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Formulation and evaluation of sustained release matrix tablet of metoprolol succinate by using xanthan gum and carbopol

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ABSTRACT

Metoprolol succinate is a β1 selective antagonist used as an Anti-hypertensive, Anti arrhythmic, Anti Angina. The aim of present investigation was to develop matrix tablets of Metoprolol succinate using different polymers.Metoprolol succinate matrix tablet was prepared by use of xanthan gum and carbopol-934 as a polymer initially by direct compression methods. Physicochemical compatibility of the drug with polymer was confirmed by IR spectroscopy and DSC. Metoprolol succinate matrix tablets were prepared by direct compression and wet granulation method using different polymers. All the formulations were evaluated for weight variation, thickness, hardness, friability and dissolution. The result of matrix tablets formulation (A-4) showed drug release 94.12% in 720 min. Therefore it was concluded that formulation (A-4) containing carbopol-934 and xanthan gum in the ratio of 80:20 showing promising result for sustained release of Metoprolol succinate, further for improvement of release profile in situ interpolymeric complexes of both carbopol and xanthan gum were tried. All the formulations were evaluated for weight variation, thickness, hardness, friability and dissolution. The results of IPC formulation B-11 showed drug release 96.29% in 720 min. It was concluded that tablets were prepared by using in-situ inter polymer complex formed with 70:30 ratio of Carbopol and Xanthan gum solution as binder. Formulation B-11 showed promising result because of its resistance in pH 1.2 HCL buffer for more than 2 hrs showed the maximum sustained release as compared to simple matrix tablet because of more acid resistance of the complex. Thus, sustained release matrix tablets of Metoprolol succinate using biocompatible polymers were successfully formulated, evaluated and found to be suitable candidates in extending the release of the drug from the matrix tablets.

Keywords: Metoprolol succinate, Sustained release Matrix tablets, Direct compression, Wet granulation method.

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INTRODUCTION

The project was designed with an aim to develop and evaluate sustained release Metoprolol succinate matrix tablet which will reduce the dosing frequency and have better patient compliance and less fluctuation in plasma concentration. In this study an attempt was made to formulate and evaluate sustained release matrix tablets of Metoprolol succinate as a model drug. The main objective of formulating matrix tablets was to achieve sustained release of Metoprolol succinate for long period of time so as to maintain the plasma drug concentration constant for whole day. It also helps in decreasing the dosing frequency by the patient compliance increases. Sustained release dosage form is a modified dosage form that prolongs the therapeutic activity of the drug. Sustained release products provide an immediate release of drug that promptly produces the desired therapeutic effect which is followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period of time. The basic rationale of a sustained drug delivery system is to optimize the Pharmacodynamics and Pharmacokinetics properties of a drug in such a way that its utility is maximized through reduction in side effect and cure or control of condition in the shortest possible time by using smallest amount of drug which is administered by the most effective route. Oral route has been the most popular and widely used for sustained delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design, ease of production and low cost. Sustained drug delivery system is one of the most useful tools that providing promising approaches to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration level of the drug in the body. Sustained release drug delivery is improve patient compliance by reduction frequency of drug administration, reduction steady-state fluctuation of drug levels, increased safety margin of low therapeutic index drug, maximum utilization of the drug, reduction in healthcare costs through improved therapy and shorter treatment period. Tablets offer the lowest cost approach to sustained

and controlled release dosage forms. Matrix tablets serves as an important tool for oral extended- release dosage. Matrix tablets may be formulated by wet granulation or direct compression methods by dispersing solid particles within a porous matrix formed of hydrophilic and hydrophobic polymers.

MATERIAL AND METHODS

Chemical: The Metoprolol succinate was obtained from Swiss Garnier Life sciences, Mehatpur and Xanthan gum from Himedia Laboratories, Mumbai and carbopol-934 from Himedia Laboratories, Mumbai, Lactose CDH Laboratory Reagent, New Delhi, Microcrystalline cellulose from Central Drug House, New Delhi, Talc and magnesium stearate from Hi-Pure Rankem, New Delhi. Other ingredient was provided by institute.

