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FORMULATION AND EVALUATION OF METOPROLOLOL SUCCINATE SUSTAINED RELEASE MATRIX TABLETS USING HPMC 100000 AND STEARIC ACID

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ABSTRACT

The objective of this study was to design and evaluate oral sustained drug delivery system for Metoprolol Succinate 50 mg, 100 mg, and 200 mg using hydrophilic polymers such as HPMC 100000 and hydrophobic excipient such as stearic acid. five batches were prepared by using Metoprolol Succinate 50 mg and HPMC 100000 in drug: polymer ratio of 1:0.5, 1:1, 1:1.5, 1:2, 1:2.5, and five batches were prepared by using Metoprolol Succinate 100 mg, HPMC 100000 and stearic acid in ratios : 1:2.5:0, 1:2.5:0.25, 1:2.5:0.5, 1:2.5:0.75, 1:2.5:1.and five batches were prepared by using Metoprolol Succinate 200 mg, HPMC 100000 and stearic acid in ratios : 1:2.5:0, 1:2.5:1, 1:2.5:1.25 1:2.75:1, 1:3:1. Matrix tablets were prepared by wet granulation method and evaluated for weight variation, content uniformity, friability, hardness, thickness and in vitro dissolution. Among the formulations studied, formulation F5 containing Metoprolol Succinate 50 mg and HPMC 100000 in drug: polymer ratio of (1:2.5) showed sustained release of drug for 10 h with cumulative percent release of 55% , formulation F6/4 Metoprolol Succinate 100 mg, HPMC 1000000 and stearic acid in ratio: (1:2.5:1) showed sustained release of drug for 10 h with cumulative percent release of 47,8%, formulation F7/4: Metoprolol Succinate 200 mg, HPMC 1000000 and stearic acid in ratios: (1:3:1) showed sustained release of drug for 10 h with cumulative percent release of 48,2%. Formulations with standard specifications were subjected to stability studies according to ICH Q1A guidelines. It was found that most of the formulations prepared conform to

compendial specifications and there was no significant change in active content and dissolution profile in the accelerated stability studies.

INTRODUCTION

Oral drug delivery is the largest and oldest segment of the total drug delivery market. It is the fastest growing and most preferred route for drug administration and the most convenient, widely utilized for both conventional and novel drug delivery systems, preferred route of drug delivery for systemic action.[1,2] Tablets are the most popular oral solid formulations available in the market and are preferred by patients and physicians. There are many obvious reasons for this, not the least of which would include acceptance by the patient and ease of administration. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages.[3,4,5] However, when administered orally, many therapeutic agents are subjected to extensive pre systemic elimination by gastrointestinal degradation and/or first pass hepatic metabolism as a result of which low systemic bioavailability shorter duration of therapeutic activity and formation of inactive or toxic metabolites.[2,4,6] The goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. Extended drug delivery systems are used in the treatment of chronic rather than he acute condition, and they process a good margin of safety.[7,8,9,10] Use of hydrophilic matrices for oral extended release of drugs is common practice in the pharmaceutical industry, Hydrophilic matrix formulation is one of the least approach for developing extended release dosage forms to allow at least a twofold reduction in dosing frequency or patient compliance when compared to conventional immediate release dosage form.[7,11,12,13]

Metoprolol Succinate: Metoprolol Succinate ((±)-1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2- propanol Succinate (2:1) Molecular Formula is (C15H25NO3)2• C4H6O4.

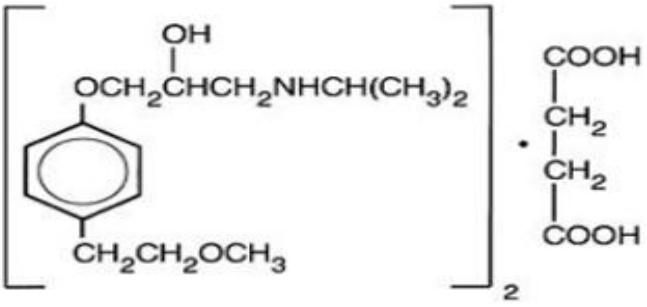

Figure 1: Metoprolol succinate.

