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FORMULATION AND EVALUATION OF ORAL FLOATABLE *IN SITU* GEL OF OFLOXACIN FOR STOMACH SPECIFIC DELIVERY

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ABSTRACT

The present investigation deals with the formulation and evaluation of sodium alginate based floating oral *In situ* gel of Ofloxacin for the eradication of Helicobacter pylori in stomach, which undergo pH dependent sol-gel transition. Sodium alginate used as a polymer and CaCO3 was used as a cross-linking agent. The formulation is in solution before administration, after administered undergoes gelation to form a gel. The formulation is carried out with pH induced ion gelation method. The *in-situ* gel is evaluated for viscosity, drug content, pH, in vitro gelling capacity, in vitro floating ability and *in vitro* release profile characteristics. From designed set of experiments, it was evident that formulation containing 2 Gram of sodium alginate and 500 milligram of calcium carbonate control the release of drug for longer duration this formulation show release of about 76.886% after 10 hour and the gel float for more than 12 hours.The study points to the potential of in situ gel in terms of better patient compliances, ease of administration, and prolonged gastric retention.

KEYWORDS: *In situ* gel, Ofloxacin, Sodium alginate, Calcium carbonate, Sustained release, pH induced ion gelation.

INTRODUCTION

The present investigation deals with the formulation, optimization and evaluation of sodium alginate based floating oral *In situ* gel of Ofloxacin. Sodium alginate used as a polymer and Calcium carbonate was used as a cross-linking agent.[1] Oral administration is most convenient and preferred means of any drug delivery to the systemic circulation. Oral sustained release drug delivery recently have been increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. *In-situ* forming polymeric formulations drug delivery systems is in solution form before administration in the body, but once administered, undergoes gelation *in-situ* to form a gel. The formulation of gel depends upon factors like temperature modulation, pH changes, presence of ions and ultraviolet irradiation, from which drug gets released in sustained and controlled manner. The system utilizes polymers that exhibit solution-to-gel phase transition due to change in specific physicochemical parameters.

Gastroretentive in situ gelling system helps to increase bioavailability of drug compared to conventional liquid dosage form. The gels formed in situ gelling system, being lighter than gastric fluids, floats over the stomach contents or adhere to gastric mucosa due to presence of bioadhesive nature of polymer and produce gastric retention of dosage form and increase gastric residence time resulting in prolonged drug delivery in gastrointestinal tract. This review attempts to discuss stomach specific in situ gelling system of Ofloxacin for the eradication of Helicobacter pylori by using the polymer sodium alginate.

Helicobacter pylori[2] (H. pylori) are reported to be an important etiologic factor in the development of the gastritis, gastric ulcer and carcinoma in human stomach. H. pylori reside mainly in the gastric mucosa layer and epithelial cells of the antral region of the stomach. There are two major reasons for the failure of H. pylori eradication with conventional dosage forms of antimicrobials. One reason may be the degradation of antimicrobial agents by gastric acid, therefore, the administration of high doses of antimicrobial agents on a daily basis is necessary for H. pylori eradication, but they are usually accompanied by adverse effects and poor patient compliance. Another reason for incomplete eradication is the probably that residence time of antimicrobial agents in the stomach is so short, that effective antimicrobial concentrations cannot be achieved in the gastric mucosa layer or epithelial cell surfaces.

Ofloxacin is a second generation fluroquinolone Soluble in aqueous solutions with pH between 2 and 5. Sparingly to slightly soluble in aqueous solutions with pH 7 (solubility falls to 4 mg/mL) and freely soluble in aqueous solutions with pH above 9.It is a broad spectrum antimicrobial agent for oral administration. It acts by inhibiting bacterial DNA gyrase enzyme which is required for DNA replication and thus causes bacterial lysis.[3]

The main principle involved in the formation of *In situ*gel is the pH induced ionic gelation. Trisodium citrate complexes with free Ca++ and maintains the fluidity of *In situ* gel until it reaches the stomach. Once the formulation reaches the stomach, in the presence of acidic environment Ca++ get releases and triggers the gelation of sodium alginate. Carbondioxide that is released at acidic pH helps the formulation to float on the gastric contents for extended period.[4]

From designed set of experiments, it was evident that formulation containing 2 grams of sodium alginate and 500milligram of calcium carbonate control the release of drug for longer duration. The *in-situ* gel exhibited the expected, viscosity, drug content, pH, *in vitro* gelling capacity, *in vitro* floating ability and sustained drug release.

