Supplementary material

SAXS Data Analysis

SAXS data were analysed with a model with form factor for a spheroidal oligomer with semi-axes, *a* and *b* (*cf*. Fig S1).

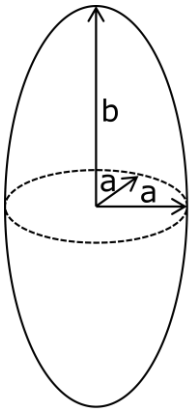

Figure S1: Depiction of spheroid with semi-axes *a* and *b*, in which *b*>*a*.

The differential scattering cross section as a function of scattering vector *q* for a sample of interacting oligomers with concentration *n* (number of particles per unit volume) can be written as follows[1]

$$\frac{d\sigma(q)}{d\Omega} = n(\Delta\rho V)^2 P(q)[1 + \beta(q)(S(q) - 1)] \quad \text{(S1)}$$

where the structure factor *S*(q) has been taken into account using the decoupling approximation.[2]

The orientationally averaged form factor for a spheroid may be written as

$$P(q) = \langle F^2(q)\rangle = \int_0^{\pi/2} F(q,\phi)^2 \sin\phi \, d\phi \quad \text{(S2)}$$

and

$$\beta(q) = \frac{\langle F(q)\rangle^2}{\langle F^2(q)\rangle} \quad \text{(S3)}$$

The amplitude of the form factor is defined as

$$F(qr) = \frac{3(\sin qr - qr\cos qr)}{(qr)^3} \quad \text{(S4)}$$

where

$$r = \sqrt{a^2 \sin^2\phi + b^2\cos^2\phi} \quad \text{(S5)}$$

and

$$\langle F(q)\rangle = \int_0^{\pi/2} F(q,\phi)\sin\phi \, d\phi \quad \text{(S6)}$$

The structure factor was based on the scattering by mass fractal objects, as described by Teixeira.[3] Fractal objects have two characteristics: self-similarity and the fractal dimension. Self-similarity means that a structural element is repeated throughout the object, and the fractal dimension can be described as the roughness or complexity of the object. The scattering, as a function of *q*, from fractal objects is based on equation 7

$$S(q) = 1 + \frac{D}{R^D}\int_0^{\infty} \frac{r^{D-1}\, exp\left(-\frac{r}{\xi}\right)\, sin(qr)}{Qr} dr =$$

$$+\frac{1}{(qR)^D}\frac{D\Gamma(D-1)}{\left[1+\frac{1}{q^2\xi^2}\right]^{\frac{D-1}{2}}}\sin[(D-1)\tan^{-1}(q\xi)] \quad \text{(S7)}$$

in which *D* is the mass fractal dimension, *R* is the size of the scatterer, and ξ is the size of the clusters. In this case, the scattering particles formed large clusters, and the parameter ξ was set to approach infinity. With this assumption, equation S7 is simplified to

$$S(Q) = 1 + \frac{D\Gamma(D-1)}{(QR)^D}\sin\left[\frac{\pi}{2}(D-1)\right] \quad \text{(S8)}$$

and the resulting equation describes the scattering as a function of *q* depending on two variables, *D* and *R*.

The parameters in the model were optimized by means of conventional least squares analysis. (Pedersen 1997; B. R. Bevington, *Data reduction and error analysis for physical sciences*, McGraw-Hill, New York, 1969) The quality of the fits were measured in terms of the reduced chi-squared parameter defined as

$$\chi^2 = \frac{1}{N-M}\sum_{i=1}^{N}\left(\frac{I_{exp}(q_i) - I_{mod}(q_i)}{\sigma_i}\right)^2 \quad \text{(S9)}$$

where $I_{exp}(q_i)$ and $I_{mod}(q_i)$ are the experimental and model intensities, respectively, at a scattering vector modulus q_i, σ_i is the statistical uncertainties on the data points, *N* is the total number of data points and *M* is the number of parameters optimized in the model fit. All our scattering data could be fitted with one single model using the four fitting parameters (*a*, *b*, *R* and *D*). In addition, the quantity $n(\Delta\rho V)^2$ was used as a scaling parameter and the residual background scattering as an additive parameter. The minor semi-axis *a* could, however, not be accurately determined for most of our samples due to lack of scattering data in the high *q*-regime.

