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FORMULATION AND EVALUATION OF IMMEDIATE AND SUSTAINED RELEASE BILAYER TABLETS OF METOPROLOL TARTRATE

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ABSTRACT: Metoprolol Tartrate is a beta-selective adrenergic receptor antagonist used in the treatment of various cardiovascular diseases. It has a short half-life of about 3-4 hours and needs to be administered frequently to maintain the therapeutic concentration. Sustained release formulation is inadequate due to lack of initial bolus dose. Hence, the main objective behind this research was to develop different Immediate and Sustained release formulations of Metoprolol Tartrate and select the best formulation for manufacturing Bilayer tablet. Immediate release layer (IRL) was formulated by using Sodium Starch Glycolate and Crospovidone as superdisintegrants and Sustained release layer (SRL) was formulated by using HPMC K100M and HPMC K15M as release retardant polymers. FTIR study revealed that the combination can be safely prepared and no interaction between drug and excipient was found. The powdered formulation exhibited good flow property. The optimized immediate release formulation (IR6) with highest invitro release of 99.11% within 30 minutes and optimized Sustained release formulation (SR7) with 98.45% of drug release at the end of 18 hours was selected for IRL and SRL respectively for formulation of Bilayer tablet. Finally the selected IRL and SRL are combined into Bilayer tablets by double compression process. The hardness and friability of prepared Bilayer tablet was found to be 6.25kg/cm3 and ≤1% respectively. Short term Stability Studies showed that prepared Bilayer tablet was stable at 400C/75% RH for a period of 3 months. The Bilayer tablet had same in-vitro drug release as that of individual layers i.e; IRL and SRL.

KEYWORDS: Bilayer tablet, immediate release, Sustained release, Metoprolol Tartrate, Stability Studies.

I. INTRODUCTION

Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost- effective dosage forms[1]. Bilayer tablet concept has long been utilized to develop sustained released formulation[2]. The most important application of the bilayer is a quick/slow release system provides an initial burst of drug release followed by a constant rate (ideally) of release over a defined period of time[3]. This type of system is used primarily when a maximum response needs to be achieved quickly, and followed by a sustained release phase to avoid repeated administration. [4]When a single constant rate for drug release does not entirely satisfy the therapeutic objective, the quick/slow delivery system may be an interesting alternative[5]. This biphasic release system can be achieved by the application of an immediate release layer to the conventional layered matrix tablet[6].

Metoprolol Tartrate is a Beta-selective adrenergic receptor antagonist which is used in the treatment of various cardiovascular diseases[7]. The aim of the present research work was to develop different immediate and sustained release formulations of Metoprolol tartrate and from the above formulations select a best formulation based on their release profiles for manufacturing bilayer tablet. The reason behind selection of Metoprolol tartrate was that, its peak plasma concentration is achieved within 1.5 to 2 hours after a single oral dose, but because of the drug's short half-life (3 to 4 hours), the therapeutic plasma concentration can be maintained only if the Metoprolol tartrate is administered frequently[8]. Sustained release formulation is inadequate to provide instant relief due to lack of initial bolus dose[9]. These characteristics make Metoprolol tartrate a suitable candidate for formulation of bilayer tablets. There is a need to prepare a bilayer tablet of Metoprolol Tartrate containing both Immediate Release layer (IRL) and Sustained Release layer (SRL).[10]Hence, the main objective behind this research was to develop different Immediate and Sustained release formulations of Metoprolol Tartrate and select the best formulation for manufacturing Bilayer tablet

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II. MATERIALS AND METHODS

Materials

Metoprolol tartrate was obtained as a gift sample from Yarrow Chem Products, Mumbai, India.Micro Crystalline Cellulose and Magnesium Stearate was purchased from Hi Media Laboratories Pvt. Ltd, Mumbai, India and rest all the other chemicals were purchased from S.D. Fine Chem. Ltd, Mumbai, India

III. METHODS

Preformulation Studies:

Melting point:

Melting point of drug was determined by capillary method in triplicate.

Standard curve for Metoprololtartrate[11]:

100 mg of Metoprolol tartrate was accurately weighed and dissolved in 100 ml of distilled water to prepare stock solution-I. 10ml of stock solution-I was taken and diluted to 100 ml with the same solvent to prepare stock solution-II. The aliquot amount of stock solution-II was further diluted with distilled water to get 10-60 µg/ml concentration of drug solution. Then the absorbance was measured in a UV spectrophotometer at 223 nm against distilled water as blank. The graph was plotted for absorbance vs concentration[72].

Compatibility study using Fourier Transform Infra-Red (FTIR) Spectrum[12]:

Infrared spectroscopy was conducted using a Thermo Nicolet FTIR and the spectrum was recorded in the region of 4000 to 400 cm-1. The interaction between drug-excipients was observed from IR-Spectral studies by observing any shift in peaks of drug in the spectrum of physical mixture of drug.

Calculation of dose[13]:

The total dose of Metoprolol tartrate for once daily formulation was calculated by the following equation, using available pharmacological data.

Dt = Dose (1+0.693xt/t1/2)

Where,

Dt = Total dose of drug,

Dose = Dose of immediate release part.

t = time in hours during which the sustained release is desired (18 hrs)

t1/2 = half life of the drug (4 hrs)

Formulation of Immidiate release Layer: Immediate release layer of Metoprolol tartrate was prepared by wet granulation technique using different concentrations of superdisintegrants such asSodium starch glycolate and Crospovidone. Iron oxide red was used as colouring agent as it differentiates IRL with SRL. Micro crystalline cellulose (MCC) and lactose were used as glident.

Table 1: Formulation of IRL

Sl.No.	Ingredients in mg	IR1	IR2	IR3	IR4	IR5	IR6
1	Metoprolol tartrate	50	50	50	50	50	50
2	Lactose	99.98	94.98	89.98	99.98	94.98	89.98
3	Sodium starch glycolate	5	10	15	-	-	-
4	Crospovidone	-	-	-	5	10	15
5	MCC	40	40	40	40	40	40
6	Iron oxide red	0.02	0.02	0.02	0.02	0.02	0.02
7	Magnesium stearate	3	3	3	3	3	3
8	Talc	2	2	2	2	2	2
9	Total	200	200	200	200	200	200

Note: All ingredients are in mg

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Manufacturing steps involved during preparation of IRL

All the ingredients were passed though sieve #80. Metoprolol tartrate was mixed with MCC geometrically and then mixed with lactose. Superdisintegrants were added and mixed for about 10 to 15 min in mortar and pestle. Wet mass was made using colour solution. The cohesive mass was passed through sieve # 16 to get uniform granules. Granules were dried at 50^{o}C for 15 min in hot air oven. Granules were lubricated and compressed into tablets of 200 mg each by adjusting hardness. The formulations are shown in Table 1.

Formulation of Sustained release Layer: Sustained release layer of Metoprolol tartrate was prepared by wet granulation technique using different concentrations of release retardant polymers such as HPMC K100M and HPMC K15M. Accurately weighed Metoprolol tartrate, polymers and others ingredients were taken in mortar and pestle and mixed well.

Table 2: Formulation of SRL

Sl.No.	Ingredients in mg	SR1	SR2	SR3	SR4	SR5	SR6	SR7	SR8	SR9
1.	Metoprolol Tartrate	155.92	155.92	155.92	155.92	155.92	155.92	155.92	155.92	155.92
2.	Lactose	19.08	14.08	9.08	19.08	14.08	9.08	19.08	14.08	9.08
3.	HPMC K100M	45	50	55	-	-	-	22.5	25	27.5
4.	HPMC K15M	-	-	-	45	50	55	22.5	25	27.5
5.	MCC	20	20	20	20	20	20	20	20	20
6.	Povidone K30	5	5	5	5	5	5	5	5	5
7.	Magnesium stearate	3	3	3	3	3	3	3	3	3
8.	Talc	2	2	2	2	2	2	2	2	2
9.	Total	250	250	250	250	250	250	250	250	250

Manufacturing steps involved during preparation of SRL

The powder was mixed with sufficient quantity for Povidone K30 solution until wet mass was formed.
The cohesive mass obtained was passed though sieve # 16. The granules were dried in a hot air oven at 50oC for 20 min. The dried granules were again passed through sieve # 22 to break the large lumps. Then granules were mixed with talc and magnesium stearate, and compressed into 250 mg tablet by adjusting the hardness. The formulations are shown in Table 2.

