Comparative Evaluation of Super Disintegrants and Binder with Formulation Development of Orodispersible Tablets

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Abstract

The objective of this work is to find a quantitative and qualitative formula for a rapidly disintegrating matrix.

For a first approach, fast disintegration matrices were formulated without active ingredient, selecting the quantity, the quality and the mode of introducing the Superdisintegrants and binder on a case-by-case basis.

An optimal rapid disintegration matrix was chosen into which an active ingredient was introduced with a disintegration time of 16 s, a Hardness of 4.95 Kp and a friability of 0.45%.

Keywords: *Rapidly disintegrating matrix; Tablet orodispersible; Placebo; Wetting time*

I. INTRODUCTION

New pharmaceutical forms are being innovated to improve patient comfort among them, orodispersible tablets or rapidly disintegrating tablets administered orally.

Rapidly disintegrating tablets have the particularity of rapidly disintegrating in the oral cavity, tongue and in contact with saliva. After deglutition the dissolution and absorption of the suspension (saliva-grain) will take place as for a conventional tablet in the gastrointestinal tract [1-3].

Orodispersible forms are convenient for pediatric patients, geriatric, disabled and also patients with persistent nausea, who are traveling or who do not have access to water. [1]

Indeed, the active principle, in the orodispersible form, is presented in a form directly available for absorption; the rapid dispersion in fine particles makes it possible to avoid any gastric ulceration and adherence to the walls of the digestive tract [2].

They are, in fact, manufactured with standard equipment (mobile mixers) present in any industry dedicated to solid forms [2].

The main disadvantage of orodispersible tablets is taste masking [2], and because of their low hardness and high friability, these tablets are difficult to handle during their use [4].

The solubility of the active ingredient (AI) of the orodispersible tablets in water is an important factor where a comparison between two matrices one containing a water-insoluble AI and the other water-soluble AI has shown that the water-insoluble AI matrix gave a smaller disintegration time than that of the soluble AI which impedes water penetration.

It has been suggested that for a freeze-drying method an insoluble AI should be used with a dose of less than 400mg and the soluble AI with a dose of less than 60mg.

Moreover, the disintegrant is the most important excipient in the formulation of the orodispersible tablets; it accelerates the release of the active ingredient by bursting of the tablet when it is in contact with water or saliva [2].

As part of its research and development activities, the SAIDAL Group has undertaken, through its research and development center (CRD), the development of a rapid disintegration matrix.

The aim of this work is to formulate tablets which rapidly disintegrate and whose active ingredient is acetylsalicylic acid, one of the non-opiate analgesics. These tablets should have great hardness and low friability.

II. MATERIAL AND METHOD

A. *Material preparation*

- *Analytical balance*

The products used were weighed using an analytical balance with an accuracy of d = 0.1 g and a capacity of (5-3640) g.

- *Granulator mixer*

The granulator mixer (LODIGE) small model (capacity 1kg), served to mix and wet the powder.

- *Oscillating granulators*

The oscillating granulator was meshed with meshes equal to 3.15mm, 1mm and 1.6mm.

- *Drying oven*

In order to maintain the residual moisture content of the mixture at lower values, drying was carried out in an oven at a temperature of 40 ° C.

- *Free-fall mixer*

The free-fall mixer (Turbula) with a capacity of 10 kg served to mix the external phase with the internal phase.

- *Tableting*

The powder mixer (FORGERAIS) was prepared on an alternative machine. The punches used were for tablets: round, non-domed, with a diameter of 10mm.

B. *Control equipment*

- *Infrared Desiccator*

To check the moisture content of the mixture an infrared desiccator was used. 5 g of the powder underwent infrared drying on a torsion wire scale for 5 minutes.

- *Standard Funnel*

A funnel standardized according to the European Pharmacopoeia 2008 was used for the flow test.

- *Compaction equipment*

A packing apparatus able to produce 250 ± 15 drops per minute, with a height of 3 ± 0.2 mm, was used. The specimen support with its fixing device had a mass of 450 ± 5g and the 250 ml test piece graduated every 2 ml had a mass of 220 ± 40 g.

