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COMPARISON OF DIFFERENT SUPERDISINTEGRANTS IN DESIGNING OF FAST DISSOLVING TABLETS OF METOPROLOL TARTRATE

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Keywords:

Fast dispersible tablet, metoprolol Tartrate, croscarmellose sodium, sodium starch glycolate, crospovidone, Indion 414

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ABSTRACT

Metoprolol tartrate which is used in the present study is widely used as antianginal properties. Oral bioavailability of metoprolol tartrate is around 40%. In the present work fast dissolving tablets of metoprolol tartrate have been prepared by direct compression method. Formulations were evaluated for precompressional parameters such as angle of repose, % compressibility and Hausner's ratio. The prepared tablets were evaluated for post compressional parameters such as hardness, friability, thickness, in-vitro dispersion time, wetting time, and water absorption ratio. The prepared tablets were characterized by DSC and FTIR studies. Stability studies were carried out as per ICH guidelines for three months. Effect of superdisintegrants [such as croscarmellose sodium, sodium starch glycolate, crospovidone, and Indion 414] on wetting time, in-vitro dispersion time and stability parameter has been studied. In-vitro dispersion time decreases with increase in concentration of indion 414 upto 9% then increases. Where as in-vitro dispersion time decreases with increase in the concentration of croscarmellose sodium and in-vitro dispersion time increases with increase in concentration of sodium starch glycolate. However in-vitro dispersion time value did not reflect major change with increase in the concentration of crospovidone. Short term stability studies on the formulations indicated that there are no significant change in the in-vitro dispersion time ($p<0.05$). No chemical interaction between drug and excipients was confirmed by DSC and FTIR studies. From this study it is concluded that fast dissolving tablets could be prepared by direct compression method using different superdisintegrants enhanced dissolution will lead to improved bioavailability, improved effectiveness of metoprolol tartrate.

INTRODUCTION: Metoprolol tartrate is a antianginal with a view to provide a convenient means of administrations to those patients suffering from difficulties in swallowing such as pediatric, geriatric, uncooperative and patients suffering from angina pectoris[1]. Oral bioavailability of metoprolol tartrate is around 40 % [2]. The present work enhance the dissolution will lead to improves the bioavailability of metoprolol tartrate (MT). The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation and solid dispersion)[3]. The dissolution of a drug can also be influenced by disintegration time of the tablets. Faster disintegration of tablets delivers a fine suspension of drug particles resulting in a higher surface area and faster dissolution.

Now a day fast dissolving tablets are gaining more importance in the market. Currently these tablets are available in the market for treating many disease conditions. More is concerned on hypertension[4], migraine[5], dysphasia[6], nausea and vomiting[7], Parkinson's disease[8], schizophrenia[9], pediatric emergency[10]. These conditions are those which require the drug to be formulated as fast dissolving tablets. Some patient prefers fast dissolving tablets to conventional tablets best of ease of administration, swallowing, pleasant taste and the availability in several flavors[11]. The pediatric and geriatrics patients are of particular concern. To overcome this, dispersible tablets[12] and fast-disintegrating tablets[13] have been developed. Most commonly used methods to prepare these tablets are; freeze-drying/Lyophilization[14] tablet molding[15] and direct-compression methods[16]. Lyophilized tablets show a very porous structure, which causes quick penetration of saliva into the pores when placed in oral cavity[14, 17]. The main disadvantages of tablets produced are, in addition to the cost intensive production process, a lack of physical resistance in standard blister packs and their limited ability to incorporate higher concentrations of active drug[12].

Moulded tablets dissolve completely and rapidly. However, lack of strength and taste masking are of great concern[18]. Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets[19]. Therefore, direct-compression appears to be a better option for manufacturing of tablets. The main objective of present work was to develop fast dissolving MT tablet by direct compression method and to study the effect of functionality differences of superdisintegrants on the tablet properties.

MATERIALS AND METHODS:

Materials: Metoprolol Tartrate was obtained as a gift sample from Emcure pharma. Ltd., Pune. Directly compressible microcrystalline cellulose (MCC), croscarmellose sodium (CCS), crospovidone (CP), sodium starch glycolate (SSG), Indion 414, aspartame and mannitol (directly compressible) were obtained from Cipla pharma. Ltd. Vikroli, Mumbai. Other reagents were of analytical grade.

