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Formulation and evaluation of amlodipine and metoprolol bilayer tablets

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ABSTRACT

Background

The objective of the present research, an attempt has been made to formulate bi-layered tablets of Amlodipine besylate and Metoprolol succinate. The main objective for combination therapy is to encourage the use of lower doses of drug to reduce the patient's blood pressure, to minimize dose dependent side effects and adverse reactions.

Materials and Methods

Various formulations of extended release part of Metoprolol succinate were developed using various polymers like HPMC K15M, HPMC K100M in different proportion and combinations by direct compression technique, Bulk density, tapped density, compressibility index, and hausner's ratio before being punched as tablets.

Results

All the evaluated parameters of the optimized formulation optimized formula showed the metoprolol succinate drug release over a period of 16 to 20 hours. and the amlodipine besylate (IR) release the max drug in 60 minutes showed compliance with pharmacopoeial standards. Results of in vitro release profile indicated that formulation 9FDT-IV was the most promising formulation as the extent of drug release from this formulation was optimum (IHS) when compared to other formulations. It was observed that tablets of batch 9FDT-IV followed the Zero order release profiles.

Conclusion

From the above results and discussion it was concluded that formulation of Extended release tablet of Metoprolol succinate containing 19.5% of HPMC K 15 M, batch 9FDT-IV can be taken as an ideal or optimized formulation of Extended release tablets for 20-hour release as it fulfils all the requirements for Extended release tablet.

Keywords: Metoprolol succinate, Amlodipine besylate, HPMC, Immediate release (IR), Sustained release (SR)

INTRODUCTION

Drugs are rarely administered solely as fine chemical substances, but those almost given formulated preparations. The principle objective of dosage form design is to be achieve a predictable therapeutic response to a drug included in the formulation.

Before a drug substance can be successfully formulated in to a dosage form, many factors must be considered. These factors can be broadly grouped in to three categories.

- Biopharmaceutical considerations (Factors affecting absorption of drugs)
- Drug related factors (Physical and chemical properties of a drug)
- Therapeutic considerations (Disease to be treated and patient factors)

Among various orally administered dosage forms (tablets, capsules, syrup, solution etc…), the tablet dosage form is the most widely used.

It is estimated that 50% of the population is affected by this problem, which results in a high incidence of ineffective therapy oral solid dosage forms.

The aim of the present study was to design and evaluate bilayer Floating tablets of Metoprolol succinate and Amlodipine besylate. An attempt was made to formulate bi-layer tablet appropriate for delivering different drugs with different release pattern like one layer of drug as IR to get rapid release & 2nd drug as SR of drug which gives effect of drug for adequate long time and reduce frequency of dose.

BILAYER TABLETS [8]

Figure 1 A: Single Layer Tablet

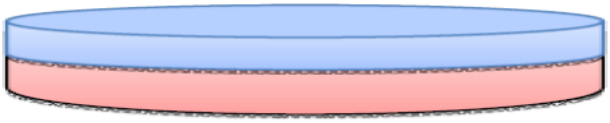
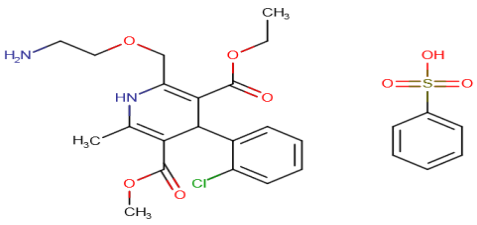


Figure 2 B: Bilayer Tablet

DRUG PROFILE

DRUG NAME: Amlodipine besylate

Structure:

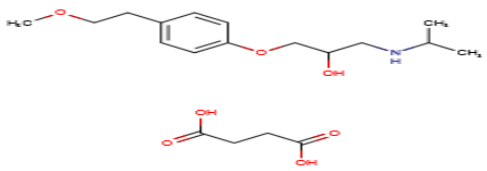


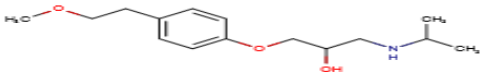
Synonyms

Amlodipine benzenesulfonate, Amlodipine besylate

- **Chemical Formula:** $C_{26}H_{31}ClN_2O_8S$
- **IUPAC Name:** 3-ethyl 5-methyl 2-[(2-aminoethoxy) methyl] -4- (2-chlorophenyl) -6-methyl-1, 4-dihydropyridine-3, 5-dicarboxylate; benzenesulfonic acid.
- **DRUG NAME:** Metoprolol

Structure





Synonyms

(RS)-Metoprolol, 1-(isopropyl amino)-3-[4-(2-methoxyethyl) phenoxy] propan-2-ol. DL-metoprolol.

Chemical Formula: $C_{34}H_{56}N_2O_{10}$

IUPAC Name: bis(1-[4-(2-methoxyethyl) phenoxy]-3-[(propan-2-yl) amino] propan-2-ol); butane dioic acid.

BILAYERED TABLETS: QUALITY AND GMP REQUIREMENTS [12]

- Providing sufficient tablet hardness.
- Preventing cross contamination
- Producing a clear visual separation between the two layers.
- High yield.
- Precise and individual weight control of the two layers.

Bilayer Tablet Press

The first layer sampling capability also offers a hardening feature, in which the main compression station will automatically Compress the first layer tablet for in-process measurement. The two feeders are zero clearance and are configured with an integrated dust extraction manifold which cleans the die table and completely eliminates any potential for cross contamination. The bi-layer execution, single-layer conversion kit and exchangeable turret offer unprecedented flexibility.

Types of bilayer tablet press

1. Single sided tablet press.
2. Double sided tablet press.

Single sided tablet press

- The simplest design is a single sided press with both chambers of the doublet feeder separated from each other.
- Each chamber is gravity or forced fed with different power, the producing the two individual layers of the tablets.
- When the die passes under the feeder, it is at first loaded with the first layer powder followed by the second layer powder.
- Then the entire tablet is compressed in one or two steps.

Limitations of single sided press

- No weight monitoring/control of the individual layers.
- No distinct visual separation between the two layers.
- Very short first layer dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping, and hardness problems.
- This may be corrected by reducing the turret-rotation speed (to extend the dwell time) but with the consequence of lower tablet output.

Double sided tablet presses

- In most double-sided tablet presses with automated production control use compression force to monitor and control tablet weight.

- The effective peak compression force exerted on each individual tablet or layer is measured by the control system at main compression of the layer
- This measured peak compression force is the signal used by the control system to reject out of tolerance tablets and correct the die fill depth when required.

Advantages

- Weight monitoring/control for accurate and independent weight control of the individual layers.
- Low compression force exerted on the first layer to avoid capping and separation of the two individual layers.
- Independence from the machine stiffness
- Increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross-contamination between the two layers

MATERIALS AND METHODS PREPARATION OF LINEARITY PLOT OF METOPROLOL SUCCINATE IN 0.1N HCL

Preparation of 0.1N HCL

Take 8.5ml of HCL and make up with 1000ml distilled Water to get 0.1N HCL

- **Standard Stock solution:** 10 mg of Metoprolol was dissolved in 100 ml 0.1N HCL to give a concentration of (100µg/ml)
- **Scanning:** From the above 100µg/ml was prepared in 0.1N HCL and UV scan was pippet out between 200 to 400 nm. The absorption max. Was found to be223nm and was used for the further analytical studies.

