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Sodium Alginate Based Oral *in Situ* Floating Gel of Metformin Hydrochloride

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ABSTRACT

The present investigation concerns with the development and optimization of an *in-situ* gelling formulation of Metformin. It is an antidiabetic drug with upper part of gastrointestinal tract as its absorption window. The polymer used in the study is Sodium alginate which forms a gel when it comes in contact with simulated gastric fluid. The principle of gelling involves supply of complexed calcium ions in form of calcium carbonate that are released in the acidic environment of the stomach. The formulations are designed with an objective to retain in stomach for an extended time period to obtain better bioavailability. Sodium alginate sols of various concentrations were prepared by dissolving variable amount of sodium alginate in distilled water at 60°C. After cooling to 40°C variable amounts of Metformin were added so as to obtain nine different formulations. The formulation (1.25% sodium alginate, 3.75% Metformin, 1.5% calcium carbonate, 2.5% sodium citrate) showed optimum drug release and the release was 90 % in 8 hours. The concentration of sodium citrate and calcium carbonate was kept optimum so as to facilitate floating. The gels were evaluated with respect to *in-vitro* gelation time, floating lag time, duration of floating and *in-vitro* dissolution. Stability study was done according to ICH guidelines. From the result it was observed that, as drug concentration in formulation increases onset of drug release increases, whereas, polymer concentration increases onset of drug release decreases and vice-versa. Hence, oral *in situ* floating gel delivery system of Metformin was developed.

Keywords: Sodium Alginate, Metformin Hydrochloride, *In-situ* gel.

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INTRODUCTION

An ideal drug delivery system (DDS) should aid in the optimization of drug therapy by delivering an appropriate to the intended site and at a desired rate. Hence, the DDS should deliver the drug at a rate dictated by the needs of body over the period of treatment [1]. GRDD in situ gelling systems are especially useful for geriatric and pediatric patients where patient is not able to take oral dosage form like tablets. In this system the gel forming polymer solutions like Gellan gum [2], Sodium alginate, Xyloglucan and Methoxy pectin [3] forms gels after coming in contact with cations at body temperature. These solutions also contain source of cation, which would liberate cation like Ca^{2+} , Mg^{2+} , K^+ and Na^+ in vivo condition [4]. These compounds when react with simulated gastric fluid pH (1.2) releases cation reacts with the simulated gastric fluid liberates cation which swells and forms a viscous cohesive gel[3] This will give continuous delivery of drug for a predetermined period with predictable and reproducible kinetics and known mechanism of release. Controlled release drug delivery systems attempt to sustain drug blood concentration at relatively constant and effective levels in the body by temporal delivery and offer various advantages such as reduce drug blood level fluctuations, minimize drug accumulation, reduces dose, improve patient compliance and minimize the size effects[5][6] Metformin is an oral hypoglycemic agent used in the treatment of Diabetes Mellitus. Due to its physicochemical and pharmacokinetic properties, Metformin had been used as model drug in development of gastro retentive systems.

MATERIALS AND METHODS

Materials

The drug Metformin Hydrochloride was procured as gift sample from (Shreya Pharmaceuticals Limited, Aurangabad, India), sodium alginate, calcium carbonate and sodium citrate were procured from (Loba Chemicals, Mumbai, India). All other chemicals were purchased and were of analytical grade.

Table 1: Formulation of floating gel

Formulation Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Sodium alginate (%w/v)	1.25	1.75	2.25	1.25	1.75	2.25	1.25	1.75	2.25
Metformin (%w/v)	2.5	2.5	2.5	3.75	3.75	3.75	5.0	5.0	5.0
Sodium Citrate (%w/v)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Calcium Carbonate (%w/v)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Experimental

Characterization of Metformin

Solubility of Metformin was checked in various solvents like water, ethanol, chloroform, dil.HCL Also Melting point of metformin was determined using melting point apparatus and compare with reported standards.



Characterization of Polymer

Prepared sodium alginate based *in-situ* solutions of metformin were checked for their clarity and the pH of the solutions. After administration of the prepared solutions in pH 1.2 buffer the pH was measured using a calibrated digital pH meter.

