DESIGN AND DEVELOPMENT OF FLOATING TABLETS OF METOPROLOL SUCCINATE

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ABSTRACT: Metoprolol succinate (MS) gastro retentive (GR) controlled release system was formulated to increase gastric residence time leading to improved drug bioavailability. Floating tablets were used to increase the gastric residence time of dosage forms. Such dosage forms are better because they reduce the inter-subject variability in absorption and lower probability of dose dumping by reducing frequency of dosing. The objective of this study was to develop floating tablets of Metoprolol succinate using natural polymer having desirable properties in order to achieve an extended retention in the upper gastrointestinal tract, which may result in enhanced absorption and there by improved bioavailability. In this work Natural gums (Okra gum, Hibiscus rosa sinensis leaves mucilage, gum karaya) are used, which where not used till date in the formulation of Metoprolol succinate floating matrix tablets. Sodium bicarbonate was used as gas generating agent. Floating tablets of Metoprolol succinate were prepared by Wet granul;ation technique using Okra gum, Hibiscus rosa-sinensis and Gum karaya which showed controlled release of the drug for a prolonged period of time.The natural polymers used showed drug release retarding nature, and the release retarding nature was in order of Gum karaya>Hibiscus rosa-sinensis>Okra gum.Compared to other gums used, Gum karaya has high viscosity value and good drug release retarding capacity.There is a similarity between the viscosities of the polymers and their release retarding profiles.The powder folw properties such as Bulk density,Tapped density ,Angle of repose, carr's Index Hausner ratio were measured.The concentration of sodium bicarbonate influences the lag time. The FT-IR studies were performed which clearly indicates that there are no drug and polymer interactions .The prepared Metoprolol succinate floating tablets complies with the specifications of the Pharmacopoeial standards.

Keywords: Metoprolol succinate ,Gum karaya, Okra gum, Hibiscus rosa sinensis, Floating tablets

INTRODUCTION:

The increased interest in developing oral controlled release dosage forms can be endorsed to their ability to maintain an effective drug concentration in the systemic circulation for a long period of time and offering improved therapeutic advantages such as ease of dosing administration, patient compliance, flexibility in formulation[1]. However, the short gastric retention time and unpredictable rapid gastric rate can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to decreased therapeutic efficacy of administered dose[2] .This limitation has led to the development of oral gastro retentive dosage forms. Several gastro retentive drug delivery approaches being designed and developed which includes: high density sinking systems that is retained in the bottom of the stomach[3], low density floating systems that causes buoyancy in gastric fluid[4] , mucoadhesive systems that causes bioadhesion to stomach mucosa[5] , swellable, expandable or unfoldable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach[6] , superporous hydrogel systems [7] and magnetic systems[8] .Under certain circumstances prolonging the gastric retention of delivery system is desirable for achieving greater therapeutic benefit of the drug substances. For example, drugs that are absorbed in the proximal part of the gastro intestinal tract and the drugs that are less soluble are degraded by the alkaline pH may benefit from the prolong gastric retention[9,10]. In addition, for local and sustained drug delivery to the stomach and the proximal small intestine to treat certain conditions, prolonging gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability, therapeutic efficacy and possible reduction of the dose size[11,12].
Generally, drugs that are suitable for Gastro retentive drug delivery systems include[13]:
1. Drugs that are locally active in the stomach.
2. Drugs that have narrow absorption window in the GIT.
3. Drugs that are unstable in the intestinal or colonic environment.
4. Drugs that are primarily absorbed in stomach.
5. Drugs that exhibit low solubility at higher P^H values.

Most of the GRDDS act by the mechanism of swelling and expanding of the polymers that are generally incorporated or by effervescence which is trapped by the swollen polymer. This results in lowering the density of the formulation that helps in gastric retention. Polymers have been successfully investigated and employed in the formulation of gastro retentive drug delivery systems. Both synthetic and natural polymers have been investigated extensively for this purpose[14]. Synthetic polymers are toxic, expensive, have environment related issues, need long development time for synthesis and are freely available in comparison to naturally available polymers. However, the use of natural polymers for pharmaceutical applications

is attractive because they are economical, readily available, non-toxic and capable of chemical modifications, potentially biodegradable and with few exceptions and also biocompatible.

A large number of plant-based pharmaceutical excipients are available today. Many researchers have explored the usefulness of plant-based materials as pharmaceutical excipients. Ability to produce a wide range of material based on their properties and molecular weight, natural polymers became a plunge area in majority of investigations in drug delivery systems[15] . Natural gums can also be modified to meet the requirements of drug delivery systems and thus can compete with the synthetic polymers available in the market[16].

PLANT BASED NATURAL POLYMERS USED IN GASTRO RETENTIVE DRUG DELIVERY SYSTEMS:

1) Hibiscus rosa-sinensis Linn: Belongs to the Malvaceae family is also known as the shoe-flower plant, China rose, and Chinese hibiscus[17,18] . The fresh leaves of Hibiscus rosa-sinensis Linn are collected, washed with water to remove dirt and debris, and dried. The powdered leaves are soaked in water for 5-6 h, boiled for 30 min, and kept aside for 1 h for complete release of the mucilage into water. The material is squeezed from an eightfold muslin cloth bag to remove the marc from the solution. Acetone is added to the filtrate to precipitate the mucilage in a quantity of three times the volume of the total filtrate. The mucilage is separated, dried in an oven at a temperature < 50 °C, collected, dried-powdered, passed through a sieve (number 80), and stored for further use in desiccators[19] .The plant contains cyclopropanoids, methyl sterculate, methyl-2-hydroxysterculate, 2- hydroxysterculate malvate and β-rosasterol. Mucilage of Hibiscus rosa-sinensis contains L-rhamnose, D-galactose, D-galactouronic acid, and D- glucuronic acid[20] . The leaves are used in traditional medicines as emollients and aperients to treat burning sensations, skin disease, and constipation[21]. In a study the use of its mucilage for the development of sustained release tablet has been reported[19] . Matrix tablet containing dried mucilage and diclofenac sodium (DS) was prepared through direct compression techniques. It was found that mucilage can be used as release-retarding agent for 12 hrs when the drug-mucilage ratio was 1:1.5.

2) Okra gum:
Okra gum, obtained from the fruits of *Hibiscus esculentus*, is a polysaccharide consisting of D-galactose, L-rhamnose and L-galacturonic acid[22]. Okra gum was evaluated as a controlled- release agent in modified release matrices, in comparison with sodium carboxymethyl cellulose(NaCMC) and hydroxypropylmethyl cellulose (HPMC), using paracetamol as a model drug[23] . Okra gum matrices provided controlled- release of paracetamol for more than 6 hrs and the release rates followed time-independent kinetics. The release rates were dependent on the concentration of the drug present in the matrix. Okra gum compared favourably with NaCMC, and a combination of Okra gum and NaCMC, or on further addition of HPMC resulted in near zero order release of paracetamol from the matrix tablet. The results indicate that Okra gum matrices could be useful in the formulation of sustained- release tablets for up to 6 hrs.

3) Gum karaya:
Karaya gum is obtained from streculia urens of family streculiaceae. It is partially acetylated polymer of galactose , rhamnose and galactoroniac acid[24]. Gum karaya is a dried gummy exudate obtained from the tree Sterculiaurens (Roxburgh), Sterculiavillosa (Roxburgh), Sterculiatragacantha (Lindley) or other species of Sterculia (Sterculiaceae). It is also known as Indian tragacanth, Sterculia gum, Karaya gum, Thapsi Gum, Katiera, Gum kadaya, Kullo,
It is used as release controlling agent in producing directly compressed matrices. It has lower hydration capacity and a higher rate of erosion. **Park *etal***[25] showed that mucoadhesive tablets prepared by karaya gum for buccal delivery had superior adhesive properties when compared to other natural guma and was able to provide zero-order drug release ,but concentrations greater than 50%w/w may be required to provide suitable sustained release.

Gastro retentive dosage forms are drug delivery systems which remain in the stomach for an extended period of time and allow both spatial and time control of drug liberation. Basically gastro retentive systems swells following ingestion and is retained in the stomach for a number of hours, while it continuously releases the incorporated drug at a controlled rate to preferred absorption sites in the upper intestinal tract. Their application can be advantageous in the case of drugs absorbed mainly from the upper part of GIT or are unstable in the medium of distal intestinal regions. They can also be used beneficially in the local therapy of the stomach. Prolonged gastric retention of the drugs may offer numerous advantages including improved bioavailability, therapeutic efficacy and possible reduction of dosage size.

Metoprolol Succinate is a selective β_1 blocker used in the treatment of hypertension. It belongs to the category of AntiHypertensive. Its IUPAC name is (±) 1-(isopropyl amino)-3-[p- (2-methoxyethyl)phenoxy]-2-propanol succinate. Metoprolol is a β 1 -selective adrenergic receptor blocking agent. This preferential effect is not absolute, however and at higher plasma concentrations, metoprolol has no intrinsic sympathomimetic activity, and membrane stabilizing activity is detectable. Metoprolol blocks β1 adrenergic receptors in heart muscle cells, thereby decreasing the slope of phase 4 in the nodal action potential (reducing Na^+ uptake) and prolonging repolarization of phase 3 (slowing down K^+ release)[26]. It also suppresses the norepinephrine-induced increase in the sarcoplasmic reticulum (SR) Ca^{2+} leak and the spontaneous SR Ca^{2+} release, which are the major triggers for atrial fibrillation[27].

