Development of Sustained Release of Gatifloxacin by Using Floating Oral in Situ Gelling System

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Article Information

Received 11 September 2019

Received in revised form 24 Dec 2019

Accepted 26 December 2019

Keywords:

Gatifloxacin,
in situ gelling,
sodium alginate,
HPMC

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DOI: [10.20510/ukjpb/7/i6/1581325597](https://doi.org/10.20510/ukjpb/7/i6/1581325597)

Abstract

Gatifloxacin is end up being one of the potential medications against *H. pylori* infection. As conventional drug delivery systems do not remain in the stomach for delayed periods, they can't convey the Gatifloxacin to the site of infection in effective concentrations. Hence it planned to develop a new floating in situ gelling system of Gatifloxacin with increased residence time using sodium alginate as gelling polymer and HPMC as thickening agent with a potential of *H. Pylori* eradication. The formulations were evaluated on the basis of Pharmacopoeial specification. Clarity, visual appearance, pH, gelling capacity, viscosity, gelation, buoyancy, water uptake, density of gel, gel strength, drug content, assessment of drug release, release kinetics were carried out as per specifications and results were found to be complied with the Pharmacopoeial specification. The formulation F6 shows good result as compared to other formulation. The findings of prepared in situ gelling formulations of Gatifloxacin increased the gastric residence time and also float in the gastric condition.

1 Introduction

Gastric retention time can be drawn out by different strategies, for example, floating drug delivery system, polymeric boiadhese system, high density system, swelling and expanding systems, modified- shape system, delayed gastric emptying devices etc. Oral in situ gel forming system is also called as stomach specific or raft forming systems have given a reasonable method for giving the controlled drug delivery within stomach with upgraded gastro-retention. The tablet/capsule floating dosage forms are steady as contrast with liquids however the issue with them is that are expected to swallow as whole unit. If there should arise an occurrence of dosage adjustment these can't be broken in equal parts as these are likewise intended controlled release and floating ability additionally relies upon dimensions of tablets. Old patients, kids some grown-up individual and patient with specific conditions experience the ill effects of dysphasia, so it gets hard for them to swallow tablet/capsule dosage forms¹.

Additionally if there should arise an occurrence of dosage adjustments these floating solid dosage forms are needed to be accessible in various strengths. Where an environment specific gel forming solution, on conversion to gel, floats on the surface

of the gastric fluids (because of less density than gastric contents).

In this method, less viscosity solution is used, which undergo change in polymeric conformation when come in contact with the gastric liquids, and a viscous gel of density lower than the gastric fluids is the contact time. This low density gel formation called as raft not slow drug release².

The most widely recognized pathogenic bacterial infections is *Helicobacter pylori*. It is related with serious gastro duodenal sickness, including peptic ulcers, gastric lymphoma, and acute chronic gastritis³. *H. pylori* resides mainly in the gastric mucosa or at the interface between the mucous layer and the epithelial cells of the antral region of the stomach.

Antibiotics required for annihilation of *H. pylori* are high in dose and in more frequencies. This is Because of the low concentration of the antibiotic reaching the bacteria under the mucosa, instability of the drug in the low pH of gastric fluid, and short residence time of the antibiotic in the stomach, leading to incomplete eradication of *H. pylori*⁴.

Recently Gatifloxacin is proved to be one of the potential drugs against *H. pylori* infection. As conventional drug delivery systems do not remain in the stomach for prolonged periods, they are unable to deliver the Gatifloxacin to the site of infection in effective concentrations⁵. Therefore, it is necessary to design drug delivery systems that not only alleviate the shortcomings of conventional delivery vehicles but also deliver Gatifloxacin to the infected cell lines. A few analysts had arranged and revealed new Gatifloxacin formulations, such as floating tablets, mucoadhesive tablets and mucoadhesive microspheres, which were able to dwell in stomach for an extended period for more effective *H. pylori* annihilation^{6,7}. The floating tablet is preferred for better and less variable gastric retention, but it has a limitation of incorporation of high dose of the drug. The drug with high dose like Gatifloxacin can be easily incorporated in liquid in situ gelling formulation that upon oral administration can float for a prolonged period of time in the stomach⁸.

Keeping the above facts in mind, we planned an attempt to developed a new floating in situ gelling system of Gatifloxacin with increased residence time using sodium alginate as gelling polymer and hydroxypropyl methyl cellulose K100 (HPMC K100) as thickening agent with a potential of *H. Pylori* eradication. The proposed new sodium alginate-based Gatifloxacin floating in situ gelling systems would have the advantage of ease of administration, as being a liquid, and also be more patient compliant.