Instruments: Digital weighing balance, Hot Air Oven, UV Spectrophotometer, FTIR Spectrophotometer, DSC, Sonicator, Stability Chamber, Tablet Dissolution Testing Apparatus, Monsanto Hardness Tester, Rotatory Flask Shaker. Dissolution apparatus USP11, Friabilator, Tablet disintegration apparatus, SEM, Differential Scanning (DSC), Tablet punching machine.

Methodology

Preformulation studies

Absorbance Maxima

Stock solution of metoprolol succinate was prepared by dissolving the 10 mg drug in 10 ml phosphate buffer (pH 6.8), from which get the concentration 100 µg/ml. Maximum wavelength (λmax) was obtained by scanning the solution in the wavelength region 200 nm to 400 nm using UV-Vis spectrophotometer.

Preparation of calibration curve

Standardization of Metoprolol succinate by UV-Visible spectrophotometry in 0.1N HCL Solution

Standard curve of Metoprolol succinate in phosphate buffer pH (7.4)

100mg of Metoprolol succinate was weighed accurately and dissolved in 100 ml of volumetric flask and volume was made up with the saline buffer (pH 7.4). 10ml of this solution was diluted to 100ml with saline buffer (pH 7.4) to obtain a stock solution of 100µg/ml. From this stock solution, aliquots of 0.2 ml to 1.4ml were taken transferred to 10ml volumetric flask and volume was made up to 10ml with saline buffer (pH 7.4). The absorbance of these solutions was measured at 243 nm against a blank saline buffer (pH 7.4). The absorbance of these solutions was measured at 243nm against a blank saline buffer (pH 7.4). The calibration curve was plotted between concentration and absorbance. The absorption maxima have shown in **Fig. 1.**

Drug Excipient Compatibility by FTIR studies

FTIR Spectroscopy

IR study was performed for identification and structural analysis of the procured drug using Shimadzu-1800 Fourier transformed infrared spectrophotometer (Koester et al.,2012). The potassium bromide (KBr) disk technique was employed using 100mg of spectroscopic grade dried KBr. KBr was ground under a hydraulic pressure at 10,000 psi. Mortar/pestle and drug excipients mixture were placed on the KBr disc with the help of capillary tube. Each KBr disc was scanned at a resolution of 400 cm^{-1} over the wavelength region of 4000-400cm^{-1} and characteristic bands was recorded. The FTIR has shown in **Fig. 2.**

a) Solubility determination:

Solubility is an important parameter for preformulation studies because:

1. It affects the dissolution of drug.

2. Bioavailability of drug is directly affected by dissolution and absorption of drug by oral administration.

3. Particle size, shape, surface area may affects the dissolution characteristics of drug hence it should be determined during Preformulation.

b) Melting point determination: The melting point of Active ingredients were determined by capillary method, using definite quantity of Active ingredients were taken and placed in apparatus and melting point was determined and matched with standards.

c) Partition coefficient: A major criterion in evaluation of the ability of a drug to penetrate the lipid membranes is its apparent oil/ water partition coefficient($K_{O/W}$) value . this value is a measure of the degree of distribution of the drug between lipophilic solvents and an aqueous phase.

$K = C_O/C_W$

Partition coefficient of metoprolol succinate was determined by dissolving the 10 mg drug in 10 ml mixture of n-octanol and 6.8 pH phosphate buffer at 37±0.50 C and shake for 24 hours in a separating funnel, then separate the two layers, finally calculate the partition coefficient and the value of Log P.

Differential scanning calorimetry (DSC)

DSC thermograms of pure drug (Metoprolol succinate) and drug excipients mixture with additives (Xanthan gum and carbopol) were carried out to investigate any possible interaction between the drug and the ulilized additives. The samples of 10mg were taken and heated in an open aluminium pans at a heating rate of 10^0C/min in a 30^0C to 300^0C temperature range using METTLER DSC. The DSC has shown in **Fig. 3.**

Formulation studies

Preparation of sustained release Matrix tablet

Tablet was prepared by direct compression method with xanthan gum and carbopol as polymers.

