

## DESIGN AND FORMULATION OF BUCCAL MUCOADHESIVE PREPARATION BASED ON SORBITAN MONOSTEARATE OLEOGEL

ELENA DINTE\*, IOAN TOMUȚĂ, RAREȘ I. IOVANOV,  
SORIN E. LEUCUȚA

*"Iuliu Hatieganu" University of Medicine and Pharmacy, Faculty of Pharmacy, Pharmaceutical Technology and Biopharmaceutics, 41, V. Babeș Street, 400012, Cluj-Napoca, Romania*

*\*corresponding author: edinte@gmail.com*

### Abstract

Eleven formulations of buccal mucoadhesive preparations based on sorbitan monostearate (SMS) oleogel in which were incorporated bioadhesive polymers, Carbopol 940 or HPMC K100M, in concentrations established according to a composite central experimental design were prepared. The drug substances, metronidazole (MZ) and ibuprofen (IB) were incorporated in a concentration of 1%. The rheological characteristics, adhesion and *in vitro* release of MZ and IB were studied. The analyse of the kinetic release showed a good correlation with Peppas model. A formulation containing SMS 6.87% and HPMC K100M 14.99% was identified for maximising consistency, mucoadhesivity and ensuring an *in vitro* prolonged drug release profile for 8 hours. The optimized formulation was characterized in terms of adhesivity, rheology and release kinetics and their reproducibility was confirmed. The optimized formulation can be considered a good candidate for application in the postextractional socket at patients presenting the risk for osteomyelitis on the background of osteonecrosis.

### Rezumat

S-au realizat 11 formulări de preparate mucoadezive bucale, constituite din oleogel de monostearat de sorbitan (SMS) în care s-au încorporat prin suspendare polimeri bioadezivi, Carbopol 940 sau HPMC K100M, în concentrații stabilite conform unui plan experimental de tip central compozit. Substanțele medicamentoase, metronidazol (MZ) și ibuprofen (IB), s-au încorporat în concentrație de 1%. S-au studiat caracteristicile reologice, de adeziune și de cedare *in vitro* a MZ și IB. Analiza cineticii de cedare a prezentat o corelare bună cu modelul Peppas. S-a calculat formularea optimizată, conținând SMS 6,87% și HPMC K 100M 14,99%, caracteristicile de interes fiind consistență și mucoadezivitate crescute și eliberare prelungită a substanțelor medicamentoase pe parcursul a 8 ore. S-au studiat caracteristicile reologice, de adeziune și de cedare *in vitro* ale formulării optimizate, iar valorile obținute practic au fost apropiate de cele estimate teoretic. Formularea optimizată poate fi considerată un bun candidat pentru aplicarea în alveola postextractională la pacienți cu risc de osteomieliță pe fond de osteonecroză.

**Keywords:** oleogel, sorbitan monostearate, mucoadhesion, buccal semisolid preparation

## Introduction

Postextraction dry socket (alveolar osteitis, osteonecrosis) occurs due to the displacement of the blood clot formed after tooth extraction or to clot insufficiency at the extraction site, exposing the nerve and the bone underneath it to infection. The etiology is multifactorial: trauma, diabetes mellitus, marked peripheral vasoconstriction, HIV, chronic alcoholism, etc., the most severe being osteoradionecrosis. In the last decades, a great number of cases of bone necrosis have also been described consequent to the treatment with bisphosphonates, compounds widely used in the management of the bone metastases secondary to various types of cancer (breast, prostate) and in the treatment of osteoporosis. The systemic treatment of dry postextraction alveolitis by the administration of oral antibiotics before the extraction is not justified because on one hand, no other infection source is present in the organism, and, on the other hand, the antibiotic does not reach to the infection site, the alveolus, due to bone necrosis (hypovascularization, hypoxia). The alternative remains the local treatment with antibiotics, antiseptics, antiinflammatory and anaesthetic drugs [1,2]. Because the conventional topical formulations are rapidly cleared from the oral cavity, the mucoadhesive semi-solid preparations can increase the efficiency by allowing the application of the drug on the pathological site, thereby increasing the contact time between formulation and mucosa [3]. Gels are semisolid preparations most appropriate and preferred for application in the oral cavity [4]. There are 2 major types of gels: hydrogels, which contain a high amount of water in their composition and oleogels (lipogels, organogels). Oleogels, are semisolid materials composed of an amphiphilic molecule, usually known as organogelator, and a hydrophobic liquid [5, 6]. The microstructure of oleogels is characterized by either permanent rigid networks or transient semiflexible meshes, both being thermoreversible. Examples of oleogels are those containing ethylcellulose, cholesterol, lecithin, sorbitan monostearate or lanolin alcohols, as organogelators, dispersed in vegetable oils, as organic solvents. The network stops the flow of liquid by altering the surface tension of the liquid. It is the network of the gelator which gives the gel structure and stickiness [7-9]. Organogelators are broadly classified into 2 categories depending on the molecular weight of the gelator: low molecular weight organogelators and polymeric organogelators. The interaction between the gelator molecule to form an aggregate and hence the fibers might be either covalent (chemical) or simply physical. Chemical gels are thermally irreversible whereas gels formed by weak non-covalent interactions (physical gels) are reversible [10, 11]. These hydrophobic gel materials do

