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CARBOXYMETHYLSTARCHES IN WET GRANULATION

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ABSTRACT

Commercialized carboxymethystarches (CMS) are both carboxymethylated and cross linked potato starch.

The influence of carboxymethylation and cross linkage on the disintegrating properties of starch are studied.

Tablets are made with acetaminophen as drug, Emcompress as diluant, Magnesium stearat as lubricant, and potato starch or its derivatives as disintegrants.

Tablets are prepared by direct compression or by wet granulation with the disintegrant intervening only in internal phasis.

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Five disintegrants were studied, with two different concentrations :

- native potato starch
- potato starch simply cross linked
- potato starch simply carboxymethylated
- two potato starches both cross linked and carboxymethylated at two different degrees

Compressibility of powders blending and grain for compression are discussed.

The hardness, the tablet disintegration and the rate of drug dissolution are studied.

. The results showed that the simply carboxymethylated starch has a totally different behaviour after direct compression or wet granulation. The poor results after wet granulation could be imputed to the bursting of starch granules during grain drying. Since it has lost its granular structure, the carboxymethylated starch will only allow a poor disintegration and a slow dissolution of the drug.

. A very similar behaviour of native and simply cross linked starch : the results of which are bad for tablets either prepared by wet granulation or direct compression.

. A very similar behaviour of the starches both carboxymethylated and cross linked, allowing a very good disponibility, either with tablets prepared by direct compression or wet granulation.

These experiments prove :

- the need for an sufficient cross linkage for CMS in a wet granulation process

- the good behaviour of commercialized CMS during a wet granulation. They serve both as binding and disintegrating agents
- the need for a good disintegrant to be insoluble.

INTRODUCTION

Carboxymethylstarches (CMS) are modified potato starches. Under the microscope they look like grains as nativ starch.

They are very hydrophilic and insoluble and, by the way, very good disintegrants.

When in contact with water, they form an apparent jelly which is in fact the accumulation of grains swelled with water and huddled together. Owing to this developped viscosity, CMS can be used not only as a disintegrating agent but also as a binding agent, in internal phasis, in wet granulation. We tried to discover how this can be done.

Commercialized CMS are both carboxymethyled and cross linked. Carboxymethylation dramatically increase the swelling of the grain, and cross linkage prevents its splitting. According to their categories, commercialized CMS are in fact, more or less carboxymethylated and cross linked.

Two points were studied :

- the possibility of using CMS in wet granulation and the comparison with tablets of the same formulation made by direct compression. Indeed, Kahn has recently underlined the fact that few authors have made this comparison on tablets of the same formulation (1). This condition seems to be obligatory for a strict interpretation.

- the important part played by the cross linkage in the disintegrating power of CMS, particulary in wet granulation. It might be thought that the cross linkage, as it decreases the swelling of the grain in contact with water could decrease disintegrating power. Yet, we have pointed out in a previous paper (2) that the disintegrating power is absolutely independant of the swelling power of disintegrant particles. This was one of the reasons which enabled us to put forward the idea that swelling is not the mechanical force which destroys the tablets.

MATERIALS

Acetaminophen(*) tablets were prepared with an equal quantity of Emcompress^{R} (**) as the diluant, 0.5 % or/and 1 % of Magnesium stearate as the lubricant. Some modified potato starches were used as disintegrant :

-"simply cross linked starch" (C.L.S.)(***)

-"simply carboxymethylated starch" (C.M.S.)(***)

-"two both carboxymethylated and cross linked starches" :

. Explotab^{R} (**) (Ex) (this modified starch presents the same degree of cross linkage and carboxymethylation as C.L.S. and C.M.S.)

(*) Acetaminophen - Bottu Laboratories - Nanterre - France

(**) E. Mendell Co. Inc., Carmel, NY 10512

(***) We thank the Research Department of Roquette Freres Society Lestrem - France, for the different samples of modified starches prepared for us.

"C.M.S.C1"(***) (this experimental carboxymethyl starch presents the same degree of substitution than Explotab but a higher degree of cross linkage).

- Native potato starch as reference (P.S.)

