.

## FORMULAREA UNOR COMPRIMATE BIOADEZIVE DE TIP MATRICE CU CONCENTRAȚII DIFERITE DE CARBOPOL ȘI CARBOXIMETILCELULOZĂ SODICĂ UTILIZÂND UN PLAN EXPERIMENTAL

**Rezumat**

***Obiective.*** *Scopul acestei lucrări de cercetare a fost studiul efectelor unor combinaţii a trei polimeri bioadezivi extensiv utilizaţi asupra proprietăţilor unor comprimate bioadezive de tip matrice cu famotidină.*

***Material şi metodă.*** *Pentru a realiza studiul a fost utilizat un plan experimental cu 2 factori şi trei nivele. Factorii de formulare utilizaţi au fost: procentul de Carbopol şi procentul de carboximetilceluloză sodică. Comprimatele au fost caracterizate prin profilul de eliberare al substanţei active, prin proprietăţile bioadezive, prin absorbţia*

*de apă şi prin profilul de eroziune.*

***Rezultate.*** *Din rezultatele obţinute s-a conclus că, deşi există o diferenţă semnificativă în cantitatea totală de polimeri utilizată în comprimate, profilurile de eliberare a substanţei active şi cele de absorbţie a apei sunt similare între formulările analizate. În ceea ce priveşte profilurile de eroziune, formulările conţinând o cantitate mai mare de polimer, în particular cele cu o cantitate mai mare de Carbopol au prezentat profiluri de eroziune mai semnificative. Bioadeziunea este favorizată de combinaţia de Carbopol şi carboximetilceluloză sodică care prezintă un efect sinergic mai pronunţat la concentraţii mai mari.*

*În intervalul de concentraţii de la 35% la 65% de polimeri bioadezivi, factorii de formulare nu prezintă un impact semnificativ asupra proprietăţilor comprimatelor analizate.*

***Concluzii.*** *Cu cât concentraţia de Carbopol (30%) şi de carboximetilceluloză sodică (30%) utilizate în formulări este mai mare, cu atât eliberarea substanţei active are loc mai lent prin difuzia prin stratul de gel şi prin eroziunea acestuia. Combinarea de Carbopol şi carboximetilceluloză sodică în cea mai mare concentraţie cercetată favorizează şi proprietăţile bioadezive ale comprimatelor.*

**Cuvinte cheie:** comprimate bioadezive, polimeri bioadezivi, plan experimental, famotidină.

## INTRODUCTION

Bioadhesion may be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended periods of time by interfacial forces. In the pharmaceutical sciences, when the adhesive attachment is to mucus or a mucous membrane, the phenomenon is referred to as mucoadhesion [1,2].

The most widely investigated group of muco-adhesives are hydrophilic macromolecules containing numerous hydrogen bond forming groups, the so-called "first generation" mucoadhesives. The presence of hydroxyl, carboxyl or amine groups on the molecules favours adhesion. They are called "wet" adhesives in that they are activated by moistening and will adhere non-specifically to many surfaces. Once activated, they will show stronger adhesion to dry inert surfaces than those covered with mucus. Unless water uptake is restricted, they may overhydrate to form a slippery mucilage [1].

Anionic polymers are the most widely employed mucoadhesive polymers within the pharmaceutical formulations due to their high mucoadhesive functionality and low toxicity. Such polymers are characterised by the presence of carboxyl and sulphate functional groups that give rise to a net overall negative charge at pH values exceeding the pKa of the polymer. Typical examples include poly(-acrylic acid) (PAA) (Carbopol) and its weakly cross-linked derivatives and sodium carboxymethylcellulose (SCMC). CP and SCMC possess excellent mucoadhesive characteristics due to the formation of strong hydrogen bonding interactions with mucin [2,3,4,5]. Also non-ionic polymers (e.g. hydroxypropylmethylcellulose, HPMC) present good mucoadhesive characteristics and are commonly used in bioadhesive formulations [4,5,6].

Famotidine (FAMO) was chosen as the model drug because of its characteristics: prolonged antisecretory effect in the therapy of duodenal, gastric, and peptic ulcer, and its low solubility (25 μg per ml) with a relatively short elimination half-life time (about 2.5-4 h) [7].

In this paper we have studied the effect of different combinations of two widely used bioadhesive polymers on the release profile, bioadhesive properties, water uptake and erosion profile. An experimental design with two factors and three levels was used in order to optimize the compositions of tablets and study the influence of the formulation factors on the properties of the formulated matrix tablets [8,9,10].

