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EVALUATION OF ANHYDROUS α-LACTOSE, A NEW EXCIPIENT IN DIRECT COMPRESSION

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SUMMARY

Different forms of lactose are available for direct compression of tablets. The use of spray-dried lactose, which has good flow and compressibility characteristics, is limited by its stability when stored under humid conditions. Sieved crystalline fractions of α-lactose monohydrate such as the 100 mesh fraction, have very good flow properties and an outstanding stability, but the compressibility is so poor, that it can be used only in combination with other filler-binders, like microcrystalline cellulose.
A third form of lactose, increasingly used in direct compression is anhydrous lactose. The commercially available products generally consist of an excess of β next to α-lactose. They both have good binding and stability characteristics, but a flowability which is less than optimum. The latter is caused by the rather irregular particle shape and the relatively high amount of fines.
A newly developed form of lactose is anhydrous α-lactose. It is prepared by dehydration of α-lactose monohydrate. Binding, flow and stability properties of this excipient were compared with the properties of other filler/binders. The results show that the

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compressibility of anhydrous α-lactose was about the same as that of anhydrous β-lactose.
The flow properties of anhydrous α-lactose were even better than the very good fluidity of α-lactose monohydrate 100 mesh. At storage under normal or humid conditions, there was no change in hardness of tablets compressed from anhydrous α-lactose.

A comparative evaluation of the effect of mixing with magnesium stearate on the binding properties of filler/binders showed that all the lactose products investigated, including anhydrous α-lactose, behave in an intermediate manner, between complete plastic deformation and complete brittle fracture. For this reason there is a limited decrease in crushing strength for tablets compressed from anhydrous α-lactose, during mixing with magnesium stearate.
Some formulation examples will show that anhydrous α-lactose is a very useful filler/binder in direct compression, of which tablets with a low weight variation,sufficient strength, a low friability, a fast disintegration and a high drug release can be prepared.

INTRODUCTION

In 1963, Gunsel and Lachman (1) published the results of a comparative evaluation between conventionally processed and spray-dried lactose. The results showed, that spray-dried lactose had improved flow and binding properties compared with the conventionally prepared lactose. For this reason, spray-dried lactose could be compressed without preceeding granulation. Since the introduction of spray-dried lactose, a number of directly compressible fillers appeared on the pharmaceutical market and the attention paid to direct compression increased because of the advantages which direct compression had over the granulation process. It should be emphasized, however, that in direct compression much higher demands must be made on the quality of the excipients. Particularly in tableting of low-dose drugs, the tablet characteristics will mainly be determined by the filler/binders

chosen. Moreover, lot-to-lot variations and other adequacies are not covered up by a granulation step. The high demands and the increasing critical approach of raw materials have resulted in the survival, without any changes in quality, of only a few products, including microcrystalline cellulose, of all filler/binders, marketed in the late 1960s. A number of the initial products were modified in order to improve their tableting characteristics (for instance spray-dried lactose) or were taken off from the market (for instance Amylose V). In recent years only a few original new products have been introduced, including calcium sulphate dihydrate (Compactrol^{R}) and different kinds of directly compressible sorbitol.

Focussing our attention on lactose for direct compression, at least three kinds are available. Spray-dried lactose has been improved in order to overcome the problem of discoloration and to increase the compressibility of the initial product. The qualities offered at present (Fast-Flo^{R}, D.C.L^{R}actose 11) are highly compressible, have a good flowability and exhibit no browning reactions. The physical stability is, however, limited, particularly when the product is stored under humid conditions (2,3). Coarse and regular grade sieved crystalline fractions of α-lactose monohydrate have very good flow properties (4,5) but lack in binding capacity (5). A granulated form of α-lactose monohydrate, Tablettose^{R}, has only a limited improved compressibility (6). Commercially available anhydrous lactose, which consists mainly of β-lactose, exhibits a good compressibility but mostly shows a fluidity that is less than optimum, in spite of the fact that it has been improved in recent years.

Consequently there was a real need for an improved lactose-based filler/binder for direct compression. To upgrade lactose to a product with high flowability as well as good compressibility and stability, anhydrous α-lactose was developed by dehydration of α-lactose monohydrate (7,8).

Objective of this study was to evaluate and compare the tableting properties of anhydrous α-lactose with a number of

currently available filler/binders. Special attention was given to the effect of mixing excipients with magnesium stearate on tablet hardness and changes in crushing strength during storage of the tablets.

EXPERIMENTAL

Materials

The directly compressible filler/binders used were: microcrystalline cellulose N.F. (Avicel[R] PH 101 and PH 102)[1], microfine cellulose (Elcema[R] G250)[2], directly compressible starch (STARCH[R] 1500)[3], dicalcium phosphate dihydrate "grob sterilisiert"[4], dicalcium phosphate dihydrate N.F. (Emcompress)[5], calcium sulphate dihydrate (Compactrol)[5], Neosorb[R] [6], Emdex[R] [5], Lactose USP Fast Flo[7], α-lactose monohydrate 100 Mesh[8], spray-dried lactose USP (D.C.Lactose 11)[8], anhydrous β-lactose USP (D.C. L[R]actose 21)[8], anhydrous α-lactose USP (D.C. L[R]actose 30)[8] and Tablettose[R] [9].

The other tablet additives used were: Crospovidone NF XV (Plasdone[R] XL)[9], colloidal silica (Aerosil[R] 200)[2] and magnesium stearate Ph.Ned. VI[10].

The drugs used were: Phenobarbitone[11] and Tetracycline hydrochloride pond[12].

Methods

Electron micrographs were made using a scanning electron microscope*(Jeol JSM-U3). The powders examined were coated with gold/palladium, using a sputter technique, giving a coating of about 300 Å.

Flow properties of blends of filler/binders and 0.5% magnesium stearate were measured by determining the minimum aperture through which the powder blend would flow without assistance, according to Klein (9).

Particle size distribution of filler/binders was determined by sieve analysis, using standard sieves (N-480) on a sieving machine.

