An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

FORMULATION DEVELOPMENT AND *IN-VITRO* EVALUATION OF BI-LAYERED SUSTAINED RELEASE TABLETS OF AMLODIPINE DESILATE AND METOPROLOL SUCCINATE

D. Tharun*, S B Thirumalesh Naik, S Sai Vikas, P Kalyan, K Siva Kumari

Department of Pharmaceutics, JNTUA-Oil Technological and Pharmaceutical Research Institute, Ananthapuramu, 515001. Andhra Pradesh, India

*Corresponding author E-mail**: tharundudi888@gmail.com**

ARTICLE INFO

Key Words

Amlodipine desilate ,Metoprolol succinate,HPMC K15, PEO, MCC

ABSTRACT

The objective of the present investigation was to develop a bi-layered tablet of Amlodipine desilate and Metoprolol succinate, shows immediate and sustain release to reduce dosing frequency, achieve patient compliance and to avoid toxicity.It was prepared byDirect compression technique According to FT-IR studies, polymers like HPMC K15, Polyethylene oxide, Mg-stearate, Aerosil,MCC,Sodium starch glycolate, Dicalcium phosphate,Iron oxide are compatible.Polymers like HPMC K 15 and PEO contributes for sustained release.The formulated bi-layered tablets satisfied all the physical evaluation parameters in required specifications.The dissolution studies of bi-layered tablets reflects USP specifications of NMT 20% by 1 hr,20-40% by 4 hrs,40-60 % by 8 hrs, and 80 % by 20 hrs.Amlodipine shows 100% Drug release within 1 hr. whereas Metoprolol takes 24 hrs.Amongst of all the prepared formulations, F8 follows Non-Fickian type and shows 1st order kinetics, M2,M5 and M10 followed Fickian type of diffusion, which was evidenced from the drug release kinetics.

INTRODUCTION:

Drug delivery has metamorphosed from the concept of pill to molecular medicine level in the past 100 years. in order to improve the therapeutic efficacy, better appreciation and integration of pharmacokinetic and pharmacodynamic principles in the design of the drug delivery system has been developed. Bilayer tablets are novel drug delivery systems where combination of two different drugs in the same dosage form, to minimize physical and chemical incompatibilities, IR and SR in the same tablet and optimized bilayer dsage form containing one immediate release drug amlodipine besilate and another extended release drug metoprolol succinate as extended release dosage form[1,2,3]. JNCVI recommended that the combination of a low dose of two drugs in fixed dose combination is an appropriate choice for initial treatment. A combination drug therpy is recommended for treatment of hypertension to allow

medications of different mechanism of action complement each other and lower the blood pressure lower than maximum dose of each. The rational for combination therapy is to encourage the use of lower drug doses for reducing the blood pressure miimaxe dose dependent side effects and adverse reactions[1].

MATERIALS

Metoprolol succinate was obtained from ParasImpex, Ahmedabad and Amlodipine from Siflondrugs, Hyderabad as an gift sample. Polymers like MCC from FMC biopolymers, Mumbai.Lactose from Himedialaboratories.Pvt.Ltd,Mumbai.Dicalc ium phosphate from All India drug supply.co, Mumbai.HPMC K4M and HPMC K15 from Colorcon Asia Pvt.Ltd, Goa.Sodium starch glycolate as excipient obtained from BioplusPvt.Ltd, Banglore. Crospovidone is obtained from Himedialaboratories.Pvt.Ltd,Mumbai.Carbo xy methyl cellulose sodium gift pack is obtained from Simla industries, Mumbai. Carbopol as a sample obtained from Jaymanchemicals,Mumbai. PEO is obtained from Rimproindia,Ahmedabad. Aerosil and Magnesium stearate is obtained from S.D.Finechemicals,Mumbai, Iron oxide from Pampa enterprises, Bangalore. Sodium hydroxide,Orthophosphoric acid, and Potassium Di-hydrogen ortho phosphate Acetonitrile is obtained from Ranchem,RFCLLtd.,Delhi.

Preformulation studies:

Standard curves of Amlodipine Besilate and Metoprolol Succinate

Assay of Amlodipine&Metoprolol in Amlodipine Besilate&Metoprolol Succinate tablets 5mg & 100mg by HPLC method[6].

Reagents and Standard – Amlodipine &Metoprolol Tablets: Water HPLC Grade and amlodipine Besilate & Metoprolol Succinate Working Standards, Acetonitrile HPLC Grade, Ortho phosphoric acid

Preparation of mobile phase: Mix a mixture of above buffer 500 mL (50%) and 500 mL of Acetonitrile HPLC (50%) and degas in ultrasonic water bath for 5 minutes. Filter through 0.45 µ filter under vacuum filtration.

Formulation of Amlodipine besilate immediate release tablets: Direct compression method is used to prepare amlodipine besilate immediate release tablets. Sodium starch glycolate, Dicalcium phosphate, MCC along with active ingredient were mixed uniformly and passed through sieve no.30.Aerosil and Magnesium stearate were passed through sieve no.60.Then,the colourant Iron oxide is passed through sieve no.100.then these 3 mixtures were homogeniouslymixed to get uniform blend,which is subjected to direct compression[9,14,15].

Formulation of Metoprolol succinate sustained release tablets: Direct compression method is used in Metoprolol succinate sustained release tablets formulation.HPMC K15,carbopol,sodium CMC,PEO,MCC,HPMC K 4M & active ingredient were mixed homogeniously and extract through sieve no.30.Aerosil & Mg-stereate were allowed to pass through sieve no.60,which acts as lubricant.Both these mixtures were mixed to obtain homogeniousblend,which allowed for direct compression[6].

Formulation of optimized bilayered tablets of Amlodipine besilate and Metoprolol succinate: Among all the formulations A8 in immediate release (Amlodipine besilate) & M7 in sustained release (Metoprolol succinate) were chosen as the best formulations after in-vitro drug release studies to formulate immediate & sustained release bi-layered tablet by usingCadmach high speed rotatory tablet press**.**

EVALUATION OF DOSAGE FORMS

Post compression studies[4,5]

Weight variation test: Randomly 20 tablets were selected and their individual weights were calculated,from which the average weight was calculated.

Friability: 10 formulated tablets were de-dusted and weighed accurately,it is subjected to friability test apparatus and rotated with a speed of 100times at 25±1 rpm for 4 minutes.The tablets were removed and de-dusted,the loss of weight was calculated by below formula.

Hardness test: Hardness of formulated tablet was detected by Monsanto tablet tester by placing tablet vertically and variation in tablet weights was observed.

Thickness: 10 tablets were randomly selected,with the help of screw guage micrometer their thickness was measured.

