

FORMULATION AND EVALUATION OF FLOATING ORAL IN SITU GEL OF DILTIAZEM HYDROCHLORIDE

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ABSTRACT

Objective: The objective of the present study was to formulate and evaluate the floating in-situ gelling system of diltiazem hydrochloride.

Methods: Sodium alginate based diltiazem hydrochloride floating in situ gelling systems were prepared by dissolving hydroxyl propyl methyl cellulose (HPMC) in 25% of water, to which calcium carbonate and diltiazem hydrochloride were added with stirring to form, a proper and a homogenous dispersion of diltiazem hydrochloride. Meanwhile, 30% of water was heated to 60 °C on a hot plate to dissolve sodium alginate and cooled to 40 °C. The resulting solution was added to HPMC solution and mixed well. To 5% of water at 60 °C, sodium methyl paraben was added and dissolved and cooled to 40 °C and was added to the above mixture and mixed well. The volume was adjusted finally to 100% with distilled water. Prepared formulae were evaluated for physicochemical properties, drug content, pH, *in vitro* gelling capacity, *in vitro* buoyancy, viscosity, water uptake and *in vitro* drug release.

Results: Formulation variables such as type and concentration of viscosity enhancing polymer (sodium alginate) and HPMC affected the formulation viscosity, gelling properties, floating behavior, and *in vitro* drug release. Formulation F5 and F6 showed the floating time of 5 min and more than 20 h respectively. A significant decrease in the rate and extent of the drug release was observed with the increase in polymer concentration in in-situ gelling preparation. Formulation F4, F5, F6 were shown to have extended drug release until the end of 7 h.

Conclusion: The prepared in situ gelling formulations of diltiazem hydrochloride could float in the gastric conditions and released the drug in a sustained manner. The present formulation was non-irritant, easy to administer along with good retention properties, better patient compliant and with greater efficacy of the drug.

Keywords: *In-situ* gel, Sodium alginate, Diltiazem hydrochloride, Floating, Drug release

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INTRODUCTION

Over the past 30 y, greater attention has been focused on the development of controlled and sustained drug delivery systems. The development of in situ gel systems have received considerable attention over the past few years due to the advantages are shown by this system like the ease of administration, reduced frequency of administration, improved patient compliance and comfort [1].

The in situ gel dosage form is a liquid before administration but converts into a gel that floats on gastric contents as it comes in contact with it [2]. Such gel conversions are due to one or more mechanisms such as physiological stimuli (e. g., temperature and pH), physical changes in biomaterials (e. g., diffusion of solvent and swelling) and chemical reactions (e. g., enzymatic, ionic and photoinitiated polymerization) [3].

In situ gel formulations are one of the challenging drug delivery systems. Since various biodegradable polymers used for the formulation of *In situ* gels, faces many fabrication problems, difficult processability, use of organic solvents, burst effect and irreproducible drug release kinetics and the natural polymers show batch to batch variations [4].

Diltiazem hydrochloride is a calcium channel blocker which is widely used in the treatment of variant angina, hypertension, and supraventricular tachyarrhythmias. It works by relaxing the blood vessels so that heart does not have to pump as hard. It also increases the supply of blood and oxygen to the heart. High blood pressure is a common condition and when not treated it can cause damage to the brain, heart, blood vessels, kidney and other parts of the body. Damage to these organs may cause heart diseases, heart attack, heart failure, stroke, kidney failure, loss of vision.

Diltiazem hydrochloride is freely soluble in distilled water, chloroform and methanol. It is rapidly absorbed (90 %) after oral

administration, but availability is only 30%-40% in systemic circulation and bioavailability varies between individuals. It has an elimination half-life of 3-5 h and is slightly prolonged after multiple dosing. Based on the above physical, chemical, biopharmaceutical properties and clinical relevance, diltiazem hydrochloride was selected as the drug candidate for developing floating oral in-situ gel for releasing the drug in a sustained manner. The objective of the present study was to develop diltiazem hydrochloride floating in-situ gel which provides sustained release of the drug for the management of hypertension or angina pectoris.