The granules of these modified starches swell more or less in water and in USP artificial gastric juice without enzyme (Table 1)

	in dry medium	in water	in gastric juice
CLS	26,7 µ	36,8 µ	29,9 µ
CMS	20,1 µ	135 µ	50,7 µ
Ex	29,7 µ	85,8 µ	40,9 µ
CMS.CL	26,2 µ	76,9 µ	43,4 µ
P.S.	23,3 µ	25,7 µ	23,4 µ

Table 1 : Particles size of the granules modified starches in different mediums (microscopic determination)

Two concentrations of disintegrant were investigated : 4 % (usual concentration) and the concentration corresponding to the continuous hydrophilic network in the tablet (3). This concentration is in most cases, the better for a fast disintegration. It can be determined according to the swelling power of disintegrant particles (4) (5).

This concentration is slightly different for each disintegrant, because the swelling of particles is different :

10.3 g of PS and CLS
2.7 g of CMS
6.3 g of Ex
6.1 g of CMS CL+

} for 100 g of a mixture of acetaminophen + an equal quantity of Emcompress

METHODS

Mixing of powders was performed in a Turbula mixer. The different powders were added in the following order, according to Ringard's theory of the disintegrant's introduction (6)

Acetaminophen + Emcompress

Disintegrant (in two additions)

Magnesium stearate

The mixing took five minutes between each addition.

The resulting mixture was either directly compressed or granulated with water.

A) Direct Compression

The mixture 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).

In few particular cases, we had to modify this upper punch displacement.

Strain gauges are sticked on the upper and lower punches, connected by means of the Wheatstone bridges to a computer. This equipment gives us the possibility of noticing for each batch of tablets the average maximum force of the upper and lower stresses. It's possible to compare the behaviour of the different mixtures under compression because all the measurements are made on the same mechanical conditions.

B) Wet granulation

The mixture of powders (without Magnesium stearate) was moistened with water until a granulable bulk was obtained. After being

granulated in a Frewitt granulator through a sieve (1,6 mm), the resulting grain was dried 16 h at 45° C and calibrated with Frewitt granulator (through a 1 mm sieve).

Compression was made in the same conditions as mentioned above, after mixing the grain with magnesium stearate in Turbula mixer.

On resulting tablets we investigated :

- the hardness (Heberlein durometer)
- the disintegration time (according to European Pharmacopea) at 37° C in water and in USP artificial gastric juice without enzyme.
- dissolution studies where conducted according to the USP method with rotating paddle (50 r/min) in USP artifial gastric juice without enzyme. Three milliliter samples were withdrawn at various time intervals and assayed for drug content using ultraviolet spectroscopy at 245 nm after suitable dilution.

RESULTS AND DISCUSSION

Each batch of tablets will be indicated by its disintegrant abbreviation (CLS, CMS...) and its concentrations : "4" for 4 %, "N" for the continuous network of disintegrant.

A preliminary study on the mixture of powders and on grains for compression, showed good flow and good tapping properties. We can notice than, after tapping, the tapped density was much lower for grains with swelling disintegrant (CMS, Explotab, CMS CL+) than with those which do not swell (CLS, PS). Grain dryring prevokes a more porous structure when the disintegrant has swelled with water.

Table I : Particles size of granules modified starches in different mediums (microscopic determination)

	in dry medium	in water	in gastric juice
CLS	26,7 µ	36,8 µ	29,9 µ
CMS	20,1 µ	135 µ	50,7 µ
Ex	29,7 µ	85,8 µ	40,9 µ
CMS CL+	26,2 µ	76,9 µ	43,4 µ
P.S.	23,3 µ	25,7 µ	23,4 µ

Compression study

Results are collected in tables II and III in which :

y_1 is the maximum upper punch stress

y_2 is the maximum lower punch stress

y_2/y_1 is indicative of stress transmission through the powder during the compression. This value must be as near to 1 as possible

y_1/hardness is indicative of the aptitude of powders to give hard tablets. This value must be the lowest possible one.

See table II and III.

The stress/hardness ratio (y_1/hardness) study, indicates the superiority of tablets prepared by wet granulation.

