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).

Table 1: Composition and morphological parameters of the produced tablets

Formulation components	Variant No.1 %	Variant No.2 %	Variant No.3 %	Variant No.4 %
Sorbitol Neosorb P 60 W	88.9	80.0	66.70	44.45
Xylitol Xylisorb 300	~	8.90	22.20	44.45
HPMC Pharmacoat 904	5.00	5.00	5.00	5.00
$CaHPO_4 \cdot 2\,H_2O$ C 72–04 Budenheim	5.00	5.00	5.00	5.00
Magnesium stearate	1.10	1.10	1.10	1.10
Tablet mass – m_t (x) (g)	0.3066	0.3066	0.3038	0.3092
Tablet surface – P_C (mm^2)	77.2	77.0	77.2	77.4
Tablet height – h (mm)	2.72	2.70	2.72	2.74
Tablet density – d_{rz}; (g/cm^3)	1.435	1.446	1.422	1.437

In relation to the percentage proportion of sorbitol (% S) the above relationship for model tablets was described by the correlation equations:

After compression (*ex tempore*)

$$\frac{1}{T} = 3.3217 \cdot 10^{-2} - 2.8278 \cdot 10^{-4} \cdot \%S \; r = 0.9954 \quad (1)$$

after 12 months storage

$$\frac{1}{T} = 3.9993 \cdot 10^{-2} - 3.6842 \cdot 10^{-4} \cdot \%S \; r = 0.9845 \quad (2)$$

after 24 months storage

$$\frac{1}{T} = 4.2966 \cdot 10^{-2} - 4.0610 \cdot \%S \; r = 0.9915 \quad (3)$$

The above relationships with constant proportions of HPMC, $CaHPO_4 \cdot 2H_2O$ and magnesium stearate in the formulation, make it possible to design a model tablet with given mechanical and morphological parameters which contains xylitol in the required proportion. This possibility depends on the morphological parameters of model tablets specified in Table 1.

With fixed experimental compressing force of a top and bottom punch (Table 2) significant reproducibility of target tablet mass (m_t), tablet density (d_{true}) as well as height (h) and its surface (P_C) was achieved.

The consequence of an increase in the proportion of xylitol in a model tablet formulation was found to be a decrease of hardness (Table 2), which results in practice in an increase in friability (W%). The loss of total model tablet mass found increases with a decrease in the proportion of sorbitol; at 44.5% xylitol in m_t of a tablet after 24 months of storage, friability amounts to 0.96%.

The limiting value of the total tablet mass loss according to FP V (FP V 1993) may not exceed 1.5% (Farmakopea Polska 1993).

Measurement and statistical analysis of the diameter of model tablets after 24 months storage indicates that the greater the increase in the proportion of xylitol (Table 1), the more their diameter increases (Table 2).

The observed relationship was described by an approximation equation

$$\log d = 1.0066 + 6.6158 \cdot 10^{-5} \cdot \%S \; r = 0.9671 \quad (4)$$

The above characteristic of model tablets which contain sorbitol and xylitol in due proportion is significant for designing recesses in blisters and for mechanical packaging of the produced form of a drug. Taking this characteristic into consideration results in reduced losses associated with mechanical damage of tablets and packaging.

The results of the investigations carried out indicate the possibility of producing a tablet of required morphological parameters in which polyols (sorbitol and xylitol) comprise 88.9% of the preparation by mass.

During storage, mechanical properties of model tablets do not change significantly.

The important effect of xylitol on the hardness and friability of model tablets was confirmed. The relationship between mechanical parameters as a function of composition was described by approximation equations which enable the preparation of a tablet formulation characterized by the required use-related values.

The determined disintegration time of model buccal tablets falls within the standard required by FP V (15–

Table 2: Selected parameters characterizing the pressing process and mechanical strength of the produced tablets

Proportion (%) of 1. Xylitol 2. Sorbitol	Pressing force of an upper punch	Pressing force of a bottom punch	Hardness (N) (x ± dx)			Disintegration time t (min) (x)	Friability W (%)	Diameter of a tablet d (x) mm (for n = 11)
			1	2	3			
1. 0	21.8 kN	20.6 kN	116 ± 17	156 ± 20	130 ± 9	14.6	0.52	10.01 ± 0.005
2. 88,90	2830 kg/cm^2	2672 kg/cm^2						
1. 8,90	23.7 kN	22.3 kN	101 ± 2	96 ± 12	97 ± 8	16.7	0.71	10.04 ± 0.02
2. 80,00	3077 kg/cm^2	2899 kg/cm^2						
1. 22,20	19.3 kN	17.5 kN	70 ± 6	58 ± 7	69 ± 7	16.6	0.74	10.06 ± 0.03
2. 66,70	2511 kg/cm^2	2273 kg/cm^2						
1. 44,45	26.1 kN	23.9 kN	48 ± 3	44 ± 5	39 ± 10	15.4	0.96	10.08 ± 0.01
2. 44,45	3384 kg/cm^2	3097 kg/cm^2						

Disintegration time, friability and tablet diameter were determined after 24 months

30 min) (Pharmakopea Polska 1993). It is interesting that an increasing proportion of xylitol in model tablets is accompanied by an increase in measurable tablet diameter during storage. Average values of disintegration time of model tablets are specified in Table 2. This property, resulting from so called "crystallographic memory" of the xylitol structure, described by the approximation equation, should be taken into consideration during design of packaging (blisters) not only to reduce losses during blistering but also to provide the required practical stability of a preparation.

