In Vitro and In Vivo Evaluation of Guar Gum Matrix Tablets for Oral Controlled Release of Water-soluble Diltiazem Hydrochloride

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ABSTRACT

The objective of the study was to develop guar gum matrix tablets for oral controlled release of water-soluble diltiazem hydrochloride. Matrix tablets of diltiazem hydrochloride, using various viscosity grades of guar gum in 2 proportions, were prepared by wet granulation method and subjected to in vitro drug release studies. Diltiazem hydrochloride matrix tablets containing either 30% wt/wt low-viscosity (LM1), 40% wt/wt medium-viscosity (MM2), or 50% wt/wt high-viscosity (HM2) guar gum showed controlled release. The drug release from all guar gum matrix tablets followed first-order kinetics via Fickian-diffusion. Further, the results of in vitro drug release studies in simulated gastrointestinal and colonic fluids showed that HM2 tablets provided controlled release comparable with marketed sustained release diltiazem hydrochloride tablets (D-SR tablets). Guar gum matrix tablets HM2 showed no change in physical appearance, drug content, or in dissolution pattern after storage at 40°C/relative humidity 75% for 6 months. When subjected to in vivo pharmacokinetic evaluation in healthy volunteers, the HM2 tablets provided a slow and prolonged drug release when compared with D-SR tablets. Based on the results of in vitro and in vivo studies it was concluded that that guar gum matrix tablets provided oral controlled release of water-soluble diltiazem hydrochloride.

KEYWORDS: guar gum, matrix tablets, oral controlled release, diltiazem hydrochloride, in vitro drug release, in vivo evaluation

INTRODUCTION

Oral drug delivery continues to rise in popularity as formulation scientists look for ways to control drug release and improve patient convenience. However, developing oral controlled release tablets for water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most of these water-soluble drugs, if not formulated properly, may readily release the drug at a faster rate and produce a toxic concentration of the drug on oral administration. In recent years, considerable attention has been focused on hydrophilic polymers in the design of oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance. Among the hydrophilic polymers, cellulose derivatives such as methyl cellulose, hydroxypropyl methylcellulose, and sodium carboxymethyl cellulose are generally considered to be stable and safe as release retardant excipients in the development of oral controlled release dosage forms. These semisynthetic polymers are quite expensive when compared with natural polymers such as guar gum, alginates, and so forth. The natural polymers are nontoxic and easily available. The objective of the present investigation was to develop oral controlled release tablets for water-soluble diltiazem hydrochloride using a natural polymer such as guar gum. Diltiazem hydrochloride was formulated as an oral controlled release dosage form using various polymers.[1-3] A number of reports appear in the literature on the utility of guar gum or modified guar gum in the design of oral controlled release tablets.[4-8]

Guar gum is a nonionic polysaccharide derived from the seeds of *Cyamopsis tetragonolobus*, family Leguminosae. It consists of linear chains of (1→4)-β-D-mannopyranosyl units with α-D-galactopyranosyl units attached by (1→6) linkages. In pharmaceuticals, guar gum is used in solid dosage forms as a binder and disintegrant.[9-11] A few reports appear on the use of guar gum, as a hydrophilic matrix, for designing oral controlled release dosage forms.[4,12,13] The efficiency of the hydrophilic matrix in controlling the drug release, in addition to other factors, is dependent on the viscosity of the hydrophilic polymer(s) incorporated in the formulation.[14,15] Hence, in the present study various viscosity grades of guar gum were evaluated for the oral controlled drug release of water-soluble diltiazem hydrochloride in the form of a matrix using in vitro dissolution studies and in vivo pharmacokinetic studies. Matrix tablets containing 2 different proportions of various viscosity grades of guar gum were prepared by wet granulation method and subjected to in vitro drug release studies to

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Table 1. Excipients in Diltiazem Hydrochloride 90 mg Tablet Formulations* Containing 20% wt/wt (LM1) Low-Viscosity, 30% wt/wt (LM2) Low-Viscosity, 30% wt/wt Medium-Viscosity (MM1), 40% wt/wt Medium-Viscosity (MM2), 40% wt/wt High-Viscosity (HM1), or 50% wt/wt High-Viscosity (HM2) Guar Gum

	Quantity Present (mg) in					
Ingredients	**LM1**	**LM2**	**MM1**	**MM2**	**HM1**	**HM2**
Low-viscosity guar gum	60	90	—	—	—	—
Medium-viscosity guar gum	—	—	90	120	—	—
High-viscosity guar gum	—	—	—	—	120	150
Microcrystalline cellulose	126	96	96	66	66	36

*Each formulation contained Starch, 15 mg; talc, 6 mg; Mg Stearate, 3 mg per tablet (300 mg).

find the utility of guar gum in providing controlled release. The guar gum matrix tablet formulation providing an optimal in vitro drug release was subjected to further studies to investigate its in vivo performance in healthy volunteers.

