International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 729-757 www.ijprajournal.com ISSN: 2456-4494

Formulation and Evaluation of In-Situ Sustained Release Gelling System of Famotidine

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Submitted: 15-05-2022 Revised: 20-05-2022 Accepted: 25-05-2022

ABSTRACT:
The main purpose of gel dosage form is to provide sustained and controlled release of drug thereby increasing the oral absorption of drug with narrow absorption window and to protect the drug from unfriendly environment.The main objective of this present work is to formulate and evaluate novel in-situ gel of famotidine for treatment of peptic ulcer.In this study different concentration of gelling polymer like sodium alginate, xanthan gum, gellan gum were prepared by dissolving it in deionized water at 70°C. all formulation were evaluated for clarity,PH, viscosity, dug release, drug content, gel strength, floating lag time, and stability study.all results were found to be satisfactory. The results shows that viscosity increases with increase in polymer concentration and drug release gets sustained. All the formulations were therapeutically efficacious and provide sustaine release of drug.the study shows that the developed formulation is an alternative to conventional dosage form.

KEYWORDS: in situ gel, novel drug delivery system, polymers.

I. INTRODUCTION

GELS:

Gels are semisolid system which contains both solid and liquid components. It consists of three dimensional solid network [3].

In-situ is a Latin phrase which translated is literally as "in position". In-situ gel drug delivery are in solution form before administration in the body, but once administered undergoes gelation in-situ, to form gel. Gelation occurs due to cross linking of polymer chain through covalent and non-covalent bond formation [6]. In-situ gelling system has become one of the best among the novel drug delivery system due to its sustained and controlled release action, improved patient compliance and comfort, reduced frequency of dosing [1,2]. In situ gel formation occurs due to one or combination of different stimuli or triggering mechanisms like change in pH, temperature or solvent exchange, ionic cross linkage, ionization, UV irradiation [3]. In-situ gel forming system via different route such as oral, nasal, ophthalmic etc. can be formulated. The system basically utilizes polymers that undergo transformation from sol to gel like consistency, due to the change in physicochemical properties [8].

- Over the past 30 years greater attention has been focused on the development of controlled and sustained drug delivery systems. The goal in designing these systems is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of the action.

- Amongst the extensive research has been carried in designing of polymeric drug delivery systems, the development of in situ gel systems has received considerable attention over the past few years. These systems are capable of releasing the drug in a sustained manner maintaining relatively constant plasma profiles and they are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. This is a characteristic property of temperature dependent, pH dependent and cation induced gelation. In situ gel forming drug delivery is a type of mucoadhesive drug delivery system.[4]

- In contrast to very strong gels, they can be easily applied or used in liquid form to the site of drug absorption, where, they swell to form a strong gel that is capable of prolonging the residence time of the active substance. Both natural and synthetic polymers can be used for the production of in situ gels

❖ **Advantages of in-situ gelling system** [6, 3]

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It shows various advantages like

- Ease of administration.
- Improved patient compliance.
- Reduced dosing frequency.
- Site specificity and local action.
- Increased bioavailability.
- Sustained and prolonged release.
- It can also be administered to unconscious patient.

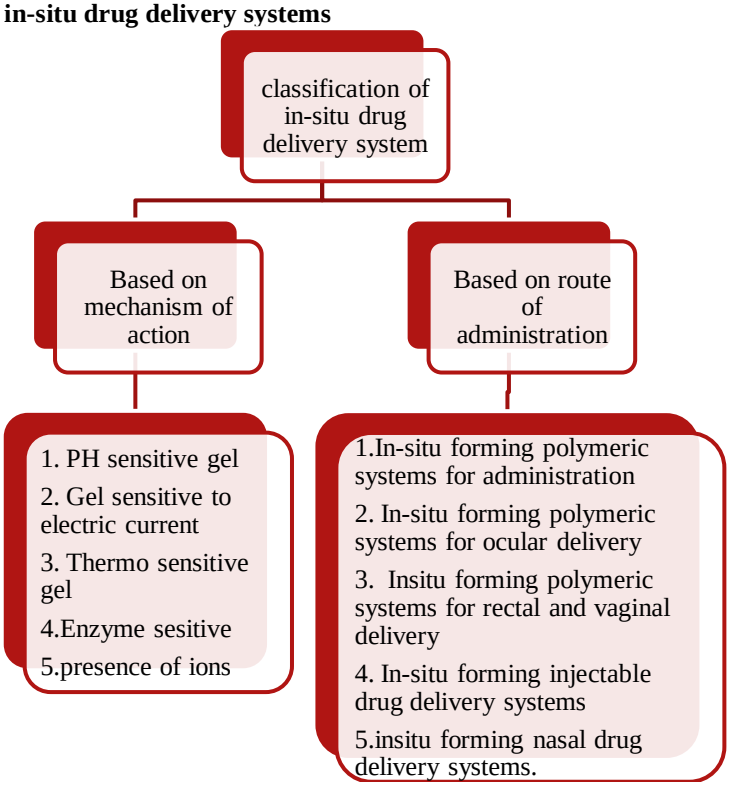
❖ **Disadvantages of in-situ gelling system**[8]

- It requires an elevated level of fluids
- Only small doses can be administered
- The solution dorm of drug is more susceptible to degradation.
- Due to chemical degradation, there is a chance of instability.
- It may results in premature dissolution due to low mechanical strength.

❖ **Importance of in-situ gelling system** [1, 2]

- It helps for the controlled and sustained release of the drug by its special 'Sol Gel transition.'
- It helps to reduce frequency of drug administration.
- Low drug dose required and there will be no drug accumulation and no side effects.
- More bioavailability of the drug.
- Increased residence time of the drug due to gel formation.
- The in situ gelling decreases wastage of the drug.
- Reduced systemic absorption of drug drained through the nasolacrimal duct may result in some undesirable side effects.

Ⅱ. Classification of in-situ drug delivery systems



ⅲ. Approaches for forming in-situ gels

There are 4 triggering mechanisms for in-situ gelling of biomaterials

1. In situ gel formation due to physiological stimuli

a. Temperature triggered in situ gel systems
b. pH triggered in situ gelling systems

2. In situ gel formation due to ion-activated system

3. In situ gel formation due to physical mechanism

a. Swelling
b. Diffusion

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4. In situ gel formation due to chemical reactions

a. Ionic cross-linking
b. Enzymatically cross linking
c. Photo-polymerization

1. In situ gel formation due to physiological stimuli

There are some polymers which undergo large and unexpected physical and chemical changes in response to small external variation or changes in their environmental conditions. Such polymers are called Stimuli-responsive polymers [3].

Some examples of multi-stimuli responsive in-situ gelling system.

Model drugs	Polymers	Stimuli	Major finding
Sparfloxacin [29]	Sodium alginate and methylcellulose	Ion and pH sensitive	Rapid gelation upon raising pH to 7.4, in vitro sustained drug release over period of 24 h, significantly enhanced corneal permeation.
Nepafenac [48]	Carboxymethyl chitosan (CMC) and poloxamer	pH-induced and thermo-sensitive	The gelation temperature of 32–33 °C and retarding the drug diffusion rate was observed.
Timolol [49]	Chitosan with gellan gum	pH-sensitive and ion-activated polymer	Enhanced transcorneal drug permeation and prolonged the retention at the corneal site.
Levofloxacin [50]	Sodium alginate and chitosan	Ion and pH-triggered	Better retention time was observed.
Ciprofloxacin [51]	Carbopol/HPMC and Poloxamer	pH-induced and thermo-sensitive	Improved therapeutic efficacy and offers sustained release of the drug over an 8 h period.

Table no 1

a. Temperature triggered in situ gel system

Temperature sensitive polymers are most widely studied class of environmentally responsive polymer systems in drug delivery. This is because change in temperature is easily applicable on both in vivo and in vitro, and controlling of temperature is also very easy. In this system, gelling of solution is triggered by body temperature, thus sustaining the drug release and no need of external heat. These hydrogels are in liquid form at room temperature (20- 25°C) and undergo gelation when comes in contact with body fluid (35-37°C) (Fig.1). The use biomaterial whose transition from sol-gel induced by increase in temperature is an amazing way to approach in situ formation. The best critical temperature range for such systems is ambient and physiologic temperature; so there is no need for external heat, as gelation is triggered by body heat. There are three type of temperature induced system:

Table no 2

TYPE	EXAMPLE
Negative thermo sensitive	Poly (N-isopropyl acrylamide)
Positive thermo sensitive	polyacrylic acid
Thermally reversible	Poloxamer, pluronics, tetronics

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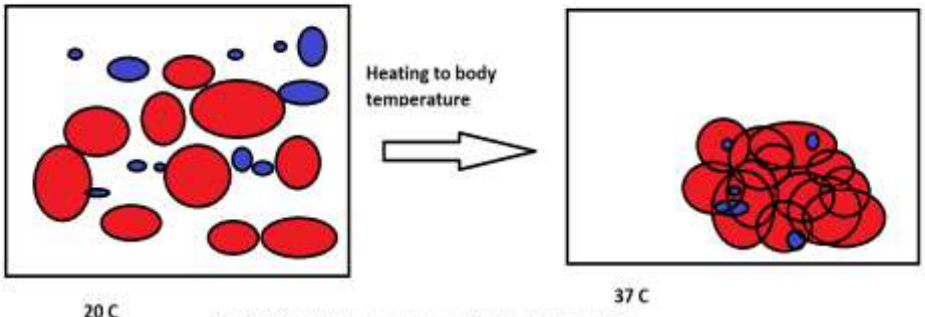

Fig. 1: Effect of temperature on in situ gel formation

b. PH triggered in-situ gelling systems;

In this system gelling is triggered due to pH changes. PH sensitive polymers or pH responsive are used in this method. In pH sensitive polymers includes pendant acidic or basic groups that either accept or release protons in counter to changes in environmental ph. The large number polymers of the ionizable groups are known as poly electrolytes. The poly electrolytes are present in the formulation causes increase in external pH that results into swelling of hydrogel that forms in situ gel.