Experimental

1. Excipients

Sorbitol: Neosorb P 60 W (Roquette-Lesterm, France; Xylitol: Xylisorb 300 (Roquette-Lestrem, France); Hydroxypropylmethyl cellulose (HPMC): Pharmacoat 904 (France); Dibasic calcium phosphate – $CaHPO_4 \cdot 2\,H_2O$ (Calcium ortho phosphate p.a.) P.OCH Gliwice (Poland), C-72-04 Budenheim; Magnesium stearate

2. Instruments and methods

"EXACTA 21" numerical tabletting machine with computer control which enables monitoring of the compression process at programmed morphological parameters of a model tablet. "TURBULA type T2C" mixer with standard glass containers $V = 3.0\ dm^3$ in which tablet feed (powder) for direct tabletting was made. Electronic micrometer produced by Mitutoyo (U.K.) Ltd; Patent EP 0053091. Measurement of morphological values of a tablet ($d = 2r$; h) was made with an accuracy of $\pm$ 0.01 mm. Hardness tester: Schleuninger Type T 2 C (Switzerland) and ERWEKA type TB – M (Germany). ERWEKA instrument to determine tablet disintegration time.

The product for direct tabletting was prepared in a TURBULA T 2C mixer by mixing Neosorb P 60W, Xylisorb 300, HPMC and $CaHPO_4\ 2\,H_2O$ for 15 min. The comparative particle size of the mixed components was maintained in a formulation. After introducing the magnesium stearate the components were mixed in alternating planes for 5 min at a speed of 20 rpm.

The compression process was carried out in an "EXACTA 21" tabletting machine using computer optimization of the morphological parameters of model tablets.

The different types of model tablets were produced in quantities of 4.5–5.0 thousand units.

Tests were made according to the requirements of FP V (Pharmakopea Polska 1993). The results obtained for each of the four model types, which are characterized by different contents of xylitol, were estimated statistically.

The evaluation of hardness of the model tablets was made with a Schleuniger T 2 C hardness tester *ex tempore* and after the first (12 months) and second (24 months) year of storage. The measurements were made for 20 tablets selected at random and were analysed statistically.

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Complexation of roxatidine acetate hydrochloride with β-cyclodextrin: NMR spectroscopic study

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A NMR spectroscopic study of mixtures of varying ratios of roxatidine acetate hydrochloride (RAH) and β-cyclodextrin (β-CD) in D_2O revealed the formation of a 1 : 1 inclusion compound. The aromatic ring of RAH selectively penetrates the β-CD cavity in preference to the piperidine ring.

Cyclodextrins (CDs) hold a variety of guests into their hydrophobic cavities (Steed and Atwood 2000; Wimmer et al. 2002) and serve as useful models for studying topochemistry and catalytic mechanism of enzymes (Bender 1988). CDs are widely used in pharmaceutical applications as a vehicle for drug delivery of poorly water-soluble drugs (Aithal and Shrinivas 1996; Frömming and Szejtli 1994). Extensive studies on inclusion complexes of various medicinally useful compounds with β-CD have been reported (Aithal and Shrinivas 1996; Frömming and Szejtli 1994; Menard et al. 1990). We report, herein, our results on the study of the inclusion complex of roxatidine acetate hydrochloride (RAH), a potent anti-ulcer drug (Murdoch 1991), with β-CD in solution by NMR spectroscopy.

The ^{1}H NMR spectra were recorded for five samples with [RAH]/[β-CD] molar ratios varying from 0.77 to 4.55 as determined by direct integration of the NMR signals. The anomeric proton (H-1) of β-CD was used as internal reference throughout this work.

The signals for RAH and β-CD protons did not interfere with each other in any spectrum. The signals for aromatic protons of the RAH molecule appeared as a singlet (H-6′), a doublet ($J = 8.1$ Hz H-2′,4′) and a triplet ($J = 8.0$ Hz H-3′) in all the cases except in the spectrum of the pure drug in which the doublet for H-2′,4′ and H-6′ singlet were found partly overlapping.

The induced chemical shift change ($\Delta\delta i$) for β-CD protons were calculated relative to reported ^{1}H NMR data (Schneider et al. 1998). Each sample spectrum denoted largest $\Delta\delta i$ for the H-3 and H-5 protons of the β-CD. The other β-CD's protons showed either much smaller or negligible deviations. The $\Delta\delta i$ data for various protons of β-CD in the presence of varying amount of RAH is given in the Table. In the presence of RAH, the peaks for H-3 and H-5 protons of the β-CD moved progressively upfield with the increase of concentration of RAH. The Fig. shows the part of the NMR spectra of samples A to E, containing signals for protons of β-CD. NMR spectra of samples A and B were recorded on a 200 MHz spectrometer while those of samples C, D & E were obtained on a 300 MHz instrument. The spectra of samples A and B