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Preparations of placebo tablets. Filler/binders were mixed with 0.5% magnesium stearate during 2 min in a Turbula[13] mixer at a rotation speed of 90 rpm. Plain filler/binders or filler/binder-lubricant blends were compressed to flat tablets, using an instrumented eccentric press at a machine speed of 18 cycles/min. The instrumentation of the machine has been reported previously by Groenwold et al (10). Tablet diameter was 9 mm, the weight was 250 mg. The compression forces used were 5 kN, 10 kN and 20 kN, respectively.

To determine the effect of mixing with magnesium stearate on the crushing strength of tablets, filler/binders and 0.5% magnesium stearate were mixed in the Turbula mixer at 90 rpm during specified time periods. The tablets were prepared by introducing manually a weighed quantity of 250 mg of the blend into a prelubricated 9 mm die of a compression device, mounted between the plattens of an instrumented hydraulic press. The samples were compressed at specified compression forces with a loading rate of 2 kN/s.

Preparation of tablets containing active ingredient. All the tablet ingredients except magnesium stearate were mixed in the Turbula mixer at 90 rpm during 15 min. After addition of the lubricant, the mixing procedure was continued for 2 min. Tablets of 500 mg (phenobarbitone) or 625 mg (tetracycline hydrochloride) were compressed with the eccentric press mentioned previously. The tablet diameter was 13 mm, the compression force used was 15 kN.

Tablet properties. The variation coefficient of the tablet weight was determined by weighing 40 individual tablets with an accuracy of $\pm$ 0.1 mg. The crushing strength of the compacts was measured not before 10 min after compression, using a motorized Schleuniger instrument. The data given are the mean of at least 10 tablets. The friability of the tablets was measured with a Roche friabilator after 100 rotations.

The disintegration time of the tablets was determined using the USP apparatus without disks. The data given are the mean of the disintegration times of 6 individual tablets.

The dissolution velocity of phenobarbitone tablets was performed according to the USP XX, suppl. 3, Add. A. Samples were removed through a 0.8 µm membrane filter at 2, 5, 10, 15, 20, 25, 30, 45 and 60 minutes. The dissolution velocity of tetracycline hydrochloride tablets was determined in 900 ml deareated water using the USP paddle apparatus at 50 rpm. Samples were removed through a 0.8 µm membrane filter at 2, 5, 10, 15, 20, 25, 30, 45 and 60 minutes. The samples were diluted with 0.1 N sulfuric acid and measured spectrophotometrically at 269 nm with 0.1 N sulfuric acid as a blanc.

Storage of tablets. Some of the tablets prepared were stored in open containers for 8 weeks at 20°C and at a relative humidity of 50% and 85%, respectively. After storage, the crushing strength was measured as described previously.

RESULTS

The principal demands for directly compressible excipients are good fluidity and sufficient binding properties. But also additional factors may play a role in the choice of a proper filler/binder. They are -among other things- sufficient stability, particularly in case of storage under humid conditions and good compatibility with drugs and other additives.

Table 1 lists the flow properties of a number of filler/binders lubricated with 0.5 percent magnesium stearate, expressed as:

- the flow through funnels of standard dimensions (9);
- the variation coefficient of the weight of 40 tablets, compressed from excipient/lubricant blends.

Although one should realize the relative value of the tests performed, the flow properties of anhydrous α-lactose can be characterized as excellent, being the best of all the filler/binders examined, even better than the good fluidity of the sieved crystalline α-lactose monohydrate 100 mesh. The good flow properties of the latter are the result of the regular form and the favorable particle size, as can be seen from the scanning electron micrograph (figure 1). The flow properties of Tablettose

TABLE 1

Flow Properties of a Series of Filler/binders, Lubricated with 0.5% Mg Stearate

Filler/binder, lubricated with 0.5% Mg Stearate	Flow class (flows through vessel nr:)	Variation coefficient of tablet weight (%)
Avicel PH 101	not through nr 5	3.2
Avicel PH 102	2	1.0
Elcema G250	2	0.35
Starch 1500	not through nr 5	2.2
Dicalcium phosphate dihydrate	1	0.9
Compactrol	2	0.3
Emdex	2	0.6
Neosorb 20/60	2	0.5
α-lactose monohydrate 100 mesh	1	0.4
Tablettose	1	1.2
Spray-dried lactose (D.C.Lactose 11)	1	0.4
Anhydrous β-lactose (D.C.Lactose 21)	1	0.45
Anhydrous α-lactose (D.C.Lactose 30)	1	0.25

(figure 2) were negatively influenced by the broad particle size distribution and the higher percentage of fines. The good fluidity of spray-dried lactose can be attributed to the rather spherical form of the agglomerates, as can be seen from figure 3. Anhydrous β-lactose (figure 4) flows quite well, in spite of the rather irregular form of the particles. The excellent flowability of anhydrous α-lactose (figure 5) can be attributed to several factors, including the more clean particle surface, the regular form, the favorable particle size and the small particle size distribution.

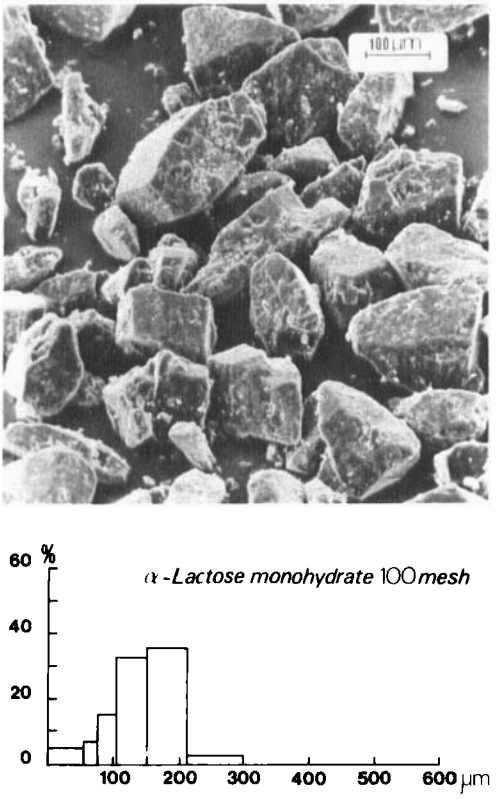
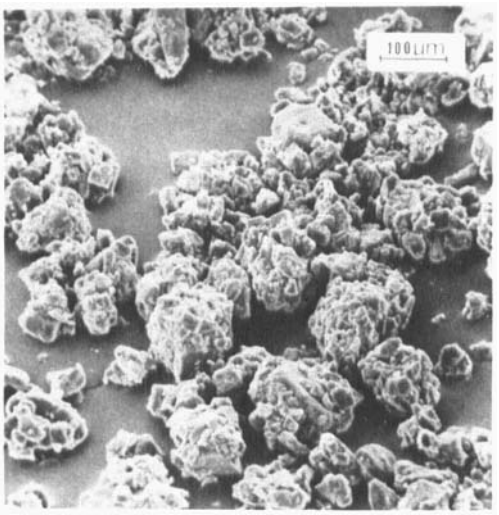


