# EVALUATION OF GELATIN MICROSPHERES WITH XANTINOL NICOTINATE

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*Abstract.* The administration of pharmaceutical forms with normal release and short half-life is done 3–4 times/day. The formulation of some preparations with prolonged release is in this case a useful widely used alternative. One method of creating preparations with prolonged release consiste in microencapsulation of drug. We presented the results of a complex study upon some gelatin microspheres with xantinol nicotinate. The experimental data confirm that the particule size has an influence upon the inflation kinetics as well as active drug release rate.

*Keywords*: microencapsulation, xantinol nicotinate, kinetic release.

## INTRODUCTION

The microspheres were manufactured by emulsifing a xantinol nicotinate solution in sun flower oil. A fraction of our microspheres were subjected to reticulation in a saturated atmosphere of glutaraldehyde.

The objectives was:

- The intimate structure of gelatine microspheres research.
- Kinetics of the swelling.
- The influence of gelatine microsphere particles on the kinetics of xantinol nicotinate release.

## MATERIALS AND METHODS

- Unreticulated gelatine microspheres with xantinol nicotinate;
- Xantinol nicotinate gelatine microspheres reticulated for 24, 48 and 72h in a saturated atmosphere of glutaraldehyde;

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- Electronic microscope ( SEM );
- Zeiss optic microscope;
- In vitro release column type device.

## RESULTS AND DISCUSSION

### THE STUDY OF GELATINE MICROSPHERES WITH SEM

The SEM analysis represented a characterizing criterium for the gelatin microspheres because this technique provides threedimensional images of studied materials [3, 6]. The intimate structure of gelatine microspheres is presented in the Figure 1.

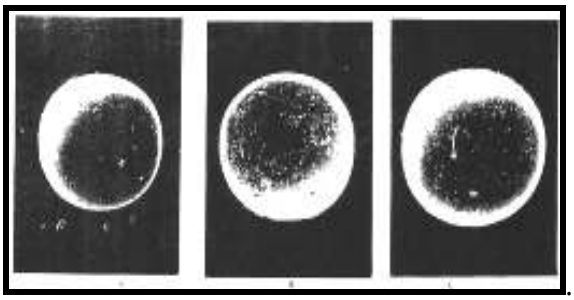

Fig. 1. – Xantinol nicotinate gelatin microspheres reticulated 24 (A), 48 (B) and 72 h (C) in a saturated atmosphere of glutaraldehyde.

### SWELLING KINETICS STUDY

Photographs were taken at differend swelling phases in order to understand the swelling process.

We used one drop of methylene blue in order to observe how the water front penetrates within the microspheres (Fig. 2).

The values of *n* parameter were calculated using Korsmeyer equation adapted for swelling process [2, 4, 7]:

$$\frac{D_t - D_0}{D_0} = kt^n \qquad (1)$$

where: $D_0$ = the size of the microsphere at time 0, $D_t$ = the size of the microsphere at time $t$, $k$ = the swelling rate, $n$ = the parameter of the transport type of water.