MATERIALS AND METHODS

Ofloxacin Yarrow chem. Medicals, Mumbai, Sodium alginate(Chemvin chemicals, Thrissur), Sodium citrate (Chemvin chemicals, Thrissur), Calcium carbonate (Chemvin chemicals, Thrissur), All Other Chemicals Used In The Study Were of Analytical Grade.

Analytical Methods

Preparation of Standard Stock Solution of Ofloxacin

The standard stock solution of ofloxacin was prepared by transferring accurately weighed 10 mg of drug to 10ml volumetric flask and dissolving it with 0.1 N Hcl to get a concentration of 1000 µg/ml. From this solution of ofloxacin, 1ml is pipetted out and diluted to 10 ml to get 100µg/ml and was kept as stock solution. This prepared stock solution was diluted with 0.1 N Hcl to getting working standard solution of concentration 2-20µg/ml.[5]

Determination of λ max

Standard stock solutions of ofloxacin was scanned in the wave length region of 200-400nm on UV-visible spectrophotometer.

Preparation of Standard Calibration Curve of Ofloxacin

Working standard solutions of ofloxacin were scanned in the UV region and absorbance were measured against 0.1 N Hcl at 293nm and the data were plotted against concentration. A calibration curve was plotted by taking concentration on x axis and absorbance on y axis.

Preformulation Studies

Preformulation testing was an investigation of a drug substance alone. It is the first step in rational development of dosage form.

Solubility studies

Excess of ofloxacin was added to 5ml of each fluids (water, phosphate buffer of pH 6.8, acidic buffer of pH 1.2) in a 25ml stoppered conical flasks and the mixtures were shaken for 24 hours at room temperature, (25±1°C) on a rotary flask shaker. After 72 hours of shaking 1ml aliquots were withdrawn and filtered immediately using a 0.45µ nylon disc filter. The filtered samples were diluted suitably and assayed for Ofloxacin by measuring the absorbance at 293 nm. Shaking was continued until three consecutive estimation were same. The solubility experiments were run in triplicate.[6]

Identification by melting point

Melting point of drug was determined using melting point apparatus.

Organoleptic properties

Physical appearance of drug was observed and compared with the official monographs.

Drug- excepient interaction studies

In order to find out the possible interactions between Ofloxacin and the polymer used in the formulation, Fourier transform infra-red spectroscopy (FT-IR) analysis was carried out on the pure substances and their physical mixtures.

FT-IR spectra of the Ofloxacin, Sodium alginate and the physical mixture of the drug with polymer were taken individually by KBr pellet technique between 4000-500cm^{-1}. This is to ensure that there is no incompatability between the drug and the polymer. Once spectra were recorded, the peaks of the pure drug, the polymer and the physical mixture of the drug and polymer were compared for any incompatability.[7]

Formulation of Ofloxacin *in Situ* Gelling Solution

The solution of sodium alginate, in different concentration were made in deionized water, in which sodium citrate and calcium carbonate were previously dissolved. The solution were heated to 60° C with constant stirring on a magnetic stirrer it was then allowed to cool to 40°C. Appropriate amount of Ofloxacin was then added to the resulting solution with continuous stirring and the formulation were prepared. The solution were then stored in amber colored bottles until use.[8]

Table No 1: Components of floating *in situ* gelling solution.

Ingredients	Formulation Code And Quantities					
	F_1	F_2	F_3	F_4	F_5	F_6
Ofloxacin	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
Sodium alginate	1g	1.5g	2g	1g	1.5g	2g
Sodium citrate	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg
Calcium carbonate	250 mg	250 mg	250 mg	500 mg	500 mg	500 mg
Distilled water	qs to 100 ml	qs to 100 ml	qs to 100ml	qs to 100ml	qs to 100 ml	qs to 100ml

Evaluation of Prepared *In Situ* Floating Solution

Determination of Physical appearance

All prepared sodium alginate based *in situ* solution of Ofloxacin were checked for their clarity and the type of the solution.

