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Formulation and Evaluation of Azithromycin Dihydrate Based In situ Gel as Floating Drug Delivery System

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ABSTRACT

Floating Drug Delivery Systems have been used to overcome some of the problems like low oral absorption of drugs with narrow absorption window as it has an advantage of sustained release of drugs over a prolonged period of time. In-situ gels are the novel approach in the context of floating drug delivery systems. The aim of this present study was to develop an oral stomach specific floating in-situ gel of Azithromycin dihydrate. In-situ gelling system was prepared by dissolving different concentrations of polymers like sodium alginate, xanthan gum in the de-ionized water already prepared with sodium citrate at 60°C to 90°C. After the heating with continuous stirring the formulation was cooled below the temperature of 40°C with the addition of certain amount of drug and calcium carbonate which acts as gas generating agent. All the formulations showed pH in the range of 6.1 to 6.7, drug content was found to be in the range of 97.29% to 99.27%. Floating lag time was less than 1 minute for all the formulations and the duration of floatation was more than 24 hours for the combination of polymers. Appearance and measurement of water uptake by the gel was also good. Stability studies were also done and was found to be at normal phase at different temperatures and at interval of times. Although, F9 showed the maximum properties of an in-situ gel with increased gastric retention time with low slowly release of the drug. Drug release was found to be decreasing as the concentration of polymer increases. However, it was concluded that the in-situ gelling system of Azithromycin dihydrate could be prepared in various concentrations of different polymers and the combination of polymers to increase the patient compliance and reduction in the frequency of dosing of the drug with the increased gastric residence time for the drug in the stomach.

Keywords: *Floating Drug Delivery System; Azithromycin Dihydrate; In-situ gelling system; Sodium Alginate; Xanthan Gum.*

Introduction

The field of drug delivery system has been greatly impacted by the development of controlled release formulations, especially for medications having a small window of absorption. However, conventional controlled release formulations are restricted by insufficient stomach retention [1] and leads to bioavailability complications [2]. In order to increase the period that these dosage forms remain in the stomach, it is necessary to decrease their density, which encourages floating in the gastric juices. From

this, a gastro-retentive sustained release dosage form is produced [3]. This latest advancement in continuous drug delivery is represented today by the floating in situ gel system. It is simple to apply a solution with low viscosity in this system, and once it reaches the gastric contents, it undergoes polymeric modifications, creating an in situ viscous gel with a density lower than the gastric fluids [4]. A unique method for achieving stomach retention and obtaining enough medication bioavailability is the floating drug delivery system (FDDS). Since these systems have a lower bulk density than gastric fluids, they can keep their buoyancy in the stomach for a long time. As a result, the medicine is released in the stomach at the proper rate and slowly. The stomach's residual system is emptied after the medication has been expelled [5]. The FDDS uses a novel approach called in situ gelling system. When in touch with gastric juices, in situ gels, which are in solution form, transform into gels. One or a combination of several stimuli, such as ionic contact, pH shift, temperature modulation, and solvent exchange, may be responsible for the phase transition of in situ gels. In situ gelling systems have the benefits of being simple to administer, requiring less frequent administration, improving patient compliance, and being comfortable. The in situ gels' time spent in the stomach increases with increasing gelling capacity, which eventually results in sustained drug delivery.

Azithromycin Dihydrate is a macrolide antibiotic [6] prescription medicine approved by the U.S. Food and Drug Administration for the treatment of certain bacterial infections [7]. Due to its limited bioavailability after oral administration tablet form indicates low bioavailability of roughly 34 ± 19% in the gastrointestinal environment, it is chosen as the active drug in the current investigation to be integrated in the in situ gelling system [6]. Therefore, in order to address the aforementioned concerns, it was decided to create a novel floating in-situ gelling system of Azithromycin dihydrate with a longer residence period using sodium alginate as the gelling polymer and xanthan gum as the thickening agent. The advantages of the novel sodium alginate based Azithromycin dihydrate floating in situ gelling systems include simplicity of administration due to their liquid form and improved patient compliance [8].

