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Research paper

Development and pharmaceutical approach for sustained-released metformin succinate tablets

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ABSTRACT

Metformin is currently marketed in the U.S. and worldwide as a hydrochloride salt and sustained-release (SR) tablets are preferred for increasing patient compliance. However, this SR tablet is large because of its high water solubility and the high dose required for efficacy, and some patients find it difficult to swallow. To overcome these challenges, the salt formation was changed, thereby changing its solubility. Ten new pharmaceutical salts were synthesized and metformin succinate was chosen among these because of its lower solubility and lower molecular weight. DSC thermograms and FT-IR spectra demonstrated that metformin HCl and succinate were different materials. However, other tablet properties related to effectiveness, such as density, compressibility, particle size distribution, stability in various artificial human fluids, and permeability were not statistically different. Metformin succinate SR tablets with an excipient portion reduced from 43% to 14% were prepared and compared with metformin HCl SR tablets *in vitro* and *in vivo*. The drug release study in buffer solutions at pH 6.8 and the pharmacokinetic parameters, C_{max}, T_{max}, and $AUC_{0-\infty}$ showed no significant differences between the two types of tablets. In conclusion, metformin succinate, which has low water solubility, can be used to reduce the size of SR metformin tablets for improving patient compliance.

1. Introduction

Metformin is an oral antihyperglycemic agent used to treat patients with type 2 diabetes mellitus [1]. Unlike insulin and the sulfonylureas, metformin does not promote weight gain; it has therefore become the first choice for treatment of type 2 diabetes and is even used in obese patients with type 1 diabetes to reduce insulin resistance [2]. Chemically, metformin (N,N–dimethylimidodicarbonimidic diamide hydrochloride) [3] belongs to the class of biguanides. It is a highly hydrophilic drug, with oral bioavailability of 50–60% [4] and plasma elimination half-life of 2.0–6.0 h [5–8] with the peak plasma concentration reached at approximately 3 h after dosage [5–8]. The biological half-life of metformin hydrochloride is 1.5–1.6 h and the drug is commonly administered at high doses (500 mg or 1000 mg) 2–3 times per day to achieve effective glucose-lowering treatment. The main absorption site is the proximal small intestine [9,10].

Metformin is currently marketed in the U.S. and worldwide as a hydrochloride salt (Glucophage™, Bristol-Myers Squibb Company) and as a cohesive white powder that is highly soluble in water (>300 mg/ml at ambient temperature) [11]. Because of its extremely high water solubility, preparing a controlled-release system for metformin hydrochloride is extremely difficult. Additionally, functional excipients are needed to modify drug release, adding to tablet size. It was previously reported that patients who have experienced difficulty in swallowing their medications were 31.3 times less likely to comply with their treatment than were patients who did not experience any difficulty in swallowing their medications [12]. This problem becomes even more severe at high doses (500 mg–1000 mg) because of increased tablet size (9 mm × 10.5 mm, Glucophage® 1000 mg tablets), and the need for daily dosing [13]. The only available alternative for such patients is the above-mentioned soluble powder (RIOMET®, 500 mg/5 ml). This composition is only available in the United States, and it has the well-known disadvantages of many syrup compositions [14].

There are continuing efforts to improve patient compliance or reduce the size of pharmaceutical dosage forms. These noticeable efforts have been focused on gastroretentive (GR) dosage forms and effervescent tablets. Controlled-released GR dosage forms that can

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remain in the stomach and release a constant amount of metformin hydrochloride into the upper part of the gastrointestinal tract would be advantageous [15–17]. However, this GR technique could not directly reduce tablet size because of metformin hydrochloride's very high solubility. By contrast, effervescent tablets are readily soluble in a glass of water; this may help patients to swallow the medication more easily [13,18]. However, excess sodium is needed to make effervescent tablets and the number of diabetic patients also having hypertensive symptoms must also be considered [19].

Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs [20–22]. Furthermore, other objectives can be achieved with a salt, such as increased chemical stability [23] and avoidance of polymorphism [23], leading to better compatibility [24] and better efficacy [25]. However, no research was found describing methods to improve patient compliance without compromising therapeutic efficacy, when decreasing the water solubility of the API by formation of a pharmaceutical salt.

The aim of this work was to reduce the solubility of metformin itself in water or fluids by changing the salt formation. This new metformin salt would also require fewer excipients to achieve its sustained-release (SR) profile. Finally, the new metformin SR tablet, reduced in size and weight, was obtained.

