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Formulation and Evaluation of Fast Melting Tablet Containing Celecoxib with β-Cyclodextrin and Hydroxypropyl β- Cyclodextrin

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Keywords: Fast melting Tablet, Hydroxypropyl β-CD, β-CD, kneading method, superdisintegrant

ABSTRACT

Celecoxib is a selective COX- II inhibitor with anti – inflammatory, analgesic and antipyretic properties. The poor aqueous solubility of the drug leads to variable dissolution rates. In the present study an attempt has been made to prepare FMT of celecoxib in the oral cavity with enhanced dissolution rate. The solid complexes prepared by kneading method. Invitro study showed that the solubility and dissolution rate of celecoxib were significantly improved by complexation with HP-βCD and βCD. Tablet formulation using 1:1 kneading complex of celecoxib, HP-βCD and βCD ith drug equivalent to 100 mg was prepared by direct compression method. The FMT of celecoxib was prepared with some carrier (polymers) and superdisintegrant such as crospovidone NF, Croscarmellose sodium. Superdisintegrant were taken in same proportion of 20. All the FMT of celecoxib (F1-F6) were prepared by direct compression technique, the blend was examined for angle of repose, bulk density, compressibility index and hausner's ratio. The prepared tablets were evaluated for hardness, drug content uniformity, friability, wetting time, and disintegration time and dissolution rate. The optimized batch F5 and F6 show the better release (99.96% and 97.59%) within 12 minutes.

INTRODUCTION

Fast melting tablet (FMT) are single-unit solid dosage form that disintegrates or dissolve rapidly (in few seconds) in mouth without need for water or chewing. These dosage forms show good stability ease of manufacture and ease of handling by patients. The drug is immediately released from the dosage form and is readily available for absorption, improving its onset of action and its bioavailability in some cases, to some extent, it is also possible to achieve absorption of some drugs across the oral mucosa directly into systemic circulation, circumventing first pass hepatic metabolism and its subsequent side effect. Fast-melting tablets (FMTs) (also called fast-dissolving tablets or fast disintegration tablets, or FDTs) provide a convenient solution for patients who have difficulties in swallowing tablets and other solid dosage forms. The solid FMT dosage form turns into a soft paste or liquid form for easy swallowing, and thus it is free of suffocation risk. The benefits of FMTs can be extended to more general patients of daily medication regimens if the FMT dosage form has improved mechanical properties, fast disintegration time, and pleasant taste. The key properties of FMTs are fast absorption of water into the core of the tablets and disintegration of associated particles into individual components for fast dissolution.

Celecoxib

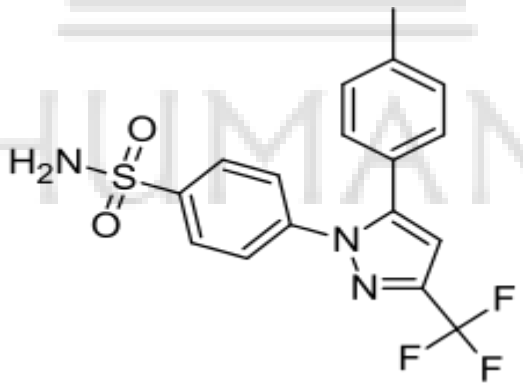

Figure no:-1 Chemical structure of celecoxib

Celecoxib is a COX-2 selective nonsteroidal anti-inflammatory drug (NSAID). It is used to treat the pain and inflammation of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute pain in adults, painful menstruation, and juvenile rheumatoid arthritis in people two years or older. It reduces the number of colon and rectal polyps in people with familial adenomatous

polyposis. For pain relief, it is similar to paracetamol (acetaminophen) and in osteoarthritis acetaminophen is the first line treatment. It was originally intended to relieve pain while minimizing the gastrointestinal adverse effects seen with conventional NSAIDs. In practice, its primary use is in people who need regular and long-term pain relief; probably, no advantage exists to using celecoxib for short-term or acute pain relief over conventional NSAIDs.

MATERIALS AND METHODS

Material

Celecoxib was obtained as a gift sample from Alkem laboratory Pvt. Ltd. Daman , HP-βCD , β-CD, croscarmellose sodium and aerosols from Ozone® International Pvt., Ltd Mumbai. crospovidone and Talc from S.D. Fine Chemicals, Mumbai, mannitol from Qauligen fine chemical, Mumbai, Lactose from Milton Chemicals, Mumbai. Magnesium Stearate from Ranbaxy Fine Chem. Ltd. Delhi.

