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Research article

FORMULATION, OPTIMIZATION AND EVALUATION OF BILAYERED TABLETS OF AMLODIPINE BESILATE AS IMMEDIATE RELEASE AND METOPROLOL SUCCINATE AS SUSTAINED RELEASE

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ABSTRACT: The purpose of the study was to develop a bilayer tablet of Amlodipine besilate (IR) and Metoprolol succinate (SR) having different release pattern, which is indicated for the management of hypertension. The study was planned in three stages. In the first stage six batches (A1, A2, A3, A4, A5 and A6) of immediate release tables of Amlodipine besilate was prepared by direct compression method using sodium starch glycolate and pre-gelatinised starch as super disintegrant. In the second stage, six batches(M1, M2, M3, M4, M5, M6) of Metoprolol succinate sustained release part was prepared using HPMC polymers as rate retardant. Preformulation studies were performed prior to compression. In the third stage compressed bilayer tablets were evaluated for weight variation, dimension, hardness, friability, drug content, and disintegration time and invitro drug release using RP-HPLC. DSC studies revealed no disturbances in the principle peaks of pure drugs Metoprolol succinate and Amlodipine besilate and it confirms the integrity and compatibility of pure drugs with their excipients. The stability studies were performed for optimised batch for three months and it showed acceptable results.

Keywords : Bilayer tablet, Amlodipine besilate, Metoprolol succinate, HPMC polymers, HPLC.

INTRODUCTION

Hypertension is the most common cardiovascular disease. The prevalence of hypertension increases with advancing age (Chobanian A.V., Bakris G.L., Black H.R. *et al*, 2003). Arterial pressure is the product of cardiac output and peripheral vascular resistance. Drugs lower blood pressure by actions on peripheral resistance, cardiac output, or both. Drugs may reduce the cardiac output by inhibiting myocardial contractility or by decreasing ventricular filling pressure. Drugs can reduce peripheral resistance by acting on smooth muscle to cause relaxation of resistance vessels or by interfering with the activity of systems that produce constriction of resistance vessels (*e.g.,* the sympathetic nervous system). In patients with isolated systolic hypertension, complex hemodynamic in a rigid arterial system contribute to increased blood pressure; drug effects may be mediated by changes in peripheral resistance but also *via* effects on large artery stiffness (Franklin, S. 2000).

Metoprolol succinate, β_1-selective adrenergic receptor blocking agent used in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism and in the prophylactic treatment of migraine. The half-life of drug is relatively short approximately 4-6hrs and in normal course of therapy drug administration is required every 4-6hrs, thus warrants the use of sustained release formulation for prolong action and to improve patient compliance (Deshmukh, V.N., Singh, S.P. & Sakarkar D.M., 2009). Ca^{2+} channel blocking agents are an important group of drugs for the treatment of hypertension. Amlodipine is a prototype second generation dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. It has a longer duration of action (i.e.) half life of 40 hours and the initial effects are cumulative over many days and more over for patient compliance in case of anti angina patients, a rapid onset of action is necessary for immediate pain relief. Hence Amlodipine can be given as a single immediate release dose (Weber M.A., 2002).

In recent times, multi-layer matrix tablets are gaining importance in the design of oral controlled drug delivery systems. Bi-layer tablets are novel drug delivery systems where combination of two or more drugs in a single unit. They are preferred for the following reasons: to co-administer two different drugs in the same dosage form, to minimize physical and chemical incompatibilities, for staged drug release, IR and SR in the same tablet, for chronic condition requiring repeated dosing. In the present study a combination drug therapy is recommended for treatment of hypertension to allow medications of different mechanism of action to complement each other and together effectively lower blood pressure at lower than maximum doses of each. The rational for combination therapy is to encourage the use of lower dose of drug to reduce the patient's blood pressure, minimize dose dependent side effects and adverse reactions (Mohamed Halith S. *et al.*, 2011).

MATERIALS AND METHODS

Materials

The following materials were obtained from The Madras Pharmaceuticals as gift samples. They were Metoprolol succinate USP, HPMC K- 100 IP, HPMC K- 4M IP, MCC PH 102 IP, Polyvinyl pyrrollidone K-30 IP, Isopropyl Alcohol IP, Purified Talc IP, Sodium Stearyl Fumarate IP,S. Amlodipine besilate IP, Dicalcium Phosphate IP, Starch 1500 IP, Colloidal Silicon Dioxide IP, Quinoline Yellow Lake, Magnesium Stearate IP, Aerosil, Sodium Starch Glycolate IP, Lactose DCL 11.

