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Research Article

Formulation and Evaluation of Ion Activated *In-Situ* Gelling System of Sucralfate for Stomach Ulcer

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ABSTRACT

In the present study an attempt was made to formulation and evaluation of ion activated Sucralfate in situ gel for stomach ulcer. The preformulation studies for the drugs included API characterization, solubility, melting point, determination of λ max, standard calibrative curve, drug and excipient compatibility study was carried out. In-situ gel of Sucralfate was formulated by ion activated method. In ion activated method, various formulations (FI-F9) were developed using excipients in various concentration of gelrite and HPMC K100M.Formulations were evaluated for various physicochemical parameters like appearance, clarity, pH, gel strength, viscosity, in-vitro gelling capacity, gelling time, in-vitro floating behaviour, drug content and in-vitro drug release studies. As the concentration of the polymer increases properties like gel strength, viscosity found to increasing but whereas the percentage of cumulative drug release from the formulation was decreased. Among all formulation F8 was selected as best formulation because of its good gelling capacity and optimum viscosity, Drug content was found to be 99.85%. It showed drug release more than 12 hours. The F8 formulation follows zero order kinetic which is depend on the concentration of the polymers and follows fickian mechanism of drug release. Stability studies was confirmed as there were no significant changes observed in physicochemical parameters.

Keywords: Sucralfate, In-situ gel, Gelrite, HMC K100M, Ion Activated Method

INTRODUCTION

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 out in designing of polymeric drug delivery systems, the development in in-situ gel systems has received considerable attention over the past few years. These systems are capable of releasing the drug in sustained manner maintaining relatively constant plasma profiles and they are liquid at room temperature but undergoes 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. In contrast to very strong gels, they can be easily applied or used in liquid form to the site of drug absorption, where they will 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 (Patel et al., 2012; Pallavi et al., 2016).

A peptic ulcer is a lesion in the mucosa of stomach or duodenum in which acid and pepsin play a major role, the term is often used to encompass any gastric or duodenal ulceration. Peptic ulcers constitute a major problem in hyperacidity patients, which is due to inflammation of the stomach duodenal mucosal lining of the GIT.

Sucralfate is an medication used to treat duodenal ulcers, epithelial wounds, chemotherapy-induced mucositis, radiation proctitis, ulcer in Behcet disease, burn wounds. Sucralfate exhibits it's action by forming a protective layer, increasing bicarbonate production, exhibiting anti-peptic effects, promoting tissue growth, regeneration, and repair. The medication has relatively safe profile as there is negligible absorption from enteral system**.**

MATERIALS AND METHODS

Materials

Sucralfate was obtained from gift sample from Vasundhara Rasayana Ltd. Gelrite was provided by Yarrow chem product, Mumbai. HPMC K 100 M was provided by Balaji drugs Ltd. All the other materials used were of analytical grade.

Preparation of In-situ Gel

In-situ Gel of Sucralfate was formulated by Ion Activated Method

Gelrite solution was prepared by adding gelrite in around 30 ml of deionised water containing sodium citrate and heat up to 90° C then cool to 40 °C. In around 35 ml water, dissolve HPMC K100 M. Then add calcium chloride & Sucralfate to it while stirring, so that there was proper & homogeneous dispersion of the drug. Mix both the solutions. In around 5 ml water, dissolve methyl paraben & sweetener, mix well. Make up the volume to 100 ml with deionised water.

Preformulation studies

Solubility

Solubility of Sucralfate was checked with 3 different solvents dilute 1 N HCl, Sodium hydroxide solution and distilled water at room temperature.

Melting point

A sample in a sealed capillary, attached to a thermometer with a rubber band, is immersed in the tube. Heating is commenced, and the temperature ranges at which the sample melts can then be observed. During heating, the point at which melting is observed and the temperature constant is the melting point of the sample. Record the temperature on the thermometer when the sample starts to melt and record the temperature again when all of the sample has melted.

Fourier Transform Infrared Spectroscopy

This study is carried out to find out the compatibility in between the drug and the various excipients, which will be used in the formulation of a dosage form.

The sample disc was prepared by triturating approximately 1 to 2 mg of the sample substance with around 10-20 mg of KBr and it is triturated and the triturate is compressed by a hydraulic press in order to form a thin disc of around 10-15 mm diameter, which will be sufficient to give an IR spectrum of a suitable intensity. This disc is then placed in a sample holder and it is scanned in the range of 4000 to 400 cm-1 in a FTIR Spectrophotometer in order to get p ta spectrum. The obtained spectra of drug and excipients are compared and it was interpreted for the functional group peaks in order to check for any major interactions.

