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FORMULATION OF A RAPIDLY DISINTEGRATING MATRIX USED FOR THE FORMULATION OF ORODISPERSIBLE TABLET

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ABSTRACT

Objective: The purpose of the present research was in the first part : to study the effect of several superdisintegrants separately (croscarmellose sodium and sodium starch glycolate, crospovidon, starch pre-gelatinized, low substituted hydroxypropylcellulose (HPC-L), in order to select the best superdisintegrants on the mouth dissolving property of piroxicam tablets. The second part of this research is the formulation of a rapidly disintegrating matrix composed of two disintegrating (crospovidon, croscarmellose) used previously. **Methods: T**otal five formulations (F1 to F5) were prepared by direct compression method. The final blend of the drug and excipients were evaluated for the powder flow properties, residual moisture, angle of repose, compressibility index and hausner's ratio. All the formulations tablets were evaluated for the weight variation, disintegration time *in vivo* and *in vitro*, hardness, friability, wetting time and water absorption ratio. **Results:** The results show that the presence of superdisintegrants is desirable for the orodispersion. The best result is one of the tablets which is formulated with the pre-gelatinized starch with a time of less than 30 s followed by the tablet containing crospovidone with 34 s. The disintegration time of the tablet containing a higher concentration of crospovidone (F7) is improved by more than 9 seconds compared to the first tablet containing crospovidone and 5 seconds compared to the tablet formulated with pre-gelatinized starch. The disintegration time of the tablet containing the mixture of the bad desintegant (croscarmellose sodium) and the best one (crospovidone) is improved by 11s compared to the tablet containing croscarmellose sodium**. Conclusion:** It was concluded that the crospovidone gives the best desintegration, and the increase its concentration improved its performances, as well as association from two desintegrationg in a rapidly desintegrating matrix giving excellent results.

INTRODUCTION

Pharmaceutical industry is going through a difficult period these last years It is indeed confronted with the increasingly competition of generic drugs. Besides this financial pressure, the pharmaceutical industry must meet the requirements and needs for the patients especially with regard to the route of administration; for

the dry forms more precisely, more than half of the population suffers from the problems of swallowing especially the children, who did not have until very recently their own drugs. By using the drugs developed for the adults, not only the administered doses could be approximate, but the existing dosage forms were badly adapted. This could raise the headache to ensure a good observance of the drug, leading to a change with the development of tablet with oral disintegration [1, 2]; it is a solid posological form which disintegrates and dissolves in the mouth in less than 3 min, under the tongue or in the oral cavity and not need water [3] at the time of the drug. the novelty of this study, is to improve the quality of certain disintegrants (such as sodium crosscarmellose) by forming a rapidly disintegrating matrix composed of the latter with another disintegrating having super power used at low concentration to rationalize its quantity in the formula. For this purpose, the objective of the present research is focused on the the effect of several disintegrants separately (croscarmellose sodium and sodium starch glycolate, crospovidon, starch pre-gelatinized, low substituted hydroxypropylcellulose (HPC-L), in order to select the best and the bad disintegrants on the mouth dissolving property of Piroxicam tablets matrix. The second part is devoted to the formulation of a rapidly disintegrating composed of two disintegrating used previously (the bad and best one).

MATERIALS AND METHODS

Materials: Piroxicam was procured from Amaratal and Co. Chennai, India. Crospovidone, Magnesium stearate and Pregelatinized starch were procured from Loba Chemie., pvt. Ltd, Mumbai, India. Sodium starch glycolate, microcrystalline cellulose and low substituted hydroxypropylcellulose were provided from S.d finechem., Pvt. Ltd, Mumbai, India.

Methods:

Formulation of Piroxicam orodispersible tablets: Different formulas were prepared as shown in Table .1. Formulas (F1- F7) were prepared by direct compression method in which all constituents were mixed and directly compressed. The first part relates to the formulation of 5 preparations (F1 to F5) of orodispersible tablets of Piroxicam using five different superdisintegrants namely crospovidone, sodium starch glycolate, pregelatinized starch, croscarmellose sodium and low substituted hydroxypropylcellulose (HPC-L) with the same concentration (5%). The second part of this consists in proposing two other formula, the formulation F6 contains croscarmellose sodium and crospovidone as superdisintegrant in 5%, concentrations, finally the formulation F7 contains crospovidone as superdisintegrant, like F5 but at a concentration of 10% concentrations. All the ingredients were sieved through 60-mesh sieve separately and collected. The drug and the ingredients were weighed and mixed in geometrical order. as show at the fig. 1, the tablets were compressed using 14 mm flat- face surface punch tablet rotary compression machine (Karnavati , Mehsana, Gujarat, India) to get tablet of 600 mg weight. The drug, superdisintegrant, was ground in a agate mortar and pestle to get a uniform mixture (Mixture 1). Then, the mixture is filtered in order to destroy any existing agglomerate.