Some suitable polymers for this approach

Cellulose acetate phthalate (CAP), carbomer and its derivatives, polyethylene glycol (PEG), pseudo latexes and poly methacrilic acid (PMC) etc. (2, 3)

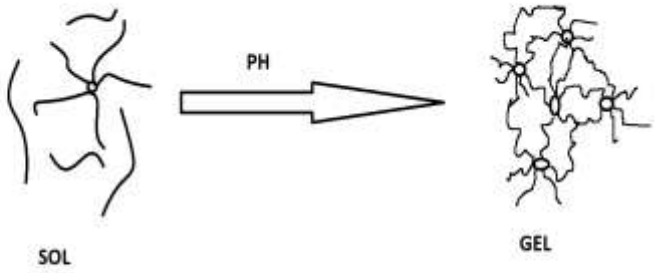

Fig. 2: mechanism of PH triggered in-situ gel system

2. In situ gel formation due to ion activated system

Here, gelling of the biomolecules solution is induced by the change in ionic strength. It is assumed that in ion activated system the osmotic gradient across the surface of the gel determines the rate of gelation. Polymers that shows osmotically induced gelation include gelrite or gellan gum, hyaluronic acid, alginates, etc. (3, 2)

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Model Drug	Polymers	Major finding
Gatifloxacin[43]	Alginate with HPMC	A higher ocular bioavailability and extended residence time in aqueous humor than conventional ophthalmic solutions.
Fluconazole[44]	HPBCD complexed gellan gum and κ-carrageenan	Showed effective control of fluconazole release and good Bioadhesive properties.
Acetazolamide[45]	Gellan gum with xanthan gum, HPMC or carbopol.	Enhanced therapeutic efficacy and more extended intraocular pressure lowering effect compared to that of marketed eye drops and oral tablet.
Terbinafine hydrochloride [46]	Gellan gum	Significantly higher C max, delayed t max, and prolonged mean residence time and increased bioavailability.

Table no 3

3. In situ gel formation due to physical mechanism

a. Swelling: In-situ gelling occurs when the material absorbs water present in the surrounding environment and then expands to occupy desired space. Example of such a substance is myverol 18-99 (glycerol mono-oleate)

b. Diffusion: This method involves diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N methyl pyrrolidone (NMP) has shown to be useful solvent for this system.

4. In situ gel formation due to chemical reaction

a. Ionic cross-linking

There are some ion sensitive polysaccharides which fall into the class of ion-sensitive ones, such as gellan gum, pectin, sodium alginate which undergo phase transition in presence of various ions. An anionic polysaccharide, Gellan gum, undergoes in situ gelling in presence of mono- and divalent cations, i.e. Ca2+, Mg2+, K+ and Na+. Gelation of the low-methoxy pectin's can be caused by divalent cations, especially ca2+.

b. Enzymatically cross linking

Enzymatic cross linking is most suitable and convenient method that can be used in formulation of in-situ gelling system. In this method gelling occurs by cross linking with the enzymes which are present in the body fluids. In situ formation catalyzed by natural enzymes has not been studied and investigated widely but it possesses some advantages over chemical and photochemical approaches. For example, under physiologic conditions, an enzymatic process works efficiently without need for potentially harmful and destructive chemicals such as monomers and initiators. Modifying the amount of enzyme provides a convenient and suitable mechanism for controlling the rate of gel formation, which allows the mixture to be injected before gel formation. [3, 2].

c. Photo-polymerization

Electromagnetic radiations are used in photo-polymerization method during formation of in situ gelling system. A solution of reactive macromere or monomers and invader can be injected into a tissues site for gelling process. The most suitable polymers for photo polymerization are the polymers that undergo dissociation by polymerisable functional group in the presence of photo initiator like acrylate or similar monomers and macromeres that are typically long wavelength ultraviolet and visible wavelengths are used. Short wavelength ultraviolet have limited penetration of tissue and biologically harmful so they are not widely used. In this method, ketone, such as 2, 2 dimethoxy-2-phenyl acetophenone, is used as the initiator for ultraviolet photo- polymerization. Camphor Quinone and ethyl eosin initiators are used in visible light systems. [2]

ivv. Ideal characteristics of polymers for preparation of in situ gel [14, 15]

- The polymer should be capable of adhering to the mucous membrane.
- It should be well compatible and should not provide any toxic effects.
- It should have pseudo plastic behavior.
- The polymer should be capable of decreasing the viscosity with increase in shear rate.
- Preferred pseudo plastic behavior of polymer.
- Good tolerance and optical clarity is more preferred.
- It should influence the tear behavior

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POLYMER	PROPERTIES
PECTIN[4]	➢ Pectin's are a family of polysaccharides, in which the polymer backbone contains mainly, α- -(1-4)--D galacturonic acid residues. ➢ Low methoxy pectin's (degree of esterification <50%) in presence of free calcium ions readily forms gels in aqueous solution, which crosslink the galacturonic acid chains in a manner described by egg-box model. ➢ Pectin used mainly for these formulations is due to its water solubility, so organic solvents are eliminated in the formulation. ➢ Divalent cations present in the stomach, carry out the transformation of pectin to gel form when it is orally administered(11)
GUAR GUM[14]	➢ Guar gum is also known as guaran of naturally occurring gum which is obtained from the endosperm of the seed. ➢ Guar gum is insoluble in hydrocarbons, fats, esters, alcohols and ketones but soluble in water. ➢ These show its dispersibility in both cold and hot water that it is soluble in both cold and hot water to form colloidal solution at low amount. ➢ Guar gum has derivatives are used in targeted delivery systems in the formation of coating matrix systems, nano-microparticles and hydrogels. ➢ It can also be used as a polymer in matrix tablets which shows controlled release.
CARBAPOL[4,5]	➢ Carbopol is a polyacrylic acid (PAA) polymer, also known as PH dependent polymer which changed to gel as the pH is raised from 4.0 to 7.4. ➢ Carbopol stays in solution form at acidic pH but transform into a low viscosity gel at alkaline Ph. ➢ HPMC is generally used in combination with carbopol to enhance viscosity of carbopol solution, and to reduce the acidity of the solution.
XYLOGLUCAN[8]	➢ Xyloglucan is also called as tamarind gum as it is obtained from endosperm of tamarind seeds (3). ➢ Xyloglucan consists of three different oligomers like heptasaccharide, octasaccharide, nonsaccharide, which differ in number of galactose side chain. ➢ It is potentially used in oral, rectal, ocular drug delivery due to its non- toxic, biodegradable and biocompatible property. ➢ Various water soluble polymers such as: carbopol system- hydroxypropylmethylcellulose

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	system, poly (methacrylic acid)-poly (ethylene glycol) come under the class of pH-induced in-situ precipitating polymeric systems.(6)
GELLAN GUM[2,5]	➢ Gellan gum (Gelrite) is a linear, anionic deacetylated exocellular polysaccharide secreted by the microbe Pseudomonas elodea with a tetra saccharide repeating unit of one α-L rhamnose, one β-D-glucuronic acid and two β- D-glucuronic acid residues. ➢ Gelation of gellan gum is temperature dependent or cation induced. ➢ This gelation involves formation of double helical junction zones followed by aggregation of the double helical segments which gives rise to a 3-dimensional network by complexation with cations and hydrogen bonding with water.(3)
ALGINIC ACID[4]	➢ Alginic acid is a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and α-L-guluronic acid residues joined by 1, 4-glycosidic linkage. ➢ Depending on the algal source, the proportion of each block and the arrangement of blocks along with the molecule varies. ➢ Dilute aqueous solutions of alginates form firm gels on addition of di- and tri-valent metal ions by a cooperative process involving consecutive glucoronic residues in the α-L- guluronic acid blocks of the alginate chain. ➢ Alginic acid is mucoadhesive, biodegradable and non-toxic polymer, due to which it is widely used as a vehicle for ophthalmic in situ gelling system.(6)
XANTHUM GUM[5]	➢ Xanthum gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram negative bacteria Xanthomonas campestris. ➢ The primary structure of this naturally obtained cellulose derivative contains a cellulose backbone (β-D-glucose residues) and a trisaccharide side chain of β-D- mannose-β-D-guluronic acid-α-D-mannose attached with alternate glucose residues of the main chain. ➢ The anionic character of this polymer is due to the presence of both glucuroniacid and pyruvic acid groups in the side chain(7,3)
CHITOSAN[9]	➢ Chitosan is a biodegradable, thermo sensitive, polycationic polymer obtained by alkaline deacetylation of chitin, a natural component of shrimp and crab shell. ➢ Chitosan is a biocompatible pH dependent cationic polymer, which remains dissolved in aqueous solutions up to a pH of 6.2(7)

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	➢ Neutralization of chitosan aqueous solution to a pH exceeding 6.2leads to the formation of a hydrated gel like precipitate. ➢ The pH gelling cationic polysaccharides solution are transformed into thermally sensitive pH dependent gel forming aqueous solutions, without any chemical modification or cross linking by addition of polyol salts bearing a single anionic head such as glycerol, sorbitol, fructose or glucose phosphate salts to chitosan aqueous solution.(7)
HPMC[4]	➢ Cellulose consists of glucan chain which has repeating β-(1, 4)-D-glucopyranose unit. ➢ Some natural polymers like HPMC, MC and EC exhibit temperature sensitive sol-gel phase transition. ➢ Cellulose material will increases its viscosity when temperature will decreases while its derivatives like HPMC, MC, will increase its viscosity when temperature is increased. ➢ MC is a natural polymer composed of native cellulose with alternate methyl substitution group on its chain. ➢ At low temperature (30C) solution is in liquid form and when temperature is increases (40-50C) and gelation occurred.(4)
POLOXAMER[5]	➢ Poloxamer are water soluble tri-block copolymer. ➢ It consists of two polyethylene oxide (PEO) and polypropylene oxide (PPO) core in an ABA configuration(4) ➢ Pluronics or Poloxamers consists of more than 30 different non-ionic surfactants. ➢ There in situ gel formation is based on temperature change. ➢ These are triblock copolymers consisting of poly (oxyethylene) and poly (oxypropylene) units that undergo alteration in solubility with alteration in surrounding temperature. ➢ Pluronic F217 gives colorless and transparent gel, and is one of the most commonly used polymer in pharmaceutical technology. ➢ A concentration of 20% weight of Pluronic F217 at 25°C is required for gelation. The solution behaves as a mobile viscous liquid at room temperature (25°C), which is altered into a semisolid transparent gel at body temperature (37°C).(3)