not require new or extensive manufacturing knowledge in order to be produced, and can be formulated in a wide viscosity range [12, 13]. Various oleogel applications have been investigated over the past few years. It is worth mentioning their potential use in the area of environmental chemistry and in the pharmaceutical and cosmetic industries [14]. Sorbitan monostearate (SMS), a hydrophobic nonionic surfactant, gelifies a number of organic solvents such as hexadecane, isopropyl myristate, and a range of vegetable oils. Gelation is achieved by dissolving/dispersing the organogelator in a hot solvent to produce an organic solution/dispersion, which, after cooling sets to the gel state [8, 15]. SMS is mainly used in pharmaceutical formulations as a water-in-oil emulsifying agent. The obtaining of stable oleogel/hydrogel semisolid formulations ("bigel") was reported in the literature [16].

Incorporation of hydrophil polymers in a lipophil matrix based on SMS oleogel could increase the bioadhesive capacity of the preparation on the buccal mucosa by the reduction of the hydration rate of the bioadhesive polymers forming a hydrogel and which in its turn is eluted with greater difficulty with the saliva.

In the present study, attempts have been made to develop and characterize an SMS oleogel based semisolid preparation, with optimized properties of forming an artificial clot, consistency, bioadhesion and release of the metronidazole and ibuprofen, for a possible application in the postextraction socket in patient with osteonecrosis.

### Materials and Methods

**Materials:** Sorbitan monostearate - SMS (Merk, Germany), olive oil (purchased from the local market), polyacrylic acid (Carbopol 940, B.F. Goodrich), hydroxypropyl methylcellulose (HPMC K100M, Colorcon, USA), ibuprofen 25 µm (BASF, Germany), metronidazole (BASF, Germany), white petrolatum, wool wax (*adepts lanae anhydricus*), PEG 400 (Merk, Germany); all other ingredients used were of pharmaceutical grade.

### Methods

#### Preparation of buccal mucoadhesive oleogel based formulations.

Oleogels of various SMS concentrations were prepared by dissolving a specified amount of SMS (see Table I) in olive oil, kept in a water bath maintained at 60°C and stirred at 500 rpm, until a homogeneous clear solution was obtained. In order to increase the plasticity of the preparations white petrolatum and wool wax were added, keeping the mixture on a water bath until it melted completely and became homogeneous. The hot solutions obtained in this way were allowed to cool down at room-temperature so as

to allow gel formation [10,17]. Finally oleogels containing SMS in a concentration of 2–9%, petrolatum 40%, wool wax 5% and olive oil up to 100g (w/w). Drug loaded organogels were prepared by dispersing the drug substances in a non-aqueous solvent. A corresponding amount of oleogel containing SMS in the concentration shown in Table I, was fluidized on water bath at 40–50°C; MZ (dissolved in PEG 400, 1:15) and IB (dissolved in PEG 400, 1:10), were incorporated and the mixtures obtained were added to the powder of bioadhesive polymer (Carbopol 940 or HPMC K100M), homogenized continuously until a homogenous paste was obtained. The final preparations contained MZ 1%, IB 1%, PEG 400 25%, bioadhesive polymers 5 to 15 % and oleogel (containing SMS 2–9%) up to 100g. All the samples were kept at room-temperature for further analysis.

**Rheologic study.** The viscosity measurements were performed on a Brookfield DV III Ultra viscometer (Brookfield Engineering Laboratories, Inc., USA), using a spiral adaptor. The determinations were made at 37°C±0.5, in the range 0.3–100 s<sup>-1</sup>, with three replicates for each experiment. Because the viscosity decreases with the shear rate, the apparent viscosity at 20.36 s<sup>-1</sup> of the preparations was determined.

*In vitro spreading capacity* was studied by measuring the spreading radius of 1 g of the preparation between two 20×20 cm glass plates at 1 min. after applying 500 g. The mass of the upper plate was standardized at 125 g.

*In vitro adhesive capacity* was assessed by measuring the detachment force of a synthetic membrane coming in contact with the preparation. The contact time was 1 minute. The measurements were made at room temperature using a modified analytical scale according to a model reported in the literature [18, 19].

