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DISINTEGRATION MECHANISMS OF TABLETS CONTAINING STARCHES. HYPOTHESIS ABOUT THE PARTICLE-PARTICLE REPULSIVE FORCE

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ABSTRACT

The disintegration of a tablet immersed in a liquid appears to be essentially a mechanical phenomenon : penetration of liquid then destruction of compressed structure

For a number of authors, the starch granule swelling is the mechanical force which destroys the tablet.

Indeed, a study on a series of experimental carboxymethylstraches indicates that those that do not swell, show the same disintegration time to those that do swell.

We can also notice that the carboxymethylstarches wich swell much less in a gastric medium, produce even shorter disintegration times in this medium.

The destruction of the cohesion forces between the constitutive elements of the tablet under the action of water may be ascribed to the creation of a repulsive force when the elements of the tablet enter into contact with water, or to a simple annibilation of the hydrogen bonds or of the capillary cohesion forces.

The hydrophilic nature of starch seems to be determinant : water penetrates into the tablet owing to hydrophilic porosity under the action of an important hydrostatic pressure.

INTRODUCTION

The mechanism of action of starches in the tablet disintegration has been developed for many years in pharmaceutical magazines.

This is the reason why we will be trying to make an objective synthesis of the various hypothesis that have been issues before adding our contribution to this imposing task. Everybody seems to agree nowadays with the idea that the disintegration of a tablet immersed in a liquid appears to be essentially a mechanical phenomenon.

Penetration of the disintegration liquid, then destruction of the compressed structure tending to the return to initial particles. This two-steps dissociation has the advantage of making admissible various issued hypothesis.

First one can consider that the disintegration will be all the faster as the liquid absorbing capacity is greater. This capacity may be increased, either by a "sucking phenomenon" due to the disintegrant, or still by the creation of a porous network propitious to the progression of water in the tablet structure.

This structure has been created by the compressive force and is maintened by more or less important cohesive forces.

Its destruction will be all the more complete as these forces will be very quickly annilihated.

For a number of authors, this is the very time when the main action of the starch swelling will take place, a mechanical force which would be enough to destroy the tablet.

This quick review concerning the mechanism of disintegration displays one essential fact : the absolute necessity of an important and fast progression of the disintegration liquid.

This idea is the underlying foundation of our reflexion and served as the guide-line to the deeper analysis of the hypothesis that have just been reported.

USUALLY ISSUED HYPOTHESIS :

The swelling of starches - This theory appeals to the mechanical influence of the disintegrant in the disintegration phenomenon. Studies about the swelling capacity of various starches abound in literature. (1), (2), (3). The measurements given by these authors are not always effectuated in the same conditions, so their results are accordingly extremely variable (6% swelling of the volume for maize starch for some authors ; and up to 78% for the others.) In any case, they are not exactly the reflected image of what happens inside a tablet in which starch is compressed among other particles. More over this tablet will have to be disintegrated easily in a glass of water at 20°C as well as in gastric juice at 37°C.

As for us, different measurements of the starch grains diameter, experimented by microscopic determination in various media have shown to us extremely variable swellings of the grains according to the samples ; (variation of the diameter from 0 to 10% : the amount of amylopectin which can vary probably promotes the swelling.) (2)

Whatever the conditions of the experiment, the increases of diameters that have been observed, do not seem sufficient to some authors to explain the disintegrating action of starch. Some other authors such as COUVREUR (4), connect the disintegration efficiency to the increasing volume of potato starch and to the porosity of the tablet.

In the case of a compressed structure, the swelling phenomenon could be reduced to the minimun BERRY & RIDOUT (5), for example have noted an increase in the disintegration time with a large compressive force. This increase can be attributed to the reduction of the speed penetration of liquid into the tablet. On the opposite, others authors show a decrease in the disintegration time above a certain compressive force. (6). The deformation and the small deterioration of the grain starches may, perhaps, be ascribed to the effect of a too strong compressive force.

At first sight, then it does not seem that the swelling should explain the whole mechanism of the disintegration, considering the great variability of the experimental results.

Indeed we carried out a study on a series of experimental carboxymethylstarches which are to be distinguished by very different swelling capacities, rising up to 200 times the initial volume.(7). Now, when the times of disintegration of the various tablets obtained with these carboxymethylstarches are compared, those that do not swell, show the same performances (sometimes even superior) to those that do swell. We present in Table 1 a few examples drawn from a work about aspirin and acetaminophen tablets containing 3% of carboxymethylstarch. We can also notice that the carboxymethylstarch which swell much less in a gastric medium produce even shorter disintegration times in this medium.