Evaluation of pre-compression parameters[14]

Determination of Bulk Density and Tapped Density:

20 g of the mixed blend (W) was introduced into a 100 ml measuring cylinder, and the initial volume was observed. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following formulae.
Bulk density = W / VO
Tapped density = W / VF
Where, W = weight of the powder mixture, VO = initial volume of the powder mixture and VF = final volume of the powder mixture[75].

Carr's compressibility Index (CI):

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20% has good flow property.

$$CI = \frac{(\text{Tapped Density} - \text{Bulk Density}) \times 100}{\text{Tapped Density}}$$

Hausner's Ratio:

It indicates the flow properties of the granules and is measured by the ratio of Tapped density to the Bulk density75.
Hausner's Ratio = Tapped density/Bulk density

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Determination of Angle of repose:
Angle of repose is an indication of the frictional forces existing between granules. It is the maximum angle possible between the surface of the pile and the horizontal plane:
tan θ = h/r
Where, **θ** = the angle of repose, **h** = height of the heap of the powder and **r** = radius of the heap of the powder.

Evaluation of post-compression parameters
Weight Variation Test:
The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit.

Hardness
The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded[75].

Thickness
Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using VernierCalipers. It was determined by checking the thickness of ten tablets of each formulation[75].

Friability
Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients. 20 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator dusted off the fines and again weighed and the weight was recorded.

Drug content[15]:
At random 20 tablets were weighed and powdered. The powder equivalent to 100 mg was weighed accurately and dissolved in 100 ml of distilled water. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatmann No.41 filter paper. Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured at 223 nm. The concentration of the drug was computed from the standard curve of the Metoprolol tartrate in distilled water.

In-vitro disintegration studies of Immediate release layer:
The disintegration time for all immediate release formulations was carried out using tablet disintegration test apparatus (Electrolab). Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The medium, pH 6.8 phosphate buffer was maintained at a temperature of 37±2 ^{0}C and time taken for the entire tablet to disintegrate completely was noted.

In-vitro dissolution studies of Immediate release layer[16]:
The in-vitro dissolution studies were carried out using USP-II (paddle) dissolution apparatus at 50 rpm. pH 6.8 phosphate buffer was used as dissolution media and its temperature was maintained at 37±0.5^{0}C. A 5 ml of sample was withdrawn at specific time intervals and same volume of fresh buffer was replaced. The withdrawn samples were diluted with pH 6.8 buffer solution, filtered and analyzed on UV spectrophotometer at 223 nm using pH 6.8 as a blank. Percentage cumulative drug release was calculated.

In-vitro dissolution studies of Sustained release layer[17]:
The in-vitro release profile of sustained release layer of Metoprolol tartrate was carried out for 18 hours using USP type-II dissolution test apparatus (DT-1200- Lab India) at 100 rpm for the first 45 minutes in 900 ml 0.1 N HCl maintaining at 37 ±0.5^{0}C and then in 900 ml 6.8 pH phosphate buffer for another 18 hours. A 5 ml sample was withdrawn at different time intervals and replaced with an equal volume of fresh medium. The samples were suitably diluted with blank dissolution medium, filtered and analyzed on UV spectrophotometer at 223 nm.

Drug release kinetics[18,19]
Investigation for the drug release from the Metoprolol tartrate bilayer tablet was done by studying the release data with zero

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order, first order kinetics and Higuchi equation. The release mechanism was understood by fitting the data to KorsmeyerPeppas model.

Stability Studies[20]: In the present study, stability studies were carried out at 40ºC/75% RH for a specific period of 3 month for the selected formulations.

IV. RESULTS AND DISCUSSIONS

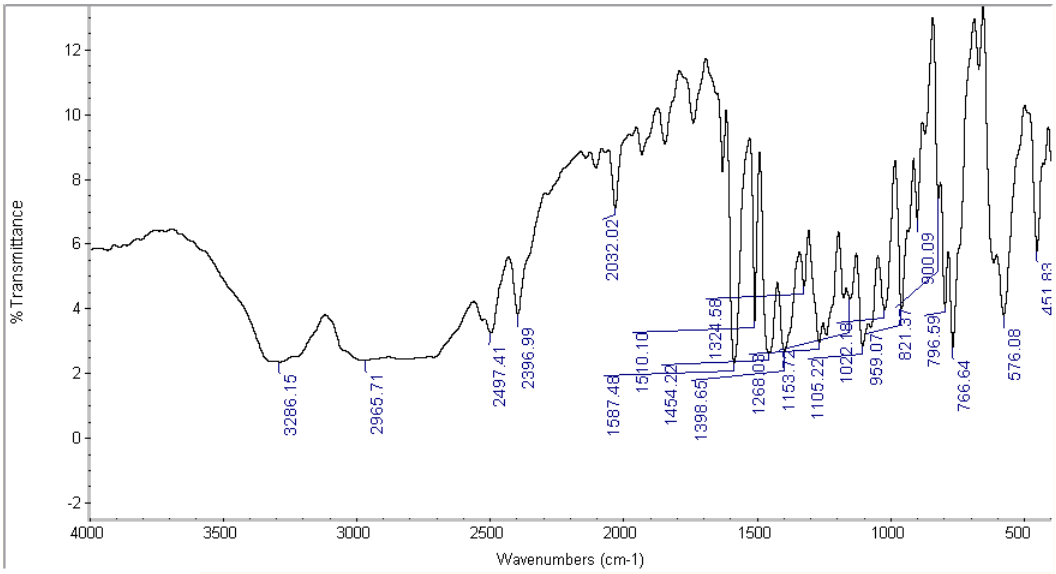
Preformulation Studies:

Melting point:

Melting point of drug was determined by capillary method. The result was found to be 120-121oC. Result obtained was similar as mentioned in literature i.e. 120°C.

Compatibility study using Fourier Transform Infra-Red (FTIR) Spectrum:

All the characteristic peaks of Metoprolol tartrate were present in the spectrum formulation mixture, indicating compatibility between drug and polymers. The spectrum confirmed that there was no significant change in the chemical integrity of the drug.



drug

Figure 1: FT-IR spectra of Metoprolol tartrate (pure drug)

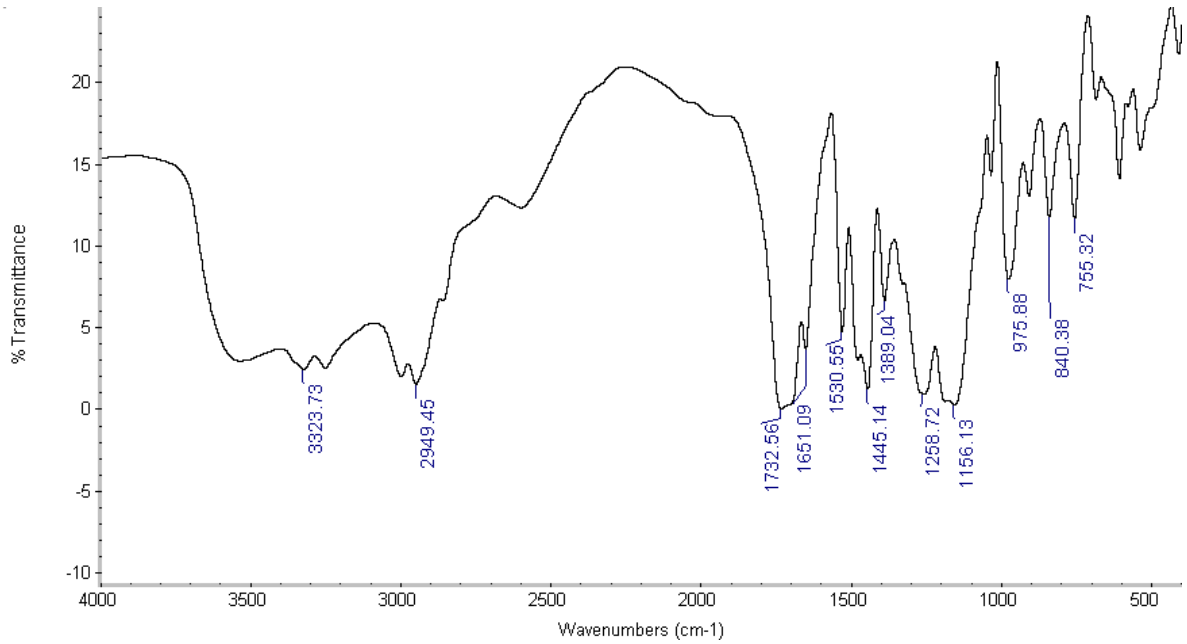


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Figure 2: FT-IR spectra of Metoprolol tartrate and microcrystalline cellulose