*In vitro assay and drug release studies* was performed using the dialysis method: 1–2 g of mucoadhesive preparation was placed in a dialysis bag (Spectra/Por Cellulose Ester Membrane MWCO: 5000–8000 Da), which was placed in 900 mL of phosphate buffer pH 6.8 in a dissolution apparatus (Pharma Test PT-DT7), maintained at 37°C and stirred at 50 rpm. Samples were collected periodically and replaced with fresh dissolution medium. MZ and IB were analysed using an HPLC validated method. The chromatographic separation was achieved on a Zorbax SC C18 (5µm, 4.6 x 150 mm) with UV detection at 319 nm for metronidazole and 225 nm for ibuprofen. The mobile phase consisted of acetonitrile and phosphoric acid 0.1% (15:85 v/v, t<sub>R</sub> 2.48 min for MZ and 65:35 v/v, t<sub>R</sub> 2.12 min for IB).

**The kinetic analysis** of the release data was done with the regression module of SigmaPlot 8, using the Peppas equation:

$$M_t / M_\infty = Kt^n \quad \text{Eq. 1}$$

where  $M_t / M_\infty$  is the fraction of drug released at time t, K is the rate constant and n is the release exponent. The n value is used to characterize various release mechanisms [20,21].

**Experimental design.** For the optimization of the formulation, a Central Composit Design with three factors and two levels was used. A design matrix of experimental runs is presented in Table I. The independent variables are represented by the concentrations of the components of the buccal mucoadhesive oleogel based formulations (SMS and the bioadhesive polymer) and the type of the bioadhesive polymer used in the preparation (HPMC K100M or Carbopol 940) (Table II). The dependent variables (the studied experimental responses) are presented in Table III.

The construction and analysis of the experimental design was performed with Modde 9.0 Software (Umetrics Sweden) [22].

**Table I**

The matrix of the experimental design

| Exp Name | Run Order | X1  | X2           | X3 |
|----------|-----------|-----|--------------|----|
| N1       | 11        | 2   | HPMC K100    | 5  |
| N2       | 8         | 9   | HPMC K100    | 5  |
| N3       | 9         | 2   | CARBOPOL 940 | 5  |
| N4       | 4         | 9   | CARBOPOL 940 | 5  |
| N5       | 10        | 2   | HPMC K100    | 15 |
| N6       | 3         | 9   | HPMC K100    | 15 |
| N7       | 6         | 2   | CARBOPOL 940 | 15 |
| N8       | 7         | 9   | CARBOPOL 940 | 15 |
| N9       | 5         | 5.5 | HPMC K100    | 10 |
| N10      | 2         | 5.5 | HPMC K100    | 10 |
| N11      | 1         | 5.5 | HPMC K100    | 10 |

X1 – SMS (sorbitan monostearate) (% w/w); X2 –Bioadhesive polymer type; X3 – Bioadhesive polymer concentration (% w/w)

**Table II**

The independent variables

| Independent variables                         |                | Levels    |     |               |
|-----------------------------------------------|----------------|-----------|-----|---------------|
|                                               |                | -1        | 0   | +1            |
| Sorbitan monostearate (SMS) concentration (%) | X <sub>1</sub> | 2         | 5.5 | 9             |
| Bioadhesive polymer type                      | X <sub>2</sub> | HPMC K100 |     | CARBO POL 940 |
| Bioadhesive polymer concentration (%)         | X <sub>3</sub> | 5         | 10  | 15            |