## MATERIALS AND METHODS

### Materials

Famotidine (FAMO) (Sms Pharmaceuticals Ltd., India), was used as model drug. Three hydrophilic polymers with bioadhesive properties were used in this study: HPMC K15M (Colorcon, UK), Sodium Carboxymethylcellulose (SCMC, Fluka, Germany) and Carbopol 71G (CP, Carbopol® 71G NF, Lubrizol, Belgium). Microcristalline cellulose (MCC) (JRS Pharma, Germany) and isomaltose (ISO) (galenIQ Palatinit Gmbh, Germany) were used as fillers. In all tablets formulations fumed silica-Aerosil (Degussa, Germany) and Magnesium stearate (Merck, Germany) where used as glidant and lubricant. The release profiles were evaluated using several release models such as Baker-Lonsdale, Korsmeyer-Peppas, Hixson-Crowell, Higuchi first order and zero order. The Akaike criterion was chosen for distinguishing among competing models.

Manuscript received: 17.02.2012
Received in revised form: 30.03.2012
Accepted: 04.04.2012
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**Experimental Design**

An experimental design with two factors and three levels was used to perform the study. Eleven experimental determinations were performed according to an experimental plan. The independent variables (formulation factors) and the variation levels are shown in Table I. The dependant variables are shown in Table II.

**Table I.** The independent variables and the formulation levels.

| Formulation Variable | Symbol | Level | | |
|---|---|---|---|---|
| | | -1 | 0 | 1 |
| Percentage of Carbopol | $X_1$ | 10 | 20 | 30 |
| Percentage of SCMC | $X_2$ | 10 | 20 | 30 |

**Table II.** Dependent variables (answers).

| Number | Answer | Symbol |
|---|---|---|
| 1 | The amount of famotidine released after 0.25h | $Y_1$ |
| 2 | The amount of famotidine released after 0.5h | $Y_2$ |
| 3 | The amount of famotidine released after 1.0h | $Y_3$ |
| 4 | The amount of famotidine released after 1.5h | $Y_4$ |
| … | … | … |
| 23 | The amount of famotidine released after 11.0h | $Y_{23}$ |
| 24 | The amount of famotidine released after 11.5h | $Y_{24}$ |
| 25 | The amount of famotidine released after 12.0h | $Y_{25}$ |
| 26 | k Peppas | $Y_{26}$ |
| 27 | n Peppas | $Y_{27}$ |
| 28 | Bioadhesion | $Y_{28}$ |
| 29 | Water uptake after 0.5h | $Y_{29}$ |
| 30 | Water uptake after 1.0h | $Y_{30}$ |
| 31 | Water uptake after 2.0h | $Y_{31}$ |
| 32 | Water uptake after 4.0h | $Y_{32}$ |
| 33 | Water uptake after 8.0h | $Y_{33}$ |
| 34 | Water uptake after 12.0h | $Y_{34}$ |
| 35 | Erosion after 1.0h | $Y_{35}$ |
| 36 | Erosion after 2.0h | $Y_{36}$ |
| 37 | Erosion after 4.0h | $Y_{37}$ |
| 38 | Erosion after 8.0h | $Y_{38}$ |
| 39 | Erosion after 12.0h | $Y_{39}$ |

The experimental design matrix is shown in Table III. The experiments were performed in the order specified in the experimental design matrix.

**Table III.** Experimental Design Matrix.

| Experiment Name | Order of Run | $X_1$ | $X_2$ |
|---|---|---|---|
| N1 | 4 | 10 | 10 |
| N2 | 5 | 30 | 10 |
| N3 | 8 | 10 | 30 |
| N4 | 1 | 30 | 30 |
| N5 | 10 | 10 | 20 |
| N6 | 3 | 30 | 20 |
| N7 | 2 | 20 | 10 |
| N8 | 7 | 30 | 20 |
| N9 | 11 | 20 | 20 |
| N10 | 9 | 20 | 20 |
| N11 | 6 | 20 | 20 |

The experimental design, the coefficient calculation, the statistic parameter calculation and the evaluation of the quality of the fit were performed using the Modde 9.0 software (Umetrics, Sweden).

**Tablet Composition**

The tablets were prepared using isomaltose and microcrystalline cellulose as excipients. The general formula of the composition of the tablets is shown in Table IV.

**Table IV.** General formula.

| Components | Composition | |
|---|---|---|
| | mg/Tablet | % |
| Famotidine | 20 | 3.33 |
| HPMC K15M | 90 | 15 |
| Carbopol | 60/120/180 | 10/20/30 |
| Sodium carboxymethylcellulose | 60/120/180 | 10/20/30 |
| Isomalt | difference | difference |
| Microcrystalline Cellulose | 90 | 15 |
| Magnesium Stearate | 3 | 0.5 |
| Aerosil | 1.5 | 0.25 |
| Total | 600 | 100 |

All the materials for the tablet preparation-FAMO 10 mg/tablet, HPMC polymer 15%, Carbopol between 10-30% and SCMC between 10%-30% (as shown in Table IV), excipients (MCC 15%) and isomaltose (the difference to the other components), glidant 0.25% and lubricant 0.5%, were mixed in planetary mixer for 10 minutes (Erweka, Germany). The powder mix was sieved through a 400-µm sieve and then mixed again for 5 minutes in the same apparatus. Tablets with 600 mg weight were prepared by direct compression using an EK-0 Tablet press (Korsch, Germany) equipped with 16 mm diameter punch and dies. The tablet hardness was between 9-10 kg force and the friability under 1%.