Development of a capillary network - It appears that the porosity of the tablet is indeed an important factor of the disintegration.

HIGUCHI (8) had already proved that the porosity varies in the reverse order of compressive force and logarithm of the time of disintegration is directly proportional to the pressure. More recently, some authors, among them NOGAMI (9), have tried to connect the evolution of the porosity to the disintegrant concentration and tried to prove its influence on the disintegration. The relations between the disintegration time, the porosity and the starch concentration are not linear. The association of different particle sizes of aspirin to maize starch or to potato starch produces perceptibly different results. The author explains this difference in behaviour by the fact that maize starch which is smaller seems to envelop the drug particles.

TABLE 1

Comparisons between disintegration times and swelling capacity of different carboxymethylstarches grains in water and gastric juice (USP without enzymes). (Potato starch in reference).

Variety of starch		dry medium	water	gastric juice (USP without enzymes)
CMS 38	Volume of sediment	1,35 ml	1,65 ml	1,60 ml
	Diameter	24,2 μ	33,8 μ	24,2 μ
	Dis.Time ASPIRIN		62 sec.	63 sec.
	ACETAMINOPHEN		375 sec.	330 sec.
CMS 48	Volume of sediment	1,60 ml	37,0 ml	8,8 ml
	Diameter	38,0 μ	116,0 μ	52,6 μ
	Dis. Time ASPIRIN		49 sec.	26 sec.
	ACETAMINOPHEN		285 sec.	225 sec.
EXPLOTAB	Volume of sediment	1,35 ml	29,0 ml	3,5 ml
	Diameter	29,7 μ	85,8 μ	40,9 μ
	Dis.Time ASPIRIN		32 sec.	24 sec.
	ACETAMINOPHEN		210 sec.	195 sec.
POTATO STARCH	Volume of sediment	1,40 ml	1,65 ml	1,70 ml
	Diameter	23,3 μ	25,7 μ	23,4 μ
	Dis.Time ASPIRIN		50 sec.	52 sec.
	ACETAMINOPHEN		367 sec.	456 sec.

The continuity of the disintegrant around the drug may induce a change in the porous volume favourable to the disintegration. In fact, we have shown that this continuity had a beneficial influence on the kinetics of the water absorption of tablets : By creating an hydrophilic network around the drug particles, the disintegrant helps disintegration. Indeed, we can see that tablets containing aspirin only with a high porosity do not disintegrate because the walls of the pores cannot be wetted. Il the pores are covered with an hydrophilic starch, water can enter very easily into the tablet (10).

We must agree the beneficial influence of the porosity in this case. We have proved that when a continuous network of starch was set up around the particles, the tablet disintegration still took place in relatively short time, even when the porosity had been reduced to the minimum by a strong compressive force (11).

Hydration heat - MATSUMARU (12) gives an explanation which seems unfortunately to be limited to a few particular instances. The author demonstrates by thermal analysis, in the case of starch that the wetting of the tablet by the disintegration liquid would cause an expansion of the air entraped in the porous structure of the tablet which might be at the origin of the mechanical destruction of this tablet.

LIST (13), when analysing the phenomenon shows that, according to the different cases, heat can be released or not and the disintegration time is not always very quick when there is an important heat development.

Hypothesis about the particle-particle repulsion - The whole contradictory facts, previously reported, has led us to look else where for the causes of the cohesion lost of the tablet constituents when it comes into contact with water.

As for us, we are enclined to think of the destruction of the cohesion forces between the constitutive elements of the tablet under the action of water. The phenomenon may be ascribed either to the creation of a repulsive force when the elements of the tablet enter into contact with water or to a simple annihilation of the hydrogen bonds or of the capillary cohesion forces.

Several facts which have been found in literature have led us to this hypothesis.

BEDIN (14) has described with details the disintegration of a tablet, after filming it under the objective of a microscope : "As soon as the disintegration liquid reaches the edges of the fragment tablet, it seems to be sucked by this fragment. The wetting of the whole fragment involves the appearance of clefts from which starch grains escape. The clefts grow larger, the agglomerates break... After the creation of a cleft in a fragment of tablet, we can notice the starch grain ejection out of this very cleft. This ejection separates the edges of the two fragments formed by the cleft."