Metoprolol has a short half-life of 3 to 7 hours, so is taken at least twice daily or as a slow-release preparation.It undergoes α-hydroxylation and O-demethylation as a substrate of the cytochrome liver enzymes CYP2D6 and a small percentage by CYP3A4, resulting in inactive metabolites[28]

NEED FOR GASTRO RETENTION[10]

- Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).
- Drugs that are less soluble or that degrade at the alkaline p^H.
- Drugs that are absorbed due to variable gastric emptying time.
- Local or sustained drug delivery to the stomach and proximal small intestine to treat certain conditions.
- Particularly useful for the treatment of peptic ulcers caused by H.Pylori infections.

CERTAIN TYPES OF DRUGS CAN BENEFIT FROM USING GASTRO RETENTIVE DEVICES[12]

- Drugs acting locally in the stomach.
- Drugs those are primarily absorbed in the stomach.
- Drugs those are poorly soluble at an alkaline P^H.
- Drugs with a narrow window of absorption.
- Drugs absorbed rapidly from the GI tract.
- Drugs those degrade in the colon.

FLOATING DRUG DELIVERY SYSTEMS

A floating dosage form is useful for drugs acting locally in the proximal gastrointestinal tract. These systems are also useful for drugs that are poorly soluble (or) unstable in intestinal fluids. The floating properties of these systems help to retain in the stomach for a long time. Various attempts have been made to develop floating systems, which float on the gastric contents and release drug molecules for the desired time period. After the release of a drug, the remnants of the system are emptied from the stomach.

Based on the mechanism of buoyancy, two different technologies have been used in development of floating drug delivery systems. These include:

a) Effervescent system.

b) Non- Effervescent system.

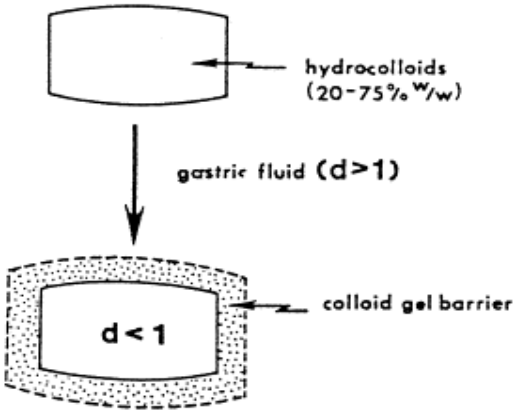
a) Effervescent Systems

Effervescent systems,[12] include use of gas generating agents, carbonates (e.g. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature.
These effervescent systems further classified into two types:

1) Gas generating systems.
2) Volatile liquid or Vacuum containing systems.

1) Gas generating systems
a) Tablets:
i) Intragastric single layer floating tablets or Hydrodynamically Balanced System

These formulations have bulk density lower than gastric fluids and thus float in the stomach that increases the gastric emptying rate for a prolonged period,(fig.2.14). These are formulated by intimately mixing the gas (CO_2) generating agents and the drug within the matrix tablet. The drug is released slowly at a desired rate from the floating system and the residual system is emptied from the stomach after the complete release of the drug. This leads to an increase in the gastric residence time (GRT) and a better control over fluctuations in plasma drug concentration.

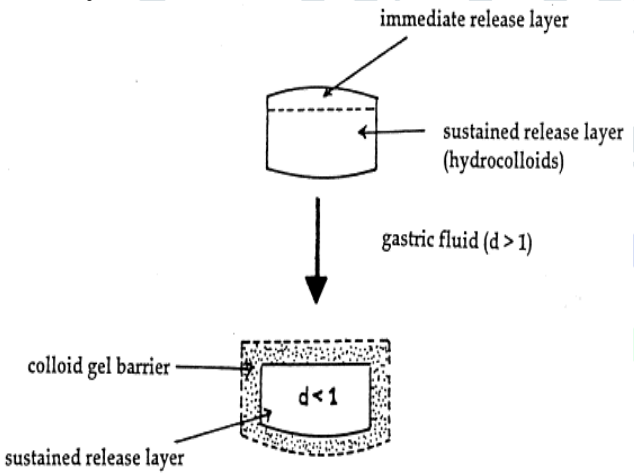


Intragastric single layer floating tablet

ii) Intragastric bilayer floating tablets:

These are also compressed tablets, containing two layers

- Immediate release layer and
- Sustained release layer.



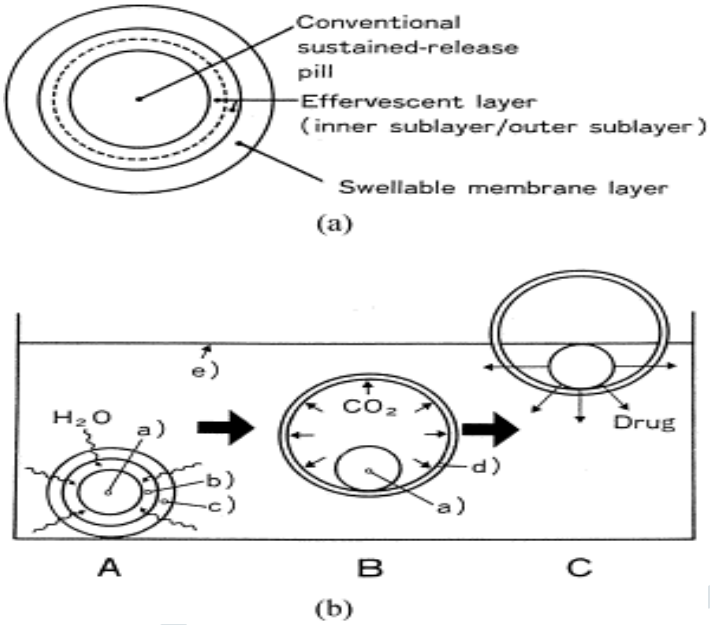
Intragastric bilayer floating tablet.

b) Floating capsules:

These floating capsules,[11]are formulated by filling with a mixture of sodium alginate and sodium bicarbonate. The systems float as a result of the generation of CO_2 that was trapped in the hydrating gel network on exposure to an acidic environment.

c) Multiple unit type floating pills:

These multiple unit type floating pills,[12] are sustained release pills, known as 'seeds', which are surrounded by two layers (fig.2.16). The outer layer is of swellable membrane layer while the inner layer consists of effervescent agents. This system sinks at once and then it forms swollen pills like balloons which float as they have lower density, when it is immersed in the dissolution medium at body temperature. The lower density is due to generation and entrapment of CO_2 within the system.



(a) A multiple-unit oral floating dosage system.(b) Stages of floating mechanism: (A) penetration of water; (B) generation of CO_2 and floating; (C) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (37^0C).

d) Floating system with Ion-Exchange resins:

Floating system using bicarbonate loaded ion exchange resin was made by mixing the beads with 1M sodium bicarbonate solution, and then the semi-permeable membrane is used to surround the loaded beads to avoid sudden loss of CO_2. On contact with gastric contents an exchange of bicarbonate and chloride ions takes place that results in generation of CO_2 that carries beads towards the top of gastric contents and producing a floating layer of resin beads[11].

2) **Volatile liquid or Vacuum containing systems**

a) Intragastric floating gastrointestinal drug delivery system:

This system floats in the stomach because of floatation chamber, which is vacuum or filled with a harmless gas or air, while the drug reservoir is encapsulated by a microporous compartment,[12] (fig.2.17)

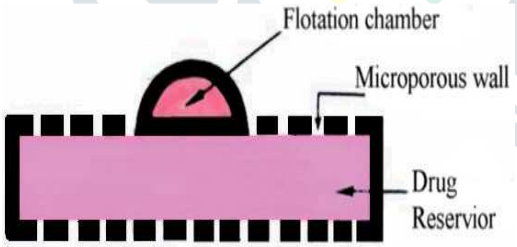


Figure 2.17: Intragastric floating gastrointestinal drug delivery device

b) Inflatable gastrointestinal delivery systems:

These systems are incorporated with an inflatable chamber, which contains liquid ether that gasifies at body temperature to inflate the chamber in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule,[12](fig.2.18). After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug is released continuously from the reservoir into gastric fluid.

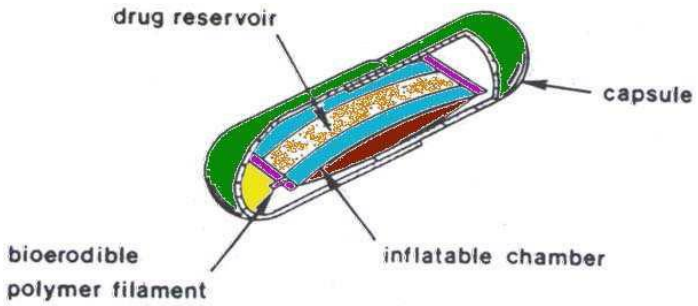
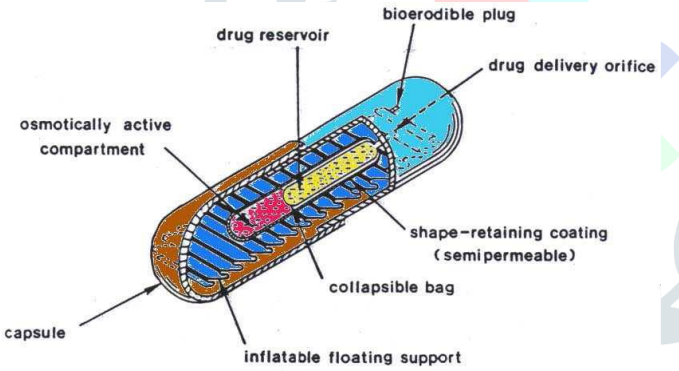


Figure 2.18: Inflatable gastrointestinal delivery system

c) Intragastric osmotically controlled drug delivery system:

This system is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule, [12] (fig.2.19). On contact with the gastric contents in the stomach, the capsule disintegrates quickly to release the intragastirc osmotically controlled drug delivery device. The inflatable support inside forms a hollow polymeric bag which contains a liquid that gasifies at body temperature to inflate the bag and it is deformable. The osmotic pressure controlled drug delivery device consists of two components, osmotically active compartment and a drug reservoir compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to liquid and vapor and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi-permeable housing. In the stomach, the osmotically active salt present in the osmotically active compartment is dissolved by absorbing the water continuously present in the GI fluid through the semi-permeable membrane. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice. The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.