**Table III**  
The dependent variables

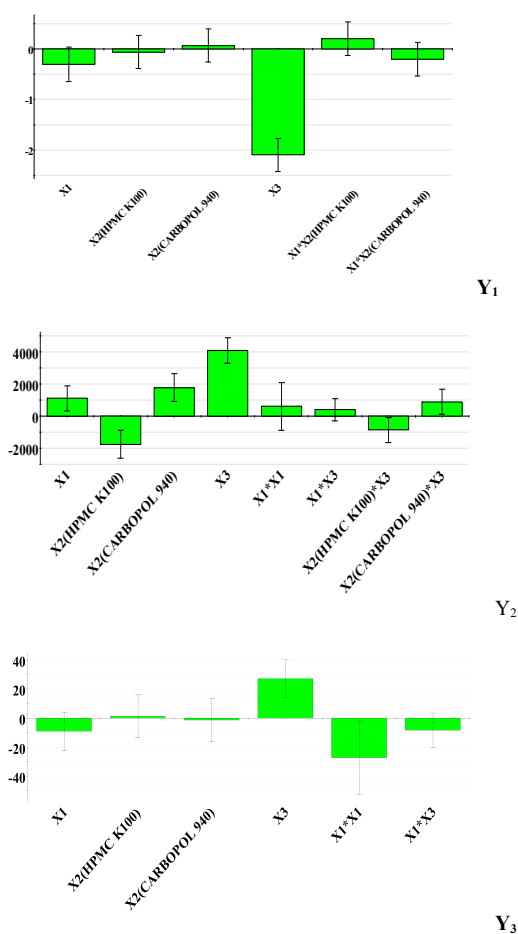
| No. | Responses                               | Symbols  | No. | Responses                             | Symbols  |
|-----|-----------------------------------------|----------|-----|---------------------------------------|----------|
| 1   | Spreading (mm)                          | $Y_1$    | 13  | Ibuprofen released at 0.5 h (%)       | $Y_{13}$ |
| 2   | Viscosity at $20\text{ s}^{-1}$ (mPa.s) | $Y_2$    | 14  | Ibuprofen released at 1 h (%)         | $Y_{14}$ |
| 3   | Detachment force (mN)                   | $Y_3$    | 15  | Ibuprofen released at 1.5 h (%)       | $Y_{15}$ |
| 4   | Metronidazole released at 0.5 h (%)     | $Y_4$    | 16  | Ibuprofen released at 2 h (%)         | $Y_{16}$ |
| 5   | Metronidazole released at 1 h (%)       | $Y_5$    | 17  | Ibuprofen released at 3 h (%)         | $Y_{17}$ |
| 6   | Metronidazole released at 1.5 h (%)     | $Y_6$    | 18  | Ibuprofen released at 4 h (%)         | $Y_{18}$ |
| 7   | Metronidazole released at 2 h (%)       | $Y_7$    | 19  | Ibuprofen released at 5 h (%)         | $Y_{19}$ |
| 8   | Metronidazole released at 3 h (%)       | $Y_8$    | 20  | Ibuprofen released at 6 h (%)         | $Y_{20}$ |
| 9   | Metronidazole released at 4 h (%)       | $Y_9$    | 21  | Ibuprofen released at 8 h (%)         | $Y_{21}$ |
| 10  | Metronidazole released at 5 h (%)       | $Y_{10}$ | 22  | k - Peppas metronidazole ( $h^{-n}$ ) | $Y_{22}$ |
| 11  | Metronidazole released at 6 h (%)       | $Y_{11}$ | 23  | n - Peppas metronidazole              | $Y_{23}$ |
| 12  | Metronidazole released at 8 h (%)       | $Y_{12}$ | 24  | k - Peppas ibuprofen ( $h^{-n}$ )     | $Y_{24}$ |
|     |                                         |          | 25  | n - Peppas ibuprofen                  | $Y_{25}$ |

### Results and Discussion

Homogeneous pastes with an increased consistency at room temperature were obtained, but these can easily be modelled by means of a spatula and can be sampled using a syringe with a flat end needle; this indicates the possibility of applying these formulations in the postextraction socket.

The experimental results obtained from the study of the rheologic, *in vitro* adhesive and drug release characteristics were fitted with the chosen model. The results obtained after the fitting and the statistical parameters calculation using data obtained from the experimental design are well for all the responses. The results of Anova test showed that the results are good for all studied responses (for all responses  $p$  is lower than 0.05 for the model and it is higher than 0.05 for the error).

Figure 1 presents, in the form of centred and scaled coefficients, the influence of the formulation factors on the rheologic and *in vitro* adhesive characteristics. The results showed that the spreading capacity of the formulations decrease significantly with the increase of the concentration of the bioadhesive polymers in the formulation.

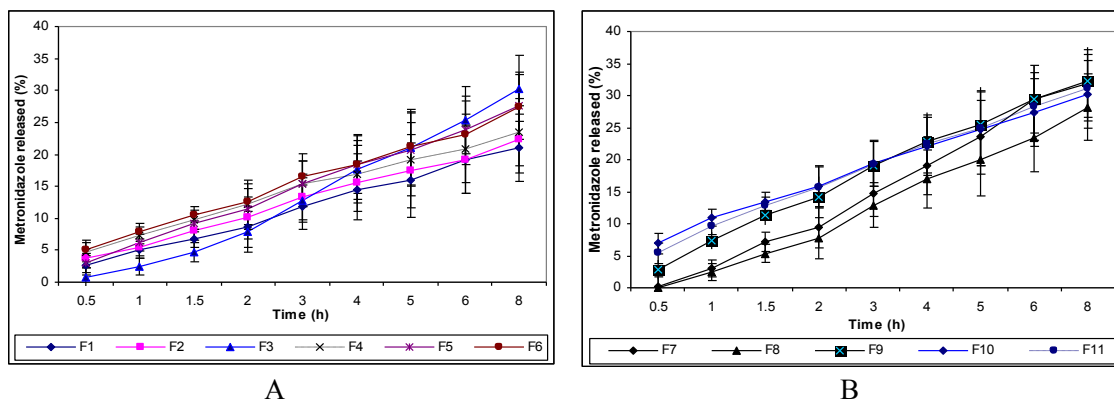
**Figure 1**

Centred and scaled coefficients illustrating the influence of the formulation factors on the rheologic and *in vitro* adhesive characteristics of the buccal mucoadhesive formulations based on SMS oleogel Y<sub>1</sub>: Spreading (mm) ; Y<sub>2</sub> : Viscosity at 20 s<sup>-1</sup> (mPa.s); Y<sub>3</sub>: Detachment force (mN)

