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Research Paper

Formulation And Evaluvation of Metoprolol Succinate Microspheres for The Management of Angina Pectoris

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ABSTRACT
Angina pectoris, characterized by chest pain, arises from inadequate blood flow to the heart muscle, disrupting the delicate balance between oxygen supply and demand, ultimately resulting in reduced blood flow to the heart.This research focuses on developing and evaluating mucoadhesive microspheres containing Metoprolol succinate, a cardio selective beta-blocker, for managing angina pectoris, hypertension, heart attacks, and arrhythmias. A drug with a short half-life (4-6 hours) was formulated into microspheres using the ionic gelation method. To optimize the formulation, a Box-Behnken design (BBD) was applied, considering three independent factors: Carbopol 934P (X_1) amount of Eudragit RL 100 (X_2) and stirring speed (RPM) (X_3). The optimized formulation was evaluated based on four dependent variables were particle size (Y_1), entrapment efficiency (Y_2), cumulative drug release (CDR) in 3 hours (Y_3), and total drug release in 12 hours (Y_4). A total of 17 formulations were tested, with all characterization tests performed in triplicate to ensure accuracy.To assess optimization data, response variables were evaluated. Formulated microspheres underwent Scanning Electron Microscopy (SEM), micrometric analysis, entrapment efficiency, and in vitro mucoadhesion and drug release studies. Response surface graphs and contour plots helped understand factor-level effects. Optimized formulation F11 (1250mg X_1, 500mg X_2, 1000rpm X_3) showed close agreement between predicted and experimental values. F11 demonstrated 83.14% entrapment efficiency and a particle size of 149.6µm.A cumulative drug release of 9.89% was observed within 3 hours, followed by a controlled release of 94.4% over 12 hours. The study revealed that polymer concentration significantly impacted the release profile. By optimizing polymer concentration and stirring speed, metoprolol succinate microspheres can be effectively formulated to achieve desired controlled release characteristics, offering a promising treatment for angina pectoris.

Keywords: *Angina Pectoris, Mucoadhesive microspheres, Ionic gelation method, Box-Behnken Design*

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I. INTRODUCTION

Angina Pectoris, or chest pain, occurs when the heart muscle receives inadequate blood flow, causing an imbalance between blood supply and oxygen demand. This condition, known as myocardial ischemia, is a common symptom of coronary artery disease (CAD). Angina typically manifests as uncomfortable pressure, squeezing, or pain in the center of the chest, and may also radiate to the neck, shoulder, jaw, back, or arm[1].

Mucoadhesive microspheres are a type of gastroretentive drug delivery system, consisting of free-flowing powders with spherical particles ranging from 1-1000µm. These microspheres enhance drug targeting and absorption by forming an intimate contact with the mucus layer. Upon adhesion to the mucosal surface, they release the drug over a prolonged period, resulting in improved drug absorption. When exposed to gastric fluids, the microspheres' gel-forming polysaccharides and polymers create a colloidal gel barrier, which slowly releases the medication at a controlled rate, achieving better gastric retention and reduced fluctuations in plasma drug concentration[2].

Microspheres (1-1000µm) made of natural or synthetic polymers can be used for targeted and controlled drug release. Adding mucoadhesive properties enhances absorption and bioavailability by increasing contact with the mucus layer and targeting the absorption site. Tailored mucoadhesive microspheres can provide

localized and controlled drug release in various mucosal tissues, including the eyes, nasal cavity, urinary tract, and GI tract[3]. Microspheres which decreases dose and toxicity, prolonged and sustained release of drug, increased safety margin of high potency drugs due to better control of plasma levels, better patient compliance and convenience due to less frequent drug administration, better processability. Types of microspheres used in drug delivery such as Bio adhesive microspheres, Magnetic microspheres, Floating Microspheres, Radioactive Microspheres, polymeric microspheres [4,5] .

Various types of systems have been developed to increase the gastro retentive of dosage form by employing range of concepts these systems are classified on the basis of principle of gastric retention[6]. Floating drug delivery system that are low density and so float over the gastric contents. Bio adhesive systems that bind with stomach mucosa and hence enable with the localized retention of the system. Swelling and expanding systems this system can enlarge size by absorbing water. High density system that remains in the stomach for longer period of time by sedimenting to the fold of stomach[6].

Gastroretentive systems are designed to prolong gastric retention, enabling controlled drug release to preferred absorption sites in the upper intestinal tract, and offering advantages for local stomach therapy and drugs with specific absorption requirements[7,8].

Angina pectoris is chest pain resulting from coronary heart disease. It occurs when the heart muscle lacks sufficient blood and oxygen due to narrowed or blocked arteries. This ischemia is often triggered by risk factors like smoking, diabetes, high cholesterol, high blood pressure, inactivity, and family history of heart disease.Coronary atherosclerosis, a buildup of fatty deposits in the arteries, is the main culprit behind angina. These plaques narrow the arteries, reducing blood flow to the heart, especially during exertion when the heart needs more oxygen. This lack of oxygen causes chest pain, a symptom of angina. In severe cases, chest pain can even occur at rest[1].

Drug therapy for coronary artery disease aims to minimize symptoms and prevent disease progression. Short-acting nitrates provide rapid relief for acute angina, while long-acting nitrates and beta blockers reduce myocardial oxygen demand. Beta blockers, such as metoprolol and atenolol, are first-line therapy, but may have adverse effects. Calcium channel antagonists, like verapamil and amlodipine, improve symptoms via vasodilation and can be used with beta blockers. Nicorandil, a potassium channel activator, can be added to control angina. Each medication has its own set of contraindications and potential interactions, emphasizing the need for careful consideration when selecting treatment options.

II. MATERIALS AND METHODS

Metoprolol succinate was a gift sample from Tablets (India) Ltd, Chennai. Eudragit RL 100 and Carbopol 934 P was purchased from We Associates, Kottayam. Sodium alginate and Calcium chloride was purchased from Nice chemicals. All other chemicals used in experiment were of analytical grade and used as such.

III.METHODOLOGY

3.1 Preformulation Studies :

Preformulation studies are crucial in drug development, investigating a drug's physical and chemical properties with and without excipients. This research focuses on preformulation studies for Metoprolol succinate, aiming in the management of Angina pectoris . Key parameters assessed include melting point, solubility, particle size, and compatibility with excipients[9,10].

3.1.1 Physical Charecterization of Drug Sample

3.1.2 Nature: The drug sample's physical nature was assessed visually and with a compound microscope.

3.1.3 Colour: The colour of the sample was observed visually against contrasting background.

3.1.4 Melting point: The melting point of drug was determined by capillary tube method. The drug was filled to capillary tube which has one end sealed. The filled capillary tube was placed inside the melting point apparatus and the temperature at which drug melted was noted[11].

3.1.5 Solubility: The solubility of Metoprolol succinate was evaluated in various solvents, including water, methanol, phosphate buffer 6.8, diethyl ether, and 0.1N HCl. To determine solubility, 100mg of the drug was accurately weighed and transferred to a stoppered tube containing 0.1ml of solvent. The solubility classification was based on the volume of solvent required for complete dissolution. If the drug dissolved in 0.1ml, it was considered very soluble. If not, additional solvent was added in increments, and the solubility was classified accordingly: freely soluble (1ml), soluble (3ml), sparingly soluble (10ml), slightly soluble (20ml), or very slightly soluble (1mg in 10ml)[12].

3.1.6 Calibration Curve of Metoprolol

UV spectrophotometry method was developed for the analysis of drug using double beam Systronics-2202 spectrophotometer.

3.1.7 Determination of λ max of metoprolol succinate

50µg/ml solution of Metoprolol succinate was taken in 0.1N HCl using serial dilution technique and scanned in range 200-400nm using UV spectrometer to find out the wavelength of maximum absorbance. 4.4.1.7

3.1.8 Preparation Of Standard Stock Solution

10 mg of pure Metoprolol succinate was accurately weighed and transferred to 50ml of volumetric flask. Drug was dissolved in0.1N HCl and volume was made up to 50ml. The concentration of drug was 1mg/ml. 2.5ml of this solution was taken in a 25ml volumetric flask and volume was made up to the mark with 0.1N HCl. Thus metoprolol succinate of strength 100µg /ml was obtained27,28 . 4.4.1.8 Procedure for plotting calibration curve of pure drug From the standard stock solution 0.5ml ,1ml ,1.5ml, 2ml, 2.5ml,3ml dilutions were made in 10ml volumetric flask and volume was made upto the mark with methanol to obtain concentration in range of 5-30 µg/ml. The spectra were recorded, absorbance were measured at 221nm and calibration curve was plotted[13,14].

3.1.9 Drug Excipients Compatibility studies

3.1.9.1 FTIR (Fourier Transform Infrared)Study

The IR spectra were recorded using FTIR spectrophotometer. The samples were prepared by mixing the drug and the excipients in 1:1 ratio and the mixtures were stored in closed containers for 1 month. FTIR spectrum of the samples was taken using potassium bromide pellet method. The physical mixtures of Metoprolol succinate and excipients were scanned in the wavelength region between 4000 and 500 cm-1 and compared to check compatibility of drug with excipient[15].

3.1.9.2 DSC (Differential Scanning Calorimetric) Analysis

DSC study was carried out using DSC-60 instrument to check the compatibility of ingredients. The samples were prepared by mixing the drug and the excipients in 1:1 ratio. Accurately weighed samples were sealed in aluminium pans and analysed in an inert atmosphere of nitrogen at flow rate of 25 ml/min[16]. A temperature range of 0°C to 300°C was used, and the heating rate was 10°C/min. DSC thermograms of pure drugs and physical mixtures of drugs and excipients were studied for their interactions[17].

a. OPTIMIZATION

Experimental design, statistical analysis and optimization

R.A. Fischer's work in the early 20th century emphasized the importance of careful experimental design and execution to avoid common problems[18,19].Design of Experiments (DOE) is a statistical methodology used to plan, analyse, and interpret controlled studies. By applying DOE, researchers can efficiently explore the relationships between independent variables (factors) and dependent variables (responses) using fewer experiments. The experimental design process involves selecting a layout type, defining settings and sequences, and identifying the study's objectives. A key goal of DOE is to optimize and assess the impact of factors on responses, ultimately informing optimization criteria based on desired outcomes[20,21].

