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Preparation of pellets with controlled release of glucose as prevention of hypoglycaemia in paediatric patients

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ABSTRACT

Hypoglycaemic episodes represent serious and frequent complications of type 1 and 2 diabetes. Theoretically, the risk of hypoglycaemic states can be affected by a dosage form based on a food supplement containing a delayed release formulation of glucose. The release of glucose should compensate for balance the peak effect of an antidiabetic treatment. In clinical practice, a diet with fibre and grains is recommended and patients are broadly educated in the topic of low and high glycaemic indexes to achieve the same effect. However, a precisely-timed release of carbohydrates can favourably target expected hypoglycaemia and concurrently decrease carbohydrate content. To study the possibility of preparing the dosage form with controlled-release carbohydrates, a dosage form of pellets containing four osmotically active substances coated by a membrane created of ethylcellulose was prepared. These pellets can be administered in a mixture with liquid or semisolid food. The resulting dissolution profiles for selected compositions showed that delayed release can be achieved for 120, 240 and 360 min *in vitro*, representing an ideal delay for clinical purposes.

1. Introduction

Day and nocturnal hypoglycaemia are common complications among diabetics and can occur in all patients treated by insulin or several groups of antidiabetic drugs. The American Diabetes Association Workgroup on Hypoglycaemia (2005) suggests a blood glucose value below 3.9 mmol/l as the definition of hypoglycaemia in all age categories. In clinical practice, mild, moderate, and severe hypoglycaemias are defined based on the activation of contraregulatory systems, severity of symptoms, and the patient's own ability to resolve the hypoglycaemia (Ryan et al., 2005). A level of blood glucose below 3.1 mmol/l may result in unconsciousness and the need for glucagon and parenteral glucose treatment. Moreover, hypoglycaemia inhibits optimal glycaemic control, worsening one's ability to pay attention and, consequently, to study, work, or operate a vehicle. Hypoglycaemic episodes are profound and prolonged in children and adolescents, exaggerated by the inability of children to recognize autonomic symptoms and the innate tendency of these age groups to eat reluctantly and irregularly (Shalitin and Moshe, 2008). After experiencing severe hypoglycaemia, children and caregivers fear its recurrence and tend to keep the values of glucose above the recommended targets which leads to poorer glycaemic control and the risk of chronic complications, which may ultimately be more detrimental to the individual's health compared to casual mild or even moderate hypoglycaemia (Ryan et al., 2005). Hypoglycaemic episodes are preventable, providing patients respect the precautions of long-term home self-management. However, some hypoglycaemias are difficult to treat by the regime precautions due to their relation to the treatment options, e.g. nocturnal hypoglycaemia, hypoglycaemia in sports, and hypoglycaemia in paediatric patients with inappropriate eating habits.

The efforts of some food manufacturers to produce food with controlled release glucose seem to be promising. Food containing sugar releases the desired amount of glucose at the desired time which is required to balance the effect of insulin or antidiabetics. Food company 'The Estee Corp. (1994)' attempted to offer a solution to this problem by applying to patent a food supplement in the form of microparticles containing saccharides with the gradual slow release of glucose, yet without any lag time in the release. Similarly, a patent application by the company Hercules Inc.

Abbreviations: ADS, Ac-Di-Sol® – Croscarmellose sodium; CI, Carr compressibility index; CMS, Carboxymethyl starch; HR, Hausner ratio; PEG, polyethylene glycol; RC, Avicel RC® 591; SEM, scanning electron microscopy.

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(1995) claims a special preparation of food containing controlled-release glucose. Nevertheless, neither of these patents make any mention of food form or lag times.

The aim of this work was to develop a dietary supplement consisting of pellets with the delayed release of glucose. Another objective was to evaluate the effect of core composition and coating quantity on the release of glucose. The dosage form of pellets was selected due to its small size, which allows children patients to swallow them easily. The concept of controlled release was chosen so the dosage form would release glucose during times when patients are not able to eat and the activity of insulin is high, e.g. night or sports. The formulation is comprised of an inert core in the form of pellets containing glucose prepared by extrusion–spheronization and coated by a membrane which releases glucose after a specific time interval during passage through the gastrointestinal tract. The resulting pellets, which release glucose in clinically suitable time intervals, may be mixed with semi-solid or liquid food or dispersed in a beverage and ingested together with food.