Method

Preparation of Inclusion Complex: [3]

1. Kneading Method: -

Thick slurry was prepared by using Drug , β-Cyclodextrin and HP- β-Cyclodextrin in the proportion of appropriate molar ratio (1:1 molar ratio) were mixed in a mortar for 30 minutes with small quantities of ethanol was added intermittently to get slurry like consistency. The paste was dried in the oven at the temperature of 45°C. Dried complex was pulverized into fine powder and sifted with sieve # 60.

2. Preparation of Tablets by Direct Compression:

Direct compression method was selected for the preparation of tablet. The weight of inclusion complex equivalent to the 100 mg of celecoxib were taken. superdisintegrant were selected for the formulation. Six different batches were made in each formulation consist of different quantities respectively. Tablets were compressed by direct compression method using 10 mm flat round punch. All the required excipient was weighed and mixed properly for direct compression the total weight of one tablet was 300 mg.

3. Phase solubility study: [4,]

Solubility studies were performed according to the method reported by Higuchi and Connors. Excess celecoxib was added to phosphate buffer pH 6.8 containing various concentration of β-cyclodextrin and HP-βCD in a series of 100 ml volumetric flask and the mixture was shaken for 48 hr at room temperature(25^{o}C) on a shaker (120 rev/min). Then, the samples were kept aside to achieve equilibrium. After equilibrium was reached aliquots were then filtered through Whatman filter paper. The filtered samples were diluted suitably and assayed for simvastatin, by measuring the absorbance at 252 nm. The phase solubility diagram was plotted absorbance against concentration. The apparent complexation constant (K1:1) of the complex was calculated as following equation (Eq.(1)) from phase solubility slope, where the intercept is the intrinsic solubility of drug in the absence of β-cyclodextrin at 25^{o}C.

$$(K1:1) = \frac{\text{Slope}}{\text{Intercept (1-Slope)}}$$

Table no1:-Formulation Design

Ingredient mg/tab	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
DPC(eq.to 100mg of Celecoxib(βcd)	150	150	-	-	-	-
DPC(eq.to 100mg of Celecoxib(HP-βcd)	-	-	120	120	-	-
DPC(eq.to 100mg of Celecoxib(βcd-HP-βcd)	-	-	-	-	170	170
Crosspovidon	20	-	20	-	20	-
Crosscarmelose sodium	-	20	-	20	-	20
Manitol	71.5	71.5	86.5	86.5	53	53
Lactose	51.5	51.5	66.5	66.5	50	50
Magnesium Stearate	3	3	3	3	3	3
Aerosile	3	3	3	3	3	3
Talc	1	1	1	1	1	1
Total	300mg	300mg	300mg	300mg	300mg	300mg

RESULTS AND DISCUSSION

Calibration Curve of Celecoxib:-

The standard calibration curve of celecoxib was obtained by plotting Absorbance vs. Concentration. Table 7.2 shows the absorbance values of celecoxib. The standard curve is shown in figure 7.1 The standard calibration curve shows the slope of 0.010 and correlation coefficient of 0.996. The curve was found to be linear in the concentration range of 5, 10, 15, 20, 25, µg/ml at 252 nm. The calculation of drug content, *in vitro* dissolution study was based on this calibration curve

