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Investigation of an active film coating to prepare new fixed-dose combination tablets for treatment of diabetes

Ju-Young Kim[a,1], Dong-Wook Kim[b,1], Yun-Mo Kuk[b], Chun-Woong Park[a,1], Yun-Seok Rhee[c], Tack-Oon Oh[a], Kwon-Yeon Weon[b,**], Eun-Seok Park[a,*]

[a] School of Pharmacy, Sungkyunkwan University, Suwon 440-746, Republic of Korea
[b] R&D center, Handok Pharmaceuticals Co., Ltd., Seoul 131-879, Republic of Korea
[c] College of Pharmacy, Gyeongsang National University, Jinju 660-701, Republic of Korea

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ABSTRACT

The aim of the present study was to formulate new fixed-dose combination tablets (FCTs) by coating a glimepiride (GLM) immediate-release (IR) layer on a metformin hydrochloride (MTF) extended-release (ER) core tablet using perforated film coating equipment.

Composition of GLM-IR coating suspension for homogeneity was studied and application of near-infrared spectroscopy (NIR) to determine the end-point of the coating process was also investigated. The final product was administered to healthy male volunteers and its pharmacokinetic parameters were analyzed.

GLM-IR coating suspension was prepared with a ratio of SLS to GLM at 0.75 for homogeneity. An inert mid-layer was introduced to prevent contact between MTF-ER core tablet and GLM-IR layer, which led to an increased release rate of GLM in pH 7.8 medium. The proportional correlation was confirmed between analytical results of GLM determined by NIRS and those by HPLC-UV. Thus, the end-point of the GLM coating process was determined by NIRS, the fast and non-destructive method. New FCTs were confirmed to be bioequivalent to the marketed product.

1. Introduction

Glimepiride (GLM) is a medium-to-long acting sulfonylurea anti-diabetic drug and acts as a secretagogue. It lowers blood sugar by stimulating the release of insulin and by inducing increased activity of intracellular insulin receptors (Davis, 2004; Katzung et al., 2009). Metformin hydrochloride (MTF) is an anti-diabetic drug of the biguanide class and improves hyperglycemia primarily by suppressing glucose production in the liver, increases insulin sensitivity, enhances peripheral glucose uptake, increases fatty acid oxidation and decreases absorption of glucose from the gastrointestinal tract (Katzung et al., 2009; Scarpello and Howlett, 2008).

For a few decades, co-administration of GLM and MTF has been clinically attempted to achieve better glucose control for diabetes patients (Charpentier et al., 2001; Nauck et al., 2009). Administration of GLM is generally once daily, while MTF is given more than twice daily. In addition, fixed-dose combination tablets (FCTs) of MTF and glyburide, another sulfonylurea drug, showed improved patient compliance of long-term diabetes treatment (Melikian et al., 2002). Therefore, there have been medicinal needs of FCTs consisting of an immediate-release (IR) part of GLM and an extended-release (ER) part of MTF for better clinical efficacy and patient compliance.

A few pharmaceutical technologies could be employed to prepare combined oral dosage forms consisting of an immediate-release part and an extended-release part. For example, multi-layer tablets can be designed for such a purpose, but expensive and specialized tableting machine is necessary (Mandal and Pal, 2008; Pattanayak and Dinda, 2011). Multi-unit dosage forms which have different release rates (e.g., coated pellets or mini-tablets) are studied as well (Li and Zhu, 2004; Tissen et al., 2011; Zeeshan and Bukhari, 2010). However there have been some limitations such as a time-consuming process to prepare these pellets/mini-tablets. Furthermore, preparation of the pellets requires expensive and specialized equipment (e.g., a fluid bed processor).

* Corresponding author at: School of Pharmacy, Sungkyunkwan University, Jangan-gu, Suwon, Gyeonggi-do 440-746, Republic of Korea. Tel.: +82 31 290 7715; fax: +82 31 290 7729.
** Corresponding author at: R&D Center, Handok Pharmaceuticals Co., Ltd., Jungnang-gu, Seoul 131-879, Republic of Korea. Tel.: +82 2 490 1301; fax: +82 2 490 1305.
E-mail addresses: kwonyeon.weon@handok.com (K.-Y. Weon), espark@skku.edu (E.-S. Park).
[1] Authors equally contributed to this work.

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For the achievement of a commercial product (Amaryl®-Mex, Handok Pharmaceuticals Co., Ltd., Korea) which was launched in Korea, we prepared a new FCT for once daily administration of GLM and MTF by coating GLM-IR layer on MTF-ER core tablet. With this active film coating method, favored oral dosage forms can be prepared with a smaller tablet diameter than multi-layer coated tablets. Further, a film coating machine and tableting machine simply used without other specialized equipment, making this process more advantageous. Because of low aqueous solubility, an aqueous coating suspension of GLM was prepared with special attention to its homogeneity.

In the pharmaceutical industry, the end-point of the coating process is generally determined by measuring the increase in tablet weight. However, the coating layer contains active ingredient in active film coating process thus near-infrared spectroscopy (NIRS), a more sensitive method, was evaluated as an analytical tool for determining the end-point. The final product was administered to healthy male volunteers and pharmacokinetic parameters of GLM in new FCTs were compared with those of the marketed product.