Methods of Preparation

The study was planned in three stages
1. Formulation of Amlodipine besilate immediate release layer and evaluation.
2. Formulation of Metoprolol succinate sustained release layer and evaluation.
3. Formulation of compressed bi-layer tablets of IR and SR part and evaluation (Jeong-Soo Kim *et al., 2011*).

Formulation of Amlodipine besilate immediate release layer

In the first stage, six batches (A1, A2, A3, A4, A5, A6) of immediate release tablet of Amlodipine besilate was prepared by direct compressed method using various ratios of Sodium Starch Glycolate and pre-gelatinised Starch as a super disintegrant and the formula was given in the **table.1**

Amlodipine besilate IR tablets were prepared by direct compression method. The microcrystalline cellulose, di-calcium phosphate, pre-gelatinised, sodium starch glycolate and the active ingredient were passed through sieve no.40 and mixed homogenously. Magnesium stearate and aerosol were passed through sieve no.60 and added as a lubricant to the above dry mixture and mixed well for five minutes. Finally the colorants quinoline yellow lake was sieved through sieve no.100 mess and then mixed with dry mix homogenously to get uniform blend without mottling.

Table .1: Formula for Amlodipine Besilate immediate release layer (in w/w %)

S. No.	Ingredients	Batch					
		A1	A2	A3	A4	A5	A6
1	S. Amlodipine Besilate	4.17	4.17	4.17	4.17	4.17	4.17
2	Lactose DCL 11	45.83	37.50	45.83	37.50	45.83	37.50
3	Starch 1500	1.67	1.67	1.67	1.67	1.67	1.67
4	Microcrystalline Cellulose PH102	41.67	50.00	41.67	50.00	41.67	50.00
5	Sodium Starch Glycolate	3.08	2.25	3.08	2.25	2.25	2.50
6	Polyvinyl Pyrolidone K 30	1.25	2.08	1.25	2.08	2.08	1.83
7	Colour	0.04	0.04	0.04	0.04	0.04	0.04
8	Aerosil	0.20	0.20	0.20	0.20	0.20	0.20
9	Magnesium Stearate	2.08	2.08	2.08	2.08	2.08	2.08

Formulation of Metoprolol succinate sustained release layer

In the second stage six batches (M1, M2, M3, M4, M5, M6) of Metoprolol succinate sustained release tablet which contains HPMC K100 and HPMCK4M in different ratios were prepared and the formula was given in the table.2

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Metoprolol succinate sustained release layer were prepared by wet granulation method. The hydroxyl propyl methyl cellulose (HPMC K100 & HPMC K4M), MCC PH101 and Metoprolol succinate were passed through sieve no. 30 and mixed homogenously. For the binder solution weighed amount of PVP K30 was added little by little in isopropyl alcohol with continuous stirring to avoid lumps. The binder solution was slowly added to the above blend and mixed well to get a final coherent mass. These granules are air dried initially and pass through mess no. 20. The resultant granules left on the sieve were milled through sieve no. of pore size 1.5mm. The granules were finally dried at 60˚C till a constant LOD reaches (3-4%). Talc and sodium starch fumarate were added to the dried granules and homogenously mixed.

Table 2: Formula for Metoprolol Succinate extended release layer (in w/w %)

S. No.	Ingredients	Batch					
		M1	M2	M3	M4	M5	M6
1	Metoprolol Succinate	15.83	15.83	15.83	15.83	15.83	15.83
2	HPMC K100	32.66	37.33	42	46.66	51.33	55.67
3	HPMC K4M	9.33	9.33	9.33	9.33	10	10
4	Microcrystalline Cellulose PH101	37.50	31.60	26.30	21.16	15.36	8.85
5	Polyvinyl Pyrolidone K 30	1.86	2.63	2.80	3.26	3.26	3.26
6	Isopropyl Alcohol	qs	qs	qs	qs	qs	Qs
7	Magnesium Stearate	0.93	1.40	1.86	-	-	-
8	Sodium Steryl Fumerate	-	-	-	1.86	2.33	4.53
9	Talc	0.93	0.93	0.93	0.93	0.93	0.93
10	Colour	0.93	0.93	0.93	0.93	0.93	0.93

Formulation of compressed bi-layer tablets

The bilayer tablet compression was made using 14/32 mm punch in a 27 station rotary tablet machine with double feed. In this, sustained release Metoprolol succinate granules were introduced first in to die cavity and a slight compression was made so that the layer was uniformly distributed. After that immediate release Amlodipine besilate granules were added through the other feed and a final compression was made (Baojian Wu *et al., 2007*).