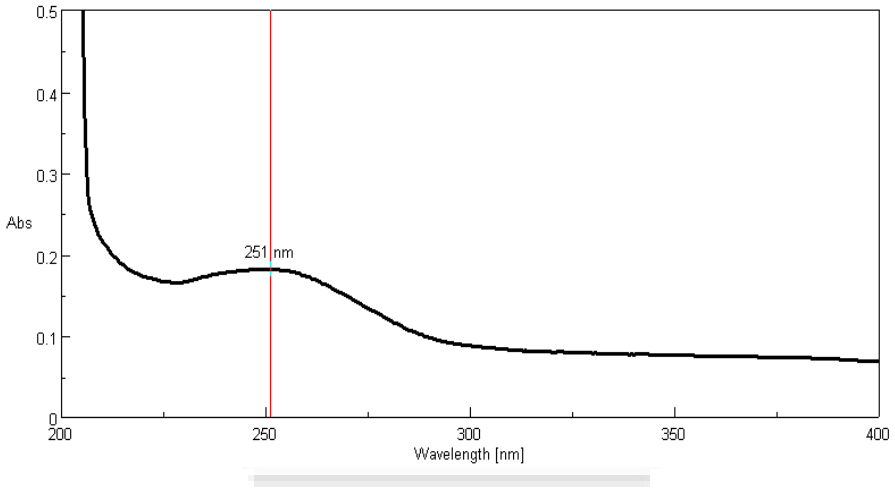

Figure no.2 UV Spectrum of Celecoxib

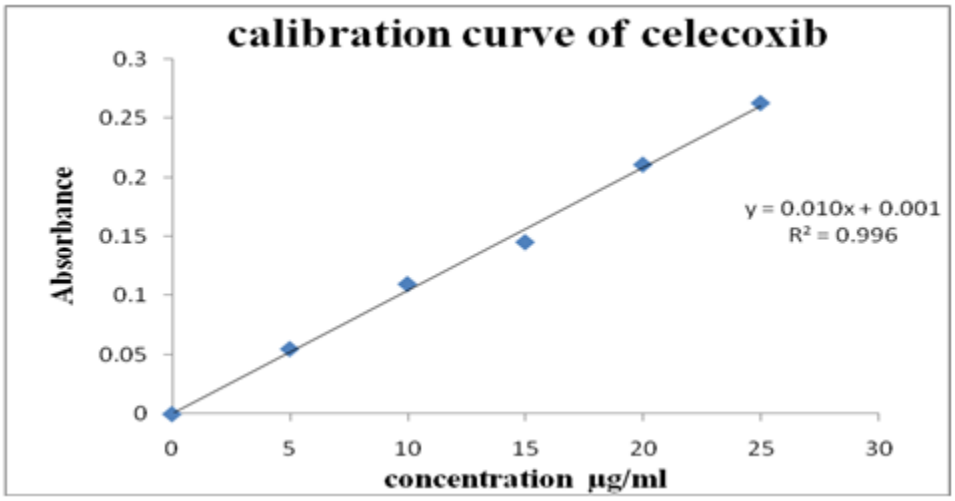

Figure no.3 Calibration Curve of celecoxib

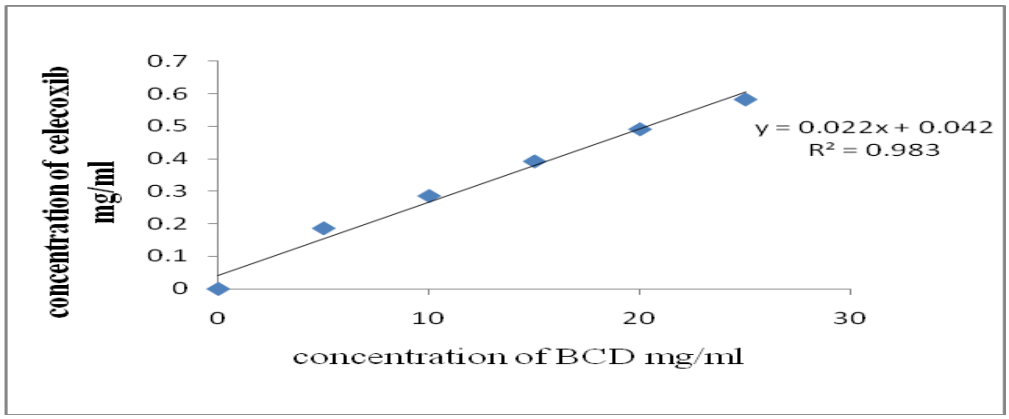

Figure no.4 phase solubility diagram of Drug: β-CD:

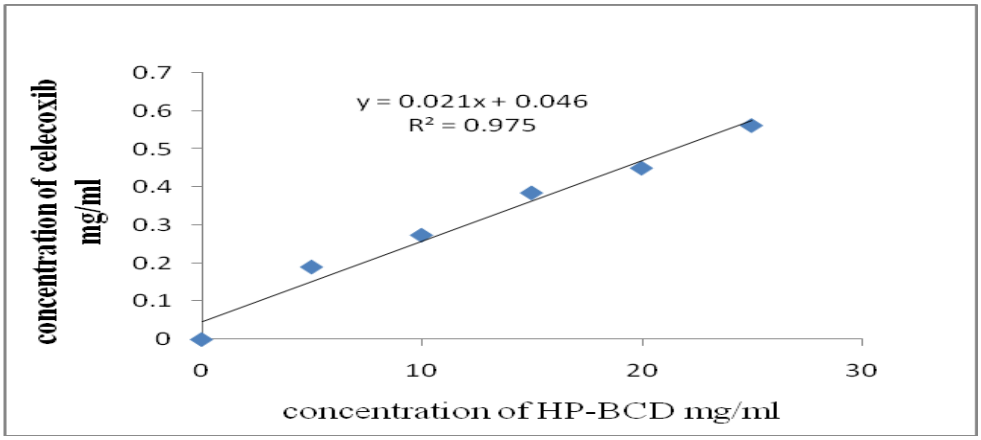

Figure no.5 phase solubility diagram of Drug: HP- βCD

Table no 2. Evaluation of Formulated Batches:

