FORMULATION & EVALUATION OF FAST DISSOLVING TABLETS OF AMLODIPINE BESYLATE BY USING CO-PROCESSED SUPERDISINTEGRANTS

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ABSTRACT

AIMS: To formulate fast dissolving tablets of amlodipine besylate using co-processed superdisintigrant and evaluate the properties of fast dissolving tablets.

Study Design: Formulation, evaluation of fast dissolving tablets of amlodipine besylate.

Place and Duration of Study: Department of Quality Assurance S. N. D. College of Pharmacy Babhulgoan Yeola Dist Nashik 423401, between July 2012 to February 2013.

Methodology: In the present study, novel co-processed superdisintegrants were developed by solvent evaporation method using crospovidone and sodium starch glycolate in different ratios (1:1, 1:2 1:3 2:1, 3:1) in the fast dissolving tablet formulations. The developed excipients were evaluated for angle of repose, Carr's index and Hausner's ratio in comparison with physical mixture of superdisintegrants. Fast dissolving tablets of Amlodipine Besylate were prepared using co-processed superdisintegrants and evaluated for pre-compression and post-compression parameters. Effect of co-processed superdisintegrants (crospovidone (polyplasdone XL) and sodium starch glycolate) on wetting time, disintegrating time, drug content, *in-vitro* release, and stability parameters have been studied.

Results: The angle of repose of the developed excipients was found to be < 30^0 Compressibility (%) index in the range of 13.14 to 14.63 % and Hausner's ratio in the range of 1.15-1.19. The prepared tablets were characterized by FTIR and DSC Studies. Based on *in vitro* dispersion time (approximately 40 sec), promising formulation CP5 was tested for *in-vitro* drug release pattern in phosphate buffer pH 6.8.

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Conclusion Among the designed formulations, the formulation (CP5) containing co-processed superdisintegrant (3:1 mixture of crospovidone and sodium starch glycolate) emerged as the overall best formulation based on drug release characteristics in phosphate buffer pH 6.8. From this study, it can be concluded that dissolution rate of amlodipine besylate could be enhanced by tablets containing co-processed superdisintegrant.

Key Words: co-processed mixture, sodium starch glycolate, crospovidone. amlodipin besylate, FDT.

1 INTRODUCTION

Hypertension is becoming an important public health challenge worldwide. Hypertension is one of the main risk factors for cardiovascular diseases, which is one of the leading causes of death in developed countries. The number of adults with hypertension in 2025 was predicted to increase by about 60% to a total of 1.56 billion. (1) The relationship between blood pressure and risk of cardiovascular disease is continuous, consistent and independent of other risks. The higher the blood pressure, the greater is the chance of ischemic heart disease, stroke, heart failure and kidney diseases. Therefore prevention, detection, treatment and control of hypertension should receive high priority (2). Many patients have difficulty to swallow tablets and hard gelatin capsules. This results in high incidence of noncompliance and ineffective therapy. (3).There is unavailability of water during travelling, to overcome these problems fast dissolving tablet is emerged. FDT dissolves rapidly in the saliva without the need for water, faster the dissolution and provide quick onset of action. The bioavailability of drug is significantly enhanced by avoiding first pass hepatic metabolism than conventional tablets. (4)

Amlodipine is a dihydropyridine calcium antagonist (calcium ion-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. It binds to both dihydropyridine and non dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extra cellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.(5) Amlodipine is an ionized compound having ionization value 8.6 (pKa = 8.6) (6).

The bioavailability of amlodipine besylate, the functionality of excipients is improved by co-processed method. (7)

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 Co-processing excipients lead to the formulation of excipient 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) Several co-processed superdisintegrants are commercially available: Ludipress (lactose monohydrate, polyvinylpyrrolidone 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).

In present study, the preparation and evaluation of FDT by using co processed superdisintegrants containing crospovidone and sodium starch glycolate was studied. The reasons for selection of crospovidone are high capillary activity, pronounced hydration capacity and little tendency to form gels. Sodium starch glycolate has high swelling capacity (10)**.** The concept of formulating fast dissolving tablets (FDT) of amlodipin besylate (anti-hypertensive) using co-processed superdisintegrants 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.