The "both carboxymethylated and cross linked starches exhibit the better compressibility (Explotab and CMS CL+) CMS CL+ seems a little better than Explotab.

Table II : Study of the compression of mixtures containing potato starch (PS), cross linked starch (CLS) only carboxymethylated starch (CMS) in different concentration : 4% and "N" corresponding to continuous network.
$DC_{0.5}$: direct compression, 0.5% of Magnesium stearat
$G_{0.5}$: wet granulation, 0.5% of Magnesium stearat
G_1 : wet granulation, 1% of Magnesium stearat

		Upper punch displacement (in 1/100mm)	y_1	y_2	y_2/y_1	Hardness	$\frac{y_1}{\text{hardness}}$
PS 4%	$DC_{0.5}$	454	12.20	10.52	0.86	2.6	4.7
	$G_{0.5}$	480	13.80	11.34	0.82	5.1	2.7
	G_1	480	14.42	13.30	0.92	5.5	2.6
PS"N"	$DC_{0.5}$	453	15.73	13.69	0.87	2.5	6.2
	$G_{0.5}$	480	15.15	12.95	0.85	4.5	3.4
	G_1	480	16.44	15.53	0.94	4.8	3.4
CLS 4%	$DC_{0.5}$		cannot be prepared				
	$G_{0.5}$	481	10.87	6.87	0.63	3.65	3.0
	G_1	481	10.77	9.34	0.87	5.1	2.1
CLS"N"	$DC_{0.5}$	452	16.43	14.63	0.87	2.25	7.5
	$G_{0.5}$		cannot be prepared				
	G_1	481	9.00	7.90	0.88	3	3.0
CMS	$DC_{0.5}$	450	13.14	11.38	0.86	3.45	3.8
	$G_{0.5}$	584	9.86	8.59	0.87	3.65	2.7
	G_1	584	8.12	7.46	0.92	5.95	1.4
CMS"N"	$DC_{0.5}$	451	12.24	10.59	0.86	3.47	3.5
	$G_{0.5}$	584	10.83	8.98	0.83	5.9	1.8
	G_1	584	10.77	9.5	0.88	6.45	1.7

Table III : Study of compression of mixtures containing "both carboxymethylated and cross linked" starch : Ex and CMS CL+ (same key as Table II).

	Upper punch displacement (in 1/100mm)	y_1	y_2	y_2/y_1	Hardness	$\frac{y_1}{\text{hardness}}$
Ex_n 4% $DC_{0.5}$	452	13.18	11.38	0.86	3.15	4.2
$G_{0.5}$		cannot be prepared				
G_1	580	15.77	14.53	0.92	5.0	3.2
Ex_n"N" $DC_{0.5}$	452	14.05	12.08	0.86	2.55	5.5
$G_{0.5}$		cannot be prepared				
G_1	581	16.68	14.68	0.88	5.8	2.9
CMS CL+ 4% $DC_{0.5}$	452	7.02	3.33	0.47	0.7	10.6
$G_{0.5}$	581	20.64	17.26	0.84	9.0	2.3
G_1	581	22.08	18.80	0.85	9.3	2.4
CMS CL+ "N" $DC_{0.5}$	451	13.46	11.58	0.86	3.3	4.08
$G_{0.5}$	583	14.39	12.21	0.85	5.5	2.6
G_1	582	18.87	16.36	0.87	8.2	2.3

It seems that, in this formulation case, 1 % of Magnesium stearate is the best concentration for grains for compression, whereas 0.5 % is sufficient for powder direct compression.

The manufacturing process (direct compression or wet granulation) has a variable influence on disintegration time.

Concerning potato starch and simply cross linked starch we can notice :

. relatively long disintegration times

. faster disintegration times after wet granulation

Table IV : Disintegration time of tablets containing the different tested disintegrants.

