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# The use of citric acid to prolong the in vivo gastro-retention of a floating dosage form in the fasted state

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**Abstract**

Gastro-retentive dosage forms have the potential to improve local therapy and decrease the variation in bioavailability that is observed with a number of commercially available immediate and modified release preparations. In this study, a dosage form has been developed, utilising freeze-dried calcium alginate beads, designed to float on the surface of the stomach contents thus prolonging the retention time.

The aim of the study was to also assess the in vivo behaviour of the radio-labelled calcium alginate beads when they were administered under fasting conditions with either water or an aqueous solution of citric acid, a potential gut transit delaying substance. The study was performed in healthy male volunteers who swallowed the radio-labelled calcium alginate beads after a 10 h overnight fast. Gamma scintigraphy was selected as the method to monitor the movement of the calcium alginate beads. The volunteers consumed no further food or drink until gastric emptying of the calcium alginate beads was complete.

The results indicated that prolonged gastric retention was achieved when the dosage form was administered with the citric acid solution when compared to retention in the absence of citric acid. Citric acid, therefore, has the potential to delay the gastric emptying of the calcium alginate beads when administered to fasted volunteers.


*Keywords:* Alginate; Beads; Gastric retention; Scintigraphy; Citric acid; Floating dosage forms

## 1. Introduction

Oral dosage forms account for the largest proportion of administered pharmaceuticals. The administration of therapeutic agents in conventional immediate release and some modified release preparations results in a high variation in bioavailability due to inter-patient variables such as posture (Bennett et al., 1984), age, gender and disease state (Mojaverian et al., 1988). The largest contributor to the efficiency of drug absorption of substances from the small intestinal region of the gastrointestinal tract is whether the stomach is in the fed or fasted state. In the fed state, gastric emptying can extend to a period of hours (Whitehead et al., 1998), whereas in the fasted state gastric emptying may be complete in minutes (Washington et al., 2001). Dosage forms that can be retained in the stomach are, therefore, advantageous because drug delivery can be controlled and the ideal of the drug in the right place at the right time can be realised.

Many physiological or technological approaches have been made to develop dosage forms that can be retained in the stomach. These approaches include large, single dose units designed to be physically retained in the stomach and/or the use of bioadhesive systems that use polymers that enable adherence of the dosage form to the gastric mucosa (Lehr et al., 1992). Products designed to float on stomach contents include hydrodynamically balanced systems and gas generating systems (Hwang et al., 1998). An alternative approach showing particular promise is that of multi-particulate calcium alginate beads (Whitehead et al., 1998).

Alternatively, chemical methods have been suggested to delay gastric emptying with the use of fatty acid meals. Fatty acids and lipids are macronutrients that are insoluble in water

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(Peckenpaugh and Poleman, 1999) and digested mainly in the small intestine. They are emulsified by bile and bile salts (Peckenpaugh and Poleman, 1999) released into the liver by the gall bladder. Lipids, therefore, require longer periods of time (approximately 4 h), to be digested (Barasi, 1997), than other nutrients such as carbohydrates (1 h) and proteins (2 h) (Barasi, 1997).

Lipids are used clinically to detect *Helicobacter pylori*, the causative organism of chronic gastritis, which produces excess quantities of urease that in turn breaks down urea to carbon dioxide and ammonia. When radio-labelled urea is administered to a patient, the level of urease activity can be determined by detecting the amount of carbon dioxide exhaled. Test meals such as the fatty acid meals are given with the radio-labelled urea as they make for increased contact time with the bacterial urease (Graham et al., 1999). However, the disadvantage of fatty acid meals is that they are not palatable and are generally not welcomed by the patient.

A recent study proposed that citric acid solutions might be used as a viable alternative to fatty acid meals. For example, citric acid solutions have been used as test meals to diagnose for *H. pylori* (Dominguez-Munoz et al., 1997) and results using such solutions have compared well with those reported after using fatty acid meals (Graham et al., 1999). Citric acid is a naturally occurring product found in many fruit species including lemons, where the concentrations are in the region of 5–8% (w/w). Pharmaceutically, citric acid is used as a flavour enhancing agent in liquid preparations and with sodium bicarbonate in the preparation of effervescent granules and tablets.