***In - vitro* drug release study for amlodipine formulations:** Formulated Amlodipine tablet was added to USP type-II dissolution apparatus which is filled with 900ml of 6.8 P^H phosphate buffer,maintained at 37 ± 0.5°C,tempetrature and paddle at 50 rpm. Sample of 5 ml. were collected with specific time intervals by replacing the equal volume of fresh medium.Filter the collected sample and subjected to HPLC.The drug release concentrations were calculated in the form of standard curve and was expressed as cumulative drug % release[14]

***In vitro* drug release for optimized bilayer tablet:** Drug release studies was performed by using USP II apparatus filled with 900 ml of (pH 1.2) 0.1N hydrochloric acid medium for first 2 hrs.then replaced with phosphate buffer(P^H 6.8) with maintained at 37 ± 0.5°C,maintain the paddle at 50 rpm.Collect the sample of 5 ml. with specific time intervals for 20 hrs. by replacing the equal volume of fresh medium

Drug release kinetics of metoprolol succinate formulations[2]: The formulated tablets of metoprolol were subjected for the drug release kinetics.All the batches may fitted to Zero order,First order & Higuchi ascertain the kinetic modeling of thedrug release in dissolution profile.Most adopted method is Bamba et.al.

Zero order: Generally, modified dosage forms like controlled and sustained released dosage forms follows Zero order kinetics(seen in planned, predictable and slower release dosage forms).It van be calculated through

$m = k \times t$ $\ln (100-Q) = \ln 100 - k_1 t$

Higuchi Model: A large number of modified release dosage form contain some sort of matrix system. In such instances, the drug dissolves from the matrix. The dissolution pattern of the drug is dictated by water penetration rate (diffusion controlled) and thus the following relationship applies as formula

$Q = k_2 t^{1/2}$

Korsmeyerspeppa's equation:

$Mt/M\infty = Kt^n$

Where, Mt is the amount of drug released at time t, M∞ is the amount of drug released after infinite time, k is a kinetic constant incorporating structural and geometric characteristics of the tablet, and n is the diffusional exponent indicative of the drug release mechanism.

RESULTS AND DISCUTIONS

Compatibility (FTIR) Study: From the FT-IR studies,it is evidenced that there is no chemical interaction between Metoprolol succinate and Amlodipine Besilate.It is observed that both the drugs were showing characteristic peaks

i.e..,1613,1374,1107,1374,3275,3426,777,1232,722,1050cm^{-1}.The interpretation valueswere clearly shown below figures.

All the formulation blend of Amlodipine Besilateshows with an angle of repose value 30˚.187'to 33˚.141' indicating passable flowability. The Carr's index was found to be in a range of 15.41% to 16.16% .Hausner's ratio was in the range of 1.175 to 1.193 indicating good flowability.

The weight variation of the tablets was in the acceptable range of 2.011% to 2.371%. Friability values of 0.53% to 0.68% showed that the formulations are physically stability. All tablets disintegrated rapidly in the USP disintegration test showing immediate release.The hardness and thick ness of all the formulated tablets were found to be 2.6 to 3.0 kg/cm^2 and 2.26 to 2.89 mm respectably.

Evaluation of Metoprolol sustained release layer:

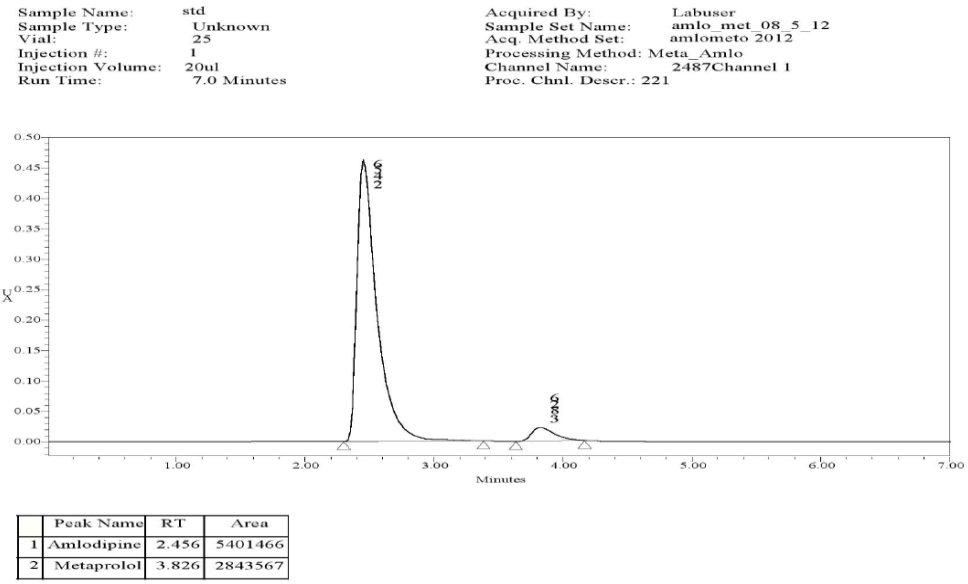
Pre compression of Metoprolol: The angle of repose values are in a range of 19˚.093' to 27˚.613' indicating excellent flowability. Carr's index of Metoprolol blend was found to be in a range of 5.240% to 6.403% indicating excellent flowability. Hausner'sratio isin the range of 1.055 to 1.068 indicating excellent flowability. As the powder material was free flowing, tablets were prepared by direct compression technique.

***In-vitro* drug release:** *In-Vitro* release studies of manufactured bilayered tablets of Amlodipine besilate and Metoprolol succinate were carried out in 900 ml of (pH 1.2) 0.1N hydrochloric acid medium for first 2 hours, which was then replaced with the same volume of a phosphate buffer solution pH 6.8 kept at 37˚C ± 0.5˚C and stirred at 50 rpm, USP Type-II dissolution apparatus. A 5mL sample was withdrawn at preselected intervals up to 20 hours and replaced with another 5 ml of a suitable fresh dissolution medium. The samples were filtered through membrane filter disc and analyzed for drug content by measuring area with HPLC. Drug concentration was calculated from the standard curve and expressed as percent drug release.

Drug release kinetics: The drug release kinetics was performed for all the Metoprolol Succinate formulations as well as for the optimised formulation, in that only M2, M5, and M10 formulations have shown Fickian type of diffusion and remaining 7formulations showed Non-fickian type of diffusion. The release kinetics of the optimized formulation showed Higuchi model and non-fickian transport.

CONCLUSION

The present investigation showed that desired controlled release matrix tablet formulation was prepared with expected drug release and can be obtained by using the release retarding polymers and channeling agents. Based on the resultsobtained, it was concluded that FTIR studies confirmed the drug excipient compatibilities. Formulated Powder blend of all the formulations were evaluated for pre-compression and post compression parametersand observed that they are in the limits.The formulated tablets are subjected to various evaluation studies like hardness, friability, content uniformity, weight variation, thickness, release kinetics ,in-vitro dissolution studies etc., Based on the *In-Vitro* dissolution study, it was found that optimized formulation was reflecting the drug release as per the USP specification limits. Hence, F8 is considered as optimized formulation. The drug release kinetics was performed for all the Metoprolol Succinate formulations and optimized formulation, in that only M2, M5, and M10 formulations showed Fickian type of diffusion and remaining 7formulations (i.e., M1, M3, M4, M6, M7, M8, M9) showed Non-fickian type of diffusion. But in optimized formulations shows Fickian type and Non Fikiantexcept F9 showed case II release.