Evaluation of Granules Flow Properties

The prepared granules were evaluated for bulk density, tap density, Carr's index, Angle of Repose, Hausner's ratio, and loss on drying (Lachman L., 1987; Nakhat P.D., 2002) and the results are as in table 3 and 4.

Table 3: Preformulation parameters of Amlodipine Besilate (A1-A6)

Batch Code	Angle of Repose (θ)	Bulk Density(g/cm^3)	Tapped Density(g/cm^3)	Carr's Index	Loss on Drying (%)
A1	33.69	0.3846	0.4166	7.68	6.5%
A2	32.38	0.3703	0.4347	14.81	5.2%
A3	34.99	0.3571	0.4347	17.85	5.2%
A4	44.16	0.3333	0.4000	16.67	5.9%
A5	36.59	0.3225	0.4000	19.36	6.2%
A6	32.38	0.3125	0.3921	20.30	6.1%

Table 4: Preformulation parameters of Metoprolol Succinate (M1-M6)

Batch Code	Angle of Repose (θ)	Bulk Density(g/cm^3)	Tapped Density(g/cm^3)	Carr's Index	Loss on Drying (%)
M1	28.95	0.3076	0.3333	7.71	4.2
M2	32.38	0.3571	0.4166	14.28	4.9
M3	32.55	0.2272	0.2500	9.21	3.9
M4	32.20	0.2777	0.2940	5.57	3.2
M5	34.90	0.3030	0.4000	24.25	4.4
M6	29.16	0.3030	0.3571	15.14	4.3

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Methods of Evaluation
Assay

Column	:	Inertsil ODS C18, 250 x 4.6mm
Detector Wavelength	:	215mm
Flow Rate	:	1.0ml/min
Injection Volume	:	50µl
Mobile Phase	:	Buffer: Acetonitrile (80:20)

Buffer Preparation
Fifty millilitre of one molar Monobasic Sodium Phosphate dilute with water to thousand millilitres, pH adjusts to 3.0 with Phosphoric acid solution. Filter and degas before use.
Standard Stock Preparation (A)
Weigh accurately thirty five milligram of Amlodipine Besilate working standard in a hundred millilitre volumetric flask dissolve in a dissolution medium make up the volume with same.
Standard Stock Preparation (B)
Weigh accurately ninety five milligram of Metoprolol Succinate working standard in a hundred millilitres volumetric flask dissolve in a dissolution medium make up the volume with same.
Procedure
Inject fifty micro litre sample preparation into the liquid chromatography and record the chromatogram. Measure the responses for the major peaks. Calculate the dissolve quantity of Amlodipine Besilate in sixty minutes and Metoprolol Succinate in first, fourth, eighth and twelfth hour from the peak areas of standard and sample preparation and percentage of potency of working standards used (United States Pharmacopoeia 1980; Ravouru Nagaraju *et al.*, 2009).
Calculation: For Amlodipine Besilate

$$\frac{\text{Sample area}}{\text{Standard area}} \times \frac{\text{Standard Weight}}{100} \times \frac{2}{50} \times \frac{500}{\text{Label Claim}} \times \frac{\text{Std. purity}}{100}$$

x 100 x 0.721 = percentage release for Amlodipine.

Calculation: For Metoprolol Succinate eq. To Metoprolol Tartarate

$$\frac{\text{Sample area}}{\text{Standard area}} \times \frac{\text{Standard Weight}}{100} \times \frac{5}{50} \times \frac{500}{\text{Label Claim}} \times \frac{\text{Std. purity}}{100} \times 100 \times 1.049$$

= percentage release for Metoprolol.

Invitro Drug Release Studies

Column	:	Inertsil ODS C18
Detector Wavelength	:	215mm
Flow Rate	:	1.0ml/min
Injection Volume	:	50µl
Mobile Phase	:	Buffer: Acetonitrile (80:20)
Diluents (1st Dilution)	:	Methanol: Acetonitrile (1:1); Mobile phase (2nd Dilution)

Buffer Preparation

Fifty millilitre of one molar Monobasic Sodium Phosphate dilute with water to thousand millilitres, pH adjust to 3.0 with Phosphoric acid solution filter and degas before use.

Standard Amlodipine Stock Preparation

Weigh accurately seventy milligram of Amlodipine Besilate working standard in a fifty millilitre volumetric flask dissolve in diluents make up the volume with diluents.

