DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(15-17), 2443-2465 (1988)

AN ATTEMPT AT BRINGING TO LIGHT A "PHASE INVERSION" IN A BINARY MIXTURE OF TWO DIMENSIONAL ROUNDED PARTICLES

C. Lefebvre, C. Barthélémy, A.M. Guyot-Hermann
Laboratoire de Pharmacie Galénique et Biopharmacie
Faculté de Pharmacie de Lille, France

J.C. Guyot
Laboratoire de Pharmacotechnie Industrielle
Faculté de Pharmacie de Lille, France

ABSTRACT

It has been demonstrated previously in our Laboratory that the disintegrant concentration corresponding to an interparticular network between drug or diluent particles in tablets may be calculated.

When the disintegrant concentration increases little by little, for a critical concentration, a sudden modification of the physical properties of the powder mixture and of the resulting tablets can be observed.

A new structure is set up in the tablet : in a way, a "phase inversion" is produced.

This experimental critical concentration is the same as the calculated critical concentration for more or less rounded particles.

An investigation into the physical properties of binary powder mixtures and of resulting tablets is carried out when increasing, little by little, the quantity of disintegrant particles : Starches and their derivatives, cross linked PVP, are more particularly studied.

The authors study :

- The flowing properties of powder mixtures

- The compressibility (Hardness/Compression forces, transmission forces through the powder mixture during compression, compression cycles...)
- The physical properties of tablets (hardness, structure hydrophilicity, disintegration time and drug dissolution).

Several formulations were studied. The results point out the setting up of the continuous network of the small particles between the larger particles for the calculated critical concentration.

The same theory may be applied to the hydrophilization of powders in hard gelatin capsules and to all the more or less rounded two dimensional particles in a mixture.

INTRODUCTION

When increasing the amount of one of the two components of a binary mixture, some authors have pointed out that a critical proportion exists. Leuenberger (1) compares the binary mixtures to a dispersion of oil droplets in water. He defines a "percolation threshold" at which, with an increasing amount of the lipophilic phase, the O/w system turns into a w/O system". The properties of the dispersion change according to the fact that the water or the oil forms the continuous phase.

This notion can be applied to the mixture of two powders.

Indeed, the study of the physical properties of binary mixtures when the amount of one of the two components is increased, allows us to point out the "percolation threshold" which represents the phase inversion.

The consequential effect on flowability and compressibility of powder mixtures and the repercussion on the compact disintegration, followed by the dissolution of the more soluble of the two components, was more particularly studied by Leuenberger (1). He points out that in the case of binary mixtures between drug and disintegrant, the disintegrating activity can only take place below a critical concentration in some of his experiments.

To the contrary, Nakaï (2) and Yuasa (3) show that a minimum amount of disintegrant is necessary for a quick tablet disintegration. As Patel and Hopponen (4) report, this critical concentration corresponds to a continuous network of disintegrant particles. A continuous disintegrant particles phase has replaced the continuous drug particles phase. It endows the mixture with its own physical properties.

As for us, owing to these observations, ten years ago, we studied more particularly this critical observation and we calculated it for the more or less isodiametrical particles of most of the disintegrants (starch and derivatives, Kollidon CL®, Polyplasdone XL®, Explotab®, Primojel®) (5) (6) (7).

We developed these calculations and their applications in tablet formulation in a previous report (8).

The equation for the calculation of the critical concentration of disintegrant in a tablet is :

$$\text{g of disintegrant necessary for 100g of drug or diluent} = 0.32 \frac{d_1}{d_2} \left[\left(\frac{D_1}{D_2} + 1 \right)^3 - 1 \right] \frac{D_{1g}}{D_1}$$

d_1 and d_2 : The real respective densities of the disintegrant and the drug or diluent

D_1 and D_2 : The diameters of the disintegrant and the drug or diluent (Ferret's diameters, determined by microscopy) (µm)

D_{1g} : The diameter of disintegrant particles in the release medium (µm)

This critical concentration corresponds to an hydrophilic, monoparticular, continuous network between drug or diluent particles which enables a fast water conduction into the tablet and, consequently, a fast disintegration.

We made the following observations during our previous works : Other properties, besides disintegration, must be pointed out at the critical concentration : flowing properties, packing properties and the compressibility of the mixture.

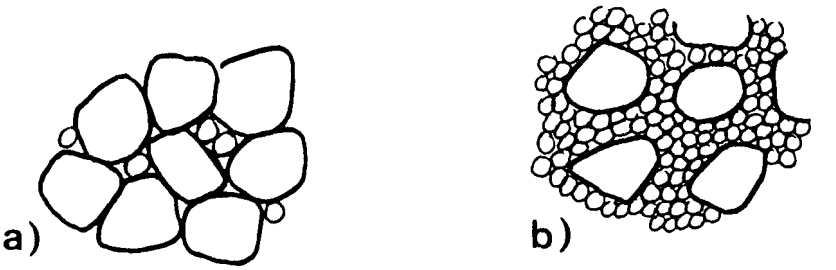


FIGURE 1

Particle arrangement
a) A continuous phase is constituted by bigger particles
b) A continuous phase is constituted by smaller particles

On the other hand, the hydrophilicity of the mixtures when increasing the disintegrant concentration, must be more particularly studied for an explanation of the consequent disintegration time.

We have taken stock of the observations made in previous works to this effect and we have studied three kinds of mixtures more carefully :

Aspirin + Maïze starch
Paracetamol DC® + Kollidon CL®
Terpin hydrate + Rize starch

We tried to point out that in these mixtures, when increasing the smaller particle concentration, we can observe a critical concentration for which, some of the physical properties, suddenly change.

