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Formulation and evaluation of bilayer tablets of amlodipine besilate and metprolol succinate

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ABSTRACT

Bilayer tablets of Amlodipine besilate (IR) Metoprolol succinate (SR) were formulated for the management of hypertension. In the formulation of immediate release sodium starch glycolate and pregelatinised starch were used as super disintegrant and was directly compressed. For sustained release portion HPMC polymers were used in granulation stage and also extragranularly. Preformulation studies were performed prior to compression. The compressed bilayer tablets were evaluated for weight variation, dimension, hardness, friability, drug content, disintegration time and invitro drug release using USP dissolution apparatus type 2 (paddle). It was found that the optimized formulation showed 9.96%, 35.56%, 52.12%, 90.46% release for Metoprolol succinate in 1, 4, 8, 20 hours respectively.However, Amlodipine besilate released 98.28% at the end of 30 minutes.The IR spectrum and DSC studies revealed that there is no disturbance in the principal peaks of pure drugs Metoprolol succinate and Amlodipine besilate. This further confirms the integrity of pure drugs and no incompatibility of them with excipients. The stability studies were carried out for the optimized batch for three months and it showed acceptable results. The kinetic studies of the formulations revealed that diffusion is the predominant mechanism of drug and release follows first order kinetics.

INTRODUCTION

In the 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 doses of drug to reduce the patient's blood pressure, minimize dose dependent side effects and adverse reactions.

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 (ie) 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.

Metoprolol is selective ß1 receptor blocker used in the treatment of hypertension and angina-pectoris. It reduces plasma rennin activity in hypertensives. It has half life of 3 to 4 hours in fast hydroxylator and about 7 hour in slow hydroxylators. Hence to improve its therapeutic efficacy and patient compliance the formulation of metoprolol succinate as sustained release is necessary for chronic use.

MATERIALS AND METHODS

Amlodipine besylate, Metoprolol succinate, HPMC K4M, HPMC K 100, PVP K 30, Microcrystalline cellulose , Dicalcium phosphate , Starch 1500, Sodium starch glycolate, Sodium stearyl fumarate, Aerosil , Purified talc,Magnesium stearate were received from Madras Pharmaceuticals,Chennai. Quinoline Yellow lake was received as a gift sample from Roha die chemicals. All other chemicals are of analytical grades.

Formulation of tablets:

Table 1: Formulation of immediate release layer of Amlodipine besilate (in mg)

Ingredients	A1	A2	A3	A4	A5	A6	A7
Amlodipine Besilate	7	7	7	7	7	7	**7**
Dicalcium phosphate	60	55	52.5	52.5	50	60	**70**
Microcrystalline cellulose PH102	50	50	50	50	50	40	**30**
Pregelatinised Starch	-	5	5	5	5	5	**5**
Sodium starch glycolate	-	-	-	2.5	5	5	**5**
Cross povidone	-	-	2.5	-	-	-	-
Aerosil	1	1	1	1	1	1	**1**
Magnesium stearate	1	1	1	1	1	1	**1**
Quinoline yellow lake	1	1	1	1	1	1	**1**

Preparation of Amlodipine besylate immediate release layer:

Amlodipine besilate immediate release tablets were prepared by using direct compression method. The microcrystalline cellulose, Dicalcium phosphate, Pregelatinised starch, sodium starch gluconate and the active ingredient were passed through sieve no. 30 and mixed

homogenously. Magnesium stearate and Aerosil were passed through sieve no.60 and added as a lubricant to the above dry mix and mixed well for 5 minutes. Finally the colorant Quinloline yellow lake was sieved through sieve no.100 mesh and then mixed with the dry mix homogenously to get uniform blend without mottling.

