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FORMULATION AND EVALUATION OF METOPROLOL SUCCINATE SUSTAINED RELEASE TABLETS

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ABSTRACT

A sustained effect of Metoprolol Succinate is required for the treatment of some chronic conditions like rheumatoid arthritis, osteoarthritis and chronic pain. Sustained release matrix tablets of Metoprolol Succinate were formulated using polymers (ethyl cellulose, Eudragit-RL100, PVP) and hydrophilic gums (guar gum, xanthan gum) in various concentrations. Hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (Na.CMC), micro crystalline cellulose and lactose were used as fillers. Nineteen different formulations of matrix tablets of Metoprolol Succinate were produced by wet granulation and direct compression methods. The flow properties of the granules and the physical properties of the compressed tablets namely, weight uniformity, crushing strength, drug content, friability and tablet thickness were evaluated. *In – vitro* release studies of the drug was performed in 0.1 N HCl for 2 hrs and phosphate buffer pH 6.8 for 10 hours. The best selected formulation F14 (containing 35% of Eudragit-RL100) sustained the drug release for 12 hrs. All the physical characteristics of the formulated tablets were within acceptable limits. The best selected formulation F14 has exhibited anomalous Non-Fickian diffusion (i.e., n<1). This was observed due to the effect of swelling/erosion of polymer (Eudragit RL-100).

KEYWORDS: Sustained release tablets, Metoprolol Succinate, Hydrophilic gums & hydrophobic polymers.

INTRODUCTION

Drug delivery system: A drug delivery system (DDS) is defined as formulation or a device that enables the introduction of a therapeutic substance in a body & improves its efficacy & safety by controlling the rate, time & place of release of drugs in the body. This process includes the administration of the therapeutic product, the release of the active ingredients by the product & the subsequent transport of the active ingredients across the biological membranes to the site of action.[1]

Sustained release indicates an initial release of drug sufficient to provide a therapeutic dose soon after administration, and then a gradual release over an extended period.[2]

Metoprolol succinate, 1-[4-(2-methoxyethyl)phenoxy]-3-[(propan-2-yl)amino]propan-2-ol, represents the β_1 – selective adrenergic receptor blocker. Metoprolol Succinate exhibits high water solubility but low permeability (class III) according to Biopharmaceutics Classification System (BCS) with only 12% of oral bioavailability. The biological half life of Metoprolol Succinate is 3-7 hrs.[7]

To reduce the frequency of administration and to improve patient compliance, a sustained release formulation of metoprolol succinate is developed. The main objective of the present work was to develop sustained release matrix tablets of water-soluble metoprolol succinate using different polymers viz. Ethyl cellulose (EC), Eudragit RL-100, PVP and natural gums like Karaya gum (KG), Guar gum (GG). The matrix tablets were prepared and evaluated for different physiochemical parameters such as appearance, weight variation, hardness, friability, drug content and *in vitro* release. Metoprolol Succinate is available in the market in various forms like tablets (Actocard 25mg, Asoprol 25mg and 50mg), extended-release tablets (Actiblok- 25mg, 50mg, 100mg), capsules (Betaloc, Lopressor, Mepol), injections (Betaloc 1mg/ml, Metolar).

MATERIALS AND METHODOLOGY

Materials: Metoprolol succinate was procured as gift sample from Systopic lab, New Delhi. Polymers like Eudragit RL-100, PVP and ethyl cellulose were procured from SD Fine Chemicals Ltd., natural gums like Xanthan gum was procured from Loba chemicals Pvt. Ltd., guar gum was procured from Merk Specialties Pvt. Ltd., Diluents like hydroxy propyl methyl cellulose, Sodium Carboxy methyl cellulose, Lactose, Micro crystalline cellulose, Lubricant

& Glidant used are Magnesium stearate & Talc, Aerosil respectively. All the other ingredients used are of lab grade chemicals.

METHODOLOGY

Formulation of tablets

The sustained release tablets of metoprolol succinate were prepared by both wet granulation and direct compression methods. The tablets obtained from these methods are compared for their release characteristics.