2. Materials and experimental methods

2.1. Materials

GLM and MTF were obtained from Sanofi-Aventis (Paris, France) and Farmhispania (Barcelona, Spain), respectively. Hydroxypropyl methylcellulose (HPMC) with 4.5 cP, 6 cP and 100 cP were obtained from Shin-Etsu (Tokyo, Japan) and sodium lauryl sulfate (SLS) was purchased from Cognis (Monheim, Germany). Glipizide as an internal standard for LC/MS/MS analysis was purchased from Sigma–Aldrich (St. Louis, MO, USA). Other materials were of USP-NF grade and solvents were of HPLC analytical grade. All the studies were carried out using distilled water.

2.2. Preparation of MTF-ER tablets

MTF-ER tablets (total weight: 1000 mg) consisted of 500 mg of MTF, 430 mg of HPMC K100 M, 35 mg of povidone K-30, 30 mg of lactose monohydrate and 5 mg of magnesium stearate. MTF-ER tablets were prepared by the wet granulation method. MTF, HPMC K100 M and povidone K-30 were mixed and granulated with distilled water using a high shear granulator (P100, Diosna & Söhne GmBH, Osnabrück, Germany). After the drying process, granules were lubricated with magnesium stearate and were compressed into tablets using a rotary tableting machine (T-200, Killian & Co., GmBH, Köln, Germany) equipped with a 20 mm × 10 mm oblong punch.

2.3. Preparation of the GLM-IR coating suspension

GLM (2.0 g) and SLS (0.2–3.0 g) were added to distilled water (80 g) in a glass beaker and homogenized using a Ultraturrex T-25 (IKA-Werke GmBH & Co. KG, Staufen, Germany) at 8000 rpm for 10 min to prepare GLM suspension. To evaluate its homogeneity, samples were collected at the bottom of the glass beaker after 3 h of stirring. Concentrations of GLM in the samples were analyzed using HPLC-UV. Excipients such as HPMC (4.5 cP), PEG 6000 and titanium oxide were added to the GLM suspension and therefore, GLM-IR coating solution contained 8.33% of HPMC, 1.81% of PEG 6000, 0.5% of titanium oxide, 0.32% of GLM, 0.24% of SLS and 88.76% of distilled water.

2.4. Measurement of particle size distribution and zeta potential of the suspension

Particle size of the suspension was measured by a laser diffraction size analyzer (Mastersizer 2000, Marvern Instruments, Malvern, UK). Samples were diluted 5 times with distilled water and dispersed at 1000 rpm for measurement. The obscuration concentration ranged from 10 to 15%. D_{v10}, D_{v50}, and D_{v90} corresponded to the diameters at which the cumulative sample volume was under 10%, 50% and 90%, respectively. Zeta potential was determined using ELS-8000 (Otsuka Electronics, Osaka, Japan). All measurements were performed in triplicate.

2.5. Formulation of new FCTs

MTF-ER tablets were coated with a 12% (w/w) HPMC (4.5 cP or 6 cP) aqueous solution for a 1% weight gain of the core tablet. Bare MTF-ER tablets and HPMC-coated MTF-ER tablets were coated with GLM-IR coating suspension. The coating process was conducted using a PC-1500 perforated pan (Glatt GmBh, Binzen, Germany). Spray rate, atomizing pressure and outlet temperature were 250 g/min, 2.0–3.0 bar and 50 ± 5 °C, respectively.

2.6. Quantitative analysis by NIRS

NIRS was evaluated as a quantitative analytical tool for GLM to determine the end-point of the coating process. Regression analysis was carried out between GLM content analyzed by NIRS and HPLC-UV (n = 410).

NIR spectra were recorded in the reflectance mode on a Model 5000 spectrophotometer (FOSS NIR Systems, Laurel, MD, USA). The instrument was controlled by Vision 3.3.0 software (FOSS NIR Systems, Laurel, MD, USA), which also provided the spectral pretreatments and multivariate partial least squares (PLS) calibration algorithms. The range of wavelength used was 1100–2500 nm.

2.7. In vitro release study

In vitro dissolutioin rate of GLM and MTF was determined in a dissolution tester (VK7000 and VK8000, Varian Inc., Palo Alto, CA, USA) following the USP apparatus II method at 37.0 ± 0.5 °C. For GLM (n = 6), The medium was 900 mL of pH 7.8 phosphate buffer (pH 7.8 medium) solution and paddle rotation speed was 100 rpm. For MTF (n = 6), medium was 900 mL of simulated intestinal fluid without enzyme (pH 6.8 medium), 500 mL of fasted state simulated intestinal fluid (FaSSIF) and 1000 mL of fed state simulated intestinal fluid (FeSSIF). Composition of FaSSIF and FeSSIF corresponded with that in the literature (Galia et al., 1998). The rotation speed was 50 rpm. Difference factor (f_1) and similarity factor (f_2) were calculated using the following equation;

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \times 100 \quad (1)$$

$$f_2 = 50 \times \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (2)$$

where n is the number of withdrawal time points, R_t is the percentage dissolved of reference product at time point t and T_t is the percentage dissolved of test at time point t (Moore and Flanner, 1996; Shah et al., 1998).

