Formulation And Evaluation of Stomach Specific Floating In- Situ Gelling System

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***Abstract*—Aim: - The aim of present study is to Design, Development and Characterization of Stomach Specific Floating In-Situ Gelling System to reduce dose frequency for prolonged period of drug action.**

Objective: -The objective of research is to Develop and Evaluate In-Situ Floating gelling system to be administered by oral route which upon exposure to Physiologic conditions changes to gel Phase. This novel drug delivery system promotes importantly ease and convenience of administration, deliverance of accurate dose as well as to prolong residence time of drug in contact with mucosa that problems generally encountered in semisolid dosage forms. In situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. Smart polymeric systems represent promising means of delivering the drugs; these polymers undergo sol-gel transition, once administered.

***Index Terms*—Floating Drug Delivery System, Gastric retention,**

I. INTRODUCTION

Floating Drug Delivery System (FDDS) is one of the novel systems of drug delivery In-situ gelling system is a new trend in FDDS. In-situ gelling system has its application in different routes of administration like oral, nasal, ophthalmic, peroral, rectal, vaginal and also Parenteral route. In situ forming polymeric drug delivery systems has many advantages such as ease of administration, increased local bioavailability, reduced dose frequency, improved patient compliance and has less complex method of production and so is cost effective

Oral Drug Delivery System- Oral delivery of drugs is by far the most preferred route of drug delivery due to ease of administration, patient compliance and flexibility in formulation. Conventional oral dosage forms provide a specific drug concentration in systemic circulation without offering any control over drug delivery. These systems achieve as well as maintain drug concentration within therapeutically effective range needed for treatment only when taken several times a day. This results in significant fluctuation in drug levels. Now-a- days most of the pharmaceutical scientists are involved in developing an ideal drug delivery system (DDS). Anatomy of Stomach: - The stomach is a j-shaped organ located in the upper left-hand portion of the abdomen just below the diaphragm. It occupies a portion of the epigastria and left hydro chondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Due to its small surface area very little absorption takes place from the stomach. It acts as a barrier to the delivery of drugs to the small intestine.

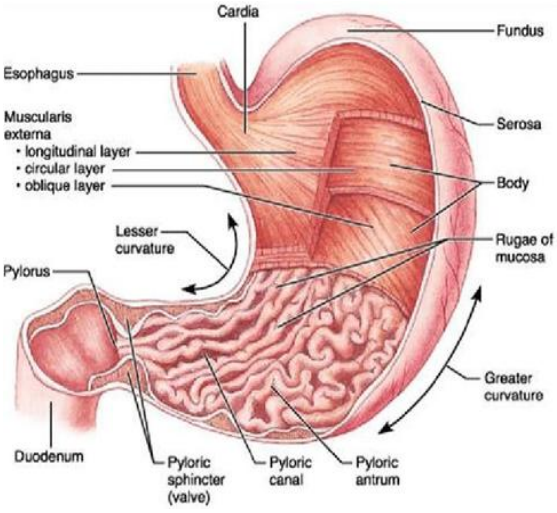


Fig. No. 1. Anatomy of Stomach

The stomach has four main regions,

- Cardia
- Fundus
- Body
- Pylorus

The main function of the fundus and body is storage, whereas that of cardia is mixing or grinding. The fundus adjusts the increased volume during eating by relaxation of the fundus muscle fibers. The fundus also

exerts a steady pressure on the gastric contents pressing them towards the distal region. To pass through the pyloric sphincter into the small intestine, particle size should be of order of 1-2mm.

Physiology of stomach- The main function of stomach is to store food temporarily, grind it and then release it to duodenum.The end portion of stomach and starting of intestine means duodenum is joined by pyloric sphincter, which a valve type unit and it can open maximum up to 12.8 ±7 mm. So dosage having higher size are retained more time in stomach. fluid volume in stomach is minimum of 25-50 ml at resting stage.pH of gastric fluid is generally 1.5-2 in fasted state and may raise up to 2-6 in fed condition but it come back down soon by secretion of more gastric acid. The main function of the fondues and body is storage, whereas that of cardiac is mixing or grinding. The fondues adjusts the increased volume during eating by relaxation of the fondues muscle fibers. The fondues also exerts a steady pressure on the gastric contents pressing them towards the distal region. To pass through the pyloric sphincter into the small intestine, particle size should be of order of 1-2 mm Gastric retention time of any dosage form is generally 1-2.5 hr in fasted state. Butin fed condition GRT is increased especially with fatty food.

Histology of Stomach-

The stomach wall is composed of the four basic layers Simple columnar epithelial cells line the entire mucosal surface of the stomach. Epithelial cells extend down into the lamina propria, where they form columns of secretary cells called gastric glands. The gastric glands contain three types of exocrine gland cells (figure 1) that secrete their products into the stomach lumen.

1. Mucous neck cells
2. Chief cells
3. Parietal cells

The chief cells secrete pepsinogen and gastric lipase. Parietal cells produce hydrochloric acid and intrinsic factor. Both mucosal surface cells and mucous neck cells secrete mucus and bicarbonate. They protect the stomach from adverse effects of hydrochloric acid as mucosa has a lubricating effect. It allows chyme to move freely through the digestive system. Food is passed out from stomach to intestine by gastric motility. There is specific motility pattern in fasted condition called 'migrating my electric complex (MMC) cycle.

Phase I (basal phase)- Period of no contraction (40-60 minutes)

Phase II (preburst phase)-

It consists of intermittent contractions that gradually increase in intensity as the phase progresses, and it lasts about 20 to 40 minutes. Gastric discharge of fluid and very small particles begins later in this phase.

Phase III (burst phase)-

Period of regular contractions at the maximal frequency that travel distally also known as housekeeper wave; includes intense and regular contractions for short period. It is due to this wave that all the un-digested material is swept out of the stomach down to the small intestine (10-20 minutes)

Phase IV- This is a short transitory period of about 0 to5 minutes, and the contractions dissipate between the last part of phase III and quiescence of phase L .

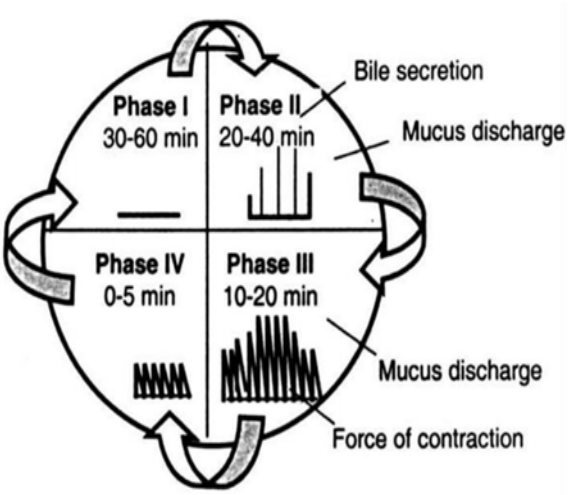


Fig. No. 2 MMC Cycle

Gastroretentive Drug Delivery System-

Dosage forms that can be retained in stomach are called gastro retentive drug delivery systems (GRDDS) GRDDS can improve controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site, thus ensuring its optimal bioavailability. Drugs having narrow absorption window are mostly associated with improved absorption at jejunum and ileum due to their enhanced absorption properties eg. large warface are or because of enhanced solubility in stomach as opposed to the more distal parts of the GIT.

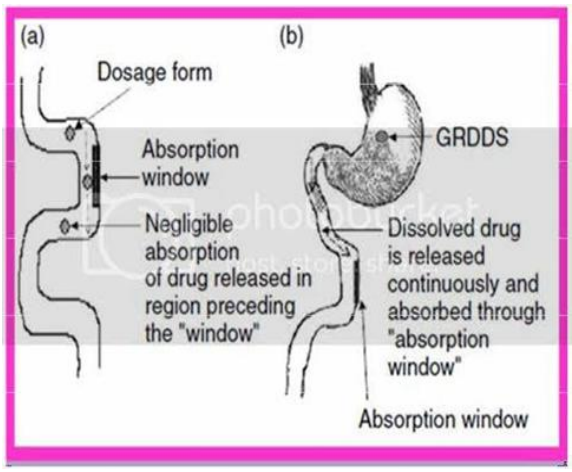


Fig. No. 3 Drug Absorption in case of a) Conventional dosage forms and b) Gastroretentive Drug delivery system.