Evaluation of prepared In-Situ Gelling System

Physical Appearance & Clarity

All the prepared batches were checked for their appearance, clarity (visually).

PH Measurement

The pH of prepared solution for all formulation was measured by digital pH meter at 25±0.5°C after it is calibrated using standard buffer solutions of pH 4, 7, 9. Then the measurements of pH were recorded as an average of three measurements.

Viscosity Study

The viscosity was measured by Brookfield DVT viscometer using LV-3 spindle. The formulation was taken into sample holder and angular velocity increased gradually from 0.3, 0.6, 1.5, 3, 6, 12, 30 and 60 rpm with await period of 30 second at each speed. The viscosity measured was performed at room temperature. For all the formulation volume of sample was adjusted with the mark given in the spindle to measure accurate viscosity. The interpretation of results or viscometer dial reading are converted to a viscosity value in units of centipoise, multiply the reading noted on dial viscometer by the appropriate factor.

Floating Behaviour

The time which is taken by the gel to reach the top from the bottom position of the dissolution flask is termed as Floating lag time/buoyant time. The floating lag time of the gel was determined by performing a visual inspection in a USP dissolution test apparatus, which contains 900 ml of 0.1 N HCl (pH of 1.2) at temperature 37±0.5°C.

Gelling Time

Gelling time was determined by mixing each of the 5 ml formulation with 0.1 N HCl (approx. 50 ml) pH 1.2 in a beaker and the gelation was assessed by visual examination. The time required for the

detection of gelation of in-situ gelling system is noted down as gelling time and the integrity of gel was also observed.

In-vitro Gelation study

The in-vitro gelling capacity of prepared formulations was measured by using visual method.5 ml of the gelation solution i.e, 0.1 N HCl of pH 1.2 was placed in a 15 ml borosilicate glass test tube and it was maintained at 37±0.5°C temperature. One ml of the formulation solution was added to gelation solution by using pipette. The formulation is transferred in such a way that the pipette is placed at surface of fluid in test tube and the formulation is slowly released from pipette. As the solution comes in contact with the gelation solution, it is expected to get converted into stiff gel like structure immediately. The gelling capacity of the resulting solution is evaluated on the basis of stiffness of gel formed. The gelling capacity of solution was graded in three categories evaluated on the basis of stiffness of formed gel and time period for which the gel retained its rigidity.

(+) Gels after few minutes dispersed rapidly.

(++) Gelation immediate remains for few hours.

(+++) Gelation immediate remains for an extended period.

Drug Content Uniformity

Prepared 10 ml of in-situ gel (containing equivalent to 50 mg of Sucralfate) from different batches was transferred to 100ml volumetric flask. To this 70 ml 0.1 N HCl was added and sonicated for 30 minutes. After that volume was adjusted to 100 ml with 0.1 N HCl. The absorbance of these solutions was measured in UV – Visible spectrophotometer at 281 nm against same dilution without drug as a blank solution.

In-vitro Diffusion Study

In-vitro drug diffusion studies were carried out using modified Franz diffusion cell. The apparatus consists of a cylindrical glass tube which was opened at both the ends. Gel sample (1 ml) was spread uniformly on the surface of egg shell membrane (previously soaked in water for overnight) and was fixed to the one end of tube such that the preparation occupies inner circumference of the tube. The whole assembly was fixed in such a way that the lower end of tube containing gel was just touched (1-2mm deep) the surface of the diffusion medium. i.e, 200 ml of pH 1.2 phosphate buffer contained in 200 ml beaker which was placed in water bath and maintained at 37±2°C. The egg shell membrane acts as a barrier between the gel phase and pH 1.2 phosphate buffer. A quantity of 1 ml samples were withdrawn from receptor fluid at the interval of 1,2,3,4,5,6,7,8,9,10,11 and 12 hrs. released drug was estimated by spectrophotometer at 281 nm and 1 ml phosphate buffer pH 1.2 was replaced each time.

Drug Release Kinetic Studies

The drug release kinetic studies were done by various mathematical models (zero order, first order, Higuchi square root, Hixson-Crowell cube root law and Korsemeyer Peppas model). The model that best fits the release data is selected based on the regression coefficient (R^2) value in various models. The model that gives high 'R^2' value is considered as the best fit of the release data. The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (R^2) was determined.