FIGURE 1

The binding properties of the different products were characterized by means of the crushing strength of tablets from plain excipients or excipients lubricated with 0.5% magnesium stearate, compressed at different compression forces (figures 6, 7, 8). As expected, high crushing strengths were found for the Avicels, both with and without lubricant (figure 6). On the other hand, the binding properties of Elcema G250 and Starch 1500 were lost by the presence of magnesium stearate.

The effect of lubricants on the binding properties will be discussed later on in this paper. Figure 7 shows the compressibility of two inorganic materials (dicalcium phosphate dihydrate and calcium sulphate dihydrate (Compactrol) as well as Emdex and Neosorb. In contradiction to the cellulose- and starch products,



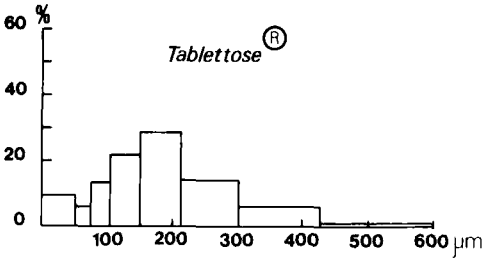


FIGURE 2

these filler/binders have no lubrication properties, so that compression without a lubricant was not possible. For this reason the excipients were mixed with 0.5% magnesium stearate before compression. In contradiction to the good compressibility of Emdex and Neosorb, figure 7 shows that the binding properties of dicalcium phosphate dihydrate and dicalcium sulphate dihydrate (Compactrol) may be characterized as moderate and poor, respectively. Likewise the lactose products cannot be compressed without a lubricant. Fig.8 shows that rather high crushing strengths were found for anhydrous β-lactose, spray-dried lactose and anhydrous α-lactose. The compressibility of α-lactose monohydrate 100 mesh is poor. For Tablettose the values were in between. The improved binding properties of spray-dried lactose, when compared with α-lactose

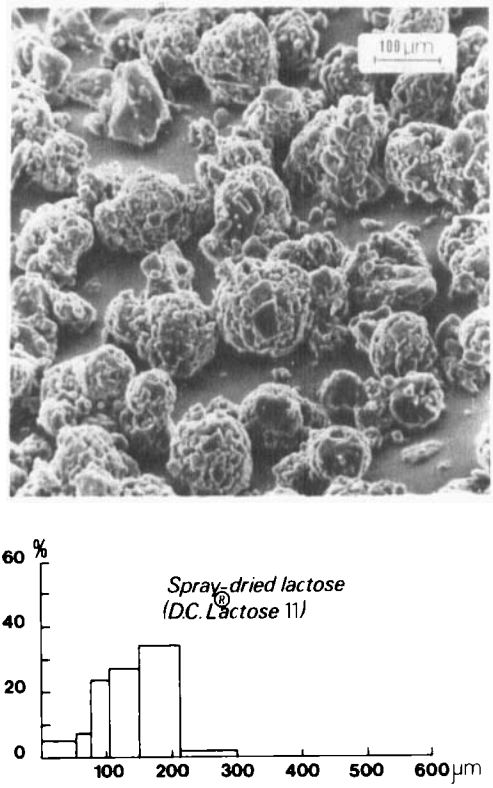


FIGURE 3

monohydrate are attributed to the presence of amorphous material, called lactose glass and the phenomenon of fracture and plastic flow under compression (11,12). Tablettose, which is also made up of aggregated crystals of α-lactose monohydrate, is less compressible than spray-dried lactose. Particles of anhydrous β-lactose are easily deformable under compression, which explains their high compressibility. As mentioned before, anhydrous α-lactose is prepared by dehydration of the hydrous form. This process introduces cracks and a large number of small pores in the crystal as can be seen from the scanning electron micrographs (figure 9) and was confirmed by mercury porosimetry (8). These results point to a strongly increased fragmentation during compression and explain the increase in binding capacity as an effect of dehydration of α-lactose monohydrate.

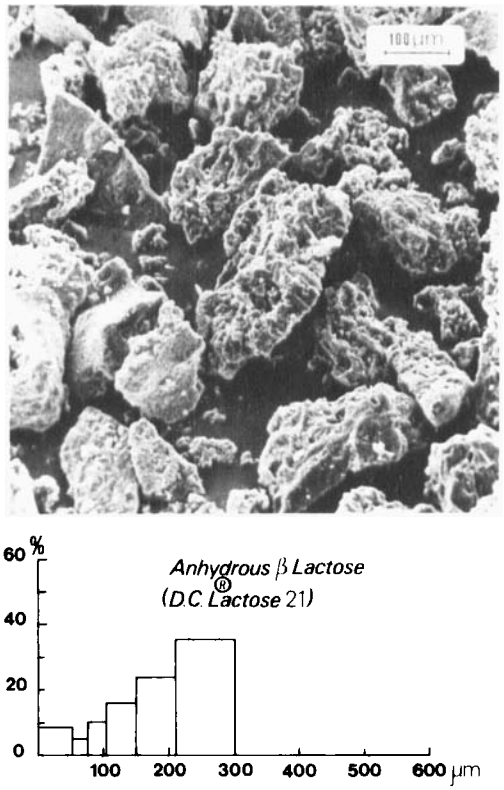
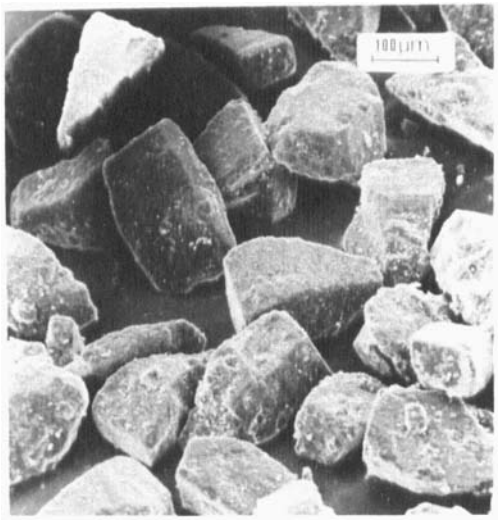