Metoprolol Succinate a cardio selective beta-blocker. It is used in the management of hypertension, angina pectoris, cardiac arrhythmias and myocardial infarction. According to the Biopharmaceutical classification system (BCS) Metoprolol Succinate comes under class I drug means that highly soluble and highly permeable. It is rapidly and completely absorbed but due to extensive first pass effect, it is bioavaiable only 50% after oral administration. Due to its short half life (3-7 hrs) drug should be administed 4 times daily.[14,15] Whenever dose is missing leads to nocturnal attack, Therapeutic level of β1 (beta 1) blockage occurs when plasma concentration is 80-300 nM. Immediate release dosage forms increase the plasma concentration above 300nM leads to more β2 (beta 2) blockage and little β1 blockade. For maintaining the therapeutic concentration and eliminating the fluctuation in plasma concentration Metoprolol Succinate is suitable agent for controlled drug delivery.[13,14] Many studies of extended-release Metoprolol tartrate tablets were formulated and developed using hydrophilic polymers such as Hydroxylpropyl methyl cellulose, Ethyl cellulose N 50, Methocel k100m Eudragit NE guar gum, Xanthan gum , Tragacanth gum as release retardants The purpose of these studies was to evaluate the influence of formulation variables (ratios of polymer on drug release from tablets.[11,12,15,16,17,18,19,20] or formulated using Eudragit NE as binder for Metoprolol fluid bed Granulator. Eudragit NE 40D is an aqueous dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate used for modified-release drugs.[19] other studies design and evaluate oral sustained drug delivery system for Metoprolol Succinate using hydrophilic polymers such as HPMC K4M and HPMC K100M, hydrophilic Ethylcellulose, natural and synthetic polymer using natural hydrophilic gums such as Xanthan Gum, Guar Gum, Pectin and Carrageenan as a release modifier.[21,22,23,24] Siddique et al (12) developed sustained release capsules containing coated matrix granules of metoprolol tartarate . Niharika et al .[25] evaluated formulations of Bi-layer tablets of Metoprolol Succinate Extended Release and Hydrochlorthiazide Immediate Release using HPMC, Ethyl cellulose as polymer, Purushothaman M.[26] prepared sustained release system for Metoprolol Succinate, designed to increase its residence time in the stomach without contact with the tablets achieved through the preparation of floating tablets by the direct compression method, Quinten et al.[27] prepared Sustained-release matrix tablets based on Eudragit RL and RS were manufactured by injection moulding; The influence of process temperature; matrix composition; drug load, plasticizer level; and salt form of Metoprolol tartrate , fumarate and Succinate on ease of processing and drug release were evaluated.

OBJECTIVE

The aim of this investigation was to develop and optimize Metoprolol Succinate 50 mg, 100 mg and 200 mg for extended release tablets using hydrophilic polymers such as HPMC 100000 and hydrophobic base Stearic acid. The sustained release matrix tablet of Metoprolol was prepared by wet granulation technique using Hydroxypropyl methylcellulose, and Stearic acid at variable concentrations. Extended release matrix tablet of Metoprolol Succinate were formulated with different combinations of polymers (Hydroxyl propyl methyl cellulose HPMC 100000) and HPMC 100000 with stearic acid by wet granulation method. The formulated tablets were subjected to Thickness, Weight variation test, Hardness test, Friability test and Drug content. Invitro dissolution studies carried out in 6.8 phosphate buffer using apparatus Type 2 (paddle) as described in the USP dissolution monograph To evaluate the influence of formulation variables (levels of HPMC100000 and levels of HPMC100000 with stearic acid on drug release during a period of time of 10 hours.

MATERIAL AND METHOD

Materials: Metoprolol Succinate was obtained from Aarti drug Laboratories Ltd Thane, India. Hydroxy propyl methyl cellulose 100000 cp was obtained from Farmasino pharmaceuticals (JIANGSU). Stearic acid was obtained from Echo chem, SDN BHD Selangor Malaysia. Talc was obtained from euro Minerals GmbH. Anhydrous calcium hydrogen phosphate was obtained from Angel yeast Co., LTD. pharmacy filial. PVP K30, Sodium Stearyl Fumarate were obtained from MSN Laboratories Ltd India.

Method: Formulations study: hydroxypropyl methyl cellulose (HPMC 100000) hydrophilic matrix and stearic acid hydrophobic matrix was used to prepare extended-release dosage forms with Metoprolol Succinate, Dibasic calcium phosphate was used as carrier and filler, povidone K-30 as binding agent Sodium stearyl fumarate and talc was used as lubricants. Different formulations were prepared by wet granulation method formulations are given in table 1.2.

The amount of drug was kept constant at 50mg/tablet. HPMC 100000 was used with variable amounts (25 , 50, 75, 100, and 125 mg per tablet) the tablet formulations are given in table 1,The final tablet weight was adjusted to 300mg by adding Dibasic calcium phosphate as filler. After getting the best formulation for tablets of 50 mg with weight of 300 mg, this formulation is adopted to prepare and study tablets of 100 mg Metoprolol Succinate with 12

mm diameter and 600 mg weigh, t also tablets of 200 mg Metoprolol Succinate with caplet shape.

Granulation Method and Preparation of tablets: Wet granulation technique was applied for formulation of tablets by using excipients such HPMC 100000, and Dibasic calcium phosphate sifted through sieve 40 mesh. The sifted materials were mixed thoroughly into Erweka blender, PVP K30 dissolved in Isopropyl alcohol was added with constant mixing for granulation. The wet mass was passed through sieve 25 mesh and the obtained granules was dried for 2 hrs in an oven at 40 c°

When using stearic acid in the tablet formulations (table 2). we dissolved stearic acid by ethanol and added to mortar containing the mixture of powder (Metoprolol Succinate , HPMC 100000, and Dibasic calcium phosphate) The thick slurry that formed was kneaded for 10 min and then dried at 45 °C. The dried mass was pulverized and sieved through sieve 25 mesh.), the result powder is granulated again with alcoholic solution of PVP and dried at 45 °C. The dried mass was pulverized and sieved through sieve 25 mesh, Finally talc and Sodium stearyl fumarate was mixed for lubrication and Gliding of granules. The obtained granules were compressed with rotary tablet press (Cadmach, Ahmadabad, India using punches and dies 8.5mm, 12 mm round and caplet, for preparation tablets weight 300 mg, 600 mg, 1200 mg.