Determination of pH

The pH of the sodium alginate based *in situ* solution of Ofloxacin can be determined by using a calibrated digital pH meter at 27°C.

Determination of viscosity

The viscosity of the solution prepared using various concentration of gelling agent is determined before and after gelling by using Brookfield viscometer DV I at suitable temperature (25±1°C) using spindle no 61 and 64.

***In vitro* gelling capacity**

The *in vitro* gelling capacity of the prepared formulation was determined by placing 5 ml of the0.1 N HCl in a 15 ml borosilicate glass tube and maintained at 37 ±1°C temperature.1 ml of formulation solution was added with the help of pipette. The formulation was transformed in such a way that places the pipette at the surface of the fluid in the test tube and the formulation was slowly released from the pipette. As the solution came in contact with the gel solution, it immediately converted into 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 gel remains as such.[9]

The *in vitro* gelling capacity was graded in 3 categories on the basis of gelation time and time period for which formed gel remains:

+ gel after few minutes, disperse rapidly
+ + gelation immediate, remains for 12 hours
+++ gelation immediate, remains for more than 12 hours.

***In vitro* buoyancy studies**

The *in vitro* floating ability of the prepared formulation was evaluated by adding 10 ml of the prepared formulation in 500ml of 0.1 N HCl, pH 1.2 at 37 °C. The parameters like time taken for the system to float over the surface of medium (Floating lag time) and the time the formed gel constantly float over the surface of dissolution medium (Floating time) can be determined.[10]

Determination of drug content

10 ml of the formulation was added to 900 ml of 0.1 N HCl of 1.2 pH and stirred for 1 hour on a magnetic stirrer.The solution was filtered, suitably diluted with 0.1 N HCl and the drug content was determined by using U V -Visible spectrophotometer at 293 nm against a suitable blank solution.[11]

***In vitro* dissolution studies**

The release rate of the drug from *in situ* gel can be determined by using USP dissolution rate testing apparatus I (basket covered with muslin cloth) at 37±0.5° C and 50 RPM speed. To mimic the the gastrointestinal condition, as per the official recommendation of USFDA, 900 ml of 0.1N of HCl was used as dissolution medium. Aliquot equal to 5ml was withdrawn at specific time intervals (1hr, 2hr, 3hr, 4hr, 5hr, 6hr, 7hr 8hr, 9hr, 10hr) and replaced with fresh buffer. The aliquot were diluted and drug release was determined spectrophotometrically at a wavelength of 293 nm respectively by comparing with standard calibration curve.

Study of Release Kinetics and Release Mechanisms

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order, first order, Higuchi's plot and Korsemeyer Peppas model repectivelly. The model that best fits the release data is selected based on the correlation coefficient (r) value in various models. The model that give high 'r' 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.

In short the result obtained from in vitro release studies were plotted in four kinetics model of data treatment as follows.

- Cumulative percentage drug release Vs Time (Zero order release kinetics plot)
- Log cumulative percentage drug retained Vs Time (First order rate kinetics plot)
- Cumulative percentage drug release Vs √Time(Higuchi 's plot)
- Log cumulative percentage drug release Vs log time (Korsmeyer Peppas plot).

Stablity Studies

Preparation of Sodium alginate based *in situ* gel of ofloxacin was stored in a glass amber coloured container

(well stoppered)for 1, 2 &3 month.The study was carried out in a temperature and humidity condition as per ICH guidelines. Stability of the preparation was monitored up to three month at accelerated stability condition (45 °C and 75 %RH) and at room temperature periodically sample was withdrawn and evaluated for pH, viscosity, drug content and drug release.

RESULTS AND DISCUSSIONS

Analyticalmethods

Determination of λ max

The pure drug of ofloxacin was analysed by UV Spectroscopy and λmax was found to be 293 nm.