An equal quantity of avicel is added to the mixture 1, once the homogeneous powder is filtered, this operation is repeated until the exhaustion of of Avicel. A first half of lactose is introduced in a polyethylene bag followed by the mixture (drug, superdisintegrant, avicel), then one introduces the second half of lactose. The powders were mixed during 10 min.. This new mixture was lubricated by using magnesium stearate and mixed during further 5 min ; the final mixture was ready for the compression.

Evaluation of powder blend: All the pre-compression parameters such as the bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio were measured by the following standard procedure:

Residual moisture of the powders: By using an infra red dessicator (Sartorius modèle MA150,Groosseron, French), the residual water content of each mixture of powders was increased, 4 g of powder was placed on a base, the device has been programmed not to exceed 105 °C the analysis lasts between 4 and 6 min. The water content of the powders w% was displayed on the screen

Angle of repose: The angle of repose for the powder blend was determined by the funnel method [4]**.** The weighed accurate quantity of powder blend was taken in a funnel (Fig 2). The height of the funnel was adjusted in such a way that its tip just touches the heap of the powder blend. This allowed to flow through the funnel freely onto the wooden surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation: $\theta = \tan^{-1}\left(\frac{h}{r}\right)$

Where 'h' and 'r' are the height and radius of the cone respectively

Bulk Density: Bulk density ρ_b is defined as the mass of the powder divided by the bulk volume, expressed as g/cm^3. Weighed quantity of powder blend from each formulation (100g) was taken in a measuring cylinder (20 ml capacity) and the initial volume of the powder blend (Vb) in the measuring cylinder was noted [5]. This was calculated by using the formula $\rho_b = \frac{M}{V_b}$

Where ρ_b is the bulk density, M the weight of the sample in g, V_b the volume of the blend (m^3).

Tapped density: It is the ratio of total mass of the powder to the tapped volume of powder. The latter was measured by tapping the powder blend for 1250 times using a settling volunometer (**Erweka SVM, Germany)**. [6]**.** The tapped density was calculated by using the following formula

$\rho_t = M / V_t$

Compressibility index and hausners ratio: The compressibility index of the powder blend was determined ~~by~~ from the Carr's compressibility index and the Hausners ratio is calculated by using the formula [7]. Hausner's ratio = ρ_t / ρ_b

The Hausner's ratio < 1.25 indicates better flow properties than higher ones > 1.25 [8].

Carr's index (%) $= 100 * \frac{\rho t - \rho b}{\rho t}$

Value below 15% indicates that the powder gives rise good flow characteristics, where values above 25% indicates rather a poor flowability [6].

***In vivo* disintegration test:** Six human volunteers were involved in the determination of the disintegration time for each tablet formula; the time required for complete disintegration of the tablet when placed on the tongue was determined by using a chronometer [13].

RESULTS AND DISCUSSION

Evaluated for powder flow properties:

The final blend of excipients was evaluated for the powder flow properties, compressibility index and Hausner ratio. The precompression parameters, evaluated within the prescribed limits, indicated a good free flow property (Table. 2). The results show that the residual moisture of the powder is less than 2% and therefore the powders did not cause any sticking problem during the compression. The results (Table 2) also show that the combination of the two disintegrants (Croscarmellose sodium and Crospovidone as super-degrading at 5% concentrations) in Formulation No. 6 did not improve the flow properties, whereas the increase in the concentration of Crospovidone in formulation No. 7 improved the flow.

Evaluation of orodispersible piroxicam tablets: The Data obtained on the post-compression parameters such as the hardness, friability, *in vivo* and *in vitro* disintegration time, wetting time and water absorption rate are presented in Table. 3.