In this work, Design Expert 13.0 software was used in order to create the experimental design and response surface plots. Data obtained from the microspheres properties were analyzed with this software, too. Polynomial models were generated for all responses including linear, quadratic as well as interaction terms[22]. The best model was chosen based on the particular statistical parameters involving coefficient of variation (CV), regression coefficient (R^2) and p-value. The following mathematical equation form was used to evaluate numerical effect of independent variables on responses:

$$\mathbf{Y = b0 + b1\ X1 + b2\ X2 + b1.2\ X1\ X2 + b1.1\ X1\ 2 + b2.2\ X2\ 2}$$

where Y is the response variable, b0 is the intercept, bi is the estimated coefficient of factors. X_1, X_2 and X_3 are the main effects representing how responses change, when an individual factor changes. Interaction term (X_1X_2) shows the effect of simultaneous change of factors on responses. Xi^2 is the quadratic effect for evaluation of non-linear correlations.

The Design of Experiments (DOE) approach was employed to optimize the inotropic gelation method, minimizing the number of experimental trials while identifying the most influential process variables on the resulting microspheres[23,24].

In this study, the Box-Behnken Design (BBD) was utilized to investigate the effects of formulation variables on microsphere properties. The concentration of polymer (Carbopol 934P and Eudragit RL 100) and stirring speed were selected as independent variables, while drug entrapment efficiency, particle size, and in vitro drug release (at 3 and 12 hours) were evaluated as dependent variables. Seventeen formulations (F1-F17) were prepared and analyzed using Design Expert software (version 13.0) to generate polynomial equations and identify optimal conditions.

Table 1:Independent and Dependent Variables

Variables (Independent variables)	Low	Medium	High
Carbopol 934 P	500	875	1250
Eudargit RL100	500	875	1250
Stirring speed	800	10000	1200
Dependent variables			
Y_1= Particle size			
Y_2 = Entrapment Efficiency			
Y_3 = Drug release in 3hrs			
Y_4= Drug release in 12 hrs			

Table 2: Experimental plan of formulation

FORMULATIONS	Carbopol 934P(mg)	Eudragit RL100(mg)	Stirring rate(rpm)
F1	875	875	1000
F2	500	1250	1000
F3	500	500	1000
F4	500	875	1200
F5	875	1250	800
F6	875	1250	1200
F7	1250	875	1200
F8	875	875	1000
F9	875	875	1000
F10	875	500	1200
F11	1250	500	1000
F12	875	875	1000
F13	875	875	1000
F14	875	500	800
F15	1250	875	800
F16	500	875	800
F17	1250	1250	1000

3.3 Formulation Of Microspheres

Mucoadhesive microspheres were prepared by Ionic Gelation Method. Weight quantity of the drug metoprolol succinate was dissolved in distilled water and stirred well.Then polymer solution was prepared by dissolving in suitable solvent and stirred for 2 hrs using magnetic stirrer at a speed of 1800rpm.For formation of microspheres,50ml of this solution was extruded drop wise from a needle of 18G in diameter from a height of about 6cm into 100ml aqueous calcium chloride solution and stirred at 100rpm[25]. Then the immediately formed beads were collected and filtered by using whatmann paper no-1.The microspheres were allowed to dry at about 30-40ºC for 8-12 hrs and stored in well closed container for further evaluation

Table 3: Formulation of Mucoadhesive of Metoprolol Succinate

	INGREDIENTS					
Formulations	**Metoprolol succinate(mg)**	**Carbopol 934P(mg)**	**Eudragit RL100(mg)**	**Sodium alginate(mg)**	**Calcuim chloride(%w/v)**	**Distilled water(ml)**
F1	200	875	875	5%	10	q.s
F2	200	500	1250	5%	10	q.s
F3	200	500	500	5%	10	q.s
F4	200	500	875	5%	10	q.s
F5	200	875	1250	5%	10	q.s
F6	200	875	1250	5%	10	q.s
F7	200	1250	875	5%	10	q.s
F8	200	875	875	5%	10	q.s
F9	200	875	875	5%	10	q.s
F10	200	875	500	5%	10	q.s
F11	200	1250	500	5%	10	q.s
F12	200	875	875	5%	10	q.s
F13	200	875	875	5%	10	q.s
F14	200	875	500	5%	10	q.s
F15	200	1250	875	5%	10	q.s
F16	200	500	875	5%	10	q.s
F17	200	1250	1250	5%	10	q.s

3.4 EVALUATION

3.4.1 MICROMETERIC PROPERTIES[26,27]

3.4.1.1 Angle of Repose

It is defined as the maximum angle possible between the surface of the pile of the powder and horizontal plane.

Procedure:

A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom is closed and 10gm of sample powder is filled in funnel. Then funnel was open to release the powder on the paper to form a smooth conical heap, is found by measuring a different directions. The height of the heap was measured by using scale. The values of angle ofrepose are calculated by using the following formula.

$$\theta = \tan^{-1}(h/r)$$

were,θ = Angle of the repose.

h = Height of the heap.

r = Radius of the heap.

Table 4: Angle of Repose Limit

Angle of Repose	**Flow Ability**
‹25	Excellent
25-30	Good
30-40	Passable
›40	Very poor

3.4.1.2 Bulk density

Bulk density is the ratio of mass of powder to the bulk volume. Bulk density largely depends onparticular shape as the particle become more spherical in shape, bulk density is increases. Bulkdensity is determined by measuring the volume of a known mass of a powder sample that has beenpassed through a screen into a graduated cylinder.

Procedure:

A known quantity of powder was poured into measuring cylinder carefully level the powderwithout compacting, if necessary and read the unsettled apparent value. Calculate the bulk density,in gm per ml, by the formula.

$$\rho b = m/Vb$$

Where, ρb= Bulk density.

m = mass of powder.
Vb= initial/bulk volume.

3.4.1.3 Tapped density

Tapped density is the bulk density of a powder which has been compacted by tapping or vibration.Tapped density was determined by placing a graduated cylinder containing a known mass ofpowder on amechanical tapping apparatus, which is operated for a fixed number of taps (100) oruntil the powder bed volume has reached a minimum. The tapped density was computed by takingthe weight of drug in cylinder and final volume.

Tapped density = Weight of powder/ tapped volume

3.4.1.4 Compressibility index (Carr's index)

The compressibility index is measures of the propensity of a powder to be compressed. As such,they are measures relative importance of inter particulate interactions. In a free flowing powder, such interactions generally less and tapped densities will be closer in value. For poorer flowingmaterials, there are frequently greater inter particulate interactions, and a greater difference betweenbulk and tapped densities will be observed. These differences are reflected in the compressibilityindex calculated by the formula.

Carr's index =Tapped density- bulk density/ Tapped density×100

Table 5: Standard values for compressibility index

% Compressibility	Flow ability
5-12	Excellent
12-16	Good
18-21	Fair
23-25	Poor
33-38	Very poor
More than 40	Very very poor

3.4.2Hausner Ratio

Hausner ratio is an indirect index of ease of powder flow. If the hausner's ratio of powder is near to1.25, indicates better powder flow. It is calculated by the following formula,

Hausner' ratio= Tapped density/Bulk density

Table 6: Standard Values for Hausner's Ratio

SL.NO	Hausner's ratio	Properties
1	1.00 – 1.11	Excellent
2	1.12 – 1.18	Good
3	1.19 – 1.25	Fair
4	1.26 – 1.34	Passable
5	1.35 –1.45	Poor
6	1.46 – 1.59	Very poor
7	> 1.60	Extremely poor

3.4.3Surface morphology:

The surface morphology and structure were visualized by scanning electron microscopy (SEM).The samples were prepared by lightly sprinkling the microspheres powder on a double sideadhesive tape which already shucked to on aluminum stubs. The stubs were then placed into finecoat ion sputter for gold coating. After gold coating samples were randomly scanned for particlesize and surface morphology.

3.4.4Percentage yield:

The percentage yields of microspheres were calculated by the weight of final product after dryingwith respect to the initial total weight of the drug and polymer[28]. The percent yields were calculatedby the formula given below.

$$\textbf{Percentage Yield} = \frac{\textit{Practical mass (microspheres)}}{\textit{Total weight of drug and excipient}} \times 100$$

3.4.5Drug Entrapment Efficiency (DEE)

Microspheres equivalent to 50 mg of the drug were taken for evaluation. The amount of drugentrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HClrepeatedly. The extract was transferred to a 50 ml volumetric flask and the volume was made upusing 0.1N HCl. The solution was filtered and the absorbance was measured after suitable dilutionspectrophotometrically at 221 nm against appropriate blank. The amount of drug entrapped inthe microspheres was calculated by the following formula.

$$\textbf{\% DEE} = \frac{\textbf{Amount of drug actually present}}{\textbf{Theoretical drug content}} \times 100$$

3.4.6 Particle Size analysis

The particle size of the microspheres was determined by using optical microscopy method.Approximately 100 microspheres were counted for particle size using a calibrated opticalMicroscope[29].

3.4.7 Swelling Index

Swelling index was determined by measuring the extent of swelling of microspheres in 0.1N HCl(pH 1.2) buffer. To ensure the complete equilibrium, exactly weighed amount of microspherewere allowed to swell in 0.1N HCl (pH 1.2) buffer. The excess surface adhered liquid dropswere removed by blotting and the swollen microspheres were weighed by usingmicrobalance[30]. The microspheres then dried in an oven at 60 °C for 5 hr until there was nochange in the dried mass of sample. The swelling index of the microsphere was calculated byusing the formula.

% Swelling index = (mass of swollen microspheres - Mass of dried Microspheres) / Mass of dried microspheres x 100

3.4.8*In vitro* Mucoadhesion Test

The mucoadhesive properties of the microspheres were evaluated by the in vitro wash-off test. A2x2 cm piece of Goat stomach mucosa was tied onto a glass slide (3×1 inch) using thread.Microspheres were spread (∽50) onto the wet, rinsed, tissue specimen, and the prepared slide washung onto one of the groves of a USP tablet disintegrating test apparatus. The disintegrating testapparatus was operated such that the tissue specimen was given regular up and down movements ina beaker containing the acidic buffer pH 1.247[31]. At the end of 1 h, the number of microspheres stilladhering to the tissue was counted.

$$\textbf{\% mucoadhesion} = \frac{\textbf{weight of adhering microsphere}}{\textit{weight of microsphere}} \times 100$$

3.4.9*In vitro* drug release study

Drug release from the mucoadhesive microspheres was investigated using USP dissolutionapparatus 1(Basket type),SGF(0.LN HCL; pH 1.2)was used as the dissolution medium and 900mlof it was poured into each dissolution vessel. Microspheres of metoprolol succinate were filled incapsule and placed inside the basket and then rotated at a speed of 50rpm,maintained at atemperature of 37± 0.5ºC.An aliquot of 1ml was withdrawn at hourly intervals up to 12hrs and thevolume was replaced with fresh medium[32]. The aliquots were diluted and the concentration ofmetoprolol succinate was determined spectrophotometrically at 221nm.