- *Precision scale*

The average weight of the tablets was measured on a precision digital scale 0.001g and with a maximum capacity of 420 g.

- *Vernier caliper*

The caliper was used to measure the thickness and diameter of the tablets with the aid of a caliper.

- *Friabilimeter*

The apparatus consisted of a transparent rotating drum having an inner diameter of about 286 mm and a height of about 39 mm.

The drum was mounted on the horizontal axis of a drive device, the rotational speed of which was 25 rpm. Consequently, at each rotation, the tablets slided and fell and were projected from the center of the drum towards the cylindrical wall along a curvilinear trajectory.

- *Durometer*

The hardness of the tablets was tested with a Durometer described in the European Pharmacopoeia 2008.

- *Disintegrating apparatus*

The disintegration test of the tablets was carried out in the disintegration apparatus described by the European Pharmacopoeia 2008.

C. *Methodology*

On the basis of a literature search, an attempt was made to optimize a qualitative and quantitative formula, as well as a manufacturing process which would be subsequently validated by transposition on an industrial scale.

- *The choice of the formula*

The proportions of the various excipients used are inspired by the "Handbook of pharmaceutical excipients and are summarized in the following table:

Table 1. Components selected for the various tests

Component	Role	Used range %
Acetylsalicylic acid	AI	
Lactose monohydrate	Thinner	
Pregelatinized corn starch	Binds and disintegrates	5-10
Povidone K 30	Binder	0.5-5
Crospovidone	Super disintegrating	2-5
Croscarmellose sodium	Super disintegrating	0.5-5
Magnesium Stearate	Lubricant	0.25-5
Talc	Lubricant	1-10

- *Working Principle*

In this work a focus was much more on choosing a binder and a super disintegrant in order to find the correct percentage and the mode of introduction in

order to obtain an orodispersible tablet with a rapid disintegration time.

D. Choice of manufacturing process

Flow and packing tests were carried out on the excipients in order to guide the selection of the manufacturing process. These tests are summarized in the following table:

Table 2. Flow test and compaction test of excipients

excipients	Flow tests	V0 (mL)	V10 (mL)	V500 (mL)	V10- V500
Lactose monohydrate m=100 g	∞	147	136	130	6
Pregelatinized starch m=100 g	∞	209	196	174	22
Crospovidone m=50 g	∞	172	165	128	37
Croscarmellose sodium m= 100 g	∞	170	163	140	23
Magnesium stearate m= 50 g	∞	145	140	124	16
Talc m= 100 g	∞	198	190	130	60

The test for flow and compaction of the excipients was non-compliant, the flow time had exceeded the limit of 10 s and the packing test (V10-V500) was greater than 20 ml, excepted for those performed on lactose monohydrate, which were compliant but this was not sufficient to obtain a mixture with good flow and settlement.

This was the reason why the recommended process was wet granulation in order to improve the rheology of the mixture.

- **Attempts**

Six placebo trials were performed (Table 3), each placebo was 500 g in weight this would be used to find a rapid disintegration matrix optimum in which the AI would be introduced and which aimed to verify the technical feasibility of the formula through the search for the conformity of the pharmaco-technical controls.

Placebo Test 01:

Manufacturing process:

Before each manufacture, the cleanliness of the equipment was checked.

• Step 01: sieving and weighing raw materials.

We weighed the exact quantities of the excipients, screened them first with a 1 mm sieve to prevent agglomeration of the powder. The quantities are shown in the above table.

• Step 02: mixing.

In a granulator mixer (LODIGE), lactose monohydrate, pregelatinized starch and Croscarmellose sodium were introduced, with shaking for 10 minutes at a speed of 310 rpm.

• Step 03: wetting and granulation

The wetting liquid (water) was introduced into the granulator mixer using a test piece until a moistened mass was obtained. The volume of water used was 185 ml.

• Step 04: dismantling

The wetted mass on an oscillating granulator equipped with a mesh screen 3, 15 mm was dismantled. A 5g sample was taken to determine the residual moisture content using an infrared desiccator (PRECISA). The residual moisture content was 15.76%.

