ELSEVIER

International Journal of Pharmaceutics 196 (2000) 207–210

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Solubilization of timolol maleate in reversed micellar systems
Measurement of particle size using SAXS and PCS

Stefan Mackeben, Christel C. Müller-Goymann *

Institute of Pharmaceutical Technology, Technical University of Braunschweig, Mendelssohnstr. 1, D-38106 Braunschweig, Germany

Abstract

Small angle X-ray scattering (SAXS) and photon correlation spectroscopy (PCS) are two methods to measure particle sizes in the order of 10 nm magnitude, which can be used to characterize reversed micellar systems, in this case reverse micelles consisting of lecithin and isopropyl myristate (IPM). In this study these micelles are loaded with different concentrations of the amphiphilic anti-glaucoma drug timolol maleate (TM). The PCS results are consistent with those yielded by SAXS, showing a decrease of particle size with higher TM concentration. In addition, SAXS is capable to give information about the particle shape. This kind of evaluation yields an ellipsoidal shape for micelles with low drug loads, which transform into nearly spherical micelles at higher drug concentrations. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: SAXS; PCS; Reverse micelles; Timolol (maleate)

1. Introduction

Reversed micellar systems (RMS) consisting of 30% lecithin in isopropyl myristate (IPM) transform into liquid crystals on the addition of water (Hamann, 1990).

It was shown on examples that in the case of a solubilized drug this transformation provides sustained drug release (Hamann, 1990; Papantoniou, 1995).

To develop an appropriate drug formulation using this transformation effect it is necessary to consider the physicochemical properties of the RMS. These properties such as viscosity, the lattice constant of the liquid crystal and the diffusion of the drug from the liquid crystal correlate closely with the interactions between the drug and the reverse micelles. Information about these interactions is gained by measuring the micellar sizes and shapes in dependence of the drug concentrations.

In this study differences in particle size of reverse micelles containing the anti-glaucoma drug timolol maleate (TM) in varying concentrations are characterized by small angle X-ray scattering

* Corresponding author. Tel. +49-531-391-5650; fax: +49-531-391-8108.

E-mail address: c.mueller-goymann@tu-bs.de (C.C. Müller-Goymann)

PII: S0378-5173(99)00423-8

(SAXS) and photon correlation spectroscopy (PCS).

2. Materials and methods

2.1. Materials

The lecithin used is Phospholipon 90 G® (Rhône-Poulenc Rorer, D-Köln), which contains at least 90% phosphatidylcholine. Isopropyl myristate was obtained from Henkel KG, D-Düsseldorf. Dr Winzer Pharma GmbH, D-Olching, kindly provided timolol maleate.

2.2. Preparation of the reversed micellar systems

To prepare a reversed micellar stock solution, 30% lecithin is dissolved in 70% IPM at a temperature of 60°C while being stirred (Papantoniou, 1995).

As TM is insoluble in IPM, the drug needs to be dissolved 1:16 in water before being added to the RMS. By this way the drug is inserted in the resulting liquid crystal. The water is removed at a temperature of 60°C under continuous stirring for circa 36 h. After this time, a clear yellowish solution without visible particles is obtained.

The declared percentages of drug concentrations further in the text refer to the 30% stock solution.

2.3. PCS

The PCS measurements are taken with a Zeta-Sizer 3 (Malvern, D-Herrenberg) equipped with a 35 mW He/Ne-Laser (Spectra Physics, Mt.View, CA). Due to the large viscosity of the stock solution, the systems are diluted 1:6 with IPM, resulting in RMS solutions which contain 5% lecithin. The scattering light is collected at an angle of 90°. For each sample the PCS measurements are repeated 3–5 times for at least 300 s each. PCS is based on the measurement of intensity changes in the scattering pattern, which are results of the diffusion of particles in the solution. Hence the gained values are the hydrodynamic diameters of the micelles.

2.4. SAXS

The SAXS measurements are carried out with a Kratky compact camera (Anton Paar, A-Graz) with a block-collimation system (Kratky and Stabinger, 1984). The scattering data are collected by a PSD-50M position sensitive detector (MBraun, D-München) and evaluated with the programs PDH and ITP-92, developed by O. Glatter (Glatter, 1977; Glatter and Kratky, 1982).

The primary scattering curve consists of the interference patterns from the scattering light of electron pairs. Therefore only those parts of the micelle can be recognized which differ from the solvent in electron density, in the samples of this study this is the hydrophilic micellar core.

There are two methods possible to obtain the micellar size, the Guinier approximation and the electron distance distribution, the latter provides information about the particle shape in addition.

- The Guinier approximation is based on the fact that the scattering curve shows Gaussian shape at small angles, of which the slope depends on the radius of gyration (Glatter and Kratky, 1982). Assuming a spherical symmetry, it is possible to calculate the micellar diameter (Fig. 3).
- The electron distance distribution $p(r)$ is obtained from the sample electron density by a Fourier transformation (Glatter, 1977). $p(r)$ describes the number of electron pairs with distance r, which means that the maximum extension of the micellar core is found at the first point of intersection with the abscissa (Fig. 2).

To avoid interparticular interferences, the primary 30% samples are diluted 1:15 to gain 2% RMS, where no concentration effects are discernible (Müller and Glatter, 1982).

3. Results and discussion

Although SAXS data give just information about the core of the micelles, the results yielded by Guinier approximation are consistent with the PCS data (Figs. 1 and 3), i.e. a low drug load increases the micelle diameter whereas with higher drug loads the micelles become smaller.

