CHAPTER IV

DISCUSSION & CONCLUSION

Starches in the native form cannot be compressed into tablets owing to two main reasons: insufficient compressibility and poor flowability despite their enormous supply and low cost. The reason for low compressibility of starches is due to their structures. Starches are composed of amylose (linear chain) and amylopectin (branched chain) arranged in a specific fashion. Generally, the amount of amylose in starches is about 20-30 %, the rest is amylopectin. Amylopectin, the major component, aligns in such a way to form micelles, the crytalline regions, giving the strength to the starches. Amylose, the minor component, mingles with amylopectin, but not in the micelles, and provides additional strength to the starches. The strength of starches is due to the fact that micelles create a large number of hydrogen bonds between adjacent hydroxyl groups, largely intermolecular. The more the number of hydrogen bonds, the more the strength and compressibility of starches. However, the number of hydrogen bonds in starches is small compared to

cellulose which is one of the strongest material in nature. This is due to the fact that outer chains of amylopectin which engage in micelles are very short, with only an average chain length of 12 A.G.U. If the engaged molecules in micelles were linear chain such as cellulose, the compressibility of starches could be sufficient to be compressed into tablets.

Poor flowability is related to the size and shape of starch granules. Most of commercial starches had small granule sizes, usually under 30 um on average, and moreover their shapes are largely irregular, not round and smooth. These factors generate forces (electrostatic, Van der Waal's etc.) and friction which are large enough to impede flowability, even with the aid of lubricants.

Traditionally, the way to solve these problems is to make wet granulation of starches with lactose using various binders such as starch paste, PVP etc. This method gives satisfactory results with most drugs. However, it has numerous drawbacks. First, the compressibility is not high enough to mix with low compressibility drugs, especially at high amount. Second, the disintegration time is rather long, especially when hard tablets are needed, for example,

for making core tablets in tablet coating. Moreover, if the particle size of drugs to be mixed is small, (under 100 um.), the segregation or demixing can take place during transferring and compression. If we solve these problems by reducing the particle size of granules, the granules will not flow freely as before.

Two different ways to solve these problems are illustrated by Starch 1500[R] and Eratab[R]. Starch 1500[R] is a trade name for partially pregelatinized corn starch. When starch is gelatinized, there are rearrangements of amylose and amylopectin components. The pregelatinized starch has more compressibility than the native starch. Even though the compressibility is sufficiently high for general purposes, but not high when compared to other directly compressible diluents (Table 38). Most of the small corn starch granules are melted to form aggregates which are much larger. This improves flowability considerably. If carefully observed, a small number of corn starch granules are not gelatinized, this is intention, these unmodified granules serve as a self lubricant. The last drawback of starch 1500[R] is that if it is kept in ambient condition with relative humidity 70 % (or more) at room temperature (the normal climate of Thailand), it cannot

Table 38   Tabletting Properties of Various Directly Compressible Diluents

Diluents	Compressional Force (Ponds)	Physical Properties of Tablets				
		Weight (mg)	Thickness (mm)	Hardness (Kp)	Friability (%)	Disintegration time (min)
Starch 1500[R]	1,000	340.0 (0.5)	3.816 (0.002)	5.9 (0.48)	2.628	12.27 (0.42)
	1,500	340.6 (0.6)	3.610 (0.017)	9.3 (0.49)	0.930	17.91 (0.98)
	2,000	341.0 (0.3)	3.504 (0.015)	12.2 (0.62)	0.706	18.27 (0.46)
	2,500	340.1 (0.5)	3.475 (0.012)	14.5 (0.35)	0.556	21.32 (0.92)
Emcompress[R]	1,000	345.0 (0.5)	2.587 (0.013)	1.65 (0.37)	3.33	5.74 (1.48)
	1,500	347.0 (0.2)	2.503 (0.011)	2.62 (0.05)	2.18	13.60 (3.08)
	2,000	347.3 (0.6)	2.432 (0.010)	3.80 (0.58)	1.61	> 60
	2,500	346.5 (0.6)	2.380 (0.080)	5.65 (0.19)	1.37	> 60
Anhydrous Lactose	1,000	345.1 (0.9)	3.697 (0.012)	4.50 (0.11)	1.48	0.34 (0.04)
	1,500	347.0 (0.2)	3.546 (0.007)	6.75 (0.37)	0.98	0.56 (0.06)
	2,000	346.5 (0.9)	3.428 (0.007)	9.0 (0.16)	0.66	2.35 (0.13)
	2,500	398.3 (0.7)	3.340 (0.013)	11.1 (0.73)	0.61	3.85 (0.16)

Table 38   Cont.

