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

Table: ^{1}H NMR chemical shift changes ($\Delta\delta_i$) of β-CD and RAH protons upon complexation

Sample	[G]/[H]	β-Cyclodextrin						Roxatidine acetate hydrochloride		
		H-2	H-3	H-4	H-5	H-6	$\Delta\delta_i$ (H-5)/ $\Delta\delta_i$ (H-3)	H-2′,4′	H-3′	H-6′
A	0.77	0.0141	−0.0176	0.0093	−0.0182	−0.0075	1.03	0.0214	0.0302	−0.0388
B	1.19	0.0107	−0.0276	0.0079	−0.0281	−0.0095	1.01	0.0155	0.0220	−0.0322
C	1.96	0.0060	−0.0495	0.0095	−0.0505	−0.0135	1.02	0.0100	0.0120	−0.0130
D	3.50	0.0140	−0.0985	0.0145	−0.0995	−0.0135	1.01	0.0070	0.0082	−0.0087
E	4.55	0.0170	−0.1455	0.0185	−0.1535	−0.0255	1.05	0.0050	0.0041	−0.0037

Negative values indicates upfield shift.

are very much alike due to small change in [RAH]/[β-CD] molar ratio but the shift of signals for H-3 and H-5 protons is obvious. The shift of signals for H-3 and H-5 protons in the spectra C, D and E is very prominent.

The penetration of the less polar portion of the guest molecule into the β-CD cavity from the wider side comprises the most common mode of complexation. Since the H-3 and H-5 protons are positioned inside the cavity, the inclusion of guest into the β-CD cavity causes major upfield shifts of these protons. This is attributed to the ring current of the aromatic ring of the guest molecule that is included in the cavity (Komiyama and Hirai 1980a, 1980b). On the other hand, most of the guest protons show downfield shift changes but the $\Delta\delta i$ values for guest protons are much smaller in magnitude compared to host protons. Rekharsky et al. (1995) have demonstrated that the magnitude of the upfield shifts of H-3 and H-5 protons of CDs, $\Delta\delta i$(H-3) and $\Delta\delta i$(H-5), and their relative ratios $\Delta\delta i$(H-5)/$\Delta\delta i$(H-3), can be used, respectively, as a quantitative measure of the stability of complex and the depth of inclusion of ligand into the cavity.

The observed high field shifts in the H-3 and H-5 peaks of β-CD in the presence of varying amount of RAH thus clearly indicate the insertion of the aromatic ring of the RAH into the β-CD cavity. Moreover, the magnitude of the shifts for H-3 and H-5 protons of β-CD increased as a function of an increasing ratio of [RAH]/[β-CD] giving a slightly curved line for $\Delta\delta i$(H-3) vs [RAH]/[β-CD] plot. A modified Hildebrand-Benesi plot (Benesi and Hildebrand 1949; Qi et al. 1991) of chemical shift change data for H-3 of β-CD in the form of ([RAH]/[β-CD])/$\Delta\delta i$(H-3) vs [RAH]/[β-CD] gave excellent linear fits supporting the 1 : 1 complex formation. As expected, all the protons of the RAH, except the aromatic proton (H-6′), showed downfield shifts on complexation. The $\Delta\delta i$ data for aromatic protons of RAH in the presence of varying amounts of β-CD is given in the Table. There was no significant change observed in the chemical shift values of protons of RAH molecule in the spectra of samples C, D and E. This is in good agreement with the earlier observation that with the increase of concentration of guest, the $\Delta\delta i$ values for guest protons decrease (Rekharsky et al. 1995). This phenomenon indicated, in analogy to many previously reported cases (Bergeron and Rowan 1976; Komiyama and Hirai 1980a, 1980b), that the phenyl ring of the RAH is selectively inserted into the β-CD cavity driven primarily by hydrophobic interactions.

