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COMPARISON OF XYLAN AND SOME COMMERCIAL MATERIALS AS DISINTEGRANTS IN TABLETS

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The disintegrant properties of xylan, a polymerization product of the pentose sugar xylose, were evaluated and these were compared with the properties of four commercial materials used for direct compression of tablets. The reference adjuvants were microcrystalline cellulose, Avicel PH 101, microfine cellulose, Elcema G 250, carboxymethyl starch, Primojel STD, and modified starch, Sta-Rx 1500.

The swelling properties of the plain materials were evaluated by measuring the particle size distribution in two electrolytes with different polarities using the Coulter Counter method. Tablets containing 0, 1.0, 2.5 or 5.0 % of the adjuvants as disintegrants, and 15 % of the drug, ascorbic acid or nitrazepam, and the rest of the base material, dicalcium phosphate, Emcompress, were compressed. The breaking strength and porosity of the tablets were evaluated. Water penetration into the tablets was studied by means of the modified Washburn equation. The disintegration time of the tablets was also determined.

Xylan, Primojel and Sta-Rx underwent extensive swelling of the primary particles in water. Swelling of cellulose microcrystals of Avicel was slight but that of cellulose aggregates

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of Elcema was extensive, probably due to the expanding structure of these aggregates. All the adjuvants tested made the tablets more hydrophilic. The swelling adjuvants, xylan and starch derivatives, were clearly more effective in tablets containing water insoluble nitrazepam than in those with water soluble ascorbic acid. On the other hand, cellulose derivatives, especially Avicel, were more effective in ascorbic acid tablets than in nitrazepam tablets. According to the results of this study, the disintegrant properties of xylan were weaker than those of Primojel STD, but almost as good as those of Sta-Rx 1500 and clearly better than those of Avicel PH 101 and Elcema G 250. An essential disintegrant mechanism of xylan is the swelling of primary particles.

INTRODUCTION

Rapid dissolution of the tablet, followed by dissolution of the drug, is usually the presupposition for effective absorption and high bioavailability of the drug in a compressed tablet. The disintegration process can be divided into three phases; wetting of the tablet, penetration of fluid into the tablet, and development of disintegrant force. There are numerous factors connected with these processes. The disintegrant, including its amount and the way it is added, is often the most important of these factors. Although action of disintegrants in tablets during disruption has been studied extensively for several decades, we still do not always understand how different disintegrants act during the disintegration process. The principal difficulty in such studies arises from the mixed effects of several possible factors. These effects are caused partly by disintegrants, partly by other materials in the tablet and partly by the manufacturing method.

Xylan is a polymerization product of the pentose sugar xylose. It is usually obtained as a by-product from the manu-

facturing of xylitol. Recently has been pointed out that it would be possible to use xylan as an filler and disintegrant in pharmaceutical tablets (1,2). The purpose of this study was to evaluate the disintegrant properties of xylan and to compare these with the properties of four commercial materials used for direct compression of tablets. The effects of disintegrant concentration, drug solubility and tablet porosity on the processes of water penetration into tablet and tablet disruption were especially examined.

MATERIALS

Xylan, a polymerization product of pentose sugar xylose, was manufactured by Kemi OY (Kemi, Finland) using the methods described in Finnish Patent No. 55516. All the xylan used was from the same lot, and its chemical purity was industrial grade (Kemi OY). The material was stored for one week at a temperature of 20 °C and a relative humidity of 20 %. The large particles were then separated by sieving the material through a 700 µm sieve.

The disintegrant properties of xylan were compared with those of microcrystalline cellulose, Avicel PH 101 (FMC, Corp., Philadelphia, USA), microfine cellulose, Elcema G 250 (Degussa, Frankfurt/Main, West-Germany), carboxymethyl starch, Primojel STD (E. Mendell Co., New York, USA), and modified starch, Sta-Rx 1500 (Staley Mfg. Co., Illinois, USA).

Dicalcium phosphate, Emcompress (E. Mendell Co., New York, USA) was used as the base material in tablets. Emcompress was chosen because it is insoluble in water and has practically no intrinsic disintegrant property (3,4).

Ascorbic acid (Acidum ascorbicum, Ph. Eur.) and nitrazepam (Nitrazepamum, Ph. Eur.) were used as drug models. These drugs were chosen because of the difference in their water solubili-

ties. Ascorbic acid is soluble 1 in 4 of water, while nitrazepam is practically insoluble in water (5).

METHODS

Determination of Particle and Powder Properties

The particle size of the materials was examined using the microscopic method in which the Feret's diameter of four hundred particles is measured (6). Particle size data were treated using a model of the normal distribution. Thus the arithmetic mean diameter was used as a comparison value for the materials. The standard error of the mean was used to describe the precision of the values for mean diameter and the standard deviation to describe the width of the particle size distribution.

The water content of the materials was determined using a Mettler Drying Unit LP 12. Three determinations were made for every material and the mean was used in the results. The possible effect of crystal water was not calculated.

Loose density was determined by pouring a quantity of 100 ml of tablet mass through a funnel in a fine stream into a glass cylinder with a diameter of 25 mm and volume of 100 ml. Six determinations were made.

The values of the particle and powder properties are in Table I.

Swelling of Particles

The swelling properties of the adjuvants were studied using the method described by Steffens et al. (7). Using a Coulter Counter ZM apparatus with an orifice tube 280 μm in diameter, the particle size distribution of the adjuvants was determined in two electrolytes. The electrolytes used were water with 1 m/V % sodium chloride and isopropanol with 4 m/V % ammonium thiocyanate. The adjuvants tested were sieved through

TABLE I
Particle and powder properties of the materials.

Material	Arithmetic mean diameter (μm)	s.e.m. (μm)	r.s.d. (%)	Water content (%)	Loose density (g/ml)
Xylan	25.5	2.0	157.2	11.7	0.733
Avicel PH 101	19.1	1.0	109.5	3.9	0.285
Elcema G 250	121.0	7.1	118.0	5.6	0.359
Primojel STD	26.4	1.2	83.4	9.4	0.749
Sta-Rx 1500	18.7	0.7	75.4	10.1	0.610
Emcompress	39.5	2.9	144.4	4.9	0.849
Ascorbic acid	7.0	0.3	90.6	0.4	0.533
Nitrazepam	2.2	0.0	18.2	0.1	0.268

s.e.m. = standard error of arithmetic mean diameter
r.s.d. = relative standard deviation of arithmetic mean diameter

a 150 μm sieve before measurements were made. Because of the large and rather inconsistent background signals under 8 μm, only particles over this size were measured.

