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CALCULATION OF DISINTEGRANT CRITICAL CONCENTRATION IN ORDER TO OPTIMIZE TABLETS DISINTEGRATION

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ABSTRACT

Many reports are available about tablet disintegration mechanisms and several theories are reported in the literature.

All of them are supported by an universally recognized fact which is the necessity of fast water penetration inside the whole tablet. This fact points out the necessity of a continuous hydrophilic network setting up in the tablet structure.

Thereby, the authors after checking the regular adhesion of most of the disintegrant particles on the surface of drug particles, have applied the coordinence equation of Ben Aim and Le Goff, in order to calculate the best disintegrant proportion in a tablet formulation. This calculation will be relevant if the disintegrant particles are more or less spherical (e.g. starch and its derivatives : polyplasdone® XL, Kollidon® CL...). However, the coordinence equation leads to a number of small spherical particles needed for statistical coating of an isolated larger one. Therefore, this quantity will correspond to a double network of the small disintegrant particles between the larger drug particles. In practice, half the quantity of disintegrant particles are enough for a total cover. According to these facts, the equation to determine disintegrant percentage is :

$$\frac{d_1}{d_2} \times \left[\left(\frac{D_1}{D_2} + 1 \right)^3 - 1 \right] \times 100$$

d_1 and D_1, real density and mean diameter of disintegrant particles,
d_2 and D_2, real density and mean diameter of drug particles.

The same equation can be applied to the diluent percentage calculation.

If disintegrant particles swell in contact with water (e.g. Explotab®, Primojel®...) a correction factor will be used :

$\frac{D_1}{D_{1g}}$ (D_{1g} = diameter of swollen disintegrant particles).

Many applications have been carried out according to this formulation process and several results are reported.

INTRODUCTION

There are many reports in the literature in order to choose the best disintegrants for tablets formulation. Nevertheless, few of these reports give information about the most effective disintegrant concentration to be used. Several authors compare the disintegrating efficiency of different disintegrants by employing them in their tablets formulations at a one and only concentration. This process is open to criticism. For example, a tablet may be quickly disintegrated with 10 % of corn starch, but no disintegration will occur with 5 %. On the contrary, 5 % of Explotab®may be a more effective concentration than 10 %.

A good knowledge of the mechanisms of the tablet disintegration is required in order to estimate the best concentration of disintegrant to introduce in a mixture for compression.

The mechanism of tablet disintegration has been widely studied. Several theories have been put forward : swelling, cappilary action, heat of wetting, annihilation of cohesion forces between particles in presence of water, followed by particle/particle repulsion.

Several mechanisms are perhaps involved in the disintegration process.

In our opinion,the last hypothesis seems to be the most appropriate, as we have developped many years ago (1). Recently,Cartilier

and his Collaborators have rejected the swelling as the determinant mechanism for the disintegration of tablets containing native starches as disintegrating agents. They rally to the theory of the annihilation of the interparticular cohesion forces, by contact with water (2).

In spite of the numerous explanations given about the disintegration process, Van Kamp and his Collaborators emphasize the role of water uptake of the tablets, whatever the disintegration theory may be : "... There is however, no doubt that water uptake must be the first step in any process of disintegration..." (3).

Disintegration effectiveness in relation to the water uptake of the tablets

Many studies were carried out in this way :

- on pure disintegrants
- on tablets batches, each one containing a different disintegrant.

The affinity of samples for water was tested

- either by measuring the weight increase of the sample after storage at 100 % relative humidity, (4)
- or by the evaluation of water intake of a powder bed (or of a tablet) after contact with water through a sintered glass filter.

Several devices, more or less sophisticated, were set up on this principle (3) (5) (6) (7) (8) (9) 10).

As it is reported by Khan and Rhodes (4), after exposition of disintegrants at 100 % R.H. :

"The results of water sorption studies... clearly demonstrate that the disintegrants with the highest water uptake are generally the most effective in most tablet systems".