Formulations of sols

All the ingredients used in the formulation were initially passed through sieve #40 before mixing. The required quantity of metformin and Sodium alginate were weighed according to the formulation. Sodium alginate sols of various concentrations were prepared by dissolving specified amount of sodium alginate in 100ml distilled water containing sodium citrate (0.25% w/v) and heated up to 60⁰C with stirring. After cooling below 40⁰C, appropriate amounts of calcium carbonate and metformin were added. Various quantities of polymers used for preparation of sodium alginate sols are depicted in Table no. 2 [2][3].

Determination of in vitro gelation time [2]

Gelation time is the time taken by sol to get converted to gel in favorable conditions. In vitro gelation time was determined by putting sols in a dissolution apparatus USP (Type II) containing 900 ml of 0.1N HCl at 37±0.5⁰C. The readings were taken in triplicate.

Determination of Floating Lag Time [2],[8]

The floating lag time is defined as the time taken by the gel to reach the top from the bottom of the dissolution flask. The floating lag time of gel was determined by visual inspection using a dissolution test apparatus USP (Type II) containing 900 ml of 0.1N HCl at 37±0.5⁰c. The readings were taken in triplicate.

Determination of Duration of floating [2]

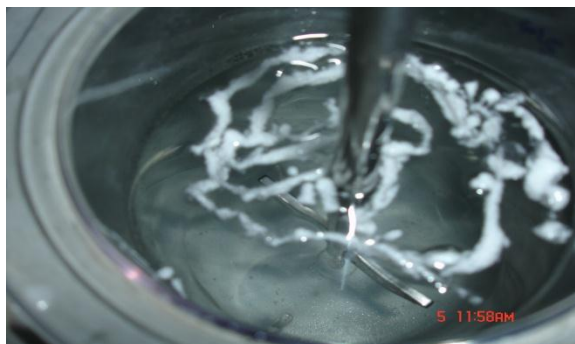
The time for which the formulation floats constantly on the surface of the medium is known as the duration of floating. The duration of floating of gels was determined by using a dissolution test apparatus USP (Type II) containing 900 ml of 0.1N HCl at 50 rpm at 37±0.5⁰c. The readings were taken in triplicate.

In Vitro Drug Release Studies

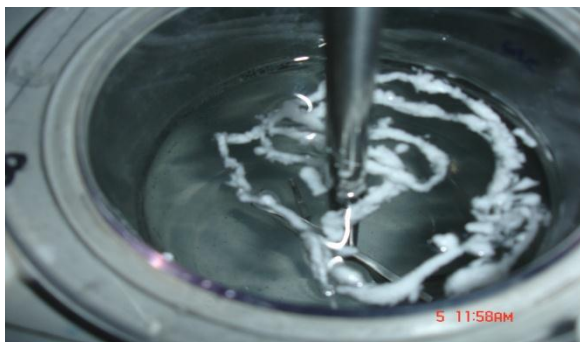
The drug release studies were performed by USP Type II dissolution test apparatus. 0.1N HCl was used as dissolution medium. The temperature and speed of the apparatus were maintained at 37±0.5⁰C and 50 rpm respectively. The samples were withdrawn at predetermined time interval and analyzed for drug concentration at 232nm by UV-Visible spectrophotometer (shimadzu UV-1700) after filtration. The readings were taken in triplicate.

Stability Studies [7]

Stability studies were conducted on metformin Hydrochloride in-situ gel containing Sodium alginate and calcium carbonate to assess their stability with respect to their physical appearance, drug content, and drug release characteristics after storing them in Stability chamber (Thermolab) at 40°C/ 75%(RH) for 6 months.



Photograph 1. Floating gel of 1.25 % Sodium alginate. Photograph 2. Floating gel of 1.75 % Sodium alginate.



Photograph 3. Floating gel of 2.25 % Sodium alginate. Photograph 4. Dissolution of Floating gel of Metformin.

RESULT AND DISCUSSION

Characterization of Metformin

Solubility Profile

10 mg of Metformin was taken and solubility profile was done as depicted in Table 2. The results of solubility profile confirmed that the drug had considerable solubility in acidic conditions.

Melting point

The melting point of Metformin was 216°C.

