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Research Article

Design, Development and Evaluation of Bilayered Tablets Containing Amlodipine Besilate as Immediate Release and Metprolol Succinate as Sustained Release

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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 were used as super disintegrant and was directly compressed. For sustained release portion HPMC polymers were used in granulation stage . 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 15.98%, 39.04%, 58.76%, 94.86%release for Metoprolol succinate in 1, 4, 8, 20 hours respectively.However, Amlodipine besilatereleased 95% at the end of 45 minutes.The IR spectrum and DSC studies revealed that there is no disturbance in the principal peaks of pure drugs Metoprolol succinate and Amlodipinebesilate. 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.

Key words: Bilayer tablets, Amlodipine besylate, Metoprolol succinate, extended release, immediate release, antihypertension, combination

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

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

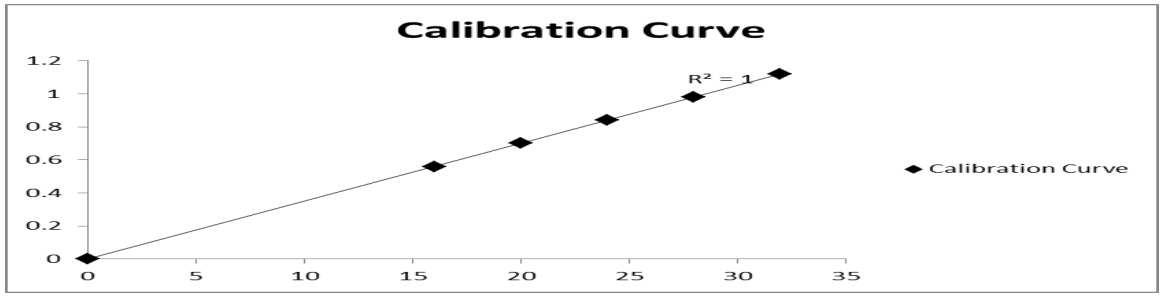
S.no	Material	Quantity in mg A1	A2	A3
1	Amlodipine besylate	10	10	10
2	Microcrystalline cellulose	80	_	50
3	Dicalcium phosphate NF	100	95	95
4	Anhydrous sodium starch glycolateNF	4	20	20
5	Magnesium sterate	1	10	10
6	Lactose BP	10	10	10
7	Magnesium sterateBp	10	20	20
8	Purified talc BP	5	5	5
9	Maizestarch BP	6	_	_
10	Sodium starch glycolateBP(typea)	_	50	_
	TOT.WT	226	220	220

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

		quantity inmg					
s.no	Ingredients	M1	M2	M3	M4	M5	M6
1	metoprololsuccinate	23.75	23.75	23.75	23.75	23.75	23.75
2	hydroxypropyl cellulose	–	–	–	150	150	150
3	mccph101	305	310	310	–	–	–
4	ethylcellulose	15	10	15	15	10	15
5	maize starch	15	15	10	15	15	10
6	glycerol	5	5	5	5	5	5
7	water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
8	methylcellulose	9	12	9	9	12	9
9	magnesiumsterate	3	3	3	3	3	3
10	totalweight	375.75	378.75	375.75	220.75	218.75	215.75

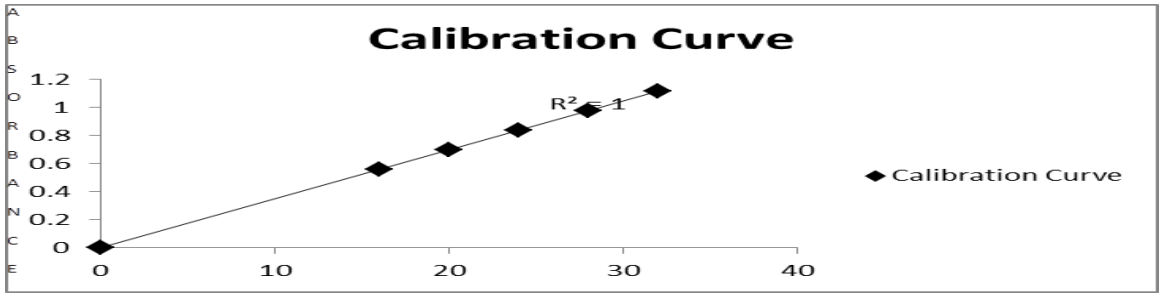
Effectively lower blood pressure at lower than maximum doses of each. The rational for Combination therapy is to encourage the use of lower doses of drug to reduce the patient's blood Pressure, minimize dose dependent side effects and adverse reactions. Amlodipine is a prototype second generation dihydropyridine 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.

