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SORBITOL INSTANT
AN EXCIPIENT WITH UNIQUE TABLETING PROPERTIES

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ABSTRACT

The manifold tableting applications of sorbitol instant - a special type of spray-dried sorbitol - are described and numerous examples of tablet formulations are given. It is shown that the unique tableting properties of sorbitol instant chiefly result from its crystalline structure, which consists of very loosely-packed, randomly oriented, interwoven filamentary crystals. Due to the large compressibility of sorbitol instant, tablet formulations for low-dose as well as for high-dose drugs are relatively simple. Even though tablet disintegration is slower compared to standard formulations based on lactose, drug dissolution can be optimized in most cases by the proper

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selection of the disintegrant. Compared to crystalline sorbitol, sorbitol instant is a more universal tablet binder.

Sorbitol instant is an example showing that the tableting characteristics of a chemical substance can be improved by adequately altering its physical and mechanical properties.

INTRODUCTION

As the result of the steadily increasing importance of direct compression during the past few years many new excipients with interesting tableting properties have become commercially available. In order to be suitable for direct compression, an excipient must possess good flowability, favorable mixing properties, and high cohesion after compression. The advantages of directly compressible materials for tablet manufacture are self-evident. Direct compression is the most economical, the most energy-efficient, and the most expeditions tableting method, since it involves the least handling of materials, no drying steps are needed, it eliminates the effect of heat and moisture on drugs, and finally, the optimization of tablet disintegration is easy. However, flexibility in formulating high-dose drugs had to be frequently compromised. When low-dose drugs were processed by direct compression problems of segregation and of content uniformity were also common thus far.

Much has been undertaken in order to develop direct compression (DC) excipients with optimum technological properties (1). As a result of these efforts DC-lactose, DC-dextrose, DC-sucrose, and several types of DC-celluloses and DC-inorganic fillers became available.

Crystalline sorbitol is also a DC-excipient.

Although sorbitol is one of the most widely used tablet fillers in the sugarless confectionery industry and many medicated lozenges are formulated on a sorbitol-basis, its uses in common tablet formulations and other solid dosage forms are still very limited at present. There are three major reasons why pharmaceutical formulators have a preference for more conventional binders or fillers. The first reason is that the hygroscopic nature of sorbitol may limit to some extent the optimum operating conditions of normal tableting equipment. Another reason is that long-term keeping properties of sorbitol tablets and the chemical stability of a sufficiently large number of drugs in these formulations have not yet been studied comprehensively. Finally, the last reason is that most crystalline types of sorbitol, which are mainly optimized for confectionery application and lozenge production, do not have many of the advantages of the well-known excipients normally used in pharmaceutical applications, like the different types of direct compression lactose or microcrystalline cellulose.

Most of the earlier drawbacks of sorbitol have now been overcome: modern pharmaceutical plants are well prepared to process materials far more hygroscopic than sorbitol, the stability of pharmaceutical formulations can be guaranteed by the careful selection of the excipients and the selection of a suitable packing, and finally, special modifications of the crystalline structure of sorbitol have recently provided materials with superior tableting properties. One of these types of directly compressible sorbitols, which has many advantageous properties, not only in conventional

applications e g lozenges or troches, but which is also especially suited for pharmaceutical tablets, is sorbitol instant (2). The purpose of this paper is to show how special modifications of the crystalline structure of sorbitol can affect its application properties and to point out its advantages and limits.

EXPERIMENTAL

1. Materials

Sorbitol Instant

Sorbitol Instant is prepared by a special spray-drying process, the raw material being a concentrated solution of very pure sorbitol. Like most types of crystalline sorbitol intended for direct compression it is constituted of more than 90 % of the γ-polymorphic form. The particle size distribution ranges from 200 µm to 850 µm, being centered around 500 µm. Compared to many other types of sorbitol, sorbitol instant is characterized by a comparatively large surface area of about 1.0 m^2/g, a low bulk density of about 0.4 g/ml, and a low tamped density of about 0.5 g/ml. The material is virtually dustless and has excellent flowability.

Two types of sorbitol instant were used for tableting: Sorbitol Instant DAB 8, NF XVI, BP 80, E 420 (Merck Cat.No. 3140) and Sorbitol Instant FG, NF XVI, FCC (Merck Cat.No. 3557). Both types of sorbitol meet the purity requirements for food application according to the FRG-Zusatzstoffverordnung and the Food Chemicals Codex. The content of water is less than 1 %. The two types of sorbitol differ in the content of mannitol, which is 0.5 - 2 % for type 3140 and 5 - 7 % for type 3557.

The tableting properties of both types of sorbitol instant are equivalent. The physical properties are listed in Table 1.

Other Materials

The following materials of other suppliers were used in this study:

Material	Trade Name	Supplier
Acetaminophen 96 %	Paracetamol-Granulat PNUU	Hoechst AG (Frankfurt/M.,FRG)
Colloidal silicon dioxide	Aerosil 200	Degussa AG (Frankfurt/M.,FRG)
Croscarmellose	Ac-Di-Sol	FMC-Corp. (Philadelphia,USA)
Crystalline sorbitol	Neosorb 20/60	Roquette Frères (Lestrem, France)
DC-dextrose	Emdex	Ed. Mendell Co. (Carmel, NY, USA)
DC-ß-lactose (anhydrous)	DC-Lactose 21	DMV (Veghel, Netherlands)
DC-sucrose	Di-Pac	Amstar Corp. (New York, NY, USA)
Fibrous cellulose	Elcema F 150	Degussa AG (Frankfurt/M.,FRG)
Microcrystalline cellulose	Avicel PH 101	FMC-Corp. (Philadelphia,USA)
Powdered triglyceride	Dynasan 114	Dynamit Nobel AG (Troisdorf-Oberlar, FRG)

All other drugs and excipients used in this investigation were taken from the standard assortment of E. MERCK - Darmstadt (FRG).

TABLE 1

Physical Properties of Sorbitol Instant

Microscopic evaluation:	agglomerated particles with rough and irregular surface
Melting point:	96° - 101°C (high values for low content of mannitol)
Bulk density:	0.38 - 0.46 g/ml
Tamped density:	0.46 - 0.52 g/ml
Surface area (BET):	0.95 - 1.05 m^2/g
Surface area (calculated from RRSB-distribution):	0.98×10^{-2} - 1.08×10^{-2} m^2/g
d'-Parameter (R= 36.8 %; RRSB-distribution):	410 - 500 µm
Flowability:	7.5 - 8.5 g/s (gravimetric) 17.0 -19.0 ml/s (volumetric)
Particle size distribution:	< 100 µm : - 100 - 212 µm : < 15 % 212 - 500 µm : 60 - 90 % 500 - 850 µm : 3 - 35 % 850 -1000 µm : < 5 % >1000 µm : -

2. Methods

Tablets were prepared in the usual way. The ingredients were passed through a 1000 µm screen and were blended for 5 - 10 min in a 2 l T2C-Turbula-mixer (W. Bachofen, Basel, Switzerland). Tablets were compressed on a Korsch EKO-DMS single punch eccentric tablet press instrumented with strain gauges (E.Korsch, West-Berlin, FRG). Flat-faced, bevel-edged punches were used throughout this work; the press ran at a speed of 54 tablets per minute. Compressional forces (upper and lower punches) and ejectional forces were monitored by using a Hottinger-Baldwin (Darmstadt,FRG)

system of measuring and recording instruments (TE - MG 372 A, SP 3540 A and Kern-Analogger AL 4). No tableting problems were observed with the formulations given in this paper (batch size was 1 - 2 kg).

