Guar Gum-Based Sustained Release Diltiazem

Syed A. Altaf,[1,2] Karen Yu,[1,3] Jagdish Parasrampuria,[1,4] and David R. Friend[1,5]

Received March 6, 1998; accepted May 8, 1998

Purpose. This study was performed to examine the use of guar gum to sustain the release of diltiazem under in vitro and in vivo conditions.
Methods. Guar gum tablet formulations were prepared and evaluated under a variety of in vitro dissolution conditions. The formulations, along with Dilacor XR®, were administered to a group of eight fasted, healthy volunteers in a four period crossover study.
Results. Varying the lot of guar gum as well as using guar from different suppliers had little effect on diltiazem dissolution. Also, dissolution of diltiazem from guar gum tablets was essentially independent of stir speed under normal conditions (USP Apparatus II). The stability of guar-based formulations under stressed conditions (40°C/75% relative humidity for 3 months) was also established. All four formulations gave similar plasma concentrations over time in the healthy volunteers pharmacokinetic study.
Conclusions. Guar gum-based matrix tablets represent a simple and economical alternative to existing diltiazem sustained release dosage forms.

KEY WORDS: guar gum; sustained release; extended release; diltiazem; dissolution; pharmacokinetics.

INTRODUCTION

The advantages of administering a single dose of drug that is released over an extended period of time, instead of numerous doses, have been obvious to the pharmaceutical industry for some time. Various drug delivery techniques have been developed to sustain the release of drugs, including triple layered tablets (Geomatrix® technology) and osmotic pumps with laser drilled holes (OROS® technology). Some of these drug delivery systems are not versatile enough to accommodate a large variety of drugs. Also, these dosage forms are intricate and relatively expensive to manufacture. For instance, the Geomatrix-based dosage forms are tablets composed of multiple layers requiring special tableting equipment and multiple components.

Hydrocolloids are often used in sustained release formulations. Guar gum, a naturally occurring highly viscous, water-soluble polysaccharide, is used in the pharmaceutical industry primarily as disintegrating or binding agents in compressed tablets (1–6). Guar gum has been used in some extended release dosage forms (7–14); however, guar gum alone may not sustain drug release satisfactorily requiring the addition of other hydrocolloids like hydroxypropylmethylcellulose (HMPC) in relatively large amounts (9).

The aim of this study was to assess factors affecting drug release from guar gum-based once-daily matrix sustained release formulations. The potential advantages of guar gum as a sustained release excipient are its high viscosity, low cost, and commercial availability (15,16). Guar gum's potential in sustaining the release of water soluble drugs, such as diltiazem, is presented in this paper. The use of guar gum as a controlled release matrix for water insoluble drugs (such as ketoprofen and nifedipine) over a 24 hour period have also been studied (17). In addition, guar gum has been purified and evaluated as an improved pharmaceutical excipient for sustained release formulations in our laboratory (18,19). The ultimate goal of this work is to provide guar gum-based sustained release systems that are inexpensive, in terms of raw material and manufacturing costs, and suitably robust to accommodate a variety of drugs.

MATERIALS AND METHODS

Materials

A water soluble drug, diltiazem HCl (Reddy-Cheminor, Ridgewood, NJ) was used as a model drug. Guar gum (Supercol® G3-NF) was supplied by Aqualon (Hercules Incorporated, Wilmington, DE). Plasdone® K-25 (Povidone USP) was obtained from ISP Technologies Inc., Wayne, NJ; Hydroxypropylmethylcellulose (K100LV) were obtained from Spectrum Chemical Mfg. Co., Gardena, CA; Polyox WSR-308, Mol. weight 8,000,000, was purchased from Union Carbide Corp. Danbury, CT; Emersol 132 NF (Lily Stearic acid, powder), Lot# 3LJ04, was purchased from Henkel, Cincinnati, OH.

Methods

Guar gum particle size was determined using conventional sieve analysis. Guar powder (100 g) was passed through six or seven tared sieves (45, 75, 90, 106, 150, 180 and 250 μm) and the mass of powder remaining on each sieve was determined to yield the particle size distribution.