• Step 05: drying

The grain thus formed was dried in a GLATT tray oven at a temperature of 40 ° C. Samples were taken at regular intervals (10 minutes) to determine the moisture content. The drying operation was stopped when a humidity level of 2-4% was reached.

For this test, after 80 minutes of drying a humidity level of 2.04% was reached.

• Step 06: Calibration

After drying, the grain obtained was we calibrated using a FREWITT oscillating granulator equipped with a 1.6 mm grid.

• Step 07: lubrication

The weight of the grain obtained was w_f = 461 g giving a yield of 92.2%, the weight of the lubricant (Magnesium Stearate) to be used was calculated in relation to this yield and was 9.22g.

The magnesium stearate, previously sieved to 1 mm, was introduced with the granulate in a free-fall mixer (Turbula) for 5 min. After this operation the mixture was ready for compression.

• Step 08: Compression

This operation consisted in compressing the granulates in an alternative machine

(FORGERAIS) equipped with a punch of 10 mm in diameter. The weight of the tablets was 350 mg.

Placebo test 02

For this test, the way in which the Pregelatinized starch was introduced was changed in order to improve the disintegration time of the tablets.

Manufacturing process

• Step 01: sieving and weighing raw materials

• Step 02: mixing

The lactose monohydrate was introduced into the granulator mixer (LODIGE); Croscarmellose sodium and half the amount of the Pregelatinized starch (internal phase) were mixed for 10 minutes at a speed of 309.7 rpm.

• Step 03: wetting and granulation

The volume of water used for wetting was 140 ml.

• Step 04: dismantling.

• Step 05: drying

Drying was stopped after 70 min and the residual moisture content of the grain at the end of the drying operation was Th = 12.62%.

• Step 06: Calibration (same step as test 01).

• Step 07: lubrication

After adding the remainder of the Pregelatinized starch (50%) to the external phase, the weight of the final mixture was w_f= 475 g, giving a yield of 95%, the mass of the lubricant (magnesium stearate) to be used was calculated in relation to this yield as 9.5 g.

The magnesium stearate was sieved to 1 mm beforehand and then introduced with the granulate into a free-fall mixer and mixed for 5 min. After this operation the mixture was ready for compression.

Placebo test 03

For this test Croscarmellose sodium was replaced by another disintegrant: Crospovidone.

Manufacturing process

The steps listed below were carried out in the same way as for the test 01.

• Step 03: wetting and granulation

The volume of water used for wetting was 140 ml.

• Step 04: dismantling

The residual moisture content was 14.59%.

• Step 05: drying

Drying was stopped after 43 min and the moisture content of the mixture was 1.87%.

• Step 06: Calibration

• Step 07: lubrication

We reweighed the weight of the final mixture 430 g, giving a yield of 86%, the mass of the lubricant (magnesium stearate) to be used is calculated in relation to this yield, it is 8.6 g.
The magnesium stearate was introduced and sieved beforehand to 1 mm, with the granulate in a free-fall mixer and mix for 5 min. After this operation the mixture was ready for compression

Placebo test 04

Manufacturing process

The steps mentioned below proceeded in the same manner as for the test 02.

• Step 03: wetting and granulation

The volume of water used for wetting was 100 ml.

Step 04: dismantling

The residual moisture content was 13.81%.

• Step 05: drying

Drying was stopped after 42 min. The moisture content of the mixture was 1.43%.

• Step 06: Calibration

• Step 07: lubrication

After adding the remainder of the Pregelatinized starch (50%) to the external phase, the weight of the final mixture was w_f= 475 g, giving a yield of 95%, the mass of the lubricant (magnesium stearate) to be used was calculated in relation to this yield as 9.5 g.

After the remainder of the pregelatinized starch (50%) was added to the external phase. We have weighed the weight of the final mixture wf = 439 g, giving a yield of 87.8%, the mass of the lubricant (magnesium stearate) to be used is calculated in relation to this yield, it is 8.78 g.