FIGURE 4

In direct compression, careful attention must be given to the mixing process, in order to obtain a homogeneous blend from which tablets with a high drug content uniformity can be compressed. Previous work (13, 14) has shown, however, that mixing with magnesium stearate forms a lubricant film around substrate particles during the mixing process. This film does not only interfere the binding of the particles (13) but can also have a marked effect on tablet disintegration and drug dissolution velocity (15,16,17). The effect of magnesium stearate on the binding properties of the celluloses and Starch 1500 was shown already in figure 6. The effect on the compressibility of the lactoses and a number of other filler/binders could not be illustrated, because these excipients could not be compressed withouta lubricant using an eccentric press.



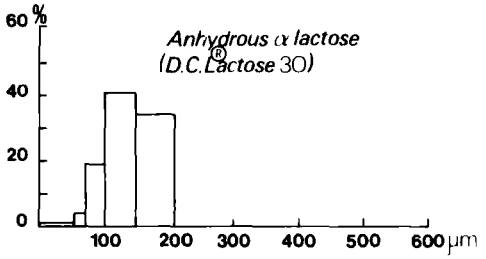


FIGURE 5

For this reason, tablets were prepared in a prelubricated die of a compression device, mounted between the plattens of a hydraulic press, using different compression forces. In the figures 10 and 11 the crushing strength of tablets from blends of filler/binders and 0.5% magnesium stearate have been plotted as a function of the mixing time of the excipient with the lubricant.

As can be seen from figure 10, the decrease in crushing strength at an increase in mixing time strongly depends on the nature of the filler/binder. Previous work (18) has shown that magnesium stearate exercises with respect to crushing strength a maximum effect on excipients which undergo complete plastic deformation under compression, and are bonded by cohesion, as was found for Starch