Guar gum purification consists of removal of insoluble materials including proteins. Briefly, guar gum is first dissolved in distilled water. The aqueous guar gum solution/suspension is then centrifuged to remove the insoluble material, generating a translucent to transparent solution. This solution is precipitated into an equal volume of 95% ethanol and the resulting wet solid is dried in a vacuum oven and ground into powder. A much more complete description of purified guar gum has been published (18).

Three oral sustained release formulations of diltiazem HCl 240 mg were developed based on the guar gum matrix. The composition of the three formulations prepared is summarized in the Table I. All ingredients except the lubricant were weighed and mixed together in a V-blender for 10 minutes. The powder mixture was dry granulated using a roller compactor (Vector TF Mini Roller Compactor). Tablets were compressed on a Manesty Beta press to an average weight of 785 mg with an average hardness of 10 kP. The tablets were then placed into size 00 capsules.

[1] CIBUS Pharmaceutical, Inc., P.O. Box 1226, Menlo Park, California 94026-1226.
[2] Present address: Gilead Sciences, Foster City, California 94404.
[3] Present address: Shaman Pharmaceuticals, Inc., South San Francisco, California 94080.
[4] Present address: Genelabs, Redwood City, California 94063.
[5] To whom correspondence should be addressed. (e-mail: drfriend1@aol.com)

0724-8741/98/0800-1196$15.00/0 © 1998 Plenum Publishing Corporation

Table I. Composition of Guar Gum-Based Tablet Formulations

Ingredients	Formulations A	B	C
Diltiazem HCl, USP	31	31	31
Purified Guar gum (Supercol® G3-NF)[a]	—	67	—
Conventional Guar gum (Supercol® G3-NF)	62	—	62
Polyethylene Oxide (Polyox, MW = 8,000,000)	—	—	5
Hydroxypropyl methylcellulose (Methocel® Premium K100LV)	5	—	—
Stearic acid, NF	2	2	2

[a] For a complete description of the purification and use of purified guar gum, see ref. 19.

Diltiazem release was determined using a USP II (Paddle) Apparatus at 50, 100, or 200 rpm in 900 mL deionized water at 37 ± 0.5°C. For pH effect experiments, dissolution was conducted at pH 1.2 for 2 h and then switched to pH 7.5 for the remaining time. Samples were collected at 0, 1, 2, 4, 7, 10, 15, and 24 hours with n ≥ 4 replicates. Samples were diluted (1:10) and assayed by UV spectrophotometer at 240 nm.

Dissolution Curve Characterization

Dissolution profiles were reduced to a meaningful set of parameters (Table II) by fitting the dissolution curves to the Weibull function (20). The two parameters used to characterize the dissolution curves were the shape parameter, b, and the scale parameter, d. The following equation was used to fit the curves:

$$F(t) = f^*(1 - \exp(-t/d)^b)$$

where, $F(t)$ *is* the percent dissolved at time t, f is the percent dissolved at infinity which was set at 100% for the calculations, d is the scale factor and b is the shape factor.

The shape parameter, b, qualitatively defines the curve, i.e., when $b = 1$ the curve becomes a simple 1st order exponential. If $b > 1$, the drug release rate is slow initially followed by an increase in release rate. The shape parameter also provides qualitative information on diffusion and disintegration processes. The effective surface area for dissolution will be maximum after a certain time in the beginning when $b > 1$, while when $b \leq 1$ no disintegration occurs at all and the rate of dissolution will decrease steadily. As can be seen from the data in Table II, all values for the shape parameter are close to 1, indicating the 1st order exponential curve for all comparisons. On the other hand, the scale parameter d gives a quantitative evaluation by differentiating the curves along the time axis. The scale parameter d was used to calculate the drug release rate constant, k ($k = 1/d$). Analysis of covariance was performed on the dissolution curves to examine if differences were significant based on a predetermined α level. The significance level, α, was set at 5%. So, the decision that the release rate constants were different was based on being ≤ 0.05 (21). Statistics were calculated using JMP® (Version 3.2.2, SAS Institute Inc., Cary, NC).