By Wet Granulation Method

Different tablet formulations containing unit dose of metoprolol succinate were prepared by wet granulation technique. Required quantities of drug and polymer were mixed thoroughly in a mortar, and a sufficient volume of granulating agent (Ethanolic solution of EC or Eudragit or PVP or IPA solution of PVP for hydrophilic gums) was added slowly. After obtaining the required cohesiveness, the mass was sieved through 18mesh. The granules were dried at 40°C for 2 hours. Once dried, talc and magnesium stearate were finally added as glidant and lubricant. The tablets were compressed using a 10-station tablet compression machine using 8 mm punches (Rimek Multistation Press). The composition of each tablet is shown in **Table 1 & 2**.

Table. 1: Formula for the sustained release tablets of metoprolol succinate for each tablet (F1-F6).

	Ingredients	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**
	Metoprolol succinate	47.5	47.5	47.5	47.5	47.5	47.5
Ethanolic solution	**Ethyl Cellulose**	7	7	0	0	0	0
	Eudragit RL-100	0	0	7	7	0	0
	PVP	0	0	0	0	7	7
	HPMC	40	0	40	0	40	0
	NA.CMC	0	40	0	40	0	40
	Lactose	150	150	150	150	150	150
	Talc	2.5	2.5	2.5	2.5	2.5	2.5
	Mg. Stearate	3	3	3	3	3	3
	Total	**250**	**250**	**250**	**250**	**250**	**250**

Ethyl cellulose: 2.8%, Eudragit RL-100: 2.8%, Povidone (PVP): 2.8%

Table.2: Formula for the sustained release tablets of metoprolol succinate for each tablet (F7-F12).

	INGREDIENTS	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
	Metoprolol Succinate	47.5	47.5	47.5	47.5	47.5	47.5
IPA solution	**Guar Gum**	48	60	72	0	0	0
	Xanthan Gum	0	0	0	48	60	72
	Lactose	140	128	116	140	128	116
	PVP	7	7	7	7	7	7
	Talc	5	5	5	5	5	5
	Mg. Stearate	2.5	2.5	2.5	2.5	2.5	2.5
	Total	**250**	**250**	**250**	**250**	**250**	**250**

Guar gum & Xanthan gum: 19-29%

By Direct Compression Method

Different tablet formulations containing unit dose of metoprolol succinate were prepared by Direct Compression technique. Required quantities of drug and polymer were mixed thoroughly, and a sufficient volume of filling agent (Micro Crystalline Cellulose) & Aerosil were added and mixed properly. Talc and magnesium stearate were finally added as glidant and lubricant. The tablets were compressed using a 10-station tablet compression machine using 8 mm punches (Rimek Multistation Press). The composition of each tablet is shown in T**able 3**.

Table. 3: Formula for the sustained release tablets of metoprolol succinate for each tablet (F13-F19).

INGREDIENTS	F_{13}	F_{14}	F_{15}	F_{16}	F_{17}	F_{18}	F_{19}
Metoprolol Succinate	47.5	**47.5**	47.5	47.5	47.5	47.5	47.5
Ethyl cellulose	50	**0**	0	0	75	87.5	100
Eudragit RL-100	50	**87.5**	100	125	0	0	0
MCC	90	**102.5**	90	65	115	102.5	90
Aerosil	5	**5**	5	5	5	5	5
Talc	5	**5**	5	5	5	5	5
Mg. Stearate	2.5	**2.5**	2.5	2.5	2.5	2.5	2.5
Total	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Ethyl cellulose: 20-40%, Eudragit RL-100: 20-50%

Evaluation of Granules: The granules were evaluated for angle of repose, bulk density, compressibility index and Hausner's ratio. The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the

surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation: **$\tan \theta = h/r$**

where h and r are the height and radius of the powder cone.

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of weighed granules from each formula was introduced into a 10-mL measuring cylinder. After 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- second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas

LBD = weight of the powder/volume of the packing

TBD = weight of the powder/tapped volume of the packing

The compressibility index of the granules was determined by using the formula

Carr's compressibility index (%) = [(TBD – LBD) × 100]/TBD

Hausner found that the ratio TBD/LBD was related to interparticulate friction and such could be used to predict powder flow properties. Hausner showed that powders with low interparticulate friction had ratios of approximately 1.2, whereas more cohesive, less free-flowing ones had ratios greater than 1.6.The Hausner's ratio was calculated by using the formula: **Hausner's ratio=TBD/LBD**

Evaluation of Tablets

The prepared tablets were evaluated for weight variation, hardness, friability, drug content. To study weight variation, 20 tablets of each formulation were weighed and average weight was calculated and then the individual tablets were weighed and weight was compared with the average weight. The drug content was determined by taking accurately weighed amount of powdered metoprolol succinate tablets (equivalent to 100 mg of metoprolol succinate) was extracted with pH 6.8 buffer and the solution was filtered. The absorbance was measured at 274 nm after suitable dilution.