On the other hand we did succeed in observing with the microscope, that in a dry medium the native starches appear like aggregates, with some isolated grains. When we added a drop of water on the slide, the aggregates immediatly disappear and a layer of isolated grains strictly individualized can be observed. The disintegrant does seem to present a real force of individualization power of its particles when it comes into contact with water.

METHODS

Disintegration times - Method of the French Pharmacopeia 9th Edition, in water at 37°C.

Tests of comparative disintegration in water and different organic solvents have been carried out both at room temperature, without a disk, with the help of a basket which only presented one cell basket. That basket was undergoing a up and down movement which is usual in the machine of the Pharmacopeia.

Hardness - The measurements were taken with a durometer HEBERLEIN

Compression - The tablets were made with a OA FROGERAIS alternative machine on some mixtures of starch and drug by direct compression. Every time, two formulations have been compressed for comparison ; the tablets have been produced with the same upper punch displacement, the volume of the compression chamber remaining constant.

MATERIALS

- Maize starch
- Modified starches :
  - . Carboxymethylstarch (CMA) ; EXPLOTAB ® (1)
  - . Highly reticulate corn starch ; VULCA 100 ® (2)
- Cristallized Aspirin (300 μ)
- Paracetamol DC ® (3)
- EMCOMPRESS Special ® (1)

RESULTS AND DISCUSSION

Particle-particle repulsion demonstration - Several authors, as we already note, have ascribed to the swelling of starch a preponderant place in the disintegration and these authors often connect the swelling of starch to the increase of the volume of the tablet, a phenomenon which is generally observed when this tablet enters into contact with water.

(1) Explotab, Edward Mendell Co. Inc., Carmel, NY 10512
Emcompress, Edward Mendell Co. Inc. Carmel, NY 10512
(2) Roquette Lestrem France
(3) Graesser Salicylates, Sandycroft, Deeside CLWYD CH52PX

Two phenomena must not be confused : the swelling of the tablet itself and the swelling of its constitutive elements.

Indeed we carried out the following experiment. We made aspirin tablets on the one hand, and some tablets with EMCOMPRESS which is insoluble, on the other hand. These tablets were prepared in the same conditions with maize starch on one hand, and high reticulate starch which cannot swell. Two different amount of starch were used for the aspirin tablets.

The results shown in table 2 demonstrate that disintegration times with reticulate starch tablets are not in any case longer than the disintegration times obtained with native starch in spite of a smaller hardness.

TABLE 2

Comparisons between the disintegration times and the hardness of tablets containing native starch and reticulate starch.

	%starch		Native starch	Reticulate starch
Aspirin	4%	Hardness	8,5 Kg	12 Kg
		Dis.Time	150 sec.	135 sec.
	8,5%	Hardness	8,5 Kg	10,3 Kg
		Dis.Time	21 sec.	10 sec.
Emcompress[R]	4,25%	Hardness	7,5 Kg	12 Kg
		Dis.Time	15 sec.	10 sec.

It is obvious to note that the tablets made with highly reticulate starch that does not swell, show in contact with water a swelling which is just as important as the swelling of the tablets made with native starch. The phenomenon can be easily observed (15).

How can this swelling be explained if the tablet's components do not swell, if not by the advent of a separation between those elements ?

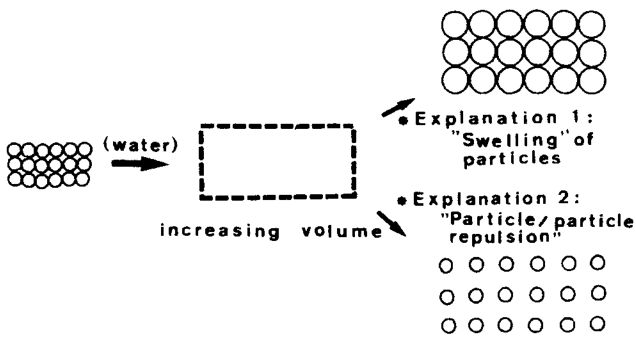

FIGURE 1
Possible explanations of the swelling of a tablet in contact with water.

Such a phenomenon occurs with other excipients which are generally considered as non-swelling such AVICEL.

This series of facts already enable us to draw a first conclusion : this disintegration is indubitably a mechanical phenomenon in which the constituent elements separate one and another under the action of water.

