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FORMULATION AND EVALUATION OF METOPROLOL SUCCINATE CONTROLLED RELEASE TABLETS USING NATURAL AND SYNTHETIC POLYMER

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ABSTRACT

The objective of the present study to develop controlled release tablets of Metoprolol succinate using Natural polymer, guar gum and synthetic polymer, carbopol as a rate controlling polymers.. It was also desired to study the effect of polymer concentration. Metoprolol succinate, β1- selective adrenergic receptor- blocking agent used in the management of hypertension, angina pectoris, cardiac arrthymias, myocardial infarction, heart failure, hyperthyroidism and in the prophylactic treatment of migraine. The half-life of drug is relatively short approximately 4-6 hrs and in normal course of therapy drug administration is required every 4-6 hrs, thus warrants the use of controlled release formulation for prolong action and to improve patient compliance. In the present investigation Natural polymer, guar gum and synthetic polymer, carbopol have been selected as matrix forming materials for the drug. The formulations are made by employing the conventional wet granulation method, to achieve prolonged release of medicaments.

INTRODUCTION: Over the past 30 years, as the expense and complication involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained release or controlled release drug delivery systems. The attractiveness of these dosage forms is due to awareness to toxicity and ineffectiveness of drug when administered or applied by conventional dosage form of tablets, capsules, injectables, ointments etc.

Usually conventional dosage forms produce wide ranging fluctuation in drug concentration in the blood stream and tissue with consequent undesirable toxicity and poor efficiency. This factor as well as factors such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery system.

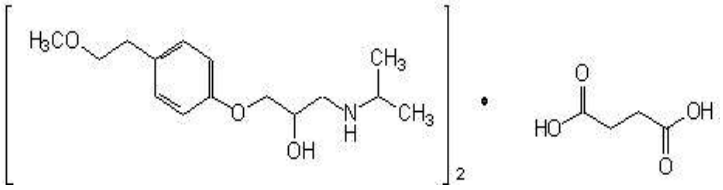
The goal in designing sustained or controlled delivery system is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery.

So, the controlled release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Controlled release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effects, increased efficacy and constant delivery.

Drug Profile:

Metoprolol Succinate: Metoprolol Succinate ((±)-1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-

propanol succinate (2:1) Molecular Formula is $(C_{15}H_{25}NO_3)_2 \bullet C_4H_6O_4$. Metoprolol succinate is a white crystalline powder. It is freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; practically insoluble in ethyl acetate, acetone, diethylether and heptane.



Metoprolol is a $beta_1$-selective (cardioselective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits $beta_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction.

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by reduction in heart rate and cardiac output at rest and upon exercise, reduction of systolic blood pressure upon exercise, inhibition of isoproterenol-induced tachycardia, and reduction of reflex orthostatic tachycardia. Prescribed dose is 25 mg to 100 mg daily in a single dose, whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. Dosages above 400 mg per day have not been studied.

MATERIALS AND METHOD:

Construction of Calibration Curve for Metoprolol Succinate: Accurately weighed 100mg of Metoprolol succinate was dissolved in methanol in a100ml volumetric flask and the solution was made up to volume with methanol.

The standard solution of Metoprolol succinate was subsequently diluted with phosphate buffer of pH 6.8 to obtain a series of dilutions containing 2, 4, 6, 8 and 10 µg of Metoprolol succinate per 1 ml of solution. The absorbance of the above dilutions was measured in Shimadzu double beam UV spectrophotometer at 275 nm using the phosphate buffer of pH 6.8 as a blank. The concentrations of Metoprolol succinate and the corresponding absorbance values are given Table 1.1. The absorbance values were plotted against concentrations of Metoprolol succinate as shown in Fig 1.1. The method obeyed Beer's law in the concentrations range of 0-10 µg/ml.

Preparation of Tablets using Guar Gum by Wet Granulation Method: Different formulations were prepared by wet granulation method. The amount of drug was kept constant at 50mg/tablet. The amount of polymer in these formulations varies from 25, 30, 35, 40, 45 and 50% w/w. The final tablet weight was adjusted to 240mg by adding lactose as filler. The different composition of the tablet formulations are given in **table 1**.

All the powders were first passed through sieve no.20. Required quantity of drug, polymer and lactose were mixed thoroughly and transferred into mortar and PVP K30 dissolved in Isopropyl alcohol was added with constant mixing. The wet mass was passed through sieve no. 10 and the obtained granules dried for 2 hrs in an oven at 40^{o}C. The dried granules were passed through a sieve no. 12. Finally magnesium stearate (1%w/w) and talc (1%w/w) was mixed for lubrication and glidant for granules. The obtained granules were then compressed with single punch tablet compression machine (Cadmach, Ahmadabad, India) using 9mm punches and dies.

Preparation of Tablets using Carbopol-934 by Wet Granulation Method: Different formulations were prepared by wet granulation method. The amount of drug was kept constant at 50mg/tablet. The amount of polymer in these formulations varies from 5, 10, 15, 20, 25 and 30% w/w. The final tablet weight was adjusted to 240mg by adding lactose as filler. All the powders were first passed through sieve no. 20. Required quantity of drug, polymer and lactose were mixed thoroughly and transferred into mortar and PVP K30 dissolved in Isopropyl alcohol was added with

constant mixing. The wet mass was passed through sieve no. 10 and the obtained granules dried for 2 hrs in an oven at 40°C. The dried granules were passed through a sieve no. 12. Finally magnesium stearate (1%w/w) and talc (1%w/w) was mixed for lubrication and Glidant for granules. The obtained granules were then compressed with single punch tablet compression machine (Cadmach, Ahmadabad, India) using 9mm punches and dies.

