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A floating-type dosage form of repaglinide in polycarbonate microspheres

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ABSTRACT

Objective: To prepare a floating type dosage form for the anti-diabetic drug repaglinide using polycarbonate (PC) microspheres capable of floating in the gastro-intestinal fluid to improve the biological half life and bioavailability of the drug.
Methods: Floating microspheres containing repaglinide were fabricated using different ratios of PC and poly(propylene glycol) (PPG) by a solvent evaporation technique using dichloromethane as the solvent. Microspheres were characterized using scanning electron microscopy (SEM) and differential scanning calorimetry (DSC). Toxicity of the microspheres was examined using NH 3T3 cells. *In vitro* drug release was examined in simulated gastric and intestinal fluids.
Results: Microspheres having encapsulation efficiency (>90%) and floating ability (>70%) were obtained. DSC studies confirmed the amorphous nature of drug in the microspheres. The microspheres were non-toxic to NH 3T3 cells *in vitro*. *In vitro* release studies showed a biphasic mode of release from all formulations.
Conclusions: It was seen that the mechanism of release of repaglinide from the microspheres was diffusion controlled and Fickian in character. Incorporation of more PPG in the system and increase in the drug payload led to faster release. The system is expected to ensure retention in the gastro-intestinal tract (GIT) for longer periods.

1. Introduction

In order to maintain therapeutically desirable drug concentrations, it is often necessary to take multiple doses of a drug which may result in significant fluctuations in drug plasma concentration. The variation of drug concentration in plasma is mainly due to the low bioavailability of drug which in turn depends upon both the physiological state and the dosage formulations. The major physiological difficulty with oral formulations is that the absorption of the drug depends on its gastric residence time (GRT). Drugs with shorter GRT can be eliminated much faster from the gastro-intestinal tract (GIT) thereby reducing the bioavailability of drug. The gastric emptying problem can be overcome by placing the dosage formulation in a specific region of GIT to prolong the residence time of the drug. This increases the retention time of the drug in the absorption region and improves its bioavailability [1,2].

Every drug has its own absorption window through GIT, but most of them are absorbed in the upper intestinal tract (UIT). Even though UIT has an excellent absorption capacity, the degree of absorption from this site is inadequate as the gastro-intestinal movement is very fast. After crossing this absorption window, the remaining drug is eliminated as waste. In order to improve the availability of such drugs, the residence time of the dosage in the UIT should be increased. These considerations have led to the development of oral controlled release dosage forms possessing gastric retention capacities in which the dosage system can reside in stomach for longer periods and release drug, which can be absorbed in stomach and in UIT.

During the past two decades, various approaches have been examined to fabricate controlled release systems which can prolong the GRT of the drug that include swelling controlled release systems [3,4], bioadhesive systems [5,6], high density systems [7,8], hydrogel-based systems [9], and floating type dosage forms

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[10–12] to name a few. Of these, floating systems have advantages over other methods [1,13]. Floating type dosage forms have been fabricated using low density systems such as sponges with a porous structure that can float in gastric fluid. They can be administered either as single or multiple unit formulations. However, single unit formulations fail to float for longer durations and thus producing gastric irritation. Multiple unit systems have the advantage they are not subjected to 'all or nothing' gastric emptying nature of single unit systems [14].

Polymers have many advantages over other materials in developing drug delivery devices [15]. Multi-particulate floating systems using many polymers have been reported. Others and us have shown that microspheres fabricated from polycarbonate (PC) are capable of floating on the gastric and intestinal fluids [16–19]. It is reported that many drugs are released in insufficient amounts from the multi-particulate formulations in gastric fluid. Therefore, various hydrophilic fillers are blended with polymers to improve the release rate of drug from floating systems [20,21]. Poly(-propylene glycol) (PPG) is one such agent used in drug dosage to improve poorly soluble drugs [22]. In the present investigation, PC and PPG blended microspheres were prepared and evaluated as a floating type delivery system.

Repaglinide, is a carbamoylmethyl benzoic acid derivative used for reducing the blood glucose level. Repaglinide is rapidly absorbed following oral administration, reaching peak concentrations 30–60 min post dosing. The drug has a fast onset and a relatively short duration of action. Repaglinide has a very fast elimination rate with a plasma half-life of 1 h [23,24]. The bioavailability of the drug is around 50%. These characteristics make repaglinide a good candidate for gastroretentive drug delivery.