In all formulations, the friability values, less than 1% and are in the respected limit of the United States Pharmacopoeia USP. The results of the disintegration time (VDT) of all formulations were found to be within the prescribed limits and meet the criteria of orodispersible tablets. The values found are in the range (25 - 39.3 seconds). The best result is obtained with the tablet formulated with the pre-gelatinized starch with less than 30 seconds, followed by the tablet containing crospovidone with 34 seconds. This result is consistent with the work of Lokendra S C *et al*. [16] which concluded that the optimum effect of desintegration time for orodispersible tablet is shown for crospovidone et Sodium starch glycolate. Conversely, the longest disintegration time is that of the tablet containing HPC-L exceeding 39 seconds. The results show that the wetting time of tablets formulated with sodium starch glycolate and croscarmellose sodium are significantly higher than others, exceeding one minute. The lowest wetting time is that of the crospovidone-containing tablet which equals 30 seconds, which is consistent with work of Kumara Swamy. S *et al* [17]. From the foregoing it has been noted that pre-gelatinized starch has the best disintegration time, it is recognized to be the earliest tablet disintegrant used nowadays [18,19], however the crospovidone has the best wetting time. This can be explained by the fact that the disintegration mechanism of crospovidone functions in part by capillarity [20,21] and shape recovery. In the opposit of pre-gelatinized starch which functions exclusively by swelling with gel formation [22] , which facilitates the ascent of the water through the pores of the tablet. The results of the water absorption rates clearly show that the croscarmellose tablet absorbs a large amount of water compared to the rest of the tablets. The tablets formulated with crospovidone stand out for their very low water absorption rates. The results show that the most water-absorbing tablets are not necessarily the ones that break down the fastest. The results for *In Vivo* disintegration time (T.D *In Vivo*), show that the disintegration of crospovidone-formulated tablets is achieved in a minimum of time compared to other tablets. The results agree well with those of the wetting time of the tablets. According to the results obtained from the *In Vitro* disintegration test, the formula containing pre-gelatinized starch as disintegrant appears to be optimal. However, The *In Vivo* wetting and disintegration tests show the formula containing crospovidone is better, with significantly lower times than the other tablets. The water absorption rate shows that the crospovidone-containing tablets are not very hydrophilic compared to croscarmellose-containing tablets. The results also indicate that the least water absorbing tablets give better results in the disintegration; this can be explained by the disintegration mechanism used by different disintegrating agent. After consulting the results, the crospovidone appeared as the disintegrator giving the best performances. However, a question remains open, in the case of a fast disintegrating matrix or increasing the concentration of the disintegrating agent in the formulation. Do these changes affect the previous results? This is why, in another formulation (F7) the concentration was increased in order to know its influence on the tablet disintegration. Also, an association of crospovidone and croscarmellose in the same formulation was carried out (F6), with the aim of proposing the formulation of a fast disintegrating matrix containing crospovidone and sodium croscarmellose. The experimental results obtained for the two new formulas (F6 = Crsmi+ crsp, F7= crsp II) is illustrated in Fig. 2. The disintegration time of the tablet containing a higher concentration of crospovidone (F7) is improved by more than 9 seconds compared to the first tablet containing crospovidone and 5 seconds with respect to the tablet formulated with pre-gelatinized starch.

Table No 1: Composition of different formulas

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
Piroxicam	20	20	20	20	20	20	20
Croscarmellose sodium	30	-	-	-	-	15	-
Low substituted hydroxypropylcellulose	-	30	-	-	-	-	-
Pregelatinized starch	-	-	30	-	-	-	-
Sodium starch glycolate	-	-	-	30	-	-	-
Crospovidone	-	-	-	-	30	15	60
Microcrystalline cellulose (Avicel 102)	156	156	156	156	156	156	156
Lactose tablettose	388	388	388	388	388	388	388
Magnesium Stearate	6	6	6	6	6	6	6

Formulations Fl, F2, F3, F4 and F5contains one superdisintegrant at 5%, Formulation F6 contain Croscarmellose sodium and Crospovidone as superdisintegrant in 5%, concentrations. Formulations F7 contain Crospovidone as superdisintegrant, like F5 but with 10%.

Table. No 2: Evaluation of the powder mixture

Formula Number	Residual moisture (w%)	Angle of repose (°)	Compressibility Index (%)	Hausner's ratio
F1	1.63±0.022	32.83±0. 26	26.19±0. 42	1.35±0. 020
F2	1. 37±0.040	32.86±0.18	23.80±0. 50	1.31±0. 036
F3	1.90±0.014	31.85±0.30	27.90±0. 30	1.38±0. 055
F4	1.51±0.031	31.81±0.32	23.80±0. 50	1.30±0. 060
F5	1.16±0.036	28.77±0.96	25.00±0. 32	1.33±0.0 15
F6	1.12±0.042	30.53±0.34	27.50±0. 26	1.37±0. 042
F7	0.75±0.056	30.12±0.21	22.50±0. 86	1.29±0. 018

Table. No 3: Evaluation of orodispersible piroxicam tablets.