Table 1: Compositions for different formulations using hydrophilic polymers hpmc.

	Formulation code					
Ingredient	F1	F2	F3	F4	F6	F7
Metoprolol	50	50	50	50	100	200
HPMC100000	25	50	75	100	200	400
Dibasic calcium phosphate	203	176	153	128	256	512
PVP	16	16	16	16	32	64
alcohol Isopropyl	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
fumerat Sodium stearyl	2	2	2	2	4	8
Talc	4	4	4	4	8	16
Total weight	300	300	300	300	600	1200

Table 2: Compositions for different formulations using hydrophilic polymer HPMC + hydrophobic excipient: Stearic acid.

Ingredient	Formulation code									
	F6	F6/1	F6/2	F6/3	F6/4	F7	F7/1	F7/2	F7/3	F7/4
Metoprolol	100	100	100	100	100	200	200	200	200	200
HPMC100000	200	200	200	200	200	400	400	400	500	600
Dibasic calcium phosphate	256	231	206	181	156	512	312	262	212	112
Stearic aced	-	25	50	75	100	-	200	250	200	200
PVP	32	32	32	32	32	64	64	64	64	64
Isopropyl Alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Sodium stearyl fumerat	4	4	4	4	4	8	8	8	8	8
Talc	8	8	8	8	8	16	16	16	16	16
Total weight	600	600	600	600	600	1200	1200	1200	1200	1200

The tablets were evaluated for various parameters such as thickness Hardness, Weight variation, friability, In Vitro Dissolution Study and Stability study.

Control the thickness of the tablets: The thickness of 20 tablets was measured individually using a micrometer calibration sensitivity 5 micron, average of twenty measurement and standard deviation was calculated. the measure the thickness of the manufactured tablets is very important because it is directly reflected on the disintegration time and dissolution rate of the tablet and their mechanical resistance and on the size of the containers needed for their packaging

Weight variation test: Twenty tablets were selected randomly from each formulation and individually weighed accurately on electronic balance (Shimadzu, Japan) and their average weight and deviations from average weight were calculated should be within the permissible.

Friability: The Friability of ten tablets was determined using Pharmatest FriabilityL9. This device subjects tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at the height of 6 inches in each revolution. Pre-weighed sample of tablets was placed in the friabilator and was subjected to 100 revolutions dedusted and reweighed. The friability (F) is given by the formula:

Friability (%) = (Wo-W) / WX100

Where, W0 is the weight of the tablets before the test.

W is the weight of the tablet after the test

Hardness test: The hardness of the tablets was determined using Hardness ERWEKA L90 tester. It is expressed in kgf. Ten tablets were randomly picked and hardness of the same

tablets from each formulation was determined. The mean and standard deviation values were also calculated 10 tester. Mean and standard deviation were computed and reported.

Drug content: Twenty tablets were randomly selected from each batch and crushed into powder, the quantity of powder equivalent to 50 mg Metoprololol Succinate was weighed and dissolved in mobile phase and diluted to 100 ml, the solution is filtered through 0.45 micron, then diluted. Drug content was determined using HPLC as described below.

In vitro drug release kinetics: A dissolution study was carried out in 900 ml of the dissolution medium (Phosphate buffer of pH = 6.8 was placed in the vessels of the dissolution apparatus USP (type II). The dissolution medium was equilibrated to 37 ± 0.5 °C, and the paddle speed set to 50 revolutions per minute. one tablet were placed in each of the vessels of the dissolution apparatus and operated at the specified rate. At specified time intervals of 1, 2, 4, 6, 8, and 10 hrs, 5 ml samples were withdrawn from dissolution medium and 5 ml of fresh dissolution medium was added to the beaker.

Stability study: The optimized formulations were put in blister: pvc/ aluminium and subjected to Stability studies test as per ICH Q1A guidelines: Optimized formulations were kept in humidity chamber maintained at 40 ±2°C and 75± 5% RH relative humidity (RH) for 3 months. Formulations were analyzed for Drug content, organoleptic color characteristics, thickness, hardness, disintegration time, weight variation and In Vitro Drug release kinetics.

RESULTS AND DISCUSSION

The drug content was determined by Agilent High Performance liquid chromatography, HPLC with auto sampler and UV-visible detector provided with Symmetry C18 column (250×4.6mm, packed with 5µm)GL science with Ultra sonic bath for mixing and eliminating gases.

Chromatographic conditions

The flow rate of the mobile phase was 1.0ml/min.

Detection was monitored at wavelength 220 nm. The column temperature was kept at ambient and Injection volume was 40 µl.