MATERIALS AND METHODS

Materials

Diltiazem hydrochloride was purchased from Gluchem Chemicals, Hyderabad; Andhra Pradesh, sodium alginate was procured from Loba Chemicals Pvt. Limited, Mumbai, calcium carbonate and sodium bicarbonate were purchased from SD Fine-Chem limited, Mumbai, HPMC was purchased from Molychem, Mumbai, sodium citrate was procured from Qualigens, Mumbai, methylparaben and hydrochloric acid were purchased from Molychem, Mumbai. All other reagents were of analytical grade.

Methods

Preparation of in-situ gel

Floating in-situ gel formulations of diltiazem hydrochloride were prepared using compositions given in table 1 [5].

Evaluation

Physicochemical properties

The colour, odour and taste of the formulated in-situ gel of diltiazem hydrochloride were determined as per the senses.

Table 1: Composition of diltiazem hydrochloride *In situ* gel formulations

Ingredients	Formulations in mg					
	F1	F2	F3	F4	F5	F6
Diltiazem HCl	30	30	30	30	30	30
HPMC	50	50	50	50	50	50
Sodium alginate	50	100	150	200	250	300
Calcium carbonate	50	50	50	50	50	50
Sodium bicarbonate	50	50	50	50	50	50
Sodium citrate	25	25	25	25	25	25
Methyl paraben	10	10	10	10	10	10

Determination of drug content

Accurately, 10 ml of the formulation (containing the equivalent of 30 mg diltiazem hydrochloride) from different batches was measured and transferred to 100 ml volumetric flasks. To this 50-70 ml of 0.1 N HCl was added and sonicated for 30 min. Volume was adjusted to 100 ml. Complete dispersion of the contents was ensured visually and the dispersion was filtered using Whatman's filter paper. From this solution, 10 ml of sample was withdrawn and diluted to 100 ml with 0.1N HCl. Contents of diltiazem hydrochloride were measured at a maximum absorbance at 237 nm using UV-Visible spectrophotometer [5].

pH measurement

pH of the prepared formulations was measured using a calibrated digital pH meter at 27 °C [6].

In vitro gelation study

To evaluate the formulation for their *in vitro* gelling capacity accurately measured 1 ml of the coloured formulation were added to 5 ml of the gelation solution (0.1 N HCl, pH 1.2) at 37 °C in a test tube with mild agitation that avoids breaking of formed gel. The *in vitro* gelling capacity was graded in three categories on the basis of the stiffness of the formed gel, gelation time and time period for which they formed gel remains as such (+) gels after few minutes, dispersed rapidly; (++) gelation immediate remains for few h; (+++) gelation immediate remains for an extended period.

Measurement of viscosity of in-situ gelling system

The viscosity of the dispersion was determined using a Brookfield digital viscometer (DV-E Viscometer). The samples (2 ml) were sheared at a rate of rpm/min using spindle number 1 at room temperature. Viscosity measurement for each sample was done in triplicate, with each measurement taking approximately 30 seconds [7-9].

In vitro floating study

The *in vitro* floating study was carried out by introducing 10 ml of the formulation into a beaker containing 900 ml of 0.1 N HCl (pH 1.2) at 37 °C without much disturbance. The time the formulation took to emerge on the medium surface (floating lag time) and the time the formulation constantly floated on the surface of the dissolution medium (Duration of floating) were recorded [10-12].

Measurement of water uptake

The water uptake by the gel of selected formulation of sodium alginate was determined by a simple method. In this study, the *in situ* gel formed in 40 ml of 0.1 N HCl (pH 1.2) was used for each formulation the gel portion from the 0.1N HCl was separated, and

the excess HCl solution was blotted out with a tissue paper. The initial weight of the gel taken was weighed, and to this gel, 10 ml of distilled water was added and after every 30 min of the interval water was decanted and the weight of the gel was recorded and the difference in the weight was calculated [13,14].