Clinical Study Design

The study was conducted with 8 healthy volunteers in an open-label, single-center four period crossover design with one week washout between periods. One capsule was dosed with 240 mL water under fasted conditions at the same time of the day for each treatment period. Samples (10 mL, venipuncture) were taken at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, 24, 28, 32, and 36 hours. Samples were analyzed using a validated HPLC procedure and the pharmacokinetic parameters C_{max}, t_{max}, $AUC_{(0-t)}$ and F_{rel} were calculated from plasma diltiazem concentrations. The clinical research followed tenets of the Declaration of Helsinki promulgated in 1964 and was approved by the institutional human experimentation committee of Corning Besselaar (now Covance). Informed consent was obtained from all volunteers.

Table II. Summary of the Comparison of Dissolution Parameters[a,b]

Variable		b (beta)	d (Td)	K = 1/Td
Vendor	Aqualon	0.82	8.61	0.12
	Meer	0.97	8.58	0.12
	TIC gums	0.92	8.60	0.12
Lot	Lot 1	0.82	8.62	0.12
	Lot 2	0.87	7.78	0.12
	Lot 3	0.85	8.62	0.12
Particle size	Less than 106 μm	0.84	6.07	0.16
	Greater than 150 μm	0.82	6.32	0.16
	Whole distribution	0.82	8.18	0.12
Hardness	6 kP	0.84	7.19	0.14
	9 kP	0.85	7.68	0.13
	12 kP	0.82	8.18	0.12
Granule size	30 to 40 mesh	0.82	8.62	0.12
	30 to 60 mesh	0.77	8.52	0.12
	30 to 100 mesh	0.70	15.77	0.06
Relative humidity				
	11%	0.68	6.01	0.17
	56%	0.77	7.87	0.13
	75%	0.77	8.25	0.12
Paddle speed	50 rpm	0.99	8.74	0.11
	100 rpm	0.99	7.40	0.14
	200 rpm	0.93	5.94	0.17
	Dilacor XR, 50 rpm	1.16	8.04	0.12
	Dilacor XR, 100 rpm	1.27	7.11	0.14
	Dilacor XR, 200 rpm	1.21	4.74	0.21
Stability	Initial	0.99	7.40	0.13
	1 month	0.97	6.55	0.15
	3 month	1.00	7.40	0.13

[a] Unless stated, all dissolution studies were performed with guar formulation A.
[b] All differences in K values within a given group (e.g., paddle speed) were statistically insignificant based on $p > 0.05$ except those of granule size where $p < 0.05$.

RESULTS AND DISCUSSION

Particle Size Characterization

Guar gum is a natural product that can potentially vary in specifications crop-to-crop and season-to-season. The effect of guar particle size distribution from three different lots of the same manufacturer on formulating once daily diltiazem dosage forms was investigated. The greatest variation in particle size occurs in the 106–150 and 150–180 μm size range where up to a 15% difference in the weight of material in this size range is observed between three different lots of guar gum obtained

from the same supplier (Aqualon) (Fig. 1A). To evaluate the effect of varying lot on dissolution, formulation A (see Table I) was manufactured from these three lots. The resulting dissolution release rate constants (Table II) were insignificantly different ($p = 0.98$) indicating that the particle size distributions examined have little effect on dissolution of diltiazem.

To assess the variability among commercial sources, three guar gum manufacturers were chosen and their guar gum used in formulation A. The particle size distribution for the TIC guar gum (see Fig. 1B) is somewhat different from Supercol G3 guar gum (Aqualon) or the Meer guar gum, in that there are slightly more fines (<90 μm) than coarse particles (>150 μm). Also, there is a higher amount of particles in the size range of 106–150 μm. The guar gum from these three different suppliers was used in formulation A and dissolution was performed. It was found that guar gum source did not affect diltiazem release based on data in Table II.

