Utility of Gastric-Retained Alginate Gels to Modulate Pharmacokinetic Profiles in Rats

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ABSTRACT: A gastric-retentive formulation amenable to dosing in rodents has the potential to enable sustained release in a preclinical setting. This may be useful to provide systemic exposure over a longer duration or to increase duration of exposure for compounds with targets localized in the gastrointestinal tract. Previous work has shown that a mixture of 1% sodium alginate and 0.625% karaya gum in the presence of a calcium chelator can form gels *in situ* that are gastric retained in rats. The aim of this work was to define the physicochemical boundaries of compounds within this technology and their relation to *in vivo* release using a series of model compounds with high permeability but varying solubility. *In vitro* data demonstrated a good correlation between solubility and initial release rates from the gels. *In vivo* studies were conducted in Sprague–Dawley rats to compare the exposure profile of compounds dosed in gel relative to a standard formulation. *In vivo* data were consistent with trends from the *in vitro* studies. These data suggest that, in conjunction with an understanding of compound solubility, sodium alginate/karaya gum gels may be a useful tool to modulate exposure profiles in rodent models in a preclinical setting. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:2440–2449, 2013

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INTRODUCTION

Pharmaceutical discovery teams often utilize tool compounds with nonoptimized pharmacokinetic (PK) properties to test the hypotheses related to the target of interest early in the discovery process. In ideal situations, researchers would be able to achieve adequate exposure in animal models to effectively evaluate the target. In some instances, infusion pumps are implanted subcutaneously to provide a constant infusion of compound supply to systemic targets in an effort to maintain adequate coverage during the study. This often requires high compound solubility in an acceptable vehicle that is also compatible with the pumps. Given that the overall trend in the industry is toward less soluble compounds, this can be very challenging. In addition, pumps need to be surgically implanted in the animal, which may have an impact on the study design and results.

Oral dosing is typically the preferred route for small molecules in the discovery setting provided that adequate exposure to a given target is achieved. A gastric-retentive formulation strategy that can be dosed to small rodents may be beneficial to provide systemic exposure over longer periods or to prolong the duration of exposure for compounds with targets localized in the gastrointestinal (GI) tract. Such a strategy may, for example, enable the reduction of oral dosing frequency in chronic studies by maintaining a desired trough concentration (C_{trough}) over a given time frame (e.g., 24 h). Furthermore, this strategy may be especially useful in avoiding potential adverse effects associated with a high maximum plasma concentrations ($C_{\max}$) as delayed compound release will temper the maximum exposure in the concentration versus time profile.

Many publications exploring the concept of gastric retention involve designing a solid dosage form for application to a commercial formulation.[1–13] The intent of this work was to apply gastric retention technology in the early discovery space to achieve extended coverage in small rodents used in the discovery

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testing funnel. Although other researchers have published on *in situ* gel approaches to test the delivery of theophylline,[14] paracetamol,[15] and ampicillin in rats,[16] to our knowledge, no one has examined the delivery of compounds with varying solubility from a gastric-retentive formulation in the same study. The present authors have previously published on the use of an alginate/karaya gum formulation capable of forming gels *in situ* when combined with a calcium source to demonstrate gastric retention of barium sulfate in Sprague–Dawley rats.[17] The purpose of this work was to define the physicochemical boundaries of compounds formulated within the alginate/karaya gum matrix to modulate *in vivo* exposure profiles compared with a standard suspension or solution dose. To this end, model compounds possessing high permeability but varying aqueous solubility were evaluated in the alginate/karaya gum *in situ* gel system. This work utilized metoprolol (high solubility), ibuprofen (medium solubility), and celecoxib (low solubility) as model compounds.

METHODS

Materials

Sodium alginate was purchased from Spectrum Chemical (New Brunswick, New Jersey). Karaya gum, calcium chloride, ibuprofen, metoprolol tartrate, and docusate sodium were purchased from Sigma–Aldrich (St. Louis, Missouri). Methylcellulose E4M was obtained from Colorcon (West Point, Pennsylvania). Celecoxib was purchased from Toronto Research (North York, Ontario, Canada). Ibuprofen, metoprolol tartrate, and celecoxib were >98% pure and used upon receipt.

Model Compound Selection

Model compounds were selected to evaluate modulation of PK profiles using gastric-retained alginate gels based on solubility and minimize the impact of parameters outside of solubility (permeability/toxicology, etc.) on the PK profiles. Therefore, the following criteria were established: the compounds should be commercially available; chemically stable in an acidic environment; highly permeable; and cover a wide range of aqueous solubility. In addition, each compound had to possess a short half-life (<3 h) in male Sprague—Dawley rats to ensure that the *in vivo* exposure profile was sensitive to the manipulation of drug absorption in the GI tract. The compounds were also required to be well tolerated based on literature data at doses of 20–25 mg/kg in rats.

Drug Solubility and Stability in 0.01 N HCl

The solubility of each compound was measured by adding excess powder to vials containing 0.01 N HCl and rocking overnight at 37°C. The following day, the supernatant concentration was measured by HPLC. Chromatograms were also evaluated to ensure chemical stability in 0.01 N HCl.

In Vitro Dissolution and Diffusion Study Using a Flow-Through Apparatus

A flow-through cell for *in vitro* diffusion and dissolution testing was assembled from various components. The top of a 10 mL syringe (Becton Dickinson, Franklin Lakes, New Jersey) was cut off, and the remaining barrel fitted snugly inside of a 10 mL polypropylene column (Thermo Scientific, Rockford, Illinois) with an inside diameter of 16 mm. Tubing was fitted to each end of the cell. A porous polyethylene disc (16 mm diameter, 3 mm thick, 30 μm pore size) was inserted on each side of the cross-linked gel to be tested. The volume inside the gel compartment was 6 mL.

Celecoxib and ibuprofen were milled to ensure that undissolved drug in the gel and control formulations were similar in particle size (<5 μm as measured by microscopy) for *in vitro* release testing. Gels were made by homogenously suspending the compound at 2 mg/mL in a solution of 1% sodium alginate/0.625% karaya gum, and then mixing with a 0.1 M calcium chloride solution. A portion of the suspension (1 mL) was cross-linked with 3 mL of the 0.1 M calcium chloride to form the gel. The solidified gel was transferred into the flow-through cell between the porous polyethylene discs. In a separate study, the drug release from a standard formulation (without gel) was measured for each compound so that the effect of the gel on release rate could be determined.

Simulated gastric fluid was used for dissolution tests and was 0.01 N HCl, pH 2.0. The simulated gastric fluid was pumped through the cell at a flow rate of 0.2 mL/min at room temperature using a peristaltic pump (variable speed pump ultra-low flow; VWR, Atlanta, Georgia). After exiting the flow-through cell, the fluid was collected and assayed at various time points by HPLC analysis for drug concentration.

Drug Encapsulation Efficiency

Immediately after gel formation for *in vitro* studies, the calcium chloride solution was removed and assayed for drug concentration to determine the encapsulation efficiency of drug in the gel. The encapsulation efficiency was calculated by the equation shown below.

$$\text{Encapsulation efficiency} = (\text{mass}_{\text{total}} - \text{mass in CaCl}_2)/\text{mass}_{\text{total}} * 100\%$$

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