Intragastric osmotically controlled drug delivery system

b) Non-Effervescent systems[12]

The Non-Effervescent floating drug delivery systems are based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The various types of this system are:

1) **Single layer floating tablets:**

These are formulated by intimate mixing of drug with a gel forming hydrocolloid, that swells on contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

2) **Bilayer floating tablets:**

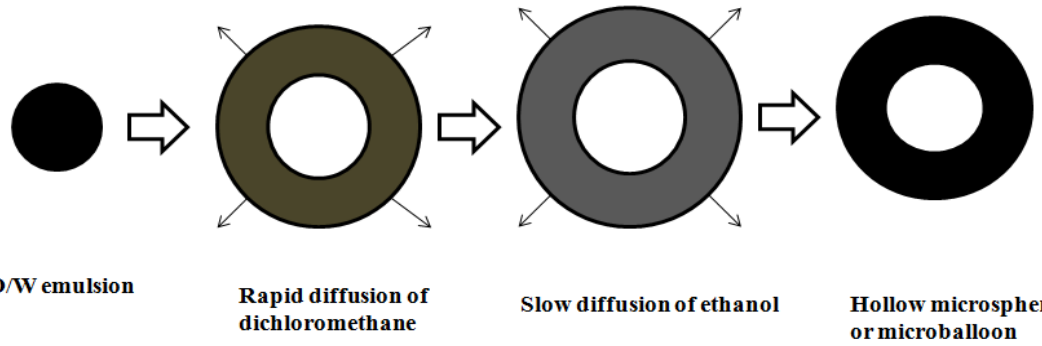
A bilayer tablet contain two layer one immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

3) Alginate beads:

Multi unit floating dosage forms were developed from freeze dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of $cacl_2$, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence, time of 1 hr, and these floating beads gave a prolonged residence time of more than 5.5 hours.

4) **Hollow microspheres:**

Hollow microspheres (microballons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method (fig.2.20). The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40^0C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro.*



Formulation of floating hollow microsphere or microballoon

ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM[12]

- The principle of Hydrodynamically Balanced System (HBS) can be used for any particular medicament or class of medicament. The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach, since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine. e.g. Chlorpheniramine maleate.

- The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.

- The efficacy of the medicaments administered utilizing the sustained release principle of HBS has been found to be independent of the site of absorption of the particular medicaments.

- Administration of a prolonged release floating dosage form tablet or capsule will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolved drug is available for absorption in the small intestine, therefore it is expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline p^H of the intestine.
- Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine.
- When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhoea, poor absorption is expected under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
- Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEM[18]:

1) Sustained drug delivery

Hydrodynamically Balanced System (HBS) type dosage forms which have bulk density less than one, relatively large in size and did not easily pass through pylorus, release the drug over a prolonged period of time by retaining in the stomach for several hours and by increasing the gastric residence time. Madopar HBS formulation has shown to release levodopa for up to 8 hour in vitro, whereas the standard formulation released levodopa in less than 30 min.

2)Site specific drug delivery

Floating drug delivery systems are particularly useful for drugs having specific absorption from stomach or proximal part of the small intestine e.g. riboflavin, furosemide etc. The absorption of Captopril has been found to be site specific, stomach being the major site followed by duodenum. This property prompts the development of a monolithic floating dosage form of Captopril which prolongs the gastric residence time and thus increases the bioavailability, which has shown AUC, approximately 1.8 times than that of conventional tablets.

3)Absorption enhancement

Drugs that have poor bioavailability, because of their absorption is restricted to upper GIT are potential candidates to be formulated as floating drug delivery systems, thereby improving their absolute bioavailability.

4)Minimized adverse activity at the colon

Retention of the drug at the stomach (HBS system), minimizes the amount of drug that reaches the colon, that prevents the undesirable activities of the drug in colon. This Pharmacodynamic aspect provides the rationale for GRDF formulation for betalactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

5) There are some cases in where the relative bioavailability of floating dosage form is reduced as compared to conventional dosage form e.g. floating tablets of amoxicillin trihydrate has bioavailability reduced to 80.5% when compared with conventional capsules. In such cases, the reduction in bioavailability is compensated by the advantages offered by FDDS e.g. patients with advanced Parkinson's disease, experienced pronounced fluctuations in symptoms while treatment with standard L-dopa. A HBS dosage form provided a better control of motor fluctuations although its bioavailability was reduced by 50-60% of the standard formulation.

6) H. Pylori, causative bacterium for peptic ulcers and chronic gastritis. Patients require high concentration of drug, to be maintained at the site of infection that is within the gastric mucosa. The floating dosage form due to its floating ability was retained in stomach and maintained high concentration of drug in the stomach. A sustained liquid preparation of Ampicillin, using sodium alginate was developed that spreads out and adheres to gastric mucosal surfaces and releases the drug continuously.

7) Floating drug delivery systems are particularly useful for drugs which are poorly soluble or unstable in intestinal fluids and acid stable drugs and for those which undergo abrupt changes in their pH-dependent solubility due to pathophysiological conditions of GIT, food and age, e.g. floating system for furosemide lead to potential treatment of Parkinson's disease. Approximate 30% drug was absorbed after oral administration

Aim and plan of the work is as follows:

The main objectives of this investigation are as follows:

- To isolate and extract natural polymers from their natural sources.
- To study the effect of sodium bicarbonate concentration and to optimize the concentration of gas generating agent.
- To conduct the compatibility studies of drug with natural polymers by IR spectral studies.
- To formulate and evaluate drug extended release floating tablets by direct compression method.
- To evaluate the formulated tablets according to the pharmacopeia standards.

- To conduct comparative release studies among the natural polymers
- To study the influence of natural polymers on release rate and to select the best

release retarding polymer among them and to evaluate the mechanism and release kinetics of drug from the prepared tablets**.**

Metaprolol succinate API and Okra gum was obtained from Hetero labs, Hyderabad. Hibiscus rosa sinensis was taken from Yucca enterprises, Mumbai. Gum karaya was obtained from Yarrow chem. Products ,Mumbai. Micro crystalline cellulose, sodium bicarbonate, Hcl, Citric acid was taken from Qualigens fine chemicals,Mumbai. Talc and magnesium stearate was taken from SD Fine chemicals,Mumbai.
Tablet Dissolution test was performed by Electrolab TDT 08L, dissolution tester, U.S.P.

Construction of Standard calibration curve for Metoprolol succinate:

The calibration curve was constructed using 0.1N HCl as buffer. Accurately weighed 100 mg of Metoprolol succinate was transferred into 100 ml volumetric flask and dissolved in 0.1N HCl. Then volume was made up to the mark with 0.1N HCl to give a stock solution1 mg/ml. Further dilutions were made with 0.1N HCl to obtain 2 to 10 µg/ml concentrations of Metoprolol succinate and the absorbance was measured at 224 nm.

VISCOSITIES OF 1% w/v DISPERSIONS OF NATURAL GUMS IN 0.1N HCL:

Viscosities of 1%w/v dispersion of natural gumsin 0.1N HCl were measured by using Brookfield viscometer.

EXTRACTION OF NATURAL GUMS

1) Abelmoschus esculentus pods mucilage (Okra gum)*[29]*

The fresh *Abelmoschus esculentus* fruits were collected and washed with water. The fruits were crushed and soaked in water for 5 to 6 hrs, boiled for 30 mins and left to stand for 1 hr to allow complete release of the mucilage into the water. The mucilage was extracted using a multi layer muslin cloth bag to remove the marc from the solution. Acetone (three times the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 40°C, collected, ground, passed through a # 80 sieve and stored.

2) Hibiscus rosa-sinensis (leaves mucilage)[30] The fresh *Abelmoschus esculentus* fruits were collected and washed with water. The fruits were crushed and soaked in water for 5 to 6 hrs, boiled for 30 mins and left to stand for 1 hr to allow complete release of the mucilage into the water. The mucilage was extracted using a multi layer muslin cloth bag to remove the marc from the solution. Acetone (three times the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 40°C, collected, ground, passed through a # 80 sieve and stored.

The fresh leaves of *Hibiscus rosa-sinensis Linn.* were collected, washed with water to remove dirt and debris, and dried. The powdered leaves were soaked in water for 5 to 6 hrs, boiled for 30 mins, and kept aside for 1 hr for complete release of the mucilage into water. The material was squeezed from an eight-fold muslin cloth bag to remove the marc from the solution. Acetone was added to the filtrate to precipitate the mucilage in a quantity of three times the volume of the total filtrate. The mucilage was separated, dried in an oven at a temperature < 50 °C, collected, dried-powdered, passed through a sieve (number 80), and stored.

PREPARATION OF METOPROLOL SUCCINATE FLOATING TABLETS

Floating tablets of Metoprolol succinate were prepared by using different drug : polymer (Metoprolol succinate +Natural polymer) ratios . The tablets were formulated by employing Direct compression method. Metoprolol succinate, sodium bicarbonate, different polymers, diluent, talc and magnesium stearate were mixed thoroughly and directly compressed employing 12 mm round shaped die. The details of composition of each formulation are given in the table below.