Materials and Method

Azithromycin dihydrate was obtained as a gift from Centaur Pharmaceuticals, Baddi. All the other excipients and materials like Sodium Alginate, Calcium Carbonate and Xanthan gum, Sodium citrate was obtained from Nice Chemicals and Loba Chemie respectively. All the used ingredients were of analytical grade and laboratory grade. Deionized water was used in the preparation of the formulation.

Preparation of in-situ gelling system

Sodium Alginate, Xanthan gum and the combination of both polymers were prepared in different concentrations (1.0% w/v – 2.0% w/v) and (0.5% w/v – 1.0% w/v) in deionized water containing sodium citrate (0.45% w/v). The gelling polymers were then heated to 60°C to 90°C with the continuous stirring and then was cooled down below to 40°C. Adequate amount of azithromycin (250 mg) and Calcium Carbonate (0.50% w/v) was gradually added (as given in the table 1) to the solution while stirring with a magnetic stirrer so that the dispersion of the drug could be proper and homogenous. These prepared solutions were stored at the room temperature until further use. The composition of various formulations of Azithromycin dihydrate floating in in-situ gels is in Table 1.

Table 1: Formulation table of Azithromycin dihydrate in-situ gelling system.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Azithromycin Dihydrate	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg
Sodium Alginate	1.0% w/v	1.5% w/v	2.0% w/v	--	--	--	--	--	--
Xanthan gum	--	--	--	0.5% w/v	0.75% w/v	1.0 % w/v	--	--	--
Sodium Alginate + Xanthan gum	--	--	--	--	--	--	1.0% w/v – 0.5% w/v	1.5% w/v – 0.75% w/v	2.0% w/v – 1.0 % w/v
Sodium Citrate	0.45% w/v	0.45% w/v	0.45% w/v	0.45% w/v	0.45% w/v	0.45% w/v	0.45% w/v	0.45% w/v	0.45% w/v
Calcium Carbonate	0.50% w/v	0.50% w/v	0.50% w/v	0.50% w/v	0.50% w/v	0.50% w/v	0.50% w/v	0.50% w/v	0.50% w/v
Water	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml

Evaluation Parameters

Physical Appearance

One of the most crucial aspects of preparation is the clarity of the solution. Visual ingredient against a black and white background was used to assess the solutions clarity [9].

pH

pH is the one of the most important factors involved in the formulation. The pH of formulation should be such that the formulation will be stable at the pH and at the same time there would be no irritation to the patient upon administration of the formulation. The pH was measured in each of the solution of sodium alginate and xanthan gum based in situ solutions of Diltiazem HCL using a calibrated digital pH meter at 25ºC [10].

In-vitro Gelation Study

The in-vitro gelling capacity of prepared formulations was measured by placing 5 ml of the gelation solution (0.1N HCL, pH 1.2) in a 15 ml borosilicate glass test tube and maintained at 37 ± 1°C temperature. Using a pipette, 1 ml of the formulation solution was added. The pipette was placed at the fluid surface of the test tube when the formulation was transferred, and it gently released the formulation as it did so. The solution was instantly transformed into a stiff gel-like structure as soon as it came into contact with the gelation solution. The stiffness of the produced gel and the length of time it lasts as such were used to assess the solution's ability to 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 [11].

(+) Gels after few minutes and dispersed rapidly.

(++) Gelation immediate and remains for 12 hours.

(+++) Gelation immediate and remains for more than 12 hours.

Drug Content

A magnetic stirrer was used to agitate 5 ml of the solution for 1 hour while 900 ml of simulated gastric fluid (0.1 mol/l HCL, pH 1.2) was added. A UV-visible spectrophotometer operating at 272 nm was used to measure the medication content in the solution after it had been filtered and appropriately diluted with simulated gastric juice [12].

Measurement of Water Uptake by Gel

A thermo-gravimetric analyser can be used to determine the amount of water that each formulation's gel absorbs. But in the current work, a straightforward method has been used to estimate the gel's water absorption. For this work, the in situ gel created in 40 ml of gastric acid buffer (pH 1.2) was employed. The gel portion of the buffer was removed from each formulation, and any extra buffer was wiped away using tissue paper. Every 30 minutes during the interval, 10 ml of distilled water was decanted and added to the gel, which was then measured again. The difference in weight between the two measurements was then calculated and reported [6].