Monsanto hardness tester was used for the determination of the hardness. The tablet was placed in contact between the plungers and the screw was rotated, the force of the fracture was recorded. The friability of 6 tablets was determined using the Roche friabilator (Cintex Friability Test Apparatus). This device subjects the tablets to the combined effect of

abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$\mathbf{F = (1- W_0 / W) \times 100}$$

Where, W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test.

The *in vitro* dissolution studies were carried out using USP apparatus type II (Electrolab Tablet Dissolution Tester) at 50 rpm. The dissolution medium consisted of 0.1 N HCl for 2 hours (900 mL) and phosphate buffer pH 6.8 for 10 hours (900 mL), maintained at 37°C ± 0.5°C. The drug release at different time intervals was measured by UV-visible spectrophotometer (Lab India, UV-3000+) at 274 nm.

Drug release kinetics

Data obtained from in vitro drug dissolution studies were fitted to various kinetic equations (zero order, first order, higuchi model and korsemeyer peppas model) to find out the mechanism of drug release from the formulation. The correlation coefficient was calculated for different models.

FTIR studies

IR spectra for metoprolol succinate and formulation F14 tablets were recorded in a Fourier transform infrared spectrophotometer (FTIR Shimadzu.) with KBr pellets method. Approximately 0.1 to 1.0 % sample is well mixed into 200 to 250 mg fine alkali halide KBr powder and then finely pulverized and put into a pellet-forming die. A good KBr pellet is thin and transparent. Opaque pellets give poor spectra, because little infrared beam passes through them. White spots in a pellet indicate that the powder is not ground well enough, or is not dispersed properly in the pellets. It analyzes the molecular interactions and stability of the formulation between the drug and excipients used.

Stability Studies

The stability study of the tablet F14 was carried out according to ICH guidelines at 25±2ºC/60±5%RH for three months by storing the sample in (Cintex, Mumbai) stability chamber.

RESULTS AND DISCUSSION

The present study was carried out to formulate & evaluate oral sustained release tablets of metoprolol succinate both by wet granulation and direct compression method. The tablets were prepared by using different hydrophilic and hydrophobic polymers viz. ethyl cellulose, Eudragit RL-100, poly vinyl pyrrolidone, guar gum and xanthan gum.

Pre-compression parameters

Evaluation properties of granules

Granulation is an important step in the preparation of tablets as the physical properties of granules play a vital role in the release of drug from the sustained release tablets. The Metoprolol succinate granules were prepared by wet granulation method. The prepared granules of different batches were evaluated for their granule size, angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio, and the results are shown in the **Table 4**.

Table. 4: Pre-compression parameters of Granules for formulations F1-F12

Batch code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Cars Index (%)	Hausner's Ratio	Angle of Repose (%)
F_1	0.43	0.50	14.29	1.17	37.30
F_2	0.40	0.43	7.50	1.08	31.33
F_3	0.38	0.45	14.67	1.17	31.76
F_4	0.39	0.42	7.06	1.08	35.31
F_5	0.40	0.44	8.24	1.09	36.18
F_6	0.43	0.48	11.43	1.13	36.03
F_7	0.46	0.52	11.76	1.13	32.74
F_8	0.42	0.49	14.29	1.17	34.00
F_9	0.44	0.47	6.67	1.07	34.82
F_{10}	0.43	0.48	9.72	1.11	36.43
F_{11}	0.44	0.51	13.51	1.16	33.07
F_{12}	0.44	0.51	14.29	1.17	36.25

The granules have an average size in the range of 0.459±0.12 to 0.701±0.13 mm, which indicates narrow size distribution. The angle of repose varied from 30.78-37.30. The low values of angle of repose indicate free flowing nature of the granules. The bulk densities of the granules were found to be in the range of 0.38-0.46 gm/ml. The tapped densities were in the range of 0.42-0.52 gm/ml. The Carr's indexes were in the range of 5.33-14.29. Hausner's ratio was found in the range of 1.06-1.17. Hence, as they complies with pharmacopoeial standards with good flow properties and may be compressed into tablets.