***In vitro* dissolution studies**

The *in vitro* dissolution tests were conducted in the PharmaTest PT-DT7 device, which was equipped with the USP no. 1 apparatus (with basket), at 100 rpm rotation speed. The dissolution media used was 900 ml HCl 0.1 M (pH=2) at 37±0.5º. A 5 ml sample was collected after 15 minutes for the first half hour and then for every 30 minutes until 12 hours. Each sample was immediately filtered through a 0.45 µm filter and replaced by fresh media to maintain a constant volume across the experiment. The sample solutions were analyzed at 265 nm by UV spectrophotometry (Jasco, V530. Japan).

**Bioadhesive study**

The measurement of the bioadhesive forces of the formulations were performed on a modified two arms balance using cellophane as a synthetic membrane. The tablets were prehydratated for 3 minutes with 50 µl of HCl 0.1 M and brought in contact with the synthetic membrane for 5 minutes to allow interaction between the hydratated polymer and the cellophane. The force necessary to detach the tablets from the synthetic membrane was calculated by using the below formula:

Detachment force (N) = [Weight (g) * 9.8]/1000.
All measurements were repeated ten times.

**Water uptake**

The water uptake study was performed in triplicate in the same conditions as the dissolution study (at 37±0.5º) in no. 1 apparatus (basket), (HCl 0.1 M, 100 rpm). A tablet was weighed together with the basket ($W_1$) and placed in the dissolution medium. At regular time intervals (0.5, 1, 2, 4, 8 and 12 hours) the tablet and basket were removed, excess surface liquid was carefully removed by a filter paper and reweighed ($W_2$).

The swelling index (SI) was calculated using the formula: $SI = (W_2 - W_1)/W_1$.

**Erosion profile**

The erosion study was peformed in triplicate in the same conditions as the water uptake study (at 37±0.5º) in no. 1 apparatus (basket), (HCl 0.1 M, 100 rpm). At given time intervals (1, 2, 4, 8 and 12 hours) the tablets were removed, placed in the exicator and reweighed until constant mass. Erosion (%) was calculated according to the following formula:

$$\% \text{ Erosion} = (I - E) / I \times 100$$

where I = the initial weight of the matrix; E = the weight of the eroded matrix [11].

**Kinetic release evaluation**

To evaluate the release profiles, several release models were tested, such as Baker-Lonsdale, Korsmeyer-Peppas, Hixson-Crowell, Higuchi first order and zero order. The mathematical models, shown in Table V, were fitted to individual dissolution data with the regression module of Kinetica 4.4 for Windows.

**Table V.** Release models studied.

| Release models | Formula |
|---|---|
| Baker-Lonsdale | $(3/2)[1-(1-(Q_t/Q_\infty)^{2/3}]-(Q_t/Q_\infty)=K_b t$ |
| Peppas-Korsmeyer | $Q_t/Q_\infty=K_p t^n$ |
| Hixson-Crowell | $Q_0^{1/3}-Q_t^{1/3}=K_s t$ |
| Higuchi | $Q_t/Q_\infty=K_h t^{0.5}$ |
| First order | $Q_t/Q_\infty=K_1 t$ |
| Zero order | $Q_t=Q_0+K_0 t$ |

Regression analyses were used to obtain the release constant *k*, correlation coefficients *R* and Akaike Information Criterion (AIC) for each model. The Akaike criterion was chosen for distinguishing among competing models. In this criterion a lower value of the indicator means a better fit. On the basis of the Akaike indicator we selected the mathematical model, which describes the release profile for all the analyzed samples with the greatest accuracy. The equation with the lower value of the indicator was judged to be the most appropriate model for each system. The mechanism of drug release was analyzed using the Peppas equation in which *k* is the release rate constant and *n* is the release exponent indicating the mechanism of drug release [12].

## RESULTS AND DISCUSSION

**Experimental design analysis. Quality of fit**

The statistical module from the Modde 9 software was used in order to fit the experimental data with the chosen experimental design and to calculate the statistical parameters, with the Partial Least Squares method. To check the validity of the experimental design the following statistical parameters were calculated: $R^2$, $Q_2$ and the ANOVA test. $R^2$ represents the fraction of the variation of the response explained by the model and $Q^2$ represents the fraction of the variation of the response that can be predicted by the model.

Values close to 1 for both $R^2$ and $Q^2$ indicate a very good model with an excellent predictive power. The values of $R^2$, $Q^2$ and the ANOVA test were good, indicating a good quality of fit for the release study, the bioadhesion and the erosion profiles. The quality of fit was not satisfying for the water uptake as there was little difference in the formulations which can be explained by the erosion of the tablets.