METHODS:

Preparation of fast dissolving tablets of MT by direct compression method: Fast dissolving tablets of MT were prepared by direct compression. All the ingredients were passed through 60-mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 200mg using 8mm round flat punches on 10-station rotary tablet machine (Rimek). A batch of 30 tablets of each formulation was prepared for all the designed formulations. Different formulations compositions are given in (Table 1)**.**

Evaluation of MT fast dissolving tablets: The prepared tablets were evaluated for hardness, thickness variation, weight variation, friability, disintegration time, wetting time, drug content, *in-vitro* dissolution studies, and stability studies.

Pfizer hardness tester was used for the determination of the hardness of tablets. Tablet was placed in contact between the plungers, and the handle was pressed, the force of the fracture was recorded. The thickness and diameter of 4 tablets (2 tablets from each batch) were recorded during the process of compression using calipers (Mitotoyo; Japan). For weight variation[13] twenty tablets were selected randomly from each formulation and weighed individually using a Shimadzu digital balance (BL-220H). The individual weights were compared with the average weight for the weight variation. The friability of a sample of twenty tablets was measured using a USP type Roche friabilator (Pharmalab, Ahmedabad, India). Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then dusted, reweighed and percentage weight loss (friability) was calculated. Drug Content Uniformity[14] , ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 10 mg of metoprolol tartrate was extracted into distilled water and liquid was filtered (0.22 μm membrane filter disc (Millipore Corporation). The metoprolol tartrate content was determined by measuring the absorbance at 223 nm (using UV-VIS spectrophotometer, Shimadzu 1700) after appropriate dilution with distilled water. The drug content was determined using standard calibration curve.

The mean percent drug content was calculated as an average of three determinations. . In the Disintegration time[15] study one tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffers at 37 ± 0.5^0 C and the time required for complete dispersion was determined. In wetting time[16] study, twice folded tissue paper was placed in a petri dish having an internal diameter of 5 cm containing 6 ml of water. A tablet was carefully placed on the surface of the tissue paper in the petri dish. The time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time. Water absorption ratio (R) was then determined according to the following equation:

$$R = 100 \times (w_a - w_b) / w_b$$

Where, w_b and w_a were tablet weights before and after water absorption, respectively.

Table 1: Composition of MT fast dissolving Tablets

Ingredient (mg)	Formulation code															
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Metoprolol Tartrate	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
Indion 414	6	12	18	24	-	-	-	-	-	-	-	-	-	-	-	-
CCS	-	-	-	-	6	12	18	24	-	-	-	-	-	-	-	-
CP	-	-	-	-	-	-	-	-	6	12	18	24	-	-	-	-
SSG	-	-	-	-	-	-	-	-	-	-	-	-	6	12	18	24
Aspartame	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Mg stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Talc	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
MC	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
MCC	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Mannitol	94	88	82	76	94	88	82	76	94	88	82	76	94	88	82	76
Total	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

The in-vitro dissolution study was carried out in the USP dissolution test apparatus (Electrolab TDT - 08 L Dissolution testers USP) type 2 (paddle). 900 ml of the dissolution medium phosphate buffer pH 6.8 was taken in vessel and the temperature was maintained at 37 ± 0.50C. The speed of the paddle was set at 50 rpm. 5 ml of the dissolution medium was withdrawn and the same amount of fresh medium was replenished to the dissolution medium. The samples were filtered through 0.22 □ m membrane filter disc and analyzed for drug content by measuring the absorbance at 223 nm. Drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved. The release studies were performed in replicates of three. The stability study of the tablets was carried out according to ICH guidelines at 40 ± 20C/75 ± 5% RH for three months by storing the samples in stability chamber (Lab-Care, Mumbai). The optimized tablets were selected for stability studies. At intervals of 1 month, the tablets were visually examined for any physical changes

and evaluated for changes in drug content and in-vitro dispersion time.

Characterization of Metoprolol Tartrate tablets:

FTIR Studies: IR spectra for drug, excipients and formulations F1, F3 and F8 were recorded in a Fourier transform infrared (FTIR) spectrophotometer (FTIR 1615, Perkin Elmer, USA) with KBr pellets.