Calibration curve of Metoprolol succinate 0.1N HCL

- **Preparation of 0.1N HCL**
- Take 8.5ml of HCL and make up to 1000ml with distilled Water to get 0.1N HCL
- **Standard Stock solution:** 100 mg of Metoprolol succinate was dissolved in 100 ml 0.1N HCL to give a concentration of (1000µg/ml)
- **Sample Preparation and Scanning:** 10ml of this solution was diluted to 100 ml with 0.1N HCL buffer respectively to get 100µg/ml stock solution. From this stock solution, aliquots of 2, 4, 6, 8, 10 ml were pipetted out and made up to 100 ml in order to get concentration ranging from 2-10µg/ml. The absorbance of the solution was measured at 223 nm by UV spectrophotometry

PREPARATION OF LINEARITY PLOT OF AMLODIPINE BESYLATE IN 0.1NHCL

Preparation of 0.1N HCL

Take 8.5ml of HCL and make up with 1000ml distilled Water to get 0.1N HCL

- **Standard Stock solution:** 10 mg of Amlodipine besylate was dissolved in 100 ml 0.1N HCL to give a concentration of (100µg/ml)
- **Scanning:** From the stock solution 100µg/ml was prepared in 0.1N HCL and UV scan was taken between 200 to 400 nm. The absorption maximum was found to be 237nm and was used for the further analytical studies.

Calibration curve of Amlodipine besylate in 0.1N HCL

Preparation of stock solution

- Accurately weighed amount of 100 mg of Drug was transferred into a 100ml volumetric flask and dissolved with few ml of methanol then volume was made up to 100 mL with 0.1 N HCL to give a concentration of (1000µg/ml).

Sample Preparation and Scanning

- 10ml of this solution was diluted to 100 ml with 0.1N HCL buffer respectively to get 100µg/ml stock solution. From this stock solution, aliquots of 2, 4, 6, 8, 10 ml were pipetted out and made up to 100 ml in order to get concentration ranging from 2-10µg/ml. The absorbance of the solution was measured at 237 nm by UV spectrophotometry.

DRUG - EXCIPIENT COMPATIBILITY STUDY

Fourier Transform infra-red (FTIR) spectroscopy

- IR is a useful analytical technique to ensure the chemical interaction between the drug & polymers used in the formulation.1-2 mg of solid fine powder of Metoprolol succinate and Amlodipine besylate.

FORMULATION OF BILAYER MATRIX TABLET (FLOATING LAYER)

Composition of Floatinglayer

Table.1: formulation table for floating layer

Ingredients(mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Metoprolol(mg)	150	150	150	150	150	150	150	150	150
NaHCO3(mg)	25	25	25	25	25	25	25	25	25
Guar gum (mg)	50	75	87.5	-	-	-	-	-	-
Carbopol 934(mg)	-	-	-	50	75	87.5	-	-	-
HPMC K100 (mg)				-	-	-	50	75	87.5
EC (mg)	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Talc(mg)	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25
PVPK30	10	10	10	10	10	10	10	10	10
Magnesium stearate (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
MCC (mg)	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s
Total weight (mg)	350	350	350	350	350	350	350	350	350

DIRECT COMPRESSION FOR IMMEDIATE LAYER

Composition of Immediate Release Layer

Table.2: formulation table for immediate release layer

Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F_6	F7	F8	F9
Amlodipine	10	10	10	10	10	10	10	10	10
Talc	3	3	3	3	3	3	3	3	3
SSG	2.5	5	7.5	-	-	-	-	-	-
CP	-	-	-	2.5	5	7.5	-	-	-
CCS	-	-	-	-	-	-	2.5	5	7.5
PVP K30	5	5	5	5	5	5	5	5	5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
MCC	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s
Total weight (mg)	150	150	150	150	150	150	150	150	150

EVALUATION OF PRECOMPRESSION BLEND

Preformulation studies

- Angle of Repose
- Carr's Index (CI)
- Hausner's Ratio

- Size & Shape
- Weight variation test
- Friability
- Thickness
- Hardness
- Drug content uniformity
- Dissolution studies

POST EVALUATION OF TABLETS

- Physical Appearance

In vitro Dissolution Studies for Floating layer of Metoprolol

Kinetic Analysis of Dissolution Data

- Zero order kinetics
- First order kinetics
- Higuchi plot
- Peppa's model

BILAYERED TABLET PUNCH

- After the batch was optimized in both immediate release layer (F9) and sustained release layer
- (F9) The optimized batch in both was compressed by using same ingredients.

Table. 3: formulation table for bi-layered tablets formulation

Sustained Release Formula(F9)	Bi-layered formulation(F10)
METOPROLOL SUCCINATE	150
PVPK30	17.25
EC	17.5
MCC	q. s
Mg. stearate	5.25
Sodium bicarbonate	35
Talc	5.25
Total weight	**350mg**
Immediate Release Formula (F9)	
AMLODIPINE BESYLATE	10
MCC	q. s
PVP K 30	3.75
Talc	3
HPC	15
Mg. stearate	3.75
Total weight	**150mg**
TOTAL WEIGHT OF THE BILAYERED TABLET: 500mg	

RESULTS AND DISCUSSION

Pre-formulation studies

Description

Table.4: Table showing the description of METOPROLOL SUCCINATE (API)

Test	Description
Colour	A white crystalline powder
Odour	Free of Odour

Table.5: Table showing the description of AMLODIPINE BESYLATE (API)

Test	Description
Colour	A White or almost white powder
Odour	Free of Odour

Solubility

Table.6: Table showing the Solubility of METOPROLOL SUCCINATE (API) in various solvents.

Solvents	Solubility
Water	Freely Soluble
Methanol	Soluble
Ethanol	Sparingly Soluble
IPA	Slightly Soluble

Table.7: Table showing the Solubility of AMLODIPINE BESYLATE (API) in various solvents.

Solvents	Solubility
Water	Slightly Soluble
Methanol	Freely Soluble
Ethanol	Sparingly Soluble
2-propanol	Slightly Soluble