But the studies carried out on the pure disintegrants cannot be sufficient for the disintegration time optimization. Other factors must be involved :

- the disintegrant concentration
- the wettability of the other components of the tablet
- the porosity of the system.

That is the reason why the studies of water uptake by capillary sucking carried out on mixture for compression or on tablets in a device similar to those of Nogami (7) ar more advisable.

Two factors must be investigated with these devices :

- the water uptake kinetics
- the water volume absorbed.

Cartilier, Tawashi and Moës show that a relationship is observed between the effectiveness of starches as disintegrating agents and their initial rate of water absorption (2).

Van Kamp and his collaborators study the influence of different formulation factors on the disintegration of tablets and bring to light to a certain extent, a relation between water uptake in the different formulation cases and the disintegration time of the tablets (3). They point out the beneficial effect of hydrophilic filler binders and the decrease of both the water uptake and the disintegration process in presence of hydrophobic lubricant as they have published in a previous work.

As for us, we have shown, in the same manner, a good relationship between the disintegration time and the initial rate of water uptake for tablets containing starches as disintegrant (9).

Surlève, in our Laboratory, has come up with the same findings with tablets containing cross linked PVP or fibrous disintegrants (Low HPC®, Ac Di Sol®, Nymcel®...) (11).

Consequently, it seems that the whole structure of the tablet must be invaded by water owing to an hydrophilic continuous network of disintegrant particles.

The necessity of setting up a continuous hydrophilic network in the tablet structure, in order to obtain a fast disintegration

It can be seen in many publications that a critical concentration of disintegrant is pointed out when increasing the amount of disintegrant in a given formulation of tablets. Below this concentration, disintegration time is very low. At this critical concentration, disintegration time, often dramatically decreases. (12) (13) (14) (15). Above this critical concentration, disintegration time

may continue to decrease slowly or remains constant at its lowest value. Sometimes, particularly with starches, the disintegration time may increase again when the amount of disintegrant is above this critical concentration.

Nakaĭ and Nakajuna have studied tablets of Aspirin or Sulfisomezole containing various amounts of corn starch. They have determined the minimum concentration of corn starch for tablet disintegration : the "critical content" (14). More recently, Yuasa and Kanaya point out this "critical amount" of disintegrant for the disintegration of tablets (16). These authors sum up the works of Patel and Hopponen (17) and those of Fukuzawa (18). They ascertain "that a directly compressed tablet which contains a drug, insoluble or slightly soluble in water, is not disintegrated until it contains more than a given minimum amount, that is the "critical amount of disintegrator".

Recently, Leuenberger and his collaborators proposed the "percolation theory" as a "novel approach to solid dosage form design" (15). They point out a theoritical percolation threshold similar to the previously described critical concentration. In the case of binary mixture of substances A and B, there is a percolation threshold for which, with an increasing amount of one of the two substances (e.g. "A"), a continuous network of "A" particules is formed. For this critical concentration, some properties change suddenly : compressibility, disintegration time and, consequently, dissolution time of enclosed "B" particles.

As for us, ten years ago, we have brought to light this critical concentration in the case of binary mixtures of starch and drug particles (12) (13).

We have shown that this critical concentration corresponds to a very great increase of water uptake of the tablet (9).

It can be advanced, as different authors do (16) (17) (18) that this critical amount of disintegrant corresponds to the setting up of a continuous hydrophilic structure allowing a fast progression of water in the whole tablet : that is to say an "hydrophilic continuous network" inside the tablet.

This continuity of the water has been filmed by Couvreur (19). By filming under the microscope, he shows the disintegration of tablets containing starch as disintegrant. The disintegration happens when water comes in contact with aggregates or strings ("chapelets") of starch grains. He points out the sudden appearance of cleft between starch grains. These clefts grow more and more and complete disintegration happens.

Hess (20) shows, owing to the scanning electron microscope, the role of the distribution of starch grains in the tablets.