	Peak Name	RT	Area
1	Amlodipine	2.456	5401466
2	Metaprolol	3.826	2843567

Fig 1: Standard curve of Amlodipine Besilate and Metoprolol Succinate

INGREDIENTS	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10
Amlodipine besilate	5	5	5	5	5	5	5	5	5	5
Microcrystalline cellulose	10	100	0	100	100	100	100	25	50	75
Sodium starch glycolate	0	10	10	0	10	10	10	10	10	10
Dicalcium phosphate	100	0	100	100	75	50	25	100	100	100
Magnesium stearate	1	1	1	1	1	1	1	1	1	1
Aerosil	2	2	2	2	2	2	2	2	2	2
Iron oxide	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16
PVP K30	5	5	5	0	0	0	0	0	0	0
Cross povidone	10	10	10	0	0	0	0	0	0	0
Tablet weight (mg)	223.16	133.16	133.16	208.16	193.16	168.16	143.16	143.16	168.16	193.16

Table 1: Formulation of Amlodipine besilate immediate release tablets:

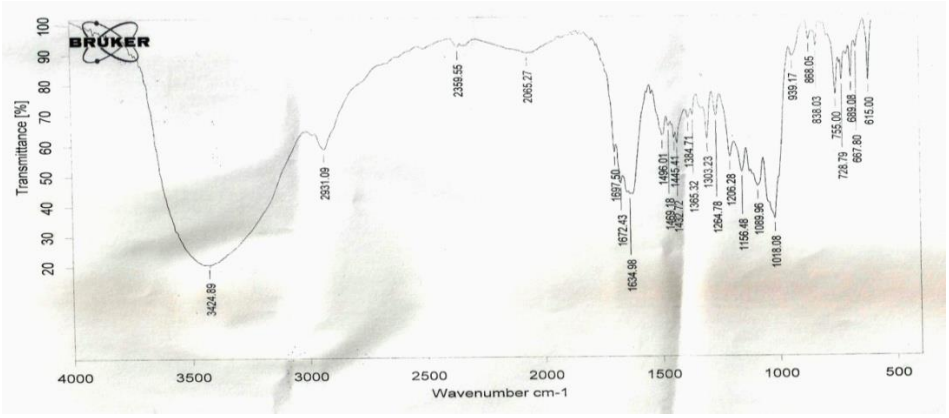


Fig 2: FTIR of Amlodipine Besilate

Table 2: Batch composition of Metoprolol succinate

INGREDIENTS	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
Metoprolol succinate	100	100	100	100	100	100	100	100	100	100
HPMC K4M	50	75	100	0	0	0	0	0	0	0
Lactose	20	25	0	25	0	0	0	0	0	0
Microcrystalline cellulose	78	25	0	25	0	0	0	0	0	0
HPMC K15	0	0	0	50	100	100	100	125	150	150
Sodium CMC	0	0	0	0	25	50	0	0	0	0
Carbopol	0	0	50	0	0	0	0	0	0	0
Poly ethylene oxide	0	0	0	0	0	0	50	50	50	25
Magnesium stearate	1	1	1	1	1	1	1	1	1	1
Aerosil	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
TABLET WEIGHT (mg)	251.5	228.5	253.5	203.5	228.5	253.5	253.5	278.5	303.5	278.5

Table 3:Batch composition of Optimized formulation

S.NO	WORKING INGREDIENTS	M7	WORKING INGREDIENTS	A8
1	Metoprolol succinate	100	Amlodipine besilate	5
2	HPMC K15	100	Microcrystalline cellulose	25
3	Poly ethylene oxide	50	Sodium starch glycolate	10
4	Magnesium stearate	1	Dicalcium phosphate	100
5	Aerosil	2.5	Magnesium stearate	1
6			Aerosil	2
7			Iron oxide	0.16
TABLET WEIGHT (mg)		**253.5**		**143.16**
TOTAL TABLET WEIGHT (mg)			**253.5+143.16**	**396.66**

Table 4:IR interpretation of Amlodipine Besilate

S.No	Type of bond	Type of vibration	Actual frequency (cm^{-1})	Observed frequency (cm^{-1})	Confirmation
1	N – H	Streching	3500	3424.89	Amine group
2	C – Cl	Streching	800 – 754	755.00	Aromatic
3	C – O	Streching	1300 – 1050	1206.28	Aliphatic ethers
4	C – H	Bending	710 – 690	689.08	Aromatic
5	S – O	Streching	1165 – 1150	1156.48	Sulphonic salts

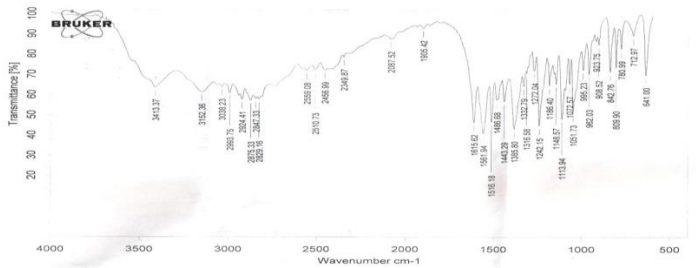


Fig 3: FTIR of Metoprolol Succinate

Table 5:IR interpretation of Metoprolol Succinate

Type of bond	Type of vibration	Actual frequency (cm^{-1})	Observed frequency (cm^{-1})	Confirmation
C=C	stretching	1600	1615.62	Aromatic
C-O	stretching	1350-1260	1272.04	2^0 alcohol
C-O	stretching	1150-1070	1148.57	Ether
C-O	stretching	1410-1300	1385.80	Phenoxide
N-H		3310-3140	3152.36	2^0 amine