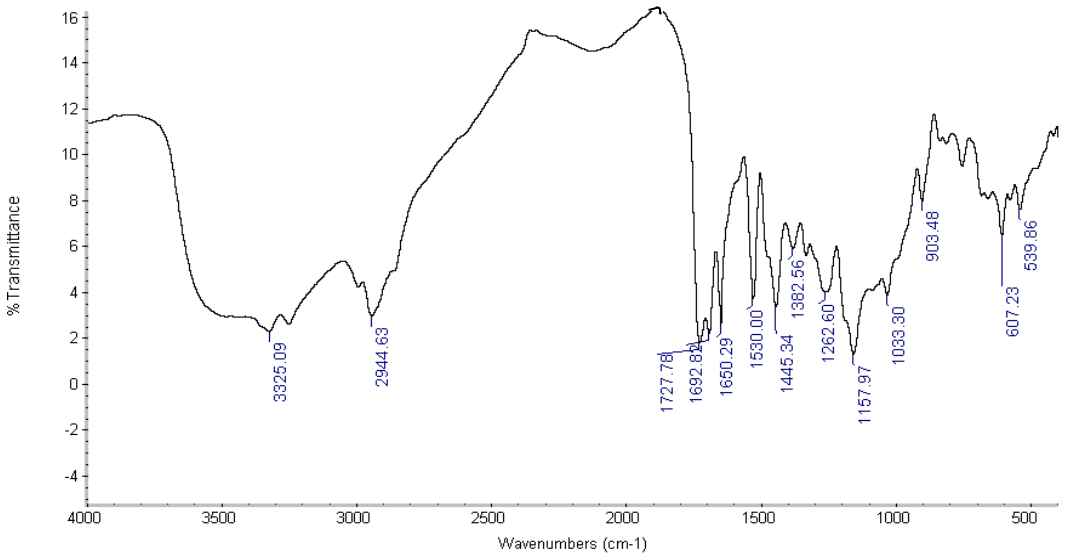

Figure 3: FT-IR spectra of Metoprolol tartrate and Sodium starch glycolate

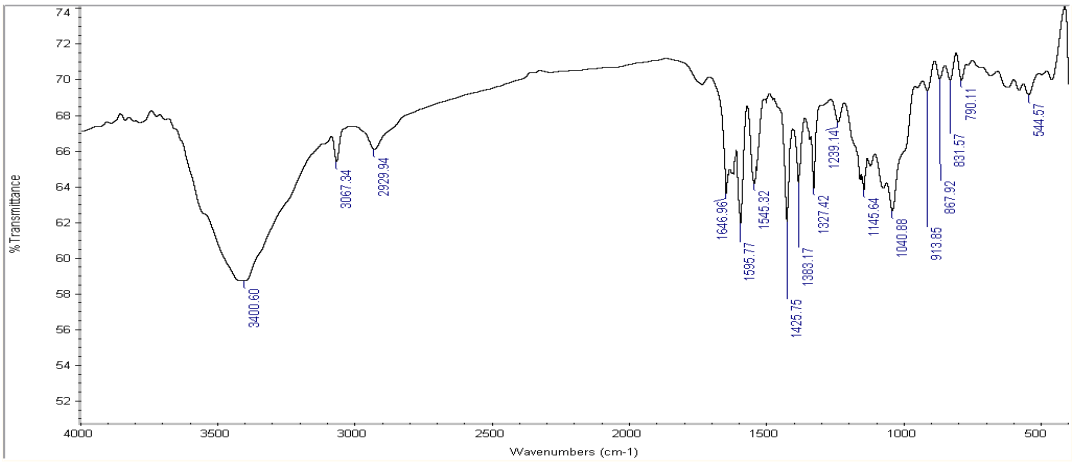

Figure 4: FT-IR spectra of Metoprolol tartrate and crospovidone

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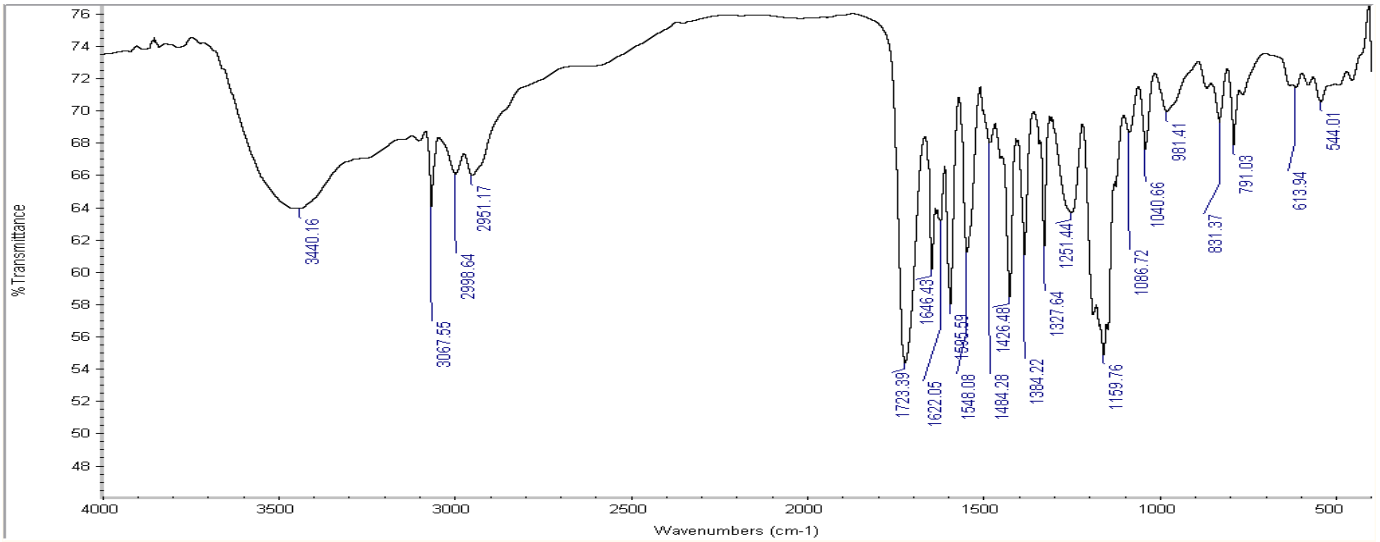