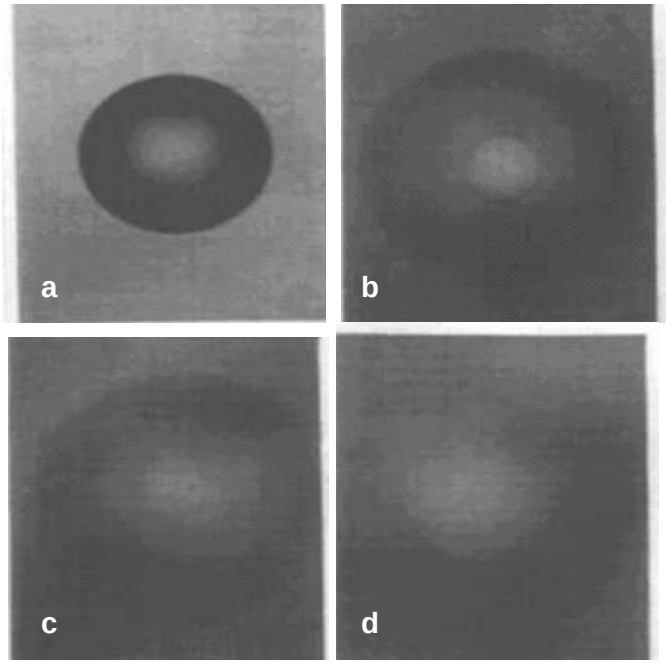


Fig. 2. – Penetration of the water front along the swelling process of the unreticulated gelatin microspheres with xantinol nicotinate ($D_0$ = 360 μm): a. initial, b. after 1 minute, c. after 2 minutes, d. after 5 minutes.

The swelling degree ($Q$) was calculated according to the ratios:

$$\frac{D_t}{D_0} = \frac{D_{10}}{D_0} = \frac{D_\infty}{D_0} = Q \qquad (2)$$

We analysed xantinol nicotinate gelatine microspheres reticulated for 72 h in a saturated atmosphere of glutaraldehyde (Table 1).

*Table 1*

The values of swelling kinetic parameters.

| $D_0$ (μm) | $D_{10} = D_\infty$ (μm) | $n$ | $k \cdot 10^2$ ($min^{-n}$) | $Q$ |
|---|---|---|---|---|
| 210 | 273.04 | 0.56 | 4.5 | 1.300 |
| 260 | 330.12 | 0.65 | 6 | 1.270 |
| 310 | 385.94 | 0.73 | 7.5 | 1.245 |

Figure 3 indicates the influence of size particles on swelling process kinetics.

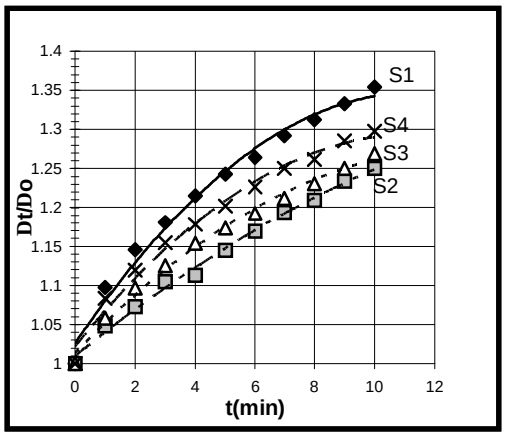


Fig. 3. – The influence of size gelatin microspheres with xantinol nicotinate on the swelling process kinetics ($S_1$:$D_0$ = 210 μm, $S_2$:$D_0$ = 260 μm, $S_3$:$D_0$ = 310 μm, $S_4$:$D_0$ = 430 μm).

## THE STUDY OF XANTINOL NICOTINATE KINETICS RELEASE FROM GELATINE MICROSPHERES

These studies were accomplished with a in vitro release column type device (distilled water as release medium, temperature 37 ± 0,1 °C, flow rate 2 ml/min.)

The experimental data were analysed through several mathematical models (0 order, 1st order, Higuchi, Korsmeyer). The release profiles are presented in Figure 4 and the values for the delivery kinetic parameters in Tables 2, 3.

The active substance release (Fig. 5b) from the designed microspheres takes place in the initial swelling phase as well as after the swelling process ended (Fig. 5a). The xantinol nicotinate release is rate determinant.

Because the gelatin microspheres were of spheric shape, we appreciated that the drug release follows a spherical simetry diffusion model (Fig. 5).

In this case, for the kinetic description of the release process from the designed microspheres, it proves necessary to evaluate the apparent diffusion coefficients ($D$) of xantinol nicotinate towards the environment. These coefficients were calculated using the following equation:

$$m_t = m_0\left[1-\frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{2}\exp\left(-\frac{n^2\pi^2 Dt}{r_0^2}\right)\right] \tag{3}$$

where: $m_0$ = the amount of xantinol nicotinate from the microspheres at time 0;
$m_t$ = the amount of xantinol nicotinate from the microspheres at time $t$;
$r$ = the radius of the microsphere [1, 5].

