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Original Research Article

Herbal carrier-based floating microparticles of diltiazem hydrochloride for improved cardiac activity

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Abstract

Purpose: *To formulate and characterize a gastroretentive floating drug delivery system for diltiazem hydrochloride using psyllium husk and sodium alginate as natural herbal carriers to improve the therapeutic effect of the drug in cardiac patients.*
Methods: *Floating microparticles containing diltiazem hydrochloride were prepared by the orifice ionic gelation technique. Various physicochemical properties of the floating microspheres were characterized, including drug content, particle size, surface morphology, in vitro drug release, and in vivo antihypertensive effect.*
Results: *The diltiazem hydrochloride microparticles exhibited a high drug content ranging from 63.23 ± 1.14 to 85.56 % ± 1.14 %. The particle size was 891.40 ± 2.14, 928.40 ± 1.79, 900.65 ± 2.22, and 1345.40 ± 1.36 µm ($p < 0.05$ compared to blank microspheres for formulations FDD1, FDD2, FDD3, and FFD4), respectively. Scanning electron microscopy showed that all the formulations had a smooth spherical surface with little pores and few cracks. The maximum floatability value was 83.11 % ± 3.18 % for FDD1. All of the formulations showed good in vitro drug release profiles, with a maximum release of 87.4 % of the drug at the end of 12 hours. The in vivo antihypertensive effects of the microparticles in human subjects were significant ($p < 0.05$ compared to normal controls), with a reduction in diastolic blood pressure from 120 to 78 mmHg at the end of 4 hours compared to diltiazem sustained-release tablets.*
Conclusion: *Psyllium husk and sodium alginate-based microspheres can be suitably prepared for the controlled delivery of diltiazem hydrochloride to cardiac patients. However, further study is required to develop the delivery system.*

Keywords: *Diltiazem, Cardiac disease, Psyllium husk, Sodium alginate, Microsphere, Microparticle, Controlled drug release, Gastroretentive, Floating drug delivery*

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INTRODUCTION

Herbal-based drug delivery systems have long been used in folk medicine, and herbal medicines of natural origin show good therapeutic activity with minimal side effects. The World Health Organization estimates that 80 % of the world's population currently uses herbal medicines for primary health care. Thus, researchers have begun to focus on herbal drugs and the use of materials of herbal origin. Herbal medicines have many advantages over traditional medicines, including a lower risk of side effects, lower cost, and widespread availability [1,2].

Gastroretention is the most feasible approach for achieving prolonged, predictable, and controlled drug delivery in the gastrointestinal tract. These systems have a lower density than gastric fluid and remain buoyant in the stomach without affecting gastric emptying for prolonged periods [3-6].

Psyllium husk is a source of mucilaginous fiber obtained from the dried seed coats of *Plantago ovata*. It forms a gel upon contact with water, and its swelling behavior makes it suitable for use as a carrier for diltiazem hydrochloride (HCl) microparticles [7,8].

Diltiazem HCl is a calcium channel blocker that inhibits the influx of calcium (Ca^{2+}) ions during membrane depolarization in cardiac and vascular smooth muscle. It is effective in the treatment of hypertension and angina pectoris due to its cardiac effects. It has 40% oral bioavailability [9], and so requires frequent dosing to avoid these drawbacks. The administration of conventional diltiazem HCl tablets causes fluctuations in the plasma drug level resulting in side effects due to reduced drug concentrations at receptor sites. Furthermore, the maintenance of a constant plasma concentration of cardiac vascular drugs is important to ensure the designed therapeutic response; as the half-life of diltiazem HCl is 3 – 4 h, multiple doses of the drug are needed to maintain a constant plasma concentration for a good therapeutic response and to improve patient compliance [10-13].

The present study was performed to develop a gastroretentive floating drug delivery system for diltiazem HCl using psyllium husk and sodium alginate as natural herbal carriers to achieve improved therapeutic effects in cardiac patients.

EXPERIMENTAL

Materials

Diltiazem HCl was obtained from Sigma-Aldrich (St. Louis, MO). Psyllium husk was obtained from the Department of Traditional Chinese Medicine, Medical College of Shihezi University, Xinjiang, China. All other reagents were of analytical grade or higher and obtained commercially.

Preparation of diltiazem HCl microparticles

Floating microparticles containing diltiazem HCl were prepared by the orifice ionic gelation technique using the composition shown in Table 1.