It can be argued that this critical concentration corresponds to a phase inversion in the mixture. The concentration for which the smaller particles become the continous phase (figure n° 1).

We have tried to connect this experimental critical concentration to our calculated critical concentration (8).

MATERIALS

1. Only for mixture study

	Origin	Average diameter	Real density
Grinded Aspirin	Cooper Melun (Fr)	20.5 µm	1.35
Grinded Terpin (batch 2)	Cooper Melun (Fr)	18 µm	1.15
Grinded Phenacetin	Cooper Melun (Fr)	263 µm	1.33
	Origin	Average diameter	Real density
Ascorbic Acid	Cooper Melun (Fr)	152 µm	1.65
Dry Flo (hydrophobic maïze starch)	Roquette Lestrem (Fr)	12.5µm	1.52

2. Materials for mixtures and tablets

Studies	Origin	Average diameter	Real density
Cristallized Aspirin	Cooper Melun (Fr)	375 µm	1.35
Paracetamol DC®	SPCI La Plaine St Denis (Fr)	50 µm	1.39
Terpin (batch 1)	Cooper Melun (Fr)	23 µm	1.15
Maïze starch	Roquette Lestrem (Fr)	12.5µm	1.52
Rize starch	Cooper Melun (Fr)	4 µm	1.52
Kollidon CL®	BASF Ludwigshafen (RFA)	10 µm	1.30

All these products are European Pharmaopoea grade.

METHODS

1. Real density determination

This determination is measured by comparison air pycnometry (Beckman apparatus).

2. Average diameter

We determine the Ferret's diameter by microscopy.

3. Mixing

For each formulation, 5 concentrations of hydrophilic agents were studied :

- the calculated critical concentration "N" corresponding to the monoparticular continuous network between drug particles,
- its fractions : N/2 and N/4, and
- its multiples : 1.5 N - 2 N

The concentrations of hydrophilic or hydrophobic agent corresponding to the critical concentration "N" for the different formulations were (for 100 g of drug) :

. Aspirin - Maïze starch : 4 g
. Paracetamol DC® - Kollidon CL® : 14 g
. Terpin (Batch 1) - Rize starch : 26 g
. Terpin (Batch 2) - Rize starch : 35 g
. Ascorbic Acid - Dry Flo® : 8 g
. Phenacetin - Potato starch : 10.8 g
. Grinded Aspirin - Rize starch : 25.5 g

One percent of magnesium stearat was added for "Paracetamol DC® - Kollidon CL®" and "Terpin - Rize starch" mixtures.

Mixing was performed in a Turbula mixer ;two,three parts of a certain quantity of an hydrophilic agent were added at intervals to the drug. When magnesium stearat is present, it was added at last. The period of mixing was five minutes long between each addition.

The pure drugs and the second agent were also studied.

4. Flow evaluation of powder mixtures

We measured the time (in seconds) for the complete discharge of 100 g of powder through the hole of a standardized funnel (9).

5. Tapping test (10)

The packing properties of powder mixtures were tested using a graduated cylinder connected to a motorized tapping device. The powder volume was noticed after 10 and 500 cycles. The $V_{10} - V_{500}$

volume difference is indicative of the packing properties of the powder.

6. Compressibility

The powder mixtures were compressed with a single punch tablet machine Frogerais OA.

Strain gauges are stuck on the upper and lower punches, connected by means of Wheatstone bridges to a computer. This equipment gives us the possibility of noticing for each batch of tablets, the maximum force average on the upper and lower punches y_1 and y_2.

- Hardness was measured by the Heberlein hardness tester
- y_1/hardness is the force required to obtain a tablet having one Newton hardness. This value is indicative of the compressibility of the mixture.

The compressibility study was performed in two steps. At first, for the basic study, we compressed each serie of powder mixture of the same two components at different relative amounts, with the same chamber volume and with the same upper punch displacement.

The second step consisted in trying to work with a more industrial aim. Each mixture of the same two components at different relative amounts, was compressed to obtain the same drug content and the same hardness of the tablets, that is to say with different chamber volume and a different upper punch displacement.

7. Hydrophilicity of powder mixtures or resulting tablets

7.1. Powder mixture

We used the very simple device of Ringard (7) : 3 g of powder mixture is disposed in a glass tube on the bottom of which is a sintered glass.

This tube is plunged into water in such a way that the water surface is :

- either at the same level as the powder in the tube (for hydrophobic mixtures)
- or at 1 mm above the sintered glass for hydrophilic mixtures.

Of course,the same process must be used for a comparative study.

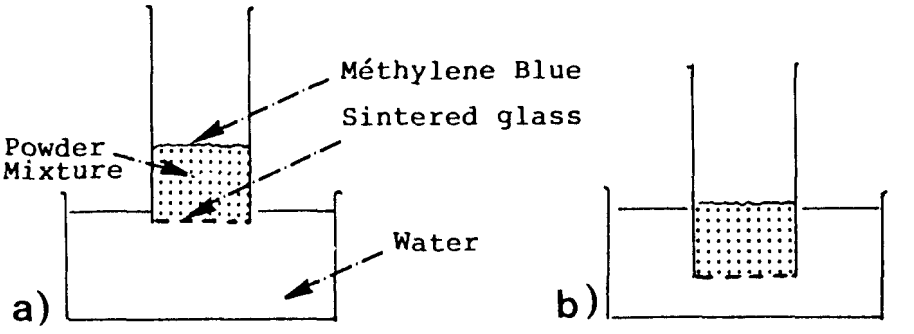


FIGURE 2

Device for the measure of the powders hydrophilicity
a) Hydrophilic mixtures b) Hydrophobic mixtures

Some methylene blue crystals were put on the surface of powder mixture.