Formulation Batches	Evaluation parameters				
	Angle of Repose	Bulk Density (gm/cm3)	Tapped Density (gm/cm3)	Carr's Index (%)	Hausner's Ratio
F1	25.30^0	0.45	0.50	20.94	1.25
F2	26.84^0	0.48	0.60	20	1.25
F3	29.15^0	0.55	0.66	16.66	1.20
F4	28.40^0	0.53	0.67	20.89	1.26
F5	22.29^0	0.51	0.63	19.04	1.23
F6	23.65^0	0.43	0.60	28.94	1.39

Table no 3. Evaluation of Formulated Batches:

Sr. No.	Formulation	Friability (%)	Weight Variation(mg ± SD)	Thickness (mm± SD)	Hardness (kg/cm.sq±SD)
1	**F1**	0.65	300.78±1.5	2.1±0.2	3.5
2	**F2**	0.44	299.79±2.1	2.1±03	3.0
3	**F3**	0.69	300.32±2.0	2.3±0.1	3.4
4	**F4**	0.44	299.78±2.0	2.2±0.4	3.5
5	**F5**	0.38	300.10±1.3	2.3±0.1	3.0
6	**F6**	0.38	300.10±1.3	2.3± 0.2	3.5

Table no 4. Evaluation of Formulated Batches:

Sr. No.	Formulation	Diameter mm ± SD	Wetting time (s)	Disintegration Time (Second)	% drug content	% drug Release in 12 min
1	**F1**	10±0.00	59±4	27	95.20%	97.72
2	**F2**	10±0.00	26±1	28	90.29%	92.58
3	**F3**	10±0.00	29±3	30	94.01%	94.43
4	**F4**	10±0.00	25±5	35	93.80%	90.26
5	**F5**	10±0.00	66±4	25	99.14%	99.97
6	**F6**	10±0.00	60±5	27	97.55%	97.59

Table no.5 Comparative Percentage drug release in 12 minutes for all formulation

TIME (min)	F1	F2	F3	F4	F5	F6
0	0.00	0.00	0.00	0.00	0.00	0.00
2	20.33	16.82	18.91	14.57	22.37	20.50
4	37.84	30.19	32.52	29.53	40.26	39.72
6	57.39	45.96	49.22	44.46	58.76	55.53
8	76.12	61.24	66.09	62.95	76.15	73.12
10	89.11	78.47	81.72	76.78	89.57	87.53
12	97.72	92.58	94.42	90.25	99.96	97.59

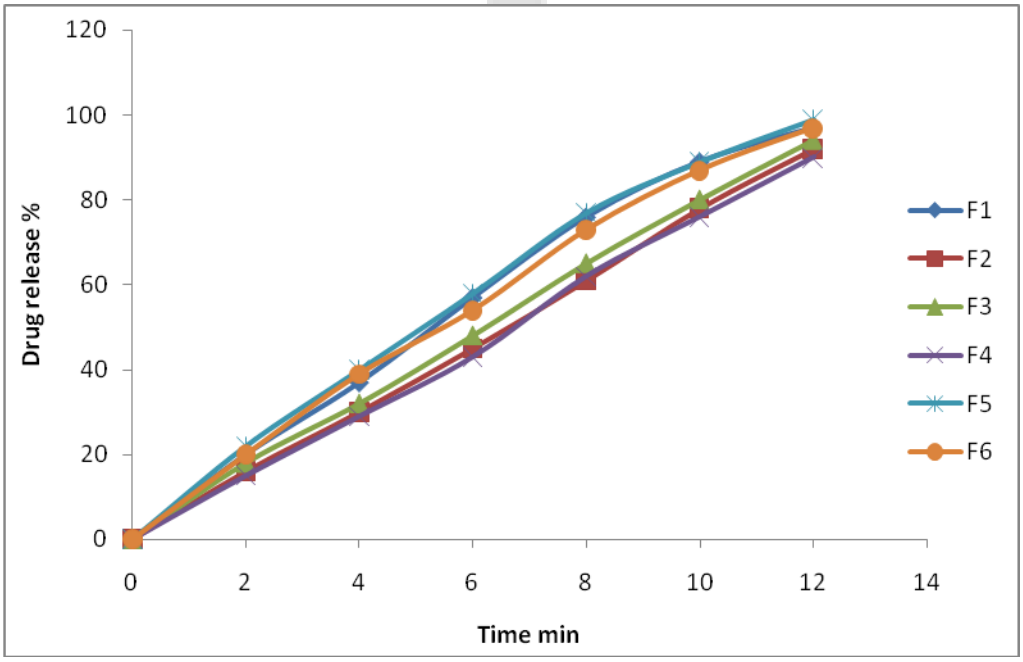

Figure no.6 Comparative Dissolution profile of all batches Formulated

IR spectroscopy analysis:

The IR spectrum of the drug agrees with its chemical structure 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl) benzenesulfonamide

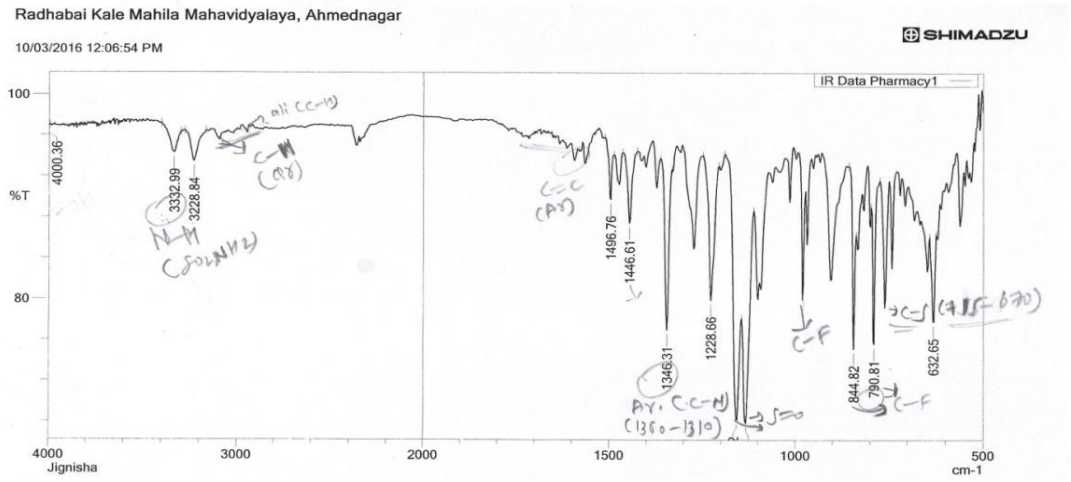

Figure no.7 IR Spectrum of Celecoxib

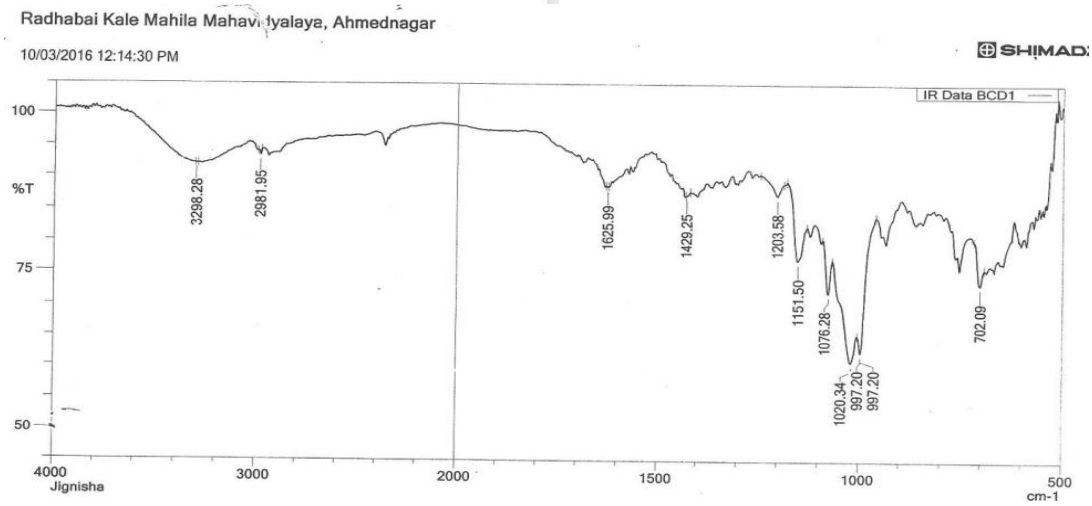