Composition of Metoprolol succinate floating tablets formulated with different natural polymers:

Ingredients	F_1 (mg)	F_2 (mg)	F_3 (mg)	F_4 (mg)	F_5 (mg)	F_6 (mg)	F_7 (mg)	F_8 (mg)	F_9 (mg)
Metoprolol succinate	100	100	100	100	100	100	100	100	100
Abelmoschus esculentus pods mucilage.	25	50	75	-	-	-	-	-	-
Hibiscus rosasinensis leaves mucilage.	-	-	-	25	50	75	-	-	-
Gum karaya	-	-	-	-	-	-	25	50	75
Micro crystaline cellulose	82.5	57.5	32.5	82.5	57.5	32.5	82.5	57.5	32.5
Sodium Bbicarbonate	25	25	25	25	25	25	25	25	25
Citricacid	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	250	250	250	250	250	250	250	250	250

EVALUATION PARAMETERS:

FLOW PROPERTIES OF POWDER BLEND[31]:

a) **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 powder blend (passed through standard sieve # 20) into a measuring cylinder and initial weight will be noted. This initial volume is called bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in g/ml and is given by

Bulk Density (g/ml) = Mass of the powder/Bulk Volume

b) **Tapped Density (D_t):** It is the ratio of total mass of the granules to the tapped volume of the granules. Volume was measured by tapping the granules for 750 times and the tapped volume will be noted, if the difference between these two volumes is less than 2%. If it is more than 2%, tapping was continued for 1200 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 g/ml and is given by

Tapped density (g/ml) = Mass of the powder/Tapped volume

c) **Angle of Repose (ɵ):** The friction forces in powder blend can be measured by the angle of repose (ɵ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of granules and the horizontal plane. The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was calculated by measuring the height and radius of the heap of granules formed. Angle of repose is calculated by using the following formula:

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

Where,
θ is the angle of repose.
h is the height of the heap(in cms)

r is the radius of the heap(in cms)

d) **Carr's index (or) % compressibility:** It indicates powder flow properties. It is expressed in percentage and is given by

Carr's Index (%) = [(Tapped density – Bulk Density) / Tapped Density] × 100

e) **Hausner ratio:** Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

Hausner's Ratio = Tapped density / Bulk Density

EVALUATION OF FLOATING TABLETS

a) **Hardness[32]:** The hardness of the tablet was measured by Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force. The hardness was measured in terms of kg/cm^2.

b) **Drug content[32]:**Twenty tablets were weighed and powdered and a quantity of powder equivalent to 100mg of Metoprolol succinate was weighed and was dissolved in 100ml of 0.1N HCl and filtered. 5ml of this was diluted to 50ml with water and drug content was estimated using UV-VISIBLE spectrophotometer at 224nm.

c) **Weight variation[33]:**Formulated tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated by using the following formula.

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

d) **Friability [33]:** The Roche friability test apparatus was used to determine the friability of the tablets. Twenty six 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.

$$\text{Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} X\ 100$$

e) **In vitro buoyancy study[34]:** This test is characterized by floating lag time and total floating time. The test was performed using USP-Type II paddle apparatus using 900 ml of 0.1N HCl at paddle rotation of 100 rpm at 37 ± 0.5^0 C. The time required for tablet to rise to surface of dissolution medium and duration of time the tablet constantly float on dissolution medium was noted as floating lag time and total floating time.

f) **In vitro dissolution test[34]:**The release of Metoprolol succinate from the tablet was studied using USP-Type II paddle apparatus. Dissolution test was carried out for a period of 12 hrs. Drug release profile was carried out in 900 ml of 0.1N HCl maintained at 37 ± 0.5°C temperatures at 75 rpm. 5 ml of samples were withdrawn at regular time intervals. The samples were replaced by its equivalent volume of dissolution medium and was filtered through 0.45 µm whattman filter paper and analyzed at 224 nm by UV spectrophotometer.

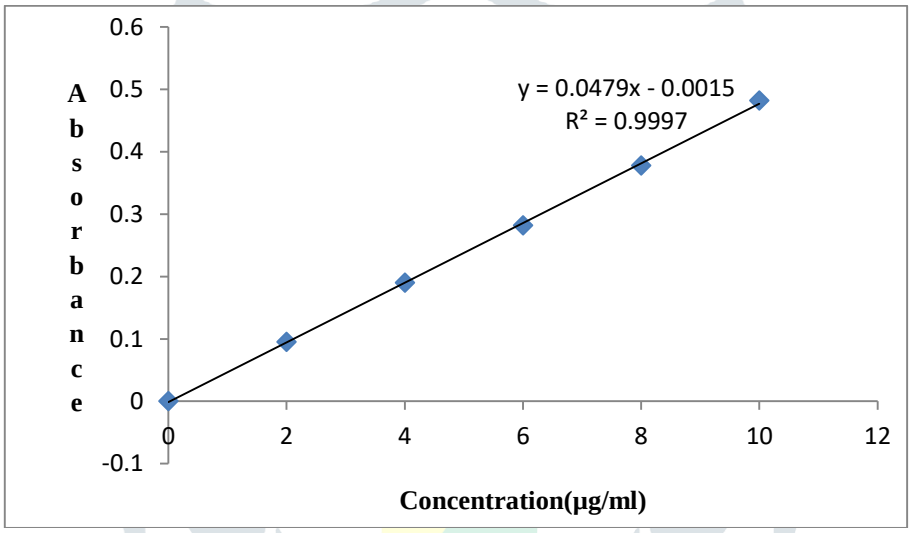
Drug-excipient compatibility study by IR spectroscopy:

The physico-chemical compatibility between Metoprolol succinate and the excipients used in the research was tested by IR spectroscopy using Perkin Fourier Transform Infrared Spectrophotometer (Laila impex research centre, Vijayawada)[35]. The samples were scanned under diffuse reflectance mold and graph was plotted by KBr spellet technique. The spectra were recorded in the wave number region between 4400cm^{-1} to 400cm^{-1}.

RESULTS AND DISCUSSION:

1) Construction of calibration cure for Metoprolol succinate in 0.1N HCl

S.no	Concentration (µg/ml)	Trial 1	Trail 2	Trial 3	Average
1	2	0.098	0.084	0.104	0.095
2	4	0.199	0.174	0.199	0.190
3	6	0.298	0.277	0.273	0.282
4	8	0.411	0.403	0.320	0.378
5	10	0.500	0.470	0.478	0.482
6	R^2	0.9994	0.9937	0.9976	0.9997



Standard Calibration Curve of Metoprolol succinate 0.1 N HCl.

2)Viscosities of 1%w/v dispersions of1%w/v dispersions of natural gums in 0.1N HCL

S.NO	Natural gum	Viscosity(Cps)
1	Gum karaya	1205.74
2	Hibiscus rosa-sinensis	1052.54
3	Okra gum	958.28

3) **Micromeritic properties of Metoprolol succinate powder blend formulated with different concentrations of Okra gum:**

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (^{0})	Compressibility index (%)	Hausner's ratio
F_1	0.52	0.62	27.14^o	13.88	1.16
F_2	0.53	0.68	29.14^o	13.91	1.16
F_3	0.57	0.66	25.14^o	12.70	1.14

4) Physical properties of Metoprolol succinate floating tablets formulated with different concentrations of Okra gum:

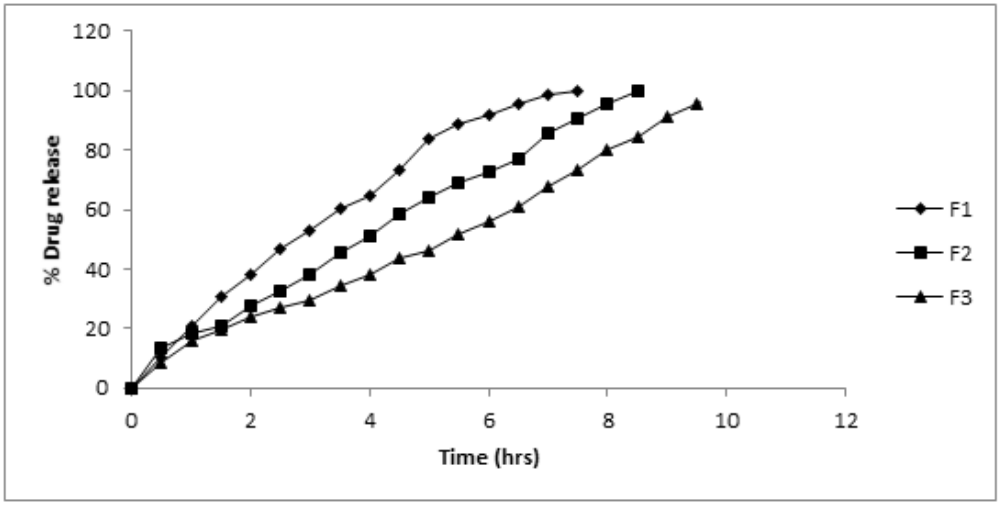
Formulation	Hardness (kg/ cm^2)	Weight variation(mg)	Friability (%)	Drug content (%)	Floating lag time (min)	Total floating time (hrs)
F_1	4.77	250.38	0.37	100.15	4	>14
F_2	4.80	251.39	0.73	100.78	3	>14
F_3	4.43	250.98	0.52	99.62	2.5	>14

5) *In vitro* release data of Metoprolol succinate floating tablets formulated with different concentrations of Okra gum:

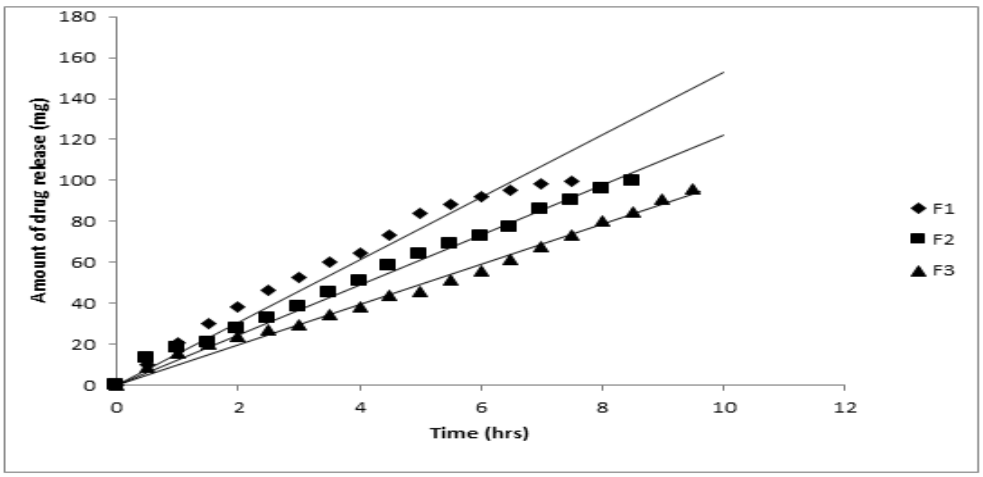
Time (hrs)	% Drug Release		
	F_1	F_2	F_3
0	0.00	0.00	0.00
0.5	10.13±0.04	13.51±0.04	9.22±0.05
1	20.69±0.07	18.22±0.06	15.74±0.06
1.5	30.39±0.04	20.83±0.07	20.50±0.04
2	38.31±0.09	27.72±0.05	24.15±0.07
2.5	46.54±0.04	32.56±0.05	26.91±0.04
3	52.69±0.11	38.32±0.11	33.24±0.05
3.5	60.40±0.12	45.36±0.08	36.58±0.02
4	64.45±0.07	50.79±0.06	40.78±0.06
4.5	73.41±0.05	58.19±0.104	43.43±0.07
5	84.06±0.08	64.03±0.04	48.96±0.08
5.5	88.53±0.04	69.07±0.08	52.91±0.03
6	91.82±0.05	72.85±0.04	58.05±0.04
6.5	95.41±0.03	77.25±0.05	64.62±0.02
7	98.36±0.06	85.71±0.06	69.94±0.08
7.5	99.49±0.04	90.49±0.05	79.29±0.06

6) *In vitro* drug release kinetic data of Metoprolol succinate floating tablets formulated with different concentrations of Okra gum:

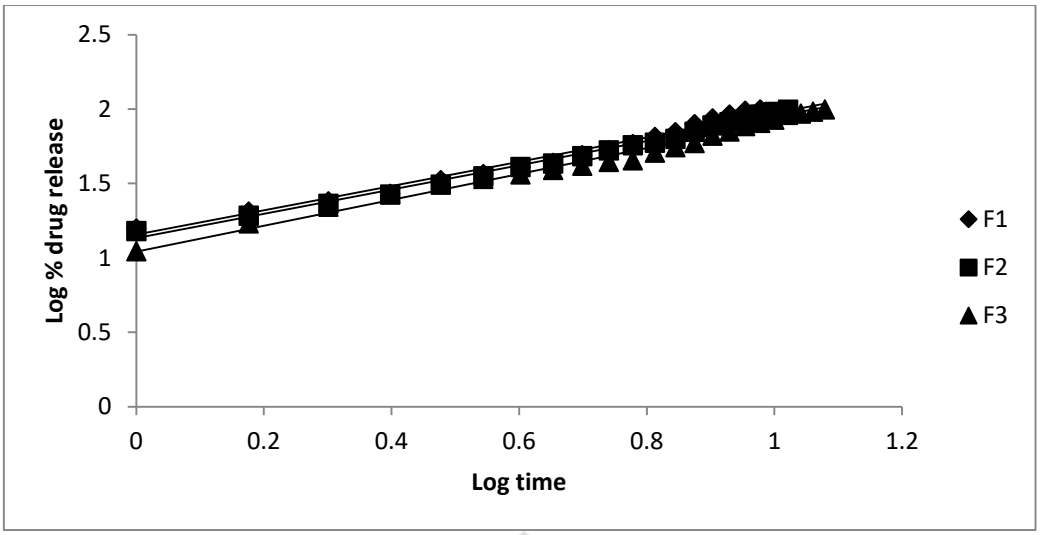
Formulation	Correlation Coefficient Value				Release RateConstant k_0 (mg/hr)	Exponential Coefficient (n)	T_{50} (hr)	T_{90} (hr)
	Zero Order	First Order	Matrix	Peppas				
F_1	0.9894	0.8304	0.9581	0.9984	13.32	0.8147	3.75	6.75
F_2	0.9910	0.8573	0.9612	0.9976	11.76	0.8206	4.25	7.65
F_3	0.9939	0.8190	0.9751	0.9966	10.52	0.9188	4.75	8.55



Comparative *in vitro* drug release profile of Metoprolol succinate floating tablets formulated with different concentrations of Okra gum



Comparative Zero order plots of Metoprolol succinate floating tablets formulated with different concentrations of Okra gum



Comparative Peppas plots of Metoprolol succinate floating tablets formulated with different concentrations of Okra gum

7)Micromeritic properties of Metoprolol succinate powder blend formulated with different concentrations of Hibiscus rosasinensis

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (^{0})	Compressibility index (%)	Hausner's ratio
F_4	0.52	0.62	27.14º	13.88	1.16
F_5	0.58	0.69	28.38º	12.10	1.13
F_6	0.54	0.65	29.26º	13.76	1.15

8)Physical properties of Metoprolol succinate floating tablets formulated with different concentrations of Hibiscus rosasinensis

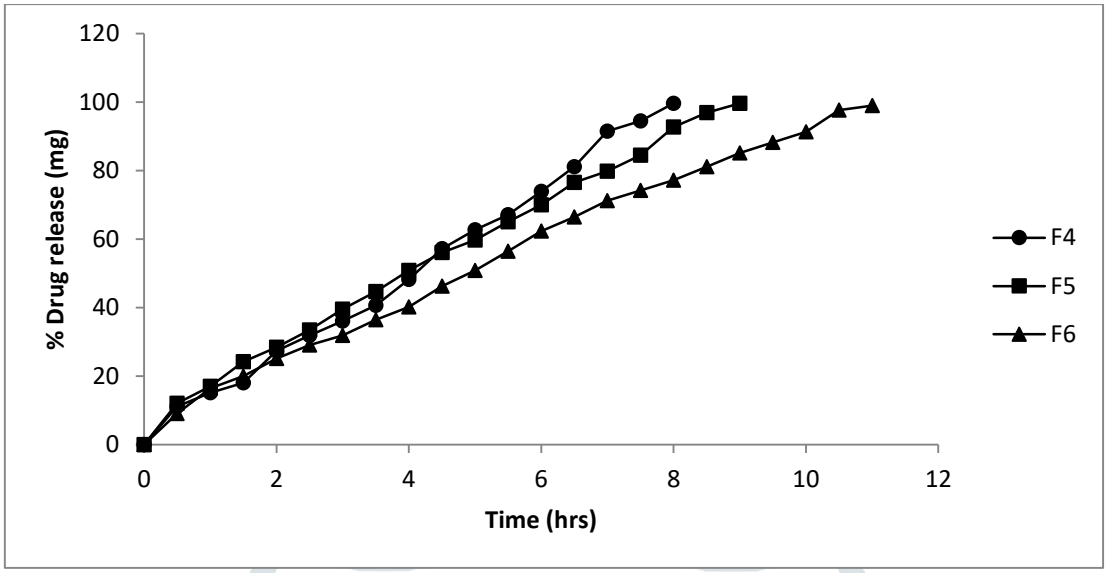
Formulation	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)	Floating lag time (min)	Total floating time (hrs)
F_4	4.77	250.38	0.37	100.15	3	>14
F_5	4.8	250.47	0.62	99.45	2.5	>14
F_6	4.7	251.39	0.37	101.89	2.2	>14

9) ***In vitro*** **release data of Metoprolol succinate floating tablets formulated with different concentrations of Hibiscus rosasinensis.**

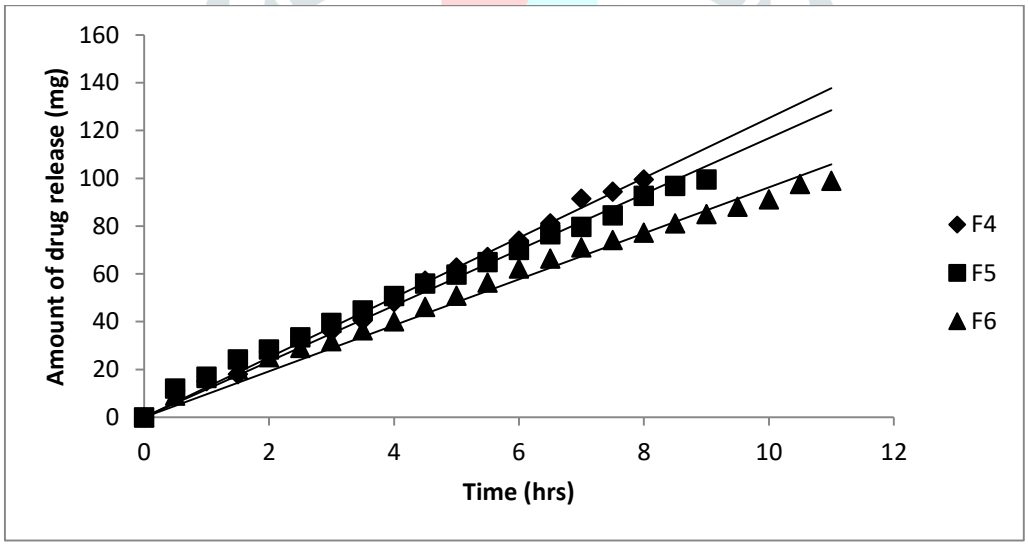
Time (hrs)	% drug release		
	F_4	F_5	F_6
0	0.00	0.00	0.00
0.5	10.98±0.06	11.97±0.05	8.61±0.06
1	15.14±0.08	17.04±0.10	15.70±0.02
1.5	18.02±0.04	24.25±0.06	19.87±0.04
2	27.42±0.05	28.38±0.05	24.08±0.01
2.5	31.86±0.15	33.47±0.07	26.94±0.03
3	36.083±0.09	39.56±0. 03	29.45±0.05
3.5	40.61±0.06	44.73±0.02	34.36±0.06
4	48.24±0.16	50.86±0.06	38.24±0.07
4.5	57.17±0.12	56.01±0.03	43.79±0.06
5	62.75±0.17	59.77±0.06	46.11±0.08
5.5	67.11±0.05	65.03±0.08	51.67±0.12
6	73.93±0.08	70.07±0.07	55.91±0.11
6.5	81.16±0.15	76.58±0.02	61.15±0.05
7	91.49±0.03	79.78±0.04	67.68±0.11
7.5	94.46±0.04	84.53±0.03	73.28±0.03
8	99.61±0.14	92.72±0.09	80.14±0.05