2. MATERIALS AND METHODS

2.1 Materials

Amlodipine besylate is procured by wockhardt Aurangabad, crosspovidone and sodium starch glycolate are gifted by Sai Tech Lab. Sinner (Nasik), Microcrystalline Cellulose, Manitol Isopropyl alcohol procured by our college.

2.2 Methods

2.2.1 Preparation of Co-processed Superdisintegrants

The co-processed superdisintegrants were prepared by solvent evaporation method. Crospovidone and sodium starch glycolate (in the ratio of 1:1, 1:2, 1:3, 2:1, 3:1) were mixed together with 10 ml of isopropyl alcohol. The contents of beaker (250 ml capacity) were mixed thoroughly and stirring continue till most of isopropyl alcohol 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 sieves and stored in airtight container till further use.(11)**.(**Table 1).

Table 1. Different batches of superdisintigrants.

Batch code	PM1	PM2	PM3	PM4	PM5	CP1	CP2	CP3	CP4	CP5
Cp	1	1	1	2	3	1	1	1	2	3
SSG	1	2	3	1	1	1	2	3	1	1

PM - Physical Mixture CP - Co-processed Superdisintegrants of Cp and SSG in different ratios (1:1, 1:2, 1:3, 2:1,3:1), Cp – Crosspovidone, SSG – Sodium Starch Glycolate

Table 2. Formulations of Amlodipin Besylate FDT Prepared by Direct Compression Method

Ingredients	Formulation code										
	CP0	PM 1	PM 2	PM 3	PM 4	PM 5	CP 1	CP 2	CP 3	CP 4	CP 5
Amlodipin Besylate	5	5	5	5	5	5	5	5	5	5	5
CP(Crospovidone + SSG)	-	6	6	6	6	6	6	6	6	6	6
Aspartame	3	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	3	3	3	3	3	3	3	3	3	3	3
Flavour	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Microcrystalline cellulose	30	30	30	30	30	30	30	30	30	30	30
Mannitol	106	100	100	100	100	100	100	100	100	100	100
Total weight (mg)	150	150	150	150	150	150	150	150	150	150	150

2.3 Preparation of Fast Dissolving Tablets

Fast dissolving tablets of amlodipine besylate 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 150 mg using LAB PRESS compression machine with 12 compression stations and 8 mm round flat punches are used for tablet compression(Table no 2).(12)

3 Evaluation of Amlodipin Besylate Fast Dissolving Tablets

3.1 Pre compression evaluation parameters

3.1.1 Angle of repose

Angle of repose is defined as the maximum angle possible between the surface of a pile of the

powder and horizontal plane. It is calculated by using following formula.

$$\text{Tan } \Theta = h / r$$

$$\Theta = \tan^{-1} (h/r)$$

Where, Θ is the angle of repose

h is height of pile

r is radius of the base of pile

3.1.2 Bulk Density:

Bulk density is defined as the mass of a powder divided by the bulk volume. Loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of accurately weighed powder was introduced into a *25* ml 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 2.5 cm at 2 sec interval. The taping was continued until no further change in volume was noted. LBD and TBD were calculated using following formula;

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

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

3.1.3 Tapped Density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. Electrolab Tap Density Tester USP ETD-1020 is used for determination of tapped density. The tapped density (pt) was calculated using the following formula

$$\rho t = \frac{M}{Vt}$$

3.1.4 Hausner Ratio

Hausner ratio is an indirect index of ease of power flow. It is calculated by the following formula.

$$\text{Hausner Ratio} = \frac{\rho t}{\rho d}$$

Where ρ_t is tapped density and ρ_d is bulk density. Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

3.2. Post compression evaluation parameters

3.2.1. Weight Variation

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. (13)

3.2.2. Thickness variation

Ten tablets from each formulation were taken randomly and their thickness was measured with a micrometer screw gauge.

3.2.3. Hardness and Friability

Hardness of the tablets was measured using the Monsanto Hardness Tester (Pharmalab, Ahmedabad, India). The friability of a sample of twenty tablets was measured using Roche friabilator (Pharma lab, Ahmedabad, India). Pre-weighed tablets were placed in the plastic chamber of 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.

