JYP

Preparation and *in vitro* Characterization of Porous Carrier–Based Glipizide Floating Microspheres for Gastric Delivery

Pandya N, Pandya M, Bhaskar VH

Department of Pharmaceutics, M.P. Patel College of Pharmacy, Jeevanshilp Campus, Kapadwanj, Gujarat - 387 620, India

Address for correspondence: *Dr Narendra Pandya; E-mail: speed_5naren@yahoo.co.in*

ABSTRACT

Floating microspheres have been utilized to obtain prolonged and uniform release of drug in the stomach for development of once-daily formulations. A controlled-release system designed to increase residence time in the stomach without contact with the mucosa was achieved through the preparation of floating microspheres by the emulsion solvent diffusion technique, using (i) calcium silicate (CS) as porous carrier; (ii) glipizide, an oral hypoglycemic agent; and (iii) Eudragit® S as polymer. The effects of various formulations and process variables on the internal and external particle morphology, micromeritic properties, *in vitro* floating behavior, drug loading, and *in vitro* drug release were studied. The microspheres were found to be regular in shape and highly porous. The prepared microspheres exhibited prolonged drug release (~8 h) and remained buoyant for >10 h. The mean particle size increased and the drug release rate decreased at higher polymer concentrations. No significant effect of the stirring rate during preparation on drug release was observed. *In vitro* studies demonstrated diffusion-controlled drug release from the microspheres. Microsphere formulation CS4, containing 200 mg calcium silicate, showed the best floating ability (88% buoyancy) in simulated gastric fluid. The release pattern of glipizide in simulated gastric fluid from all floating microspheres followed the Higuchi matrix model and the Peppas-Korsmeyer model.

Key words: Calcium silicate, emulsion solvent diffusion method, floating controlled drug-delivery system, glipizide, microspheres

INTRODUCTION

To develop oral drug-delivery systems, it is necessary to optimize both the residence time of the system within the gastrointestinal tract and the release rate of the drug from the system. Various attempts have been made to prolong the residence time of the dosage forms within the stomach.[1,2] Prolongation of the gastric residence time (GRT) of delivery devices could be achieved by promoting adhesion to the mucous membranes,[3] which acted by preventing passage of the microspheres through the pylorus[4] or by maintaining them in a buoyant fashion in gastric juice.[5–7] With regard to the floating devices, Innuccelli *et al*,[8–10] reported that an air-contained multiple-unit compartment system showed excellent buoyancy *in vitro* and prolonged GRT relative to the controls *in vivo* in

Access this article online	
Quick Response Code:	Website: www.jyoungpharm.in
	DOI: 10.4103/0975-1483.80292

the fed state. However, in the fasted state, the intragastric buoyancy of the devices did not influence GRT. Yuasa *et al*,[11] attempted to prepare an intragastric floating and sustained-release preparation, which derived its buoyancy from the air trapped in the pores of calcium silicate when these particles were covered with polymer. Murata *et al*,[12] prepared calcium-induced alginate gel beads that, upon oral administration, were capable of floating on gastric juice.

Glipizide is a second-generation sulfonylurea prescribed to treat NIDDM (non- insulin-dependent diabetes mellitus). Its short biological half-life (3.4 h) and the site of the absorption in the stomach necessitates development of controlled-release dosage forms that are retained in the stomach, which would increase the absorption, improve drug efficiency, and decrease dose requirements.[13] An objective was to develop a multiparticulate floating delivery system, consisting of highly porous carrier material like calcium silicate (CS), glipizide as the drug, and Eudragit® S (ES) as the polymer, which would be capable of floating on gastric fluid and delivering the therapeutic agent over an extended period of time.

MATERIALS AND METHODS

Materials

Glipizide was supplied as a gift sample by Micro Labs, (Bangalore, India); CS was purchased from Sigma Chemicals (Mumbai, India); and ES (Eudragit® S) was received as a gift sample from M/s Rohm Chemische GmBH (Fabrik, Germany). Ethanol, dichloromethane (DCM), and the other solvents were purchased from SD Fine Chemicals (Mumbai, India). All chemicals were of analytical-reagent grade and were used as received.

Preparation of glipizide-absorbed CS

CS (1.0 g) was dispersed in 10 mL ethanolic solution of glipizide (50 mg) to prepare a slurry. The slurry was ultrasonicated for 10 min in an ice bath at 40% voltage frequency using a probe sonicator (Soniweld, Imeco Ultrasonics, Mumbai, India) to entrap the drug solution inside the pores of the porous carrier. The excess ethanolic solution was removed by filtration and then by drying in vacuum, which resulted in the glipizide-absorbed CS powder.[14]

Preparation of floating microspheres

Microspheres were prepared by the emulsion solvent diffusion method established by Kawashima *et al*.[14] as follows: The glipizide-absorbed CS was added into the polymer solution of ES (1 g) in ethanol and DCM (2:1) and sonicated using the probe sonicator (Soniweld). The resulting suspension was poured into a 200 mL aqueous solution of polyvinylpyrollidine (0.75% w/v) in a 500 mL beaker at 40ºC. The emulsion/suspension was stirred at 500 rpm employing a 2-bladed propeller-type agitator (Remi, Mumbai, India) for 3 h. The microspheres were separated by filtration using Whatman filter paper (No. 41, Whatman, Brentford, UK), washed with water, and dried at room temperature in a desiccator for 24 h. The microspheres of glipizide without CS (WC) were also prepared using the same method for comparative study.

Process variables

Amount of polymer: 500, 1000, and 1500 mg; stirring rate: 250, 500, 750, and 1000 rpm; Temperature of the preparation: 20, 30, 40, and 50°C; volume of aqueous phase: 200, 300, 400, and 500 mL; solvent ratio (ethanol: DCM): 1:1, 2:1, and 3:1; amount of carrier: 50, 100, 150, 200, and 250 mg.

Preparation of nonfloating microspheres

Nonfloating microspheres were prepared using the procedure reported by Choi *et al*.:[15] ES (1.0 g) and glipizide (50 mg) were dissolved in 10 mL of ethanol/DCM mixture (2:1), followed by addition of 1 mL of aqueous phase containing 0.25% w/v of Tween 80. The initial water/oil (w/o) emulsion was prepared by stirring the mixture for 20 s. The w/o emulsion was slowly added into 500 mL of corn oil, the second oil phase containing 0.02% w/v of Span 80 as a surfactant, with stirring at 500 rpm at 25ºC. The mixture was stirred for 1 h and the hardened microspheres were collected by filtration. The collected microspheres were washed with n-hexane thrice and soaked in fresh hexane with gentle shaking for 24 h. The microspheres were separated and then dried in an oven overnight at 50°C.

Characterization of microspheres

Micromeritic properties

The microspheres were characterized by their micromeritic properties, such as particle size, true density, tapped density, compressibility index, and flow properties.[16] The size was measured using an optical microscope, and the mean particle size was calculated by measuring 200–300 particles with the help of a calibrated ocular micrometer. The tapping method was used to determine the tapped density and percent compressibility index as follows:

Tapped density = mass of microspheres / volume of microspheres after tapping