DSC studies: DSC scan of about 5mg accurately weighed MT and tablet mixtures were performed by using an automatic thermal analyzer system (DSC60, Shimadzu Corporation, Japan). Sealed and perforated aluminium pans were used in the experiments for all the samples. Temperature calibrations were performed using indium as standard. An empty pan sealed in the same way as for the sample was used as a reference. The entire samples were run at a scanning rate of 10°C/min from 50-300°C.

RESULTS AND DISCUSSION: The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property is given in Table 2. The data obtained from post-compression parameters in all the formulations, friability is less than 1%, indicated that tablets had a good mechanical resistance. Drug content was found to be in the range of 99 to 101%, which is within acceptable limits. Hardness of the tablets was found to be in the range of 2.00-2.90 kg/cm2.

In-vitro dispersion times were found to be in the range of 21-62 sec. The water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in the range of 52- 85% and 42- 58 sec respectively is given in Table 3. It is observed that in-vitro dispersion time of tablets decreased from (27-21 sec) with increase in concentration of Indion 414 upto 9% and then increases. In case of CCS in-vitro dispersion time of tablet deceased from (41-34 sec) with increase in concentration but in-vitro dispersion time increased with increase in concentration of SSG in tablets. At higher level, formation of viscous gel layer by SSG might have formed a thick barrier to the further penetration of the disintegration medium and hindered the disintegration or leakage of tablet contents. In case of tablet containing CP increasing the level of CP had no much greater effect on in-vitro dispersion times of the tablets.

The dissolution profiles of formulations are shown in Fig 1 - 5. The dissolution profile of formulations are shows the release of drug 97.33 to 99.67 % and the promising formulations i.e. F1, F3, F8 shows drug release within 6 min. Among the entire formulations F1 shows maximum drug release around 99.67 % within 6 min. The stability study for tablets was carried out for three months. No significant ($p<0.05$) changes in physical characteristics shown in Table 4.

Table 2: Pre-compression parameters of powder blend

Formulation code	Bulk density (gm/cc) ± SD, n=3	Tapped density (gm/cc) ± SD, n=3	Angle of repose (degree) ± SD, n=3	Carr's index (percent) ± SD, n=3	Hausner's Ratio ± SD, n=3
F1	0.52 ± 0.007	0.63 ± 0.01	31.25 ± 1.56	17 ± 1	1.21 ± 0.03
F2	0.53 ± 0.007	0.63 ± 0.01	32.02 ± 1.20	15 ± 1.51	1.18 ± 0.04
F3	0.53 ± 0.007	0.64 ± 0.02	33.1 ± 1.70	17 ± 1.20	1.20 ± 0.03
F4	0.55 ± 0.007	0.65 ± 0.01	32.20 ± 0.88	15 ± 2.51	1.18 ± 0.03
F5	0.50 ± 0.007	0.63 ± 0.01	32.43 ± 1.48	20 ± 1.58	1.26 ± 0.03
F6	0.52 ± 0.007	0.63 ± 0.02	32.72 ± 1.22	17 ± 1.55	1.21 ± 0.04
F7	0.51 ± 0.007	0.62 ± 0.38	34.87 ± 1.32	17 ± 1.39	1.21 ± 0.04
F8	0.54 ± 0.007	0.65 ± 0.02	3.04 ± 1.34	16 ± 2.20	1.20 ± 0.03
F9	0.52 ± 0.007	0.62 ± 0.01	2.28 ± 1.26	16 ± 2.01	1.19 ± 0.03
F10	0.52 ± 0.007	0.63 ± 0.01	33.52 ± 1.20	17 ± 2.12	1.21 ± 0.04
F11	0.54 ± 0.007	0.64 ± 0.02	34.19 ± 1.26	15 ± 1.51	1.18 ± 0.03
F12	0.55 ± 0.007	0.65 ± 0.01	32.26 ± 1.20	15 ± 1.39	1.14 ± 0.03
F13	0.52 ± 0.007	0.62 ± 0.02	33.03 ± 1.56	16 ± 1.20	1.19 ± 0.04
F14	0.53 ± 0.007	0.63 ± 0.01	33.72 ± 1.41	15 ± 1.67	1.18 ± 0.02
F15	0.51 ± 0.007	0.62 ± 0.02	32.85 ± 1.33	17 ± 1.41	1.21 ± 0.03
F16	0.52 ± 0.007	0.63 ± 0.02	34.14 ± 1.67	17 ± 2.51	1.21 ± 0.03