We noted the time for the capillary rise of water to the surface : at this time, the methylene blue is dissolved and colours the powder surface in intense blue.

7.2. Tablets

We used another very simple device conceived after Nogami (9) (see the diagram on Figure n°3). The apparatus is filled with water thanks to the vacuum. After the water level balance is obtained, we lay a tablet on the wet sintered glass : we noted the amount of time required for the meniscus displacement. We could draw the water uptake kinetics of the tablet.

8. Disintegration time

The disintegration time was measured in distilled water at 37°C according to the USP XXI method.

9. Dissolution rate

For some tablet formulations we carried out a dissolution test according to the USP XXI method (Paddle method) in artificial gastric

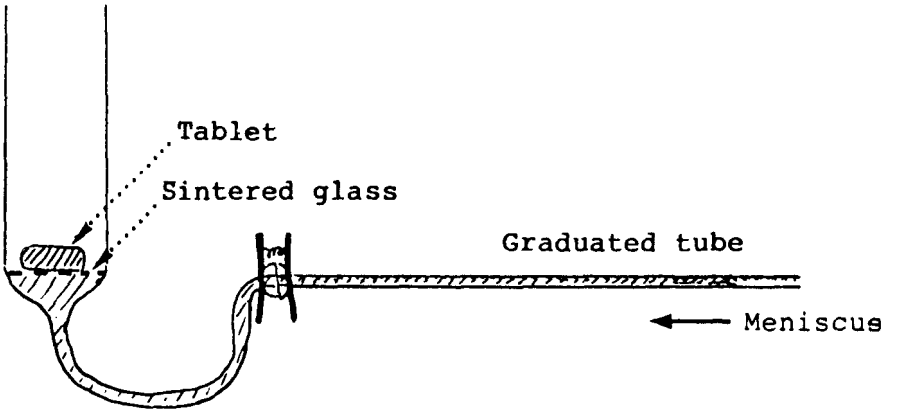


FIGURE 3

Apparatus for the measure of the tablets hydrophilicity

juice without enzyme (800 ml, 50 rpm). The drug concentrations were measured by spectrophotometry at the maximum absorbance of the drug.

RESULTS

1. Flowability

The times for the complete discharge of the powder mixtures are displayed in Table I.

Aspirin has a good flowability : no effect can be observed by the addition of maïze starch, so, all the results are good.

Terpin has a very bad flowability : no effect of the addition of rize starch is observed whatever its amount may be; so,all the results are bad. However, with Paracetamol DC®- Kollidon CL®mixtures, we can see a very clear increase in the discharge time when the Kollidon CL®concentration is higher than the concentration corresponding to the calculated continuous network.

2. Packing properties

The differences in tapped volume "V_{10}- V_{500}" after 10 and 500 cycles of the tapping device are displayed in Table II.

TABLE I

Discharge time of the different mixtures with an increasing amount of small (hydrophilic) particles.

Mixture	pure drug	N/4	N/2	N	1.5N	2N	pure disintegrant
Aspirin+ maïze starch	8.9	7	7.4	8.3	7.2	6.1	no flow
Paracetamol DC®+ Kollidon CL®	12	34	8.3	12.5	26 very difficult	no flow	no flow
Terpin batch 1 + rize starch	no discharge if not shaken						
Terpin batch 2 + rize starch							
Grinded aspirin + rize starch	← the wall-flasks were covered with powder				no flow		the wall-flasks were clean →

TABLE II

Influence of the amount of small disintegrant particles on the "V_{10}-V_{500}" value of some experimented mixtures.

Mixture	pure drug	N/4	N/2	N	1.5N	2N	pure disintegrant
Crist. aspirin + maïze starch	10	11	11	9	6	9	45
Paracetamol DC® + Kollidon CL® (1% Mg stearate)	27	31	39	37	47	51	65
Terpin (batch 2) + rize starch (1% Mg stearate)	36	38	46	39	45	44	40
Grinded aspirin + rize starch	34	45	46	53	59	52	64
Phenacetin + potato starch	21	-	9	14	16	16	16
Ascorbic acid + Dry Flow	9	8	9	9	9	11	26

TABLE III

Hydrophilicity of mixtures : Time for rise of water to the powder surface in minutes.

Mixture	pure drug	$\frac{N}{4}$	$\frac{N}{2}$	N	1.5N	2N	pure disintegrant
Crist. Aspirin + Maïze starch	> 12h	> 2h	90	61	56	35	
Paracetamol DC® + Kollidon CL®	56	19	18	19	27	29	11
Terpin (batch 1) + Rize starch	> 12h	> 3h <12h	100	88	92	65	15
Terpin (batch 2) + Rize starch	> 12h	> 3h	120	90	54	50	15
Phenacetin + Potato starch	> 12h	no rise of water					3
Ascorbic acid + Dry Flo®	3	3	5	23	34	48	0
Phenacetin + Lactose (previous work (10))	> 12h		110	42	27	26	2

Aspirin and ascorbic acid show good packing properties so, no effect of the added maïze starch can be observed.

A very slight change in the "V_{10} - V_{500}" values is observed for the other formulations when the concentration of the small disintegrant particles are nearly the "N" calculated concentration. However, no sudden change is observed.

3. Hydrophilicity of the powder bed

The time for the complete rise of water to the surface of the standardized powder bed is reported in table III (figure 4).