Figure-1-Standard Calibration Curve For Amlodipine Besylate In 0.1nhcl



CONCENTERATION IN µG/ML

Figure-2-Standard Calibration Curve For Metoprolol Succinate In 6.8 Phosphatebuffer



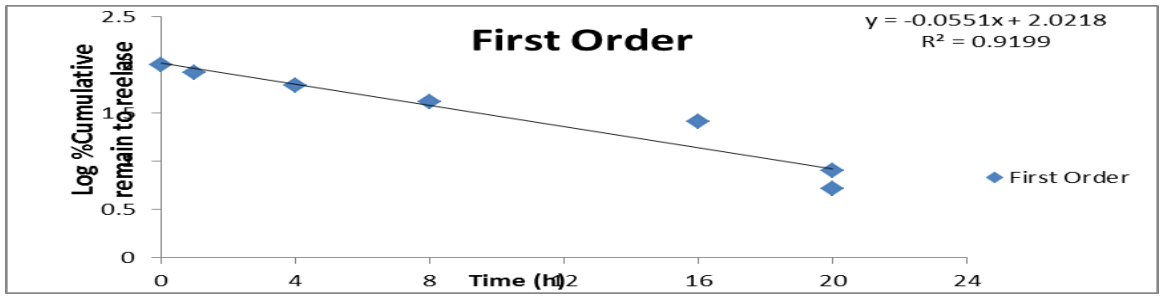
CONCENTERATION IN µg/ml

Figure-3-Zero Order Release For M6

TIME VS. %CUMULATIVE DRUG

Figure-4 –First Order Release For M6

TIME VS. LOG% CUMULATIVE DRUG



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

Table 3. Pre compression Parameters of Metoprolol Succinate (M1-M6)

S.No	Formulation of SR granules	Bulk density	Tapped density	Carr's Index (%)	Hausner's ratio	Particle size (µ)	Angle of repose θ
1	M1	0.604	0.698	13.6	1.42	489.8	41.26
2	M2	0.602	0.648	13.6	1.40	511.8	40.06
3	M3	0.587	0.638	12.4	1.32	512.7	37.12
4	M4	0.544	0.634	11.6	1.26	499.2	34.60
5	M5	0.523	0. 610	11.3	1.14	497.6	34.10
6	M6	0.504	0. 590	11.0	1.10	482.9	32.06

Table 4 : Pre compression Parameters of Amlodipine Besilate(A1-A3)

S.No	Formulation of IR blend	Bulk density	Tapped density	Carr's Index (%)	Hausner's ratio	Particle size (µ)	Angle of repose θ
1	A1	0.422	0.533	11.1	1.22	300.2	28.20
2	A2	0.420	0.522	10.7	1.20	299.2	30.18
3	A3	0.390	0.490	10.5	1.16	313.98	28.36

Figure-5- Peppas Model For M6

Log T vs log %of release

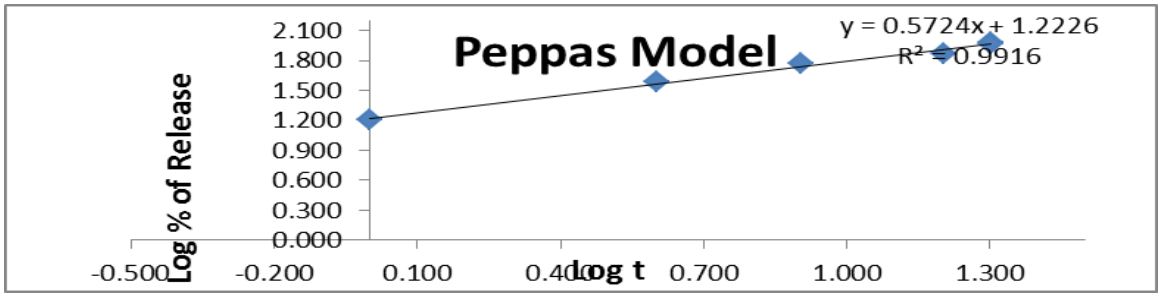
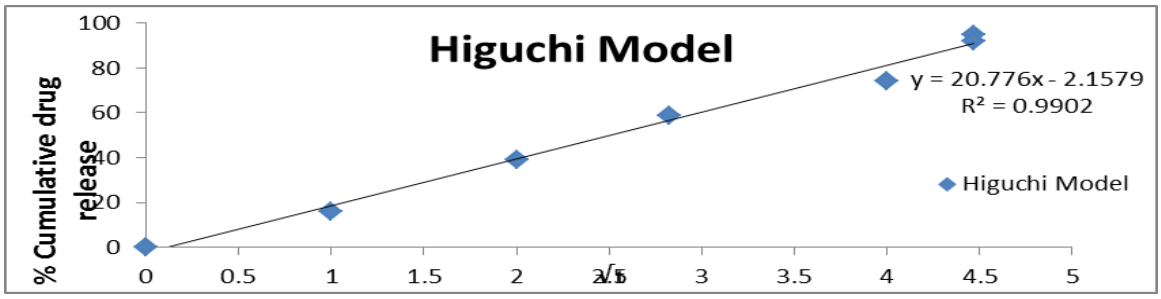


Figure-6- Square Time Vs Cumulative Drug



slow hydroxylators. Hence to improve its therapeutic efficacy and patient compliance the formulation of metoprolol succinate as sustained release is necessary for chronic use.