Several approaches have been proposed to retain the dosage forms in the stomach. These methods include bio adhesive system, swelling system, expanding system and floating system. In fact the buoyant dosage unit enhances gastric residence time (GRT) without affecting the intrinsic rate of emptying. Unfortunately floating devices administered in a single unit form (Hydro dynamically balanced system) HBS are unreliable in prolonging the GRT owing to their 'all-or-nothing' emptying process and, thus they may causes high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastrointestinal tract.

Requirements for gastric retention Considering physiological factors in the stomach, it must be noted that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms.

Drugs which require gastric retention: -

- Drugs acting locally in the stomach e.g. Antacids and drugs for H. Pylori viz. Misoprostol
- Drugs that are primarily absorbed in the stomach e.g. Amoxicillin
- Drugs those are poorly soluble at alkaline pH e.g. Furosemide, Diazepam, Verapamil, etc.
- Drugs with a narrow window of absorption e.g. Cyclosporine, Methotrexate, Levodopa, etc.

Advantages of Oral Gastro retentive Release Dosage Form:-

- Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. Furosemide
- Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the
- Risk of resistance especially in case of antibiotics. e.g. ß-lactum antibiotics. (penicillin and cephalosporin)

Factors affecting gastric retention time of the dosage form

- ❖ Density -GRT is a function of dosage form buoyancy that is dependent on the density.
- ❖ Size.Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.
- ❖ Shape of dosage form: Tetrahydron and ring-shaped devices with a flexible modules of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 at 24 hr compared with other shapes.
- ❖ Single or multiple unit formulation: Multiple unit formulations show a more predictable relese profile and insignificant impairing of performance due to failure of units, allow co more predictable release profile and administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

Introduction of Floating Drug Delivery System: Floating Drug Delivery System is one of the novel system of drug delivery. Various dosage forms are formulated in the form gastro retentive floating systems such as microspheres, micro beads, tablets, capsules, films etc. In-situ gelling system is a new trend in floating DDS. nce and has less complex method of production and so is cost effective In-situ gelling system have its application in different routes of administration like oral, nasal, ophthalmic, peroral, rectal, vaginal and also parenteral route. In situ forming polymeric drug delivery systems has many advantages such as ease of administration, increased local bioavailability, reduced dose frequency, improved patient compliance. Gastro retentive FDDS

have bulk density lower than gastric fluid and hence remain buoyant in stomach without affecting the gastric emptying rate for a long period of time. When the gel so formed float on gastric fluid

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEMS

Effervescent systems

These buoyant delivery systems utilize matrices prepared with swellable polymers such as Methocel or polysaccharides, e.g., chitosan, and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. Gas can be introduced into the floating chamber by the volatilization of an organic solvent (e.g., ether or cyclopentane) or by the carbon dioxide produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salts.

Non-effervescent systems

Non-effervescent floating drug delivery systems are normally prepared from gel- forming or highly swellable polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment.

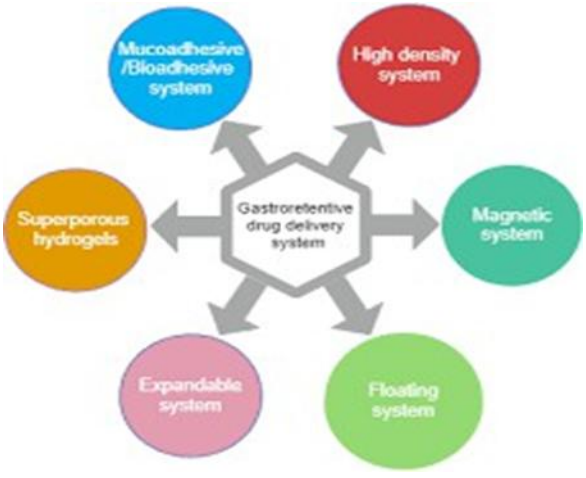


Fig. No. 4 Approaches Related to GRDDS

Floating oral In Situ Gel Oral in situ gel forming system also known as stomach specific or raft forming systems have provided a suitable way of providing the controlled drug delivery within stomach with enhanced gastro-retention. The tablet/capsule floating dosage forms are stable as compare to liquids but the problem with them is that they are needed to swallow as whole unit. In case of dosage adjustment these cannot be broken in halves as these are also designed for controlled release and floating ability also depends on dimensions of tablets. Elderly patients, children some adult persons and patient with certain conditions suffer from dysphasia, so it becomes difficult for them to swallow tablet/capsule dosage forms. Also in case of dosage adjustments these floating solid dosage forms are needed to be available in different strengths Oral floating in-situ gel formulation have some advantages like ease of administration, enhance bioavailability of the drug, reduce dosing frequency, improve patient compliance and its production is less complex and so lowers the investment.

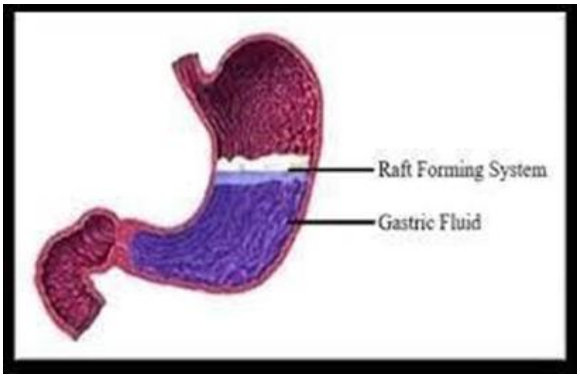


Fig. No. 5. Schematic illustration of the barrier formed by a raft forming system.

Mechanism of Control Release System

The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft (Fig.3). This raft floats on gastric fluids because of low bulk density created by the formation of CO2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO2 to make the system less dense and float on the gastric fluids28. An antacid raft forming floating system contains a gel forming agent (e.g. sodium alginate), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft), which when comes in contact with gastric fluids, the raft floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagu

Advantages of Control release system:

- They are used for the symptomatic treatment of heartburn and oesophagitis. It can be used in LPR. GERD, Laryngopharyngeal Reflux (LPR) refers to the backflow of stomach contents into the laryngeal and pharyngeal region.
- It does not interfere with the activity of promotility agent, antisecretory agents such as cimetidine.

Approaches used for the formulation of the Control release drug delivery system:

Raft forming drug delivery systems are a revolution in oral drug delivery. These systems are liquids at room temperature but undergo gelation when comes in contact with body fluids or change in pH. These have a unique property of temperature dependent and action-induced gelatin. Gelatin involves formation of the double helical junction zones followed by aggregation of the double helical segments which form three dimensional networks by complication with captions and hydrogen bonding

Swelling:

Formation of a gel occurs when the liquid effervescent system comes in contact with gastric fluid. In situ formation of gel occurs when materials absorb water from the surrounding environment and expand to occur at the desired space. Swelling of the polymer occurs by absorption of water which further causes formation of the gel. Certain biodegradable lipid substance such as mineral 18-99 (glycerol mono oblate), is a polar lipid that swells in water to form allotropic liquid crystalline phase structures .