Standard Preparation

Take five millilitre from the above Amlodipine stock solution adds 47.5mg of Metoprolol Succinate working standard in a hundred millilitre volumetric flask. Add about ten millilitres of diluents, sonicate to dissolve, make up to the mark with diluents. Again dilute 10ml from the above solution to fifty millilitres with mobile phase.

Sample Preparation

Transfer about ninety five milligram equivalent of Metoprolol Succinate in a two hundred millilitre volumetric flask, dissolve with diluents and make up the volume with the same. Centrifuge the solution. Filter the supernatant liquid with 0.45 micron membrane filter. Dilute ten millilitres from the solution to fifty millilitres with mobile phase.

Procedure

Separately inject fifty micro litre of the standard preparation and assay preparation into the chromatograph, record the chromatograms and measure the responses for the major peaks (Arunachalam A. *et al.*, 2010; Narmada G.Y. *et al.*, 2009; United States Pharmacopoeia, 2007).

Assay of Amlodipine IR Part

$$\frac{\text{Sample area}}{\text{Standard area}} \times \frac{\text{Standard Weight}}{100} \times \frac{5}{50} \times \frac{100}{\text{Sample weight}} \times \frac{50}{5} \times \frac{\text{Std. purity}}{100}$$

$$\times U = \frac{\text{Drug in mg}}{\text{Label Claim}} \times 100 = \text{percentage of drug}$$

Where, U = conversion factor x Average weight

Assay of Metoprolol SR Part

$$\frac{\text{Sample area}}{\text{Standard area}} \times \frac{\text{Standard Weight}}{100} \times \frac{5}{50} \times \frac{100}{\text{Sample weight}} \times \frac{50}{5} \times \frac{\text{Std. purity}}{100}$$

$$\times U = \frac{\text{Drug in mg}}{\text{Label Claim}} \times 100 = \text{percentage of drug}$$ Where, U = conversion factor x Average Wt.

RESULTS

Six batches (AM1, AM2, AM3, AM4, AM5, AM6) of compression bilayer tablets were evaluated for average weight, hardness, disintegration test, content uniformity, assay and invitro drug release. The data are given in the table 5, 6 and 7 and chromatographic representations are given in Fig 1 to Fig 7.

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Table 5: Physicochemical evaluation of formulated bilayer tablets

Parameters	Batch Code					
	AM1	**AM2**	**AM3**	**AM4**	**AM5**	**AM6**
Average weight (in mg)	405.08	426.62	426.91	425.50	426.40	424.50
Hardness (Kg/cm^2)	2.77	3.22	3.30	5.10	5.12	4.52
Thickness test (in mm)	4.32	4.16	4.22	4.20	4.22	4.22
Friability test (in %)	5.82	6.11	5.86	0.27	0.24	0.23
Disintegration test	14'54"	9'18"	4'54"	4'48"	4'54"	4'54"
Drug content (%)						
Metoprolol Succinate	80.36	84.63	85.02	87.23	88.92	89.58
Amlodipine besylate	102.24	102.46	103.62	104.21	105.56	105.86

Table 6. Comparative dissolution study of AM1-AM6

Time	Percentage drug release					
	AM1	**AM2**	**AM3**	**AM4**	**AM5**	**AM6**
1st hour	41.26	34.5	26.9	24.4	18	17.24
4th hour	-	63.27	59.9	49.28	40.03	39.165
8th hour	-	-	-	72.68	54.6	57.065
20th hour	-	-	-	-	97.5	81.48

USP limits for drug release for Metoprolol Succinate SR

Time	Amount of drug release
1st hour	NMT 20%
4th hour	20-40%
8th hour	40-60%
20th hour	NLT 80%

Table 7: Dissolution data for Metoprolol Succinate formulation (AM6)

Sl. No.	Area First Hour	Results in %	Area Fourth Hour	Results in %	Area Eighth Hour	Results in %	Area Twentieth Hour	Results in %
J1	74227	14.80	166652	33.23	234615	46.78	345091	68.81
J2	67209	13.40	150420	29.99	218133	43.49	334608	66.73
J3	82256	16.40	210844	42.04	306505	61.11	430319	85.80
J4	101500	20.23	216974	43.26	311498	62.11	437080	87.15
J5	104736	20.88	215617	42.99	323687	64.54	453515	90.43
J6	89187	17.78	218082	43.48	322794	64.36	451275	89.98
AVG.		**17.24**		**39.165**		**57.065**		**81.48**

