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Design and evaluation of compound metformin/glipizide elementary osmotic pump tablets

Defang Ouyang, Shufang Nie, Wei Li, Hong Guo, Hui Liu and Weisan Pan

Abstract

A simple elementary osmotic pump (EOP) system that could deliver metformin hydrochloride (MT) and glipizide (GZ) simultaneously for extended periods of time was developed in order to reduce the problems associated with multidrug therapy of type 2 non-insulin-dependent diabetes mellitus. In general, both highly and poorly water-soluble drugs are not good candidates for elementary osmotic delivery. However, MT is a highly soluble drug with a high dose (500 mg) while GZ is a water-insoluble drug with a low dose (5 mg) so it is a great challenge to pharmacists to provide satisfactory extended release of MT and GZ. In this paper sodium carbonate was used to modulate the solubility of GZ within the core and MT was not only one of the active ingredients but also the osmotic agent. The optimal EOP was found to deliver both drugs at a rate of approximately zero order for up to 10 h in pH 6.8, independent of environment media. In-vivo evaluation was performed relative to the equivalent dose of conventional MT tablet and GZ tablet by a cross-study in six Beagle dogs. The EOP had a good sustained effect in comparison with the conventional product. The prototype design of the system could be applied to other combinations of drugs used for cardiovascular diseases, diabetes, etc.

Introduction

The oral osmotic pump tablet has many advantages, such as reducing the risk of adverse reactions, improving patient compliance, in-vivo predictability of release rate based on in-vitro data, etc. There has been an increasing interest in the development of oral osmotic pumps in the past 20 years, and various types of oral osmotic pump have been developed and studied to deliver drugs possessing different aqueous solubility. In the 1970s, Theeuwes (1975) developed the elementary osmotic pump (EOP) and put forward its basic theory. However, EOPs are only suitable for moderately soluble drugs. A number of design options are available in the field of oral osmotic pumps to deliver various drugs possessing different solubility properties. One effective way to improve the drug-release rate is to increase drug solubility. For some drugs, it is feasible to convert them into ionic substances by reacting them with or adding alkali/acid (Lu et al 2002). Okimoto et al (1999) used $(SBE)_{7m}$-β-CD as a solubilizer and osmotic agent to prepare an osmotic pump tablet for poorly water-insoluble drugs such as testosterone. Moreover, for water-insoluble drugs it is possible to release drugs in the form of a suspension. Finding an appropriate polymer is therefore pivotal to the success of this osmotic tablet. Liu et al (2000) used polyethylene oxide as a suspending agent to prepare a nifedipine monolithic osmotic tablet system. Later, controlled porosity oral osmotic pumps were developed for the delivery of drugs (Haslam & Rork 1989). Various types of oral osmotic pumps, their advantages and formulation aspects have been reviewed (Verma et al 2000, 2002). In addition, a large body of patent literature describes new and novel osmotic systems (Santus & Baker 1995).

Chronic diseases, such as diabetes, asthma and heart diseases, are treated using multidrug therapies, which are vulnerable to incidences of side-effects, poor patient compliance and slow improvement of patients. Metformin hydrochloride (MT) and glipizide (GZ) are oral hypoglycaemic agents belonging to the biguanide group and second-generation sulfonylurea, respectively (Carruthers et al 2000). Generally, they

Department of Pharmacy, Shenyang Pharmaceutical University, Shenyang 110016, China

Defang Ouyang, Shufang Nie, Wei Li, Hong Guo, Hui Liu, Weisan Pan

School of Chemistry & Pharmacy, Jiamusi University, Jiamusi 154007, China

Hong Guo

Wuhan General Hospital, Wuhan 430070, China

Hui Liu

Correspondence: Defang Ouyang, Department of Pharmacy, Shenyang Pharmaceutical University, Shenyang 110016, China. E-mail: ouyangdf@21cn.com

are individually used in the treatment of type 2 non-insulin-dependent diabetes mellitus. MT acts by decreasing hepatic glucose production and improves insulin sensitivity by increasing peripheral glucose uptake. Because of its shorter and variable biological half-life of 1.5–4.5 h, it should be repeatedly administered (250 mg two or three times a day) to maintain an effective plasma concentration. GZ lowers glucose concentrations by stimulating the release of insulin from pancreatic β-cells. GZ has a similar biological half-life (2–4 h), depending on the individual, and the dose is 2.5 mg two or three times a day. The combination of MT with GZ is more effective than individual therapy because of the synergism (Katzung 2001). Although controlled drug delivery systems are available separately for both drugs, a system that can deliver both drugs simultaneously at a controlled rate may ensure improved patient compliance. In addition to improved patient compliance, as a once-daily formulation it may improve the safety profile and activity of drugs exhibiting short biological half-lives. Recently, a modified push–pull osmotic system was developed to deliver a slightly water-soluble theophylline base and freely soluble salbutamol sulfate simultaneously (Prabakaran et al 2004). However, the modified push–pull osmotic system needed a sophisticated technique.