The viscosity of the formulations increased significantly with the increase of the total concentration of the bioadhesive polymers in the formulation; as the type of bioadhesive polymer is concerned, it was noted that Carbopol 940 determined an increase of the viscosity while HPMC K100M determined the decrease of this parameter. The *in vitro* adhesive capacity, reflected by the increase of the detachment force, increased with the increase of the concentration of the bioadhesive polymers in the

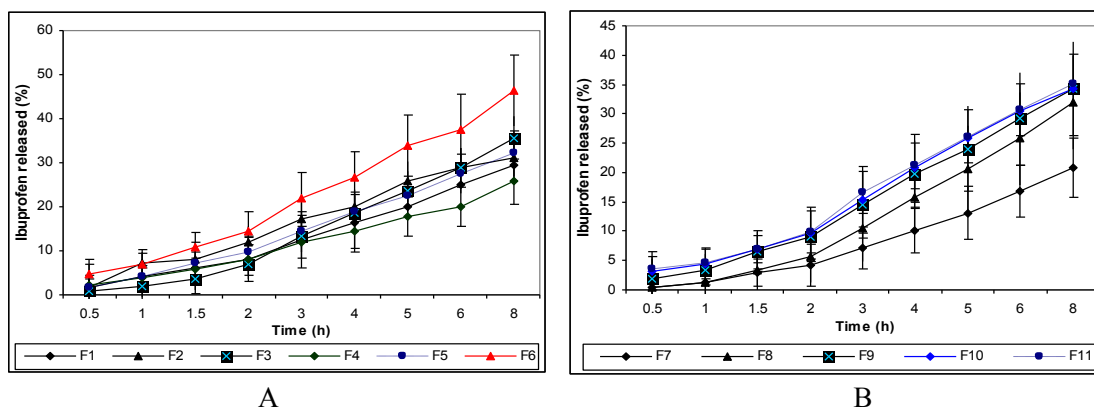
formulation, being not specially influenced by one of the two polymers used in the formulation.

Figure 2 represents the release curves of MZ (A-formulations F1-F6 and B-formulations F7-F11) and Fig.3. represents the release curves of IB (A-formulations F1-F6 and B-formulations F7-F11), from the studied buccal mucoadhesive formulations based on SMS oleogel.



**Figure 2**

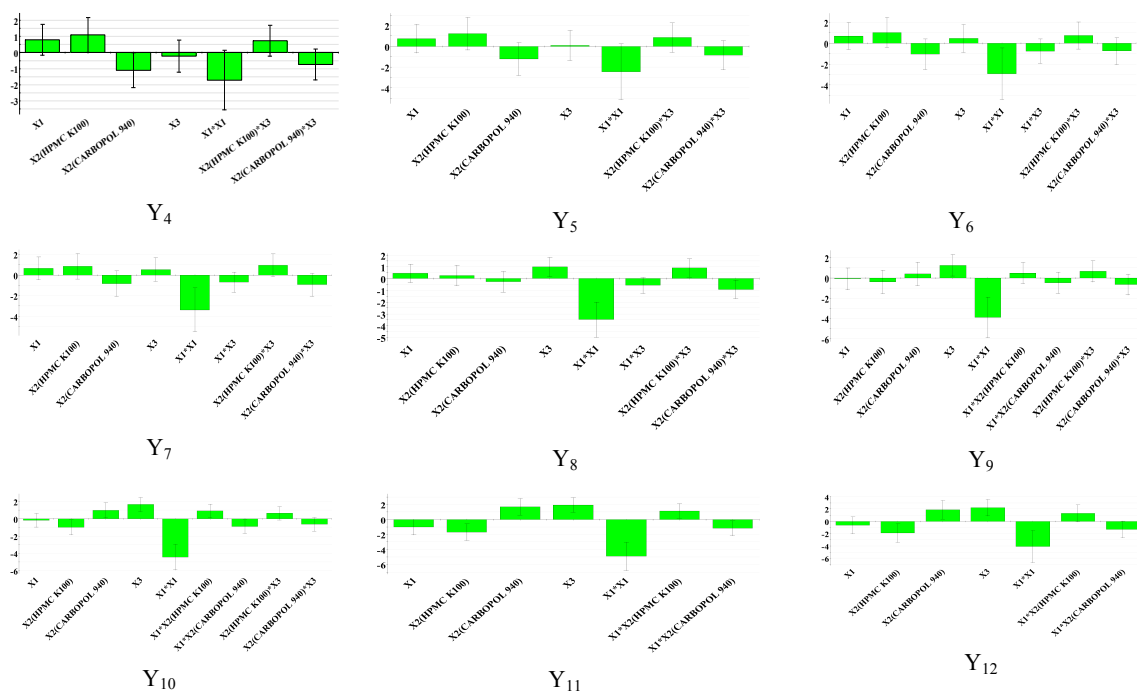
*In vitro* release of metronidazole from buccal mucoadhesive formulations based on SMS oleogel (A: F1-F6 and B: F7-F11, according to Table I)