Granule Size Optimization

During scale-up it is important to have the manufacturing procedure at its most efficient. To optimize the manufacturing process, the effect of granule size on diltiazem release was studied. Granules were collected following dry granulation (roller compaction) at 30 to 40 mesh (600–425 μm), 30 to 60 mesh (600–250 μm) and 30 to 100 mesh (600–150 μm) screens. A difference in the diltiazem dissolution rate constant is observed (Table II) from tablets made from 30 to 100 mesh granules compared with those made from 30 to 40 and 30 to 60 mesh granules. Formulations prepared with the 30/60 or 30/100 mesh granules behaved similarly with respect to dissolution. The difference in dissolution rate constant was statistically significant ($p < 0.05$). The difference in drug release is possibly due to the greater percentage of fines which causes the tablet to hydrate faster leading to rapid gelling of the polymer, which in turn slows the drug release. In terms of granule yield optimization during dry granulation, the 30 to 40 mesh screen required 7 compression cycles to attain the desired quantity of granules. The 30 to 60 mesh needed 4 compression cycles and the 30 to 100 mesh used only one compression cycle to get the same amount of granules.

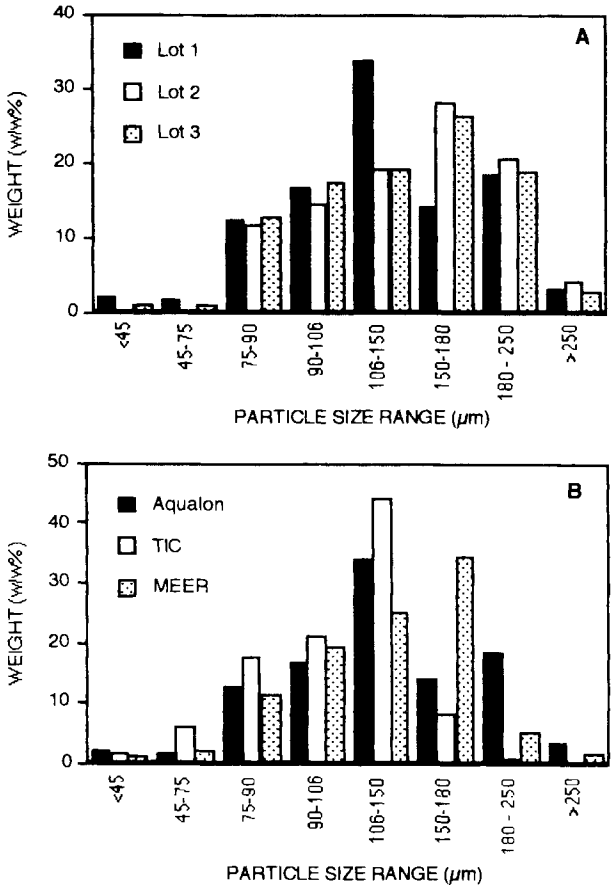

Fig. 1. Particle size distribution of 3 different lots of guar gum. Panel A: Supercol G3-NF (Aqualon); Panel B: Particle size distributions of guar gum from three different guar gum suppliers (Aqualon, Meer, and Tic Gums).

Effect of Relative Humidity and Hardness

The effect of relative humidity (RH) on granules used to prepare formulation A was investigated by equilibrating granules at relative humidity levels of 11%, 56%, and 75%. The granules were then compressed into tablets with an average hardness of 11 kP with the exception of tablets made from granules equilibrated to 11% RH, in which case the hardness of only 3.3 kP was achieved. The resulting dissolution rate constants show insignificant differences (Table II). Even though the tablets made from the 11% RH had a hardness of only 3.3 kP, the release profiles were within 10% drug release ($p = 0.862$, Table II) of the others, indicating the robustness of the guar gum matrix tablets.

The effect of fluctuations in tablet hardness on dissolution of diltiazem was also evaluated using formulation A. The tablet hardness was adjusted to 6, 9 and 12 kP. The results show that the change in hardness does not significantly affect the dissolution profiles (Table II).