Figure 5: FT-IR spectra of Metoprolol tartrate and HPMC K100M

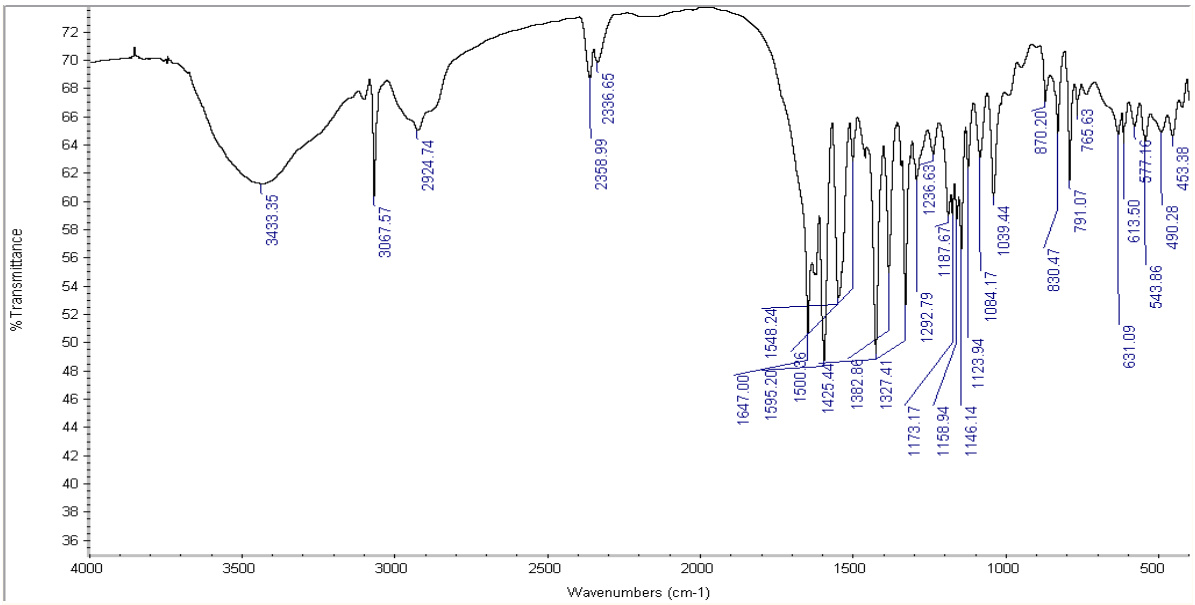

Figure 6: FT-IR spectra of Metoprolol tartrate and HPMC K15M

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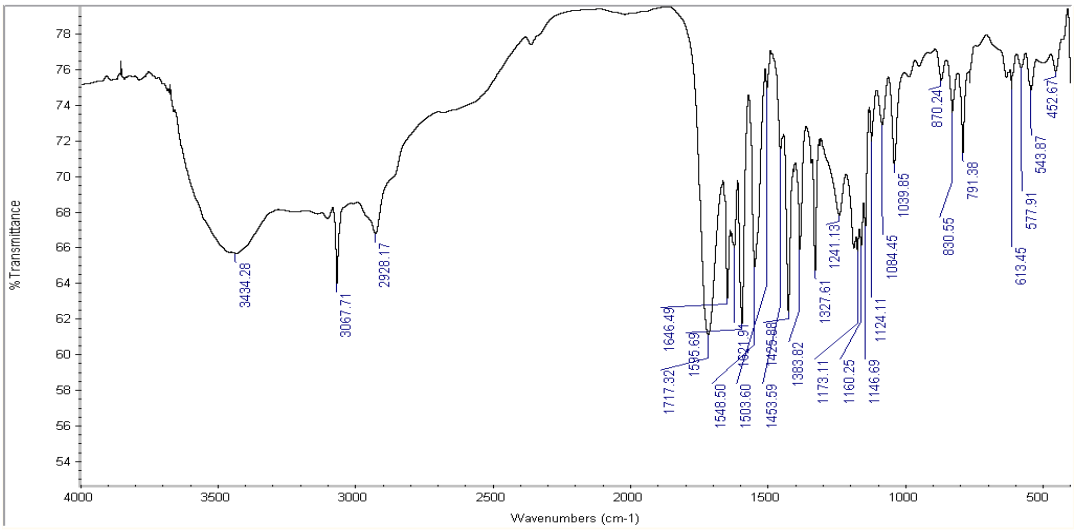


Figure 7: FT-IR spectra of IRL formulation (IR6) of Metoprolol tartrate

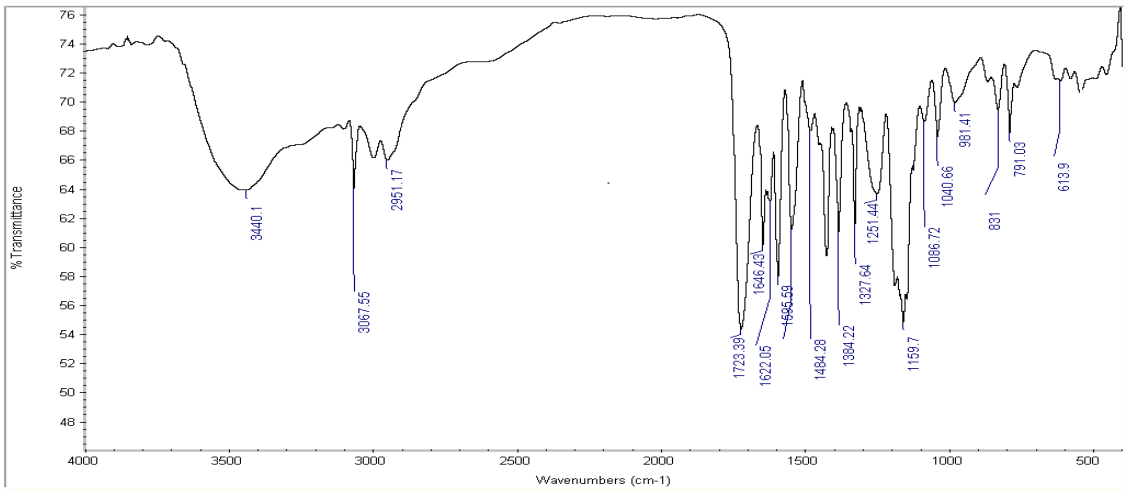
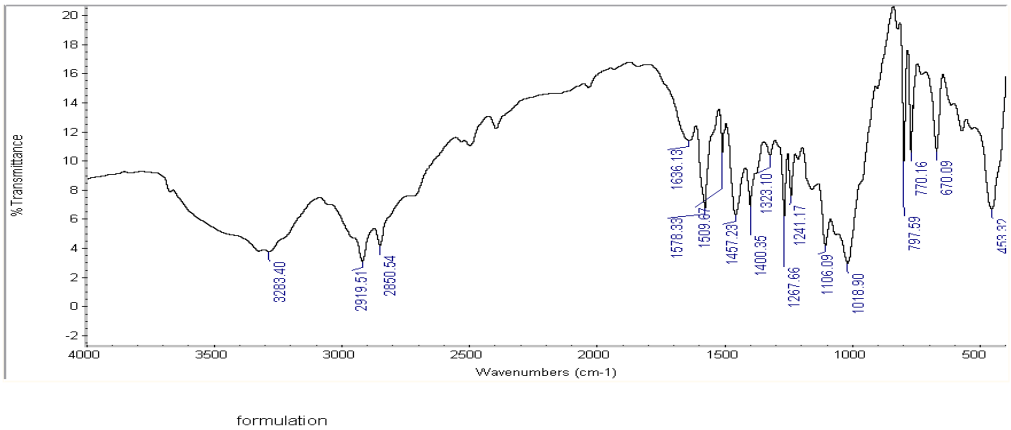


Figure 8: FT-IR spectra of SRL formulation (SR7) of Metoprolol tartrate



formulation

Figure 9: FT-IR spectra of Metoprolol tartrate bilayer formulation

Calculation of dose

Therefore maintenance dose = 205.925-50 = 155.92 mg

Hence, the formulation should release 50 mg of drug within 1 hour and 155.92 mg drug in 18 hours.

Evaluation of pre-compression parameters

The present study revealed that all powder blends showed good flow property.

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Table 3: Pre-compression parameters for IRL and SRL

Formulation (n=3)	Bulk Density Mean ± SD	Tapped Density ± SD	Carr's Index± SD	Hausner's ratio ±SD	Angle of Repose (^{0}) ± SD
IR1	0.587±0.002	0.673±0.005	12.77±0.217	1.14±0.030	17.59±0.36
IR2	0.566±0.005	0.667±0.004	15.14±0.226	1.17±0.020	16.36±0.25
IR3	0.573±0.004	0.680±0.003	15.73±0.109	1.18±0.020	19.42±0.13
IR4	0.585±0.003	0.678±0.003	13.71±0.177	1.15±0.013	21.14±0.16
IR5	0.582±0.010	0.659±0.007	11.68±0.206	1.13±0.090	17.13±0.03
IR6	0.566±0.004	0.637±0.006	11.14±0.157	1.12±0.025	19.10±0.07
SR1	0.592±0.005	0.684±0.003	13.45±0.206	1.15±0.009	18.64±0.27
SR2	0.591±0.008	0.686±0.002	13.84±0.328	1.16±0.017	18.48±0.03
SR3	0.605±0.004	0.681±0.003	11.16±0.186	1.12±0.009	18.20±0.08
SR4	0.623±0.005	0.713±0.002	12.62±0.127	1.14±0.010	22.48±0.28
SR5	0.596±0.004	0.708±0.004	15.09±0.249	1.18±0.028	18.31±0.07
SR6	0.591±0.004	0.727±0.002	18.70±0.397	1.23±0.029	18.16±0.14
SR7	0.615±0.003	0.704±0.004	12.64±0.673	1.14±0.028	23.47±0.09
SR8	0.572±0.001	0.713±0.002	19.77±0.436	1.24±0.024	19.34±0.07
SR9	0.620±0.002	0.696±0.001	10.91±0.181	1.12±0.017	17.396±0.02

Evaluation of post-compression parameters: The present study revealed that all the formulations were within the Pharmacopeal limits.