In these expriments, the calculated critical concentration corresponding to the phase inversion is clearly brought to light in a rather abrupt manner :

- between 0.5 N and N for Terpin/Rize starch mixtures, and Ascorbic Acid/Dry Flo mixtures,

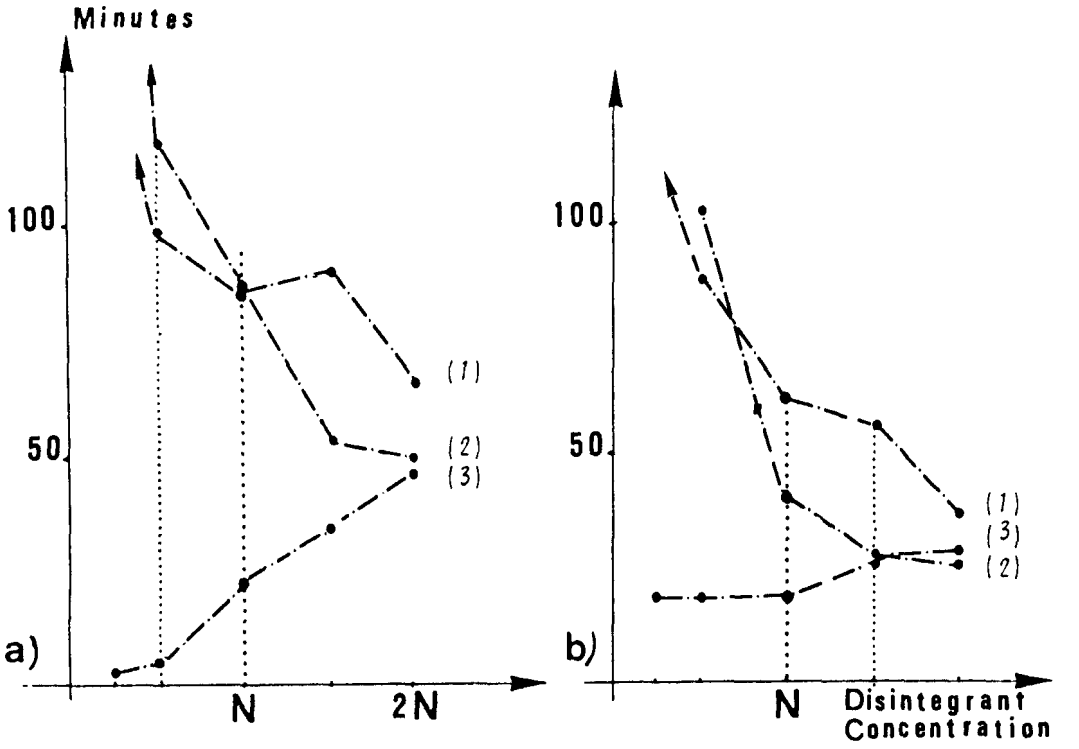


FIGURE n°4

Hydrophilicity of powder mixture when the small hydrophilic particles concentration increases (concentration is expressed as multiples or fractions of the critical concentration "N")
a) Terpin batch 1 + Rize starch (1), Terpin batch 2 + Rize starch (2), Ascorbic acid + Dry Flo® (3)
b) Aspirin + Maïze starch (1), Phenacetin + Lactose (previous work (10)) (2), Paracetamol DC® + Kollidon CL®(3)

- at the "N" concentration for Paracetamol DC®/Kollidon CL®, Phenacetin / Lactose and Aspirin/Maïze starch mixtures.

No rise of water is observed through the Phenacetin/Potato starch mixtures. However, Phenacetin seems better hydrophilized by the soluble Lactose.

For the Paracetamol DC®/Kollidon CL® mixture, we observe an unusual fact:

The hydrophily of the powder-bed decreases when Kollidon CL® begins to constitute the continuous phase.

This phenomena is perhaps in connection with the relative hydrophily of the Paracetamol DC® which is covered with gelatine.

For "Ascorbic acid/Dry Flo" mixtures, we see clearly the setting up of hydrophobicity when the hydrophobic Dry Flo® constitutes the continuous phase.

4. Effect of inversion phase on mixture compressibility

As we have previously explained, we have assimilated the compressibility of the mixtures containing increasing disintegrant concentrations, to the ratio of the forces recorded on the upper punch y_1 upon the tablet hardness.

We have shown in figure n° 5a the results of previous works and in figure n° 5b (from table IV) the results of our present systematic experiments.