Melting Point

Table.8: Table showing the melting point of METOPROLOL and AMLODIPINE API's

Material	Observed Melting Point
METOPROLOL	120 °C
AMLODIPINE	199-201^{0}C

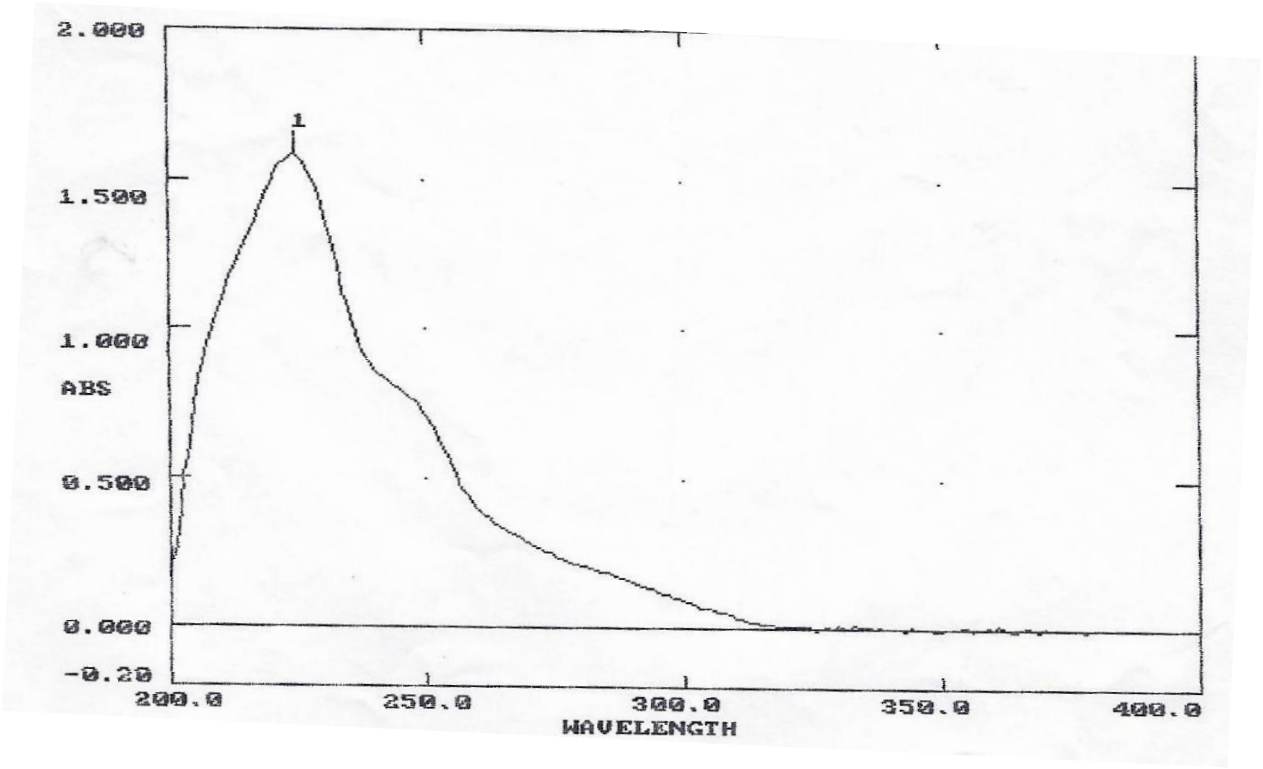


Fig.3: Spectophotometry for Metoprolol Succinate In 0.1n Hcl At 223nm

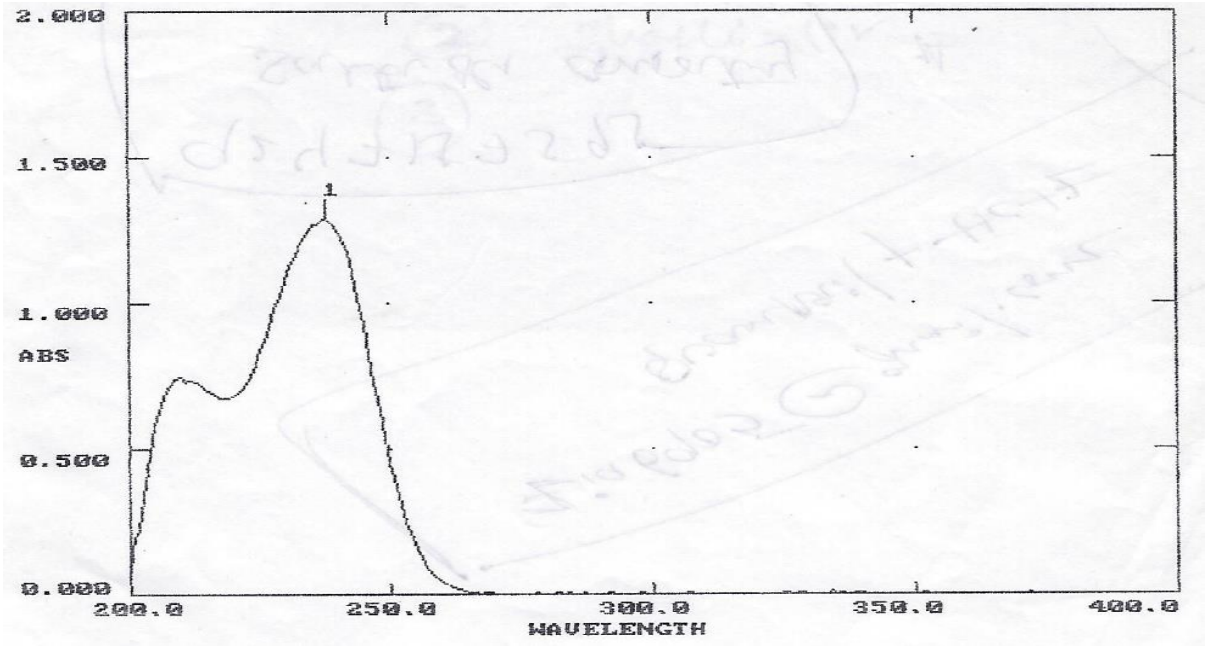


Fig.4: Spectophotometry for Amlodipine Besylate in 0.1n hcl at 237nm.

Preparation of standard calibration curve of METOPROLOL SUCCINATE

Table.9: standard calibration curve of METOPROLOL SUCCINATE in 0.1N HCL

Concentration	Absorbance at 223nm
0	0
2	0.123±0.01
4	0.307±0.02
6	0.434±0.01
8	0.602±0.03
10	0.744±0.02

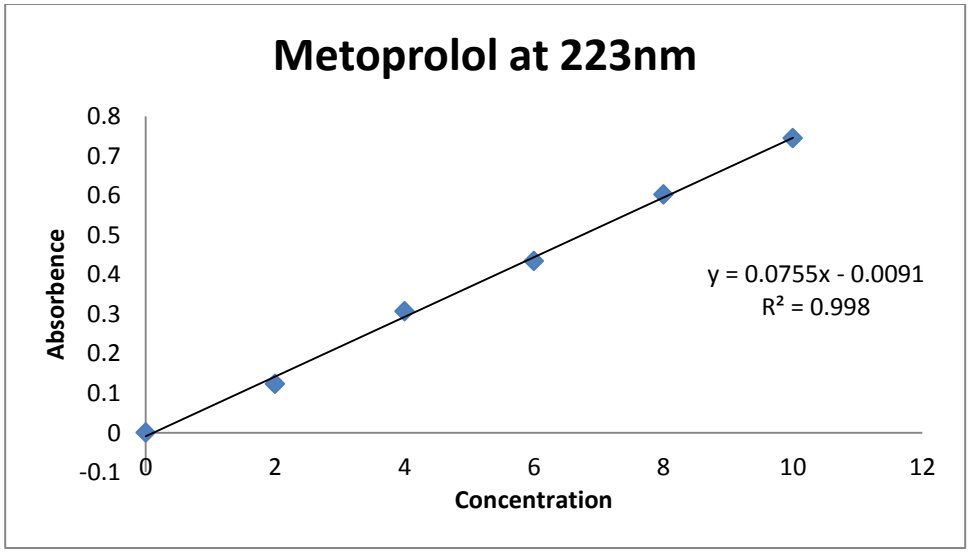


Fig.5: calibration curve of METOPROLOL in 0.1N HCL.