Stability Studies

With the recent trend towards globalization of manufacturing operation, it is imperative that the final product be sufficiently rugged for marketing worldwide under various climatic conditions including tropical, sub-tropical and temperate. Stability studies for F6 and F8 were performed for three months, at room temperature (30 ± 20ºC) and at 40ºC. Stability studies were carried out as per ICH guidelines [13,14].

Results and Discussion

Appearance

All the formulations were visually examined and found to be clear and transparent. The result of the particular evaluation is tabulated in the below Table 2 [9]:

Table 2: Appearance of Azithromycin dihydrate of in-situ gel formulations.

Formulations	Appearance
F1	Clear and transparent
F2	Clear and transparent
F3	Clear and transparent
F4	Clear and transparent
F5	Clear and transparent
F6	Clear and transparent
F7	Clear and transparent
F8	Clear and transparent
F9	Clear and transparent

pH

pH is one of the most important factors involved in the formulation. The pH was measured in each of the solution of sodium alginate and Xanthan gum based in situ solutions of Azithromycin using calibrated digital pH meter at 25°C. The result of the particular evaluation is tabulated in the below Table 3 [10].

In-vitro Gelation Study

The in-vitro gelling capacity of prepared formulations was measured by placing 5 ml of the gelation solution (0.12 N HCL, pH 1.2) in a 15 ml borosilicate glass test tube and maintained at 37 ± 1°C temperature. 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. The result of the particular evaluation is tabulated in the below Table 4 and Figures 1 and 2 [11].

Table 3: pH value of Azithromycin dihydrate in-situ gel formulations.

Formulations	pH value
F1	6.1
F2	6.3
F3	6.4
F4	6.5
F5	6.0
F6	6.1
F7	6.2
F8	6.7
F9	6.2

Table 4: In-vitro Gelation study of Azithromycin dihydrate in-situ gel formulations.

Formulations	In-vitro floating lag time (min)	In-vitro floating time (h)	Gelling Capacity
F1	<1	>24	(+)
F2	<1	>24	(+)
F3	<1	>24	(++)
F4	<1	>24	(+)
F5	<1	>24	(++)
F6	<1	>24	(++)
F7	<1	>24	(++)
F8	<1	>24	(+++)
F9	<1	>48	(+++)

Figure 1: In situ gelation of formulation F3 and F7 respectively.

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Figure 2: In situ gelation of formulation F8 and F9 respectively.

Drug Content

The solution was filtered, suitably diluted with simulated gastric fluid and the drug concentration was determined by using a UV-visible spectrophotometer at 272 nm against a suitable blank solution. The result of the particular evaluation is tabulated in the below Table 5 [12].

Table 5: Drug Content of Azithromycin dihydrate in-situ gel formulations.

Formulations	Drug Content (%)
F1	98.52
F2	98.84
F3	99.16
F4	98.76
F5	98.85
F6	99.27
F7	97.29
F8	97.99
F9	99.09

Measurement of water uptake by the gel

The water uptake by gel was directly proportional to the polymer concentration. As the concentration of the gelling polymers was increased the water uptake by the gel also increased. The % of water uptake by gel also influenced the drug release from the gel. As the % of water uptake by gel increased the drug release was found to decrease.

Formulation F6, F8 and F9 showed higher % of water uptake by gel than all the other formulations. The % of water uptake by the gel is graphically represented in the below mentioned graph [6] (Figure 3).