2.8. Stability test

New FCTs collected from 3 different batches ($n = 3$ for each batch) were packed in a polypropylene bottle and were placed under accelerated conditions ($40 \pm 2\,^{\circ}C/75 \pm 5\%$ RH) for 6 months. Content of GLM, MTF and impurities of each drug was determined using HPLC-UV.

2.9. HPLC-UV analysis of MTF and GLM

A validated HPLC-UV method was employed to determine concentrations of MTF and GLM. Agilent 1100 series HPLC system (Agilent Technologies, Santa Clara, CA, USA) was used. HPLC conditions for MTF and its impurity were as follows: column – 4.6 mm × 25 mm, 5 μm, stainless steel column with benzene sulfonic acid group, mobile phase – 1.7% (w/v) $NH_4H_2PO_4$ aqueous solution (pH was adjusted to 3.0), injection volume – 10 μL, flow rate – 2.0 mL/min, column temperature – 40 °C, wavelength – UV 218 nm. The conditions for GLM and its impurities were: column – Sheseido capcell pak C18 (4.6 mm × 250 mm, 5 μm, Japan), mobile phase – 0.1% Na_2PO_4 aqueous solution:ACN = 1:1 (pH was adjusted to 3.0), injection volume – 10 μL, flow rate – 1.4 mL/min, column temperature – 40 °C, wavelength – UV 228 nm.

2.10. Pharmacokinetic study

2.10.1. Study design

An open, randomized, crossover pharmacokinetic study was performed, which was fully approved by the Korean Food and Drug Administration. Healthy male volunteers ($n = 12$) were enrolled in the present study. Body weight ranged between 50 and 90 kg and age ranged between 19 and 45 years old. Written informed consent was obtained from all volunteers, and the institutional ethics committee approved the protocol.

Tested treatments were as follows:

(1) New FCTs of the present study (Amaryl®-Mex, FCTs containing GLM-IR 2 mg and MTF-ER 500 mg, Handok Pharmaceuticals Co., Ltd., Korea), q.d.
(2) Amaryl®-M (FCTs containing GLM-IR (2 mg) and MTF-IR (500 mg), Handok Pharmaceuticals Co., Ltd., Korea), q.d.

The wash-out period between the treatments was 1 week. Blood samples were collected at predetermined time points via a catheter. Plasma was obtained from the blood samples by centrifugation at 3000 rpm for 10 min. Plasma was thereafter stored at −40 °C until analysis.

2.10.2. Determination of GLM concentrations in plasma

Concentrations of GLM in plasma were determined using a previously described method with a modification (Kim et al., 2004; Salem et al., 2004). Plasma samples (200 μL) were transferred into eppendorf tubes and were spiked with 100 μL of 50 ng/mL internal standard solution (glipizide in methanol). The samples were mixed by vortexing for 20 s prior to centrifugation at 13,000 rpm for 10 min. Supernatant (10 μL) was injected into a high turbulence liquid chromatography (HTLC) system (Aria HTLC system, Cohesive Technologies, Franklin, MA, USA). After on-line extraction, samples were eluted on an HPLC–MS/MS system (1100 series, Agilent Technologies, Santa Clara, CA, USA/API 4000, Applied Biosystems, Carlsbad, CA, USA). A C_{18} analytical column (Luna C_{18}, 50 mm × 2.0 mm, 3.0 μm, Phenomenex, Torrance, CA, USA) was used. GLM (491.3 > 352.4) and the internal standard (446.2 > 321.4) were detected by the multiple reaction monitoring (MRM) scan mode with positive ion detection.

The samples were calibrated against a standard curve in the range of 0.2–500 ng/mL. The pharmacokinetic parameters such as area under the plasma concentration–time curves from time 0 to 24 h ($AUC_{24\,h}$), peak plasma concentrations (C_{max}) and time to reach C_{max} (t_{max}) were calculated from the data obtained using a non-compartmental method operated on a commercial software program WinNonlin® (Pharsight, St. Louis, MO, USA). Log-transformed AUC_{24} which were set up as the primary pharmacokinetic parameter of individual subjects were averaged per treatment group. The point estimator was obtained for the difference between those averages and their 90% confidence interval at 0.05 significance level was generated.

2.11. Statistical analysis

All statistical analyses were performed using a *t*-test with Minitab™ software (release 13.32, Minitab Inc., State College, PA, USA) and values of $p < 0.05$ were considered statistically significant.

3. Results and discussion

3.1. Preparation of MTF-ER tablets

The release rate of MTF-ER tablets was compared to that of the marketed product (Glucophage™ XR, Merck Santé s.a.s, France) as displayed in Fig. 1. In pH 6.8 medium, FeSSIF and FaSSIF, difference factor and similarity factor between MTF-ER tablets and the marketed product were summarized in Table 1.

The release rate of MTF in FeSSIF and FaSSIF was investigated because bioavailability of MTF could be affected by food intake (Marathe et al., 2000; Nicklin et al., 1996). Similarity factor and difference factor are tools to evaluate equivalence between two *in vitro* profiles. Difference factors between 0 and 15 and similarity factors between 50 and 100 suggest that two release profiles are similar (FDA, 1997; Moore and Flanner, 1996).