Table 4: Post-compression parameters for IRL and SRL

Batch code	Weight variation Mean ± SD (n=3)	Hardness(kg/cm^2) Mean ± SD (n=3)	Thickness (mm) Mean ± SD (n=3)	Friability (%) Mean ± SD (n=3)	Drug content (%) Mean ±SD (n=3)	In-vitro disintegration time (sec) Mean ± SD
IR1	199.39±0.067	4.15±0.05	2.80±0.04	0.71±0.09	99.62±0.19	110.13±1.52
IR2	200.23±0.042	4.18±0.10	2.86±0.10	0.57±0.04	98.60±0.82	86.06±2.08
IR3	200.58±0.060	4.35±0.03	2.90±0.07	0.55±0.06	98.65±0.28	72.33±2.51
IR4	201.35±0.091	3.97±0.07	2.87±0.03	0.63±0.05	97.61±0.94	98.33±3.05

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IR5	200.14±0.052	4.10±0.04	2.72±0.06	0.73±0.03	99.43±0.32	59.23±2.08
IR6	250.05±0.091	4.03±0.11	2.79±0.09	0.59±0.04	98.51±0.81	30.30±1.52
SR1	252.46±0.041	5.78±0.10	3.34±0.09	0.32±0.06	96.38±0.19	--
SR2	251.19±0.029	6.33±0.02	3.30±0.14	0.35±0.02	99.60±0.03	--
SR3	252.54±0.059	6.14±0.04	3.31±0.03	0.63±0.03	97.43±0.28	--
SR4	248.75±0.014	5.83±0.06	3.28±0.05	0.26±0.02	98.57±0.85	--
SR5	250.65±0.037	6.14±0.03	3.30±0.06	0.41±0.06	98.43±0.27	--
SR6	251.30±0.031	6.52±0.02	3.33±0.03	0.45±0.03	98.63±0.61	--
SR7	253.20±0.046	6.14±0.04	3.28±0.08	0.59±0.06	99.47±0.04	--
SR8	251.25±0.055	6.16±0.02	3.30±0.04	0.37±0.04	98.51±0.20	--
SR9	249.42±0.094	6.46±0.03	3.32±0.07	0.52±0.03	99.49±0.93	--

In-vitro dissolution studies of Immediate release layer:

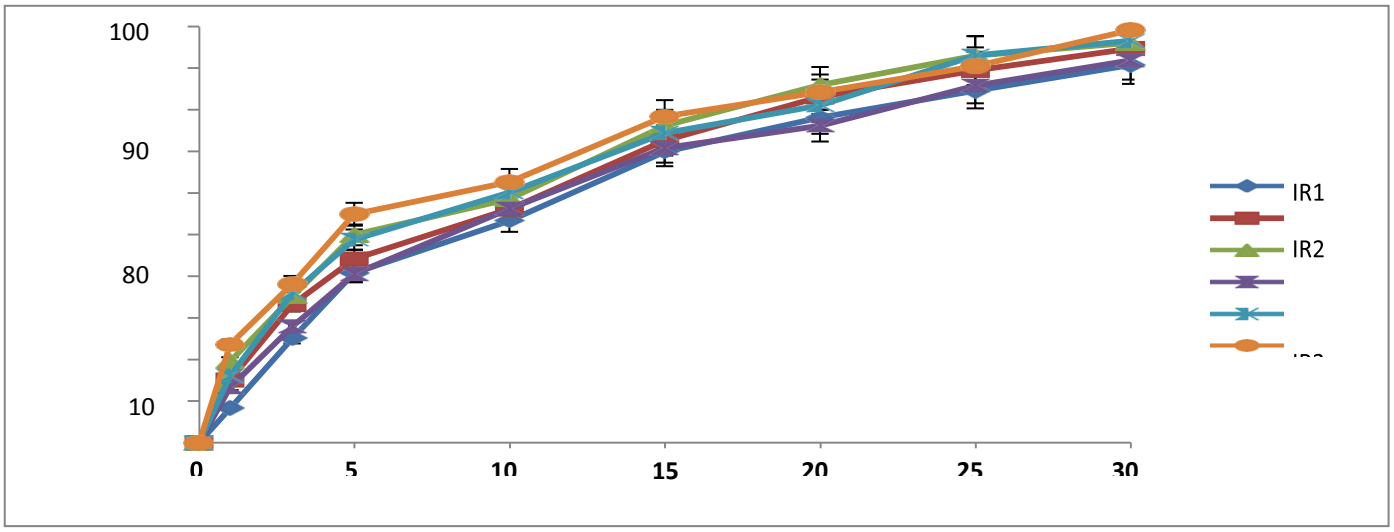

Figure 10: Comparative release profile of immediate release layer

In-vitro dissolution studies of Sustained release layer:

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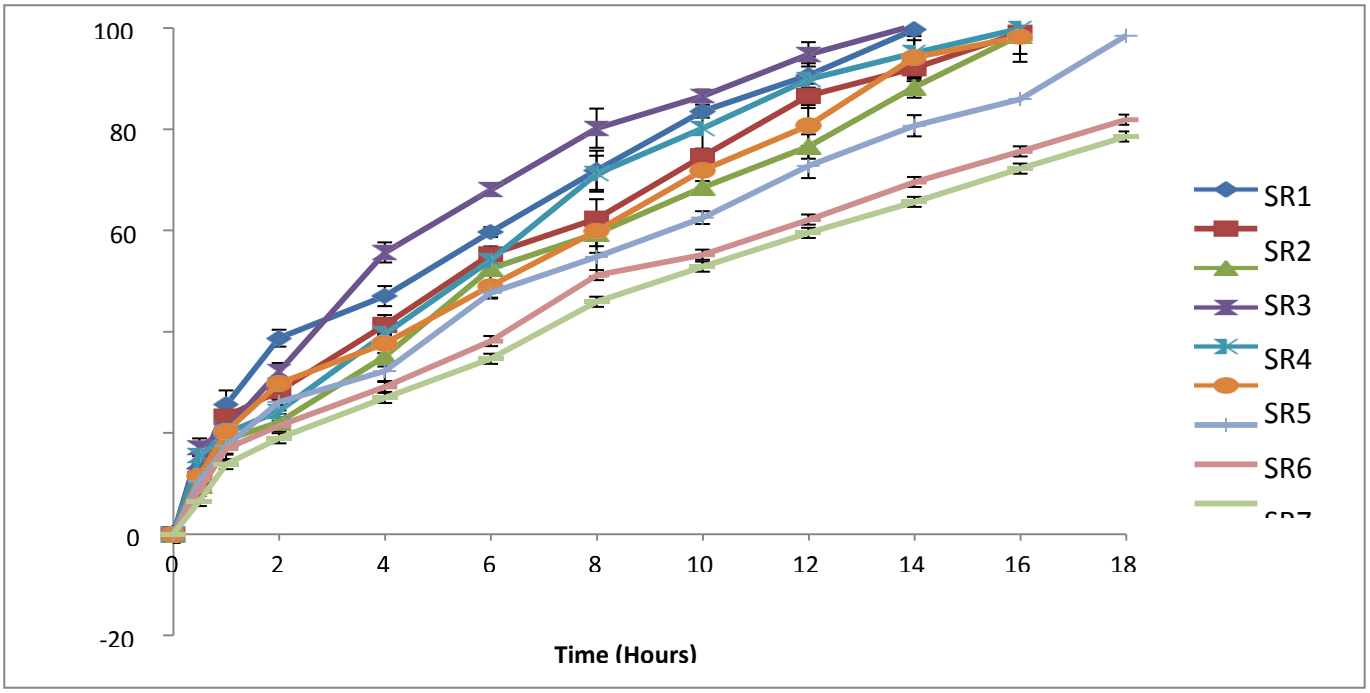

Figure 11: Comparative release profile of sustained release layer

In-vitro drug release profile of the immediate release and sustained release formulations are shown in Figure 1 and 2 respectively. Among all formulations of immediate release layer, formulation IR6 containing 7.5% Crospovidone as superdisintegrant showed the highest percentage of drug release (99.11%) at the end of 30 minutes and was chosen as the optimized formulation. The release profile of the formulation IR6 was highest, which might be due to combined action of Crospovidone and MCC. The result also suggested increase in the concentration of superdisintegrants drastically increases the release profile of the drug. Formulation IR6 disintegrated within 30.30 second which was comparatively quicker than the remaining formulations. Hence Formulation IR6 was chosen as the Optimized formulation for the IRL.

The formulation SR7 [containing combination of HPMC K100M and HPMC K15M in the ratio of 1:1 of the 18 % concentration of total weight] was selected as optimized sustained release layer based on dissolution profile as it showed more than 95% of drug release after 18 hours. Formulation SR1 and SR4 released almost all the drug at the end of 14 hours whereas formulations SR2, SR3, SR5 and SR6 released drug at the end of 16 hours. Hence these formulations were omitted from the study. In case of the formulation SR8 and SR9 only 81.87% and 78.56% of drug was released at the end of 18 hours, hence these formulations also did not meet our requirement. Formulations SR8 and SR9 showed floating behaviour so these batches were withdrawn from the dissolution studies. The formulation SR7 was selected as optimized sustained release layer based on dissolution profile as it showed more than 95% of drug release after 18 hours. The formulation was found to contain combination of HPMC K15M and HPMC K100M in the ratio of 1:1 of the 18 % concentration of total weight. Based upon the data of in-vitro release studies, formulation of bilayer tablet is shown in Table 5.