The results obtained after the fit and after the statistical parameters calculation using the data obtained in the experimental plan for the release and the Peppas parameters are the following: $R^2$ was over 0.85 for all the results; $Q^2$ was over 0.7 for almost all results. With two exceptions, ($Y_4$ and $Y_8$), the validity of the model was over 0.7. The reproducibility is acceptable for all the results. The results of the ANOVA test showed that p for the model was less than 0.05 for all the experiments, and p for the error was over 0.05 for all the experiments.

***In vitro* release of famotidine**

The results indicate that the percent of famotidine released depends on the formulation factors studied in the experimental design. FAMO was slowly released over 12 hours from all the experimental formulations. The release varied between 59% and 77% depending on the percentage and the combination of the bioadhesive polymers used (Figure 1).

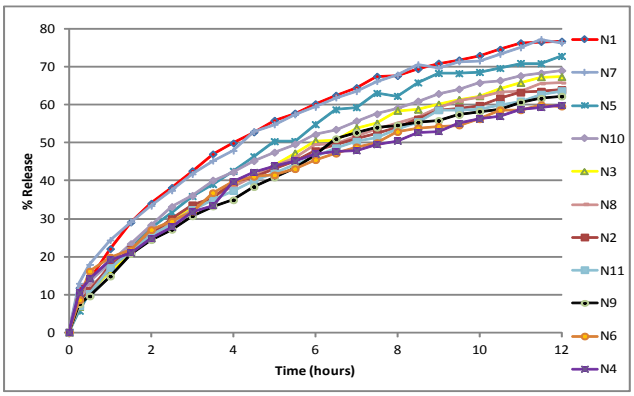



**Figure 1.** The amount of famotidine released in time from tablets.

The release of famotidine was the slowest from formulations N4 and N6 (containing 75% and 65% respectively of polymers combination) followed by formulations with 55% of polymers (N9, 11). The fastest release was obtained for formulation N1 (35% polymers) and formulations containing 45% of polymer combination (N5 and N7). The difference of the release profiles are not significant (< 20%) taking into consideration that the difference in total polymer concentration between the formulations with the highest and lowest total polymer content is 40%. In formulations containing the same concentration of total polymers the release is slightly faster in case of the tablets containing more CP than SCMC. This fact might be explained by the erosion profiles of the tablets and the pH dependancy of Carbopol.

**Influence of formulation factors on the dissolution profile (responses $Y_1$-$Y_{25}$)**

Figure 2 shows the influence of the formulation factors on the $Y_1$, $Y_7$, $Y_{13}$ and $Y_{25}$ answers. According to the obtained results, at the first times of release ($Y_1 - Y_3$) the formulation factors did not influence the release profile of famotidine. After 1 hour of dissolution, the increasing percentage of Carbopol in the formulations determined a faster release profile. This can be explained by the pH dependant nature of Carbopol. The low pH of the release medium (HCl pH 2) results in fewer ionized carboxyl groups on Carbopol (average pKa 6.2) which result in lower repulsion forces between the chains and thus less gel formation [12,13]. The gel formation is mainly due to the presence of SCMC and HPMC.

The presence of the interactions $X_1$*$X_1$ and $X_2$*$X_2$ demonstrate a nonlinear influence of the factors over the concentration interval.

**Influence of the formulation factors on the kinetics of release**

In order to study the release profile of famotidine from bioadhesive matrix tablets, six well known kinetic release models were evaluated. Table VI provides the summary of the model fitting and statistical parameters for kinetic release characterization of the prepared formulations N1-N19. The best fitting for the drug profile release for all the experiments was obtained with the Peppas equation.

In order to analyze the influence of the formulation factors on the kinetic release, the parameters of the Peppas equation (*k* and *n*) where introduced as responses ($Y_{26}$ - *k* and $Y_{27}$ - *n*) in the experimental design. The coefficients of the equation used to fit the experimental data with the chosen model at kinetic release evaluation are presented as scaled and centred coefficients in figure 3.

The influence of the formulation factors on *k* parameter is similar with the influence of formulation factors on the *in vitro* release of famotidine at different time point intervals. The percentage of CP ($X_1$) has a positive influence on the *k* parameter of the Peppas equation, meaning that increasing the concentration of this polymer from 10 to 30% is in favour of a faster release profile. This result is in concordance with the data obtained by the statistic parameters of the release profiles. There are no big interactions between the factors. The influence is not linear in the concentration interval indicated by the presence of the factors $X_1$*$X_1$ and $X_2$*$X_2$.