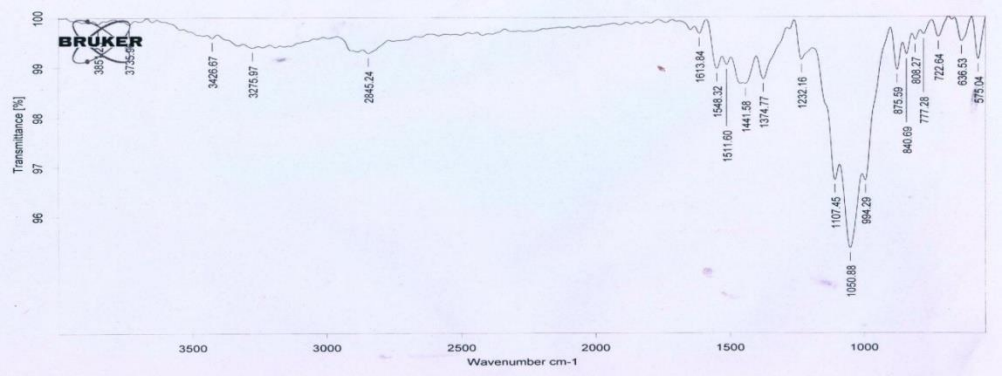


Fig 4: FTIR of Placebo (mixture) IR interpretation of Metoprolol Succinate

Table 6: IR interpretation of Metoprolol Succinate

Type of bond	Type of vibration	Actual frequency(cm^{-1})	Observed frequency(cm^{-1})	Confirmation
C = C	Stretching	1600	1613.84	Aromatic
C – O	Stretching	1350-1260	1374.77	2^0 alcohol
C – O	Stretching	1150-1070	1107.45	Ether
C – O	Stretching	1410-1300	1374.77	Phenoxide
N – H		3310-3140	3275.97	2^0 amine
N – H	Streching	3500	3426.67	Amine group
C – Cl	Streching	800 – 754	777.28	Aromatic
C – O	Streching	1300 – 1050	1232.16	Aliphatic ethers
C – H	Bending	710 – 690	722.64	Aromatic
S – O	Streching	1165 – 1150	1050.88	Sulphonic salts

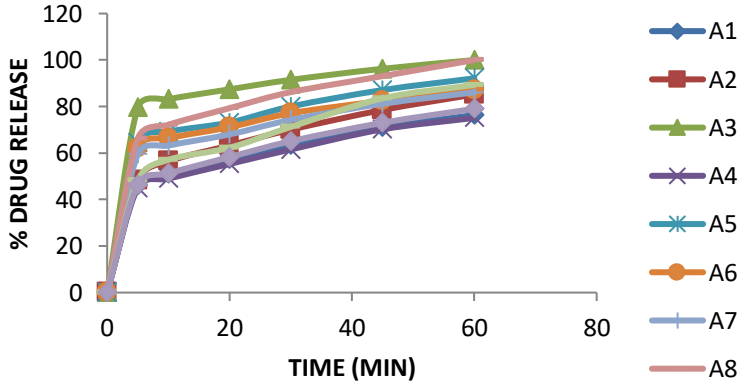


Fig 5: Graphical representation of amlodipine

Evaluation of Amlodipine immediate release layer:

Table 7: Pre-compression parameters of amilodipine

Formulation	Angle of repose(θ) Avg ± SD	Bulk density (g/mL) Avg ± SD	Tapped density (g/mL) Avg ± SD	Compressibility Index (%) Avg ± SD	Hausner'sRatio Avg ± SD
A1	31˚.251'±0.742	0.517±0.022	0.612±0.011	15.52±1.231	1.184±0.021
A2	30˚.754'±0.881	0.514±0.014	0.611±0.031	15.88±1.343	1.189±0.035
A3	32˚.125'±1.240	0.524±0.028	0.621±0.026	15.62±1.262	1.185±0.031
A4	31˚.075'±0.951	0.531±0.031	0.631±0.022	15.45±1.316	1.183±0.032
A5	33˚.141'±0.980	0.519±0.024	0.619±0.018	16.16±1.241	1.193±0.024
A6	30˚.663'±0.815	0.523±0.020	0.603±0.014	15.41±1.256	1.175±0.022
A7	30˚.298'±0.765	0.511±0.017	0.618±0.011	16.62±1.134	1.187±0.021
A8	30˚.367'±0.569	0.502±0.021	0.621±0.028	15.44±1.230	1.191±0.023
A9	30˚.530'±0.779	0.521±0.018	0.611±0.016	15.43±1.342	1.185±0.025
A10	30˚.187'±0.812	0.518±0.016	0.621±0.012	15.72±1.201	1.187±0.024

Post-compression parameters of amilodipine

Table 8: Post-compression of amilodipine

Formulation	Weight variation (%) Avg ± SD	Friability (%) Avg ± SD	Disintegration time(sec) Avg ± SD	Hardness(kg/cm^2) Avg ± SD
A1	2.011±0.219	0.66±0.021	21.52± 0.67	3.0±0.194
A2	2.266±0.328	0.56±0.020	20.94±0.51	2.8±0.120
A3	2.310±0.429	0.52±0.016	17.64±0.24	2.6±0.114
A4	2.118±0.231	0.68±0.021	13.73±0.62	3.0±0.213
A5	2.197±0.310	0.54±0.038	11.69±0.69	2.8±0.172
A6	2.291±0.330	0.58±0.021	21.19±0.60	2.9±0.160
A7	2.301±0.117	0.53±0.010	20.66±0.39	3.0±0.193
A8	2.071±0.291	0.59±0.015	15.53±0.51	2.6±0.054
A9	2.108±0.102	0.63±0.022	16.11±0.33	2.8±0.151
A10	2.371±0.017	0.62±0.028	18.33±0.75	3.0±0.182

***In vitro* drug release of Amlodipine:**

Table 9:*In vitro* drug release of Amlodipine

Percentage drug release of amlodipine layer										
Time	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**	**A10**
0	0	0	0	0	0	0	0	0	0	0
5	46.08	48.21	79.48	45.04	64.42	62.10	59.45	66.19	48.26	46.34
10	51.06	56.37	83.14	49.00	69.18	66.36	63.20	72.16	57.08	51.20
20	57.25	63.27	87.39	55.30	73.14	71.12	68.02	79.30	62.28	58.26
30	63.29	70.03	91.47	61.53	80.00	77.11	74.25	86.20	71.22	65.07
45	71.14	78.51	96.24	70.19	87.08	82.48	81.20	93.06	83.50	73.00
60	76.30	85.21	100	75.12	92.14	87.17	86.07	100	89.32	79.03

Table 10: Pre compression of Metoprolol

Formulation	Angle of repose(θ) Avg ± SD	Bulk density (g/mL) Avg ± SD	Tapped density (g/mL) Avg ± SD	Compressibility Index (%) Avg ± SD	Hausner's Ratio Avg ± SD
M1	23˚.699'±0.013	0.497±0.011	0.531±0.010	6.403±0.021	1.068±0.041
M2	24˚.139'±0.022	0.477±0.021	0.508±0.011	5.731±0.032	1.061±0.012
M3	24˚.546'±0.011	0.458±0.042	0.486±0.021	5.761±0.041	1.061±0.011
M4	25˚.371'±0.023	0.466±0.051	0.494±0.031	5.668±0.040	1.060±0.013
M5	26˚.331'±0.024	0.446±0.043	0.471±0.036	5.307±0.012	1.056±0.048
M6	27˚.613'±0.030	0.469±0.041	0.497±0.062	5.633±0.011	1.059±0.054
M7	19˚.093'±0.020	0.458±0.013	0.485±0.053	5.567±0.010	1.059±0.062
M8	23˚.734'±0.014	0.465±0.014	0.492±0.047	5.488±0.016	1.058±0.051
M9	24˚.764'±0.010	0.442±0.032	0.467±0.028	5.353±0.027	1.056±0.034
M10	26˚.552'±0.013	0.434±0.034	0.458±0.018	5.240±0.029	1.055±0.041