Table 5: Composition of the Metoprolol tartrate bilayer tablet

Sl. No	Ingredients	IRL formulation batch (IR6)	SRL formulation batch (SR7)	Bilayer tablet
1.	Metoprolol tartrate	50	155.92	205.92
2.	Lactose	89.98	19.08	109.06
3.	Crospovidone	15	--	15
4.	HPMC K100M and HPMC K15M (1:1)	--	45	45
5.	MCC	40	20	60

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6.	Povidone K30	--	5	5
7.	Iron oxide red	0.02	--	0.02
8.	Magnesium stearate	3	3	6
9.	Talc	2	2	4
10.	Total	200	250	450

In the visual inspection of the tablets two distinct layers were clearly visible, where upper layer was red in colour indicating IRL of bilayer tablets. This red colour was due to presence of iron oxide red used as coloring agents. Hardness and friability was found to be 6.25±0.15 kg/cm^3 and less than 1% respectively indicating the stability against physical strokes. Thickness was found to be 6.28±0.14 mm and content uniformity was 99.23±0.53 indicating uniform distribution of drug in both layers. In-vitro drug release is showed in Figure 3. The release pattern of the drug from bilayer tablet showed same dissolution profile as the individual layers of immediate and sustained release. When subjected to dissolution studies formulated bilayer tablets showed higher release in the first 30 minutes as IR layer disintegrated with immediate release of the drug. Further dissolution was continued for 18 hours and drug release data showed that the release was retarded which might be due to simultaneous imbibition of dissolution medium by the tablet with the formation of gel layer by the polymers HPMC K100 M and HPMC K15M which swell when in contact with the dissolution medium thereby leading to the formation of a thicker gel layer with a decrease in the drug release. Hence it can be concluded that biphasic release of Metoprolol tartrate had been achieved due to addition of proper proportion of crospovidone in the IR layer and combination of rate retarding polymer (HPMC K100M and HPMC K15M) in the SRLayer

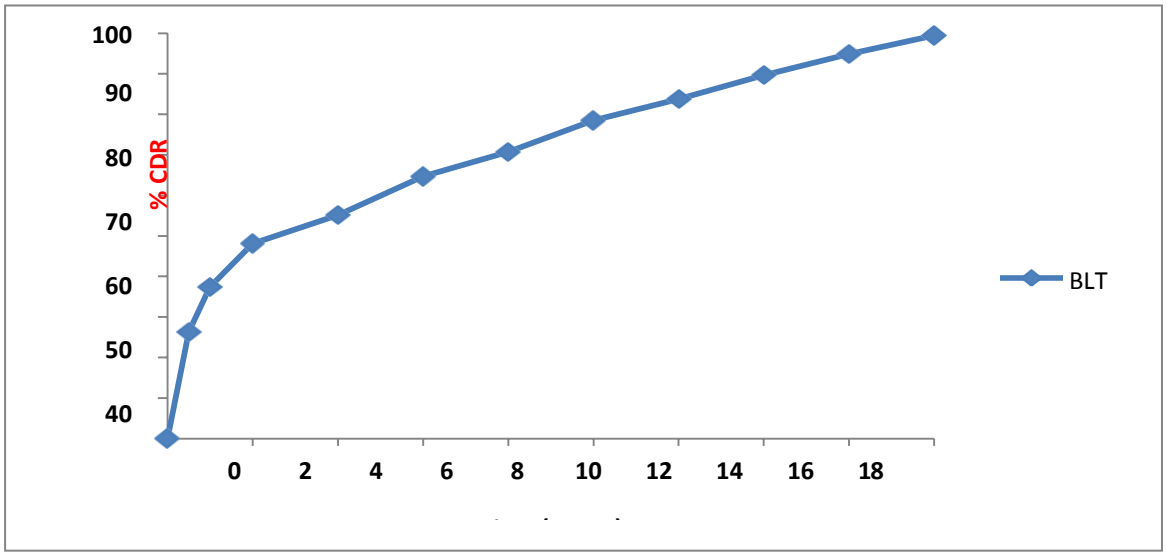

Figure 12: Dissolution profile of Metoprolol tartrate bilayer tablet

Drug release kinetics

The mechanism of drug release from the prepared IRL and SRL formulations of Metoprolol tartrate were performed by using different kinetic equations (Zero order, First order, and Higuchi). The release mechanism was understood by fitting the data to KorsemeyerPeppas model. The release kinetics of immediate release layer formulations (IR1-IR6) was found to follow first order kinetics, as the values for 'r' is (0.991 to 0.997) and values of 'n' was more than 0.89, hence the mechanism of drug release was Super case II transport. The release kinetics of sustained release layer (SR1-SR9) was found to follow zero order release kinetics as the value for 'r' was (0.994 to 0.998) which was comparatively higher in comparison to first order (0.820 to 0.895) and Higuchi's square root of time (0.880 to 0.976) and values of 'n' was found in between 0.606 to 0.663 indicating release mechanism was non-fickian release. The Figure 13-20show the different release kinetics pattern and release mechanism of the tablet formulations.

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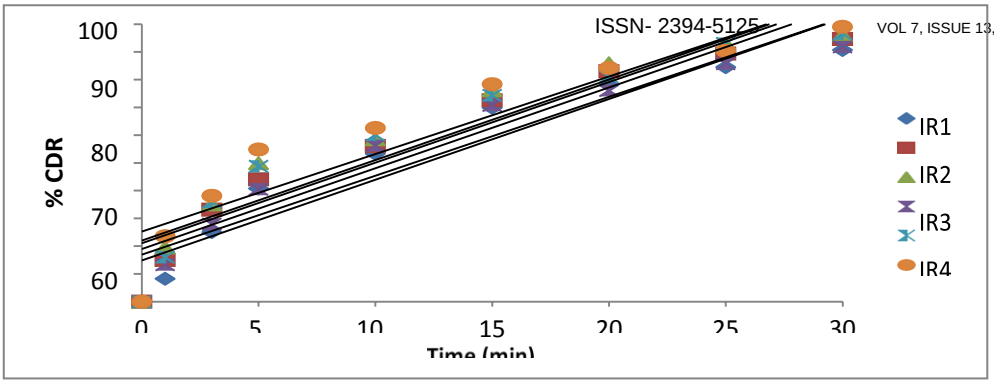

