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Formulation and Evaluation of Dispersible Tablet of Furosemide for Pediatric Use

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***Abstract*—**The objective of this work is to formulate a dry dispersible form of furosemide in the context of pediatric dose adjustment. To achieve this, we have produced a set of formulas that will be tested in process and after compression. The formula with the best results will be improved to optimize the final shape of the product. Furosemide is the most widely used pediatric diuretic because of its low toxicity. The manufacturing process was chosen taking into account all the data relating to the active ingredient and the excipients used and complying with the specifications and requirements of dispersible tablets. The process used to prepare these tablets was wet granulation. Different excipients were used: lactose, maize starch, magnesium stearate and two superdisintegrants. The mode of incorporation of super-disintegrant changes with each formula. The use of super-disintegrant in the formula allowed optimization of the disintegration time. Prepared tablets were evaluated for weight, content uniformity, hardness, disintegration time, friability and *in vitro* dissolution test.

***Keywords*—**Formulation, dispersible tablets, wet granulation, superdisintegrants, disintegration.

I. Introduction

MANY drugs are only available in adult dosage form, therefore the administration of an accurate dosage for children is critical [1], [2]. To reduce the dosage of adult dosage forms for pediatric use is at the hospital level either by crushing the tablets in a mortar or by opening capsules. Therefore, children are often given drugs whose dosage form is not suitable for them. This practice may jeopardize the efficacy and safety of the treatment. Over these last years, WHO and UNICEF have joined efforts to promote the development of pediatric pharmaceutical formulations for children of various ages, including dispersible tablets disintegrating in water or a small amount of breast milk. The drugs most prescribed by pediatricians are for the cardiovascular system and account for 70% of the dosage adjustment requests from the pediatrics service of Béni Messous Hopsital. Between 2012 and 2014, 1605 dosage reduction requests for Furosemide. This number increased by 10% and reached 1765 requests [3]. The dose is 5 mg, following a statistical study carried out in collaboration with pediatricians. The use of dispersible tablets for reconstitution is a good way in pediatrics formulation as a solid pharmaceutical form offers greater stability compared with a formulated liquid.

The dispersible tablets are uncoated tablets or film-coated tablets intended to be dispersed in water before administration, giving a homogenous dispersion. The tablets must disintegrate in water in less than 3 minutes; the dispersed particles must be fine enough to pass through a mesh of maximum mesh of 710 µm [4], [5].

In pediatrics, dispersible tablets have the advantage of being used in very young children (0-6 months). For their administration they require only a minimum quantity of water, as they can be dispersed in breast milk.

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II. Materials and Methods

A. Materials

Furosemide was obtained as gift sample fromHongkong Yuancheng Gongchuang Tec, Lactose was obtained as gift sample fromChina Meheco), Starch maize, Croscarmellose, Crospovidone and Magnesium stearate were obtained as gift sample from Roquette.

B. Methods

1.Formulation of Dispersible Tablets of Furosemide

The present work consists of formulation of a dispersible tablet of furosemide dosed at 5 mg for use in pediatrics [6]. It is a dry pharmaceutical form comprising a binding agent, a binding agent, one or two disintegrating agents and a lubricating agent. Dispersible tablets usually disintegrate within three minutes when placed in water or in a small amount of breast milk. In order to optimize this disintegration time, two superdisintegrants have been introduced into the formula.

Four formulas were prepared. For formula F1 and F2, one disintegrant was used at time. On the other hand, for formulas F3 and F4 two disintegrants were used by varying their mode of introduction into the internal or external phase (Table I).

The tablets were prepared by a wet granulation process. In this formulation, the maize starch was used as binder; it has the advantage to having a dual role: Binding and disintegrating. The use of corn starch as a binder in the formula is intended firstly to produce a dense grain having a good flow facilitating compression, and secondly to improve the disintegration of tablets and by therefore accelerate the kinetics of release of the active ingredient [7]-[9], [10].

All manufactured formulas are evaluated to select the optimal formula.

All the raw materials (except lubricant) were passed through sieve 500 µm separately, then weighed and mixed in a granulator mixer Lödige for about 10 min. The binder solution is prepared by dispersing maize starch in water at a

concentration of 5%. The amount of maize starch weighed for each formula is dispersed in a sufficient volume of distilled water heated prior to 90 °C. Mix the preparation for 10 minutes. The binder solution is poured into the powder mixture. Once the dispersion of binder solution is complete, maintain agitation for 1 min.