Diluents	Compressional Force (Ponds)	Physical Properties of Tablets				
		Weight (mg)	Thickness (mm)	Hardness (Kp)	Friability (%)	Disintegration time (min)
Avicel PH 100[R]	1,000	341.4 (1.22)	3.617 (0.016)	> 20	0.035	3.77 (0.20)
	1,500	342.7 (0.29)	3.394 (0.013)	> 20	0.034	7.43 (1.10)
	2,000	342.4 (0.48)	3.273 (0.020)	> 20	0.017	10.65 (0.23)
	2,500	341.8 (1.56)	3.215 (0.020)	> 20	0.00	15.75 (5.91)
Elcema P 100[R]	1,000	342.0 (0.4)	3.788 (0.033)	11.1 (0.39)	1.276	54.73 (7.45)
	1,500	340.9 (0.3)	3.548 (0.005)	15.95 (0.71)	0.410	> 60
	2,000	341.1 (0.4)	3.439 (0.005)	19.92 (0.09)	0.350	> 60
	2,500	341.8 (0.5)	3.382 (0.013)	> 20	0.078	> 60
MFB	1,000	344.0 (0.8)	3.776 (0.013)	18.52 (0.41)	0.497	2.20 (0.45)
	1,500	344.2 (0.3)	3.531 (0.006)	> 20	0.216	4.32 (0.69)
	2,000	343.0 (0.1)	3.382 (0.021)	> 20	0.136	7.98 (1.11)
	2,500	343.2 (0.3)	3.307 (0.001)	> 20	0.05	10.55 (2.30)

disintegrate within 30 min.(Table 19).

Eratab[R] solves the problems in the different way. It is made up of spherical rice starch aggregates (agglomerates) probably prepared by flash drying (Fig. 77). Flash drying employs the same principle as spray drying. Rice starch is selected to be modified for many reasons. First, its size is the smallest of commercial starches. Small particles have a natural tendency to adhere together, so it is easier to prepare starch aggregates made up of small granules than the large ones.Second,rice starch has the highest compressibility compared to other commercial starches(Lerk, C.E. et al, 1987). Finally, its price is low, though not the lowest, and it is one of the most available of all starches in Thailand, the rice producing country. The compressibility of Eratab[R] is high, the highest of non-cellulose type directly compressible diluents (Table 20). However, its compressibility is only a half of Avicel[R] (microcrytalline cellulose). Its flowability is good, and disintegration time is the lowest of all water insoluble diluents, second only to anhydrous lactose,the water-soluble one.This short disintegration time is due to a large number of pores between each granule forming starch aggregates which let the water
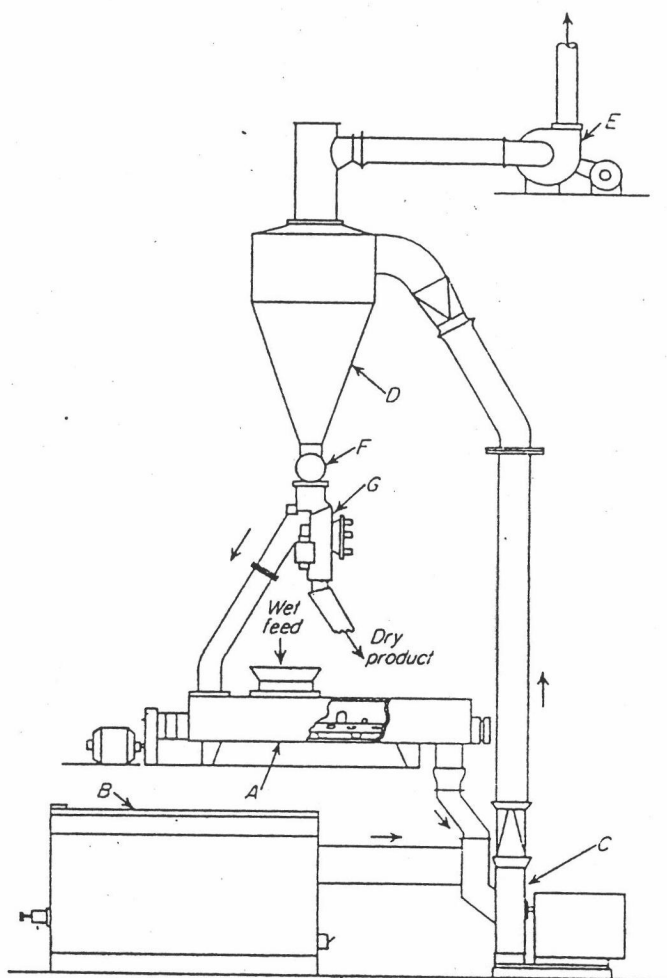
Flash dryer with disintegrator. *A*, paddle-conveyor mixer; *B*, oil-fired furnace; *C*, hammer mill; *D*, cyclone separator; *E*, vent fan; *F*, star feeder; *G*, solids flow divider and timer.

