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Formulation, Evaluation and Optimization of Orally Disintegrating Tablet of Piroxicam

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Abstract: Objective of this study was to formulate directly compressible orally disintegrating tablets of piroxicam with sufficient mechanical integrity, content uniformity, and acceptable palatability to assist patients of any age group for easy administration. Effect of varying concentrations of different superdisintegrants such as crospovidone, croscarmellose sodium, and sodium starch glycolate on disintegration time was studied. Tablets were evaluated for weight variation, thickness, hardness, friability, drug content, in vitro disintegrating time, wetting time and in vitro drug release. The results of disintegration time and wetting time of tablets prepared using crospovidone was significantly superior compared to other two superdisintegrants evaluated. Release of drug was quick from formulations containing 7% crospovidone (F8) compared to the other orally disintegrating tablet prepared. Differential scanning calorimetric studies did not indicate any excipients incompatibility, either during mixing or after compression.

Keywords: Orally disintegrating tablets, piroxicam, crospovidone, croscarmellose sodium, sodium starch glycolate.

Introduction

Recent developments in the technology have prompted scientists to develop orally disintegrating tablets with improved patient compliance and convenience. ODTs are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing and water.[1] orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. Additionally, pediatric patients may suffer from ingestion problems as a result of underdeveloped muscular and nervous control.[2, 3] Moreover, patients traveling with little or no access to water, limit utility of orally administered conventional tablets or capsules.[4] Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action.[5] Moreover,drug candidates that undergo pre-gastric absorption when formulated as ODTs may show increased oral bioavailability.[6] It provides good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients.[7] It is easy to administer for pediatric, geriatric, and institutionalized patients (especially for mentally retarded and psychiatric patients). Many technologies have come up for fast dissolve tablets like Zydis, OraSolv, DuraSolv, FlashTab and WowTab.Technologies like Zydis, FlashTab have resulted in tablets with a very low disintegration time, but poor mechanical strength.[8,9] On the other hand, techniques like OraSolv, DuraSolv have resulted in products with sufficient mechanical strength but a comparatively longer disintegration time [10].

In the present research work, orally disintegrating tablets of piroxicam is formulated using wet granulation technique. Piroxicam is a NSAID (Non-steroidal anti inflammatory) drug, analgesic and anti-pyretic drug which use in Musculo-skeletal disorders like osteoarthritis. Piroxicam has bad taste and has the half life of 30hr and has poor water solubility. So in case of pain, osteoarthritis, gout it required immediate

release of drug from the dosage form, which make piroxicam suitable candidate for the orally disintegrating tablets. [11]

Materials and Method

Piroxicam was gifted from the Sifavittor, Italy. Mannitol, Sodium starch glycolate was purchased from the Roqutte pharma, Nasik India. Cross carmellose sodium was gifted from the FMC biopolymer, Shangai, China. Crospovidine XL was gifted from the ISP petrochemicals. Aspartame Fine grade, Nutra sweet, India and Magnesium stearate were gifted from the Dr. paul Lohman.

Preparation of ODT Tablets

Sift all intragranular ingredients through the 30#. Aspartame was passed through 30# and magnesium stearate was passed through 60#. Mixed all intragranular ingredients in rapid mixer granulator for 10 minute where, impeller at 150 rpm. Granulation was carried out with water in rapid mixer granulator for 1 minute with the help of impeller at 150 rpm. Kneading was given by chopper for proper granulation of materials at 1500 rpm. Granules were dried in the rapid dryer for 20 to 30 minute at 60 to 65˚C. Dried granules were sifted through 30#. Sodium starch glycolate or Croscarmellose sodium or Crospovidone XL was added in dried granules and mixed for 10 minute in conta blender at 18 rpm. Aspartame was added to above blend and mixed for 5 minute in conta blender at 18 rpm. Magnesium stearate was added to above blend and mixed for 5 minute in conta blender at 18 rpm. 5.5 mm round FFBE (flat faced beveled edges) punch was used during compression. The tablet was prepared using a Rotary compression machine (Cadmach, Ahmadabad, India)

Evaluation parameters of prepared piroxicam ODT

Compatibility study (Differential Scanning Calorimetry analysis)

DSC study was carried out using DSC-60 instrument (M/s Shimadzu, Japan) to check the compatibility of ingredients. DSC thermo grams of pure drug (piroxicam), superdisintegrants Sodium starch glycolate, croscarmelllose sodium and crospovidone XL, Aspartame, mannitol and magnesium stearate were individually taken for their identical endothermic reaction. Finally physical mixture of all above ingredients was scanned for DSC.