Tablet hardness was measured by use of a Heberlein-type hardness tester (Model TBH 28, Erweka, Heusenstamm, FRG). Friability was determined by means of a Roche-type friabilator (100 revolutions within 4 min). The disintegration time (average of 6 tablets) was determined by use of a disintegration tester (Model ZT 3, Erweka, Heusenstamm, FRG), according to the method described in the European Pharmacopoeia.

Drug dissolution was determined according to the method described in the USP XXI, apparatus 2 being used (Sotax AT-6, Basel, Switzerland). The testing fluid was 0.1 M hydrochloric acid; the concentration of the dissolved drug was measured spectrophotometrically (Kontron Uvikon 810, Zürich, Switzerland). Every determination was carried out 6 times.

RESULTS AND DISCUSSION

1. Sorbitol Instant

The large surface area and the low bulk density of sorbitol instant are determined by its very loose crystalline matrix, which is made up of interwoven filamentary crystals. This structure can be easily seen by scanning electron microscopy. It is this structure that imparts to sorbitol instant its unique tableting properties.

The better ratio of compressional force to tablet hardness for sorbitol instant is a function of its crystalline structure: during tableting the initially loosely-packed filamentary crystals are easily compacted and the

interpenetration of the crystals results in improved tablet hardness and a smooth surface, which seals up the tablet against atmospheric moisture. The compressibility profiles of a series of direct compression excipients are shown in Figure 1. Sorbitol instant is the excipient which gives the hardest tablets for all compressional forces.

In Table 2 the hygroscopicity of tablets made of the same direct compression excipients is compiled. The hygroscopicity is expressed in terms of weight increase of the tablets after storage at room temperature in an atmosphere of 65 % relative humidity. The least hygroscopic materials are lactose and sucrose, as expected. It is interesting to notice, however, that tablets made of sorbitol instant are significantly less hygroscopic than tablets made of crystalline sorbitol. This is certainly the result of the extreme hardness and the distinctly sintered structure of the tablets made of sorbitol instant (3). The effect of the compressional force on the hygroscopicity was almost negligible for all excipients.

The individual particles of sorbitol instant are very irregularly shaped, because they are composed of a large number of very small particles agglomerated together. As a result of this, the granules of sorbitol instant exhibit many irregularities, indentations, and small cavities. These indentations can act as sites of preferential accumulation of other powdered substances and they give another notable property to this type of sorbitol: the capability of forming ordered mixtures or even supersaturated ordered mixtures. Sorbitol instant can thus be used as an excellent carrier or vehicle for drugs in stable solid mixtures with no tendency of segregation; it has wide practical appli-

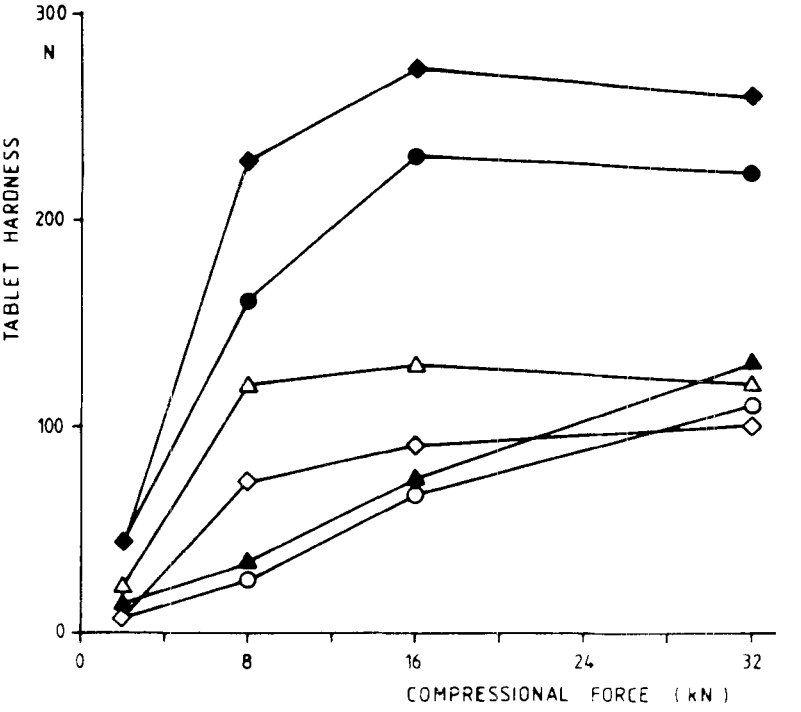

FIGURE 1

Compressibility profiles of DC-excipients (tablet diameter: 11 mm; tablet weight: 360 mg; lubricant: 1 % magnesium stearate).
-◆- sorbitol instant, -●- DC-dextrose, -△- granulation of powdered sorbitol (no binder), -◇- crystalline sorbitol, -▲- DC-ß-lactose, -○- DC-sucrose

cability, e g in premixes, master-batches, reconstitution syrups or suspensions, and in general direct compression formulations (4).

2. Lozenges

The preparation of sugarless lozenges using Sorbitol instant does not require fundamental deviations from the standard techniques applicable to other crystalline types. Formulations having 90 % or more of

TABLE 2

Hygroscopicity of Tablets Made of Different Direct Compression Excipients (tablet diameter: 11 mm; tablet weight: 360 mg; compressional force: 2 - 32 kN; storage conditions: room temperature, 65 % relative humidity)

Excipient	Weight increase after storage		
	1 week	2 weeks	4 weeks
Sorbitol instant	0.6 %	0.6 %	0.8 %
Crystalline sorbitol	1.1 %	1.2 %	1.3 %
DC-dextrose	0.7 %	0.9 %	1.1 %
DC-lactose	0.1 %	0.1 %	0.1 %
DC-sucrose	0.1 %	0.2 %	0.2 %

sorbitol instant are directly compressed by adding 0.5 - 1 % of magnesium stearate or 4 - 5 % of stearic acid or the same quantity of a pulverized glyceride, e g glycerol tristearate. No other tableting adjuvants are needed. The nature of the remaining ingredients is not important: flavours, refreshants, colorants, or drugs, such as sodium fluoride, benzocaine, cetylpyridinium chloride, magnesium peroxide, dextromethorphan, etc can be used. If the particle size of these ingredients is sufficiently small, very smoth and palatable tablets are always obtained, the grittiness being significantly reduced compared to tablets of normal crystalline sorbitol. Tablet hardness can be adjusted within broad limits by applying different compressional forces during tableting. The maximum tablet hardness obtainable far exceeds that obtained with ordinary sorbitol: a factor of two or more is easily attained (3, 5). Even if the tablets made of

sorbitol instant are much harder than those of ordinary sorbitol, the volume of the tablets is approximately 10 % larger, an advantage for products marketed on a volume basis. However, if tablet hardness is fixed, sorbitol instant enables a lower compression setting, which reduces the wear of the equipment. Friability of lozenges made of sorbitol instant is very small (0.1 - 0.2 %).