Post compression parameters of Metoprolol

Table 11: Post compression of Metoprolol

Formulation	Weight variation	Friability (%)	Hardness(kg/cm2)	Thickness(mm)
M1	2.161±0.045	0.75±0.011	4.4±0.156	4.71±0.01
M2	2.951±0.173	0.88±0.021	4.6±0.114	4.70±0.02
M3	3.527±0.416	0.82±0.032	4.1±0.245	4.66±0.02
M4	3.367±0.174	0.85±0.010	4.3±0.112	4.72±0.02
M5	2.758±0.192	0.76±0.022	4.0±0.158	4.70±0.03
M6	4.159±0.057	0.72±0.033	4.7±0.312	4.67±0.03
M7	2.469±0.127	0.71±0.021	4.2±0.158	4.72±0.03
M8	2.494±0.066	0.68±0.024	5.0±0.315	4.71±0.02
M9	3.095±0.071	0.55±0.025	4.9±0.214	4.69±0.01
M10	2.585±0.053	0.81±0.028	4.2±0.132	4.72±0.02

Table 12 : Percentage drug release of metaprolol formulations

Percentage drug release of metaprolol formulations										
TIME	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
0	0	0	0	0	0	0	0	0	0	0
1	21.33	30.06	14.24	19.23	30.06	12.36	20.02	19.45	16.34	26.02
4	50.22	42.21	32.09	46.08	61.04	44.14	39.17	31.14	28.26	51.39
8	69.16	58.18	55.17	67.26	91.14	58.13	58.42	49.34	46.07	73.08
20	92.20	96.44	89.04	94.18	100	95.29	96.50	79.01	75.03	98.01

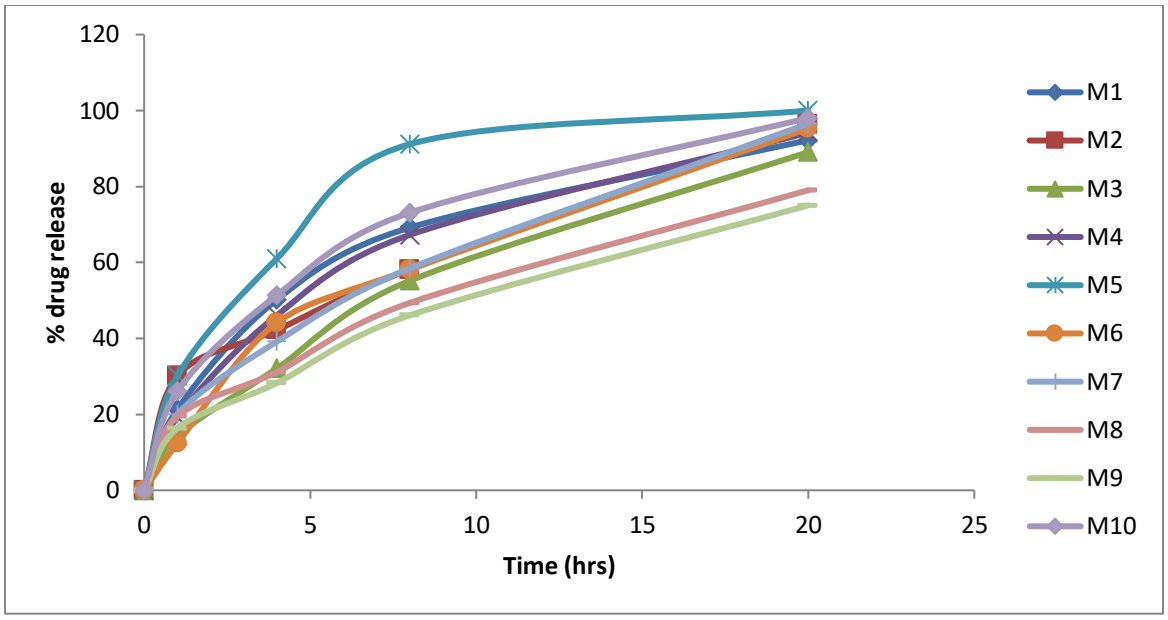


Fig 6: Graphical representations of % drug release of Metaprolal formulations

***In-Vitro* drug release kinetics of the Metoprolol formulations**

***Table 13: In-Vitro* drug release kinetics of the Metoprolol formulations**

Formulation code	Zero order		First order		Higuchi		Korsmeyer-peppas		Drug release mechanism
	r^2	Slope	r^2	Slope	r^2	Slope	r^2	Diffusion exponent (n)	
M1	0.822	4.112	0.993	-0.053	0.979	21.21	0.976	0.495	Non-fickian diffusion
M2	0.898	4.162	0.968	-0.07	0.987	20.62	0.957	0.384	Fickian diffusion
M3	0.942	4.206	0.996	-0.047	0.99	20.38	0.996	0.621	Non-fickian diffusion
M4	0.863	4.288	0.999	-0.06	0.99	21.7	0.985	0.538	Non-fickian diffusion
M5	0.705	4.333	0.982	-0.1	0.921	23.4	0.942	0.42	Fickian diffusion
M6	0.911	4.461	0.985	-0.065	0.988	21.96	0.968	0.678	Non-fickian diffusion
M7	0.932	4.41	0.975	-0.072	0.997	21.56	0.998	0.525	Non-fickian diffusion
M8	0.923	3.563	0.993	-0.032	0.994	17.48	0.98	0.472	Non-fickian diffusion
M9	0.935	3.438	0.994	-0.029	0.994	16.75	0.986	0.514	Non-fickian diffusion
M10	0.829	4.317	0.993	-0.083	0.984	22.23	0.991	0.45	Fickian diffusion

Evaluation of bilayered tablets (Optimized formulation):

Table 14: Optimized formulation post compression evaluation studies:

Formulation	OPTIMIZED FORMULATION POST COMPRESSION EVALUATION			
	Thickness (mm)	**Hardness (kg/cm^2)**	**Friability (%)**	**Weight variation (%)**
A_8M_7	5.72±0.02	4.0±0.158	0.62±0.015	2.869±0.134