In the present study, a simple EOP system that could deliver MT and GZ simultaneously for an extended period of time was developed and evaluated to reduce the problems associated with the multidrug therapy of type 2 non-insulin-dependent diabetes mellitus. MT is highly soluble and high dose (500 mg) while GZ is water insoluble and low dose (5 mg). Gan et al (2002) developed a cyclodextrin complex osmotic tablet for GZ. However, it needed a complicated process and the amount of excipient was very high. It is a great challenge to pharmacists to use less excipient and provide satisfactory extended release of MT and GZ. In this paper sodium carbonate was used to improve the solubility of GZ within the core and a compound MT/GZ osmotic pump tablet was successfully designed and the optimal EOP evaluated in vitro and in vivo.

Materials and Methods

Materials

MT (Kunsan Shuanghe Pharmaceutical Company, China), GZ (Shanghai Fifteenth Pharmaceutical Factory, China), cellulose acetate (CA, 54.5–56.0 wt% acetyl content; Shanghai Chemical Company, Shanghai, China), polyethylene glycol (PEG) 1500 (Pudong Gaonan Chemical Company, Shanghai, China), sodium carbonate (Tianjin Chemical Factory, China) and PVP K90 (ISP Technologies, Inc) were used. The other chemicals used were of analytical grade.

Determination of both drugs

The content of MT was determined at 233 nm by UV. The concentration of GZ was determined at 275 nm by HPLC. Briefly, 20 μL of the filtrate was injected onto an ODS C_{18}, 250×4.6 mm, 5 μm particle size column. Acetonitrile/methanol/pH 7.0 phosphate buffered saline (5:6:11) was used as the mobile phase and pumped with the help of two LC-10 VP pumps (Shimadzu) at the rate of 1 mL min^{-1}.

Preparation of core tablets

Granules were prepared by the wet granulation method. MT, GZ, PVP and sodium carbonate were mixed well, 70% alcohol solution was added to make granules by passing through a mesh (1150 μm) and the granules were kept at 40°C for 2 h. After this, the granules were passed though a mesh (1000 μm) and lubricated with magnesium stearate. Granules were compressed by a single station-punching machine with concave punches (diameter 12 mm). The average hardness of compressed tablets was 80 ± 5 N. The core compositions are listed in Table 1.

Coating and drilling

Core tablets were coated using a coating pan. CA (2%, w/v) containing 40% PEG-1500 was used as the coating solution. The diameter of the coating pan was 230 mm, the pan-rotating rate was 40 rpm and the spray rate of the CA solution was 4 mL min^{-1}. Coated tablets were dried at 40°C for 12 h. The average weight increase after coating was 40 mg per tablet. The coated tablets were drilled by a mechanical drill to obtain a uniform orifice diameter of 0.6 mm.

In-vitro drug release

The in-vitro release of the EOP was carried out using 500 mL of pH 6.8 phosphate buffer as the medium in USP paddle apparatus at 37°C and 50 rpm. Five-millilitre samples were taken at 1, 2, 3, 4, 6, 8 and 10 h and filtered through 0.45 μm filter membrane. Five millilitres of fresh dissolution medium was added after each sampling. Determination of MT: the filtrate was diluted with pH 6.8 phosphate buffer (dissolution medium) and determined at 233 nm by UV. Determination of GZ: the filtrate was determined at 275 nm by HPLC.