3.5 RELEASE KINETICS

Kinetic study was carried out by fitting the in vitro drug release data into Zero order, First order,Higuchi model, Hixon-Crowell Cube Root Law model and Korsmeyer peppas models. The bestoutfit model was confirmed by the value of R2 which is near to 149[33].

3.5.1 Zero Order Kinetics

Plot made between cumulative % drug release vs. time. Mathematical relation shows that therelease is independent of drug concentration.

$$\mathbf{Q = Q^0 + k^0 t}$$

Where, Q is the amount of drug released or dissolved; Q0 is the initial amount of drug in thesolution (most times, $Q^0 = 0$); $k^0$is the zero order release constant expressed in units ofconcentration/time.

3.5.2 First Order Kinetics

Plot made between log cumulative % drug retained vs. time would yield a straight line with a slopeof -k/2.303. Mathematical relation shows that the release is proportional to amount of drugremaining.

$$\mathbf{\log C = \log C^0 - kt/2.303}$$

Where, C0 is the initial concentration of drug; k is the first order rate constant; t is the time.

3.5.3 Hixson Crowell Model

A plot of cube root of % cumulative drug remaining in matrix vs. time was made. Thismathematical model describes drug release as dissolution from erodible matrix formulations. Here,the relation shows that the particles regular area is proportional to the cube root of its volume.

$$W^0 1/3 - Wt1/3 = \kappa t$$

where, W0 is the initial amount of drug in pharmaceutical dosage form; Wt is the remaining amountof drug in the pharmaceutical dosage form at time 't' and κ (kappa) is a constant incorporating thesurface volume relation.

3.5.4 Higuchi Model

A plot made between cumulative % drug releases vs. √t. Mathematical relation shows that therelease is proportional to square root of time.

$$Qt = KH\ t1/2.$$

Where, Qt is the amount of drug released at time 't'; KH is the release rate constant for the Higuchimodel.

3.5.5 Korsmeyer Peppas Model

Plot made between log of cumulative % drug release vs. log time. The Korsmeyer Peppas powerlaw equation predicts that the fraction release of drug is exponentially related to the release time andadequately describes the release of drug from slabs, cylinders and spheres. This was used to find outthe mechanism of drug release.

$$Mt/\ M\infty = ktn$$

Where, Mt/ M∞ is a faction of drug released at time 't' k is the release rate constant; n is therelease exponent. The _n value is used to characterize different release mechanism of drug. If n isless than 0.5, then the system follows fickian diffusion mechanism, if n value is greater than 0.5 andless than 1.0, then the drug transport mechanism follows non-fickian or anomalous diffusion. Ifrelease exponent is more than 1, the system follows case II transport mechanism.

3.6Stability studies

Stability study was done to check out the quality of drug substance or product varies with timeunder the influence of a variety of environmental factors such as temperature, humidity, and light;to establish a retest period for the drug substance or a shelf life for the drug product andrecommended storage condition. Here the microspheres were loaded at accelerated condition at400C±20 and 75% RH in a stability chamber. Samples were withdrawn after 3months and continuefor 6 month and analysed suitably for the drug entrapment efficiency and dissolutioncharacteristics[34].

IV.RESULTS AND DISCUSSION

4.1 PERFORMULATION STUDY

4.1.Identification of drug

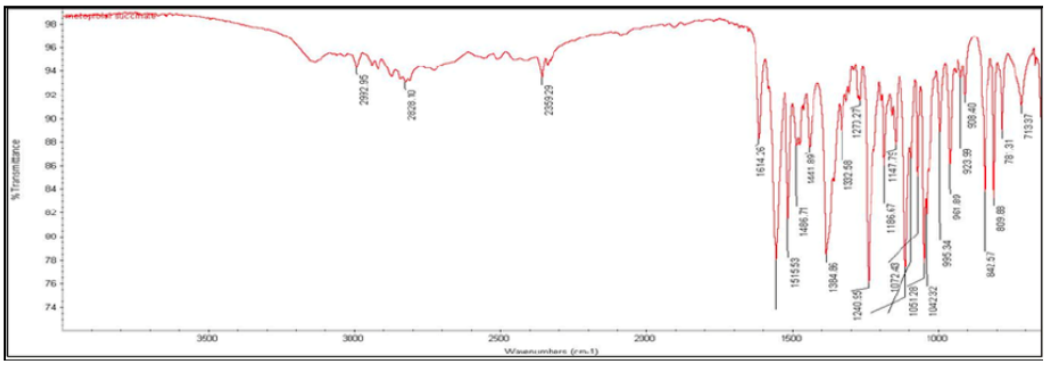


Figure 1: Reference spectrum of Metoprolol succinate

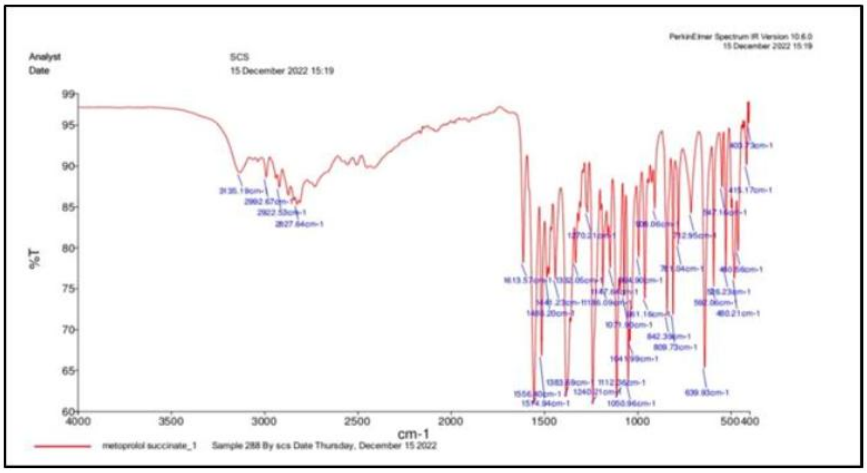


Figure 2: IR Spectrum of Metoprolol succinate (Sample)

Table 7: Functional Group and their observed peak value

Sl.NO	Type of bond	Type of Vibration	Actual frequency (cm^{-1})	Observed frequency (cm^{-1})	Confirmation
1	C=C	Stretching	~ 1600	1613.57	Aromatic
2	N-H	Stretching	3310-3140	3135.19	2° Amine
3	C-O	Stretching	1350-1260	1240.21	2° Alcohol
4	C-O	Stretching	1150-1070	1050.96	Ether
5	C-O	Stretching	1410-1300	1383.69	Phenoxide

The sample spectrum was compared with the reference spectrum. There were no significant changesin the functional groups.The frequency of observed functional groups NH, C-O, C=C,were withinthe standard limits .The finger print region has not changed significantly. So the drug wasconfirmed to be Metoprolol succinate.

4.1.2 Organoleptic evaluations

Table 8: Physical Properties of Metoprolol Succinate

Character	Metoprolol succinate
Color	White
Odor	Odourless
Appearance	Crystalline powder

4.1.3 Determination of Melting Point

The standard melting point of Metoprolol succinate is in the range of 137-140°C. The observedvalue was 140°C which is within the range as per official monograph. So the drug was identified asMetoprolol succinate.

4.1.4 Determination of solubility of Drug

Table 9: Solubility of drug

Sl.no:	Solubility	Solvents
1	Freely soluble	Water
2	Soluble	Methanol, phosphate buffer,0.1N HCL
3.	Slightly soluble	Dichloromethane ,2-propanol
4.	Insoluble	Acetone,diethylether,ethylacetate

The solubility was determined by dissolving the drug in different solvents like water, Methanol,0.1N HCl, Phosphate buffer 6.8. The results of solubility analysis are given in the table It wasvery freely soluble in water and soluble in 0.1 N HCl, Phosphate buffer 6.8.

4.2 Analytical Method for the Determination of Drug

4.2.1 Determination of λ max of Metoprolol succinate

The 10 µg/ ml sample was prepared and scanned between 200 to 400 nm. The drug showedmaximum absorption at 221 nm in 1.2 HCl buffer.

Table 10: Standard callibration curve data of metaprolol succinate

Sl.no	Concentration	Absorbance
1	0	0
2	5	0.172
3	10	0.328
4	15	0.476
5	20	0.662
6	25	0.791
7	30	0.969

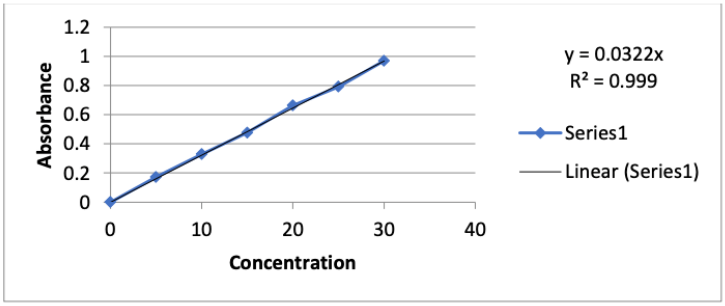


Figure 3: Calibration curve of Metoprolol succinate 0.1N HCL

Various concentrations [5,10.15,20,25 and 30µg/ml] of the drug were prepared as shown in TableNo. 10 and the standard graph was plotted [Fig. No:3].The y- intercept and R2 values were foundto be 0.032,0.999 respectively.