Calibration curve of Ofloxacin

The absorbance of Ofloxacin standard solution having concentration range 2-20 µg/ml in 0.1N HCl was determined. The curve was found to be linear and obeys Beer – Lambert's law in the range of 2-20µg/ml at λmax 293 nm.

Preformulation Study

Solubility studies

Solubility of drug has been carried out and the drug shows highest solubility in buffer of pH 1.2

Determination of melting point

Melting point was determined using melting point apparatus.Temperature was noted at which solid drug changes into liquid and From the result the melting point of drug was found to be 250°C which complies with official standard indicating the purity of the sample.

Determination of organoleptic property

It occurs as off-white powder and it is odourless.

Identification and compatability studies by FTIR studies

FTIR spectrum of Ofloxacin is shown in figure no:1, 2 and peak value obtained in table no -3. FTIR studies of physical mixture of drug and excipients were carried out the peaks obtained were found to be similar with that of reference. After spectral comparison it was confirmed that no incompatibility reaction took place between drug and excipients.

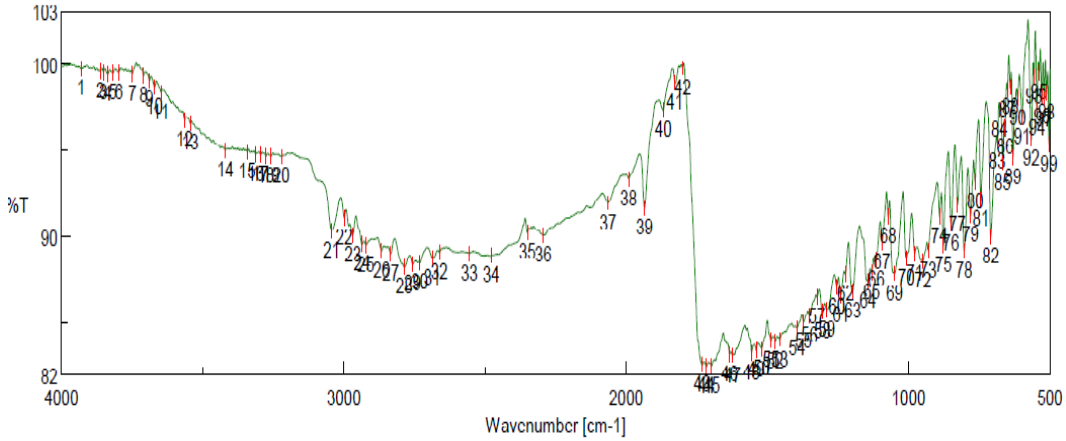

Fig. 1: FTIR spectrum of Ofloxacin.

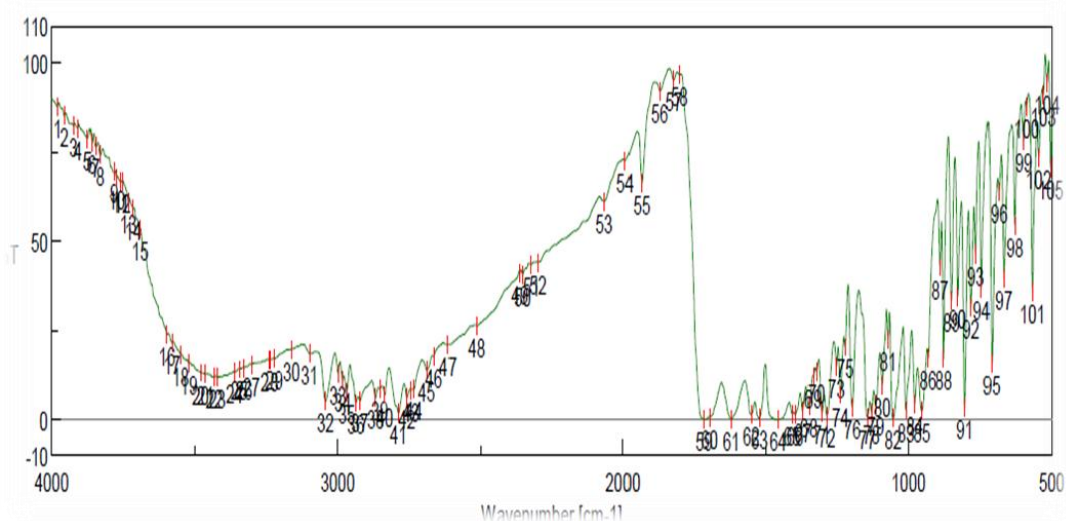

Fig. 2: FTIR spectrum of Ofloxacin + Sodium alginate.