STANDARD GRAPH OF AMLODIPINE BESYLATE (0.1 NHCL)

Table.10: standard calibration curve of Amlodipine in 0.1N HCL

Concentration	Absorbance at 313nm
0	0
2	0.182±0.02
4	0.366±0.01
6	0.527±0.02
8	0.685±0.04
10	0.874±0.01

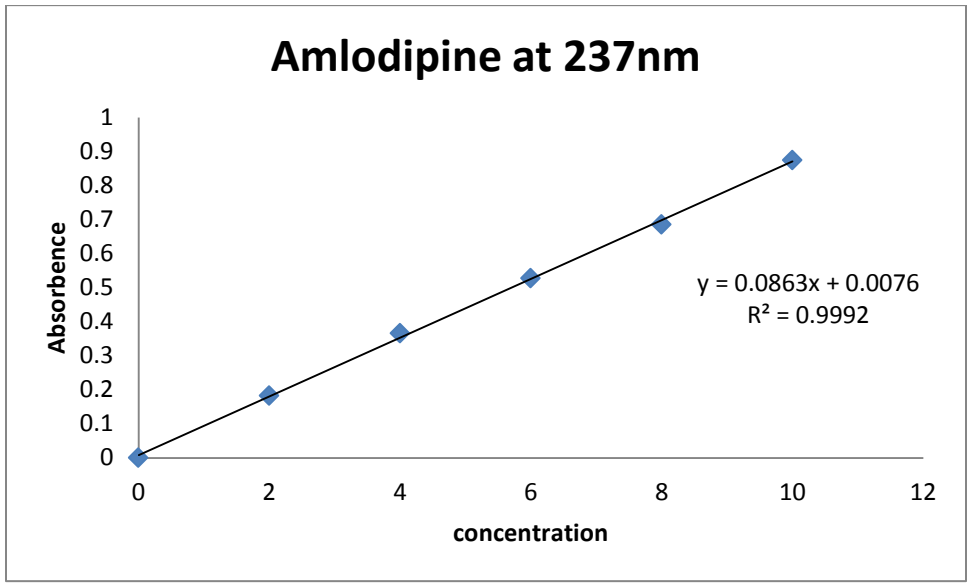


Fig.6: calibration curve for Amlodipine in 0.1N HCL at 237nm

COMPATIBILITY STUDIES

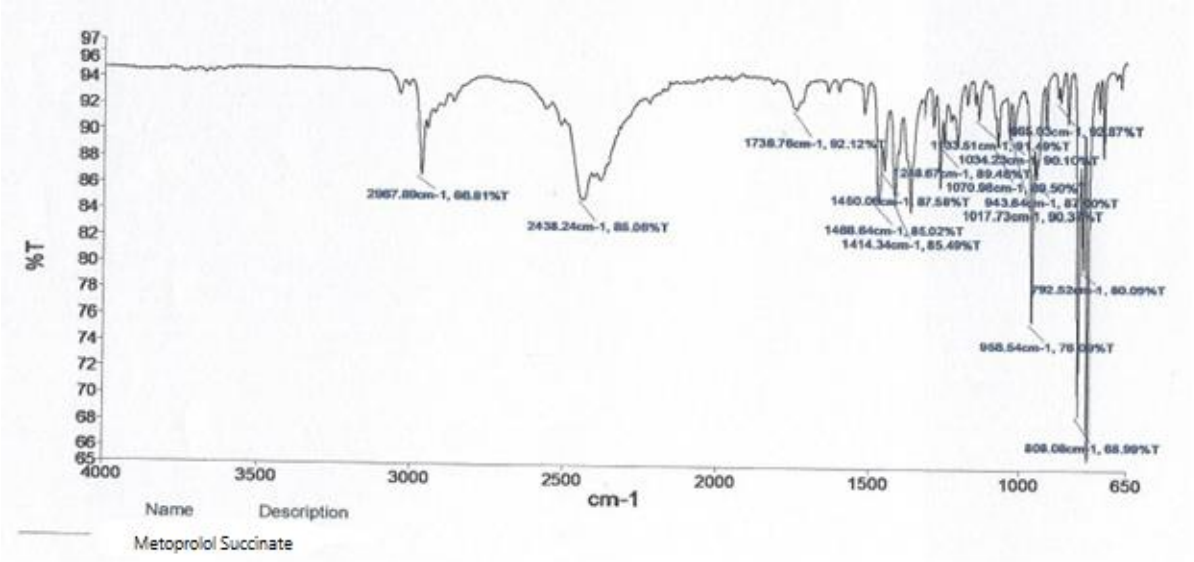


Fig.7: FTIR spectra of METOPROLOL pure drug

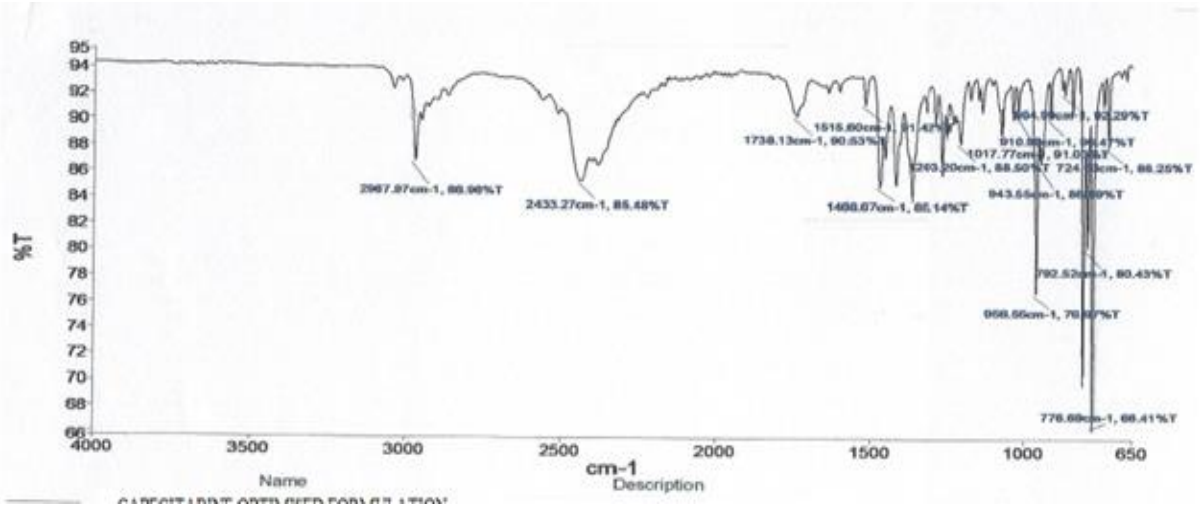


Fig.8: FTIR spectra of METOPROLOL Optimized formulation

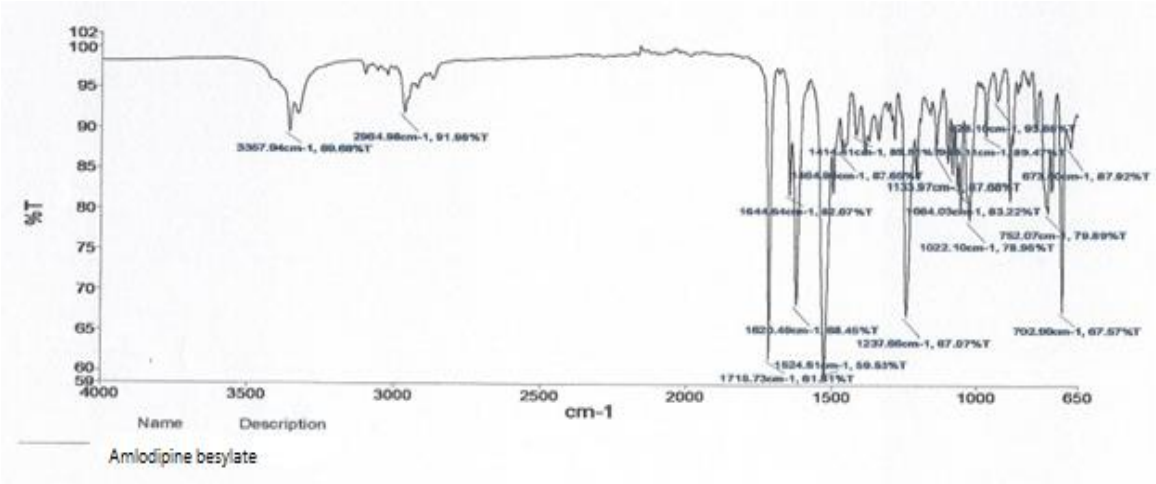


Fig.9: FTIR spectra of Amlodipine pure drug

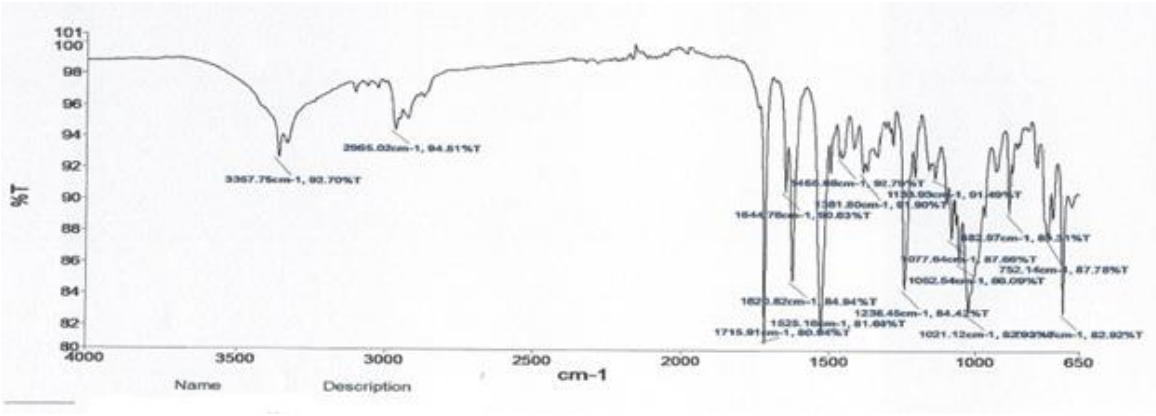


Fig.10: FTIR spectra of Amlodipine Optimized formulation

EVALUATION OF PRECOMPRESSION PARAMETERS FOR FLOATING LAYER OF METOPROLOL

Table.11: Pre-Compression Parameters for floating layer of Metoprolol Succinate

Formulations	Angle of repose (^{0})	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio
F1	29.34±0.33	0.36±0.04	0.41±0.04	12.19±0.15	1.13±0.03
F2	32.32±0.32	0.33±0.04	0.40±0.03	16.42±0.13	1.20±0.05
F3	24.20±0.33	0.31±0.03	0.36±0.04	13.89±0.14	1.16±0.02
F4	27.06±0.31	0.31±0.04	0.38±0.05	18.42±0.11	1.22±0.03
F5	26.30±0.33	0.34±0.05	0.42±0.04	14.29±0.13	1.17±0.04
F6	29.51±0.32	0.3±0.04	0.37±0.03	18.91±0.11	1.23±0.01
F7	27.43±0.33	0.35±0.03	0.42±0.05	16.66±0.13	1.20±0.04
F8	28.43±0.32	0.34±0.02	0.4±0.04	15.0±0.15	1.17±0.01
F9	27.18±0.31	0.33±0.04	0.40±0.02	17.5±0.12	1.21±0.02