MATERIAL AND METHOD

Materials: Amlodipine besylate, Metoprolol succinate was received giftSample from Concept Pharmaceutical, Aurangabad. HPMC K4M,Microcrysatalline cellulose was received gift sample from ColorcornAsia Pvt. Ltd. Goa. Starch 1500, Sodium starch glygolate, Sunset yelLow was received gift sample from Concept pharmaceutical,Aurangabad. All other chemicals are of analytical grades

Formulation of tablets:

Preparation of Amlodipine besylate immediate release layer: Amlodipine besilate immediate release tablets were prepared by using direct compressionmethod. The Microcrystalline Cellulose, Dicalcium phosphate,

Table 5. Evaluated results of bilayer tables

S.No	Evaluation tests	M1	M2	M3	M4	M5	M6
1	Weight Variation (%)	-1.82 to +2.54	-2.42to +2.81	-1.56 to +3.12	-1.94 to +2.92	-2.23 to +2.63	-1.21 to +2.21
2	Average Thickness (mm)	4.20	4.20	4.22	4.21	4.20	4.20
3	Average Hardness	2.8	3.2	3.8	4.5	3.6	3.4
4	Friability (%)	0.01	0.01	0.6	0.82	1.21	1.41
5	Disintegration test	8.35	7.10	6.52	6.0	5.30	5.32
6	Drug content (%)						
	Metoprolol Succinate	80.67	85.43	89.98	96.82	97.42	100.20
	Amlodipine besylate	83.77	85.89	87.26	91.88	96.65	97.22

Figure-7 Invitrorelease Curve Of Metoprolol Succinate

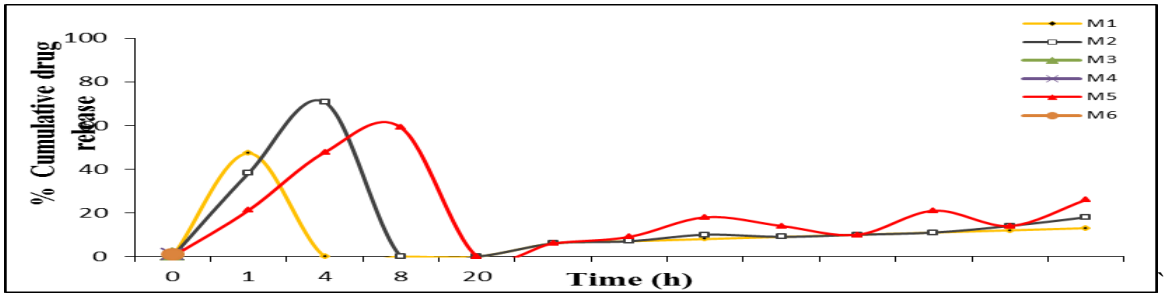


Figure-8

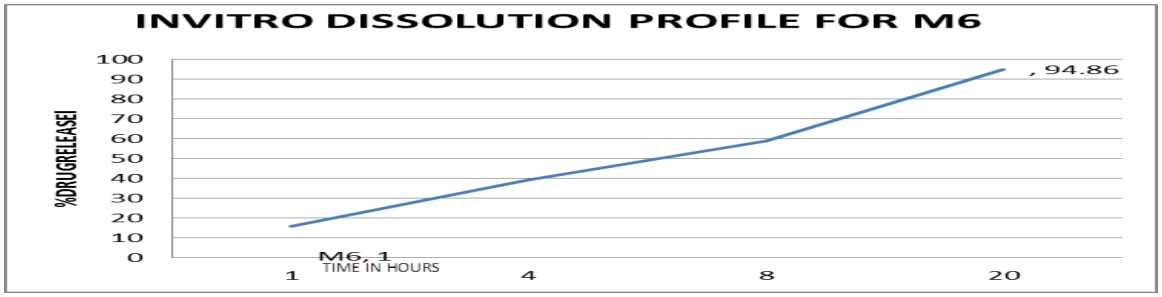
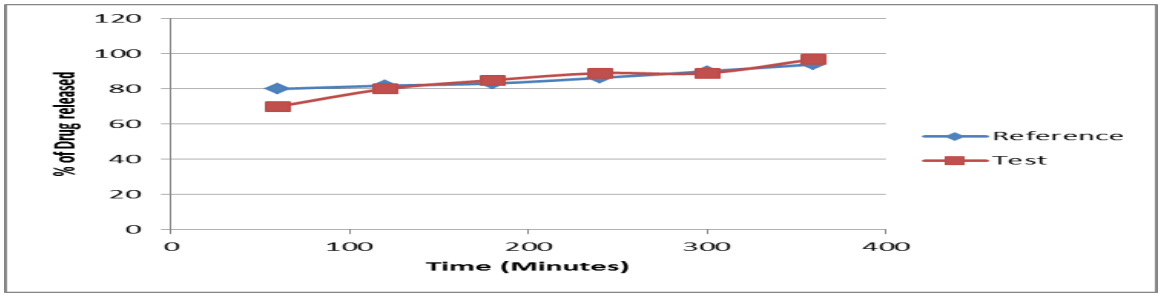


Figure-9 Reference Vs Test



sodiumstarch glycolate and the active ingredient were passed through sieve no. 30 and mixed homogenously.