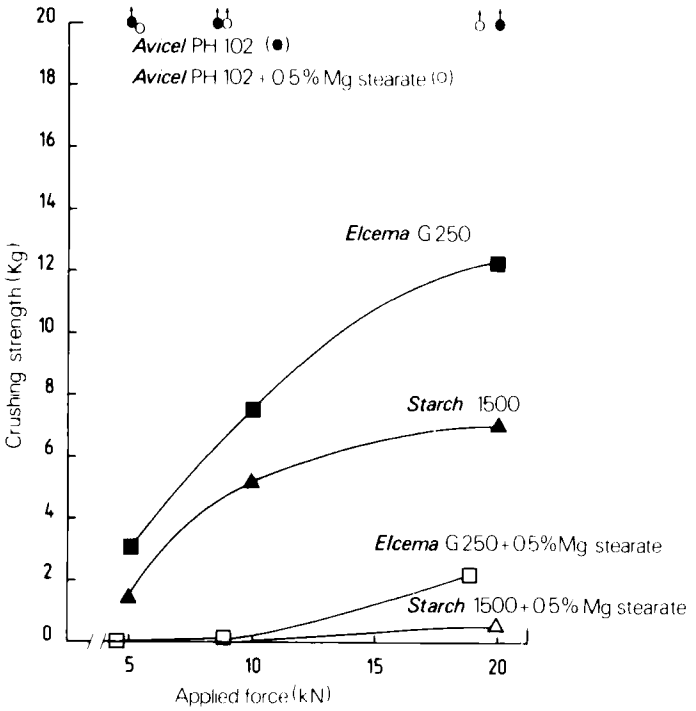


FIGURE 6

Compressibility Profiles of Filler/binders
Both Lubricated and Unlubricated

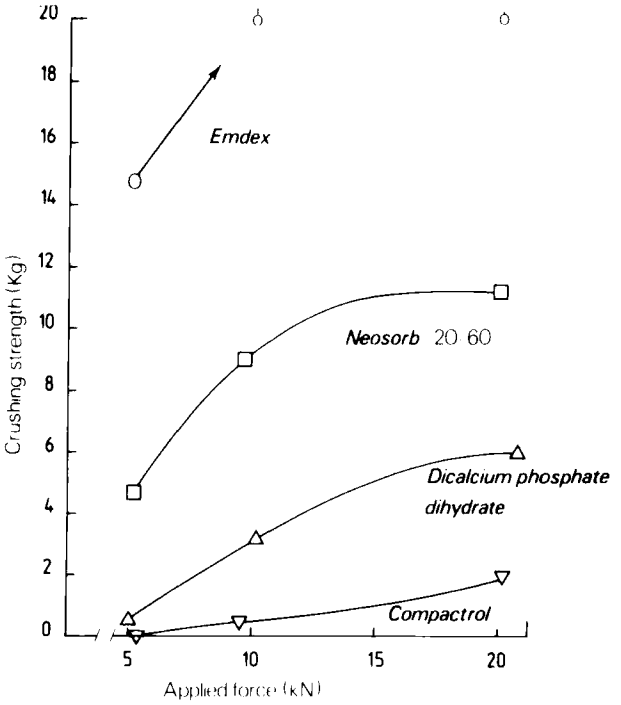


FIGURE 7

Compressibility Profiles of
Lubricated Filler/binders

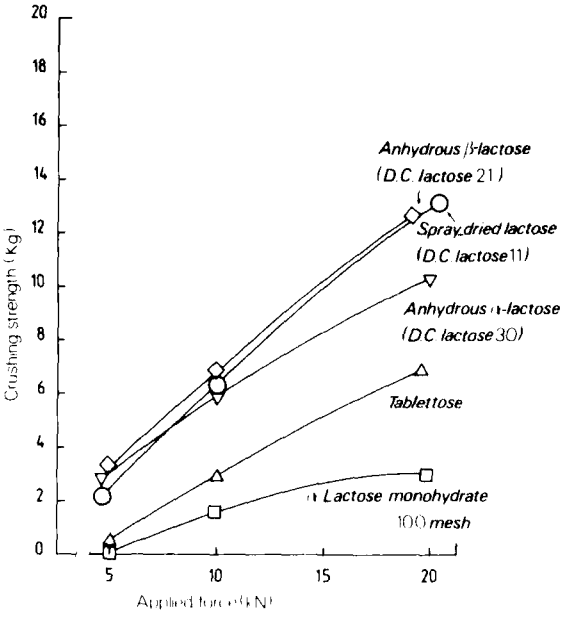


FIGURE 8

Compressibility Profiles of
Lubricated Lactoses for Direct Compression

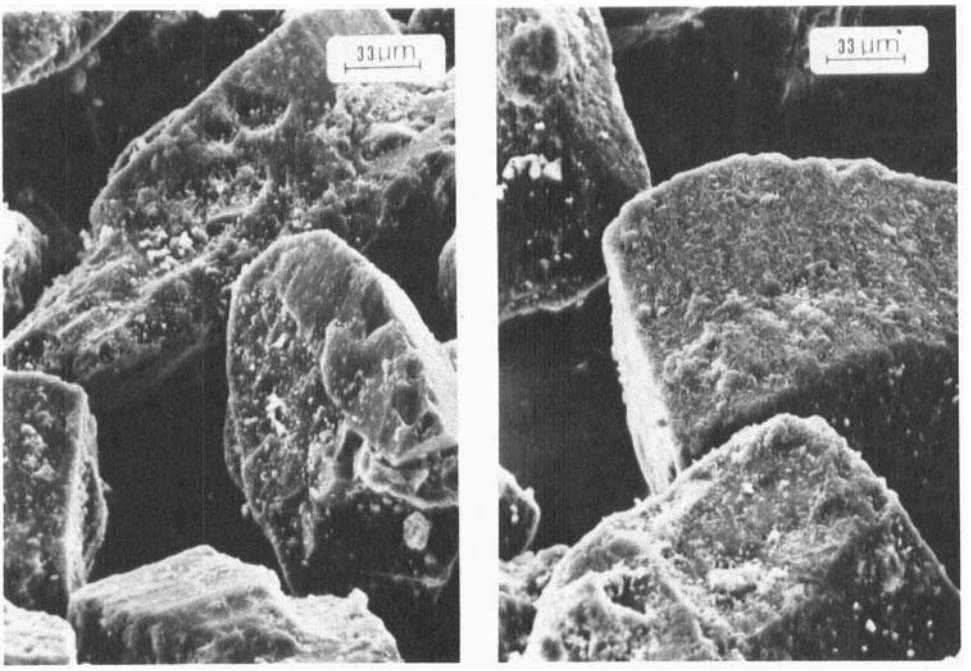


FIGURE 9

α-Lactose Monohydrate 100 Mesh (Left) and
Anhydrous α-Lactose (Right)

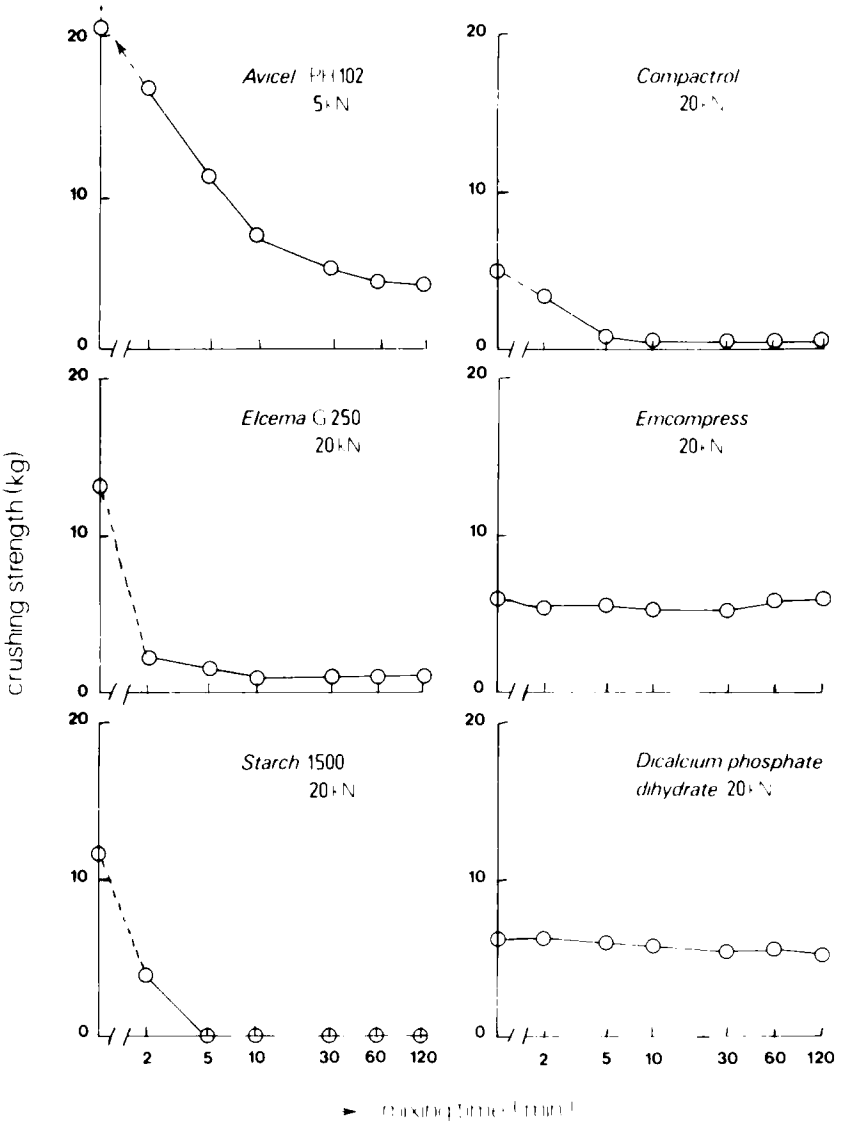


FIGURE 10

Crushing Strength versus Mixing Time
for Tablets Compressed from Filler/Binders
with 0.5% Magnesium Stearate