Tablet.12: Post Compression Parameters for floating layer of Metoprolol Succinate

Formulations	Weight variation	Hardness	Thickness (mm)	Friability (%)	Drug content (%)
F1	351±0.5	4.5±0.06	2.2±0.04	0.42±0.007	98.3±0.3
F2	352±0.6	4.4±0.04	2.3±0.04	0.45±0.006	98.56±0.2
F3	349±0.4	5.0±0.02	2.4±0.03	0.51±0.002	97.12±0.1
F4	351±0.5	4.6±0.05	2.2±0.04	0.50±0.001	98.8±0.1
F5	350±0.4	4.5±0.04	2.1±0.05	0.43±0.003	99.12±0.2
F6	349±0.6	4.4±0.06	2.3±0.03	0.45±0.002	98.31±0.1
F7	350±0.4	4.2±0.05	2.4±0.04	0.42±0.005	99.29±0.1
F8	351±0.5	4.2±0.07	2.3±0.03	0.44±0.004	98.14±0.2
F9	350±0.4	4.4±0.06	2.1±0.04	0.46±0.002	99.56±0.4

INVITRO DISSOLUTION STUDIES FOR FLOATING TABLETS

In-Vitro Drug Release Studies for Floating tablets

Table.13: Cumulative percentage drug release of Metoprolol Succinate Floating layer

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
0.5	57±0.2	35±0.1	25±0.8	91.32±0.3	41.11±0.5	25.7±0.6	37.5±0.2	18.10±0.3	11.05±0.1
1	65.8±0.2	52.61±0.3	37.66±0.6	100.1±0.2	63.27±0.6	37.3±0.4	56.9±0.4	28.63±0.2	22.57±0.3
2	84.1±0.4	64.63±0.2	52.82±0.5	101.4±0.1	81.06±0.3	45.2±0.1	78.3±0.3	38.19±0.5	36.18±0.4
3	98.4±0.4	73.92±0.4	66.35±0.1		97.66±0.4	56.8±0.3	87.4±0.2	56.20±0.8	43.73±0.4
4		85.32±0.1	75.82±0.2		100.11±0.2	67.7±0.2	90.5±0.4	70.28±0.6	53.60±0.1
6		99.50±0.4	82.91±0.4			76.9±0.1	100.28±0.1	89.71±0.5	67.25±0.2
8			97.8±0.1			88.5±0.1		99.42±0.2	76.52±0.3
10						100.3±0.1			88.15±0.4
12									97.51±0.4