Study of disponibility in vitro

A) Disintegration time

Disintegrant concentration		4 %	Continuous network "N"
PS	$DC_{0.5}$	9min 30sec	5 min
	$G_{0.5}$	2min 5sec	60 sec
	G_1	3 min	2 min
CLS	$DC_{0.5}$	cannot be prepared	3 min
	$G_{0.5}$	2min 30sec	cannot be prepared
	G_1	4min 15sec	1min 35sec
CMS	$DC_{0.5}$	1min 25sec	3 min
	$G_{0.5}$	2min 30sec	5 min
	G_1	6 min	8min 30sec
Ex_n	$DC_{0.5}$	18 sec	18 sec
	$G_{0.5}$	cannot be prepared	
	G_1	27 sec	27 sec
CMS CL+	$DC_{0.5}$	20 sec	20 sec
	$G_{0.5}$	24 sec	15 sec
	G_1	30 sec	25 sec

. a very good improvement by the constitution of a continuous network which is a confirmation of our previous works (3) (7)

Concerning the "simply carboxymethylated starch" : it presents a very particular behaviour : after direct compression, disintegration is very fast, but after wet granulation disintegration is slow.

Table V : Dissolution rate of the acetaminophen in tablets prepared either by direct compression or wet granulation.
$\bar{m}$: average of four experiments CV : variation coefficient

%magnesium stearat		0.5%				1%	
Manufacturing process		Direct compression		Wet granulation		Wet granulation	
Disintegrant	Time	$\bar{m}$	CV	$\bar{m}$	CV	$\bar{m}$	CV
PS 4%	7min5	15.6%	36.2%	18.2%	3.3%	9.0%	1.7%
	15min	23.7%	22.8%	26.7%	9.2%	19.1%	9.6%
	30min	38.2%	18.4%	43.1%	15.6%	32.4%	5.5%
	45min	49.6%	17.3%	55.0%	14.0%	42.1%	6.5%
	60min	57.7%	15.7%	61.8%	16.0%	52.3%	0.8%
PS "N"	7min5	19.4%	18.6%	37.7%	16.3%	14.9%	6.2%
	15min	19.4%	18.6%	49.1%	5.4%	25.7%	8.4%
	30min	56.9%	25.2%	69.0%	1.9%	41.5%	14.6%
	45min	69.2%	20.2%	82.9%	5.2%	52.9%	18.5%
	60min	76.9%	16.7%	91.4%	5.0%	60.3%	20.0%
CLS 4%	7min5	cannot be prepared		19.7%	16.5%	15.0%	5.2%
	15min			30.7%	13.9%	25.8%	9.0%
	30min			54.9%	17.5%	37.6%	0.6%
	45min			67.2%	15.0%	47.7%	3.5%
	60min			78.0%	11.4%	54.5%	2.1%
CLS "N"	7min5	26.6%	31.6%	cannot be prepared		13.0%	1.6%
	15min	41.8%	27.3%			20.7%	3.0%
	30min	61.9%	19.2%			32.5%	1.7%
	45min	77.5%	19.1%			43.8%	6.7%
	60min	89.0%	17.5%			50.8%	9.8%

Tablet VI : Dissolution rate of the Acetaminophen in tablets prepared either by direct compression or wet granulation