Stability studies

The stability study was done for the optimized batch (Batch AM6) as per ICH guidelines at 40°C and RH 75±5% (Yasir M. *et al., 2010*) and the results were given in Table 8

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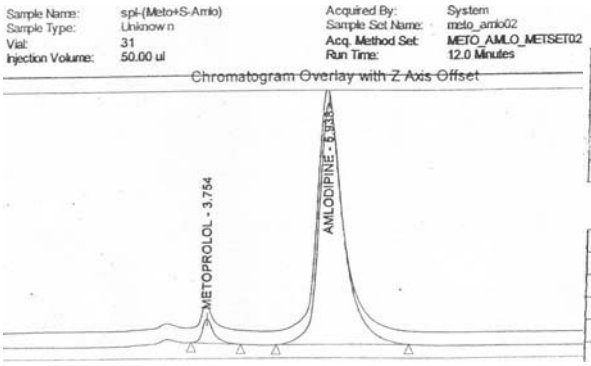


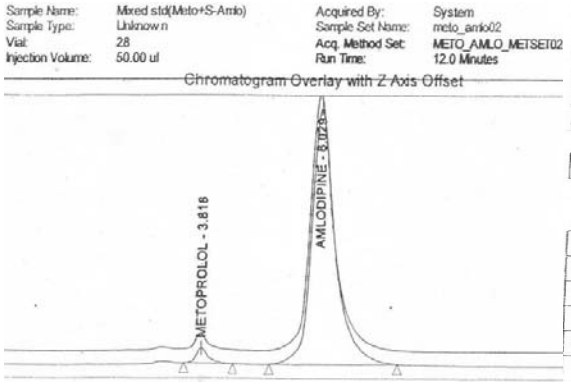
Component Summary Table
Name: AMLODIPINE

	Vial	Inj	Name	RT	Area
1	31	1	AMLODIPINE	5.938	3536518
2	31	2	AMLODIPINE	5.911	3527141
Mean				5.924	3531829.500
Std. Dev.				0.019	6630.540
% RSD				0.3	0.2

Component Summary Table
Name: METOPROLOL

	Vial	Inj	Name	RT	Area
1	31	1	METOPROLOL	3.754	166948
2	31	2	METOPROLOL	3.735	169036
Mean				3.744	167991.750
Std. Dev.				0.013	1476.793
% RSD				0.3	0.9

Fig 1: Chromatogram of Metoprolol succinate and S. Amlodipine besilate test sample.



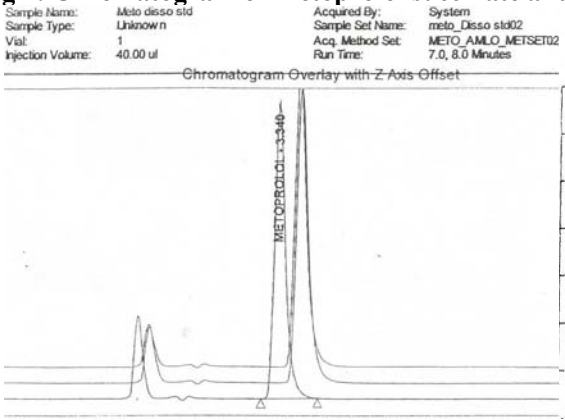
Component Summary Table
Name: AMLODIPINE

	Vial	Inj	Name	RT	Area
1	28	1	AMLODIPINE	6.029	3506713
2	28	2	AMLODIPINE	6.002	3497818
Mean				6.015	3502265.250
Std. Dev.				0.019	6290.068
% RSD				0.3	0.2

Component Summary Table
Name: METOPROLOL

	Vial	Inj	Name	RT	Area
1	28	1	METOPROLOL	3.818	96936
2	28	2	METOPROLOL	3.799	96369
Mean				3.808	96652.500
Std. Dev.				0.013	400.930
% RSD				0.4	0.4

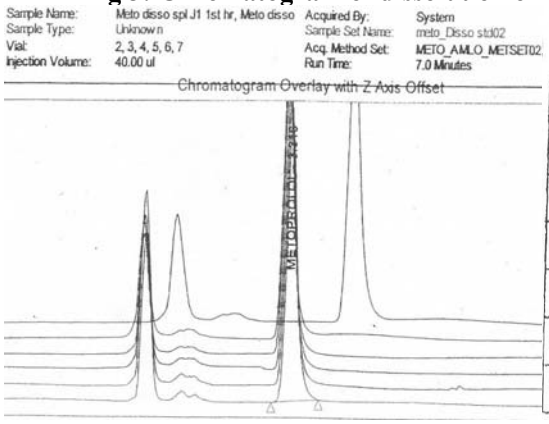
Fig 2: Chromatogram of Metoprolol succinate and S. Amlodipine besilate mixed standard.