The swelling occurs especially in polar liquids. Thus the difference between cumulative volume of particles measured in water and that measured in isopropanol indicates the swelling potential of the adjuvant (7).

Preparation of The Masses

All materials were first sieved through a 700 μm sieve. In all the masses the drug content was 15 m/m %. The concentration of adjuvant added as a disintegrant was 0, 1.0, 2.5 and 5.0 m/m %. The base material, Emcompress, was added for obtaining 100 m/m %. The total weight of the masses was 250 g. The masses were mixed in a Turbula 2P mixer for 15 minutes with a rotation speed of 90 rpm, using a 2000 ml glass vessel. The lubricant, magnesium stearate, making up 0.5 m/m %

of the weight of drug-adjuvants mixture, was mixed manually by means of cards before tableting.

Compression and Evaluation of The Tablets

Flat faced tablets, 13 mm in diameter and 400 mg average weight were compressed using the Korsch EK-0 instrumented single-punch machine (8,9). Compressional pressure was adjusted to produce tablets with breaking strength of 3, 5 and 7.5 kg for ascorbic acid tablets and 5, 7.5 and 11 kg for nitrazepam tablets. Breaking strength was measured as the mean of twelve tablets using a Schleuniger 2E apparatus. The accurate breaking strenght of tablets as well as their dimensions were measured about 24 hours after tableting.

The porosity of tablets was determined by an air comparison pycnomoter (Beckman model 930) using helium as the inert gas. The test was performed ten times using a lot of twenty tablets.

The disintegration time of twelve tablets was determined in distilled 37° C water using a USP disintegration apparatus, Erweka XT 2, according to the technique described in the European Pharmacopoeia.

Penetration of water into the tablets was studied using an apparatus similar to that described by Ganderton and Selkirk (10). All tablets containing nitrazepam were studied, as well as the strongest tablets containing ascorbic acid. Three tablets were used for each determination. Distilled water at 20±1° C was used in this test. The tablet was placed onto the sinter of the apparatus. The amount of water penetrated through the sinter into the tablet was observed as a function of time using the capillary pipet connected to the apparatus.

Three parameters were obtained from the test of water penetration. Firstly, the total volume of penetrated water was determined. Secondly, the penetration index and, thirdly, the rate coefficient of penetration were obtained using the volume of penetrated vater, V, as a function of time, t. These parameters

were calculated from the modified Washburn equation (11,12,13):

$$V = K^m t^m \qquad (1a)$$

which can also be written in a logarithmic form as

$$\log V = m \log K + m \log t \qquad (1b)$$

where K is the rate coefficient and m is the penetration index. Thus plotting the penetration volume as a function of time on a double logarithmic scale, m can be calculated from the slope and then K from the value of m and the intercept of the linear portion of the curve. For all lots of tablets studied the linear portion began at the time of ten seconds. The end point varied between thirty and sixty seconds. The equation for this line was calculated using all the points from three measurements in the linear region. The total number of points used in calculations of the method of least squares varied between 12 and 18. The coefficient of determination, r^2, was over 0.887 for all the nitrazepam tablets and over 0.959 for all the ascorbic acid tablets.

The surface changes of tablets during water penetration were also studied. Tablets were placed on wet filter paper, the edges of which were immersed in $20 \pm 1^{\circ}$ C water. Thus the water that penetrated into the tablet was continously replaced by new water. Tablets were allowed to stand on the filter paper for five minutes, then they were photographed.

RESULTS AND DISCUSSION

Swelling of Particles

Particle size distributions for particles over 8 μm measured in two electrolytes with different polarities are in Fig. I. These two distributions were clearly different for all