%magnesium stearat		0.5%				1%	
Manufacturing process		Direct compression		Wet granulation		Wet granulation	
Disintegrant	Time	$\bar{m}$	CV	$\bar{m}$	CV	$\bar{m}$	CV
CMS 4%	7min5	62.2%	16.4%	29.6%	16.8%	18.6%	12.6%
	15min	76.9%	8.8%	54.1%	9.3%	32.1%	12.8%
	30min	83.6%	10.2%	81.5%	13.0%	56.5%	8.9%
	45min	86.7%	9.6%	93.4%	4.9%	75.2%	6.5%
	60min	94.7%	4.1%	98.3%	0.8%	84.1%	2.9%
CMS "N"	7min5	78.4%	18.4%	17.1%	14.6%	13.3%	13.9%
	15min	91.9%	8.9%	28.4%	12.6%	22.4%	4.1%
	30min	101 %	1,9%	54.9%	14.9%	37.3%	7.8%
	45min			70.9%	13.4%	49.1%	5.6%
	60min			80.2%	11.5%	60.0%	9.2%
Ex 4%	7min5	76.0%	5.1%			87.1%	10.4%
	15min	92.8%	3.6%			94.4%	2.1%
	30min	98.2%	2.8%	cannot be prepared		96.8%	2.0%
	45min	98.6%	2.0%			97.2%	1.8%
	60min	99.0%	2.2%			97.4%	1.8%
Ex R	7min5	60.5%	14.8%			85.8%	4.2%
	15min	80.8%	9.0%			91.3%	2.1%
	30min	92.3%	4.0%	cannot be prepared		92.1%	1.7%
	45min	94.4%	1.4%			93.7%	2.2%
	60min	95.2%	1.7%			94.0%	2.3%
CMS CL+	7min5	56.3%	13.5%	88.5%	4.7%	85.4%	7.7%
	15min	86.1%	9.7%	97.7%	1.4%	91.7%	8.9%
	30min	96.3%	7.4%	98.6%	0.7%	98.9%	1.4%
	45min	97.8%	7.0%	98.9%	0.8%	99.1%	1.6%
	60min						
CMS CL+ "N"	7min5	58.7%	24.9%	89.3%	9.7%	91.5%	8.1%
	15min	76.5%	8.9%	99.0%	4.5%	96.3%	3.4%
	30min	87.3%	7.2%	99.5%	3.5%	96.9%	3.1%
	45min	95.4%	0.3%				
	60min	97.0%	1.0%				

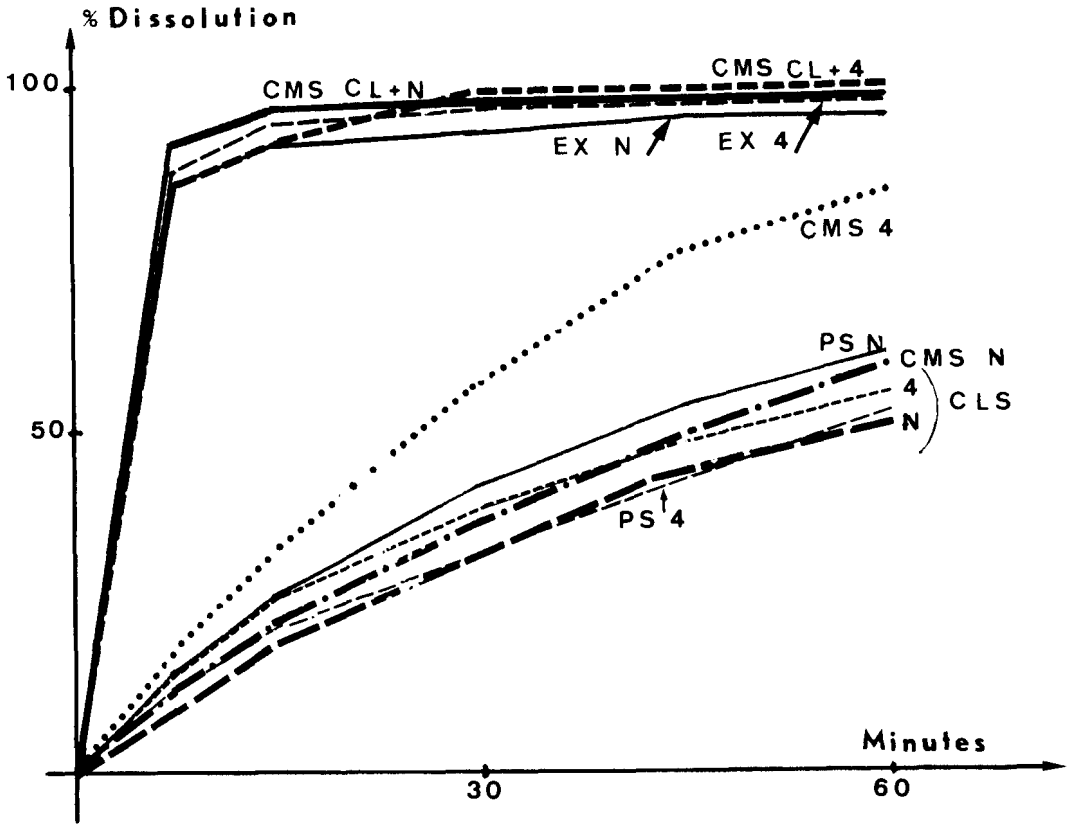


FIGURE 1

Kinetics of dissolution of Acetaminophen from tablets prepared by wet granulation. (4 : 4% of disintegrant, N : Concentration of disintegrant corresponding to the continuous network).