Figure 13: Comparative Zero Order release profile of IRL formulation

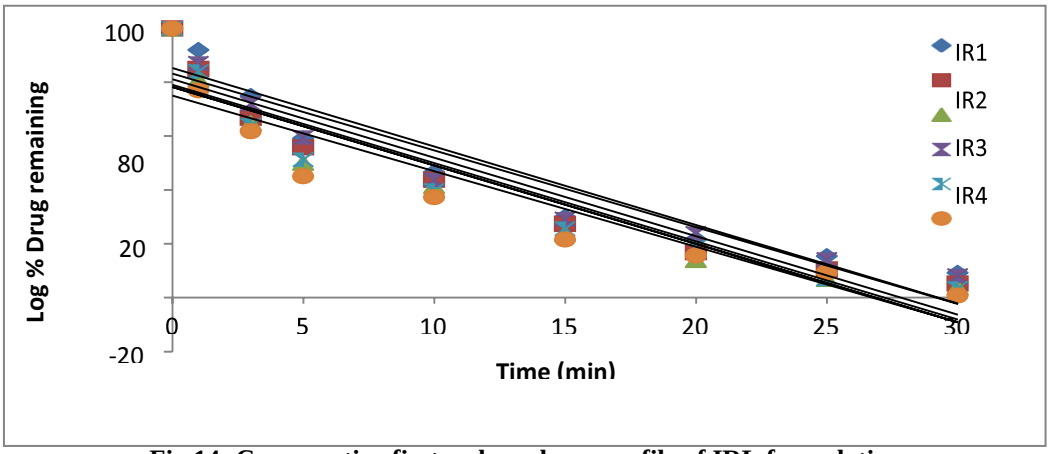

Fig 14: Comparative first order release profile of IRL formulation

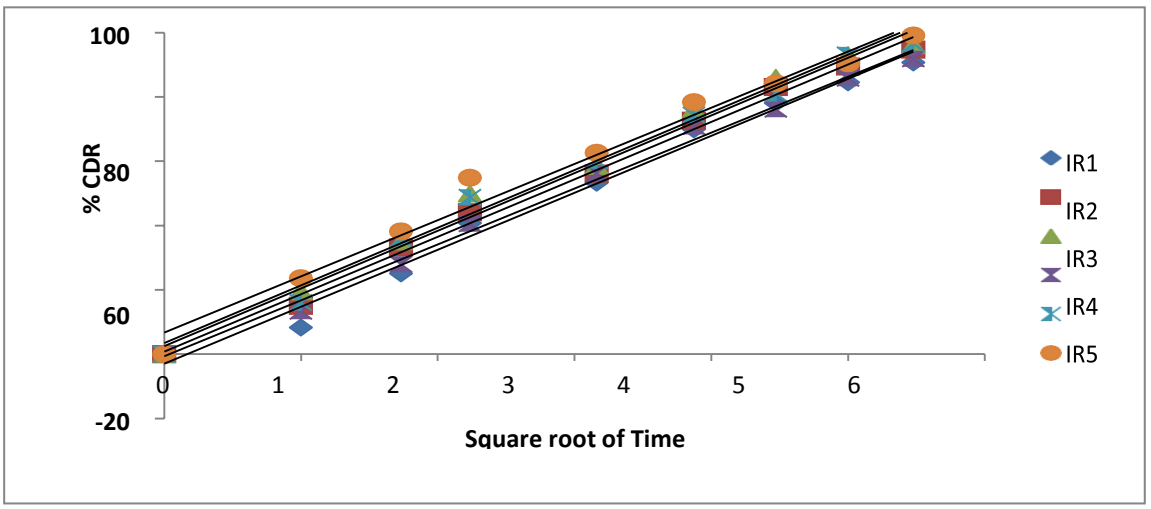

Figure 15: Comparative Higuchi release profile of IRL formulation

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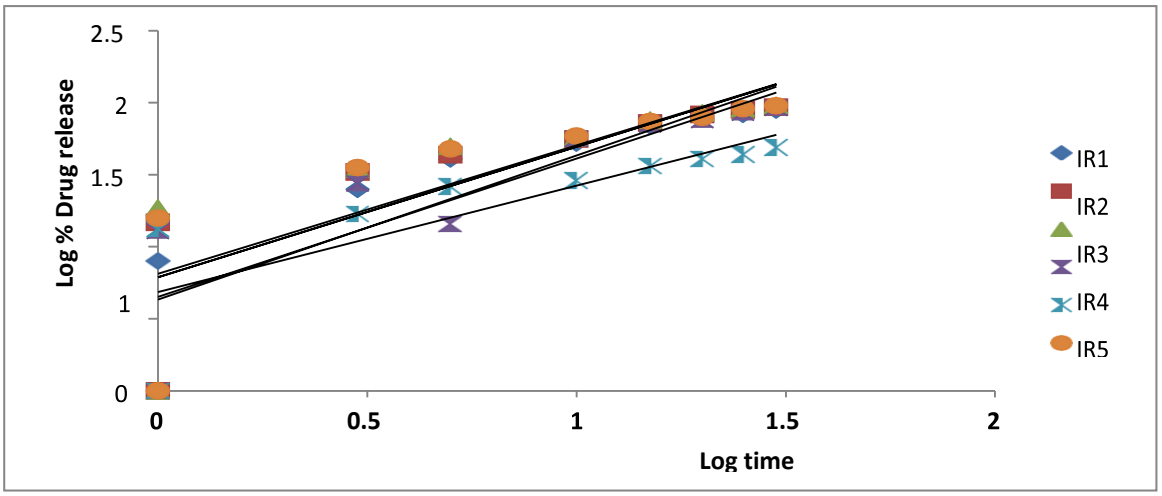