Uniformity of weight

The weights of 20 tablets and individual as well as was carried out using mettler toledo PG-403 S.

Crushing Strength

A significant strength of ODT is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of crushing strength for an ODT is usually kept in a lower range to facilitate early disintegration in the mouth. The crushing strength of the tablet may be measured using conventional hardness testers.

The crushing strength of the tablets was measured using Dr. Schleuniger pharmatron model SY hardness tester[12].

Friability of tablet

To achieve % friability within limits for an ODT is a challenge to the formulator since all methods of manufacturing of ODT are responsible for increasing the % friability values. Thus, it is necessary that this parameter should be evaluated and the results are within bound limits (0.1-0.9%).

Friability test was done using Roche friability tester. Friability of the tablet determined using Roche friabilator (Electrolab USP friabilator). This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25rpm and dropping a tablet at 1 height of 6 inches in each revolution. Preweighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were de-dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula[12].

$$\%\ Friability = \frac{W_0 - W}{W_0} \times 100$$

Wetting time

For measurement of wetting time five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimeters of water-containing Eosin, a water-soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time[12].

Modified disintegration test

For measurement of disintegration time, a petridish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of petridish and the time for the tablet to completely disintegrate into fine particles was noted[13].

In- vitro dissolution test

USP dissolution apparatus 1 and 2 can be used. USP 1 Basket apparatus may have certain applications, but sometimes tablet fragments or disintegrated tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible dissolution profiles. Kancke proposed USP 2 Paddle apparatus, which is the most suitable and common choice for ODTs, with a

paddle speed of 50 rpm commonly used. Typically, the dissolution of ODT is very fast when using USP monograph conditions; hence, slower paddle speeds may be utilized to obtain a profile. The release rate piroxicam from orally disintegrating tablets was determined using United State Pharmacopoeia (USP) dissolution testing apparatus II (paddle method, Electrolab, TDT-06T, Mumbai, India). The dissolution test was performed using 900 ml of 0.1 N HCl ($_P$H=1.2), at 37 ± 0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at 5, 10, 15, 20, 30, 45 and 60min. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a 0.45 µ membrane filter. Absorbance of these solutions was measured at 333 nm using a Shimadzu UV-1700 UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve[14].

Accelerated stability study of best batch

In order to determine the change in in-vitro release profile on storage, stability study of optimized batch was carried out at 40^0 C in a humidity chamber having 75% RH. Sample were withdrawn after three-week interval and evaluated for change in in-vitro drug release pattern, hardness and disintegration time.

Result and Discussion

Compatibility study (Differential Scanning Calorimetry analysis)

DSC curves obtained for pure piroxicam, SSG, croscarmellose sodium, crospovidone, mannitol, Aspartame, magnesium stearate and physical mixture of all ingredients were shown in figure 4.2. Pure powdered piroxicam showed a sharp melting endotherm at 197.41 °C. DSC scan of mannitol, Aspartame showed sharp endotherm at 168.30°C, 191.80°C & 254.86°C, 194.10°C respectively due to melting whereas during scanning of SSG, croscarmellose sodium, crospovidone and magnesium stearate, melting endotherm at 86.46°C, 96.11°C, 88.52°C, 96.25°C and 116.14°C were observed respectively. DSC thermograms of physical mixture of drug and excipients showed the melting peak of the drug at 197.41°C and broad endothermic peak at 116.94°C. Physical mixture of all above ingredients showed their identical peaks at defined temperature range. Presence of all peaks indicates that all ingredients are compatible with drug means there is no incompatibility between the selected ingredients

Evaluation of precompression properties

For each designed formulation, blend of drug and excipients was prepared and evaluated for precompression properties shown in table 2. Bulk density was found to be between 0.44±0.01 to 0.60±0.02gm/cm^3 and tapped density between 0.61±0.01 to 0.75±0.01 gm/cm^3 for all formulations. From density data % compressibility was calculated and was found to be between 14.51±0.01percent to 25.8±0.04 percent. Angle of repose was found to be in the range of 25.1±0.03 to 26.66±0.02. Hausner ratio was found below 1.16±0.01 to 1.36±0.03. All the formulation shows the fair to good flow properties for compression and hence tablets were prepared.

Evaluation of prepared piroxicam ODT

In all of the formulations, tablet weight and hardness were from 59.6±3 to 61.0±3 and 3 to 4.5 kg/cm^2 respectively (Table 3). Friability values were less than 1% in all cases shows good mechanical strength at the time of handling and transport. In Vitro Disintegration Time Disintegration time is an important criterion for selecting an optimum ODT formulation. Several methods have been described for evaluating in vitro ODT formulations. In vitro DT was determined following the procedure described by Gohel et al., 2004.[15] It was observed that increasing the superdisintegrant concentration from 1 to 7% resulted in a decrease in DT up to the 10 sec. as depicted in figure 2. Also, Disintegrating Time of formulations containing Crospovidone was 10 sec. lower than those containing Cross crmellose sodium 18 sec. at the concentration level of 7% which might be attributed due to Crospovidone's rapid water absorbing nature involving both capillary and swelling mechanisms, building up the pressure internally leading to the faster disintegration[16]. CP polymers are densely cross-linked homopolymers of Nvinyl 2 pyrrolidones. Their porous particle morphology enables them to rapidly absorb liquids into the tablet by capillary action and to generate rapid volume expansion and hydrostatic pressures that result in tablet disintegration. As reported, in addition to its unique particle size and morphology, disintegrant properties of CP are not affected by pH and consequently being non-ionic does not bind to ionic drug moieties.[17] In addition, CP can also be used as a solubility enhancer to improve dissolution and, unlike other superdisintegrants, does not form a gel at higher concentrations Wetting time was determined for all of the formulations.

Wetting time of formulations containing Crospovidone was less compared to formulations containing Cross camellose sodium or Sodium starch glycolate at equivalent concentrations. Faster wetting of tablets containing Crospovidone might be due to its rapid water absorbing nature involving both capillary and swelling mechanisms. Dissolution of the ODT at lower paddle speeds yield more discriminating dissolution profiles since ODT formulations disintegrate rapidly.[18] Dissolution profiles reveals that an increase in

superdisintegrant concentration from 1% to 7% resulted in increased cumulative % drug released in the first 5 min. The % drug released from the batch F8 containing Crospovidone was higher then the % drug relesed from the batch F6 containing Cross carmellose sodium although both having the same concentration level of 7% at 5min. All of the ODT formulations released 80.0% of the drug within 15 min (Figure 4). Sample withdrawn after two month shown no more drastically change in in-vitro drug release profile Results of the stability study had shown no remarkable change in the release profile of the piroxicam ODT after the stability. Disintegration time of the tablets is like same after the stability study.

Conclusion

Considering wetting time, in vitro DT, %friability and cumulative % drug released, crospovidone can successfully utilized for preparation of ODTs.

Table 1: Composition of Orally Disintegrating Tablets of Piroxicam

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
(Intragranular)								
Piroxicam	20	20	20	20	20	20	20	20
Mannitol (Pearlitol SD-200)	38.8	38.2	38.2	38.2	36.4	36.4	34.9	34.9
purified water	QS	QS	QS	QS	QS	QS	QS	QS
(Extra granular)								
Sodium starch glycolate	--	1.2 (2%)	--	--	--	--	--	--
Croscarmellose sodium	0.6 (1%)	--	1.2 (2%)	--	3 (5%)	--	4.2 (7%)	--
Crospovidone-XL	--	--	--	1.2 (2%)	--	3 (5%)	--	**4.2** (7%)
Aspartame	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Magnesium .stearate	0.3	0.3	0.3	0.3	0.3	0.3	0.6	0.6
Total weight	60	60	60	60	60	60	60	60

* All ingredients are in milligram

Table 2: Evaluation data of precompression properties

Batch No.	**Angle of Repose (^{0})**	**Bulk Density (gm/cm^3)**	**Tapped Density(g m/cm^3)**	**Carr's Index (%)**	**Hausner's Ratio**
F1	31.56±0.01	0.49±0.01	0.63±0.02	22.22±0.01	1.28±0.01
F2	33.9±0.04	0.60±0.02	0.75±0.01	20.00±0.03	1.25±0.02
F3	32.1±0.02	0.57±0.01	0.69±0.02	17.39±0.02	1.21±0.02
F4	28.6±0.01	0.53±0.02	0.72±0.03	26.38±0.01	1.35±0.03
F5	28.8±0.03	0.47±0.03	0.61±0.01	22.95±0.02	1.29±0.01
F6	34.0±0.02	0.44±0.01	0.60±0.02	26.66±0.02	1.36±0.03
F7	34.7±0.01	0.53±0.02	0.62±0.01	14.51±0.01	1.16±0.01
F8	**31.3±0.01**	**0.54±0.01**	**0.68±0.01**	**20.58±0.01**	**1.25±0.01**

* Shown results were for n=3

Table 3: Evaluation data of prepared piroxicam orally disintegrating tablet

Batch	Disintegration time (sec)	Wetting time (sec)	Hardness (kg/cm^2)	Friability (In %)	Q_5 (%drug released)	Avg.wt (mg)
F1	37±1	55±2	3-4	0.66±0.03	26.5±1	60.1±2
F2	70±3	90±1	3-4	0.58±0.01	25.8±2	61.0±3
F3	35±1	47±2	3.5-4.5	0.65±0.02	27.8±2	59.6±3
F4	32±2	42±1	3-4	0.41±0.01	32.4±1	60.2±1
F5	20±1	35±3	3-4	0.57±0.01	32.6±3	60.2±2
F6	12±1	16±1	3-4	0.50±0.02	34.5±1	60.0±2
F7	18±1	33±1	3-4	0.33±0.01	34.2±1	59.9±1
F8	**10±1**	**12±1**	**3-4**	**0.42±0.01**	**36.6±1**	**60.3±1**

* Shown results were for n= 3

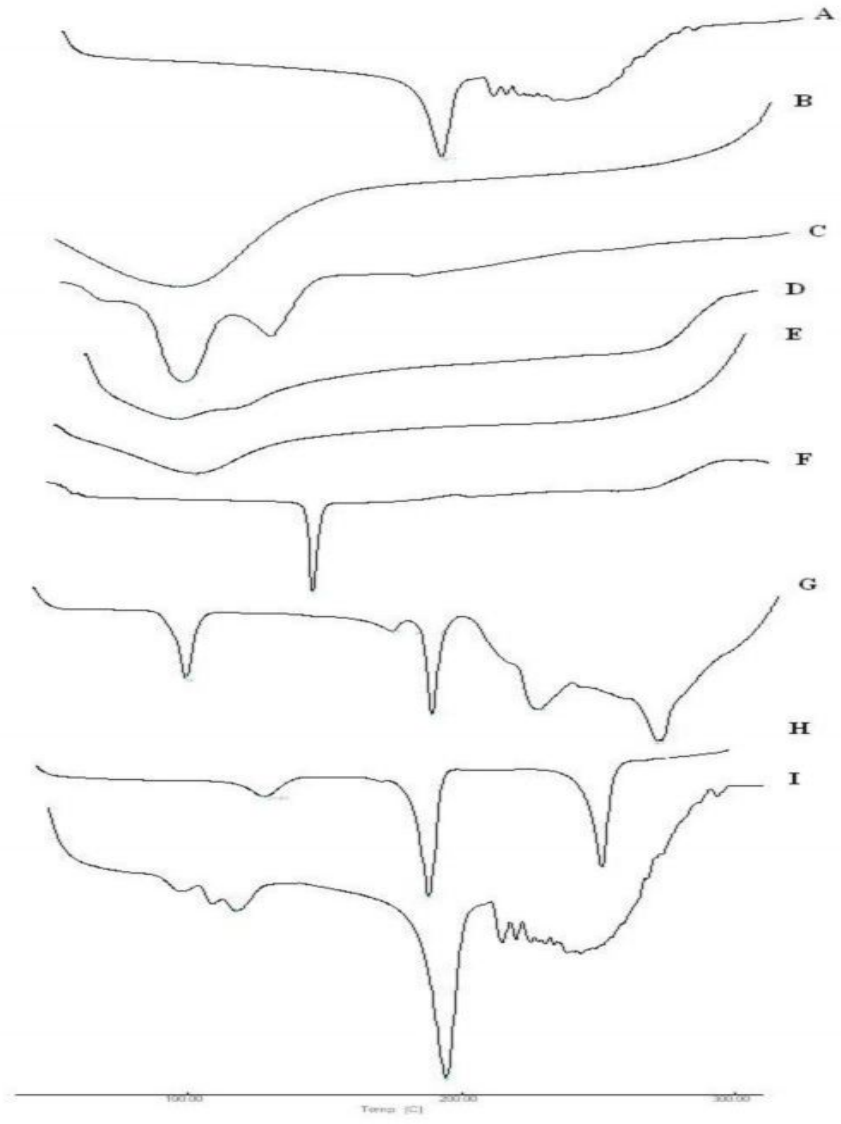

Figure 1: DSC thermogram

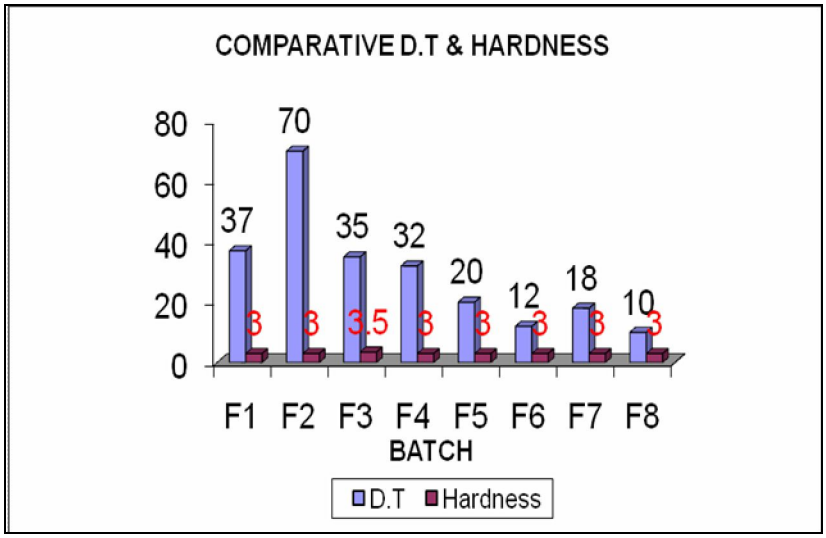

Figure 2: Comparative graph of Disintegration time & hardness

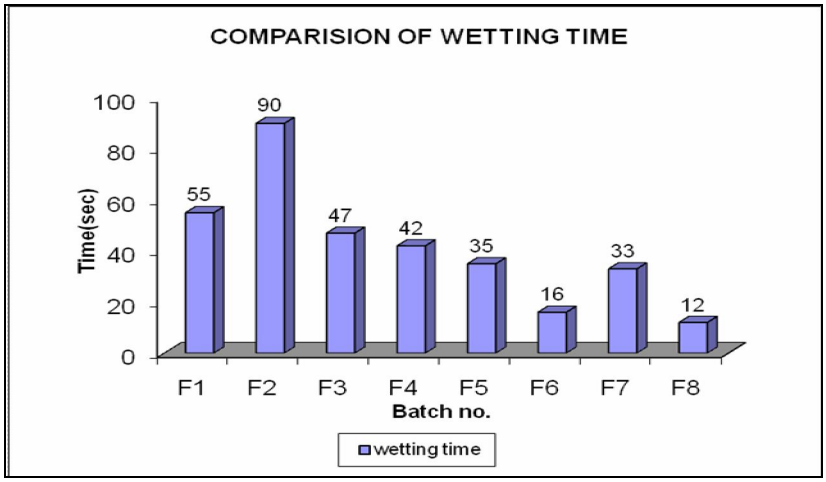

Figure 3: Comparative graph of wetting time for different preliminary batches

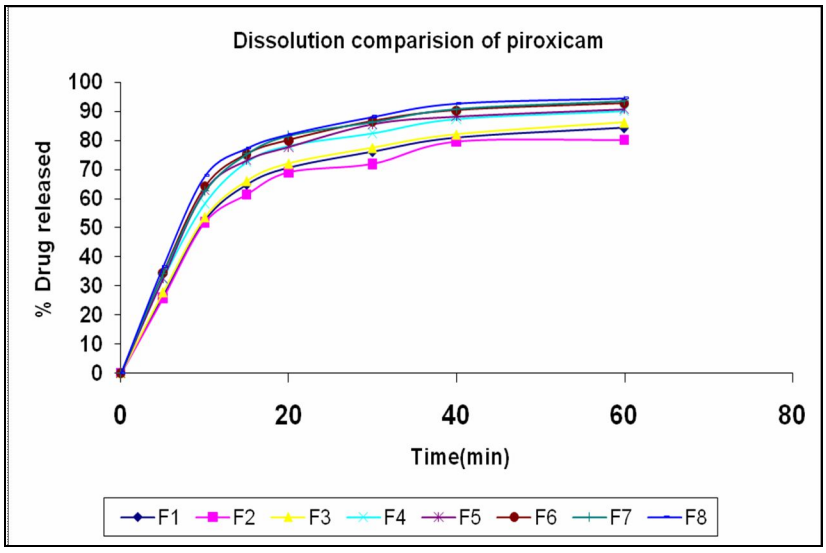

Figure 4: ***Release profiles of preliminary trails***

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