Table 2: Formulation of sustained release layer of Metoprolol succinate (in mg)

Ingredients	M1	M2	M3	M4	M5	M6	M7	M8
Metoprolol Succinate	47.5	47.5	47.5	47.5	47.5	47.5	**47.5**	47.5
MCC PH 101	41.5	71.5	101.5	41.5	67.75	67.75	**37.75**	7.75
HPMC K100	180	150	120	150	120	60	**75**	90
HPMC K4M	-		-	30	30	15	**15**	15
PVP K 30	25	25	25	25	25	25	**25**	25
Isopropyl alcohol (in ml)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	**q.s.**	q.s.
Lubrication stage:								
Talc	3	3	3	3	3	3	**3**	3
SSF	3	3	3	3	6.75	6.75	**6.75**	6.75
HPMC K100	-	-	-	-	-	60	**75**	90
HPMC K4M	-	-	-	-	-	15	**15**	15

Table 3: Polymer percentage in Metoprolol succinate portion (avg wt. 300mg)

Polymer	M1	M2	M3	M4	M5	M6	M7	M8
HPMC K100	60%	50%	40%	50%	40%	40%	50%	60%
HPMC K4M	-	-	-	10%	10%	10%	10%	10%

Preparation of Metoprolol succinate sustained release layer:

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 were air dried initially and passed through mesh no. 20.The resultant granules left on the sieve were milled through sieve of pore size 1.5mm.The granules were finally dried at 60ºC till a constant LOD reaches(3-4%).Talc and sodium starch fumarate were added to the dried granules and homogenously mixed.

Evaluation of Granules Flow Properties [1,2]

The prepared granules were evaluated for parameters like bulk density, tap density, Carr index, Angle of repose, and Hausner's ratio, loss on drying. The results are as in table 4 and 5.

Tablet compression:

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 the die cavity and a slight precompression 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.

Evaluation of tablets:

The crushing strength of tablets were evaluated by using Monsanto type hardness tester the value was 7.0 to 7.8 kg/cm^2. The friability was with in the limit (less than 1).

Table 4 : Pre compression Parameters of Amlodipine Besilate

Trial	Angle of Repose (θ)	Bulk density (g/cm^3)	Tapped Density (g/cm^3)	Carr's index	Hausner ratio
A 1	26.4 º	0.663	0.820	19.146	1.237
A 2	25.8º	0.701	0.828	15.338	1.181
A 3	26.7º	0.698	0.822	15.085	1.178
A 4	26.0º	0.695	0.818	15.037	1.177
A 5	26.5º	0.696	0.820	15.122	1.178
A 6	25.4º	0.694	0.824	15.777	1.187
A 7	28.3º	0.698	0.812	14.039	1.163
A 8	28.0º	0.702	0.800	12.250	1.140

Table 5: Pre compression Parameters of Metoprolol Succinate

Trial	Angle of Repose (θ)	Bulk density (g/cm^3)	Tapped Density (g/cm^3)	Carr's index	Hausner ratio
M 1	30.4 º	0.373	0.442	15.610	1.185
M 2	30.8º	0.375	0.445	15.730	1.187
M 3	29.7º	0.375	0.446	15.919	1.189
M 4	32.0º	0.376	0.438	14.155	1.165
M 5	31.5º	0.378	0.444	14.864	1.175
M 6	32.4º	0.385	0.436	11.697	1.132
M 7	34.3º	0.380	0.438	13.242	1.153
M 8	28.0º	0.384	0.439	12.528	1.143

ASSAY USING HPLC: [5,6]

Chromatographic conditions:

Stationary phase : Cosmosil $C_{18/33}$ (150mm×3.9 mm) column ,Isocratic MobilePhase: Mixture of buffer (0.7% aqueous triethylamine, pH 3.0 adjusted with orthophosphoric acid), Acetonitrile in the ratio of 80:20 (v/v) ,flow rate of the mobile phase was 1.0 mL/min, injection volume was 50µL.detector signal was monitored at a wavelength of 215 nm. The overall runtime was 60 minutes.

Preparation of Standard for Simultaneous estimation:

Amlodipine stock solution*:* Accurately 70mg of amlodipine besilate working standard was dissolved in 50ml methanol- Acetonitrile mixture (1:1).

Mixed standard*:* Five milliliters of amlodipine stock solution and 47.5mg metoprolol succinate working standard were transferred to a 100ml volumetric flask and the volume was made up with methanol, ACN mixture (1:1). From this 5ml was transferred and made up to 25ml with the mobile phase in a 25mL volumetric flask.

Test solution: Twenty bilayer tablets were crushed in a dry mortar homogenously and powder equivalent to 100mg of metoprolol succinate was transferred into a clean and dry 1000ml volumetric flask. Five hundred millilitres of methanol was added to disintegrate tablets completely by using ultrasonicator for 20 minutes and made up to the volume with mobile phase. This solution was filtered through 0.45µm membrane filter.