Diffusion: Diffusion is the method which involves diffusion of a solvent from polymer solution into surrounding tissue, which further results in precipitation or solidification of polymer matrix. Solution of polymer that can be used for such mechanism is N- methyl pyrrolidone (NMP). Raft formation based on chemical mechanism

Ionic cross linking: There are various polysaccharides that undergo phase transition in the presence of various ions. Polysaccharides falling into the class of ion-sensitive ones are most widely used 40. lon sensitive polysaccharides such as carrageen an, gellan gum (Gel rite®), pectin, and sodium alginate undergo phase transition in the presence of various ions such as K+, Ca+, Mg+ and Na+. Various polysaccharides undergo gelatin in the presence of various monovalent, divalent cations. Alginic acid undergoes gelatin in the presence of divalent/polyvalent cations like Ca2+ due to the interaction with guluronic acid block in alginate chains. K-carrageenan forms rigid, brittle gels in response to small amount of K+, i-carrageenan forms elastic gels mainly in the presence of Ca2+. Gellan gum commercially available as Gelrite is an anionic polysaccharide that undergoes in situ gelling in the presence of mono- and divalent cations, including Ca2+, Mg2+, K+ and Na+. Gelatin of the low-methoxy pectin can be caused by divalent cations, especially Ca2+

Physiological stimuli mechanism (pH dependent gelling): Formation of gel in the system also occurs due to change in the pH of the medium. Various pH dependent polymers are used which cause the formation of in situ gel in the system. Various polymers such as PAA (Carpool®, carbomer)

Temperature dependent gelling: These hydro gels are liquid at room temperature (20°C-25°C) and undergo gelation when in contact with body fluids (35°C-37°C), due to an increase in temperature. This approach exploits temperature-induced phase transition. Some polymers undergo abrupt changes in solubility in response to increase in environmental temperature (lower critical solution temperature, LCST)[43,44]. At the LCST, hydrogen bonding between the polymer and water becomes unfavorable, compared to polymer- polymer and water-water interactions, and an abrupt transition occurs as the solvated macromolecule quickly dehydrates and changes to a more hydrophobic structure.

MARKETED FORMULATION

Madopar HBS: An anti-Parkinson's agent, is a commercially available product marketed by Hoffmann- LaRoche. It contains 100 mg levodopa and 25 mg benserazide, a peripheral dopa decarboxylase inhibitor. It consists of a gelatin capsule, designed to float on the surface of the gastric fluids. After the gelatin shell dissolves, a mucous body is formed that consists of the active drugs and other substances. The drugs diffuse from the hydrated boundary layers of the matrix at the desired rate.

Valrease : Is another floating capsule, marketed by Hoffmann-La Roche. It contains 15 mg diazepam, which is more soluble at low pH; therefore absorption

is more desirable in the stomach. The drug components form a soft gelatinous mass in the stomach and are released gradually. The HBS system maximizes the dissolution of the drug by prolonging the gastric residence time.

Liquid Gaviscon: A floating liquid alginate preparation, is used to suppress gastro esophageal reflux and alleviate the symptoms of heart burn. The formulation consists of a mixture of alginate, which forms a gel of alginic acid, and a carbonate or bicarbonate component, evolving CO_2 upon reaction with the acidic content of the stomach. The formed gel entraps the CO_2 formed, and consequently floats on the stomach contents.

Topalkan® **:** Is a third-generation aluminum magnesium antacid, which also contains alginic acid in its formula. It has antiseptic and protective effects with respect to the thucous membrane of the stomach and esophagus, and provides, together with magnesium salts, a floating layer of the preparation in the stomach.

DRUG & EXCIPIENTS PROFILE

Febuxostat: Febuxostat is a xanthine oxidase inhibitor used for the management of chronic hyperuricemia in adults with gout who have an inadequate response or intolerance to allopurinol. Structure of Febuxostat

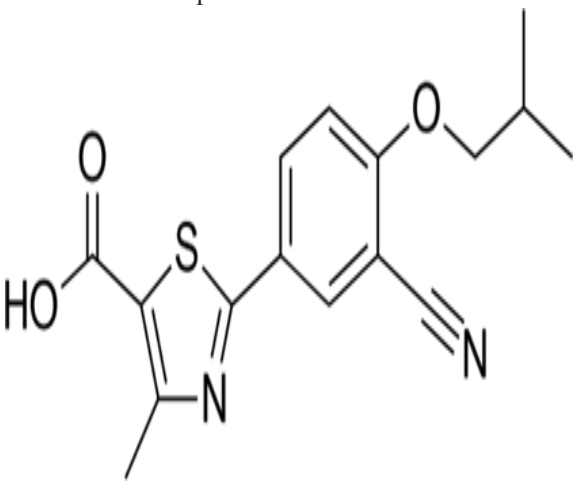


Fig. No. 6. Strucure of Febuxostat

Description : Febuxostat is indicated for the chronic management of hyperuricemia in adult patients with gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable. It is not recommended for the treatment of asymptomatic hyperuricemia or secondary hyperuricemia.

Chemical Formula -C16H16N2O3S Molecular Weight - 316.375n Melting Point - 207.0 to 211.0

Solubility- freely soluble in dimethyl formamide, soluble in dimethyl sulphoxide and sparingly soluble in ethanol.

Storag - Store at room temperature away from light and moisture

Mechanism of Action- The primary mechanism of action of febuxostat evaluated in trials was the inhibition of xanthine oxidase, evidenced by the increase in serum and urine xanthine concentrations, decrease in serum and urine uric acid levels, and lack of significant reduction in total purine synthesis.

Pharmacodynamics Of Drug:- Febuxostat is a novel, selective xanthine oxidase/dehydrogenase inhibitor that works by decreasing serum uric acid in a dose-dependent manner. In healthy subjects, febuxostat decreased the mean serum uric acid and serum xanthine concentrations, as well as the total urinary uric acid excretion. Febuxostat at daily doses of 40-80 mg reduced the 24-hour mean serum uric acid concentrations by 40 to 55%.[10] Closely related to the drug-induced reduction of serum uric acid levels and mobilization of urate crystals in tissue deposits, febuxostat is associated with gout flares.

Unlike allopurinol and oxypurinol, febuxostat has no inhibitory actions against other enzymes involved in purine and pyrimidine synthesis and metabolism, because it does not structurally resemble purines or pyrimidines.

Dose of febuxostat :- The current approved dosages for febuxostat in the US are 40
and **80** mg daily (FDA 2009)

Hyperuricemia : Diuretics are one of the most important causes of secondary raise serum uric acid level by an increase of uric acid reabsorption and/or decrease in uric acid secretion. Several drugs may also increase uric acid production. hyperuricemia. Drugs

POLYMERS PROFILE

1. ALGINATE
2. SODIUM XANTHAN GUM
3. SODIUM CITRATE
4. CALCIUM CARBONATE

II. MATERIALS AND EQUIPMENTS

MATERIALS:

Sr. No.	Chemicals	Source
1	Febuxostat	Swapnaroop Research Pvt. Ltd., Aurangabad Maharashtra
2	Sodium Alginate	Loba Cheme Pvt. Ltd. Mumbai
3	Guar Gum	Thomas Baker Pvt. Ltd. Mumbai
4	Xanthan Gum	Research Lab Fine Chem Mumbai
5	Tragacanth	Loba Cheme Pvt. Ltd. Mumbai
6	Calcium Carbonate	Loba Cheme Pvt. Ltd. Mumbai
7	Sodium Citrate	Loba Cheme Pvt. Ltd. Mumbai
8	Methyl Paraben	Loba Cheme Pvt. Ltd. Mumbai
9	Propyl paraben	Loba Cheme Pvt. Ltd. Mumbai

Table No.1: List Of Chemicals and Its Source

EQUIPMENTS

Sr. No.	Instrument	Company
1	Electronic Digital Balance	Citizon, Mumbai
2	Magnetic Stirrer	OMEGA Scientific industries
3	Dissolution Apparatus	AMETEK Dissolution Apparatus USA
4	FTIR	Agilent cary 630 ATR FTIR
5	pH Meter	Hanna Instruments
6	Brookfield viscometer	Ametek B.V.

Preformulation Studies of Drug & Excipients

Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients. Preformulation studies are the first step in the rational development of dosage form of a drug substance. The objectives of preformulation studies are to develop a portfolio of information about the drug substance, so that this information is useful to develop formulation. Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product. The goals of the program therefore are: To establish the necessary physicochemical characteristics of a new drug substance.To determine its kinetic release rate profile. To establish its compatibility with different excipients. Hence, a preformulation study on the obtained sample of drug includes physical test determination and compatibility studies.