Table 6. Comparative dissolution study of M1-M6 with various ratios of polymer

Time	Percentage drug release					
	M1	M2	M3	M4	M5	M6
1 hour	47.28	38.23	27.50	29.57	21.19	15.98
4 hour	-	70.70	58.37	52.93	47.75	39.04
8 hour	-	-	69.27	82.63	59.11	58.76
20 hour	-	-	-	-	93.46	94.86

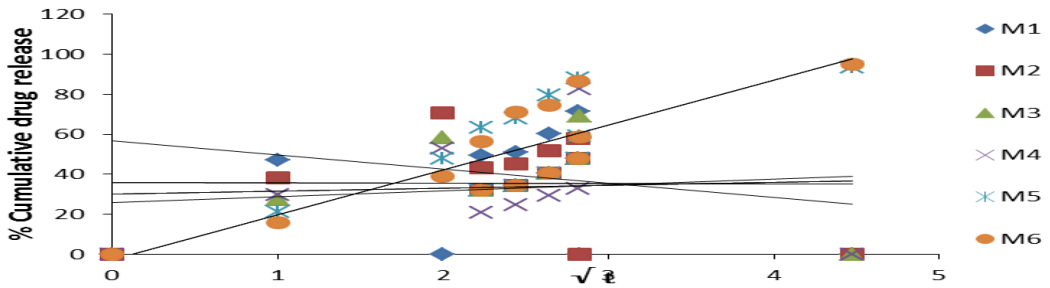
Table No-7 USP limits for drug release for Metoprolol Succinate SR

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

Table No.8- Stability studies of film coated tablets (M6)

S. No	Time	Percentage drug release							
		Metoprolol succinate							
		Initial		st		rd		th	
			RT	0 25±2 C/ 60±5% RH	0 40 ±2 C /75±5% RH	0 25±2 C/60±5%RH	0 40 ±2 C /75±5% RH	0 25±2 C/60±5%RH	0 40 ±2 C /75±5% RH
1	1 h	15.98	15.60	15.95	15.17	15.92	15.02	15.88	15.17
2	4 h	39.04	39.00	38.28	39.78	38.75	38.77	37.20	39.11
3	8 h	58.76	57.12	56.18	58.16	57.25	58.17	57.14	58.64
4	20 h	94.86	95.76	94.84	94.06	93.88	95.12	94.80	94.67
	Amlodipine besylate								
5	45 min	95.42	96.45	95.02	95.10	95.36	95.28	93.88	93.23

Figure-10-Higuchi Plots For All Metoprolol Succinate Tablets



Magnesium stearate and purifiedtalc were passed through sieve no.60 and added As alubricant to the above dry mix and mixed well for 5 minutes, Homogenously to get uniform blend .

Preparation of Metoprolol succinate sustained release layer: Metoprolol Succinate sustained release layer were

Table 9- Noc-No Obseravable Changes

S. No	Metoprolol succinate with HPC , MAIZESTARCH,METHYL CELLULOSE MCCPH101 (1:1:1), , Mg.Streate (1:0.5:0.5) & Amlodipine besylate with MCC PH 101, Lactose, DCP,S.S.G,TALC (1:1:1:1)	Sample intervals				
		st 1 day	th 7 day	th 15 day	st 21 day	th 30 day
	Conditions	Physical changes				
1	o o	Noc	Noc	Noc	Noc	Noc
2	o o	Noc	Noc	Noc	Noc	Noc
3	Room temperature	Noc	Noc	Noc	Noc	Noc
4	0 0	Noc	Noc	Noc	Noc	Noc
5	0 0	Noc	Noc	Noc	Noc	Noc
6	0 0	Noc	Noc	Noc	Noc	Noc