Table No. 2: FTIR characters of Ofloxacin.

Sr. no	Functional Group	Reference Wave Number (Cm^{-1})	Peak Observed$_{(Cm^{-1})}$
1.	O-H stretching	3050-3000	3043.12
2.	Aromatic, cyclic enes	3000-2950	2998.77
3.	Alkyl group CH_3	2750	2967.91
4.	Acidic C=O stretching	1750-1700	2833.88
5.	N-H bending	1650-1600	2755.78
6.	Alkyl CH_3 CH_2	1550-1500	1716.34
7.	CH_2 stretching	1450-1400	1305.57
8.	O-H bending	1400-1350	1240
9.	C-O-C stretching	1250-1200	1223.61
10.	C-F stretching	1050-1000	978.697
11.	=CH out of plane bending	950-800	823.318

Evaluation of Prepared Floating *In Situ* Solution

Six formulations (F_1-F_6) were prepared with 1, 1.5 and 2g of polymers, different concentration of calcium carbonate(0.25g, 0.5g) and keeping all other ingredients constant. The formed *in situ* gel were evaluated for the physical appearance, pH, viscocity, *in vitro* buoyancy, *in vitro* gelling capacity, drug content and in vitro dissolution studies by using standard procedure and were reported in table no 4, 5 respectively.

In situ solution should be clear and free of any particular matter, and appear as yellowish white colour, pH values of the formulation are acceptable in this range thus the formulation was stable and do not effect drug properties, so there was no need for pH adjustment. The data obtained for viscosity determination shows that Viscosity was directly proportional to the polymer concentration, so viscosity of *in situ* formed gel of the formulation was taken as one of the dependent parameters for optimization of formulation. The floating lag time and duration of floating of the prepared six formulations were evaluated and floating lag time was found to be in between 40.33-56 seconds and duration of floating was found to be more than 12 hrs. Drug content of the formulations showed that the drug was uniformly distributed in to gels.

Table No. 3: Evaluation of floating *in situ* gel.

Formulation code	Clarity & Colour	pH	Floating lag time(sec)	Floating time(hrs)	Gelling capacity	Drug content (%)
F_1	Clear and yellowish white	7.36 ± 0.0577	51 ± 1.732	<12	++	95.9 ± 0.3605
F_2	Clear and yellowish white	7.56 ± 0.1154	56 ± 1	>12	+++	91.91 ± 0.0737
F_3	Clear and yellowish white	7.233 ± 0.1154	53 ± 3.606	>12	+++	95.233±0.4041
F_4	Clear and yellowish white	7.2 ± 0.1	45.33 ± 0.577	>12	+++	91.016±0.7910
F_5	Clear and yellowish white	6.866 ± 0.2086	41.66 ± 1.528	>12	+++	97.64 ± 0.293
F_6	Clear and yellowish white	6.9 ± 0.11	40.33 ± 0.577	>12	+++	98.263 ±0.6069

Table No. 4: Viscosity in centipoise of *in situ* gel formulation (F_1-F_6) before and after gelling.

Formulation code	Viscosity before gelling (Cp)	Viscosity after gelling (Cp)
F_1	5.5166 ± 0.0057	1277.33 ± 1.1547
F_2	6.81 ± 0.03	2208.66 ± 0.5773
F_3	7.89 ± 0.0550	2476.33 ± 1.5275
F_4	5.263 ± 0.0665	2042.66 ± 2.5166
F_5	6.9033 ± 0.0665	2148 ± 1
F_6	8.13 ± 0.0953	2534.66 ± 3.0505

***In Vitro* Dissolution Study**

All the 6 formulations were subjected to in vitro dissolution study using USP dissolution apparatus I covered with muslin cloth.