3.2.4. Fourier Transform Infrared Spectroscopy (FTIR)

The samples of amlodipine besylate and co-processed mixture of crosspovidone and sodium starch glycolate are scanned by using Model ALPHA Brucker ECO-ATR. The scanning range was from 4000-400 cm^{-1}.

3.2.5. Drug Content Uniformity.

For the content uniformity test, ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 10 mg of amlodipin besylate was extracted into distilled water and liquid was filtered (0.22 µm membrane filter disc. The amlodipin besylate content was determined by measuring the absorbance at 235.7 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. (14)

3.2.6. In Vitro Dispersion Time

One tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffers at 37±0.5ºC and the time required for complete dispersion was determined.

3.2.7. Wetting Time and Water Absorption Ratio (R)

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:

$$R = 100 \times (Wa - Wb)/ Wb$$

Where;

Wb and **Wa** were tablet weights before and after water absorption, respectively.

3.2.8. *In Vitro* Drug Release Study

In vitro dissolution studies of the promising fast dissolving tablets of amlodipin besylate, all formulations were performed according to USP XXIII Type-II dissolution apparatus employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffers at 37±0.5ºC as dissolution medium. One tablet was used in each test. Aliquots of the dissolution medium (5 ml) were withdrawn at specific time intervals (1, 2, 3, 4, 5, 10, 15, 20, 25 & 30 min) and replaced immediately with equal volume of fresh medium. The samples were analyzed for drug content by measuring the absorbance at 237.5 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. (15)

3.2.9 Stability Studies

The promising formulations were subjected to short term stability study by storing the formulations at 40°C/75% RH up to three month. The formulations **PM1 PM5 CP1 CP5 w**ere selected. After one month the tablets were again analyzed for the hardness, friability, drug content uniformity and dispersion time. The increase in the disintegration time was observed in case of tablets prepared with physical mixture method. This may be due to increase in the hardness of the tablets during storage. Decrease in the disintegration time was observed in tablets prepared by co-processed mixture method. No change was observed in the disintegration time and hardness of tablets prepared by other technique. No significant change was observed in the drug content of all formulation.

4 RESULTS AND DISCUSSION

Co-processed superdisintegrants were prepared by solvent evaporation using crospovidone and sodium starch glycolate in different ratios (1:1, 1:2, 1:3, 2:1,and 3:1).The co-processed superdisintegrants were evaluated for their flow and compression properties in comparison with physical mixture of superdisintegrants. The angle of repose of co processed superdisintegrants was found to be $<25^0$ which indicate excellent flow in comparison to physical mixture of superdisintegrants ($<30^0$) due to granule formation, Carr's index in the range of 10- 15% and Hausner's ratio in the range of 1.14-1.18.Tapped

density was determinened by using Electrolab Tap Density Tester USP ETD-1020.Bulk density and tapped density of superdisintigrants (physical and co-processed mixture) was found to be within range 0.32-0.44 and 0.41-0.51 respectively.

Table3.Pre-compression Parameters of Co-processed and Physical Mixture of Superdisintegrants

Formulation Code	Parameters				
	Bulk density (g/cc)	Tapped density(g/cc)	Angle of repose	Carr's index (percent)	Hausner's Ratio
PM 1	0.35	0.41	29.14	14.63	1.171
PM 2	0.38	0.44	27.50	13.72	1.165
PM 3	0.40	0.46	25.10	13.14	1.160
PM 4	0.41	0.48	25.15	13.55	1.172
PM 5	0.44	0.51	25.00	13.77	1.176
CP 1	0.36	0.42	24.45	14.23	1.167
CP 2	0.38	0.44	23.40	13.75	1.159
CP 3	0.32	0.38	22.90	14.15	1.180
CP 4	0.35	0.42	22.82	14.31	1.175
CP 5	0.40	0.47	22.50	14.16	1.179

Total ten formulations and control formulation were designed. As the blends were free flowing (angle of repose $<30^0$ and Carr's index <15% Table 4), tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specification i.e., below 7.5%. Drug content was found to be in the range of 97 to 101%, which is within acceptable limits. Hardness of the tablets was found to be in the range of 3.1-3.40 kg/cm^2. Friability below 1% was an indication of good mechanical resistance of the tablets. 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 53-78% and 30-85 sec respectively. Among all the designed formulations, formulation CP5 was found to be promising and displayed an *in vitro* dispersion time of 40 sec, which facilitates faster dispersion.