Procedure:
From the standard solution 50µl was injected and the peak areas were recorded. Then 50µl of sample was injected and the chromatograms were recorded and the responses of the major peaks were measured.

***INVITRO* DISSOLUTION STUDIES BY HPLC:**[6,7,8]
Preparation of dissolution medium: (phosphate buffer pH 6.8)
Accurately 50 ml of 1M sodium dihydrogen phosphate solution was made up to 1000ml and pH was adjusted using orthophosphoric acid.

Preparation of amlodipine besilate standard for immediate release studies:
Accurately 7mg of amlodipine besilate was weighed and transferred into a 500ml volumetric flask and made up with 0.1N HCl . From this 5ml was diluted to 50ml with 0.1 N HCl. Again a second dilution of 5ml to 50ml was done using the above solution.

Preparation of Standard for Sustained release studies:
Accurately 47.5mg Metoprolol succinate was transferred to a 100ml volumetric flask and the volume was made up with phosphate buffer pH 6.8. From this 5ml was transferred and made upto 50ml with the same buffer.

Procedure:
In vitro drug release studies of Metoprolol succinate and Amlodipine besilate was studied using dissolution apparatus USP .XXII Rotating paddle Method. For the dissolution medium 500 ml of 0.1N HCl buffer (pH 1.2) was used. Tablet was placed in a basket and rotated at a speed of 75 rpm maintained at a temperature of 37 $\pm$ 0.5^{o}C. Five milliliters of the sample was withdrawn at periodic time interval of 5, 10,15,20,25 and 30 minutes and was made up to 10ml with 0.1 N HCl buffer solution. Five ml of fresh dissolution medium was replaced after each time of withdrawal of sample. The samples were analyzed in HPLC at 239nm after filtering through 0.45 µm millipore filters for determination of amlodipine besilate.

This is followed by study in simulated intestinal fluid (PH 6.8 Phosphate buffer solution) used in 500 ml dissolution medium. The dissolution samples 5 ml was collected at an interval of 1, 4, 8 and 20hrs with replacement of equal volume of fresh dissolution medium. The sample was made up to 10 ml with PH 6.8 buffer solution. The aliquots withdrawn were filtered through 0.45 µm millipore filters. The concentration of metoprolol succinate in the dissolution media was estimated by HPLC method as described earlier at 215 nm.

Table 9: USP limits for drug release for Metoprolol Succinate SR

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

Stability Studies: [9]

The tablets were packed in blister packing and kept for 3 months at 40^{o}C / 75% RH and 25^{o}C / 60% RH in a stability chamber (Oswald, Mumbai).At the interval of 1 month tablets were withdrawn and evaluated for appearance, average weight, assay and in vitro drug release.

Differential Scanning Calorimetry Analysis: [10, 11, 12]

In the present study, samples in the range 5-10 mgs were taken in an aluminum 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 was 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.

Fourier transform infrared spectroscopic analysis:[7,11]

In the present study FTIR spectra of the Metoprolol succinate pure drug, Amlodipine besilate pure drug, and placebo of both layers and optimized bilayer formulation were recorded using a Fourier transform infrared spectrophotometer (BOMEM –MB 100 FTIR). Samples were prepared as KBr disks using a hydraulic pellet press and scanned from 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1}.

Kinetic Studies: [13]

The following plots were made: cumulative % drug release vs. time (zero order kinetic model); log cumulative of % drug remaining vs. time (first order kinetic model); cumulative % drug release vs. square root of time (higuchi model). The regression coefficient R^2 value nearer to 1 indicates the model best fits the release mechanism.