Mobile phase: Acetonitril: buffer (330: 660)

The buffer is prepared from 50 ml of 1 M monobasic sodium phosphate and 8.0 ml of 1 M phosphoric acid, diluted with water to 1000 ml, adjusted if necessary with phosphoric acid 1 M or potassium phosphate 1 M to a PH of 3.0.

Standard stock solution

Accurately weighed 50 mg Metoprolol Succinate working standard transferred into a 100 ml clean dry volumetric flasks, added about 70 ml of mobile phase (or dissolution medium in case of dissolution) and sonicated to dissolve it completely and make volume up to the mark with the same solvent. Calibration standards were prepared by appropriately mixed and further diluted stock standard solutions in the concentration range from 0.01-0.06 mg/ml for assay and from 0.0025-0.06 mg/ml for dissolution. Samples in triple injections were made for each prepared concentration. Peak areas were plotted against the corresponding concentration to obtain the Linearity graphs.

Standard dilution

1 ml of standard stock solution is transferred into a clean 10 ml volumetric flask and made up to the mark with same solvent.

Linearity and range

Linearity of the method was studied by the injecting the mixed standard solutions with the concentration range from 0.010mg/ml- 0.06 mg/ml for the assay and range from 0.0025 mg/ml -0.06 for the dissolution for Metoprolol Succinate levels of target concentrations were prepared and injected three times into the HPLC system keeping the constant injection volume. The peak areas were plotted against the concentrations to obtain the linearity graphs.

Table 3: Shows precision, accuracy, method of analysis of Metoprolol Succinate with calculated concentrations of the standard chain.

Concen-tration	0.010 mg/ml	0.020 mg/ml	0.030 mg/ml	0.035 mg/ml	0.040 mg/ml	0.045 mg/ml	0.05 mg/ ml	0.055 mg/ml	0.060 mg/ml
Y1	55.5	113.5	161.2	186.8	213	235.3	264.9	287	319.1
Y2	55.7	113.4	161.1	186.1	214	235.5	264.9	288	320.7
Y3	55.6	113.45	161.15	186.45	213.5	235.4	264.9	287.5	319.9
Average	55.6	113.45	161.15	186.45	213.5	235.4	264.9	287.5	319.9
RSD %	0.1798	0.0440	0.0310	0.1877	0.2341	0.0424	0	0.1739	0.2500

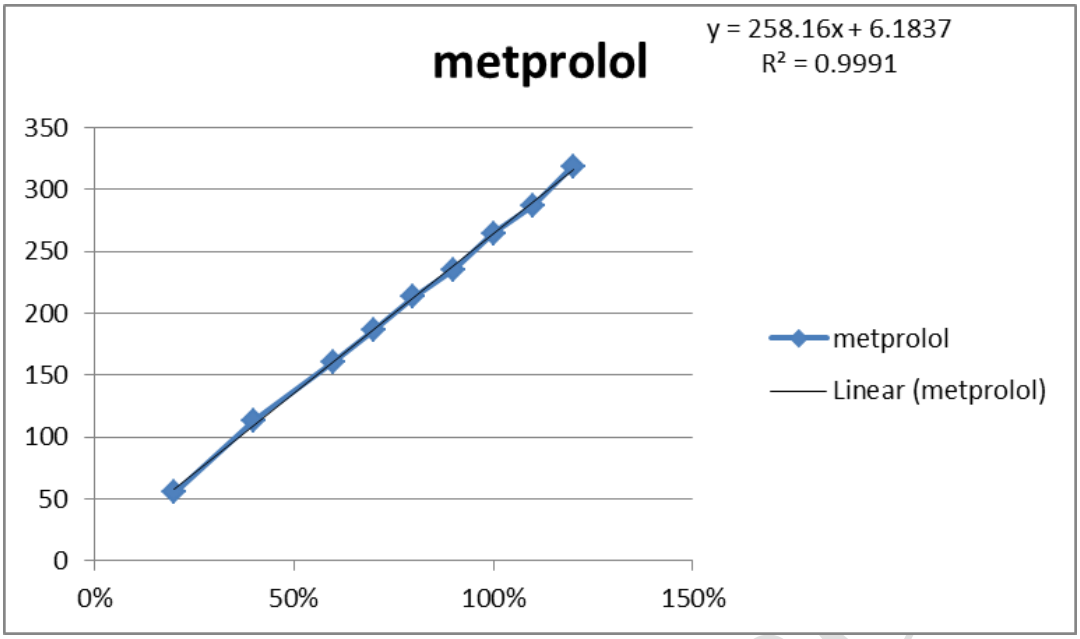

Figure 1: Linear relationship between theoretical and calculated concentrations of the standard series of assay.

The standard deviation and the relative standard deviation of the studied concentrations of samples were calculated, and it was found that the relative standard deviation was between RSD % = 0 - 0.2500. Regression coefficient was calculated in the representative figure of these concentrations, so R^2 =0.9991, and the regression equation for this line was determined. Y = 258.16 x + 6.1837 R^2 = 0.9991 .

Table 4: Shows precision, accuracy, method of the dissolution of Metoprolol Succinate with calculated concentrations of the standard chain.