Procedure

The sustained release matrix tablet was prepared by using carbopol-934 and xanthan gum as a polymers. Metoprolol succinate tablets were prepared by direct compression method each tablet contained 50mg Metoprolol succinate and different concentration of polymers. Lactose was used as a filler and MCC as directly compress material. The drug delayed release and lactose were weight accurately and mixed thoroughly in pestle and mortar. Different ratios of carbopol-934 and xanthan gum were added to the mixture containing drug and lactose. After uniform mixing of all ingredients like microcrystalline cellulose (MCC), magnesium stearate, talc was added. The mixed powder was than directly compressed using single punching machine. The formulation of Metoprolol succinate has shown in **Table 1** and **Table 2.**

Formulation of sustained release matrix tablet by direct compression method

Matrix tablet prepared by different ratio of polymer by using different ratio of binder solution.

Preparation of solution

2% xanthan gum: 1 gm of xanthan gum was soaked overnight in 50ml in water after 10hrs. The mixture was stirred vigorously by mechanical stirrer to make suspension

2% carbopol-934 solution: 1 gm of carbopol solution was dissolved in 50ml of 2% glacial acetic acid solution with stirring occasionally until a clear solution is obtained

Preparation of inter polymer complex for matrix tablets: In situ IPC was prepared by using xanthan gum and carbopol as binder solution using wet granulation method. 50 mg of Metoprolol succinate was thoroughly mixed with other ingredients like xanthan gum and carbopol-934. The drug and lactose weight accurately and was mixed thoroughly mixed in pestle and mortar. The binder solution 2% w/v carbopol solution and 2% w/v xanthan gum in different ratio was added drop wise until a damp mass was formed. The damp mass passed through sieve no 16 and the granules were dried at 40^0c in the oven after drying MCC talc and magnesium stearate were added to the granules the mixture was then compressed by tablet punching machine. Then different ratios of both solution xanthan gum and carbopol-934 were mixed with continuous stirring to check the maximum interaction. For this different ratios were checked. Interaction increases as the concentration of xanthan gum amount in the interactions mix was increasing. Carbopol-934: Xanthan ratio with the viscosity of supernatant liquid is equivalent to water which showed that all polymeric content in the solution interacted and formed precipitates. The precipitates obtained was collected and compressed into tablet and this tablet was then checked for stability in the buffer of ph 1.2, ph7.4 and ph 6.8 for 2 hrs and 6 hrs respectively. As we found that interaction was maximum at 70:30 thus for preparation of tablet 70:30 ratio was selected. The tablet was prepared by keeping varying concentration of carbopol and xanthan gums are used for preparation of tablets.

Formulation of sustained release matrix tablet by wet granulation method

Evaluation of powder mixture and tablet characteristics:

Pre-compression studies-The powder mixture was prepared by direct compression technique. The various parameter of powder like angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio were determined before punching the tablets. The flow ability of powder mixture was found fair to good with an angle of repose 25.4^0c-33.4^0c. The results of bulk density, tapped density, tapped density, compressibility index and Hausner's ratio and compressibility index were found satisfactorily within acceptable limits. The Pre-compression data has shown in **Table 3.**

Bulk Density (D_b)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in gm/ml and is given by

$(D_b)=M/V_b$

Where, M and V_b are mass of powder and bulk volume of the powder respectively.

Tapped Density (D_t)

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes was noted. Tapping was continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2% (in a bulk density apparatus).it is expressed in gm/ml and is given by

$D_t = M/Vt$

Where M and Vt are the mass of powder and tapped volume of the powder respectively.