It is also possible to improve the tableting characteristics of crystalline sorbitol by carefully controlling the crystallization of molten material (6). The products obtained have higher compressibilities than ordinary crystalline sorbitol and their use in lozenge production is advantageous. The unique tableting and mixing properties of sorbitol instant are, however, not attained.

3. Chewable Tablets

Chewable tablets with a content of sorbitol instant from 50 % to 75 % can be readily prepared by direct compression. In most cases it is not possible to make similar tablets by direct compression using ordinary crystalline sorbitol as a substitute for the instant material. This is attributed to the capability of sorbitol instant to adsorb comparatively large quantities - in some cases up to 20 % - of the active ingredients of the tableting mixture by forming supersaturated orderd mixtures, which are still directly compressible. This effect naturally depends markedly on the nature and on the particle size of the active ingredients (4). Sorbitol instant can thus bind the fines of tableting mixtures and in this way decrease their detrimental effect on tableting.

Numerous formulations of chewable tablets could be given, but we will confine ourselves to a few typical formulations which were selected to demonstrate the versatility of sorbitol instant. Ascorbic acid tablets have been considered in detail elsewhere (7). Two formulations of multivitamin tablets, one antacid formulation and one aspirin formulation will be given in this paper. The composition and the properties of a saccharated and a sugarless multivitamin tablet are given in Table 3. It should be noted that the taste properties and the cooling effect of both formulations can be improved by adding 100 - 200 mg of xylitol, at the expense of sorbitol, without affecting the properties of the tablets noticeably. Tablet hardness and chewing qualities can be altered by adding 100 - 200 mg of microcrystalline cellulose or pregelatinized starch, likewise at the expense of sorbitol. The use of pregelatinized starch seems to improve long-term stability of the tablets (8).

The vitamin premix used was composed as follows: 2.7 % thiamine mononitrate, 3.4 % riboflavine, 3.1 % pyridoxine hydrochloride, 10.1 % vitamin B 12 trituration (0.1 % on mannitol), 0.9 % folic acid, 15.0 % calcium pantothenate, 21.5 % niacinamide, 0.3 % biotin and 43.0 % tocopherol acetate (50 % spray-dried). Thus, one tablet approximately corresponds to the daily human vitamin requirements.

Details of an aspirin and of an antacid calcium carbonate tablet are given in Table 4. Since fine crystalline aspirin was used to reduce grittiness when the tablets are chewed, an additional granulation step by slugging is required. The antacid mixture is free-flowing and easily compressible. It is possible to alter the chewing characteristics of both formulations

TABLE 3

Multivitamin Tablets

	Saccharated	Sugarless
Vitamin premix	66 mg	66 mg
DC-ascorbic acid 90 %	105 mg	105 mg
DC-sucrose	900 mg	-
Sorbitol instant	645 mg	1140 mg
Pulverized triglyceride	70 mg	70 mg
Microencapsulated flavor	8 mg	8 mg
Saccharin sodium	-	5 mg
Magnesium stearate	6 mg	6 mg
Tablet weight	1800 mg	1400 mg
Weight variation	0.5 %	0.4 %
Tablet diameter	18 mm	15 mm
Compressional force	18 kN	10 kN
Tablet thickness	5.7 mm	6.8 mm
Tablet hardness	100 N	150 N
Friabilit	0.9 %	0.2 %

TABLE 4

Aspirin and Antacid Tablets

	Aspirin	Antacid
Aspirin fine crystalline	500 mg	-
Calcium carbonate	-	450 mg
Sorbitol instant	400 mg	520 mg
DC-dextrose	400 mg	-
Microcrystalline cellulose	120 mg	- *
Talc	70 mg	-
Saccharin sodium	5 mg	- *
Microencapsulated flavors	5 mg	- *
Magnesium stearate	-	30 mg
		* optional
Tablet weight	1500 mg	1000 mg
Weight variation	0.8 %	0.3 %
Tablet diameter	18 mm	15 mm
Compressional force	15 kN	20 kN
Tablet thickness	5.0 mm	4.2 mm
Tablet hardness	90 N	90 N
Friability	1.4 %	0.6 %

by adding microcrystalline cellulose or pregelatinized starch.

The antacid tablet of Table 4 was also selected to point out the favorable properties of very simple formulations including high percentages of sorbitol instant. Tablet hardness increases continually as the compressional force is raised, without any tendency of capping; the disintegration time - which is of minor importance for chewable tablets - also increases, but to a much lesser extent (Figure 2). The variation of tablet thickness and friability as a function of the compressional force are shown in Figure 3. The values of the friability are low (around 0.6 %) for tablets having usual hardness (90 - 100 N).

4. Medicated Tablets

Sorbitol instant can also be used in general pharmaceutical formulations, giving tablets with superior properties. As a first step, commonplace formulations of acetaminophen tablets based on sorbitol instant, DC-ß-lactose and DC-sucrose were compared (Table 5). It can be seen that sorbitol instant was the binder which gave the least friable tablets, even at very low compressional force. The compressibility profile of the sorbitol formulation is shown in Figure 4. Tablet hardness increases with increasing compressional force, but a limit of tablet hardness is soon reached, beyond which capping begins. The disintegration time of the tablets is not much affected by the compressional force. The onset of capping is even more clearly seen in Figure 5, which shows friability and tablet thickness as a function of the compressional force. The sharp minimum of the friability defines the optimum compressional force of