MATERIALS AND METHODS

Materials

Diltiazem hydrochloride was a gift sample from M/s Kopran Limited (Mumbai, India). Microcrystalline cellulose (Avicel, FMC Type pH-105), starch, magnesium stearate, and talc used were of USP/NF quality. Low-viscosity guar gum (viscosity of 1% aqueous dispersion at 25°C is 86 cps; particle size $\leq$ 75 μm), medium-viscosity guar gum (viscosity of 1% aqueous dispersion at 25°C is 4200 cps; particle size $\geq$ 75 μm), and high-viscosity guar gum (viscosity of 1% aqueous dispersion at 25°C is 5650 cps; particle size $\geq$ 75 μm) were the gift samples from M/s Dabur Research Foundation (New Delhi, India) and were used as received. Verapamil was obtained from M/s Sigma-Aldrich Corporation (St. Louis, MO). Water (HPLC grade), acetonitrile (HPLC grade), triethylamine (AR grade), orthophosphoric acid (AR grade), cyclohexane (AR grade), diethyl ether (AR grade), and dipotassium hydrogen phosphate (AR grade) were obtained from M/s Qualigen Fine Chemicals (Mumbai, India).

Methods

Preparation of Diltiazem Hydrochloride Matrix Tablets

Matrix tablets of diltiazem hydrochloride using various viscosity grades of guar gum, in 2 different proportions, were prepared by wet granulation method using 5% starch paste as the binder. Microcrystalline cellulose (MCC) was used as diluent. The composition of different formulations used in the study is given in Table 1. In all the formulations, guar gum was sieved (<250 μm) separately and mixed with diltiazem hydrochloride (<150 μm) and MCC (<250 μm). The powders were blended and granulated with 5% starch paste. The wet mass was passed through a mesh (1680 μm) and the granules were dried at 50°C for 2 hours. The dried granules were passed through a mesh (1190 μm), and these granules were lubricated with a mixture of talc and magnesium stearate (2:1). The lubricated granules were compressed at a compression force of 4500 to 5500 kg using 9-mm round, flat, and plain punches on a single-station tableting machine (M/s Cadmach Machinery Co Pvt Ltd, Ahmedabad, India). Matrix tablets of each composition were compressed (100 No.) and tested for their hardness, drug content, and drug release characteristics with the required number of tablets for each test. The hardness of the matrix tablets was determined by using a Monsanto hardness tester (M/s Campbell Electronics, Mumbai, India).

In Vitro Drug Release Studies

Drug release studies were performed using USP dissolution rate test apparatus (Apparatus 1, 100 rpm, 37°C) for the first 2 hours in pH 1.2 buffer (900 mL) and then the dissolution medium was replaced with pH 7.4 phosphate buffer (900 mL) and tested for drug release for another 10 hours.[5,6] Thus, the dissolution testing conditions were representing the use of simulated gastric and intestinal juices without enzymes. One milliliter of the dissolution samples was taken at different time intervals replacing with an equal quantity of drug-free dissolution fluid. The samples were suitably diluted with blank dissolution fluid and analyzed for diltiazem hydrochloride content by high performance liquid chromatography (HPLC). During the in vitro drug release studies, all formulations were observed for physical integrity at different time intervals. D-SR tablets were used as the reference formulation, and were also subjected to in vitro drug release studies so as to choose the optimal amount of guar gum in the matrix tablets.

HPLC Analysis of Diltiazem Hydrochloride

The quantitative determination of diltiazem hydrochloride was performed by HPLC. A gradient HPLC (Shimadzu HPLC Class VP series, Shimadzu Corporation, Kyoto,

Japan) with 2 LC-10AT VP pumps, a variable wavelength programmable UV/VIS Detector SPD-10A VP, a CTO-10AS VP column oven (Shimadzu), an SCL-10A VP system controller (Shimadzu), and a reversed-phase C-18 column (250 mm × 4.6 mm ID; particle size 5 μm) (Shimadzu) were used. The HPLC system was equipped with the software Class-VP series version 5.03 (Shimadzu).