Figure 77   Diagram of Flash Dryer

(Perry & Chilton, 1973).....

penetrate into the core easily. In addition, the pores also serve as reservior for small drug particles or dyes to help prevent segregation. The last reason for fast disintegation and high compressibility of Eratab is that spherical starch aggregates are gelatinized at the surface during flash drying. This surface gelatinization can be done by flash or spray drying only. This process produces the optimum degree of gelatinization that makes the starch aggregates not too viscous when they contact with water and much more rigid after compressed into tablets.

Effects of Concentration on Properties of Starch Aggregates

There was the optimum concentration (50 % w/w) that could produce the starch aggregates that were large enough (89 um when determined by S.E.M. or 102 um when determined by sieve analysis) to flow freely and has just sufficient compressibility to be compressed into tablets (3.8 kp, 1000 lb) and short disintegration time (3 min.). It will be seen that the more the concentration, the larger the diameter of starch aggregates. The 50 % w/w is the maximum concentration that can be prepared by ordinary method and not too

viscous to be carried to the atomizer by peristaltic pump.

Effects of Temperature on Properties of Starch Aggregates

Again,there was a narrow range of temperature that could produce starch aggregates. At below 130 $^{\circ}$C, the starch aggregates would not dry completely.Above 135 $^{\circ}$C, the starch dispersion became gel which clogs the atomizer.

The two temperatures produced starch aggregates with nearly equal diameters and flowability, but the difference was seen when the starch aggregates were compressed into tablets. Hardness and disintegration time of the starch aggregates spray-dried at 130 $^{\circ}$C were clearly higher than 135 $^{\circ}$C, but the friability was much lower. This can be explained in term of degree of gelatinization. The starch aggregates dried at 130 $^{\circ}$C had higher degree of gelatinization than at 135 $^{\circ}$C. At higher temperature, water absorbed or trapped in the starch aggregates dried more quickly and completely than at 130 $^{\circ}$C. Gelatinization process must employ water to transfer heat to the granules. If the quantity of water is not sufficient for all regions of the granules,

the whole granules cannot gelatinize completely. In case of starch aggregates, gelatinization took place only at the surface because the quantity of water around the granules was low(the concentration of starch dispersion is high) and duration of drying was very short, only a few seconds.

If the gelatinization occurred to all regions of the granules, the whole granules would melt and deform when observed by S.E.M.such as Starch 1500[R]. Therefore, starch aggregates dried at 130 $^{\circ}$C had higher compressibility (hardness), longer disintegration time, and less fragility than at 135 $^{\circ}$C because they gelatinized more completely.