As given in Table 1, difference factors smaller than 15 and similarity factors larger than 50 in 3 different medium indicated that release rates of MTF-ER tablets and the marketed product were equivalent. Thus, MTF-ER tablets were employed as core tablets for coating in further study.

3.2. Preparation of coating suspension containing GLM

When GLM was dispersed in distilled water, it was observed that drug particles were not wet but were floated on the medium due to its practically insoluble property (Seedher and Kanojia, 2008). During the coating process, homogeneity of the coating solution/suspension should be retained. Thus, the effect of SLS on homogeneity of GLM suspension was investigated. SLS is an anionic surfactant employed in pharmaceutical formulations and cosmetics (Rowe et al., 2006). It was already reported that aqueous solubility of GLM could be enhance by addition of SLS (Seedher and Kanojia, 2008).

As displayed in Fig. 2(A), when the ratio of SLS to GLM was less than 0.25, the content of GLM in the collected sample was only 16–21% after 3 h. This meant that GLM particles were still not dispersed homogenously. On the other hand, with a ratio of 0.75 or 1.00, content of GLM in the samples reached 95%. As shown in Fig. 2(B), the D_{v50} of GLM in the suspension was not affected by

Table 1
Comparison of dissolution profiles of MTF-ER tablets and marketed products.

	In pH 6.8 medium	In FeSSIF	In FaSSIF
Difference factor (f_1)	5.6	10.2	5.9
Similarity factor (f_2)	68.8	66.2	78.1

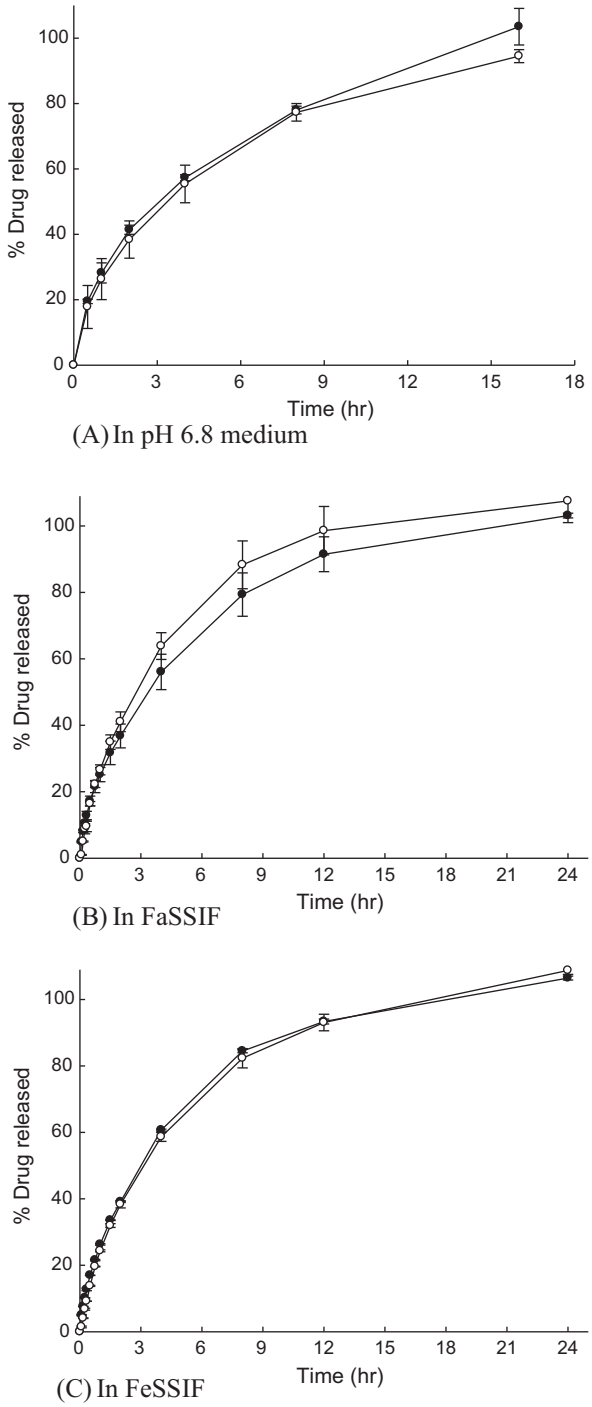

Fig. 1. Release profiles of MTF from MTF-ER tablets (○), Glucophage™ XR (●); (A) in pH 6.8 medium, (B) in FaSSIF and (C) in FeSSIF ($n = 6$, mean ± S.D).