2 Material and Methods

2.1 Formulation of Gatifloxacin in situ gelling solution

Take a beaker and make a solution of Calcium carbonate (CaCO_3) in water by dissolving it. Then, take 10 ml of 0.1N HCl solution; dissolve 0.2 g of Gatifloxacin. Now, take another beaker; add alginate into water which contains trisodium citrate with continuous stirring. Mix above three solutions. Now make solution of propylparaben and; methylparaben in purified Water in ration of 9:1 with aspartame. Now, different concentrations of HPMC was add in respective batches. These solutions were mixed with the above solutions (Table 1). The resulting alginate in situ gel solution containing Gatifloxacin was check for lag time, viscosity, and gelling property. In all batches, concentration of all ingredients was not changed only concentration of ingredients like Aspartame preservatives and; trisodium citrate was kept constant⁹⁻¹¹.

2.2 Characterization of in situ gel

2.2.1 Determination of the visual appearance

All the formulations was visually inspect for their appearance and clarity.

2.2.2 Measurement of the pH

The pH for each of the formulations was measure using a calibrated pen pH meter. The readings was record three times for

each of the formulation and the averages of the readings was consider¹².

Table 1: Quantity of raw materials for preparation of *in situ* ocular gel

Ingredient (mg)	F1	F2	F3	F4	F5	F6
Gatifloxacin	2000	2000	2000	2000	2000	2000
Sodium alginate	250	500	750	250	500	750
HPMC-K100	100	200	300	100	200	300
CaCO_3	400	400	400	700	700	700
NaHCO_3	50	50	50	50	50	50
Trisodium citrate	200	200	200	200	200	200
Methylparaben	90	90	90	90	90	90
Propylparaben	10	10	10	10	10	10
Aspartame	200	200	200	200	200	200
Distilled water (ml)	50	50	50	50	50	50

2.2.3 In vitro gelation study

5 ml of the simulated gastric fluid (0.1N HCl, pH 1.2) in a 15ml test tube maintained at 37°C followed by the addition of 1 ml of the formulation using a pipette. The pipette was position facing the surface of the fluid in the test tube and slowly the formulation was released from the pipette. When the formulation came in contact with the gelation medium, it was quickly converted into a gel-like structure. Based on the stiffness of gel as well as the duration, for which the gel remains as such the in vitro gelling capacity was investigate¹³.

The in vitro gelling capacity was mainly divided into three categories based on gelation time and time period the formed gel remains.

- (+): Gels in few second and disperse immediately
- (++) : Immediate gelation does not disperse rapidly
- (+++) : Gelation after few minutes remains for extended periods.

2.2.4 Determination of viscosity

Viscosities of the formulations are determined with the help of Brookfield's digital Viscometer using S21 spindle at 50 rpm and measurement was done for 6 times with fresh samples being used each time and the average reading was take.

2.2.5 In vitro buoyancy study

The studies was conducted in a USP Type II dissolution apparatus using simulated gastric fluid (0.1N HCl, pH) as the dissolution medium at $37 \pm 0.5^\circ\text{C}$. About 10 ml of the in situ gel formulation was placed in the dissolution medium. The time taken by the in situ gel formulation on the surface of the medium (floating lag time) and time period for which the formulation remained buoyant (duration of floating) was note¹⁴.

2.2.6 Determination of the drug content

5 ml of the formulation equivalent to 10 mg of the drug was add to 80 ml of 0.1N HCl, pH 1.2, and stirred for 1 h in a magnetic stirrer. After 1 h, the solution was filtered and diluted with 0.1 N HCl, pH 1.2. The drug concentration was then determined by ultraviolet (UV) visible spectrophotometer at 292 nm against a suitable blank solution¹⁵.

2.2.7 Measurement of water uptake by the gel

To conduct this study, the in situ gel formed in 40 ml of 0.1N HCl, pH 1.2 was use. From each of the formulation, the gel part was separate from the buffer and the excess buffer was blotted out with the help of Whatman filter paper. The gel was initially weighed and its weight was note, followed by the addition of 10 ml distilled water to this gel. After every 30 min interval, water was decant and weight of the gel was note and difference between initial and final weight was calculated and record¹⁶.

2.2.8 Measurement of density of gel

30 ml of the *in situ* formulation was poured into a beaker containing 50 ml of 0.1N HCl. 10 ml of the gel formed was take in measuring cylinder and weight of the gel was measured. Using the weight as well as the volume of the gel, the density was calculate. This method was followed for all the formulations¹⁷.