In vitro drug release studies of six formulations F_1, F_2, F_3, F_4, F_5, F_6 were performed. The release profile obtained for the *in situ* gel were represented in fig 3.For F_1, in the first hour about 11.269% and at the end of 9^{th} hour about 96.035% cumulative amount of drug was released. For F_2, in the first hour about 4.183% and at the end of 10^{th} hour about 95.02% cumulative amount of drug was released. For F_3, in the first hour about 3.813% and at the end of 10^{th} hour about 98.14% cumulative amount of drug was released. For F_4, in the first hour about 8.889% and at the end of 10^{th} hour about 84.31%cumulative amount of drug was released. For F_5, in the first hour about 3.597% and at the end of 10^{th} hour about 87.17% cumulative amount of drug was released. For F_6, in the

first hour about 3.781% and at the end of 10th hour about 76.886% cumulative amount of drug was released.

From the drug release profile of Ofloxacin *in situ* gel it was found that the formulation containing sodium alginate 2gm and calcium carbonate 500 mg as polymer and cross linking agent (F_6) showed best release profile(76.886%).

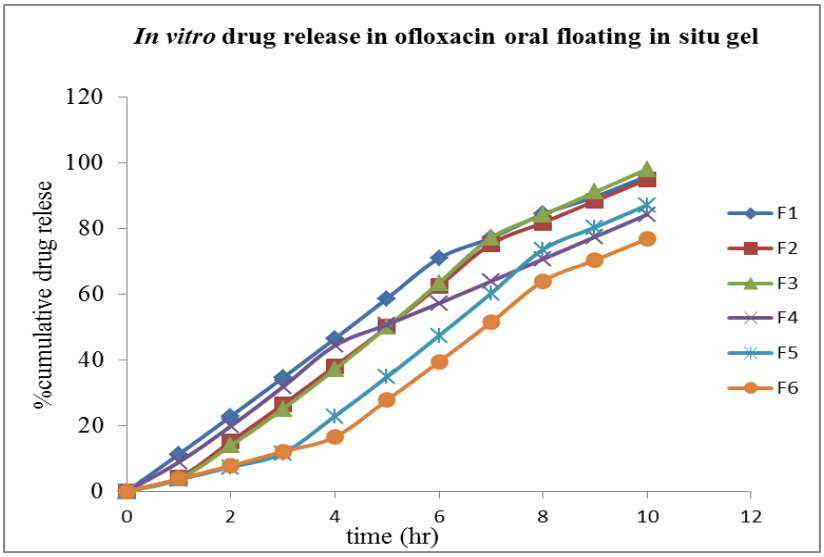

Fig. 3: Drug Release in Ofloxacin Floating *In Situ* Gel Formulations.

Study of Release Kinetics and Release Mechanism

The drug release data of Ofloxacin were fitted to various models to know the release kinetics and mechanisms.

It was found that the in vitro drug release of optimized batch F_6 was explained by zero order as the plots shows highest linearity (R^2 = 0.967) and follows Fickian diffusion.

Table No. 5: Various drug release kinetics of selected formulation (F_6).

Formulation code	R^2 Value			
	Zero order model	First order model	Higuchi model	Korsmeyer Peppas model
F_6	0.967	0.899	0.812	0.982

Stability Study

Stability studies carried out for the formulation F_6 for a period of 3 months showed that the prepared floating oral *in situ* gel passes stability studies with no much significant change in physical appearance, pH, drug content. The data are shown in table below.

Table No. 6: Stability study data of optimized formulation.

