A New Ternary Polymeric Matrix System for Controlled Drug Delivery of Highly Soluble Drugs: I. Diltiazem Hydrochloride

Hyunjo Kim¹ and Reza Fassihii,²

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Purpose. The purpose of this study was to develop a new ternary polymeric matrix system that is easy to manufacture and that delivers a highly soluble drug over long periods of time.

Methods. Pectin, hydroxypropylmethylcellulose (HPMC), and diltiazem HCl granulated with gelatin at optimized ratios were blended at different loading doses and directly compressed. Swelling behavior, dissolution profiles, and the effect of hydrodynamic stress on release kinetics were evaluated.

Results. Diltiazem release kinetics from the ternary polymeric system was dependent on the different swelling behavior of the polymers and varied with the drug loading dose and hydrodynamic conditions. Drug release followed either non-Fickian or Case II transport kinetics. The relative influence of diffusion and relaxation/dissolution effects on release profiles for different drug loadings was calculated by a non-linear regression approach. Photographs taken during swelling showed that the anisotropic nature of the gel structure, drug loading dose, swelling capacity of polymers used, and the design of delivery system all play important roles in controlling the drug release and dissolution/erosion processes.

Conclusions. Zero-order delivery of diltiazem HCl from a simple tablet matrix was achieved. The ternary polymeric system developed in this study is suitable for controlled release of highly soluble drugs. It offers a number of advantages over existing systems, including ease of manufacturing and of release modulation, as well as reproducibility of release profiles under well defined hydrodynamic conditions. Our delivery system has the potential to fully release its drug content in a controlled manner over a long time period and to dissolve completely.

KEY WORDS: ternary polymeric system; highly soluble drugs; controlled drug delivery; pectin; HPMC; gelatin system; simple hydrophilic matrix; diltiazem hydrochloride.

INTRODUCTION

The use of single or multiple unit dosage forms as controlled drug delivery devices encompasses a wide range of technologies (1–5) and polymeric as well as nonpolymeric excipients. Controlled release delivery systems provide greater safety and efficacy for drugs in therapeutics than conventional dosage forms. Their purpose is to optimize the drug input rate into the systemic circulation in order to achieve a desirable and predictable pharmacodynamic response and pharmacokinetics as well as to improve patient compliance, minimize side effects, and maximize drug product efficacy. The use of controlled release products for chronic administration frequently is indicated. For example, calcium-channel blockers with a well established safety profile and therapeutic effectiveness, such as nifedipine, diltiazem, and verapamil, (6–8) are extensively used in the management of angina and hypertension. Their worldwide sale exceeds 8 billion dollars (9). For delivery system design, physicochemical properties and intrinsic characteristics of the drug (e.g., high or low solubility, limited absorption, presystemic metabolism) may impose specific constraints during product development. To overcome such constraints and limitations, delivery system designs are diverse and often produce one of the following delivery-rate kinetics: first order (10), square or cubic root of time law (11,12), zero order (4,5), and non-Fickian diffusion including Case II transport (13–15).

Diltiazem is a benzothiazepine derivative with active metabolites. Its oral absorption is greater than 90%, its bioavailability ranges from 30 to 60% due to extensive variable first-pass metabolism, and its elimination half-life is 3–6 h. The protein binding is greater than 90% and it has a high clearance from plasma. The water solubility of diltiazem exceeds 50%. Daily doses of 120 to 360 mg are usually used for angina and hypertension. The drug was approved by the FDA in 1988, and is currently available as once-a-day dosage forms, such as Cardizem® CD and Dilacor XR®. Cardizem CD consists of diltiazem drug particles coated with thin and thick polymeric membranes which become semipermeable upon exposure to aqueous fluid and provide extended drug release for 24 hours. Dilacor XR® consists of 3 or 4 tablets in a capsule. Each tablet consists of three layers. The faster hydrating core layer contains 60 mg of the active drug. Two external layers sandwiched around the core limit drug release from the lateral side of a cylindrical shaped tablet. The tablet matrix is hydrophilic. Upon swelling, it results in continuous drug diffusion over a 24-hour period through the side wall of a constrained tortuous swollen structure. Both products deliver diltiazem for 24 hours and are effective in controlling mild-to-moderate hypertension, with low incidence of adverse effects and improved patient compliance.

The production of both formulations is complicated and cumbersome. Therefore a once-a-day, extended-release diltiazem tablet which consists of a simple matrix and which can be manufactured with high-speed tableting machines will represent significant advance. Such a tablet could also be used to deliver other highly soluble drugs.

In the past, many controlled-release systems for low or sparingly soluble drugs have been developed, but considerable difficulties have been experienced in the formulation of highly ionized and soluble drugs, especially at relatively high doses (e.g., >100 mg) (16,17). We recently reported the application of binary, hydrophilic polymeric matrix system for modulating the drug release rate. The tablet matrices were produced by direct compression, using various ratios of pectin:hydroxypropylmethylcellulose (HPMC) and sparingly soluble drugs (14,15). Both non-Fickian and Case II transport kinetics were easily achieved for periods of up to 24 hours by different combination of these two polymers.

The objectives of the present work were to develop a new simple matrix tablet based on pectin:HPMC:gelatin for the constant delivery of a highly soluble drug (e.g., diltiazem), and to evaluate the effect of the formulation variables and hydrodynamic stress on the drug release. The dissolution pro-
files of our formulations were compared with that of a commercially available product (Dilacor XR™).

