Development of Novel Mucoadhesive Pellets of Metformin Hydrochloride

Jingshu Piao¹, Ji-Eun Lee¹, Kwon-Yeon Weon², Dong-Wook Kim², Jung Suk Lee³, James D. S. Park³, Yuichi Nishiyama⁴, Ikuo Fukui⁴, and Jin-Seok Kim¹

¹Sookmyung Women’s University, Seoul 140-742, Korea, ²Handok Pharmaceuticals Co., Ltd., Seoul 135-755, Korea, ³Richwood Trading & Pharmaceuticals Co., Ltd., Seoul 100-095, Korea, and ⁴Shin-Etsu Chemical Co., Ltd., Niigata, Japan

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Mucoadhesive polymer-coated pellets containing metformin hydrochloride were prepared by the powder-layering technique using a centrifugal fluidizing (CF)-granulator. Four high-viscosity polymers were applied to make the pellets: 1) hydroxymethylcellulose (HPMC), 2) sodium alginate (Na-Alg), 3) HPMC/Carbopol, and 4) sodium carboxymethylcellulose (Na-CMC). The physical crushing test, mucoadhesive test, zeta-potential test, in vitro release study and observation of gastroretention state of the dosage form were performed to investigate the pellets. The strong adhesive interaction between the Na-CMC-coated pellets and the mucin disc was obtained by mucoadhesive test. Na-Alg was most effective among the polymers used in changing the value of zeta potential of the mucin solution by the interaction between a polymer and a mucin particle. Results from drug dissolution study showed that over 95% of the drug from all the four pellets was released before 2 h, while Na-CMC- and Na-Alg-coated pellets showed a moderate sustained-release in SGF (simulated gastric fluid) and SIF (simulated intestine fluid), respectively. In conclusion, Na-CMC and Na-Alg seem to be promising candidates for mucoadhesive formulation and further studies to improve the sustained-release property are underway for achieving the ultimate goal of once-a-day formulation of metformin hydrochloride.

Key words: Powder-layering, CF-granulator, Mucoadhesion, Polymer, Pellets, Metformin hydrochloride

INTRODUCTION

Type 2 diabetes, formerly known as adult-onset diabetes or non insulin-dependent diabetes mellitus (NIDDM), is the most common form of diabetes. People can develop type 2 diabetes at any age, even during childhood. This form of diabetes usually begins with insulin resistance, a condition in which muscle, liver, and fat cells do not use insulin properly. At first, the pancreas keeps up with the added demand by producing more insulin. In time, however, the pancreas loses the ability to secrete sufficient insulin in response to meals to maintain normoglycaemia (Adikwu et al., 2004; Kim et al., 2004; Hotamisligil et al., 1993; Briede et al., 2007).

Metformin, a biguanide glucose-lowering agent, is widely used for management of type 2 diabetes (Briere et al., 2007; Stepensky et al., 2001; Dunn and Peters, 1995; Bailey et al., 1996; Hu et al., 2006; Stepensky et al., 2002). Metformin does not lead to weight gain, increased episodes of hypoglycaemia, or the promotion of insulin secretion (Cayley, 2002). Although the mechanism of action of metformin is not understood completely, it is known to decrease hepatic glucose output, reduce the rate of intestinal glucose absorption and increase the glucose uptake by muscle cells or adiposities (Bailey et al., 1996; Hu et al., 2006; Stepensky et al., 2002; Cayley, 2002). Oral bioavailability of metformin is 40–60% in human, due to its principal absorption in the upper gastrointestinal tract.
Many studies have attempted to design an oral, sustained-release form of metformin with various polymers for increasing gastrointestinal retention time, and thereby reducing the dosing frequency and increasing patient compliance (Stepensky, 2002). Hydroxypropylmethylcellulose (HPMC), a hydrophilic polymer that has been widely used to prolong drug release, was employed as a matrix-forming polymer to design an oral sustained-release matrix tablet of metformin hydrochloride (Mandal et al., 2007; Ofori-Kwakye et al., 2004). Sodium alginate (Na-Alg) microspheres of metformin hydrochloride have been successful in sustaining drug release for 8 h (Balasubramaniam et al., 2007). Kar et al. (2007) reported that ethyl cellulose is a retardant material when used to prepare controlled-release microspheres of metformin hydrochloride. Adikwu et al. (2004) applied detarium gum for making a mucoadhesive formulation. Moreover, chitosan- and Na-Alg-based bioadhesive vaginal tablets have also been reported by El-Kamel et al. (2002).

