International Journal of Pharmaceutics, 53 (1989) 139–143
Elsevier

IJP 01796

The characterisation by small-angle X-ray scattering of a pharmaceutical gel with a lamellar structure

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(Received 7 November 1989)
(Modified version received 30 December 1988)
(Accepted 12 January 1989)

Key words: Gel; Lamellar structure; Small angle X-ray scattering

Summary

A pharmaceutical gel containing 0.5% w/w cetrimide, 10% w/w cetostearyl alcohol and water has been analysed using small-angle X-ray scattering (SAXS). The scattering curve is in direct agreement with the perceived structure of the system i.e. a series of cetostearyl alcohol bilayers separated by water indicating a water layer thickness of the order of 34 nm. Using a one-dimensionally ordered lamellar stack lattice model the distribution of the water layer thickness has been estimated to be of the order of ±1 nm.

Introduction

Pharmaceutical creams and gels, although belonging to the oldest of the currently used dosage forms, have a complicated microstructure an understanding of which is essential in the optimisation of their formulation and stability. Many are prepared using a surfactant and fatty alcohol with the interaction resulting in the formation of a gel network consisting of bilayers of the fatty alcohol swollen with water. Introduction of an oil phase does not appear to affect the formation of the network while alcohol in excess of that required to form the network is present as particles built up of bilayers of its semihydrate (Junginger, 1984; Patel et al., 1985a; Eccleston, 1986). Small-angle X-ray scattering (SAXS) of such systems has generally been limited either to examining the lamellar phase of the alcohol semihydrate (Eccleston, 1975) or the gel network of gels and emulsions with water contents below 70% w/w (Junginger, 1984). The aim of the present work is to assess the usefulness of SAXS in analysing a pharmaceutical gel containing 90% w/w water which has been well characterised physically by other techniques (Patel et al., 1985a; Louden et al., 1985; Dissado et al., 1987; Rowe and McMahon, 1987) and to test the applicability of using a one-dimensionally ordered lamellar stack lattice model to assess the distribution of the water layer thickness.

Theoretical considerations

The theoretical small angle scattering from one-dimensionally ordered systems is particularly well documented and has been applied extensively in the interpretation of the intensity curves from

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semicrystalline polymers (Crist, 1973; Burmester and Geil, 1972; Vonk, 1982). In a vast number of polymeric materials the morphology is believed to consist of arrays of alternating crystalline and amorphous regions or phases. For a perfect one-dimensional array of stacked lamellae the scattering intensity is confined to a series of maxima the positions of which are given by Bragg's Law ($n\lambda = 2d\sin(\theta)$ where d is the interplanar spacing and the remaining symbols have their usual meaning) which yields $d_i/d_1 = 0.5, 0.33, 0.25, 0.2, 0.167$, etc for i increasing from 1. The breadth of each maximum is influenced by a number of factors including distributions in the thicknesses of both phases together with the total length of the one-dimensional array.

The effects of these distributions on the scattering data can be readily simulated if one assumes the somewhat ideal case of flat parallel lamellar surfaces of infinite lateral extent. Conceptually two different models can be employed in the construction of such a lamellar array and these are named the lattice and stacking models. In the lattice model the structure is assembled by firstly defining a lattice according to some probability density distribution $H(z)$ where z is the distance between consecutive lattice points. Each point is then occupied by a lamella of thickness x the distribution of which is determined by $H'(x)$. The one-dimensional scattering function for this two phase system is then given by (Bramer, 1972):

$$I_1(Q) \propto \frac{(\rho_1 - \rho_2)^2 n}{Q^2} \left\{ (1 - |F_x(Q)|^2) + |1 - F_x(Q)|^2 \, Re\left[\frac{1 + F_z(Q)}{1 - F_z(Q)} \right] \right\}$$

where F_z is the Fourier transform of $H(z)$

F_x is the Fourier transform of $H'(x)$

$\rho_1 - \rho_2$ is the electron density contrast between phases

n is the number of lamellae and

$Q = 4\pi/\lambda \sin(\theta)$ where λ is the wavelength and θ is half the scattering angle.

In the above expression n is taken to be large. The introduction of a linear shape function to describe overall stack size leads to an additional intensity expression for the scattering intensity (Hosemann and Bagchi, 1962) but the influence of stack size becomes noticeable only when the number of lamellae is small ($n \leq 10$). In essence the resultant structure obtained using the lattice model is dominated by the first phase. Fluctuations in this phase destroy any long range order whilst deviations in the thickness of the second component do not affect the overall lattice spacings.