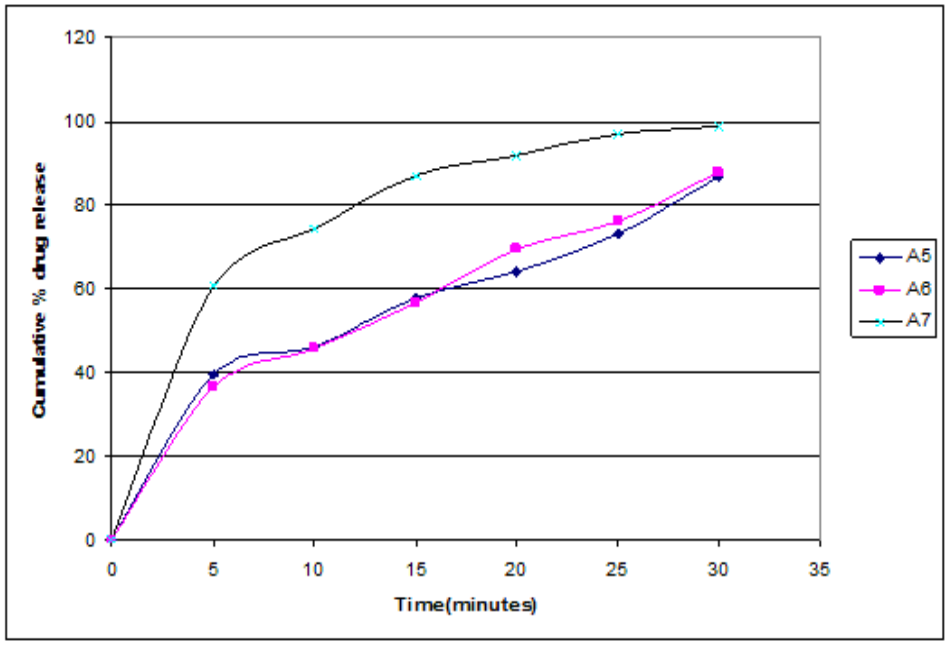
RESULTS AND DISCUSSION

Various formulations of bilayer were prepared and evaluated with an aim of presenting Metoprolol Succinate as sustained release and Amlodipine besilate as immediate release for improving the patient's compliance.

In the design of amlodipine besilate immediate release part, Formulation A1 had problem in compression due to lack of binder hence in formulation A2 pregelatinised starch was added as

binder. It showed good tablet integrity but disintegration time was more. In A3 formulation crosspovidone was used as superdisintegrant. But A3 had bulges and black spots on the tablet. So the use of Crosspovidone was discarded in the further formulations. In formulation A4, SSG was selected as super disintegrant and it disintegrated in 2 minutes and 5 seconds.The increase in disintegrant (i.e.) SSG in A5 decreased the disintegration time to 1 minute 5 seconds. But the drug release was only 86.71 % after 30 minutes. In the A6 formulation concentration of MCC PH 102 was decreased and a little increase in the release profile (89.65%) was observed. So in the A7 formulation MCC PH 102 was reduced further and this showed marked increase in the drug release (99.24%) and hence optimized as the immediate release layer.

Figure 1: *Invitro* release curve of Amlodipine Besilate IR



In the design of Metoprolol sustained release part formulation M1, to control the release of Metoprolol Succinate, 60% HPMC K100 was used. It showed very low release of 57% at the end of 20th hour. It may be due to higher polymer concentration, which retards the drug release from the polymer- drug matrix. Hence the polymer content was reduced to 50% in the M2 formulation which gave a release of 59.33% at the end of 20th hour.In M3 formulation 40% of HPMC K100 was used which gave satisfactory 20th hour release (88.90%) but failed in the 1st , 4th , 8th hour release which were 35.12%, 48.67%, 68.77% respectively.The above release problems were assumed to be aroused due to high polymer viscosity, hence in the formulations M4 , 10% HPMC K4M was added along with 50% HPMC K100 . The drug release was only 60.24% at the end of 20th hour. Moreover the tablet had sticking problem. So in M5 formulation, 40% HPMC K100 and 10% HPMC K4M were added and the concentration of lubricant was increased. The release was 68.96% for this formulation which still did not met with the specification due to increase in polymer drug binding.