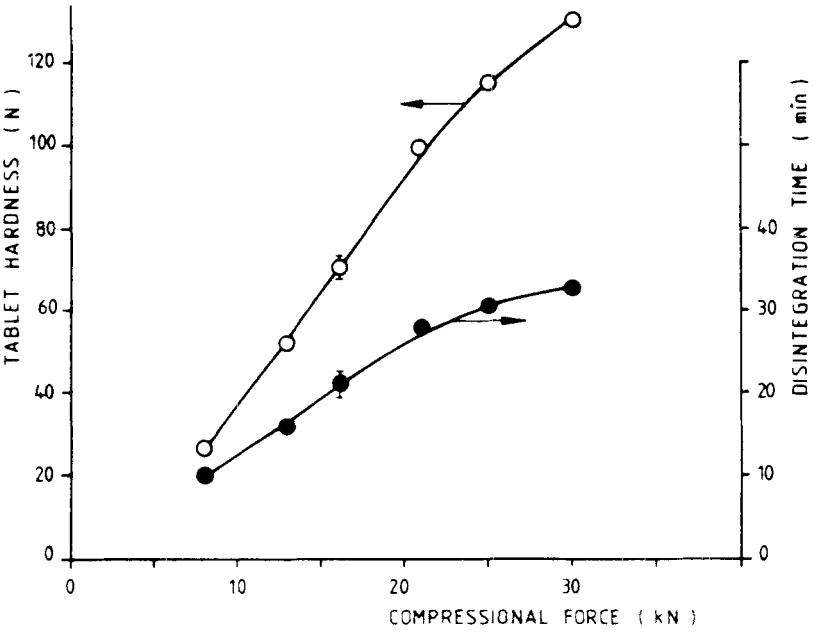

FIGURE 2

Effect of compressional force on tablet hardness and disintegration time of calcium carbonate/sorbitol instant tablets (see also Table 4)

13 kN. It should be noted, however, that the capping tendency observed in this case is not a consequence of sorbitol instant or the other two binders used; it is caused by the poor compressibility of the acetaminophen granulation.

It was in fact impossible to obtain acceptable tablets if the binders in the formulations of Table 5 were omitted, or if ordinary crystalline lactose was used instead. The acetaminophen formulation presented here is only one example of the binding power and anti-capping action of sorbitol instant. Similar effects are observable in many tableting mixtures; the

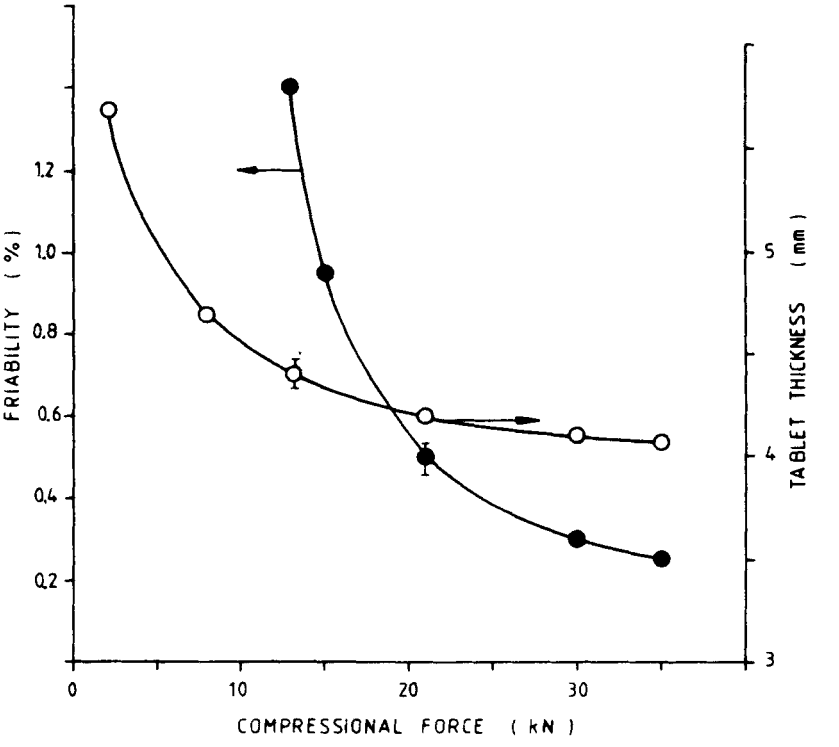

FIGURE 3

Effect of compressional force on tablet thickness and friability of calcium carbonate/sorbitol instant tablets (see also Table 4)

TABLE 5

Acetaminophen Tablets - 300 mg

Acetaminophen (96 %)	313 mg	313 mg	313 mg
DC-ß-lactose	180 mg	-	-
Sorbitol instant	-	-	180 mg
DC-sucrose	-	180 mg	-
Microcrystalline cellulose	50 mg	50 mg	50 mg
Sodium starch glycolate	33 mg	33 mg	33 mg
Colloidal silicon dioxide	9 mg	9 mg	9 mg
Magnesium stearate	15 mg	15 mg	15 mg
Tablet weight	600 mg	600 mg	600 mg
Weight variation	0.6 %	0.4 %	0.4 %
Tablet diameter	13 mm	13 mm	13 mm
Compressional force	15 kN	14 kN	9 kN
Tablet thickness	4.0 mm	4.1 mm	4.3 mm
Tablet hardness	39 N	32 N	39 N
Friability	1.1 %	1.6 %	0.6 %
Disintegration time	3 min	4 min	4 min

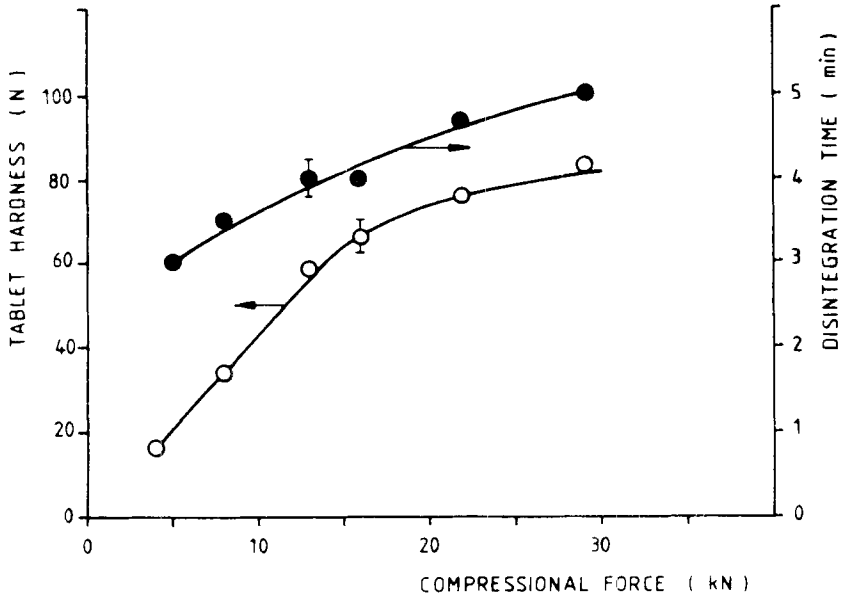

FIGURE 4

Effect of compressional force on tablet hardness and disintegration time of acetaminophen/sorbitol instant tablets (see also Table 5)