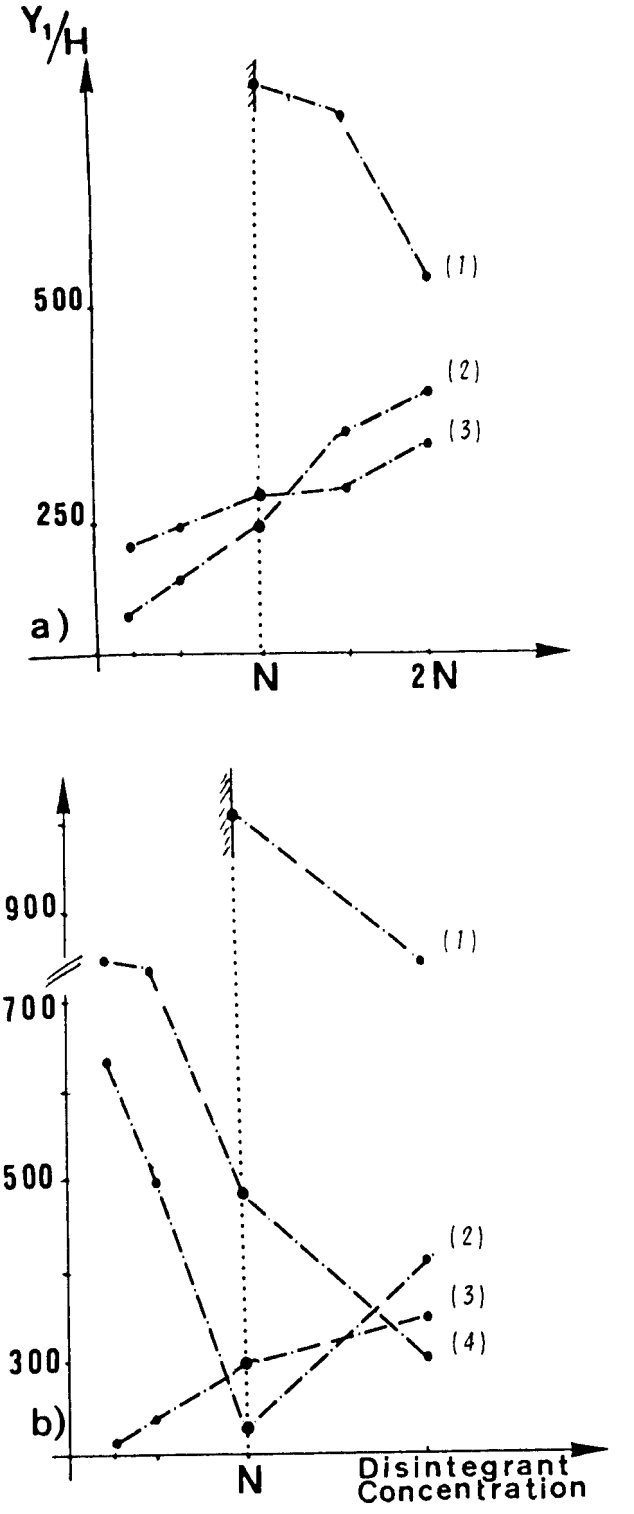
When the concentration of the small particles increases in the binary mixtures, we can point out the critical concentration as follows. We can do it :

- very clearly for Terpin/Rize starch mixture,
- clearly but in a minor degree for other mixtures.

This critical concentration corresponds to the setting up of the calculated continuous network of smaller particles.

5. Water uptake kinetics of tablets, consequential effect on disintegration time and dissolution rate of drug

5.1. The whole water volume which penetrates into the tablet is indicative of the volume of the hydrophilic components in this tablet. The time to obtain the saturation of the tablet by the water is more significant. We have shown that the time necessary to obtain 90 % of the whole saturation is quite indicative of the disintegration time and of the dissolution properties of the drug contained in the tablet (13). The setting up of the hydrophilic continuous network is clearly evidenced.



When the disintegrant concentration is below the critical concentration, the time necessary to obtain 90 % water uptake is high. For the critical concentration corresponding to the continuous hydrophilic network, this time decreases suddenly owing to this continuous hydrophilic network. It either continues to decrease or it increases slightly when increasing the disintegrant concentration. This calculated critical concentration corresponds to the phase inversion. The hydrophilic phase becomes the continuous phase and it may conduct the water quickly into the whole tablet structure.

This phenomenon is well brought to light for Terpin/rize starch tablets in figure n° 8.

The water uptake is faster for the N/2 disintegrant concentration than for the N/4 one, for N concentration than for the N/2 one.

But, when the continuous network is obtained no further improvement is observed.

Note : It must be pointed out that, in a tablet, the disintegrant must be hydrophilic but insoluble. The internal viscosity developed by soluble particles would reduce the water uptake.

5.2. These results have a consequential effect on disintegration time as we can see in figure n° 9.

A very surprising result is observed for Terpin/Rize starch tablets. In spite of its better water uptake for the N, 1.5 N and 2 N

FIGURE n° 5

Compressibility (y_1/H) variation when the disintegrant concentration increases (concentration is expressed as multiples or fractions of the critical concentration "N")

a) Terpin + Rize starch (*1*), Paracetamol DC®+ Kollidon CL® (*2*), Aspirin + Maïze starch (3)
b) Results of previous works (11) (12). Aspirin + Polyplasdone INF (1 % of Magnesium stearate) (*1*), Phenacetin /Emcompress + Polyplasdone XL (*2*), Aspirin + Esma Farin 16 (3), Aspirin + Polyplasdone INF (0.5 % of Magnesium stearate) (4).

TABLE IV

The y_1/Hardness variation when the amount of small disintegrant particles is increased in the mixture for compression.

	y_1 (N)	Hardness (N)	y_1/Hardness
Kollidon CL®	13 470	31.2	440
2 N	8 370	21.1	404
1.5 N	9 220	26.5	355
N	10 780	42.8	257
0.5 N	12 780	68.3	191
0.25 N	13 110	85.6	156
Paracetamol DC®	18 590	103.5	183
Maïze starch	3 580	0	meaning less
2 N	18 190	60.6	352
1.5 N	15 400	52.7	298
N	13 400	49.5	276
0.5 N	12 950	53.2	248
0.25 N	9 160	40.7	229
Aspirin	4 950	27.4	181
Rize starch	2 040	0	meaning less
2 N	8 760	16.3	537
1.5 N	9 100	12.5	728
N	15 350	20.4	752
0.5 N	no correct tablets : capping		
0.25 N			meaning less
Terpin	no tablet		