By photography under the microscope, Ringard (13) found the lower disintegration time for the tablets in which it can be seen, that starch grains are adjacent close to each other

Hess (20) attributes this fast moving of water, to the hydrophilic porosity of starch chains.

Nakaĭ (14) studies this phenomenon thoroughly. When the associated drug crystals have hydrophilic surfaces, one starch grain can be further from the other : "For the tablets of sulfisomezole which were coated with Aerosol OT, the distance between starch grains, necessary for tablet disintegration, was longer than that in tablets of intact crystals".

The importance of wettability of drug particles cannot be disregarded in the continuous hydrophilic network.

Importance of the relative size of the particles in the setting up of a continuous hydrophilic network

Nakaĭ and coll. (14) observe that "the tablets of small particles require a larger amount of corn starch to disintegrate in water than those of larger ones".

Other authors have reported nearly the same observation (17) (21). The critical concentration seems to be dependent on the particle size of the associated drug.

As for us, we have prepared tablets with binary mixtures of different starches with two dimensional particles of Aspirin and we have made the same conclusion (13).

It appears that a minimal threshold of disintegrant concentration is generally necessary for a good disintegration efficiency. This concentration is function of the relative sizes of the particles.

Attempt at a calculation in order to realize a continuous network of hydrophilic particles in a tablet : coordination concept

We have first considered the case of binary mixtures of particles of which we know particle size.

To realize a continuous network of hydrophilic "A" particles between drug "B" particles a first solution is evident : a complete coating of B particles with A particles.

We tried to calculate the weight of starch (potatoes - maïze - rice starches) in order to obtain the complete coating of Aspirin particles

- by means of the projected area of A particles on the whole surface of a B particles of average diameter.
- by the Tawashi's equation.

Results were meaningless.

In fact, this binary mixture is a bed of two dimensional, more or less rounded, packed particles. We can apply to these particles the co-ordination equation of Ben Aïm and Le Goff (22).

The mixtures constituted by more or less rounded particles ("Drug + disintegrant" or "diluent + disintegrant") can be assimilated to a close disordered packing of two dimensional spheres.

Disintegrant particles must be the smaller.

If the ratio of small spherical particles is varying in a binary mixture of two dimensional spheres, there is a concentration for which each large spherical particle is surrounded with small particles, and, consequently, isolated from the other large particles.

The number of small spherical particles which can be close to a larger one is named : "contact co-ordination".

But, there are only few diameter ratios for which a continuous coating of small particles, touching each an other, can be set up in contact with the surface of a larger one.

In reality, the coating by small spherical particles cannot be absolutely regular as Ben Aïm and Le Goff have pointed out (22).

In application of an experimental work about the "wall effect" in a close packing of spheres, they studied the disturbance caused by a large spherical particle when we plunge it in a bed of small spheres (23).

Owing to this study they propounded an equation giving a much more realistic idea of the co-ordination.

The co-ordination ($\overline{Cc}$) would be the number of small spherical particles needed for statistical coating of an isolated larger one. The small particles are touching or very near a larger one.

$$\overline{Cc} = \frac{1 - \varepsilon o}{D_1^3} \left[(D_1 + D_2)^3 - D_2^3 \right] \qquad (1)$$

D_1 : average diameter of small particles

D_2 : average diameter of large particles

εo : porosity of the close packing particles

The porosity of the close packing of the two dimensional spherical particles depends on the diameters ratio D_1/D_2 and of the proportion of small particles in the mixture. This proportion may be represented as the "volumic ratio" : $V_1/(V_1+V_2)$

V_1 : volume of small spherical particles

V_2 : volume of large spherical particles

Ben Aïm and Le Goff draw the curve representing the porosity variation as a function of the volumic ratio $V_1/(V_1+V_2)$ (23) for some D_1/D_2 diameter ratios (figure 1). This graph has been set up from experimental data and from results found in the literature.

The porosity of a close packing of one dimensional spheres is nearly 0.36.