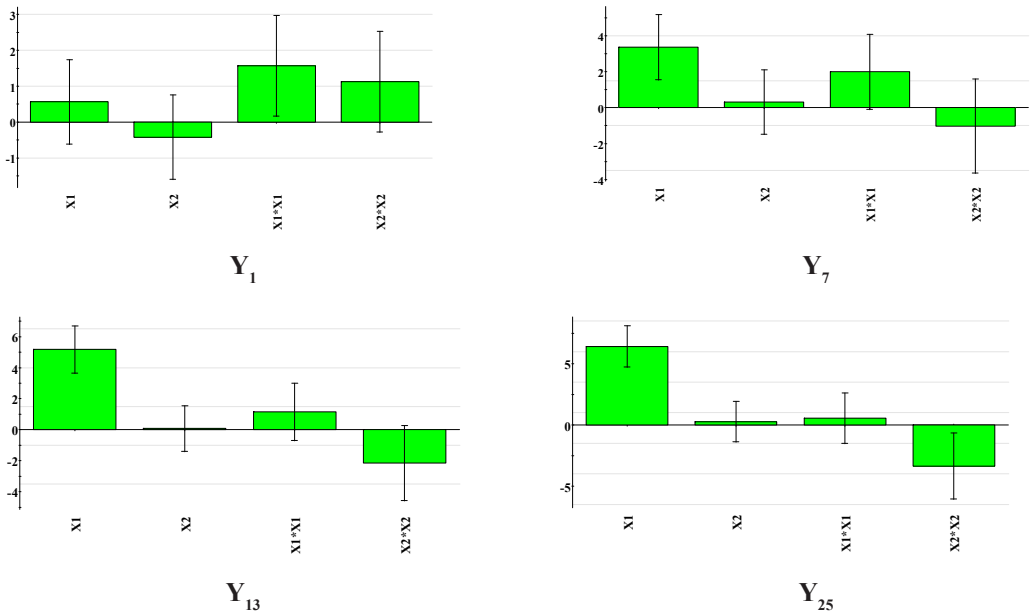
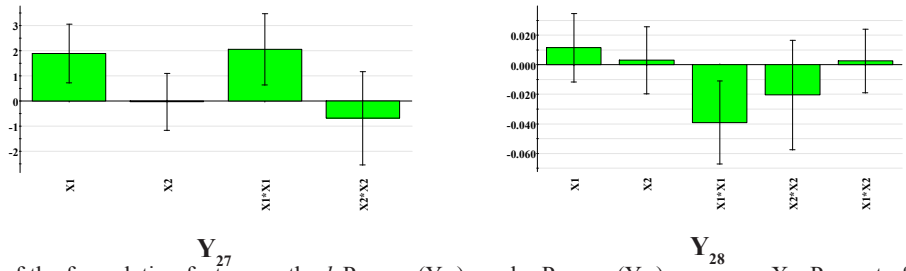



**Figure 2.** The influence of the formulation factors on the percent of famotidine release at different time intervals ($Y_1$, $Y_6$, $Y_{13}$ and $Y_{16}$ answers). $Y_1$ - Percent of famotidine released after 0.25h; $Y_6$ - Percent of famotidine released after 3.0h; $Y_{13}$ - Percent of famotidine released after 6.0h; $Y_{25}$ - Percent of famotidine released after 12.0h; $X_1$- Percent of CP; $X_2$ - Percent of SCMC.

**Table VI.** Results of the kinetic release characterization.

| Exp. Nr. | Baker and Lonsdale | | | Peppas | | | | Hixon and Crowell | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | R | AIC* | k | R | AIC* | k | n | R | AIC* | k |
| N1 | 0.9966 | 98.471 | 0.007 | 0.9961 | 103.504 | 196.531 | 0.4559 | 0.8948 | 182.769 | 0.027 |
| N2 | 0.9967 | 110.323 | 0.013 | 0.9975 | 105.684 | 253.569 | 0.4573 | 0.9346 | 184.402 | 0.040 |
| N3 | 0.9979 | 85.516 | 0.007 | 0.9975 | 91.955 | 198.261 | 0.4521 | 0.8923 | 183.147 | 0.027 |
| N4 | 0.9953 | 120.992 | 0.014 | 0.9961 | 118.382 | 251.168 | 0.4672 | 0.9429 | 182.607 | 0.041 |
| N5 | 0.9946 | 115.317 | 0.008 | 0.9984 | 87.180 | 186.566 | 0.5088 | 0.942 | 174.049 | 0.029 |
| N6 | 0.9933 | 120.333 | 0.008 | 0.9983 | 88.795 | 178.499 | 0.5206 | 0.9467 | 171.588 | 0.029 |
| N7 | 0.9915 | 128.019 | 0.008 | 0.9984 | 87.883 | 179.327 | 0.5320 | 0.9549 | 169.351 | 0.030 |
| N8 | 0.9885 | 137.721 | 0.009 | 0.9979 | 97.738 | 178.234 | 0.5472 | 0.9634 | 166.267 | 0.031 |
| N9 | 0.9944 | 120.079 | 0.010 | 0.998 | 96.573 | 206.964 | 0.5001 | 0.9458 | 176.383 | 0.033 |
| N10 | 0.9833 | 152.872 | 0.011 | 0.9943 | 128.291 | 197.498 | 0.549 | 0.9717 | 165.944 | 0.036 |
| N11 | 0.9883 | 134.845 | 0.008 | 0.995 | 115.553 | 170.961 | 0.5372 | 0.9526 | 169.257 | 0.028 |