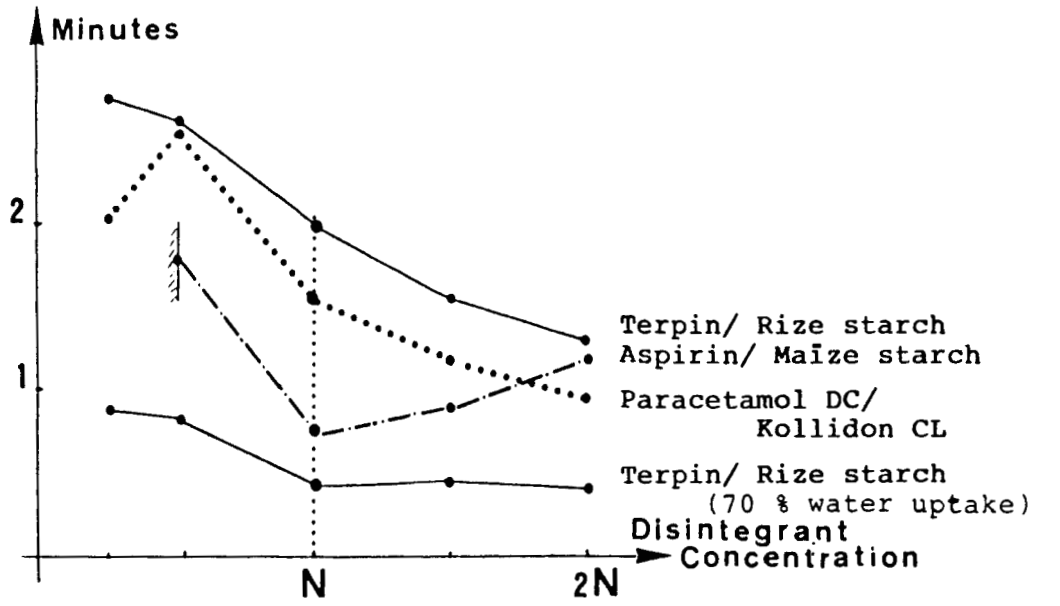


FIGURE n° 6

Time to obtain 90 % water uptake of tablets containing different disintegrant concentrations (expressed as N or its fractions)

