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TABLETS OF HAMAMELIS DRY EXTRACT BY DIRECT COMPRESSION : COMPARATIVE STUDY OF NATURAL STARCHES AND STARCH DERIVATIVES

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ABSTRACT

Tablets of hamamelis dry extract are made by direct compression. The rheological properties of natural starches and of various starch derivatives (split starches, pregelatinized starches, starch glycolates...) are compared. 50 mg hamamelis dry extract (20 % w/w) formulations were prepared with these different disintegrants ; for each formulation mechanical properties of both powder mixture and resulting tablets were assessed.

INTRODUCTION

Leaf extracts of *Hamamelis virginiana* (Hamamelidaceae) are known for their astringent and vasoconstritive properties. As their composition is mostly determined and as specific assay methods applicable to routine controle are available (1-7), it seemed worthwhile for us to take up the pharmaceutical development of these extracts. The present work aims to develop high-dose tablets of hamamelis dry extract by direct compression.

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In this case, appropriate formulation depends on the properties of both the active ingredient and the excipients (8, 9). Accordingly, the rheological properties of hamamelis dry extract and selected excipients were studied in order to assess their qualities and potential faults. Our work was particularly directed towards starches, excipients used as disintegrants but also presenting binding properties. We performed a comparative study of the rheological properties of natural starches and of various starch derivatives available on the market (split starches, pregelatinized starches, starch glycolates...). Afterwards, 50 mg hamamelis dry extract (20 % w/w) formulations were prepared with the different starches and starch derivatives tested ; for each formulation mechanical properties of both powder mixture and resulting tablets were assessed.

MATERIALS AND METHODS

Raw Materials

The active ingredient consisted of dry extract of *Hamamelis virginiana*.

The excipients for direct compression were lactose fast flo® (FMC Corp. Seppic) and Avicel PH 101® (FMC Corp. Seppic). The following starches were tested as disintegrants. Maize starch, wheat starch, potato starch (Coopération Pharmaceutique Française), starch HAUSSY AD® (Avebe-Doittau Emuldo S.A.). Maize starch derivatives : -Pregelatinized starch - Lycatab PGS ®, Pregeflo M® (Roquette Frères, S.A.), Snow flake 12018 ® (Ceresta France) ; - Physically modified starch - Starch 1500 ® (Colorcon SARL). Potato starch derivatives : - Modified and spray-dried starch - Amylogum CLS ® (Avebe-Doittau Emuldo S.A.) ; - Starch glycolate - Explotab® (SPCI), Glycolys D®, Primojel® (Avebe-Doittau Emuldo S.A.), Sodium starch Glycolate ® (Yung Zip Chemical ind. Corp. Promecome) ; - Pregelatinized starch - Pregeflo P 250® (Roquette Frères S.A.). Talc and magnesium stearate were used as lubricants (Coopération Pharmaceutique Française).

Methods

Study of the rheological properties of the raw materials

This was carried out using a Hosokawa® powder characteristics tester. This apparatus has been designed to measure mechanically compressibility, angle of repose, spatula angle, fall angle and dispersibility for any powder. These parameters and particle size distribution allow the determination of the flowability and floodability properties of powders.

Mixing of raw materials and compression

After mixing for 5 minutes in a Turbula T2C® mixer, the formulations were compressed with a Korsch® tabletting machine fitted with 8 mm punches.

Manufacturing in-process controls

Samples of 10 tablets were taken periodically during the manufacturing process. Weight of each sample was determined using a precision balance ; its mean crushing strength was measured with a Vanderkamp VK 200® tablet handness tester.

Study of tablets properties

The mean thickness of the tablet was measured with a Hoko® apparatus and its mean crushing strength with a Vanderkamp VK200® tablet hardness tester. Each test was carried out on a sample of 10 tablets taken at random from the production batch. Weight uniformity was assessed on a sample of 20 tablets using a precision balance (10). Friability was measured with a Roche® Friabilator, which subjects a sample of 10 tablets to friction and impacting for 5 minutes ; the weight loss of the sample is then measured. Disintegration time, which should not exceed 15 minutes, was determined with an Erweka type ZT2 apparatus (10).

RESULTS AND DISCUSSION

Choice of excipients

Published data on excipients for direct compression (8, 9) indicate three suitable materials :

- a diluent, lactose fast flo® possessing favourable flow properties and a compressibility appreciably higher than that of other lactoses ; this excipient had been previously used by us for formulation of procyanidins high-dose tablets by direct compression (11).
- a microcrystallin cellulose binder, Avicel PH 101® , incorporated in a proportion of between 15 and 25 %.
- a starch or starch derivative, used as disintegrant and binder.