Fig 7: Optimized formulation dissolution profile by HPLC at 5th Min

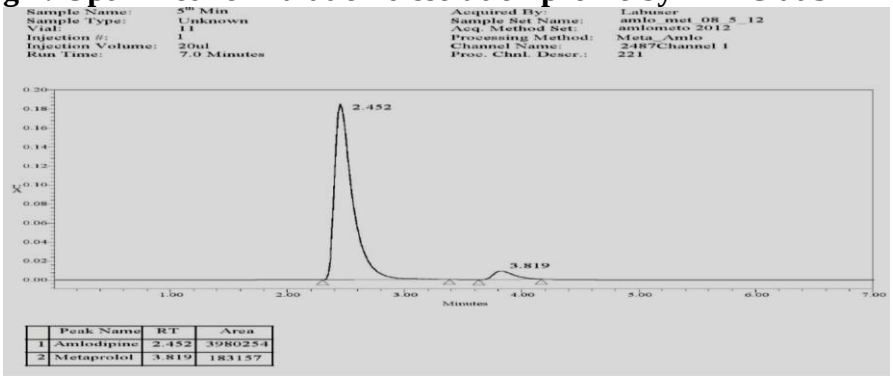


***Table 15: In-Vitro* dissolution profile of optimized formulation**

TIME	OPTIMIZED FORMULATION INVITRO DRUG RELEASE			
	AMLODIPINE		**METOPROLOL**	
	AREA	**% DR**	**AREA**	**% DR**
5Min	3980254	66.1869	183157	5.7853
10Min	4339272	72.1586	304187	9.6083
20Min	4768246	79.2903	402127	12.7020
30Min	5183654	86.1980	502127	15.8607
45Min	5596127	93.0569	553157	17.4726
1Hour	6014016	100	633187	20.0005
4 Hours	6012116	99.9843	1237682	30.0947
8 Hours	6012916	99.9776	1841664	58.1728
20 Hours	6013016	99.9706	3047662	96.2667