We introduced the magnesium stearate, sieved beforehand to 1 mm, with the granulate in a free-fall mixer and mix for 5 min. After this operation the mixture is ready for compression.

Table 3. The centesimal and quantitative formulas for the various tests

Placebo	P1		P2		P3		P4		P 5		P6		P7with AP	
	%	(g)	%	g	%	g	%	g	%	g	%	g	%	g
Acetylsalicylic acid													33,33	166,66
Lactose monohydrate	86	428	85.5	427.5	85.5	427.5	85.5	427.5	85.5	428	85.5	427.5	52.16	260.8
Croscarmellose sodium	5	37.5	5	25					2.5 (External phase)	12.5	2.5 (External phase)	12.5		
Crospovidone					5	25	5	25	2.5 (Internal phase)	12.5	2.5 (Internal phase)	12.5	5	25
Pregelatinized maize starch	72.5	25	7.5 (50% in internal phase and 50% in external phase)	37.5 (18.75 in internal phase and 18.75 in external phase)	7.5	37.5	7.5 (50% in internal phase and 50% in external phase)	37.5 (18.75 in internal phase and 18.75 in external phase)	7.5	37.5			7.5	37.5
PVP K30											5	25		
magnésium Stéarate	2	10	2	10	2	10	2	10	2	10	2	10		
Talc													2	10

Placebo test 05

During this test we had associated two disintegrants, one in the internal phase and the other in the external phase.

Manufacturing process

The steps mentioned below proceed in the same manner as the previous tests.

• Step 01: sieving and weighing raw materials

• Step 02: mixing

Lactose monohydrate, Pregelatinized starch and Crospovidone (internal phase) were introduced into the granulator mixer (LODIGE)

• Step 03: wetting and granulation

The volume of water used for wetting was 110 ml.

• Step 04: dismantling

The residual moisture content was 13.69%.

• Step 05: drying

Drying was stopped after 45 min and the moisture content of the mixture was 2.03%.

• Step 06: Calibration

• Step 07: lubrication

After the addition of 12.5 g of Croscarmellose sodium to the external phase, the weight of the final mixture was wf= 447.1g with a yield of 89.42%. The mass of the lubricant (magnesium stearate) to be used was calculated in relation to this yield and was 8. 94 g.

The magnesium stearate was introduced, sieved beforehand to 1 mm, with the granulate in a free-fall mixer and mix for 5 min. After this operation the mixture is ready for compression.

Placebo test 06

We have done the fifth process while changing the binder.

Manufacturing process

• Step 02: mixing

Introduce lactose monohydrate, Crospovidone and PVP K30 into the granulator mixer (LODIGE);

• Step 03: wetting and granulation

The volume of water used for wetting was 83 ml.

• Step 04: dismantling

The residual moisture content was 12.51%.

• Step 05: drying

Drying was stopped after 50 min and the moisture content of the mixture was 1. 60%.

• Step 06: Calibration

• Step 07: lubrication

After the addition of Croscarmellose sodium to the external phase, the weight of the final mixture was re-weighed wf = 419.7 g, giving a yield of 83.94%, and the corresponding mass of the lubricant (magnesium stearate) to be used was calculated as 39 g.

The magnesium stearate was sieved to 1 mm beforehand and then introduced with the granulate into a free-fall mixer and mixed for 5 min. After this operation the mixture was ready for compression.

To deduce the optimal matrix, compliance of all the pharmaco-technical controls of each placebo was considered.