Figure 2: *Invitro* release curve of Metoprolo Succinate SR

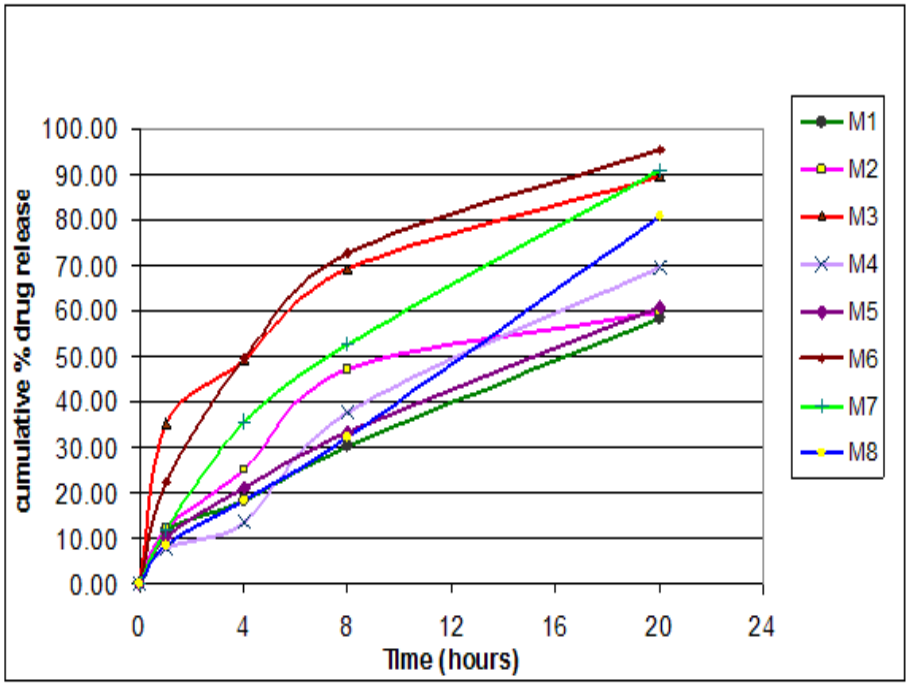
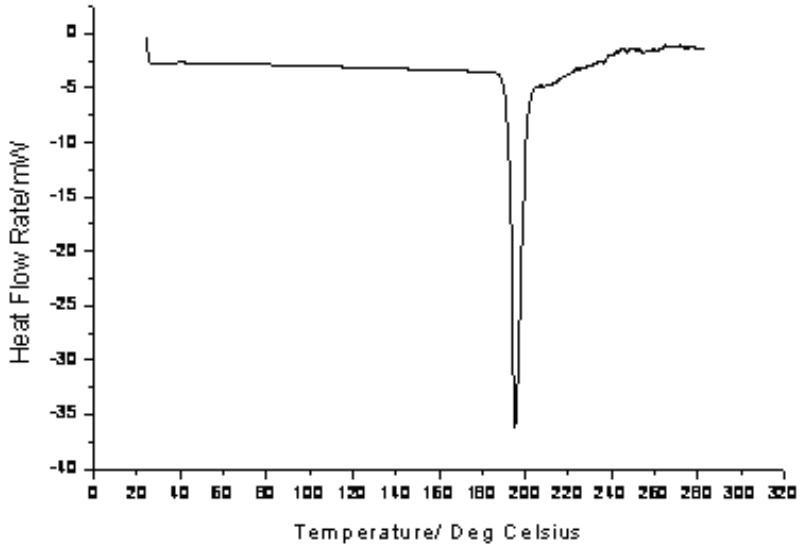


Figure 3: DSC thermogram of Amlodipine Besilate pure drug



Hence to overcome this problem in the following formulations M6, M7 and M8 half portion of HPMC polymer was added in the lubrication stage instead of completely granulating those along with the drug. In M6 formulation combination of 40% HPMC K 100 and 10 % HPMC K4M

were used and the release increased to 94.46% at the end of 20th hour.Hence to achieve the invitro drug release HPMC K100 concentration was increased to 50% and 60% in M7 and M8 formulation. The releases were 90.46 % and 80.24% respectively for M7 and M8.The decrease in release in M8 formulation was due to higher polymer concentration hence M7 formulation was finalized for sustained release Metoprolol Succinate.