| Exp. Nr. | Higuchi | | | First Order | | | Zero Order | | |
|---|---|---|---|---|---|---|---|---|---|
| | R | AIC* | k | R | AIC* | k | R | AIC* | k |
| N1 | 0.9942 | 111.653 | 179.975 | 0.9269 | 174.101 | 0.0935 | 0.7928 | 198.334 | 61.393 |
| N2 | 0.9957 | 117.285 | 232.857 | 0.9652 | 169.018 | 0.1468 | 0.7956 | 130.551 | 79.431 |
| N3 | 0.9952 | 106.549 | 180.192 | 0.9247 | 174.645 | 0.0937 | 0.7895 | 198.512 | 61.449 |
| N4 | 0.995 | 122.291 | 235.222 | 0.9722 | 164.974 | 0.1501 | 0.807 | 211.244 | 80.273 |
| N5 | 0.9983 | 86.176 | 189.882 | 0.9649 | 161.786 | 0.1019 | 0.8614 | 194.750 | 65.133 |
| N6 | 0.9979 | 91.332 | 186.028 | 0.9679 | 159.209 | 0.0986 | 0.8728 | 192.369 | 63.888 |
| N7 | 0.9976 | 96.298 | 191.211 | 0.9744 | 155.461 | 0.1030 | 0.8832 | 192.212 | 65.751 |
| N8 | 0.9962 | 110.300 | 195.957 | 0.981 | 150.075 | 0.1072 | 0.8945 | 191.872 | 67.479 |
| N9 | 0.998 | 94.573 | 207.010 | 0.9701 | 161.853 | 0.1178 | 0.8514 | 200.344 | 70.932 |
| N10 | 0.9924 | 133.204 | 217.909 | 0.9885 | 143.625 | 0.1289 | 0.8911 | 198.618 | 75.012 |
| N11 | 0.9939 | 118.448 | 184.208 | 0.9721 | 156.252 | 0.0971 | 0.8829 | 190.957 | 63.355 |




$Y_{27}$ $Y_{28}$

**Figure 3.** Influence of the formulation factors on the *k* Peppas ($Y_{27}$) and *n* Peppas ($Y_{28}$) response. $X_1$- Percent of CP; $X_2$ – Percent of SCMC.

The influence of formulation factors on the *n* parameter are negligible meaning that the release profiles of the formulations are similar all having a Higuchi release gouverned by difusion and erosion of the gel layer (*n* close to 0.5).

**Measurement of bioadhesion**

Figure 4 presents the influence of the formulation factors on the bioadhesive properties of the formulated tablets ($Y_{28}$).

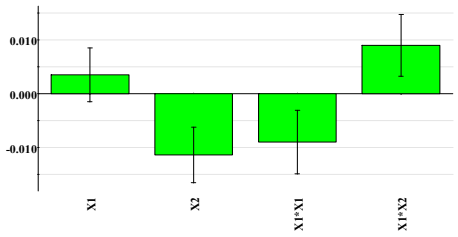



**Figure 4.** Influence of the formulation factors on the bioadhesive properties of matrix tablets. $X_1$- Percent of CP; $X_2$ - Percent of SCMC.

The factor which has a positive influence on the bioadhesive properties of the tablets, increasing them, is the concentration of CP in the formulations. Increasing the percentage of CP in the formulations favors the bioadhesive properties. This influence is nonlinear over the concentration interval.

There are also some interactions between the percentage of CP (X1) and SCMC (X2) which are very intense. The two factors have a synergic effect on the bioadhesive properties, increasing them.

**Water uptake. Influence of formulation factors on the water uptake profile**

Regarding the water uptake, the formulation presented similar values for all the studied formulations (range between 13.53% for N1 and 16.13% for N6). The results are presented in Figure 5.

