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Steady-State Pharmacokinetics of a Novel Extended-Release Metformin Formulation

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Abstract

Background and objective: Metformin is an effective treatment for type 2 diabetes mellitus. The pharmacokinetic characteristics of the conventional immediate-release (IR) formulation of metformin (Glucophage®), however, necessitate two- or three-times-daily dosing. Development of a novel extended-release (XR) formulation of metformin (Glucophage® XR) using GelShield Diffusion System technology provides a once-daily dosing option. The objective of this study was to assess the steady-state pharmacokinetics of metformin XR tablets.

Study design: This was an open-label, multiple-dose, five-regimen, two-sequence clinical study lasting 5 weeks.

Methods: Subjects were 16 healthy volunteers aged 18–40 years. Three 1-week regimens of metformin XR (500, 1000 and 1500mg once daily) were administered sequentially. Subjects were alternately given either metformin XR 2000mg once daily or metformin IR 1000mg twice daily during weeks 4 and 5. The pharmacokinetic properties of metformin XR were assessed on two separate days at steady state and compared with those of metformin IR.

Results: Absorption of metformin XR was slower than that of metformin IR (time to maximum plasma concentration = 7 versus 3 hours). Maximum plasma concentrations (C_{max}) following the administration of metformin XR 2000mg once daily was 36% higher than that following the evening dose of metformin IR 1000mg twice daily. The extent of absorption, determined by area under the plasma concentration-time curve (AUC), was equivalent for both formulations. The mean accumulation ratio of metformin XR was 1.0, indicating no accumulation with multiple-dose administration. Intrasubject variabilities in C_{max} and AUC of metformin were comparable between metformin XR and metformin IR. This novel formulation of metformin XR was well tolerated at single doses up to 2000mg once daily for 7 days, and adverse events were similar to those reported with metformin IR.

Conclusion: The pharmacokinetic parameters of metformin XR tablet using GelShield Diffusion System technology were similar to those of metformin IR. Metformin XR was well tolerated at single doses up to 2000mg once daily.

The biguanide metformin is an established and effective treatment for type 2 diabetes mellitus. The drug in its conventional form, immediate-release (IR) metformin (Glucophage® [1]; Bristol-Myers Squibb Company, Princeton, NJ, USA), is administered orally two or three times daily and has been in use in the US since 1995.

The pharmacokinetic characteristics of metformin IR are not conducive to the slow and controlled release of metformin desirable for a once-daily formulation. Absorption of metformin IR in the gastrointestinal tract appears to be limited by permeability, with absorption occurring almost exclusively in the upper gastrointestinal tract and with poor permeability in the lower gastrointestinal tract.[1] Introduction of the drug into the jejunum via an intubation technique was associated with a 2.5-fold greater area under the plasma concentration-time curve (AUC) compared with introduction into the ileum. No absorption was apparent when the drug was introduced into the colon.[1] The absolute bioavailability of a 500mg dose of metformin IR is 50–60% and decreases as the dose increases, suggesting some form of saturable absorption or permeability/transit time-limited absorption.[2,3] Food causes a reduction in the bioavailability of metformin IR.[4] Additionally, metformin is highly soluble in water,[5] which usually results in rapid dissolution from a dosage form. These obstacles are compounded by the high unit dose of metformin IR, specifically, 500mg per tablet.

Drugs that have limited absorption in the upper gastrointestinal tract, such as metformin, are usually regarded as poor candidates for incorporation into modified-release formulations. Most oral modified-release delivery systems function by delivering a drug for absorption over an extended period and along the length of the gastrointestinal tract following administration. However, such delivery devices might not be suitable for metformin because of the relatively narrow window of absorption. In addition, the high water solubility of metformin means that large amounts of polymer are required to control its release from conventional modified-release formulations. This makes the application of many existing extended-release (XR) technologies inappropriate for metformin. A number of mechanisms may be used to produce a dosage form that delivers a drug over an extended period in the upper gastrointestinal tract; however, many of these mechanisms have important limitations. For example, coadministration of metformin and propantheline – a drug that reduces gastrointestinal motility – has been shown to extend the period during which metformin plasma levels are maintained.[6] However, administration of propantheline for the sole purpose of extending residence in the upper gastrointestinal tract has many disadvantages, including the potential for undesirable anticholinergic adverse effects. Various other delivery devices have been proposed that could extend the residence time of metformin in the upper gastrointestinal tract, including: (i) floating or buoyant systems that float on gastric contents; (ii) bioadhesive systems that adhere to the gastric mucosa/mucus layer; and (iii) systems with a large size, either intrinsically or through swelling/expanding systems designed to prevent passage through the pylorus. To overcome these difficulties, a novel, biphasic, controlled-release delivery system – the GelShield Diffusion System, which can be included under the third category just described – has been developed and used for the XR formulation of metformin (Glucophage® XR, Bristol-Myers Squibb Company, Princeton, NJ, USA).[7]