TABLE 3

Disintegration Times of tablets containing maize starch or 3 % of carbomethyl-starch in various media with variable dielectric constant (ε).

		maize starch	maize starch + EMCOMPRESS	EXPLOTAB + EMCOMPRESS
Hardness		7,8 Kg	7,5 Kg	6,5 Kg
ε	Dis. Medium			
78	Water	30 sec.	15 sec.	4 sec.
33	Methanol	30-45 sec. macrogranular	none	none
33	Dioxane/ Water	30-45 sec. microgranular	30 sec.	30-45 min. macrogranular
24	Ethanol	6 min. 30 sec. macrogranular	none	none
21	Acetone	none	none	none
21	Dioxane/ Water	30-45 sec.	2 min.	none
10	Dioxane/ Water	3-6 min.		
2	Dioxane	none	none	none

We have looked for the causes of this repulsion between tablet's components.

Demonstration of the necessity of the presence of water in this phenomenon - We have made maize starch tablets and they have been disintegrated in variable constant dielectric* media. We have also studied tablets containing EMCOMPRESS, which is insoluble in water and organic solvents,mixed on the one hand with 4,25 % of maize starch, mixed on the other hand with 3 % EXPLOTAB. This carboxymethylstarch swells strongly into contact with water.

These results have been reported in Table 3.

Three observations can be made :

- The disintegration time becommes longer with the decrease in dielectric constant of the medium. Yet the disintegration time is not direct fonction of the dielectric constant of the medium

All things considered, with the equivalent dielectric constant, the medium which contains water still allows the disintegration even for very low dielectric constants (ε = 10 for pure starch tablets).

- The carboxymethylstarch which swells, absorbs more water and needs more of it in the medium to provoke a fast disintegration after a complete tablet soaking.

* Dielectric constant = ε

- A number of tests on aspirin tablets and paracetamol tablets have confirmed these results but the conclusions were more difficult to draw as the dissolution of these drugs were superposed on the phenomena of disintegration.

This research shows the preponderance of the necessary presence of water in the mechanism of disintegration, independantly of the dielectric constant of the medium.

The presence of hydroxyles in the disintegration medium appears to be a factor likely to induce the disintegration of pure starch tablets since methanol enables a fast disintegration of them and since ethanol whose dielectric constant is 24 still permits some sort of disintegration which cannot be obtained with acetone whose dielectric constant is 21.

A sort of affinity between hydroxyles of the medium and those of starch could consequently be necessary to provoke the disintegration. For compound formulation tablets in which they are not only cohesion connections between starch granules, the water alone seems to have a sufficient affinity for starch grains to induce the separation and the breaking up of the tablet structure.

<u>Attempt at a physical interpretation of these observations</u> - These various observations can easily be related to the fundamental theories concerning the phenomena of particle-particle cohesion in presence of a liquid or moisture.

Moisture can in fact influence cohesion between particles in three ways :

- by adsorption on the surface and modification of surface energy.

- by modification of conductivity and consequently by electrostatic discharges.

- by condensation in capillars close to surface contact.

Varying with the importance of moisture or with quantity of water in contact with the particles, either a cohesion of these particles, will be noted,or, on the opposite, a release of particle-particle force will be seen.

SHOTTON & HARB (16) have demonstrated this variation of cohesion between starch grains according to the increase of moisture ; after reaching a maximum, the cohesion falls off when moisture gets very important. Hence the idea arises that the presence of water brought by starch into the tablet structure, may annihilate the cohesion forces keeping the particles joining one and another.

NEWITT, CONWAY, JONES, (17) studied the theorical case of two contiguous wettable spheres, having one contact point. A drop of water is laid on this contact point. The authors then show that these spheres are subject on the one hand to an attractive force due to the surface tension