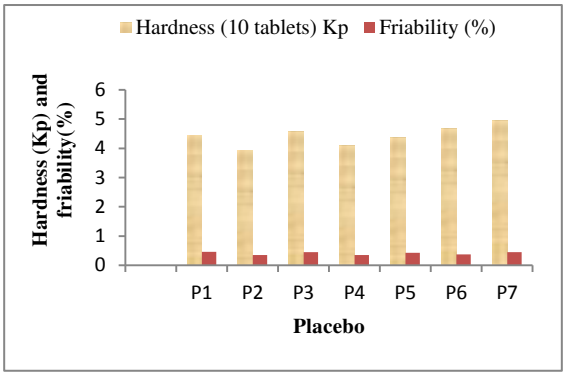

Figure 1. Representation of the results of the friability and hardness tests of each placebo

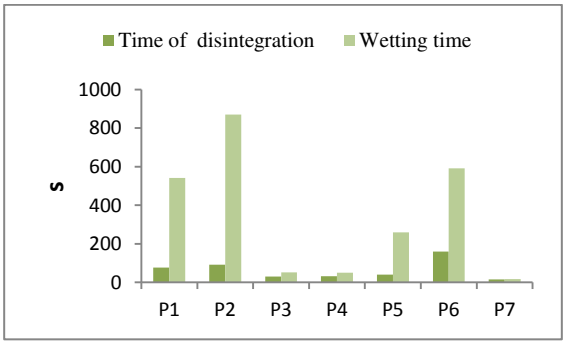

Figure 2. Variability of wettability time and disintegration time for each placebo

According to Figures 1 and 2, the representation of the results of the friability and hardness tests of

placebos was almost the same. We had good hardness and good friability for all the placebos, so we could not distinguish the optimal matrix according to these analyzes.

Regarding the first histogram which represents the variation of wettability time, disintegration time and water content absorbed for each placebo, the disintegration time increased with that of the wettability time and the placebo 03 gave the time of Disintegration and fastest wettability. Therefore, it this test would be retained as an optimal matrix.

Test 07 with the AP

Manufacturing Formula

The formulated tablets are dosed with 100 mg of acetylsalicylic acid with a weight of 300 mg, we have taken the same formula of the test 03.

The magnesium stearate is incompatible with acetylsalicylic acid, so we replaced it with talc which does not present any incompatibility with the latter.

Manufacturing process

The steps mentioned below are carried out in the same way as the test 03

• Step 03: wetting and granulation

The volume of water used for the wetting is 120 ml.

• Step 04: dismantling

The residual moisture content is 13,38%.

• Step 05: drying

We stopped drying after 43 min. The moisture content of the mixture is 2,37%.

• Step 06: Calibration

AI I was incorporated into the grain. The particle sizes of the AP and that of the grain obtained must be close in order to avoid the phenomena of segregation and demixing.

• Step 07: lubrication

We weighed the weight of the final mixture PF = 281.26 g, giving a yield of 86.99%, the mass of AI to be used was calculated in relation to this yield and was 144.97 g.

The weight of the mixture w_f = 426.25 g, give a yield of 85.25%. The mass of talc to be used in relation to this yield was 8.52 g.

PA was introduced and then talc, previously sieved to 1 mm, combined with the granulate in a free-fall mixer and mix for 5 min. After this operation the mixture is ready for compression.

• Determination of AP

The AP was assayed in the finished product (tablet) to verify the uniformity of tablet content, this method is described in the US Pharmacopeia (USP 30) as follows:

• Witness: in an Erlenmeyer we put:

150 mg of PA (raw material); 10 ml of 0,5 N sodium hydroxide (NaOH);

- 02 drops of phenol phthalene as a color indicator;

- Obtaining a colored solution in pink; Titrate with 0,5 N sulfuric acid ($H_2 SO_4$) using a burette until discolored;

- Note the volume of $H_2 SO_4$ used

- $V_{H2\ SO4}$= 4 ml.

Test:

Same protocol as previous step; In this case the tablet was used instead of the raw material; The test was carried out several times in order to validate the following obtained results:

Table 4. Dosage results of AP in tablets

Tablets	1	2	3	4	5	6
$V_{H2\ SO4}$ (ml)	5.5	5.5	5.5	5.5	5.5	5.5

$$WAP = 150 * \frac{10-Vsample}{10-Vstandard} \quad (1)$$

WAP = 112.5 mg.

V standard: Volume of the sulfuric acid used for the control. (Burette drop for the sample).

V sample: Sulfuric acid volume for the sample.

WAP: The weight of the active ingredient.