The controlled-release delivery system uses a heterogeneous, two-phase approach, composed of an inner solid particulate phase and an outer solid continuous phase (figure 1). For the metformin XR tablet, the inner solid particulate phase contains individual granules of metformin-associated XR polymer. The outer solid continuous phase consists of a different XR polymer containing no metformin; the granules or particles of the inner phase are dispersed within it (figure 1). Following administration, the polymers in the outer solid phase hydrate and cause the tablet to develop into a gel-like mass. The initial size of the tablet and its transformation into a nondisintegrating gel may help temporarily

1 The use of trade names is for product identification purposes only and does not imply endorsement.

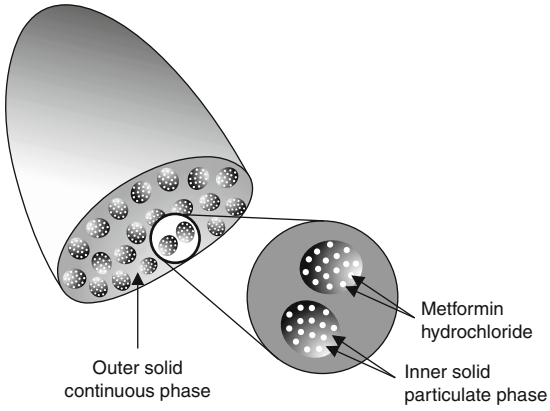

Fig. 1. Diagram of the fabrication of the extended-release metformin (Glucophage XR®) tablet. The tablet consists of fine particles created from a polymer that is intimately associated with metformin hydrochloride (inner solid particulate phase). This polymer-drug combination is then embedded in a continuous matrix of a second hydrophilic polymer (outer solid continuous phase).

prevent transit of the tablet through the pylorus (when administered with food), thereby effectively prolonging gastric residence. Hydrophilic polymer systems for extended oral drug delivery have been established for many decades,[8] and the impact of size on gastric retention of such nondisintegrating dosage forms is also well known,[9-12] but the Gel-Shield Diffusion System represents a novel technology within this field.

On release from the inner solid particulate phase, metformin diffuses through the outer phase and is released for absorption. The rate of release from metformin XR is significantly slower than from metformin IR, as indicated by *in vitro* testing where metformin IR releases 90% of its contained drug within 30 minutes compared with 90% released over about 10 hours, relatively independent of pH and agitation conditions, for metformin XR. These characteristics indicate good control of drug release from metformin XR with low potential for dose dumping. When administered with the evening meal, the Gel-Shield Diffusion System of metformin XR works in concert with the normal physiology of slowed gastrointestinal emptying nocturnally and following a meal, resulting in extended absorption of metformin and permitting once-daily dosing.[13] Over time, the disintegration of the hydrated polymer mass or its pliability enables it to pass through the pylorus, or it may be broken up by normal peristalsis in the gastrointestinal tract. The biologically inert components of metformin XR occasionally remain intact during gastrointestinal transit and are eliminated in the faeces as a soft hydrated mass.[14]

In a preliminary single-dose pharmacokinetic study that compared extended- and immediate-release formulations of metformin, metformin XR produced a similar AUC and similar percentage of urinary recovery as metformin IR (1000mg).[15] Peak plasma concentration (C_{max}) was somewhat lower for metformin XR than metformin IR (978 versus 1226 ng/mL), and time to C_{max} (t_{max}) was longer (3.5 versus 5.1 hours, respectively). Based on these favourable findings, the present study was conducted to assess the steady-state pharmacokinetic properties of multiple doses of metformin XR tablets administered to healthy volunteers. Plasma concentrations of metformin following multiple metformin XR once-daily administration were compared with those of twice-daily metformin IR administration.

