STUDIES OF PENTOXIFYLLINE MICROSPHERES

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Abstract. For this aim, the microencapsulation of the drug (pentoxifylline) was used for creating the preparations with extended release because the drug has short half life (cca 1 h) and frequent administration a day. The microspheres are prepared by emulsification of a gelatin solution in an oil phase. The cross-linking is the glutaraldehyde. In this study, the gelatin microspheres are characterized physicochemically (particle size, particle density, crystalline form of drug, drug content, release kinetics). The release profiles from the studied formulations were evaluated by dissolution models in order to establish the release mechanism and kinetics.

Key words: gelatin, microspheres, pentoxifylline, dissolution testing.

INTRODUCTION

Microencapsulation was used to modify and retard drug release. In pharmaceutical sustained release preparations, the microcapsules offer the advantage that can be widely distributed throughout the gastrointestinal tract. This potential improves drug absorption and reduces side effects related to localized buildup of irritating drugs against the gastrointestinal mucosa [1].

Many techniques for the preparation of microcapsules have been developed and the techniques have been comprehensively reviewed.

Many different materials and microencapsulation processes can be used. The emulsifying drug solution in a mineral oil technique has been described in the literature [1, 4, 9].

The microspheres were prepared developing the method proposed by Tanaka *et al*. [1]. The gelatin microspheres were manufactured by emulsifying a pentoxifylline solution in sunflower oil. A fraction of our microspheres was subjected to reticulation in a saturated atmosphere of glutaraldehyde (48 and 72 h), and in an acetonic solution of glutaraldehyde (35%) for 2 h.

The purpose of this study was:

- Characterization of the experimental gelatin microspheres.
- Fit data to various postulated drug release models.

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- To study the effect of reticulated degrees to drug ratio on the *in vitro* dissolution.

MATERIALS AND METHODS

MATERIALS

- Unreticulated gelatine microspheres with pentoxifylline.
- Pentoxifylline gelatine microspheres reticulated for 48 and 72h in a saturated atmosphere of glutaraldehyde and in an acetonic solution of glutaraldehyde (35%) for 2 h.
- Pycnometer.
- Spectrophotometer Lambda 2, Perkin-Elmer.
- X-ray.
- *In vitro* release column type device.

METHODS

Density determination

The density of the designed microspheres was determined using the pycnometric method:

$$\rho = \frac{(b-a)\rho_1}{(d-a)-(c-b)} \quad (1)$$

where ρ is the density of the microspheres, a is the weight of the pycnometer empty, b is the weight of the pycnometer with the microspheres, c is the weight of the pycnometer with designed microspheres and the solvent and d is the weight of the pycnometer with the solvent (acetone, $\rho^{20}_{acetone} = 0.79$ g/cm^3) [7].

Determination of size from designed gelatin microspheres

The determination of diameter was measured by a special calibrated system VEB Metallwebereii Neustadt Orla.

X-ray diffractometry

The X-ray diffraction patterns were recorded using an X-ray diffractometer TUR M-61. The experimental parameters of the procedure were set as follows: Ni filter, $K\alpha_1$ radiation, tube settings 30 kV, 20 mA, angular speed 1° (2θ) per minute.

Drug content

The drug content of the designed microspheres was determined spectrophotometrically (λ = 274 nm) after drug extraction in distilled water at 37 °C and stirring at 200 r.p.m. (2h).

In vitro dissolution

To determine the release of pentoxifylline from designed microspheres we used *in vitro* column type device.

Dissolution medium used is distilled water at 37±0.1 °C, flow rate 2 ml/min. Samples were taken at appropriate intervals up to 3 hours. The sample was analyzed by measuring the UV absorbance at 274 nm. Drug concentration in each sample solution was calculated from a standard curve. The *in vitro* dissolution of pentoxifylline from the designed microspheres was reported as the average of six determinations.

The best fit of the release-data was initially tested with the mathematical models [3–5, 7–9] as follows:

- Zero-order kinetics

$$w = w_0 - k_0 t \tag{2}$$

- First-order kinetics

$$\ln w = \ln w_0 - k_1 t \tag{3}$$

- Square-root of time (Higuchi model)

$$w = k\sqrt{t} \tag{4}$$

- Korsmeyer empiric model

$$\ln \frac{w}{w_0} = n \ln t + \ln k \tag{5}$$

where w_0 is the amount of xantinol nicotinate from the microspheres at time 0 and w = the amount of xantinol nicotinate from the microspheres at time t.

RESULTS AND DISCUSSION

DENSITY DETERMINATION

In Table 1 the experimental data such as the density are presented.

Table 1

Density of the gelatin microspheres with pentoxifylline (P)

Type of microspheres	ρ (g/cm^3)
Unreticulated gelatin microspheres with P.	0.826
P. gelatin microspheres reticulated 48 h	0.858
P. gelatin microspheres reticulated 72 h	0.947
P. gelatin microspheres reticulated 2 h in an acetonic solution of glutaraldehyde (35%)	0.942

DETERMINATION OF SIZE FROM DESIGNED GELATIN MICROSPHERES

Due to choosing the right technological parameters, we obtained the most of microspheres within the size domain of 400 – 630 μm (Fig. 1).