TABLE 1.1: FORMULATIONS OF TABLETS

Ingredients	Formulation Code											
	A1	A2	A3	A4	A5	A6	B1	B2	B3	B4	B5	B6
Metoprolol succinate	50	50	50	50	50	50	50	50	50	50	50	50
Guar gum(25-50%w/w)	60	72	84	96	108	120	-	-	-	-	-	-
Carbopol-934(5-30%w/w)	-	-	-	-	-	-	12	24	36	48	60	72
Lactose	115.6	103.6	91.6	79.6	67.6	55.6	163.6	151.6	139.6	127.6	115.6	103.6
PVP K30	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2
Isopropyl Alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium Stearate	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Talc	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8
Total Weight (mg)	240	240	240	240	240	240	240	240	240	240	240	240

Evaluation of Granules: (Table 2)

Angle of Repose: The angle of repose of granules was determined by the fixed funnel method. The accurately weighed granules were taken into a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches 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 by using the following equation:

$$\tan \theta = h/r$$

Where h = height, r = radius of the powder cone.

Bulk Density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of powder from each formulation into a 100mL graduated cylinder. After the initial volume was observed, the cylinder was fixed on the density apparatus and the time knob was set for tapping and measured the final volume after tapping. The bulk density of the powder was calculated.

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

Compressibility Index: 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 to 30% is defined as the free flowing material.

$$\text{Carr's index (\%)} = \frac{\text{TBD - LBD}}{\text{TBD}} \times 100$$

TABLE 1.2: EVALUATION OF GRANULES

Formulation code	Angle of repose (θ)	Loose bulk density (g/mL)	Tapped bulk density (g/mL)	Compressibility index (%)	Hausner's ratio
A1	23.699±0.013	0.497±0.011	0.531±0.010	6.403±0.021	1.068±0.041
A2	24.139±0.022	0.477±0.021	0.508±0.011	5.731±0.032	1.061±0.012
A3	24.546±0.011	0.458±0.042	0.486±0.021	5.761±0.041	1.061±0.011
A4	25.371±0.023	0.466±0.051	0.494±0.031	5.668±0.040	1.060±0.013
A5	26.331±0.024	0.446±0.043	0.471±0.036	5.307±0.012	1.056±0.048
A6	27.613±0.030	0.469±0.041	0.497±0.062	5.633±0.011	1.059±0.054
B1	19.093±0.020	0.458±0.013	0.485±0.053	5.567±0.010	1.059±0.062
B2	23.734±0.014	0.465±0.014	0.492±0.047	5.488±0.016	1.058±0.051
B3	24.764±0.010	0.442±0.032	0.467±0.028	5.353±0.027	1.056±0.034
B4	26.552±0.013	0.434±0.034	0.458±0.018	5.240±0.029	1.055±0.041
B5	27.463±0.011	0.428±0.041	0.451±0.016	5.099±0.031	1.054±0.010
B6	29.234±0.014	0.432±0.052	0.479±0.046	9.812±0.030	1.108±0.016

All values are expressed as Mean± SD, n=3

Evaluation of Tablets:

Thickness: The thickness of the tablets was determined by using vernier calipers. Five tablets from

each batch were used, and average values were calculated. Results were shown in table 1.3.

Hardness: Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in constant with the tablet and zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet is fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force. The results were showed in the table 1.3.

Weight Variation Test: Formulated matrix tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated by using the following formula.

$$\% \text{ Weight Variation} = \frac{\text{Average Weight - Individual Weight}}{\text{Average Weight}} \times 100$$

The Results were shown in table 1.3.

Friability: The Roche friability test apparatus was used to determine the friability of the tablets. 20 pre-weighed tablets were placed in the apparatus and operated for 100 revolutions and then the tablets were reweighed. The percentage friability was calculated according to the following formula. Results were shown in table 1.3.

$$\text{Friability (\%)} = \frac{\text{Initial wt. of Tablets – Final wt. of Tablets}}{\text{Initial wt. of Tablets}} \times 100$$

Drug Content: Twenty tablets of each formulation were collected and powdered. Powder equivalent to 100mg of Metoprolol succinate was weighed and added to 5ml of methanol and diluted with 6.8 phosphate buffer make up the volume to 100ml it was allowed to sonication for 15min. The solution was filtered and the absorbance was measured with suitable dilutions by using Shimdzu UV spectrophotometer at 275nm. Results were shown in table 1.3