TABLE I
DIFFERENT FORMULAS USED IN FORMULATION OF DISPERSIBLE TABLETS OF FUROSEMIDE

Ingredients	F1	F2	F3	F4
Lactose	73%	73%	68%	68%
Starch Maize	20%	20%	20%	20%
Crospovidone	5%	-	5%	5%
Croscarmellose	-	5%	5%	5%
Magnesium Stearate	2%	2%	2%	2%

The wet mass was passed through 1 mm sieve and the wet granules obtained are dried at 50 °C in the hot air oven. The dried granules were passed through 600 µm sieve. The lubricant was added to the mixture and mixed for about 2 min. Finally, an amount of the blend was compressed into tablets of 50 mg using 6 mm round flat punches using two stations alternative tablet machine (FROGERAIS).

C. Control of Granules

1.Flow Test

This test was carried out according to the European pharmacopoeia 8th Edition. Using the chronometer, we measure the time taken by 100 g of powder to flow through a standardized funnel. The flow time must be less than 10 seconds. Otherwise, a modification of the formula or the manufacturing process must be considered [11].

2.Compressibility: Carr's Index

A sample of 100G of formulas granules was introduced in to a volumetric cylinder to occupy a volume (V_0) and the volume of powder was measured after 10 settlements (V10), 500 settlements (V500) and after 1250 settlements (V1250). The Carr's Index was calculated using:

$$\text{Compressibility Index} = 100 \times (V_f - V_0) / V_0$$

The Carr's index informs us about the compressibility of powder. Carr has established a qualitative correspondence between the value of the compressibility index and the flowability of a grain.

TABLE II
COMPRESSIBILITY AND FLOWABILITY PROPERTIES OF POWDERS

Carr's Index (%)	Flowability
5-11	Excellent
12-17	Good
18-22	Fair
23-28	Poor
29-34	Very poor
>35	Extremely poor

3.Particles Sizes

The granulometric analysis was carried by the sieving method. We superimpose 8 sieves (bottom receiver, 90 µm, 125 µm, 180µm, 250 µm, 355 µm, 500 µm, 710 µm, 1000 µm). A sample of 100 g of granule is placed on the upper sieve. The apparatus is shaken for 10 minutes. The granules will be distributed on the different sieves according to their size. The difference in weight between the empty sieves and the sieves after analysis gives the percentage of refusal on each sieve. The histogram giving the percentage of refusal on each sieve is plotted as a function of the mesh size of the sieves.

D. Evaluation of the Prepared Tablet

All the tablets were evaluated for the following parameters:

1.Weight Variation

Randomly, 20 tablets were selected after compression and the mean weight was determined. The variations in average weight results should not exceed 10%.

2.Hardness

The crushing strength of the tablets was measured using a PHARMATEST hardness tester. 10 tablets from each formulation batch were tested randomly and the average reading was recorded.

3.Friability

20 tablets were weighed and placed in an ERWEKA friabilator and the equipment was rotated at 25 rpm for 4 min. The tablets are recovered from the drum and weighed again. The determination of friability rate of the tablets is according to:

$$PercentFriability = \frac{(FinalWeight - InitialWeight)}{InitialWeight} \times 100 \quad (1)$$

4.*In vitro* Disintegration Time

The disintegration time is the time required for the tablet to disintegrate without leaving a palpable mass in the disintegrating apparatus. This time is expressed in seconds or minutes.

The test is carried out using as medium distilled water at 37 °C. Six tablets were placed individually in each tube of disintegration test apparatus. The values reported are mean ± standard deviation.

5.*In vitro* Dissolution Studies

In vitro dissolution studies were performed only for the optimum formula by using type apparatus 2 at 50 rpm/min and 900 ml of phosphate buffer pH 5.8 was used as dissolution medium. The dissolution test is carried out at 37 ± 5 °C. A sample of 10 ml is taken from the dissolution medium at specific time intervals. Absorption of filtered solution sample was read by UV-Visible spectrophotometer at λ=277 nm.

III. RESULTS AND DISCUSSION

Furosemide tablets were prepared by wet granulation

method. Four formulas were prepared using different superdisintegrants. All batches of the tablets were evaluated for various pre and post compression parameters. Table III shows the data obtained from the pre-compression examinations of the tablets which includes flow test and Carr's Index. The post compression parameters such as hardness, friability, disintegration time were evaluated.

The results of flowability studies of the granules reveal acceptable flowability for tablet represented by the flow test and Carr's Index. The Values were listed in Table II.

TABLE III
RESULTS OF CONTROL GRANULES

Formula no	Flow test (Second)	Carr's Index
F1	10	14
F2	12	18
F3	8	22
F4	6	11

The results presented above show satisfactory flow except for the formula F2. The granules of formulas F1 and F2 have good compressibility properties. On the other hand, those of the formula F3 have an average compressibility. The granules of formulas F4 have excellent compressibility.