Figure 11: DSC thermogram of Amlodipine Besilate pure drug

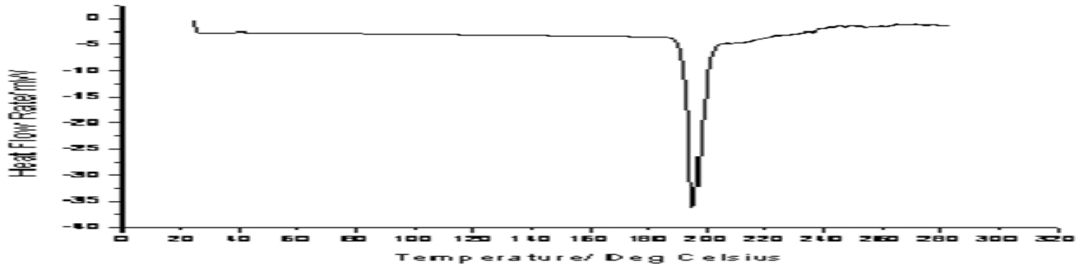


Figure 12: DSC thermogram of Amlodipine Besilate –$_{A3}$

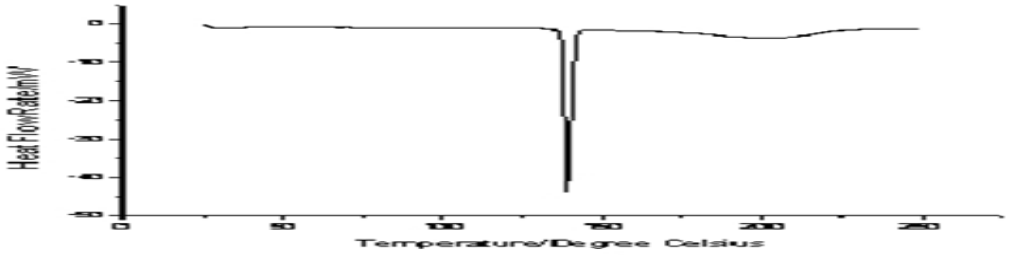
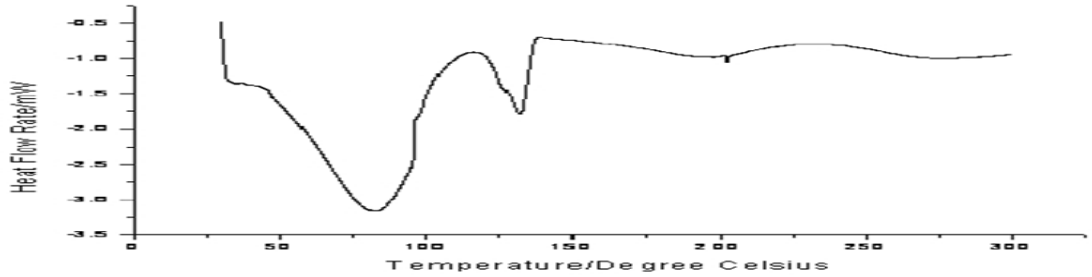


Figure 13: DSC thermogram of Metoprolol succinate pure drug



prepared by wet granulation method. Thehydroxyl propyl cellulose , ETHYLCELLULOSE, MCC PH101, and metoprololsuccinate were passed through sieve no.30 and mixed Homogenously. For the binder

Table No-10- Drug Release M6 Formulation

Time (Hr)	Log Time	SQRT Time	% Cumula Release	Log % Release	% Drug remaining	Log % Drug remaining
0		0	0		100	2
1	0.000	1.000	15.98	1.204	84.02	1.924
4	0.602	2.000	39.04	1.5915	60.96	1.785
8	0.903	2.828	58.76	1.7691	41.24	1.615
20	1.301	4.472	94.86	1.9771	5.14	0.711

solutionweighed amount of methylcellulose was added little by little in glycerol Inwater with continuousstirring to avoid lumps. The binder solution was slowly Added to the above blend and mixed wellto 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.thegranules were finally dried at 60ºc till a constant LOD reaches(3-4%). MAGNESIUMSTERATE, maize starch 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's Index Angle of repose, and Hausner's ratio, loss on drying. The results are as in table 3and 4.

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.

Methods: Simultaneous estimation of Metoprolol succinate and Amlodipinebesylate by UV spectroscopy6 ,7

Preparation of stock solution of Metoprolol succinate Metoprolol succinate equivalent to 20 mg of metoprolol wasaccurately weighed and transfer to 100 ml volumetric flask. About 90ml of 0.1 N HCl was added and sonicated to dissolve. The volume wasmade up to the mark with 0.1 N HCl. The final dilution contained 500µg/ml of metoprolol.

Preparation of stock solution of Amlodipine besylate Amlodipine besylate equivalent to 10 mg of amlodipine wasaccurately weighed and transfer to 100 ml volumetric flask. About 90ml of 0.1 N HCl was added and sonicated to dissolve. The volume was made up to the mark with 0.1 N HCl. The final dilution contained 200µg/ml of amlodipine.

Preparation of synthetic mixture of Metoprolol and Amlodipine 10 ml of each of the stock solutions of metoprolol andamlodipine were transferred to 10 ml volumetric flask. The volumewas made up to mark with 0.1 N HCl. The resultant solution contained 50 µg/ml of metoprolol and 20 µg/ml of amlodipine.

Preparation calibration curve:

i) For Amlodipine besylate: 100 mg of Amlodipine besylate was accurately weighed and dissolved in 25 ml of methanol in 100 ml volumetric flask and the volume was made up to the mark using methanol, to make (1000 µg/ml) standard stock solution (I). Then 1 ml stock solution (I) was taken in another 100 ml volumetric flask and further dilute in 100 ml of methanol to make (10 µg/ml) standard stock solution(II), then final

concentrations were prepared 16, 20, 24, 28, 32 µg/ml with 0.1N HCL The absorbance of standard solution was determined using UV/ VIS spectrophotometer at 244nm. Linearity of standard curve was assessed from the square of correlation coefficient (r2) which determined by least-square linear regression analysis.

ii) For Metoprolol succinate: 100 mg of Metoprolol succinate was accurately weighed and dissolved in 25 ml of 6.8 pH buffer in 100 ml volumetric flask and the volume was made up to the mark using 6.8 pH buffer, to make (1000 µg/ml) standard stock solution

(I). Then 1 ml stock solution (I) was taken in another 100 ml volumetric flask and make up the volume with phosphate buffer pH 6.8 to get(10 µg/ml) standard stock solution(II), then final concentrations of 10, 20, 30, 40, 50, 60, 80 and 100 µg/ml were prepared from stock II. The absorbance of standard solution was determined using UV/ VIS spectrophotometer at 223 nm. Linearity of standard curve was assessed from the square of correlation coefficient (r2) which determined by least-square linear regression analysis.