4.3 FTIR STUDIES

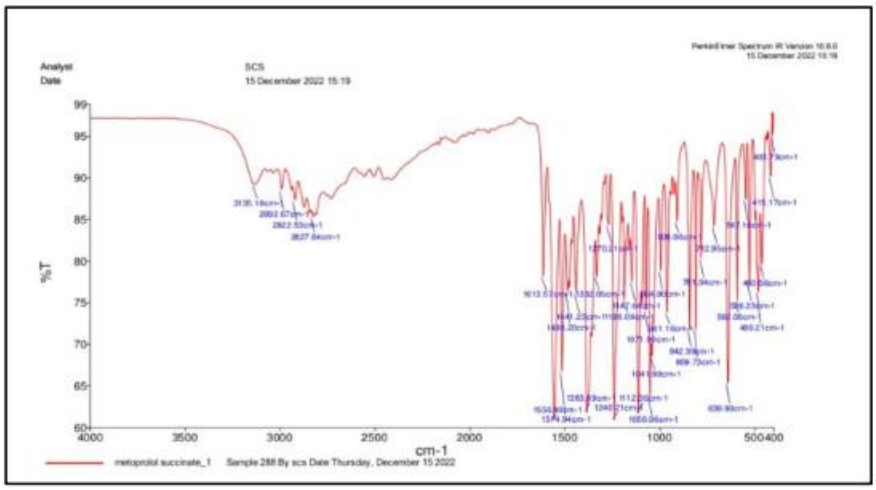


Figure 4: FTIR of Metoprolol succinate

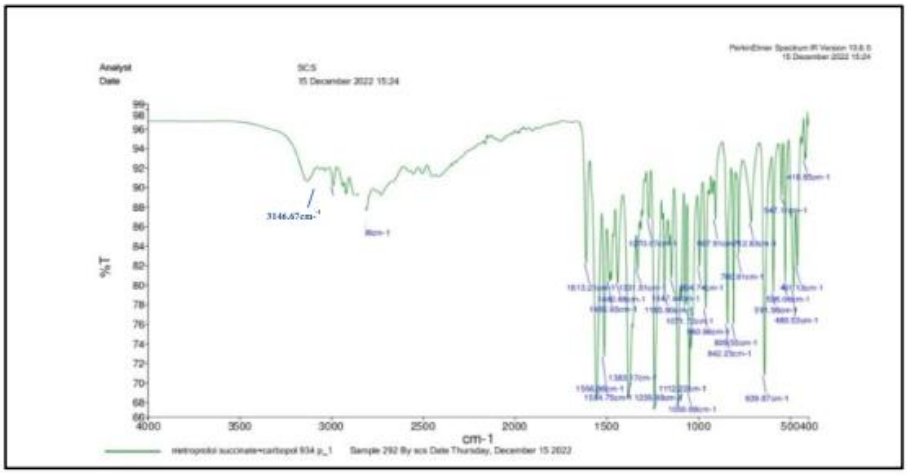


Figure 5: FTIR of Metoprolol succinate + Carbopol 934 P

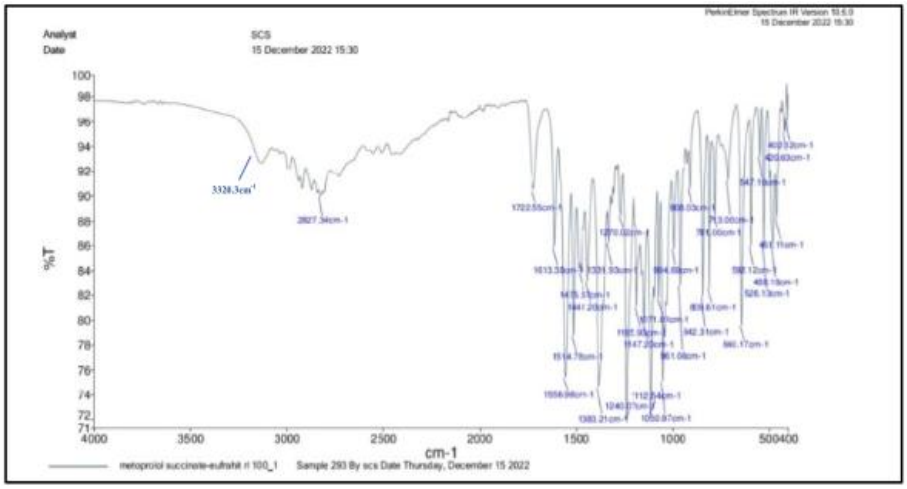


Figure 6: FTIR of Metoprolol Succinate+ Eudragit RL 100

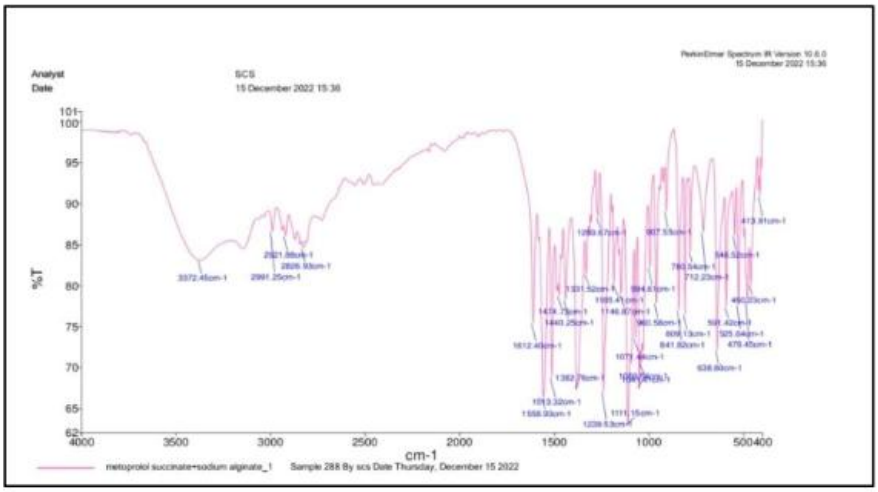


Figure 7: FTIR of Metoprolol Succinate + Sodium Alginate

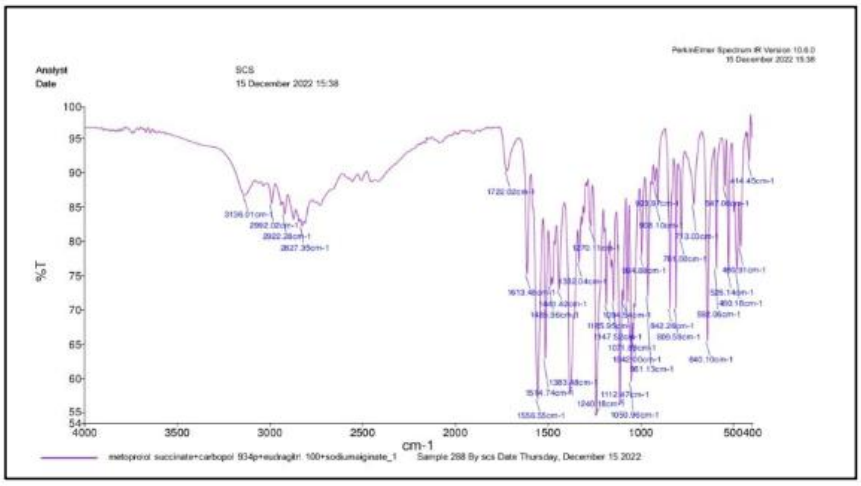


Figure 8: FTIR of Metoprolol Succinate + Eudragit RL 100 + Carbopol 934 P + Sodium Alginate

Table 11: Comparison of FTIR spectra of Metoprolol + Carbopol 934 P + Eudragit RL 100 + Sodium Alginate

Sl. no	Functional group	Metoprolol succinate	Metoprolol succinate+ Carbopol 934 P	Metoprolol succinate+ Eudragit RL 100	Metoprolol succinate+ Sodium alginate	Metoprolol succinate+Eudragit RL 100+ Carbopol 934P+ Sodium alginate
1	**C =C**	1613.57	1613.21	1613.38	1612.40	1613.48
2	**N-H**	3135.19	3146.67	3320.3	3312..45	3136.01
3	**C-O**	1240.21	1239.98	1240.07	1239.53	1240.18
4	**C-O**	1050.96	1050.89	1050.97	1050.54	1050.96
5	**C-O**	1383.69	1383.17	1383.21	1382.76	1383.48

4.3.1DSC

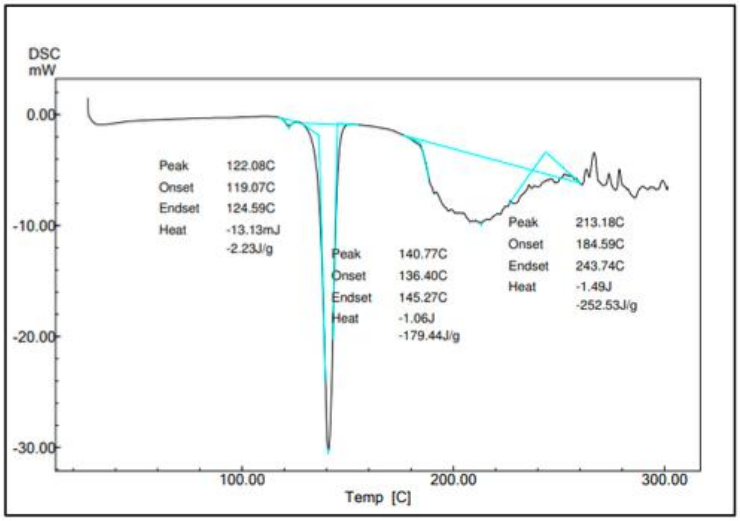


Figure 9: DSC curve of Pure Metoprolol Succinate

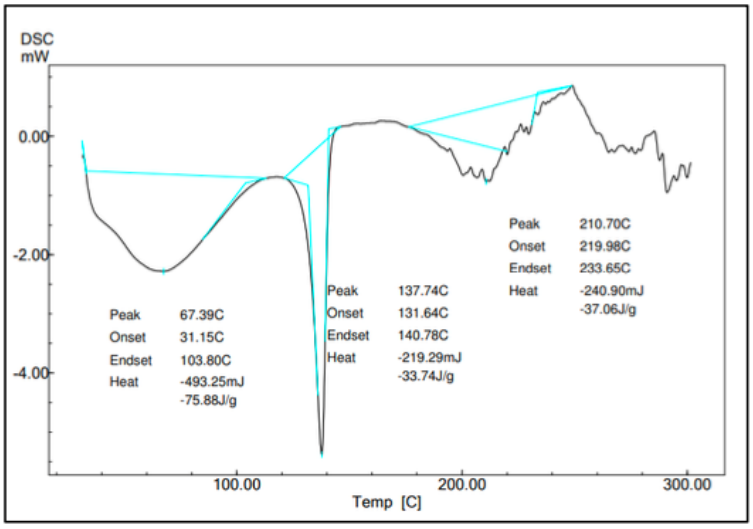


Figure 10: DSC curve of Metoprolol Succinate + Eudragit RL 100 + Carbopol 934 P + Sodium Alginate

The DSC studies were carried out for drug [Metoprolol succinate] and drug-excipients physical mixtures.The results are given in Fig. No(9,10). The recorded DSC thermograms showed the profile of Metoprololsuccinate with melting point at 140˚C. Drug when combined with excipients, showed melting point at 137ºC.The melting point remains almost the same, indicated that the drug and excipients are compatible with eachother.