Table 3: Post- compressional parameters of fast dissolving tablets

Formulation code	Hardness ± SD, n=3	Friability ± SD, n=3	Thickness ± SD, n=3	Drug Content* ± SD, n=3	Wetting time ± SD, n=3	*In-vitro* dispersion time (sec) ± SD, n=3	Water absorption ratio ± SD, n=3
F1	2.5 ± 0.11	0.56 ±0.12	4.60 ±0.12	99.18 ± 0.72	47 ± 2.51	27 ± 2.78	80 ± 1
F2	2.3 ± 0.11	0.66 ± 0.11	4.75 ±0.15	99.81 ± 1.07	49 ± 2.0	25 ± 1.0	82 ± 1.52
F3	2.2 ± 0.10	0.62 ± 0.13	4.71 ±0.10	99.54 ± 0.50	48 ± 2.40	21 ± 1.0	85 ± 1.35
F4	2.1 ± 0.12	0.58 ±0.11	4.80 ± 0.10	98.12 ± 0.73	40 ± 1.89	30 ± 2.0	78 ± 1.58
F5	2.8 ± 0.18	0.57 ± 0.12	4.85 ± 0.17	99.30 ± 0.87	50 ± 2.20	41 ± 1.5	67 ± 1.21
F6	2.1 ± 0.10	0.67 ±0.09	4.87 ± 0.15	99.23 ± 0.90	48 ± 1.0	40 ± 1.7	70 ± 1.57
F7	2.1 ± 0.15	0.75 ± 0.07	4.72 ± 0.12	100.03 ± 1.07	43 ± 2.25	39 ± 2.8	72 ± 1.20
F8	2.3 ± 0.21	0.78 ± 0.06	4.65 ± 0.09	99.63 ± 0.39	44 ± 2.15	34 ± 1.45	76 ± 1.05
F9	2.2 ± 0.10	0.59 ± 0.07	4.61 ± 0.19	99.50 ± 0.77	46 ± 1.0	49 ± 1.28	61 ± 1.73
F10	2.3 ± 0.21	0.65 ± 0.11	4.58 ± 0.21	99.96 ± 0.27	42 ± 2.25	52 ± 1.11	58 ± 1.85
F11	2.2 ± 0.15	0.60 ± 0.13	4.64 ± 0.15	99.56±0.76	40 ± 1.75	50 ± 2.15	63 ± 1.88
F12	2 ± 0.10	0.52 ± 0.14	4.71 ± 0.25	100.09±0.76	41 ± 1.35	53 ± 1.55	57 ± 1.15
F13	2.1 ± 0.05	0.61 ± 0.13	4.69 ± 0.14	100.65±1.23	42 ± 1.21	45 ± 2.10	60 ± 1.18
F14	2.2 ± 0.20	0.73 ± 0.08	4.73 ± 0.28	99.08±2.65	47 ± 1.79	52 ± 1.21	55 ± 1.08
F15	2.4 ± 0.15	0.82 ± 0.07	4.59 ± 0.20	100.76±0.33	49 ± 1.71	59 ± 1.08	52 ± 1.05
F16	2.5 ± 0.42	0.77 ± 0.07	4.65 ± 0.08	99.99±1.79	42 ± 2.41	62 ± 2.0	48 ± 1.81