TABLE 1.2: EVALUATION OF TABLETS

Formulation code	Thickness* (mm)	Hardness* (kg/cm^2)	Friability** (%)	Weight variation *** (%)	Drug content* (%)
A1	4.71±0.01	4.4 ±0.156	0.75 ±0.011	2.161±0.045	98.33±0.051
A2	4.70±0.02	4.6 ±0.114	0.88 ±0.021	2.951±0.173	98.80±0.051
A3	4.66±0.02	4.1 ±0.245	0.82 ±0.032	3.527±0.416	99.45±0.034
A4	4.72±0.02	4.3 ±0.112	0.85 ±0.010	3.367±0.174	98.23±0.069
A5	4.70±0.03	4.0 ±0.158	0.76 ±0.022	2.758±0.192	98.48±0.086
A6	4.67±0.03	4.7 ±0.312	0.72 ±0.033	4.159±0.057	98.72±0.415
B1	4.72±0.03	4.8 ±0.158	0.71 ±0.041	2.469±0.127	97.78±0.173
B2	4.71±0.02	5.0 ±0.315	0.68 ±0.054	2.494±0.066	98.59±0.173
B3	4.69±0.01	4.9 ±0.214	0.55 ±0.025	3.095±0.071	96.99±0.051
B4	4.72±0.02	4.2 ±0.132	0.81 ±0.028	2.585±0.053	99.76±0.069
B5	4.72±0.03	4.3 ±0.161	0.67 ±0.016	3.199±0.064	98.78±0.259
B6	4.69±0.03	4.5 ±0.102	0.77 ±0.019	4.151±0.053	98.14±0.219

All values are expressed as Mean± SD; * n=3; ** n=10, and *** n=2

***In-Vitro* Dissolution Study:** The *in vitro* dissolution study was carried out using USP Type II dissolution apparatus. The study was carried out in 900 mL of 0.1N HCl for first 2 hours and then 900 mL of phosphate buffer (pH 6.8) from 3 to 12 hr. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37±0.5^{o}C. The paddle was lowered so that the lower end of the stirrer was 25 mm above from the base of the beaker. The tablet was then introduced into the dissolution jar and the paddle was rotated at 75 rpm.

At different time intervals, 5 mL sample was withdrawn and analyzed by using spectrophotometrically at 275 nm, and using pH 6.8 as a blank for the drug release. At each time of withdrawal, 5 mL of fresh dissolution medium was replaced into the dissolution flask.

Infrared Spectroscopy: Infrared (IR) spectroscopy was conducted using a Shimadzu FTIR 8300 Spectrophotometer (Shimadzu, Tokyo, Japan) and the spectrum was recorded in the wavelength region of 4000 to 400 cm^{-1}. The procedure consisted of dispersing a sample (drug alone or mixture of drug and

excipients) in KBr and compressing into discs by applying a pressure. The pellet was placed in the light path and the spectrum was obtained.

TABLE 1.4: DISSOLUTION DATA OF METOPROLOL SUCCINATE TABLETS FORMULATED WITH GUAR GUM

Time	Percentage of Metoprolol Released ($\bar{x}$ ± s d)					
	A1	A2	A3	A4	A5	A6
0.5	2.003 ±0.06	1.952±0.04	1.885±0.04	1.716±0.02	1.648±0.03	1.598±0.02
1	2.621±0.04	2.503±0.08	2.418±0.06	2.248±0.02	2.130±006	1.995±0.04
1.5	3.192±0.07	3.107±0.06	2.988±0.02	2.885±0.06	2.648±0.09	2.444±0.08
2	3.834±0.12	3.748±0.03	3.662±0.08	3.542±0.04	3.326±.0.02	3.065±0.07
2.5	10.787±0.28	10.617±0.48	10.277±0.19	9.886±0.06	9.326±0.24	9.086±0.38
3	12.652±0.36	12.531±0.56	11.633±0.22	11.122±0.24	10.271±0.36	9.997±0.24
3.5	18.027±0.06	16.674±0.44	12.878±0.36	12.583±0.02	11.222±0.64	10.541±0.52
4	20.825±0.16	19.633±0.42	18.085±0.34	13.866±0.62	11.991±0.42	11.172±0.46
4.5	26.674±0.18	22.933±0.38	19.895±0.25	16.151±0.08	12.765±0.24	11.773±0.56
5	31.374±0.28	24.077±0.66	24.039±0.22	20.274±0.52	13.442±0.32	12.241±0.48
5.5	34.075±0.32	26.232±0.26	24.194±0.44	22.409±0.54	14.088±0.48	12.881±0.36
6	36.222±0.44	28.567±0.42	29.372±0.36	24.048±0.36	18.340±0.56	13.507±0.28
6.5	40.531±0.58	31.251±0.18	29.061±0.54	25.696±0.42	19.788±0.36	14.254±0.08
7	44.798±0.66	34.793±0.24	34.764±0.46	27.859±0.28	21.244±.0.42	16.769±0.12
7.5	49.762±0.24	37.679±0.08	35.988±0.42	29.358±0.32	22.820±0.22	19.220±0.52
8	54.415±0.32	40.580±0.34	42.408±0.28	31.202±0.24	24.179±0.24	20.841±0.48
8.5	58.250±0.70	44.496±0.36	43.515±0.22	33.392±0.42	25.657±0.26	22.470±0.74
9	62.778±0.12	46.764±0.48	50.812±0.24	35.088±0.54	27.312±0.28	24.108±0.64
9.5	66.824±0.26	51.061±0.24	49.108±0.34	37.636±0.36	29.144±0.24	25.585±0.56
10	69.879±.0.08	55.381±0.12	55.246±0.52	40.365±0.48	31.322±0.32	26.902±0.42
10.5	72.948±0.24	59.723±0.36	57.057±0.28	42.603±0.46	33.343±0.48	28.393±0.26
11	76.876±0.32	64.256±0.48	59.383±0.24	44.851±0.42	35.037±0.54	29.892±0.42
11.5	80.824±0.08	67.813±0.22	61.438±0.22	47.280±0.32	36.571±0.62	31.567±0.36
12	84.960±0.08	72.212±0.12	63.560±0.32	49.721±0.24	38.112±0.36	33.251±0.24