Table 1: Composition of microparticles of diltiazem HCl (DHCl)

Formulation	DHCl (mg)	Sodium alginate (%w/v)	Psyllium husk (%w/v)
FDD_1	100	200	150
FDD_2	100	100	150
FDD_3	100	150	100
FDD_4	100	250	50

Sodium alginate and psyllium husk were dissolved in purified water to form a firm gel, and the gas-forming agent sodium carbonate was dispersed in the purified water to form a homogeneous polymer mixture. The drug was added to the polymeric solution and mixed thoroughly with a magnetic stirrer to form a homogeneous mixture. Gelation medium containing 2 % calcium chloride in glacial acetic acid was prepared. The homogenous polymer solution was extruded into the gelation medium using a 21-G needle. The distance between the tip of the needle and surface of the gelation medium was maintained at 10 cm. The mechanical strength of the microparticles was improved by gentle stirring for 30 minutes at room temperature. The prepared microparticles were collected, washed twice with distilled water, dried at room temperature for 24 hours, and stored in desiccators [14].

Assessment of microparticle size and shape

The size of the microparticles was determined using an optical microscope fitted with an ocular and stage micrometer. Scanning electron microscopy (SEM) was performed to determine the surface morphology of the formed microparticles. The preparations were mounted directly onto the sample stub and coated with gold film (~200 nm) under reduced pressure (0.130 Pa) (JSM-1600; JEOL Ltd., Tokyo, Japan).

Determination of drug content

The drug content was determined by dissolving a 50 mg equivalent of diltiazem HCl microspheres in 100 mL of 0.1 N HCl.

This solution was then stirred on a magnetic stirrer for 24 hours and filtered. Next, the samples were withdrawn, filtered, diluted appropriately, and measured spectrophotometrically at 243 nm to determine the drug content.

Evaluation of bulk density

The bulk density of the prepared gastroretentive floating microspheres was determined using a standard bulk density apparatus.

Buoyancy test

In vitro floating behavior studies were performed by placing 50 microparticles in 50 mL glass flasks. To exclude floating due to non-wet surfaces, an additional 50 mL of 0.1 N HCl containing 0.02 % w/v Tween 20 was added followed by horizontal shaking (37 °C, 75 rpm). The flasks were allowed to stand for 5 minutes without agitation, and the particles were counted. This procedure was repeated after 2, 4, 6, and 8 hours. The percentage of floating microspheres was calculated using the following equation.

In vitro drug release studies

The *in vitro* release profile of the microspheres was evaluated using an eight-station USP dissolution test apparatus with 900 mL of acid buffer (pH 1.2) as the dissolution medium. It was maintained at 37 ± 0.5 °C at 50 rpm. Aliquots of an accurately weighed 100 mg equivalent of drug microspheres were added and dissolution was performed for 2.5 h. Samples (5 mL each) were withdrawn every 30 minutes and replaced with an equal volume of fresh medium to maintain sink conditions. The samples were filtered, diluted appropriately, and analyzed spectrophotometrically for drug release at 243 nm. The dissolution medium was then replaced by 900 mL of phosphate buffer (pH 6.8) maintained at 37 °C ± 0.5 °C at 50 rpm. This study was continued for 12 h.

In vivo antihypertensive effect

This study was conducted in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects [15]. The study was approved by the ethics committee of Medical College of Shihezi University (approval no. TEK-1345523). The antihypertensive effect was studied in 60 hypertensive men aged 35 – 45 years with a diastolic pressure of 100 – 120 mmHg. Each subject provided written consent prior to participation. The exclusion criteria included patients with obesity, patients on multidrug therapy, liver or renal failure patients, and smokers. The *in vivo* antihypertensive effect of the selected formulation (50 mg of diltiazem containing an equivalent amount of microspheres in capsules of size 000) was examined in 30 hypertensive men in comparison to a group of 30 hypertensive men administered oral diltiazem tablets (10 mg). The patients were administered the sample preparation (with about 250 mL of water) or tablets in the morning after an overnight fast. The diastolic blood pressure was measured in mmHg at different time intervals (Figure 2).

Statistical analysis

The results are expressed as mean ± standard deviation (SD) and were analyzed by Student's t-test. The level of statistical significance was set at $p < 0.05$.

RESULTS

The drug content of the microsphere formulations are show in Table 2. The bulk densities of all formulations indicate good flow properties and floatability. The bulk density was between 0.177 ± 0.0322 and 0.232 ± 0.0232 g/mL.

SEM showed that all of the formulations had a smooth spherical surface with little porosity and few cracks (Figure 1A to Figure 1D).