Stability Studies

The purpose of stability study is to provide evidence that the quality of a drug substance or drug product will not vary with time under the influence of a variety of environmental factors such as temperature, humidity and light during the storage period before consumption of the product. Stability Studies were performed for the formulation which was selected as best as per ICH guidelines. The formulation was selected in an aluminium foil and stored at specified condition 40+2°C and 75+5°% RH for a month. Samples were periodically taken and evaluated for physicochemical parameter, drug content and in-vitro release using the same procedure mentioned previously.

RESULTS & DISCUSSIONS

The study is important as organic property determination is a preliminary test for each and every drug. The nature, colour and the odour of Sucralfate are complying with their specifications that is mentioned as in the various literature sources description of drug.

Solubility studies were carried out in different solvents as per IP . Solubility studies are important because the drug has to dissolve in solvents and also in the dissolution medium. Sucralfate was found to be soluble in dilute HCl and sodium hydroxide.

Melting point carried out. Melting point of Sucralfate was found to be 220°C that is within the standard range which showed that the standard range procured pure drug (Sucralfate) which is free from impurities.

Determination of λmax of Sucralfate was carried out and the λmax of Sucralfate in dilute HCl was found to be 281 nm.

Drug and polymer compatibility studies were carried out by FT-IR technique to study any interaction of polymer with the drug in the formulation. The pure Sucralfate showed principle absorption peaks at 3398 (O-H stretching allopathic),1634(C-O stretching),1225(C-C stretching pyran ring),1053(C-C stretching furan),998(C-C bending in mono substituting ring). The FT-IR study show that there is no interaction between drug and polymer because it shows the characteristic peak of drug and polymers. Therefore, the drug and the polymer used are compatible with each other.

The in-situ gels formulations (F1-F9) are evaluated for their appearance and clarity. All formulations F1-F9 were transparent in their appearance and their clarity is clear shown in Table II.

The pH of prepared solution was measured by pH meter. The formulation was found to be in the range of 6.48-7.15. The measurement of pH of each formulation were in triplicate and the average values along with standard deviations are noted in Table II.

The rheological properties of the solutions are important in viscosity of their proposed oral administration. The formulation should have an optimum viscosity that will allow easy swallowing as a liquid, which then undergoes a rapid sol-gel transition due to ionic interaction. The prepared formulations were evaluated for their rheological properties using Brookfield viscometer at various shear rates. The order of viscosity of all formulations were F9>F8>F7>F6>F5>F4>F3>F2>F1as shown in Table II. The formulation showed a marked increase in concentration of gelrite and HPMC K 100M. The formulation obeys non- Newtonian flow (pseudoplastic flow).

The floating lag time of all prepared formulations from F1-F9 was determined by using the buffer 0.1 N HCl (pH 1.2) the floating lag time was found to be in between 12-35 sec for the formulation and results are shown in Table II. We can conclude that the higher polymer concentrations will help in shortening of the time that is being taken by formulation to float completely over the surface of the dissolution medium in agreement with other reports. This may be due to the higher cross-linking density at the higher polymer concentrations, which could effectively trap CO2 bubbles so that density of the gel is reduced rapidly to induce buoyancy.

The floating duration of all prepared formulations from F1-F9 was determined by using the buffer 0.1 N HCl (pH 1.2) and it was found out that all the formulations were able to float for more than the period of 8 hours except F1 formulation (7 hrs). Result of the floating behaviour of all the formulations F1-F9 is shown in Table II.

Gelling time of the formulation was assessed by visual examination. Gelling time found to be varied according to the concentration of the polymer used proportionally. The Gelling time of formulation F1-F9 was found to be 8-20 seconds.

The immediate gelation occurred due to the ion cross-linking of the gelrite chains by the divalent cation's gelation. Formulation F1 formed gelation within few minutes but it was dispersed rapidly due to less concentration of gelrite. Formulation F2-F9 shows formed gelation immediately and remains for few hours which shows good property of gelation. In case of formulation F5-F9 formed immediate gel and remains for extended period of time but they form stiff gel due to higher concentration of gelrite and HPMC K 100 M.