The mobile phase used was a mixture of acetonitrile and water (37:63) containing 0.35% wt/vol of triethylamine (pH adjusted to 3.0 with 5% orthophosphoric acid). The filtered mobile phase components were pumped from the respective reservoirs at a flow rate of 0.95 mL/min. The column temperature was maintained at 40°C. The eluent was detected by UV detector at 240 nm, and the data were acquired, stored, and analyzed. A standard curve was constructed for diltiazem hydrochloride in the range of 5 to 50 μg/mL using verapamil as internal standard. A good linear relationship was observed between the concentration of diltiazem hydrochloride and the ratio of the peak area of drug to that of internal standard with a high correlation coefficient (r = 0.9998). The method was found to be precise (intraday and interday variation was found to be less than 1.5%) and accurate (mean recovery 98.5%). The standard curve, constructed as described above, was used for estimating diltiazem hydrochloride in guar gum matrix tablets, D-SR tablets, or in dissolution fluids.

Kinetics of Drug Release

The cumulative amount of diltiazem hydrochloride released from guar gum matrix tablets and D-SR tablets at different time intervals was fitted to zero-order kinetics using the least squares method of analysis to find out whether the drug release from the formulations was providing a constant drug release. The data were further fitted to first-order kinetics to find the fitness to first-order kinetics. The data were also fitted to the model developed by Korsmeyer et al[16] in order to find out the drug release mechanism from the formulations. The percent of drug released from the formulations was plotted against time on a log-log scale, and analyzed for linearity using least squares method. The correlation coefficients were calculated and used to find the fitness of the data.

Drug Release Studies in Rat Cecal Content Medium

Earlier reports indicated the susceptibility of guar gum to the action of colonic bacterial enzymes.[17] Hence it is essential to study the influence of colonic bacterial enzymes on the release of diltiazem hydrochloride from the guar gum matrix tablets.

The guar gum matrix tablet formulations that provided controlled release on par with D-SR tablets (LM2, MM2, and HM2) were subjected to in vitro drug release studies in simulated gastrointestinal (GI) fluids and simulated colonic fluids (rat cecal contents medium). Drug release studies were performed using a USP dissolution rate test apparatus (apparatus 1, 100 rpm, 37°C) for the first 2 hours in pH 1.2 buffer (900 mL). Then, the dissolution medium was replaced with pH 7.4 phosphate buffer (900 mL) and tested for drug release for 3 hours. At the end of the time periods, 2 samples each of 1 mL were taken and estimated for diltiazem hydrochloride by HPLC as described above.

The susceptibility of guar gum to the enzymatic action of colonic bacteria was assessed by continuing the drug release studies in rat cecal content medium obtained as per the procedure described earlier.[17] At different time intervals, a 1-mL sample was withdrawn without a prefilter and replaced with 1 mL of rat cecal medium or fresh phosphate-buffered saline (PBS) bubbled with CO_2, and the experiment was continued up to 19 hours. The dissolution sample was subjected to HPLC analysis to estimate the amount of diltiazem hydrochloride released at different time intervals.

Stability Studies

Stability studies were conducted on diltiazem hydrochloride matrix tablets containing 50% wt/wt of high-viscosity guar gum (HM2) to assess their stability with respect to their physical appearance, drug content, and drug release characteristics after storing them at 40°C/relative humidity (RH) 75% for 6 months.[18]

In Vivo Pharmacokinetic Evaluation in Human Volunteers

The Ethics Committee of M/s Sipra Labs Pvt Ltd (Hyderabad, India) approved the protocol of the study, which complied with the recommendations of the Helsinki Declaration. Six healthy male volunteers (60 to 70 kg, age between 25 and 30 years) participated in the study, and all were nonsmokers and did not drink alcohol. The biochemical examination of the volunteers revealed normal function of the kidney and liver. The nature and purpose of the study, and its possible consequences, were fully explained to them. An informed written consent was obtained from every volunteer. None of the volunteers were on drug treatment 1 week prior to participation in the study. The volunteers were free to withdraw from the study at their discretion.

The volunteers were divided into 2 equal groups (Group I and Group II), and a crossover study was followed. A marketed sustained release tablet containing 90 mg of diltiazem hydrochloride (D-SR tablets) was chosen as a reference formulation and administered orally to 3 volunteers (Group I). The Group II (n=3) volunteers were administrated guar gum matrix tablet HM2 containing 90 mg of diltiazem hydrochloride. After a washout period of 10 days,

Group I volunteers received guar gum matrix tablet HM2 and Group II volunteers received the D-SR tablets. Both tablet formulations were administered with 150 mL of water after a 12-hour overnight fast. Food and drinks were withheld for at least 2 hours after dosing. Blood samples were collected from each volunteer's antecubital vein via a hypodermic syringe (rinsed with dilute heparin solution) over a period of 24 hours (0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours). The blood samples were immediately centrifuged at 5000 rpm and the plasma separated and stored at −40°C until analysis by HPLC.