**Figure 3**

*In vitro* release of ibuprofen from buccal mucoadhesive formulations based on SMS oleogel (A: F1-F6 and B: F7-F11, according to Table I)

The next figures present the influence of the formulation factors, in the form of centered and scaled coefficients, on the *in vitro* release of MZ (Fig 4) and IB (Fig 5) respectively, from the buccal mucoadhesive formulations based on SMS oleogel.



**Figure 4**

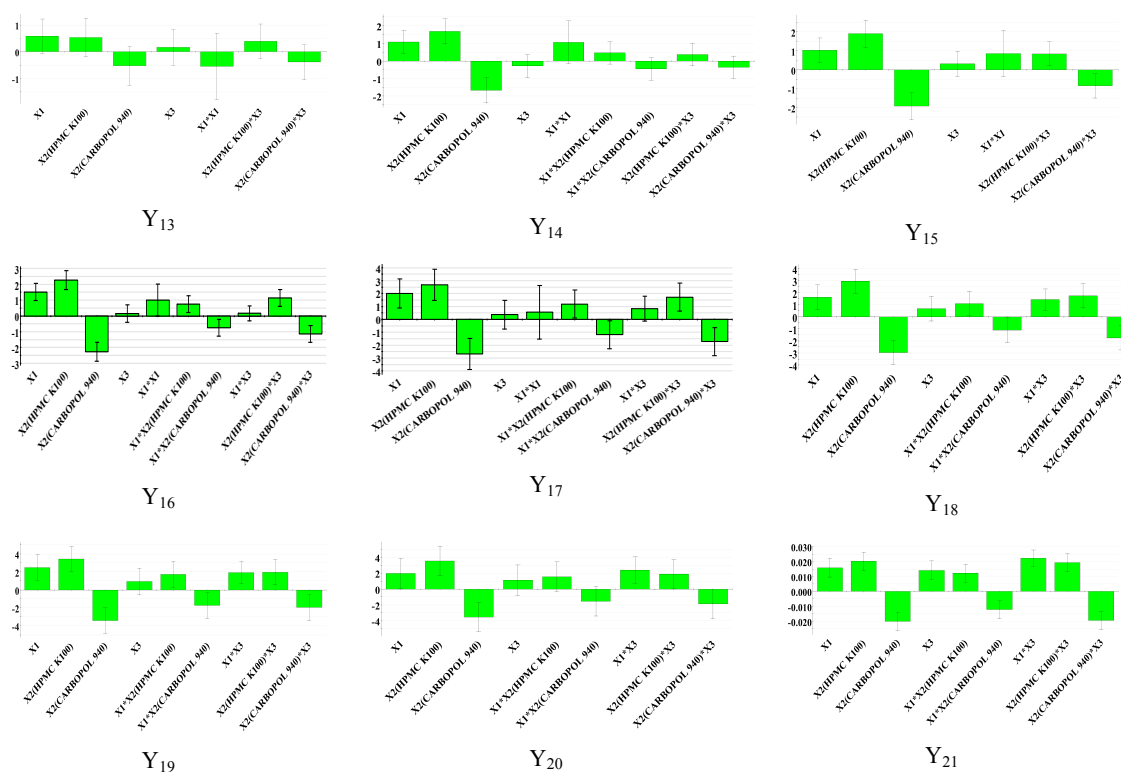
Centered and scaled coefficients illustrating the influence of the formulation factors on the *in vitro* release of MZ from buccal mucoadhesive formulations based on SMS oleogel  
 Y4: MZ released at 0.5 h (%); Y5: MZ released at 1h (%); Y6: MZ released at 1.5 h (%); Y7: MZ released at 2 h (%); Y8: MZ released at 3 h (%); Y9: MZ released at 4 h (%); Y10: MZ released at 5 h (%); Y11: MZ released at 6 h (%); Y12: MZ released at 8 h (%)

Comparative analysis of the influence of the type of bioadhesive polymers on the release of MZ revealed that HPMC K100M determined the reduction of the release of MZ, while Carbopol 940 increased the amount of released MZ.