This study has performed a comparative analysis of the crushing test, mucoadhesive test, zeta-potential test, in vitro release study and observation of gastroretention state of the pellets coated with mucoadhesive polymers such as HPMC, Na-Alg, HPMC/Carbopol, and Na-CMC.

MATERIALS AND METHODS

Materials

Metformin hydrochloride (Farmhispania, Spain) was used as active agent in this study. Sugar spheres (Nonpareil 101, Frenund, Japan) was used for the core seed. HPMC 2208 (Shin-Etsu, Japan), Carbopol 934NF (Noveon, USA), Na-Alg (Protannal® LF240D; FMC Biopolymer, USA), or Na-CMC (Blanose 7M8SF; Hercules, USA) were applied as an outer-layer coating of pellets prepared by a powder-layering technique (Deshpande et al., 1997). Five percent (w/v) of polyvinylpyrrolidone (PVP) ethanol solution was used as a binder in order to coat the pellets with the polymer powder. Mucin from porcine stomach type III was purchased from Sigma. Gelatin minicapsules (Qualicaps®, Japan) were purchased from Jeung Do Bio & Plant Co., Ltd (Seoul, Korea). Methanol and acetonitrile were of HPLC grade, and other chemicals were of HPCL or analytical grade.

Preparation of pellets

The mucoadhesive pellets containing metformin hydrochloride were prepared by centrifugal fluidizing (CF)-granulator (CF-360, Freund Industrial, Japan). First, drug-layered pellets were prepared by spraying metformin hydrochloride powder of 1000 g with 10% PVP ethanol solution as a binder on 500 g of the Nonpareil 101 using the CF-granulator. Then, four adhesive polymers such as HPMC, Na-Alg, HPMC/Carbopol, and Na-CMC of 500 g with the binder were sprayed on drug-loaded pellets of 250 g using the CF-granulator. During the working process, inlet air temperature was maintained at 60°C, and sample temperature was 20°C. The powder feed rate was 5 g/min and the binder spray rate was 11 g/min in this study.

Crushing strength test

The strength of pellets was evaluated using a texture analyzer (Stable Micro Systems, UK). The probe (p20 type) was moved at a speed of 0.1 mm/s down onto the pellet. After contact to the pellet, the force to crush the pellet was measured when the probe was down to 50% of the height of the pellet. The arithmetic mean of the force was used as the crushing strength in this study (Steckel and Mindermann-Vogly, 2004). All measurements were performed in quadruplicate.

Mucoadhesive test

The mucoadhesive properties of pellets were evaluated using a texture analyzer. Mucin discs were manufactured by compression of mucin (250 mg) using an IR press with a 13 mm diameter and a compression force of 3 tons was applied for 10 s. These were then horizontally attached to the lower and upper ends of the Texture Profile Analysis (TPA) probes using double-sided adhesive tape. Samples of each pellet were swollen in pH 1.2 simulated gastric fluid (SGF) for 5 min and were placed on the lower mucin disc and the analytical probe containing the mucin disc was lowered onto the surface of each pellet and a downward force of 0.1 N was applied for 3 min to ensure intimate contact between the mucin disc and the sample. The probe was then moved up in a vertical direction at a constant speed of 0.5 mm/s and the force required to detach the mucin disc from the surface of each formulation was determined from the resultant force-time plot (Jones et al., 1997). All measurements were performed in quadruplicate.

Interaction between mucin particles and the polymers

The mucoadhesion of polymers with commercially available porcine mucin particles were evaluated.