Concerning the "both carboxymethylated and cross linked starches" : we can notice strickingly short disintegration time whatever the manufacturing process is. Cross linkage in addition to carboxymethylation brings some particularly interesting properties for the use of carboxymethylated starches in wet granulation.

B) Dissolution studies

Results are collected in tables V and VI.(figures 1 and 2).

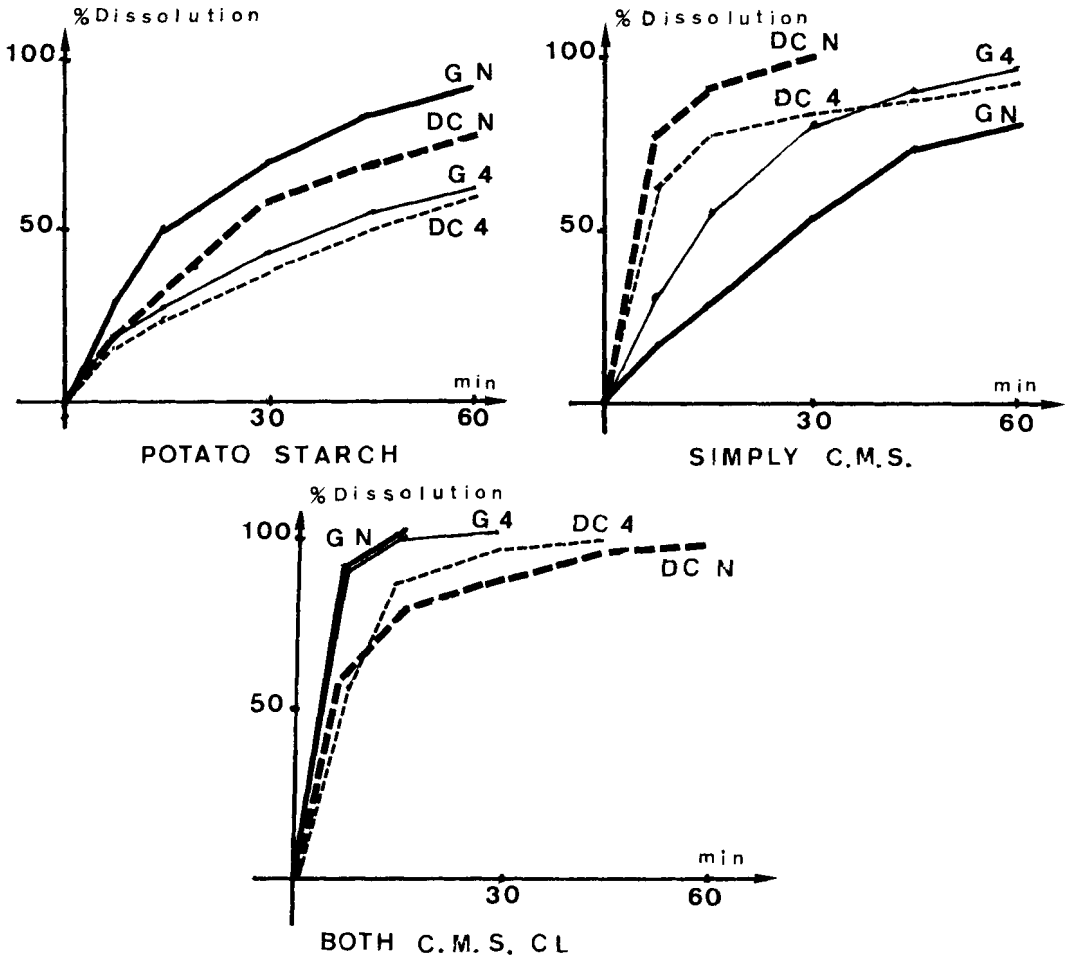
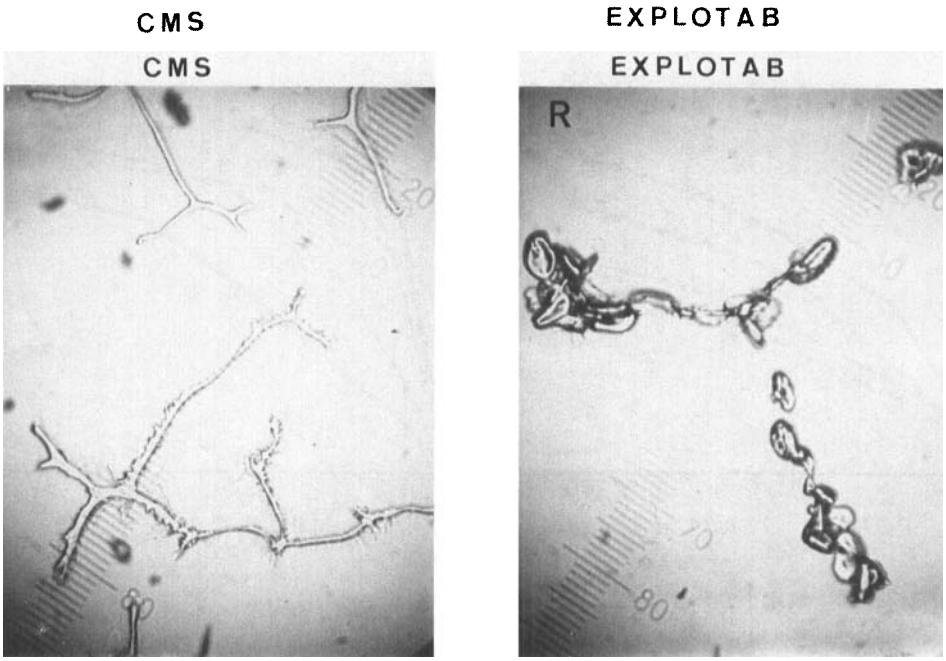