Post-compression parameters

Evaluation of tablets: The sustained release tablets of metoprolol succinate were prepared both by wet granulation and direct compression methods. The tablets were evaluated for their weight variation, hardness, friability, drug content uniformity and the results are tabulated in the **Table.5**. With a tablet designed to contain specific amount of tablet formula, the weight variation of the tablet being made is routinely measured to help ensure that a tablet contains the proper amount of drug. The weight variation was within the prescribed limits and it varied between 249±1.10 to 251±1.93 mg.

Table. 5: Post- compression parameters of all formulations F1-F19.

Batch code	Hardness (kg/cm^2)	Friability (%)	Wt. Variation (mg)	Drug Content (%)
F_1	3.4	0.20	250±1.73	110.849
F_2	3.5	0.33	251±1.93	96.698
F_3	4.1	0.27	249±2.02	101.415
F_4	3.8	0.88	249±1.10	94.34
F_5	3.6	0.27	250±1.51	91.981
F_6	3.5	0.33	251±1.84	99.057
F_7	3.9	0.26	249±1.83	101.415
F_8	4.3	0.40	250±2.02	106.132
F_9	4.1	0.40	250±2.13	91.981
F_{10}	4.0	0.40	250±2.05	94.34
F_{11}	3.8	0.33	249±2.00	96.698
F_{12}	4.5	0.40	250±1.63	99.057
F_{13}	5.1	0.40	249±2.35	96.698
F_{14}	**4.9**	**0.47**	**250±1.75**	**103.774**
F_{15}	3.8	0.61	250±1.70	101.415
F_{16}	3.7	0.68	249±1.70	94.34
F_{17}	4.6	0.33	250±2.26	99.057
F_{18}	3.7	0.33	250±1.95	108.491
F_{19}	4.6	0.54	249±1.97	96.698

Tablets require a certain amount of strength or hardness or resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. Hardness was in the range of 3.4 to 5.2 kg/cm^2. Tablet hardness is not an absolute indicator of strength since some formulations, when compressed into very hard tablets, tend to "cap" on attrition, losing their crown portions. Therefore, another measure of a tablet's strength, its friability, is often measured. Friability was less than 1% (i.e. 0.20 to 0.61%) in all the batches, which indicates tablet ability to withstand shock during the time of transportation and handling. Drug content uniformity was in the range of 91.98 to 110.85%. All the physical characteristics of the formulated tablets were within acceptable limits.

The rate of drug absorption for acidic drug moieties that are absorbed high in the GI tract is often determined by the rate of drug dissolution from the tablet. If the attainment of high peak blood levels for the drug is a product objective, obtaining rapid drug dissolution from the tablet is usually critically important. The rate of dissolution may thus be directly related to the efficacy of the tablet product, as well as bioavailabity differences between formulations. *In vitro* Dissolution studies for sustained release matrix tablet formulations were carried out using 0.1N HCl for 2hrs and in phosphate buffer pH 6.8 upto 10hrs as the drug is targeted for release in intestine. As the tablet has to pass the GI tract before entering into the intestine acidic media is used for dissolution considering 2hrs as normal gastric emptying time. The *in vitro* release data for formulations was presented in **Tables 6, 7 and 8** respectively. Formulations F1 to F6 were prepared by using Ethyl cellulose: 2.8%, Eudragit RL-100: 2.8%, Povidone (PVP): 2.8%. **Figure.1** shows the release profile of formulations F1 to F6. Formulations F7 to F12 were prepared with Guar gum and Karaya gum 19-29%. **Figure.2** shows the release profiles of formulations F7 to F12. Formulations, F13 to F19 containing Ethyl cellulose: 20-40%, Eudragit RL-100: 20-50%. **Figure.3** shows the release profiles of formulations F13 to F19. The best selected formulation F14 containing 35% of Eudragit RL-100 by using Direct compression method has sustained the drug release for more than 12 hours.

