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Synchrotron radiation small- and wide- angle scattering study of dispergation of Equoral®, a novel drug delivery system with cyclosporine A

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Equoral® oral solution is a novel drug delivery system for cyclosporine consisting mainly of non-ionic surfactants, polyglycerol esters and polyoxyethylated fatty acids aggregates, and gives microdispersions in the aqueous enviroment. To simulate dispergation, Equoral® was mixed with varying amounts of water. Changes in the structure of the prepared aggregates were studied using synchrotron x-ray small- and wide-angle scattering. A lamellar phase is the most probable structure, arising spontaneously after dispergation of Equoral® in the region of 30–70 wt% H_2O.

Cyclosporine A, an immunosuppressive drug introduced into the therapeutic practice in 1980's, is used primarily to prevent graft rejection after solid organ transplantation, for prophylaxis of graft-versus-host disease, and for treatment of autoimmune diseases. The low water solubility of cyclosporine does not allow formulation as a simple preparation. The first registered dosage form (Sandimmune®, Novartis, Switzerland) was designed as an emulsion pre-concentrate with the mean size of dispersed droplets above 1 μm. Current brand leader formulation (Neoral®, Novartis, Switzerland) is a microemulsion pre-concentrate with dispersed particles smaller than 100 nm. Equoral® (IVAX Pharmaceuticals Ltd., Czech Republic) is a new cyclosporine formulation consisting mainly of non-ionic surfactants, polyglycerol esters and poloxyethylated fatty acids aggregates (Andrýsek 2003; Andrýsek et al. 2003). It gives coarse dispersion with average particle size between 1 and 150 μm when dispersed in the aqueous environment. Simulating dispergation, dramatic changes of viscosity were observed when Equoral® was mixed with different amounts of water. In these dispersions, the viscosity begins to increase from about 30 wt% of water, reaching a maximum between 60–70 wt% of water and then decreases sharply at 80 wt% of water (Murdan et al. 2003). In the present communication, we study the microscopic structure of Equoral® dispersions with different amounts of water using the synchrotron radiation small- (SAXS) and wide-angle (WAXS) scattering.

In Fig. 1, the typical scattering patterns show the dependencies of scattered radiation intensity (in relative units) on the reciprocal spacing $s = 2 \sin\theta/\lambda$, where 2θ is the scattering angle. The samples at 0–10 wt% H_2O exhibited a broad diffuse SAXS reflection. In the region of 30–70 wt% H_2O, two sharp peaks appeared superimposed on a weak broad diffuse reflection. After background subtraction these SAXS patterns were fitted with 3 Lorentzians. Supposing that the sharp peaks are the first and second order diffraction peaks of one-dimensional lamellar phase, the repeat period d of this phase was calculated from the positions of maxima of fitted sharp peaks by using the Bragg equation. The repeat period d was found to increase non-linearly with the water content in the sample, indicating lamellar phase swelling (Fig. 2). At the highest H_2O content studied (80 wt%) the sharp peaks were not observed and the SAXS pattern consisted of the broad diffuse reflection shifted to lower s values. The changes in

