Research Article

DESIGN OF FAST DISSOLVING TABLETS OF METOPROLOL TARTRATE USING NOVEL CO-PROCESSED SUPERDISINTEGRANTS

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ABSTRACT

In the present work, fast dissolving tablets of Metoprolol tartrate were prepared using novel co-processed superdisintegrants consisting of crospovidone and croscarmellose sodium in the different ratios. Metoprolol tartrate is effective β-blocker which is having anti-anginal properties and used in the treatment of myocardial infarction and oral bioavailability of is around 40%. Effects of co-processed superdisintegrants on different parameters have been studied. Drug compatibility with excipients was checked by FTIR and DSC studies. No chemical interaction between drug and excipients was confirmed by DSC and FTIR studies. Stability studies were carried out as per ICH guidelines for three months. The values of pre-compressional parameters evaluated were within prescribed limits and indicated good free flowing property. In all the formulations, the post-compressional parameters evaluated were within prescribed IP limits. The wetting time is an 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 42 to 146 sec. The *in-vitro* disintegration time were found to be in the range of 14 -132 sec. Among all the designed formulations, formulation CP1 was found to be promising formulation, which facilitates its faster dispersion in the mouth. The formulations CP1 containing 4% w/w of co-processed superdisintegrant (1:1 mixture of CP and CCS) was found to be promising and has shown an *in-vitro* dispersion time of 14 sec, wetting time of 28 sec. Stability studies on promising formulation indicated that there were no significant changes in drug content and *in-vitro* dispersion time ($p<0.05$). From this study, it can be concluded that dissolution rate of metoprolol tartrate could be enhanced by tablets containing co-processed superdisintegrant.

Keywords: Co-processed superdisintegrants, metoprolol tartrate, croscarmellose sodium, and crospovidone.

INTRODUCTION

Metoprolol tartrate (MT) is a selective beta1-adrenoreceptor blocking agent. Metoprolol tartrate is (±)-1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol (2:1) dextro-tartrate salt used in Essential hypertension, prevention after a myocardial infarction, tachycardia, coronary heart disease (prevention of angina attacks), treatment of heart failure[1].

For poorly soluble orally administered drugs the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation, solid dispersion etc). Another prerequisite for the fast dissolution may be the disintegration time of tablets. Because, faster disintegration of tablets delivers a fine suspension of drug particles and thus, greater dissolution of the drug[2]. Solid oral dosage forms, especially tablets, remain one of the most popular because of advantages like patient convenience, ease of storage and dispensing, dose accuracy and easy manufacturability.

Major challenge for tablets manufacturing comes from the flow properties of the materials to be compressed. Most of the formulations (> 70%) contain excipients at higher concentration than active drug[3]. In recent years drug formulation scientists have recognized that single-component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately[4]. Hence, there is a need to have excipients with multiple characteristics built into them such as better flow, low/no moisture sensitivity, superior compressibility and rapid disintegration ability[5]. Excipients with improved functionality can be obtained by developing new chemical excipients, new grade of existing materials and new combination of existing materials[6]. New combinations of existing excipients are an interesting option for improving excipients functionality because all formulations contain multiple excipients. One such approach for improving the functionality of excipients is co-processing of two or more excipients. Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual[7]. Co-processing excipients lead to the formulation of excipients granules with superior properties, compared with physical mixtures of components or individual components, like improved flow properties, improved compressibility, better dilution potential, fill weight uniformity, and reduced lubricant sensitivity[8]. Physical mixtures, as the name suggests, are simple admixtures of two or more excipients typically produced by short duration low-shear processing. Co-processed excipients are appropriate for consideration as new monographs because one or more of the components may be formed in situ, or the component may not be isolated prior to co-processing.