Table. 6: *In vitro* release data for Formulations F1-F6.

TIME (hrs)	% Drug Release					
	F_1	F_2	F_3	F_4	F_5	F_6
0	0	0	0	0	0	0
0.5	9.00	8.05	9.47	7.58	7.11	7.58
1	12.84	11.89	13.79	11.41	9.99	9.52
1.5	18.59	19.06	18.60	15.26	14.31	14.78
2	23.91	27.69	24.39	22.03	21.49	21.49
2.5	31.06	33.07	30.65	30.52	28.64	28.19
3	36.91	44.72	37.38	35.93	33.60	33.59
3.5	41.45	50.18	44.16	45.39	41.71	43.49
4	48.25	56.56	50.97	55.80	48.07	50.32
5	59.56	61.63	57.37	60.45	57.16	61.65
6	72.71	68.97	69.62	70.05	65.84	67.23
7	80.80	75.45	82.83	79.70	77.71	79.01
8	91.60	82.41	92.09	86.50	86.63	91.93
10	100.12	93.66	99.56	96.54	98.56	100.27
12		101.56		103.45	102.55	

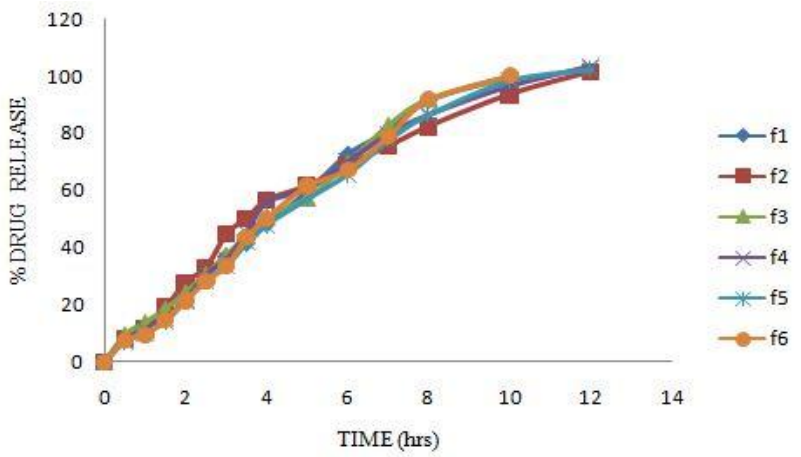

Fig. 1: Drug release profile for Formulations F1-F6.

Table. 7: *In-vitro* release data for formulations F7-F12.

TIME (hrs)	% Drug Release					
	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
0	0	0	0	0	0	0
0.5	12.32	14.21	9.47	17.53	16.37	9.95
1	19.02	19.94	15.21	24.68	26.27	15.69
1.5	25.76	24.77	18.61	28.56	32.51	21.93
2	30.18	30.58	27.24	35.32	38.53	27.26
2.5	41.55	37.70	35.73	42.02	45.02	35.75
3	50.50	44.14	41.59	48.46	46.11	41.61
3.5	61.11	52.00	51.05	54.04	54.57	51.07
4	69.04	57.98	60.57	63.20	60.86	57.82
5	79.24	65.38	67.45	73.73	68.75	69.27
6	88.60	76.38	73.93	83.38	78.22	79.78
7	97.06	86.53	89.38	91.75	85.20	86.77
8	103.27	95.40	91.95	98.77	95.55	93.35
10		102.46	99.41	108.52	106.55	102.50
12						

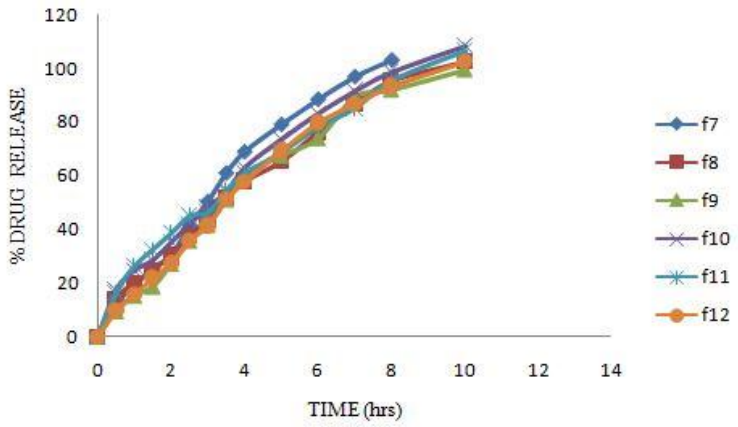

Fig. 2: Drug release profile for formulations F7-F12.