RESULTS AND DISCUSSION:

TABLE 1: CALIBRATION CURVE FOR THE ESTIMATION OF THE METOPROLOL SUCCINATE

Concentration (µg/ml)	Absorbance ($\bar{x}$ ±s d)
0	0
2	0.057 ± 0.002
4	0.108 ± 0.003
6	0.158 ± 0.003
8	0.219 ± 0.004
10	0.266 ± 0.002

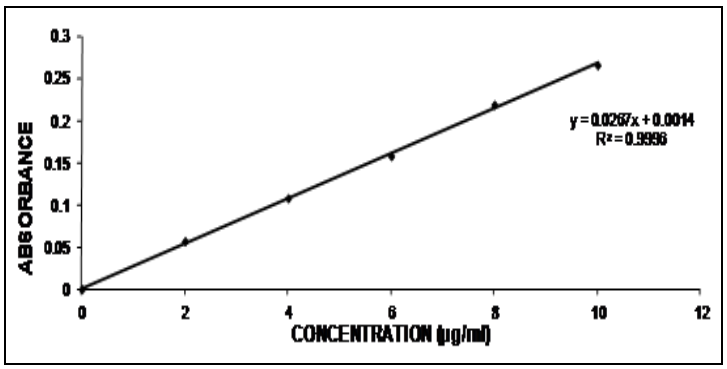


FIG. 1: CALIBRATION CURVE FOR THE ESTIMATION OF METOPROLOL SUCCINATE

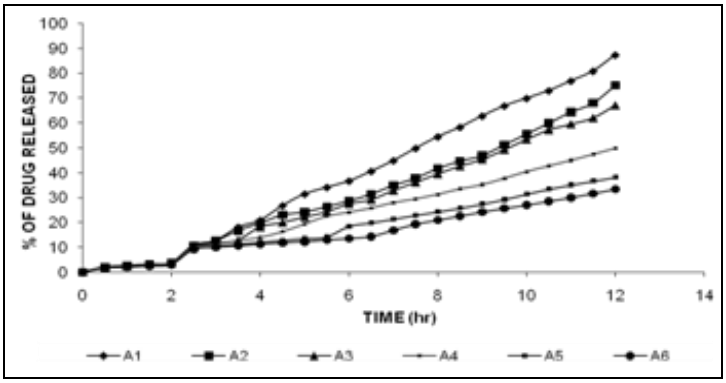


FIG. 1.2: DISSOLUTION PROFILES OFMETOPROLOL SUCCINATE TABLETS FORMULATED WITH GUAR GUM

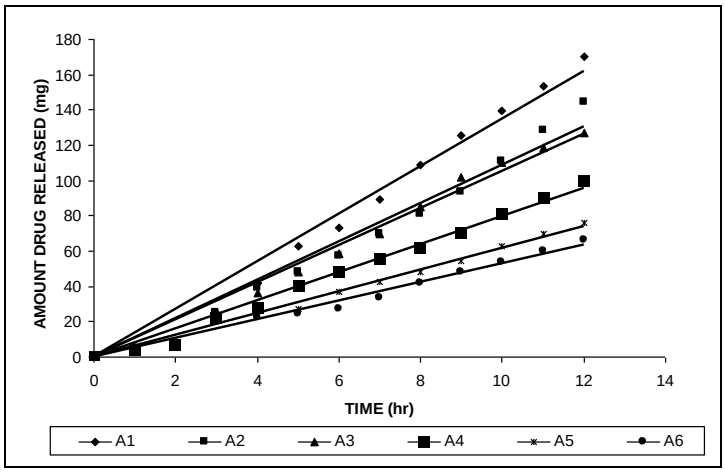


FIG: 1.3 ZERO ORDER PLOTS OF METOPROLOL SUCCINATE TABLETS FORMULATED WITH GUAR GUM

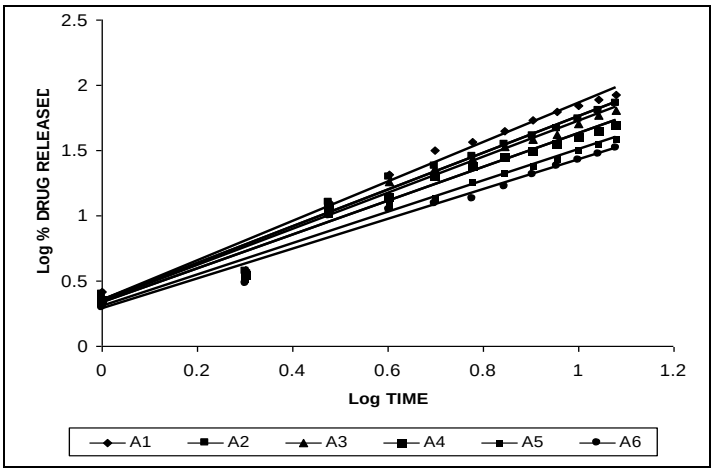


FIG: 1.4 PEPPAS PLOTS OF METOPROLOL SUCCINATE TABLETS FORMULATED WITH GUAR GUM

TABLE 1.5: DISSOLUTION KINETICS OF METOPROLOL SUCCINATE TABLETS FORMULATED WITH GUAR GUM

Formulations	Correlation coefficient				K value (mg/hr)	T_{50} (hr)	T_{90} (hr)	N
	Zero order	First order	Matrix	Peppas				
A1	0.9958	0.9311	0.8728	0.9837	6.7358	7.4	13.4	1.3788
A2	0.9858	0.9366	0.8691	0.9824	5.4095	9.2	16.6	1.2830
A3	0.9902	0.9674	0.8809	0.9828	5.2566	9.5	17.1	1.2958
A4	0.9881	0.9841	0.9007	0.9818	3.9971	12.5	22.5	1.1894
A5	0.9945	0.9868	0.9014	0.9813	3.0827	16.2	29.2	1.0965
A6	0.9903	0.9841	0.9011	0.9761	2.6472	18.9	34.0	1.0432

TABLE 1.6: DISSOLUTION DATA OF METOPROLOL SUCCINATE TABLETS FORMULATED WITH CARBOPOL-934

Time	Percentage of Metoprolol Released (x ± s d)					
	B1	B2	B3	B4	B5	B6
0.5	2.323±0.01	2.053±0.06	2.019±0.02	1.716±0.06	1.648±0.02	1.598±0.06
1	3.348±0.03	3.144±0.02	2.958±0.04	2.872±0.04	2.636±0.04	2.501±0.08