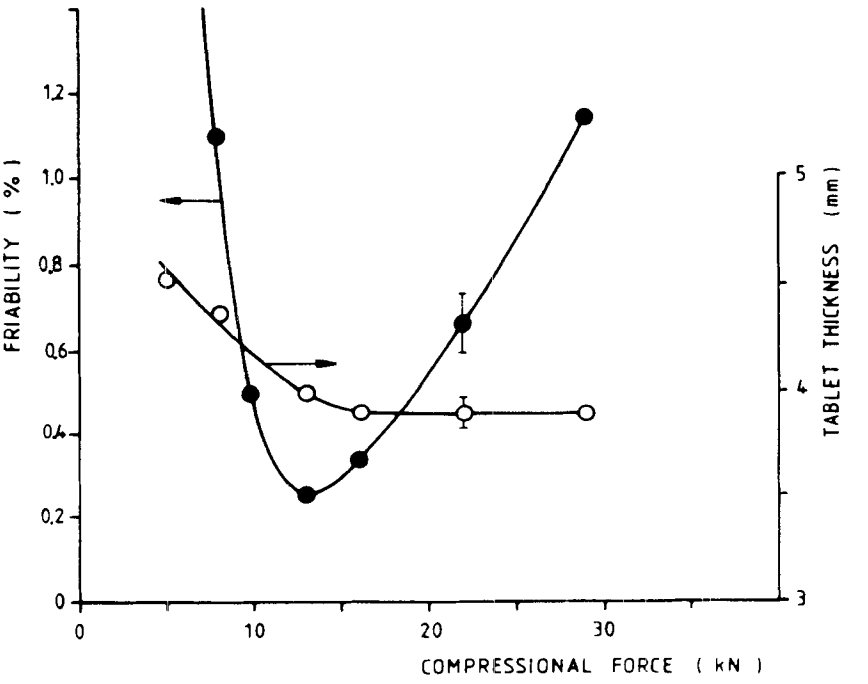

FIGURE 5

Effect of compressional force on tablet thickness and friability of acetaminophen/sorbitol instant tablets (see also Table 5)

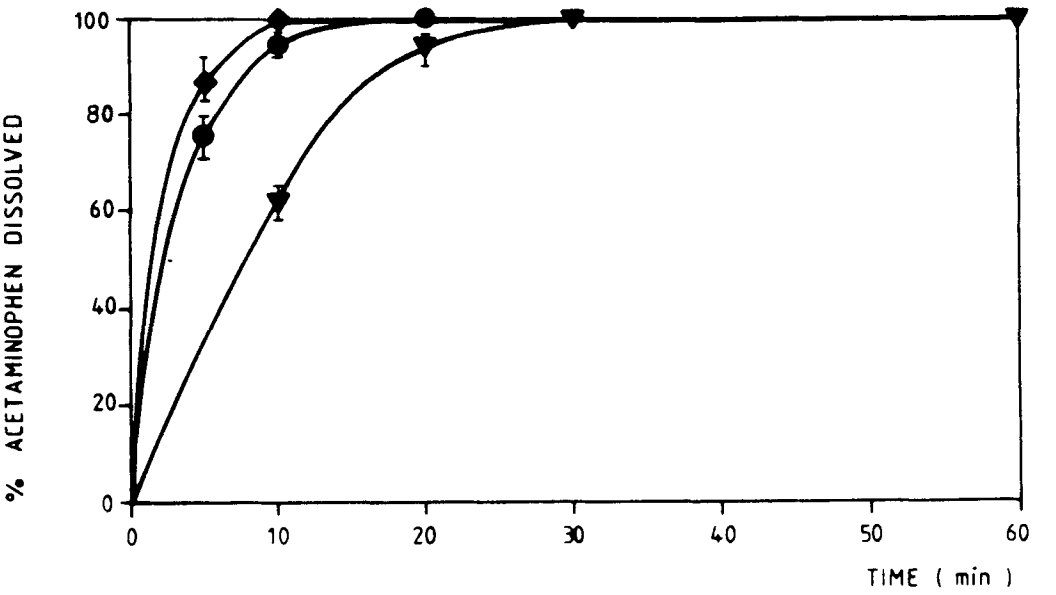

FIGURE 6

In vitro dissolution of acetaminophen tablets (see also Table 5). —◆— sorbitol instant, —●— DC-ß-lactose, —▼— DC-sucrose

quantities of sorbitol instant needed are about 10 - 30 %.

In vitro dissolution of acetaminophen from tablets of Table 5 is very good for sorbitol instant and DC-lactose, and satisfactory for DC-sucrose (Figure 6).

The next step was to investigate the use of sorbitol instant in connection with a new low-dose research drug of very low solubility. A simple lactose formulation (A), a lozenge-type sorbitol instant formulation (B) and a formulation of sorbitol instant with a disintegrant (C) were compared (Table 6).

TABLE 6

Tablet Formulations for a New Research Drug

	A	B	C
Drug	4 mg	4 mg	4 mg
Lactose monohydrate	81 mg	-	-
Sorbitol instant	-	95 mg	78 mg
Fibrous cellulose	6 mg	-	-
Microcrystalline cellulose	-	-	10 mg
Corn starch	5 mg	-	-
Croscarmellose	-	-	7 mg
Colloidal silicon dioxide	3 mg	-	-
Magnesium stearate	1 mg	1 mg	1 mg
Tablet weight	100 mg	100 mg	100 mg
Weight variation	1.1 %	0.9 %	0.6 %
Tablet diameter	7 mm	7 mm	7 mm
Compressional force	16 kN	3 kN	4 kN
Tablet thickness	2.0 mm	2.3 mm	2.2 mm
Tablet hardness	48 N	55 N	47 N
Friability	0.2 %	0.3 %	0.3 %
Disintegration time	1 min	5 min	3 min

Since sorbitol is very easily soluble in aqueous media, tablets made of the lozenge-type formulation (Table 6, formulation B) actually do not disintegrate, they rather dissolve instead. This is a phenomenon commonly observed with water-soluble adjuvants. Therefore, a powerful disintegrant is needed in sorbitol-based tablets. Starch, which gives excellent results in lactose formulations (see Tables 6 - 9, formulations A), is unsuitable for sorbitol, which can be a limitation in certain applications.
In principle, however, all disintegrants of high swelling capacity, e g crospovidone, sodium starch glycolate or croscarmellose can be used, the choice depending mainly on the results of the compatibility

TABLE 7

Moxaverine Tablets

	A	B	C
Moxaverine	27 mg	27 mg	27 mg
Lactose monohydrate	143 mg	-	-
Sorbitol instant	-	171 mg	155 mg
Fibrous cellulose	12 mg	-	-
Microcrystalline cellulose	-	-	10 mg
Corn starch	10 mg	-	-
Croscarmellose	-	-	6 mg
Colloidal silicon dioxide	6 mg	-	-
Magnesium stearate	2 mg	2 mg	2 mg
Tablet weight	200 mg	200 mg	200 mg
Weight variation	0.6 %	0.4 %	0.4 %
Tablet diameter	9 mm	9 mm	9 mm
Compressional force	12 kN	3 kN	3 kN
Tablet thickness	2.4 mm	2.7 mm	2.9 mm
Tablet hardness	38 N	64 N	39 N
Friability	0.2 %	0.3 %	0.3 %
Disintegration time	1 min	6 min	3 min