Figure no.8 IR Spectrum of β-Cylodextrin

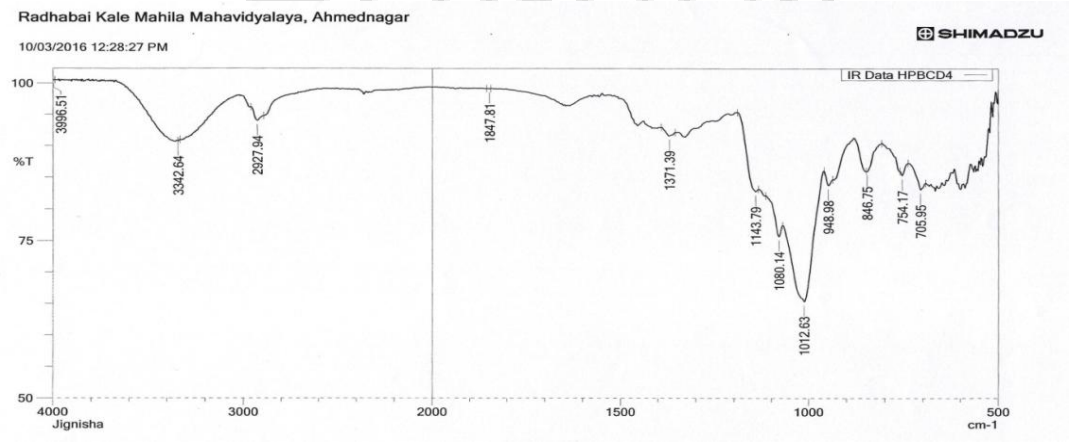

Figure no.9 IR Spectrum of Hydroxypropyl β-Cylodextrin

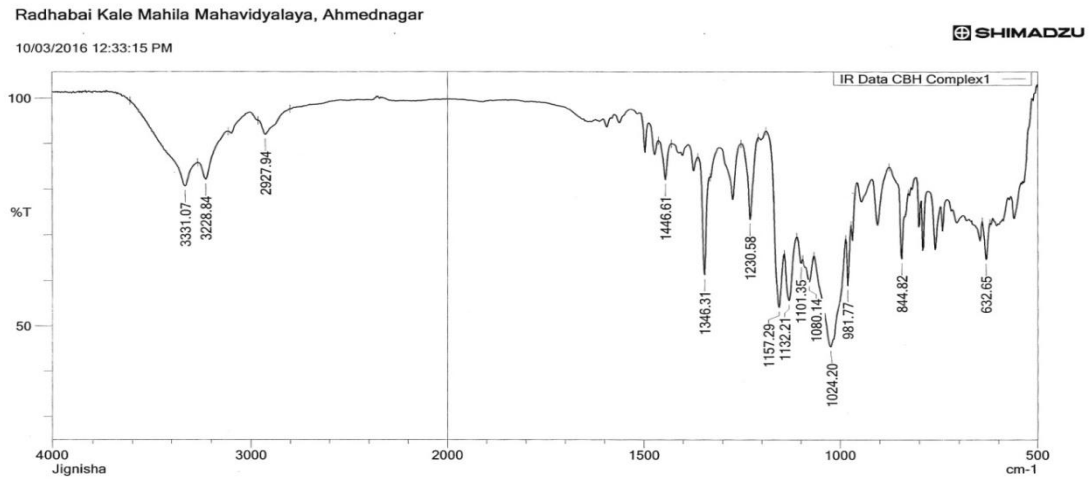

Figure no. 10 IR Spectrum of Complex of drug - β-Cylodextrin Hydroxypropyl β-Cylodextrin