Figure 16: Comparative Korsemeyerpeppas release profile of IRL formulations

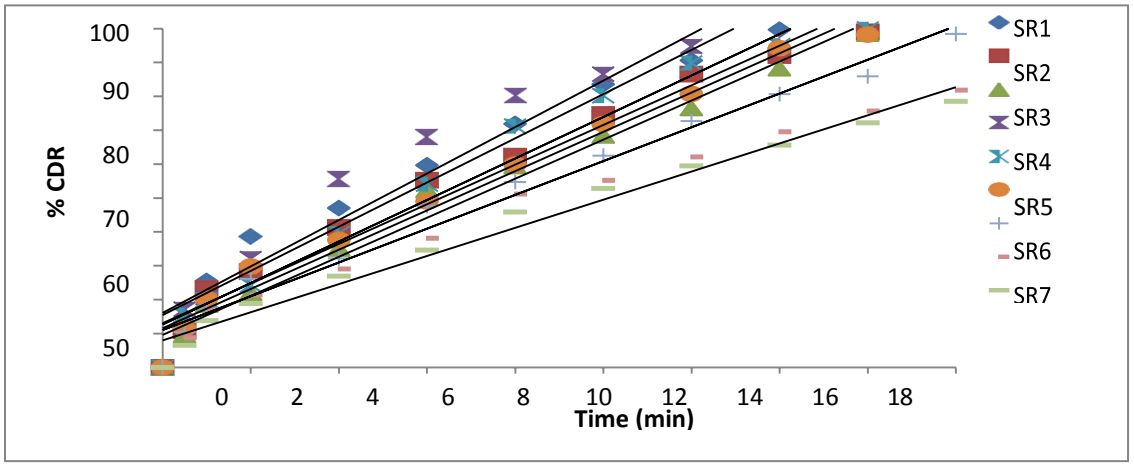

Figure 17: Zero order kinetics for SRL formulations

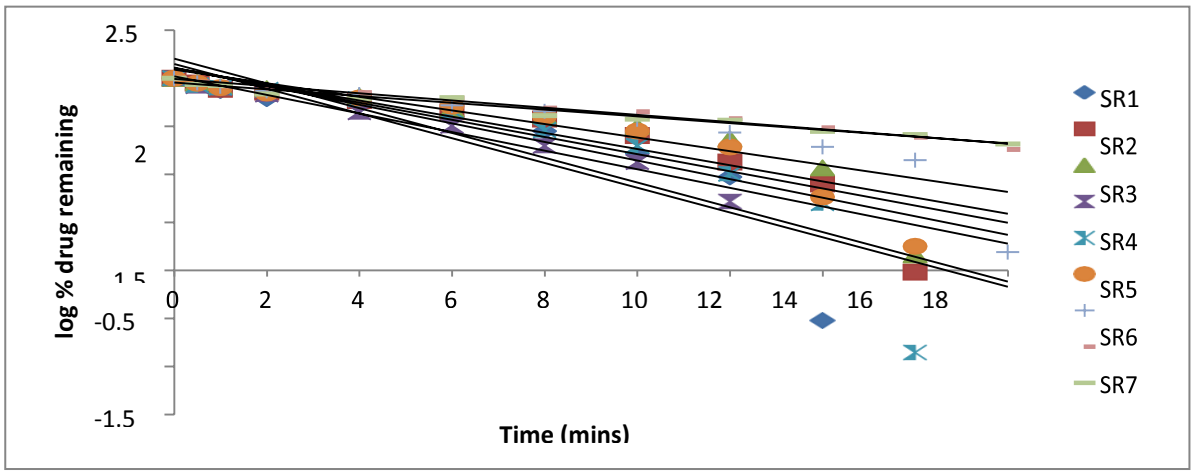

Figure 18: First-order kinetics for SRL

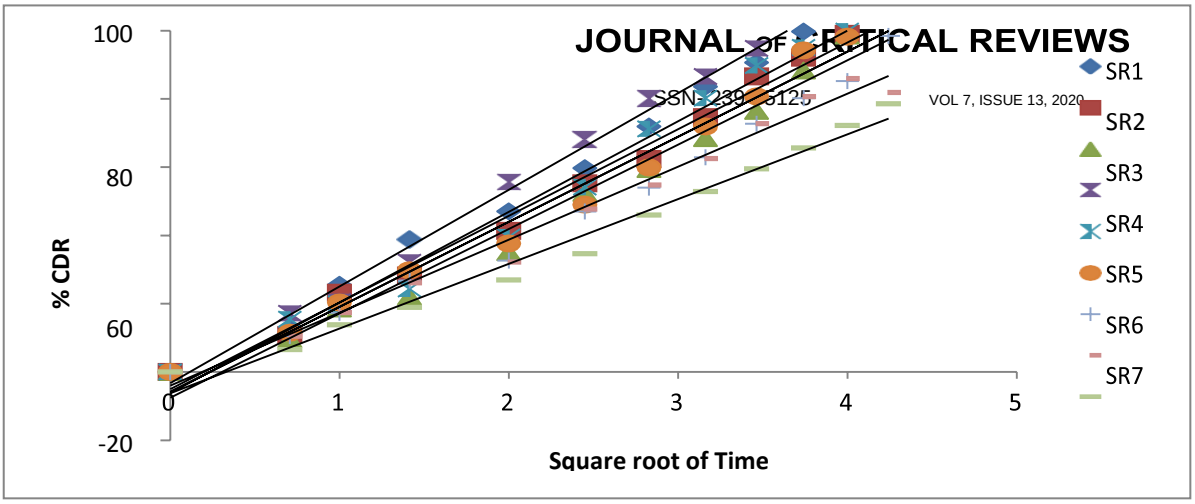

Figure 19: Higuchi Model for SRL formulations

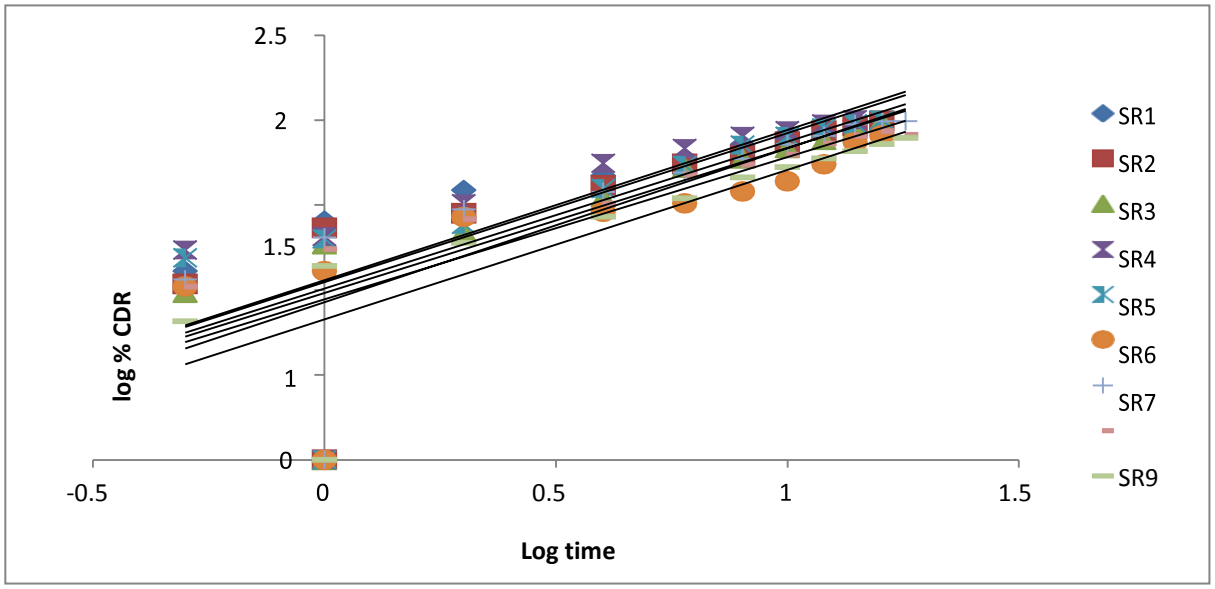

Figure 20: Korsmeyer'speppas release kinetics SRL formulations

Stability studies: Result showed that there was no significant change in hardness, drug content and in vitro drug release within 3 months of the stability period.

Time period	**lardness Kg/cm^3**	**content (%)**	**o drug release (%CDR)**
Initial	6.25	99.23	99.45
15th day	6.25	99.23	99.43
30th day	6.25	99.22	99.24
45th day	6.22	99.19	99.15
60th day	6.21	99.08	99.12
90th day	6.20	99.02	99.09

Table 6: Results of stability studies data

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IV. CONCLUSION

Based on the above observations, it can be concluded that the formulated bilayer tablets of Metoprolol tartrate using superdisintegrants and release retardant polymers were capable of exhibiting all the properties of bilayer tablet. Such formulation might reduce the dose intake, minimize dose related adverse effect, cost and ultimately improve the patient compliance and drug efficiency during the treatment ofhypertension. In summary, the release profiles of bilayer tablet formulations were quite promising for once a day formulation for the treatment of hypertension.

V. REFERENCES

[1] Jaysukh J Hirani1*, Dhaval A Rathod andKantilal R Vadalia (2009)Orally Disintegrating Tablets: A Review Tropical Journal of Pharmaceutical Research. 8: 161-172

[2] Shila VD, Ashwini EP, Manoj MB and Shashikant D (2013) A review on novel approach -bilayer tablet technology. Int J Pharm Sci Rev Res.21: 46-52.

[3] Soma C, Reddy SC, Tabasum SG and Varma V (2012). An overview on bilayer tablets. Int J Pharm Tech. 4:2143-26.

[4] Mehraj UD, Shahista MD and Tarkeshwar PS (2014)An overview on bilayered tablet technology.Am-Euras J Sci Res. 9:06-15.

[5] Naisarg DP, Ronak KG andJalpa S (2012) Bilayer tablet: An emerging trend. Int J Pharm Res Dev. 4:102-111.

[6] Carla M, José M and Joao F (2007) Compressed matrix core tablet as a quick/slow dual-component delivery system containing Ibuprofen. AAPS Pharm Sci Tech. 8:76: E1-E8.

[7] The Indian Pharmacopoeia. (2014) Government of India, ministry of health and family welfare, the Indian pharmacopoeia commission, Ghaziabad.II:2213-5.

[8] Albers S, Elshoff JP, Völker C, Richter A and Laer S (2005) HPLC quantification of metoprolol with solid-phase extraction for the drug monitoring of paediatric patients. Biomed Chromato. 19:202-07.

[9] Swaisland HC, Ranson M, Smith RP, Leadbetter J, Laight A, McKillop D and Wild MJ (2005) Pharmacokinetic drug interactions of Gefitinib with Rifampicin, Itraconazole and Metoprolol. ClinPharmaco. 44:1067-81.

[10] Singh PK and Kumar S (2011) Bilayer and floating bioadhesive tablets: Innovative approach to gastro-retention. J Drug Deli Therap. 1:32-5.

[11] Rath S, Panda SK, Sarangi RR, Dash AK, Rath SK and Nayak (2011). UV-spectrophotometric method for simultaneous estimation of Metoprolol and Amlodipine in bulk and their formulation. Int J Bio Pharma Res. 2:50-04.

[12] Raju KN, Velmurugan S, Deepika B and Vinushitha S (2011) Formulation and in-vitro evaluation of buccal tablets of Metoprolol tartrate. Int J Pharm Pharma Sci. 3:239-46.

[13] Girish SS, Devendra KJ andDhananjay MM (2007) Preparation and in vitro evaluation of bilayer and floating-bioadhesive tablets of Rosiglitazonemaleate. Asian J Pharm Sci. 2:161-169.

[14] Liberman H andLachmann L (1991). The theory and practice of industrial pharmacy. 3rd Ed.Bombay: Varghese Publication House.171-93.

[15] Vishwakarma D, Patel KR and Patel NM (2012) Formulation and Evaluation of Metoprololtartrate Fast Dissolving Tablet.Ame J PharmtechRes.2 :412-23.

[16] Swati Sanjay Gaikwad, SandipAnnajiChafle, Princy Sunil Morris and Jasmine GevAvari. (2016) Development and evaluation of bilayer tablets of combination of antibiotics for the treatment of sexually transmitted disease Brazilian Journal of Pharmaceutical Sciences 52: 555-566.

[17] Hiremath SN, Patil SD, Swamy PV and Ali MY (2010) Once-daily sustained release matrix tablets of Metoprolol tartrate: Formulation and in-vitro evaluation. Indian J Pharm Edu Res.44: 66-70.

[18] Jalalil MB, Adibkial K, Valizadeh H, Shadbad Mohammad RS, Nokhodchi A, Omidil Y, Mohammadi G, Nezhadi SH and Hasan M (2008) Kinetic analysis of drug release from nanoparticles. J Pharm Pharmaceut Sci. 11:167-77.

[19] Dash S, Murthy PN, Nath L and Chowdhury P (2010) Kinetic modelling on drug release from controlled drug delivery systems. ActaPoloniaePharmaceutica Drug Res. 67:217-23.

[20] ICH Q1A (R2) Stability testing guidelines: Stability Testing of new drug substances and products. [Online]. [Cited 2008 Nov 10]; Availablefrom:URL:http://www.tga.health.gov.au/docs/pdf/euguide/inch/273699r2en.pdf