Several co-processed superdisintegrant are commercially available: Ludipress (lactose monohydrate, poly vinyl pyrrolidone and crospovidone), Starlac (lactose and maize starch), Starcap 1500 (corn starch and pregelatinized starch), Ran Explo-C (microcrystalline cellulose, silica and crospovidone), Ran Explo-S (microcrystalline cellulose, silica and sodium starch glycolate), PanExcea MH300G (microcrystalline cellulose, hydroxy propyl methyl cellulose and crospovidone)[9]. The widely used superdisintegrants are crospovidone (CP), croscarmellose sodium (CCS) and sodium starch glycolate (SSG). In the present investigation, using physical mixture and co-processed superdisintegrant containing CP and CCS was studied. The reasons for selection of CP are high capillary activity, pronounced hydration capacity and little tendency to form gels[10]. The concept of formulating fast dissolving tablets (FDT) of MT (excellent antihypertensive and anti-diuretic effect) using co-processed superdisintegrant helps to increase the water uptake with shortest wetting time and thereby decrease the disintegration time of the tablets by simple and cost effective direct compression technique. Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets[11]. Hence, if a physical mixture of superdisintegrants is used in high-speed tableting, the problem of segregation of the disintegrants may be encountered. One of the reasons for preparing the co-processed superdisintegrant was to avoid the problem of segregation. A blend of swelling and wicking types of excipients may also prove to be efficient because the medium (usually water) required for swelling will be brought into the tablet more easily if a wicking (hydrophilic) type of superdisintegrant is also present. In the present investigation, the preparation and evaluation of fast dissolving tablets of MT by using physical mixture and co-processed superdisintegrant containing CP and CCS (in the ratio of 1:1, 1:2 and 1:3) was studied. The compositions of which are given in **(Table 1)**.

Table 1: Formulations of MT FDT Prepared by Direct Compression Method

Formulation code	CP0	PM1	PM2	PM3	CP1	CP2	CP3
Metoprolol tartrate	25	25	25	25	25	25	25
Superdisintegrants (CP+CCS)	--	6	6	6	6	6	6
Aspartame	3	3	3	3	3	3	3
Sodium stearyl fumarate	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	3	3	3	3	3	3	3
Pine apple flavour	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Microcrystalline cellulose (Avicel PH-102)	30	30	30	30	30	30	30
Mannitol (Pearlitol SD 200)	86	80	100	80	80	80	80
Total weight in mg/tab	150	150	150	150	150	150	150

PM - Physical Mixture of crospovidone and croscarmellose sodium in different ratios (1:1, 1:2, 1:3), CP - Co-processed Superdisintegrants of crospovidone and croscarmellose sodium in different ratios (1:1, 1:2, 1:3), CP0 - Control formulation (without superdisintegrants), CP - Crospovidone, CCS- Croscarmellose sodium.

MATERIAL AND METHODS

MT was obtained as a gift sample from Emcure Pharma. Ltd, Pune. Superdisintegrants like crospovidone, croscarmellose sodium (Maruti Chem. Ahmedabad), Aspartame, Directly compressible mannitol (Pe arlitol SD 200), microcrystalline cellulose (MCC, PH-102), and sodium stearyl fumerate (Aan Pharma Pvt Ltd., Rakanpur-Gujarat). Talc and Magnesium stearate purchased from SD. Fine Chem., Mumbai. All other materials used were of pharmaceutical grade.

Preparation of co-processed superdisintegrant[12]: The co-processed superdisintegrant were prepared by solvent evaporation method. A blend of CP and CCS (in the ratio of 1:1, 1:2 and 1:3) was added to 10 ml of ethanol. The contents of the beaker (250 ml capacity) were mixed thoroughly and stirring was continued till most of ethanol evaporated. The wet coherent mass was granulated through # 44-mesh sieve. The wet granules were dried in a hot air oven at 60º C for 20 minutes. The dried granules were sifted through # 44- mesh sieve and stored in airtight container till further use.

Preparation of fast dissolving tablets by direct compression method[13]: Fast dissolving tablets of MT were prepared by direct compression. All the ingredients (except granular directly compressible excipients) were passed through #60-mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 150mg by direct compression method using 7 mm bi concave punches on a 'Rimek mini press 1' a 10 station rotary compression machine.

Evaluation of MT tablets: The prepared tablets were evaluated for hardness, friability, *in-vitro* dispersion time, wetting time, drug content, *in-vitro* release study, FTIR and DSC studies, and stability studies. The hardness [13] of the tablets was measured using the Pfizer hardness tester. The friability[13] of a sample of twenty tablets was measured using a USP type Roche friabilator. 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. Thickness of the tablets was with a micrometer screw gauge. Ten tablets from each formulation were taken randomly and their thickness was measured. For the content uniformity test[14], ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 10 mg of MT was extracted into distilled water and liquid was filtered (0.22 μm membrane filter disc). The MT 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. The *in-vitro* dispersion time[15] were determined by taking one tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37 ± 0.5^{0}C and the time required for complete dispersion was determined.