Table no 4

V. FORMULATION OF INSITU

TYPE	API	POLYMER
FOR OPTHALMIC[25]	Moxifloxacin hydrochloride Linezolid Gatifloxacin	HPMC 50 LV HPMC K 4M Xanthan gum Hydroxyl ethyl cellulose

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		Carbopol 934P
FOR NASAL[24]	Vitamin B12 Chlorpheniramine maleate Ondansentron Flumarizine hydrochloride zolmitriptan Salbutamol sulphate	Pluronic F68 Pluronic F127 Carbopol 934P Chitosan Gellan gum
FOR PARENTRAL[56]	Gatifloxacin Doxycylin Leuprolide	Sodium alginate Gellan gum Alginic acid Poloxamer Pluronic F127
FOR ORAL[4]	Clotrimazole Ofloxacin Nifedipine Roxatidine Omeprazole diltiazem	Gellan gum Chitosan Carbopol Xanthan gum

Table no 5

vi. Method of preparation

1. Solution polymerization or cross linking [4]

In this method, multifunctional cross linking agents are mixed with ionic or neutral monomers. The polymerization is initiated thermally or by UV light or by redox initiator system. Solvent present minimizes the temperature control problem as well as serves as heat sink. The finished hydrogels requires washing with distilled water for removal of the unreacted materials, cross linking agent and the initiator. One of the best example of this method is poly (2-hydroxyethyl methacrylate) hydrogels from hydroxyethyl methacrylate, using ehtylene glycol dimethacrylate as cross linking agent.

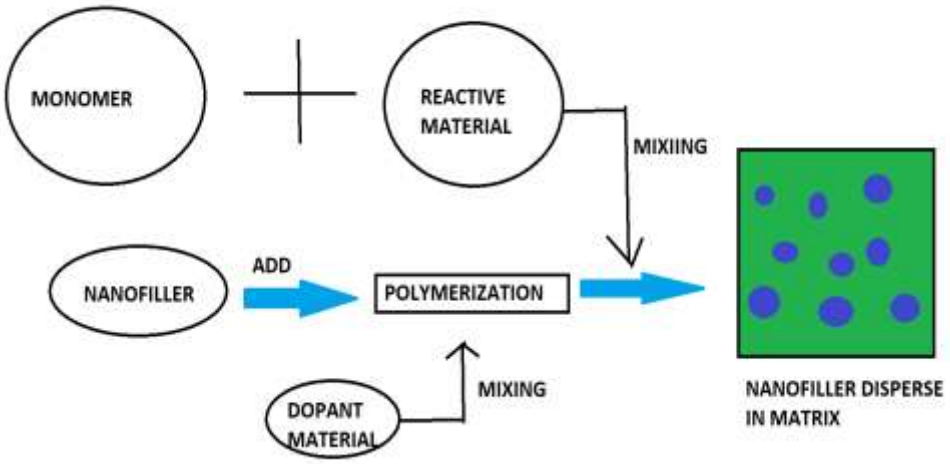

Fig.3: solution polymerization

2. Suspension polymerization [5]

This method is widely used for preparation of spherical hydrogel microparticles with size ranging from 1µm to 1mm. In this method, the monomer solution is dispersed in the non- solvent forming fine droplets, which are stabilised by addition of stabilizer. The initiation of the polymerization is by thermal decomposition of

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free radicals. The prepared microparticles require further washing to remove unreacted monomers, cross linking agent and initiator. Hydrogel microparticles of poly (vinyl alcohol) and (hydroxyl ethyl methacrylate) have been prepared by suspension polymerization method.

3. Polymerization by irradiation [6]

High energy radiations such as gamma and electron beam are used to prepare the hydrogels of unsaturated compounds. The irradiation of aqueous polymer solution results in the formation of radicals on the polymer chains, which results in formation of microradicals. Recombination of the microradicals on different chains results in the formation of covalent bonds, and finally a cross linked structure is obtained. Polymerization microradicals may interact with oxygen during radiation, that's why radiation is performed in an inert atmosphere using nitrogen or argon gas. Example of this method include poly (vinyl alcohol), poly (ethylene glycol) and poly (acrylic acid).

4. Chemically crossed linked hydrogels [3]

Polymers which contain functional groups like - OH, -COOH, -NH2 are soluble in water. Due to presence of such functional groups on the polymer chain, it can be used to prepare hydrogels by forming covalent linkages between polymer chains and complimentary reactivity, such as amine-carboxylic acid, isocyanate -OH or -NH2 or by Schiff's base formation. Gluteraldehyde can be used as a cross linking agent for preparation of hydrogels of polymers containing -OH groups such as poly (vinyl alcohol) and also polymers containing amine groups (albumin, gelatin, polysaccharides). This cross linking agent reacts with the functional groups present on the polymer via addition reaction. Since cross linking agents are highly toxic, unreacted agents have to be extracted. Also the reaction has to carried out in organic solvents since water can react with the cross linking agent. The drugs are loaded after the formation of hydrogel, hence the release is typically first order

5. Physically cross linked hydrogel [4]

Almost all of the covalent cross linking agents are known to be toxic, even in small traces. Hence to overcome this problem and to avoid a purification step, hydrogels are prepared by reversible ionic cross linking. Chitosan, a polycationic polymer reacts with positively charged components, either ions or molecules forming a network through ionic bridges between the polymeric chains. In case of anionic molecules, phosphate containing groups, particularly sodium triphosphate is widely studied. Ionic cross linking is an effortless and easy-going procedure. Compared to covalent cross linking, no auxillary molecules such as catalysts are required. Chitosan is also known for forming polyelectrolyte complex with poly (acrylic acid).

vii Evaluation and characterization [5]

Following parameters are used for evaluation and characterization of in situ gel:

Appearance: Gel formulations were visually inspected for clarity, color and homogeneity

Surface pH: The pH values of different formulations were measured using a calibrated digital pH meter at room temperature in triplicate

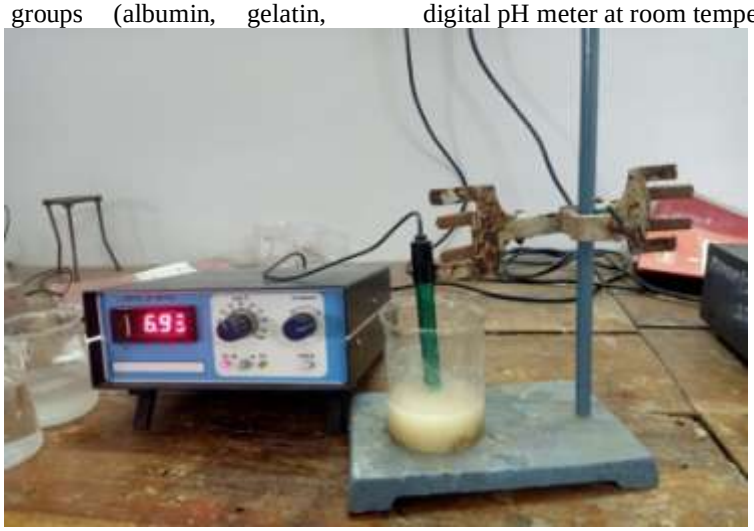

Fig 4 Ph Meter

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Viscosity: Viscosities of the formulations are determined with the help of Brookfield's digital Viscometer (DV-II) +Pro using S63 spindle at 50 rpm and measurement was for done for 6 times with fresh samples being used each time and average reading was taken.

Fig 0 Viscosity

In-vitro Floating Studies: Floating studies of in-situ gelling solution were carried out in 500 ml of 0.1N HCl (pH 1.2) in a beaker. 10 ml of solution was added to HCl with mild agitation. The parameters like the time taken for the system to float over the surface of the medium (floating lag time) and the time the formed gel constantly float over the surface of the dissolution medium (floating time) can be estimated.

Fig 6 Floating Lag Time

In-vitro Gelling Capacity: To evaluate the formulations for their in-vitro gelling capacity by visual method, colored solutions of in-situ gel forming drug delivery system were prepared. The in-vitro gelling capacity of prepared formulations was measured by placing five ml of the gelation solution (0.1N HCl, pH 1.2) in a 15 ml borosilicate glass test tube and maintained at 37 ± 1 ºC temperature. One ml of colored formulation solution was added with the help of a pipette. The formulation was transferred in such a way that places the pipette at surface of fluid in test tube and formulation was slowly released from the pipette. As the solution comes in contact with gelation solution, it was immediately converted into a stiff gel-like structure. The gelling capacity of the solution was evaluated on the basis of stiffness of formed gel and time period for which the formed gel remains as such. The color was added to give visualized appearance to formed gel. The in-vitro gelling capacity was graded in three categories on the basis of gelation time and time period for which the formed gel remains.

Determination of Drug Content: 10 ml of in- situ gel was measured and transferred to 100 ml of the volumetric flask containing 0.1N HCl and stirred for 1 h on magnetic stirrer. The solution was filtered and suitably diluted with (0.1N HCl, pH 1.2 medium), and the drug concentration was determined by using a UV-visible spectrophotometer at 273 nm against a pH 1.2 medium as the blank solution.