The mechanism by which citric acid delays gastric emptying has been open to discussion. According to studies by Hunt and Knox (1962), the retardation of gastric emptying is achieved if sufficient oral intake of citric acid occurs to cause pH of the duodenal contents to fall below pH 6. It was proposed that a local negative feedback mechanism stimulates the release of bicarbonate and secretin in response to high levels of citric acid that neutralises the acidic environment and allows gastric emptying to re-commence (Hunt and Knox, 1962). The time for neutralisation of excess acid is responsible for the retardation of gastric emptying. In other studies Hunt and Knox also suggested that parameters such as acid volumes, molecular weights of acids (Hunt and Knox, 1969) and concentrations of acid salts (Hunt and Knox, 1973) may affect gastric emptying. These findings were substantiated by Leodolter et al. who also achieved delayed gastric times when using 0.1 M citric acid, resulting in a pH of the citric acid solution of 3.0–3.5 (Leodolter et al., 1999).

In this work, floating calcium alginate beads were made based on previous methods (Whitehead, 1998) and tested in an in vivo gamma scintigraphy study. The aim of the study was to assess the gastro-retention of placebo calcium alginate beads when they were administered under fasting conditions with aqueous vehicles. The first arm of the study investigated the behaviour of the calcium alginate beads when they were administered with 100 ml of water. In the second arm of the study the calcium alginate beads were administered with 100 ml of citric acid 1% (w/v) solution in order to determine whether citric acid influenced gastric emptying.

## 2. Materials and methods

Sodium alginate (ISP Alginates, Surrey, England), anhydrous citric acid (Thornton and Ross, Huddersfield, England), calcium chloride (BDH Chemicals, Poole, England) and stannous chloride (BDH Chemicals, Poole, England) were used as-received. Technetium-99m ($^{99m}TcO_4$), as pertechnetate in sodium chloride 0.9%, was obtained from The Manchester Royal Infirmary, Department of Nuclear Medicine (Manchester, England).

### 2.1. Choice of radio-label

Technitium-99m ($^{99m}TcO_4^-$) is the radioisotope of choice for nuclear medicine imaging studies. It has a short half-life of 6.03 h and is easy and inexpensive to produce. $^{99m}Tc$ is eluted as pertechnetate ($^{99m}TcO_4^-$), with sodium chloride 0.9% from a molybdenum-99 generator.

### 2.2. Preparation of the radio-labelled dosage form

Floating radio-labelled calcium alginate beads were prepared as follows. An amount of sodium alginate (sufficient to make a 2%, w/v, final solution), was weighed and incorporated into approximately three-quarters of the final volume of glass distilled water. The sodium alginate solution was left overnight to de-aerate. On the day of bead preparation, 1.25 ml of stannous chloride (0.1%, w/v), was removed from a stock solution and placed in a glass vial. The $^{99m}TcO_4$ eluate was added to the stannous chloride, the vial stoppered and the solution shaken to ensure sufficient mixing. The stannous chloride/$^{99m}TcO_4$ mix was added to the sodium alginate solution and stirred. The sodium alginate/stannous chloride/$^{99m}TcO_4$ solution was then weighed and made up to volume to give a final concentration of 2% (w/v) sodium alginate. The resulting solution was passed through a 21 G needle from a height of 21 cm at a rate of 0.54 ml $min^{-1}$ into a stirred solution of 0.02 M calcium chloride. Following curing for 30 min, the radio-labelled calcium alginate beads were removed using an Endecotts sieve of mesh size 10 from the calcium chloride solution and ‘snap frozen’ with liquid nitrogen. The calcium alginate beads were then freeze-dried overnight using an Edwards Modulyo 4 freeze-dryer (West Sussex, England), that maintained a temperature of −40 °C and a pressure of 80 $Nm^{-2}$.

### 2.3. Assessment of the efficiency of the radio-labelling process of the calcium alginate beads

The efficiency of the radio-labelling process of the calcium alginate beads was assessed on the day following completion of the freeze-drying process. A Packard Cobra II Auto Gamma Counter (Meriden, USA), was used to obtain the counts per minute for sample of calcium alginate beads ($n = 10$) and 1 ml of calcium chloride supernatant solution that had been used to cure the calcium alginate beads. The counts per minute for the calcium alginate beads and the supernatant were then compared and the amount of radioactivity that was associated with the calcium alginate beads was, therefore, determined.