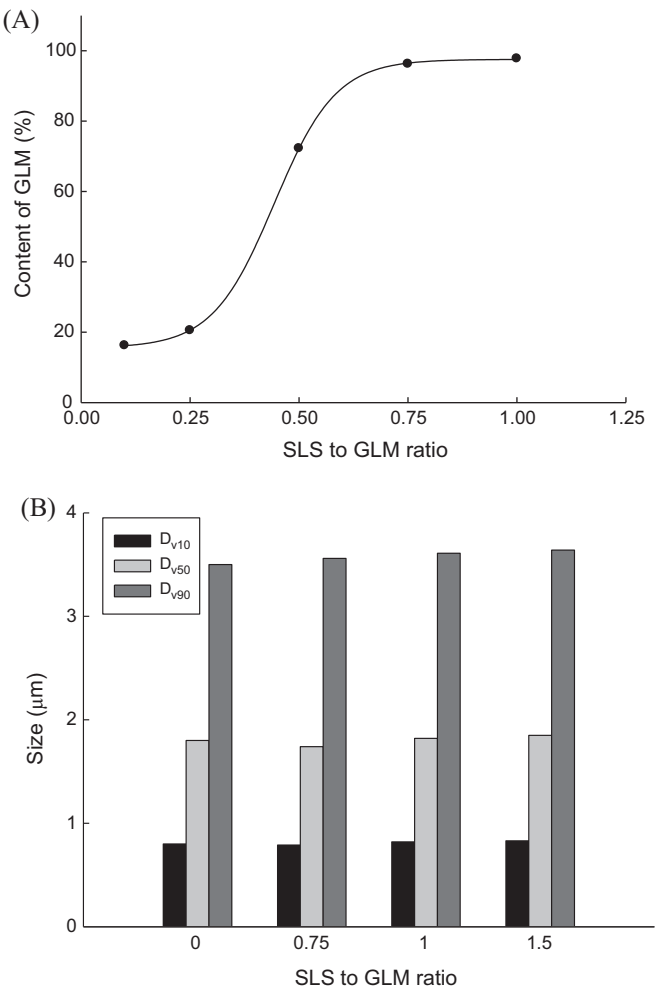

Fig. 2. Effect SLS to GLM ratio (A) on homogeneity of GLM suspension ($y = 82.0102/(1+\exp((-x+0.4430)/0.0709)) + 15.5326$, $r^2 = 1.0000$) and (B) on size distribution of GLM particles.

the SLS to GLM ratio. It was also observed that the homogenization step did not increase the amount of impurities of GLM ($p > 0.05$, data not shown). Thus, a homogeneous and chemically stable GLM suspension could be prepared by homogenization with a ratio of SLS to GLM at 0.75.

HPMC and PEG 6000 were added to GLM suspension (with ratio of SLS to GLM at 0.75), serving as a coating material and a plasticizer, respectively. Titanium oxide was also added into GLM-IR coating suspension. As displayed at Fig. 3(A), the magnitude of zeta-potential was decreased by addition of HPMC and PEG 6000, which was caused by adsorption of polymer onto the drug particles (Duro et al., 1998; Lucks et al., 1990). When titanium oxide was incorporated as well, the magnitude of zeta-potential for GLM-IR coating suspension was increased to −32.3 mV. The isoelectric point of titanium oxide was reported as 3.50 (Xu et al., 2003). Because pH of GLM suspension was 4.28, titanium oxide particle was negatively charged when added to the suspension. Hence, titanium oxide served as an electrostatic stabilizer as well as a white pigment. Since the zeta potential of GLM-IR coating suspension was still smaller than −30 mV after addition of excipients, it was still physically stable (Everett, 1988). The D_{v50} of GLM particles was not affected by incorporation of these excipients, as shown in Fig. 3(B).

3.3. Preparation of new FCTs containing GLM and MTF

The effect of an inert mid-layer on release rate of GLM was investigated. As depicted in Fig. 4, only 40% of GLM was released in 60 min without an inert mid-layer. On the other hand, 85% of GLM was released in 60 min when an inert mid-layer containing HPMC (4.5 cP) was part of the coating.

During the release test, the medium easily diffused to the core tablet through the hydrophilic coating layer, which led to swelling of HPMC with a high viscosity grade in the core tablet. When the HPMC matrix was swollen, a viscous hydrogel surrounding the matrix was established (Baumgartner et al., 2005; Conti et al., 2007). This viscous hydrogel was thought to make GLM-IR layer stick on the core tablet and retard the release rate of GLM. When inert HPMC layer was introduced, it could prevent contact between

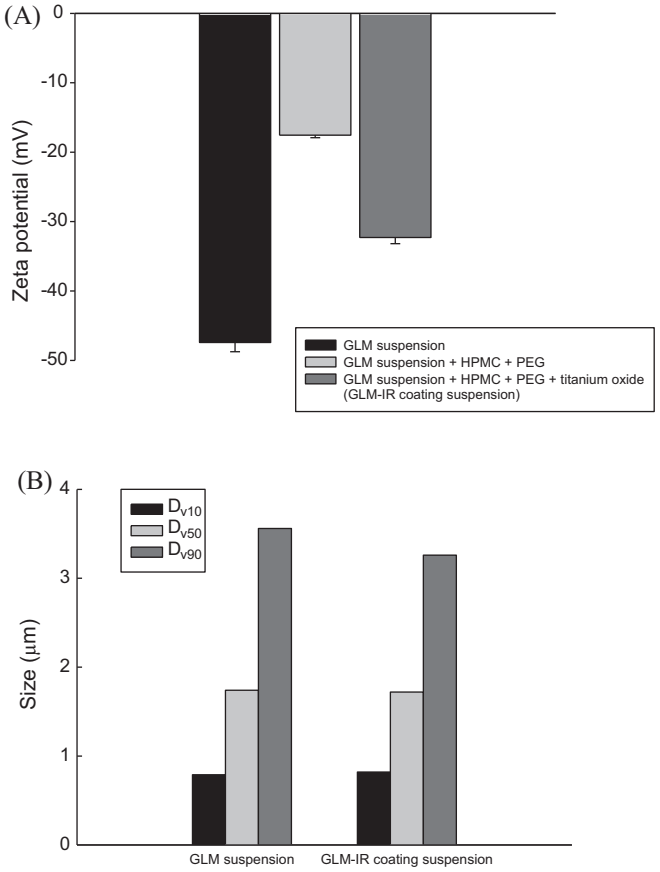

Fig. 3. (A) Zeta potential ($n = 3$, mean ± S.D.) and (B) size distribution of GLM suspension and GLM-IR coating suspension.

