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Zinc sulphate release and morphology of matrices prepared for the individual therapy of Wilson's disease

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Authors dedicate this study to Professor István Rácz on the occasion of his 70th birthday.

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Hydrophobic zinc sulphate wax matrices with different drug loadings were prepared for the individual hospital therapy of Wilson's disease. The drug release parameters, scanning electron microscopy (SEM) and energy dispersive X-ray spectroscopy (EDS) of the samples were analysed. The release mechanisms from matrices of 75% and 80%w/w zinc sulphate loadings were described with good correlation by the semi-empirical Fikkian diffusion based release model. Besides the zinc sulphate diffusion through the pores of the wax matrices, the parallel diffusion of zinc sulphate from the matrix surface is dominant in the case of samples of 83% and 90%w/w drug loadings. The combination of SEM and EDS analysis visualizes the morphology of the matrices and the related composition thus explaining the differences in the release characteristics.

Wilson's disease is a genetic disorder of copper transport resulting in the accumulation of copper in organs such as the liver and the brain, which leads to progressive hepatic and neurological damage (Sarkar 2000). Zinc application is now the recommended therapy for long-term management of this disease (Brewer 2000). Zinc has shown clinical efficacy at doses of 50 mg three times daily in the stimulation of metallothionein synthesis and reduction of copper absorption. The mean plasma elimination half-lives of most highly water soluble drugs, like zinc sulphate, are relatively short (2–4.5 h), which necessitates several applications a day (Khan 1995). Long-acting sustained and controlled release preparations make a once-a-day dose treatment possible. Waxy-type excipients were successfully applied as release-controlling agents (Dredan et al. 1998). The aim of the present study was to formulate zinc sulphate sustained release matrices for the individual treatment of Wilson's disease and to evaluate the release characteristics and the related morphology.

Along with the increase of the proportion of the wax matrix base in the samples, the rates of drug release decreased. The nonlinear parameter estimation of the release model applied for matrices, described by eq. (1), was made with the Solver function of the computer package Microsoft Excel 5.0. The Table summarises the values of K, n and MDT obtained for the drug release profiles from each zinc sulphate matrix. As it was expected, along with the increase of the matrix base of samples, the MDT values were also increased. The $n < 0.5$ values refer to the combined mechanism of drug release, thus parallel diffusion occurs through the hydrophobic pores and from the surface of the matrices. Preceding the release of the zinc sulphate through the pores of the matrices, the zinc sulphate from the matrix surface can be dissolved into the dissolution medium. The zinc sulphate dissolution from the matrix surface is more dominant in the case of samples of 83% and 90% drug loadings. The low correlation coefficients ($r^2_{83.3\%} = 0.8678$; $r^2_{90\%} = 0.8552$) between the measured release data and those calculated by eq. (1) can be explained by the diffusion mechanism of the salt from the wax surface. In the case of 66% drug loading, the higher amount of matrix base decreased the total porosity of the matrix, thus less than 30% of the embedded salt

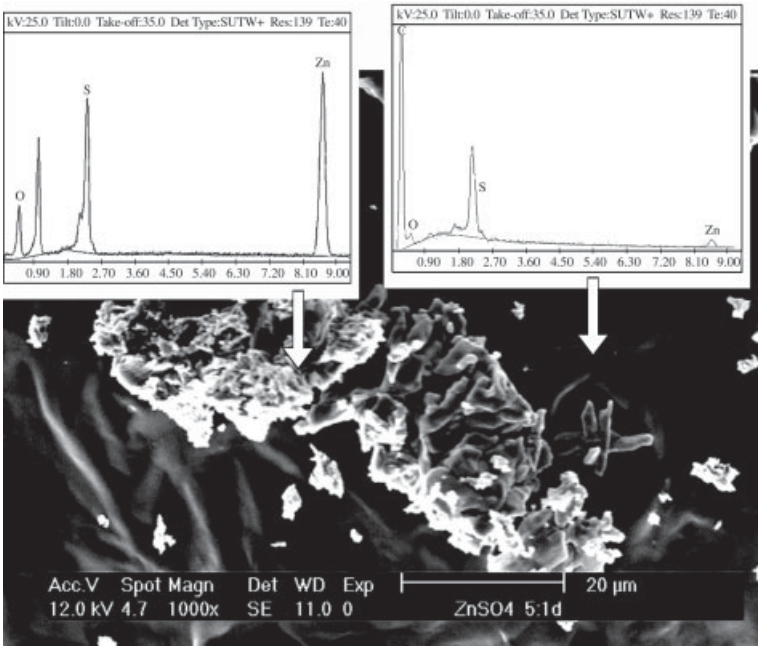

Fig.:
(a) Scanning electron microscopic photo (magnification: 1000x) and (b) EDX spectra of the matrix surface of 83.3%w/w zinc sulphate loading

Table: Analysis of release data (eq. 2) from zinc sulphate matrices of different drug loadings