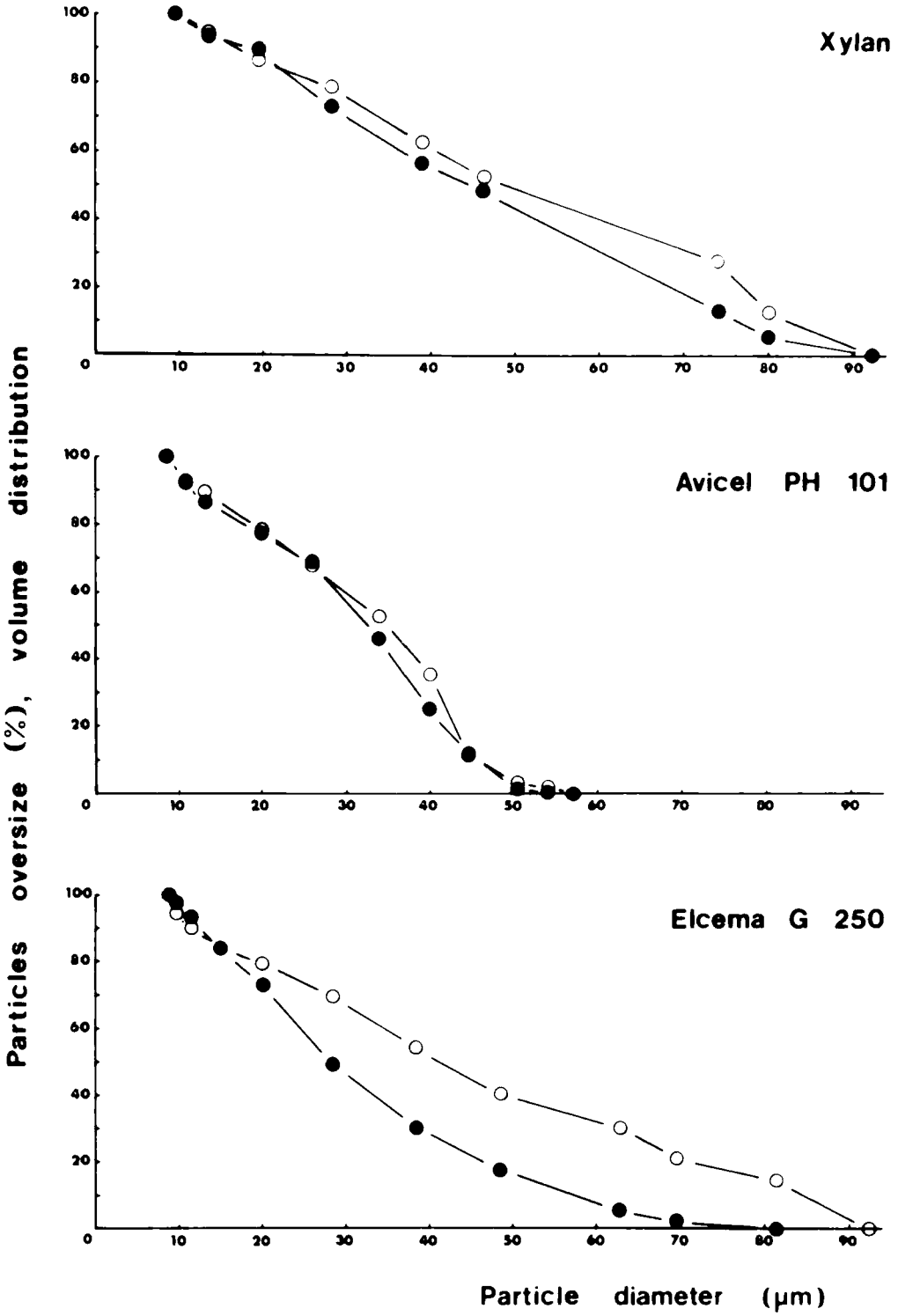

FIGURE I A
Cumulative volumes of particles larger than about 8 µm measured in 1 m/V % sodium chloride in water (○) and in 5 m/V % ammonium thiocyanate in isopropanol (●) using the electrical sensing zone (Coulter Counter) method.

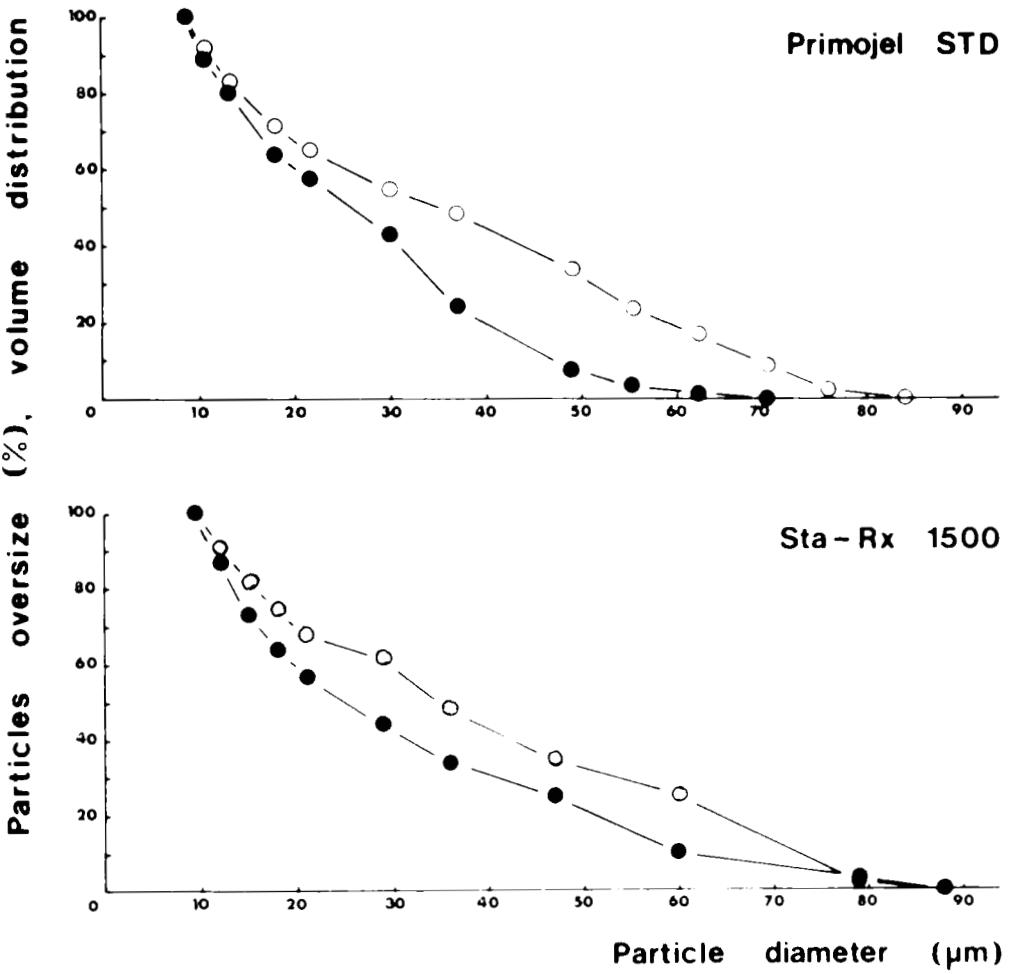

FIGURE I B
Key as in Figure I A.

adjuvants except Avicel. By designating the cumulative volume of particles in isopropanol as 1, the cumulative volumes in water were calculated, taking into account the percentages of particles in each size group as a frequency parameter. The comparison values thus obtained were 1.54 for xylan, 1.15 for Avicel, 3.43 for Elcema, 3.10 for Primojel, and 1.41 for Sta-Rx.

The fact that Elcema swelled more than Avicel and Primojel more than Sta-Rx confirm results obtained using other methods for determining the magnitude of swelling (14,15). Xylan particles swelled about as much as Sta-Rx particles. According to the scanning electron microscopic examination the structure of the particles of xylan, Primojel and Sta-Rx are fairly intact (2). Thus the swelling of these materials most probably is real swelling of primary particles. Cellulose derivatives are formed from separate and aggregated cellulose fibers (Elcema) or microfibers/microcrystals (Avicel). The swelling of Avicel was rather small and it appeared especially in large particles of Avicel. Thus the primary particles probably did not swell much but rather the structure of their aggregates broke and thus the material expanded slightly. Because the particle size of Elcema is much larger than that of Avicel (see Table I) and Elcema is composed mainly of mechanically aggregated cellulose fibers, the swelling or expanding of these aggregates was much clearer for Elcema than for Avicel. The trends observed by Gissinger and Stamm (15) for several Elcema brands with different particle sizes were the same. The larger, more aggregated particles swelled more. Thus swelling of aggregated cellulose particles is apparently not true swelling but is rather the expansion of particle structure owing to the hydrogen and mechanical bonds being broken by the penetrated water. Possibly, however, some crystal differences between Avicel and Elcema, may also create some true differences in swelling between these adjuvants.

Water Penetration into The Tablets

Values for constants of the modified Washburn equation obtained from water penetration measurements are in Tables II and III. Carli et al. (13) showed that low values for the penetration index, m, and also the rate coefficient, K, are related to the microstructure and are characterized by a broad

TABLE II

Effect of disintegrant on the penetration of water into ascorbic acid tablets. E=porosity of tablet, V_m=volumetric maximum water uptake, V_m/V_p=ratio of volumetric maximum water uptake to calculated pore volume. m=penetration index and K=rate coefficient obtained from the Washburn equation.