In-vitro Drug Release Studies: The drug release study was carried out using USP Type II paddle-

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type apparatus at 37°C ± 0.5°C and at 50 rpm using 900 ml of a dissolution medium having 0.1N HCl (pH 1.2). In-situ gel equivalent to 100 mg of famotidine was used for the test. 5 ml of sample solution was withdrawn at predetermined time intervals, filtered througha 0.45 µm membrane filter, dilute suitably, and analyzed by ultraviolet spectrophotometer at 273 nm. The same amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Each dissolution study was carried out for a period of 8h.

Stability Studies: We can define stability as, the extent to which the product maintains the its properties and characteristics that it possesses at the time of its manufacture within the prescribed limit and throughout its storage period. Stability testing is carried out to ensure that drug products retain their properties until the end of their expiry dates. The purpose of the Accelerated Stability Study was to provide evidence on the quality of a drug moeity or drug product that varies with time under the influence of various environmental factors such as temperature, humidity, and light.

The optimized formulation was subject to stability studies in accordance with ICH (International Conference of Harmonization) guidelines at temperature 40±1 ℃ / 75±5 percent Relative Humidity for a period of 1 month. The sample was extracted after 30 days and tested for pH, viscosity, product quality, physical examination , and analysis of in-vitro drug release.

Fig 7 Stability Chambar

II. RESULT AND DISCUSSION

PREFORMULATION STUDY

RESULT OF PREFORMULATION STUDY

Table 6 Organoleptic Character

Parameter	Observation
Description	white to pale yellow crystals or powder
Color	white to pale yellow
Odour	Odourless

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MELTING POINT DETERMINATION:
The observations for melting point of received famotidine are as follows:

Table 7 Melting Point

Sr. No.	Temperature (^{o}C)
1.	163.55
2.	164
3.	163.25
Average (n=3)	163.6

COMPATABILITY STUDY:
FTIR OF STANDARD FAMOTIDINE

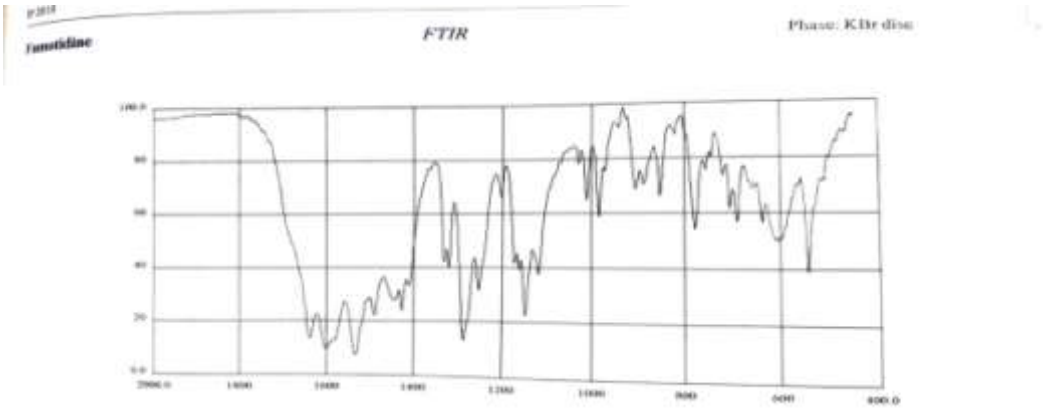

Fig 8 FTIR of Pure Drug

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Volume 7, Issue 3 May-June 2022, pp: 729-757 www.ijprajournal.com ISSN: 2456-4494

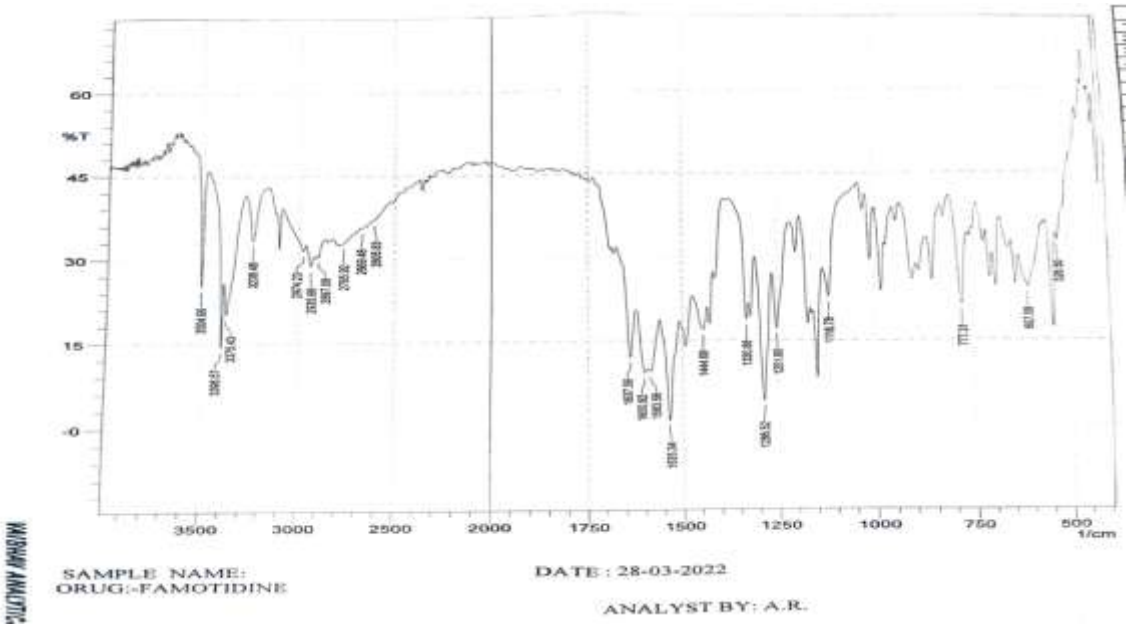

Fig 9 FTIR Received

Table 8 FTIR Received

Functional group	Standard	Observed
C-H Aromatic streach	770-790	777.31
C=C Aromatic streach	1678-1668	1637.56
N-H Streach	3400-3300	3375.5
C-N Streach	1250-1020	1251.8
S=O	1350-1300	1330.88

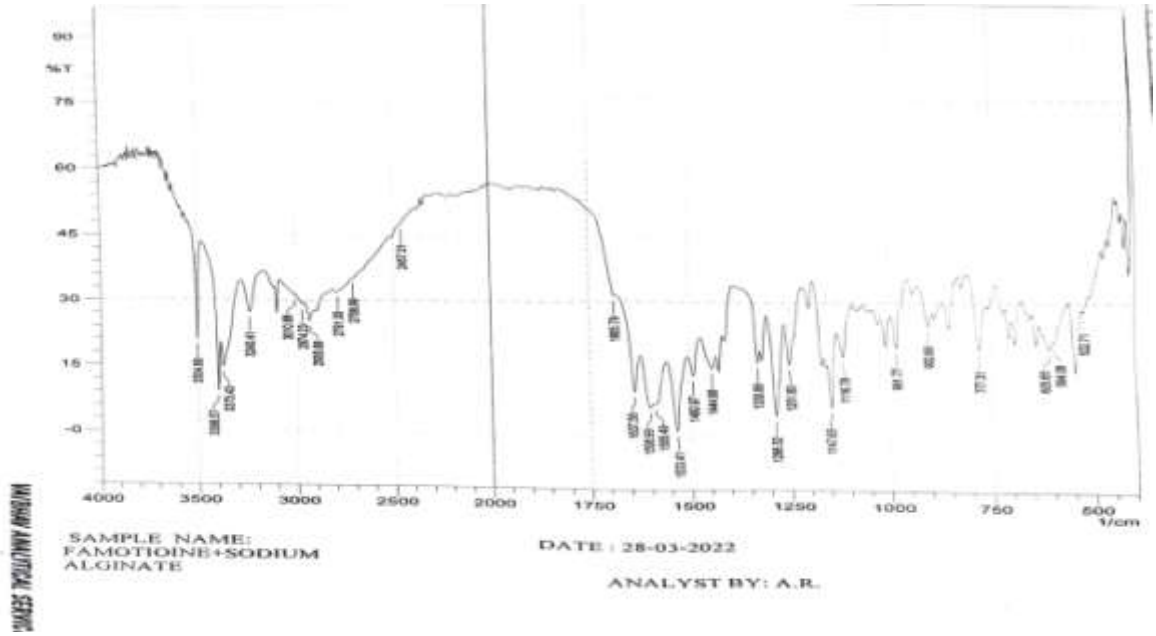

Fig 10 FTIR of Drug and Polymer

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Table 9 **FTIR of Drug and Polymer**

Functional group	Standard	Observed
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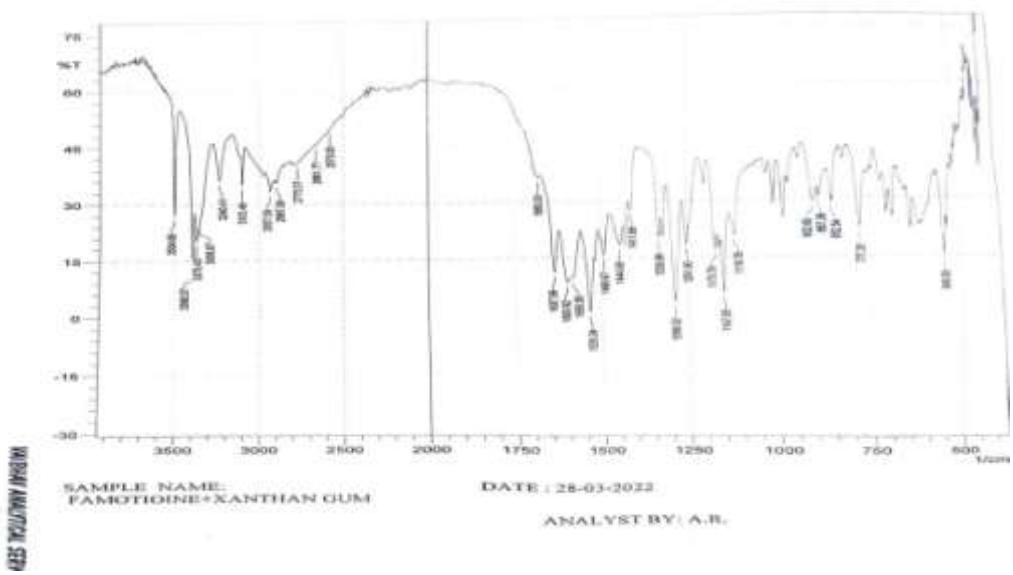