Methods

Subjects

Sixteen volunteers were enrolled in the study (nine men and seven women). Their mean age was 27 ± 6.0 years (range 19–40 years). Mean height and bodyweight for the group were 172 ± 11cm (range 160–193cm) and 71 ± 14kg (range 53–103kg), respectively. All volunteers enrolled in the study were Caucasian who were in good health based upon recent medical history, laboratory determinations and physical examination. Informed consent was obtained before enrolment.

Exclusion criteria for the pharmacokinetic study included bodyweight >15% higher or lower than the desirable weight-for-height range, donation of blood within the last 60 days, a history of clinically significant allergies to biguanides, exposure to any investigational agent within 60 days of enrolment or participation in any other clinical trials concurrent with this study, smoking more than ten cigarettes per day,

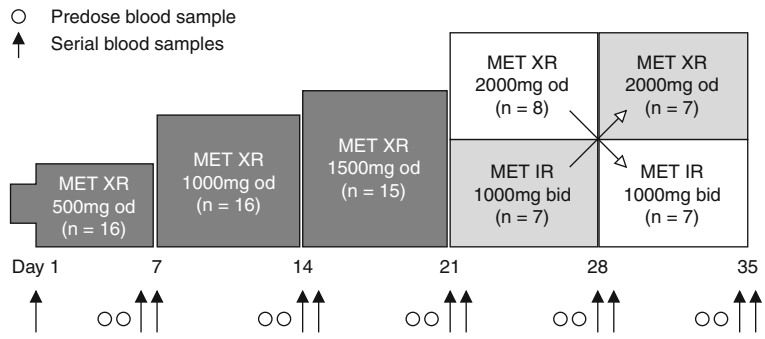

Fig. 2. Design for study of steady-state pharmacokinetics of extended-release (XR) metformin (MET). **bid** = twice daily; **IR** = immediate-release; **od** = once daily.

and a history of gastrointestinal disease or recent use (within 2 weeks of administration) of medication that might affect the gastrointestinal tract. Women who were pregnant or nursing were also excluded.

Study Design

This was an open-label, randomised, multiple-dose, five-regimen, two-sequence clinical study. The total duration of the study was 35 days. Analyses of variance were used to compare pharmacokinetic properties of metformin XR and metformin IR. A sample size of 16 was selected to provide 90% confidence intervals for the difference between the 2000mg dose of metformin XR (administered once daily) and the 1000mg dose of metformin IR (administered twice daily) of ±0.087 for log(C_{max}) and ±0.12 for log(AUC from 0 to 24 hours [AUC_{24}]). These calculations were based on the assumption that C_{max} and AUC_{24} are log normally distributed and the standard deviations are similar to 0.14 for log(C_{max}) and 0.23 for log(AUC) obtained for metformin XR and 0.13 for log(C_{max}) and 0.12 for log(AUC) obtained for metformin IR in an earlier study.[15]

Treatments and Administration

Five 1-week regimens of metformin were administered sequentially, with no washout period between treatments (figure 2). Metformin XR was supplied by Bristol-Myers Squibb Company, Princeton, NJ, USA, and metformin IR was supplied by the investigator, GFI Pharmaceutical Services, Inc., Evansville, IN, USA.

All subjects received metformin XR on days 1–21. Subjects were given one metformin XR 500mg tablet on the evenings of days 1–7. Two tablets once daily were administered on days 8–14, and three tablets once daily on days 15–21. On the evening of day 22, half of the subjects (n = 8) received four metformin XR 500mg tablets, whereas the remaining subjects received two metformin IR 500mg tablets twice daily. There was no morning dose of metformin IR on day 22. On the evenings of days 23–28, half of the subjects received metformin XR tablets, with the remainder receiving the twice-daily regimen of metformin IR. On day 29, the treatments were reversed. The first dose of metformin IR was given in the evening of day 29, and there was no morning dose. Subjects receiving metformin IR in the last period continued the twice-daily regimen from days 29 to 35, with the other subjects receiving evening doses of metformin XR.