Disintegrant and its concentration (m/m %)	E (%)	V_m (ml)	V_m/V_p (%)	m (-)	K ($ml^{1/m}/g^{1/m}s$)
--------	---	15.3	0.055	128	0.213	$5.34 \cdot 10^{-7}$
Xylan	1.0	14.2	0.073	215	0.535	$3.21 \cdot 10^{-4}$
	2.5	15.3	0.093	251	0.784	$2.07 \cdot 10^{-3}$
	5.0	14.0	0.120	353	1.052	$7.28 \cdot 10^{-3}$
Avicel PH 101	1.0	14.7	0.038	109	0.468	$2.20 \cdot 10^{-4}$
	2.5	14.2	0.052	153	0.719	$1.22 \cdot 10^{-3}$
	5.0	13.6	0.063	191	1.091	$4.91 \cdot 10^{-3}$
Elcema G 250	1.0	14.3	0.057	163	0.492	$1.20 \cdot 10^{-4}$
	2.5	15.3	0.087	235	0.762	$1.45 \cdot 10^{-3}$
	5.0	14.4	0.123	342	1.037	$4.26 \cdot 10^{-3}$
Primojel STD	1.0	14.1	0.100	303	0.879	$2.36 \cdot 10^{-3}$
	2.5	14.7	0.137	381	0.874	$3.34 \cdot 10^{-3}$
	5.0	13.8	0.213	626	0.968	$4.66 \cdot 10^{-3}$
Sta-Rx 1500	1.0	14.8	0.077	220	0.648	$8.06 \cdot 10^{-4}$
	2.5	14.3	0.097	277	0.985	$4.09 \cdot 10^{-3}$
	5.0	14.5	0.125	347	0.972	$5.76 \cdot 10^{-3}$

distribution of pore size shifted towards the small pores, whereas high m and K values are characterized by a well-defined and narrow pore-size distribution, shifted towards the large pores. These authors also showed that increasing compressional pressures decrease m and K.

The rate coefficient, K, and penetration index, m, obtained for nitrazepam tablets with different porosities and without a disintegrant support the effect of pressure shown by Carli et al. (13) (see Table III). With increasing pressures, the pores became smaller and water penetrated the tablet more slowly. The values of K indicate that all the adjuvants used as disintegrants accelerated water penetration both into the ascorbic acid tablets and into the nitrazepam tablets (see

TABLE III

Effect of disintegrant and porosity of tablet on the penetration of water into nitrazepam tablets. Terms as in Table II.

Disintegrant and its concentration (m/m %)		E (%)	V_m (ml)	V_m/V_p (%)	m (-)	K ($ml^{1/m}/g^{1/m}s$)
--------	---	19.3	0.043	84	0.460	$2.14 \cdot 10^{-4}$
	---	15.8	0.020	50	0.435	$3.28 \cdot 10^{-6}$
	---	13.8	0.028	82	0.272	$4.85 \cdot 10^{-7}$
Xylan	1.0	20.2	0.078	147	0.887	$3.91 \cdot 10^{-3}$
	1.0	17.9	0.068	148	0.852	$3.62 \cdot 10^{-3}$
	1.0	13.8	0.053	156	0.758	$9.92 \cdot 10^{-4}$
	2.5	19.8	0.117	229	0.777	$4.46 \cdot 10^{-3}$
	2.5	15.6	0.112	280	1.355	$4.77 \cdot 10^{-3}$
	2.5	12.8	0.098	306	1.405	$5.56 \cdot 10^{-3}$
	5.0	18.5	0.162	331	0.632	$4.94 \cdot 10^{-3}$
	5.0	15.4	0.148	379	1.360	$1.12 \cdot 10^{-2}$
	5.0	12.9	0.153	478	1.612	$9.07 \cdot 10^{-3}$
Avicel PH 101	1.0	20.0	0.037	73	0.621	$1.09 \cdot 10^{-3}$
	1.0	15.9	0.042	105	0.528	$3.33 \cdot 10^{-4}$
	1.0	12.4	0.021	70	0.697	$1.97 \cdot 10^{-4}$
	2.5	17.8	0.048	104	0.530	$6.58 \cdot 10^{-4}$
	2.5	14.9	0.045	122	0.411	$9.01 \cdot 10^{-5}$
	2.5	11.7	0.032	110	0.483	$8.07 \cdot 10^{-5}$
	5.0	22.0	0.078	126	0.532	$1.77 \cdot 10^{-3}$
	5.0	14.9	0.052	137	0.710	$1.28 \cdot 10^{-3}$
	5.0	13.3	0.051	155	0.770	$1.35 \cdot 10^{-3}$
Elcema G 250	1.0	20.9	0.055	100	0.584	$1.24 \cdot 10^{-3}$
	1.0	15.3	0.042	111	0.550	$2.02 \cdot 10^{-4}$
	1.0	13.3	0.037	112	0.436	$4.88 \cdot 10^{-5}$
	2.5	19.3	0.080	160	0.835	$3.37 \cdot 10^{-3}$
	2.5	15.0	0.062	163	0.776	$1.38 \cdot 10^{-3}$
	2.5	13.3	0.052	158	1.131	$9.64 \cdot 10^{-4}$
	5.0	19.4	0.120	235	0.801	$5.93 \cdot 10^{-3}$
	5.0	16.0	0.107	261	1.047	$4.54 \cdot 10^{-3}$
	5.0	14.1	0.088	251	1.257	$3.62 \cdot 10^{-3}$
Primojel STD	1.0	18.8	0.238	486	1.058	$1.60 \cdot 10^{-2}$
	1.0	17.4	0.223	496	0.938	$1.70 \cdot 10^{-2}$
	1.0	13.2	0.223	697	1.478	$1.65 \cdot 10^{-2}$
	2.5	18.0	0.388	826	0.823	$3.05 \cdot 10^{-2}$
	2.5	15.5	0.390	975	0.913	$2.12 \cdot 10^{-2}$
	2.5	12.8	0.373	1203	1.172	$1.93 \cdot 10^{-2}$
	5.0	19.8	0.580	1094	0.481	$8.41 \cdot 10^{-2}$
	5.0	14.3	0.597	1658	0.617	$5.86 \cdot 10^{-2}$
	5.0	12.4	0.597	1990	1.049	$4.82 \cdot 10^{-2}$
Sta-Rx 1500	1.0	17.8	0.065	141	0.874	$2.80 \cdot 10^{-3}$
	1.0	15.5	0.045	115	0.898	$1.28 \cdot 10^{-3}$
	1.0	13.8	0.046	135	0.689	$6.63 \cdot 10^{-4}$
	2.5	20.0	0.128	242	0.835	$7.82 \cdot 10^{-3}$
	2.5	16.4	0.120	286	0.860	$5.42 \cdot 10^{-3}$
	2.5	14.3	0.112	311	1.156	$7.09 \cdot 10^{-3}$
	5.0	18.8	0.188	376	0.678	$1.01 \cdot 10^{-2}$
	5.0	16.0	0.202	493	1.381	$1.82 \cdot 10^{-2}$
	5.0	12.1	0.198	660	1.701	$1.58 \cdot 10^{-2}$