10) ***In vitro*** **drug release kinetic data of Metoprolol succinate floating tablets formulated with different concentrations of Hibiscus rosasinensis:**

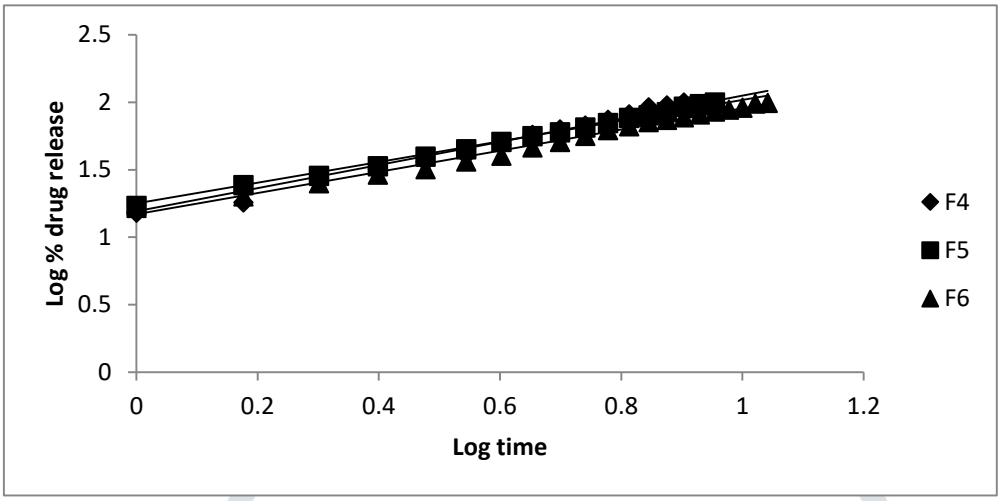
Formulation	Correlation Coefficient Value				Release Rate Constant (mg/hr)k_0	Exponential Coefficient (n)	T_{50} (hr)	T_{90} (hr)
	Zero Order	First Order	Matrix	Peppas				
F_4	0.9916	0.8094	0.9581	0.9984	12.50	0.8756	4	7.2
F_5	0.9943	0.7903	0.9632	0.9979	11.0	0.7938	4.54	8.1
F_6	0.9957	0.7956	0.9780	0.9912	9.98	0.7455	5.01	9.01



Comparative *in vitro* drug release profile of Metoprolol succinate floating tablets formulated with different concentrations of Hibiscus rosasinensis



Comparative Zero order plots of Metoprolol succinate floating tablets formulated with different concentrations of Hibiscus rosasinensis



Comparative Peppas plots of Metoprolol succinate floating tablets formulated with different concentrations of Hibiscusrosasinensis

11) Micromeritic properties of Metoprolol succinate powder blend formulated with different concentrations of gum karaya

Formulation	Bulk Density (g/ml)	Tapped density (g/ml)	Angle of repose (^{0})	Compressibility index (%)	Hausner's ratio
F_7	0.52	0.62	27.14º	13.88	1.16
F_8	0.49	0.58	29.37 º	14.82	1.14
F_9	0.57	0.68	26.32 º	15.93	1.18

12) Physical properties of Metoprolol succinate floating tablets formulated with different concentrations of gum karaya:

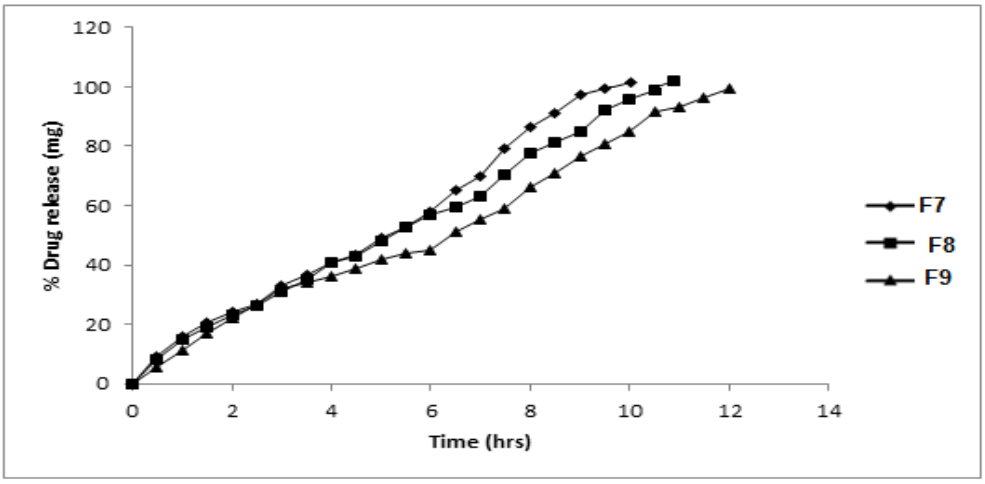
Formulation	Hardness (kg/ cm^2)	Weight variation(mg)	Friability (%)	Drug content (%)	Floating lag time (min)	Total floating time (hrs)
F_7	4.77	250.38	0.37	100.15	3	>14
F_8	4.28	250.78	0.37	99.78	3	>14
F_9	4.43	249.36	0.52	99.56	3	>14

13) *In vitro* release data of Metoprolol succinate floating tablets formulated with different concentrations of gum karaya:

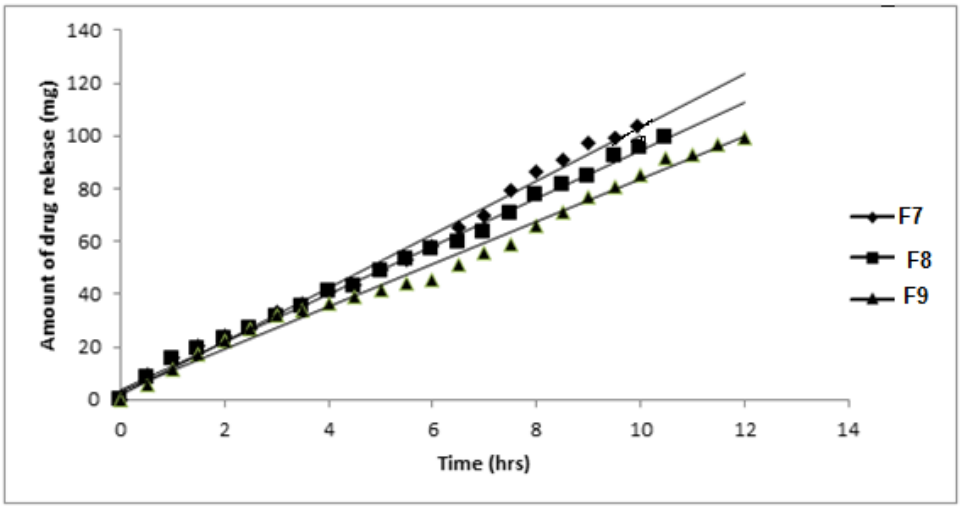
Time (hrs.)	% of drug released		
	F7	F8	F9
0	0.00	0.00	0.00
0.5	8.30±0.09	9.06±0.05	5.57±0.05
1	15.15±0.08	16.46±0.06	11.14±0.07
1.5	19.25±0.04	20.03±0.07	17.02±0.05
2	23.07±0.05	25.14±0. 06	22.04±0.06
2.5	26.60±0.12	29.01±0.07	26.85±0.07
3	31.07±0.16	31.87±0.06	31.91±0.09
3.5	35.26±0.05	36.46±0.07	33.91±0.07
4	40.71±0.12	40.10±0.04	36.32±0.08
4.5	43.13±0.13	46.28±0.06	39.03±0.06
5	48.24±0.04	50.83±0.07	41.88±0.04
5.5	52.87±0.03	56.41±0.04	44.78±0.03
6	57.18±0.09	62.32±0.07	45.43±0.07
6.5	59.34±0.05	66.46±0.03	51.05±0.06
7	63.06±0.08	71.17±0.07	55.45±0.08
7.5	70.51±0.06	74.25±0.05	59.42±0.05
8	77.69±0.07	77.27±0.06	66.60±0.06
8.5	81.50±0.06	81.13±0.03	70.42±0.09
9	84.74±0.07	85.18±0.07	76.85±0.11
9.5	91.96±0.09	88.24±0.04	80.03±0.07
10	95.55±0.07	91.35±0.06	85.05±0.08