Drug-Excipient Compatibility Study

Incompatibility studies were done by inducing astress at different temperatures such as freezer (100C-200C), Cold (20C- 80C), room temperature, 25Ċ±2Ċ/60%±5%RH,30Ċ±2Ċ/65%±5%RH ,40Ċ±2Ċ/75%±5%RH ,polymers and diluents and 1:0.5 other ingredients. The study was carried out for one month(1st. 7th, 15th, 21st and 30th day) and observation for thephysical changes such as colour, liquefaction etc., weregiven in the table 9.

Content uniformity

Ten tablets were selected randomly and crushed,from that average weight of one tablet was dissolved using20ml methanol and 20ml of 0.1N HCl until drugs get dissolved then added the dissolution media(0.1N HCl for amlodipine besylate and for metoprololsuccinate(phosphatebufferph6.8) to make volume 100ml , 0.45µ membrane filter. Standard also performed with the same concentration then this would read at 244nm ,223nm by uv spectroscopy.

$$\text{Amount of drug} = \frac{\text{sample absorbance}}{\text{Std .absorbance}} \times \frac{\text{std.dilution}}{\text{sample dilution}} \times \text{conversion factor} \times 100$$

$$\text{Conversion factor} = \frac{\text{Molecular weight of Metoprolol Succinate}}{\text{Molecular weight of Metoprolol tartrate}}$$

$$\text{Conversion factor} = \frac{\text{Molecular weight of Amlodipine besylate}}{\text{Molecular weight of Amlodipine}}$$

$$\% \text{ Purity} = \frac{\text{Amount}}{\text{Label claim}} \times 100$$

Label Claim = 25 mg (Metoprolol Succinate) and 10mg (Amlodipine besylate)

In vitro dissolution study of Metoprolol succinate sustained releasematrix layer tablet: Drug release studies were carried out using USP dissolutiontest apparatus 2 at 50 rpm, 37±0.5°C, and pH 1.2 buffer (500ml) for 2hours, since the average gastric emptying time is about 2 hours. Thedissolution medium was replaced with pH 6.8 phosphate buffer (500ml) and experiment continued for another 20 hours. At the different timeintervals,1,4,8,20hours, 5ml of the sample was withdrawn and replaced with 5ml ofdrugfree dissolution medium. The samples withdrawn were analyzedby UV spectrophotometer at 223nm.

In vitro dissolution study of amlodipine besylate immediate releaselayer tablet: Amlodipine besylate immediate release tablets drug releasestudies carried out using USP dissolution rate test apparatus (apparatus 2, 100 rpm, 37±0.5°C) for 45miniutes in 0.1 N HCl (500ml). 5ml of the sample was withdrawn and replacedwith 5ml of the 0.1 N HCl. The dissolution samples were obtained at the endof 45 miniutes replacing with drug-free dissolution medium.The samples withdrawn were analyzed by a UV spectrophotometer At 244nm.

AT – Absorbance of test preparation

AS – Absorbance of standard preparation

WS – Weight of standard

DS – Dilution of standard preparation

DT – Dilution of test preparation

LC – Label claim (mg per tablets)

P – Potency of standard

D – Sum of correction factors for all previous time points

Correction factor = V × R / 500

V – Volume withdrawn at last time point

R – Percentage of drug released at last time point

Stability Studies: [9]

Figure 14: DSC thermogram of Metoprolol succinate tablet (M6)

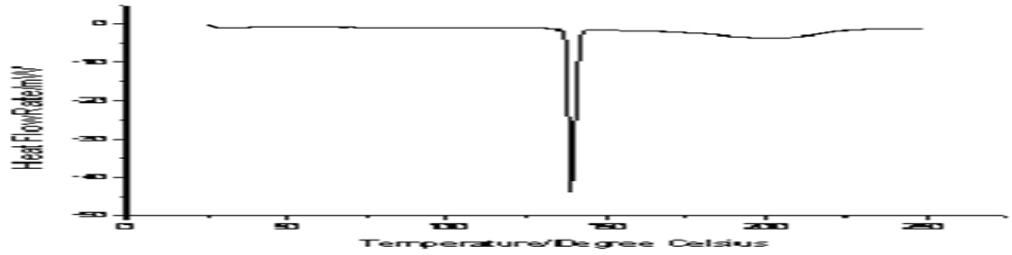
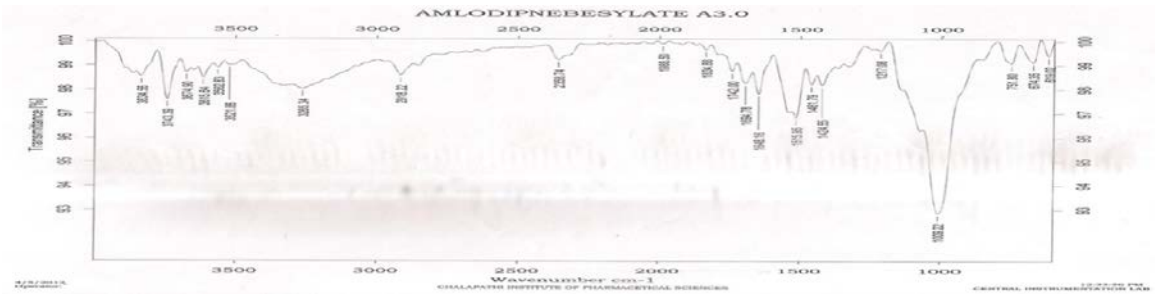


Figure-**15-**Ftir Of Amlodipine Besylate Formulation A3



The tablets were packed in blister packing and kept for 3 months at 40oC / 75% RH and 25oC / 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 R2 value nearer to 1 indicates the model best fits the release mechanism.