These excipients require lubricants. Talc (2 %) and magnesium stearate (1 %) were selected.

Rheological properties of raw materials

The development of a formulation for direct compression depends essentially on the properties of the excipient so long as the proportion of active material does not exceed 10 %. Beyond this figure, it depends also on the mechanical properties of the active ingredients. The properties of the excipient then have to correct any mechanically unfavourable properties these may have (8). A study of the rheological properties of both active material and excipients was thus undertaken.

The excipients have to flow well and be good binders. These properties can be assessed with the Hosokawa® powder characteristics tester in excipients other than lubricants (12). Since previous work had already shown the excellent rheological properties of lactose fast flo® and Avicel PH 101® (11), only starches and starch derivatives were tested.
The rheological properties of the hamamelis dry extract were also studied using this device.

For each powder, angle of repose, compressibility, spatula angle and uniformity of particle size were determined. The flowability of the powder was then estimated from these four parameters. In addition, the fall angle, difference angle (angle of repose - fall angle) and the dispersibility allowed the floodability of each powder to be evaluated.

TABLE 1

Rheological properties of raw materials : flowability parameters

Raw material	Apparent density (g/cm³) Aerated A	Packed P	Mean A+P/2	Compressibility %	Angle of repose (°)	Spatula angle (°)	Uniformity
Hamamelis extract	0.586	0.871	0.728	32.7	42.9	65.5	3.1
Maize starch	0.498	0.736	0.617	32.3	43	60.5	6
Wheat starch	0.440	0.743	0.591	40.8	45.3	61.2	6.2
Starch Haussy AD®	0.448	0.693	0.570	35.3	44.7	71.2	8.5
Potato starch	0.681	0.970	0.825	29.8	41	72.2	5.6
Lycatab PGS®	0.400	0.580	0.490	31	36.9	72.5	5.4
Pregeflo M®	0.490	0.710	0.600	31	35.6	66.6	3.8
Snow flake 12018®	0.373	0.508	0.440	26.6	33.6	55.6	5.6
Starch 1500®	0.618	0.828	0.723	25.4	32.2	64	8.7
Amylogum CLS®	0.335	0.527	0.431	36.4	37.7	64	4.2
Explotab®	0.774	0.919	0.846	15.8	30	50.4	5.9
Glycolys D®	0.745	0.979	0.862	23.9	32.5	48.1	5.8
Pregeflo P250®	0.487	0.698	0.592	30.2	35.7	57.5	5.8
Primojel®	0.818	1.016	0.917	19.5	28.5	50.3	5.8
Sodium starch glycolate®	0.859	1.024	0.941	16.5	29.7	53	6.2

TABLE 2

Rheological properties of raw materials : floodability parameters

Raw material	Fall angle (°)	Difference angle (°)	Dispersibility (%)
Hamamelis extract	24	18.9	12.4
Maize starch	27	16	32
Potato starch	19.6	21.4	30
Starch Haussy AD®	24.7	20	30
Wheat starch	24.8	20.5	19.4
Lycatab PGS®	18.1	18.8	14.1
Pregeflo M®	14.3	21.3	20.7
Snow flake 12018®	24	9.6	18.9
Starch 1500®	18.4	13.8	21.6
Amylogum CLS®	20.7	17	15
Explotab®	13	17	35.6
Glycolys D®	13.7	18.8	35.5
Pregeflo P 250®	14.1	21.2	20.2
Primojel®	15.7	12.8	33.6
Sodium starch glycolate®	13.3	16.4	30.1

The values obtained for the hamamelis extract and the fourteen disintegrants tested are set out in tables 1 and 2.

This study of the rheological properties of raw materials allowed the hamamelis extract and the different disintegrants to be classified according to the Hosokawa standards (12) :

An index, between 0 and 25, is assigned to each parameter ; the sum of compressibility, angle of repose, spatula angle and uniformity indices gives the flowability index ; floodability index is the sum of flowability, fall angle, difference angle and dispersibility indices.