Table. 8: *In-vitro* release data for formulations F13-F19.

TIME (Hrs)	% Drug Release						
	F_{13}	F_{14}	F_{15}	F_{16}	F_{17}	F_{18}	F_{19}
0	0	**0**	0	0	0	0	0
0.5	7.58	**4.74**	5.68	9.00	9.47	9.47	8.05
1	10.02	**9.50**	11.89	17.57	19.00	19.47	14.26
1.5	14.39	**13.82**	14.84	24.77	28.11	28.58	19.07
2	19.29	**18.63**	22.54	28.69	33.94	36.79	24.39
2.5	26.89	**24.76**	31.03	35.36	36.95	45.35	30.12
3	32.50	**31.61**	38.36	40.46	46.57	50.76	36.72
3.5	39.94	**37.04**	42.58	47.38	52.00	56.65	42.24
4	46.53	**41.61**	48.60	52.52	55.68	63.01	49.25
5	50.93	**51.57**	55.53	63.49	62.94	70.30	57.65
6	60.27	**60.24**	65.63	73.15	74.27	76.29	69.43
7	74.56	**69.64**	75.31	79.28	82.08	82.76	79.14
8	85.76	**77.29**	84.58	86.49	89.05	89.71	87.82
10	97.90	**86.11**	94.34	95.64	97.65	99.77	96.53
12	103.47	**93.14**	99.43	101.55	104.56	105.53	103.69

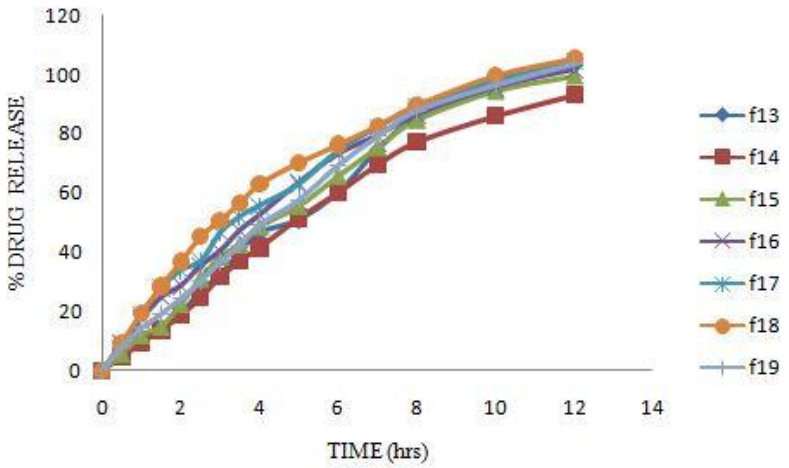

Fig. 3: Drug release profile for formulations F13-F19.

Kinetics and mechanism of drug release

The drug release mechanism was studied by comparing the correlation coefficients for different release models (**Table.9**). Kinetic results shown in **Table 9** reveal that the correlation coefficient (R^2) value is higher for Korsmeyer – Peppas plot than all other plots. From Korsmeyer – Peppas study, the 'n' value of the optimized formulation is 0.992 show that the release mechanism of formulation was controlled by anomalous Non-Fickian diffusion (i.e., n<1). The drug release from the best selected formulation sustained for 12hrs and data fitted to Peppas equation indicated a case II transport suggesting that drug release is mainly through swelling/erosion mechanism of polymer (Eudragit RL-100).

Table. 9: Correlation coefficient (R^2) values of optimized formulation (F_{14}) containing 35% of Eudragit RL-100.