Compressibility Index

The compressibility index of the power was determined by Carr's compressibility index

Carr's index (%)=$\{D_t-D_b) \text{ X } 100\}/D_t$

Hausner's Ratio

Hausner's Ratio is an ease of index of powder flow .it is calculated by using the following formula Hausner's Ratio= Tapped Density/ Bulk Density

Angle of repose

Funnel method was used to measure the angle of repose of powder. The accurately weighted powders 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 powder (2.0 cm above hard surface). The powder 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:

Angle of Repose ɵ= Tan-1 H/R

Where H= Height of the powder cone.

R= Radius of the powder cone

Characterization of sustained release tablets

After compression of powder, the tablets was evaluated for physical organoleptic characteristics like colour , odor, taste, diameter, thickness, hardness, friability, and disintegration time, wetting time.

General appearance

The general appearance of a tablet, its visual identification and over all 'elegance' is essential for consumer acceptance. It includes tablet's size, shape, colour, presence or absence of an odor, taste, surface texture, physical flaws.

Thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by suing filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

Uniformity of weight

IP procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be satisfactory method of determine the drug content uniformity. The uniformity of weight has shown in **table. 4.**

Post-compression studies- the post-compression data has shown in **table 5.**

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet, the resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on hardness. Hardness of the tablet of each formulation was determined using Pfizer Hardness Tester.

Friability

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (w_0 initial) and transferred into Friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolution. The tablets were weighed again (w). The % friability was then calculated by

$F\ \% = (1-w_o/w) \times 100$

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

Wetting time

The method was followed to measure tablets wetting time a piece of tissue paper(12 cm X 10.75cm) folded twice was placed in a small Petri dish (ID=65cm) containing 6 ml of saline buffer (Ph 6.8). atablet was put on the paper, and the time for the complete wetting was measured. Three trials for each batch were performed and the standard deviation was also determined.

Content uniformity

Ten randomly selected tablets were weighted and average weight was calculated. The tablets were powdered in a glass mortar pestle. The weight equivalent to 10mg Metoprolol succinate was weighed the weighed amount was dissolved in small amount of methocel in separate volumetric flask using magnetic stirrer the volume was adjusted of 1.0 ml from these solution were diluted to 10ml saline buffer (Ph6.8) in separate volumetric flask. The content of each formulation was estimated by UV spectroscopy at 274 nm.

In vitro dissolution studies

In vitro drug release studies from the prepared matrix tablets were conducted using USP type II apparatus at 37°C at 50rpm. Dissolution mediums used were 900mL of 0.1N HCl and phosphate buffer of pH 6.8. The release rates from matrix tablets were conducted in HCl solution (pH 1.2) for 2h and changed to phosphate buffer (pH 6.8) for further time periods. The samples were withdrawn at desired time periods from dissolution media and the same were replaced with fresh dissolution media of respective pH. The samples were analysed by UV-Visible Spectrophotometer (Lab India 3000+). The amounts of drug present in the samples were calculated with the help of appropriate calibration curves. The In Vitro Figures has shown in Fig. 4 to Fig. 9.

RESULT AND DISCUSSION

Solubility

The solubility study of drug was carried out and it showed that is freely soluble water and it shows that is freely soluble in water and slightly soluble in ethanol, different buffers, dichloromethane, 2- propanol and methanol , insoluble in acetone , heptanes and diethyl ether.

Absorption Maxima (λ_{max})

The drug Metoprolol succinate was standardized by UV method in 0.1N HCl and pH 6.8 Buffer separately and 228 nm in 0.1N HCl and pH 6.8 buffer respectively and the linearity range was 5-30mcg/ml in both the media.

DSC thermogram of Metoprolol succinate (Figure 5) showed a sharp endothermic peak at 130^0c corresponding to the sharp melting point and representing its typical crystalline nature.

DSC thermogram of drug excipients mixture (Figure 6) showed endothermic peak of metoprolol succinate. This represented that there was no chemical incompatibility between drug and the excipients. The slight changes were due to mixing of drug and excipients that resulted in broader peaks

Evaluation of granules for in situ inter polymer complex (IPC)

The in vitro drug release data was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's Korsmeyer model in order to determine the mechanism of the drug release. The results of linear regression analysis data including regression coefficient r value of zero order and first order were 0.982 and 0.910.