Concen-tration	0.0025 mg/ml	0.005 mg/ml	0.010 mg/ml	0.015 mg/ml	0.020 mg/ml	0.025 mg/ml	0.030 mg/ml	0.035 mg/ml	0.040 mg/ml	0.045 mg/ml	0.05 mg/ml	0.055 mg/ml	0.060 mg/ml
Y1	102.5	182.9	357.7	583.8	706.1	857	1034.6	1224.6	1401.7	1585.7	1779.5	1978.9	2196.5
Y2	102.8	184.6	361.3	588.8	707.6	854.9	1034.2	1225.6	1402.5	1586.1	1781.3	1981.5	2187.3
Y3	102.65	183.75	359.5	586.3	706.85	855.9	1034.4	1225.1	1402.1	1585.9	1780.4	1980.2	2191.9
Mean	102.65	183.75	359.5	586.3	706.85	855.93	1034.4	1225.1	1402.1	1585.9	1780.4	1980.2	2191.9
CV (%)	0.1193	0.3776	0.4088	0.3481	0.0866	0.1002	0.0157	0.0333	0.0232	0.0102	0.0412	0.0536	0.1713

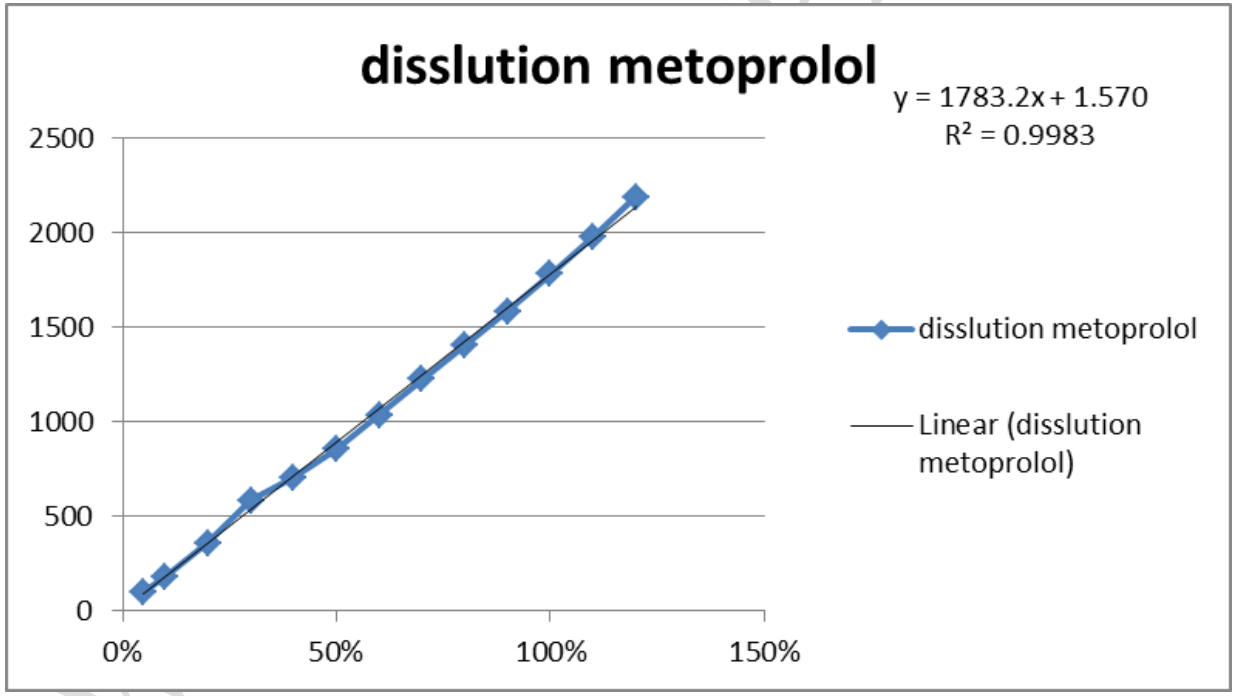

Figure 2: Linear relationship between theoretical and calculated concentrations of the standard series of dissolution.

The standard deviation and the relative standard deviation of the studied concentrations of samples were calculated, and it was found that the relative standard deviation was between RSD % = 0.0102- 0.4088. Regression coefficient was calculated in the representative figure of these concentrations, so R^2 =0.9991, and the regression equation for this line was determined.

Y = 1783.2 x + 1.57 R^2 =0.9983

Evaluation parameters of compressed tablet of metoprolol succinate

All tablets were evaluated for various parameters such as thickness, hardness, Weight variation, friability, In Vitro Dissolution Study and Stability study.

The details of physicochemical properties with a standard deviation of tablets manufactured using hydrophilic polymers HPMC100000 are given in table 5: all the formulations of Metoprolol 50 mg with diameter of 8.5 mm showed uniformity in thickness and weight variation. The thickness was in range of 4.38±0.04 mm to 4.61±0.13, the weight was in range of 298.09±2.43 to 312.80±1.39. In the present study, the friability for all the formulations was below 0.5 % in range of % (0,121-0.397). The hardness was 6.35±0.52 to 6.85±0.48. Good uniformity in drug content was found among different batches of tablets and percentage of drug content was more than 98.2±0.79 it was in range of (98.2±0.79 -103.2±0.78 %).