FIGURE 2

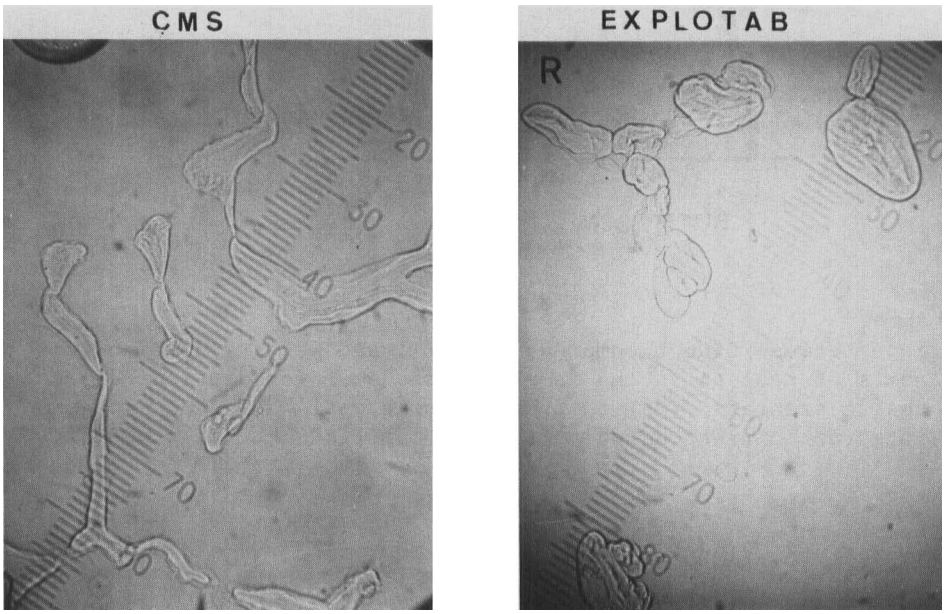
Comparison between Direct compression (DC), and Wet granulation (G) for 3 sorts of tablets in the same conditions of formulation (0.5 % of Magnesium stearat). ("4" : 4% of disintegrant, "N" : Concentration of disintegrant corresponding to the hydrophilic continuous network).