Component Summary Table
Name: METOPROLOL

	Vial	Inj	Name	RT	Area
1	1	1	METOPROLOL	3.340	500915
2	1	1	METOPROLOL	3.318	500381
3	1	2	METOPROLOL	3.299	497767
Mean				3.319	499687.500
Std. Dev.				0.020	1684.457
% RSD				0.6	0.3

Fig 3: Chromatogram of dissolution of Metoprolol succinate (standard)



Component Summary Table
Name: METOPROLOL

	Sample Name	Vial	Inj	Name	RT	Area
1	Meto disso spl J1 1st hr	2	1	METOPROLOL	3.316	74227
2	Meto disso spl J2 1st hr	3	1	METOPROLOL	3.302	67209
3	Meto disso spl J3 1st hr	4	1	METOPROLOL	3.290	82256
4	Meto disso spl J4 1st hr	5	1	METOPROLOL	3.277	101500
5	Meto disso spl J5 1st hr	6	1	METOPROLOL	3.268	104736
6	Meto disso spl J6 1st hr	7	1	METOPROLOL	3.252	89187

Fig 4: Chromatogram of dissolution of Metoprolol succinate (sample after 1st Hour)

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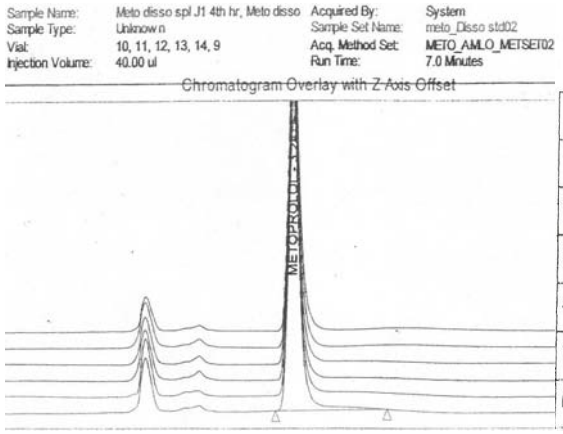
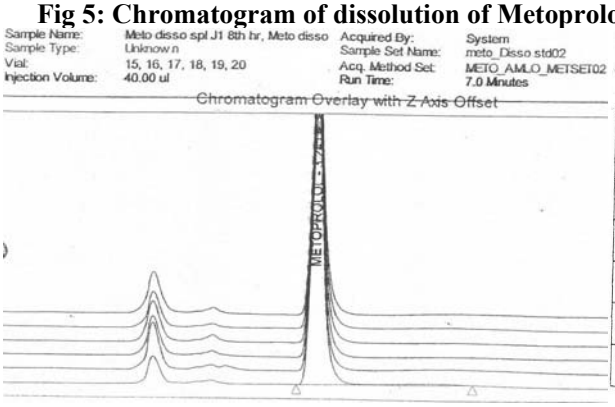


Component Summary Table
Name: METOPROLOL

	Sample Name	Vial	Inj	Name	RT	Area
1	Meto disso spl J1 4th hr	9	1	METOPROLOL	3.247	166652
2	Meto disso spl J2 4th hr	10	1	METOPROLOL	3.244	150420
3	Meto disso spl J3 4th hr	11	1	METOPROLOL	3.238	210844
4	Meto disso spl J4 4th hr	12	1	METOPROLOL	3.236	216974
5	Meto disso spl J5 4th hr	13	1	METOPROLOL	3.240	215617
6	Meto disso spl J6 4th hr	14	1	METOPROLOL	3.242	218082

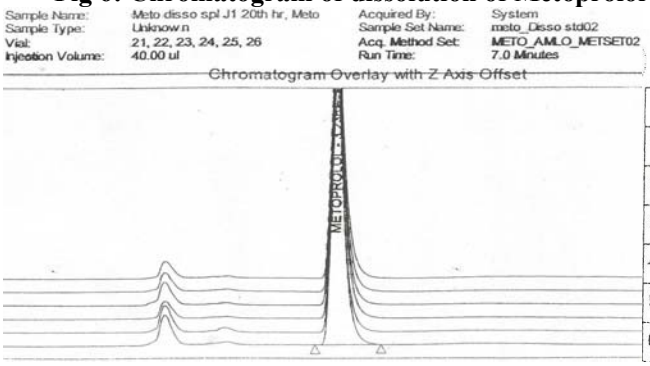
Fig 5: Chromatogram of dissolution of Metoprolol succinate (sample after 4th Hour)