Kinetic model	R^2 values
Zero Order Plot	0.971
First Order Plot	0.772
Higuchi Plot	0.951
Korsmeyer – Peppas Plot	0.992

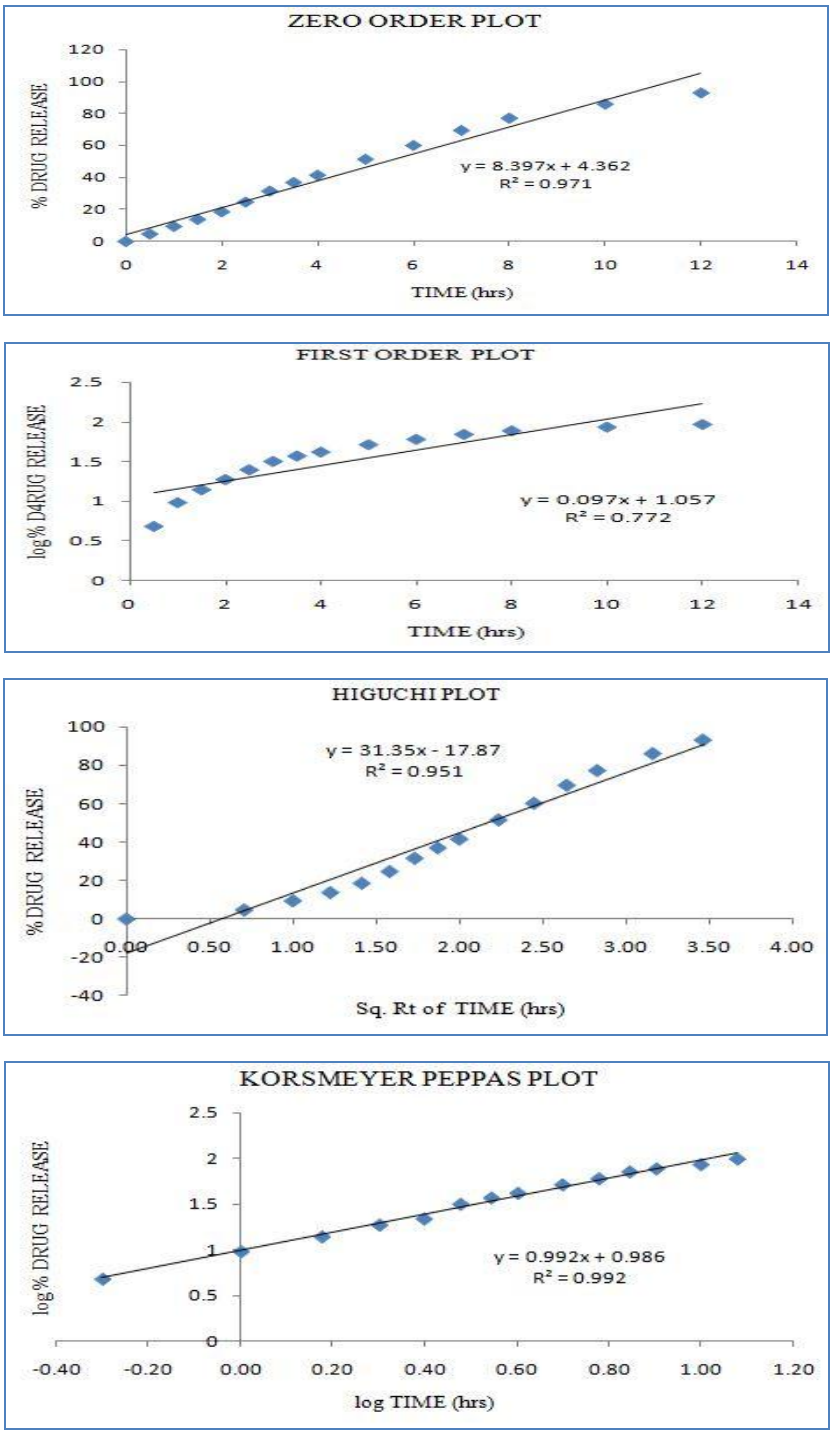

Fig-4: Kinetic plots for optimized formulation (F_{14}) containing 35% of Eudragit RL-100

FTIR (Drug- Excipient compatibility Studies)

The interaction study between the drug and optimized formulation was evaluated using Fourier Transform IR spectrophotometer. Similar peaks were observed in the optimized formulation and drug, along with absence of interface peaks indicating there is no unwanted reaction between metoprolol succinate and other excipients used in the study.

Table. 10: FTIR studies of optimized formulation (F_{14}) containing 35% of Eudragit RL-100.