In a close packing of two dimensional spheres, the porosity tends to 0.36 when the diameters ratio D_1/D_2 tends to 1.

For each curve, corresponding to a diameters ratio D_1/D_2, the minimum of porosity corresponds to the filling by the smaller particles of the void between the touching large ones.

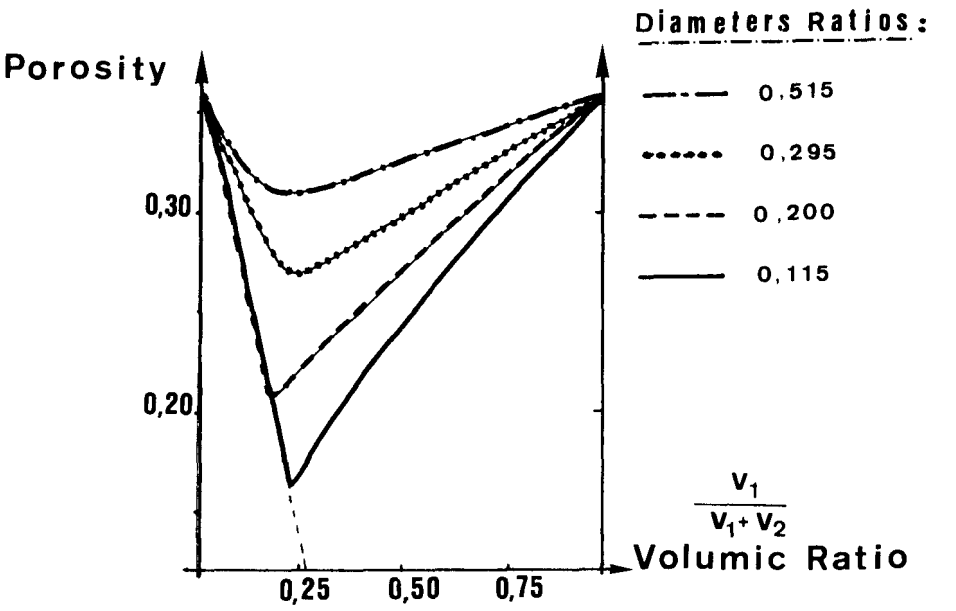

FIGURE 1

Porosity variation in binary mixtures when the volumic ratio increases, for different diameters ratios D_1/D_2 (from 23).

In fact, the volumic ratio $V_1/(V_1+V_2)$ is generally low in the case of disintegrants (V_1) and drugs (V_2) mixtures. So, we can take 0.36 as the porosity's value in the equation (1) :

$$\bar{Cc} = \frac{0.64}{D_1^3}\left[(D_1 + D_2)^3 - D_2^3\right] \qquad (2)$$

For a more practical pharmaceutical use, the number of $\bar{Cc}$ particles must be substituted by the weight of disintegrant for the coating of 1 g of drug or diluent. For that, real density of the products must be known.

The weight of the more or less rounded particles of disintegrant required for the coating of one more or less rounded particle of drug or diluent (width/length > 0.3), is :

$$\bar{Cc} \times \frac{\pi D_1^3}{6} \times d_1 \qquad (3)$$

d_1 : real density of disintegrant

D_1 : average diameter of drug or diluent particles.

This disintegrant weight will be necessary for the weight of one particle of drug or diluent :

$$\frac{\pi D_2^3}{6} \times d_2 \qquad (4)$$

d_2 : real density of drug or diluent

D_2 : average diameters of drug or diluent particles

So, the weight of disintegrant needed for the coating of 1 g of drug or diluent is :

$$\bar{C}c \times \frac{D_1^3 \times d_1}{D_2^3 \times d_2} \qquad (5)$$

If we replace $\bar{C}c$ by its value, we obtain the final equation :

$$\text{Weight of disintegrant needed for the coating of 1 g of drug or diluent} = 0.64 \frac{d_1}{d_2}\left[\left(\frac{D_1}{D_2}+1\right)^3 - 1\right] \qquad (6)$$

We have tried to use this equation for the optimization of the tablets disintegration in comparison with the experimental results.