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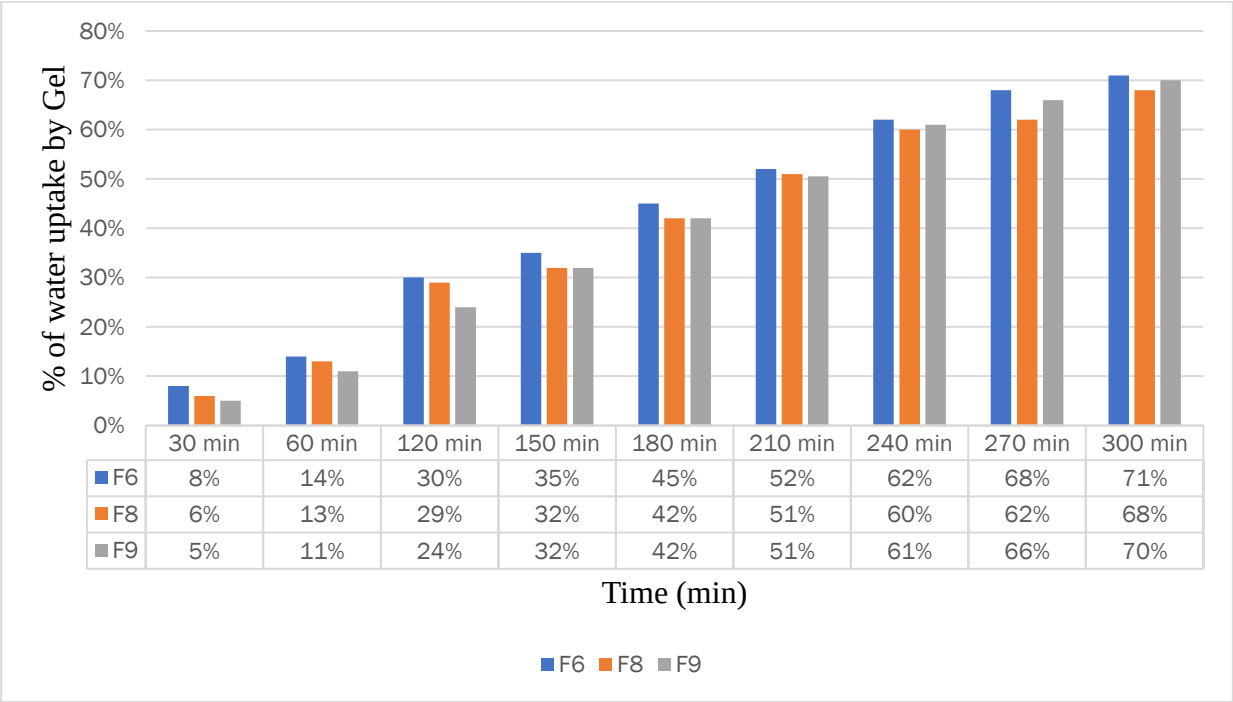

Figure 3: Percentage of water uptake by the gel.

Stability Studies

Stability studies were carried out for the drug content, viscosity and pH of the formulations. The result of the particular evaluation is tabulated in the below Table 6 [13,14].

Table 6: Stability studies of selected Azithromycin dihydrate in-situ gel formulations (F6, F8).

Time interval (months)	F6		F8	
	pH	% Drug content	pH	% Drug content
0	6.1	99.27	6.7	97.99
1	6.0	99.12	6.5	97.19
2	5.8	99.08	6.4	96.84
3	5.4	99.03	6.3	96.59

Conclusion

The novel stomach specific floating in-situ gel of Azithromycin dihydrate has been successfully and effectively prepared by Sodium alginate, Xanthan Gum and the combination of both the polymers. Based on the findings and the experimental setup employed in the study, the F9 formulation demonstrated sustained drug release from the gel. In fig. 4, the gel produced by formulation F9 is depicted. The created formulations satisfied all requirements to be an in situ gelling floating system, forming and floating instantly in the stomach's pH circumstances. This study showed that in situ gels created by the release of azithromycin dihydrate and the oral administration of the combination of polymers are sustained for at least 8 hours. It was observed that aqueous solutions of several gelling polymers demonstrated the viability of in vitro gel formation. According to the study, the viscosity and percentage of water absorbed by the gel similarly increased with an increase in polymer content, but the release of drugs from the in situ gel dropped. The study showed that using combination polymers allows for a better sustained release of medication from in situ gelling systems. Thus, it can be inferred that the stomach could be the target organ for the release of azithromycin dihydrate, which would then be sustained over time. To create the best and most effective formulation of the azithromycin dihydrate in situ gelling technology, more research is required.

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Conflict of Interest

None declared.

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