Results confirm that cross linkage brings more interesting properties for the use of carboxymethylated starches in wet granulation.

Dissolution is in any case much faster with the "both carboxymethylated and cross linked starches" (Explotab and CMS CL+). The



a)- After wetting, followed by drying



b)- After wetting, drying, followed by a second addition of water.

FIGURE 3

Aspect under the microscope (x100) of"simply carboxymethylated starch (CMS), and"Both carboxymethylated and cross linked starch" (Explotab).

more cross linked CMS CL+ is a little better in wet granulation and seems to be more adapted to this manufacturing process.

Other results confirm those of the disintegration studies :

. poor results for potato starch and "simply cross linked starch"

. poor results for the "simply carboxymethylated starch" after wet granulation.

. in any case, a part from the very particular "simply carboxymethylated starch", the Acetaminiphen dissolution from tablets prepared with an identical formulation (0,5 % of Magnesium stearat) is faster after wet granulation than after direct compression.

CONCLUSION

A) About carboxymethylation and cross linkage advisability

In this study, the "both carboxymethylated and cross linked starches" appear as very good disintegrants in wet granulation as well as in direct compression. In internal phasis during wet granulation, they are both binding and disintegrating agents.

CMS CL+ seems the best adapted to wet granulation. It is more cross linked than Explotab. In fact, a certain degree of starch cross linkage seems particulary suitable for wet granulation. A simply carboxymethylated starch is a bad disintegrant, at least in this case.

One explanation can be given by studying modified starch granules under the microscope, in dry medium, in water, after the drying of wet granules and after a second addition of water.

These phasis reflect what goes on inside the tablet during the manufacturing process : wet granulation, drying and disintegration in water. We can notice :

- Simply carboxymethylated starch (CMS) swells much more in water than " both carboxymethylated and cross linked " starch (CMS CL+ and Explotab).
- After drying, long filaments are observed for CMS. For Explotab and CMS CL+, the granule structure is kept.(figure 3a).
- After the second addition of water, more or less swelled filaments are observed in the case of CMS. Whereas perfectly individualized grains are observed for the both carboxymethylated and cross linked starch.(figure 3b).

In the first case, the non cross linked granule has splitt. It is more or less dissolved in water. The resulting viscosity decreases the water penetration in tablets : disintegration is slow.

In the second case, hydrophilic granules keep their granular structure which allows fast water penetration in tablets. The disintegration time is short.

All these observations confirm that a good disintegrant must be hydrophilic and insoluble.

B) About using CMS in wet granulation

Wet granulation seems to give better tablets than direct compression as for as the technology of the manufacturing process but also as for as the "in vitro disponibility" are concerned.

The both carboxymethylated and cross linked starches are particularly suitable for wet granulation process.

ACKNOWLEDGEMENTS

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REFERENCES

1 - Khan K.A., Drug Dev. and Ind. Pharm., 7(4), 421-438 (1981)

2 - Guyot-Hermann A.M., Ringard J., Drug Dev. and Ind. Pharm., 7(2), 155-178 (1981)

3 - Ringard J., Guyot-Hermann A.M., J. Pharm. Belg. 33(2), 89-110 (1978)

4 - Tapé L.G., Robert H., Guyot-Hermann A.M., Il Farmaco (in press : 1982)

5 - Ringard J., Guyot-Hermann A.M., Labo Pharma, n°316, 7-18 (1982)

6 - Ringard J., Etude de l'influence d'un réseau hydrophile et continu sur la désagrégation des comprimés et la dissolution de leurs principes actifs
Thèse Doctorat es Sciences Pharmaceutiques - Lille - 1977

7 - Ringard J., J. Pharm. Belg., 34(4), 204-211 (1979)