The drug content of the developed formulations F1-F9 was found to be in the range of 95.85 to 99.85% which were within the limit (not <94% and not > 106 %) as specified in USP. This study conclude that that drug is uniformly distributed in the formulation.

The in-vitro drug release study of Sucralfate from all the formulations of ion activated method were conducted for a period of 12 hours in 0.1 N HCl (pH 1.2). In ion activated method the highest drug release was observed 94.10% in F8 formulation lowest drug release was 73.92 % in F1 formulation.

All the prepared formulation was fitted in zero order release, first order release, model and Higuchi model and Korsemeyer peppas model based on in-vitro drug release data. The in-vitro drug release showed highest regression value for zero order kinetics which is depend on the concentration of polymers, because the value of r^2 was found to be greater in this model. The data obtained from Korsemeyer-peppas plot; the value of 'n' was found to be <0.5 which indicates that the mechanism of drug release was fickian. So, the result obtained from the release kinetics indicate that the drug release from the ion activated in-situ gel occurs by fickian mechanism for drug release which follows zero order kinetic model.

The selection of the best batch depends on viscosity, drug content, in-vitro diffusion drug release from the formulation. Formulation F8 may select as the best batches. They have good gelling capacity and optimum viscosity compared to other formulation. F8 show drug content 99.85% respectively, which were within the limit (not, 94% and not>106%) as specified in USP. The viscosity of batch F8 was found to be 16000 – 240 cps which is favourable for swallowing and has good ability for gelation. In-vitro drug release of F8 where 94.10% after 12 hours which may release complete release in 14 hours. So the F8 were selected as best formulation.

Stability studies was carried out on the selected best formulations F8 as per ICH guidelines formulations was stored in sealed aluminium foil at 45°C RH for 30 days. Formulation was periodically evaluated for physiochemical parameters such as pH, viscosity, floating time, drug content, in-vitro drug release and no significant changes were observed while comparing with the initial results which ensures the stability of the formulation.

Formulation code (gm)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Sucralfate	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Gelrite	0.25	0.25	0.25	0.50	0.50	0.50	0.75	0.75	0.75
HPMC K100 M	0.50	0.75	1.0	0.50	0.75	1.0	0.50	0.75	1.0
Sodium Citrate	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
Calcium chloride	0.016	0.016	0.016	0.016	0.016	0.016	0.016	0.016	0.016
Sodium saccharine	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005
Methyl Paraben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Deionised water	100ml	100ml	100ml	100ml	100ml	100ml	100ml	100ml	100ml

Table 1 Formulation chart of Ion Activated In-situ Gelling System

Parameters		F1	F2	F3	F4	F5	F6	F7	F8	F9
Physical Appearance & Clarity	Appearance	Transparent	Transparent	Transparent	Transparent	Transparent	Transparent	Transparent	Transparent	Transparent
	Clarity	Clear	Clear	Clear	Clear	Clear	Clear	Clear	Clear	Clear
PH Measurement	pH ± SD (n=3)	6.56 ±0.02	6.70 ±0.09	6.48 ±0.45	6.89 ±0.10	7.01 ±0.24	7.15 ±0.05	6.74 ±0.14	6.52 ±0.26	6.80 ±0.22
Floating	Floating lag time	35	30	28	26	23	18	15	14	12
	Floating duration	7	7	8	8	8	12	12	12	>12
Gelling Time & Capacity	Gelling time	20	17	15	14	12	10	11	9	8
	In-vitro gelling capacity	+	++	++	++	+++	+++	+++	+++	+++
%Drug Content		98.2 %	97.8 %	95.85%	96.4 %	96.95%	98.4 %	95.75%	99.85%	99.3 %