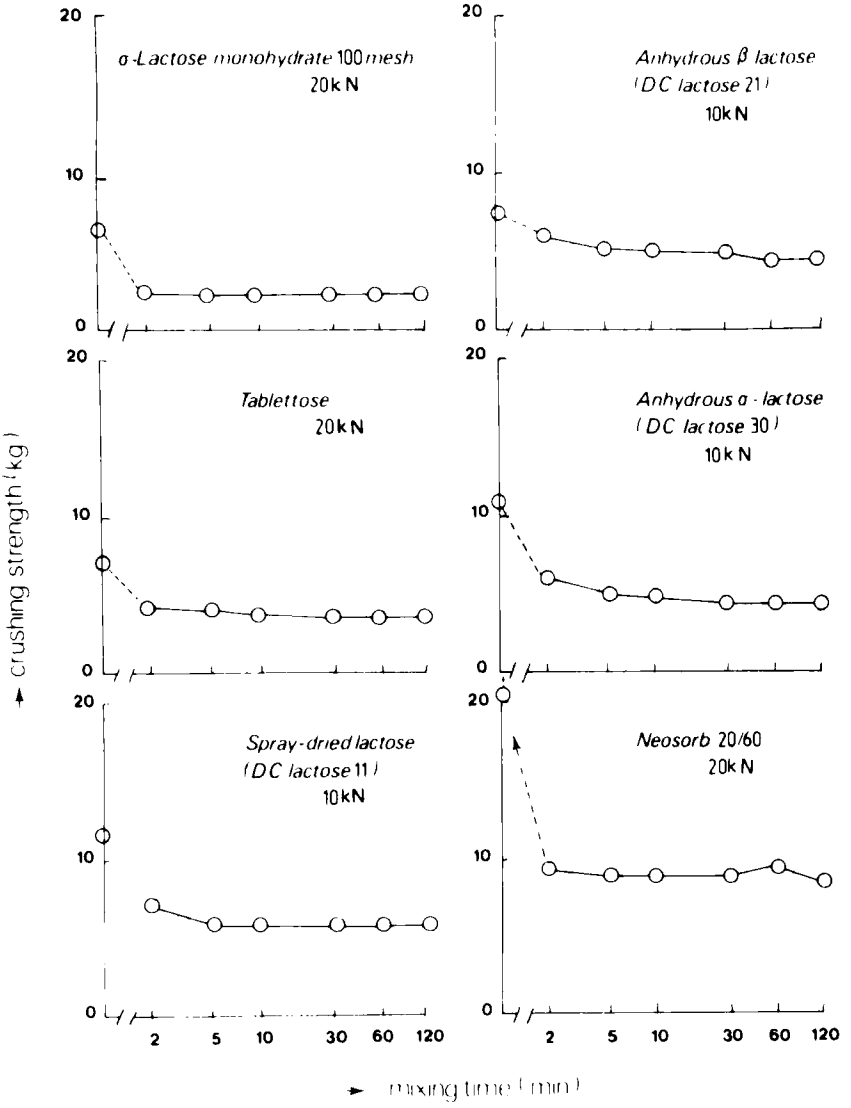


FIGURE 11

Crushing Strength versus Mixing Time
for Tablets Compressed From Filler/Binders
with 0.5% Magnesium Stearate

1500 and the celluloses. The binding properties of excipients which undergo complete fragmentation under pressure were practically unaffected by magnesium stearate, because clean, lubricant-free surfaces are formed during compression. An example of such a fragmentating product is dicalcium phosphate dihydrate (figure 10).

Most directly compressible filler/binders including all the lactose products investigated, behave, however, in an intermediate manner between complete plastic deformation and complete brittle fracture, so that the effect of magnesium stearate on the binding properties depends on the extent of fracture of the particles during compression. Figure 11 shows for the lactoses and Neosorb indeed a decrease in crushing strength at an increase in mixing time with magnesium stearate, but the decrease is limited to the first few minutes of mixing, because a lower level in the tablet hardness will be maintained by fragmentation of the product. The relatively low sensitivity of anhydrous β-lactose, when compared to the other lactoses, can be attributed to the high specific surface of the product.

In direct compression, special attention should be paid to the physical stability of the tablets, because some filler/binders are known to soften the tablets when stored under humid conditions (19). The figures 12 and 13 show the changes in crushing strength of tablets compressed from plain filler/binders lubricated with 0.5% magnesium stearate, during storage at 20°C and 50% or 85% relative humidity. The hardness of tablets, compressed from the cellulose products (figure 12) decreased when stored under normal conditions. A stronger decrease can be seen at storage under humid circumstances. This effect is caused by moisture pick up and the loosening of the interparticular bonds but should be reversible when the tablets are removed from the humid environment (20). Of the inorganic materials, tablets from dicalcium phosphate dihydrate have an excellent stability with respect to crushing strength; the tablets from Compactrol got somewhat harder when stored at 85% relative humidity. Tablets, compressed from Emdex softened during storage under normal conditions. When stored

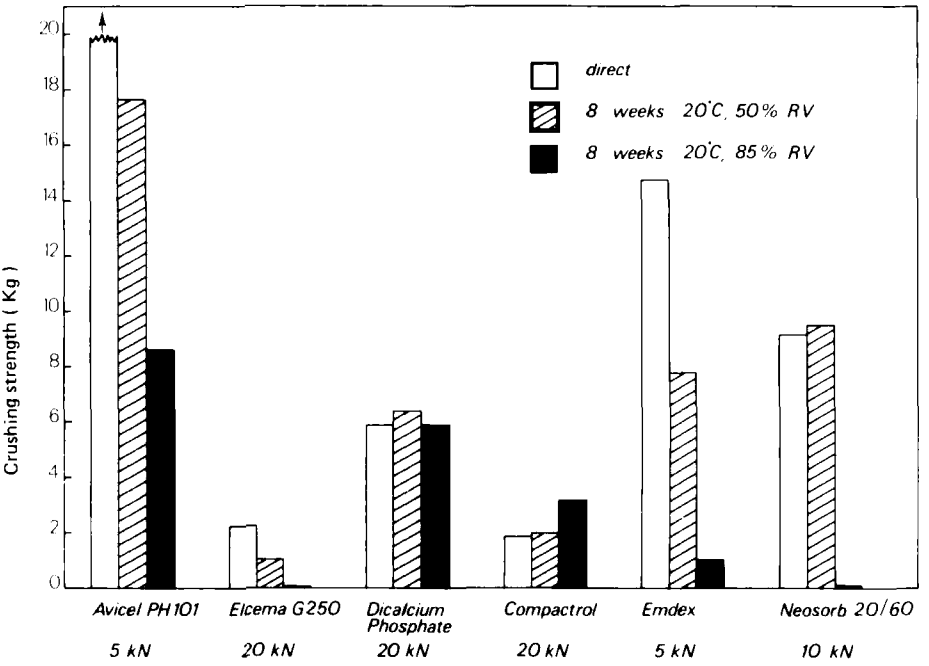


FIGURE 12
Effect of Storage on Hardness of Tablets from Filler/Binders + 0.5% Magnesium Stearate