1.5	4.547±0.05	4.325±0.04	4.206±0.04	3.934±0.02	3.781±0.02	3.442±0.06
2	5.449±0.02	5.159±0.02	4.988±0.08	4.833±0.06	4.476±0.06	4.254±0.02
2.5	11.332±0.56	11.293±0.63	10.329±0.42	9.279±0.12	9.105±0.36	8.865±0.15
3	12.930±0.36	12.941±0.24	11.769±0.36	10.342±0.26	10.336±0.31	9.555±0.21
3.5	19.178±0.53	18.385±0.36	12.896±0.44	11.411±0.24	11.186±0.51	10.164±0.28
4	23.219±0.35	21.522±0.48	18.104±0.54	12.603±0.22	12.124±0.52	10.945±0.17
4.5	26.720±0.41	24.002±0.04	20.227±0.24	13.852±0.32	13.084±0.07	11.629±0.15
5	31.251±0.18	26.831±0.52	22.361±0.03	18.896±0.24	13.998±0.08	12.248±0.25
5.5	35.638±0.22	29.845±0.36	24.507±0.36	20.686±0.34	16.597±0.03	12.787±0.35
6	39.711±0.35	32.874±0.24	27.339±0.24	22.822±0.36	18.711±0.27	13.631±0.41
6.5	44.987±0.18	36.088±0.16	30.691±0.08	24.801±0.21	20.161±0.35	14.210±0.56
7	50.290±0.25	39.318±0.43	33.387±0.06	26.959±0.20	21.450±0.21	16.775±0.63
7.5	53.766±0.27	42.566±0.12	35.928±0.12	28.622±0.18	22.746±0.19	18.889±0.43
8	57.260±0.41	45.999±0.42	38.819±0.24	30.799±0.16	24.217±0.12	20.339±0.41
8.5	61.728±0.14	49.450±0.43	40.883±0.48	31.976±0.14	25.189±0.11	21.629±0.21
9	66.163±0.56	53.088±0.58	43.968±0.54	34.001±0.32	26.504±0.15	22.924±0.24
9.5	69.720±0.45	56.744±0.55	46.395±0.34	35.700±0.36	27.656±0.17	24.226±0.36
10	73.802±0.14	60.587±0.42	50.520±0.32	37.913±0.42	28.983±0.37	25.198±0.48
10.5	78.241±0.19	64.619±0.23	53.487±0.40	40.137±0.48	30.653±0.33	26.680±0.54
11	82.197±0.21	68.166±0.18	57.312±0.18	42.204±0.50	32.669±0.26	27.832±0.15
11.5	85.836±0.22	71.730±0.08	60.987±0.22	45.462±0.15	34.696±0.25	29.159±0.16
12	89.328±0.33	73.794±0.12	63.164±0.22	47.894±0.33	36.396±0.45	30.830±0.18