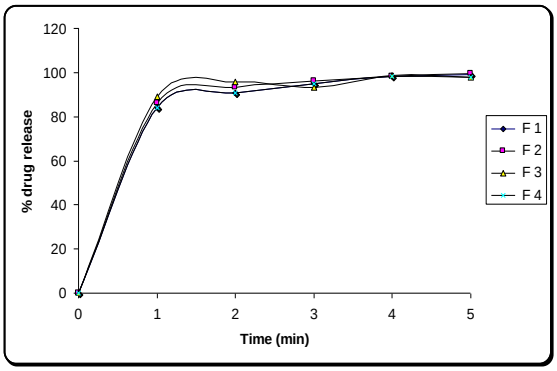

Fig 1: Dissolution profiles of formulations F1 – F4

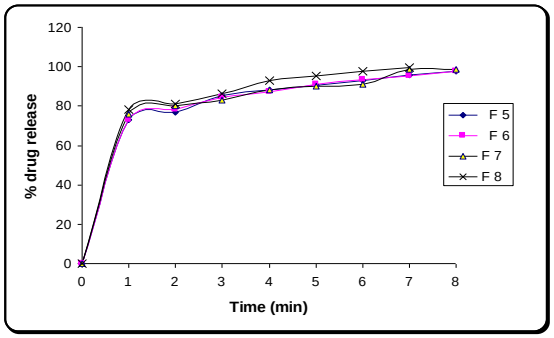

Fig 2: Dissolution profiles of formulations F5 - F8

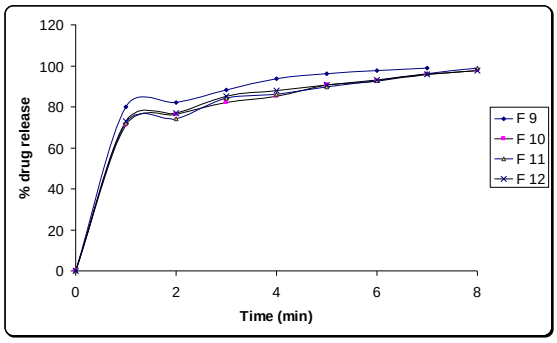

Fig 3: Dissolution profiles of formulations F9 – F12

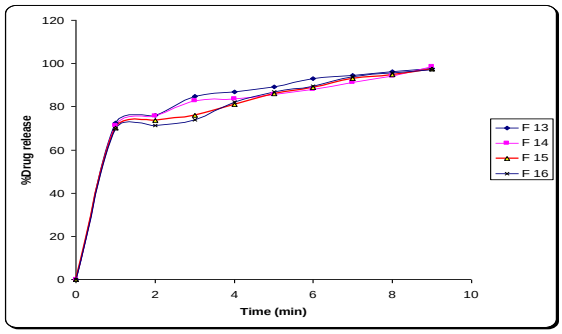

Fig 4: Dissolution profiles of formulations F13 – F16

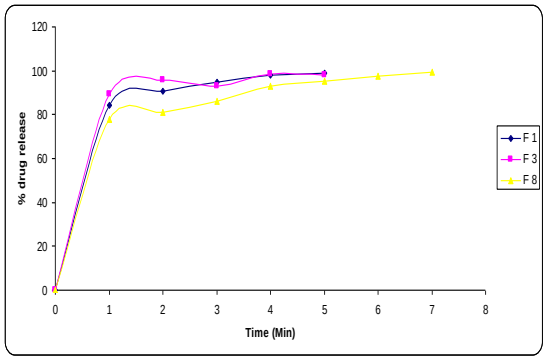

Fig 5: Dissolution profiles of best formulations F1, F3, and F8

Table 4: Stability studies for optimized metoprolol tartrate tablets

Formulation code	Period in days	Hardness Kg/cm² ± SD, n=3	percentage Friability ± SD, n=3	Dispersion time (sec) ± SD, n=3	Drug content ± SD, n=3
	30	2.5 ± 0.14	0.53± 0.12	27 ± 2.36	99.11 ± 0.64
F 1	60	2.6 ± 0.16	0.53 ± 0.16	28 ± 2.46	99.26 ± 0.54
	90	2.6 ± 0.12	0.54 ± 0.14	28 ± 2.66	99.22 ± 0.62
	30	2.3 ± 0.18	0.63 ± 0.11	24 ± 1.24	99.16 ± 0.42
F 3	60	2.3 ± 0.14	0.63 ± 0.11	25 ± 1.34	99.28 ± 0.34
	90	2.3 ± 0.10	0.63 ± 0.11	26 ± 1.11	99.36 ± 0.44
	30	2.2 ± 0.14	0.77 ± 0.11	35 ± 1.26	99.64 ± 0.26
F 8	60	2.2 ± 0.12	0.77 ± 0.08	36 ± 1.38	99.54 ± 0.32
	90	2.2 ± 0.16	0.77 ± 0.04	37 ± 1.34	99.36 ± 0.16

The IR spectrum of the pure drug MT (Racemic mixture) used in the present study shows characteristic absorption bands in the following IR region (Fig 6).

IR (KBR) cm-1: OH absorption at 3454 which is the normal range of absorption band for aliphatic hydroxyl group. Secondary immine (NH) has given a weak absorption in the form of a hump. Merged

with aromatic C-H at 3030 and aliphatic C-H of CH_3 and OCH_3 at 2980. The C-O absorption is found at 1589 merged with C=C of aromatic. These data are in support of the structure of the drug taken for study.