Table 4. Pre-compression Parameters of Amlodipin Besylate FDT Formulations Prepared by Direct Compression Method

Formulation code	Parameter				
	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose(degree)	Carr's index (percent)	Hauser's Ratio
CP 0	0.47±0.030	0.53±0.031	31.25±1.023	12.90±2.985	1.177±0.019
PM 1	0.45±0.031	0.53±0.025	29.14±1.025	14.81±1.56	1.172±0.021
PM 2	0.46±0.016	0.54±0.024	27.45±0.956	14.52±1.25	1.172±0.025
PM 3	0.47±0.021	0.55±0.031	25.15±0.911	12.96±1.364	1.169±0.027
PM 4	0.47±0.012	0.54±0.026	27.5±0.892	14.02±1.89	1.152±0.015
PM 5	0.46±0.016	0.54±0.020	26.7±1.012	12.96±1.715	1.165±0.013
CP 1	0.47±0.024	0.54±0.030	24.15±1.123	13.23±1.62	1.159±0.014
CP 2	0.465±0.020	0.53±0.024	23.30±1.002	14.51±1.31	1.142±0.019
CP 3	0.47±0.024	0.54±0.025	23.05±0.856	13.21±1.65	1.162±0.017
CP 4	0.46±0.021	0.52±0.022	22.8±0.752	13.22±1.82	1.152±0.019
CP 5	0.47±0.26	0.53±0.019	22.5±0.926	13.11±1.62	1.155±0.021

Overall, the formulation CP5 containing co-processed superdisintegrant (3:1 mixture of crospovidone and sodium starch glycolate) was found to be promising and has shown an *in vitro* dispersion time of 40 sec, wetting time of 35 sec and water absorption ratio of 78% when compared to the formulation PM5 containing physical mixture of superdisintegrants (3:1 mixture of crospovidone and sodium starch glycolate) which shows 50 sec, 40 sec and 65% values respectively and control formulation (CP0) which shows 105 sec, 85 sec and 42% values respectively for the above parameters (Table 5).

Table 5. Evaluation of Amlodipin Besylate FDT Formulations (1)

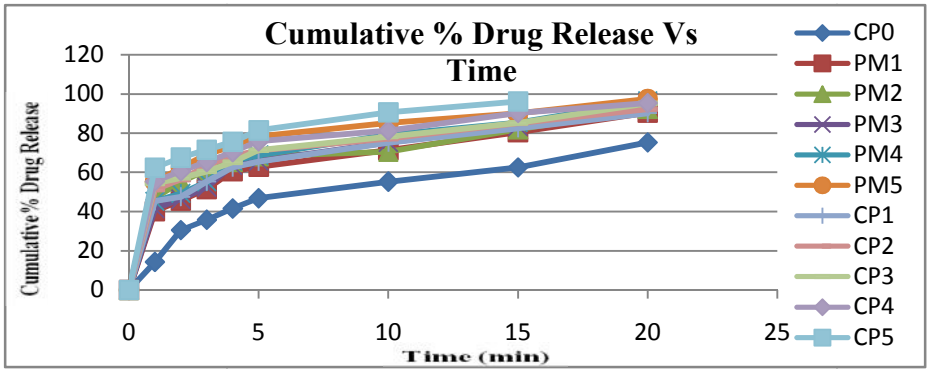
Formulation code	Parameter			
	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	*In vitro* Dispersion time (sec)
CP 0	3.15±0.152	0.72±0.034	3.28±0.0032	105± 5.5
PM 1	3.16±0.143	0.65±0.032	3.32±0.036	60±2.5
PM 2	3.22±0.124	0.61±0.021	3.48±0.016	70±5.8
PM 3	3.12±0.125	0.65±0.032	3.52±0.020	65±2.4
PM 4	3.21±0.123	0.71±0.021	3.26±0.024	60±3.5
PM 5	3.25±1.13	0.75±0.034	3.36±0.016	50±2.5
CP 1	3.32±1.02	0.63±0.045	3.42±0.042	55±5.2
CP 2	3.24±1.145	0.61±0.034	3.24±0.030	62±2.5
CP 3	3.35±1.143	0.55±0.043	3.26±0.020	57±2.54
CP 4	3.19±1.132	0.51±0.045	3.46±0.016	50±2.8
CP 5	3.25±1.234	0.50±0.035	3.48±0.030	40±2.5