The details of physicochemical properties with standard deviations of Metoprolol 100 mg, 200 mg tablets are given in table 6. Tablets are prepared using formula with acceptable dissolution rate (formula F5). Metoprolol 100 tablet was in diameter of 12 mm and 200 mg was of caplet shape. All the tablet containing 100 mg and 200 mg showed acceptable properties for weight variation, thickness, drug content, hardness and friability were within acceptable official USP limits.

Table 5 : Parameters of compressed tablet of metoprolol succinate.

Formulations	Thicknesses mm	Weight Variation	(Friability% ± 0.5)	Hardness (kg)	Drug Content %
F1	4.52±0.02	312.80±1.39	0.127	6.35±0.52	99.4±0.52
F2	4.46±0.03	310.21±2.12	0.210	6.55±0.88	101.7±0.44
F3	4.61±0.13	308.33±1.45	0.311	6.55±0.65	98.2±0.79
F4	4.38±0.04	310.80±1.63	0.221	6.85±0.48	102.6±0.88
F5	4.52±0.03	298.09±2.43	0.121	6.35±0.55	101.1±0.59
F6	6.42 ±0.02	610.05±4.51	0.397	12.8 ±0.7	100.5±0.50
F7	6.55±0.03	1216.37±3.89	0.33	14.05±0.6	103.2±0.78

Table 6: Parameters of compressed Tablet of Metoprolol Succinate.

Formulations	Thicknesses mm	Weight Variation	(Friability% ± 0.5)	Hardness (kg)	Drug Content %
F6	5.42 ±0.02	610.05±4.5	0.39	12.8 ±0.7	100.5±0.50
F6/1	5.46±0.03	610.21±2.1	0.28	12.5±0.8	101.7±0.44
F6/2	5.61±0.13	608.33±1.4	0.26	13.9± 0.6	98.2±0.79
F6/3	5.48±0.04	615.80±1.6	0.26	12.85±0.4	102.6±0.88
F6/4	5.52±0.03	628.09±2.4	0. 33	12.1±0.55	101.1±0.59
F7	6.35±0.03	1216.37±3	0.33	14.5±0.6	103.2±0.78
F7/1	6.45±0.03	1216.37±3	0.35	12.85±0.	103.2±0.78
F7/2	6. 55±0.03	1231.4±3	0.43	18.8±0.8	98.9±0.65
F7/3	6. 60±0.03	1248.44±2	0.49	16.8±0.4	99.9±0.65
F7/4	6. 65±0.03	1242.44±3	0.35	17.88±0.4	98.9±0.59

In-Vitro drug dissolution studies

Dissolution studies were performed as mentioned in the experimental methods and the results were tabulated below in tables.[7,8,9]

Formulations containing HPMC 100000 with increasing concentrations (Table 1) show that the F1, F2, F3, and F4 formulations had decreased drug release with an increased HPMC ratio. Rapid release of the tablets were outside the USP limits that may be due to the low polymer level in tablets, Formula No 5 gave the required drug release. The formula F5 was considered as a model formula for preparing 100 mg and 200 mg tablets of Metoprolol Succinate (formula F6, F7). Results of liberation as shown in Table7 were found out of USP limits.

To formula F6 containing 100 mg Metoprolol Succinate, we added 25, 50, 75 and 100 mg of Stearic acid per tablet (table 2), and a study of their drug release was performed. The table shows that formulas F6/3, F6/4 containing 50 mg or 75 mg Stearic acid showed acceptable release according to USP.

The formula F6/4 was considered as a model formula for preparing 200 mg tablets of Metoprolol Succinate (coded F7/2). the results of the liberation as shown in Table 8 were found out of USP limits. Then we added to the formula F7/2 increasing percentages of Stearic acid, resulting in tablet sticking to punches of the compression machine. Therefore we used HPMC 100000 in increasing proportions, so we obtained the acceptable release given by formula F7 /4.

Table 7: Dissolution profile of metoprolol succinate compressed tablet.

Times	Cumulative percentage drug release ± 5 %							
	USP	F1	F2	F3	F4	F5	F6	F7
1h	≤25%	46	42	38	27	20	35.8	38.2
2h		60	49	43	38	27	43.5	48
4h	20-40%	76	66	56	47	34	56.5	57.9
8h	40-60%	86	76	65	58	51	67.3	70.8
10h		98	87	76	68	58	78.8	82.6