Determination of in-vitro gelation time

Gelation time for all the formulations are depicted in Table 3. All formulations showed instantaneous gelation when they came in contact with simulated gastric fluid. Formulation containing calcium carbonate gelled instantaneous, this may be due to calcium carbonate present in the formulation as insoluble dispersion and which become soluble in the acidic medium and release calcium ions, which cause gelation of polymer. As after gelation solution will form aggregation of double helical three dimensional networks and will retard the drug release, gelation time have direct effect on drug release profile of formulation.

Determination of Floating Lag Time [8]

Floating lag times for all the formulations are depicted in Table 3. sodium alginate showed instantaneous floating when came in contact with stimulated gastric fluid. The basic mechanism behind floating was calcium carbonate is present in the formulation as insoluble dispersion and became soluble in the acidic medium. Released calcium ions and CO₂ gas, caused gelation of polymer and released gas get entrapped in gel matrix, which caused the matrix system to float.

Determination of Duration of Floating

Duration of floating for all formulation were studied in 0.1N HCl maintained at 37.5°C at 50 RPM and are depicted in Table 3. Upon contact with acidic medium calcium carbonate effervesced, releasing carbon dioxide and calcium ions, which causes gelation and cross linking by Ca⁺⁺ ions occurred to provide a gel barrier at the surface of the formulation. The released carbon dioxide got entrapped in the gel matrix producing buoyant formulation, these three-dimensional gel matrixes restrict the further diffusion of carbon dioxide and drug molecules and has resulted in extended period of floating and drug release respectively. The amount of CO₂ content are responsible for the observed floating lag time and duration of floating. Similarly an increase in the polymer concentration resulted in decreased floating lag time and an increase in floating duration of the prepared systems [8-10].

Table 2: Solubility profile of Metformin.

Sr. No.	Solvents	Distilled water	Methanol	Chloroform	Ethanol	0.1N HCL
01	ml of solvent required	10.0	10.0	10.0	10.0	10.0
02	Remark	Soluble.	Sparingly soluble.	Insoluble.	Sparingly soluble.	Soluble.

Table 3: Characterization of in situ sodium alginate formulations for oral delivery of metformin

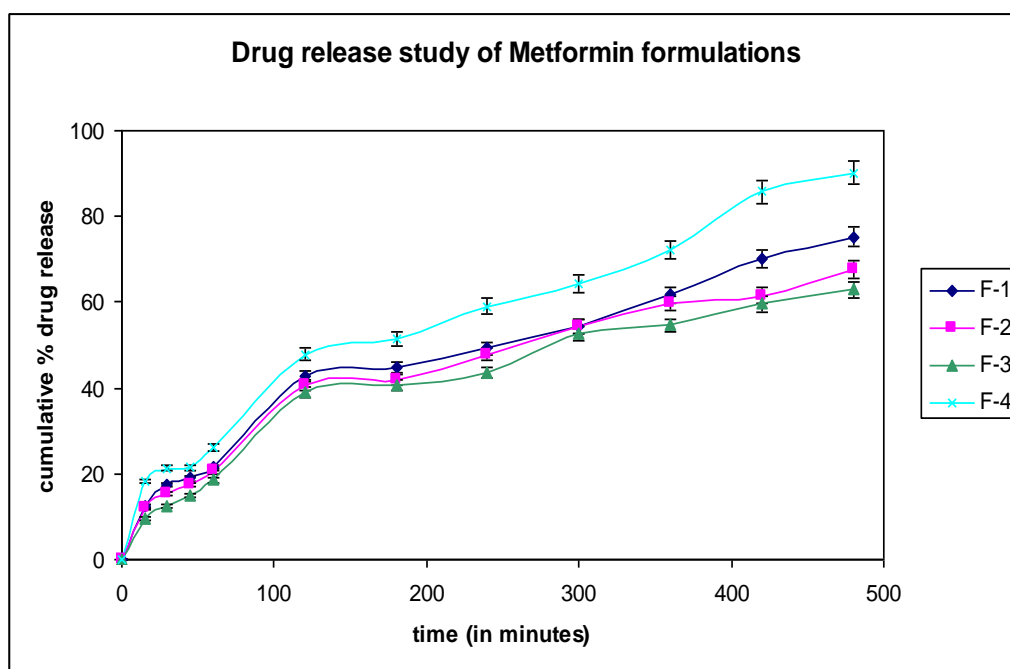
Formulation Parameters	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Gelation	+++	++	++	+++	++	++	+++	++	++
Floating Lag Time (min)	< 4	< 4	< 4	< 4	< 4	< 4	< 4	< 4	< 4
Floating Duration (hrs)	> 8	> 8	> 8	> 8	> 8	> 8	> 8	> 8	> 8