As shown in figure 1, potato starch glycolates (Explotab®, Primojel®, sodium starch glycolate®, Glycolys D®) are free flowing powders, with excellent fluidity.
Maize starch derivatives are characterized by weaker but still adequate flowability properties and variable floodability.
As concerns natural starches, these disintegrants have rather poor rheological properties, with the exception of potato starch.
Figure 1 also confirms the poor flowability properties of the hamamelis extract. Fortunately the favourable flow qualities of most of the excipients should correct these poor mechanical properties. This is a most welcome finding as it is our purpose to develop a formulation for tablets containing an important proportion of active material (20 %).

Tablet formulation

Twenty-one formulations of tablets containing 50 mg of hamamelis dry extract were tested. The active content was set at 20 % w/w. The different compositions are shown in tables 3 , 4 and 5.

Mechanical properties of powder mixtures (figure 2)

The powder mixtures with potato starch glycolates as disintegrants (formulations 15, 16, 19, 20, 21) exhibited escellent mechanical properties (regular flow, no sticking or clogging...), as could be expected from their measured rheological properties.

On the contrary, powder mixtures containing natural starches and especially wheat starch, presented poor flowability and floodability qualities. Formulations 1 to 4 were characterized by an irregular flow of the mixtures.

As concerns the other formulations, and particularly those containing maize starch derivatives, the mechanical properties of the powder mixtures were satisfactory.