Drug loading (%w/w)	$K \times 100\ h^n$	n	MDT (h)	Correlation coefficient
66.7	4.81 (±0.21)	0.45 (±0.02)	4.27 (±0.31)	0.9777
75.0	4.40 (±0.17)	0.48 (±0.02)	3.44 (±0.16)	0.9972
80.0	4.23 (±0.12)	0.50 (±0.02)	3.22 (±0.15)	0.9933
83.3	18.03 (±0.68)	0.29 (±0.01)	1.45 (±0.09)	0.8678
90.0	37.69 (±0.95)	0.17 (±0.01)	0.74 (±0.05)	0.8552

could be released after 12 h. The zinc sulphate release from matrices of 75% and 80% drug loadings can be described with good correlation ($r^2_{75\%} = 0.9972$; $r^2_{80\%} = 0.9933$) by the semi-empirical model commonly applied for matrices (eq.1). To interpret the difference in drug release characteristics, the morphology and the related composition of various matrices were carried out. The SEM photo (Fig. a) demonstrates the surfaces of matrices of 83% drug loading containing zinc sulphate without being embedded into the wax matrix base. The morphology of the matrices of 90% drug loading was very similar. The results of energy-dispersive X-ray spectroscopy confirmed the co-location of zinc sulphate at the matrix surface, the absence of C of the EDX spectra (Fig. b) refers to the lack of organic matrix base around the zinc sulphate crystals. The diffusion-controlled matrix release is most close to the samples of 75% and 80% zinc sulphate loadings.

Experimental

Zinc sulphate of Ph.Eur. 4 ($M_w = 287.5$) was used. The chosen matrix base material was white beeswax (melting range of 62–65 °C, Ph.Eur.4). To prevent the sedimentation of the zinc sulphate, 5%w/w glycerol monostearate 40–55 (Ph.Eur. 4) was added to the matrix base. The thermosoftening matrix material in all cases was heated in a double jacketed vessel mixer (Erweka SG 3/W, Erweka, Germany) to 70 ± 1 °C. The zinc sulphate crystals were mixed into the molten mass to obtain the following drug loadings: 67%, 75%, 80%, 83%, 90%w/w. The molten mass was filled into hard gelatine capsules before congealing to form a skeletal sustained release dosage form. For the determination of dissolution profiles of the samples, the paddle method of USP23 at 100 rpm was used (Erweka DT 6RE, Germany). The study was conducted in 200 ml of pH = 6.8 phosphate buffer solution at 37 °C. Sampling times were the following: 5, 10, 20, 30, 60, 120, 240, 480, 720 min. The dissolved zinc sulphate concentrations were measured by complexometric titration according to the Ph. Eur. Monograph. Dissolution data were analysed using the equation proposed by Ritger and Peppas (1987) to describe the mechanism of drug release from matrices.

$$M_t/M_\infty = Kt^n \quad (1)$$

where M_t corresponds to the amount of drug released in time t, M_∞ is the total amount of drug that must be released at infinite time, K is the release rate constant and n is the release exponent indicating the type of drug release mechanism. The model-independent mean dissolution time (MDT) was calculated as follows (Rao et al. 2003):

$$MDT = n/[(n+1)\,(K^{(1/n)})] \quad (2)$$

The surface characteristics of matrices were examined by means of a scanning electron microscope (Philips XL 30, The Netherlands). The specimens were mounted to aluminium stubs with double adhesive tape. To reduce the charging, the specimens were vacuum coated with gold. Examination was carried out at 12 kV and 25 kV accelerating voltage and 100–1000 times magnifications were used. Magnifications of scanning electron microscopic images are measured by the micrometer-line on the pictures; the accuracy of these magnifications was ±2%. Samples for the energy-dispersive spectroscopic (EDAX) investigations were in their original (not cleaned) form. Accuracy of EDS-investigations – in the lack of pure element standards – is assumed to be ±2% in the concentration range of 10–20%, while it is assumed to be ±0.3% in the range below 1%. Sensitivity of EDS-measurements is about 0.2–0.3%. Chemical analysis results are therefore qualitative ones.

References

Sarkar B (2000) Copper transport and its defect in Wilson's disease: characterisation of the copper-binding domain of Wilson's disease ATPase. J Inorg Biochem 79: 187–191.

Brewer GJ (2000) Recognition, diagnosis, and management of Wilson's disease. Proc Soc Exp Biol Med 223: 39–46.

Khan MZI (1995) Trends in oral delivery of drugs. Drug Dev Ind Pharm 21: 1037–1070.

Dredán J, Zelkó R, Antal I, Bihari E, Rácz I (1998) Effect of chemical properties on drug release from hydrophobic matrices. Int J Pharm 160: 257–260.

Ritger PL, Peppas NA (1987) Simple equation for description of solute release: part I, Fickian and non Fickian release from nonswellable devices in the form of slab, spheres, cylinders or disk. J. Controlled Rel 5: 23–36.

Rao VM, Engh K, Qiu Y (2003) Design of pH-independent controlled release matrix tablets for acidic drugs. Int J Pharm 252: 81–86.