4.5 PREPARATION OF MUCOADHESIVE MICROSPHERES

Figure 11:Prepared Mucoadhesive Microsphere

4.6 EVALUATIONS
4.6.1 MICROMERTIC PROPERTIES
Table No:12 Evaluation of pre-compression parameters

Table 12: Evaluation of pre-compression parameters

Sl.NO	Formulation	Angle of Repose(Ɵ)	Bulk density (g/cc)	Tapped Density (g/cc)	Compressibility Index	Hauser's ratio
1	F1	28.06± 0.31	0.45± 0.045	0.52± 0.09	15.60± 0.2	1.15± 0.02
2	F2	27.58± 0.15	0.45± 0.045	0.50± 0.07	12.23± 0.6	1.11± 0.04
3	F3	28.44± 0.11	0.44± 0.044	0.50± 0.09	12.58± 0.8	1.13± 0.08
4	F4	28.36±0.13	0.45± 0.045	0.52± 0.04	15.19± 0.1	1.15± 0.06
5	F5	28.52±0.19	0.44± 0.044	0.52±0.01	15.48± 0.6	1.18± 0.08
6	F6	29.32± 0.19	0.45± 0.045	0.51± 0.04	13.48± 0.8	1.13± 0.09
7	F7	29.69± 0.19	0.51± 0.045	0.59± 0.04	14.48± 0.8	1.15± 0.09
8	F8	28.52± 0.19	0.44± 0.044	0.52± 0.01	15.48± 0.6	1.18± 0.08
9	F9	27.58± 0.15	0.45± 0.045	0.50± 0.07	12.23± 0.6	1.11± 0.04
10	F10	28.35±0.12	0.45±0.045	0.52±0.04	15.17±0.1	1.14±0.05
11	F11	27.45±0.13	0.45± 0.044	0.50±0.06	12.24±0.5	1.13±0.06
12	F12	28.12±0.12	0.45±0.045	0.51±0.10	15.65±0.3	1.15±0.03
13	F13	28.64±1.09	0.50±0.045	0.58±0.04	14.48±0.8	1.15±0.09
14	F14	27.55±0.14	0.45±0.045	0.50±0.06	12.24±0.5	1.12±0.03
15	F15	28.34±0.12	0.44±0.043	0.50±0.06	12.54±0.67	1.12±0.08
16	F16	27.67±0.14	0.45±0.046	0.49±0.07	12.23±0.6	1.11±0.04
17	F17	29.23±0.18	0.45±0.045	0.51±0.04	13.46±0.7	1.13±0.09

The micrometric properties for all the formulations were expressed in terms of bulk density, tappeddensity, Carr's index, Hausner's ratio and angle of repose. As given in table No:21 the values ofCarr's index were found to be in the range of 12.23-15.65%, indicating good compressibilityHausner's ratio was recorded below 1.18, which represents good flowability. The angle of reposewas found to be below 29°, showing the free-flowing nature of the microspheres. The micrometricproperties of all the formulations indicated that microspheres were free flowing in nature.

4.6.2 Particle size Determination

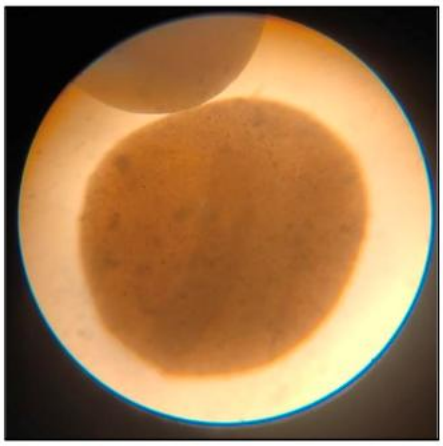


Figure 12 : Microscopic view of mucoadhesive microspheres of Metoprolol succinate

The particle size of the microspheres was determined by using optical microscopy method.The particle size of all the 17 batches varied from 132.01- 164.6µm. The size also depends on theconcentration of polymers.

4.6.3 Percentage Yield

Table 13: Percentage yield of microspheres

Formulation code	Percentage Yield(%)
F1	62.60±1.21
F2	63.40± 1.87
F3	70.95±1.31
F4	82.65±1.24
F5	75.33±1.56
F6	70.91±1.30
F7	82.74±1.37
F8	75.33±1.33
F9	67.80±2.10
F10	70.95±1.31
F11	86.65± 1.09
F12	66.10±2.54
F13	82.65±1.37
F14	71.67±1.43
F15	84.34±1.24
F16	76.98±1.46
F17	80.54±1.11

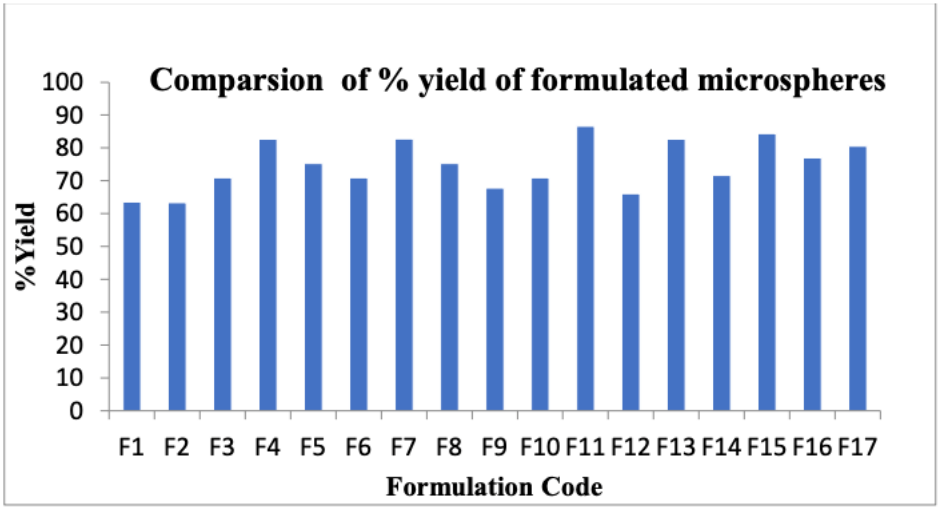


Figure 13: Comparison of percentage yield of formulated microspheres

It was observed that an optimum concentration of polymer and crosslinking agent is required, belowor above this concentration microspheres are not formed. The percentage yield of differentformulations is shown in Table no.25. The percentage yield of F11was found out to be maximum,followed by F4, F13 and F15. The percentage yield was found to be in the range of 62.60±1.21-86.75±1.09 %. Formulation F11 showed best yield of 86.75±1.09 %.

4.6.4 Entrapment Efficiency

Assessing the drug loading capacity of microspheres, the drug entrapment efficiency is importantvariable was given in table No:22 . And ranges from 64.59- 83.14%. The maximum entrapmentefficiency was 83.14% of formulation F11. It shows entrapment efficiency is increased due to anincrease in the concentration of carbopol

934,Eudragit RL 100 and increasing stirring speed. Theentrapment efficiency is highly depending on the amount of Carbopol 934P.

4.6.5 Scanning Electron Microscopy

From SEM study, it was found that microspheres were spherical and rough as shown in fig No:14The pores on microsphere surface could help in drug release by diffusion mechanism**.**

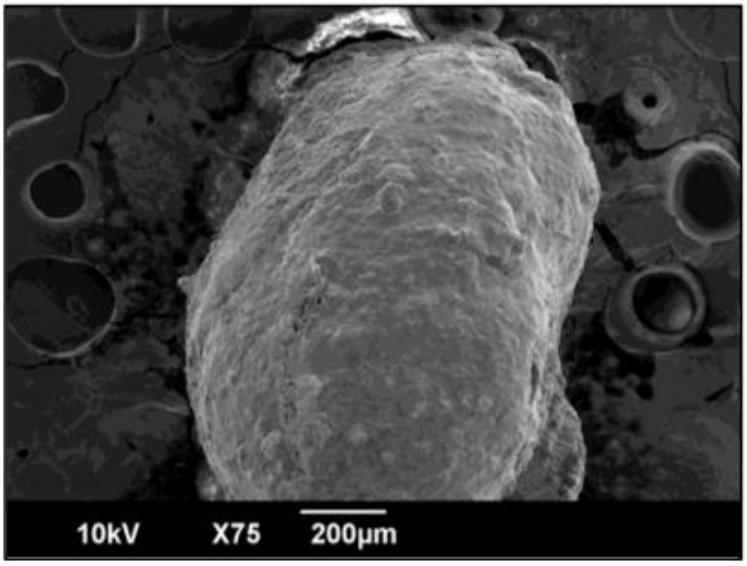


Figure 14: SEM photograph showing structure of microsphere

4.6.6 Percentage Mucoadhesion

Percentage mucoadhesion after 12hrs is shown in Table No(14).The percent mucoadhesionincreased with increase in concentration of mucoadhesive polymer**.**

Table 14: Percentage mucoadhesion of prepared microspheres

Formulation code	Percentage Mucoadhesion (%)
F1	64± 1.95
F2	73±0.96
F3	75±0.67
F4	77±0.81
F5	65±1.73
F6	66±1.74
F7	72±0.86
F8	67±1.95
F9	66±1.93
F10	68±1.74
F11	88± 0.5
F12	73±0.83
F13	82±0.13
F14	69±1.77
F15	74±0.87
F16	65±1.84
F17	78±0.89

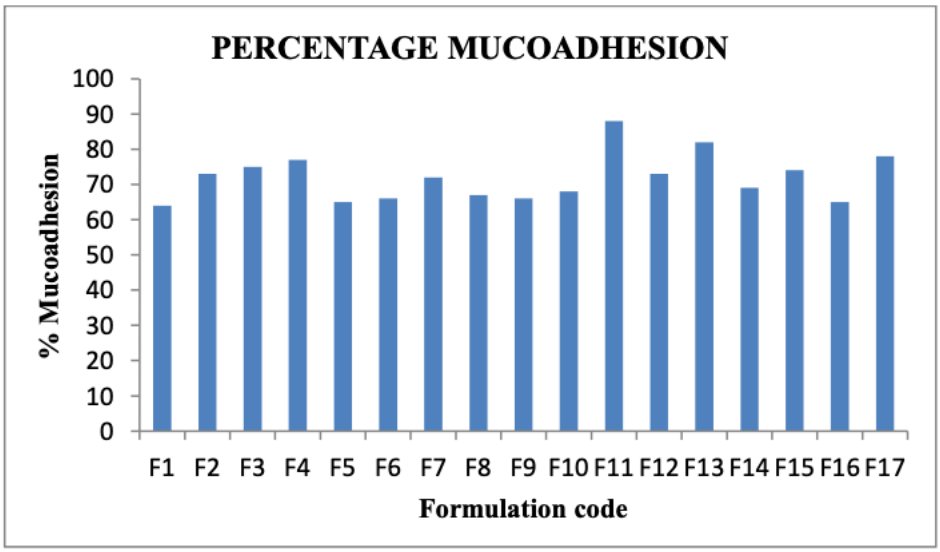


Figure 15: Percentage Mucoadhesion of Microspheres

Prepared microspheres were found good mucoadhesion strength. Percent mucoadhesion of the allbatches of microspheres were found to be in the range of 64±1.95- 88± 0.5% . It was observed thatmucoadhesion of the microspheres significantly increased with increasing polymer concentration.Increase in polymer concentration was attributed to increase in viscosity: produce stronger mucusgel network which helps to increase

mucoadhesion .The percentage mucoadhesion of microspheresadhering to tissue after 12hrs is displayed in Table no:.14 Compared to other formulationsF4,F11,F17 batches showed highest percent mucoadhesion.