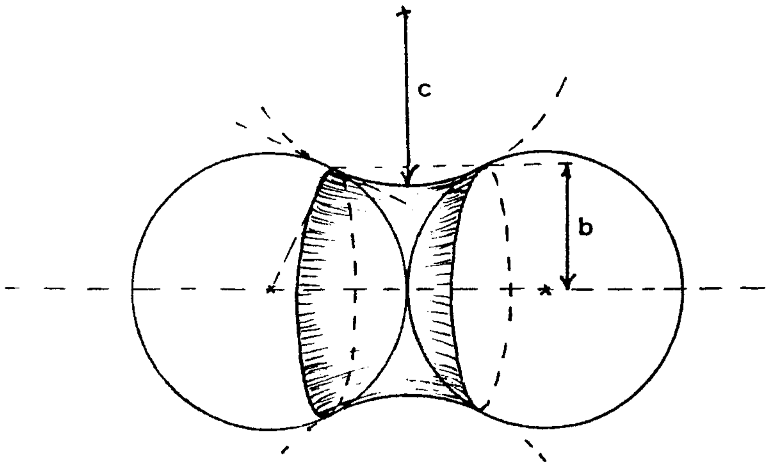

FIGURE 2
Wetting of two contiguous wettable spheres

(Fa = $2\pi b\gamma$, γ being the surface tension of liquid and b the radius of the wetting circle of the spheres) and on the other hand to a capillary force, described by LAPLACE' formula : $\pi b^2\gamma(\frac{1}{c} - \frac{1}{b})$, c and b being the radii of curvature meniscus.

But this applies to non-porous spheres. There is every reason for supposing that starch grain is soaked inside by water which enables this grain to convey this water in the very heart of the tablet even its porosity had been strongly reduced.

As for us we indeed display the beneficial influence on the disintegration rate, of creation of continuous network of starch grains inside the tablet. Water penetrates the tablet with a high capillary pressure under favour of pores with hydrophilic walls, or independtly of any porosity, from one starch grain to another one and so on(10).This penetration force is approximately three times as important in a wettable structure as for aceton or methanol, considering its particularly high surface tension (72 for water, 22 and 24 for the other two solvents).

As the weight of intergranular water increases, it annihilates the cohesion force due to the surface tension and water gets in between the grains and separates them. Besides this mechanical phenomenon, breaking up of hydrogen bonds by presence of water, is another sure cause for the release of particle-particle forces.

It is to be noted finally that some repulsion may appear between two non wettable particles if the water is brought in, for instance, by a netword of hydrophilic starch : The capillary force due to shape of the meniscus becomes repulsive (18).

The idea then may be developped that the presence of water introduced by starch into the tablet structure destroys the cohesion force keeping the constituent particles close to one another. This could be applied, in all probability, to all hydrophilic and non soluble disintegration

TABLE 4
Grains diameter and disintegration time of tablets in different medium

grains mean diameter		disintegration time
dry medium	11.9 μ	
water	12.8 μ	30 sec (microgranular)
methanol	10.7 μ	fragmentation from 18 sec
acetone	10.4 μ	none

agents. It could be the basis of the intern mechanical phenomenon of disintegration.

This mechanism consequently appears to be of the same type as the one which provokes the opening of a book when it is plunged into water : water getting between pages owing to the hydrophilic surface, induces their separation.

One cannot nevertheless be too positive. Recently LIST (13) has shown that a very slight increase in the disintegrant volume which cannot be perceived by a visible increase in the grains diameter could display sufficient forces to activate the disintegration. It would be impossible to disprove this hypothesis. However, without any intent to deny the possible interference of such a mechanism, we could realize that the starch grain shrink slightly in a acetonic or methanolic medium : now tablets containing pure maize starch disintegrate in a methanolic medium and they do not in an acetonic medium. The slight shrinking of the grain in a methanolic medium does not hinder the disintegration. The dislocation of the tablet could then be ascribed to this shrinking since there is no disintegration in acetone although the starch grain also shrinks in it.(Table 4)

CONCLUSION

The hydrophilic nature of starch seems to be determinant in the disintegration-process.

Water penetrates into the tablet owing to :

- an hydrophilic porosity
- a continuous starch network which can convey water from one grain to the other and so on, under the action of an important hydrostatic pressure because of its surface tension which is quite high compared to the surface tensions of organic solvents.

Water penetrates between starch grains because of its very large affinity for their surface and divides them by its weight and also because it breaks all the hydrogen bonds, Van Der Waals forces and capillary forces.

Conveyed into tablet by a sufficiently well distributed hydrophilic network, water could also provoke repulsion between two contiguous hydrophobic particles which are not bound by too strong forces similar to those resulting from superficial melting of touching crystals.

To sum up, the more hydrophilic the grains will be, the faster the disintegration process will be.

We could determine with the carboxymethylstarches that the graft of hydrophilic fonction increased starches performances, on condition that this graft, which make grain more brittle, should not increase the solubility, because, the viscosity then created would restrain penetration of water.

Perfect hydrophily and insolubility consequently appear to be the essential criteria of an ideal disintegrating agent.

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