Description: The drug was analyzed for color, odor and taste.

Melting point Melting point determination of Febuxostat was done by open capillary method

Solubility Characteristic: A semi quantitative determination of solubility can be made by adding a solute in small incremental amount to fixed volume of solvents, distilled water, 0.1 N.HCl pH 1.2, methanol, alcohol, isopropyl alcohol. After each addition, the system is vigorously shaken and examined usually for any undissolved particles.

FTIR study of Febuxostat: FTIR study is another identification test Febuxostat API. The FTIR spectra of pure Febuxostat was determined.

Spectroscopy

UV-visible Spectroscopy Determination of ƛ max

The UV absorption spectrum of Febuxostat was obtained using a UV-visible Spectrophotometer. 10 mg of drug dissolved in 0.1 N.HCL and The spectrum was scanned from 315 nm

Standard calibration curve of Febuxostat-

- Preparation of standard solution - Dissolve 10 mg

Febuxostat in 100 ml Water in volumetric flask having conc. 100µg/ml

- Preparation of working solution -

From stock solution pipette out Transfer to 100ml, (2, 4, 6, 8, 10,12 ml) were transferred into a series of 10 mL volumetric flasks. The volume was adjusted to the mark with the Water to get desired concentrations (2, 4, 6, 8, 10, 12 µg/mL) for RSV. Measure the absorbance at 315nm using UV-visible spectrophotometer. Plot graph between Conc. vs. Abs. Calculate coefficient of correlation (should between 0.9-1) & slope.

Drug polymer interaction studies:

The compatibility of drug and polymers under experimental conditions is important prerequisite before formulation. It is essential to verify that the drug does not react with the polymer and excipients in process condition and does not affect the shelf- life of product or any other unwanted effects on the formulation. The physical mixture of drug & polymers were used for determination of Infrared spectrums. The pure drug, the mixture of polymers (sodium alginate and pectin), and a mixture of drug with the polymers were mixed separately with IR grade KBr in the ratio of 100:1. The base line correction was done using dried KBr. Infrared spectra of the mixture were taken over a wave number range of 4000-400/cm. Also the infrared spectra of the drug and polymers were run individually.

FORMULATION OF IN SITU GEL

1. Floating in-situ gel formulations of Febuxostat were prepared using compositions.
2. Take 100ml beaker, in that beaker take sodium alginate and add with polymer, the mix with 60ml distilled water, now heat the mixture at 60 °C till solution occurs using a heating magnetic stirrer.
3. Take another 100ml beaker, in this add sodium citrate along with calcium carbonate, then mix with 30ml distilled water, heat the mixture at 60 °C till solution occurs.
4. Now take another beaker, add 5ml methanol! with drug, then three mixtures, are mixed at 60°C.

Sr. No.	Quantity of Ingredients (gm/100ml)	Batches Of Formulation								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Febuxostat	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
2	Sodium Alginate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
3	Guar gum	0.125	0.150	0.175	-	-	-	-	-	-
4	Xanthan Gum	-	-	-	0.125	0.150	0.175	-	-	-
5	Tragcanth gum	-	-	-	-	-	-	0.125	0.150	0.175
6	Calcium Carbonate	0.225	0.225	0.225	0.225	0.225	0.225	0.225	0.225	0.225
7	Sodium Citrate	0.225	0.225	0.225	0.225	0.225	0.225	0.225	0.225	0.225
8	Methyl Paraben	0.020	0.020	0.020	0.020	0.020	0.020	0.020	0.020	0.020
9	Deionisd Water	upto 100ml	upto 100ml	Upto 100ml	Upto 100ml	Upto 100ml	Upto 100ml	upto 100ml	upto 100ml	Upto 100ml

Physical appearance

All the prepared in situ solutions of Febuxostat were checked for their clarity and the pH of the solutions. after administered of the prepared solutions in 0.1 N.HCL, the time required for gel formation and consistency of gel formed was checked visually.

PH Determination: The pH of the prepared in-situ gelling system after addition of all the ingredients was measured using pH meter.

In vitro gelation study : To evaluate the formulations for their in-vitro gelling capacity by visual method, solutions of in situ gel forming drug delivery system were prepared, the in vitro gelling capacity of the formulations was measured by placing 5 ml of the gelation solution (0.1 N HCL) in a 15 ml borosilicate glass tube and maintained at 37^0C temperature, one ml of formulation solution was added with the help of pipette the formulation was transferred in such way that places the pipette at surface of fluid in test tube and formulation was slowed released from the pipette. As the solution comes in contact with gelation solution, it was immediately converted into stiff gel

like structure. The gelling capacity of solution was evaluated on the basis of stiffness of formed gel and time period for which formed gel remains. The in-vitro gelling capacity was graded in three categories on the basis of gelation time and time period for which formed gel remains

In-vitro floating study : In vitro floating study was determined using USP dissolution apparatus II having 500 mL simulated gastric fluid (SGF pH 1.2). The temperature of media was kept 37˚C. 10 mL prepared in situ gel formulations were drawn up using disposable syringe and placed into the Petridis (4.5 mm internal diameter) and finally Petridis containing formulation was kept in the dissolution vessel containing medium without much disturbance. The time at which the formulation emerge on the medium surface (floating lag time) and the time up to which the formulation constantly floated on the dissolution medium surface

Determination of drug content : 10 ml of solution was added to100 ml of simulated gastric fluid (0.1 N.HCL) and stirred for 1 hour on a magnetic stirrer. the solution was filtered, suitably dusted with simulated gastric fluid and the drug concentration was determined by using UV-visible spectrophotometer at 315 nm against suitable blank solution.

Viscosity Measurement of The In-Situ Gelling Solutions-

Viscosity before gel (Sol) were determined using Brookfield's Digital Viscometer with Spindle number 62. The temperature of the 100ml sample was kept at 25℃ ± 1℃ during each measurement which lasted 60 sec, and the experiment were performed in triplicate. The average values are given in results. Viscosity After gel were determined using same Brookfields Viscometer with spindle No.62. 250ml of 0.1N HCL was added to 25ml of In-Situ gelation solution. After 2min sample was analysed. The temperature of the sample was kept at 25℃ ± 1℃ during each measurement which lasted 60 sec, and the experiment were performed in triplicate. The average values are given in results.

In-Vitro dissolution studies : The in vitro dissolution was carried out using USP Dissolution testing apparatus type- II. The tablets were placed in the pH 1.2 (simulated gastric fluid pH) for 2 hrs and Ph 6.8 (simulated intestinal fluid pH) for 12 hrs, then the apparatus was run at 37°C+0.5°C and a rotating speed of 50 rpm in a 900 ml dissolution medium. The 5 ml aliquots were withdrawn at intervals of 1 hour, 2 hours, 3 hours,4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, and replacement was done each time with equal amounts of fresh dissolution medium maintained at same temperature. Each 5 ml aliquot was filtered through Whatmann filter paper (No.41). 5 ml of sample was diluted up to 10 ml and absorbance was measured at 280 nm using UV spectrophotometer. Drug concentrations in the sample were determined from standard calibration curve. Then calculate amount & % drug release. Amount of drug in mg/ 900 ml = [Conc. (µg/ml) x 900x dil. factor]/1000 % Drug release = [Amount of drug release in mg/900 ml]/Label claim (ml).

Kinetics of drug release : In order to understand the mechanism and kinetics of drug release, the results of the in-vitro dissolution study of the optimized batch was fitted with various kinetic equations like.