Effect of Dissolution Media pH

The solubility of diltiazem HCl is known to be relatively independent of pH (22,23). To evaluate the effect of pH on guar gum-based tablets and Dilacor XR, the dissolution was conducted in simulated gastric fluid (SGF, pH 1.2), simulated intestinal fluid (SIF, pH 7.5) and SGF for 2 hours followed by a switch to SIF (pH 1.2/7.5). Dissolution in SGF was similar to the dissolution in deionized water. A difference in release was observed between the pH 1.2 and pH 7.5. The diltiazem in SIF yielded a much slower release. In case of dissolution media switch, the dissolution rate increased steadily for the first 7 hours and became constant over the remaining time. Also, differences in the rate constants can be observed from the three dissolution curves, the rate of drug release is slower at pH 7.5 compared to the release at pH 1.2 and pH 1.2/7.5. Dissolution from formulation A and Dilacor XR was similar (Fig. 2A and 2B) even though the matrix for both the formulations is different. The probable reason for the similarity in dissolution curves of both types of dosage forms is due to the changes in solubility of diltiazem HCl. As the pH is increased from acidic to alkaline, the solubility of the drug decreases (23).

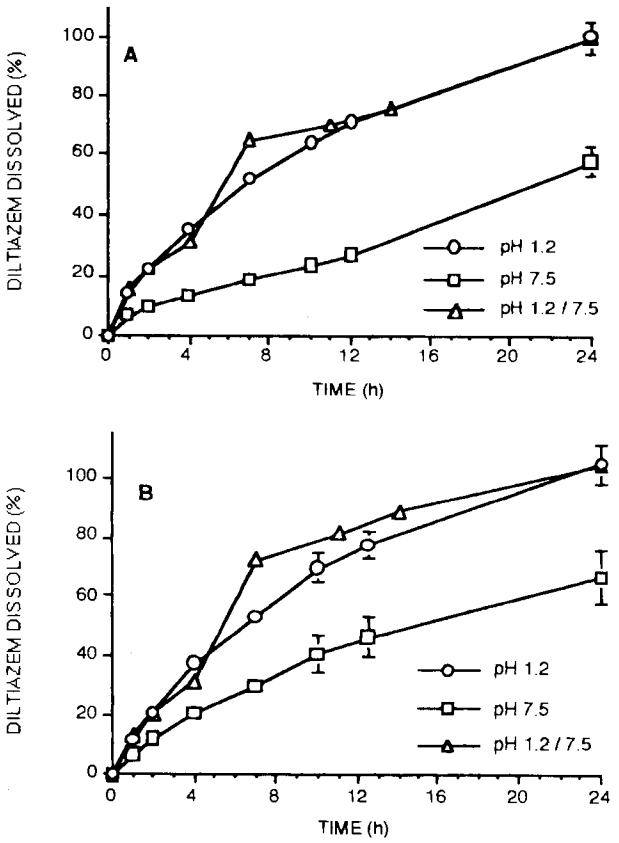

Fig. 2. Effect of pH on diltiazem dissolution from formulation A (panel A) and Dilacor XR (panel B). Error bars are SD (n = 4–6).