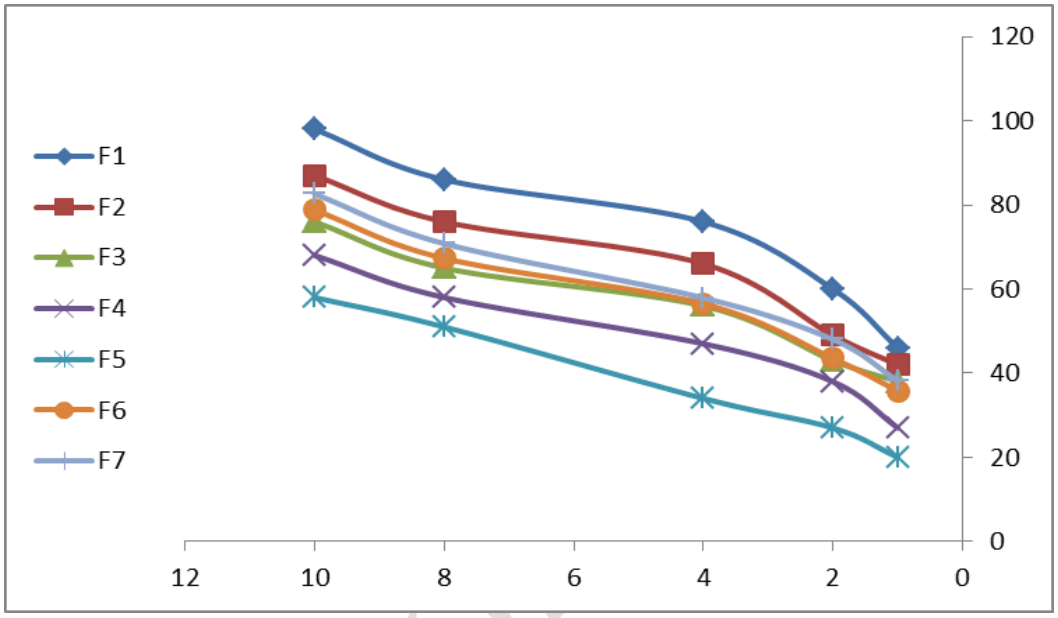

Figure 1: comparison of cumulative % drug release profiles of Metoprolol Succinate: 50,100 and 200 mg.

Table 8: Dissolution profile of Metoprolol Succinate100 compressed tablet.

Times	Cumulative percentage drug release ± 5 %					
	USP	F6	F6/1	F6/2	F6/3	F6/4
1h	≤25%	35.8	32.8	29	18	15.14
2h		43.5	40.5	36	29	22
4h	20-40%	56.5	54.9	46	35	30.7
8h	40-60%	67.3	60.3	55.5	48	38.3
10h		78.8	70.1	68	60	47.8

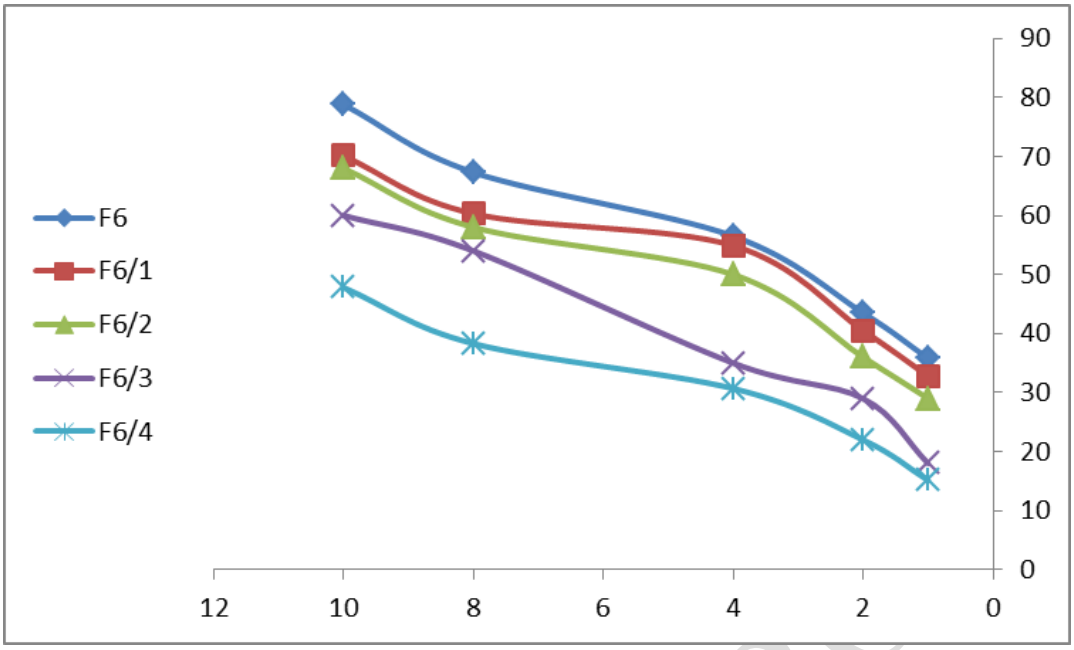

Figure 2: Comparison of cumulative % drug release profiles metoprolol succinate100 mg.

Table 9: Dissolution profile of metoprolol succinate200 compressed.