EXPERIMENTAL

Materials

Diltiazem hydrochloride was obtained from Sigma Chemicals (St. Louis, MO 63178). Granular gelatin type A and magnesium stearate both USP grades were obtained from AMEND Drug and Chemical Co. (Irvington, NJ). Pectin type 621 [designated as high methoxylated pectin citrus with a degree of methoxylation of 65–72%] obtained from Pectagel Co. (Great Neck, NY). Hydroxypropylmethylcellulose (HPMC) 2208 was supplied by Dow Chemicals as METHOCEL, K4M having nominal viscosity of 4,000 cps in water at 2% w/v level. All other chemicals were of reagent grade.

Methods

Granulation

The required quantities of diltiazem hydrochloride and gelatin (1:1 ratio) were sieved through a 40 mesh screen and blended in a cube mixer for 10 minutes. The powder blend was transferred into a mortar and ethanol was gradually added as a granulating agent with continuous mixing. The wet homogeneous mass was dried overnight in an air convection type oven at 30°C. The dried mass was sieved through a #20 mesh U.S.-standard sieve and stored in an air tight container for further use.

Tablet Preparations

Tables containing the equivalent of 5, 10, and 20% w/w diltiazem powder and granules (using diltiazem hydrochloride:gelatin mixture) were blended together with a pectin:HPMC (1:2) mixture and directly compressed with a Carver press (Model C, FRED S. Carver Inc. 1569 Morris St, Wabash, IN 46992), using a 11 mm flat-faced punch and die. The pectin:HPMC (1:2) ratio was chosen as the optimum blend for its desirable swelling and erosion characteristics (14,15). Powder mixtures were blended in a cube mixer for 10 minutes. 1% w/w magnesium stearate was added to all formulations and mixed for an additional 5 minutes prior to compression. Tablets were compressed at 2,000 lbs unless otherwise stated, to give tablet hardness values of 10 Kp as determined by laboratory hardness tester (Erweka hardness tester, Model 2E, Schleuniger, CH-8033, Zurich). Each tablet weighed 500 mg. Tablets containing various drug loadings were prepared in a similar manner.

Dissolution Studies

Representative samples from each tablet batch were subjected to dissolution study in 900 ml deionized water at 37°C, using a USP 23 dissolution apparatus II (paddle method) at 50 rpm. The system was automated using an HP diode array UV spectrophotometer (Model 8452A) with continuous sampling, using a peristaltic pump (HP Flow control, 89092A) and McKinet software (HP 89532K Multicell Kinetics Software) for data analysis. Measurements were done at the wavelength of 238 nm. No interference due to the dissolved pectin, HPMC or gelatin was evident. Each experimental run on three tablet was done at least in duplicate. In addition, HPLC analysis of diltiazem samples according to the method described in USP 23 confirmed that no degradation products were formed during the entire dissolution period.

Matrix Erosion/Weight-Loss

In order to establish a correlation between drug fraction released and matrix erosion, individual tablets were removed during the dissolution studies at selected time intervals and carefully dried at 60°C under vacuum to a constant weight. The amount of drug released and the total matrix weight loss were calculated for each interval.

Tablet Hydration (Dimensional Changes)

Triplicate determinations of tablet hydration for the ternary polymeric combinations were performed by placing individual tablets on a perforated stainless steel platform in deionized 37°C water in transparent glass dishes. Axial and radial thickness and aspect ratios (diameter divided by the thickness) as well as changes in the volume \( V = \pi R^2 t \) of the tablets were measured over a 20-hour period. Normalized swelling thicknesses (swollen thickness divided by the original thickness) were measured, and photographs of tablet swelling at different time points were taken using an Olympus microscope (SZH 10, Japan) connected to a Kodak 8650 PC color printer.

RESULTS AND DISCUSSION

Once the basic pharmacodynamics and pharmacokinetics of a drug are characterized and understood, the goal of the controlled-release delivery systems is to provide desirable delivery patterns so that predictable plasma drug levels can be achieved. Among the physiological variables in the GI tract which may affect drug absorption are pH, gastrointestinal motility, luminal and brush border enzymes, antitranporter, the existence of enzyme gradients along the intestine, and variation in the absorbing capacity of the GI epithelia. In addition, the transit time of the delivery system and the presence of food, liquids, and complexing agents are likely to influence the absorption process. When designing a new delivery system, in addition to the above biopharmaceutical considerations and a recognition of the biochemical basis of membrane transport, the manufacturing difficulties and formulation factors need to be taken into consideration as well.

Some aspects of a new extended-release dosage form for highly soluble drugs developed in our laboratory will be presented. All dissolution studies were performed in deionized water (pH 7.0 ± 0.4 throughout the dissolution study) because we have shown (14,15) that matrix swelling was not influenced by variations in ionic strength and pH. This was attributed to the fact that the pectin (an anionic material) was highly methoxylated (degree of methoxylation > 70%) and to the nonionic nature of HPMC. The latter polymer constituted more than 70% of the matrix composition. Type A gelatin within the pectin:HPMC matrix used in this study remained insensitive to variations in pH. In addition, diltiazem hydrochloride is freely soluble in water, and its release from this experimental formulation was not affected by the pH variation in the dissolution medium.