In vitro drug release study

The dissolution studies were performed in triplicate using type I (basket method) dissolution apparatus. The dissolution medium used was 900 ml of 0.1 N HCl maintained at 37 °C. The stirring rate was adjusted to 50 rpm. This speed was believed to stimulate the *in vivo* existing mild agitation and was slow enough to avoid the breaking of gelled formulation. At predetermined time intervals 1 ml samples were withdrawn and replaced by fresh dissolution medium, filtered through what Mann's filter paper, diluted and assayed at a maximum absorbance at 237 nm using double beam UV-Visible spectrophotometer [15-17].

RESULTS AND DISCUSSION

In this study, six formulations of sodium alginate based floating oral *in-situ* gelling systems of diltiazem hydrochloride were prepared using sodium alginate as release retarding gel forming a polymer. Viscosity enhancing polymer HPMC was added to sodium alginate solution in an attempt to improve viscosity and to obtain slower drug release than those formulations containing sodium alginate alone. Calcium carbonate was used as a source of calcium ions and as a gas generating agent [18]. In addition sodium, bicarbonate was also included in the formulations as an additional gas generating agent to enhance floating behaviour of the *In situ* gelling system of diltiazem hydrochloride.

Physicochemical properties

The formulated oral *In situ* gelling system of diltiazem hydrochloride was found to be off white in colour with characteristic odour and a bland taste.

Drug content

The percentage drug content for all formulation was determined and shown in table 2. The drug content was found to be in the range of 105-120% for all the formulations indicating a uniform distribution of the drug.

pH measurement

The measurement of pH is very important for oral preparations. Otherwise, it leads to irritation to the throat. All the formulations had a slightly alkaline pH. The pH of formulations was found in the range of 8.15-8.30 as shown in table 2.

Table 2: Evaluation of in-situ gel (n=3) (average±SEM)

Formulation code	Drug content (%)	pH	Gelling study	Floating lag time (min)	Duration of floating	Viscosity (cps)
F1	109.2±0.51	8.15±0.03	(+)	-	Did not float	4.97±0.01
F2	105.9±0.44	8.26±0.03	(+)	-	Did not float	22.093±0.01
F3	108.2±0.38	8.27±0.02	(+)	-	Did not float	884.269±0.01
F4	118.2±0.44	8.29±0.01	(++)	-	Did not float	1595.5±0.09
F5	119.5±0.31	8.25±0.02	(+++)	3	5 min	>1595.5
F6	120±0.43	8.30±0.03	(+++)	10	>20 h	>1595.5

Gelling Study: (+) Gels after few minutes dispersed rapidly, (++) Gelation immediate remains for 12 h, (+++) Gelation immediate remains for more than 12 h

In vitro gelation study

Gelling studies were carried out using 0.1N HCl/pH 1.2 and the obtained data were represented in table 2. Gelation occurs when the insoluble calcium carbonate solubilizes when it comes 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 [18].

It was noted that formulation F5 and F6 containing 250 mg and 300 mg of sodium alginate 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.

Viscosity studies

The formulation should have an optimum viscosity that will allow ease of administration and swallowing as a liquid and produce satisfactory gel strength for use as a delivery vehicle. Results of viscosity for formulations F1 to F6 are shown in table 2. 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 (250 mg and 300 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.

In vitro floating study

The formulated floating in-situ gelling system of diltiazem hydrochloride employed NaHCO_3 or CaCO_3 as a gas generating

agent. The *in vitro* floating test revealed the ability of F6 formulation to maintain buoyant for more than 12 h (table 2). Regarding the floating lag time, it was observed that formulae F5 and F6 showed floating within 3 and 10 min respectively. The basic mechanism behind floating was because calcium carbonate solubilized and effervesced upon contact with acidic medium releasing calcium ion and carbon dioxide (CO_2). The evolved CO_2 gas was entrapped in the gel causing floatation. The incorporation of sodium bicarbonate improves floating behavior by providing an additional source for CO_2 gas generation [19, 20]. The calcium ion reacted with polymers produced a cross-linked three-dimensional gel network and swelled structure of polymers might restrict the further diffusion of CO_2 and drug molecule and has resulted in an extended period of floating lag time and drug release of the formulation (F5 and F6) respectively.