Formula number	Hardness (N)	Friability (%)	VDT (s)	*In Vivo* disintegration time (s)	WAR (%)	WT (s)
F1	80±0.56	0.10±0.038	35.5±0.69	37.20±0.76	85.78±0.99	65±0.12
F2	80±0.45	0.01±0.002	39.3±0.56	27.80±1.12	71.40±1.73	59±0.45
F3	80±0.65	0.07±0.087	29.6±1.13	27.45±1.35	68.83±1.59	48±0.78
F4	80±0.22	0.03±0.048	38.0±0.26	33.25±1.07	74.33±1.66	63±0.13
F5	80±0.16	0.01±0.018	34.3±0.83	20.82±1.89	59.46±1.98	30±1.98
F6	75±1.80	0.19±0.0 22	28.9±1.76	27.00±1.69	72.43±1.08	56±0.38
F7	79±1.10	0.09±0.029	25.0±1.96	21.00±1.85	64.16±1.89	32±1.66

* All values are expressed as mean±SD, n=5.

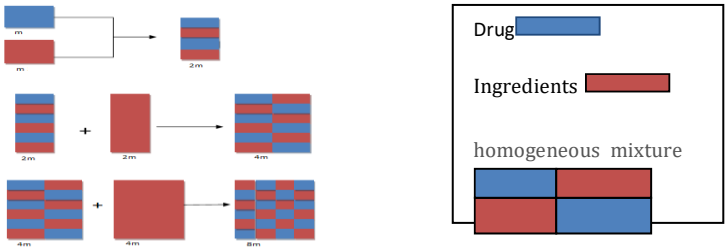

Fig. 1: Diagram of the protocol of mixture of the powders

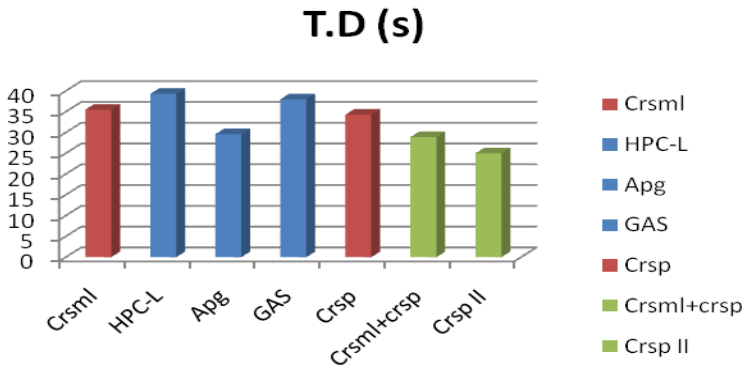

Fig .2: Comparaison disintegration time for the 7 formulas

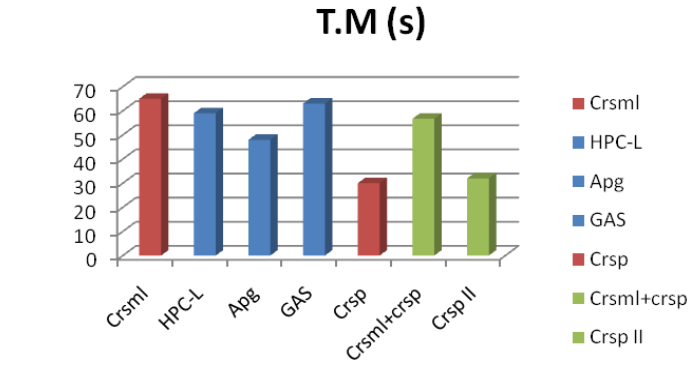

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Fig .3: Comparison of wetting time for the 7 formulas