Figure 4: DSC thermogram of Amlodipine Besilate tablet (A7)

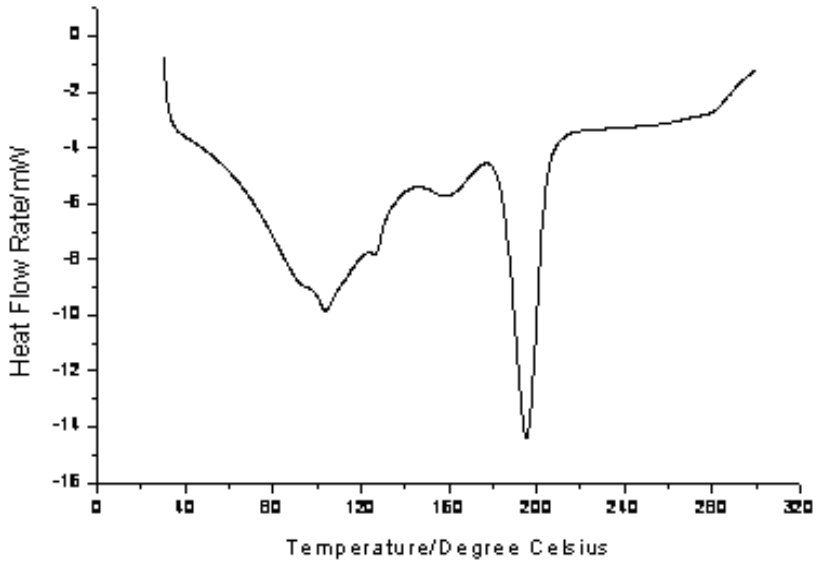


Figure 5: DSC thermogram of Metoprolol succinate pure drug

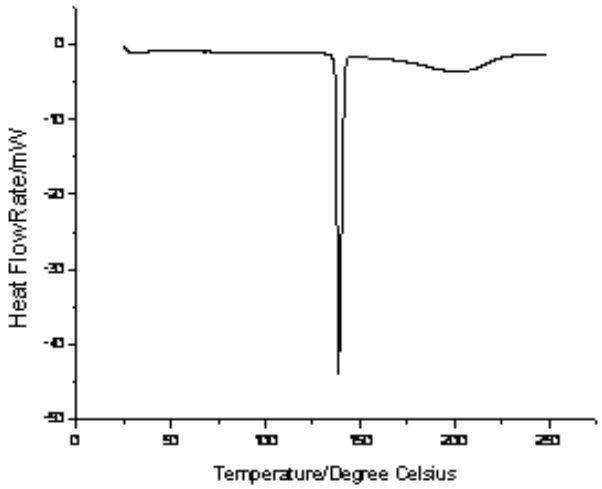


Figure 6: DSC thermogram of Metoprolol succinate tablet (M7)