In vitro dissolution study

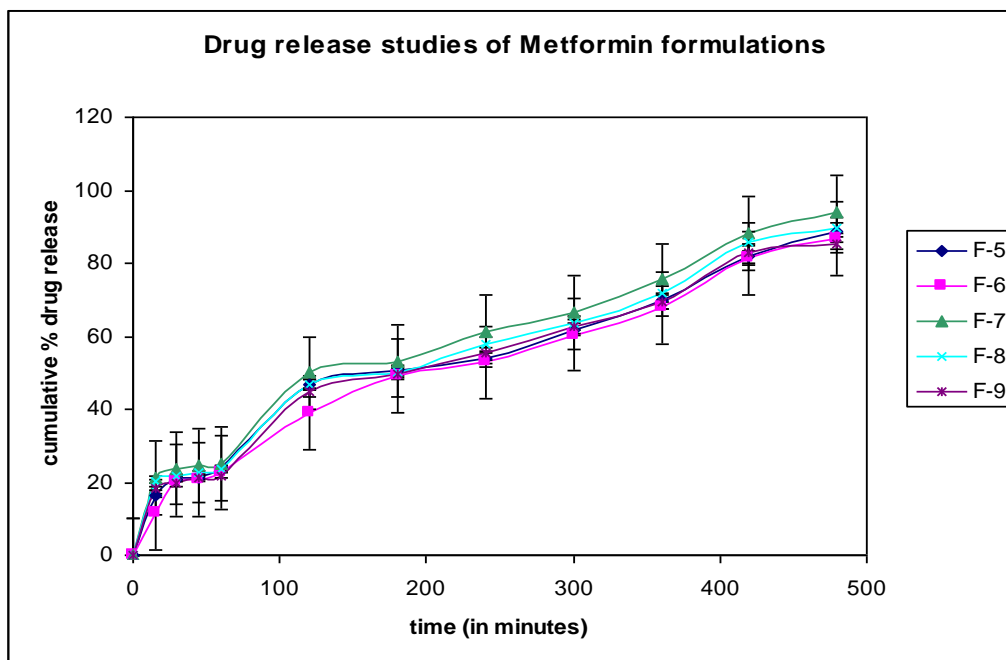
For all formulations the dissolution studies were carried out in set of three each in 0.1N HCl at 50 rpm in USP apparatus Type-II. Effect of polymer at various concentrations on in vitro drug release from in situ gels are shown in Graph no 1 and 2 . A significant decrease in the rate and extent of drug release was observed with the increase in polymer concentration in in-situ gels. The release of drug from these gels was characterized by an initial phase of high release (burst effect). However, as gelation proceeds, the remaining drug was released at a slower rate followed by a second phase of moderate release. This bi-phasic pattern of release is a characteristic feature of matrix diffusion kinetics. The initial burst effect was considerably reduced with increase in polymer concentration [11].

F-4 and F-5 formulations showed 90.09 % and 88.54 % drug release in 8 hrs. From this result it is observed that rate of release decreased with increasing polymer concentration. F-1, F-4 and F-7 formulations showed percentage release of 12.35 %, 18.21 % and 21.26 % after 15 min. This data suggest that as the drug loading was increased the percentage release also increases. F-4 has optimum release of 90.09 % in 8 hours. This formulation had rapid onset of action and optimum release.

Graph 1



Graph 2



Stability Studies

At the end of the testing period, the prepared formulations of gels were observed for changes in physical appearance, analyzed for drug content, and subjected to in vitro drug release studies. No visible changes in the appearance of the gels were observed and a significant change was not seen in the drug content and drug release at the end of the storage period [7].

CONCLUSION

From the findings one conclude that, as drug concentration in formulation increases onset of drug release increases, whereas, polymer concentration increases onset of drug release decreases and vice-versa, hence for development of therapeutically effective drug delivery of *in-situ* gel proper combination of drug and polymer must be used.

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