2. Material and method

2.1. Materials

Metformin HCl (Farmhispania, Spain) and sodium hydroxide (Merck, Germany) were obtained. Adipic acid, benzoic acid, besylic acid, glutaric acid, oxalic acid, pimeric acid, stearic acid, succinic acid, toluic acid, and tosylic acid were provided (ACROS, USA). Hydroxypropylmethylcellulose (HPMC, Shin-Etsu, Japan), lactose monohydrate (DFE Pharma, New Zealand), polyvinyl pyrrolidone (povidone k30, BASF, Germany), and magnesium stearate (Peter Greven, Germany) were kindly donated. PCcaps™ capsules were obtained (Capsugel, USA). Ammonium phosphate monobasic 98% (Daejung, Korea), methanol (HPLC grade, Daejung, Korea), and acetonitrile (HPLC grade, Daejung, Korea) were used and all other reagents were of analytical grade and used without further purification.

2.2. Preparation of various metformin salts

The theory for synthesis of a new metformin salt is shown in Fig. 1. A mixture of metformin HCl (10 g, 60.4 mmol) and sodium hydroxide (2.42 g, 60.4 mol) was added to 30 ml purified water in a reactor and mixed for 30 min. The solution was allowed to evaporate in a vacuum at 40–45 °C. Then 100 ml ethanol was added to the reactor to ensure dissolution. Meanwhile, each salt formation (adipate, benzoate, besylate, glutarate, oxalate, pimerate, stearate, succinate, toluate, and tosylate) was solubilized separately in 120 ml of 75% methanol. Each solubilized salt was added to the reactor containing metformin and gently agitated for 2 h, maintaining temperature at less than 10 °C. After filtration, the filtrate was washed with 20 ml ethanol. Each new metformin salt was dried at 60 °C for six hours. Each metformin salt was identified by NMR and purified by HPLC.

2.3. Solubility test

The solubility tests of the synthesized metformin salts were performed in purified water to check the changes in solubility. Each new metformin salt (equivalent to 10 g metformin) was placed in 30 ml of water in a volumetric flask. The flasks were then placed in a thermostatic vibrator and vibrated at 50 rpm at room temperature for 180 min. The samples were taken out and filtered through a 0.45-μm syringe filter, and then analyzed for metformin content by the RP-HPLC method. Samples were assessed in triplicate.

2.4. Preparation of metformin SR tablets

Based on the results of the above solubility test, four types of salts, glutarate, oxalate, stearate, and succinate, were selected. The five metformin salts (including hydrochloride) were each blended in a high shear-speed mixer (DIOSNA Dierks & Söhne GmbH, German) with chopper for 30 min to deagglomerate metformin and then mixed with HPMC (SR 90 grade, high viscosity), lactose, and povidone k30 for 15 min. The blends were granulated with purified water in a high shear-speed mixer. Granules obtained were placed in a fluid bed dryer (Glatt, German) for drying. Magnesium stearate was added to the dried granules after they passed through an ASTM #50 mesh. The SR metformin tablets were compressed by Manesty F3 (Bosch Packaging Technology, England) with oval-type punches and die. Formulation details are presented in Table 1.

2.5. In vitro dissolution study

Drug release studies of SR metformin tablets were performed using a USP II paddle method equipped with a TYP PTFC 2 autosampler (Pharma Test, Hainburg, Germany). The dissolution medium was 900 mL of pH 6.8 phosphate buffer solution and was maintained at a constant temperature of 37 ± 0.5 °C. The paddle rotation rate was 50 rpm.

Six samples were taken at each of 0, 0.5, 1, 2, 4, 8, 12, 16, and 20 h,

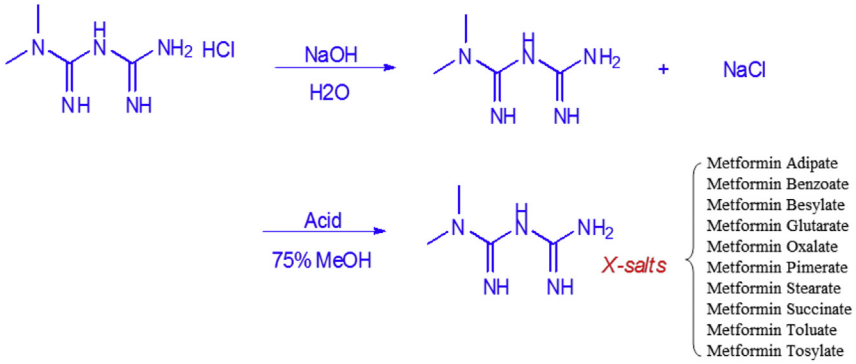

Fig. 1. The synthesis method of metformin new salts.