The granulometric analysis of the various formulas shows a homogeneous distribution of the particle size for formulas F1 and F4. However, the of formulas F2 and F3 shows a heterogeneous distribution with a high fines content of greater than 20%.

The post compression parameters of all prepared tablets are reported in Table IV.

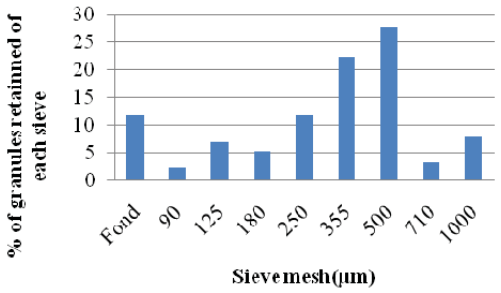

Fig. 1 Particle size distribution of granules of formula F1

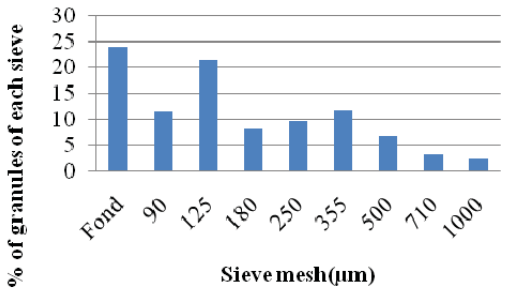

Fig. 2 Particle size distribution of granules of formula F2

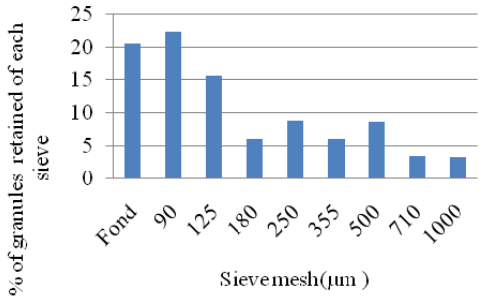

Fig. 3 Particle size distribution of granules of formula F3

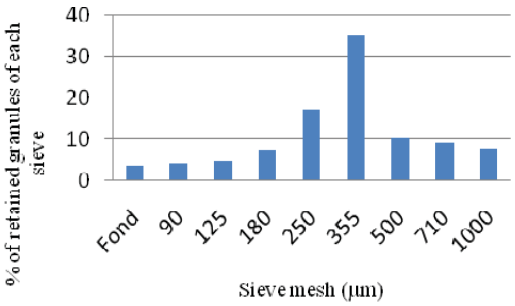

Fig. 4 Particle size distribution of granules of formula F4

TABLE IV
RESULTS OF CONTROLS OF PREPARED TABLETS

Formula	Weight Variation	Hardness	Friability	Disintegration time
F1	49,7	6,4	0,77	2min52sec
F2	50,2	4,7	0,89	2min57sec
F3	52,5	3,1	1,1	1min
F4	51,3	8,3	0,66	1min10sec

The results of controls carried out on the tablet are satisfactory to the standard of pharmacopeia except for formula F3. The tablets obtained with formula 3 were friables. The disintegration time is less than 3 min for all the formulas.

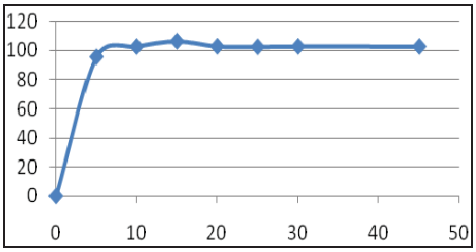

Fig. 5 Dissolution profile of optimum formula F4

The results of dissolution study (Fig. 5) show that the release of Furosemide from selected formula F4 and conventional tablet shows release of 100 less than 15 min.

IV. CONCLUSION

The development of tablets is delicate and requires a thorough knowledge of the physical and mechanical properties of powdered raw materials, because these tablets result from

the transformation of a powder or a granule into a tablet, something that is not in all the easy cases. Indeed, the powder or the granules to be compressed must have particular physical and mechanical properties:

- A good flow;
- An agglomeration under pressure.

Now the granule or the powder rarely spontaneously exhibit these properties, in practice the vast majority of the active ingredients require both the addition of adjuvants and a special treatment: granulation, to obtain the two essential qualities of tablets:

- Sufficient cohesion between the grains;
- A fast disintegration.

In view of the results obtained from all the tests carried out, the formula the formula that meets the criteria mentioned above is F4.

Formulation of dispersible tablet of furosemide for pediatric by wet granulation method using two superdisintegrants Crospovidone and Croscarmellose sodique allowed the application of the tablets having exhibited fast disintegration time with good mechanical properties.

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