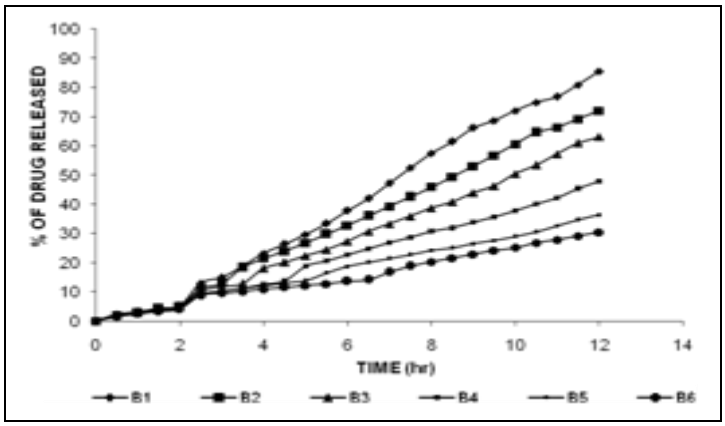


FIG: 1.5 DISSOLUTION PROFILES OF METOPROLOL SUCCINATE TABLETS FORMULATED WITH CARBOPOL-934

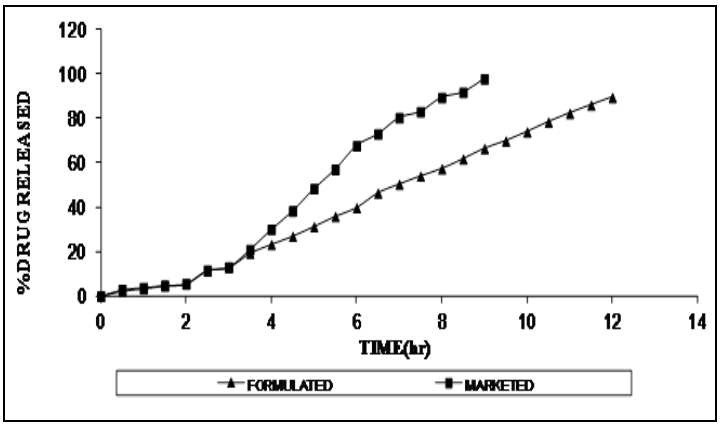


FIG: 1.8 DISSOLUTION PROFILES OF METOPROLOL SUCCINATE TABLET & MARKETED TABLET

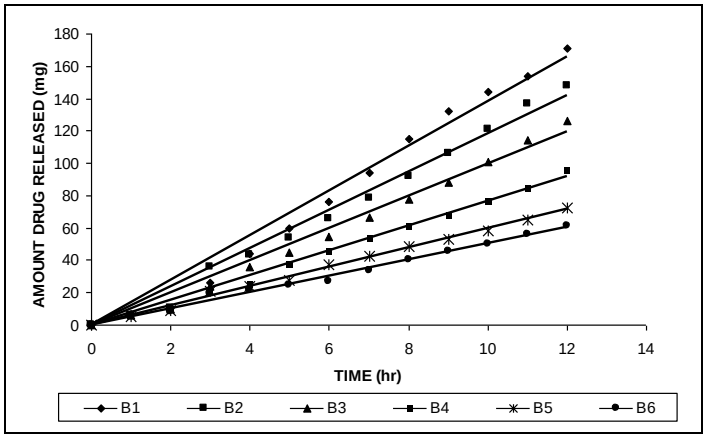


FIG: 1.6 ZERO ORDER PLOTS OF METOPROLOL SUCCINATE TABLETS FORMULATED WITH CARBOPOL-934

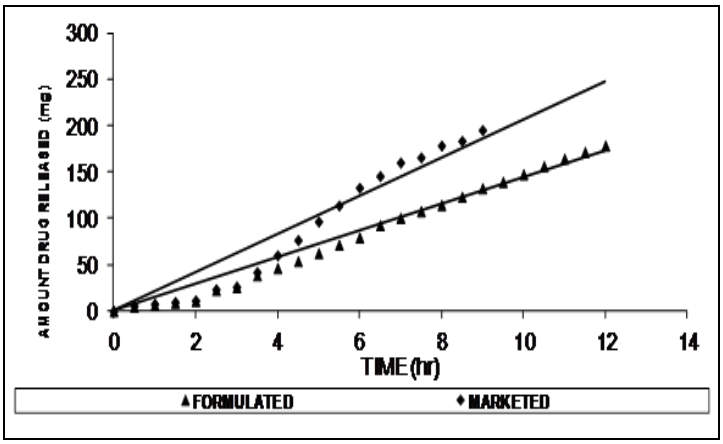


FIG: 1.9 ZERO ORDER PLOTS OF METOPROLOL SUCCINATE TABLET & MARKETED TABLET

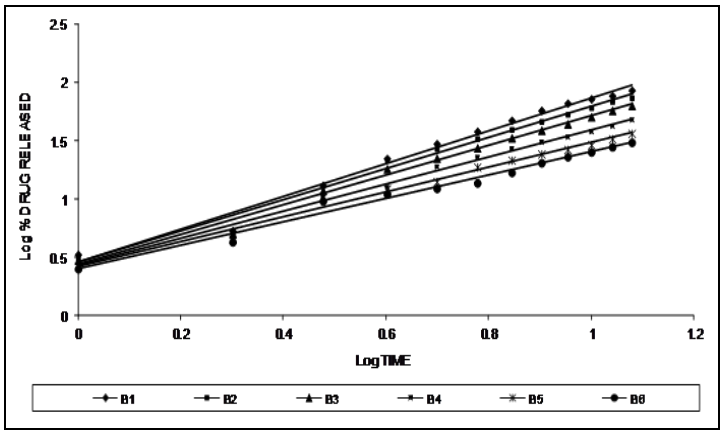


FIG: 1.7: PEPPAS PLOTS OF METOPROLOL SUCCINATE TABLETS FORMULATED WITH CARBOPOL-934

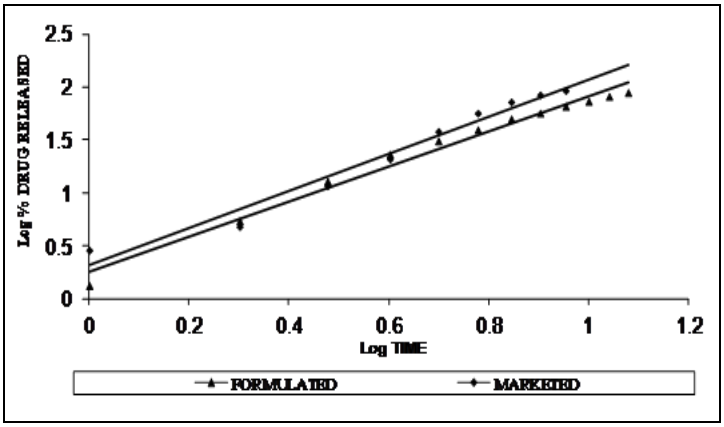


FIG: 1.10 PEPPAS PLOTS OF METOPROLOL SUCCINATE TABLET & MARKETED TABLET

TABLE: 1.7 DISSOLUTION KINETICS OF METOPROLOL SUCCINATE TABLET FORMULATED WITH CARBOPOL-934

Formulations	Correlation coefficient				K value (mg/hr)	T_{50} (hr)	T_{90} (hr)	n
	Zero order	First order	Matrix	Peppas				
B1	0.9977	0.9362	0.8758	0.9945	6.9122	7.2	13.0	1.2972
B2	0.9925	0.9518	0.8838	0.9909	5.8946	8.5	15.3	1.2460
B3	0.9922	0.9626	0.8830	0.9920	4.9423	10.1	18.2	1.1897
B4	0.9959	0.9839	0.8989	0.9880	3.8055	13.1	23.7	1.1121
B5	0.9888	0.9953	0.9233	0.9935	2.9874	16.7	30.1	1.0124
B6	0.9942	0.9918	0.9197	0.9900	2.5232	19.8	35.7	0.9551

TABLE: 1.8 DISSOLUTION DATA OF METOPROLOL SUCCINATE TABLET & MARKETED TABLET

Time (hr)	Percent of Metoprolol Released (X± S D)	
	Formulated (B1)	Marketed
0.5	2.323±0.01	2.88±0.03
1	3.348±0.03	3.823±0.05
1.5	4.547±0.05	4.806±0.02
2	5.449±0.02	5.659±0.07
2.5	11.332±0.56	11.661±0.22
3	12.930±0.36	13.024±0.31
3.5	19.178±0.53	20.931±0.35
4	23.219±0.35	29.986±0.27
4.5	26.720±0.41	38.247±0.21
5	31.251±0.18	47.239±0.18
5.5	35.638±0.22	56.937±0.11
6	39.711±0.35	67.537±0.36
6.5	44.987±0.18	72.796±0.33
7	50.290±0.25	80.107±0.10
7.5	53.766±0.27	84.902±0.19
8	57.260±0.41	89.252±0.26
8.5	61.728±0.14	93.587±0.32
9	66.163±0.56	97.643±0.25
9.5	69.720±0.45	-
10	73.802±0.14	-
10.5	78.241±0.19	-
11	82.197±0.21	-
11.5	85.836±0.22	-
12	89.323±0.33	-

DISCUSSION: The present investigation was carried out on the formulation and evaluation of oral controlled release tablets of Metoprolol succinate, which is having a short biological half-life and meant for treatment of Hypertension, Angina pectoris and Heart failure. Matrix tablets containing drug and polymer are one of the simplest approaches for controlled release of drug. In the present investigation tablets were prepared by wet granulation method. The Synthetic polymer, Carbopol and Natural polymer, Guar gum were used as a rate controlling polymers. Though they were used in the preparation of matrix tablets, the influence of polymer nature and concentration on the properties of the tablets were investigated.