All metformin doses were administered with 240mL of water. Each dose of the metformin XR tablet and the evening dose of the metformin IR tablet were administered after a standard dinner. Dinner was provided at 7:00pm and was eaten within 25 minutes. The evening dose of metformin was administered 5 minutes after completion of dinner. A standard breakfast was provided at approximately 7:00am and was eaten within 15 minutes. The morning dose of metformin IR was administered approximately 15 minutes after completion of breakfast.

Pharmacokinetic and Statistical Evaluation

Serial venous plasma samples were collected on two consecutive days at steady state for each treatment. Night-time samples were collected through a venous catheter, and natural sleep was encouraged as much as possible during sampling. Serial samples were collected predose and at 1, 2, 4, 6, 8, 12, 16, 20 and 24 hours after drug administration (evening dose) on days 1, 6, 7, 13, 14, 20, 21, 27, 28, 34 and 35 for the various treatments (figure 2). During administration of metformin IR, blood samples were collected predose and 1, 2, 4, 6, 8, 12, 13, 14, 16, 18, 20 and 24 hours after each morning dose on days 27, 28, 34 and 35. Additionally, predose blood samples were collected before the evening dose on days 4, 5, 11, 12, 18, 19, 25, 26, 32 and 33 (figure 2).

Plasma samples were assayed for metformin by means of a validated gas chromatography-mass spectrometry method. The lower limit of quantitation was established at 10 ng/mL of metformin in plasma, and the standard curve range was 10–2500 ng/mL. The plasma standard curves had R^2 values of ≥0.995. The overall between- and within-run variability of the analytical quality controls (QCs) in plasma was <11.2%. The mean observed concentrations of the analytical QC samples deviated <14.4% from the nominal values.

The following parameters were calculated for the metformin treatments using noncompartmental methods: C_{max} (ng/mL), t_{max} (hours), AUC from time zero to infinity on day 1 (AUC_∞; ng • h/mL), AUC_{24} post-dose (ng • h/mL), and terminal elimination half-life ($t_{1/2}\beta$; hours). To obtain AUC_{24} values for metformin IR, we added the morning and evening AUC from 0 to 12 hours (AUC_{12}) post-dose values. For C_{max}, t_{max} and $t_{1/2}\beta$, the evening dose of the twice-daily regimen was used. An ANOVA model appropriate for a two-by-two crossover design was used to compare metformin XR 2000mg once daily with metformin IR 1000mg twice daily for C_{max}, AUC_{24} and $t_{1/2}\beta$. To estimate intrasubject variability for C_{max} and AUC_{24}, an ANOVA was performed at each dose of metformin XR and for morning and evening doses of metformin IR. The model included day of administration and was blocked by subjects. The square root of the mean square error for $\log(C_{max})$ and $\log(AUC_{24})$ was taken as the estimate of intrasubject variability.

Results

Fourteen subjects completed all regimens in the study; two subjects discontinued the study for unspecified personal reasons.

Pharmacokinetic Profile of Extended-Release (XR) Metformin

The pharmacokinetic parameters of metformin after multiple doses of metformin XR are shown in

Table I. Mean pharmacokinetic parameters for metformin by treatment[a]

Parameter	Metformin XR					Metformin IR[b]
	500mg, single dose	500mg od[c]	1000mg od	1500mg od	2000mg od	1000mg bid
No. of subjects	16	16	16	15	14	15
C_{max} (ng/mL)	645 (115)	603 (166)	1080 (259)	1441 (362)	1780 (288)	1321 (234)
t_{max}, (h)[d]	7 (4–8)	6 (4–8)	7 (4–8)	7 (5–8)	7 (4–9)	3 (1.5–6)
AUC (ng • h/mL)[e]	6666 (1751)	6316 (1996)	12 587 (3164)	16 820 (4160)	20 451 (4114)	20 544 (4445)
$t_{1/2}\beta$ (h)	3.5 (0.7)	5.2 (1.6)	4.5 (0.8)	4.8 (0.5)	5.2 (1.2)	5.1 (1.0)

a Values are mean (SD), unless specified otherwise.

b C_{max}, t_{max} and $t_{1/2}\beta$ values reflect the 7:30pm dose.

c Accumulation ratio = 1.0 (0.2).

d Values are median (range).

e AUC_∞ for 500mg single dose; all others, AUC_{24}.