In the stacking model alternating crystalline and amorphous regions are arranged on top of each other with the result that each phase is more equally weighted in the construction of the lattice. However, when the long range order results from thickness fluctuations in one phase only both models become equivalent (Crist 1973).

The equation above is perfectly general and can be applied to any system which approximates to a periodic one-dimensional lamellar stack.

Materials and Methods

The gel sample containing 0.5% w/w cetrimide (a cationic surfactant consisting of a mixture of dodecyl, tetradecyl and hexadecyl trimethyl ammonium bromide), 10% w/w cetostearyl alcohol (consisting of cetyl and stearyl alcohol with minor amounts of C_{12}, C_{14} and C_{20} alcohols) and purified water to 100% was prepared using the technique described by Patel et al. (1985b). In essence this involved heating both the alcohol and aqueous phases to 80 °C, mixing them and stirring gently with a paddle stirrer for 1 h before homogenisation and cooling. Examination of the gel using cryogenic scanning electron microscopy (Rowe and McMahon, 1987) showed the presence of a convoluted network (Fig. 1).

SAXS measurements were performed on a Compact Kratky Camera (Kratky and Stabinger, 1984) mounted on a Philips PW1730 generator fitted with a long fine-focus Cu-target X-ray tube. In order to reduce the effect of the Kβ radiation on the data a 10 μm nickel filter was placed in front of the collimation system. The final collimation geometry was chosen to compromise both signal count rate and resolution of the data; the

Fig. 1. Freeze fracture scanning electron micrograph of gel showing convoluted bilayer network. Bar = 3.3 μm.

entrance slit was set to 80 μm and receiving slit 200 μm. The sample was contained in a quartz capillary cell length 25 mm and cross-section 1 mm and examined at room temperature. The data were collected using a Philips step scanning proportional counter and each angular point was measured for 240s.

The data were corrected for scattering from the quartz and water by appropriate subtraction of a water blank cell and the effect of slit length smearing by the X-ray beam removed using Vonk's desmearing algorithm (Vonk 1971).

Results and Discussion

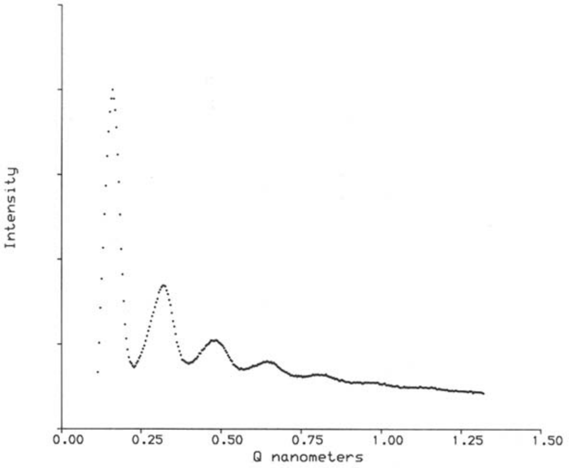

Fig. 2. Experimental small angle scattering data on gel.

The SAXS curve for the gel is shown in Fig. 2. The intensity is plotted along the ordinate in arbitrary units and the abscissa is scaled in units of Q ($Q = 4\pi/\lambda \sin(\theta)$ where $\lambda = 0.15404$ nm). The data show a periodic decay in intensity from the minimum Q value (9×10^{-2} nm^{-1}) out to high Q where the function eventually becomes flat. The positions of the peaks are listed in Table 1 together with the corresponding long-spacing values d which emanate from Bragg's equation. The ratios of these d-spacings index within experimental error to those expected for a lamella system assuming the peak at 39.0 nm represents the first order. Although the camera was restricted to d-values smaller than ca. 65.0 nm no larger d-spacing peaks could occur and still be indexed with the same series. Other morphologies were also considered, e.g. cylindrical domains, but the geometrical series of these structures failed to account for the positions of the maxima.

These data are in direct agreement with the perceived structure of the system i.e., a series of cetostearyl alcohol bilayers separated by water (Patel et al., 1985a). The 39.0 nm spacing then

TABLE 1

Comparison of experimental and theoretical d spacings

Peak position Q (nm^{-1})	d Spacing (nm)	Predicted spacing (nm) *
0.161	39.0	39.0
0.322	19.6	19.5
0.482	13.0	13.0
0.643	9.8	9.8
0.804	7.8	7.8
0.964	6.5	6.5
1.134	5.5	5.6

* Calculated using the indexing formula for a lamella system as explained in the text.

represents the spacing between the bilayers. If it is assumed that the bilayer thickness is of the order of 4.8 nm (Eccleston, 1975) then the water layer is of the order of 34.0 nm. This is much larger than that observed on comparable systems, admittedly with lower water content, where spacings of 16.0–20.0 nm were reported (Junginger, 1984).