Table 2 Evaluation studies results

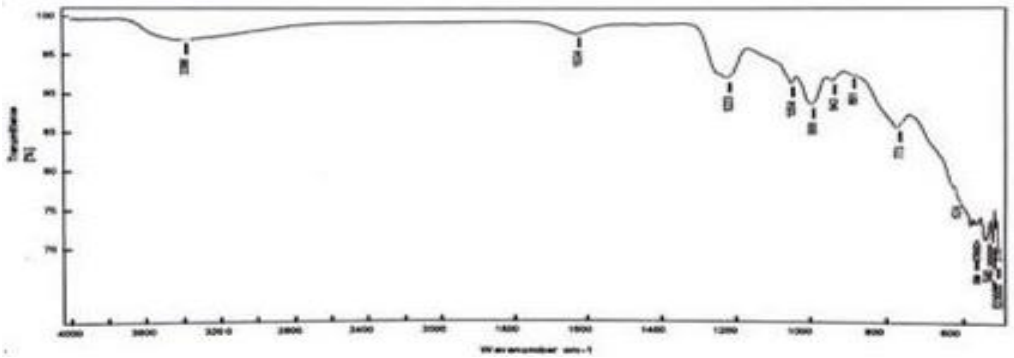


Fig:1 FT-IR Spectra of Sucralfate

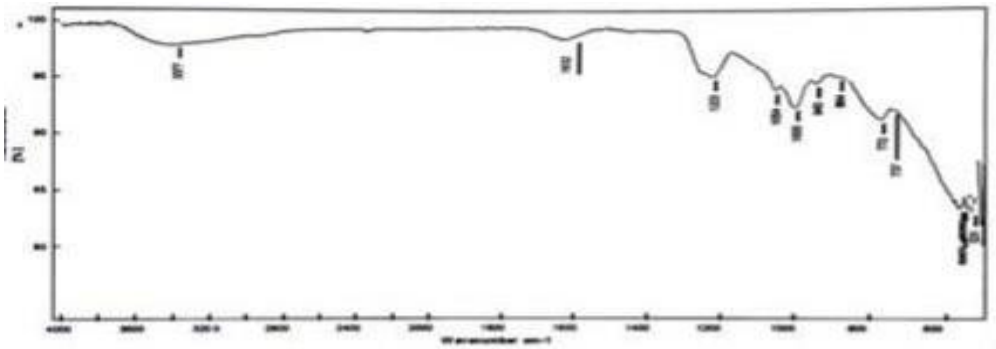


Fig:2 FT-IR Spectra of Sucralfate + HPMC K100

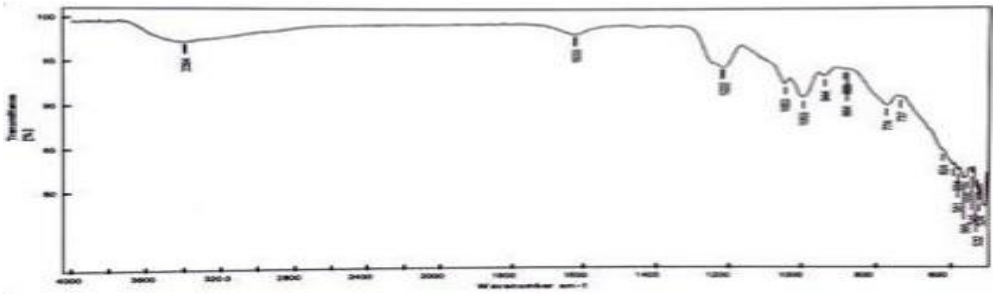


Fig:2 FT-IR Spectra of Sucralfate + Gelright

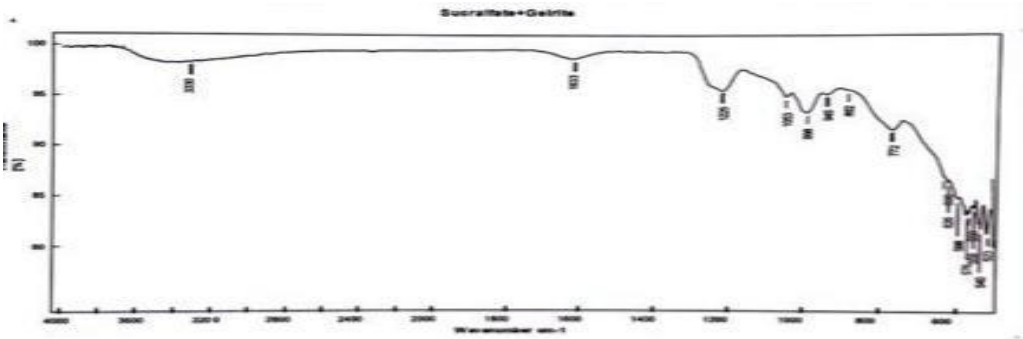


Fig:2 FT-IR Spectra of Sucralfate Formulation