*Table 2*

The values for the delivery kinetic parameters ($D_0 \in$ 400–500 μm).

| Type of microspheres | The release rate | | | | $D \cdot 10^6$ ($cm^2 \cdot min^{-1}$) |
|---|---|---|---|---|---|
| | 0 order ($g \cdot min^{-1}$) | 1st order ($min^{-1}$) | Higuchi ($g \cdot min^{-1/2}$) | Korsmeyer | |
| Unreticulated gelatin microspheres with XN | 0.000287 | 0.0281 | 0.00268 | 0.03856 | 7.803 |
| Xantinol nicotinate gelatin microspheres reticulated 24 h | 0.000203 | 0.0215 | 0.00183 | 0.01962 | 1.700 |
| Xantinol nicotinate gelatin microspheres reticulated 48 h | 0.000104 | 0.0126 | 0.00089 | 0.0076 | 1.020 |
| Xantinol nicotinate gelatin microspheres reticulated 72 h | 0.000061 | 0.0092 | 0.00053 | 0.00526 | 0.821 |

*Table 3*

The values for the delivery kinetic parameters ($D_0 \in$ 500–630 μm).

| Type of microspheres | The release rate | | | | $D \cdot 10^6$ ($cm^2 \cdot min^{-1}$) |
|---|---|---|---|---|---|
| | 0 order ($g \cdot min^{-1}$) | 1st order ($min^{-1}$) | Higuchi ($g \cdot min^{-1/2}$) | Korsmeyer | |
| Unreticulated gelatin microspheres with XN | 0.000185 | 0.0117 | 0.00172 | 0.01947 | 6.332 |
| Xantinol nicotinate gelatin microspheres reticulated 24 h | 0.000132 | 0.0142 | 0.00122 | 0.01064 | 1.113 |
| Xantinol nicotinate gelatin microspheres reticulated 48 h | 0.000065 | 0.0113 | 0.00056 | 0.0066 | 0.922 |
| Xantinol nicotinate gelatin microspheres reticulated 72 h | 0.000044 | 0.0082 | 0.00038 | 0.00525 | 0.659 |