at high humidity, the tablets liquefied as an effect of moisture pick-up by the sugars. In contrast to Emdex, tablets from Neosorb did not change in hardness during storage under normal conditions. At a high humidity, however, the tablets liquefied too.

In contrast to Emdex and Neosorb, lactoses are not hygroscopic with the exception of spray-dried lactose, which contains the slightly hygroscopical amorphous lactose. The crushing strength of tablets from α-lactose monohydrate is stable (figure 13), even when stored under humid conditions. Tablets, compressed from spray-dried lactose tend to increase in hardness during storage under normal conditions. At 85% relative humidity, softening is possible, as shown for Fast-Flo tablets. This effect, which is caused by the conversion of the amorphous glass-lactose to α-lactose monohydrate, is strongly dependent on the structure and composition of the product used. Tablets from anhydrous β-lactose

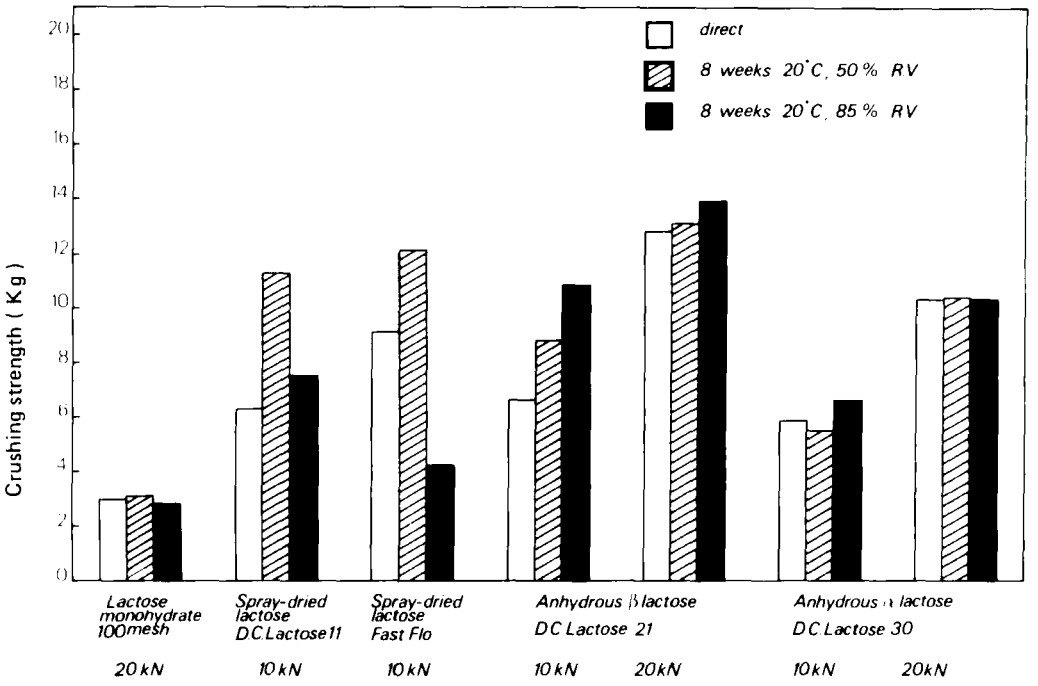


FIGURE 13
Effect of Storage on Hardness of Tablets from Filler/Binders + 0.5% Magnesium Stearate

increased in hardness, especially when stored under humid conditions. This effect almost completely disappeared, when a higher compression force was used. For all the other excipients investigated, the effect of storage on crushing strength was not dependent on the applied compression force. Tablets compressed from anhydrous α-lactose show neither a decrease nor an increase in hardness during storage, so they are as stable as tablets from crystalline α-lactose monohydrate.

When flow properties, binding properties and stability of a number of filler/binders are compared (Table 2), it can be seen that there is no universal excipient for direct compression with excellent overall properties. It must be concluded, however, that anhydrous α-lactose is full of promise.

To test the improved properties of anhydrous α-lactose with respect to the hydrous form under realistic conditions, comparative

TABLE 2
Evaluation of Filler/Binders
++ = Excellent, + = Good, Δ = Moderate, - = Poor

Filler/Binders lubricated with 0.5% Mg Stearate	Flow Properties	Binding Properties	Effect of Storage of the Tablets
Avicel PH 101	-	++	Δ
Avicel PH 102	Δ	++	Δ
Elcema G250	+	-	Δ
Starch 1500	-	-	
Dicalcium phosphate dihydrate	Δ	Δ	++
Compactrol	+	-	+
Emdex	+	++	-
Neosorb 20/60	+	+	-
α-lactose monohydrate 100 mesh	+	-	++
Tablettose	Δ	Δ	+
Spray-dried lactose (D.C.Lactose 11)	+	+	Δ
Anhydrous β-lactose (D.C.Lactose 21)	+	+	+
Anhydrous α-lactose (D.C.Lactose 30)	++	+	++

evaluations were performed by means of different directly compressible formulations. Two illustrative examples are given in the Tables 3 and 4. Table 3 concerns a formulation of phenobarbitone tablets with 20% active ingredient, using crystalline α-lactose monohydrate 100 mesh or anhydrous α-lactose (D.C.Lactose 30) as filler/binder. Phenobarbitone is known to have inferior flow- and binding properties. Tablets compressed from blends containing α-lactose monohydrate as filler/binder had a low variation coefficient of tablet weight, but an extremely high friability. As could be expected, α-lactose monohydrate 100 mesh improves only the flow