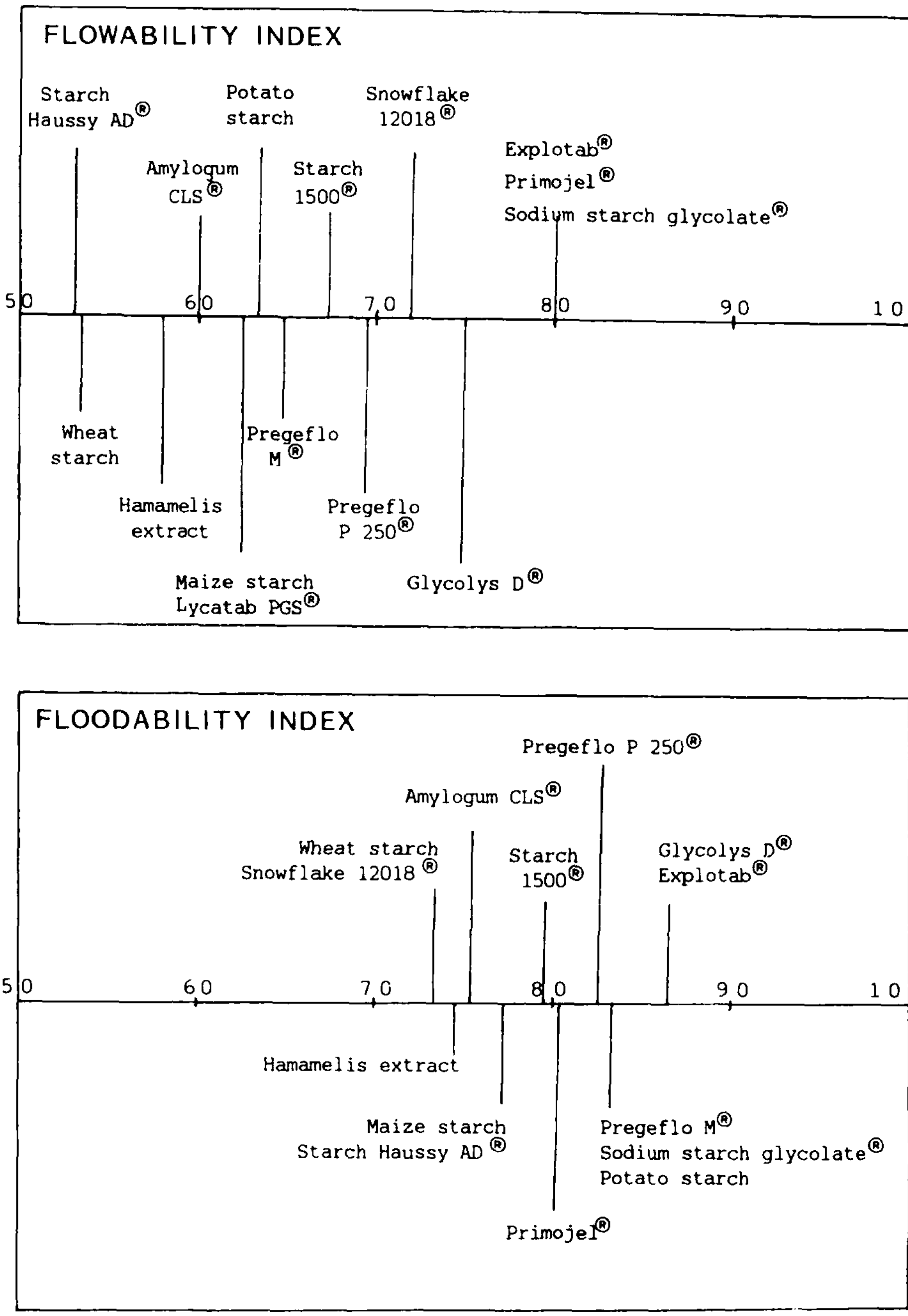

FIGURE 1

Rheological properties of disintegrants and hamamelis extract. Classification according flowability and floodability index (12)

TABLE 3

Formulation of hamamelis dry extract tablets. Natural starches as disintegrants (% by weight)

Raw material	Formulation n° 1	2	3	4
Hamamelis dry extract	20	20	20	20
Lactose fast flo®	46	46	46	46
Avicel PH 101®	19	19	19	19
Maize starch	12			
Potato starch		12		
Starch Haussy AD®			12	
Wheat starch				12
Magnesium stearate	1	1	1	1
Talc	2	2	2	2

TABLE 4

Formulation of hamamelis dry extract tablets. Maize starch derivatives as disintegrants (% by weight)

Raw material	Formulation n° 5	6	7	8	9	10	11	12
Hamamelis dry extract	20	20	20	20	20	20	20	20
Lactose fast flo®	46	43	40	46	43	46	43	46
Avicel PH 101®	19	19	19	19	19	19	19	19
Lycatab PGS®	12	15	18					
Pregeflo M®				12	15			
Snow flake 12018®						12	15	
Starch 1500®								12
Magnesium stearate	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2

TABLE 5

Formulation of hamamelis dry extract tablets. Potato starch derivatives as disintegrants (% by weight)

Raw material	Formulation n° 13	14	15	16	17	18	19	20	21
Hamamelis dry extract	20	20	20	20	20	20	20	20	20
Lactose fast flo®	46	43	46	46	46	43	46	46	50
Avicel PH 101®	19	19	19	19	19	19	19	19	19
Amylogum CLS®	12	15							
Explotab®			12						
Glycolys D®				12					
Pregeflo P 250®					12	15			
Primojel®							12		
Sodium starch glycolate®								12	8
Magnesium stearate	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2