TABLE 8

Prednisolone Tablets

	A	B	C
Prednisolone	20 mg	20 mg	20 mg
Lactose monohydrate	150 mg	-	-
Sorbitol instant	-	178 mg	162 mg
Fibrous cellulose	12 mg	-	-
Microcrystalline cellulose	-	-	10 mg
Corn starch	10 mg	-	-
Croscarmellose	-	-	6 mg
Colloidal silicon dioxide	6 mg	-	-
Magnesium stearate	2 mg	2 mg	2 mg
Tablet weight	200 mg	200 mg	200 mg
Weight variation	0.8 %	0.7 %	0.7 %
Tablet diameter	9 mm	9 mm	9 mm
Compressional force	15 kN	3 kN	3 kN
Tablet thickness	3.0 mm	3.2 mm	3.2 mm
Tablet hardness	52 N	46 N	39 N
Friability	0.5 %	0.4 %	0.4 %
Disintegration time	1 min	3 min	3 min

TABLE 9

Praziquantel Tablets

	A	B	C
Praziquantel	150 mg	150 mg	150 mg
Lactose monohydrate	359 mg	-	-
Sorbitol instant	-	443 mg	400 mg
Fibrous cellulose	36 mg	-	-
Corn starch	30 mg	-	-
Croscarmellose	-	-	43 mg
Colloidal silicon dioxide	18 mg	-	-
Magnesium stearate	6 mg	6 mg	6 mg
Wetting agent	1 mg	1 mg	1 mg
Tablet weight	600 mg	600 mg	600 mg
Weight variation	0.8 %	0.5 %	0.9 %
Tablet diameter	13 mm	13 mm	13 mm
Compressional force	12 kN	4 kN	5 kN
Tablet thickness	3.9 mm	4.3 mm	4.3 mm
Tablet hardness	51 N	58 N	53 N
Friability	0.3 %	0.3 %	0.3 %
Disintegration time	2 min	18 min	7 min

studies with the active ingredients. The pharmaceutical properties of tablets made with crospovidone, however, changed drastically after long-term storage, especially under moist conditions. No adverse effects were found for croscarmellose, a result which is in agreement with other investigators (9). Since croscarmellose gave the shortest disintegration times in most cases, and compatibility studies including a large number of drugs confirmed our initial preference for this disintegrant, all subsequent work was done using croscarmellose. A certain amount of microcrystalline cellulose improved the tableting properties of the mixture further.

The effect of the compressional force on tablet hardness and on the disintegration time of a simple

formulation based on sorbitol instant, croscarmellose and microcrystalline cellulose (Table 6, formulation C) is shown in Figure 7. It can be seen from this figure that tablet hardness can attain high values, without affecting much the disintegration time. There is no capping tendency within the whole range of compressional forces investigated. This ist shown in Figure 8, where tablet thickness and friability are plotted as a function of the compressional force.

An interesting effect is that drug dissolution does not correlate with disintegration time for the formulations given in Table 6. Even though lactose tablets disintegrated very quickly, drug dissolution was slow (Figure 9). This is due mainly to the effect that the lactose tablets (formulation A) disintegrate into comparatively large fragments, which delays the dissolution of the very sparingly soluble drug. Tablets made of sorbitol instant and croscarmellose (formulation C) disintegrate more slowly, but as the particles formed are very small, and sorbitol dissolves at once, the drug is immediately and uniformly dispersed in the liquid, an effect which accelerates its dissolution. Formulation B was investigated for comparative reasons only (Figure 9).

In order to complete the investigations two more drugs of low solubility - moxaverine and prednisolone - and one high-dose drug of very low solubility - praziquantel - were chosen. Again, lactose formulations (A), lozenge-type sorbitol formulations (B) and sorbitol instant/croscarmellose formulations (C) were used for comparative studies. The results are compiled in Table 7 for moxaverine, in Table 8 for prednisolone and in Table 9 for praziquantel.

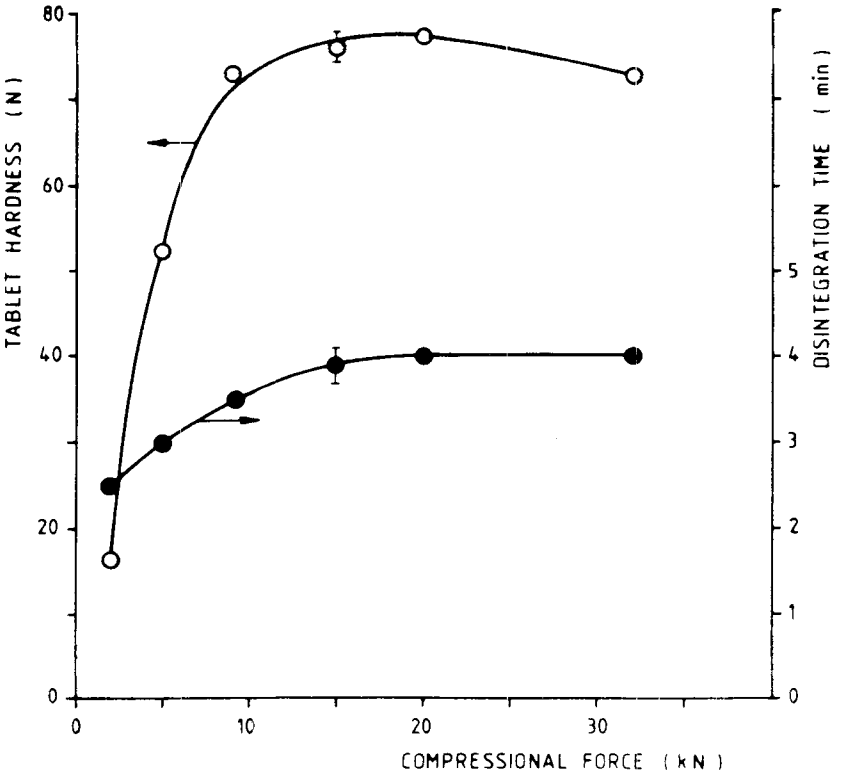

FIGURE 7

Effect of compressional force on tablet hardness and disintegration time of a sorbitol instant/croscarmellose formulation (Table 6, formulation C)

The properties of the tablets need not to be commented in each individual case. Compared to lactose, the use of sorbitol instant made it always possible to use considerably lower compressional forces.