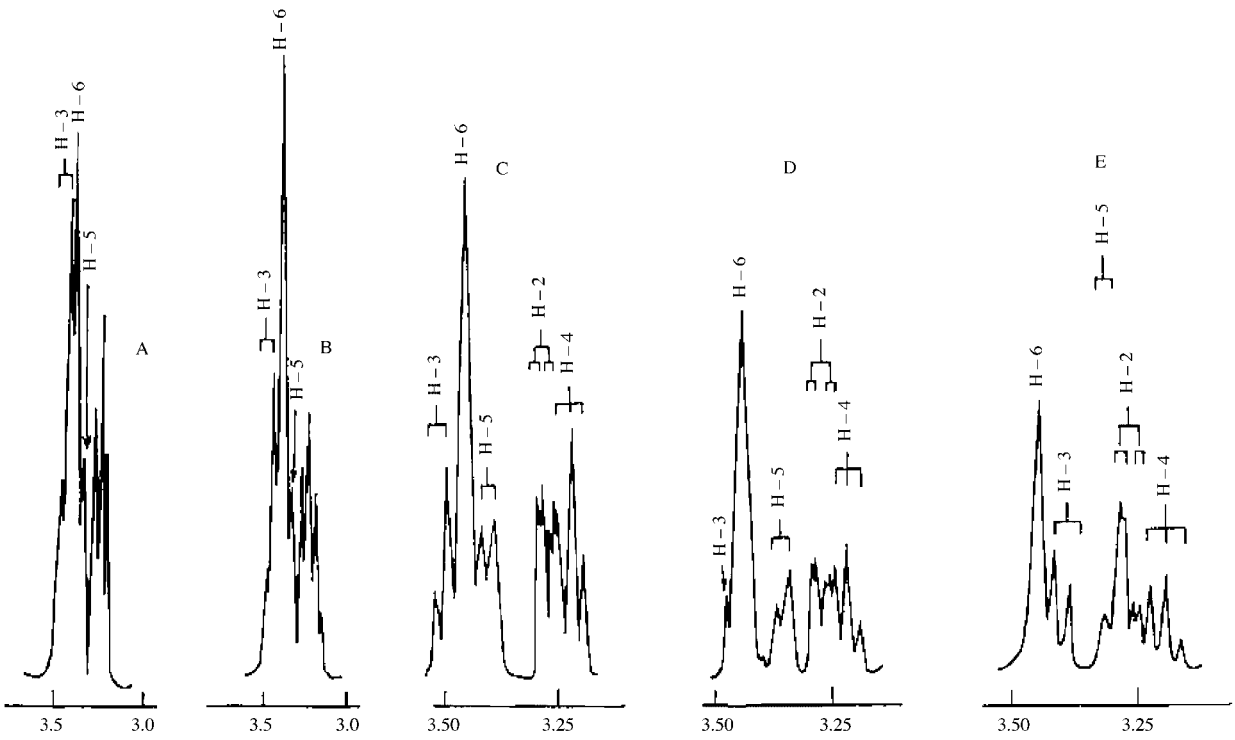

Fig.: Typical ^{1}H NMR spectra at a variety of guest to host [G]/[H] ratios for the complexation of Roxatidine Acetate Hydrochloride [RAH] with β-cyclodextrin in D_2O. Note the large upfield shifts of H-3 and H-5 in sharp contrast to the small shift changes observed for H-2, H-4 and H-6

The $\Delta\delta i$ values for H-2 and H-4 of β-CD and H-6′ aromatic proton of RAH need special attention. Normally the signal for all the β-CD protons show upfield shifts (if any) while all the guest protons show downfield shifts. The downfield shifts of H-2 and H-4 of β-CD and upfield shift of H-6′ of RAH may be attributed to their interaction through solvent. The ratios $\Delta\delta i$(H-5)/$\Delta\delta i$(H-3) were calculated for all the samples. The relatively smaller values (1.01–1.05) for $\Delta\delta i$(H-5)/$\Delta\delta i$(H-3) ratios compared to those reported for other complexes (1.2–3.0) suggest that the penetration of the aromatic ring in the β-CD cavity is not deep which is expected due to the presence of two bulky groups in the meta position of aromatic ring.

Finally, the ^{1}H NMR spectroscopic study of RAH in the presence of β-CD shows that a 1 : 1 RAH-β-CD complex is formed in solution which is in rapid equilibrium with free β-CD and RAH since the spectra consisted of mainly one set of resonances. Moreover, the aromatic ring of the RAH selectively penetrates into the β-CD cavity driven by hydrophobic interactions

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A new triterpenoid: taraxerol-3-β-*O*-tridecyl ether from *Derris triofoliata*

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The new triterpenoid taraxerol-3-β-*O*-tridecyl ether was isolated from the aerial part of *Derris triofoliata*. The structure was established on the basis of spectral data.

The genus *Derris* (Leguminous family) is widely spread in southeast Asia. It is employed for pest control in horticulture, agriculture and in poultry (Gupta et al. 1999). Some species are also used in folk medicine (Sekine et al. 1999; Mahidol et al. 1997). *D. triofoliata*, a woody climber growing in the coastal forest throughout south east Asia, is used for poisoning fish by local people. The whole plant is also used as a stimulant, antispasmodic, and counter-irritant (Ramachandran et al. 1986). Previous investigations of leaves of *Derris trifoliata* have yielded hydrocarbons, wax esters (Misra et al. 1987), sterols, amyrin, lupeol (Ghosh et al. 1985), and two flavonol glycosides: rhamnetin-3-*O*-β-neohesperidoside and quercetin-3-*O*-β-neohesperidoside (Ramachandran et al. 1986). We have investigated the chemical constituents of the aerial parts of *D. triofoliata*, and report here the isolation and characterization of a new etherified triterpenoid.

Compound **1**, prismy crystalline ($CHCl_3$–CH_3OH), was formulated as $C_{43}H_{76}O$ from ESI-MS (m/z 647 $[M + k]^+$, 631 $[M + Na]^+$). Its ^{1}H and ^{13}C NMR spectra showed great similarity to that of taraxerol (Sakurai et al. 1987). In ^{1}H NMR, eight tertiary methyls at δ 1.09 (3 H, s), 0.98 (3 H, s), 0.95 (3 H, s), 0.93 (3 H, s), 0.91 (6 H, s), 0.82 (3 H, s) and 0.80 (3 H, s) were typical for triterpene; an oxymethine proton at δ 3.20 (1 H, dd, J = 11.0, 4.6 Hz, H-3) was observed; a downfield one proton double doublet centered at δ 5.53 (J = 11.3, 3.2 Hz, H-15) indicated the presence of an olefinic bond, and was assigned to the olefinic proton at C-15 of the taraxerane skeleton (Talapatra et al. 1981); Two geminal methylene protons at δ 1.92 (1 H, dd, J = 14.7, 2.9 Hz, H-16a) and 2.03 (1 H, m, H-16b) could be discerned in the ^{1}H NMR spectra; Chemical shifts for one oxymethine carbon at δ 79.08 (C-3), olefinic carbons at δ 158.10 (C-14) and 116.88 (C-15) were all observed. Thus, the carbocyclic nucleus of compound **1** proved to be that of a typical taraxerol. Additional signals as one oxymethylene carbon at δ 63.11, one terminal methyl carbon at δ 14.11, multiple methylene carbon signals at δ 29.34 ∼ 29.70 indicated that the hydroxyl of taraxol was substituted by a long alkane. And