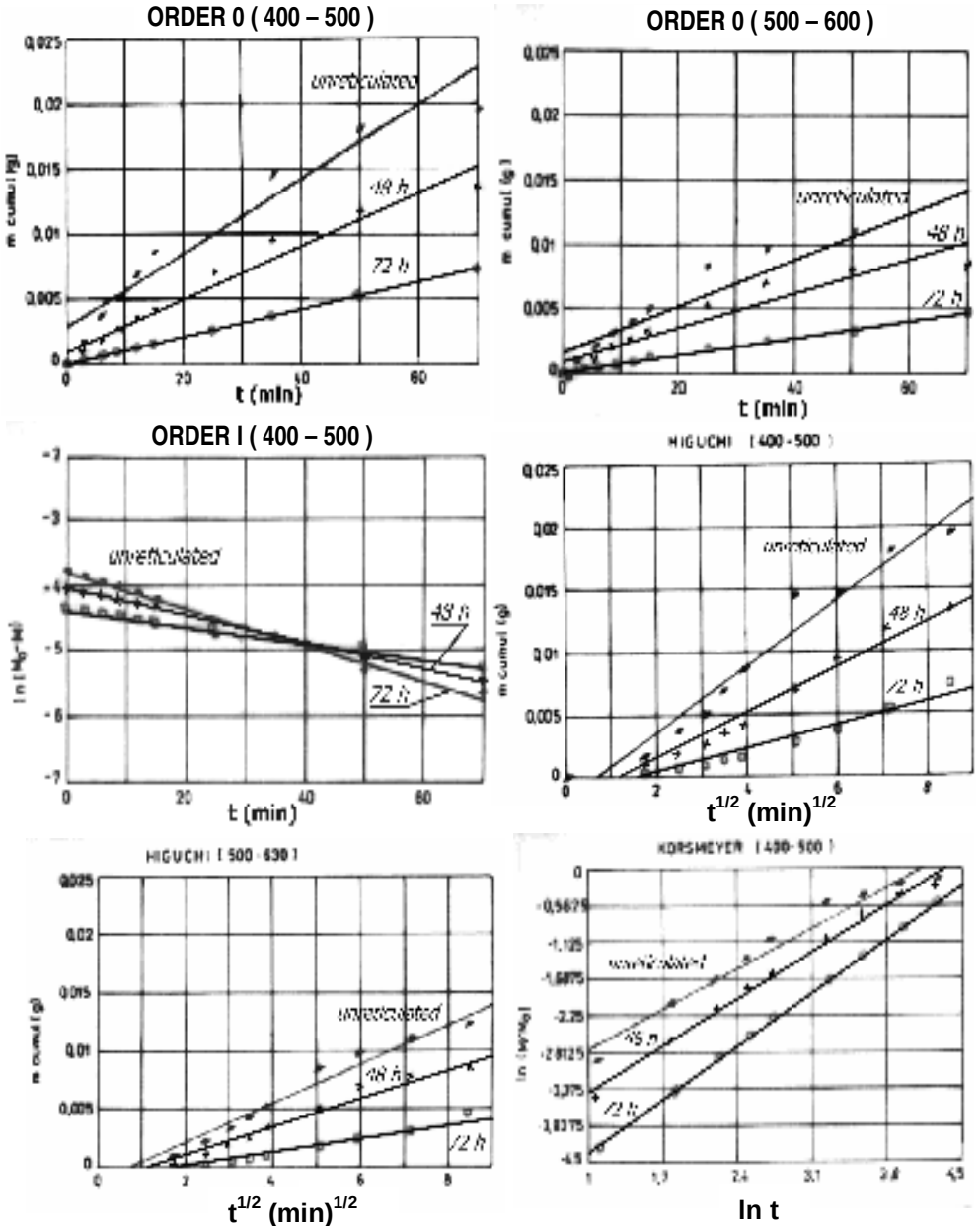


Fig. 4. – Release kinetic profiles of xantinol nicotinate from gelatin microspheres with diameters between 400–500 μm and 500–630 μm (unreticulated gelatin microspheres, xantinol nicotinate gelatin microspheres reticulated 48 h or 72 h in a saturated atmosphere of glutaraldehyde).

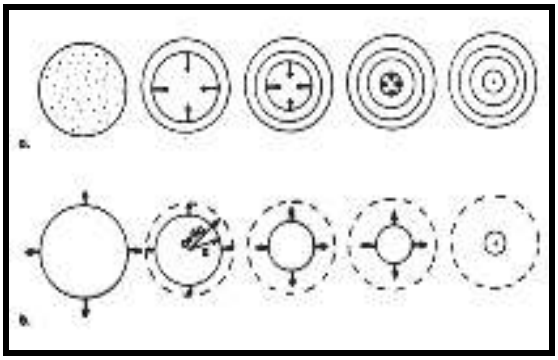

Fig. 5. – The release mechanism of xantinol nicotinate from gelatin microspheres.

The apparent diffusion coefficients values are listed in Tables 2, 3.

## CONCLUSION

1. By SEM we determined a spherical shape with smooth surface for all designed microspheres (Fig. 1).

2. The experimental data confirmed that the particle size influences the swelling kinetics as well as active principle release rate. The particle size influences the transport type of water within the microspheres. At smaller particule size the transport mechanism matches Fick's model. At higer size the mechanism becomes abnormal (Table 1).

3. The process of xantinol nicotinate release is rate determinant. An increase in the microspheres size was correlated with a decrease of both the swelling and the drug release rates (Tables 2, 3).

4. We proposed a diffusional model for the delivery of xantinol nicotinate from unreticulated and for differently reticulated gelatin microspheres (Fig. 5).

5. We evaluated the apparent diffusion coefficient of xantinol nicotinate throughout the swelled gelatin matrix. These coefficients are lower for the microspheres with higher diameters.

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