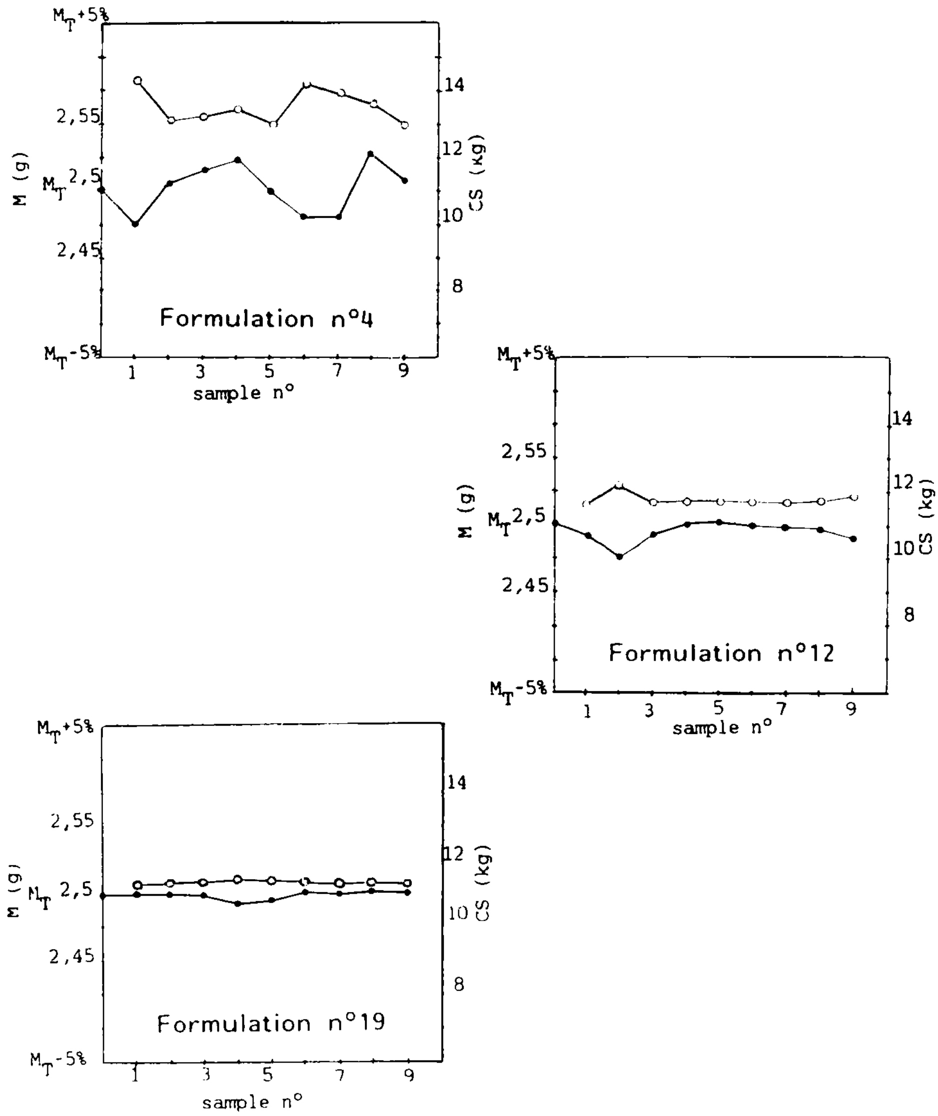

FIGURE 2
Examples of manufacturing cards
● weight (M) of a sample of 10 tablets
○ crushing strength (CS) of tablets
M_T = theorical weight of a sample

TABLE 6

Formulations with natural starches as disintegrants.

Mechanical properties of tablets

Parameter	Formulation n° 1	2	3	4
Diameter (mm)	8.0	8.0	8.0	8.0
Thickness (mm)	4.5	4.5	4.5	4.6
Crushing strength (kg)	10.5	12.0	13.0	13.5
Friability (%)	0.21	0.25	0.21	0.14
Disintegration time (min)	5.75	8.25	6.0	6.0

TABLE 7

Formulations with maize starch derivatives as disintegrants.

Mechanical properties of tablets

Parameter	Formulation n° 5	6	7	8	9	10	11	12
Diameter (mm)	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
Thickness (mm)	4.7	4.6	4.7	4.6	4.6	4.7	4.7	4.6
Crushing strength (kg)	12.0	11.5	11.75	11.75	10.25	11.5	11.0	11.75
Friability (%)	0.2	0.2	0.19	0.10	0.19	0.18	0.08	0.07
Disintegration time (min)	18.5	17.5	15.75	15.5	14.75	11.0	11.25	8.0

TABLE 8

Formulations with potato starch derivatives as disintegrants.

Mechanical properties of tablets

Parameter	Formulation n° 13	14	15	16	17	18	19	20	21
Diameter (mm)	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
Thickness (mm)	4.6	4,6	4.7	4.6	4.6	4.6	4.7	4.4	4.5
Crushing strength (kg)	11.0	11.0	9.5	12	12	10.5	10.5	8.5	9.5
Friability (%)	0.15	0.16	0.10	0.13	0.19	0.10	0.18	cleavage	0.13
Disintegration time (min)	14.5	15.0	3.75	4.75	15.75	15.5	4.5	6.0	6.75

Properties of finished tablets

The tablets obtained all passed the weight uniformity test (10). The relevant mechanical properties of the tablets are set out in tables 6, 7 and 8. They were assessed in terms of the following standards (13). Disintegration time : < 5 min : good ; 5 to 10 min : adequate ; > 10 min : poor. Friability : maximum

1 %. Crushing strength : > 6 kg : good ; 3 to 6 kg : adequate ; < 3 kg : poor.

The comparative study of the 21 formulations tested, confirmed the differences existing between natural starches and starch derivatives in their rheological properties. Moreover, this study allowed these materials to be classified according to their disintegrating power . The best results were again observed with three potato starch glycolates, Explotab®, Primojel® and Glycolys D®. Two tablet formulations containing 50 mg of hamamelis dry extract can therefore be selected : formulation 16, Glycolys D®-based, and formulation 19, Primojel®-based. Indeed, the tablets obtained exhibited the most satisfactory characteristics (crushing strength, friability, disintegration).

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