The release of IB was greater in the formulations containing HPMC K100M; also, the release of IB increased with the increase of the concentration of SMS and of HPMC K100M in the formulation. After 3 hours of release, interaction effects were noted between the polymer type and polymer concentration, which influenced the released amount of IB (HPMC K100M increases the release and Carbopol 940 decreases the release).

As the degree of hydration of the hydrophil polymers with the dissolution medium increased a rise of the rate constants of the drug

substances was noted. This can be accounted for by the increase of the diffusion rate of the drug substances from the formulation and also by the easier erosion of the superficial layer of the preparation. It was noted that the HPMC K100M containing formulations presented a slower hydration, while those containing Carbopol 940 showed a faster hydration, resulting in non-homogeneous preparations.



**Figure 5**

Centered and scaled coefficients illustrating the influence of the formulation factors on the *in vitro* release of IB from buccal mucoadhesive formulations based on SMS oleogel  
Y<sub>13</sub>: IB released at 0.5h (%); Y<sub>14</sub>: IB released at 1 h (%); Y<sub>15</sub>: IB released at 1.5 h (%); Y<sub>16</sub>: IB released at 2 h (%); Y<sub>17</sub>: IB released at 3 h (%); Y<sub>18</sub>: IB released at 4 h (%); Y<sub>19</sub>: IB released at 5 h (%); Y<sub>20</sub>: IB released at 6 h (%); Y<sub>21</sub>: IB released at 8 h(%)

The analysis of the release data revealed a good correlation with Peppas model, which revealed a combined release mechanism, MZ and IB being released by the erosion of the oleogel and by diffusion from the

hydrogel layer resulting from the hydration of the bioadhesive polymers included in the formulation.

Table IV presents the results obtained by the analysis of the release kinetics and the values of the constant release rate revealed that MZ is released at a higher rate than IB.

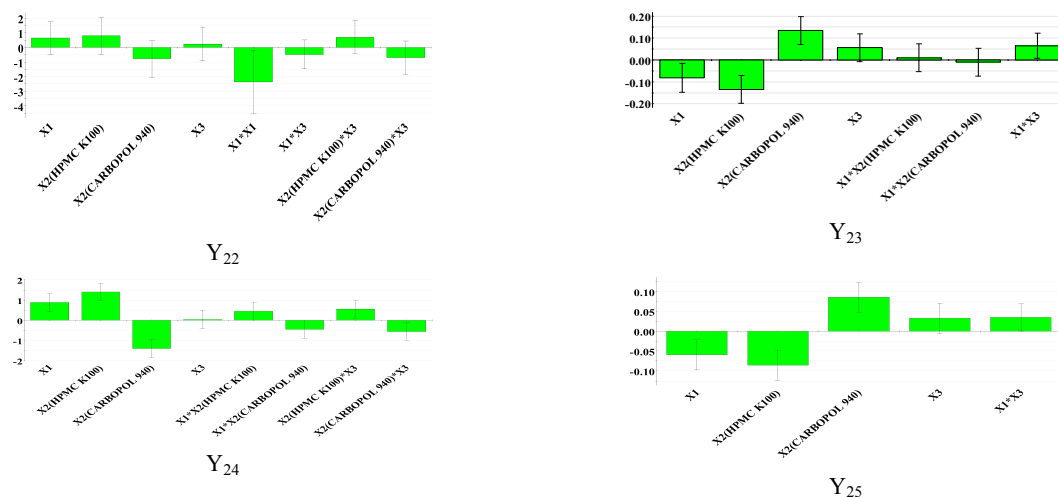
Fig. 6. presents the influence of the formulation factors, in the form of centered and scaled coefficients, on the *in vitro* release kinetic parameters: kinetic release constant and „n” exponent of Peppas equation, with which were fitted the release data of MZ and IB.

The results revealed the fact that SMS determined the reduction of the release rate of MZ and the increase of the release rate of IB. Also, the release rate of IB was increased by the presence of HPMC K100 M in the formulation and it was reduced by the presence of Carbopol 940. These results are in agreement with those obtained by the quantitative estimation of the release of MZ and IB from the studied formulations.