Scattering data for 2.5-7.5 mg cm^{-3} pramlintide

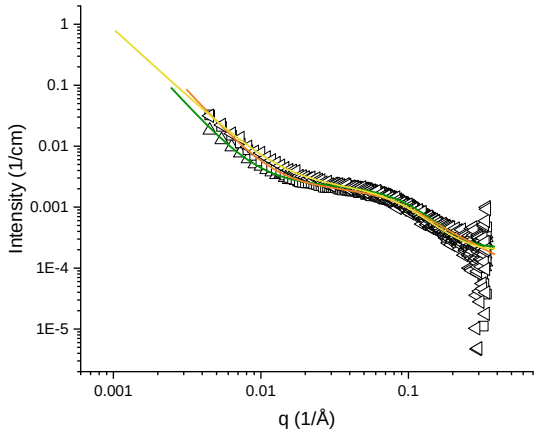

Figure S2: SAXS curves for 2.5-7.5 mg cm^{-3} pramlintide in water 7.5 mg cm^{-3}I (△), 5 mg cm^{-3} (□), 2.5 mg cm^{-3} (◁) and fitted result as solid line.

Table S1: Dimensions of scattering particles in 2.5-7.5 mg cm^{-3} pramlintide in water obtained from model fitting.

Concentration (mg cm^{-3})	Semi-axis *b* (nm)	Volume (nm^3)	Molecules/ particle	R (nm)	D
7.5	3.5±0.2	14.8	2.3	8.3±0.4	2.7±0.1
5	3.5±0.2	14.6	2.2	6.3±0.3	2.6±0.1
2.5	3.9±0.4	16.2	2.5	6.4±0.4	2.2±0.1

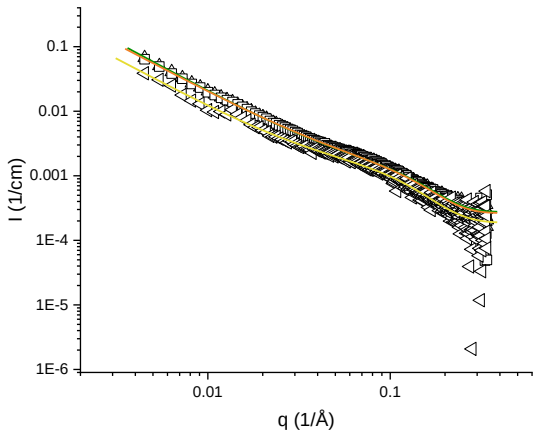

Figure S3: SAXS curves for 2.5-7.5 mg cm^{-3} pramlintide in 1 mM NaSCN 7.5 mg cm^{-3} (△), 5 mg cm^{-3} (□), 2.5 mg cm^{-3}I (◁) and fitted result as solid line.

Table S2: Dimensions of scattering particles in 2.5-7.5 mg cm^{-3} pramlintide in 1 mM NaSCN obtained from model fitting.

Concentration (mg cm^{-3})	Semi-axis *b* (nm)	Volume (nm^3)	Molecules/ particle	R (nm)	D
7.5	2.4±0.2	10.0	1.5	1.5±0.1	1.5±0.1
5	2.4±0.2	10.0	1.5	1.4±0.1	1.5±0.1
2.5	2.8±0.5	11.7	1.8	2.2±0.2	1.5±0.1

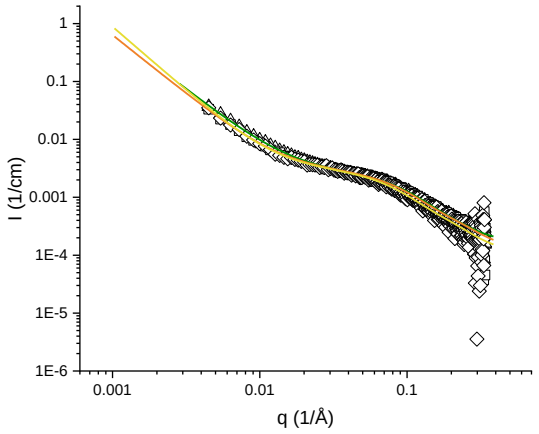

Figure S4: SAXS curves for 2.5-7.5 mg cm^{-3} pramlintide in 1 mM NaCl 7.5 mg cm^{-3} (△), 5 mg cm^{-3} (□), 2.5 mg cm^{-3} (◁) and fitted result as solid line.