Measurement of water uptake by the gel

The formulation exhibited water uptake which is observed in the range of 10-107% as shown in table 3. 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 diltiazem hydrochloride. From the study, it was concluded that formulation F6 containing 300 mg of the sodium alginate resulted in 100% water uptake, in turn, a good release of the drug from the polymer.

Table 3: Water uptake by gel (n=3) (average±SEM)

Formulation code	F1	F2	F3	F4	F5	F6
Initial Wt (g)	10.04±0.14	10.26±0.03	10.48±0.03	11.3±0.04	16.22±0.04	18.49±0.02
Time (H)	Water gain (g)					
0	10.04±0.06	10.26±0.26	10.48±0.05	11.3±0.03	16.22±0.04	18.49±0.03
1	11.6±0.09	12.22±0.06	12.08±0.02	10.84±0.03	17.11±0.04	21.44±0.03
2	Dissolved	Dissolved	12.52±0.02	10.89±0.02	18.27±0.02	28.99±0.02
3	Dissolved	Dissolved	Dissolved	11.32±0.04	19.35±0.02	38.12±0.03
4	Dissolved	Dissolved	Dissolved	13.06±0.03	20.40±0.03	38.40±0.02

In vitro drug release study

The *in vitro* release study of diltiazem hydrochloride from all six formulae in 0.1 NH_4Cl was conducted for a period of 7 h and the result was shown in fig. 1. The effect of polymer concentration on *in vitro* drug release from the formulation is shown in fig. 1. A significant decrease in the rate and extent of the drug release was observed with the increase in polymer concentration in in-situ gelling preparation. These may be attributed to the increase in density of the polymer matrix and also an increase in diffusion path length which the drug molecules have to pass. The sodium alginate and HPMC with a primary role in the sol-gel phenomenon and buoyant also affected the release rate to some extent. Formulation F4, F5, F6 was shown to have extended drug release until the end of 7 h.

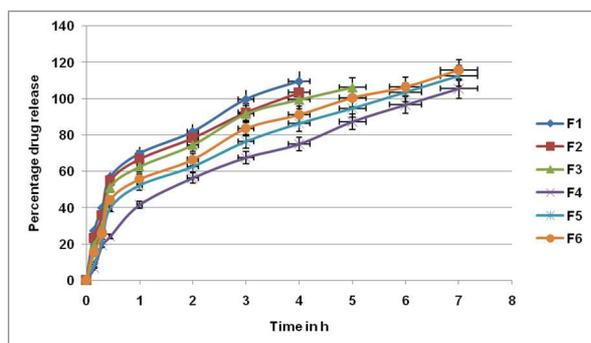


Fig. 1: *In vitro* drug release of diltiazem hydrochloride gel (F1, F2, F3, F4, F5, F6) in 0.1 NH_4Cl (n=3) (average±SEM)

CONCLUSION

In the present study, various in-situ gelling liquid oral formulation of diltiazem hydrochloride was prepared. The study as shown that by modifying the concentration of viscosity enhancing polymer and the use of HPMC, calcium carbonate, the release can be modulated to the desired rate. The incorporation of the sodium bicarbonate inappropriate amount was able to shorten the floating lag time and thereby affecting even the drug release behaviour from the in-situ gel. The prepared floating in-situ gel of diltiazem hydrochloride has the feasibility of sustaining the drug release while remaining in the stomach. So this system is of promising use in the treatment of angina pectoris.

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CONFLICT OF INTERESTS

Declared none

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