Fig 11 FTIR of Drug and Polymer

Table 11 FTIR of Drug and Polymer

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C=C Aromatic streach	1678-1668	1637.56
N-H Streach	3400-3300	3375.5
C-N Streach	1250-1020	1251.8
S=O	1350-1300	1330.88

Ftir of in-situ gel of famotidine

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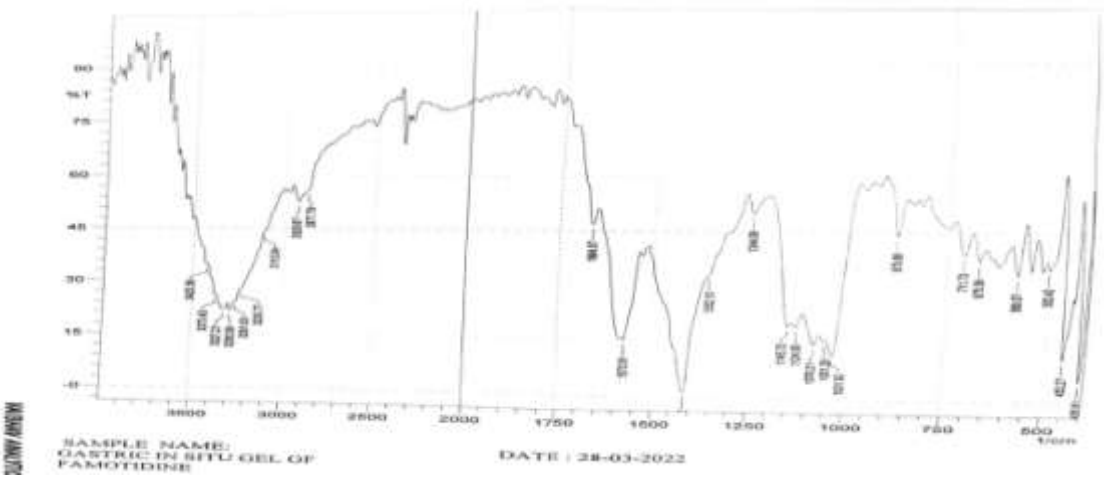

Fig 12 FTIR of Final Formulation

Table 12 FTIR of Final Formulation

Functional group	Standard	Observed
C-H Aromatic streach	770-790	777.31
C=C Aromatic streach	1678-1668	1637.56
N-H Streach	3400-3300	3375.5
C-N Streach	1250-1020	1251.8
S=O	1350-1300	1330.88

Standard calibration curve of famotidine

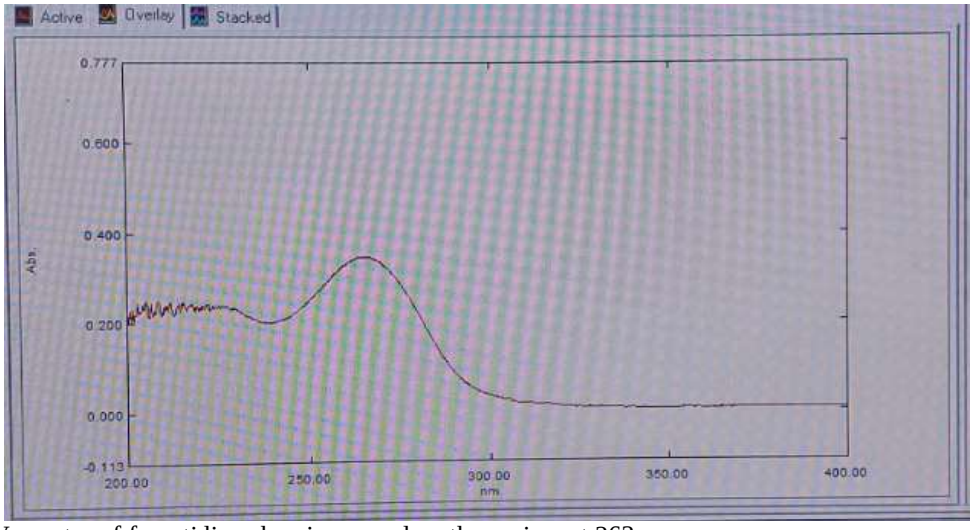

Fig 13 UV spectra of famotidine showing wavelength maxima at 263nm

Table 13 Standard calibration curve of Famotidine

CONC (µg/ml)	I	II	III	AVERAGE Abs at 263 nm
1	0.111	0.121	0.119	0.117
2	0.141	0.138	0.130	0.136
3	0.252	0.196	0.230	0.226

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4	0.315	0.320	0.322	0.319
5	0.342	0.336	0.330	0.336
6	0.364	0.354	0.350	0.356
7	0.414	0.407	0.410	0.410
8	0.456	0.440	0.451	0.449

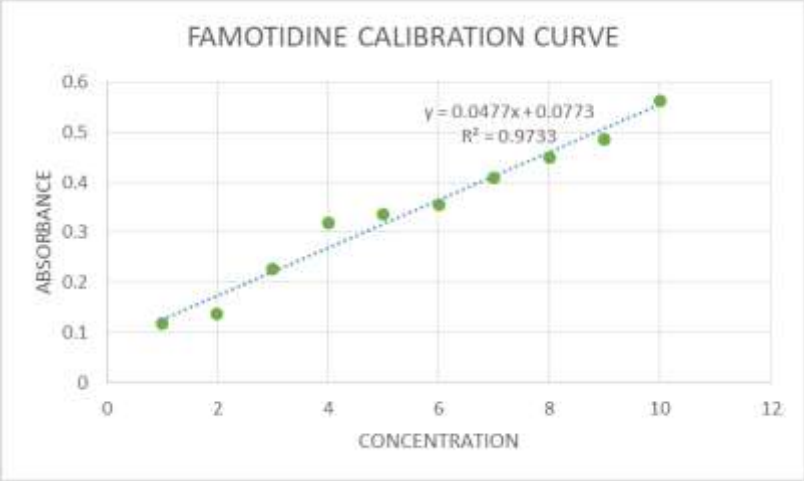

Fig 14 Famotidine Calibration Curve

DISCUSSION OF PREFORMULATION STUDY

Melting point determination:

- Melting point of famotidine was found to be in range of 163-164^{o}C as reported in literature, thus indicating purity of the drug sample. If any impurity is present, it causes variation in the melting point of given drug.

IR SPECTROSCOPY:

- The IR spectrum of the pure famotidine sample recorded by FTIR spectrometer was compared with standard functional group frequencies of famotidine.
- The functional group frequencies of the famotidine were in the reported range which indicates that the obtained sample of famotidine was pure.

COMPATABILITY STUDY:

- The interaction between drug and polymers was not seen by comparing the FTIR spectra of the mixture of drug, sodium alginate and xantahn gum with the pure drug IR spectra.

Frequencies of functional groups of pure drugs is not affected by the presence of polymers and other excipients, and it was concluded that there was no interaction between the drug and the polymer used in this study

PRILIMINARY STUDY

Table 14 Result of preliminary study 1

FORMULATION CODE	PH	APPEARANCE	VISCOSITY (cp)	CLARITY TEST	IN-VITRO GELLING CAPACITY	IN-VITRO FLOATING STUDIES(sec)
A1	7.25	VISCOUS LIQUID	175.12	PASSES	++	45
A2	6.72	VISCOUS LIQUID	150.32	PASSES	+++	30
A3	6.84	VISCOUS LIQUID	120.13	PASSES	+++	35
A4	6.95	VISCOUS	230.45	PASSES	+++	40

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		LIQUID				
A5	6.99	VISCOUS LIQUID	218.12	PASSES	+++	25

Good	+++
Moderate	++
poor	+

Discussion

Trial A1: gelling polymer sodium alginate alone as polymer was used and no retardant polymer were used in A1 so the viscosity was less due to which drug release can be fast and sustained release cannot obtained.

Trial A2: retardant polymer gellan gum was used alone and the viscosity and drug release was not expected and the thickness of gell was less

Trial A3: Retardant polymer xanthan gum was used alone and the viscosity was goo but not as desired and the gelling lag time was more

Trial A4: gelling polymer sodium alginate with the retardant polymer gelan gum was used and the viscosity was good as desired and gelling time was also good

Trial A5: gelling polymer sodium alginate was used along with retardant polymer xanthan gum and gelling lag time, viscosity, gel strength every thing was as required for good gel. So xanthan gum along with sodium alginate was used for the in-situ gel prepration of famotidine.