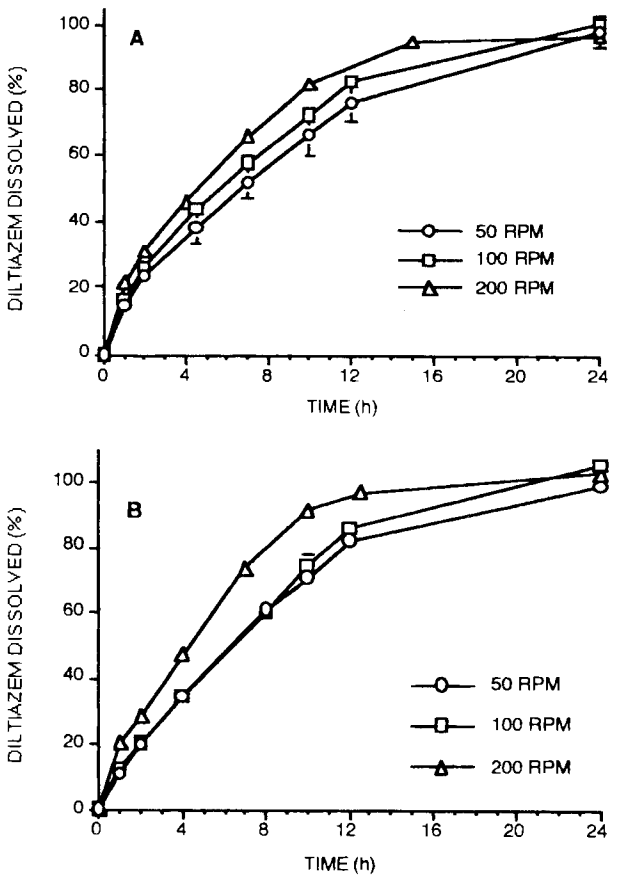

Fig. 3. Effect of paddle speed (50, 100, and 20 rpm) on diltiazem dissolution in distilled water from formulation A (panel A) and Dilacor XR (panel B). Error bars are SD (n = 4–6).

Stir Speed Effect on Dissolution

Paddle speeds of 50, 100, and 200 rpm (USP Apparatus II) were evaluated for their effect on diltiazem dissolution from formulation A and Dilacor XR (Fig. 3). An insignificant difference in diltiazem release was observed at 50 and 100 rpm paddle speeds. At 200 rpm paddle speed, dissolution exhibits some differences at the later time-points. Although both formulations showed a qualitative increase in dissolution rate at 200 rpm, these differences were statistically insignificant.

Stability of Diltiazem Formulations

The guar gum formulations were stored at 40°C/75% RH for 1 and 3 months to evaluate the effect of accelerated conditions on diltiazem dissolution. Dissolution profiles from formulation A immediately after manufacture and at 1 and 3 month storage under accelerated conditions were nearly identical (data not shown). The dissolution rate constants of the initial, one and three month dissolution data from formulation A are given in Table II. The results show that the dissolution profiles over the three months do not change significantly ($p = 0.979$). Assay values were within ±2% of initial values after 1 and 3 months storage (accelerated).

Dissolution and Human Pharmacokinetics

In vitro dissolution profiles of diltiazem at 100 rpm in distilled water from formulations A, B, C and Dilacor XR are shown in Fig. 4. These data indicate that dissolution of diltiazem from the guar gum-based formulations is similar to Dilacor XR. Since the three guar formulations diltiazem formulations differ only slightly in composition, these dissolution profiles are expected.

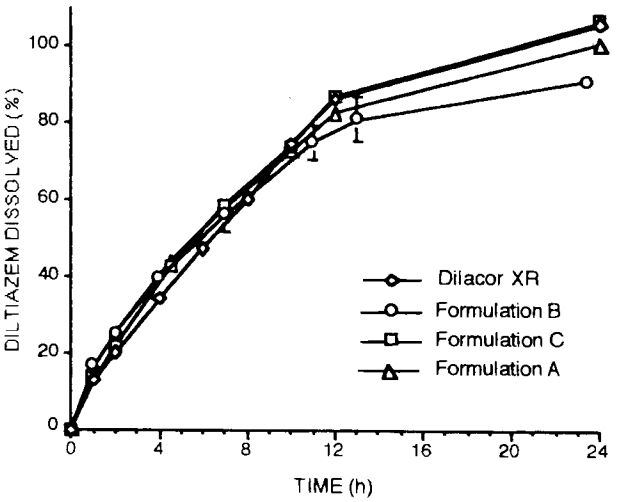

Fig. 4. Dissolution of diltiazem at 100 rpm (USP Apparatus II) in distilled water from guar gum formulations A-C and Dilacor XR. Error bars are SD (n = 4–6).