Tablets were prepared by direct compression of a binary mixture of Aspirin with different kinds of Starches at different percentages (5 - 10 - 15 - 20 - 25 %). (Results : Table I).

The mixtures were compressed with a Frogerais OA single punch tablet machine using 1 cm^2 area flat punches. We tried as much as possible to produce the tablets with the same upper punch displacement ; the volume of the compression chamber remaining constant (depth = 1 cm).

Comments

The case number 6 is aberrant. The Aspirin particles having a diameter of 40 µm cannot be coated by potato starch grains of 28 µm of average diameter.

Cases number 1 and number 5 : The starch percentages tested are not adequate : lower percentages should have been for case number 1 higher percentages for case number 5.

TABLE I

Comparison of experimental and calculated critical concentration of disintegrant

n° experiment	D_1/D_2	Components of the mixture	Calculated critical concentration g/g	Experimentally : % of starch for the best disintegration time
1	0.024	Rice starch + crist. Aspirin	0.055	0.050(1)
2	0.038	Maïze starch + crist. Aspirin	0.085	between 0.05 and 0.10
3	0.085	Potato starch + crist. Aspirin	0.199	0.10
4	0.200	Rice starch + grind. Aspirin	0.52	0.20
5	0.312	Maïze starch + grind. Aspirin	0.90	0.25(2)
6	0.70	Potato starch + grind. Aspirin	2.8	0.15

(1) a lower percentage was not tested

(2) a higher percentage was not tested

Concerning the other cases, it seems that the experimental critical concentration is more or less half of the calculated concentration.

This constatation seems to be consistent. In fact, a complete coating of larger particles produces, after being brought together a double interparticular network between larger particles. (figure 2).

A simple network of hydrophilic disintegrant particles between drug particles is sufficient for the water conduction.

So, we have to modify equation (6) : for the optimization of tablet disintegration, when the disintegrant particles are more or less rounded (starches and derivatives, Kollidon CL®, Polyplasdone XL®), it seems that the quantity of the disintegrant

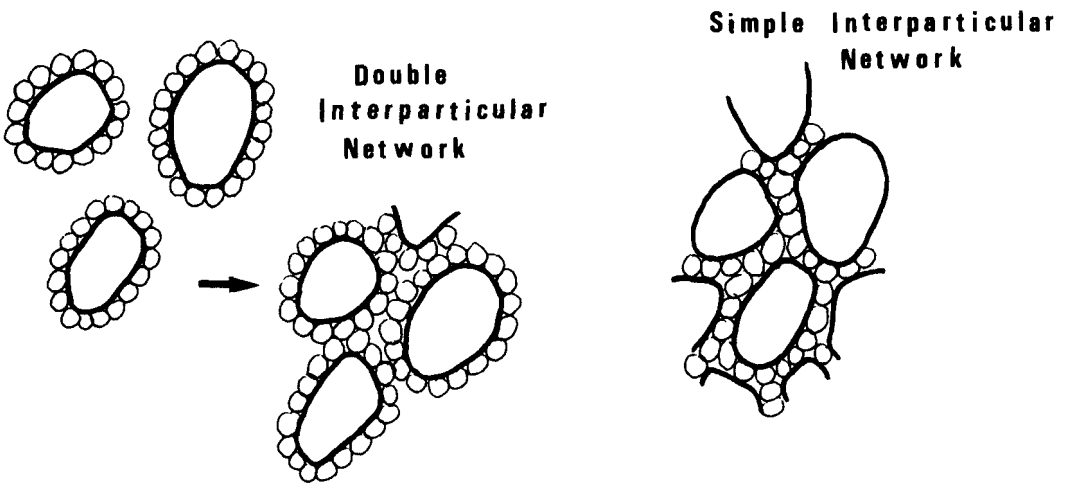

FIGURE 2

Two kinds of particles arrangement

must be :

$$\text{g disintegrant for 1 g of drug} = 0.32 \frac{d_1}{d_2} \left[\left(\frac{D_1}{D_2} + 1 \right)^3 - 1 \right] \qquad (7)$$

Many applications of this equation were carried out. Results were in practice very often in keeping with this equation. Some of them are related in the figure 3.