Zero order (% Release -Kt),

First order (log % Unreleased -Kt). Higuchi's model (% Release -Kt0.5) and Pappas Korsmeyer equation (% Release-Ktn) (or) Empirical equation (Power law expression) of $Mt / M\infty = K t$

Where ,

Mt-Amount of drug release at time t Men - Amount of drug release at infinite time K - Constant characteristics, and N-Diffusional exponent

Ifn=0.5 indicates Fickian diffusion mechanism (Higuchi matrix) Lindicates n=0.5 to 1 indicates Anomalous Transport or Non Fickian transport.

n= indicates Case II Transport (Zero order release) n> lindicates Super case-II transport

Sr. No.	Test	Observation
1	Colour	White coloured power
2	Odour	Characteristic odour
3	Taste	Blistering,crusting,irritation,itching.
4	Melting point determination	207˚C to 211^{0}c

Table No. 4 Physical appearance & Melting point determination

The organoleptic character and melting point was found to be as per standard drug so drug used in the formulation was found to be pure according to I.P. specification.

Sr. No	Solvent	Solubility
1	Ethanol	Sparingly, Soluble
2	Methanol	Highly Soluble
3	Dimethyl formamide	Soluble
4	Dimethyl sulphoxide	Soluble
5	Buffer 0.1 N.HCL	Soluble

Table No. 5 Detection of Solubility

The solubility of pure drug in 10mg/10ml of solvent was carried out and it reveals that it is soluble in Methanol and Buffer 0.1 N.HCL, practically Sparingly, Soluble in Ethanol, Highly soluble in methanol, Dimethyl formamide and Dimethyl sulphoxide.