the GLM-IR layer and the core tablet. Although the inert mid-layer also contained HPMC, its much lower viscosity grade did not cause the decrease in release rate. However, when HPMC 6 cP was layered, only 45% of GLM was released in 60 min. It was certain that the release rate of GLM could be retarded when viscosity grade of HPMC in the inert mid-layer was over 4.5 cP.

Release profiles of new FCTs are displayed in Fig. 5. Released amount of GLM from new FCTs was 95% in 45 min. Compared with the marketed product (Amaryl®, Sanofi-Aventis, France) there was

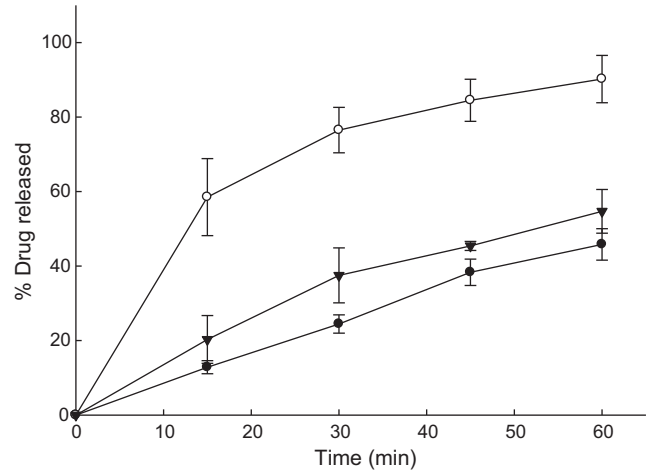

Fig. 4. Effect of inert mid-layer on release rate of GLM from new FCTs; without the mid-layer (●), with inert mid-layer containing HPMC 4.5 cP (○), with inert mid-layer containing HPMC 6 cP (▼) ($n = 3$, mean ± S.D).

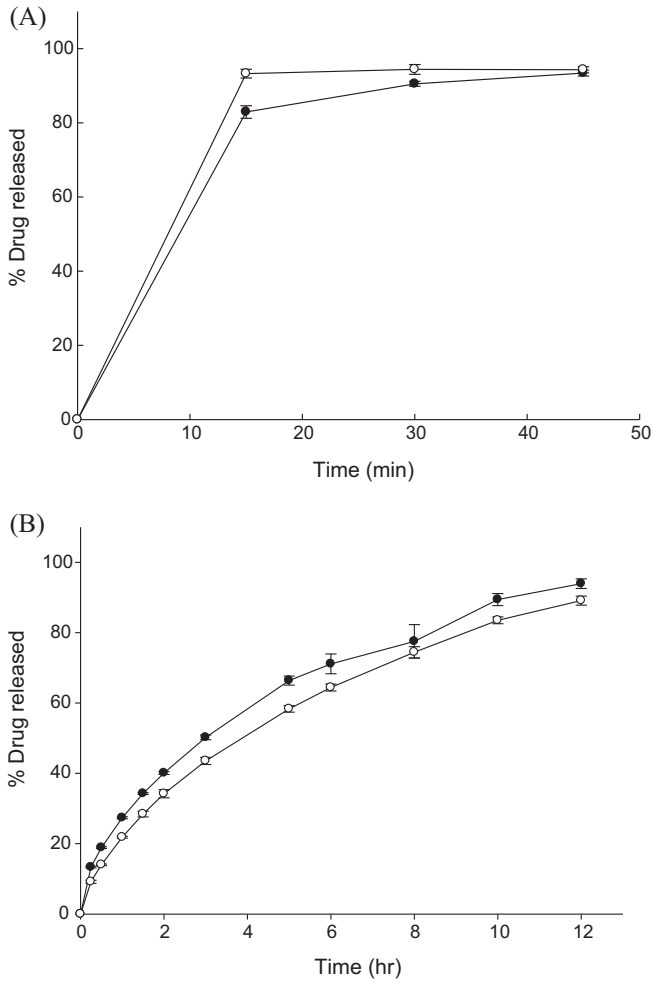

Fig. 5. (A) Release profiles of GLM from new FCTs (●) and Amaryl® (○). (B) Release profiles of MTF from new FCTs (●) and Glucophage™ XR (○) ($n = 12$, mean ± S.D).

no significant difference in the amount of drug released ($p > 0.05$). Release rate of MTF was equivalent (similarity factor: 61.7) to that of the marketed product (Glucophage™ XR, Merck Santé s.a.s, France) as well. As a result, new FCTs which had equivalent release rates of GLM and MTF to those of the marketed product can be prepared by introducing an inert mid-layer containing HPMC 4.5 cP.