Table 5. Evaluation of Amlodipin Besylate FDT Formulations (2)

Formulation code	Wetting time (sec)	Water absorption ratio (%)	% drug content	Weight Variation
CP 0	85±2.3	42±1.5	97.68±2.1	
PM 1	51±3.1	55±2.1	98.58±2.2	
PM 2	59±4.5	58±2.5	97.27±1.2	
PM 3	55±2.5	60±2.6	98.15±2.4	143-
PM 4	51±2.5	62±2.8	97.57±2.62	157mg
PM 5	41±2.8	65±2.5	101.15±2.5	±7.5
CP 1	49±1.8	52±1.9	97.58±2.4	
CP 2	52±3.5	55±2.53	97.33±2.56	
CP 3	45±4.2	65±2.15	97.58±2.54	
CP 4	41±3.5	73±2.5	98.2±2.25	
CP 5	30±4.2	78±3.5	99.85±2.5	

The percentage drug release by each tablet in the *in vitro* drug release studies were based on the mean content of the drug present in respective tablet. The result of *in vitro* disintegration of all the tablets were found to be within prescribed limit and satisfy the criteria of FDT. Overall the FDT formulations of amlodipine besylate showed an average of 80.56 to 96.15% drug release range at the end of 15 min and it was also observed that formulations CP 5 took shortest time to release the maximum amount of drug whereas the other formulations took more than 15 min to release the drug.

Fig. 1. In vitro cumulative release of Amlodipine besylate (SD n=3)



Formulations **PM1, PM5, CP1, CP5,** subjected for one month stability studies. After one month there is No change was observed in the disintegration time and hardness of tablets prepared by other technique. No significant change was observed in the drug content of all formulation.

Amlodipine undergoes a polymorphic change during preparation of FDTs and to test for possible intermolecular interactions between Amlodipine besylate and mixture of drug and co-processed polymer, FTIR was used. The FTIR spectra of pure Amlodipine, Amlodipine with -processed polymer are depicted in (figure 2). All the principal IR peaks of Amlodipine were present in formulations this clearly indicates that there is no interaction between Amlodipine and excipients.

The drug and co-processed mixture of crosspovidone and sodium starch glycolate were subjected to DSC studies; the spectra are shown in fig 3 and 4. Drug alone shows sharp endothermic peak near217.93^{0}C. In the spectra of the complex the peaks is at 215.34^{0}c . peak is widened and slightly shifted indicating complex formation, and compatibility with each other.

Fig. 2. IR Spectra Pure Drug, and Drug + Co-Processed Mixture

(red- pure drug , blue-mixture)