Tables II and III). Water penetrated more rapidly (i.e., K was larger) as the concentration of disintegrant increased. These results support the findings that several disintegrants made the tablets more hydrophilic (16,17,18). Values for the penetration index, m, tended in most cases to increase with increasing concentrations of disintegrant, indicating that the more disintegrant used, the larger the pores appeared during water penetration into tablets. This observation agrees very well with the values of V_m/V_p which can be used to describe the extent of extension of the tablet during water penetration. The particles were forced further apart, and larger empty spaces were created for the water to penetrate.

As the concentration of disintegrant increased, the decreasing porosity of the nitrazepam tablets caused a smaller decrease in rate of water penetration, K, and in many cases a larger increase in the penetration index, m (see Table III). Thus the disintegrants used reduced the retarding effect of decreasing capillary diameter on water penetration. Both the increasing hydrophilicity of pore walls and expanding pores due to swelling of particles are possible reasons for this. According to the volumetric maximum uptake of water, V_m, Primojel clearly at all concentrations studied and xylan and Sta-Rx at least at the larger concentrations drew about the same amount of water inside the tablet despite the original porosity of the tablet. Only the disintegrant concentration affected the level of maximum uptake. The decreasing porosity, however, decreased the rate of penetration and thus also decreased the rate of expansion of the tablet. For Avicel and Elcema both the porosity and the disintegrant concentration affected maximum water uptake. This emphasizes the differences between xylan and starch derivatives and cellulose derivatives in type of disintegrant action.

According to all the parameters (Tables II and III), xylan and starch derivatives seem to be more effective disintegrants

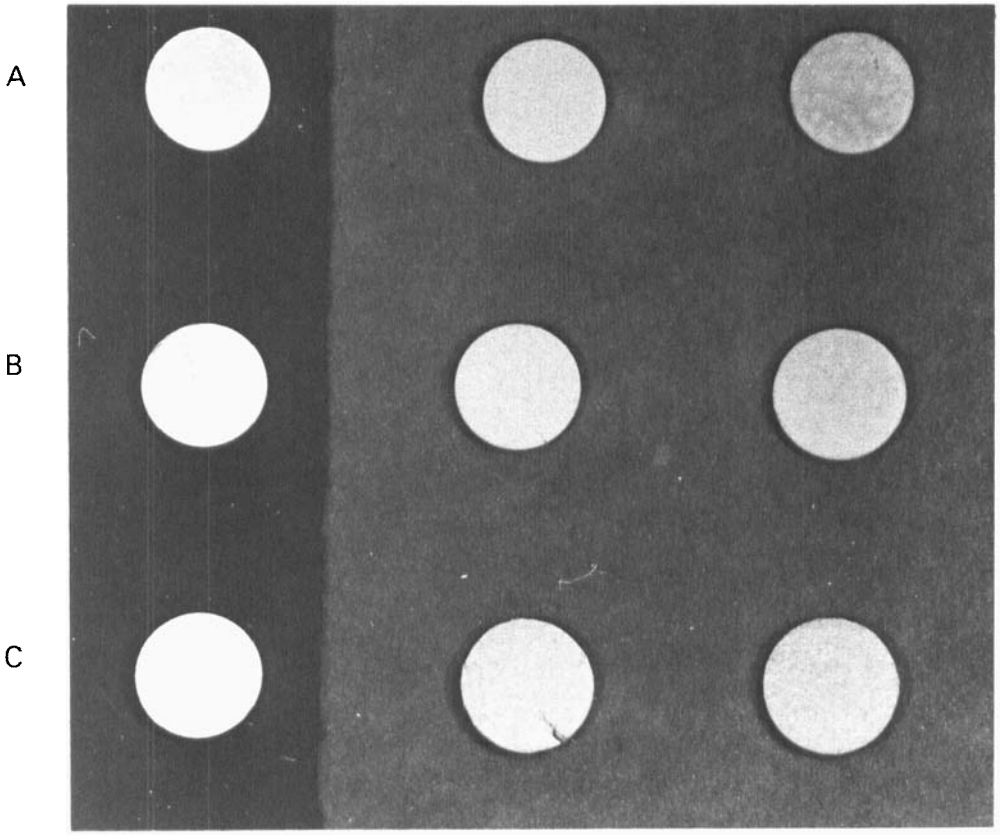

FIGURE II

Tablets before (darker background) and after (lighter background) expansion onto wet filter paper. Expanded tablets on the right contained 15 m/m % ascorbic acid, and those on the left contained 15 m/m % nitrazepam. Dicalcium phosphate was used as the base material in these tablets. The following disintegrants (concentration 5 m/m %) were used: A) no disintegrant, B) Avicel PH 101, C) Elcema G 250, D) Primojel STD, E) Sta-Rx 1500, F) xylan.