HPLC Analysis of Diltiazem Hydrochloride in Human Plasma

The quantitative determination of diltiazem hydrochloride in human plasma was performed by HPLC using the equipment as described above. An aliquot of plasma (0.5 mL) was accurately measured into a 10-mL glass tube with a Teflon-lined cap, followed by the addition of 100 μL of verapamil hydrochloride (internal standard) solution (0.5 μg) along with 0.2 mL of water, 0.25 mL of 1.0 M dipotassium hydrogen phosphate, and 3.0 mL of cyclohexane:diethylether (2:1). The samples were shaken using a reciprocating test tube shaker for 15 minutes and the organic phase from the test tube was transferred into another test tube containing 0.5 mL of 0.01 M hydrochloric acid. These tubes were shaken to extract the drug and internal standard into the aqueous phase. After extraction, 20 μL of the aqueous phase was injected into the HPLC column through which mobile phase components (acetonitrile: water containing 0.35% wt/vol of triethylamine, pH adjusted to 3.0 with 5% orthophosphoric acid) were pumped from the respective reservoirs in the ratio of 37:63 vol/vol at a flow rate of 0.95 mL/min. The eluents were monitored at 240 nm, and the sensitivity range of the detector was set at 0.0001 AUFS (absorbance units full scale). The peak area ratio of diltiazem hydrochloride to that of internal standard (verapamil) was determined, and this was used to estimate the plasma concentration of diltiazem hydrochloride from the regression equation. The regression equation was set up by spiking drug-free plasma with varying amounts of diltiazem hydrochloride (10 to 200 ng/0.5 mL) and fixed quantity of internal standard (0.5 μg), and treating the plasma as described above. The peak area ratio of diltiazem hydrochloride to internal standard was obtained. A good linear relationship ($r=0.9996$) was observed between the peak area ratio and plasma concentration of diltiazem hydrochloride in the range of 20 to 200 ng/0.5 mL. However, the lower detection limit was found to be 10 ng/0.5 mL. The interday and intraday variation was found to be less than 2.8% (coefficient of variation) indicating high precision of the HPLC method. There was a high recovery (97.8% to 99.5%) of diltiazem hydrochloride indicating that the HPLC method was highly accurate.

Pharmacokinetic Analysis

The maximum plasma concentration (C_{max}) and the time required to reach C_{max} (T_{max}) were directly read from the arithmetic plot of time vs plasma concentration of diltiazem hydrochloride. The overall elimination rate constant (k_e) was calculated from the slope of the terminal elimination phase of a semilogarithmic plot of concentration vs time after subjecting it to linear regression analysis. The elimination half-life ($t_{1/2}$) was obtained by dividing 0.693 with k_e. The absorption rate constant (k_a) was calculated using method of residuals.[19] The area under the plasma diltiazem hydrochloride concentration vs time curve ($AUC_{0-\infty}$) was determined by means of trapezoidal rule. The relative bioavailability of diltiazem hydrochloride from guar gum matrix tablets in comparison to reference formulation (D-SR tablets) was calculated by dividing its $AUC_{0-\infty}$ with that of D-SR tablet dosage form.

RESULTS AND DISCUSSION

Since the guar gum was found to have poor flow properties, wet granulation method was used to improve the flow properties of guar gum.[20] The hardness of the tablets ranged from 4.5 to 5.5 kg/cm^2. All the formulations satisfied the content of the drug as they contained 98% ± 5% of diltiazem hydrochloride.

In Vitro Drug Release Studies

Matrix tablets containing 20% wt/wt (LM1) low-viscosity, 30% wt/wt (MM1) medium-viscosity, or 40% wt/wt (HM1) high-viscosity guar gum were found disintegrated within 45 minutes of dissolution testing in pH 1.2 buffer, whereas the matrix tablets containing 30% wt/wt (LM2) low-viscosity, 40% wt/wt (MM2) medium-viscosity, or 50% wt/wt (HM2) high-viscosity guar gum retained their shape for up to 12 hours of dissolution testing. The D-SR tablets were found swollen and retained their shape for up to 12 hours of testing. This indicates that the marketed sustained release tablets of diltiazem hydrochloride were formulated as matrix tablets with hydrophilic polymer(s) for controlling the drug release. The mean amounts of diltiazem hydrochloride released at different time intervals from the matrix tablets LM2, MM2, HM2, and D-SR formulation are shown in Figure 1. All 3 guar gum matrix formulations, LM2, MM2, and HM2, appear to control the release of diltiazem hydrochloride, but with a varying degree. When the guar gum matrix tablets of diltiazem hydrochloride come into contact with the dissolution medium, they take up water and swell, forming a gel layer around the matrix. Then the dissolved drug diffuses out of the swollen guar gum matrix at a rate determined by the amount and viscosity of guar gum in the tablet formulation. All the formulations, LM2, MM2, HM2, and D-SR, showed a bipha-