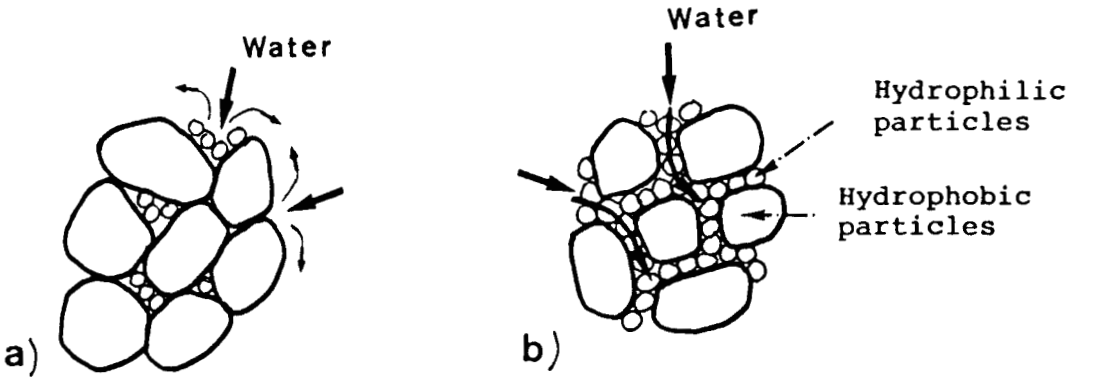


FIGURE n° 7

a) Water penetration is not possible
b) Water penetration is possible

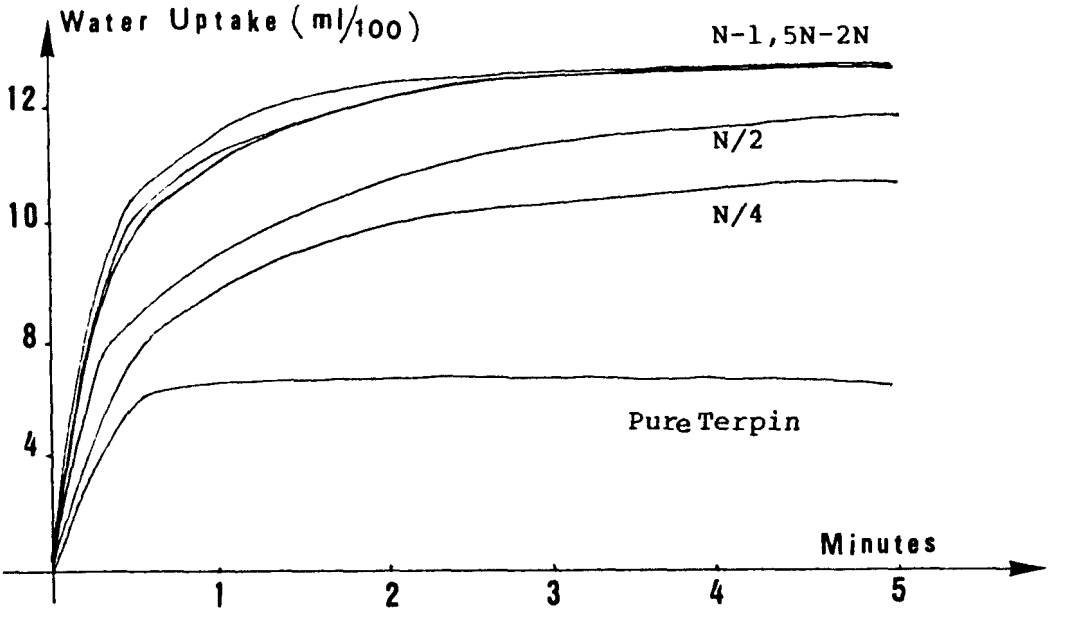


FIGURE n° 8

Water uptake kinetics of Terpin/Rize starch tablets

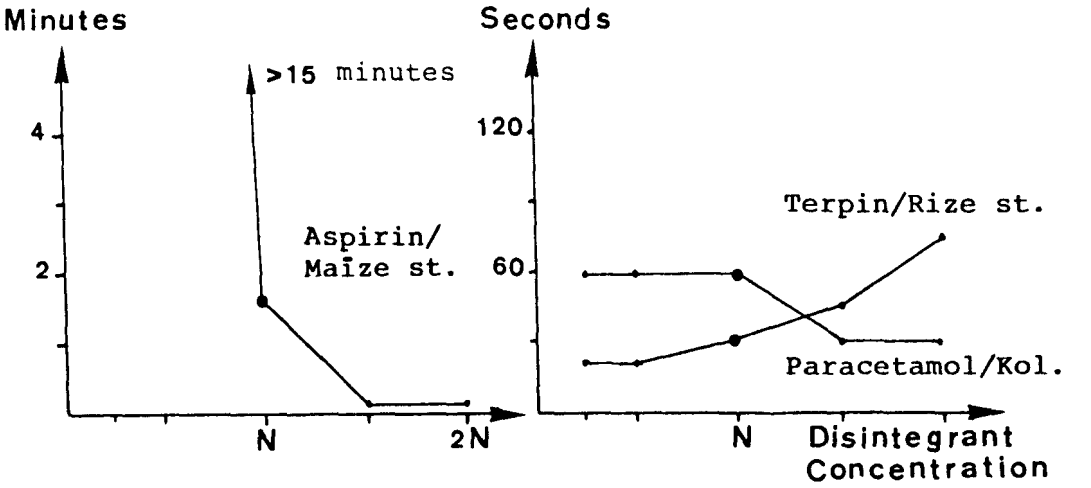


FIGURE n° 9

Disintegration time of the different tablets when the disintegrant concentration increases (N : continuous network).

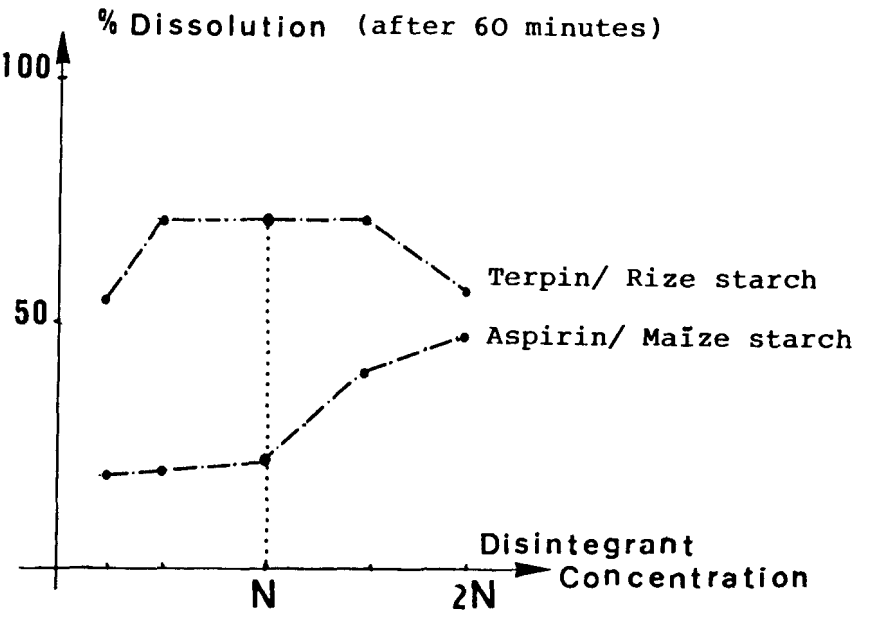


FIGURE n° 10

Dissolution rate of drugs after 60 minutes

disintegrant concentrations, the disintegration time increases. Two facts are to be considered together :

- Contrary to the two other kinds of tablets, the whole absorbed water volume does not increase when the disintegrant amount passes beyond the N concentration. There wouldn't be a sufficient quantity of water for a rapid disintegration.
- This result is in connection with the fact that the disintegration time of tablets of pure Terpin is shorter (20 sec.) than those of pure rize starch (1 min 15 sec.).

The phase inversion setting up in the continuous hydrophilic phase is particularly clear for the tablets containing hydrophobic drug (Aspirin/Maïze starch).

It is less pronounced for such hydrophilic drugs as the Paracetamol DC®(which is covered in hydrophilic gelatine). Water may penetrate more easily owing to possibility of wetting Paracetamol DC® particles.

5.3. The hydrophilization of the structure set in the tablet on and after the critical disintegrant concentration, also has a consequential effect on the dissolution data which are clearer for hydrophobic drug (figure n° 10).

INDUSTRIAL APPLICATION

The critical concentration N is sometimes a very important threshold for the flowability of binary mixture (e.g. paracetamol® DC/Kollidon CL®) and for the compressibility of some binary mixtures (e.g. Terpin/Rize starch). It may be useful to know its value. However, the mechanical problems arise immediatly as soon as the mixing and the compression begin.

But in the practical field, it seems that the knowledge of the critical concentration, corresponding to the phase inversion, is of great interest for the setting up of an hydrophilic structure in the tablet allowing its fast disintegration and the best dissolution rate of the drug.

In industrial application, binary mixtures are uncommon. But the low percentage of the lubricant does not interfere with the theory as we have shown in the case of Paracetamol DC® and Terpin.

Perhaps, the critical concentration zone would be more sharp without a lubricant. But, tablets must be feasible. So, for industrial application, we have tried to compress the mixture in order to obtain tablets presenting a determined hardness and containing a certain weight of drug.

For each mixture proportion of the two mixtures "Aspirin/Maïze" starch and "Paracetamol DC®/Kollidon CL®", the tablet machine was settled in order to obtain tablets of the same hardness.

These tablets of the same hardness and containing an increasing amount of the small disintegrant particles have been essayed for disintegration and drug dissolution.