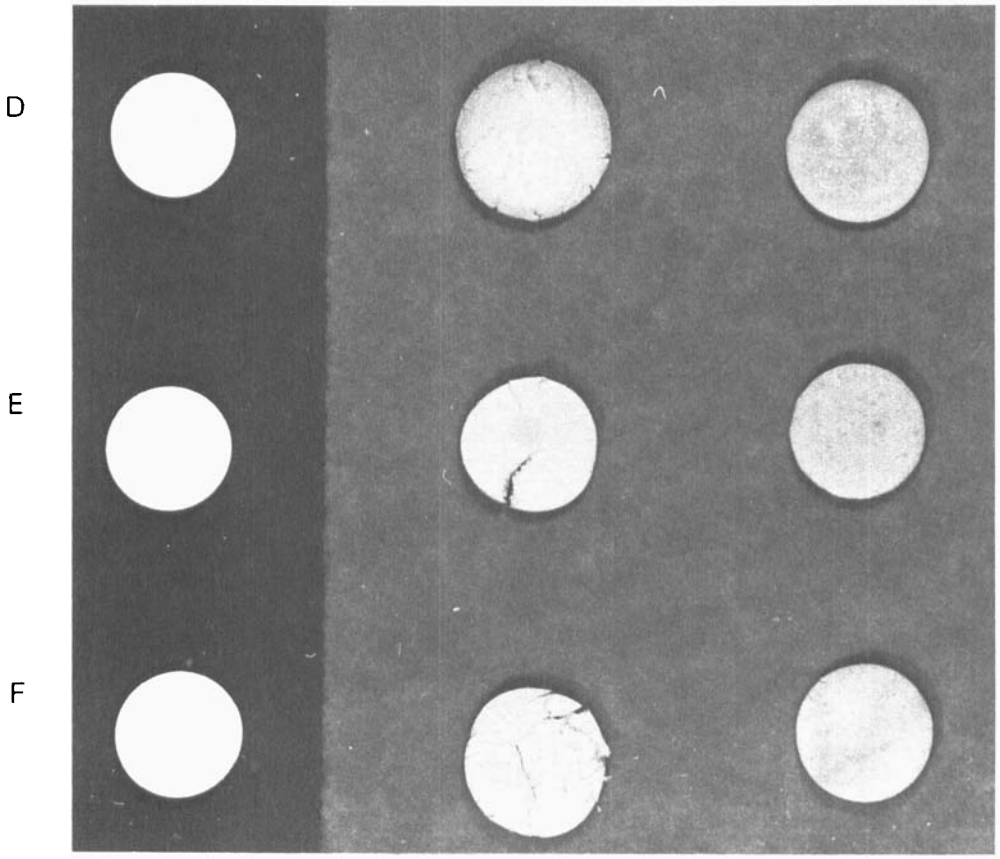

Figure 2 (Continued)

in nitrazepam tablets than in ascorbic acid tablets and cellulose derivatives behaved on the contrary. Differences in the swelling properties of these materials may partly explain these findings. The primary particles of xylan, Sta-Rx and Primojel swelled inside both kinds of tablets. These materials broke the nitrazepam tablets at least partly by means of the

swelling of particles (see Fig. II). In ascorbic acid tablets the drug dissolved rapidly, and the tablet became more porous. Thus there was more space for the particles to swell without breaking the tablet. The rate of water penetration into ascorbic acid tablets containing these swelling disintegrants decreased compared with the corresponding nitrazepam tablets with nearly the same initial porosities (see K and E values in Tables II and III). This supports the finding of Graf et al. (19) for several swelling disintegrants that they retarded water penetration as the solubility of the drug increased. Inside the slightly expanded but rather intact ascorbic acid tablets (see V_m/V_p values in Tables II and III and Fig. II), the swelling particles partly filled the voids, and thus water could not penetrate the tablets so easily. The penetrating water became more viscous, owing to dissolved ascorbic acid; this might also have decreased the rate of penetration. Although in water the nitrazepam tablets contained fewer small pores than did tablets containing ascorbic acid, the nitrazepam tablets contained many relatively large cracks. The water penetrated easily through these cracks.

Accordingly, in addition to increasing the hydrophilicity of the tablet, the swelling of particles may also be an important mechanism by which xylan and starch derivatives act. The increased volume of the particles due to swelling is, however, not large enough to break the tablet apart (20,21,22). Even if swelling is not the primary reason, in any case it enlarges the voids and facilitates the creating of cracks, especially inside the intact insoluble tablet. This allows the penetrating water to distroy the cohesive forces and create repulsive forces between the particles. Values for the penetration index, m, of the Washburn equation for ascorbic acid tablets containing xylan, Sta-Rx and Primojel are clearly smaller than those for the

corresponding nitrazepam tablets with nearly the same porosities (see Tables II and III). According to Carli's theory (13), both the values of K and m indicate that the pores for water to penetrate were smaller in ascorbic acid tablets than in nitrazepam tablets. Thus in theory, the swelling of particles should be more effective in water insoluble tablets. Dissolution of the drug, however, breaks bonds inside the tablet and weakens it, a process that can affect the disintegration of tablets considerably.

The Avicel particles swelled only slightly (see Fig. I). In tests of water penetration, the behaviour of this material was almost opposite that of xylan and starch derivatives. Ascorbic acid tablets containing Avicel absorbed more water and more rapidly than did the corresponding nitrazepam tablets. Increasing values for V_m/V_p and the constant, m, of the Washburn equation indicate that ascorbic acid tablets expanded more and contained larger voids than did the corresponding nitrazepam tablets (see Tables II and III). Thus rapid dissolution of ascorbic acid seems to have enabled microcrystalline cellulose in small concentrations to act as a disintegrant. This finding agrees with that of Sixsmith (23) for microcrystalline cellulose at concentrations of 2-8 % in lactose tablets but disagrees with that of Lerk et al. (24) for concentrations of 10-40 % in maltose-dextrose and Emcompress tablets. Large amounts of Avicel are evidently so hydrophilic that this material also acts very effectively in insoluble tablets. Reier and Shangraw (25) pointed out that the most probable mechanism by which this material acts is that the hydrogen bonds between cellulose particles are broken by the penetrated water and the particles are forced further apart. All results from the water penetration tests in this study, support this theory (see Tables II and III). At the concent-

rations used, tablets containing Avicel clearly did not become as hydrophilic as tablets containing xylan and the starch derivatives. Thus Avicel was much less effective in nitrazepam tablets, which also maintained their dense structures during water penetration, than in looser ascorbic acid tablets. At small concentrations in the tablet, Avicel seems to demand a certain amount of penetrated water surrounding particles before it can act effectively as a disintegrant.

According to all parameters used, the disintegrant properties of Elcema are intermediate between those of Avicel and the other materials. List and Muazzam (26,27,28,29) and Colombo et al. (30) have emphasized that the most important factor in the swelling of particles is not the extent of swelling but the force of swelling, meaning that the pushing effect due to swelling must be strong enough to break the tablet apart. Obviously, the pressure of swelling was only moderate for Elcema, although it swelled extensively. The firm structure of nitrazepam tablets was partly responsible for preventing cellulose aggregates from swelling and expanding. Swelling of this adjuvant was more evident in the porous ascorbic acid tablets. In water penetration tests it is difficult to determine which part of the effect of Elcema was due to swelling of aggregates, which due to swelling of primary cellulose particles, and which to effects like those found in Avicel.