RESULTS AND DISCUSSION

Preformulation studies: Preformulation Study Was Carried Out To Formulate Desired Metoprolol Succinate Sr And Amlodipine Besylateir Tablets, Compatibility Studies Performed On The Physical Mix Of Metoprolol Succinate And Amlodipine Besylate Withdifferent Tablet Excipients At Temperature Such As Freezer,Cold 25ċ±2ċ/60%±5%Rh,30ċ±2ċ/65%±5%Rh ,40ċ±2ċ/75%±5%Rh , Hpc , Mccph101, Lactose, Dcp, Purified Talc,Maize Starch,Glycerol,Methyl Cellulose, , Anhydrous Sodium Starch Glycolate,And Magnesium Stearate Result Showed That No Physical Changes In Thevalue Of Metoprolol Succinate And Amlodipine Besylate Upto 1st, 7th, 15th, 21st And 30th Day, Which Indicates That Metoprolol And Amlodipine Is Stable In Various temperature . . Calculated Value Of (Metoprolol Succinate And Amlodipine Besylate)

Percentage Compressibility(54.23% & 12%), Hausner's Ratio (1.10 & 1.17), Angle Ofrepose (Θ=68.8.& 26.7), Loss On Drying (0.52% & 1.6%) And Hygroscopicity (0.12% & 0.19) Of All Excipientsindicates That Metoprolol Succinate Was Not Suitable For Direct Compression As Well As Having Very Poor Flow Property So Almost Lot Of Chances In Weight Variation During Filling Of Dye By The Blend And Granules Can Dry At450c In Fbd. But AmlodipineBesylate Has A Shownsignificant Propriety For Direct Compression With Slightly Hygroscopic In Nature.

Physical properties of granules F1-F6

Figure-16-Ftir Of Amlodipine Besylate Formulation A0

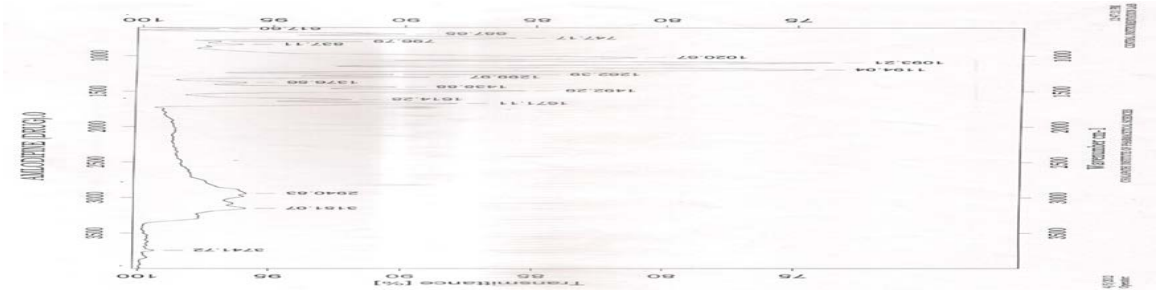


Figure-17-Ftir Of Metoprolol Succinate Formulation $_{M6}$

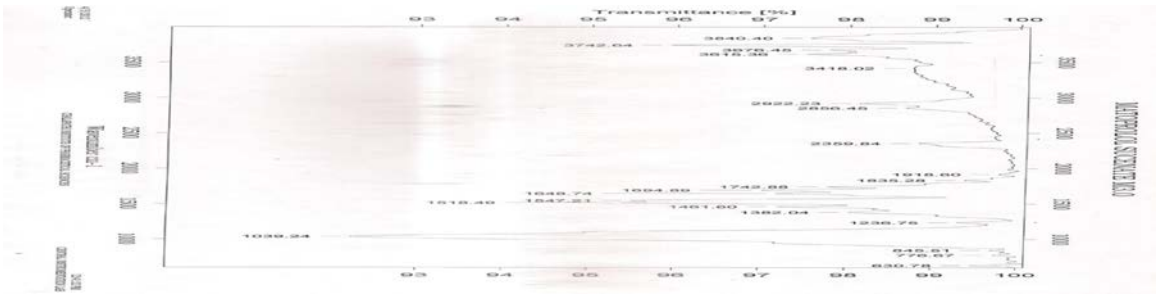
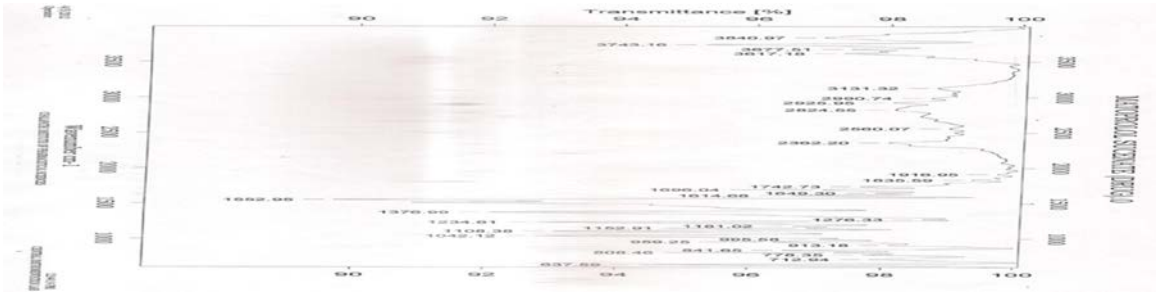