Table 15 Result of preliminary trial 2

FORMULATION CODE	PH	APPEARANCE	VISCOSITY (cp)	CLARITY TEST	DRUG CONTENT (%)	IN-VITRO GELLING CAPACITY	IN-VITRO FLOATING STUDIES(sec)
B1	7.25±0.23	VISCOUS LIQUID	102.35±0.035	PASSES	94.66±0.031	++	45±0.23
B2	6.72±.56	VISCOUS LIQUID	182.14±0.056	PASSES	93..32±0.021	+++	30±0.36
B3	6.84±0.24	VISCOUS LIQUID	220.17±0.045	PASSES	92.56±0.089	+++	50±0.14
B4	6.95±0.34	VISCOUS LIQUID	224.57±0.069	PASSES	95.81±0.083	+++	30±0.23
B5	6.99±0.41	VISCOUS LIQUID	231.52±0.054	PASSES	94.32±0.002	+++	55±0.45
B6	7.1±0.36	VISCOUS LIQUID	242.52±0.036	PASSES	93.32±0.085	+++	35±0.56
B7	6.93±0.52	VISCOUS LIQUID	257.34±0.045	PASSES	98.66±0.086	+++	30±0.78
B8	7.15±0.54	VISCOUS LIQUID	268.36±0.023	PASSES	97.66±0.074	+++	45±0.54
B9	6.69±0.21	VISCOUS LIQUID	271.48±0.024	PASSES	96.66±0.088	+++	55±0.25

DISCUSSION:

Preliminary study 2 was carried out to determine the polymer concentration necessary for drug delivery. To study the effect of polymer concentration on parameters such as solution's viscosity, pH, floating lag time, and physical

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property of gel, Batches B1 to B9 were prepared as shown in Table . The concentration of sodium alginate was ranged from 1 to 2% (w/v). The concentration of xanthan gum was ranged from 0.4 to 0.6% (w/v). In B1, B2, B3, 0.4% xanthan gum was added and sodium alginate was added 1%,1.5%,2% respectively all of them gave good result but among them B3 was found best in its gelling time, Ph, drug release and viscosity floating lag time was found good in B4,B5,B6 0.5% xanthan gum was added and sodium alginate was added 1%,1.5%,2%...the polymer concentration increased so viscosity and gelling capacity also improved. And in B7,B8,B9 0.6% xanthan gum was added and among all 0.4% xantahn gum concentration was found to be optimum

Table 16 3^2 Full Factorial Study

FORMULATION CODE	PH	APPEARANCE	VISCOSITY (cp)	CLARITY TEST	DRUG CONTENT(%)	IN-VITRO GELLING CAPACITY	IN-VITRO FLOATING STUDIES(sec)
F1	7.25±0.32	VISCOUS LIQUID	182.14±0.024	PASSES	97.99±0.031	++	45±0.26
F2	6.72±0.25	VISCOUS LIQUID	242.52±0.025	PASSES	95.5±0.021	+++	30±0.24
F3	6.84±0.45	VISCOUS LIQUID	271.48±0.058	PASSES	92.66±0.089	+++	15±0.85
F4	6.95±0.25	VISCOUS LIQUID	102.35±0.035	PASSES	98.3±0.083	+++	50±0.54
F5	6.99±0.56	VISCOUS LIQUID	268.36±0.056	PASSES	93.45±0.002	+++	20±0.63
F6	7.1±0.85	VISCOUS LIQUID	220.17±0.089	PASSES	97.36±0.085	+++	40±0.24
F7	6.93±0.45	VISCOUS LIQUID	257.34±0.024	PASSES	98.3±0.086	+++	24±0.85
F8	7.15±0.85	VISCOUS LIQUID	231.52±0.045	PASSES	95.99±0.074	+++	32±0.21
F9	6.69±0.54	VISCOUS LIQUID	224±0.023	PASSES	96.30±0.088	+++	35±.21

Good	+++
Moderate	++
Poor	+

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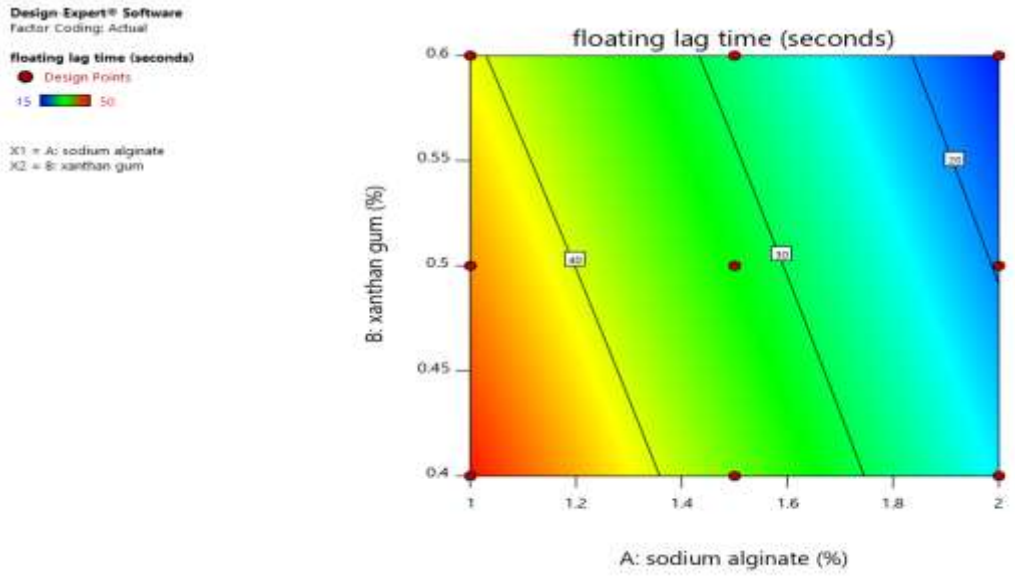

Fig 15 Contour plot of floating lag time

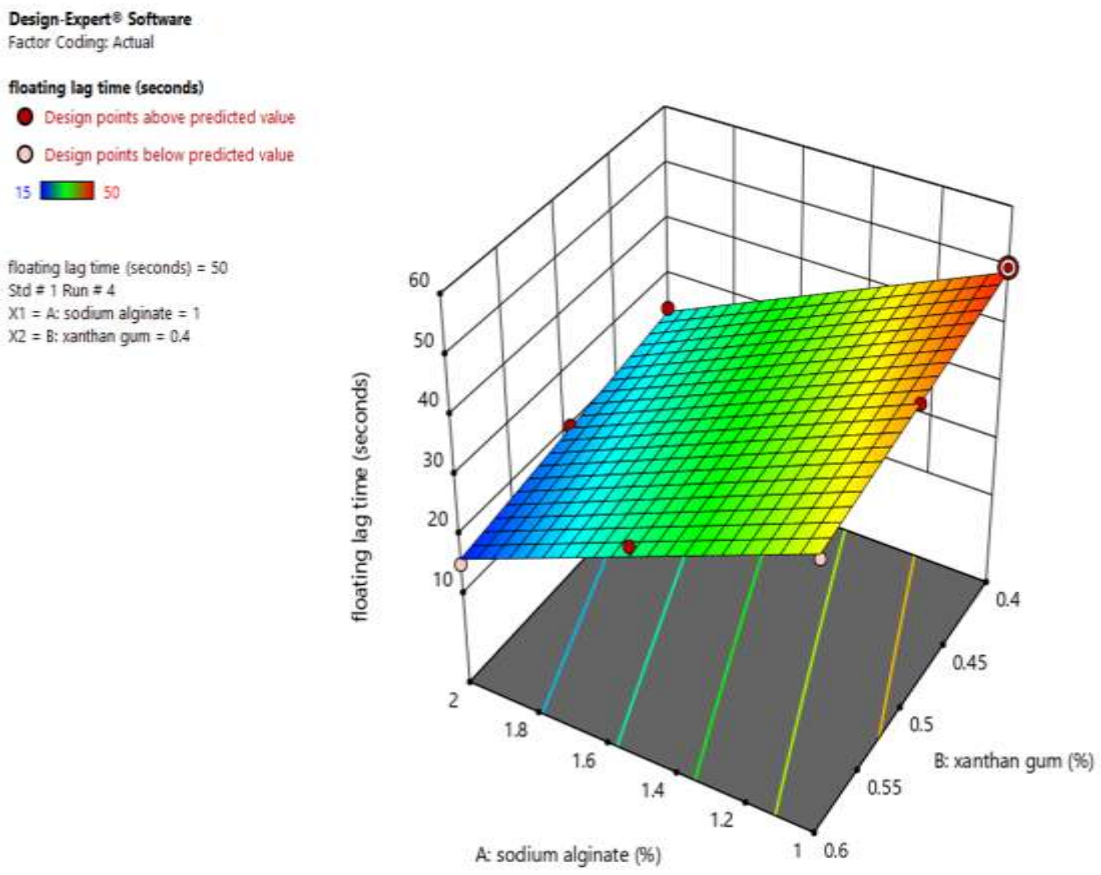

Fig 16 Surface plot of floating lag time

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Table 17 Anova for floating lag time

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1058.92	5	211.78	89.70	0.0018	significant
A-sodium alginate	962.67	1	962.67	407.72	0.0003	
B-xanthan gum	96.00	1	96.00	40.66	0.0078	
AB	0.2500	1	0.2500	0.1059	0.7663	
A^2	0.0000	1	0.0000	0.0000	1.0000	
B^2	0.0000	1	0.0000	0.0000	1.0000	
Residual	7.08	3	2.36			