When this drug is taken along with Indion 414 and prepared a tablet to know what will be the interaction between the drug and the Indion 414. The IR revealed the factor that the hydrogen binding has taken place between the drug OH group and C=O of Indian 414 which has resulted into shifting of peak for OH from 3454 to 3400 the NH absorption has given a absorption peak at 3290. Other absorption peaks from the drug have remained unaffected. However C=O of Indian 414 which is part of the tricyclic ring system has shown a strong absorption at 1735.

Hence one of the C=O has undergone hydrogen bonding with the drug to give rise to adduct which is not a chemical reaction product. This hydrogen bond can undergo cleavage during metabolic process. The same drug Metoprolol tartrate is taken with CCS for tableting the tablet will prepared is subjected for IR reading. Which has shown presence of all the absorption peaks of drug along with a strong C=O of carboxylic cluster peak at 1734. It is clear from these observations that tablet that we obtain is a physical mixture containing -H bonding between drug and the CCS. Thus the conclusion from the IR spectra of the drug and formulations is that there is no interaction between drug and polymer.

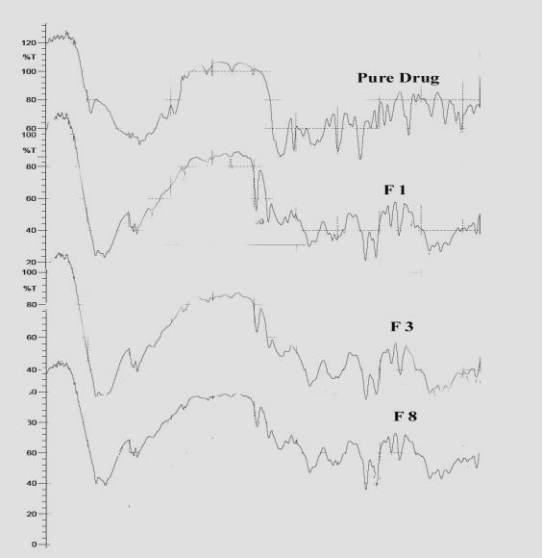

Fig 6: IR spectrum of MT, IR spectrum of formulation F1, F3, F8

In DSC study when the drug MT is taken to study its properties at higher temperature it has exhibited melting peak at 123^0C with very little variation with the literature reported temperature. This is probably due to the error in experimental determination. When the tablet containing drug and CCS is taken for same parametric determination it has started melting slowly at 162^0C to 167^0C since tablet contains mixture of the drug and 'CCS' in almost equiproportion which has resulted in a physical mixture. Suppose if it is a reaction product it should have shown sharp melting range having melting at a particular degree Celsius. It is a physical mixture and also 'CCS' is a sodium salt of the carboxylic acid because of these two factors large range of variation has been observed. In our next experiment when the tablet is prepared from pure drug and the Indion 414 the observations made during is observed since it is a mixture of two organic molecules.

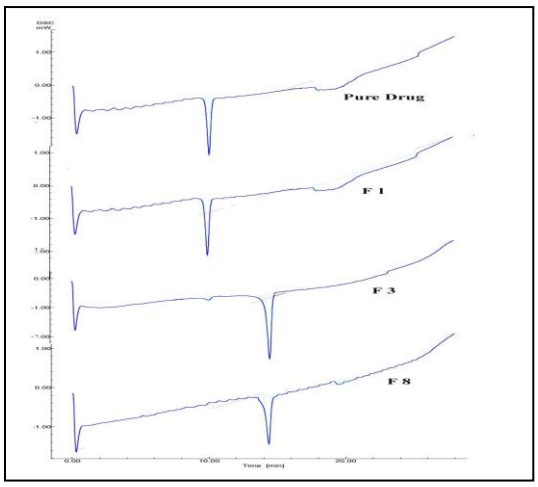

Fig 7: DSC thermograms of MT, formulation F1, F3, F8

CONCLUSION: In present study, four types of superdisintegrants in different concentrations differed in their ability to disintegrate the model Metoprolol tartrate tablets. Such difference can potentially affect drug dissolution and is proposed as model formulation for disintegrants performance testing and quality control purposes. Hence, enhanced dissolution of fast dissolving tablets of metoprolol tartrate will lead to improved bioavailability, improved effectiveness and hence better patient compliance.

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