TABLE 3

Formulations for Phenobarbitone Tablets 100 mg

	1	2
Phenobarbitone	20.0 %	20.0 %
α-Lactose monohydrate 100 mesh	75.3 %	
Anhydrous α-Lactose (D.C.Lactose 30)		75.3 %
Plasdone XL	4.0 %	4.0 %
Aerosil 200	0.2 %	0.2 %
Magnesium stearate	0.5%	0.5 %
Tablet weight (Ø 13 mm)	500 mg	500 mg
Variation coefficient of tablet weight	0.5 %	0.5 %
Compression force	15 kN	15 kN
Ejection force	240 N	300 N
Friability	15 %	2 %
Crushing strength	3.6 kg	7.6 kg
Disintegration time (- disks)	7 s	235 s

properties, not the binding properties. Substitution of α-lactose monohydrate by anhydrous α-lactose resulted both in a decreased friability from 15% down to 2% and in an increased crushing strength from 3.6 up to 7.6 kg. The weight variation was as low as for tablets containing α-lactose monohydrate. The increased disintegration time is partly the result of the increased crushing strength but may also be caused by the higher initial solubility and dissolution rate of anhydrous α-lactose, compared with the hydrate form. Figure 14 shows an excellent dissolution rate of phenobarbitone for both formulations.

The second example is for tablets containing 40% tetracycline hydrochloride. Table 4 and figure 15 show, that in spite of the high percentage of an active ingredient with a bad compressibility

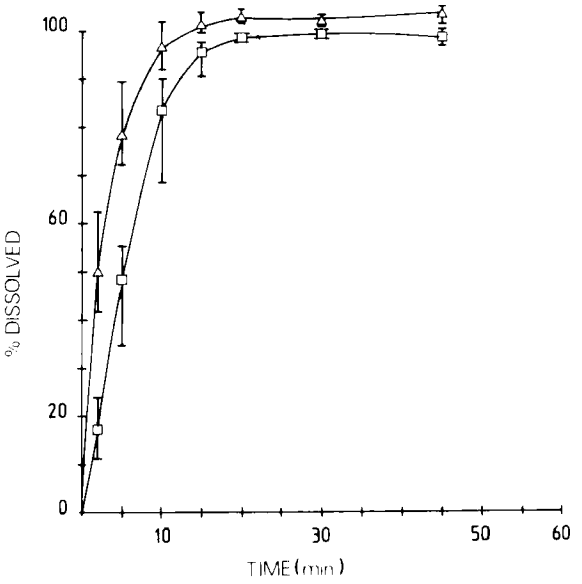


FIGURE 14

Dissolution Profiles of Phenobarbital Tablets

Δ-Δ Formulation 1; □-□ Formulation 2

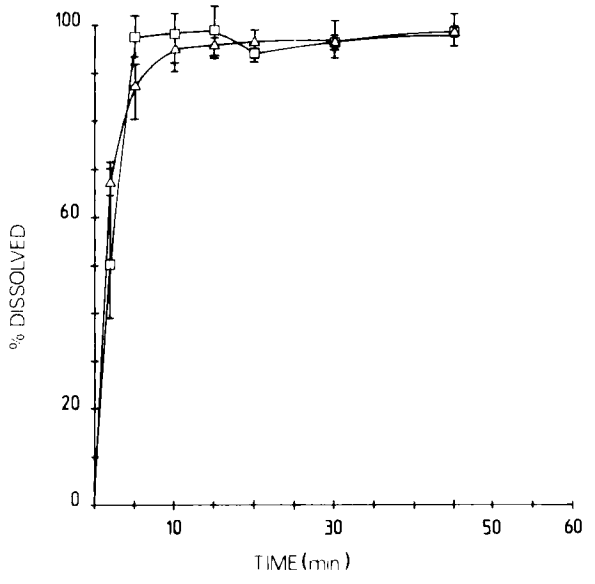


FIGURE 15

Dissolution Profiles of Tetracycline Hydrochloride Tablets

Δ-Δ Formulation 1; □-□ Formulation 2

TABLE 4

Formulations for Tetracycline Hydrochloride Tablets 250 mg

	1	2
Tetracycline hydrochloride	40.0 %	40.0 %
α-Lactose monohydrate 100 mesh	54.3 %	
Anhydrous α-lactose (D.C.Lactose 30)		54.3 %
Plasdone XL	4.0 %	4.0 %
Aerosil 200	0.2 %	0.2 %
Magnesium Stearate	1.5 %	1.5 %
Tablet weight (Ø 13 mm)	625 mg	625 mg
Variation coefficient of tablet weight	0.6 %	0.3 %
Compression force	15 kN	15 kN
Ejection force	250 N	310 N
Friability	4 %	2 %
Crushing strength	4.9 kg	9.1 kg
Disintegration time (- disks)	34 s	190 s

and poor flow properties, good quality tablets may be prepared with anhydrous α-lactose as a filler/binder.

In conclusion, the recently developed anhydrous α-lactose, which meets the specifications of anhydrous lactose USP XX, can be considered as a valuable replenishment on the market of directly compressible filler/binders because of its very good tableting properties and optimum stability, when compared with other excipients.

FOOTNOTES

[1] FMC Europe S.A., Brussels, Belgium.

[2] Degussa, Frankfurt am Main, W-Germany.

[3] Colorcon Ltd, Orpington, England.

[4] Chemische Fabrik Budenheim Rudolf A. Oetker, Budenheim bei Mainz, W-Germany.

[5] Edward Mendell, New York , U.S.A.

[6] Roquette Frères, Lille, France

[7] Foremost-McKesson Inc., San Francisco, U.S.A.

[8] DMV, Veghel, The Netherlands.

[9] GAF Corp., Frechen, W-Germany.

[10] Lamers and Indemans, 's-Hertogenbosch, The Netherlands.

[11] Bergel Nederland b.v., Alkmaar, The Netherlands.

[12] Centrachemie b.v., Etten-Leur, The Netherlands.

[13] Model 2P, W.A. Bachofen, Basle, Switzerland.

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