Disintegration of Tablets

High water solubility of a drug or tablet adjuvant, with some rare exceptions, enhances disintegration (19,24). For tablets lacking disintegrants and containing the virtually insoluble nitrazepam, disintegration time was longer than that for corresponding tablets containing water-soluble ascorbic acid (see Fig. III). Differences between the disintegrant

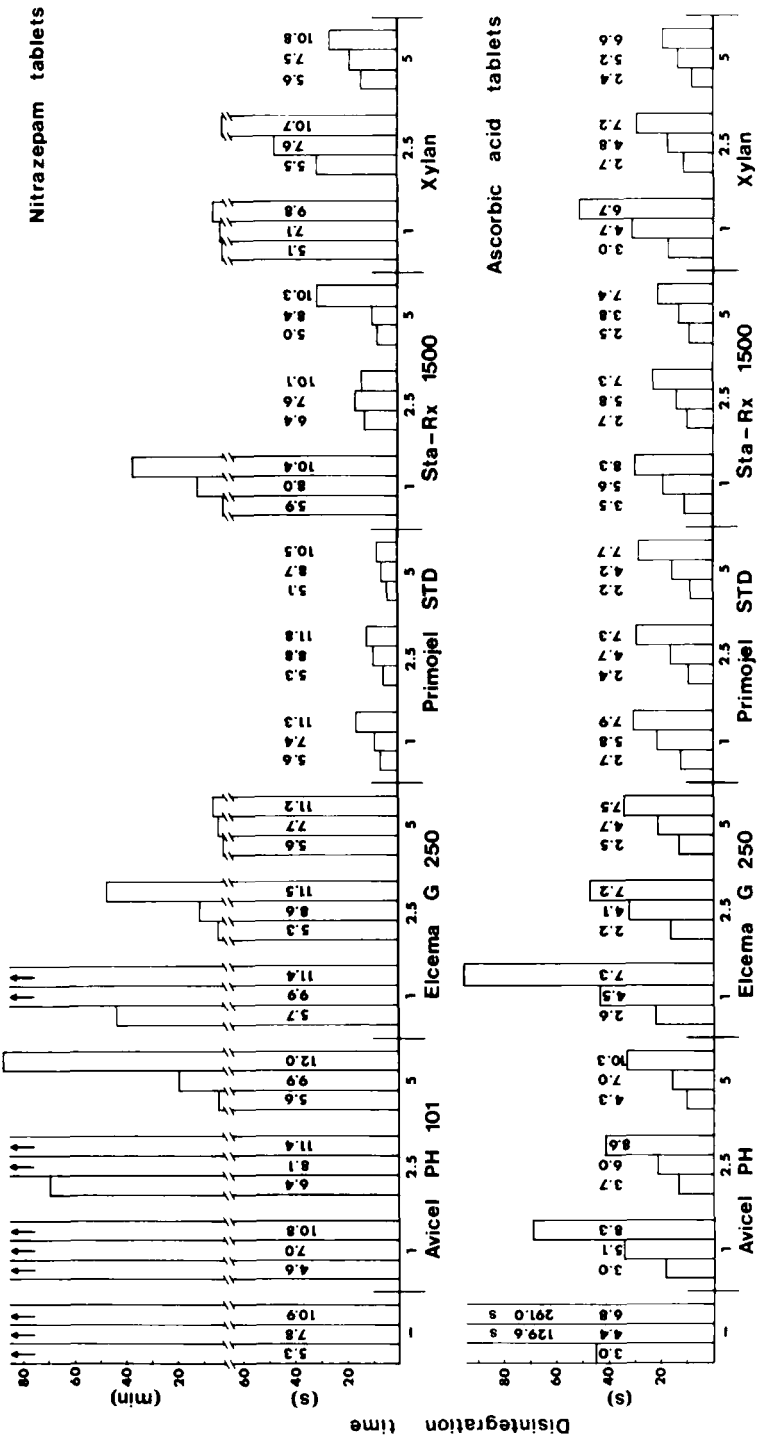

FIGURE III

Disintegration time for tablets containing either 15 m/m % nitrazepam (upper figure) or 15 m/m % ascorbic acid (lower figure) as the drug. Dicalcium phosphate was used as the base material in these tablets. Disintegrants and their concentrations (m/m %) in the tablets are under the columns. The breaking strengths of tablets are inside or above the columns. Arrows indicate disintegration times over 120 minutes.

potencies of the materials tested were greater in nitrazepam tablets than in ascorbic acid tablets. Based on their efficacy in nitrazepam tablets containing 1 m/m %, the descending order of the disintegrants was: Primojel, xylan, Sta-Rx, Elcema and Avicel. For the other two concentrations of disintegrant the order was similar, except that Sta-Rx at a concentration of 2.5 m/m % was slightly more potent than xylan.

For all ascorbic acid tablets the disintegration times were rather short. The potencies of the disintegrants in these tablets were about the same. The difference between the potencies of disintegrants in ascorbic acid tablets compared with nitrazepam tablets was clearly greater for cellulose derivatives than for xylan and starch derivatives. At all concentrations studied for Primojel and at the concentrations of 2.5 and 5 m/m % for xylan and Sta-Rx, respectively, the absolute effectiveness of these disintegrants was even weaker in ascorbic acid tablets than in corresponding nitrazepam tablets with nearly the same porosities. On the other hand, at all concentrations cellulose derivatives were more potent in ascorbic acid tablets than in nitrazepam tablets. Avicel accelerated disintegration of ascorbic acid tablets more than Elcema did, but in nitrazepam tablets Elcema was more effective than Avicel.

Results obtained in disintegration tests completely support observations obtained in tests of water penetration. Thus water penetration seems to be the step that limits the rate of disintegration for the tablets studied, a finding in agreement with those of Nogami et al. (31), Couvreur et al. (18), Lagas et al. (32) and Colombo et al. (30).

Xylan, Sta-Rx and Primojel, all of which had particles swelled, seemed to be relatively more potent in water insoluble tablets. Thus the greater expansion of dense nitrazepam tablets

in tests of water penetration correlates well with findings for disintegration. The results of this study support, however, only partly previous findings that disintegration accelerates with decreasing porosity of the tablets, owing to more effective swelling in dense tablets (33,34). In spite of disintegrant concentration, all disintegration times increased when the original porosity of tablets decreased or when breaking strength increased. Thus the phase when the tablet becomes wet and water penetrates into it, which is retarded with decreasing porosity, is probably also the rate limiting step for effective swelling of particles and thus for disintegration of tablets.

Microcrystalline cellulose, which even at concentrations used did not draw water inside the tablets very actively, acted much more effectively in tablets containing water soluble ascorbic acid than in those with insoluble nitrazepam. This agrees with the finding of Khan and Rhodes (35) that microcrystalline cellulose is a relatively ineffective disintegrant in insoluble tablets. Thus the effectiveness of this material greatly depends on the original porosity of the tablets as well as the porosity created during water penetration. As the porosity of tablets decreased and their breaking strength increased, the disintegration times increased relatively more for Avicel than for xylan and starch derivative tablets. A certain amount of water must be available for Avicel before it can act effectively as disintegrant. Thus the process of water penetration also limits the rate of disintegration for tablets containing this material.