The results were similar to the previous ones. A very sudden decrease in disintegration time for the Aspirin tablets, when the

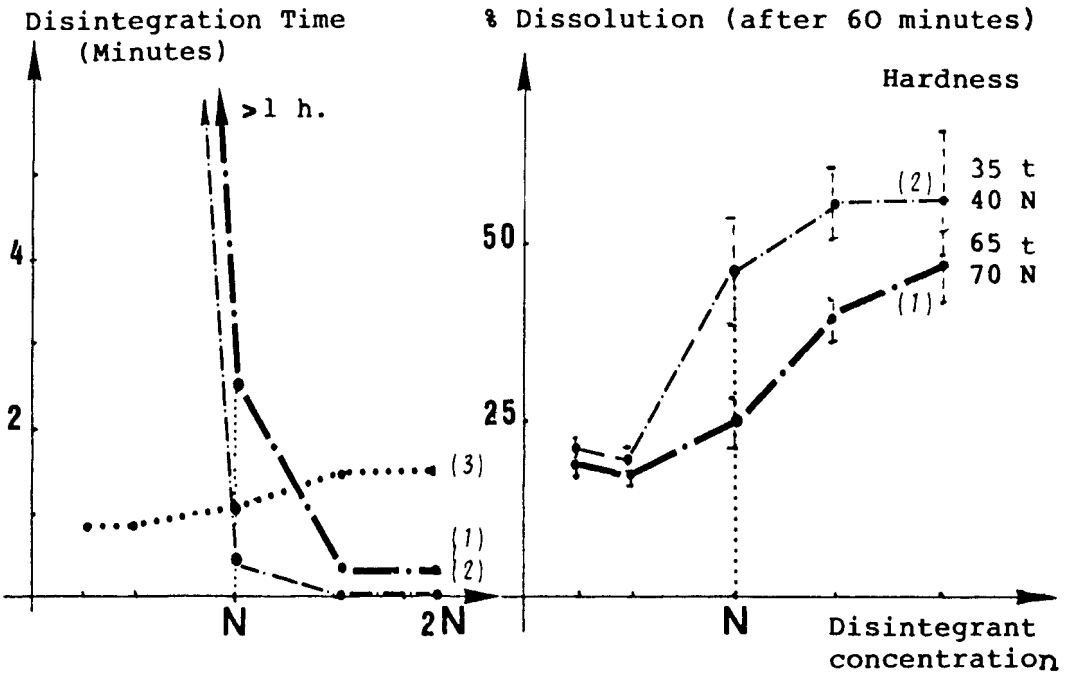


FIGURE n° 11

Disintegration time of tablets containing Aspirin ——·— or Paracetamol ····· and dissolution rate of Aspirin : (1) Aspirin tablets, Hardness: 35 to 40 N- (2) Aspirin tablets, Hardness: 65 to 70 N - (3) Paracetamol tablets (whatever the Hardness may be).

starch concentration is the calculated concentration for the starch continuous phase.

The results are more attenuated for the hydrophilic Paracetamol DC®. Disintegration time is the same whatever the hardness may be, and the dissolution rate is 100 % before 10 minutes.

CONCLUSION

When increasing the amount of smaller particles in a binary mixture, we can point out a more or less critical concentration for which the mechanical properties of the mixture change: flowability, compressibility.

This critical concentration corresponds to the calculated concentration for the setting up of a continuous network of the smaller particles between the bigger ones.

However, the nature of the bigger particles takes a prominent part in the phenomenon, and this critical concentration is not always perceptible.

When the samller particles are hydrophilic such as disintegrant particles, and when the bigger particles are a hydrophobic drug, the calculated critical concentration for the phase inversion is very clearly confirmed as we have demonstrated in this work and those previously published.

These results corroborate our formulation theory for the optimization of the disintegration of tablets. The continuous hydrophilic network set up in the tablets by means of the calculation method of Ringard and Guyot-Hermann (8).

ACKNOWLEDGEMENTS

The authors thank very much Madame Grimmelpont for her very kind help for the English translation.

REFERENCES

1. H. Leuenberger, B.D. Rohera and Ch. Haas, Intern. J. Pharm., 38, 109 (1987)
2. Y. Nakaï and S. Nakajima, Yakugaku Zasshi, 97, 11, 1168 (1977)
3. H. Yuasa and Y. Kanaya, Chem. Pharm. Bull., 34, 12, 5133 (1986)
4. Patel and Hopponen, J. Pharm. Sci., 55, 1065 (1966)
5. J. Ringard, Thèse es Sciences Pharmaceutique - Lille (1977)
6. J. Ringard and A.M. Guyot-Hermann, J. Pharm. Belg., 33, 2, 99, (1978)
7. J. Ringard and A.M. Guyot-Hermann, Labo Pharma Probl. Tech., 30, 7 (1982)
8. J. Ringard and A.M. Guyot-Hermann, 7th Pharmaceutical Technology Conference, Londres (1988)

9. H. Nogami, T. Nagai, E. Fukuoka and T. Sonobe, Chem. Pharm. Bull. 17, 7, 1450 (1969)
10. D. Leblanc, LG. Tapé, A.M. Guyot-Hermann and H. Robert, 3e Congrès Intern. Technol. Pharm., Paris (1983)
11. C. Bollaert and A.M. Guyot-Hermann, Labo Pharma Probl. Tech., 32, 682 (1984)
12. A.M. Guyot-Hermann and J.C. Guyot, 3e Congrès Intern. Technol. Pharm., Paris (1983)
13. J. Ringard, A.M. Guyot-Hermann and H. Robert, Labo Pharma Probl. Tech., 25, 409 (1977)