Pharmacokinetic study

In-vivo evaluation of the EOP was performed relative to the equivalent dose of conventional MT tablet and GZ

Table 1 Core tablet formulations

Ingredients (mg)	Formulation 1	Formulation 2	Formulation 3
MT	500	500	500
GZ	5	5	5
Sodium carbonate	0	5	10
PVP K90	30	30	30
Magnesium stearate	3	3	3
70% alcohol	Appropriate	Appropriate	Appropriate

tablet by a cross-study in six Beagle dogs. The dogs were open-labelled and fasted for 12 h. Five-millilitre samples of blood were collected pre-dose and at the following times post-dose: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 14 and 24 h. Samples were immediately centrifuged at 3500 rpm for 10 min. The plasma was separated and frozen at −20°C until required. Concentrations in plasma vs time data were evaluated using 3P97 Professional (Chinese Pharmacological Association software). Determination of MT and GZ in plasma were as shown by Chen et al (2003) and Zhong et al (1999). All studies were conducted in accordance with the Principles of Laboratory Animal Care (NIH publication no. 85-23, revised in 1985) and were approved by the Department of Laboratory Animal Research at Shenyang Pharmaceutical University.

Statistical analysis

Results from the various formulations were analysed with the SPSS statistical package using an analysis of variance to assess any significant ($P < 0.05$) differences.

Results and Discussion

Tablet formulation design

Previous studies have shown that the solubility of GZ increases in higher pH media. The solubility of GZ in saturated Na_2CO_3 solution was $137.7 \pm 0.8\,\mu g\,mL^{-1}$. Sodium carbonate was therefore chosen as a solubilizer for GZ to modulate the microenvironment pH within the core during the dissolution process. Figure 1 shows that GZ released from the osmotic pump without sodium carbonate was incomplete. Incorporation of sodium carbonate could modulate the solubility of GZ within the core, leading to complete release of GZ from the osmotic systems. However, sodium carbonate had no significant influence ($P > 0.05$) on the release of MT, as shown in Figure 2. On the other hand, the use of PVP K30 in the core tablet as a binder was to overcome the difficulty of the poor compressibility and compactibility of high-dose MT. MT was not only one of the active ingredients but also the osmotic agent. Based on the results obtained, the optimal formulation of these EOPs was: 5 mg sodium carbonate; 30 mg PVP K90; membrane weight 40 mg per tablet; 40% PEG-1500 in CA membrane; 0.6 mm orifice.

Evaluation of the optimal EOP

To investigate the influence of release media on drug release, dissolution tests of the optimal formulation were conducted in 0.1 M HCl containing 0.25% sodium dodecyl sulfate for the first 2 h and changed to pH 6.8 phosphate buffer for the following 8 h. Figures 3 and 4 show the release profiles of the EOP in these release media. When the pH of the media was increased, the release rates of drugs were not significantly different ($P > 0.05$). It may therefore be expected that the drug release from this EOP will be independent of the gastrointestinal fluid.

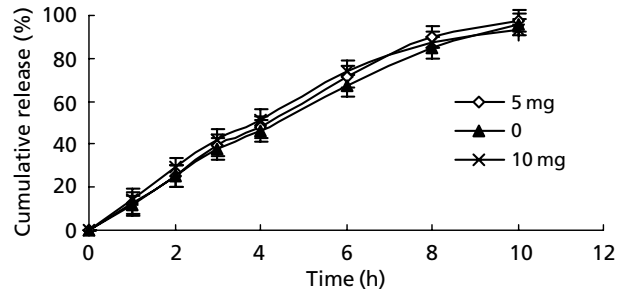

Figure 1 Influence of sodium carbonate on MT release profiles (n = 6).

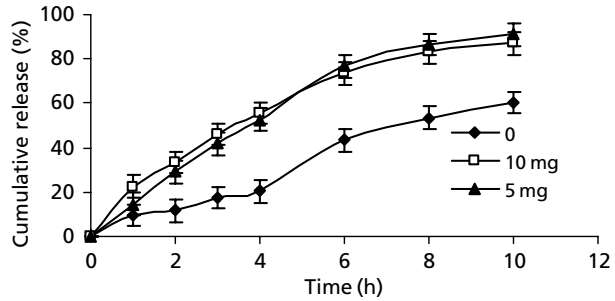

Figure 2 Influence of sodium carbonate on GZ release profiles (n = 6).