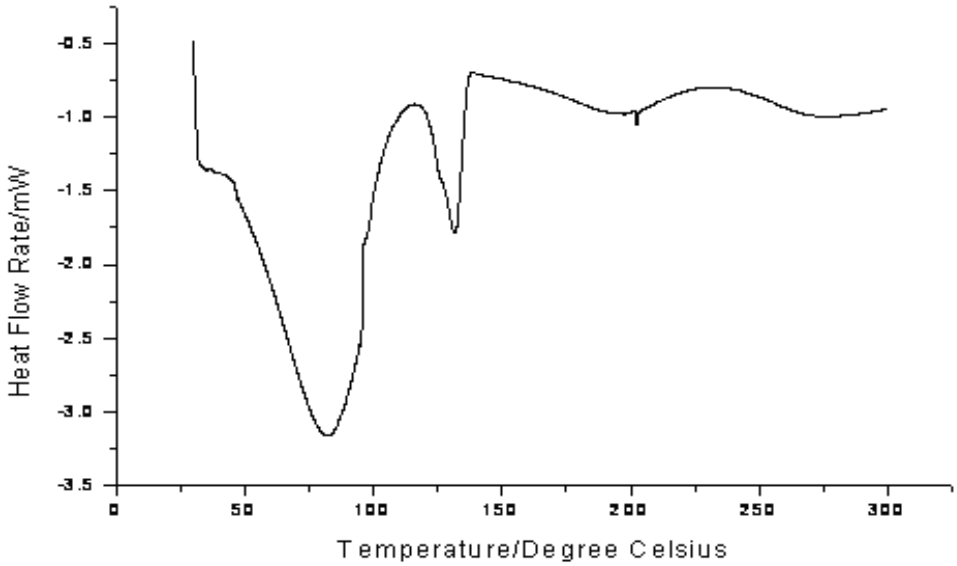
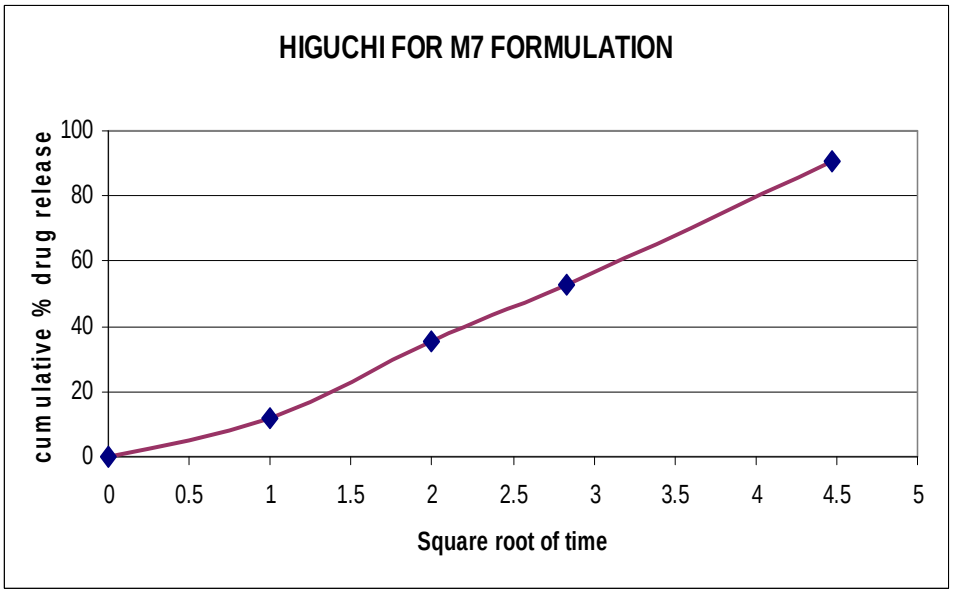


Figure 7: Higuchi plot of Metoprolol Succinate AM7 formulation

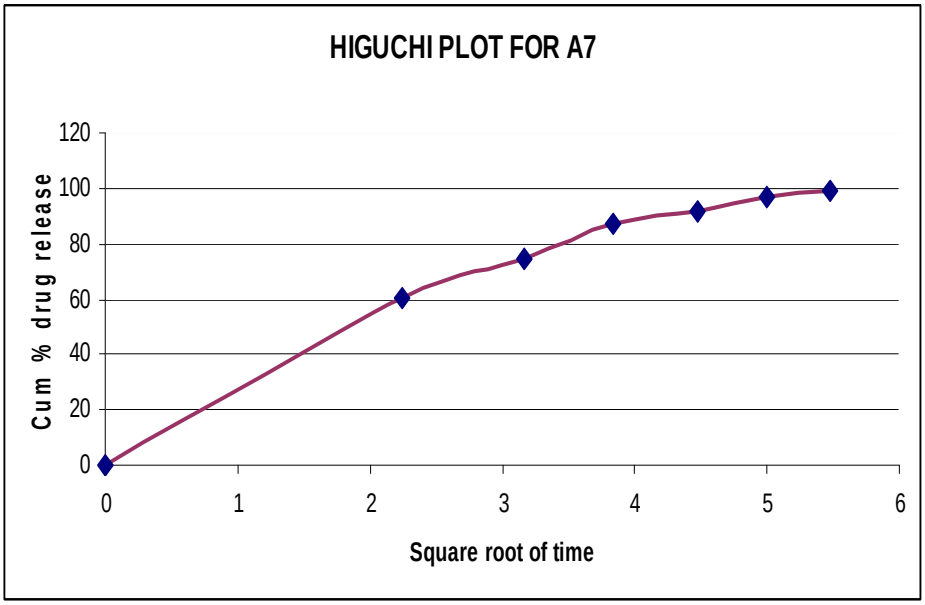


The stability studies confirmed that the formulation AM7 is stable. The DSC and FTIR studies further confirms that there is no interaction between the excipients and the actives.