A buoyancy study showed an optimum floating time of more than 8 hours for the formulations. The percentage buoyancy was 83.11 ± 3.18, 76.34 ± 1.15, 79.99 ± 1.89 and 75.22 ± 1.44 % for FDD_1, FDD_2, FDD_3, and FFD_4, respectively.

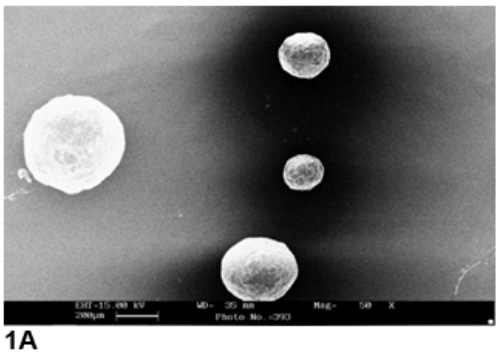
At the end of 12 h, the percentage of the drug that had been released was 87.4, 80.3, 83.1 and 75.2 % for $FDDD_1$, FDD_2, FDD_3, and FDD_4, respectively (Figure 2).

The *in vivo* antihypertensive results showed that the diastolic blood pressure decreased from 120 to 78 mmHg at the end of 4 hours and maintained this level for 10 hours. On the other hand, diltiazem tablets reduced the patients'

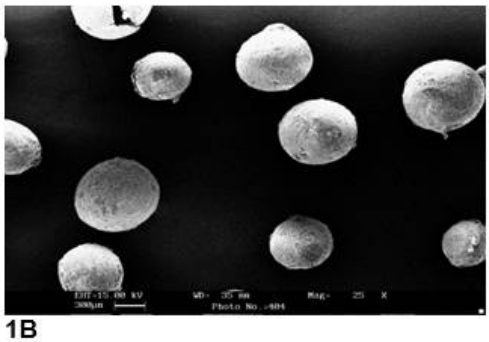
Table 2: Physical characteristics of the diltiazem HCl microspheres

Code	Drug content (%)	Particle size* (µm)	Bulk density* g/mL (ρb)	Buoyancy (%)
FDD_1	85.56 ± 1.14	891.40 ± 2.14[a]	0.232 ± 0.0232[a]	83.11 ± 3.18[a]
FDD_2	80.12 ± 1.24	928.40 ± 1.79[a]	0.210 ± 0.0322[a]	76.34 ± 1.15[a]
FDD_3	81.77 ± 3.11	900.65 ± 2.22[a]	0.179 ± 0.0172[a]	79.99 ± 1.89[a]
FDD_4	63.23 ± 1.14	1345.40 ± 1.36[a]	0.177 ± 0.0322[a]	75.22 ± 1.44[a]

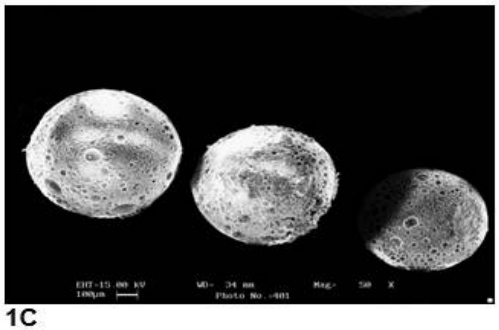
*****All values are expressed as means ± SD, $n = 3$; [a]$p < 0.05$ compared to blank microspheres



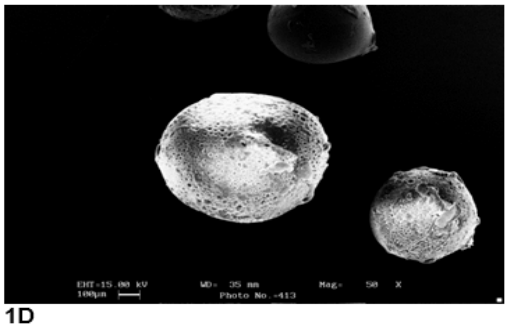
1A



1B



1C



1D

Figure 1: Scanning electron micrographs of floating microspheres: (1A) FDD_1 (50×); (1B) FDD_2 (25×); (1C) FDD_3 (50×); and (1D) FDD_4 (50×)

diastolic pressure from 110 to 97 mm Hg at the end of 4 hours (Figure 3).

DISCUSSION

Prolonged release of diltiazem from floating microparticles not only increased the therapeutic efficacy and patient compliance but also produced a more reliable plasma drug profile as compared to diltiazem tablets.