Dissolution rates are shown in Figures 10 - 12 for moxaverine, prednisolone, and praziquantel, respectively. As expected the lozenge-type formulations B (drug, sorbitol instant, lubricant) gave insufficient dissolution rates. The lactose formulation A, taken as a standard, gave excellent result with moxaverine

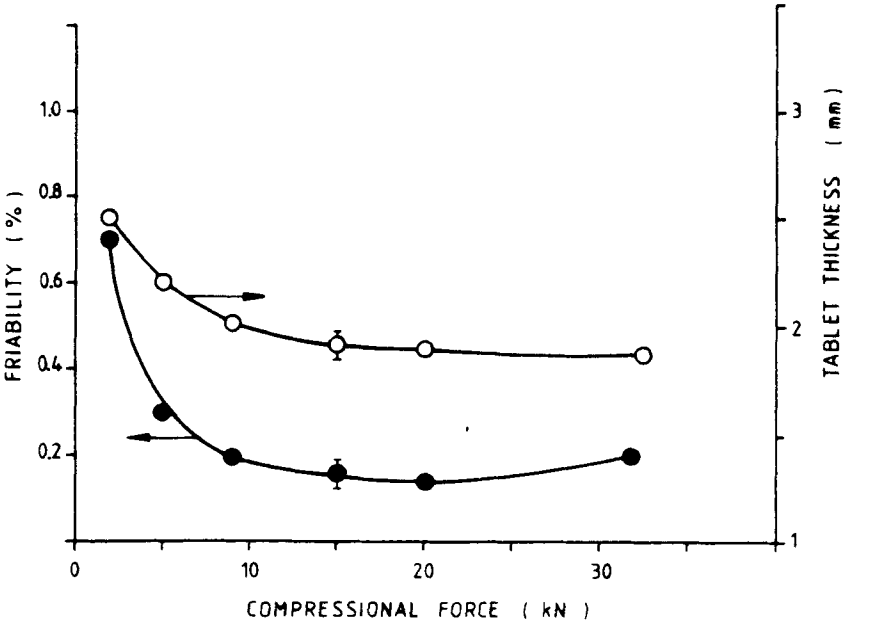

FIGURE 8

Effect of compressional force on tablet thickness and friability of a sorbitol instant/croscarmellose formulation (Table 6, formulation C)

(Figure 10), but in this case the sorbitol instant/croscarmellose formulation C also performed well. For prednisolone and praziquantel the fastest dissolution rate was obtained with sorbitol instant/croscarmellose (Figures 11 - 12).

All these results indicate that the following approximate simple formulation should give good results for a variety of drugs:

Drug:	4 - 50 %
Sorbitol instant:	30 - 80 %
Microcrystalline cellulose:	5 - 10 %
Croscarmellose:	3 - 7 %
Magnesium stearate:	1 %

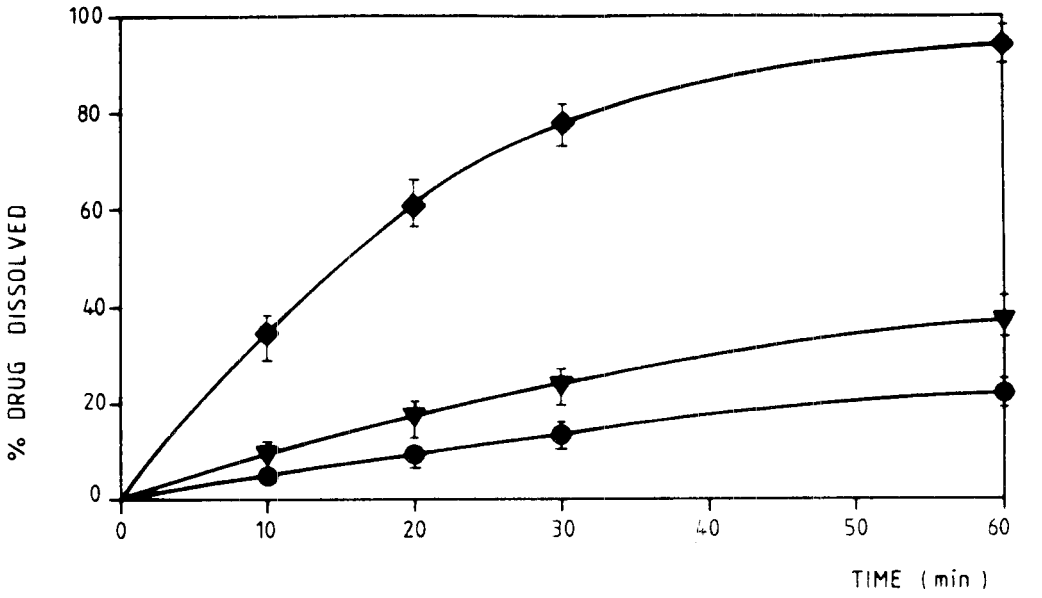

FIGURE 9

Dissolution rate of a drug of very low solubility in different formulations (see also Table 6). —●— lactose, —▼— lozenge-type/sorbitol instant, —◆— sorbitol instant/croscarmellose

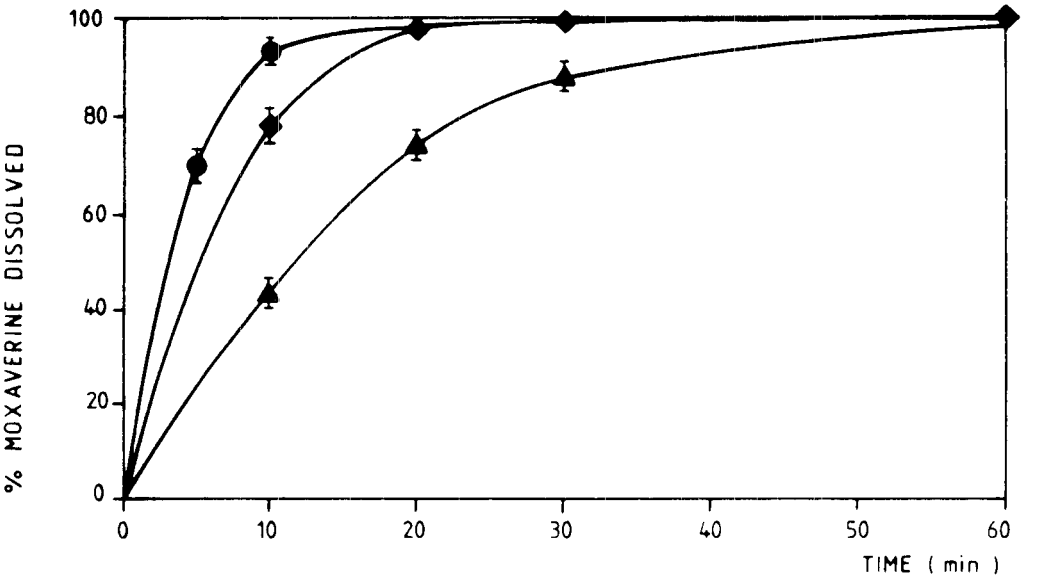

FIGURE 10

Dissolution rate of moxaverine in different formulations (see Table 7). —●— lactose, —▼— lozenge-type/ /sorbitol instant, —◆— sorbitol instant/croscarmellose