Effects of Feed Rate on Properties of Starch Aggregates

When feed rate was increased 3 and 5 times of the starting value, 4.32 g/sec, the mean weight diameters of starch aggregates did not alter. Paradoxically, moisture content decreased as feed rate increased, while bulk and tapped density, and % compressibility did not vary much from the starting values.

When compressed into tablets, the lowest feed rate gave high friability values for all three pressures, slightly exceeding 1.0 % limit. Disintegration time

values were low, while hardness were low but acceptable. When feed rate was increased 3 and 5 times,friability, disintegration time and hardness were all lower.

The explanation for these phenomena, is that low feed rate yielded starch aggregates with higher degree of gelatinization than of high feed rate. The quantity of heat supplied to the droplets of starch dispersion was the same for every feed rate (the other process variables were fixed). When the feed rate or the number of droplets per unit time was small, the heat penetrated all droplets more completely than when the number of droplets was large(high feed rate). Thus, low feed rate yielded starch aggregates with higher compressibility and longer disintegration time than of high feed rate.

Effects of Crosslinking on Properties of Starch Aggregates

When rice flour was crosslinked for 2, 6, and 10 hrs. before spray dried into starch aggregates,the mean diameter, flowability and the other physical properties of starch aggregates did not vary with crosslinking time. After compressed into tablets, hardness and

disintegration time increased as degree of crosslinking increased. In other words, the physical properties of starch aggregates after crosslinked were the same, while the tabletting properties were different. This suggested that the effects of crosslinking were not external, but internal. The explanation was that crosslinking gave more strength to the starch granules by replacing hydrogen bonds in starch molecules with covalent bonds which were much stronger. The amount of covalent bonds increases with crosslinking time, hence the hardness of starch aggregates(which showed the strength of starch granules) also increased with crosslinking time.

Effects of Deproteinization and Crosslinking on Properties of Starch Aggregates

When rice flour was deproteinized before crosslinked and spray dried, the properties of starch aggregates changed. The physical properties such as mean weight diameter, flowability did not differ from those not deproteinized. But, when compressed into tablets, the effects of crosslinking on deproteinized flour clearly observed. The hardness of starch aggregates prepared from deproteinized flour was much higher than from that

not deproteinized or the native flour. The hardness increased with crosslinking time and reached the maximum at 18.8 kp. (1,000 lb.) for the 6-hr. crosslinked starch aggregates but declined to 7.8 kp. for the 10-hr. crosslinked which was lower even than the value for the native flour . Disintegration time values were good for every form of starch aggregates, all were lower than 5 minutes even when hardness values were above 20 kp.

All friability values were also lower than 1.0 % limit except for the 10-hr. crosslinked. The explanation for these effects is that the protein which co-existed with starch molecules, bound with the hydroxyl groups of starch molecules in some way (Lee, 1983), this hindered the reaction of functional groups of sodium trimetaphosphate with the hydroxyl groups of starch. When the protein was eliminated, sodium trimetaphosphate could bind with the hydroxyl groups more effectively. This caused the increasing of the number of covalent bonds in starch molecules and helped increasing the hardness of starch aggregates to the utmost degree. When the crosslinking time increased, the viscosity and swelling power of starch aggregates decreased. Beyond certain limit, the starch granules

lost the capacity to gelatinize. This is due to the reason that hydrogen bonds were all replaced by covalent bonds. When there was no gelatinization, there was no rearrangement of starch molecules which led to higher rigidity and strength of the granules. This caused the hardness to decrease for the 10-hr. crosslinked.Moreover disintegration time also increased because the starch granules in starch aggregates did not swell when immersed in water.