The regression coefficient r value of Higuchi and Korsmeyer and Peppas were found to be 0.972 and 0.989.it indicated the release of drug from these formulations was governed by diffusion controlled process. The peppas model is widely used to confirm whether the release mechanism is Fickian diffusion, non-Fickian diffusion or zero order. 'n' value could be used to characterize different release mechanism. The 'n' value for first order were 0.001x and Higuchi's and Korsmeyer peppas were 3.899x and 0.720x.

When Korsmeyer et al., equation was fitted to dissolution data values, the exponent 'n' was found to be 0.813 indicating the drug release by non- fickian diffusion. The higuchi and Korsmeyer peppasplts are shown in fig. 11, fig, 12.

Stability studies

The stability study on the final formulation B-11 indicated that there was slight acceptable difference in average weight, friability, hardness, and in vitro drug dissolution after 3 month at 40^0c /75% RH. It has shown in **table 6**.

Table 1: composition for sustained release matrix tablet of Metoprolol succinate

Ingredients (mg)	A-1	A-2	A-3	A-4
Metoprolol Succinate (mg)	50	50	50	50
Xanthan gum (mg)	20	40	60	80
Carbopol-934(mg)	80	60	40	20
Lactose (mg)	5	5	5	5
MCC (mg)	70	70	70	70
Magnesium stearate (mg)	5	5	5	5
Talc (mg)	**20**	**20**	**20**	**20**

Table 2: Composition for sustained release matrix tablet of Metoprolol succinate

Ingredients (mg)	B-5	B-6	B-7	B-8	B-9	B-10	B-11
Metoprolol Succinate(mg)	50	50	50	50	50	50	50
Xanthan gum (ml)	80	80	80	80	80	80	80
Carbopol-934(ml)	20	20	20	20	20	20	20
MCC(mg)	70	70	70	70	70	70	70
Magnesium Stearate(mg)	5	5	5	5	5	5	5
Lactose (mg)	5	5	5	5	5	5	5
Talc (mg)	20	20	20	20	20	20	20
Binder solution(ml)	70:30 (q.s.)	60:40 (q.s.)	50:50 (q.s.)	40:60 (q.s.)	30:70 (q.s.)	20:80 (q.s.)	10:90 (q.s.)

Table 3: Pre-compression parameter of granules of in situ IPC for matrix tablets

Formulation	Angle of repose	Bulk density	Tapped density	Carr's index	Hausner's Ratio
B-5	33.4±0.02	0.409±0.01	0.445±0.02	10.44±0.01	1.182±0.02
B-6	28.7±0.03	0.420±0.01	0.450±0.03	12.90±0.02	1.150±0.03
B-7	24.2±0.02	0.320±0.03	0.364±0.01	13.48±0.03	1.190±0.01
B-8	26.4±0.01	0.317±0.03	0.312±0.01	14.60±0.01	1.180±0.01
B-9	28.9±0.02	0.325±0.01	0.448±0.01	13.80±0.02	1.192±0.01
B-10	27.6±0.01	0.330±0.02	0.440±0.02	13.48±0.02	1.187±0.03
B-11	28.9±0.01	0.325±0.02	0.448±0.03	13.50±0.01	1.192±0.02

Table 4: uniformity of weight

Average of tablets (mg)	Maximum % difference allowed
130 or less	10
130-324	7.5
More than 324	5

Table 5: Post-compression parameters of in situ IPC for matrix tablets.

Formulations	Thickness	Hardness	Friability	Weight Variation
B-5	4.1±0.01	4.9±0.01	0.65%	245±0.12
B-6	4.2±0.01	5.7±0.02	053%	244±0.15
B-7	4.4±0.01	5.0±0.02	0.59%	248±0.12
B-8	4.2±0.02	4.6±0.01	0.39%	243±0.14
B-9	4.8±0.01	5.6±0.02	0.68%	249±0.14
B-10	4.4±0.01	5.1±0.02	0.59%	252±0.12
B-11	4.3±0.02	5.1±0.01	0.65%	240±0.12

Table 6: Accelerated stability study of metoprolol succinate matrix tablets of B-11 batch at 40^{0}c & 75% RH.