Drug Polymer Compatibility Study

Expected Group	Group Frequency
N-H	3612 cm^{-1}
C=O	1639 cm^{-1}
S=O	1039cm^{-1}

Table No. 6: FTIR Study of Febuxostat

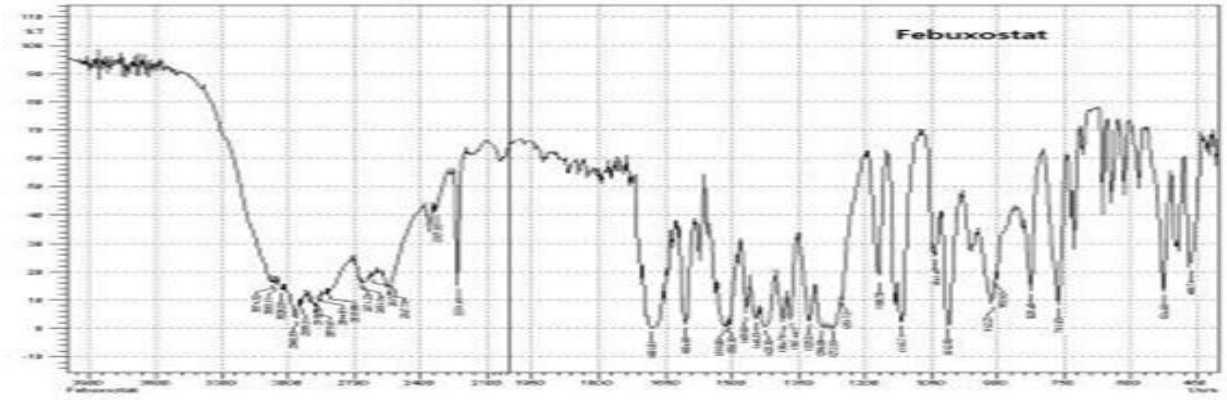


Fig. No. 1. FTIR of Febuxostat Drug

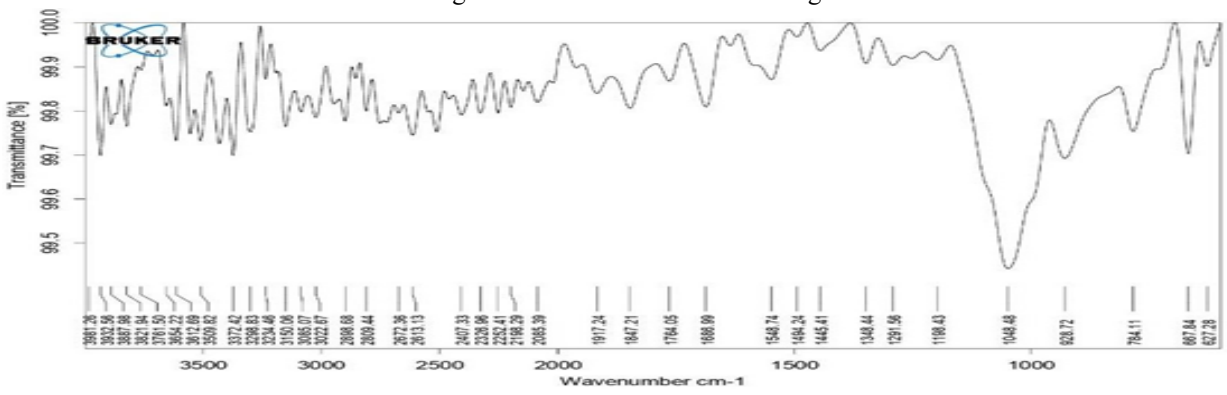


Fig No. 2. FTIR Of GUAR GUM

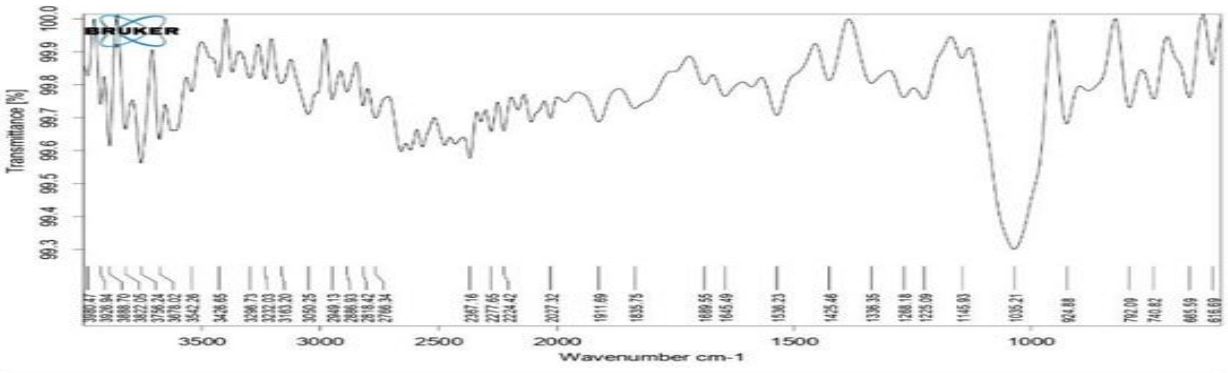


Fig. No. 3. FTIR of Xanthan gum

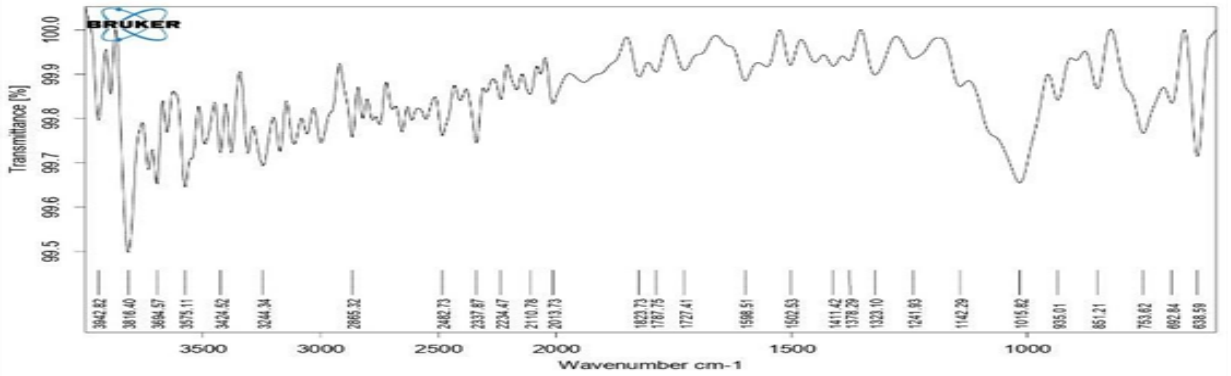


Fig. No. 4. FTIR Of Sodium Alginate

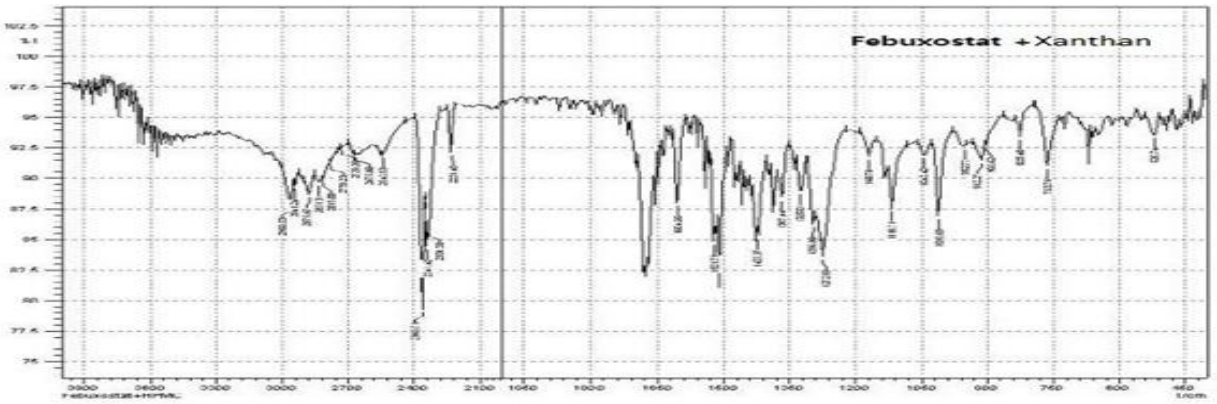


Fig. No. 5. FTIR of Febuxostat & Xanthan gum

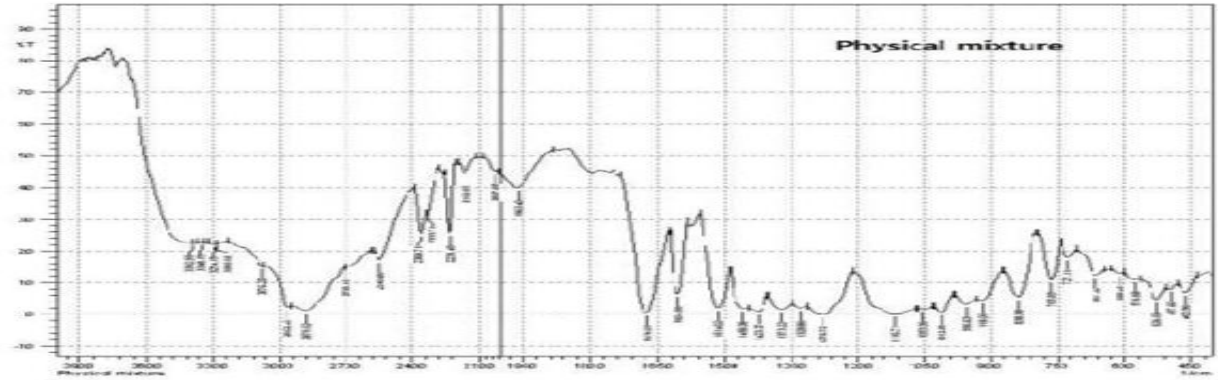


Fig. No. 6. FTIR Of Drug+ Sodium Algiante+Sodium citrate+Xanthan Gum+ Calcium Carbonate

pH Determination

Sr. No.	Batch Code	pH
1	F1	6.3
2	F2	6.5
3	F3	6.64
4	F4	6.5
5	F5	6.2
6	F6	6.4
7	F7	6
8	F8	6.4
9	F9	6.7

Table No. 7. PH Of Formulations

Determination of λmax : Febuxostat showed the maximum wavelength at 315nm, which matches with the standard.

1] Calibration curve

Standard Calibration curve of Febuxostat in 0.1N HCL

Sr. No.	Concentration (um/ml)	Mean Absorbance at 315nm
1	0	0.1078
2	2	0.2678
3	4	0.3436
4	6	0.4623
5	8	0.6241
6	10	0.7426
7	12	0.9969

Table No. 8 Standard Calibration curve

The linearity range of Febuxostat was found between 2-12µg/ml in 0.1 N HCL.the values of Febuxostat in 0.1 N HCL at 315 nm are shown in table no 4.caliberation curve of Febuxostat is shown in fig. the regression value (R2) of calibration curve of Febuxostat was found 0.991 which demonstrate the good linearity.

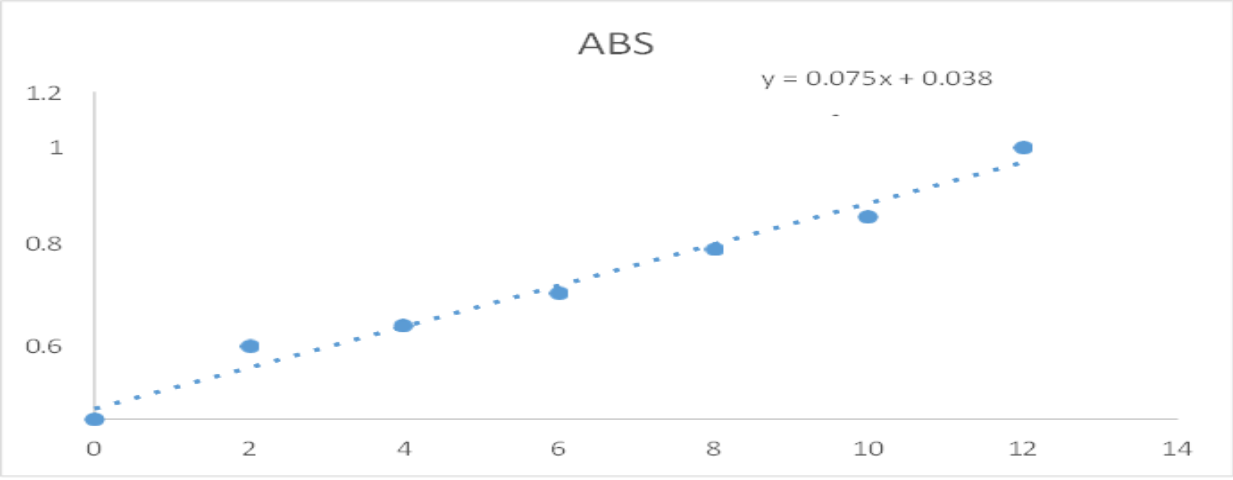


Fig. No.7. Standard Callibration curve of Febuxostat

1] Determination of Drug Content (%)

Batch Code	% Drug Content
F1	94.52
F2	93.26
F3	94.50
F4	99.98
F5	92.87
F6	92.20
F7	90
F8	91.20
F9	94.20

Table No.9 % Drug Content

All the Batches should the drug content more than 90% As the concentration of In situ gel increases. All the Batches should have better gelling properties as,