Table S3: Dimensions of scattering particles in 2.5-7.5 mg cm^{-3} pramlintide in 1 mM NaCl obtained from model fitting.

Concentration (mg cm^{-3})	Semi-xis *b* (nm)	Volume (nm^3)	Molecules/ particle	R (nm)	D
7.5	3.5±0.1	14.7	2.2	5.6±0.2	2.0±0.1
5	3.9±0.2	16.2	2.5	6.7±0.3	2.0±0.1
2.5	4.3±0.3	18.2	2.8	7.2±0.5	2.2±0.1

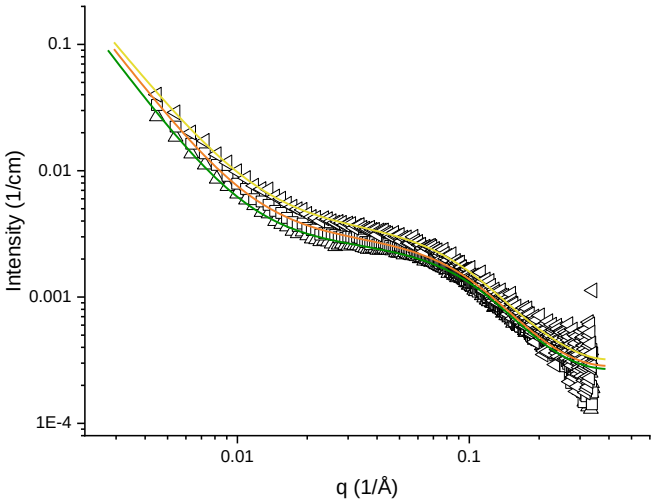

Figure S5: SAXS curves for 2.5-7.5 mg cm^{-3} pramlintide in 1 mM NaF, 7.5 mg cm^{-3} (△), 5 mg cm^{-3} (□), 2.5 mg cm^{-3} (◁) and fitted result as solid line.

Table S4: Dimensions of scattering particles in 7.5-2.5 mg cm^{-3} pramlintide in 1 mM NaF obtained from model fitting.

Concentration (mg cm^{-3})	Semi-axis *b* (nm)	Volume (nm^3)	Molecules/ particle	R (nm)	D
7.5	3.4±0.2	14.2	2.2	7.7±0.4	2.5±0.1
5	3.6±0.2	15.0	2.3	7.4±0.3	2.4±0.1
2.5	3.8±0.3	15.9	2.4	7.3±0.4	2.3±0.1

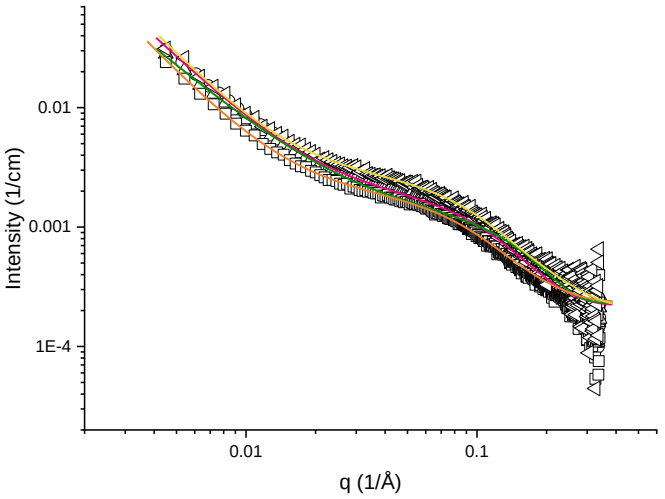

Figure S6: SAXS curves for 2.5-7.5 mg cm^{-3} pramlintide in 1 wt% DMSO 7.5 mg cm^{-3} (△), 5 mg cm^{-3} (□), 2.5 mg cm^{-3} (◁) and fitted result as solid line.