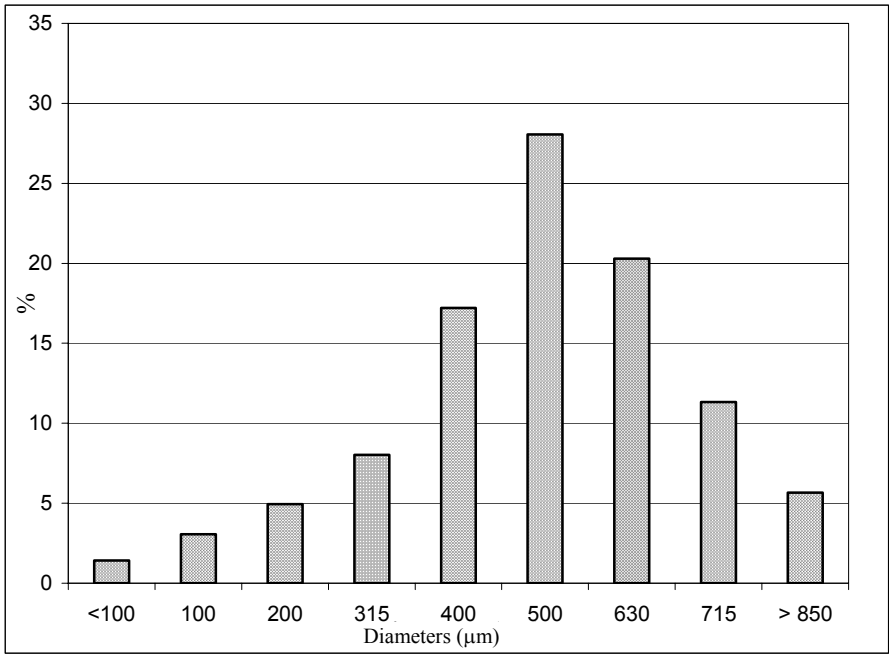

Fig. 1. – Values of the diameters of gelatin microspheres with pentoxifylline (each data point averaged at least four determinations).

X-RAY DIFFRACTOMETRY

No drug peaks were shown in the X-ray diffraction patterns of the gelatin microspheres (Fig. 2). The drug is dispersed in the gelatin network in the amorphous state.

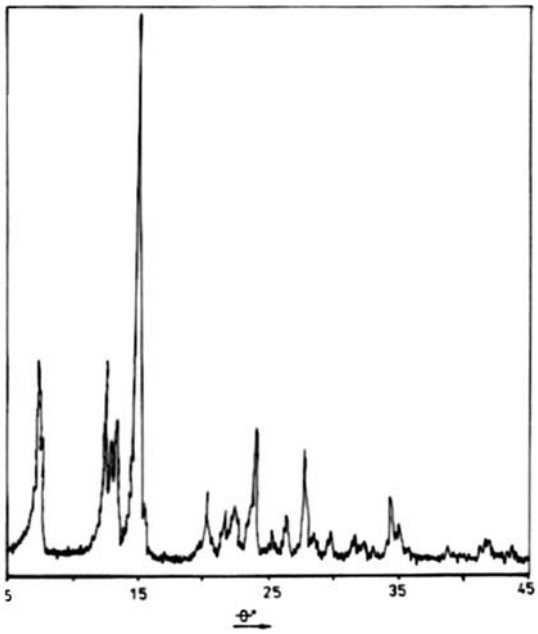

Fig. 2. – X-ray diffraction patterns for pentoxifylline.

DRUG CONTENT

The total drug content of gelatin microspheres is given in Table 2.

Table 2

Drug content (g/g of microspheres)

Type of microspheres	w_P
Unreticulated gelatin microspheres with P.	0.206
P. gelatin microspheres reticulated 48 h	0.209
P. gelatin microspheres reticulated 72 h	0.209
P. gelatin microspheres reticulated 2 h in an acetonic solution of glutaraldehyde (35%)	0.154

*each data point averaged at least six determinations

The effect of the type of reticulation was evaluated. The reticulation in a saturated atmosphere with glutaraldehyde does not affect the drug loading. The reticulation in an acetonic solution of glutaraldehyde (35%) produced a decrease of drug loading, swelling degree and drug release rate.

Also, during the reticulation process, the initial spherical shape of the microspheres in the solution makes their characterization more difficult (Fig. 3).