Wetting time and water absorption ratio (R)[16]: 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. Measurement of wetting time of a tablet was shown in **Fig 1.**

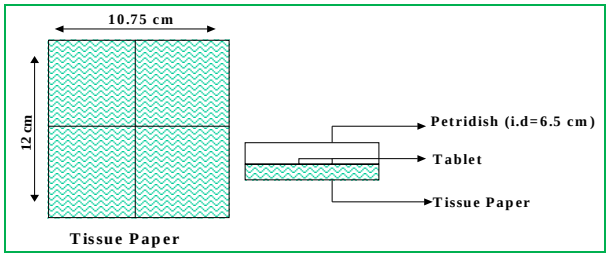

Figure 1: Simple method for the measurement of wetting time of a tablet.

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.

***In-vitro* drug release study[17,18]:** *In-vitro* dissolution studies of the fast dissolving tablets of MT formulation were performed according to USP XXIII Type-II dissolution apparatus (Electrolab, model TDT-06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37 ± 0.5^0 C as dissolution medium. One tablet was used in each test. Aliquots of the dissolution medium (5 ml) were withdrawn at specific time intervals and replaced immediately with equal volume of fresh medium. The samples were filtered through 0.22 μm 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.

Characterization of MT tablets:

FTIR Studies: IR spectra for drug MT and powdered tablets were recorded in a Fourier transform infrared spectrophotometer (FTIR 1615, Perkin Elmer, USA) with KBr pellets.

DSC Studies: 5 mg of MT and tablet formulations were sealed in perforated aluminium pans for DSC scanning using an automatic thermal analyzer system (Mettler Toledo, USA). Temperature calibrations were performed using indium as standard. An empty pan sealed in the same way as the sample was used as a reference. The entire samples were run at a scanning rate of 10^0 C/min from 50-300^0 C.

Stability studies: The stability study of the tablets was carried out according to ICH guidelines at 40 ± 2^{0}C/75±5%RH for three months by storing the samples in stability chamber (Lab-Care, Mumbai). The stability study of the tablets was carried out according to ICH guidelines at 40 ± 2^{0}C/ 75 ± 5%RH for three months by storing the samples in stability chamber (Lab-Care, Mumbai).

RESULTS AND DISCUSSION

Co-processed superdisintegrant were prepared by solvent evaporation using CP and CCS in different ratios (1:1, 1:2, and 1:3). The co-processed superdisintegrant were evaluated for their flow and compression properties in comparison with physical mixture of superdisintegrant. The angle of repose of co-processed superdisintegrant was found to be <30^0 which indicate excellent flow in comparison to physical mixture of superdisintegrant (<30^0) due to granule formation, Carr's index in the range of 15.22 to 17.46 % and Hausner's ratio in the range of 1.17 to 1.27 **(Table 2).** Fast dissolving tablets of MT were prepared using above co-processed superdisintegrant and physical mixtures of superdisintegrant. Directly compressible mannitol (Pearlitol SD 200) was used as diluents to enhance mouth feel. A total of six formulations and control formulation CP0 (without superdisintegrant) were designed.

The data obtained from post-compression parameters such as hardness, friability, thickness, drug content, water absorption ratio, wetting time, and *in-vitro* disintegration time. The results are shown in **(Table 3)**. In all the formulations, hardness test indicated good mechanical strength results were ranges from 2.86 to 3.24 kg/cm^2, friability is less than 1%, ranges from 0.48 to 0.72% indicated that tablets had a good mechanical resistance. Thickness of the tablets range from 2.14 to 2.20 mm. Drug content was found to be in the range of 97.88 to 99.92 %, which is within acceptable limits. 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 67-85% and 42-146 sec respectively. The *in-vitro* disintegration time were found to be in the range of 14 -132 sec. The graphical representation of comparison of hardness and *in-vitro* disintegration time were shown in **Fig 2.** Among all the designed formulations, formulation CP1 was found to be promising and was displayed an *in-vitro* dispersion time, which facilitates its faster dispersion in the mouth. The formulations CP1 containing 4% w/w of co-processed superdisintegrant (1:1 mixture of CP and CCS) was found to be promising and has shown an *in-vitro* dispersion time of 14 sec, wetting time of 28 sec when compared to the formulation CP2 containing physical mixture of superdisintegrant (1:2 mixture of CP and CCS) which shows *in-vitro* dispersion time of 28 sec, wetting time of 42 sec and control formulation (CPO) which shows 132 sec, 146 sec values respectively for the above parameters **(Table 3).**

The dissolution of MT from the tablets was shown in **Fig 3**. *In-vitro* dissolution studies on the promising formulations CP1and CP2 are promising fast dissolving tablet formulations containing co-processed superdisintegrant in 1:1 and 1:2 ratios, and PM1 is formulation containing physical mixture of superdisintegrant in 1:1 ratio, D_4 is percent drug released in 4 min, D_8 is percent drug release in 8 min, D_{12} is percent drug release in 12 min, D_{16} is percent drug release in 16 min, D_{20} is percent drug release in 20 min, and $t_{50\%}$ is time for 50 % drug released, $t_{90\%}$ is time for 90% drug released are shown in **Table 4**.