S.No.	Parameter	Initial	1 month	2 month	3 month
1	Average Weight (mg)	250	250.15	250.17	250.17
2	Friability (%)	0.68	0.67	0.67	0.67
3	Hardness (kg/cm^2)	5.7±0.02	5.6±0.02	5.6±0.02	5.5±0.01
4	% drug release (up to 24 hrs)	98.58±0.01	97.60±0.02	97.60±0.02	97.60±0.02

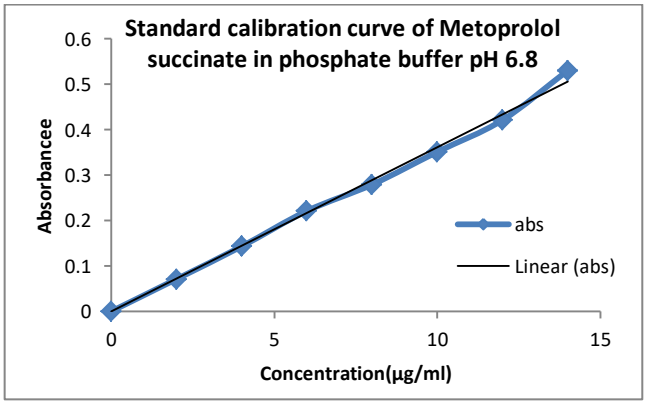

Fig. 1: Standard calibration curve of Metoprolol succinate in phosphate buffer pH 6.8