III. RESULTS AND DISCUSSION

In this work, a rapid disintegration matrix using excipients conventionally used in the manufacture of conventional tablets was formulated. The various tests carried showed the effect of these excipients and their mode of introduction in the formula.

Croscarmellose sodium acted as a disintegrant, giving a disintegration time greater than 1 min. Replacement of Croscarmellose sodium with Crospovidone significantly reduced disintegration

time to 30 seconds. This could be explained by the fact that Croscarmellose sodium swelled rapidly in water and had a specific surface area of 0.81-0.83 $m^2\ g^{-1}$. Moreover, Crospovidone had a high capillarity, a high hydrating capacity with a tendency to form a gel and a specific surface area of 1.2 to 1.4$m^2\ g^{-1}$ enabling it to ensure better disintegration.

All the tests carried out with Crospovidone as disintegrant, alone or in combination with another disintegrant and with the Pregelatinized starch as binder, made it possible to obtain a disintegration time of less than 1 min.

The use of the Pregelatinized starch, which could act as a binder as well as a disintegrant, had shown that the change in its mode of incorporation into the formula had no impact on the pharmaco-technical controls and this for the same disintegrant.

The use of polyvinylpyrrolidone (PVP K30) as a binder in place of the Pregelatinized starch was most appropriate since it had dual role: binder and disintegrant.

According to the results of the pharmaco-technical checks carried out on the various tests carried out, the matrix of test 03 proved to be the optimum matrix in which the AI will be incorporated. The disintegration time of test 07 performed with the AI was increased from 30 to 16 seconds. This was due to the fact that the increase of the porosity of the system was due to the incorporation of the PA which was in the form of grain.

We obtained orodispersible tablets with a weight of 309.8 mg and a content 112.5 mg in AP.

IV. GENERAL CONCLUSION

During this course, we carried out seven formulation tests. All the obtained tablets had pharmacological technical characteristics (Table 5), in particular the disintegration time, since according to the European pharmacopoeia; this must be less than 3 minutes.

Table 5. The results of the pharmacological technical tests of the various tests

	The results						
tests	**placebo 01**	**placebo 02**	**placebo 03**	**placebo 04**	**placebo 05**	**placebo 06**	**placebo**
Appearance and color	Tablets white and round						
The average weight (20 tablets) mg	354,65	357,8	356,6	376,8	340,8	353,7	309,8
Thickness(10 tablets) mm	2,92	3,26	2,98	3,19	2,83	2,83	2,49
Diameter (10 tablets) mm	9,51	10,11	9,58	9,68	9,56	9,56	9,64
Hardness (10 tablets) Kp	4,45	3,94	4,58	4,09	4,37	4,67	4,95
Friability (%)	0,46%	0,35%	0,45%	0,35%	0,43%	0,37%	0,45%
Time of disintegration	1mn17s	1mn31s	30 s	31 s	40 s	2 mn 39 s	16 s
Wettability test							
Absorbed water (%)	49,03	44,22	41,05	44,08	43,44	35,03	45,28 %
Wetting time	541 s (9mn 1s)	870 s (14mn 30s)	51 s	50 s	259 s(4 mn 19s)	591 s (9 mn 51 s)	17 s

The first six placebos trials would be used to select an optimal matrix to which the active ingredient would be associated.
At the end of this work a formula of a matrix with rapid disintegration was developed.

The quantitative formulas were adapted to the equipment and to the operating conditions available on the laboratory scale because of the satisfactory control results.

The manufacturing process chosen was compression after wet granulation to improve the rheology of the mixture to access the compression. The operating conditions were not modified. They were taken from the literature and previous works.

A rapid disintegration matrix with AI was obtained with a disintegration time of 16 s and a hardness of 4.95 Kp and friability of 0.45%.

It is recommended to the CRD to validate the optimal formula, masking the taste of the active ingredient, the biopharmacy test, the toxicological test and the stability studies to move to a production scale.

Finally through this work the path of a formulation as a first step towards production was perceived. It was also an opportunity to face the true industrial field, particularly the research and development, aspects.

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