Content of GLM in the new FCTs ranged from 93.1 to 108.1% when analyzed using HPLC-UV. Content uniformity of GLM was verified by USP criteria (data not shown) (US Pharmacopeia, 2006). Hardness and friability of new FCTs were 301.8 ± 12.4 N and less than 0.2%, respectively.

3.4. Application of NIRS

NIRS is a promising tool in process analytical technology due to its quickness and non-destructiveness. It has been reported that NIRS could be used to monitor physical properties of tablets (e.g. hardness, porosity, disintegration time), release rate and content of active ingredients (Cahyadi et al., 2010; Donoso and Ghaly, 2005; Gendre et al., 2011; Saeed et al., 2009; Shah et al., 2007). In addition, the usefulness of NIRS to measure physical properties of the coating layer (e.g. coating thickness and mass) is also well documented (Cahyadi et al., 2010; Gendre et al., 2011; Lee et al., 2010). However, it is rarely reported to monitor content of the active ingredient during active film coating (Buchanan et al., 1996).

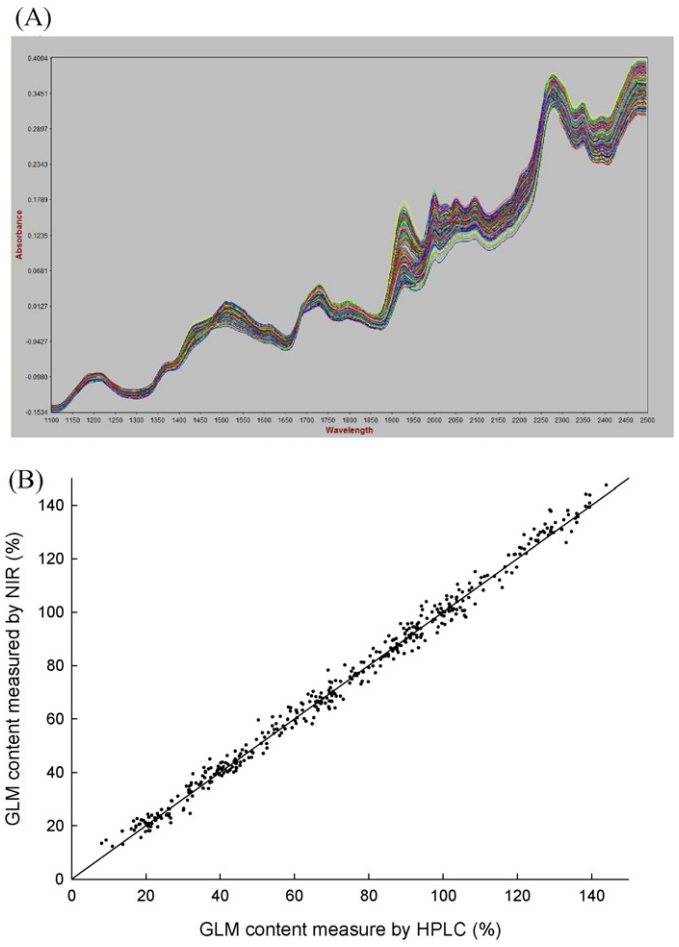

Fig. 6. (A) NIR spectrum of GLM, and (B) a correlation plot of GLM content measured by NIRS versus that by HPLC-UV ($n = 410$, $y = x + 1.4651 \times \exp(-5)$, $r^2 = 0.9916$).

NIR spectrum of GLM is shown in Fig. 6(A). Content of GLM in the coating layer was determined using PLS calibration algorithms in the range of 1100–2500 nm. As shown in Fig. 6(B), coefficient efficiency (r^2) between results analyzed by HPLC-UV and NIRS was 0.9916 with a range of 0.2–2.96 mg of GLM per tablet. Considering the result, it was obvious that NIRS could be used to determine content of GLM in the coating layer in spite of low amount.

Content of GLM in new FCTs determined by NIRS versus the coating time curve is shown in Fig. 7. With a spray rate of 250 g/min, it was observed that 100% (2 mg GLM/tablet) of coating was achieved within 310 min. Hence, the end-point was determined by collecting tablets coated for about 310 min and checking content of GLM in the samples by NIRS.

A major challenge of the active film coating process is determination of the end-point of the coating process which could accompany trouble in content uniformity and quality control. In this study it was quickly and non-destructively handled by applying NIRS without any disturbance in the coating process.

3.5. Stability test

Results of the stability test are displayed in Table 2. There was no significant change in content of GLM for 6 months ($p < 0.05$). Although peaks of glimepiride–sulfonamide and other impurities were detected in chromatograms, the amount did not exceed regulatory limitations (European Pharmacopoeia, 2011)

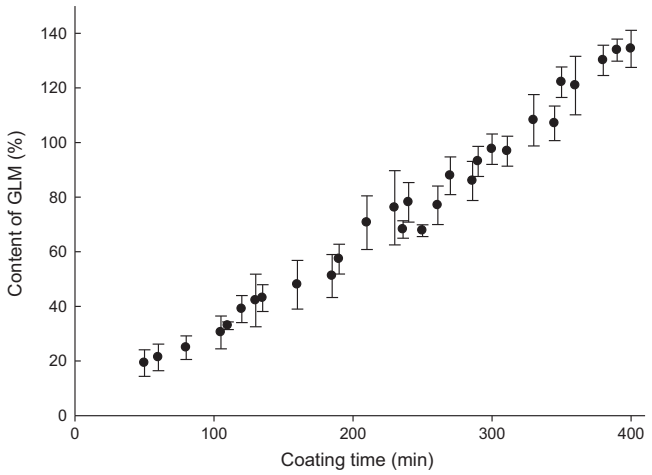

Fig. 7. GLM content measured by NIRS in new FCTs collected at predetermined time during coating process ($n = 5$–10, mean ± S.D).