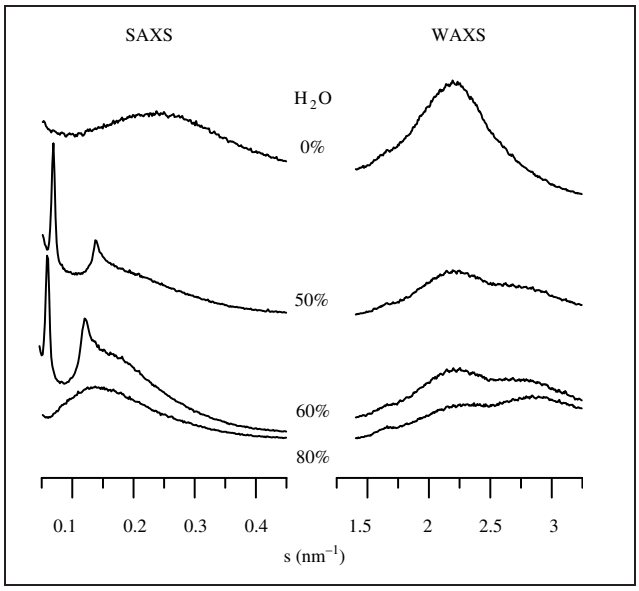

Fig. 1: SAXS and WAXS scattering paterns of samples with different compositions

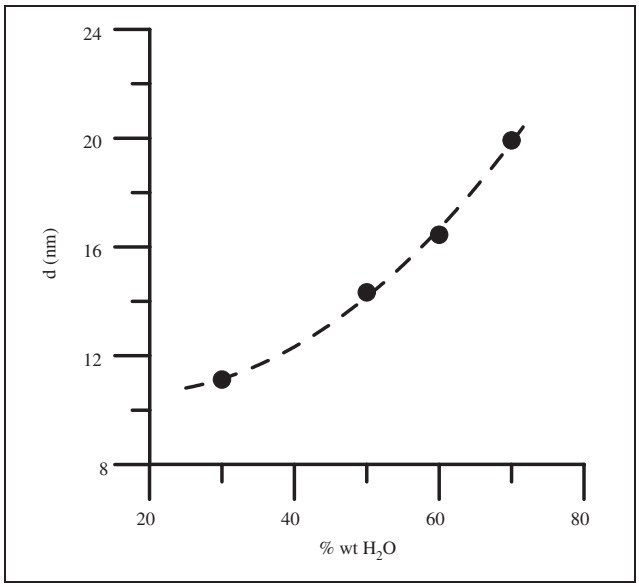

Fig. 2: Dependency of the repeat period (d) on the water content

the SAXS patterns were accompanied by the changes in the WAXS patterns, indicating changes in the short-range ordering of constituents. On the initially symmetric peak with maximum at 2.2 nm^{-1}, a shoulder and then a second peak at 2.8 nm^{-1} appeared in the region of 30–70 wt% H_2O. However, this second peak was also observed in the sample containing 80 wt% H_2O.

In conclusion, we have found the formation of a lamellar phase in aqueous Equoral® dispersions in the range 30–70 wt% H_2O. This could be the cause of previously observed changes in the viscosity of formulations with different water contents. Outside this range, the long range order has not been found though the short range order is preserved.

Experimental

Equoral® oral solution, 100 mg/ml, batch 16001QB001 (IVAX Pharmaceuticals Ltd., Czech Republic) was taken for preparation of the samples. The samples were prepared by addition of the proper amount of distilled water (in wt%). Small and wide angle synchrotron radiation x-ray scattering measurements were performed at the A2 soft-condensed matter beam line at HASYLAB at the Deutsches Elektronen Synchrotron (DESY) in Hamburg, with monochromatic radiation of wavelength $\lambda = 0.15$ nm (Dommach 2003). The samples were equilibrated at 20 °C for 5 min before exposure to radiation. The SAXS detector was calibrated with a silver behenate standard sample (Huang et al. 1993) and the WAXS detector by the tripalmitate standard sample (Chapman 1962; Kellens et al. 1990). Data reduction and normalization were done with the programs STAFO and OTOKO (Boulin et al. 1986).

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The effect of xylitol on the stability and morphological parameters of tablets with sorbitol made by direct tabletting of formulation components

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Model tablets of polyols (sorbitol and xylitol) comprised 88% by mass, were produced using a direct compression method. Morphological and mechanical parameters of the model tablets were investigated *ex tempore* as well as after 12 and 24 months' storage. The effect of xylitol on selected morphological parameters of practical relevance during storage was estimated. The results obtained are a basis for further work on the use of polyols (sorbitol, xylitol and other sugar alcohols) in the production of oral forms of drugs, particularly buccal tablets.

Technological problems observed in the production of buccal tablets or tablets with controlled dissolution rate containing xylitol result from the high plasticity of the xylitol structure whose presence in a composite system decreases the mechanical strength (friability and hardness) of this preparation type (Farmakopea Polska 1993; Garr 1990; Goczo et al. 2001; Molokhia et al. 1982; Schmidt and Vortisch 1987; Wade and Weller 1994). Hence investigations were started into the effect of an increase in xylitol content (0–50%) on selected morphological and mechanical parameters of tablets with constant bulk density (g/cm^3).

The friability coefficient, hardness and effective disintegration time of model tablet forms were investigated. The results obtained enabled not only the relationship between the content of sorbitol and xylitol in a tablet and its real mechanical strength to be observed but also the effect of programmed compression force (kN) on effective decomposition time.

The results of investigations carried out on model tablets with $m_t = 0.300$ g, in which polyols (sorbitol and xylitol) comprise 88.9% of formulation components, indicate that at constant compression parameters the increase in the proportion of xylitol is accompanied by a proportional specific decrease in hardness.

Experimental data given in Tables 1 and 2 enable the relationship between the percentage content of sorbitol and xylitol in model tablet formulations and their measured and statistically determined hardness (T) to be analyzed *ex tempore* and after one and two years of storage (temp. 25 ± 0.1 °C).