Table 2: Pre-compression parameters of MT FDT by co-processed superdisintegrant and physical mixture of superdisintegrant

Formulation code	Angle of Repose (θ) (±SD), n=3	Compressibility (%) (±SD), n=3	Hausner's Ratio (±SD), n=3
PM1	28.46 (1.22)	17.46 (0.22)	1.27 (0.03)
PM2	27.96 (2.12)	16.86 (0.16)	1.26 (0.05)
PM3	26.74 (1.42)	15.78 (0.44)	1.24 (0.02)
CP1	25.12 (1.32)	16.66 (0.38)	1.17 (0.04)
CP2	24.66 (0.84)	15.46 (0.44)	1.19 (0.03)
CP3	23.64 (0.74)	15.22 (0.42)	1.20 (0.05)

Note: *Values in parenthesis are standard deviation (±SD)*

Table 3: Evaluation of MT FDT Formulations

FC	Hardness test (kg/cm^2) ±SD, n=6	Friability (%) ±SD, n=10	Thickness (mm) ±SD, n=4	Drug content (%) ±SD, n=6	Wetting time (sec) ±SD, n=6	Disintegration time (sec) ±SD, n=6	Water absorption ratio (%), ± SD, n=3
CP0	2.86 (0.12)	0.52 (0.04)	2.19 (0.02)	99.46 (1.10)	146 (2.42)	132 (1.12)	83 (1.30)
PM1	3.12 (0.14)	0.61 (0.06)	2.18 (0.03)	98.74 (1.20)	46 (1.14)	32 (2.14)	76 (1.05)
PM2	3.16 (0.18)	0.64 (0.05)	2.20 (0.02)	98.36 (1.60)	54 (2.16)	39 (2.12)	72 (1.20)
PM3	3.19 (0.24)	0.72(0.04)	2.22 (0.04)	99.78 (1.30)	62 (2.12)	44 (1.14)	67 (1.21)
CP1	3.24 (0.12)	0.56 (0.03)	2.16 (0.03)	98.24 (1.20)	28 (2.16)	14 (2.12)	85 (1.35)
CP2	3.14 (0.22)	0.52 (0.02)	2.14 (0.02)	99.92 (0.90)	42 (1.22)	28 (1.14)	80 (1.12)
CP3	3.22 (0.24)	0.48 (0.05)	2.16 (0.04)	97.88 (1.20)	52 (2.12)	34 (1.12)	76 (1.05)

Note: *Values in parenthesis are standard deviation (±SD);* ***FC-*** *Formulation code.*

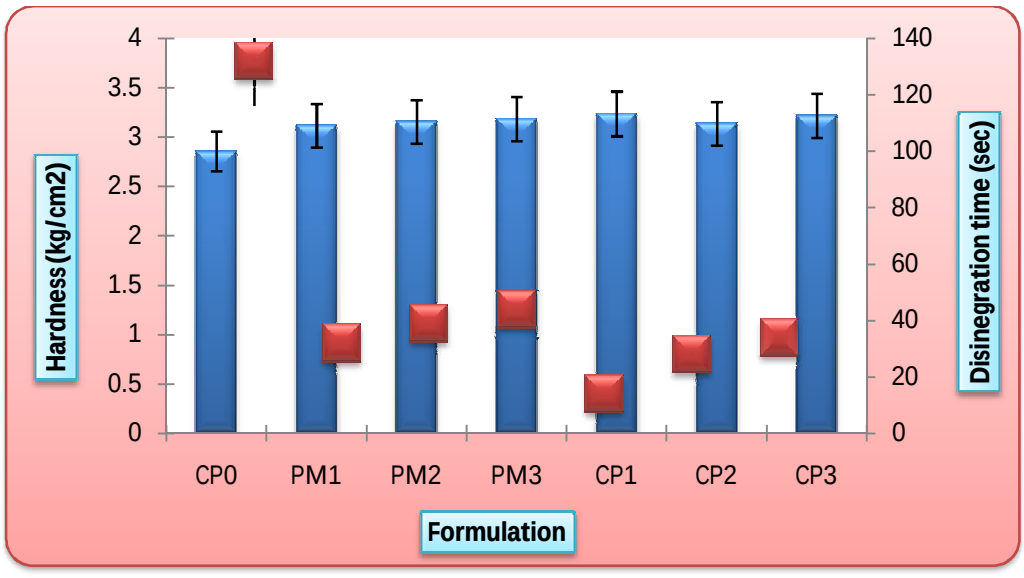

Figure 2: Graphical representation of Hardness and *In-vitro* Disintegration time of tablets containing Metoprolol Tartrate.