3.6. In vivo study

GLM plasma concentration versus time curves are shown in Fig. 8 and pharmacokinetic parameters are summarized in Table 3. Mean AUC_{24} of GLM of new FCTs and the marketed product (Amaryl®-M, Handok Pharmaceuticals Co. Ltd., Korea) were 793.2 ± 206.0 μg h/L and 752.3 ± 180.6 μg h/L, respectively. Pharmacokinetic parameters including C_{max}, AUC_{24} and $t_{1/2}$ were not significantly different between two treatments ($p < 0.05$).

As shown in Table 3, 90% confidence interval of point estimator for AUC_{24} was 0.98–1.12. Since 90% confidence interval of point estimator which fall within 0.80–1.25 indicates bioequivalence between two products, GLM in new FCTs and the marketed product is bioequivalent (FDA, 2001).

GLM is classified as biopharmaceutical class system (BCS) II drug and dissolution is the rate-limiting step of drug absorption (Frick et al., 1998). Thus decrease in release rate might lead to decreased absorption rate and prolonged t_{max} of GLM. As shown in Fig. 8 and Table 3, new FCTs and the marketed product showed similar C_{max} and t_{max} values. Hence, it was supposed that equivalent release rate of GLM achieved by applying the inert mid-layer led to bioequivalence between the new FCTs and the marketed product.

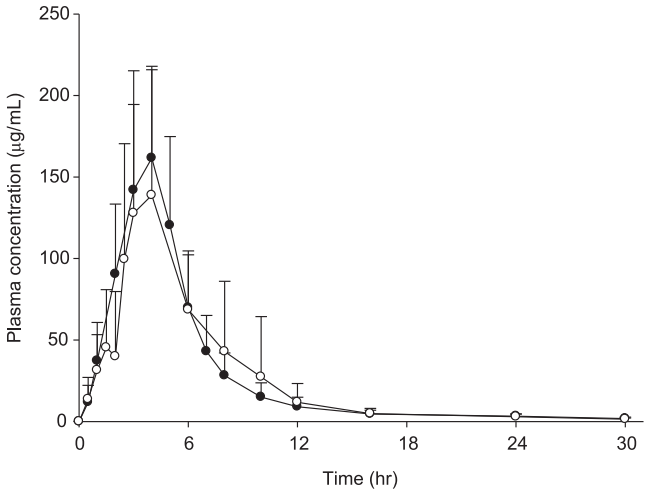

Fig. 8. Mean plasma concentration–time profiles of GLM after oral administration of new FCTs (●) and Amaryl®-M (○) to healthy male subjects. ($n = 12$, mean ± S.D.)

Table 2
Results of stability test of new FCTs ($n = 9$, mean ± S.D).

	Content		Increase of main impurity	
	GLM	MTF	GLM Glimepiride-sulfonamide	MTF 1-Cyanoguanodine
Initial	99.93 ± 1.42%	98.60 ± 0.56%	0.13 ± 0.06%	ND[a]
2 Month	100.10 ± 1.67%	98.73 ± 0.90%	0.33 ± 0.06%	ND
4 Month	99.87 ± 2.67%	99.40 ± 0.70%	0.83 ± 0.06%	ND
6 Month	98.97 ± 2.00%	99.87 ± 0.75%	1.57 ± 0.12%	ND

[a] Not detected.

Table 3
Pharmacokinetic parameters of GLM after oral administration of new FCTs and Amaryl®-M to healthy male subjects ($n = 12$, mean ± S.D).

Group	t_{max} (h)[a]	C_{max} (μg/L)	AUC_{24} (μg h/L)	$t_{1/2}$ (h)	Point estimator (for AUC_{24})
New FCTs ($n = 12$)	4.0 (2.0–5.0)	179.6 ± 46.5	793.2 ± 206.0	9.2 ± 2.3	1.05 (0.98~1.12)[b]
Amaryl®-M ($n = 12$)	3.5 (2.6–8.0)	179.6 ± 56.0	752.3 ± 180.6	8.2 ± 3.2	

[a] t_{max}, median (min–max).
[b] 90% confidence interval.

4. Conclusion

In the present study, new FCTs were comprised of the following 3 layers: (a) an MTF-ER core tablet, (b) an inert mid-layer and (c) an outer GLM-IR layer. It was concluded that the inert mid-layer was necessary to prevent contact between MTF-ER core tablet and GLM-IR layer which retarded the release rate of GLM. A homogeneous aqueous coating suspension of GLM was successfully prepared by incorporating SLS. The coating suspension did not contain organic solvent and thus was considered eco-friendly. In addition, the active film coating method simply required a tableting and coating machine, making it more productive and less costly.

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