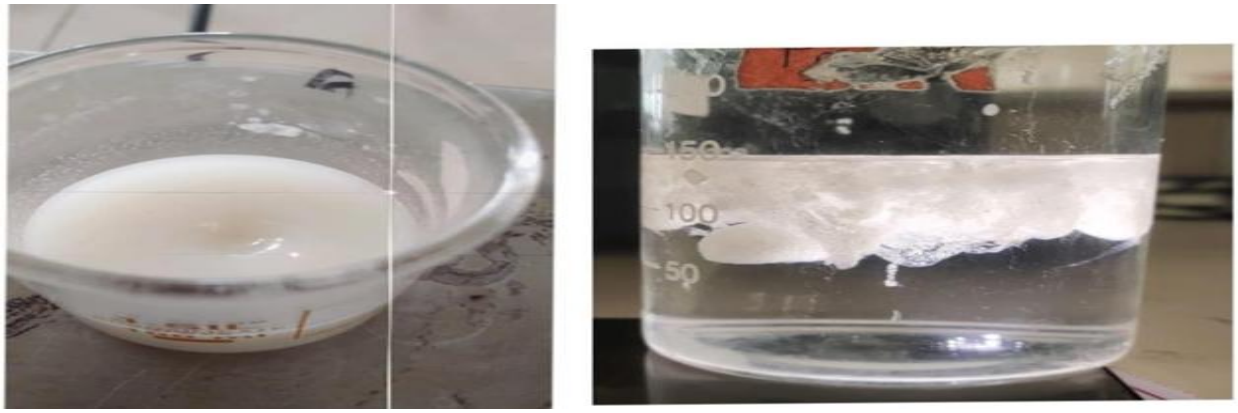
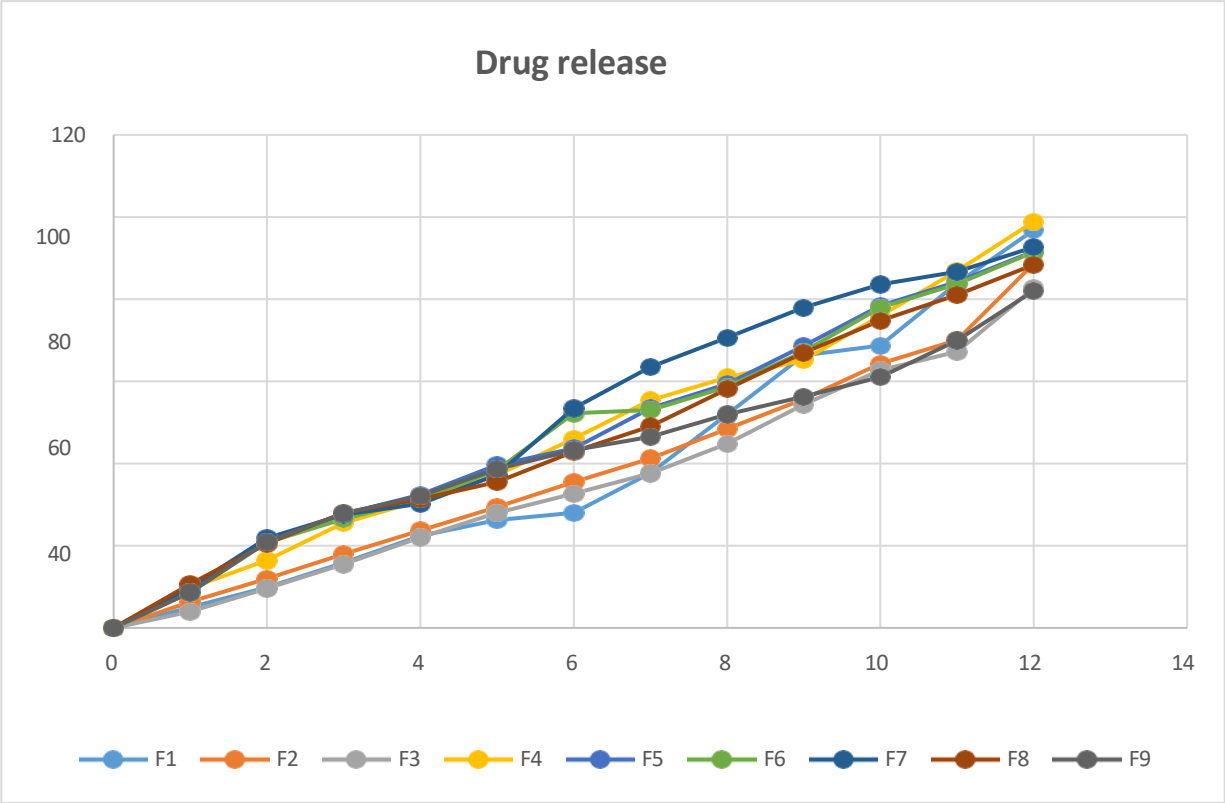


Image No. 17. Solution to Gel Conversed Form Of Batch F4

1] In-Vitro Drug Release Study

Time (Hr)	% Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	5.04	6.36	3.96	9.732	9.852	8.652	9.852	10.656	8.676
2	9.888	11.988	9.588	16.488	21.264	20.772	21.816	20.52	20.976
3	15.9	17.94	15.54	25.596	27.708	26.508	27.588	28.056	27.816
4	22.344	23.712	22.032	31.044	32.388	31.284	30.228	31.368	32.124
5	26.292	29.412	27.984	37.176	39.684	38.388	37.284	35.508	38.664
6	28.056	35.544	32.688	46.092	43.692	52.284	53.448	42.864	43.272
7	37.692	41.244	37.584	55.38	53.484	53.04	63.516	49.092	46.524
8	51.96	48.444	44.856	60.996	59.424	58.656	70.656	58.164	51.972
9	66.36	55.644	54.324	65.232	68.592	67.248	78.012	66.996	56.328
10	68.76	64.356	62.712	75.972	78.42	77.988	83.616	74.784	61.068
11	83.88	70.008	67.26	86.868	84.252	83.688	86.688	81.084	69.96
12	96.84	88.668	82.692	98.868	91.632	91.488	92.688	88.392	82.056

Table No. 10. Dissolution data of Batches of F1, F2 and F3



Time (Hr) Fig. No. 8 . % Cumulative Drug release of Batch F1, F2, F3

The in-vitro drug release of the in situ floating gel were carried out in 0.1 N HCL from 0 to 12 hrs by USP type -II apparatus and the values shown in table no 10. The plot of % drug release v/s time (hrs) was ploted and depicted as shown in figure no 16, in vitro drug release study was conducted on the formulations for a period of 12 hours during which the highest drug release of 98.869 %was observed with formulation F4 and the least drug release of 96.98% with F1 during the 12 hour dissolution study. The effect of polymer concentration on in vitro drug release is shown in table. A significant decrease in rate and extent of drug release was observed with increase in polymer concentration. This is attributed to increase in the density of polymer Shaft. It was also due to increase in the diffusional path length which the drug molecules have to travel.

Vicocity Mearurement of In-Situ Gel

Sr. No.	Batch Code	Viscosity (cp) at pH 6-7	
		Before Gelation (Sol)	After Gelation(Gel)
1	F1	486	1538
2	F2	655	1789
3	F3	273	1978
4	F4	985	1679
5	F5	993	1879
6	F6	970	2078
7	F7	900	1689
8	F8	998	2057
9	F9	970	2467

Table No. 11 Viscosity of Formulations

In-Vitro Floating Study

Sr. No	Batch Code	Floating Lag Time (Sec)	Floating Duration (Hr)
1	F1	20	>12
2	F2	25	>12
3	F3	27	>12
4	F4	18	>12
5	F5	22	>12
6	F6	29	>12
7	F7	20	>12
8	F8	24	>12
9	F9	30	>12

Table No. 12 Floating Behavior of Formulations

In Vitro Gelling Study

Sr. No.	Batch Code	Gelling Capacity
1	F1	+++
2	F2	+++
3	F3	+++
4	F4	+++
5	F5	+++
6	F6	+++
7	F7	+++
8	F8	+++
9	F9	+++

Table No. 13. Gelling Capacity of Formulatins

Stability Study of optimized Batch F4

Evaluation Parameter	Time Period Of Sampling	
	Initial	After 1 Month
pH	6.5	6.2
Viscosity (cps)	985	972
In Vitro Gelling capacity	+++	+++
Floating lag time (sec)	18	17
Floating time (hr)	>12	>12
Drug content (%)	99.98%	98.80%
Drug Release	98.868	98.21

Table No. 14 Results of stability study of F4 Batch

It was observed that at the end of one month duration stability study, there was no remarkable change in the drug content, in vitro drug release profile and other evaluation parameter of the in situ gelling solution of Verapamil Hcl after exposing to accelerated stability condition. So, the in situ gelling solution of optimized batch F3 might be considered as stable formulation.