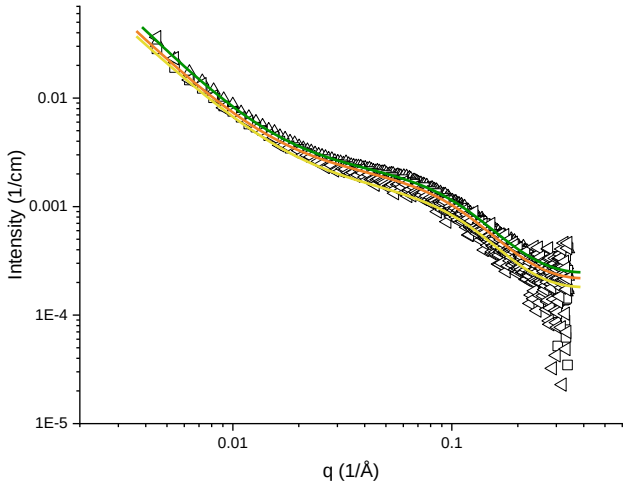

Figure S7: SAXS curves for 2.5-7.5 mg cm^{-3} pramlintide in 5 wt% DMSO 7.5 mg cm^{-3} (△), 5 mg cm^{-3} (□), 2.5 mg cm^{-3} (◁) and fitted result as solid line.

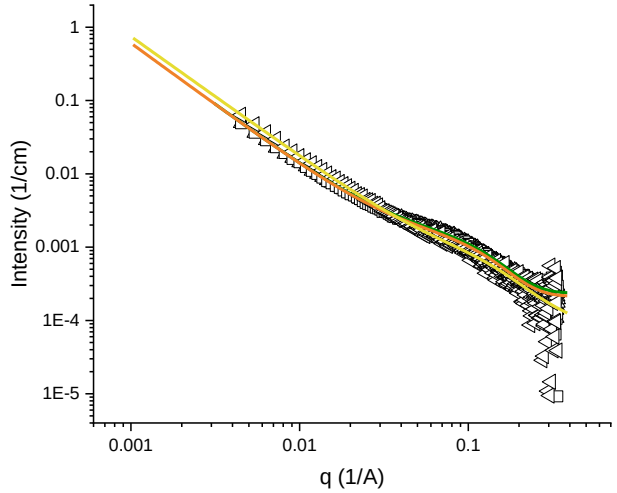

Figure S8: SAXS curves for 2.5-7.5 mg cm^{-3} pramlintide in 10 wt% DMSO 7.5 mg cm^{-3} (△), 5 mg cm^{-3} (□), 2.5 mg cm^{-3} (◁) and fitted result as solid line.

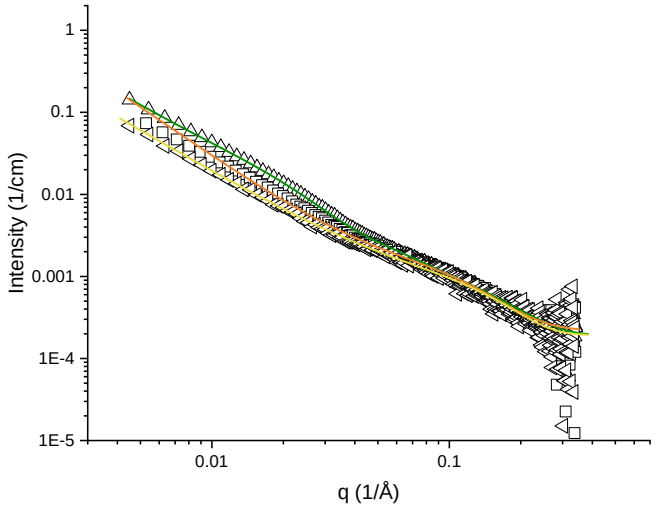

Figure S9: SAXS curves for 2.5-7.5 mg cm^{-3} pramlintide in 20 wt% DMSO 7.5 mg cm^{-3} (△), 5 mg cm^{-3} (□), 2.5 mg cm^{-3} (◁) and fitted result as solid line.

Table S5: Dimensions of scattering particles in 7.5-2.5 mg cm^{-3} pramlintide in 1-20 wt% DMSO obtained from model fitting.