With higher drug concentrations the maximum extension of the micelles approaches the micelle diameter from the Guinier approximation (Fig. 3, Table 1), becoming equal in the range of standard deviations at a load of 4% TM. This indicates that the micelles have an ellipsoidal shape at zero or low drug concentration and become more spherical at higher drug loads. In addition this statement is substantiated by the *p(r)*-curves (Figs. 2 and 3) (Glatter, 1977), which show a transition from a Gaussian (4% TM) to an asymmetric form at lower drug loads that indicates an ellipsoidal shape.

Finally the measurements show that SAXS enables to recognize very small shape and size differences in the order of Ångström magnitude.

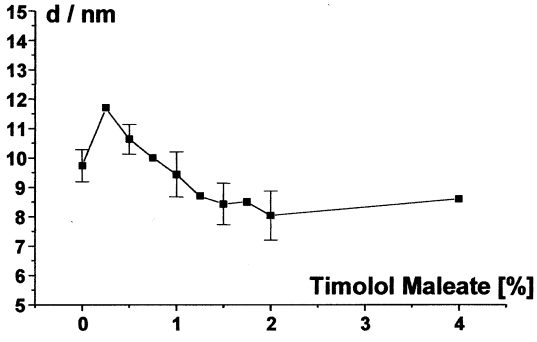

Fig. 1. Hydrodynamic diameter measured by PCS. Data without standard deviation are measured just once.

Table 1
Diameter calculated by the radius of gyration (Guinier) and maximum micellar core extension in dependence of the drug concentration

TM (%)	d_{gyr} [Å]	d_{max} [Å]
0.0	40 ± 1	62 ± 2
0.25	41 ± 1	61 ± 2
0.5	41 ± 1	59 ± 2
1.0	40 ± 1	58 ± 2
1.5	39 ± 1	53 ± 2
2.0	39 ± 1	46 ± 2
4.0	37 ± 1	37 ± 2

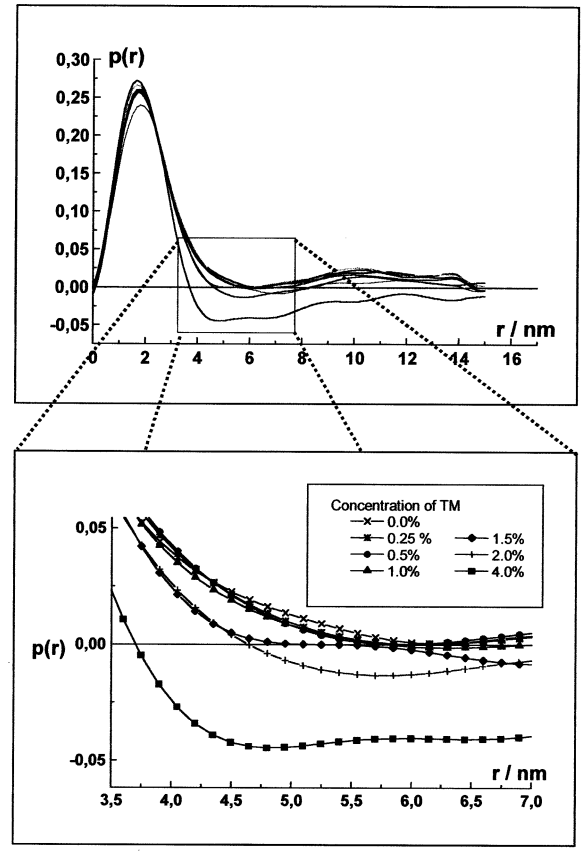

Fig. 2. Electron distance distribution $p(r)$ for RMS with different drug loads (upper). Abscissa intersections of $p(r)$ which show the extension of the micellar core (lower).

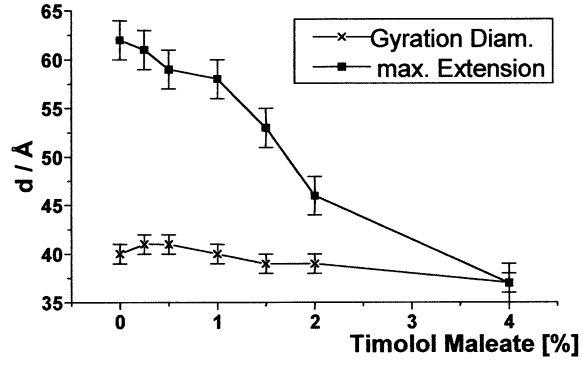

Fig. 3. Diameter calculated from the radius of gyration in comparison to the maximum micelle extension.

Acknowledgements

The authors wish to thank Dr Winzer Pharma GmbH for the donation of timolol maleate.

References

Glatter, O., 1977. A new method for the evaluation of small angle scattering data. J. Appl. Cryst. 10, 415–421.

Glatter, O., Kratky, O., 1982. Small angle X-ray scattering. Academic Press, London.

Hamann, H.-J., 1990. Wechselwirkungen mesogener Arzneistoffe mit kolloidalen Lecithinassoziaten am Beispiel des Fenoprofens. PhD Thesis, TU Braunschweig, Germany.

Kratky, O., Stabinger, H, 1984. X-ray small angle camera with block-collimation system an instrument of colloid research. Coll. Poly. Sci. 262, 345–360.

Müller, K., Glatter, O., 1982. Practical Aspects to the use of indirect Fourier transformation methods. Makromol. Chem. 183, 465–479.

Papantoniou, I., 1995. Invers mizellare Lösungen mit modifizierter Wirkstofffreisetzung durch applikationsinduzierte Transformation in lyotrope Mesophasen. PhD Thesis, TU Braunschweig, Germany.