Component Summary Table
Name: METOPROLOL

	Sample Name	Vial	Inj	Name	RT	Area
1	Meto disso spl J1 8th hr	15	1	METOPROLOL	3.241	234615
2	Meto disso spl J2 8th hr	16	1	METOPROLOL	3.238	218133
3	Meto disso spl J3 8th hr	17	1	METOPROLOL	3.235	306505
4	Meto disso spl J4 8th hr	18	1	METOPROLOL	3.235	311498
5	Meto disso spl J5 8th hr	19	1	METOPROLOL	3.235	323687
6	Meto disso spl J6 8th hr	20	1	METOPROLOL	3.235	322794

Fig 6: Chromatogram of dissolution of Metoprolol succinate (sample after 8th Hour)



Component Summary Table
Name: METOPROLOL

	Sample Name	Vial	Inj	Name	RT	Area
1	Meto disso spl J1 20th hr	21	1	METOPROLOL	3.236	345091
2	Meto disso spl J2 20th hr	22	1	METOPROLOL	3.233	334608
3	Meto disso spl J3 20th hr	23	1	METOPROLOL	3.232	430319
4	Meto disso spl J4 20th hr	24	1	METOPROLOL	3.227	437080
5	Meto disso spl J5 20th hr	25	1	METOPROLOL	3.228	453515
6	Meto disso spl J6 20th hr	26	1	METOPROLOL	3.230	451275

Fig 7: Chromatogram of dissolution of Metoprolol succinate (sample after 20th Hour)

Table 8: Stability data for Amlodipine Besilate and Metoprolol Succinate

Test	Storage Time (Months)		
	After 1st month	After 2nd months	After 3rd months
Average weight (in mg)	424.45	424.21	424.12
Dissolution	% Release	% Release	% Release
Amlodipine Besilate	105.78	105.69	105.52
Metoprolol Succinate (Time in Hrs)	% Release	% Release	% Release
1st Hour	17.19	17.04	16.92
4th Hour	39.09	38.98	38.91
8th Hour	56.97	56.82	56.73
20th Hour	81.42	81.34	81.26
Assay for Amlodipine Besilate	105.62	105.53	105.36
Assay for Metoprolol Succinate	89.52	89.39	89.26

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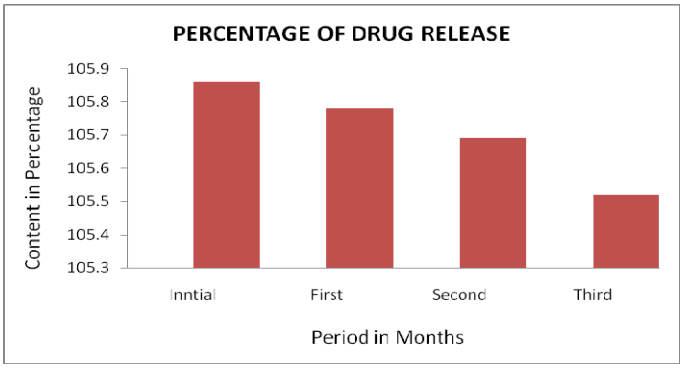