The disintegrant concentration needed for the setting up of the continuous network in the tablet structure is not always, the best concentration. It corresponds more often to a very sudden decrease of the disintegration time owing to a good water conduction into the whole tablet.

The case of swelling particles

Some disintegrant particles swell considerably that is to say, essentially, Carboxymethylated starches : Explotab® and Primojel®.

Experiments with these disintegrants induce us to add a correcting factor to the equation (7) for a more general application.

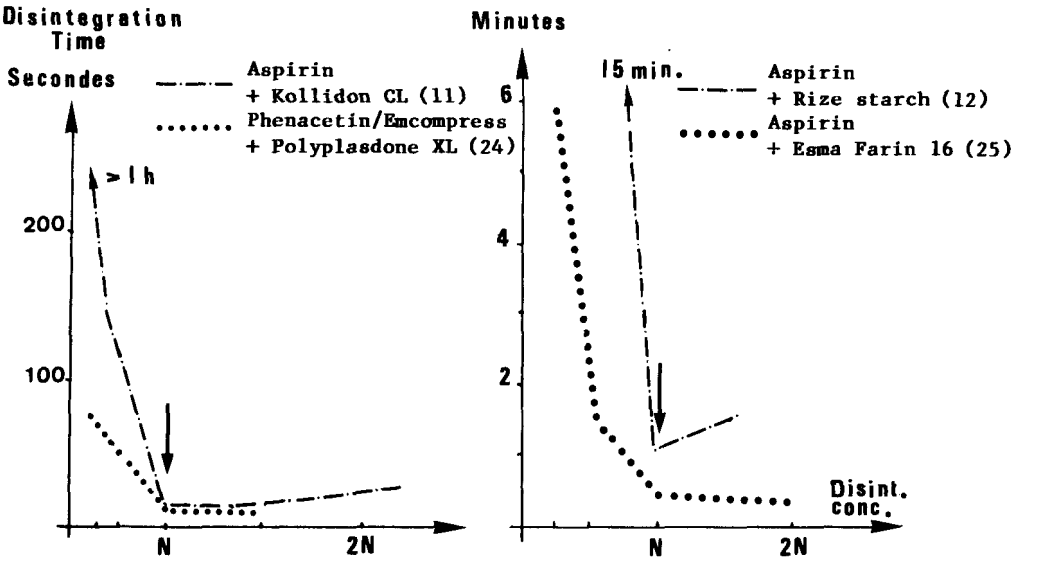

FIGURE 3

Some examples of the effectiveness of the disintegration time when the continuous network of disintegrant particles is realized. (Disintegrant concentration is expressed in fractions or multiples of the network concentration).

In fact, when we applied the equation (7) for the calculation of the best quantity of carboxymethylated starch to use, we obtain tablets showing slow disintegration time and slow drug release. A smaller quantity of disintegrant must be used. (Figure 4).

We can explain this observation as it follows : If a continuous network of carboxymethylated starch particles is set up in the tablets, we obtain an hydrophilic matrix by contact with water, by forming a gelified barrier. So, the swelling of disintegrant particles must be taken in account.

The diameter of the disintegrants particles must be measured by microscopy in their dry state (D_1) and also in the disintegration medium (water or artificial gastric medium) (D_{1_S}). For instance, if the particle diameter doubles in water, only half the quantity needed for the continuous network in the dry tablet structure must be used. It was nearly the case in our example.