4.6.7 Swelling Index

Swelling index of microspheres

Table 15: Swelling index of Microspheres

Formulation code	Swelling Index
F1	83.14±0.82
F2	81.16±2.3
F3	80.22±2.30
F4	79.26±3.09
F5	77.14±3.20
F6	82.28±3.89
F7	79.12±3.2
F8	78.24±1.5
F9	76.26±3.6
F10	74.22±2
F11	85.12± 0.91
F12	76.69±3.05
F13	74.23± 2.98
F14	80.12± 2.23
F15	71.55± 1.08
F16	76.54±3.05
F17	72.54±3.05

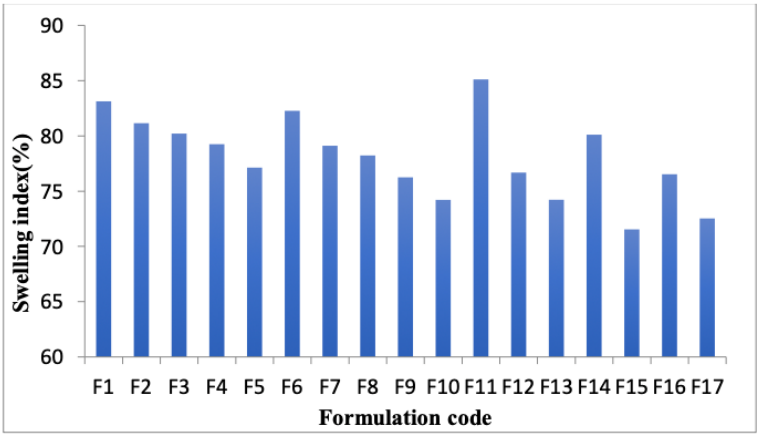


Figure 16: Swelling index of Mucoadhesive Microspheres

Percent swelling is more in case of F11 as compared to other formulations probably because F11contains less amount of Eudragit RL 100 .The percent swelling was found in the range of 71.55±1.08 -85.12±0.91%.

4.6.7 In *vitro* Drug Release

Table 16: Cumulative Drug Release of Microspheres

% Cumulative drug release													
Time	0	1	2	3	4	5	6	7	8	9	10	11	12
F1	0	4.75	6.21	11.17	12.17	28.55	35.01	39.06	54.62	70.85	72.06	76.96	86.26
F2	0	5.06	8.75	10.89	14.14	28.76	29.56	31.23	45.98	61.73	69.15	71.26	82.56
F3	0	4.96	9.27	10.89	12.24	20.45	25.86	36.97	51.65	68.24	71.28	85.76	86.08
F4	0	7.70	10.9	11.48	12.9	23.45	26.56	31.72	46.53	67.95	77.95	78.97	80.6
F5	0	6.72	9.53	11.25	15.76	29.87	31.08	40.85	50.54	57.96	75.98	79.51	86.75
F6	0	3.41	9.65	10.45	15.94	29.65	30.68	39.97	50.65	57.12	74.97	78.99	84.34
F7	0	5.70	6.79	10.03	11.01	27.67	37.97	40.18	42.23	61.56	65.96	73.68	86.67
F8	0	4.34	6.67	11.45	11.50	28.98	34.87	39.87	54.53	70.46	72.87	77.56	83.99
F9	0	4.78	6.45	10.78	12.01	28.03	35.62	38.98	54.85	69.97	72.45	77.1	84.01
F10	0	7.76	9.87	10.76	15.75	25.65	33.09	38.34	51.98	56.07	78.65	87.10	87.7
F11	0	6.11	8.68	9.89	22.31	31.03	36.01	43.44	57.37	72.75	80.68	88.13	94.4
F12	0	4.99	7.01	11.44	11.99	27.96	35.97	38.56	53.86	70.34	71.89	77.12	84.56
F13	0	4.75	6.99	11.34	11.76	28.46	36.96	39.01	54.01	70.53	72.14	73.89	76.76
F14	0	7.87	9.65	11.56	15.53	26.13	32.85	38.20	51.65	56.84	78.60	83.12	91.99
F15	0	5.14	6.88	9.43	10.66	27.35	37.52	40.27	42.16	61.06	76.15	80.84	85.46
F16	0	6.87	7.75	11.3	14.44	25.96	27.75	31.94	52.95	56.96	66.97	83.12	87.12
F17	0	4.72	5.07	8.87	10.53	25.34	27.43	33.48	48.96	65.99	78.20	79.67	81.87

4.6.8 Effect of Drug Release in 3hrs

Drug release from the mucoadhesive microspheres was investigated using USP dissolution apparatus 1(Basket type),SGF(0.LN HCL; pH 1.2)was placed in 900ml dissolution medium. The minimum drug release in 3 hours was 9.89% of formulation.The drug release depends on the concentration of polymers (Table no:16) has shown that increase the amount of carbopol 934P(X1= 1250mg), however the amount of Eudragit RL 100(X2=500mg) and stirring speed (X3=1000rpm)minimum amount of drug is released.

Table 17: ANOVA response for release 3hrs

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	6.98	9	0.7753	16.64	0.0006	significant
A-Carbopol 934p	2.88	1	2.88	61.83	0.0001	
B-Eudragit rl 100	0.6786	1	0.6786	14.57	0.0066	
C-stirring speed	0.1378	1	0.1378	2.96	0.1291	
AB	0.9900	1	0.9900	21.25	0.0025	
AC	0.1640	1	0.1640	3.52	0.1027	
BC	0.2500	1	0.2500	5.37	0.0537	
A^2	0.3278	1	0.3278	7.04	0.0328	
B^2	0.6454	1	0.6454	13.86	0.0074	
C^2	0.7130	1	0.7130	15.31	0.0058	
Residual	0.3261	7	0.0466			
Lack of Fit	0.1544	3	0.0515	1.20	0.4169	not significant

The **Model F-value** of 16.64 implies the model is significant. There is only a 0.06% chance that an F-value this large could occur due to noise.**P-values** less than 0.0500 indicate model terms are significant. In this case A, B, AB, A^2, B^2, C^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.The **Lack of Fit F-value** of 1.20 implies the Lack of Fit is not significant relative to the pure error. There is a 41.69% chance that a Lack of Fit F-value this large could occur due to noise. Non- significant lack of fit is good -- we want the model to fit.

Table 18: Fit Statistics

Std. Dev.	0.2158	**R^2**	0.9554
Mean	11.05	**Adjusted R^2**	0.8980
C.V. %	1.95	**Predicted R^2**	0.6251
		Adeq Precision	14.1517

The **Predicted R^2** of 0.6251 is not as close to the **Adjusted R^2** of 0.8980 as one might normally expect; i.e. the difference is more than 0.2. This may indicate a large block effect or a possible problem with your model and/or data. Things to consider are model reduction, response transformation, outliers, etc. All empirical models should be tested by doing confirmation runs. **Adeq Precision** measures the signal to noise ratio. A ratio greater than 4 is desirable.

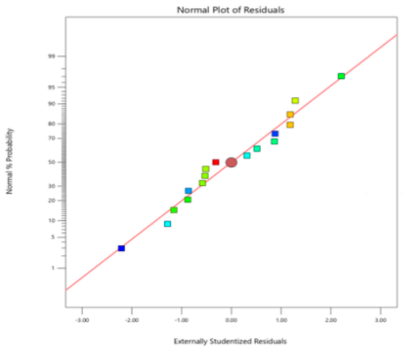


Figure 17 : Normal plot of residual

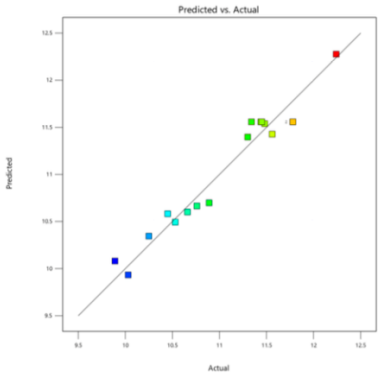


Figure 18: Predicted Vs Actual plot

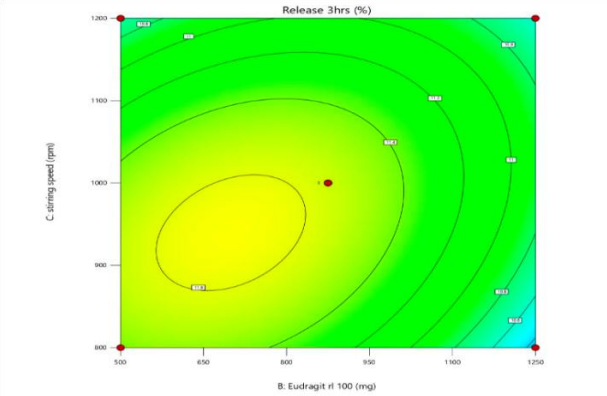


Figure 19: Contour Surface Plot showing effect of Eudragit RL 100 and stirring speed on drug release in 3hrs