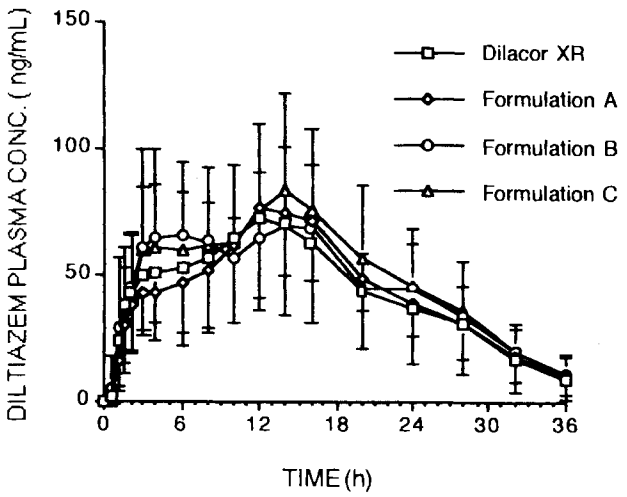

Fig. 5. Plasma concentrations of diltiazem from guar gum formulations and Dilacor XR (all 240 mg diltiazem HCl) in 8 healthy volunteers under fasted conditions in a four period, cross-over design. Error bars are SD (+ for formulations B and C, − for formulation A and Dilacor XR).

All three guar gum-based formulations sustained the release of diltiazem in vivo over 24 hours in a manner similar to Dilacor XR. Plasma diltiazem concentration plots (Fig. 5) indicated that the absorption of diltiazem from all four formulations was fairly constant over a period of 16–24 hours postdose. Of the three guar formulations, Formulation A produced plasma concentrations most similar to those of Dilacor XR. At the same time, formulation B, prepared from purified guar, demonstrated reduced variability in C_{max} (%CV = 27) when compared with the other guar gum formulations (%CV = 36 and 50 for formulation A and C, respectively) and Dilacor XR (%CV = 45). Table III summarizes the pharmacokinetic parameters for the clinical formulations.

CONCLUSIONS

These studies were performed to examine the ability of guar gum to be used in sustained release matrix formulations. The effect of different lots of guar gum and of different manufacturers on diltiazem dissolution was insignificant. Also, dissolution of diltiazem from guar gum formulations was nearly independent of stir speed under normal dissolution conditions.

Table III. Diltiazem Pharmacokinetic Parameters (Geometric Means) and 95% Confidence Intervals

Formulation	$AUC_{(0-36)}$ (ng · hr/mL)	C_{max} (ng/mL)	t_{max} (h)
Dilacor XR	1340	69.5	11
	803 to 2235	44.3 to 109.0	4 to 16
Formulation A	1484	79.0	12
	1116 to 1974	57.5 to 108.6	6 to 14
Formulation B	1588	83.6	9
	1204 to 2094	66.1 to 105.6	4 to 16
Formulation C	1599	81.1	14
	1030 to 2481	50.0 to 131.6	3 to 16

The stability of guar-based formulations under stressed conditions was also established. All three guar gum formulations provided prolonged diltiazem release similar to Dilacor XR under both in vitro and in vivo conditions. Based on the results from this study it is concluded that the guar gum-based tablets offer a simple and effective method to formulate diltiazem in a sustained release dosage form.

ACKNOWLEDGMENTS

The GMP manufacturing and stability of the clinical trial batches were conducted for CIBUS Pharmaceutical Inc. by Penn Pharmaceuticals Ltd., Gwent, UK. HPLC analysis of stability samples were performed by Susan Larrabee at CIBUS Pharmaceutical. Guar gum characterization and purification was performed by Dr. Mark Gebert. Acknowledgments are extended to Dr. Walter Doll and Philip Fowler at University of Kentucky for their assistance with the dissolution studies. The clinical study was performed by Corning Besselaar Clinical Research Unit, Madison, WI. The plasma samples were analyzed by Hazelton Wisconsin, Madison, WI.