Formulation code	Storage condition	Sampling interval	pH	Drug content (%)	Viscosity		Drug release (%)
					Before gelling	After gelling	
F_6	Room temperature	30 days	6.9±0.17	97.86±0.793	8.13±0.095	2534.66±3.050	76.83%
		60 days	6.9±0.11	97.54±0.625	8.10±0.175	2533.93±2.251	76.88%
		90 days	6.9±0.17	97.13±0.385	8.13±0.023	2534.65±3	75.65%
	40±2°C	30days	6.9 ± 0.02	97.22±0.25	8.13±0.21	2534.32 ±2.25	76.32%
		60 days	6.9 ±0.06	97.51 ±0.13	8.13 ±0.15	2534.72 ±2.36	76.59%
		90 days	6.9 ± 0.1	96.98±0.21	8.13±0.26	2534.95 ±3.21	76.86%

DISCUSSION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body and then maintain the desired drug concentration. A well designed drug delivery system can overcome some of problems of conventional therapy and enhance therapeutic efficacy of the given drug. There were various approaches in delivering therapeutic substance to the target site in sustained and controlled release fashion. One such approach is floating drug delivery system. In this study oral floating *in situ* gel of Ofloxacin was formulated using different concentration of sodium alginate, calcium carbonate as polymer, cross-linking agent, and their evaluation were performed and the results are obtained.

a. Identification of drug and compatibility studies

Drug identification was done by performing melting point determination and FT-IR studies. From the result the melting point of drug was found to be 250°C which complies with official standard indicating the purity of the sample. FTIR studies peak of Ofloxacin obtained at 3043.12cm^{-1} 2998.77 cm^{-1}, 2967.91 cm^{-1}, 2833.88 cm^{-1}, 2755.78 cm^{-1}, 1716.34 cm^{-1}, 1305.57 cm^{-1}, 1240 cm^{-1}, 1223.61 cm^{-1}, 978.69 cm^{-1}, 827.312 cm^{-1} showed that the peaks are identical to reference indicating the identity of drug. The FTIR spectrum of pure drug, polymers and physical mixtures of drug and polymer (figure 1.2)and (table1) shows that no interaction took place between drug and polymer. However, some additional peaks were observed with physical mixtures, which could be due to the presence of polymer used in the study. Thus indicating that drug and polymer are compatible with each other.

i. Physico –chemical parameters

Physical parameters like physical appearance and solubility studies were carried out. The results tabulated table nos3 shows that these parameters comply with pharmacopoeial specifications.

ii. Analytical methods

The drug was scanned in UV region (200-400nm) to find out the wave length of maximum absorption(λ_{max}).The λ_{max} was found to be 294 nm. So the standard calibration of Ofloxacin was developed at this wave length. Standard calibration curve of Ofloxacin was determined in 0.1N HCl (pH 1.2) by plotting absorbance against concentration at 294 nm. The calculation of drug content, *in vitro* release and stability studies are based on this calibration curve.

b. Formulation of floating *in situ* gel

Oral floating in situ gel was formulated by pH induced ion gelation method. After the formulation of six *in situ* gels (F_1-F_6) they were subjected to physic-chemicalevaluations like physical appearance, pH, viscosity, *in vitro* gelling capacity, *in vitro* buoyancy study, *in vitro* drug release and drug content. From the results obtained the best formulation was selected.

Effect of formulation variables on *in situ* gel

Effect of polymer concentration and cross linking agent on *in situ* gel

It was observed that on increasing polymer concentration (Sodium Alginate) from 1-2gm and cross linking agent (Calcium carbonate) from 0.25-0.5gm the viscosity increases and the floating lag time, drug content decreased. From these studies, formulation containing 2gm of sodium alginate and 0.5gm of calcium carbonate (F_6) was found to be good.

c. Evaluation of floating *in situ* gel

The prepared six formulations were evaluated for various parameters.

Results are shown in table no 3.4

Determination of physical appearance

Prepared formulations were evaluated visually for their clarity. *in situ* solution should be clear and free of any particular matter, and appear as yellowish white colour.

Determination of pH

pH values of formulations F_1, F_2, F_3, F_4, F_5, F_6 is as shown in Table no. The values are acceptable, in this range the formulation was found to be stable and do not effect drug properties, so there was no need for pH adjustment.