Properties of Commercial Modified Starch Products

Starch 1500^R had the smallest mean weight diameter of all products tested, only 80 um. This helped prevent segregation during mixing process with the fine drug powder. Despite the small size, its flowability was good. After compressed into tablets, its hardness values were fairly good, but disintegration time were too long, more than 30 minutes at all three pressures. The disintegration time values in this experiment were different from other places. Table 41 showed the disintegration time values of Starch 1500 reported by Limmatvapirat (1991). The results came from the same batch of Starch 1500^R, compressed and evaluated by the same instruments. The difference was

that the bottle of Starch 1500^R employed was not tighthy closed to prevent moisture and it was evaluated a year later. Comparing % moisture content of the two evaluations, they were nearly equal, 11.5 & 11.1 %. The possible reason is that Starch 1500^R is pregelatinized corn starch which, if dissolved in water, will turn into starch paste with increasing viscosity. In this case, the process of solubilization took place gradually and slowly at the surface of starch 1500^R particles without noticeable change in flowability or other physical properties. After immersed in water, the thin film of starch paste around Starch 1500^R particles swelled to give a viscous layer that blocked the penetration of water into the core of tablets and made the tablets not disintegrate within the limit of USP requirement.

Eratab^R had the mean weight diameter which was nearly equal to Starch 1500^R for the same purpose as Starch 1500^R. Eratab^R had a little higher moisture content but its flowability was as good as Starch^R 1500. When compressed into tablets, its hardness values were a little higher, reaching 12.7 kp. (1,000 lb.) which was very high compared to other directly compressible diluents, except the cellulose-type. Its disintegration

time was the lowest of all products tested, only 1:45
min. at 1,000 lb.

Viscosities of Crosslinked Rice Flours

All viscosities were measured at 40 $^{\circ}$C after
retrodegradation (set back) had taken place, which
resembled the actual condition for starch aggregates
after spray dried and left in the room condition.
Lower temperature was not suitable because it took too
much time and moisture might evaporate which caused
abnormal higher viscosity. The viscosity of native
flour was high at 600 B.U. When crosslinked for 2
hrs., it fell down to the minimum at 26 B.U., and rose
up a little to 30 B.U. for the 6-hr. crosslinked. When
crosslinked for 10 hrs., the viscosity increased
sharply, reaching 250 B.U. Nonetheless,these phenomena
might be caused by 2 main factors : protein binding
with starch and protein binding with crosslinking agent
(sodium trimetaphosphate). Because protein had many
different functional groups such as carboxyl, amino,
sulfhydryl etc., these groups could interact with
hydroxyl groups of starch in various ways forming
hydrogen bond, electrostatic, Van der Waal's forces,
ionic bond etc. (Lee, F.A. 1983) These forces made

water molecules solvate starch molecules (when heated) more difficult. Therefore the starch granules couldnot swell to their full capacity which lessened viscosity (protein had a helical structure as well as starch,therefore it was very easy for functional groups of the protein to bind with functional groups of starch). This was the reason why the native rice flour has lower viscosity than the deproteinized. When using sodium trimetaphosphate as a crosslinking agent, its functional groups were hindered by the protein and couldnot react with free hydroxyl groups of starch. At 2-hr. crosslinking time, the viscosity was now at the minimum. This was probably the time that sodium trimetaphosphate reacted with the starch molecules, the parts which were not bound with protein completely or nearly so. When the crosslinking time was increased to 6 and 10 hrs., the effects of high alkalinity and heat might cause the sodium trimetaphosphate to react with various founctional groups of protein (protein was well known to be a compound which was extremely sensitive to environmental conditions such as pH, heat etc.). One possible reaction was the forming of ester linkages between carboxyl groups and phosphate groups of sodium trimetaphosphate which was a kind of crosslinking

reaction (Creighton, T.E. 1990). The rate of this reaction increased with time. Therefore, the amount of sodium trimetaphosphate remaining to react with starch molecules was reduced and caused an increase in the swelling and viscosity of starch granules as crosslinking time increased.

Viscosities of Deproteinized and Crosslinked Rice Flour

When the protein content of rice flour was reduced from 8 % to 2 %, the viscosity of heated rice flour dispersion increased from 600 B.U. to 640 B.U. This result showed that protein had the interferring effects on viscosity of rice flour as discussed before. After crosslinked for 2, 6, 10 hrs., viscosities decreased to 450, 34, 25 B.U. respectively. These results demonstrated that crosslinking time had the effects on viscosity of deproteinized rice flour. When crosslinking time increased, the viscosity decreased. This was due to the reason that when degree of crosslinking increased, the number of covalent bonds that replaced hydrogen bonds in starch granules increased and this made the starch granules more rigid and less swell when heated. Hence the viscosity that resulted from the swelling 'of starch granules

decreased instead of increasing as in the case of the native rice flour.