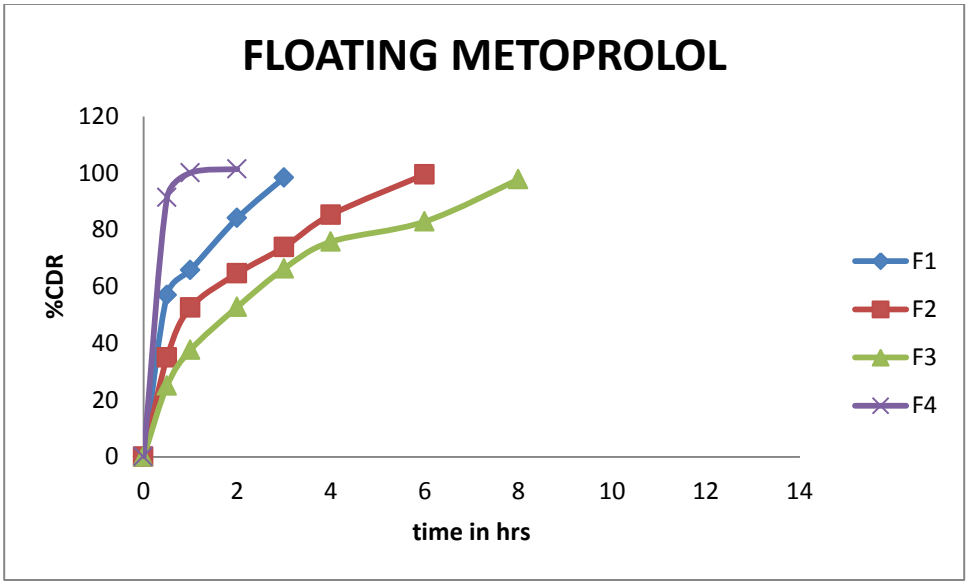


Fig.11: Dissolution graph for Floating Tablets F1-F4

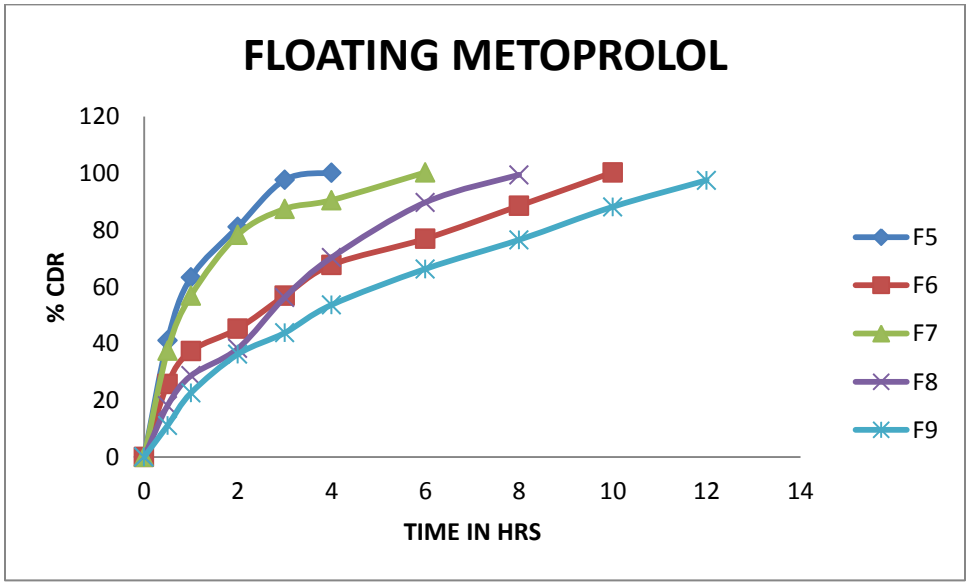


Fig.12: Dissolution graph for Floating Tablets F5-F9

EVALUATION PARAMETERS FOR IMMEDIATE RELEASE LAYER OF AMLODIPINE BESYLATE

Table.14: pre-compression parameters of Amlodipine Besylate

Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio
F1	28.4±0.21	0.31±0.02	0.37±0.02	16.21±0.06	1.19±0.06
F2	27.13±0.20	0.34±0.03	0.41±0.02	17.07±0.05	1.20±0.06
F3	26.34±0.23	0.31±0.02	0.36±0.04	13.88±0.06	1.16±0.04
F4	27.5±0.19	0.30±0.03	0.37±0.03	16.21±0.05	1.19±0.07
F5	28.4±0.15	0.32±0.02	0.37±0.01	13.51±0.04	1.15±0.05
F6	25.64±0.2	0.35±0.01	0.40±0.02	12.5±0.07	1.14±0.04
F7	25.42±0.17	0.31±0.02	0.36±0.03	13.88±0.06	1.16±0.02

F8	26.35±0.19	0.35±0.01	0.41±0.02	14.63±0.02	1.20±0.01
F9	27.9±0.21	0.31±0.04	0.35±003	11.42±0.02	1.12±0.08

Pre-compression parameters for immediate release layer of amlodipine besylate

Table.15: Post compression parameters for Amlodipine immediate release tablets

Formulations	Average weight (mg)	Hardness Kg/cm^2	Thickness (mm)	Friability (%)	Drug content (%)
F1	149±0.5	3.2±0.02	2.2±0.01	0.48±0.03	87.10±0.2
F2	149±0.2	3.4±0.02	2.3±0.02	0.26±0.01	76.46±0.2
F3	151±0.1	3.1±0.01	2.5±0.01	0.31±0.05	72.21±0.1
F4	150±0.5	3.3±0.04	2.2±0.03	0.42±0.04	80.15±0.4
F5	151±0.6	3.1±0.02	2.1±0.02	0.26±0.03	72.14±0.4
F6	149±0.4	3.2±0.02	2.3±0.01	0.31±0.02	94.74±0.5
F7	152±0.2	3.6±0.01	2.4±0.02	0.50±0.01	68.14±0.2
F8	148±0.1	3.5±0.03	2.1±0.04	0.43±0.02	76.41±0.1
F9	150±0.4	3.4±0.04	2.1±0.01	0.28±0.02	99.44±0.2

Post compression evaluation parameters for Amlodipine Besylate immediate release formulation

Table.16: Dissolution for immediate release tablet of Amlodipine

Time 0	F1 0	F2 0	F3 0	F4 0	F5 0	F6 0	F7 0	F8 0	F9 0
5	20.56±0.1	21.77±0.6	17.56±0.6	16.2±0.2	11±0.3	25.9±0.2	12.45±0.3	14.72±0.3	32.74±0.6
10	32.93±0.3	36.15±0.4	24.39±0.5	28.57±0.2	21.02±0.2	38.7±0.4	24.75±0.4	28.45±0.1	49.25±0.4
15	50.47±0.4	48.56±0.2	37.78±0.4	32.85±0.2	32.34±0.1	49.83±0.2	33.75±0.2	42.39±0.2	60.76±0.8
30	67.82±0.1	59.38±0.4	52.68±0.2	49.8±0.4	49.28±0.2	69.8±0.1	46.20±0.1	52.43±0.2	87.32±0.2
45	76.41±0.2	70.15±0.3	64.94±0.1	72.15±0.4	61.89±0.1	80.15±0.2	60.07±0.2	68.49±0.6	94.26±0.5
60	89.12±0.2	76.83±0.1	72.27±0.1	81.75±0.4	73.37±0.4	96.3±0.6	66.75±0.2	72.12±0.4	99.3±0.4