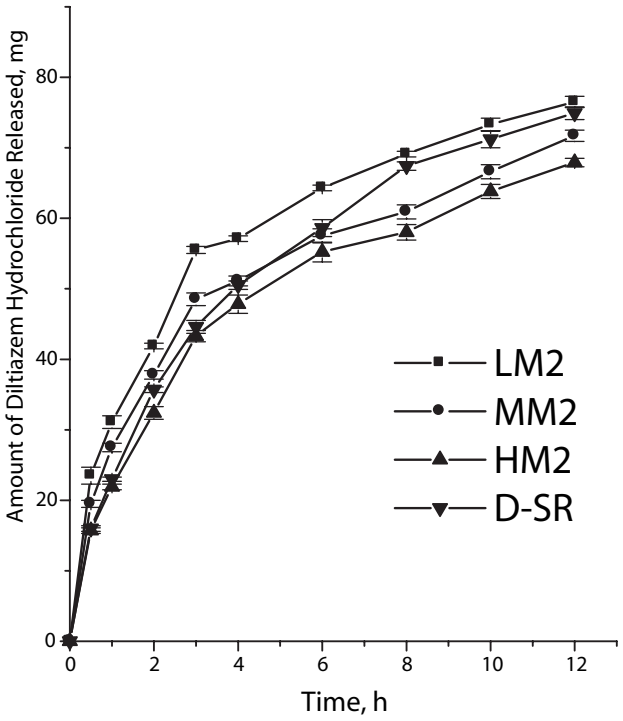

Figure 1. Mean (± SD) amount of diltiazem hydrochloride released from D-SR tablets (n=3) and matrix tablets (n=3) containing 30% wt/wt low-viscosity (LM2), 40% wt/wt medium-viscosity (MM2), or 50% wt/wt high-viscosity guar gum (HM2) in dissolution study.

sic release profile. There was a faster drug release from 0 to 3 hours, followed by a slower release from 3 to 12 hours. Such a biphasic release pattern may be beneficial in providing the initial therapeutically effective plasma concentration followed by an extended plasma concentration. The drug present on the surface of the matrix tablet might have resulted in the initial fast release of the drug from the formulation.

The correlation coefficients obtained for first-order kinetics were found to be higher (–0.9987 ± 0.001 to –0.9989 ± 0.002) when compared with those of zero-order kinetics (0.9812 ± 0.001 to 0.9950 ± 0.001), indicating that the drug release from all the formulations followed first-order kinetics (Table 2). When the percent of diltiazem hydrochloride released from formulations LM2, MM2, HM2, and D-SR was fitted to the model developed by Korsmeyer et al[16] the mean diffusional exponent values (n) ranged from 0.28 ± 0.005 to 0.38 ± 0.001 and the kinetic constants ranged from 33.0 ± 0.01 to 38.98 ± 0.87 (Table 2), indicating that diltiazem hydrochloride release from guar gum matrices and D-SR tablets followed Fickian diffusion. Thus, the results of the present study showed that the release of diltiazem hydrochloride from guar gum matrix tablets and D-SR tablets followed first-order kinetics via a diffusion-controlled mechanism.

The first-order release rate constants from MM2 and HM2 were 0.04 ± 0.001 h^{-1} and 0.04 ± 0.001 h^{-1}, which were equal to that obtained from D-SR tablets (0.04 ± 0.002 h^{-1}), showing that both the formulations were controlling the release of diltiazem hydrochloride to the same extent. However, the ability of the guar gum formulations to control the release of water-soluble diltiazem hydrochloride was dependent on the amount and viscosity of the gum. It may be noted that the release rate constant from the formulation LM2 was 0.05 ± 0.006 h^{-1} showing that more amount of low-viscosity guar gum is needed for further control of drug release. The formulations MM2 and HM2 might be contributing their tough control of drug release owing to the larger amount and higher viscosity of gum. It is expected that higher viscosity gums are required in lower quantity in providing a controlled release. But in the present study, low-viscosity guar gum was able to provide controlled drug release as that of medium- and high-viscosity-grade gums, but in a smaller quantity (30% wt/wt). This may be because of the difference in particle size of the various viscosity grades of guar gum used in the present study. The particle size of the low-viscosity guar gum was less than 75 μm, whereas that of the medium-