Functional Group	Observed Functional group peak in drug	Observed Functional group peak in tablet
O-H	1020	1020
C-N	1300	1313
CH3-O	2852	2852
N-H Bending	1612	1610
C-H (Aliphatic)	2922	2922
C-H (Aromatic)	3044	3128

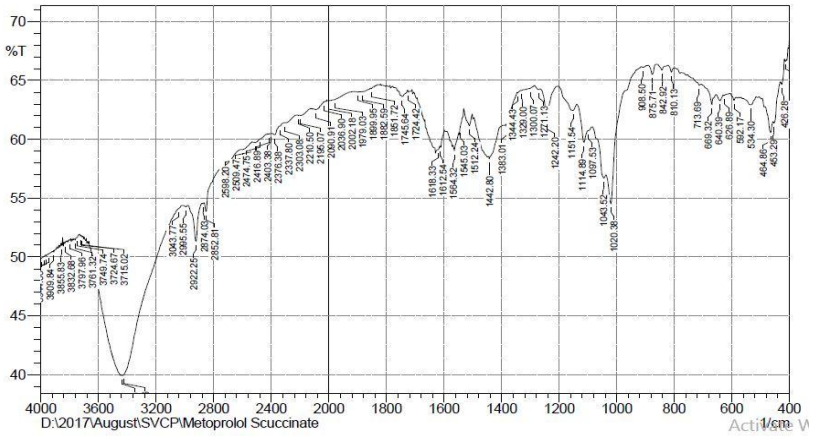

Fig. 5: FTIR studies of Drug.

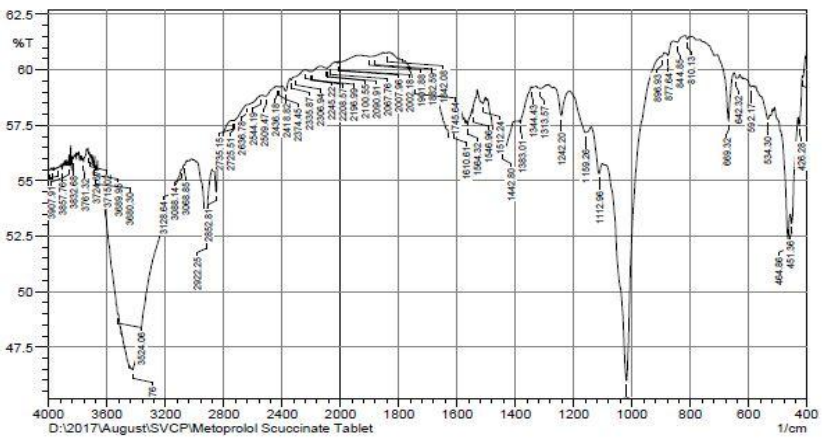

Fig. 6: FTIR spectra of MS formulation F14.

Stability studies

Stability studies of the optimized formulation F_{14} are done as per the ICH guidelines for 3 months at 25ºC and 60% RH and the drug was found to be stable after 3 months. The formulation was tested for drug content, hardness and friability. There was not much change in drug content and hardness at the end of three months. The results from stability studies are shown in the **Table.11**.

Table. 11: Stability studies data of optimized formulation (F_{14}).

Duration of period	Drug content (%)	Hardness test (kg/cm^2)	Friability (%)
Initially	**103.77**	**4.9**	**0.47**
First month	**103.50**	**4.85**	**0.47**
Second month	**103.39**	**4.81**	**0.48**
Third month	**103.15**	**4.77**	**0.50**

CONCLUSION

Metoprolol succinate, β-1 selective adrenergic receptor blocking agent used in the management of hypertension, Observations of all the formulations for physical characterization have shown that the formulations show optimum results. The formulated matrix tablets were evaluated for different parameters like thickness, hardness, friability, weight variation, drug content and *in vitro* drug release studies. Among the formulations studied the optimized formulation F14 containing 35% of Eudragit RL-100 showed 93.14% release of drug for 12hrs. The drug release from the best selected formulation sustained for 12hrs and data fitted to Peppas equation indicated anomalous Non-Fickian diffusion (case II transport) suggesting that drug release is mainly through swelling/erosion mechanism.

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