2.2.9 Measurement of gel strength

30 g of the gel was take in a 50 ml beaker and a 50 g weight was place on the center of the surface of the gel and allowed to penetrate through the gel. The time taken by the 50 g weight to penetrate 5 cm down through the gel was noted for all the formulations. The same method was followed for 6 times for each fresh formulation and average time was noted¹⁸.

2.2.10 In vitro drug release study of the in situ gel formulation

The drug release of the formulations was determined using a USP dissolution apparatus (Type II) with a paddle stirrer at 50 rpm. This slow speed is necessary to avoid breaking of the gelled formulation. 500 ml of the simulated gastric fluid (0.1N HCl, pH1.2) was use as the dissolution medium and the temperature was maintained at $37 \pm 0.5^\circ\text{C}$. 10 ml of the formulation was introduced into the dissolution vessel without disturbing the dissolution medium resulting in the formation of in situ gel. At each time interval, 3 ml of the sample was withdrawn and replenished with fresh medium. The samples collected were

filtered, suitably diluted, and analyzed at 292 nm using UV spectrophotometer¹⁰.

2.2.11 Kinetic modeling

The prepared formulation was adopted to study the kinetics of drug release. The in vitro drug release data were analyzed by fitting them into different kinetic models namely zero-order, first-order, Higuchi and Korsmeyer-Peppas in order to investigate the release mechanism of Gatifloxacin from the formulation.

3 Results and Discussions

The six different formulation (F1 to F6) of Gatifloxacin in situ gelling system were prepared by using sodium alginate as gelling polymer and HPMC as thickening agent.

3.1 Appearance and clarity

During preparation of *in-situ* gel of Gatifloxacin, the appearance and clarity of formulation on varying the concentration of polymer in drug has been observed. The appearance and clarity of Gatifloxacin formulation is displayed in table 2. It depicted that the uniformly distribution of drug in formulation.

Table 2: Appearance and clarity analysis of formulations

Formulations	Appearance	Clarity
F1	Off white	Clear
F2	Off white	Clear
F3	Off white	Clear
F4	Off white	Clear
F5	Off white	Clear
F6	Off white	Clear

3.2 pH

The pH of the various formulations observed and displayed in table 3. The pH of the formulation was found to be in range of $7.68 \pm 0.19 - 8.05 \pm 0.34$. The pH of all the formulations was within the orally acceptable range. Therefore, it will not cause any irritation on administration of the formulations.

3.3 In vitro gelation

The gelling capacity of all formulations demonstrated in table 3. The formulations were free running and did not produce any gelation at room temperature.

Gelation occurs when the insoluble calcium carbonate solubilize and in contact with acidic medium releasing carbon dioxide and calcium ions. The calcium ions interact with the anionic polymer (sodium alginate) in the formulation causing instantaneous gelation and provide a gel barrier that restricts drug release. It was observed that F2 and F5 containing 500 of sodium alginate while F3 and F6 holding 750 mg of sodium alginate. These

resulted in the gelation which remained for more than 12 h providing the sustained release of the drug, which concludes that as the concentration of anionic polymer increases the gelling capacity also increases.

3.4 Viscosity studies

The findings of viscosity of formulations are displayed in table 3. The formulations showed an increase in viscosity with increasing the concentration of gel forming polymer sodium alginate as a consequence of the increase in chain interaction. The concentration of sodium alginate (500 mg and 750 mg) was found to produce a satisfactory viscosity increase which provides sustained release of the drug. Calcium carbonate also contributes to increasing the viscosity of the formulations.

3.5 *In vitro* buoyancy study

The results of Buoyancy studies are shown in Table 3. The lag time of formulation were found to in range of 82.14±0.47 to 115.31±0.53 second.

When the formulation comes in contact with the acidic environment, gelation as well as cross-linking of the calcium ions

Table 3: pH, gelling capacity, *in vitro* buoyancy, viscosity, lag time, drug content, density, gel strength and gelling capacity of formulations

Formulation	pH	Gelling capacity	Viscosity (cps)	Lag time (s)	Drug content (%)	Density (gcm ³)	Gel strength (s)	Gelling capacity
F1	7.68±0.19	++	221.63±0.53	115.31±0.53	94.16±0.19	0.51±0.21	18.24±0.51	++
F2	7.76±0.23	+++	263.17±0.84	95.12±0.28	92.36±0.73	0.76±0.13	26.41±0.38	++
F3	7.73±0.52	+++	305.21±0.37	88.72±0.61	96.21±0.51	0.81±0.16	49.73±0.64	++
F4	8.05±0.34	++	258.34±0.71	112.49±0.17	95.57±0.36	0.56±0.08	21.47±0.44	++
F5	7.82±0.47	+++	310.72±0.82	93.56±0.23	98.32±0.24	0.79±0.32	38.31±0.32	++
F6	8.02±0.14	+++	379.41±0.69	82.14±0.47	97.46±0.16	0.85±0.05	55.17±0.16	++

Values are mean ± S.D

3.7 Density of gel

Density is an important evaluation parameter as far as the buoyancy ability of the gastroretentive dosage form is concerned. For the formulation to float on the gastric contents, it should have a density less than or equal to that of the gastric contents (~1.004 gcm⁻³). The density of all the formulations given in Table 3 has density less than the specified value. As a result, the floating of the gastroretentive *in situ* gel is promoted in the stomach.