14) *In vitro* drug release kinetic data of Metoprolol succinate floating tablets formulated with different concentrations of gum karaya:

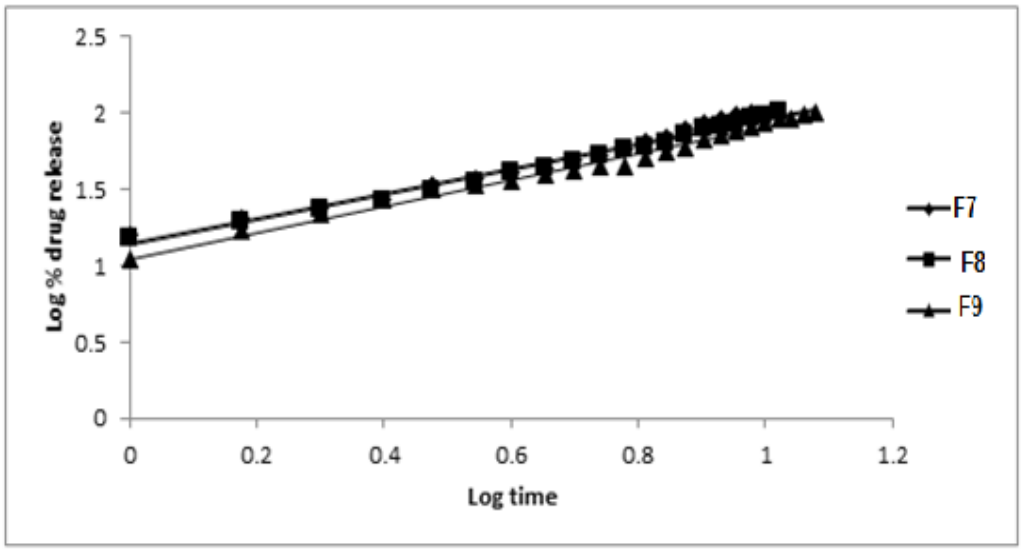
Formulation	Correlation Coefficient Value				Release Rate Constant (mg/hr)k_0	Exponential Coefficient (n)	T_{50} (hr)	T_{90} (hr)
	Zero Order	First Order	Matrix	Peppas				
F_7	0.9912	0.9878	0.9581	0.9984	9.52	0.8756	5.25	9.45
F_8	0.9616	0.9547	0.9863	0.9971	8.90	0.7619	5.61	9.91
F_9	0.9032	0.9820	0.9988	0.9958	8.32	0.6752	6.0	10.81



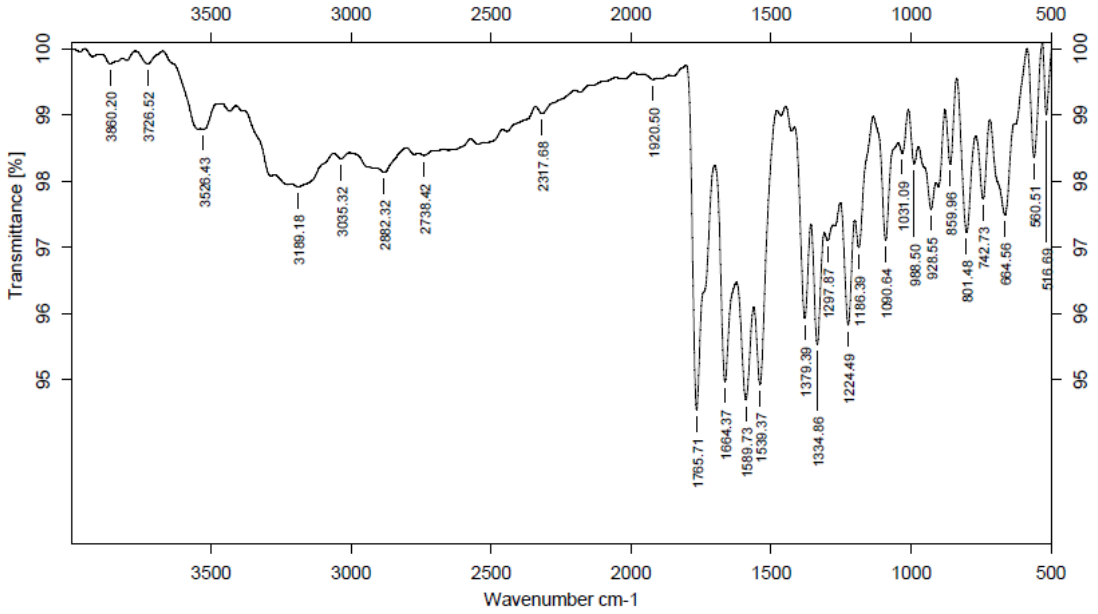
Comparative *in vitro* drug release profile of Metoprolol succinate floating tablets formulated with different concentrations of gum karaya



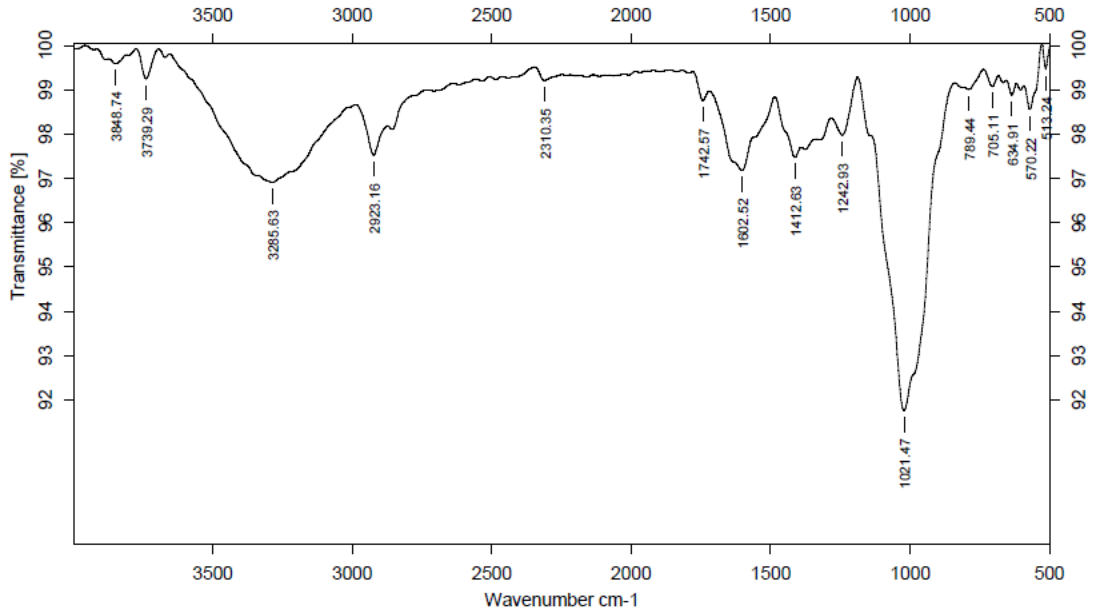
Comparative Zero order plots of Metoprolol succinate floating tablets formulated with different concentrations of gum karaya



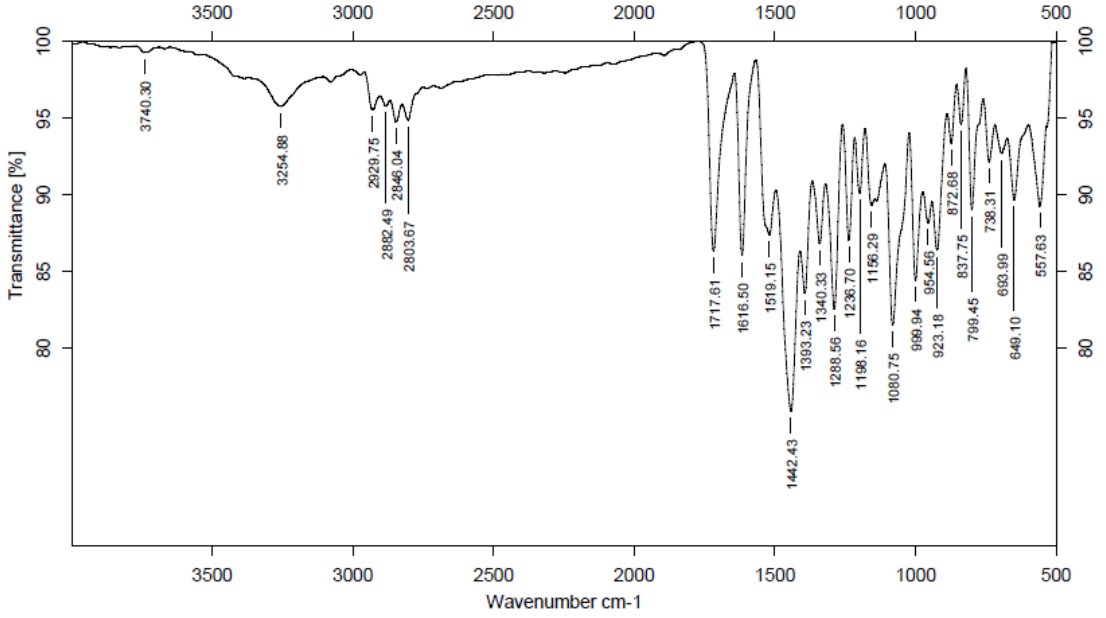
Comparative Peppas plots of Metoprolol succinate floating tablets formulated with different concentrations of gum karaya