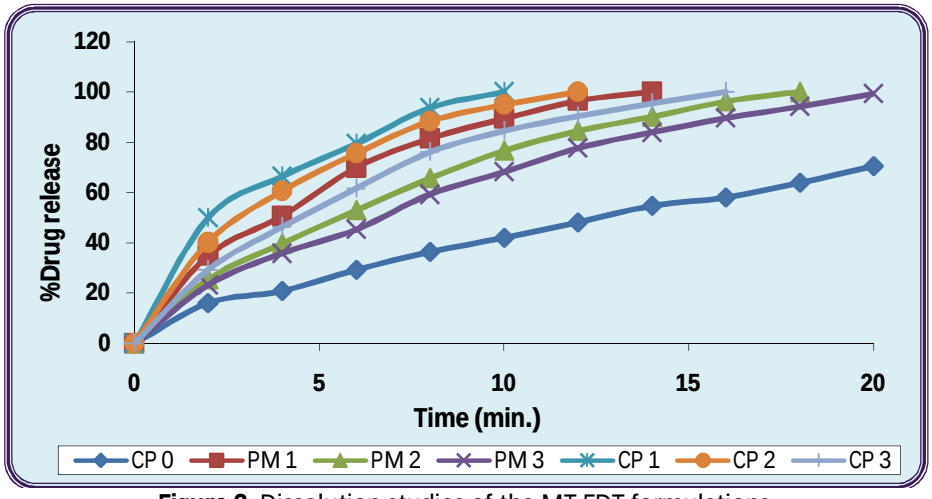

Figure 3: Dissolution studies of the MT FDT formulations

Table 4: *In- vitro* dissolution parameters of different fast dissolving MT tablet formulations

Formulation Code	Parameters						
	D_4	D_8	D_{12}	D_{16}	D_{20}	$T_{50\%}$	$T_{90\%}$
CP0	20.86	36.36	48.13	58.05	69.41	12.5 min	> 20 min
CP1	66.42	93.73	--	--	--	2.01 min	7.68 min
CP2	60.63	88.35	100	--	--	3.30 min	9.48 min
PM1	50.69	81.52	96.42	--	--	3.94 min	10.06 min

CP0 is control formulation, CP1and CP2 are promising fast dissolving tablet formulations containing co-processed superdisintegrant in 1:1 and 1:2 ratios, and PM1 is formulation containing physical mixture of superdisintegrant in 1:1 ratio, D_4 is percent drug released in 4 min, D_8 is percent drug release in 8 min, D_{12} is percent drug release in 12 min, D_{16} is percent drug release in 16 min, D_{20} is percent drug release in 20 min, and $t_{50\%}$ is time for 50 % drug dissolution, $t_{90\%}$ is time for 90% drug dissolution.

Table 5: Tablet parameters after stability studies

Formulation	Period	Drug content (%)	Wetting time(sec) (± SD), n=6	Dispersion time (sec) (± SD), n=6
CP1	1 Month	98.24 (1.20)	28 (2.16)	14 (2.12)
	2 Month	98.20 (1.40)	28 (2.10)	14 (2.16)
	3 Month	98.12 (1.26)	28 (1.14)	14 (1.14)
CP2	1 Month	99.92 (0.90)	42 (1.22)	28 (1.14)
	2 Month	99.82 (1.12)	42 (1.16)	28 (1.12)
	3 Month	99.74 (1.24)	42 (1.12)	28 (2.16)

This data reveals that among all the formulation CP1 shows nearly faster drug release. The formulations CP1 50 % of drug released in 2.01 min, and 90 % $_{of}$ drug released in 7.68 min. The formulation CP2 shows 50 % of drug released in 3.30 min, and 90 % $_{of}$ drug released in 9.48 min. Whereas CP0 control formulations 50 % of drug released in 12.5 min and 90 % of drug released were more than 20 min. The stability study for all the formulations were carried according to ICH guidelines by storing the tablets in a stability chamber (Lab care, Mumbai) at $40^0 \pm 2^0$ C/ 75 ± 5% RH for three months. There was no significant change in *in-vitro* dispersion time, wetting time and drug content of the formulation CP1 and CP2 **(Table 5).**