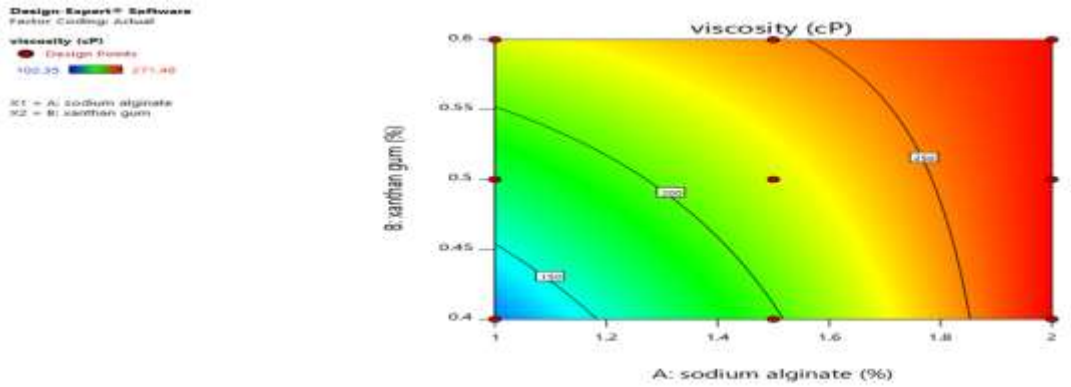

Fig 17 Contour plot of viscosity

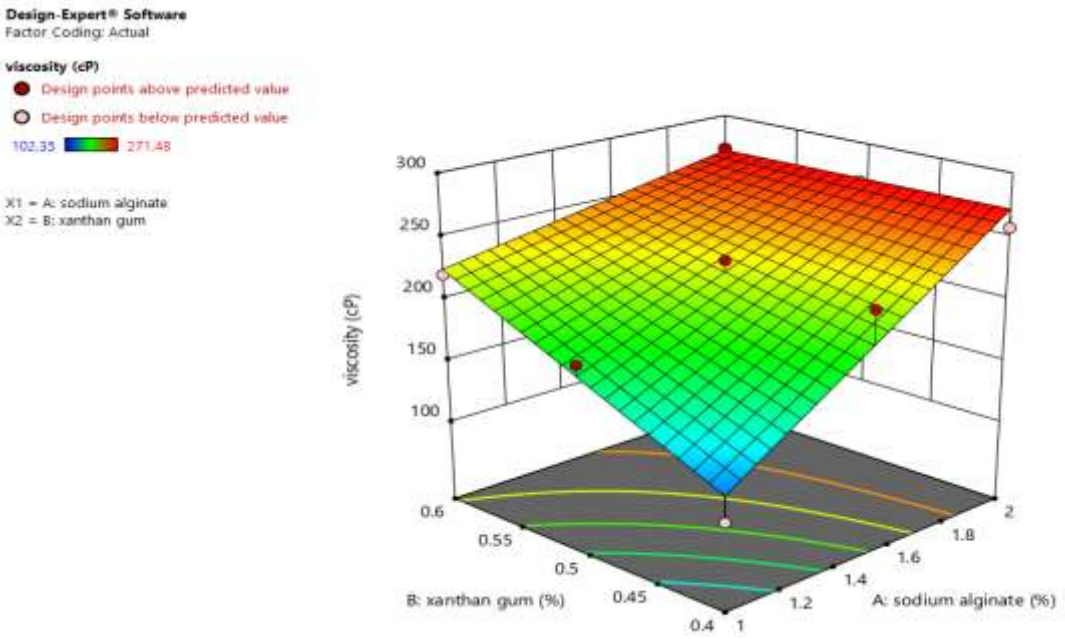

Fig 18 Surface plot of viscosity

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Table 18 Anova for viscosity

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	20694.21	3	6898.07	21.85	0.0027	significant
A-sodium alginate	14261.33	1	14261.33	45.18	0.0011	
B-xanthan gum	3745.50	1	3745.50	11.87	0.0183	
AB	2687.39	1	2687.39	8.51	0.0331	
Residual	1578.15	5	315.63			
Cor Total	22272.37	8				

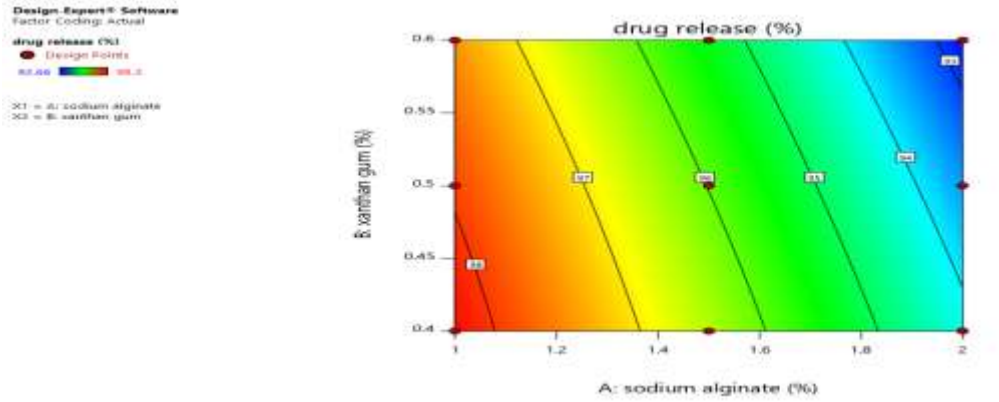

Fig 19 Contour plot of % drug release

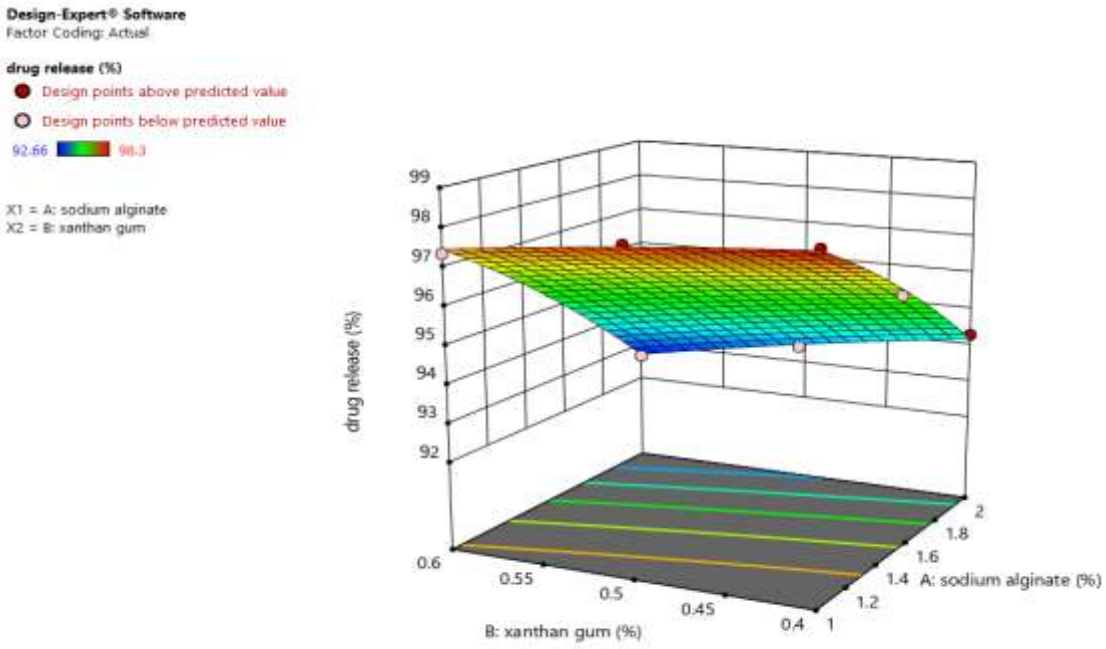

Fig 20 Surface plot of % drug release

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Table 19 anova for drug release

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	31.38	5	6.28	203.9	0.0005	significant
A-sodium alginate	29.22	1	29.22	949.15	0.0001	
B-xanthan gum	1.9	1	1.9	61.86	0.0043	
AB	0.1225	1	0.1225	3.98	0.14	
A^2	0.1284	1	0.1284	4.17	0.1338	
B^2	0.0108	1	0.0108	0.3494	0.596	
Residual	0.0923	3	0.0308			
Cor Total	31.47	8				

Table 20 Cumulative % In-vitro drug release:

Time (hour)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	26.49	26.33	24.25	26.69	25.82	25.22	26.06	24.42	24.15
2	32.71	36.67	36.34	40.55	40.04	38.45	39.68	35.95	36.67
3	44.7	42.52	41.85	44.49	42.77	41.74	42.98	41.2	40.09
4	48.19	49.55	50.49	59.85	49.85	59.74	50.45	58.93	48.74
5	52.8	59.01	58.88	62.66	51.31	68.69	55.83	62.19	57.51
6	58.96	61.5	62.03	71.93	59.81	77.59	65.57	69.98	66.55
7	63.33	72.1	79.32	72.36	70.12	78.25	75.21	70.35	68.25
8	84.52	78.36	80.12	82.68	71.32	82.98	85.36	71.38	72.65

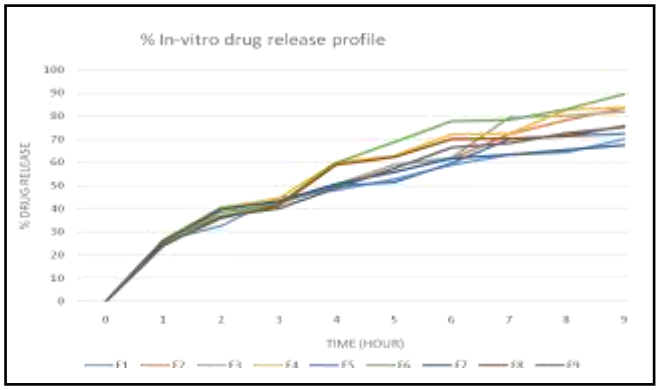

Fig 21 In-Vitro cumulative drug release vs time graph

DISCUSSION OF FACTORIAL STUDY

Based on preliminary trials, a factorial design of 3^2 factors was employed to develop famotiding in-situ gel. The design was used to study the effect of independent variables, i.e. sodium alginate (X1) concentration and xanthan gum (X2) concentration on the dependent variables floating lag time (Y1), viscosity(Y2) and drug release percentage in 8 hours (Y3).

All factors were studied at all possible combinations in a 3^2 factorial design, as it is considered to be most efficient in estimating the influence of individual variables using minimal experimentation. In this analysis, the influence on dependent variables of independent variables such as concentration of sodium alginate (X1) and concentration of xanthan gum (X2) viz. floating lag time (Y1), viscosity (Y2), and percent release of drugs (Y3) have been studied and are shown in Table. The influence of independent variables on response variables is shown in three-dimensional surface plots.