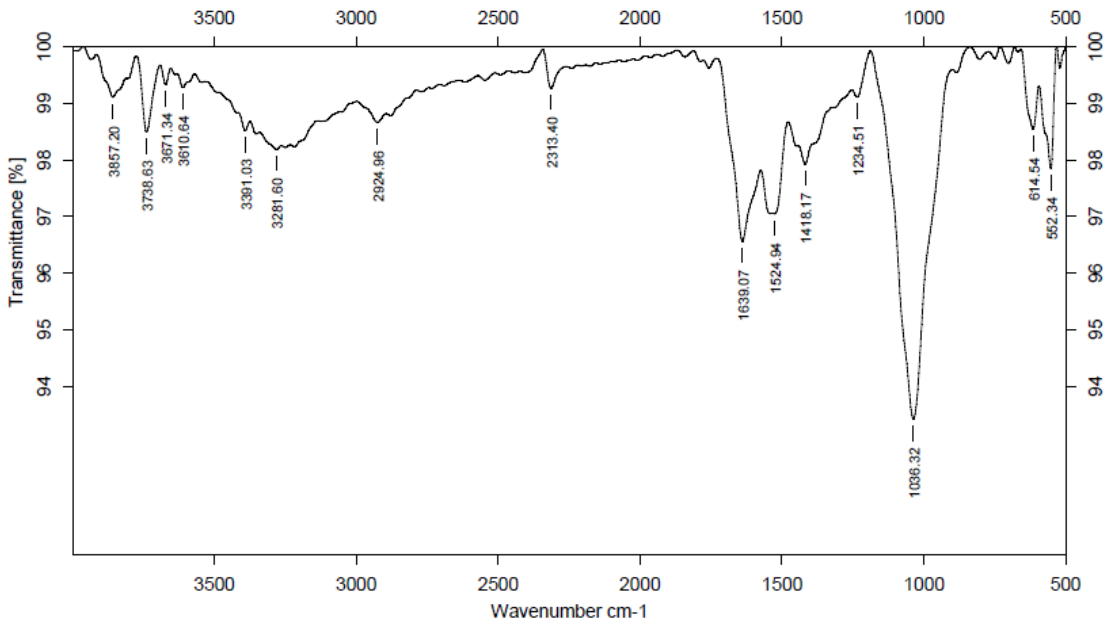
IR Spectrum of Metoprolol succinate



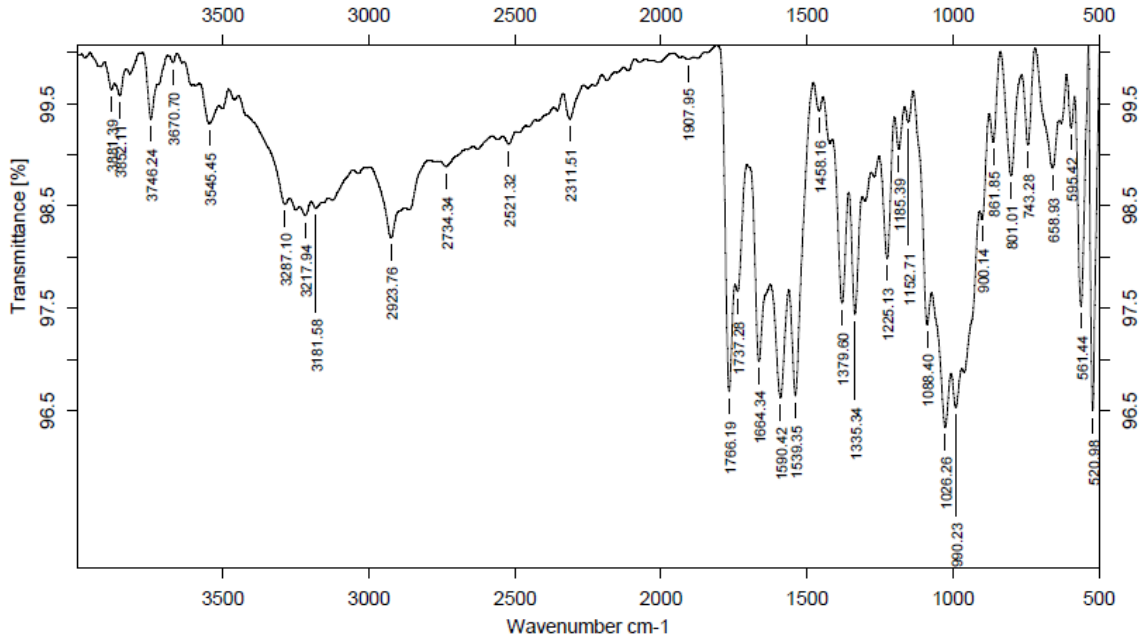
IR Spectrum of Okra gum



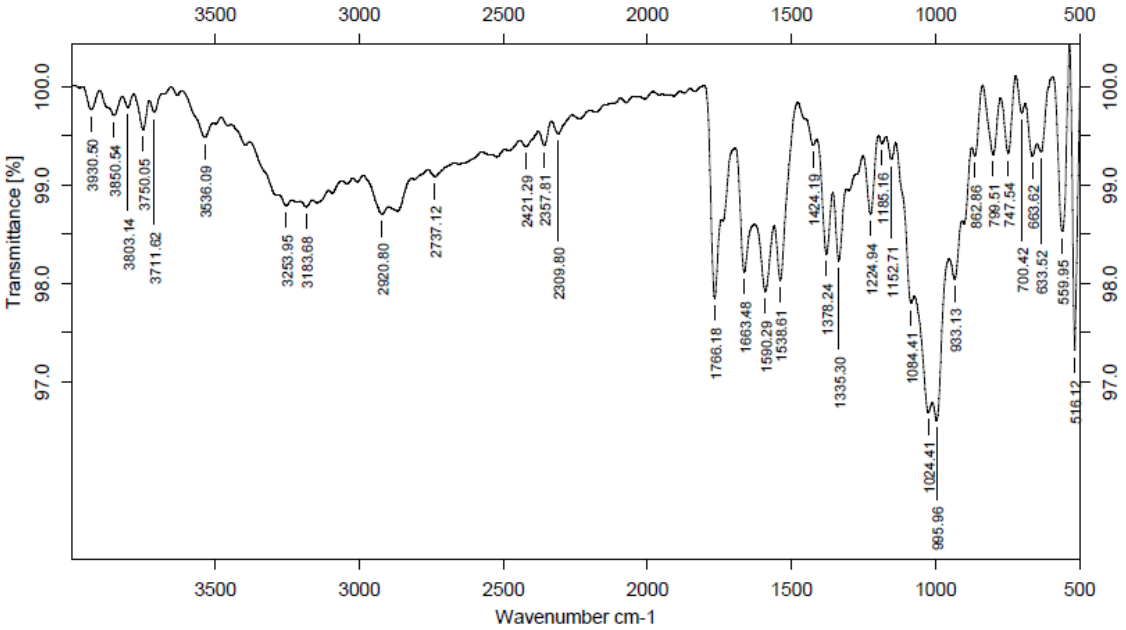
IR Spectrum of Hibiscus rosa sinensis



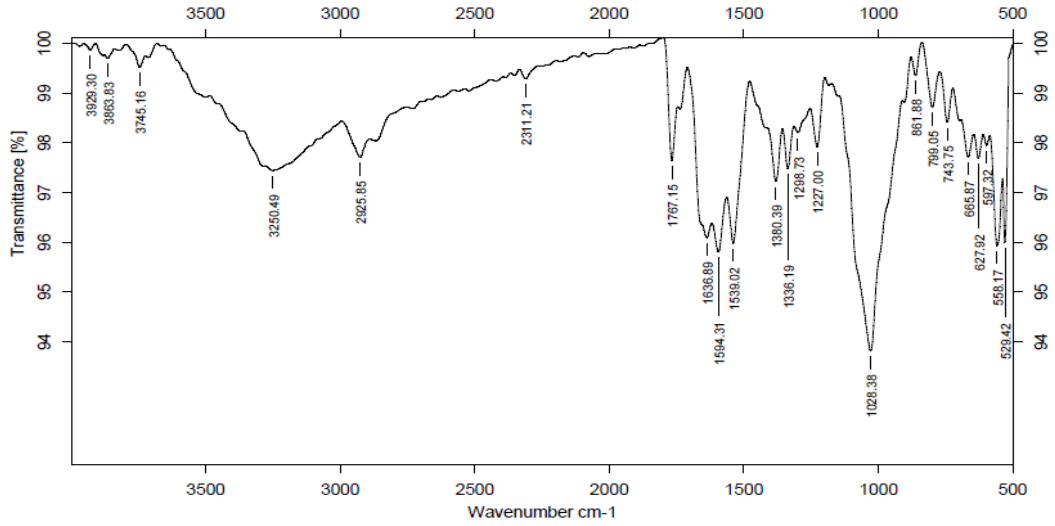
IR Spectrum of Gum karaya



IR Spectrum of Metoprolol succinate and Okara Gum



IR Spectrum of Metoprolol succinate and Hibiscus rosasinensis gum.



IR Spectrum of Metoprolol succinate and Gum karaya

SUMMARY AND CONCLUSION:

Floating tablets of Metoprolol succinate prepared using Okra gum, Hibiscus rosa-sinensis and Gum karaya showed controlled release for a prolonged period of time.The natural polymers used showed drug release retarding nature and the release retarding nature was in order of Gum karaya>Hibiscus rosa-sinensis>Okra gum.Compared to other gums used Gum karayahas high viscosity value and good drug releaseretarding capacity.There is a similarity between the viscosities of the polymers and their

release retarding profiles.The concentration of $NaHCO_3$ influences the lag time. In this investigation 12.5 % sodium bi carbonate was selected as optimized concentration.The FT-IR studies clearly indicates that there are no drug and polymer interactions.Prepared Metoprolol succinate floating tablets complies with the specifications of the Pharmacopoeial standards.From this study it could be concluded that natural polymers can be used in the preparation of floating tablets.

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