Fig 8: Stability data for representation of Amlodipine besilate

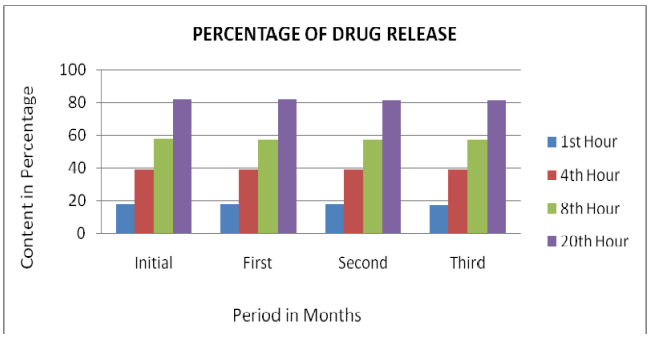

Fig 9: Stability data for representation of Metoprolol succinate

Differential Scanning Calorimetry Analysis

In the present study, samples in the range 5-10 mgs were taken in an aluminium crucible with lid and weighed accurately in a microbalance. For the tablet sample the individual layer was
carefully scraped with a stainless steel file and a portion from the resulting powder were weighed before analysis. In Differential scanning calorimeter (Mettler Toledo GmbH, DSC 821e/700) argon gas was flown over all the samples at a rate of 50 ml/min in the study. Heat flow rates were measured over a temperature range of 30°C - 300°C at a heating rate of 15°C/min for Amlodipine Besilate pure drug, placebo and tablet samples. Similarly temperature range of 25°C - 250°C at a heating rate of 5°C/min was used for Metoprolol Succinate pure drug, placebo, and tablet samples. DSC thermogram of pure drugs and along with their excipients (Rashmi Dahima *et al., 2010;* Praneeth Kumar Siripuram *et al., 2010;* Sahoo S.K. *et al., 2008*) were shown in Fig 10, 11, 12 and 13

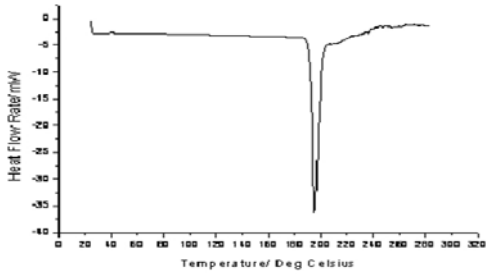

Fig 10: DSC thermogram of Amlodipine drug

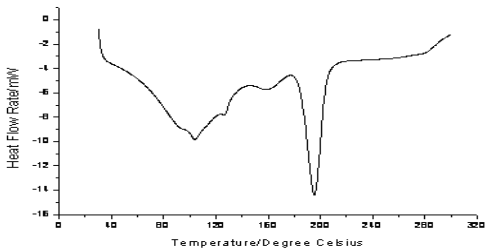

Fig 11: DSC thermogram of Amlodipine besilate pure besilate tablet (AM6)

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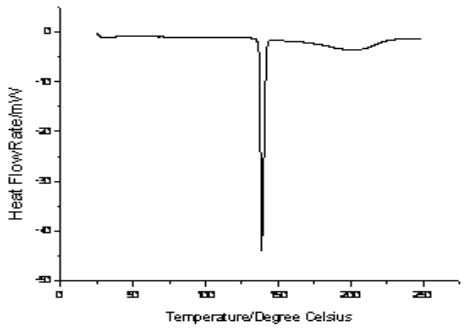

Fig 12: DSC thermogram of Metoprolol succinate pure drug

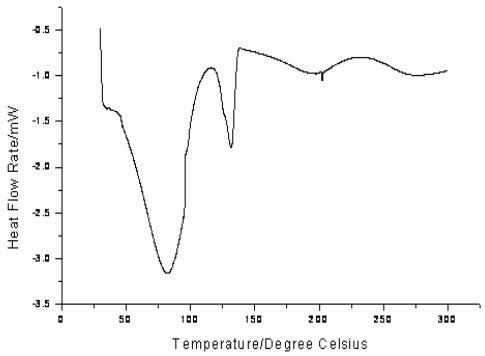

Fig 13: DSC thermogram of Metoprolol succinate tablet (AM6)

DISCUSSION

Prior to compression the granules were evaluated for angle of repose, bulk density, tapped density, Carr's index, loss on drying. The compressed bilayer tablets were also evaluated for weight variation, dimension, hardness, friability, drug content, disintegration time and *invitro* drug release. The angle of repose, bulk density, tap density, Carr's index showed that all batches AM1, AM2, AM3, AM4, AM5, AM6 had good flow property. Hence all six batches were taken up for further studies. The average weight, hardness, thickness for the batches AM1, AM2, AM3, AM4, AM5, AM6 were within the limit. Batches AM1, AM2, AM3, AM4 had faster initial invitro drug release, whereas batch AM5 had drug release profile within the USP limit. Therefore for the reproducibility of AM5 formulation, AM6 formulation was developed with change in polymers concentration. Hence batch code AM6 was taken up for further studies.

In the above studies AM6 formulation showed promising results. It was further supported by DSC analysis which showed that AM6 had no interaction with excipients. The stability studies were carried out for the optimized batch AM6 for three months and it showed acceptable results.

CONCLUSION

Based on the observation, it was concluded that batch AM6 exhibited desirable properties and optimized drug release .The *invitro* drug release of batch AM6 was followed the USP limits. Hence batch AM6 was considered as a desirable batch. The results demonstrated the effective use of compression – bilayer tablets of Metoprolol succinate and Amlodipine besilate as an ideal drug release formulation for treatment of hypertension.

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