3.8 Gel strength

All the formulations showed good gel strength which ranged from as low as 18.24 s for F1 to higher values of 55.17 for F6 formulations which have the combination of sodium alginate and

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 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 12 h. Therefore, the extended duration of floating was responsible for the sustained release of drug.

3.6 Drug content

This was measured for formulations F1 to F6 in triplicate, and results are illustrated in table 3. The drug content capacity for F1 to F6 was ranged between 96.24±0.62% to 98.63±0.73%. The F2 revealed lowest drug content capacity while F5 displayed highest drug content capacity; and it was the highest drug content capacity compared to other formulations.

polymer (Table 3). Gel strength gives an indication about the tensile strength of the gelled mass. It demonstrates the ability of the gelled mass to withstand the peristaltic movement in *in-vivo*. Table 3 gives the gel strength of all the formulations.

3.9 Gelling capacity

The gelling capacity was measured for formulations F1 to F6 in triplicate, and results are illustrated in table 3. The gelling capacity of the prepared formulation was determined by placing a drop of the formulation in a vial containing 2 ml of freshly prepared simulated tear fluid and visually observed.

3.10 Water uptake by the gel

The formulation exhibited water uptake and results are displayed in table 4. The release of the drug from the polymer

matrix depends on the amount of water associated with the system. The release of the drug may involve the penetration of the water into the matrix and simultaneously release the drug via diffusion or dissolution. The water associated with the formulation at any point in the time can be determined by the

simple test for all the formulation of sodium alginate based in situ gel of Gatifloxacin. From the study, it was concluded that formulation F3 and F6 containing 750 mg of the sodium alginate resulted in 100% water uptake, in turn, a good release of the drug from the polymer.

Table 4: Water uptake by gel

Formulation	Weight gain (g)				
	0 h (Initial Weight)	1 h	2 h	3 h	4 h
F1	11.23±0.12	13.51±0.57	Dissolved	Dissolved	Dissolved
F2	18.31±0.62	19.12±0.48	19.34±0.85	20.24±0.53	21.83±0.92
F3	20.11±0.34	20.73±0.51	21.42±0.48	22.16±0.21	23.72±0.47
F4	13.42±0.73	13.87±0.22	14.25±0.14	Dissolved	Dissolved
F5	19.63±0.66	20.13±0.31	21.36±0.28	23.42±0.43	26.21±0.25
F6	22.17±0.43	24.35±0.29	37.17±0.54	41.24±0.77	45.13±0.31

Values are mean ± S.D

3.11 Assessment of *in vitro* drug release

The *in vitro* releases of drug from Gatifloxacin in situ gel are illustrated in fig 1. The F1 and F4 released 50% drug from formulation at 4 hr, while other formulations take more than 4 hr for release of 50% drug from formulation. The formulation F6 has maximum drug release as compared to other formulations at 12 hrs.

The *in-vitro* drug release data of the check-point batch were analyzed for determining the kinetics of drug release. It was found that, all the formulations (F1 to F6) follow the zero order kinetics as the co-efficient of regression (R^2) was more near to unity as compared to the regression value of first order and Higuchi order. By using Korsmeyer-Peppas equation, the n values obtained were between 0.8152 and 0.9908 for all formulations. These values are characteristic of anomalous kinetics (non-Fickian) and super case-II transport, suggesting that more than one mechanism may be involved in release kinetics, referring to combination of diffusion and erosion based drug release mechanism. This mechanism could result from an increased plasticization at the relaxing boundary.

4 Conclusion

The present study suggested that the Gatifloxacin has enhanced gastric residence time by formulating with sodium alginate as a gelling polymer and HPMC as a thickening agent. Further it was noted formulation slowly released Gatifloxacin for the 12 h.

5 Conflicts of Interest

None

6 Author's Contributions

RP, PKS and VS have equally contribution on this study and performed the experimental work. All authors reviewed and approved the final manuscript.

Fig 1: *In vitro* drug release from in situ gel

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