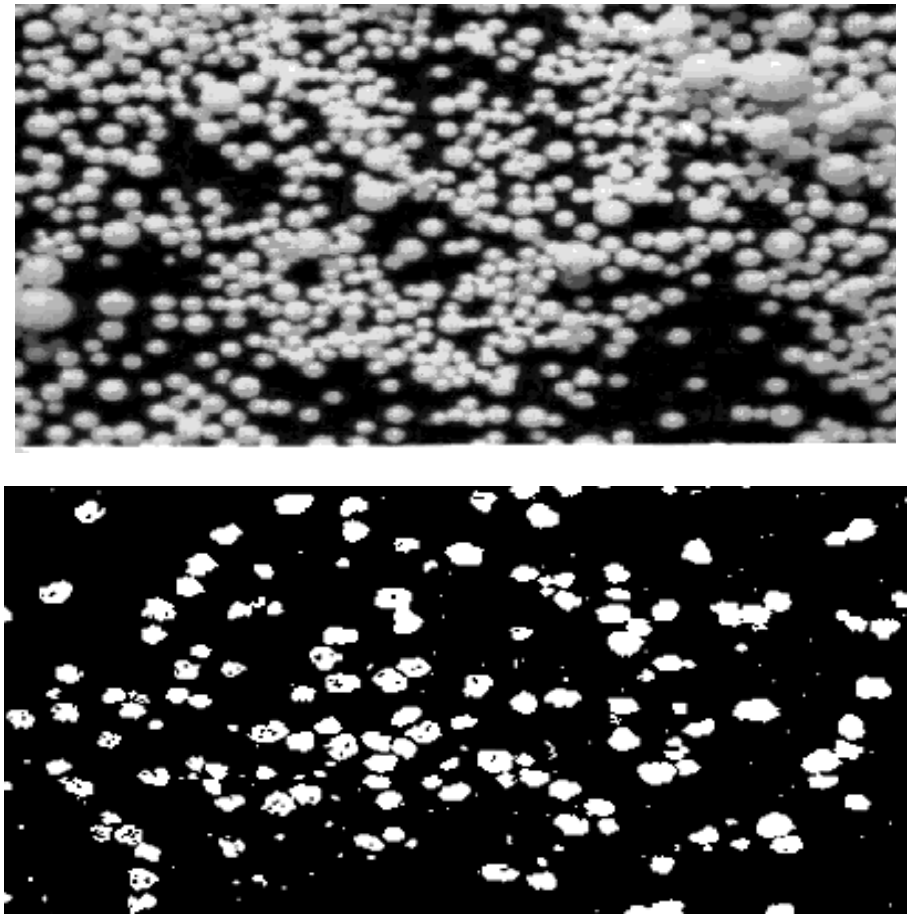

Fig. 3. – Pentoxifylline gelatin microspheres reticulated in a saturated atmosphere with glutaraldehyde (up) and in an acetonic solution of glutaraldehyde (35%) (down).

IN VITRO **DISSOLUTION**

The active substance release from the designed microspheres takes place in the initial swelling phase as well as after the swelling process ended. The pentoxifylline release is rate determinant.

The values for the released kinetic parameters are presented in Table 3.

Because the gelatin microspheres were of spherical shape, we appreciated that the drug release follows a spherical symmetry diffusion model [6].

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 pentoxifylline towards the environment.

These coefficients were calculated using the following equation:

$$w = w_0 \left[1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{2} \exp\left(- \frac{n^2 \pi^2 D t}{r_0^2} \right) \right] \quad (6)$$

where r is the radius of the microsphere [2].

The apparent diffusion coefficient values are listed in Table 3.

Table 3

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

Type of microspheres	The release rate				$D \cdot 10^6$ ($cm^2 \cdot min^{-1}$)	*DE* (%)
	0 order ($g.min^{-1}$)	1st order (min^{-1})	Higuchi ($g.min^{-1/2}$)	Korsmeyer		
Unreticulated gelatin microspheres with pentoxifylline	0.000253	0.0305	0.00214	0.0760 n = 0.6592	3.058	61.9
Pentoxifylline gelatin microspheres reticulated 48 h	0.000178	0.0181	0.00152	0.0284 n = 0.7946	1.533	39.4
Pentoxifylline gelatin microspheres reticulated 72 h	0.000110	0.0119	0.00094	0.0169 n = 0.8415	0.869	31.3
Pentoxifylline gelatin microspheres reticulated 2 h in an acetonic solution of glutaraldehyde (35%)	0.000093	0.0106	0.00085	0.0072 n = 1.0037	0.772	24.2

DE = dissolution efficiency.

CONCLUSIONS

1. An increase in the microspheres density was correlated with an increase of reticulation degree.

2. The reticulation in an acetonic solution of glutaraldehyde (35%) influences the spherical shape, the drug loading, the swelling and the release process.

The reticulation in a saturated atmosphere with glutaraldehyde does not affect these parameters. The gelatin microspheres with pentoxifylline reticulated 48 and 72 h in saturated atmosphere with glutaraldehyde keeps the spherical shape and the drug loading, which represents an advantage for this method of reticulation.

3. The pentoxifylline was dispersed in the gelatin network in the amorphous state.

4. The drug release from the gelatin microspheres takes place in the initial swelling phase as well as after the swelling process ended. Because the gelatin microspheres have a spherical shape, we appreciated that the drug release follows a spherical symmetry diffusion model.

5. The process of pentoxifylline release is rate determinant. The values of the kinetic parameters decrease as the reticulation degree increases.

6. We evaluated the apparent diffusion coefficient of pentoxifylline throughout the swollen gelatin matrix. These coefficients are decreasing with an increase of reticulation.

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