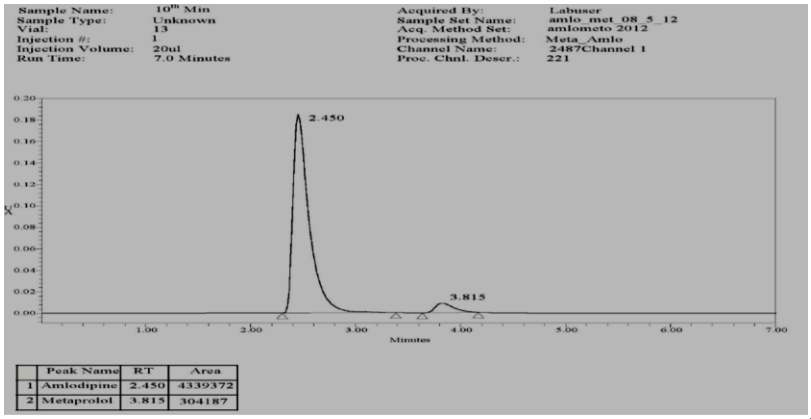


Fig 8: Optimized formulation dissolution profile by HPLC at 10th Min

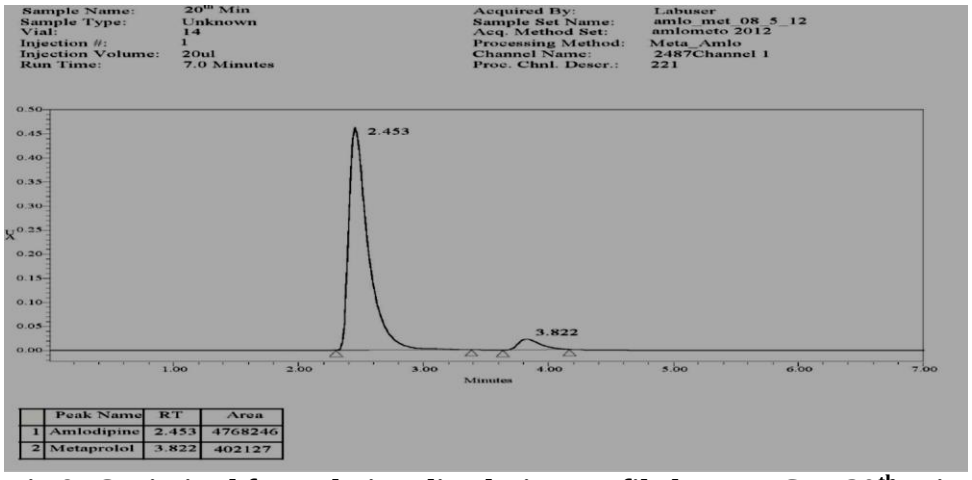


Fig 9: Optimized formulation dissolution profile by HPLC at 20th Min

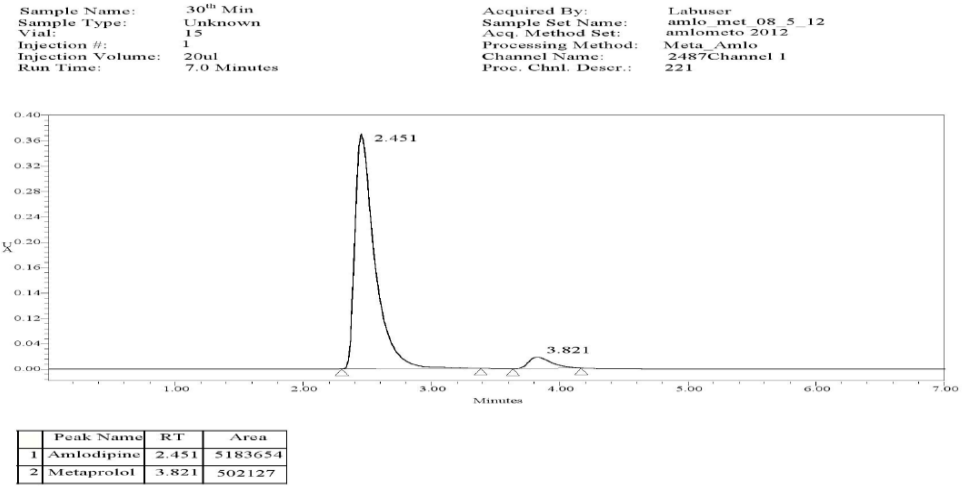


Fig 10: Optimized formulation dissolution profile by HPLC at 30th Min

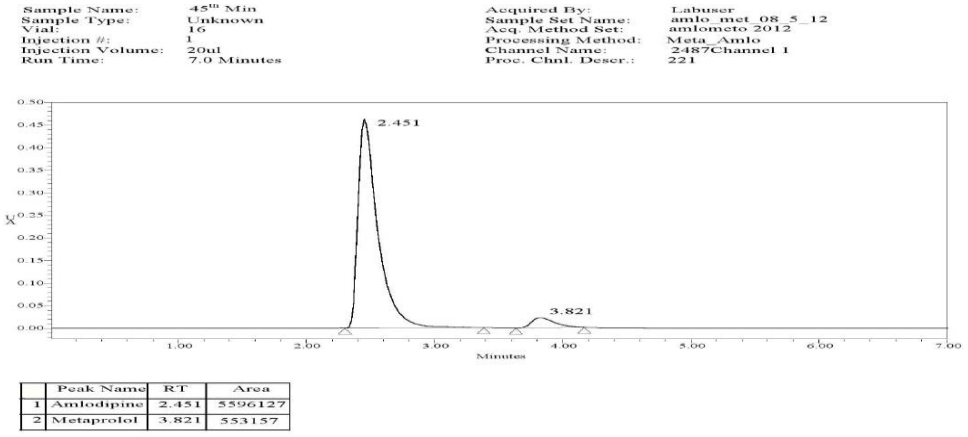
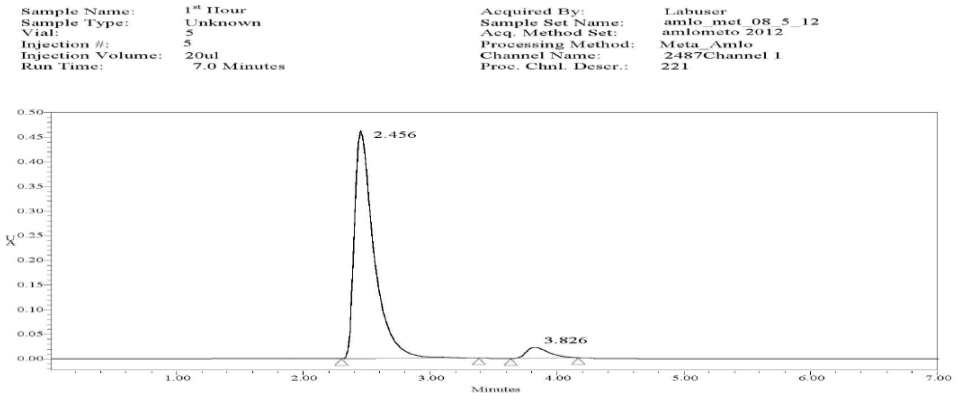
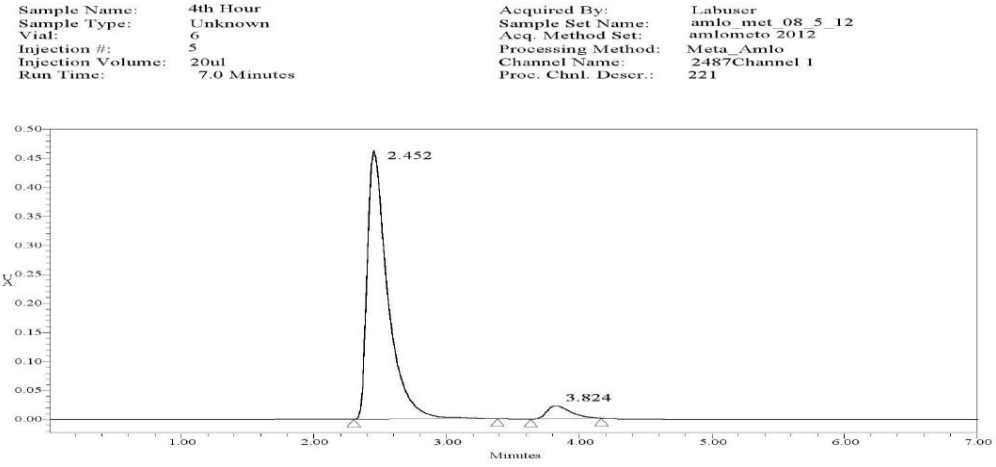


Fig 11: Optimized formulation dissolution profile by HPLC at 45th Min



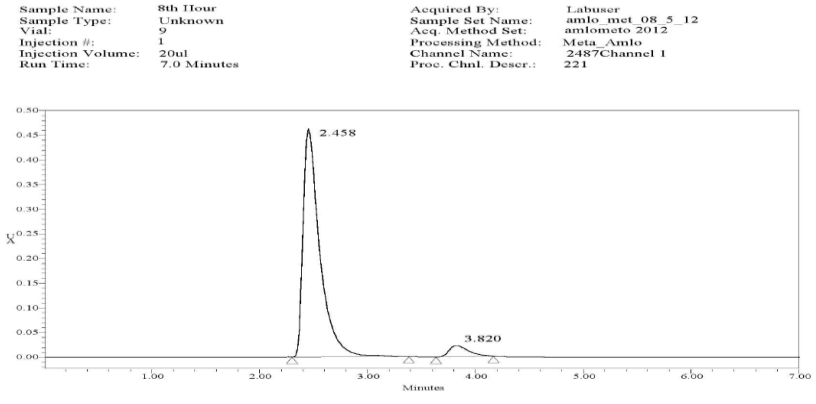
	Peak Name	RT	Area
1	Amlodipine	2.456	6014016
2	Metaprolol	3.826	633187

Fig 12: Optimized formulation dissolution profile by HPLC at 1st hour



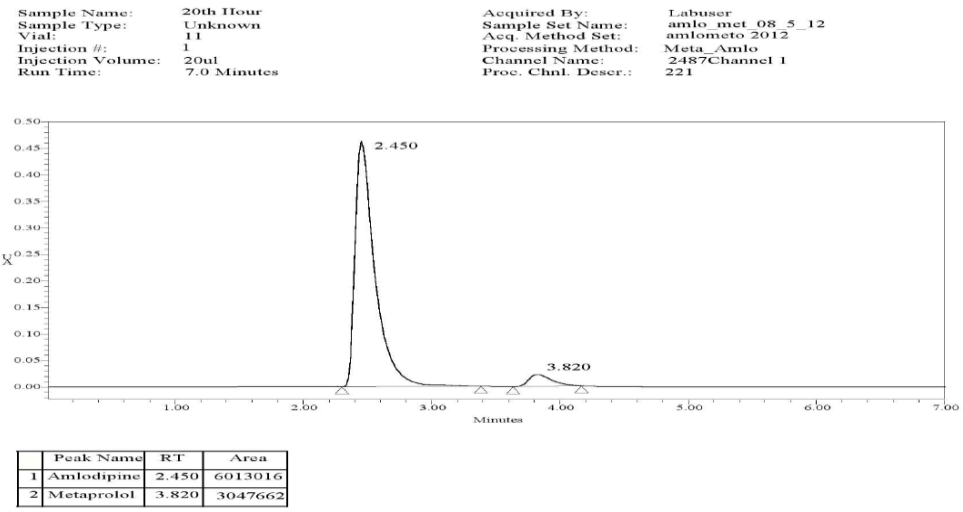
	Peak Name	RT	Area
1	Amlodipine	2.452	6012116
2	Metaprolol	3.824	1237682