Swelling Power of Crosslinked Rice Flour

The swelling power of the native rice flour was high at 696.3 %. When crosslinked for 2 hrs., it went down to the minimum at 444.8 %. Then they rose up a little to 479.8 and 574.8 % for those crosslinked 6 and 10 hrs. respectively. These results were similar to the viscosities of crosslinked rice flour, and the explanation for these results was on the same basis.

Swelling Power of Deproteinized and Crosslinked Rice Flour

The swelling power of deproteinized rice flour was high at 787.3 %, higher than the native flour. This result showed that protein interferred the swelling of starch granules. When it was eliminated, the viscosity increased appreciably.

After crosslinked for 2, 6, 10 hrs., the viscosities were 650.0 , 498.7 , and 473.5 % respectively. The explanation for these results was the same as before for the viscosities of

deproteinized and crosslinked rice flour.

CONCLUSION

1. Rice starch was found to be the most suitable starch to be developed into a directly compressible diluent by using spray-drying technique and crosslinking reaction, when compared to other kinds of locally available commercial starch including tapioca, glutinous rice, corn, and mung bean starch.

2. Rice starch in the form of rice flour dispersion(in water) was spray-dried under optimum conditions to yield spherical starch aggregates which gave much higher compressibility, lower disintegration time and faster flowability, when compared to native flour.

3. The various spray drying variables including concentration and feed rate of starch dispersion, drying temperature and atomizing pressure, all played the significant effects on tabletting properties of starch aggregates.

50 % starch dispersion (or higher) gave starch aggregates with acceptable compressibility, flowability and disintegration.

Lower feed rate gave higher compressibility and disintegration time than higher feed rate.

Temperature range which yielded satisfactory s.a. was between 130-135 $^{\circ}$C. 130 $^{\circ}$C gave the starch aggregates with higher compressibility and disintegration time.

Atomizing pressure used had to be 1.5 bar. Above this pressure, at 2.0 bar, the product was too small and stuck to the wall of the chamber. Below 1.5 bar, the product was too large and fell down to the bottom of the chamber at 1.0 bar.

4. When rice flour was crosslinked for various length of time before spray-dried, the tabletting properties of starch aggregates improved.

5. When rice flour was first deproteinized, and then crosslinked, and spray-dried, the starch aggregates obtained yielded the best tabletting properties (Fig.78).

Deproteinized rice flour, crosslinked for 6 hrs. gave the product with the best tabletting properties, i.e. highest compressibility, 18.8 kp (1,000 lb), lowest disintegration time, 3 min. (1,000 lb.) and fast flowability also (Angle of Repose = 29.41°, flow rate = 13.46 g/sec)