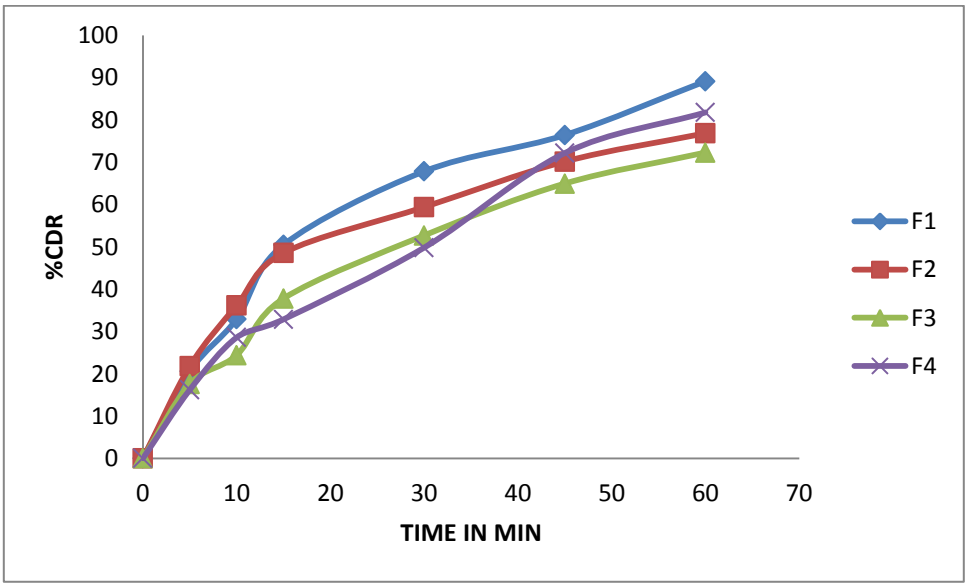


Fig.13: Dissolution graph for formulations F1-F4

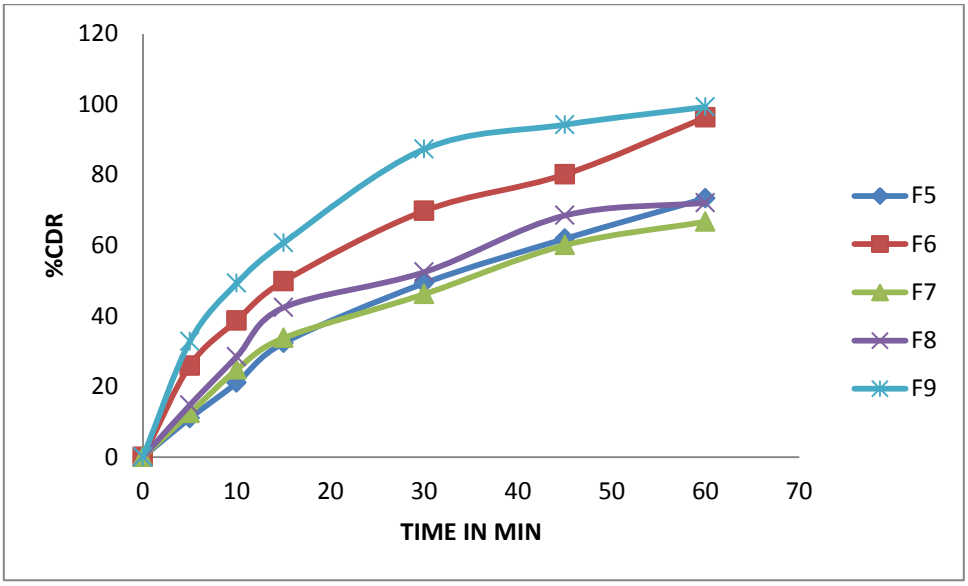


Fig.14: Dissolution graph for formulations F5-F9

KINETIC RELEASE MODELS

Table.17: Release kinetics for F9 formulation for Floating layer SR

	ZERO % CDR Vs T	FIRST Log % Remain Vs T	HIGUCHI %CDR Vs √T	PEPPAS Log C Vs Log T
Slope	7.62343632	-0.14628534	34.08261421	-1.101791717
Intercept	14.42186711	2.199834844	-16.1312068	2.153780181
Correlation	0.988676295	-0.93585635	0.979283304	0.758374413
R 2	0.94380817	0.805827116	0.92299579	0.62213175