Table 2. Mean (± SD) Dissolution Kinetic Parameters of Diltiazem Hydrochloride From Matrix Tablets (n = 3) Containing 30% wt/wt Low-Viscosity (LM2), 40% wt/wt Medium-Viscosity (MM2), or 50% wt/wt High-Viscosity Guar Gum (HM2) and D-SR Tablets (n = 3)

Matrix Formulation	Zero-Order Release Rate (mg.h^{-1})	First-Order Rate Constant (h^{-1})	Kinetic Constant (K)	Diffusional Exponent [n]
LM2	2.44 ± 0.12	0.05 ± 0.006	33.0 ± 0.01	0.38 ± 0.01
	(r = 0.9950 ± 0.001)	(r = 0.9987 ± 0.001)	(r = 0.9979 ± 0.001)	(r = 0.9977 ± 0.001)
MM2	2.55 ± 0.25	0.04 ± 0.001	38.98 ± 0.87	0.28 ± 0.005
	(r = 0.9980 ± 0.002)	(r = 0.9988 ± 0.001)	(r = 0.9928 ± 0.001)	(r = 0.9929 ± 0.001)
HM2	2.65 ± 0.04	0.04 ± 0.001	34.1 ± 1.16	0.32 ± 0.008
	(r = 0.9891 ± 0.004)	(r = 0.9989 ± 0.001)	(r = 0.9958 ± 0.996)	(r = 0.9957 ± 0.996)
D-SR tablet	3.38 ± 0.09	0.04 ± 0.002	33.0 ± 0.86	0.38 ± 0.001
	(r = 0.9812 ± 0.001)	(r = 0.9989 ± 0.002)	(r = 0.9979 ± 0.001)	(r = 0.9979 ± 0.001)

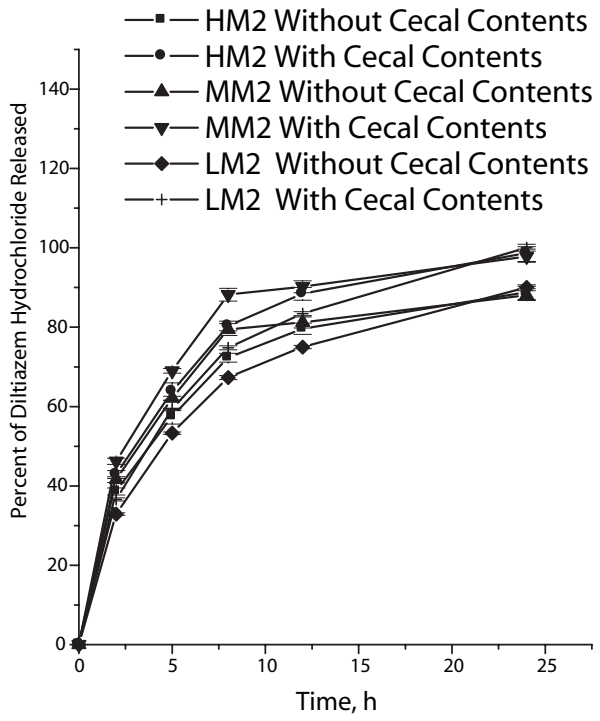

Figure 2. Mean (± SD) percent of diltiazem hydrochloride released from HM2, MM2, and LM2 tablets (n=3) in dissolution study with and without rat cecal contents in the dissolution medium.

and high-viscosity guar gums used in the present study was more than 75 μm. The finer low-viscosity guar gum might have swollen completely providing a stronger gel to control the diffusion of the drug. Altaf et al[21] prepared and evaluated guar gum tablet formulations under a variety of in vitro dissolution conditions. Varying the lot of guar gum as well as using guar gum from different suppliers had little effect on diltiazem dissolution. All the formulations gave similar plasma concentrations over time in the healthy volunteer's pharmacokinetic study. But in the present study, the extent of controlled drug release varied with the amount and viscosity of guar gum.

Drug Release Studies in Rat Cecal Contents Medium

In the presence of rat cecal contents, the swollen matrix tablets LM2 were found intact for up to 8 hours, and cracks developed at the end of 10 hours. The matrix tablets LM2 were found completely disintegrated at ∽12 hours of testing and released the entire quantity of diltiazem hydrochloride in the rat cecal content medium (Figure 2). This may be because of the enzymatic action of colonic bacteria on the completely swollen low-viscosity guar gum matrix tablet. Hence, further studies were not performed on the matrix tablet LM2.