A potential complication to the interpretation of the data is the fate of the cetrimide particularly when if offers such a high electron density contrast to X-rays. Recent data from Laser Raman Spectroscopy (Louden et al., 1985) would suggest that the majority of the cetrimide is present in the water phase. If this is so then the scattering function for such micelles so formed would comprise a smooth decay (Berr et al., 1986) and would not account for the oscillatory behaviour observed in this work. Even if the cetrimide was present in the bilayer then all that would be observed would be an increase in scattering intensity, a consequence of the improved contrast.

Such is the quality of the data that one may estimate the distribution width of the water layer using the lattice model outlined above and simulating curves assuming a delta function to describe the bilayer and a normal distribution for the water phase (Figs. 3 and 4). The peak positions in the simulations are acceptable but in general the peaks are too narrow. The reasons for this are unclear. Increasing the breadth of the water layer distribution rapidly dampens the higher angle peaks and fails to account for the number of experimentally observed maxima. Neither can a change in the bilayer thickness of between 3.6 to 6.0 nm (to account for the molecular weight distribution of the cetostearyl alcohol used) account for this discrepancy. It is anticipated that both instrumental broadening and inadequacies in the one-dimensional model could account for this peak shape. However, despite these limitations the results of varying the distribution of lamellar separation (Fig. 3) would indicate a narrow distribution estimated to be of the order of ±1.0 nm.

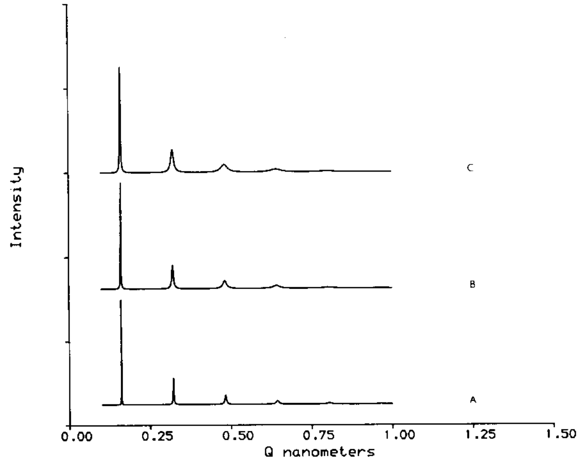

Fig. 3. The effect of varying the distribution of the lamella separation (water layer) assuming a mean separation of 39.0 nm and a bilayer thickness of 4.8 nm. A: 39.0±1.0 nm. B: 39.0±1.5 nm. C: 39.0±2.0 nm.

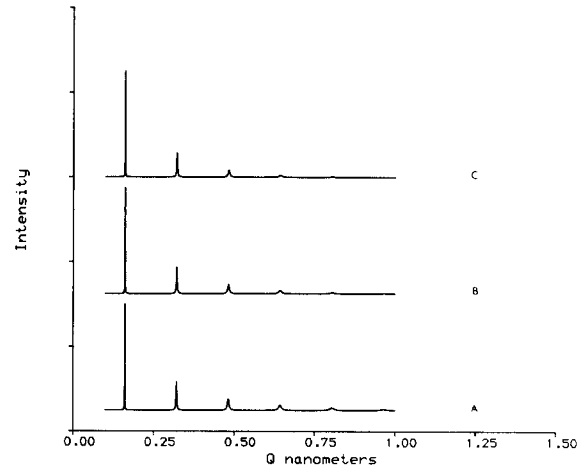

Fig. 4. The effect of varying the bilayer thickness assuming a lamella separation of 39.0 nm and variation in separation of ±1.0 nm. A: bilayer thickness 3.6 nm. B: bilayer thickness 4.8 nm. C: bilayer thickness 6.0 nm.

In conclusion it can be seen that SAXS is capable of analysing gels with high water content prepared from a surfactant and long chain fatty alcohol with interlamellar spacings of the order of 40.0 nm. Using a lattice model but recognizing its limitations it can be demonstrated that there is a very narrow distribution in the thickness of the water layer.

Acknowledgements

The authors would like to thank Mrs. Pat Howard, ICI C&P Limited for her valuable assistance.

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