Fig 13: Optimized formulation dissolution profile by HPLC at 4th hour



	Peak Name	RT	Area
1	Amlodipine	2.458	6012916
2	Metaprolol	3.820	1841664

Fig 14: Optimized formulation dissolution profile by HPLC at 8th hour



	Peak Name	RT	Area
1	Amlodipine	2.450	6013016
2	Metaprolol	3.820	3047662

Fig 15: Optimized formulation dissolution profile by HPLC at 20th hour

Optimized formulation drug release

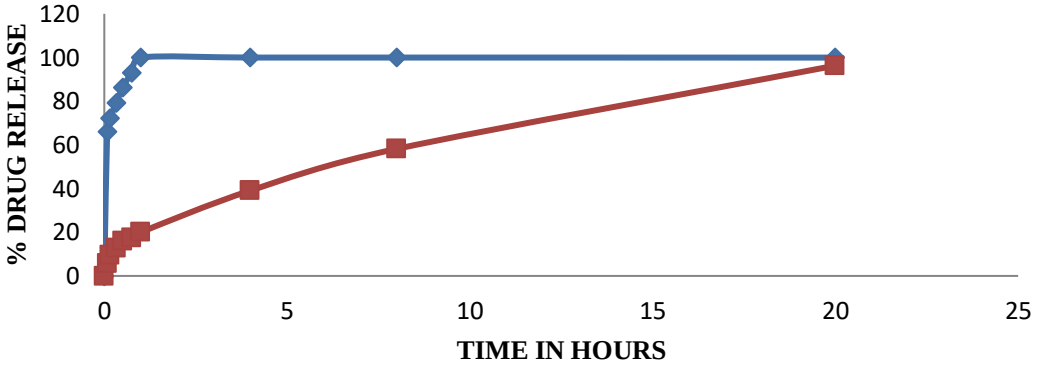


Fig 16: *In-Vitro* dissolution of optimized formulation

Table 16: Drug release kinetics:

Zero order		First order		Higuchi		Korsmeyer-peppas		Drug release mechanism
r^2	Slope	r^2	Slope	r^2	Slope	r^2	Diffusion exponent (n)	
0.955	0.075	0.969	-0.001	0.981	2.864	0.98	0.477	Non-fickian diffusion

The release kinetics of optimized formula (F8) has its release kinetics showing non-fickian transport and followed first-order release.

REFERENCES

1. Jayaprakash S, Mohamed SH, Kulathuran KP, Priya B, Mohamed PUF, Boopathi M, "Formulation and evaluation of amlodipine besilate and metoprolol succinate". *Der pharmacia letter,* 2011; 3(4):143-154.
2. Atram SC, Udavant YK, Salunke RJ, Neb GB, Shahi SR, Gulecha BS, Padalkar AN, "Formulation of

bilayer tablet containing metoprolol succinate and amlodipine besylate as a model drug for antihypertensive therapy". *Journal of Pharmacy Research,* 2009; 2(8):1335-1347.

3. Mujoriya RZ, Venkateshvarlu, Singh DC, Gupta VA, Bisen A, Bondre AB, "Formulation development and evaluation of metoprolol succinate er and amlodipine besilate bilayer tablet". *Research J. Pharm. and Tech.*,oct.-dec. 2010; 3(4): 1-4.
4. Lachman L, Lieberman, "*The theory and Practice of Industrial Pharmacy*", Vagulerr publishing house, Third edition; 1986; 293-345.
5. Swarbrick J. and Boylan J, *"Encyclopedia of Pharmaceutical Technology"*, Volume 14: 345-348,385
6. Sathyaraj A and Abhinav K, "Formulation and evaluation of metoprolol succinate controlled release tablets using natural and synthetic polymer". *International Journal of Pharmaceutical Sciences and Research,* 2012; 3(1):247-256.
7. Chandrasekhar RK, Abbulu K, Bhaskarrao R, "Preformulation parameters characterization to design, development and formulation of metoprolol succinate extended release tablets for oral use". *Int. J. Pharm & Ind. Res,* 2011; 1(4):289-294.
8. Gokul G, Pande SD, Anwar A, Lalit J, Tushar B, "Development and characterisation of fast disintegrating tablet of amlodipine besylate using mucilage of plantagoovata as a natural superdisintegrant". *International Journal of PharmTech Research.*2011; 3(2):938-945.
9. Ajay LB, Santosh NS, Monali SS, Kunal DI, Vishnu PC, Bhanudas SK, "Fabrication of controlled release metoprolol succinate matrix tablet : influence of some hydrophilic polymers on the release rate and *In-Vitro* evaluation". *International Journal of Pharma World Research.*2010;1(2).
10. Vineet B, Vikesh S, Narendra G, SalimMd, Sharma PK, "Formulation and evaluation of fast disintegrating sublingual tablets of amlodipine besylate using different superdisintegrants". *Int J Pharmacy Pharm Sci.* 2010;2(3):89-92.
11. Rashmi D, Ashish P, Sanjay N, "Formulation and evaluation of mouth dissolving tablet containing amlodipine besylate solid dispersion". *International Journal of PharmTech Research.*2010;2(1):706-715.
12. Ashutosh SK, Vijayakumar G, Karthikeyan M, Manidipa S, Ravisankar V, Arunachalam A, "Formulation and evaluation of sustained release tablets of metoprolol succinate". *International Journal of Pharmaceutical & Biological Archives.*2010; 1(5): 416 – 420.
13. Narmada GY, Mohini K, PrakashRao B, Gowrinath DXP, Kumar KS, "Formulation, evaluation and optimization of fast dissolving tablets containing amlodipine besylate by sublimation method". *Ars Pharm*. 2009; 50(3): 129-144.
14. Aqil M, Ali A, Ahad A, Sultana Y, Najmi AK, Saha N, "A validated hplc method for estimation of metoprolol in human plasma". *ActaChromatographica.*2007; 19:130-140.
15. Amlodipine besylate tablets by Dr Reddy's Laboratories

http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=16386

16. Raymond C, Rowe, Paul J Sheskey and Sian C Owen. "Handbook of Pharmaceutical Excipients".6th edition, published by *Royal Pharmaceutical Society of Great Britain*. 2009, 663-666.
17. Raymond C, Rowe, Paul J Sheskey and Sian C Owen. "Handbook of Pharmaceutical Excipients".6th edition, published by *Royal Pharmaceutical Society of Great Britain*. 2009, 185-188.
18. Sharma Y.R. "Elementary Organic Chemistry". 4th edition, published by S. Chand publications 2011, 68-151.
19. United States Pharmacopoeia 30, National Formulary 25, Asian Edition, United states Pharmacopoeial convention Inc., Rockville, 2007, 2647-2648.-400,401-418.