The matrix formulations MM2 and HM2 were intact for up to 12 hours of dissolution testing. At the end of 12 hours of study, 90.2% ± 1.5% and 88.4% ± 1.6% of diltiazem hydrochloride was released in rat cecal content medium (simulated colonic fluids) from matrix formulations MM2 and HM2, respectively, whereas 81.2% ± 1.4% and 79.6% ± 1.4% of drug was released in dissolution medium without rat cecal contents (control). However, the swollen guar gum formulations MM2 and HM2 disintegrated between 12 and 24 hours of study, and thereby released the remaining quantity of drug (Figure 2). At the end of 24 hours of dissolution study, MM2 tablets released 97.8% ± 1.4% of drug with rat cecal contents and 88.0% ± 1.2% of drug without rat cecal contents (control) in the dissolution medium. However, the formulation HM2 tablets released 98.7% ± 2.2% of drug with rat cecal contents and 88.8% ± 1.9% of drug without rat cecal contents (control) in the dissolution medium. It appears that both MM2 and HM2 are providing more or less the same extent of controlled drug release. However, the formulation HM2 seems to be providing a tougher control of drug release when compared with the formulation MM2. Based on the results of in vitro drug release studies in simulated GI fluids and simulated colonic fluids, the matrix tablet HM2 was considered as the optimal formulation in providing controlled release of water-soluble diltiazem hydrochloride. Hence, further studies were performed only with the formulation HM2 (matrix tablet containing 50% wt/wt of high-viscosity guar gum).

Stability Studies

At the end of the testing period, the matrix tablets 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 matrix tablets were observed at the end of the storage period. The drug content was found to be 98.4% ± 2.3%. At the end of 12 hours of dissolution testing, the amount of diltiazem hydrochloride released from HM2 matrix tablets before storage was 68.1 ± 2.1 mg whereas that released from the HM2 formulation after storage was 69.9 ± 0.4 mg. There was no significant difference in the mean amount of diltiazem hydrochloride released from HM2 matrix tablets after storing for 6 months at 40°C/75% RH, indicating that the formulation could provide a minimum shelf-life of 2 years.[18] However, a detailed investigation is necessary to determine the exact shelf life.

In Vivo Pharmacokinetic Evaluation

The mean plasma concentration of diltiazem hydrochloride following oral administration of guar gum matrix tablets HM2 (dose 90 mg) or D-SR tablets (dose 90 mg) of diltiazem hydrochloride is shown in Figure 3. The T_{max} of diltiazem hydrochloride from matrix tablets HM2 was 1.8 ± 0.3 hours, and the peak concentration (C_{max}) at that time

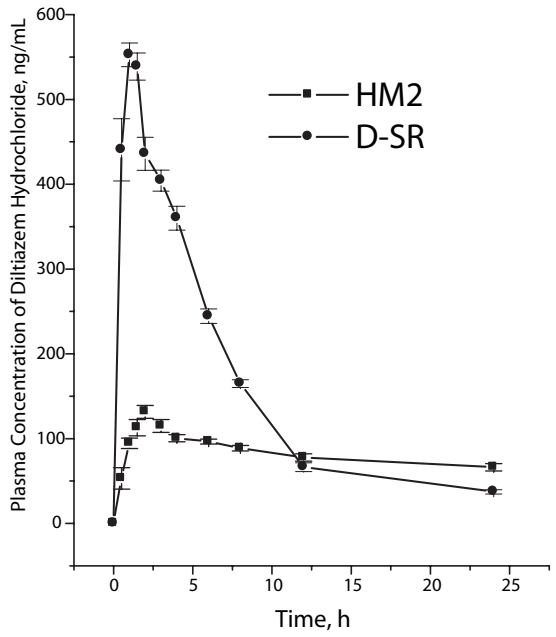

Figure 3. Mean (± SEM) plasma concentration of diltiazem hydrochloride after oral administration (dose 90 mg) of matrix tablet containing 50% wt/wt of high-viscosity guar gum (HM2 tablet) or D-SR tablet in human volunteers (n = 6).

was 134.4 ± 16.7 ng/mL. In the case of D-SR tablets of diltiazem hydrochloride, the C_{max} was 562.4 ± 20.4 ng/mL, which was significantly ($P < .001$) different from that obtained from guar gum matrix tablets HM2 (Table 3). The mean T_{max} value after administration of D-SR tablets was 1.2 ± 0.3 hours, which was significantly different ($P < .05$) from that obtained from guar gum matrix tablets (HM2) of diltiazem hydrochloride. The absorption rate constant (k_a) of the drug from D-SR tablets was 5.6004 ± 0.8506 h^{-1}, and that obtained from the guar gum formulation was 1.5778 ± 0.2385 h^{-1}, wherein the difference in the value of absorption rate constant was statistically significant ($P < .001$). Thus, the lower C_{max}, prolonged T_{max}, and decreased k_a of diltiazem hydrochloride in human volunteers indicated that the drug release from the guar gum matrix tablets is slow thereby providing a prolonged and controlled in vivo delivery of the drug. These in vivo absorption characteristics are in confirmation with the observed in vitro drug release rate of the drug from the guar gum matrix tablets.