Figure-18-Ftir Of Metoprolol Succinate Formulation $_{M0}$



The Metoprololsuccinate Granules And Amlodipinebesylate And Blends From Formulations (M1-M6 &A1-A3 Respectively) Were Evaluated For Bulk Density, Tappeddensity, Compressibilityindex (Carr'sIndex),Hausner's Ratio, Particle Size And Angle Of Repose Results Are shown In (Table 3 & 4) Promisingly Indicates That The flow of all formulation was good Throughout the formulations Due To Particle Sizes Lies Around 482 And 300µm Respectively. SR Part Of Metoprolol Succinate And IR Part Of amlodipine Besylate Tablet (M1-M6 & A1-A3) Was Found within The Specified Limit For Weight Variation Of All Trialbatches Passed, Hardness Of All Formulations Was In The Range Of 2.8 – 4.5kg/Cm2 . It Should Lies Within The uspspecification. Friability value for the trial batches was not in the more than 0.25% due to Polymer concentration formulations.

Bilayer tablet were compressed at an average weight of 400mg were ±3.0%, which falls within the acceptable weight variation range of ±5% as per USP. Layer separation and disintegration was failed from A1 - A3, the decrease the MCC PH101 up 23% and increase super disintegrant 9% can overcome above problems All ten tablets were found that the labeled amount of drug (25& 10 mg), hence passes the test for content uniformity and the assay limit for the tablets were found to be 80-100 &83-97%, shown in the table VI.

In-vitro drug release study

The expectation was to sustain the release of formulations in order to increase The polymers such ashpc & MCCPH101, ETHYLCELLULOSE concentrations Graduallyup to 82% and 70% , 4% respectively. The desired release Pattern is shown in table VI as per USP monograph.

The trial batch (M1-M3) contains MCCPH101 and ETHYLCELLULOSE Were 81% ,82%, 82% and 4%, 2.6%, 4%respectively, M4 has 70%HPC 4% ETHYL CELLULOSE but theserelease profile was not desired. At formulation M5, end of 8th and 12thh 60% and 93% of the drug was released. The drug release profile obtained Was nearest at intervals 1stand 4thh and more than specified limit at interval of 8thh. The trial batch (M6) contains 70% of HPC, 4%ETHYLCELLULOSE As rate controllingpolymer to that of tablet weight and contains 6.8% of MAIZESTARCH As diluents, .4% of METHYLCELLULOSE as binder and 1.2% of magnesium stearate As lubricants. The granules were compressed. At a hardness of 4.5 kg/cm2. Percentage of drug content determined as 100.2 and 97.22% was relates As per monograph. Dissolution study was carried out at the end of 20thh 94.86% of the drug was released. The drug releaseprofile obtained was within the specified limit at all Intervals of standard, 1st, 4th, 8th and 20th hour shown in Figure 8.

The drug release data obtained for M6 was plotted according to different modes of data Treatment are shownin fig 3,4,5,6..

The linear regression value was calculated and it was found to be 0.99.So it is obvious that the release of drug from the sustained release tablets were not obeyed Zero-order kinetics.The linear regression value was calculated and it was found to be 0.997.So it was obvious that the release of drug from the sustained release tablet follows first-orderKinetics. Drug release from polymer matrix depends uponthe concentration. The plot was linear and the linear regressioncoefficient value is 0.999. So it is obvious that the drug release obeyed diffusion mechanism from the SR matrix. The release exponent 'n' was 0.859. So it indicates a coupling of the diffusion and least considerable swelling mechanism—so-called anomalous diffusion—and may indicate that the drug release is controlled by more than one process. Incompatibility study of Metoprolol succinate and Amlodipine besylate with excipients

CONCLUSION

The present work has been observed that using of HPC , EC, MCCPH101 retarded the sustained drug release acceptably; formulation (M6) has shown a drug release NLT 80% in 20h was in accordance with the USP. when compared with all the formulations. M6 bilayer tablet was sufficiently produce sustained (SR) and immediaterelease (IR) and anomalous non-fickiantransport of diffusion from first order release, considerable swelling and diffusion mechanism involved from the matrix of the formulation was observed

In conclusion, in the present research, bilayer sustained and immediate release tablet formulation was successfully prepared for a once daily administration. Hence A3M6 was optimised formulation

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