Evaluation of Granules: The granules of different formulations A1, A2, A3, A4, A5, andA6 were evaluated for angle of repose, LBD, TBD, compressibility index and Hausner's ratio. The results were reported in table 1.2.

From the above studies, the results of angle of repose (<30) indicate good flow properties of the granules. This was further supported by compressibility index (<15), also Hausner's ratio (<1.25). All these results indicate that the granules having free flowing nature.

The granules of different formulations B1, B2, B3, B4, B5, andB6 were evaluated for angle of repose, LBD, TBD, compressibility index and Hausner's ratio. The results were reported in table 1.2.

From the above studies, the results of angle of repose (<30) indicate good flow properties of the granules. This was further supported by compressibility index (<15), also Hausner's ratio (<1.25). All these results indicate that the granules having free flowing nature.

Evaluation of Tablets: The results of physicochemical evaluation of tablets for the formulations A1, A2, A3, A4, A5, andA6 are shown in table 1.3.

From the above results, all the formulations showed uniform thickness, hardness of the tablets was satisfactory and the percentage friability for all the formulations was below 1% indicating that friability is within the prescribed limits. Good and uniform drug content (>98%) was observed within the batches of different tablet formulations. The results of physicochemical evaluation of tablets for the formulations B1, B2, B3, B4, B5, andB6 are shown in table 1.3.

From the above results, all the formulations showed uniform thickness, hardness of the tablets was satisfactory and the percentage friability for all the formulations was below 1% indicating that friability is within the prescribed limits. Good and uniform drug content (>98%) was observed within the batches of different tablet formulations.

***In vitro* Dissolution Studies:** The results of *in vitro* release studies for the formulations A1, A2, A3, A4, A5, and A6 in 0.1 N HCL for first 2hrs and next 3-12 hrs in 6.8 phosphate buffer. The data was depicted in table 1.4.