Determination of viscosity

The viscosity of all the formulations were studied before and after gelling using Brookfield viscometer at a speed of 100 and 2.5 rpm with spindle number 61 and 64 and it was found that the viscosity is in the range of 5.51-8.13 Cp before gelling and the formulations were found to be easily pourable. The viscosity was found to be in between 1277.33 - 2534.66 Cp after gelling which shows that viscosity was directly proportional to the polymer concentration. Hence viscosity of *in situ* formed gel of the formulation was taken as one of the dependent parameters for optimization of formulation.

***In vitro* gelling capacity**

In vitro gelling capacity of formulations F_1, F_2, F_3, F_4, F_5, F_6 were performed and it was found that the gelation occurs immediately (less than 3sec)and formed gel remains for 12 hrs and more which was suitable for the study.

- For F_1 gelation occurs immediately and weakly stiff gel is formed and it remains for 12 hrs in the gastric fluid.
- For F_2-F_6 gelation occurs immediately and stiff gel is formed and it remains for more than 12 hrs in the gastric fluid.

***In vitro* buoyancy studies**

The floating lag time and duration of floating of the prepared six formulations were evaluated and floating lag time was found to be in between 40.33-56seconds and duration of floating was found to be more than 12 hrs. Longer the floating lag time faster will be the drug emptied from the stomach.

Determination of drug content

Drug content of the formulated gel was estimated by UV spectrophotometer at 294nm and drug content was calculated from calibration curve. Drug content of the formulations showed that the drug was uniformly distributed in to gels. The drug content values of the formulations F_1, F_2, F_3, F_4, F_5, F_6 was found to be 95.9 %, 91.91%, 95.23 %, 91.01%, 97.64%, 98.26% respectively.

***In vitro* drug release studies**

In vitro drug release studies of six formulations F_1, F_2, F_3, F_4, F_5, F_6 were performed. The release profile obtained for the *in situ* gel were tabulated in table no5 and shown

in figure no 3.From the drug release profile of Ofloxacin *in situ* gel it was found that the formulation containing sodium alginate 2gm and calcium carbonate 500 mg as polymer and cross linking agent (F_6) showed best release profile. Hence formulation F_6 was selected for studying the kinetics and mechanism of drug release.

Drug Release Kinetics

The data obtained from the *in vitro* drug release studies of formulation F_6 was fitted into the various kinetic models and it was found that the drug release seems to follow zero order kinetics as it is evidenced by regression coefficient (r^2 = 0.967) which is better than first order (r^2 = 0.899) and Higuchi's plot with regression coefficient (r^2 = 0.812). Therefore it was ascertained that the drug permeation from the formulation F_6 follows nearly zero order kinetics. To confirm the exact mechanism of drug permeation from the formulation, the data was fitted according to the Korsmeyer Peppas model.

The value of slope of the plot n gives an indication of the release mechanism. When n =1 the release is independent of time i.e., zero order, if n=0.5 then the release is by Fickian diffusion. When n=0.5-1, diffusion is non - Fickian and when n>1.0 then it is super case II transport. In this study the regression coefficient (r^2) of Korsmeyer Peppas model was found to be closer to 1 and slope value n was found to be 0.982 this suggest that the drug release from the *in situ* gel (F_6) followed non fickian mechanism.

Stability studies

Accelerated stability studies were carried out as per ICH guidelines. From the stability studies data (Table No-6) which was carried out for the formulation F_6 for a period of 3 months showed that the prepared floating oral *in situ* gel passes stability studies with no much significant change in physical appearance, pH and drug content.

CONCLUSION

Ofloxacin oral floating in situ gel was formulated successfully with pH induced ion gelation method for the delivery of drug in gastric region for more than 12 hrs. The in situ gel formulated with 2 gms of sodium alginate and 0.5 gms of calcium carbonate was found to be the better formulation with lesser floating lag time, prolonged floating duration and with higher viscosity and gastric retention. The floating lag time decreases as the concentration of calcium carbonate increases and there by prolongs the gastric retention. The viscosity increases with increase in sodium alginate concentration and there by regulate the drug release from the formulation. Drug release and viscosity suggested that developed floating in situ gel could perform better than conventional dosage form leading to improve efficacy and better patient compliances. From the stability study it could be concluded that the optimized formulation was stable at room temperature.

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