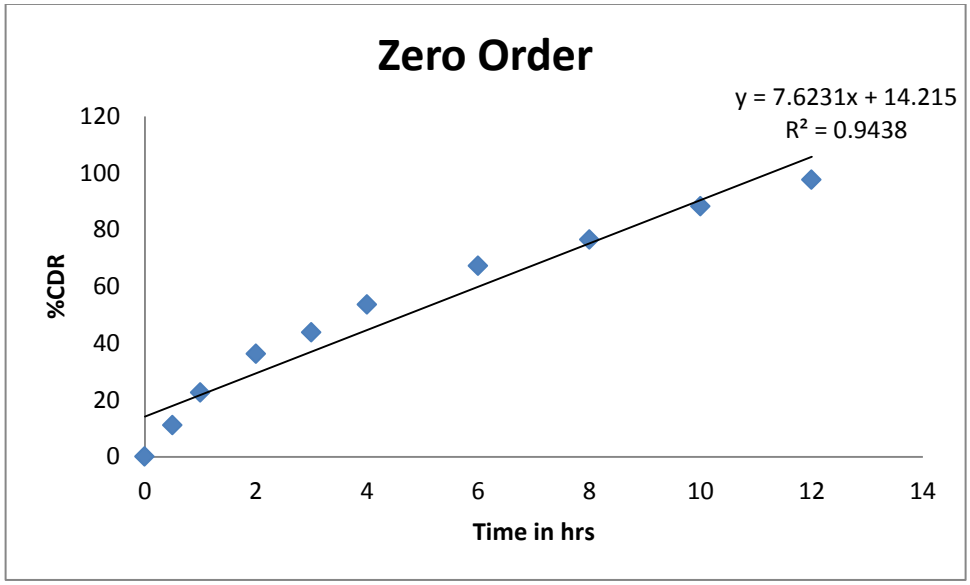


Fig.15: zero order release graph for F9 sustained release formulation

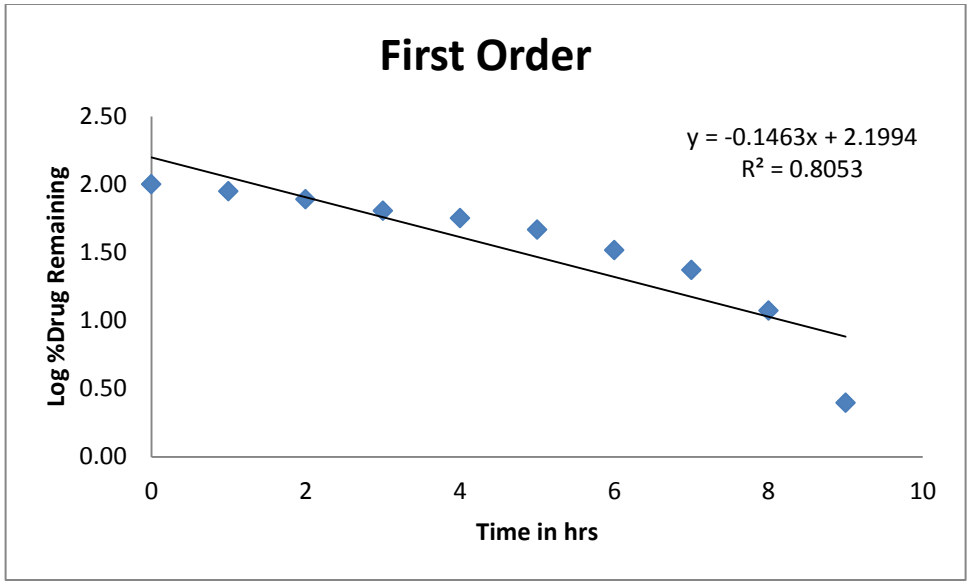


Fig.16: First order release graph for F9 sustained release formulation

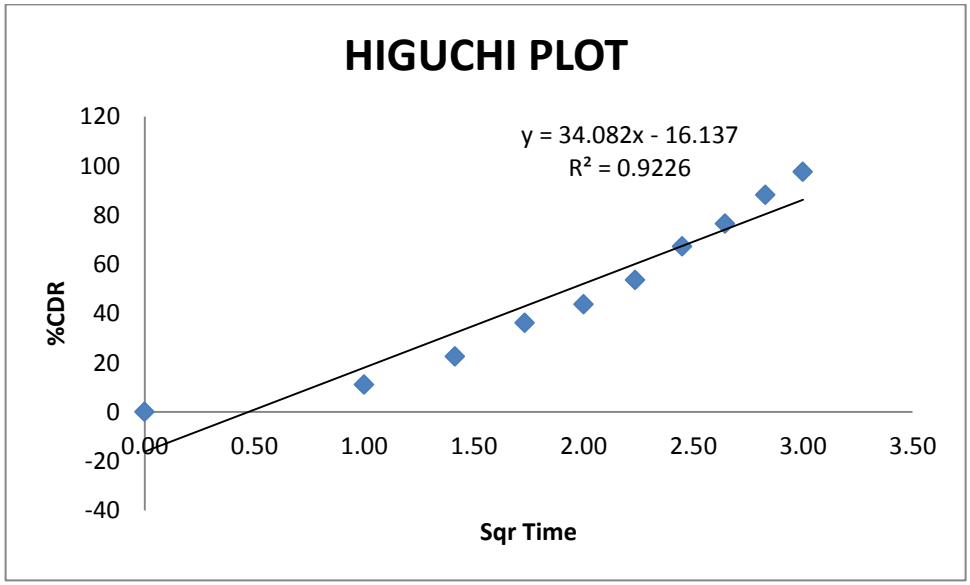


Fig.17: Higuchi model graph for F9 sustained release formulation

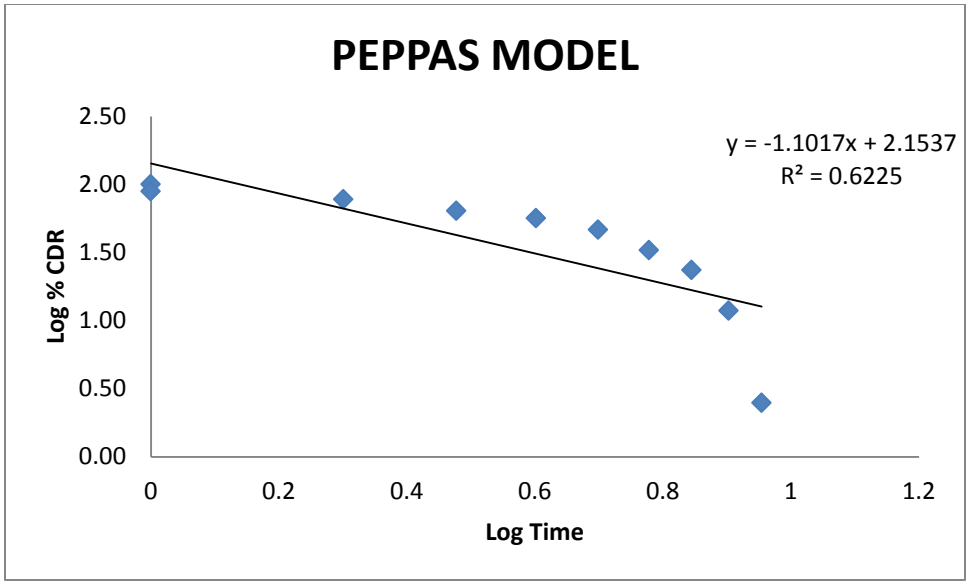


Fig.18: Peppa's model for F9 sustained release formulation

BILAYERED TABLET COMPRESSION

After the batch was optimized in both Amlodipine Besylate immediate release layer (F9) and Metoprolol Succinate Floating layer (F9) the optimized batch in both was compressed by using same ingredients.

DISSOLUTION STUDY (BILAYERED TABLETS)

Table.18: Dissolution data for bi-layered tablet

Time	Bi-layered tablet (IR)	SR
15min	42.74±3.46	0
30min	99.3±4.15	0
1hr		20.57±3.69
2hr		37.26±3.66
3hr		47.36±3.46
4hr		59.62±4.32
6hr		68.29±4.23
8hr		79.31±3.42
10hr		89.47±4.18
12hr		97.52±3.22

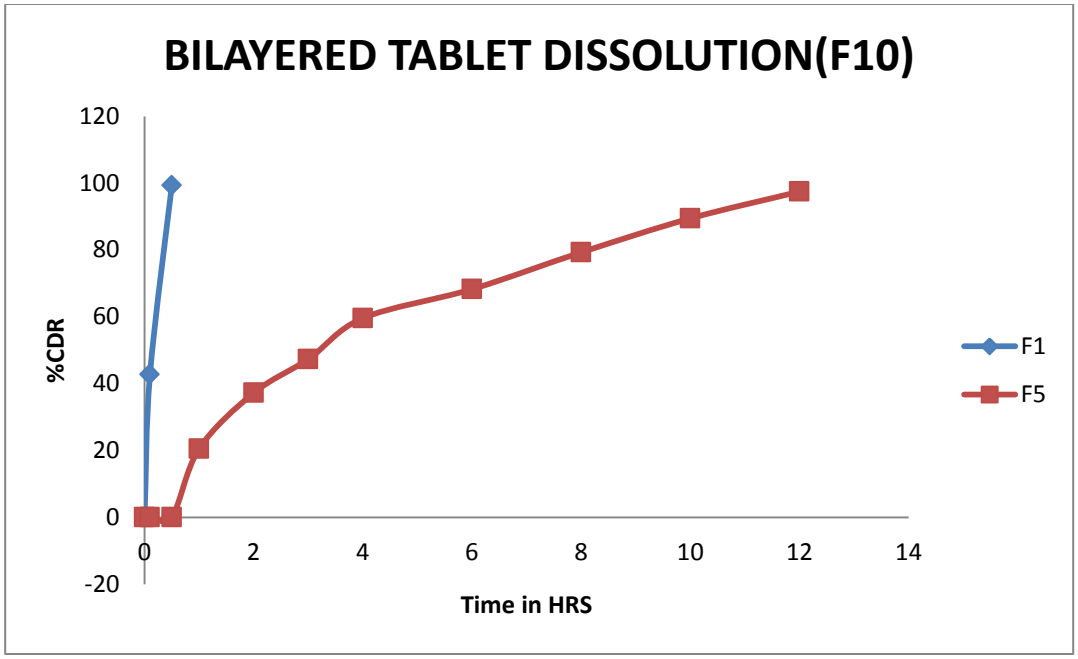


Fig.19: Dissolution diagram for Metoprolol Succinate and Amlodipine Besylate Bi-layered Tablets

Post pressure parameters

- Normal weight: 500±0.2mg
- Hardness: 5.3±0.026
- Thickness: 4.1±0.028

SUMMARY AND CONCLUSION

- ✓ The Bi-layered tablets containing Metoprolol succinate and Amlodipine besylate were successfully prepared by direct compression method respectively.
- ✓ The physiochemical evaluation results for the powdered blend of all trials pass the official limits in angle of repose, compressibility index.
- ✓ The prepared blend for IR release were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability. The optimized formulation F9 contains the average thickness of 2.1±0.01, average hardness of 3.4±0.04, average weight of 150±0.4, friability of 0.28±0.02.
- ✓ The prepared dry mixer for floating tablets were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability. The optimized formulation F9 contains the average thickness of 2.2±0.04, average hardness of 4.4±0.07, friability of 0.45±0.005.
- ✓ The F9 formulation which releases the Metoprolol succinate in sustained manner in up to 12 hours and Amlodipine besylate immediate release F9 formulation showed 99% drug release with in 60min.
- ✓ The Bi-layered Tablet (IR+SR) showed 97.52% Cumulative Drug release within 12hrs.

"Hence it may be summarized that the tablets prepared by direct compression method for sustained release layer and immediate release layer might be a perfect and effective formulation to treat the disorder".

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