TABLE: 5.9 DISSOLUTION KINETICS OF METOPROLOL SUCCINATE TABLET & MARKETED TABLET

Formulations	Correlation coefficient				K value (mg/hr)	T_{50} (hr)	T_{90} (hr)	n
	Zero order	First order	Matrix	Peppas				
Formulated (B1)	0.9977	0.9362	0.8758	0.9945	6.9122	7.2	13.0	1.2972
Marketed	0.9843	0.8497	0.8318	0.9698	10.3250	4.8	8.7	1.4787

The drug release from formulations followed zero order kinetics, as the plot observed in between amount of drug released Vs time (fig. 1.3), the corresponding release rate constant values were shown in table 1.5. To ascertain mechanism of drug release from the above formulations plots log % drug released Vs log time were plotted (fig. 1.4). The release data analyzed as Peppas equation, value of 'n' was found to be in the range of 1.0432 to 1.3788 indicating that these fallow nonfickian diffusion mechanism of drug.

The above results indicated increasing concentration of Guar gum content the drug released was retarded.

The results of *in vitro* release studies for the formulations B1, B2, B3, B4, B5, andB6 in 0.1 N HCL for first 2hrs and next 3-12hrs in 6.8 phosphate buffer. The data was depicted in table 1.6.

The drug release from formulations followed zero order kinetics, as the plot observed in between amount of drug released Vs time (fig. 1.6), the corresponding release rate constant values were shown in table 1.7. To ascertain mechanism of drug release from the above formulations plots log % drug released Vs log time were plotted (fig. 1.7). The release data analyzed as Peppas equation, value of 'n' was found to be in the range of 0.9551 to 1.2972 indicating that these follow nonfickian diffusion mechanism of drug.

The above results indicating, increasing concentration of Carbopol-934 content drug release was retarded.

FTIR: The possible interaction between the Metoprolol succinate and the polymers such as Guar gum and Carbopol-934 was studied by IR spectroscopy. The IR spectra for Metoprolol succinate, Guar gum, Carbopol-934 and its physical mixtures are shown in Figure.

Pure Metoprolol succinate showed.

C-O Str (1° Alcohol) : 1045.52cm^{-1}

C-O Str in C-O-C : 1110.84 cm^{-1}

C-O Str in C=C-O-C : 1238.39 cm^{-1}

C=C Ring Str : 1563.06 cm^{-1}

N-C Str : 3147.67 cm^{-1} wave number as major peaks

In the mixture of Metoprolol succinate and Guar gum, a peak observed with pure Metoprolol succinate was present at the same range showed below.

C-O Str (1° Alcohol) : 1048.17 cm^{-1}

C-O Str in C-O-C : 1110.06 cm^{-1}

C-O Str in C=C-O-C : 1238.04 cm^{-1}

C=C Ring Str : 1562.12 cm^{-1}

N-C Str : 3151.23 cm^{-1}

In the mixture of Metoprolol succinate and Carbopol-934, a peak observed with pure Metoprolol succinate was present at the same range showed below.

C-O Str (1° Alcohol) : 1039.38cm^{-1}

C-O Str in C-O-C : 1110.70 cm^{-1}

C-O Str in C=C-O-C : 1236.81 cm^{-1}

C=C Ring Str : 1563.05 cm^{-1}

N-C Str : 3148.67 cm^{-1}

The results revealed no considerable changes in the IR peaks of Metoprolol succinate when mixed with excipients compared to pure Metoprolol succinate. These observations indicated the incompatibility of Guar gum and Carbopol-934 with Metoprolol succinate. The FTIR studies revealed that there is no interaction between drug and polymers.

CONCLUSION: The objective of the present study to develop controlled release tablets of Metoprolol succinate using Natural polymer, guar gum and synthetic polymer, Carbopol as a rate controlling polymers. The formulations were made by employing conventional wet granulation method. The granules for tablets prepared according to the formulas given, granulation is a key process in the production of dosage form involving the controlled release of a drug from matrix type particles. Micromeritic properties of granules such as angle of repose, LBD, TBD, and compressibility index for evaluated. The results were found to be within the specified limits of I.P.

The tablets of different formulations made were subjected to evaluation test, such as thickness, hardness, friability, weight variation, and drug content. The results obtained from the evaluation parameters found to be within the specified limits of I.P. The *in vitro* drug release characteristics were studied in 0.1N HCL for first 2hrs and phosphate buffer pH 6.8 for next 3-12hrs all the results were reported. The drug-polymer compatibility studies were done by FTIR spectral analysis. All the tablets were found to be within the I.P limits.

The drug and polymers were found to be compatible, the formulation A1 containing 25% Guar gum released 85% of the drug in 12hrs, while the formulation A6 containing 50% Guar gum release 30% of the drug in 12hrs.

The formulation B1 containing 5% Carbopol-934 released 89% of the drug in 12hrs, while the formulation B6 containing 30% Carbopol-934 release 37% of the drug in 12hrs.

Though both the Natural and Synthetic polymer retards the drug release, the tablets prepared using Carbopol-934(5%) require lower amount and better release than the tablets prepared using Guar gum (25%). The drug release from the formulation B1 followed by zero order kinetics and diffusion controlled mechanism (non-Fickian).

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