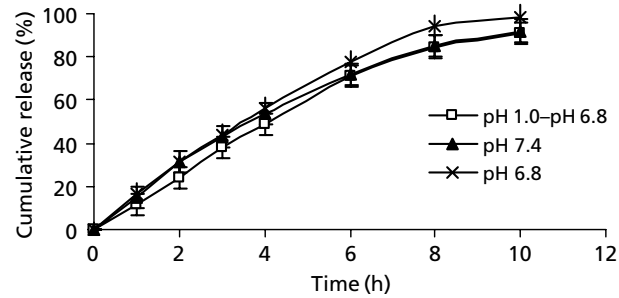

Figure 3 Influence of environmental media on MT release profiles (n = 6).

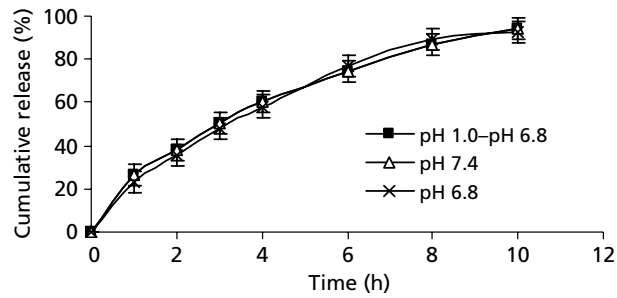

Figure 4 Influence of environmental media on GZ release profiles (n = 6).

Preparation of the EOP was simple since it was not necessary to consider a push compartment or which side should be drilled. Compared to the modified push–pull osmotic system, less excipient was used in this EOP and satisfactory drug-release rates were obtained. The optimal EOP was found to be able to deliver MT and GZ at a rate of approximately zero order up to 10 h in pH 6.8 ($r = 0.9795$ and 0.9472, respectively), the cumulative release at 10 h was 95 and 94%, respectively, and the drug-release rate can be adjusted to what we need by changing the membrane weight and the percentage of PEG-1500 in the membrane. Furthermore, this EOP was independent of the environment media. In conclusion, the EOP designed in this study could be a good controlled delivery system for combination drugs.

In-vivo evaluation

The mean plasma concentrations vs time profile are illustrated in Figures 5 and 6. It can be seen that the EOP had a good sustained effect. From 3P97 software, the relative bioavailabilities of MT and GZ were 89.1 and 102.2%, respectively. In-vitro/in-vivo correlation of EOP was investigated using the percentage dissolved vs the percentage absorbed. The correlation coefficients of MT and GZ were 0.9655 and 0.9526, respectively.

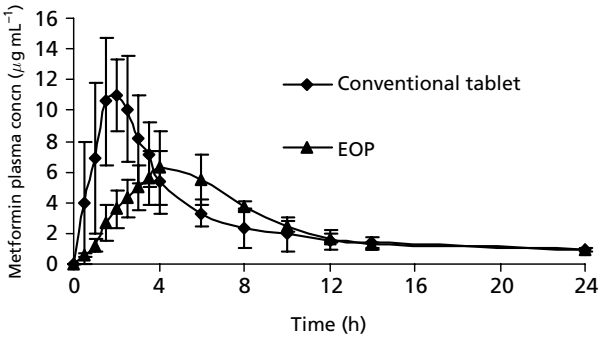

Figure 5 Mean plasma concentrations of MT vs time profile (n = 6).

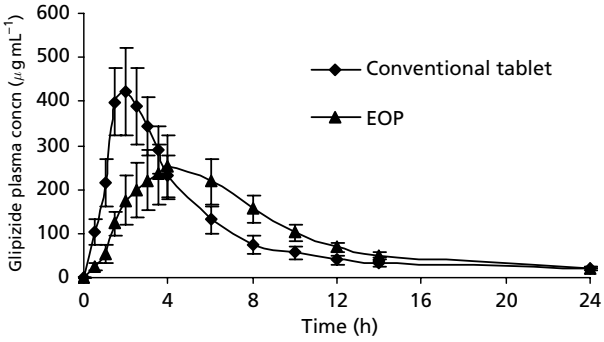

Figure 6 Mean plasma concentrations of GZ vs time profile (n = 6).

Conclusions

The present study developed an oral osmotic system that can deliver MT and GZ simultaneously. The release rate of both drugs can be effectively modified by the addition of sodium carbonate, which can manipulate pH within the tablet. The elementary osmotic system could be effective in the multidrug therapy of diabetes by delivering both drugs simultaneously in a controlled manner. The prototype design of the system could be applied to other combinations of drugs (one slightly water-soluble or insoluble drug and another freely water-soluble drug) used in cardiovascular diseases, diabetes, etc.

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