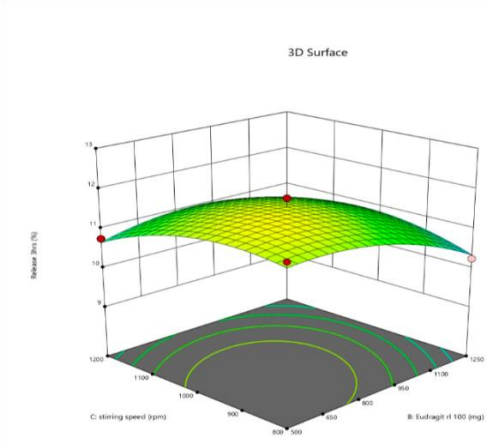


Figure 20: Response surface plot showing effect of Eudragit RL 100 and stirring speed on drug release in 3hrs

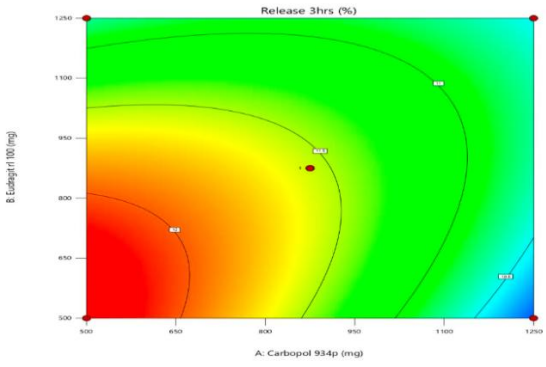


Figure 21: Contour surface plot showing effect of Eudragit RL 100 and Carbopol 934 P on drug release in 3hrs

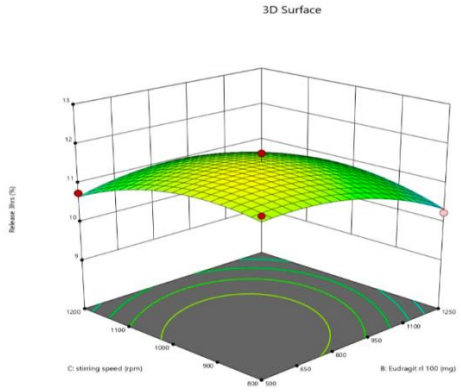


Figure 22: Response surface plot showing effect of Eudragit RL 100 and stirring speed on drug release in 3hrs

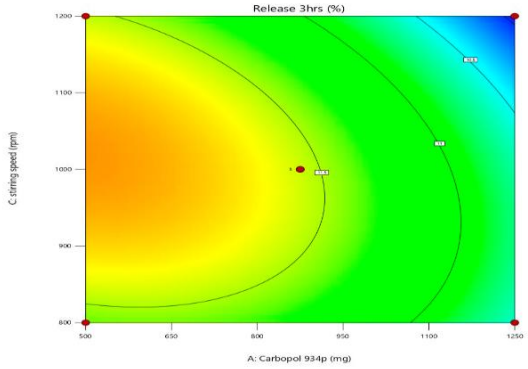


Figure 23: Contour surface plot showing effect of Carbopol 934 P and stirring speed on drug release in 3hrs

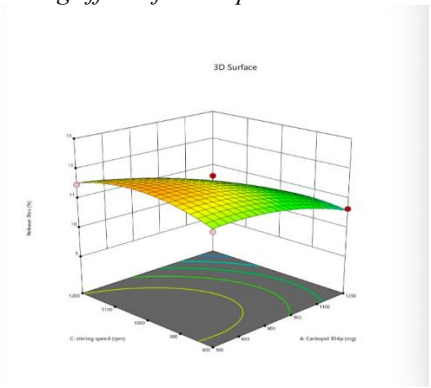


Figure 24: Response Surface plot showing effects of Carbopol 934 P and stirring speed on drug release in 3hrs

4.6.9 RELEASE KINETICS

Table 19: Kinetic Profile of Mucoadhesive Microspheres

Formulation Code	Zero order R^2	First order R^2	Higuchi model R^2	HixonCrowell Model R^2	Korsemeyer – Peppas	
					R^2	N
F1	0.954	0.875	0.793	0.861	0.943	1.41
F2	0.985	0.864	0.743	0.875	0.985	1.96
F3	0.943	0.753	0.771	0.863	0.945	1.19
F4	0.927	0.853	0.732	0.782	0.956	2.53
F5	0.912	0.834	0.753	0.892	0.932	1.10
F6	0.972	0.864	0.762	0.885	0.987	1.23
F7	0.935	0.851	0.781	0.864	0.947	1.11
F8	0.936	0.864	0.731	0.783	0.975	2.32
F9	0.945	0.853	0.763	0.891	0.951	1.76
F10	0.953	0.825	0.752	0.864	0.997	2.28
F11	0.952	0.863	0.782	0.899	0.954	1.65
F12	0.936	0.865	0.793	0.821	0.997	1.65
F13	0.942	0.855	0.764	0.832	0.971	1.07
F14	0.964	0.835	0.782	0.831	0.946	2.11
F15	0.965	0.858	0.773	0.843	0.934	1.38
F16	0.942	0.833	0.794	0.852	0.965	1.31
F17	0.974	0.853	0.764	0.862	0.972	1.46

To determine the release mechanism that gives the best description to the pattern of drug release,the in vitro release data were fitted to zero-order, first-order, Hixson Crowell equation and Higuchimatrix model. The release data were also kinetically analysed using the Korsmeyer– Peppas model. he release kinetics data indicates that therelease of drug from microspheres best fits to zero order release kinetics.The data was fitted with Higuchi equation which gave almost a linear plot with highest R^2 indicating the mechanism of drug release was diffusion. The dissolution data was also plotted inaccordance with Hixon- crowell cube root law.The diffusion exponent (n) was calculated for all formulations .In F11 the slope of the graph wasfound to be 1.65 which suggests that diffusion mechanism of drug release from mucoadhesivemicrospheres followed Super case –II diffusion.

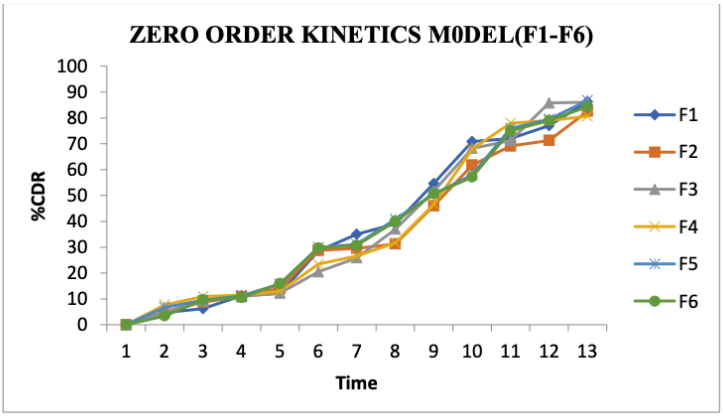
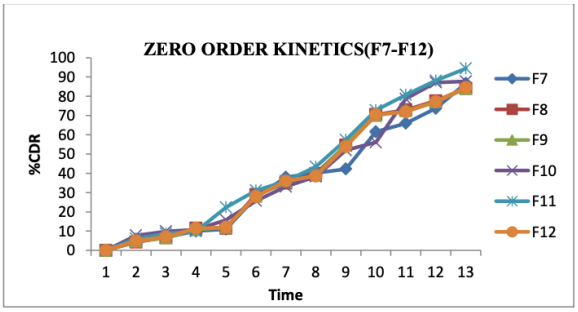


Figure 25: Zero order plot for microsphere [F1-F6]



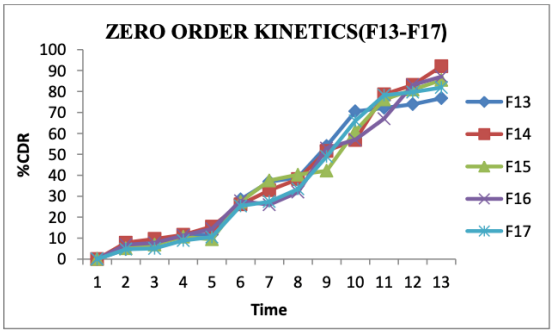
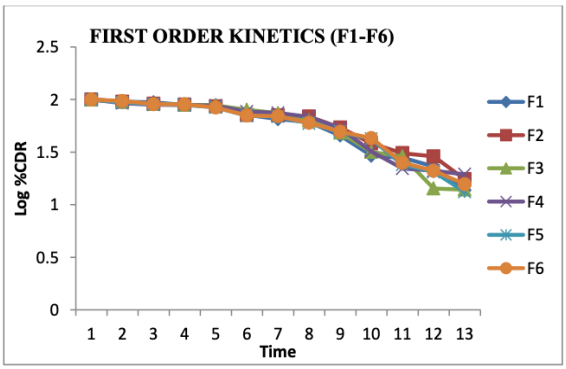


Figure 26: Zero order plot for microsphere [F7-F12]Figure 27: Zero order plot for microsphere[F13-F17]



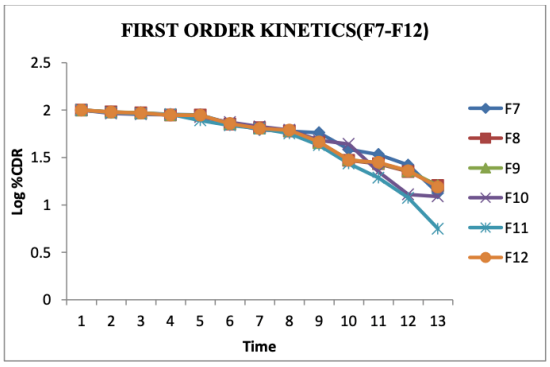


Figure 28: First order plot for microsphere [F1-F6]Figure 29: First order plot for microsphere [F7-F12]

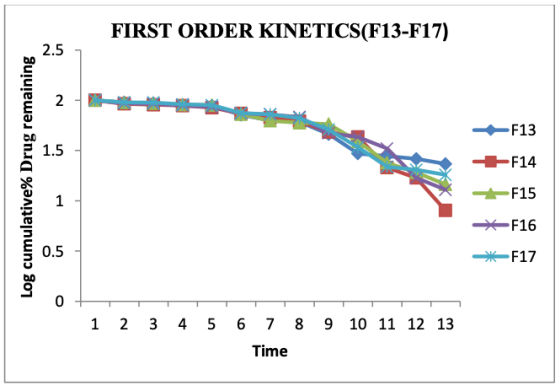
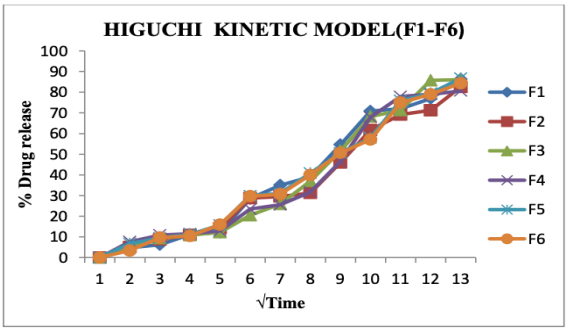