2. Materials and methods

2.1. Materials

Glucose anhydrous was obtained from Dr. Kulich Pharma, Czech Republic. Microcrystalline cellulose (Avicel® PH 101), microcrystalline cellulose and carboxymethylcellulose sodium (Avicel® RC 591), and croscarmellose sodium (Ac-Di-Sol®) were purchased from FMC Biopolymer, Belgium. Polyethylene glycol 8000 was acquired from Merck Schuchardt OHG, Germany. Carboxymethyl starch (Vivastar® P 5000) was bought from JRS Pharma, Germany. Aqueous ehylcellulose dispersion (Surelease® type B NF) was obtained from Colorcon, USA.

2.2. Preparation of cores

Cores were prepared according to the previous article (Franc et al., 2014). Individual raw materials from Table 1 were mixed in a dry state in a blender (TEFAL Kaleo, Type: 676210, France) at 400 rpm for 60 s. Purified water was added in such an amount to create a dough-like consistency. The wet mass was then mixed for another 60 s under identical conditions and then transferred to a screw extruder and extruded axially through a die (aperture size 1.0 mm, screw rate 110 rpm). The resulting ropes were spheronized in a spheronizer at 1000 rpm for 5 min. Extrusion and spheronization were performed using an integrated unit (Pharmex 35T, Wyss & Probst Eng, Germany). The resulting pellets were dried in a hot air oven (Horo, Type 38A, Germany) at 50 °C for 4 h.

2.3. Coating of pellets

The cores were coated by a 15% aqueous ethylcellulose dispersion (Surelease® Type B NF) in a Wurster-type fluid bed coating unit (M-100, Medipo, Czech Republic) under the following conditions: spray nozzle diameter 1.0 mm; atomization pressure 1.2 bar, spray rate 11 ml/min and inlet air temperature 65 °C. The final coating represented 12.5% or 25% of the total pellet mass, resulting in two different samples for each composition. The pellets were dried in a hot air dryer (Horo, Type 38A, Germany) at 70 °C for 2 h.

Table 1
Compositions of pellets.

Compounds	Concentration% (w/w)			
	ADS	RC	PEG	CMS
Glucose	80.0	75.0	75.0	80.0
Avicel PH 101	15.0	–	–	15.0
Ac-Di-Sol	5.0	–	–	–
Avicel RC 591	–	25.0	–	–
PEG 6000	–	–	25.0	–
CMS	–	–	–	5.0

2.4. Physical evaluation of cores and coated pellets

Particle size and size distribution were evaluated through sieve analysis using a set of stainless steel sieves with apertures ranging from 0.125 to 2.00 mm (Retsch GmbH & Co. KG, AS 200 basic, Germany). Pellet flow properties, i.e. flowability, bulk and taped densities, angle of repose, Hausner ratio, and Carr compressibility index were evaluated according to European Pharmacopoeia. Friability and hardness were measured according to the published method (Rabišková et al., 2007). Sphericity and aspect ratio of the cores and the coated pellets were measured using an optical microscope (DN 25 Lambda, Intarcho-micro, Czech Republic) equipped with a charged coupled device camera (Alphaphot-2, Nikon, Japan) and an image analysis (Leco IA 32, Leco Instruments, USA). Core moisture content was determined using a halogen moisture analyser (HX204, Mettler Toledo, Switzerland). The thickness of the coating was determined from scanning electron microscopy images as the mean diameter of four measurements.

2.5. In vitro drug release

The glucose release of each coated sample was determined using a dissolution apparatus (Sotax AT-7 Smart, Switzerland). The paddles apparatus was employed at 50 and 100 rpm. The dissolution medium consisted of water in a volume of 1000 ml at 37 ± 0.5 °C. The samples were withdrawn after 60, 120, 240, 360, and 540 min and subsequently analysed for glucose content using the high-performance liquid chromatography with evaporative light scattering detector. Each experiment was performed twice and results are expressed as mean values ± standard deviation of active substance in% dissolved at the given sampling time.

2.6. Microscopic evaluation of cores and coated pellets

Samples of cores, coated pellets, pellets after dissolution and cut pellets were imaged using scanning electron microscopy (SEM; JCM-6000 NeoScope™ Benchtop SEM, JEOL, USA).

Samples of pellets after dissolution were obtained as follows. The pellets were subjected to dissolution for further examination of changes in the coating. They were withdrawn after 360 min. This time was chosen since it is the time at which the greatest difference in dissolution profiles occurs. Therefore it was assumed that these differences would be visible on the surface of the pellets. Afterwards, the pellets were drained in a Petri dish using filter paper and left under laboratory conditions for 24 h to dry completely.

To obtain cut samples, single pellets were captured with a pair of tweezers, placed on a hard surface, and cut transversely using a razor blade.

3. Results and discussion

The pellets themselves must have physical parameters, such as density, size, shape or mechanical resistance, appropriate for subsequent coating. All evaluated parameters meet the requirements of European Pharmacopoeia.