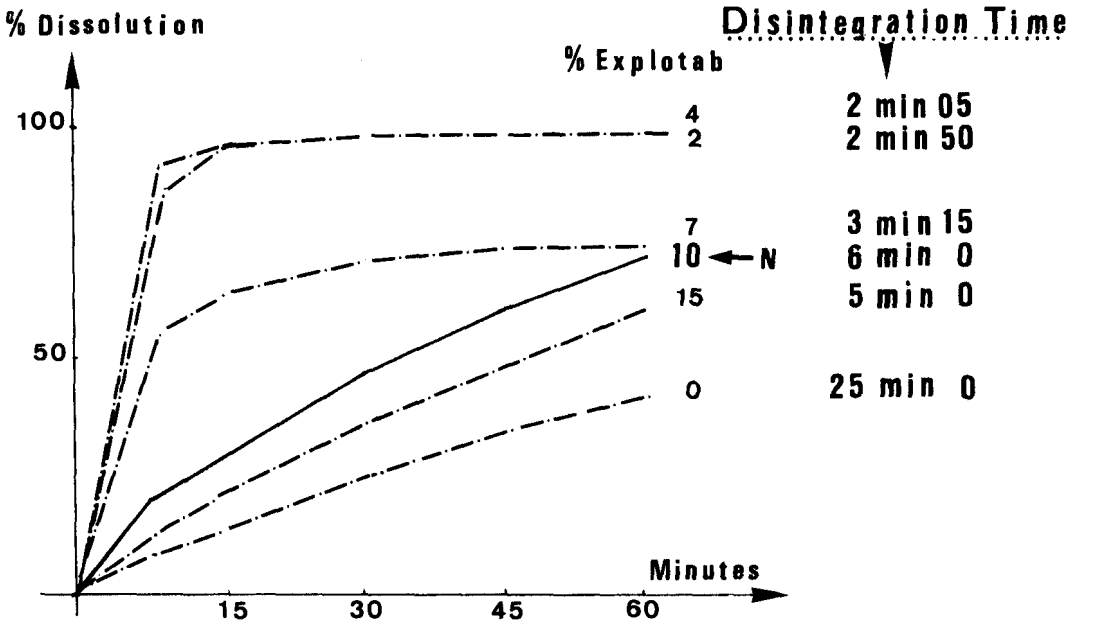

FIGURE 4

Disintegration time and dissolution kinetics of paracetamol from tablets containing different amount of Explotab® (26)

The definitive general equation

Eventually, the definitive general equation for calculation of the most effective concentration of disintegrant presenting a rounded form is :

$$\text{g disintegrant for 1 g of drug or diluent} = 0.32 \frac{d_1}{d_2} \left[\left(\frac{D_1}{D_2} + 1 \right)^3 - 1 \right] \frac{D_1}{D_{1_s}}$$

d_1 and d_2 are the real densities of respectively the disintegrant and the drug or diluent (air comparison pycnometer)

D_1 and D_2 are the average diameters determined by microcospy (Ferret's diameter)

D_{1_s} : The disintegrant diameter in disintegration medium .

Limits of the applications of this equation

This calculation can be applied only for rounded disintegrant particles. Nevertheless, most of the usual disintegrants belong to this category : Starches and its derivatives , Kollidon CL®, Polyplasdone XL®. For the fibrous disintegrants, we have developped an empiric method (11). We tested the hydrophilicity of different mixtures for compression containing different concentrations of disintegrant. This test is carried out with a very simple device, by measuring the time for the capillar rise of water in a standardized powder bed (26).

As it can be seen in the table I , the diameters ratio D_1/D_2 must be at most 0.300. For superior values of this ratio, the coating of a big particle by the smaller particles would need too high concentration of disintegrant particles, for the preparation of correct tablets.