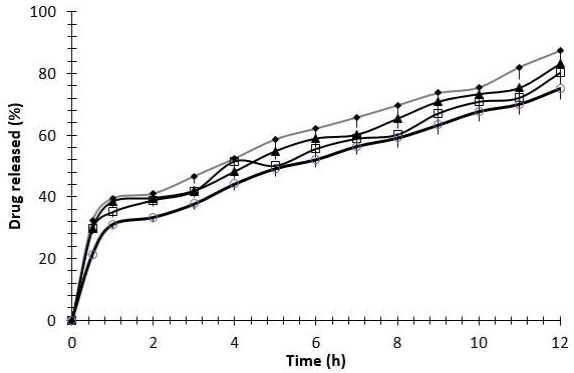


Figure 2: *In vitro* drug release profiles for floating microspheres of diltiazem: F_1 (–♦–), F_2 (–□–), F_3 (–▲), and F_4 (–○–)

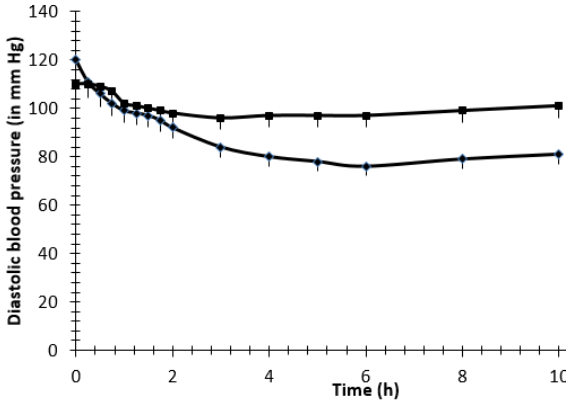


Figure 3: *In vivo* antihypertensive effect of floating microsphere formulation FDD_2 (–♦–) vs. conventional tablets (–■–)

The particles ranged in size from 891.40 ± 2.14 to 1345.40 ± 1.36 µm. The mean particle size varied significantly according to the different proportions of polymers used, which may have been due to differences in the viscosity of the polymer solution [16-20]. The particles in formulation FDD_1 (containing a greater quantity of psyllium husk) were larger than those in the other formulations. This is not surprising since psyllium husk contributed significantly to the viscosity of the polymer solution. Previous studies also suggested that psyllium husk-based extended release drug preparations were effective in delivering the loaded drugs. An increase in psyllium husk concentration was shown to increase both the viscosity of the dispersed phase and the entrapment efficiency of microparticles [21-23].

All of the formulations showed significant drug loading, which may have been due to strong intermolecular bonding between the polymer and drug. Thus, the drug was uniformly distributed and an optimum drug concentration was obtained at the site of action.

Determinations of bulk density are important with respect to floating drug delivery to ensure good flow properties and floatability. Previous studies also suggested the floating behavior of diltiazem microspheres (maximum floatability: 85.31 %). As the size of the microparticles increased, the bulk density decreased due to an increase in space between the molecules.

In vitro buoyancy testing showed a maximum percent buoyancy of 83.11 ± 3.18 % at the end of 8 hours. The good floating behavior of the particles was attributed to the low density and hollow nature of the microparticles. Previous studies also suggested that hollow cavities in microparticles occurred due to the production of air bubbles during their formulation.

The formulations yielded a gradual and more sustained release of the drug over the study period. These results show that diltiazem-loaded microparticles could be used once daily for the treatment of arrhythmia, angina, and other cardiac disorders. In the first few hours, the microspheres provided an initial burst of release due to rapid dissolution of the drug from the surface of the microparticles [24,25]. This can be considered as the loading dose, with the rest of the drug release considered as the maintenance dose. The release kinetics indicates that the drug release from the formulations followed a matrix diffusion process. Based on the obtained particle size, morphology, drug content, *in vitro* release, and release kinetics, formulation FDD_1 was selected for testing of its *in vivo* antihypertensive effects. The results confirm that FDD_1 efficiently reduced the patients' diastolic blood pressure from 120 to 78 mmHg at the end of 4 h, in comparison with diltiazem tablets. *In vitro* drug release, buoyancy and *in vivo* antihypertensive data indicate that formulation FDD_1 would reside in the gastric region for a long period and thus increase drug absorption.

CONCLUSION

Psyllium husk and sodium alginate have been used as natural herbal carriers for formulations of diltiazem floating microparticles to achieve drug release in the treatment of hypertension. The floating microparticles display good floating, suitable *in vitro* drug release profile and good *in vivo* antihypertensive effects. Thus, the formulation has potential for use as a drug delivery system, but additional studies are required to confirm these findings.

DECLARATIONS

Acknowledgement

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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