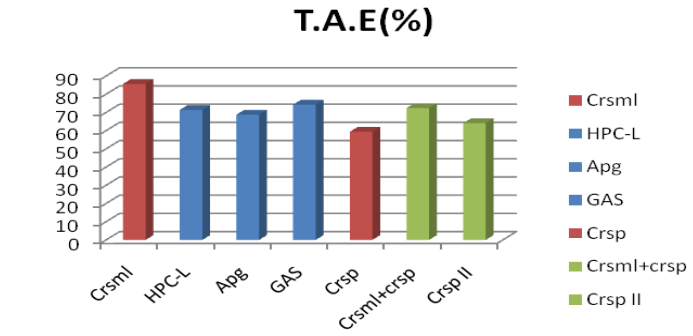

Fig. 4 : Comparison of water absorption rate for the 7 formulas

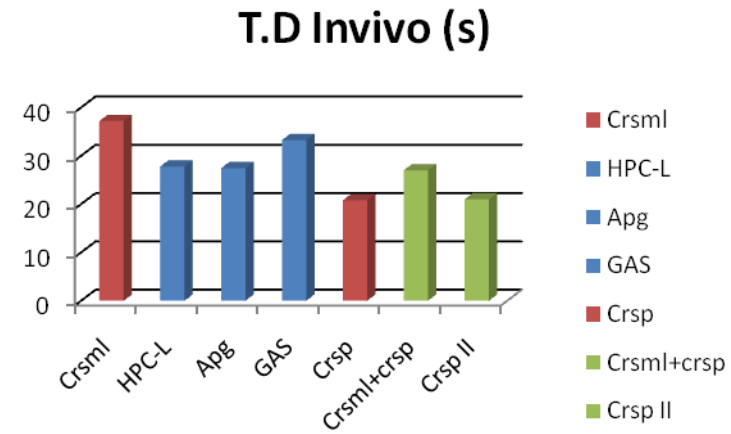

Fig. 5: Comparison of disintegration time *In Vivo* for the 7 formulas

The time of disintegration of the tablet containing both disintegrants, croscarmellose and crospovidone (F6), is improved compared to the two tablets containing the two disintegrating separately. The wetting time of the tablet formulated with the mixture of the two disintegrators is slightly smaller than that of the tablet containing only croscarmellose, but remains quite significant compared with the wetting time of the tablet containing crospovidone. Fig.3 shows the improvement of this time. The wetting time of the second tablet containing crospovidone is not different from that of the first one, increasing the concentration in the tablet did not affect the wetting time of the tablet. The water absorption rate of the tablet containing the two disintegrating agents is lower than that of the tablet containing croscarmellose alone, it is also higher than the one of the tablet containing only crospovidone, the influence of the two action mechanisms of the various disintegrants is felt, one of them proceeding by swelling and the other by capillarity the mass of water absorbed by the tablet or both tablets are associated, and therefore less than that absorbed by the croscarmellose tablet. Fig. 4 shows the difference in the water content absorbed by the different tablets. The second crospovidone tablet has absorbed more water than the first one but remains lower than the other water masses absorbed by different tablets. Fig. 4, shows the difference concerning the water absorption rate. The *In Vivo* disintegration time of the tablet where the two disintegrants are associated is lower than the croscarmellose tablet but remains higher than that of the crospovidone Fig. 5 shows the difference between these different formulas. The previous figure put forward the improvement of the crospovidone II (F7) tablet compared to the first crospovidone-containing tablet (F5). The *In Vivo* disintegration times of the crospovidone tablets are essentially the same and there has been no improvement due to the increase in disintegrating agent concentrations.

CONCLUSION

The results showed that the presence of a superdisintegrants is desirable for orodispersion. The best result was obtained on the tablet which is formulated with the pre-gelatinized starch with a time less than 30 s followed by the tablet containing crospovidone with 34 s. The disintegration time of the tablet at higher crospovidone concentration (F7) is improved by more than 9 s compared to the first tablet containing crospovidone and 5 s compared to the tablet formulated with pre-gelatinized starch. The disintegration time of the tablet containing the mixture of the bad desintegant (croscarmellose sodium) and best one (crospovidone) is improved by 11 s compared to the tablet containing croscarmellose sodium. Combining the two disintegrators gave good results, the improvement of the *In Vivo*, *In Vitro* disintegration times and wetting time of the tablet containing the two disintegrating tablets compared to the croscrmellose-containing tablet, in the opposite of the tablet containing only crospovidone. The influence of both disintegrants and their mechanisms of action ~~is~~ observed on the obtained results. Increasing the disintegrating agent for the tablet having a high concentration of crospovidone induced no change except for the *In Vitro* disintegration time and the water absorption rate. The disintegrating power of crospovidone did not depend much on its concentration in the tablet.

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