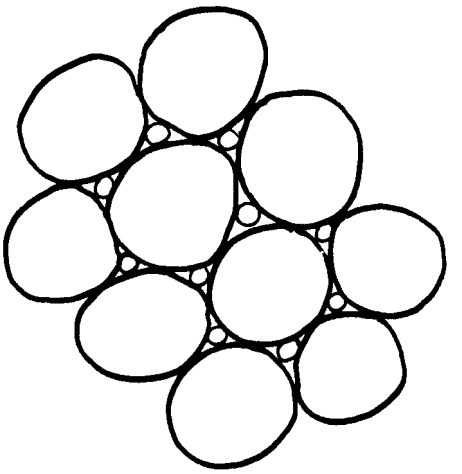

FIGURE 5

There is also an inferior limit to the diameters ratio D_1/D_2. When the drug particles are very fine, a disintegrant presenting a sufficiently fine particle size for the setting up of a continuous network between drug particles does not exist (figure n° 5). The theoretical limit is conditioned by the void space between disintegrant particles. In fact, the real limit is higher. The theoretical limit needs a too high concentration of disintegrant.

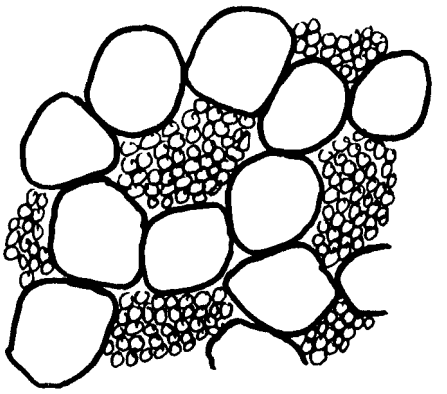

FIGURE 6

In practice, when drug particles are very fine, they form aggregates and the network of disintegrant particles enclose these aggregates in its meshes (figure n° 6). In this case, no calculation is possible.

The best diameters ratio D_1/D_2 seems to be nearly 0.2 : we can choose the disintegrant according to this observation, every time that it is possible.

Finally, it must be pointed out that this calculation is drawn up from the study of close packed spheres. The shape of particles must not be too different from the spherical form. It is effective for the usual non fibrous disintegrants. As for drug particles, our experience has conducted us to the limit ratio width/length = 0.3

PRACTICAL

Applications of this formulation theory

The diameter determination

In order to class the particles as spherical particles, the microscopic determination of Ferret's diameters seems to be the most appropriate method. It must be pointed out that the commercial literature of the manufacturers of excipients gives particle sizes determined by sieving. The data may be erroneous on account of the formation of aggregates. It is the case of cross linked PVP. Commercial literature gives a particle size of about 200 µm, but, under the microscope, we have found 6 at 8 µm for the individual particles of Kollidon CL® or Polyplasdone XL®. It is this value which must be used in the equation.

The real density determination

These values are found in the literature or determined by air comparison pycnometry.

The carrying out of mixing of powders

It seems that it is preferable to add the powders in the mixer in the following sequence :

- first, the totality of the drug,
- then, the disintegrant in three times,
- and finally, the lubricant can be added.

The mixer used for these experiments is either a Turbula mixer or a Lödige mixer.

When we investigate mixture samples under the microscope, we can see the fine disintegrant particles adsorbed on the drug crystals surfaces.

The mechanism of this adsorption is not well known. For some authors it could be an electrical phenomenon, for the other it would be independant of relative humidity and would be owed to crystalline defect on the crystalline particle surfaces (27).

In some rare cases, no adsorption is observed.

CONCLUSION

The hydrophilic continuous network seems to be a necessity for a fast tablet disintegration.

The disintegrant concentration corresponding to this continuous network can be calculated for the more or less isodiametrical particles of the most usual disintegrants : Starches and derivatives, Kollidon®CL, Polyplasdone®XL.

We have studied more accurately the structure of tablets containing the critical concentration of disintegrant and we have pointed out the phase inversion produced when this concentration is reached. These observations will be reported in a next presentation.

This formulation theory can be also applied to the hydrophilisation of powders in hard gelatin capsules.

The continuous hydrophilic network theory and the calculation of the critical concentration needed for its setting up, have given us a great number of satisfying results, in our laboratory as in industrial scaling up.

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