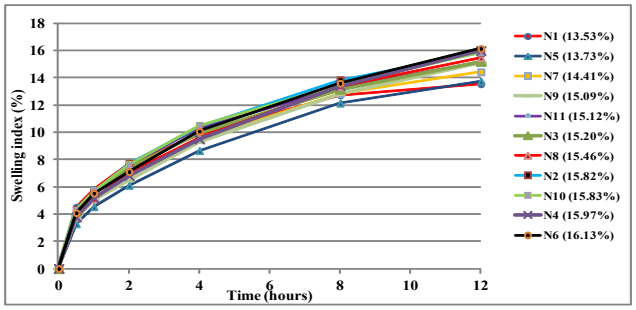



**Figure 5.** The amount of water uptake of the matrix tablets.

Regarding the influence of the formulation factors on the water uptake (Figure 6): there is no or little influence of the formulation factors up to 4 hours. The high concentration of polymers does not permit fast relaxation of the polymer chains. In time, the penetration of water allows the formation of the gel layer and encourages the water uptake. The Carbopol in the formulation presents a pH-dependant swelling. At the beginning, the low pH of the medium determines the presence of unionized carboxylic groups which hinder the relaxation of the polymer chains. After 4 hours the micro environmental pH begins to rise through the formation of the gel layer of HPMC and though the ionization of the carboxylic groups is favored. This leads to the repulsion between the carboxylic groups and relaxation of the polymeric chains with positive influence on the water uptake properties [13,14].

These similar water uptake values, even though the total mass of polymers in the formulations differs from 35% to 75%, can also be explained by the erosion profiles.

**Erosion profile. Influence of formulation factors on the erosion profile**

The results indicate that extent of the erosion depends on the formulation factors studied in the experimental design. The erosion varied between 13% and 62% depending on the percentage of the total composition of bioadhesive polymers used (Figure 7).

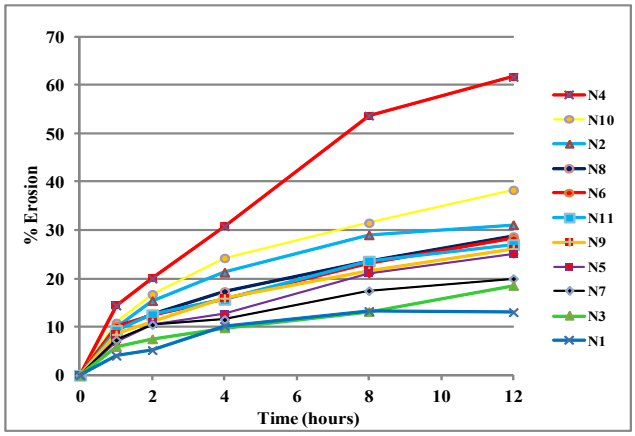



**Figure 7.** The amount of erosion of the matrix tablets.

All the histograms regarding the erosion profile (Figure 8) show a similar influence of the formulation factors on the erosion profile throughout the prelevation interval. The percentage of SCMC and CP has a negative influence on the erosion profile. There is an interaction of the two factors which has a positive effect of on the erosion profile. This result is also sustained by Figure 7. The formulations containing a high concentration of both

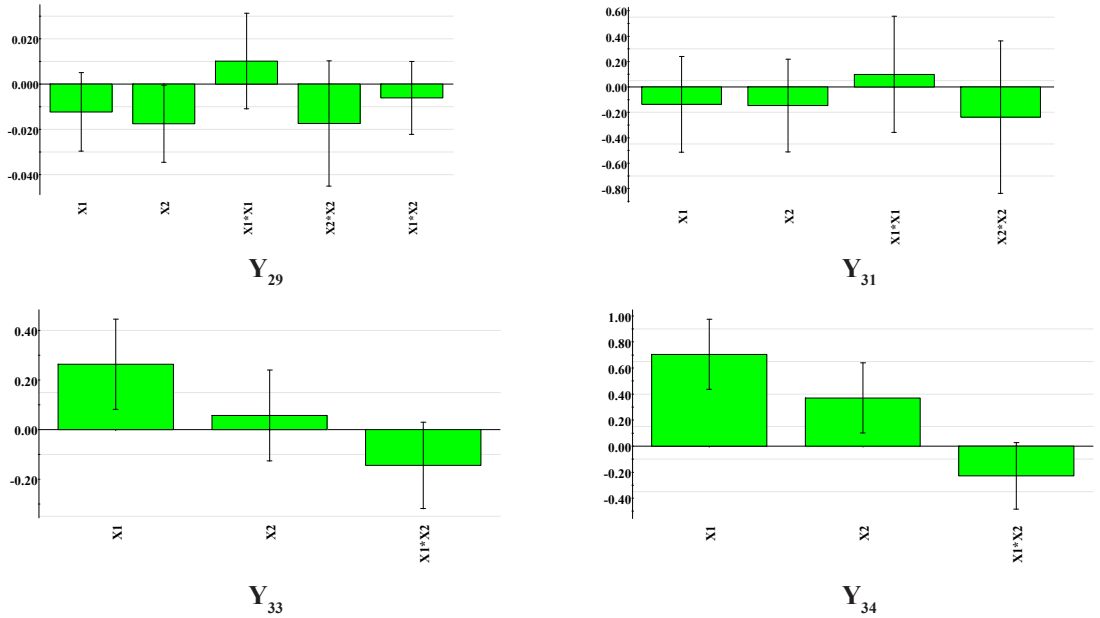



**Figure 6.** Influence of the formulation factors on the water uptake of matrix tablets ($Y_{29}$, $Y_{31}$, $Y_{33}$ and $Y_{34}$ answers). $Y_{29}$ - Percent of water uptake at 0.5h; $Y_{31}$ - Percent of water uptake at 2.0h; $Y_{33}$ - Percent of water uptake at 4.0h; $Y_{34}$ - Percent of water uptake at 12.0h; $X_1$- Percent of CP; $X_2$ - Percent of SCMC.