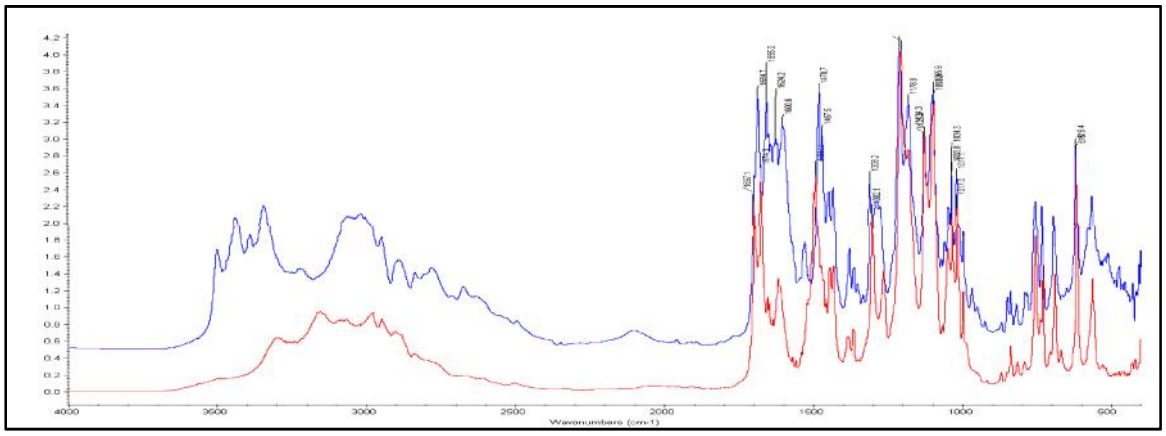


Fig 3 DSC of Pure Drug

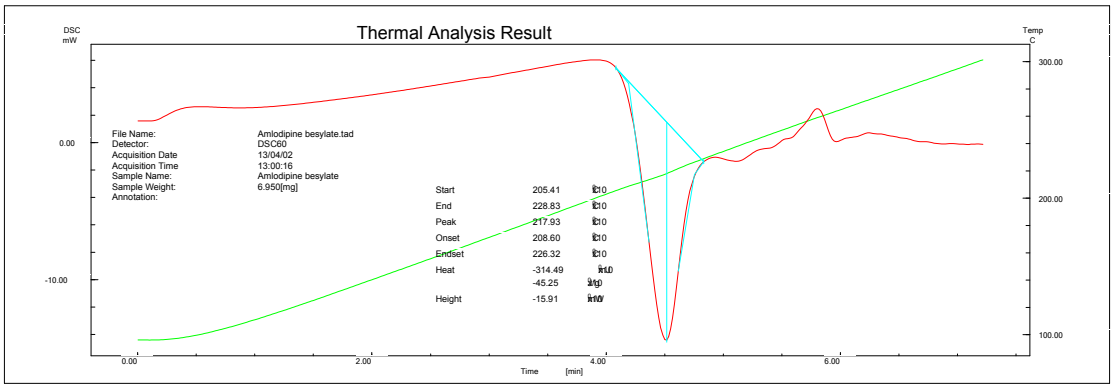
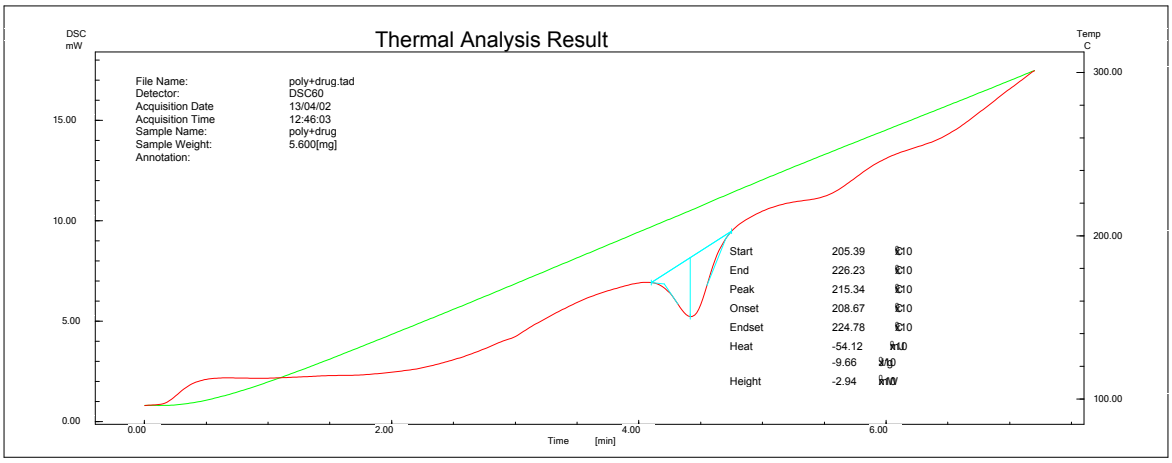


Fig 4 DSC of drug + polymer



5 CONCLUSION

The use of Co-processed superdisintegrants consist of crospovidone and sodium starch glycolate in formulation exhibit good flow and compression characteristics. Amlodipin Besylate tablets containing co-processed superdisintegrants exhibit quick disintegration and improved drug dissolution. It can be concluded from the present work that co-processed superdisintegrants of crospovidone and sodium starch glycolate are superior to physical mixtures of crospovidone and sodium starch glycolate used in Amlodipin Besylate fast dissolving tablets.

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