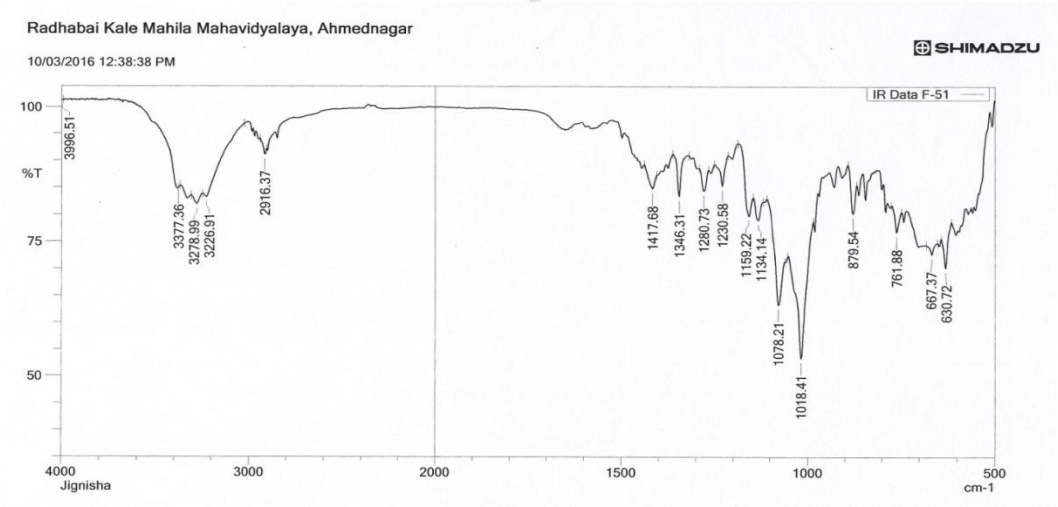

Figure no. 11 IR Spectrum of Celecoxib drug loaded Formulation F5

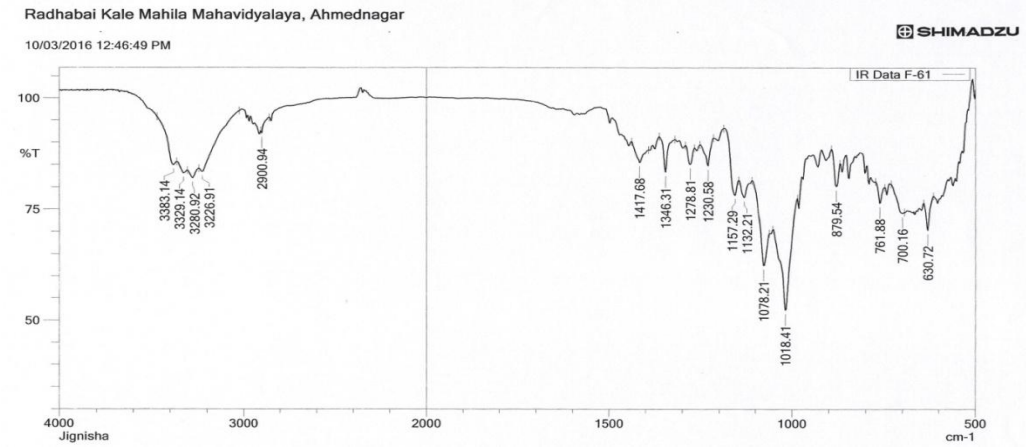

Figure no.12 IR Spectrum of Celecoxib drug loaded Formulation F6

Differential Scanning Calorimetric Analysis:-

Differential Scanning Calorimetry (DSC) is a thermoanalytical technique used for analyzing thermal transitions involving thermal energy with a great sensitivity. The DSC thermogram of celecoxib exhibited single, sharp endothermic peak at 162.71°C corresponding to its melting point. DSC Curve of formulation F5 and F6 Showing peak at164.35 and 164.36 which is near to melting point of celecoxib , indicating the formation of amorphous inclusion complex . Showing the molecular encapsulation of the drug inside the HP-β-CD cavity.