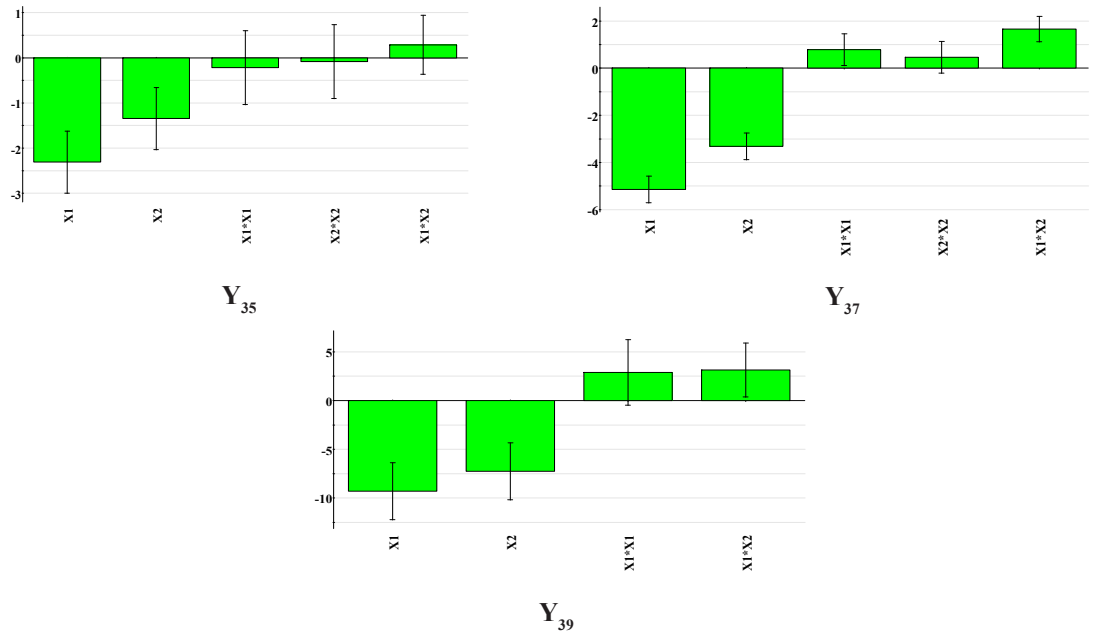



**Figure 8.** Influence of the formulation factors on the erosion of matrix tablets ($Y_{35}$, $Y_{37}$ and $Y_{39}$ answers). $Y_{35}$ - Percent erosion at 0.5h; $Y_{37}$ - Percent of water uptake at 4.0h; $Y_{39}$ - Percent of water uptake at 12.0h; $X_1$- Percent of CP; $X_2$ - Percent of SCMC.

polymers (N4, N10 and N2) show the greatest erosion while the formulations with less high concentration of polymers (N8 and N6) show the least amount of erosion. This leads to the conclusion that the higher the concentration of the two polymers, the bigger the interpenetration of the chains. We can conclude the following: because the gel layers formed by the two polymers are different in strength, the higher the concentration of CP and SCMC, the more susceptible the tablet will be for erosion.

## CONCLUSIONS

In the present study we have used an experimental optimization design to determine the influence of different combination of two of the most used bioadhesive polymers on the release profile, the bioadhesive properties, the water uptake and the erosion of matrix tablets with famotidine.

The total concentration of the polymers used beside HPMC (15% fixed amount) in the formulations varied from 35% to 75%. Despite the big difference between total polymer content in the tablets, the dissolution profiles were similar (< 20%) between different formulations which were best described by Peppas model. The slowest release was obtained for the highest amount of bioadhesives used and the fastest for the tablets with 35% of total polymer content. In formulations containing the same concentration of total polymers the release is slightly faster in case of the tablets containing more CP than SCMC. The water uptake profiles were also similar between all formulations. Regarding the erosion profiles, the formulation with the higher amount of polymer, in particular with higher amount of CP showed a marked erosion due to difference in gel strength.

In terms of bioadhesiveness the combination of CP and SCMC showed a synergic effect of bioadhesive properties, increasing the adhesive properties with increasing concentration.

In conclusion, over the range of 35% to 75% of total polymer concentration the formulation factors do not have a massive impact on the properties of bioadhesive maxtrix tablets, the biggest difference being visible in the erosion profiles.

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