Table 3. Mean (± SD) Pharmacokinetic Parameters of Diltiazem Hydrochloride After Oral Administration (dose 90 mg) of D-SR Tablets or Matrix Tablets Containing 50% wt/wt of High-Viscosity Guar Gum (HM2) in Human Volunteers (n = 6)

	Volunteers Orally Administered With	
Pharmacokinetic Parameter	**D-SR (Reference Formulation)**	**HM2**
$AUC_{0-\infty}$ (ng/mL/h)	3988.0 ± 216.4	4614.6 ± 921.6
Relative Bioavailability (%)	—	116.8 ± 28.1
$t_{1/2}$ (h)	5.6 ± 0.2	25.5 ± 3.9†
k_a (h^{-1})	5.6004 ± 0.8506	1.5778 ± 0.2385†
T_{max} (h)	1.2 ± 0.3	1.8 ± 0.3*
C_{max} (ng/mL)	562.4 ± 20.4	134.4 ± 16.7†

*Significant at $P < .05$.
†Significant at $P < .001$.

The area under the plasma diltiazem hydrochloride concentration vs time curves ($AUC_{0-\infty}$) for the D-SR tablets (dose 90 mg) and guar gum matrix tablets (dose 90 mg) were 3998.0 ± 216.4 ng.h/mL and 4614.6 ± 921.6 ng.h/mL respectively (Table 3), which were not significantly different. There was no difference in the extent of absorption of diltiazem hydrochloride from guar gum matrix tablets HM2 when compared with D-SR tablets as shown by less than 20% of change in the relative bioavailability (116.8% ± 28.1%) of the drug (Table 3). This indicates that diltiazem hydrochloride contained in guar gum matrix tablets was completely absorbed.

The elimination half-lives of diltiazem hydrochloride following oral ingestion of D-SR tablets and guar gum matrix tablets were 5.6 ± 0.2 hours and 25.5 ± 3.9 hours, respectively, which were significantly different ($P < .001$). Thus, the prolonged $t_{1/2}$ is another important indication on the in vivo performance of the controlled release guar gum matrix tablets in providing a prolonged drug delivery. There was a prominent difference in the in vitro release and in vivo release of diltiazem hydrochloride from D-SR tablets. The in vitro drug release studies showed that D-SR tablets provided a controlled release of diltiazem hydrochloride, but not in the in vivo condition. It appears that D-SR tablets could not withstand the GI movements in vivo and thereby released the drug quickly within 2 hours resulting in faster absorption of the drug. This in turn might have produced high peak concentrations of the drug with a quicker T_{max}, and thereby quickly eliminated from the systemic circulation (Figure 3 and Table 3). The results of in vivo pharmacokinetic study indicate that the guar gum matrix tablets are superior to D-SR tablets in providing oral controlled release of water-soluble diltiazem hydrochloride.

The in vitro drug release studies showed that the hydrophilic guar gum matrix tablets of diltiazem hydrochloride (HM2) provided slow release of the drug. When tested in human volunteers, the slow and continuous release of the drug from the formulation might have resulted in slow and complete absorption of the drug from stomach and small intestine due to high absorption area. However, on reach-

ing the colon, the guar gum matrix tablet might have been disintegrated by colonic bacteria, thereby releasing remaining quantity of the drug, yet resulting in slow absorption of the drug due to less absorption area of the colon. This, in turn, resulted in controlled and prolonged drug concentration in the blood. Thus, the elimination $t_{1/2}$ of the drug from guar gum tablets after oral administration was prolonged (Table 3). The in vivo evaluation of guar gum matrix tablets of diltiazem hydrochloride in human volunteers showed delayed T_{max}, lower C_{max}, decreased k_a, unaltered bioavailability, and prolonged $t_{½}$ indicating a slow and prolonged release of diltiazem hydrochloride from guar gum matrix tablets. The successful outcome of the present study warrants further studies in patient volunteers to assess the ability of the guar gum matrix formulations of diltiazem hydrochloride in providing an effective and safe therapy for hypertension.

CONCLUSION

The results of in vitro drug release studies in simulated GI fluids and colonic fluids showed that matrix tablet containing 50% wt/wt of guar gum (HM2) was able to control the release of water-soluble diltiazem hydrochloride. The in vivo pharmacokinetic evaluation of HM2 tablets in human volunteers showed a slow and prolonged release of diltiazem hydrochloride indicating the potential for clinical studies.

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