With the data from kinetic analysis , for the final M7 formulation, the zero order plot gave the r^2 value 0.9479 whereas first order plot gave 0.9904. Thus we confirm that the drug release rate depends on the concentration of drug. The best linearity was found in Higuchi's equation plot (r^2

= 0.9901) indicating the release of drug from matrix is based on Fickian diffusion. For the A7 formulation, the the zero order plot gave the r^2 value 0.7353 whereas first order plot gave 0.9819.Thus we confirm that the drug release rate depends on the concentration of drug. The best linearity was found in Higuchi's equation plot (r^2 = 0.9403) indicating the release of drug from matrix is based on Fickian diffusion.

Figure 8: Higuchi plot of Amlodipine Besilate AM7 formulation



CONCLUSION

The aim of the present study was to develop an optimized formula for bilayer tablet containing Metoprolol succinate and amlodipine besilate for the management of hypertension. Metoprolol succinate was planned to design as the sustained release part and amlodipine besilate as the immediate release part.

After preformulation studies it was decided to prepare Amlodipine besilate part by direct compression and Metoprolol Succinate by wet granulation method.

For sustained release portion HPMC polymer was used in granulation stage and also extragranularly.In the formulation of immediate release sodium starch glycolate and pregelatinised starch were used as super disintegrant.

Prior to compression the granules were evaluated for angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio. The compressed bilayer tablets were also evaluated for weight variation, dimension, hardness, friability, drug content, disintegration time and *invitro* drug release.

In the above studies AM7 formulation showed promising results. It was further supported by FTIR and DSC analysis which showed that AM7 had no interaction with excipients.

The stability studies were carried out for the optimized batch AM7 for three months and it showed acceptable results. The kinetic studies of the formulations revealed that diffusion is the predominant mechanism of drug release.

So AM7 formulation was considered as the optimized formulation.

REFERENCES

[1] Lachman L, Liberman H, Kanig J., The theory and practice of industrial Pharmacy,Varghese Publishing House, Mumbai , 3rd edition,**1987**, 171-195, 293-345.
[2] N.H.Indurwade, T.H.Rajyagures, Nakhat P.D., *Indian Drug* **2002**, 39(8) 405-409.
[3] Aulton" Pharmaceutics the science of dosage forms design",Chirchillivingstone, 2nd edition,**2002**, 199-206.
[4] United States Pharmacopoeia 20, National Formulary, Asian Edition, United States Pharmacopoeial convention Inc., Rockville, **1980**, Disintegration {701}, 276.
[5] Ravouru Nagaraju, Durgumahanthi Sai Meera, Rajesh Kaza, Vakati Venkata Arvind and Vobalaboina Venkateswarlu., *Current Drug Discovery Technologies*, **2009**, 6, 299-305.
[6] A Arunachalam, S Sethuraman, D Vinaykumar, R Senthilraj, Kishore Konam, A Umarunisha., *Int. J. Pharm Sci Bio* **2010**, 1(4),250-255.
[7] Narmada GY, Mohini K, Prakash Rao B, Gowrinath D P, Kumar KS., *ARS Pharmaceutica***, 2009**,50,129-144.
[8] United States Pharmacopoeia 30, National Formulary 25, Asian Edition, United states Pharmacopoeial convention Inc., Rockville, **2007**, 2647-2648.
[9] Yasir M, Asif M, Bhattacharya A, Bajpai M, *Int.J. ChemTech*, **2010**, 2(2), 792-799.
[10] Rashmi Dahima, Ashish Pachori, Sanjay Netam., *International Journal of ChemTech Research*, **2010**, 2(1), 706-715.
[11] Praneeth Kumar Siripuram, Suresh Bandari, Raju Jukanti, and Prabhakar Reddy Veerareddy., *Dissolution Technologies*, Aug **2010**, 34-39.
[12] S.K.Sahoo, M.K.Jena, S.Dhala and B.B.Barik., *Indian J.Pharma. Sci*.,**2008**, 70(6),795-798.
[13] M.Harris Shoaib, Jaweria Tazeen, Hamid A Merchant and Rabia Ismail Yousuf., *Pak. J. Pharm. Sci.*, **2006**, 19(2), 119-124.