When compared with other directly compressible diluents (Table 38 - 39), it was seen that its
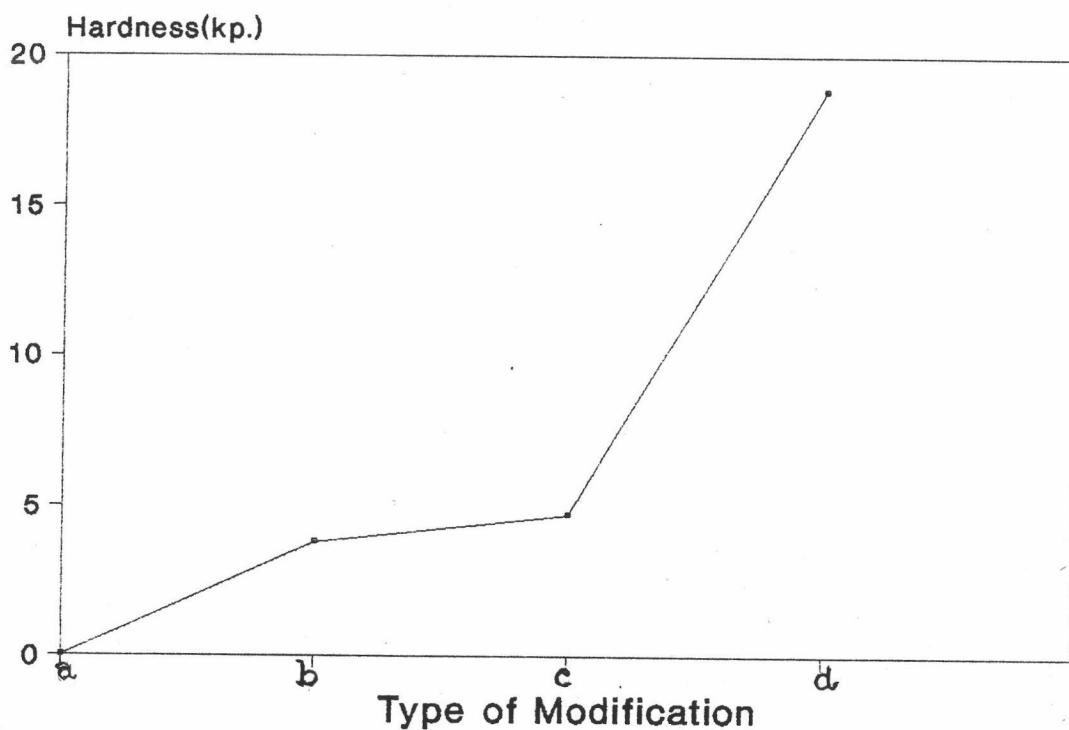
a = rice flour (unmodified) cannot be compressed into tablets

b = starch aggregates tablets, modified by spray-drying only

c = starch aggregates tablets, crosslinked for 6 hrs. before spray-dried

d = starch aggregates tablets, deproteinized and crosslinked for 6 hrs.

before spray-dried

Fig. 78   Comparison of Hardness of Starch Aggregates

Tablets prepared by various types of

Modification

compressibility was very high (second only to cellulose-type diluents by a narrow gap), its disintegration time was very low(third behind anhydrous lactose and microcrystalline cellulose from bagasse) and its flowability was good also(much better than cellulose-type diluents). So, this product was very suitable for use as directly compressible diluent, and it seemed to be the best all-round directly compressible diluent ever developed considering every property including price which should not exceed 60 Baht/kg.(retail price). However this was only the first step to the goal. Further testing with drugs in various formulations (in large scale) will prove the usefulness of this product in the future.

Table 39   Physical Properties of Various Directly
            Compressible Diluents.

Diluents	Physical Properties of Diluents					
	Bulk Density (g/ml, ± SD)	Tapped Density (g/ml, ± SD)	True Density (g/ml, ± SD)	Compressibility (%)	Angle of Repose (°, ± SD)	Moisture Content (%)
Avicel PH 101[R]	0.292 (0.001)	0.455 (0.004)	1.532 (0.019)	35.93 (0.84)	38.67 (1.07)	6.3 (0.1)
Elcema P 100[R]	0.211 (0.001)	0.462 (0.001)	1.494 (0.014)	54.29 (0.35)	44.20 (1.14)	8.3 (0.5)
MFB	0.277 (0.002)	0.522 (0.002)	1.513 (0.014)	47.03 (0.32)	42.30 (1.10)	5.8 (0.2)
Starch 1500[R]	0.562 (0.004)	0.794 (0.005)	1.449 (0.007)	29.11 (0.82)	32.09 (3.36)	11.1 (0.1)
Encompress[R]	0.885 (0.003)	1.073 (0.003)	2.258 (0.016)	17.50 (0.01)	29.84 (1.33)	15.5 (0.2)
Anhydrous Lactose	0.519 (0.002)	0.796 (0.008)	1.548 (0.004)	22.30 (0.85)	32.78 (0.48)	0.2 (0.1)