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EVALUATION

Surface pH: Measurement of pH is most important for oral preparations; otherwise it leads to throat irritation. The pH of formulation was found to be satisfactory and was in the range of 6.69- 7.25. The formulations were liquid at room temperature. All the formulation has pH around neutral or slightly alkali. Maximum pH 7.25 was observed in F1 formulation, and minimum pH 6.69 was observed in F9 formulations. The pH of all the formulation was found to be orally acceptable range and satisfactory. Therefore, it will not cause any irritation while administration.

Viscosity: Different types of viscosity-enhancing polymers (gellan gum and xanthan gum) were added to sodium alginate solution in an attempt to improve viscosity and to obtain slower drug release than those formulations containing only sodium alginate. The viscosity order of the formulation: F1 to F9 is F3 > F5 > F7 > F2 > F8 > F9 > F6 > F1 > F4. The increase in viscosity of the formulations that were observed with the increase in the concentration of polymer can be related to the increasing crosslinking of the polymer. Formulations containing xanthan gum have higher viscosities because of the viscosity enhancement property of xanthan gum.

In-vitro Floating Studies: When the formulation comes in contact with the acidic environment, gelation as well as cross-linking of the calcium ions takes place providing a gel barrier on the surface of formulation. The carbon dioxide released is entrapped in the gel matrix giving buoyancy to the formulation. Then the polymeric network further restricts the diffusion of carbon dioxide as well as drug release. The floating ability of the formulations mainly depends on the concentration of the gelling polymer, carbon dioxide, and cation source. All the in-situ gel formulations had a floating lag time of <2 min and all the formulations floated for more than 7-8 h. Therefore, the extended duration of floating was responsible for the sustained release of drug.

In-vitro Gelling Capacity: Gelling capacity is the main pre-requisite of in-situ gel formulation. The in-vitro gelling capacity was determined using simulated gastric fluid in which the solution must undergo rapid transition to gel. All the formulations showed immediate gelation and remained for extended period of time when come in contact with simulated gastric fluid maintained at 37 ± 2 °C.

Drug content: Drug must be uniformly distributed throughout the sample. This is important in relation to batch to batch uniformity and thus efficacy of the preparation. If the drug is not distributed uniformly throughout the formulation, it could either lead to the availability of sub-therapeutic dose or toxic dose. The percentage drug content of all prepared formulations was found to be in the range of 86.66 ± 0.09 – 98.3 ± 0.06%. The formulations exhibit fairly uniform drug content. Formulation F7 showed maximum drug content of 98.3±0.086 %.

In-vitro drug release: The in-vitro drug release studies, it was observed that as the concentration of gelling agent increase, release of drug from the gastroprotective in-situ gel prepared decreases. There was a drastic decrease in the drug release due to the presence of xanthan gum which acts as a drug release retardant polymer as well as viscosity enhancing agents. Xanthan gum hydrates rapidly without lumping and increases the viscosity. Even at low concentrations, xanthan gum imparts high viscosity.

KINETIC STUDY

Data Analysis: The linear regression coefficient of each kinetic model was calculated, and pattern of drug release from the dose was predicted. The drug release of F7 showed first-order kinetics with the Higuchi model drug release mechanism.

Table 21 Kinetic Study

FORMULATION	ZERO ORDER	FIRST ORDER	HIGUCHI MODEL	KORSMEYER PEPAS
CODE	R^2	R^2	R^2	R^2
F1	0.994	0.936	0.993	0.958
F2	0.993	0.930	0.981	0.934
F3	0.984	0.973	0.985	0.950
F4	0.995	0.946	0.991	0.952
F5	0.991	0.963	0.990	0.953
F6	0.988	0.973	0.988	0.953
F7	0.994	0.943	0.989	0.949
F8	0.992	0.946	0.984	0.941

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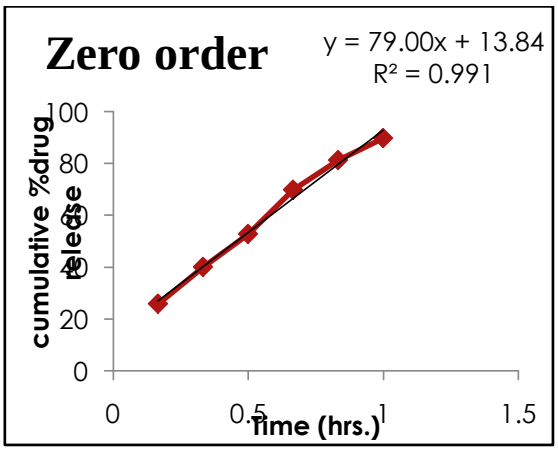
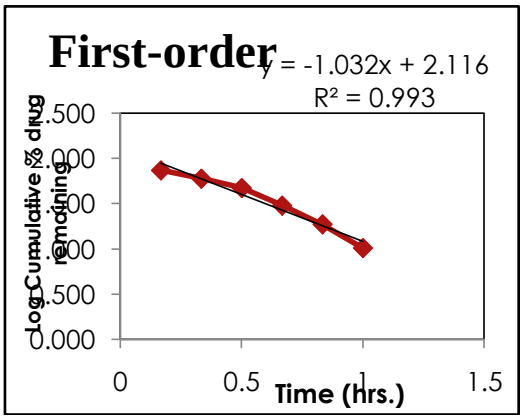
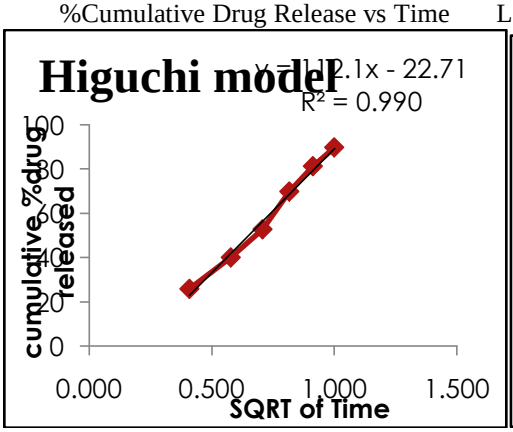
F9	0.987	0.973	0.985	0.948



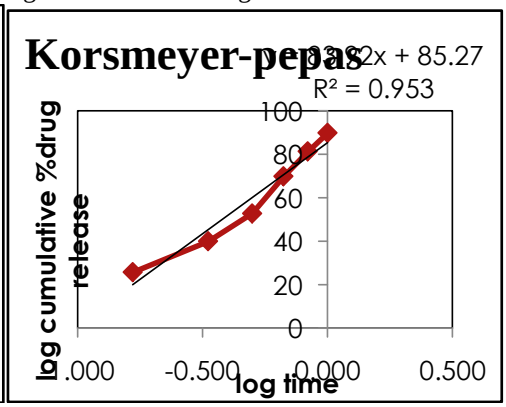
%Cumulative Drug Release vs Time



Log %Cumulative Drug Retained vs Time



Cumulative Drug Release plotted against log time



Log %Cumulative Drug Release plotted vs square root of time

SELECTION OF OPTIMIZED BATCH

- The optimized batch was selected on the basis of visual inspection, surface pH, viscosity, in-vitro floating study, in-vitro gelling capacity, drug content, and in-vitro drug release.
- Based on that formulation F7 was considered as optimized formulation for in-situ gel of famotidine among all formulations from F1 to F9

The formulation F7 was selected as the optimized formulation which has viscosity 257.34 ± 0.24 cp which is easy for swallowing and good ability for gelation immediately after oral administration with drug content of 98.30 ± 0.086% and showed in- vitro drug release of 90.32% at the end of 8 h. It follows first-order release kinetics with Higuchi model release mechanism.

Table 22 Formula of Optimized Batch F7

INGREDIENTS	quantity
FAMOTIDINE (mg)	40
SODIUM ALGINATE (%)	2
XANTHAN GUM (%)	0.4
SODIUM CITRATE(%)	0.45
CALCIUM CARBONATE (%)	0.016
SODIUM METHYL PARABEN (%)	0.2
SODIUM PROPYL PARABEN (%)	0.02

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Stability study

The optimized formulation F7 was selected for stability studies. The selected Formulation F7 were stored at and 40 ºC ± 2 ºC / 75% RH ± 5% RH for a period of 1 month. The parameters analyzed include appearance, in-vitro floating, in-vitro gelling capacity, viscosity, drug content and invitro drug release. From the stability study it was confirmed that the optimized formulation is stable at its storage temperature.

Table 23 Result of stability study of optimized formulation F7

parameter	Initial	after 1 month
Appearance	viscous liquid	viscous liquid
Viscosity	257.34	258.65
Floating lag time (sec)	24	25
Gelling capacity	+++	+++
Drug content (%)	98	96
cumulative % drug release	85	84

Storage at 40°C and 75% RH for 1 month

III. CONCLUSION

CONCLUSION

- Stomach specific floating in-situ gel containing famotidine 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 F7 was selected as the optimized formulation which has viscosity 257.34 ± 0.32 cp with drug content of 98.66 ± 0.086% and showed in- vitro drug release of 90.32% at the end of 8 h. It follows first-order release kinetics with Higuchi model release mechanism. The selected formulation was evaluated for stability.
- The present study has been a successful attempt to formulate gastro retentive in-situ gel of famotidine, an orally administrated antiulcer drug with a view to improving its oral bioavailability and provide sustained release of the drug. The developed formulations met 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 famotidine can be an effective formulation that shows improved efficacy, prolonged-release, patient compliance and cost-effective over conventional formulations.

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Volume 7, Issue 3 May-June 2022, pp: 729-757 www.ijprajournal.com ISSN: 2456-4494

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