Times	Cumulative percentage drug release ± 5 %					
	USP	F7	F7/1	F7/2	F7/3	F7/4
1h	≤25%	38.2	29	23	20.14	16.6
2h		48	40	28	26.4	22.4
4h	20-40%	57.9	50.2	38.2	34.7	31.6
8h	40-60%	70.8	68	56	47.3	39.5
10h		82.6	72.4	66	59.8	48.2

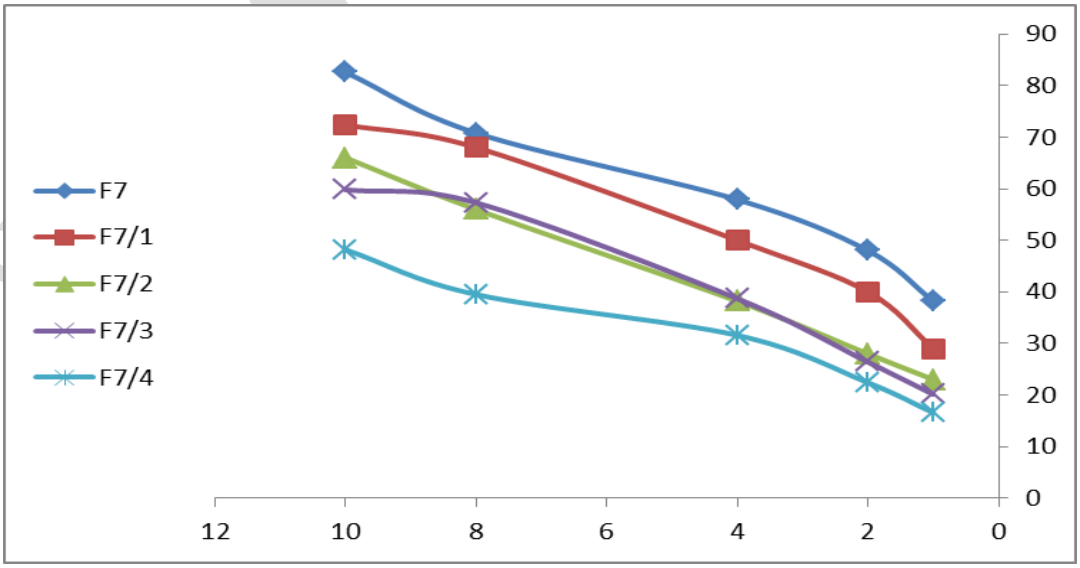

Figure 3: Comparison of cumulative % drug release profiles metoprolol Succinate 200 mg.

Accelerated stability studies of the optimized formulations

The stability studies during 3 months were shown in Table 6. Samples were analyzed for the physical changes, percent drug content and dissolutions at interval of 30, 60 and 90 days. there was no significant reduction in the content of active drug and no significant differences in in-vitro dissolution profiles of initial and accelerated stability samples of optimized formulations F5, F6/4, F7/4 up to 3 month, therefore, there were no evidence of degradation of drug during stability study.

Table 9: Cumulative percentage drug release (40°c/HR75%±5%) percentage drug release ± 5 % up to 3 month.

Times	USP %	Formulation code					
		F5		F6/4		F7/4	
		initial	40°c, RH75%	initial	40°c/RH75%	initial	40°c/RH75%
1h	≤25%	20	22,4	15.14	15.48	15.14	16.14
2h	-	27	30.8	22	22.8	22	23.1
4h	20-40%	35.7	37	30.7	31.1	30.7	32.7
8h	40-60%	51	53.2	38.3	38.3	38.3	39.9
10h	-	58	61.9	47.8	47.9	47.8	48.8

CONCLUSION

The objective of the present study was to develop an extended release tablets of Metoprolol Succinate 50, 100, 200 mg by using HPMC100000 and Stearic acid, and employing conventional wet granulation method. The best obtained formulation (F5) that contains Metoprolol Succinate 50 mg and HPMC 100000 in drug: polymer ratio of (1:2.5) showed sustained release of drug for 10 h with cumulative percent release of 55%. The formula F5 was used to prepare tablets of 100 mg and 200 mg Metoprolol Succinate (F6, F7 respectively), and found that the dissolution test of both formula F6, F7 was not comply with needed specifications, so Stearic acid was used with Formulation F5 in different proportions to get the final accepted formulations F6/4, F7/4. The formulation F6/4: Metoprolol Succinate 100 mg, HPMC 1000000 and Stearic acid in ratios (1:2.5:1) showed sustained release of drug for 10 h with cumulative percent release of 47, 8%. The optimized formulation to prepare Metoprolol Succinate 100mg F6/4 was used to prepare tablets of 200 mg Metoprolol but it was found that drug release was not acceptable.The formulation F7/4 : Metoprolol Succinate 200 mg, HPMC 1000000 and Stearic acid in ratios (1:3:1) showed sustained release of drug for 10 h with cumulative percent release of 47, 8%. There is no incompatibility between excipients used and the active substance for all formulations studied for a period of 3 months, and no degradation of the active substance appeared during

the study of stability, but the drug release increased slightly. The percent drug contained and dissolutions and were found within USP specified limit.

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