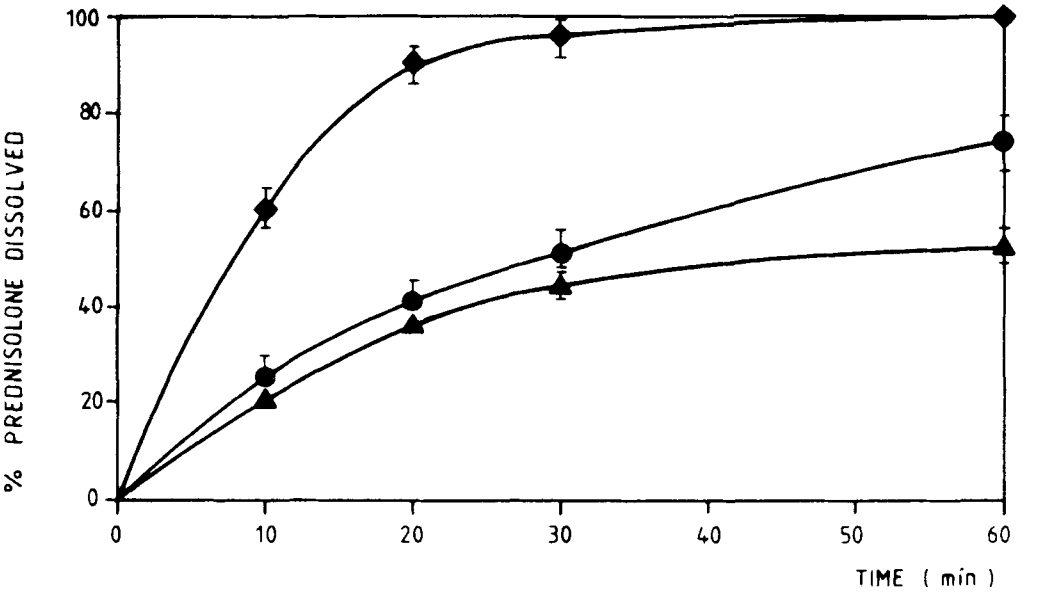

FIGURE 11

Dissolution rate of prednisolone in different formulations (see Table 8). —●— lactose, —▼— lozenge-type/ sorbitol instant, —◆— sorbitol instant/ croscarmellose

Several other drugs and vitamins were tested in this formulation. Excellent tablets were obtained in almost all cases. If the amount of disintegrant is reduced, tablets of very high hardness and very low friability (less than 0.1 %) can be made. They are well suited for film-coating. The use of ordinary crystalline sorbitol in similar formulations always gave tablets with much inferior characteristics. This is understandable, since crystalline sorbitol has much lower compressibility (see Figure 1) and it is not well suited for the formation of ordered mixtures.
On the other side, sorbitol should not be used in combination with hygroscopic drugs, since the pharmaceutical properties of the tablets changed markedly during

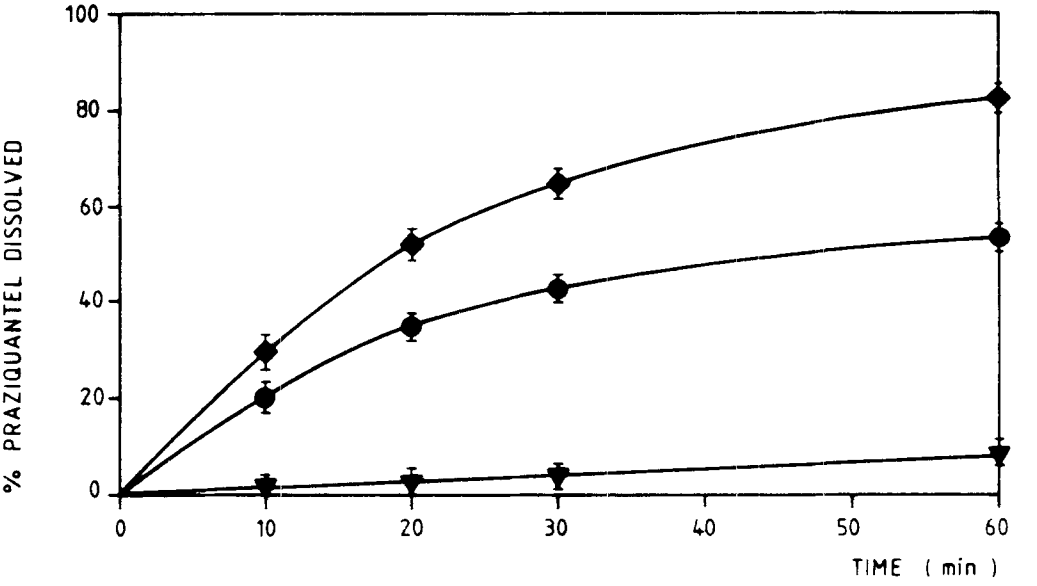

FIGURE 12

Dissolution rate of praziquantel in different formulations (see Table 9). —●— lactose, —▼— lozenge-type/ /sorbitol instant , —◆— sorbitol instant/croscarmellose

storage, especially under moist conditions. This is in accordance with general observation (9, 10).

Stability tests of tablets of all formulations given in this section were run under realistic conditions. Tablets were stored for 12 weeks in sealed bottles at 20°C, 30°C and 40°C, and in open bottles in an atmosphere of 65 % relative humidity at 25°C. Tablet hardness and disintegration time were found to remain unchanged within the range of ± 20 % after storage under the conditions mentioned above. Increase in weight due to absorption of moisture after storage at 65 % relative humidity (12 weeks, 25°C) was less than 2 % in all cases. No chemical degradation of the drugs used in the tablets was detected

after storage (all conditions) by thin-layer chromatography. Long tern stability studies are under way.

CONCLUSIONS

As shown in this paper, sorbitol instant offers many advantages, not only in the classical field of lozenge production but also in the manufacture of chewable sugarless tablets and medicated pharmaceutical tablets. Several examples of practical relevance have been presented, including even so-called problem drugs. In all these applications the unusually high compressibility of sorbitol instant and its bindung and anti-capping action is certainly the most important feature. It should, however, not be overlooked that sorbitol instant is also one of the best carriers for drugs in stable solid mixtures known so far. The formation of ordered mixtures on the basis of sorbitol instant, which show almost no tendency of segregation, provides new possibilities of rendering many tableting mixtures directly compressible, which otherwise could only be processed after a granulation step. The low bulk density and the irregular shape of the particles of sorbitol instant facilitate blending with several other low density adjuvants, e g cellulose, starch, colloidal silicon dioxide, glidants, and disintegrants.

Nevertheless, the natural hygroscopicity of sorbitol limits some of its uses. High percentages of sorbitol should not be used in combination with hygroscopic drugs or other hygroscopic excipients. Drugs of low chemical stabilily do not usually give good results in high-percent sorbitol formulations, if the tablets are stored under moist conditions. As a rule, however, optimized formulations comprising sor-

bitol instant give tablets of good stability, if the packing material is properly selected and the storage conditions are adequate.

It was shown in this paper that some inherent and inconvenient properties of a chemical substance can be outweighed by the special and favorable physical characteristics of a tailored excipient made of it. Sorbitol instant should thus not be regarded as a mere tablet filler; it is in fact a valuable adjuvant with many unique properties.

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