Solvent	Concentration (mg cm^{-3})	Semi-axis *b* (nm)	Volume (nm^3)	Molecules/ particle	R (nm)	D
1% DMSO	7.5	2.0±0.3	8.2	1.3	3.1±0.2	1.6±0.1
	5	3.1±0.1	13.0	2.0	4.7±0.2	1.9±0.1
	2.5	3.6±0.2	14.9	2.3	6.0±0.3	2.1±0.1
5% DMSO	7.5	3.3±0.2	13.8	2.1	5.6±0.2	2.0±0.1
	5	3.8±0.4	14.1	2.1	6.0±0.5	2.0±0.1
	2.5	3.1±0.1	13.0	2.0	4.7±0.2	1.9±0.1
10% DMSO	7.5	2.7±0.2	11.3	1.7	2.6±0.1	1.7±0.1
	5	2.7±0.2	11.2	1.7	2.4±0.1	1.7±0.1
	2.5	2.3±0.4	9.53	1.5	1.6±0.1	1.7±0.1
20% DMSO	7.5	16.4±0.2	68.7	11	6.2±0.1	1.7±0.1
	5	2.8±0.2	11.8	1.8	2.1±0.2	2.0±0.1
	2.5	2.3±0.4	9.67	1.5	1.6±0.1	1.7±0.1

Dynamic light scattering (DLS)

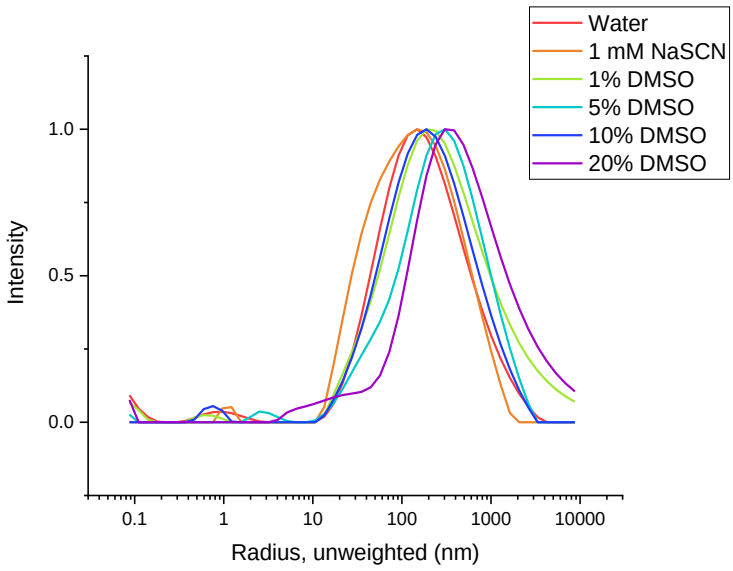

Figure S10: Distribution of hydrodynamic radii of 10 mg/ml pramlintide in water, 1 mM NaSCN, and 1-20% DMSO

Cryogenic transmission electron microscopy (cryo-TEM)

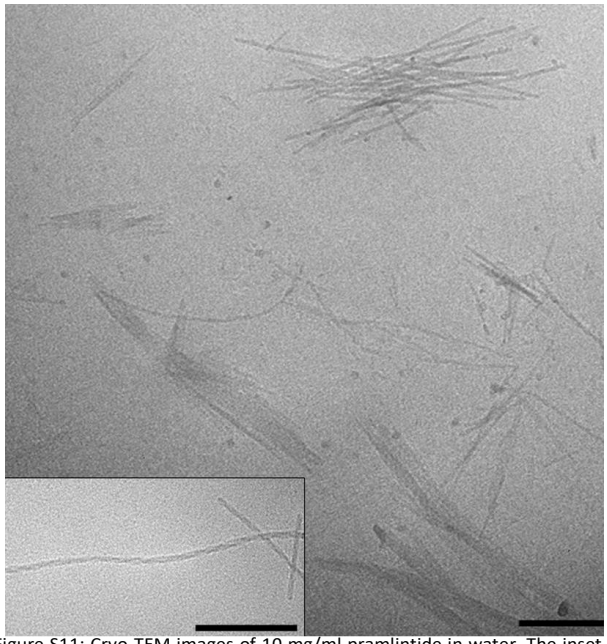

Figure S11: Cryo-TEM images of 10 mg/ml pramlintide in water. The inset shows detail of fibrils suggesting a twisted structure. The scale bar represents 200 nm.

References

1 J. S. Pedersen, *Adv. Colloid Interface Sci.*, 1997, **70**, 171–210.
2 M. Kotlarchyk and S. Chen, *J. Chem. Phys.*, 1983, **79**, 2461–2469.
3 J. Teixeira, *J. Appl. Crystallogr.*, 1988, **21**, 781–785.