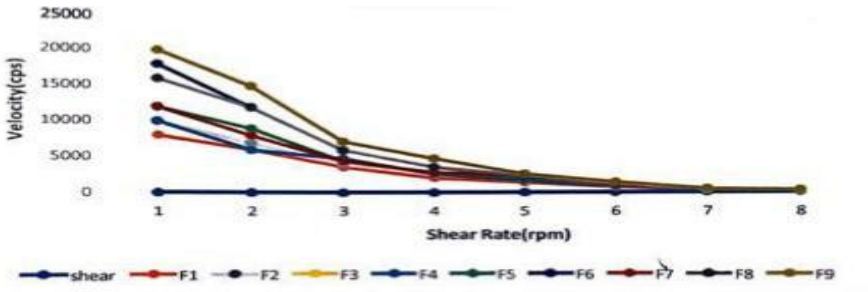


Fig:3 Viscosity of Ion Activated Formulation F1-F9 Before Gelling

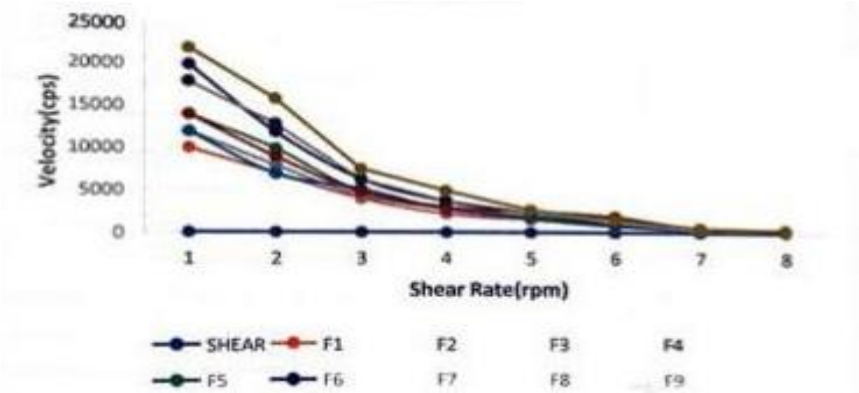


Fig:4 Viscosity of Ion Activated Formulation F1-F9 After Gelling

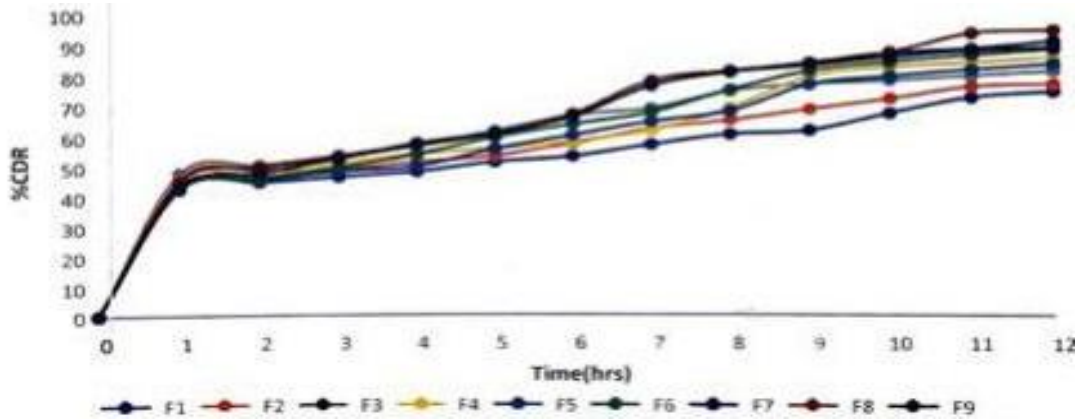
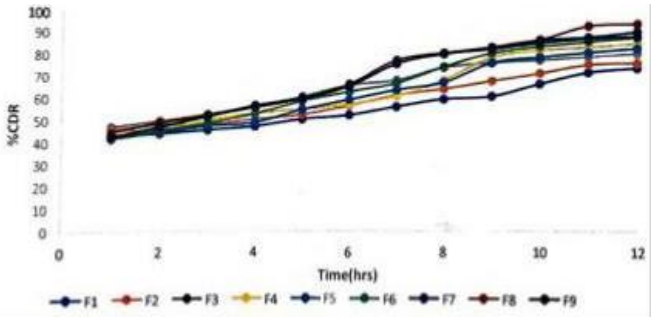
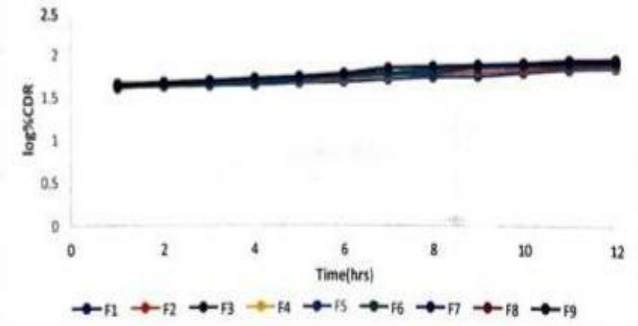