REFERENCES

1. A. M. Sakr and H. M. Elsabbagh. Correlation of water absorption with the disintegration effectiveness of guar gum. *Pharm. Ind.* **37**:457–459 (1975).
2. E. M. Rudnic, C. T. Rhodes, J. F. Bavitz, and J. B. Schwartz. Some effects of relatively low levels of eight tablet disintegrants on a direct compression system. *Drug Dev. Ind. Pharm.* **7**:347–358 (1981).
3. M. Z. Iqbal, M. Amin, and N. A. Muzaffar. Comparative evaluation of guar gum as disintegrating agent. *J. Pharmacy* **1**:17–34 (1979).
4. L. E. Eatherton, P. E. Platz, and F. P. Cosgrove. *Drug Standards* **23**:42–47 (1955).
5. W. Feinstein and A. J. Bartilucci. Comparative study of selected disintegrating agents. *J. Pharm. Sci.* **55**:332–334 (1966).
6. H. M. Elsabbagh, A. M. Sakr, and S. E. Abd-Elhadi. Effect of guar gum on the dissolution rate of ephedrine hydrochloride and sulphadimidine tablets. *Pharmazie* **33**:730–731 (1978).
7. P. J. Waaler, M. Anderson, C. Graffner, and B. W. Muller. Optimization of a matrix tablet formulation using a mixture design. *Acta Pharm. Nord.* **4**:167–170 (1992).
8. H. E. Huber and G. L. Christenson. Utilization of hydrophilic gums for the control of drug substance release from tablet formulations II. Influence of tablet hardness and density on dissolution behavior. *J. Pharm. Sci.* **57**:164–166 (1968).
9. H. L. Bhalla and Y. D. Sanzgiri. An improved controlled release tablet of salbutamol sulphate. *Indian J. Pharm. Sci.* **49**:22–25 (1987).
10. S. K. Baveja, K. V. Ranga Rao, and J. Arora. Chemical investigations of some galactomannan gums as matrix tablets for sustained drug delivery. *Ind. J. Pharm. Sci.* **30B**:133–137 (1991).
11. H. L. Bhalla and S. O. Gulati. Sustained release theophylline tablets. *Indian Drugs* **24**:338–342 (1987).
12. P. J. Waaler, C. Graffner, and B. W. Muller. Optimization of a matrix tablet formulation using a mixture design. *Acta Pharm. Nord.* **4**:9–16 (1992).
13. P. J. Waaler, K. Arnesen, C. Graffner, and B. W. Muller. Optimization of the amount of xanthan gum and guar gum in a matrix tablet formulation using a central composite design. *Acta Pharm. Nord.* **4**:291–296 (1992).
14. P. J. Waaler, C. Graffner, and B. W. Muller. Biopharmaceutical studies of naftidrofuryl in hydrocolloid matrix tablets. *Int. J. Pharm.* **87**:229–237 (1992).
15. K. Yu, D. Wong, J. Parasrampuria, and D. R. Friend. Guar Gum, In: Analytical Profiles of Drug Substances and Excipients, Vol. 24, H. G. Brittain, Ed., Academic Press, Orlando, Florida, pp. 397–442 (1996).

16. A. M. Goldstein, E. Alter, and J. K. Seaman. Guar gum In: Industrial gums, polysaccharides and their derivatives, 2nd ed. New York, NY: Academic Press.: pp. 303–321, (1973).
17. D. R. Friend, S. A. Altaf, K. L. Yu, and M. S. Gebert. Development of a zero-order nifedipine dosage form using COSRx technology. *Proc. Int. Sym. Control. Rel. Bioact. Mat.* **24**:311–312 (1997).
18. M. S. Gebert and D. R. Friend. Purified guar galactomannan as an improved pharmaceutical excipient. *Pharm. Develop. Tech.* (1998) in press.
19. M. S. Gebert, J. Parasrampuria, and D. R. Friend. Purified galactomannan as an improved pharmaceutical excipient. *Pharm. Res.* **13**:S180 (1996).
20. F. Langenbucher. Parametric representation of dissolution-rate curves by the RRBSW distribution. *Pharm. Ind.* **38**:472–477 (1976).
21. S. Bolton. Statistical Inference: Estimation and Hypothesis Testing, Pharmaceutical Biostatistics, Marcel Dekker, USA, pp. 105–161 (1984).
22. R. Bodmeier, X. Guo, R. E. Sarabia, and P. F. Skultety. The Influence of Buffer Species and Strength on Diltiazem HCl Release from Beads Coated with the Aqueous Cationic Polymer Dispersions, Eudragit RS, RL 30D. *Pharm. Res.* **13**:52–56 (1996).
23. G. A. McClelland, S. Sutton, K. Engle, and G. M. Zentner. The solubility-modulated osmotic pump: in vitro/in vivo release. *Pharm. Res.* **8**:88–92 (1991).