III. SUMMARY & CONCLUSION

Summary: In situ Floating oral drug delivery system posses potential advantages like simple manufacturing processes and ease of administration. this study reports that oral administration of aqueous solutions of Febuxostat containing Xanthan gum and sodium alginate results in formation of in situ gel at the stomach site, by using sodium alginate and Xanthan gum as gelling agents, attempt was made to developed in situ gelling systems of Febuxostat, an Hyperuricemia agent, to increase gastric resident time and to provide site specific delivery of Febuxostat. Preliminary study was carried out for optimization of different types and concentration of polymer such as, sodium alginate, xanthan gum etc. from above all polymers, sodium alginate and Xanthan gum were selected as they have better gelling capacity as compare to other polymer. 1% concentration of calcium carbonate (cross linking agent) was selected on the basis of floating lag time.0.3% w/v of sodium citrate provided stability to in situ gelling solution and prevented gelation outside the gastric environment. The optimized formulation showed in vitro sustains drug release up to 12 hours. From the release kinetic study it was concluded that the all formulations follow the higuchi model as best fit model and release from in situ gelling system showed diffusion controlled. Stability study revealed that there was no significant change in physical appearance, pH, viscosity, gelling capacity, drug content and in vitro drug release. This present investigation has demonstrated the feasibility of forming gel in the in vitro condition with aqueous solutions of sodium alginate and Xanthan Gum containing Ca++ ions in complexes form. Febuxostat can be targeted in stomach with in situ gel formation and drug release from gel formulation for 12 hr in In-vitro condition. Furthermore it was observed that, gel remained buoyant for 12 hr and release Febuxostat for 12 hr. The prepared formulation were evaluated for different parameters like physical appearance and pH, floating behavior, in vitro gelling capacity, drug content, and in vitro release.

IV. CONCLUSION

Stomach specific floating in-situgel containing Febuxostat was prepared using sodium alginate, gellan gum and release retardant polymer xanthan gum. The prepared formulations were evaluated for visual inspection, surface pH, viscosity, in-vitro floating study, in-vitro gelling capacity, drug content, and in-vitro drug release. The formulation F4 was selected as the optimized formulation which has viscosity 985 CPs with drug content of 99.98 and showed in- vitro drug release of 98.868% at the end of 12 h. It follows first-order release kinetics with Higuchi model release mechanism. The selected formulation was evaluated for stability. The formulation was stable at room temperature and accelerated temperature six months. The present study has been a successful attempt to formulate gastro retentive in-situ gel of Febuxostat, an orally administrated hyperuricemia drug with a View improving its oral to bioavailability and provide sustained release of the drug. The developed formulations all prerequisites to become gastro retentive in-situ gel system that gelled and floated instantaneously in the pH conditions of the stomach. Hence, it can be concluded that stomach specific in-situ forming gel of Febuxostat can be an effective formulation that shows improved efficacy, prolonged-release, patient compliance and cost-effective conventional formulations.

REFERENCES

[1] R. Bashir, A. Majeed, T. Ali,S. Farooq, N. Ahmad Khan, Floating Oral In-situ Gel: A Review. JDDT, 2019; 9(2): pp.442.

[2] B. Padmasri, R. Nagarju, D. Prasanth. a comprehensive review on in situ gels: Int J App Pharm, Vol 12,2020: pp.24-25.

[3] R. Pahwa, S. Bhagwan, V. Kumar, K. Kohli, .Role of Natural Polymers in the Development of Floating Drug Delivery Systems. Journal of Pharmacy Research 2010, 3(6): pp. 1312-1318.

[4] Patil P, Chavanke D, Wagh M, a review on ionotropic gelation method: novel approach for controlled gastroretentivegelispheres, international journal of pharmacy and pharmaceutical sciences, 2012;vol 4, suppl 4, 27-32,

[5] Dahiya M, Neeta, Mehta M, Satija S, Pandey P, relevance of ionotropic gelation technique in the development of floating multiparticulate drug delivery systems, International Journal of Advanced Scientific Research, 2016; Vol. 1(4), 54-59.

[6] Deshmukh P.P.M, and Barhate A.N, FORMULATION AND EVALUATION OF MICROSPHERES OF GLIBENCLAMIDE BY IONOTROPIC GELATION METHOD,Indo American Journal of Pharmaceutical Research, 2017; 471-479.

[7] Pillay V. and Danckwerts M.P. a crosslinked calcium-alginate- pectinate cellulose acetophthalategelisphere system for linear drug release, taylor & francis, 2002; drug delivery, 9:77-86.

[8] Garg S, Sharma S. Gastro retentive drug delivery system, Indian J pharma 2003: available at: URL: http// www.bbrefing.com

[9] Chawla g, Gupta P, Koradia V, Bansal A.K, Gastroretation : A mean nto address regional v gariability in intestinal drug absorption. Pharma tech 2003 Jully: 27(7):50-68. 7.

[10] Welling PG,Dobrinska MR.Dosing consideration and bioavilablity assessment of controlled drug delivery system. in:Robinson JR.Lee VHL.editors.controlled drug delivery fundamentals and application 2ndedition.new York:Marcel Dekkar Ine:1987:253-264.

[11] Tortora GJ. Derrickson B. Principles of anatomy and physiology in: 11th ed. 12.

A. John Wiley and Sons. New York. 2006; p 911-916.

[12] Wilson KJW, Waugh A. Anatomy and physiolology in health and illness. In: 9th ed. Churchill Livinstone. London. 1996; p 294-298.

[13] Amnon Hoffman et al., expandable gastroretentive dosage forms, J. cont. Rel (2003) 90, 143-162.

[14] Badoni A.. Ojha A, Gnanarajanl G., Kothiyal P., Review on Gastro Retentive Drug Delivery System, The Pharma Innovation, 2012.1(8), 32-42.

[15] Guyton A. C, Movement of food through the alimentary tract. In: Human Physiology and Mechanisms of Disease, W.B. Saunders Co., London, 1982, 3. 487- 497.

[16] Kavitha K., Yadav S.K and Tamizh M.T, The Need of Floating Drug Delivery System: A Review. RJBPS. 2010, 1(2). 396-405.

[17] Rocca JG,Omidian H,Shah K.progress in gastroretentive drug delivery system. 2003; available at;URL:http://bbriefings.com/pdf/17/ACF8D8E.pdf

[18] American Journal of Clinical Nutrition, found at American Journal of Clinical Nutrition website

[19] Kwon H. Kim, Brahma N. Singh, Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention, J. cont. Rel. (2000) 63, 235 259.

[20] Amnon Hoffman et al., expandable gastroretentive dosage forms, J. cont. Rel. (2003)90, 143-162.

[21] R. Talukder and R. Fassihi, Gastroretentive Delivery Systems: A Mini Review, Drug Dev. Ind. Pharm, (2004)30:10, 1019-1028.

[22] weta Arora et al. Floating Drug Delivery Systems: A Review, AAP Pharm SciTech (2005) 6:3, Article 47.

[23] Stanly s. David, formulation strategies for absorption window, (2005) 10:4. February.

[24] E. A. Klausner, E. Lavy, M. Friedman. A. Hoffman, "Expandable gastro retentive dosage forms Journal of Controlled Release 90 (2003) 143-162.

[25] Bhardwaj L. Sharma PK, Malviya R. A Short Review on Gastro Retentive Formulations for Stomach Specific Drug Delivery: Special Emphasis on Floating In situ Gel Systems. African Journal of Basic & Applied Sciences 2011; 3 (6): 300-312.

[26] Ripathi P, Ubaidulla U, Khar RK, Vishwavibhuti. Floating drug delivery system. International Journal of Research and Development in Pharmacy and Life Sciences.2012; 1(1): 1-10)

[27] . Chaturvedi, S., Kumari, P., Singh, S., Agrawal, V., Approaches to increase the gastric residence tim;e: floating drug delivery systems- A Review, Asian J Pharm Clin Res., 6(3):1-9 (2013). 29. Shah, S., Patel, J., Patel, N., Stomach specific floating drug delivery system: