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FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF PIROXICAM BETA CYCLODEXTRIN AND TIZANIDINE HCl BY USING SUPERDISINTEGRANTS

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ABSTRACT

Orodispersible tablets of Piroxicam Beta Cyclodextrin and Tizanidine HCl combination were formulated using superdisintegrants to impart fast disintegration. Eleven formulations were prepared based on different concentrations of two superdisintegrants cross carmelos sodium and kyron . Direct compression techniques were used to study the nature and concentrations of superdisintegrants on various features of these tablets. Pre-compression studies like bulk density, tapped density,angle of repose,compressibilityIndex, Hausner's ratio and compatability studies such as Fourier transform infrared spectroscopy were perfomred. Various features such as Hardness, Thickness, Diameter, weight variation, Friability, Disintegration, Dissolution studies, Wetting time, and stability studies were evaluated. Out of these eleven formulations,F9 was considered to be a good formulation because it gave 95% release in 12 minutes.

Keywords: Piroxicam BetaCyclodxtrin, Tizanidine HCl , Orodispersible Tablets

INTRODUCTION

Around the world, the most accepted dosage forms are tabletss, because of its usefulness, patient compliance and economic feasibility, and easy route of administration. **(Dey, 2010; G.Abdelbary, 2005; Stirnimann, 2013)**. Tablets have severed trouble faced by people

in swallowing them, hence for the main issue of dysphagia **(H.Omidin, 2008; Nunn, 2005)**. Thus the conventional dosage forms result in high incidence of noncompliance and ineffective therapy with respect to swallowing especially in the case of pediatric, geriatric, and mentally retarded persons **(Fu, 2004)**. However, it offers several advantages with respect to its stability, administration without water, accurate dosing, easy manufacturing, small packaging size, and handling. Its ease of administration in the population makes it a very popular dosage form, due to presence of superdisintegrants it gets dissolved quickly upon introduction into the mouth, resulting in rapid absorption of drug which in turn provides rapid onset of action **(Behnke, 2003)**. It is solid unit drug delivery system that disintegrates/dissolves in salivainless than 60 seconds. Today ODTs **(Orodispersible tablets)** are more widely available as OTC (over the counter)products for the management of many conditions such as allergies, cold and flu symptoms **(Elbary, 2012)**. The advantage of this convenient administration has encouraged both academia and industry to generate new fast-disintegrating formulations and technological approaches in this field **(Dobetti, 2000)**. The European pharmacopeia implemented this term "Orodispersible" that a tablet which is to be placed in the mouth afterward it absorbs quickly prior to the process of ingestion i.e. before 3 minutes **(Bandari, NU, 2014)**.

Tizanidine HCl is a centrally acting alpha -2 adrenergic agonist muscle relaxant with a slight bitter taste and half-life of about 2.5 hours **(Masareddy, 2011)**. The skeletal muscle relaxant Tizanidine HCl is endorsed by the US FDA and the European office by treating spasticity and is supplied as tablets for oral administration **(Vitale, 2013)**.

Piroxicam is a non-specific inhibitor of cyclooxygenase, belonging to a large group of NSAIDs and pain relieving drug. It is highly effective for the treatment of pain of various characteristics and inflammation **(GT, 2010)**. Piroxicam Beta Cyclodextrin is viable in the patients with rheumatic sickness and other conditions of pain, when rapid pain relieving is required for the treatment of intense distress, the quicker onset of activity and less toxicity of Piroxicam Beta Cyclodextrin might be an advantage over the parent compound **(Lee, 2012)**.

MATERIALS AND METHODS

Materials

Active ingredients Piroxicam Beta Cyclodextrin and Tizanidine HCl were as a gift from Medisave pharmaceutical (pvt)

limited Lahore. All the excipients, Avicel 102, Cross carmelose, kyron and Magnesium stearate were also taken from the same Pharmaceutical Company.

Preparation of orally disintegrating tablets

Orally disintegrating tablets of Piroxicam Beta Cyclodextrin and Tizanidine HCl were prepared by direct compression method. All the ingredients were passed through sieve no 60 mesh sieve separately **(Table No 1)**.

3^2 Full Factorial Designs

3^2 full factorial design was followed to formulate distributions of the excipients (Shahtalebi, 2015) **(Table No 2)**.

Evaluation of micromeritics properties of powder blend

Angle of repose

The angle of repose of powder mixture for direct compression was determined by funnel method. The powder was taken in a funnel; the height of the funnel was adjusted to fixed height. The powder was allowed to flow through funnel freely onto the surface until maximum cone height means not break at any point. The radius of the powder heap was measured and angle of repose **(Padmavathy, 2011)** was calculated using the following equation.

$$\text{Ø}=\tan^{-1}h/r$$

Where h= height r =radius

Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined; powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5cmuntil no further change in the volume was noted.

Bulk density is calculated by using formula:

$$\text{Bulk density} = \frac{\text{Weight of the powder}}{\text{Bulk volume of the powder}}$$

Tapped density is calculated by using formula **(H.K.Stulzer, 2008)**.

$$\text{Tapped density} = \frac{\text{Weight of the powder}}{\text{Tapped volume of the powder}}$$

Compressibility index

The compressibility index of the formula was determined by using formula(Ganesh, 2010).

$$\text{Compressibility index (\%)} = (\text{TBD-LBD}) \times 100)/\text{TBD}$$

$$\text{Where, LBD} = \frac{\text{Weight of the powder}}{\text{Volume of the packing}}$$

$$\text{TBD} = \frac{\text{Weight of the powder}}{\text{Tapped volume of the packing}}$$

Tapped density

It was determined by using a graduated cylinder containing a known mass of drug-excipients blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10cm at 2-seconds intervals. The tapping was continued no further change in the volume was noted**.**

Hausner's Ratio

The Hausner's ratio is considered as subsidiary way to conduct the flow of powder. If the calculated value comes from lower side, then it exhibits good flow and higher values shows poor flowability **(P, 2006)**.

Post evaluation of tablets

All the formulated Orodispersible tablets containing Piroxicam Beta Cyclodextrin and Tizanidine HCl were subjected to the following quality control tests **(Table No 3)**.

Weight variation

The weight variation test was carried out in order to ensure uniformity in the weight of the tablets. Randomly, 20 tablets were selected from each formulation and the mean weight was determined. The individual weights of the tablets were also determined accurately and the weight variation was calculated **(Fssihi, 2008)**.

Hardness

Hardness of tablets is defined as the force applied across the diameter of the tablet in order to break the tablet. The force is measured in kg and the hardness of about 3-5 kg/cm^2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Monsanto Hardness Tester **(Arora, 2013)**.

Friability test

Friability is the loss of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche Friabilator was employed for finding the friability by rotating at 25 rpm for 4 mins. 20 tablets from each formulation were weighed and placed in Roche Friabilator. The tablet's weight loss was calculated again **(Nawale, 2013)** using the formula

% friability = (w1-w2)100/w1

w1=Weight of the tablet before test

w2= Weight of the tablet after test

Disintegration test

The USP device to test disintegration was six glass tubes that are open at the top, andheld against 10 screens at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is dipped in 1 liter beaker filled of distilled water at 37 ± 2^0 C, such that the tablets remains below the surface of the liquid on their upward movement and the descend not closer than 2.5 cm from the bottom of the beaker **(P. S. Zade, 2009)**.

Wetting time

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers were placed in a petridish with 10 cm diameter, ten milliliter of water containing eosin, water soluble dye was added to

petridish and a tablet was carefully placed on the surface of the tissue paper. The time required of the tablet was noted as wetting time and the wetting time was measured **(Gohel, 2004)**.

Thickness

Thickness of the tablets is important for uniformity of tablet size. Thickness was measured using vernier caliper. 20 tablets from each type of formulation were used and average values calculated were expressed in mm **(P., 2010)**.

In vitro drug release studies

The Piroxicam Beta Cyclodextrin and Tizanidine HCl tablets were subjected to in-vitro drug release studies inpH 6.8 for 30mins to access the ability of the formulations for providing immediate drug delivery. Drug release was carried out in several stages, dissolution test apparatus using 900 ml for Piroxicam Beta cyclodextrin and 500 ml for Tizanidine HCl of dissolution medium (pH 6.8 Phosphate buffer maintained 37±10). The tablets were kept in the cylindrical basket and rotated at 100 rpm for Tizanidine HCl and 50 rpm for Piroxicam Beta Cyclodextrin respectively (as shown in figures 01, 02, 03, and 04). 3ml of the sample from the dissolution medium was withdrawn at each time interval for every one minute and 3 ml of fresh medium was replaced each time. The samples absorbance of Piroxicam Beta Cyclodextrin at 242 and Tizanidine HCl absorbance at 228 were measured at UV spectrophotometer.

Stability studies

The stability studies were performed on formulation F9. Results for hardness, disintegration time show no appreciable change up to 3 months of accelerated studies. The stability studies of the formulation F9 is shown in **Table 4 and 5** for three months at accelerated conditions of 40±20^{0}C, 75±2% RH. The formulation was found to be stable, with insignificant change in the hardness, disintegration time and drug contents.

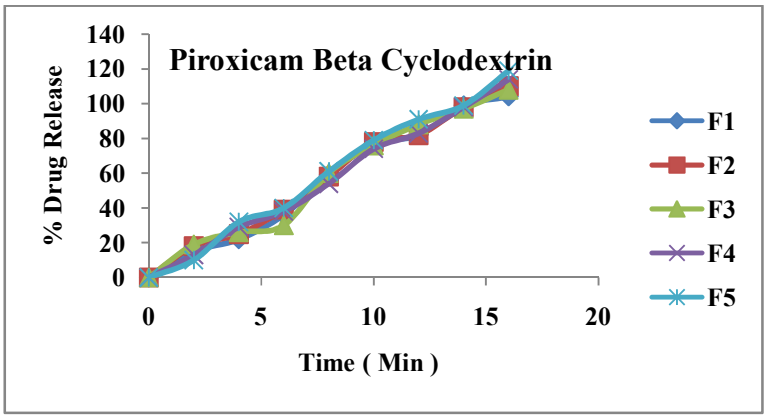

Fig 01: Drug release profile of Piroxicam Beta Cylcodextrin (F1-F5)

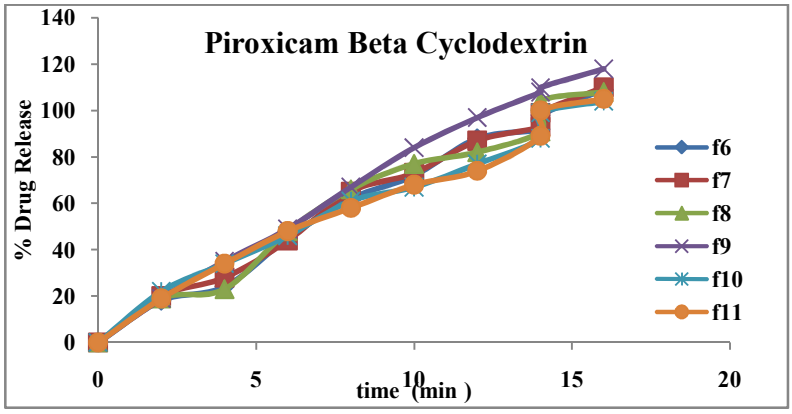

Fig 02: Drug release profile of Piroxicam Beta Cylocdextrin (F6-F11)

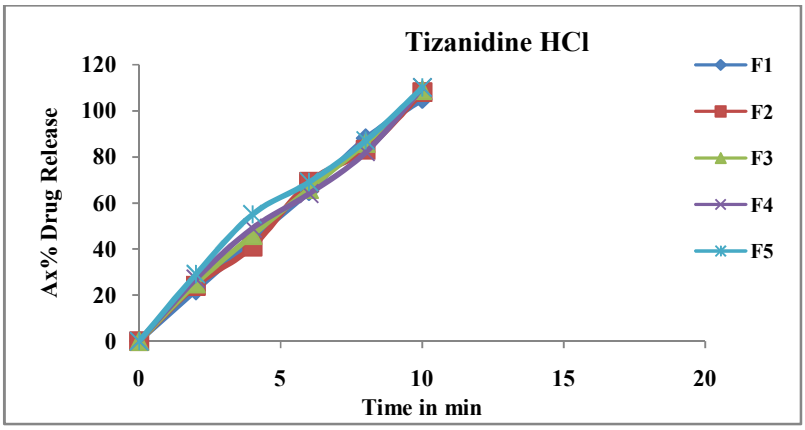

Fig 03: Drug release profile of Tizanidine HCl(F1-F5)

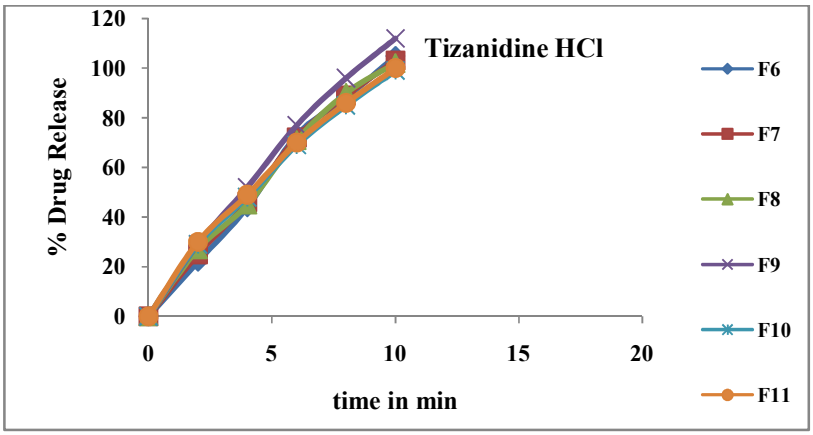

Fig 04: Drug release profile of Tizanidine HCl (F6-F11)

Table No 1: Composition of disintegrating tablets of Piroxicam Beta Cyclodextrin and Tizanidine HCl

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Angle of repose	26.21	25.02	23.81	24.80	25.92	24.98	24.30	24.97	25.45	25.81	26.80
Bulk density	0.569	0.534	0.572	0.544	0.543	0.522	0.543	0.542	0.544	0.543	0.563
Tapped density	0.656	0.654	0.655	0.653	0.652	0.651	0.655	0.654	0.655	0.653	0.652
Compressibility index	13.26	18.34	17.48	16.69	16.71	19.81	17.09	17.12	16.94	16.84	13.65
Hausner's ratio	1.152	1.224	1.145	1.200	1.200	1.200	1.206	1.206	1.204	1.202	1.158

Table No 2: Formulations of Piroxicam Beta Cyclodextrin and Tizanidine HCl

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Tizanidine HCl	2	2	2	2	2	2	2	2	2	2	2
Piroxicam BCD	20	20	20	20	20	20	20	20	20	20	20
Cross Carmelose	6	12	18	6	12	18	18	12	18	12	-
Kyron	9	9	9	18	18	18	18	27	27	-	18
Manitol	30	30	30	30	30	30	30	30	30	30	30
Avicel 102	159	159	159	159	159	159	159	159	159	159	159
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2
Aspartame	2	2	2	2	2	2	2	2	2	2	2

Table No 3: Evaluation of Orodispersible Tablets

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Weight Variation	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Hardness kg/cm^2	4.382	4.391	4.389	4.373	4.397	4.387	4.401	4.386	4.372	4.389	4.387
Thickness (mm)	4.39	4.38	4.40	4.36	4.39	4.39	4.42	4.39	4.38	4.40	4.41
Disintegration time (sec)	79	72	69	72	77	73	80	71	75	76	73
Friability	0.79	0.77	0.76	0.75	0.72	0.78	0.75	0.71	0.72	0.73	0.71
Wetting time (sec)	66	63	52	55	49	51	49	59	60	50	66
Content uniformity	99.93	99.98	99.98	99.92	99.91	99.87	99.90	99.89	98.99	97.93	99.99

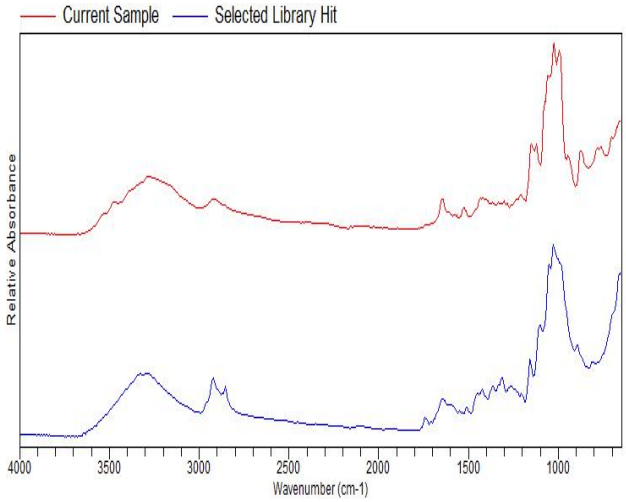

Fig 05: FTIR Scan of F9

Table No 4: Stability data at 40^{0}C

Sr. No	Evaluation	1st month	2nd month	3rd month
1	Hardness (kg/cm^2)	3.96 ±0.18	4.0±0.25	4.3±0.25
2	Disintegration time (sec)	68±1	67±1	67±1

Table No 5: Stability data at 75^{0}C

Sr. No	Evaluation	1st month	2nd month	3rd month
1	Hardness (kg/cm^2)	4.2±0.26	4.1±0.18	4.0±0.25
2	Disintegration time (sec)	69±1	68±1	67±1

CONCLUSION

Piroxicam Beta Cyclodextrin and Tizanidine HCl Orodispersible tablets were prepared by direct compression method using cross carmelose sodium, kyron, Avicel 102, Manitol, Magnesium stearate, and Aspartame. The tablets were disintegrated rapidly and had acceptable hardness and

friability. In-vitro drug release from the tablets shows significantly improved drug dissolution. Hence it could be concluded that direct compression based Piroxicam Beta Cyclodextrin and Tizanidine HCl orodispersible tablets would be quite effective in providing quick onset of action without need of water for swallowing on administration.

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