**Table IV**  
Kinetic parameters of MZ and IB from buccal mucoadhesive formulations consisting of hydrophil polymers and SMS based oleogel

| Metronidazole |        |         |        | Ibuprofen |        |        |        |
|---------------|--------|---------|--------|-----------|--------|--------|--------|
| Exp. No       | Peppas |         |        | Exp. No   | Peppas |        |        |
|               | R      | K       | n      |           | R      | k      | N      |
| N1            | 0.9963 | 5.4242  | 0.6749 | N1        | 0.9976 | 4.4670 | 0.9261 |
| N2            | 0.9976 | 6.4117  | 0.6132 | N2        | 0.9892 | 7.1011 | 0.7476 |
| N3            | 0.9930 | 4.1057  | 0.9884 | N3        | 0.9927 | 3.7000 | 1.1147 |
| N4            | 0.9966 | 8.0125  | 0.5327 | N4        | 0.9990 | 4.4127 | 0.8523 |
| N5            | 0.9969 | 6.9941  | 0.6747 | N5        | 0.9965 | 5.3322 | 0.8852 |
| N6            | 0.9988 | 8.3275  | 0.5749 | N6        | 0.9980 | 8.2829 | 0.8411 |
| N7            | 0.9886 | 5.1673  | 0.9155 | N7        | 0.9965 | 2.0841 | 1.1272 |
| N8            | 0.9916 | 4.2217  | 0.9394 | N8        | 0.9938 | 2.8955 | 1.1809 |
| N9            | 0.9926 | 8.6379  | 0.6632 | N9        | 0.9953 | 5.0185 | 0.9498 |
| N10           | 0.9987 | 11.0043 | 0.4986 | N10       | 0.9932 | 5.7373 | 0.8931 |
| N11           | 0.997  | 10.1463 | 0.5579 | N11       | 0.9936 | 6.0341 | 0.8752 |

Based on the results obtained from the study of the mucoadhesive buccal formulations consisting of SMS oleogel and Carbopol 940 or HPMC K100M, the optimization procedure was applied; constraints were made on the mathematical model chosen and the optimal formulation was obtained, the interest characteristics of which were an increased viscosity and adhesivity, an average spreadibility and a mean release rate of the drugs. Table V presents the values calculated for the independent and dependent variables for the designed optimized formulation.

**Figure 6**

Centered and scaled coefficients illustrating the influence of the formulation factors on the kinetic parameters of MZ and IB from buccal mucoadhesive formulations based on SMS oleogel

$Y_{22}$ : k - Peppas MZ ;  $Y_{23}$  : n - Peppas MZ ;  $Y_{24}$  : k - Peppas IB;  $Y_{25}$ : n - Peppas IB

**Table V**

Optimized formulation – composition and results

| Independent variables                           |            | Dependent variables                         |           |              |
|-------------------------------------------------|------------|---------------------------------------------|-----------|--------------|
| Symbol                                          | Value      | Responses                                   | Predicted | Obtained     |
| X1-SMS (% , w/w)                                | 6.87       | Spreading (mm)                              | 13,4586   | 12,98±2,35   |
| X2-Bioadhesive polymer type                     | HPMC K100M | Viscosity at 20 s <sup>-1</sup> (mPa.s)     | 12290     | 11989±710    |
|                                                 |            | Detachment force (mN)                       | 581       | 567±17       |
| X3-Bioadhesive polymer concentration (% , w/w): | 14.99      | k - Peppas metronidazole (h <sup>-n</sup> ) | 10.263    | 9.9833±0.38  |
|                                                 |            | n - Peppas metronidazole                    | 0.6398    | 0.6287±0.02  |
|                                                 |            | k - Peppas ibuprofen (h <sup>-n</sup> )     | 7.0398    | 6.9654±0.67  |
|                                                 |            | n - Peppas ibuprofen                        | 0.8658    | 0.8721±0.071 |

This optimized formulation was prepared and studied from the point of view of the rheologic, *in vitro* adhesive and drug release characteristics and the values obtained for these parameters (Table V) were very close to the estimated ones; this result confirmed the validity of the mathematical model chosen for the statistic optimization of the formulation. The optimized formulation showing convenient viscosity and *in vitro* adhesivity properties can be considered a good candidate for its use as an artificial clot forming agent following its application in the oral cavity and which is able

to isolate the postextraction socket from the septic buccal medium, in this way reducing the risk of infection in patients with osteonecrosis.

### Conclusions

Mucoadhesive buccal preparations with MZ and IB were obtained, these consisting of SMS oleogel and bioadhesive polymers (Carbopol 940 or HPMC K100M) starting from an experimental design.

The influence of the formulation factors on the rheologic, *in vitro* adhesive and drug release characteristics was analyzed. The *in vitro* adhesive capacity increased with the rise of the concentration of the bioadhesive polymers in the formulation, being not influenced in a particular manner by one of the two polymers used in the preparation. Analysis of the drug release kinetics revealed a good correlation with Peppas model. Examination of the contour plots led to the determination of the region where acceptable values of the response are obtained. The characterization of the optimized formulation led to the results very close to the predicted ones, that demonstrated the validity of the optimization model. Based on these results, the developed mucoadhesive formulation based on SMS oleogel and bioadhesive polymers may be tried as an artificial clot forming drug carrier for buccal application in patients presenting the risk for osteomyelitis on the background of osteonecrosis.

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