The IR spectrum of the pure drug MT (Racemic mixture), and PM1, CP1 and CP2 formulations were used in the present study shows characteristic absorption bands in the following IR region **(Fig 4).**

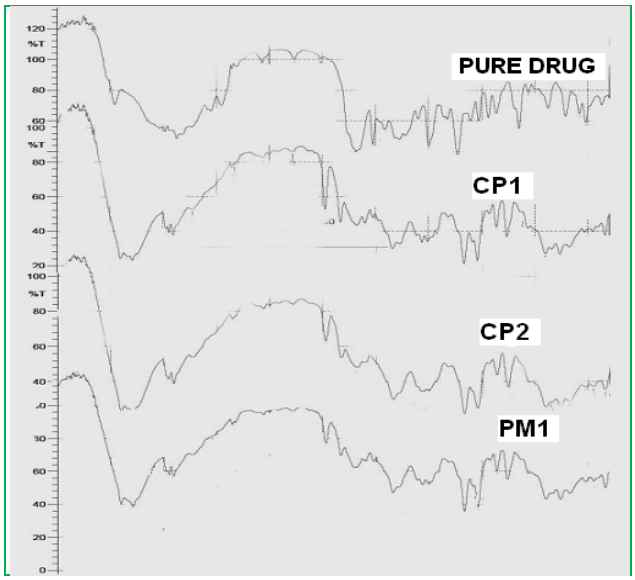

Figure 4: FTIR spectrum of pure drug MT, spectrum of formulation CP1, CP2 and PM1.

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. The drug Metoprolol tartrate is taken with CCS and CP shows 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.

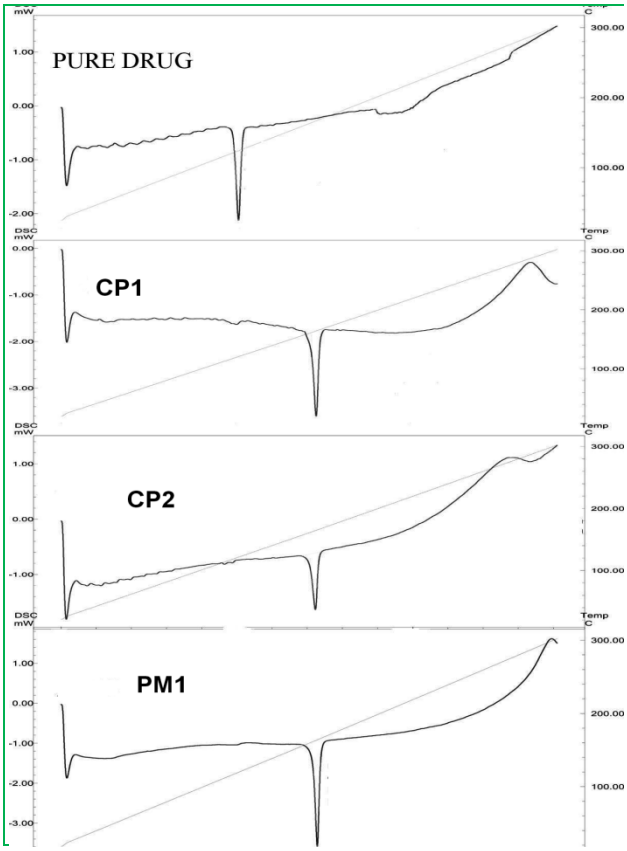

Figure 5: DSC thermograms of pure drug MT, CP1, CP2 and PM1 tablets.

In DSC study **(Fig 5)** when the drug MT and PM1 , CP1, and CP2 formulations were 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+CP' 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+CP' is a sodium salt of the carboxylic acid because of these two factors large range of variation has been observed.

CONCLUSION

MT tablets containing co-processed superdisintegrant exhibit quick disintegration and improved drug dissolution. Co-processing excipients lead to the formulation of excipients granules with superior properties, compared with physical mixtures of components or individual components, like improved flow properties, improved compressibility, better dilution potential, fill weight uniformity, and reduced lubricant sensitivity. It can be concluded from the present work that co-processed superdisintegrant of CP and CCS are superior to physical mixtures of CP and CCS used in MT fast dissolving tablets.

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