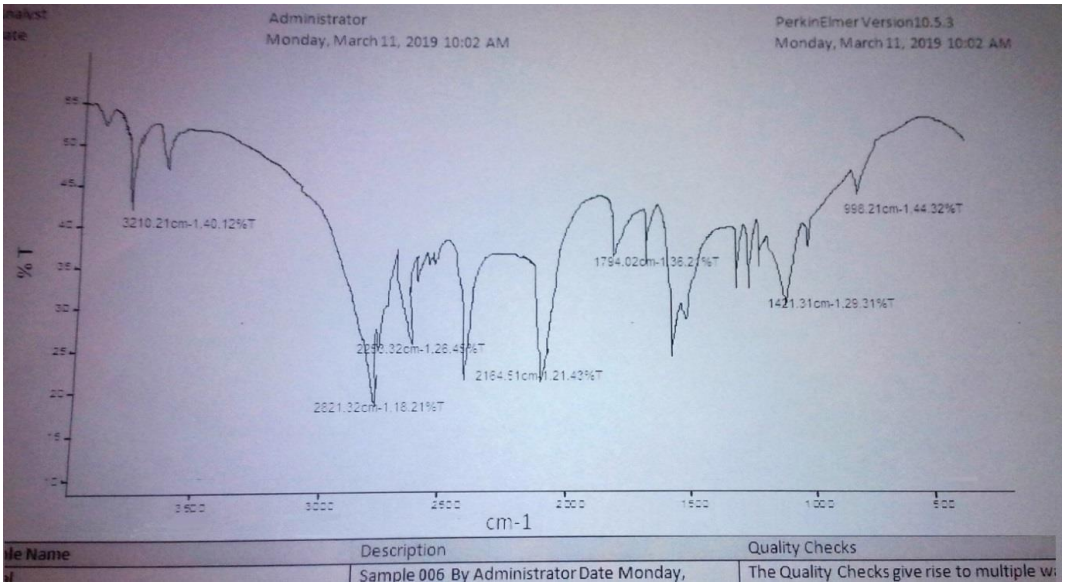

Fig. 2.FTIR of Metoprolol

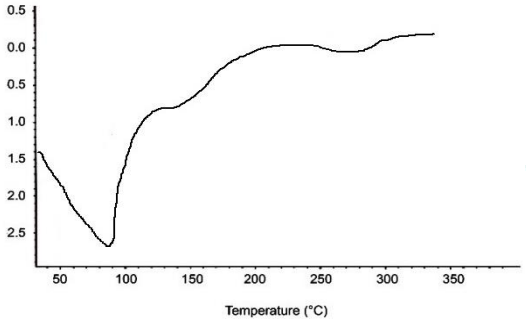

Fig. 3.DSC of Metoprolol

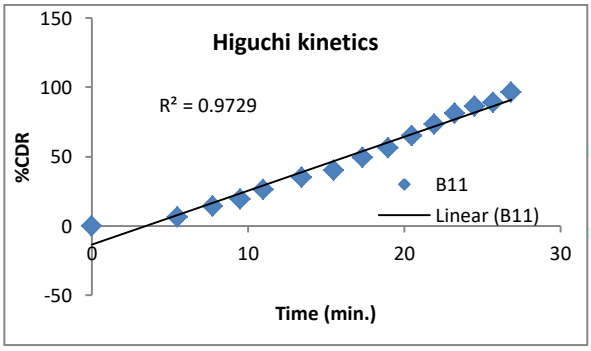

Fig. 4.Higuchi release of B-12 formulation

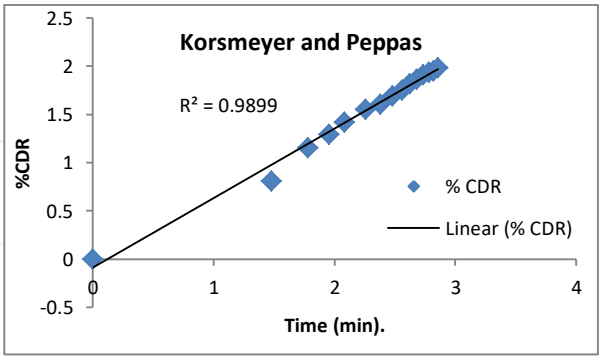

Fig. 5.Higuchi release of B-12 formulation

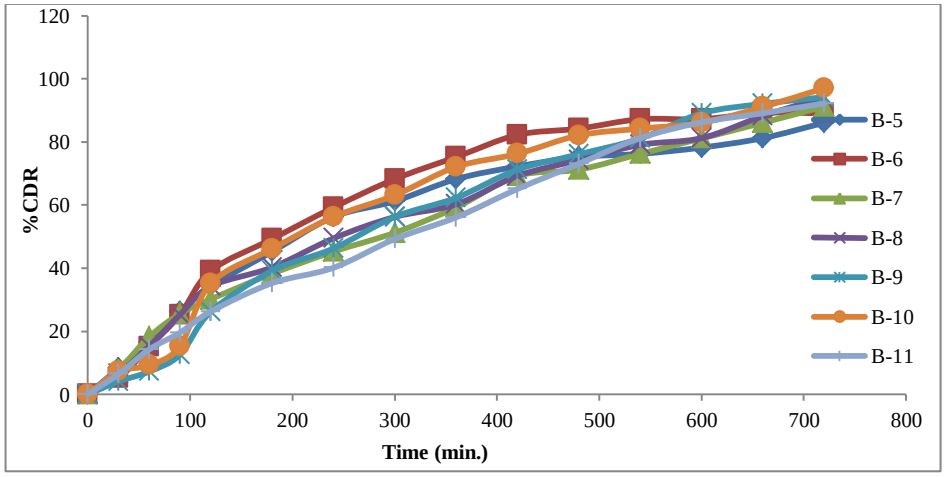

Fig. 6.Drug release profile of B-5 to B-11 batches

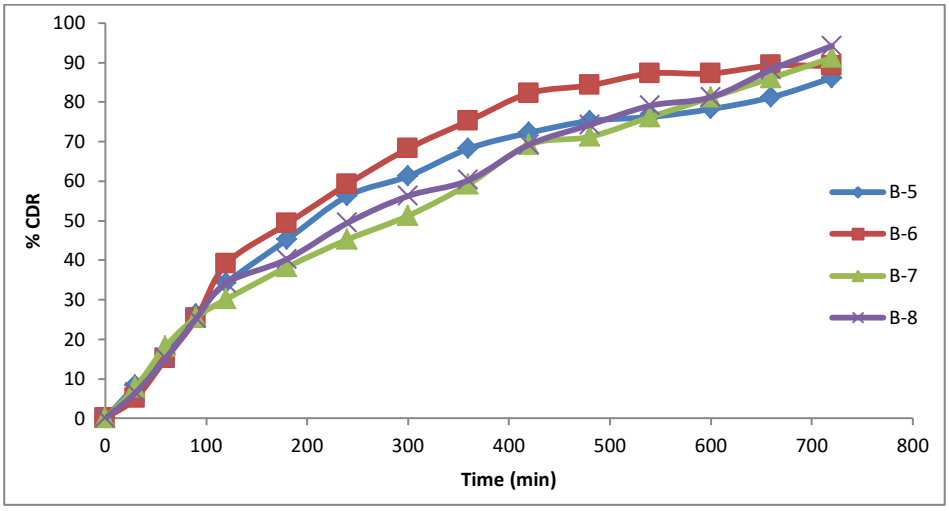

Fig. 7.Drug release profile of B-5 to B-8

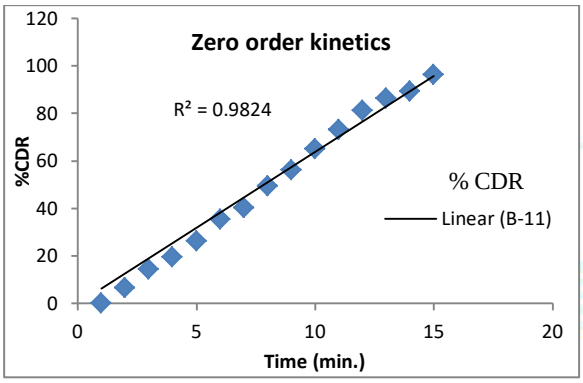

Fig. 8.Zero order release of B-11 formulation

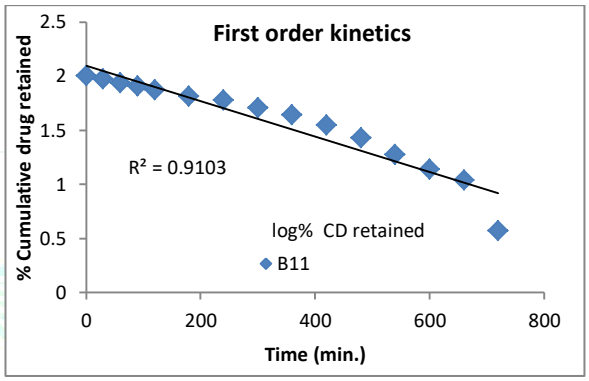

Fig. 9.First order release of B-11 formulation

CONCLUSION

It was concluded that B-11 worked in best way.Metoprolol succinate sustained release matrix tablets were prepared successfully using Xanthan gum and Carbopol-934 polymer of different viscosity. The sustained release system includes any drug delivery system that achieves prolonged release of medicament. The present study was carried out to formulate and evaluate the matrix tablets of Metoprolol succinate containing natural polymer Xanthan gum and synthetic polymer, Carbopol. In this study natural polymer, Xanthan gum and synthetic polymer, Carbopol have been selected as matrix forming material for the drug. The formulation is made by employing the direct compression as well as wet granulation method, to achieve prolonged release of medicament.

The tablets were prepared by using in-situ inter polymer complex formed with 10:90 ratio of Carbopol and Xanthan gum solution as binder. Formulation B-11 showed promising result because of its resistance in pH 1.2 HCL buffer for more than 2 hrs. From the in- vitro studies of the both methods the tablets formed by in situ inter polymer complex method showed the maximum sustained release as compared to simple matrix tablet because of more acid resistance of the complex.

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