Floating type dosage forms of repaglinide have been reported using calcium silicate as a porous carrier and Eudragit S as polymer with an incorporation efficiency of 75% by Jain et al. [2]. No release was seen in the gastric fluid (GF) since the polymer did not undergo dissolution in acidic pH. Repaglinide encapsulated in floating microspheres of cellulose acetate butyrate and poly(ethylene oxide) showed up to 40% burst release in GF [21]. Floating microspheres with ethyl cellulose and ethyl cellulose in combination with hydroxypropyl methyl cellulose for repaglinide delivery has also been reported [25]. Entrapment efficiency was in the range of 50–75% and drug release was examined only in GF. Microballons of Eudragit polymers containing repaglinide with an entrapment efficiency of 65% have also been reported [26]. The entrapment efficiency of the drug in most of these studies below 75% and release studies have been done either at the gastric pH or the intestinal pH.

In this study, a floating type microsphere dosage form based on PC blended with PPG for repaglinide has been fabricated with an entrapment efficiency of >90% and release studies have been performed in the gastric pH for 4 h followed by release in the intestinal pH *in vitro*.

2. Materials

Repaglinide was received as a gift from Octis Research laboratory (Dehradun, India). PC was obtained from GE Plastics India Pvt. Ltd (Mumbai, India). PPG (molecular weight 1000 Da) and poly(-vinyl alcohol) (PVA), molecular weight 160 kDa) were procured from Fisher Scientific, Hyderabad, India. All other chemicals were of analytical grade obtained from SD-Fine Chemicals (Mumbai, India). Simulated gastric fluid (SGF) and intestinal fluid (SIF) were prepared according to the US Pharmacopoeia. Tissue culture plates were from Tarsons, Mumbai, India. Cell culture grade dimethyl sulfoxide (DMSO) was from MP Biomedicals, Illkrich, France. Dulbecco's Minimum Essential Medium (DMEM) and fetal calf serum (FCS) were obtained from Himedia Laboratories (Mumbai, India) and NIH 3T3 mouse embryo fibroblast cells were from National Center for Cell Science (NCCS) Pune, India.

3. Methods

3.1. Preparation of drug-loaded microspheres

Repaglinide-loaded PC microspheres were prepared by a solvent evaporation method as previously reported [18,19] with some modifications. Briefly, 5 mL of a 25 or 30% solution of PC in dichloromethane (DCM) with different ratios of PC and PPG containing drug payloads of 10 and 20% was dispersed in 150 mL of an aqueous phase containing 0.75% PVA and 1% isopropanol. The mixture was continuously stirred at 600 rpm using a propeller type stirrer for 1 h at 37 ± 2 °C. After the solvent was evaporated, the microspheres were filtered, washed with distilled water and dried in air at room temperature overnight. The various formulation conditions employed for the microsphere preparation are listed in the Table 1.

3.2. Floating ability

The floating efficiency of microspheres was determined by placing 10 mg of microspheres in a 100 mL beaker containing 50 mL SGF (pH 1.2) containing 0.02% Tween 20. The beaker was shaken continuously at 100 rpm for 12 h at 37 °C in a temperature-controlled shaking water bath (Julabo, Germany). After 12 h, the buoyant and sunk particles were collected and dried separately. Both fractions were weighed and buoyancy was determined by the following equation.

Percentage of floating microspheres = (Weight of floating microspheres/Total microsphere weight)*100

3.3. Drug entrapment efficiency

In an Erlenmeyer flask, 10 mg of repaglinide-loaded PC microspheres was accurately weighed and dissolved in 2 mL DCM following which 50 mL of 1 M HCl was introduced, the flask was stoppered and stirred magnetically for 6 h at 60 °C. After evaporation of DCM completely, the solution was filtered and the absorbance of the filtrate was read at 243 nm at appropriate dilution using 1 M HCl as blank in a UV–visible spectrophotometer (Jasco-V550, Japan). The amount present in the microspheres was computed from a standard curve for the drug prepared at different concentrations and the entrapment efficiency was calculated using the following formula:

Drug entrapment (%) = (Obtained drug content/Theoretical drug content)*100

Table 1
Formulation parameters, encapsulation efficiency and buoyancy of repaglinide-loaded PC microspheres.

Formulation Code	PC (wt %)	Drug-loading (wt %)	PC: PPG ratio	Encapsulation Efficiency (%)	Buoyancy(%)
F1	25	10	90:10	99.16	88.14
F2	25	10	95:5	93.15	87.8
F3	25	20	90:10	99.06	89.50
F4	25	20	95:5	94.78	87.47
F5	30	20	90:10	91.01	77.82
F6	30	20	95:5	92.83	74.41
F7	30	10	95:5	90.21	72.72
F8	30	10	90:10	93.78	77.47