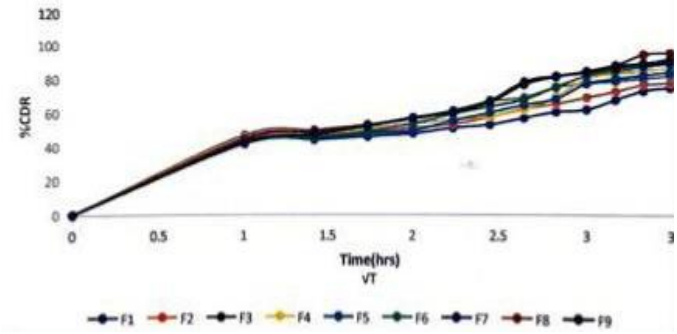
Fig:5 Invitro Drug Release of Formulations (F1-F9)



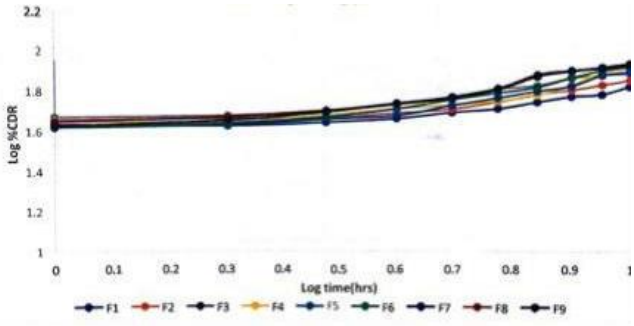
Zero Order Kinetic Drug Release of Formulations (F1-F9)



Kosemeyer Peppas Kinetic Drug Release of Formulations (F1-F9)



First Kinetic Drug Release of Formulations (F1-F9)



Higuchi Drug Release of Formulations (F1-F9)

CONCLUSION

In the present work, In-situ gel formulation was prepared and evaluated for treating stomach ulcer. The main criteria are to deliver the drug in stomach for an extended period of time. The preformulation studies for the drugs included API characterization for their organoleptic properties and other properties such as solubility and melting point and all these characteristics were in compliance with their specifications as per the standards. Drug and excipient compatibility study was carried out by FT-IR technique and found that there was no interaction between each other. In-situ gel of Sucralfate was formulated by ion activated method, Various formulation (FI-F9) was developed using excipients in various concentration of Gelrite and HPMC K 100M. Formulation was evaluated for various physicochemical parameter like appearance, clarity pH, Gelling agent, viscosity, in-vitro gelling capacity, in-vitro floating behaviour, Drug content and diffusion studies. By analysing the result, the various properties of the prepared gelling system were found to be proportional to the concentration of polymer that has been used in the formulation. As the concentration of the polymer increases properties like viscosity found to be increasing. F8 was selected as best formulation because of its good gelling capacity and optimum viscosity. Drug content was found to be 99.85%. It should 94.10% cumulative drug release for 12 hours. The in-vitro drug release showed highest regression value for zero order kinetics which is depend on the concentration of polymers, because the value of was found to be greater in this model. The data obtained from Korsemeyer- peppas plot; the value of 'n' was found to be <0.5 which indicates that the mechanism of drug release was fickian. So, the results obtained from the release kinetics indicate that the drug release from the ion activated in-situ gel occurs by fickian mechanism for drug release which follows zero order kinetic model. Stability studies were carried out for F8 formulation as per ICH guidelines and the stability was confirmed as there were no significant changes observed in physicochemical parameters such as physical appearance, pH, viscosity, in-vitro gelling capacity, gelling time, in-vitro floating behaviour, Drug content and in-vitro diffusion studies. Hence the prepared in-situ gel of Sucralfate was found to be prepared successfully. The oral in-situ gel improves patient compliance by reducing the frequency of the dosing.

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