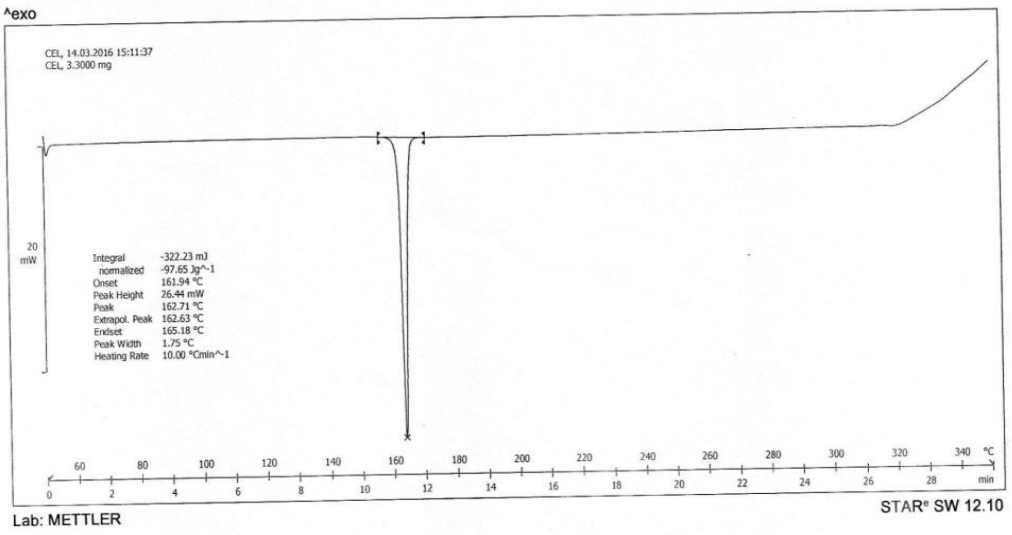

Figure no.13 DSC graph of pure Celecoxib

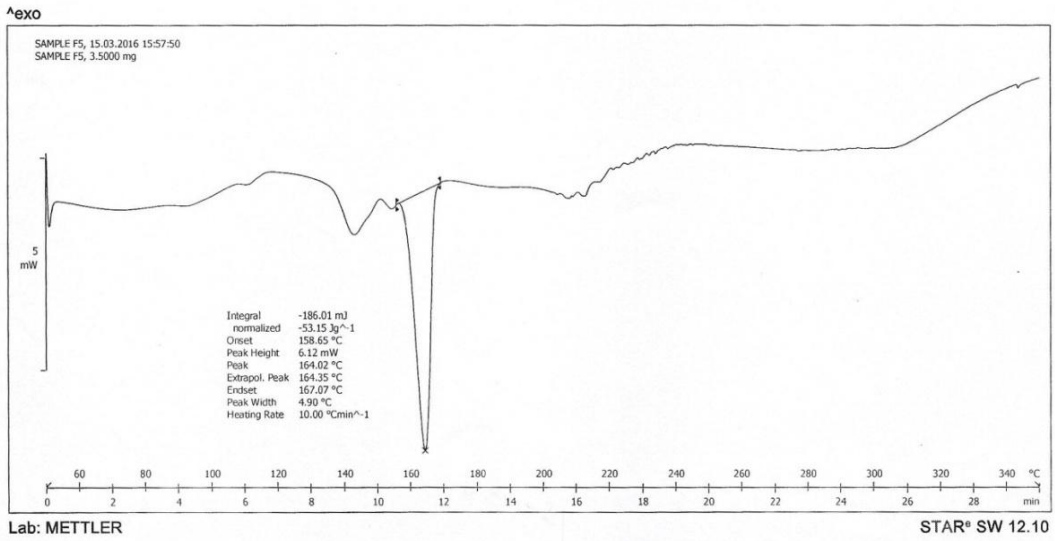

Figure no.14 DSC graph of Celecoxib drug loaded Formulation F5

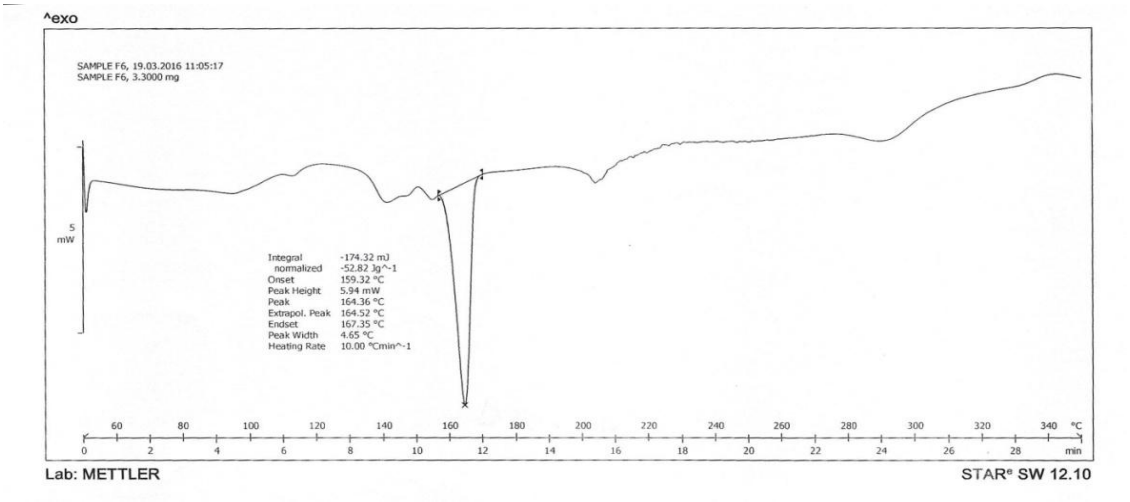

Figure no.15 DSC graph of Celecoxib drug loaded Formulation F6

CONCLUSION

On the basis of the study selection of drug candidate and the type of formulation lead to the formulation of fast melting tablet; thus the FMT of Celecoxib tablets were formulated successfully. The present research work is to enhance the solubility of poorly soluble drug celecoxib and conversion into granules using β-Cyclodextrins and HP-β. Among all the formulations, formulation F5 prepared with crospovidone (20%) and lactose as diluent showed 99.97% drug release within 12 min and disintegrate within 25 sec and formulation F6 prepared with croscarmellose sodium (20%) and mannitol as diluent showed 97.59% drug release within 12 min and disintegrate within 27 sec. Thus, formulation F5 and F6 was considered as the best among the other formulations. The release kinetic showed that the F5 follows Korsmeyer peppas model as its R^2 value is 0.9989. and F6 follows Korsmeyer peppas model as its R^2 value is 0. 9932. Therefore this research work concludes the successful way shown formulation and evaluation of FMT containing celecoxib with β-CD and HP- β-CD.

Acknowledgement:-

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