In disintegration tests and in water penetration tests, Elcema behaved as an intermediate material between Avicel and those adjuvants that merely swelled. Thus Elcema is more effective than swelling adjuvants in ascorbic acid tablets but not as effective as Avicel. The disintegration mechanisms of

Elcema probably combine those of Avicel and those of xylan and starch derivatives.

CONCLUSIONS

The disintegrant properties of xylan were weaker than those of carboximethyl starch, Primojel STD, but almost as good as those of modified starch, Sta-Rx 1500. In water all these adjuvants underwent extensive swelling of the primary particles. Swelling of cellulose microcrystals of Avicel was slight but that of cellulose aggregates of Elcema was extensive, probably due to the expanding structure of these aggregates.

The adjuvants tested as disintegrants, including xylan, made the tablets more hydrophilic. Thus more water penetrated rapidly into tablets containing these materials. Porosity of the tablets did not affect the maximum volume of water taken into tablets containing swelling disintegrants. Only the concentration of the disintegrant was significant. Both porosity and concentration affected the amount of water that penetrated into tablets containing cellulose derivatives.

Xylan and starch derivatives were clearly more effective in tablets containing water insoluble nitrazepam than in those with water soluble ascorbic acid. On the contrary, cellulose derivatives, especially Avicel, were more effective in ascorbic acid tablets than in nitrazepam tablets. At the beginning of water penetration process, water penetrated more easily into ascorbic acid tablets than into nitrazepam tablets. Ascorbic acid dissolved from the tablet, and larger pores formed inside tablet. Water reached the particles of cellulose derivatives much faster and broke the bonds more easily in ascorbic acid tablets than in dense nitrazepam tablets. On the other hand, after dissolving of ascorbic acid there was more space for the particles of xylan and starch derivatives to swell and partially

refill the formed voids without breaking the tablet. Inside dense nitrazepam tablets the swelling particles enlarged voids and facilitated the creating of cracks. Thus the penetrated water was allowed to destroy the cohesive forces and create repulsive forces between the particles.

Results obtained in the disintegration test supported those obtained in the water penetration test. Thus the penetration of water into tablets seemed to be the step that limited the rate of disintegration of tablets.

In conclusion, xylan seems to be a possible disintegrant for tablets. An essential disintegrating mechanism of xylan is the swelling of primary particles. In addition to the properties examined in this study, many other factors can affect the usefulness of xylan in pharmaceutical products.

REFERENCES

1. M. Juslin and P. Paronen, J. Pharm. Pmarmacol., in press
2. P. Paronen, "Xylan as A Direct Compression Adjuvant for Tablets," Dissertation, University of Kuopio, Kuopio 1983
3. W. Feinstein and A.J. Bartilucci, J. Pharm. Sci., 55, 332 (1966)
4. K.A. Khan and C.T. Rhodes, J. Pharm. Sci., 64, 166 (1975)
5. E.G.C. Clarke, "Isolation and Identification of Drugs," The Pharmaceutical Press, London, 1971
6. T. Allen, "Particle Size Measurements," Chapman and Hall Ltd, London, 1975
7. K.J. Steffens, P.H. List and U.A. Muazzam, Acta Pharm. Technol., 26, 254 (1980)
8. P. Puumalainen, M. Juslin and J. Nyyssönen, Pharm. Ind., 40, 979 (1978)
9. M. Juslin and P. Paronen, J. Pharm. Pharmacol., 32, 796 (1980)

10. D. Ganderton and A.B. Selkirk, J. Pharm. Pharmacol., 22, 345 (1970)
11. F. Carli and L. Simioni, J. Pharm. Pharmacol., 31, 128 (1979)
12. F. Carli and L. Simioni, Int. J. Phar. Tech. Prod. Mfr., 2, 23 (1981)
13. F. Carli, I. Colombo, L. Simioni and R. Bianchini, J. Pharm. Pharmacol., 33, 129 (1981)
14. K.A. Khan and C.T. Rhodes, J. Pharm. Sci., 64, 447 (1975)
15. D. Gissinger and A. Stamm, Drug Dev. Ind. Pharm., 6, 511 (1980)
16. D. Ganderton and D.R. Fraser, J. Pharm. Pharmacol., 22, Suppl., 95S (1970)
17. D.R. Fraser and D. Ganderton, J. Pharm. Pharmacol., 23, Suppl., 18S (1971)
18. P. Couvreur, J. Gillard and M. Roland, Ann. Pharm. Franc., 34, 123 (1976)
19. E. Graf, A.H. Ghannem and H. Mahmoud, Pharm. Ind. 44, 200 (1982)
20. J.T. Ingram and W. Lowenthal, J. Pharm. Sci., 55, 614 (1966)
21. J.T. Ingram and W. Lowenthal, J. Pharm. Sci 57, 393 (1968)
22. A.M. Guyot-Hermann and J. Ringard, Drug Dev. Ind. Pharm., 7, 155 (1981)
23. D. Sixsmith, J. Pharm. Pharmacol., 29, 82 (1977)
24. C.F. Lerk, G.K. Bolhuis and A.H. DeBoer, J. Pharm. Sci., 68, 205 (1979)
25. G.E. Reier and R.F. Shangraw, J. Pharm. Sci., 55, 510 (1966)
26. P.H. List and U.A. Muazzam, Pharm. Ind., 41, 459 (1979)
27. P.H. List and U.A. Muazzam, Pharm. Ind., 41, 1075 (1979)
28. P.H. List and U.A. Muazzam, Pharm. Ind., 42, 406 (1980)
29. P.H. List and U.A. Muazzam, Pharm. Ind., 43, 481 (1981)

30. P. Colombo, C. Caramella, U. Conte, A.L. LaManna, A.M. Guyot-Hermann and J. Ringard, Drug Dev. Ind. Pharm. 7, 135 (1981)
31. H. Nogami, T. Nagai and H. Uchrida, Chem. Pharm. Bull., 14, 152 (1966)
32. M. Lagas, C.F. Lerk and D.D. Breimer, Pharm. Weekbl. Sci. Ed., 2, 541 (1980)
33. P.M. Hill, J. Pharm. Sci., 65, 1694 (1976)
34. K.A. Khan and D.J. Rooke, J. Pharm. Pharmacol. 28, 633 (1976)
35. K.A. Khan and C.T. Rhodes, Can. J. Pharm. Sci., 10, 62 (1975)