Figure 30: First order plot for microsphere [F13- F17]



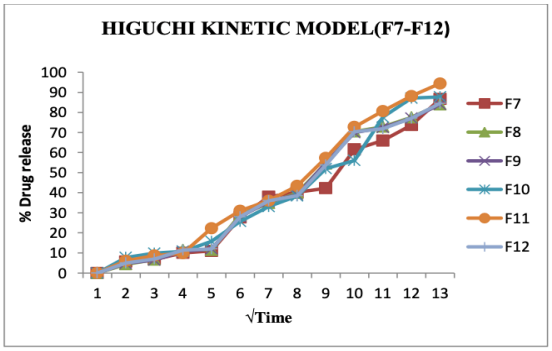


Figure 31: Higuchi plot for microsphere [F1-F6]Figure 32: Higuchi plot for microsphere [F7-F12]

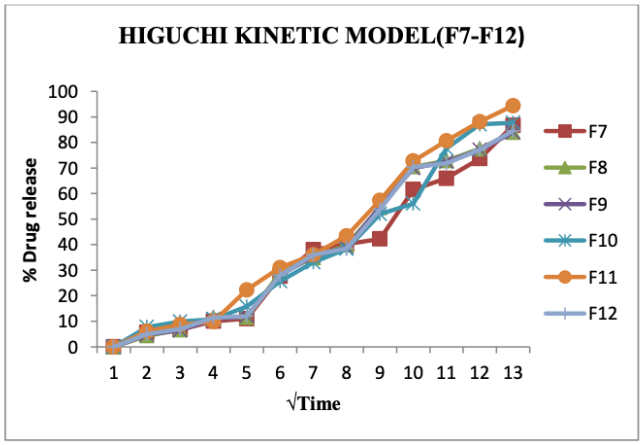
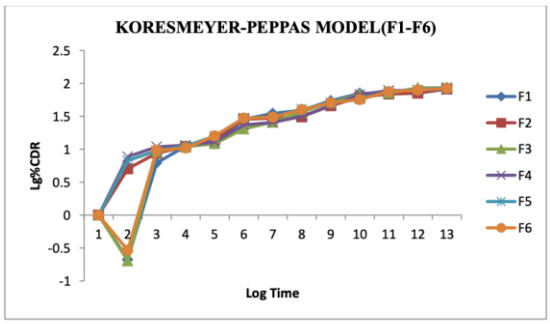


Figure 33: Higuchi plot for microsphere [F13 - F17]



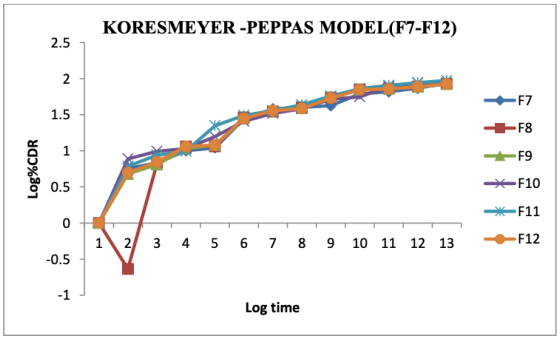


Figure 34: Koresmeyerpeppas model [F1-F6]Figure 35: Koresmeyerpeppas model [F7 -F12]

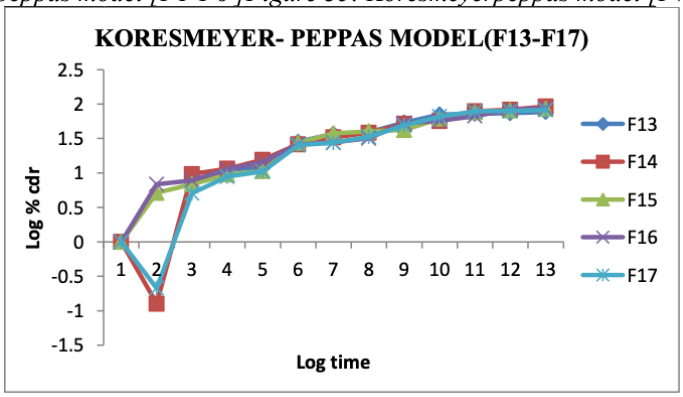
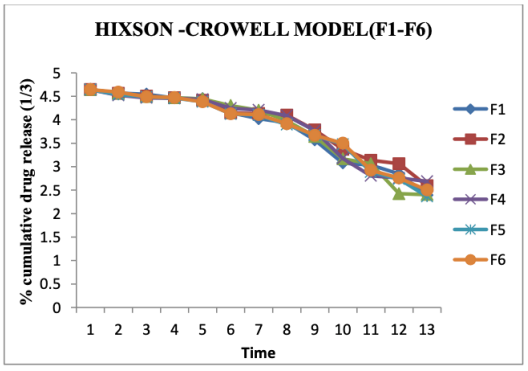


Figure 36: Koresmeyerpeppas model [F13-F17]



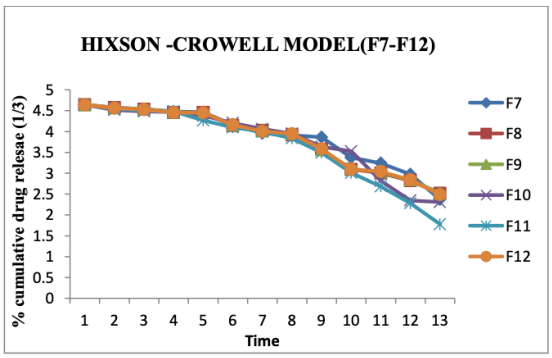


Figure 37: Hixson crowell plot of microspheres [F7 - F12] *Figure 38: Hixson crowell plot of microsphere [F1-F6]*

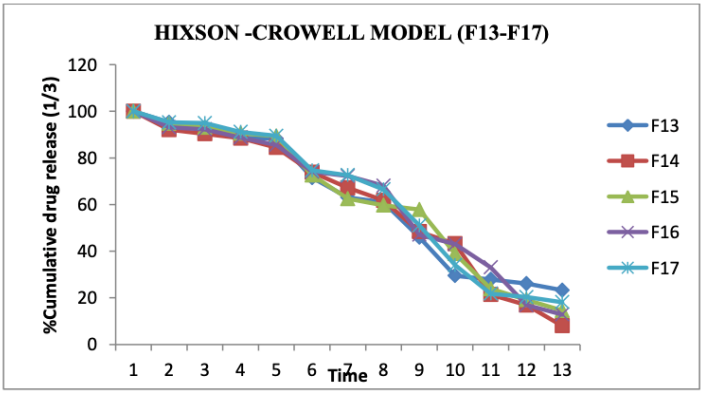


Figure 39: Hixson Crowell model [F13-F17]

Optimization and evaluation of optimized formulation

The optimized formulation was achieved at X1 = 1249.9 mg, X2 = 500 mg and X3 = 1003 rpm with the corresponding desirability (D) value of 0.987,which was nearest to the batch F11. Finally, three batches of the optimized formulations were prepared to confirm the validity of the optimal parameters and predicted responses calculated. All of the responses were evaluated for each optimized formulation. The comparisons of predicted and experimental results are shown in TableNo20. It can be seen that the experimental values were in very close agreement with the predicted values, indicating the triumph of the BBD pooled with a desirability function for the assessment and optimization of Metoprolol succinate microspheres formulations. Thus it can be concluded that batch F11 may be considered as optimized formulation.

Table 20: Predicted and observed response of optimized formulation

Independent variables	**Optimized levels**	
Carbopol 934P(X_1)	1250mg	
Eudragit RL 100(X_2)	500 mg	
Stirring speed(X_3)	1000rpm	
Dependent variables	**Predicted response**	**Observed response**
Particle size(Y_1)	144.7	149.6
Entrapment Efficiency(Y_2)	83.24	83.24
Drug release in 3hours(Y_3)	9.97	9.89
Drug release in 12hours(Y_4)	94.13	94.4

4.6.10 Stability study of Mucoadhesive microspheres

Table 21: Stability study of mucoadhesive microspheres of F11

Duration	**Drug Entrapment efficiency**	**%Cumulative drug release pH 1.2**	
Initial	83.14%	9.89%	94.4%
3 month	81.09%	10.88%	91.5%

The results of stability studies indicate no significant changes in the formulation after 3months.Drugentrapment efficiency was found to be 81.09%.*Invitro* drug release were 10.88% forand 91.5% for 12 hrs. There was no significant change in the formulation. Hence it was found thatformulation was stable. Further studies can be carried out until 6 months.

4.7 CONCLUSION

Angina pectoris is the chest pain ,pressure or discomfort that occurs to the poor blood flow to the heart muscle.There are approximately 10 million people in the united states who have angina and there are over 500,000 cases diagnosed per year.

Metoprolol succinateis a beta -1- selective (cardio selective) adrenoreceptor blocking agent used in the management of hypertension, myocardial infraction, angina pectoris and cardiac arrhythmias. Metoprolol succinate is considered as the first line treatment for angina pectoris. The conventional dosage form of metoprolol succinate does not provide a better absorption in targeted site and prolonged action and it shows some side effects. So that metoprolol succinate is formulated as microspheres by ionic gelation method. Microspheres constitute an important part of novel drug delivery system by virtue of their small size and efficient carrier capacity. Drug action can be improved by developing new drug delivery system, such as Mucoadhesive microsphere drug delivery system So, the development of oral controlled release dosage form would clearly advantageous. In this preparation, Carbopol 934 P is used as mucoadhesive polymer and Eudragit RL 100 is used as a copolymer that increases the stability of the drug. The limited number of experiments an optimized formulation with controlled release and good mucoadhesion can be developed appropriate stastical software. The formulation F11 was found to be the optimum formulation which is shown in confirmation design. So the study show that metoprolol succinate microspheres can be successfully developing by optimizing the concentration of polymers and stirring speed in order to achieve the desired controlled release characteristics for the treatment of angina pectoris. Thus, metoprolol succinate microspheres that are retained in the stomach which increase the drug absorption, improves stability and decrease dosing frequency which provides better patient compliance as compare to conventional dosage form.

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