AUC = area under the plasma concentration-time curve; **AUC_{24}** = AUC from 0 to 24 hours post-dose; **AUC_∞** = AUC from time zero to infinity; **bid** = twice daily; **C_{max}** = maximum plasma concentration; **IR** = immediate-release; **od** = once daily; **$t_{1/2}\beta$** = terminal elimination half-life; **t_{max}** = time to reach C_{max}; **XR** = extended-release.

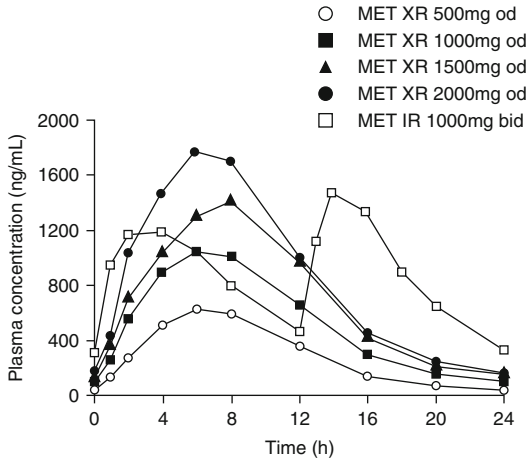

Fig. 3. Mean plasma concentration-time profiles of metformin (MET) at steady state after a once-daily (od) dose of MET extended-release (XR) 500mg, 1000mg, 1500mg or 2000mg, and a twice-daily (bid) dose of MET immediate-release (IR) 1000mg.

table I. Analysis of minimum plasma concentrations indicated that steady state was reached by day 6 for each of the metformin XR treatments. The mean accumulation ratio was 1.0, indicating no accumulation upon multiple dose administration with metformin XR. Mean plasma concentration-time profiles demonstrated that the increase in plasma concentration from the metformin XR tablet was slower than that reported with metformin IR; plasma concentrations peaked about 2–3 hours later (figure 3). The median t_{max} of metformin after administration of metformin XR was 7 hours, compared with 3 hours for metformin IR. Mean C_{max} following the metformin XR 1500mg dose was 1441 ng/mL, which was similar to the mean C_{max} after the evening dose of metformin IR (1321 ng/mL). Geometric mean C_{max} at the highest dose of metformin XR (2000mg once daily) was 36% higher than at the evening dose of the 1000mg twice-daily metformin IR treatment (90% CI 1.29, 1.44) [table II]. This difference in C_{max} was smaller when the C_{max} values following the morning dose of metformin IR were considered. Bioavailability of metformin with the 2000mg once-daily dose of metformin XR was 100% relative to the same total daily dose of metformin administered as metformin IR 1000mg twice daily, measured by metformin AUC (90% CI 0.93, 1.07).

Analysis of average day 6 and day 7 steady-state data revealed that C_{max} and AUC_{24} values increased somewhat less proportionately to the dose of metformin XR (figure 4). Figure 5 illustrates the within-subject variability in AUC_{24} following treatment with the formulation. Estimates of within-subject standard deviations are shown in table III. For metformin XR, the standard deviation ranged from 0.11 to 0.24 (coefficient of variation [CV] 9.1–19.7%). For metformin IR, the standard deviation ranged from 0.09 to 0.17 (CV 8.5–19.2%). These data suggest that the within-subject variability was low and similar for both formulations.

Safety Profile of XR Metformin

A total of 137 adverse events were reported during the study. Similar to the adverse events reported with metformin IR, the most common treatment-related adverse events possibly or probably associated with metformin XR were related to the gastrointestinal system and included abdominal pain, decreased appetite, diarrhoea, heartburn, flatulence and nausea/vomiting. Other treatment-related events possibly or probably associated with metformin XR were headache, rash, dizziness, blurred vision and muscle cramps. There appeared to be no relationship between frequency of events and dose of metformin XR. The intensity of all adverse events was rated as mild or moderate. No serious adverse events occurred during the study.

Table II. Statistical comparison of pharmacokinetic parameters by treatment

Parameter	Adjusted geometric means		Ratio of geometric means	
	Metformin XR 2000mg od	Metformin IR 1000mg bid	Point estimate	90% CI
C_{max} (ng/mL)	1 763	1 297	1.36	1.29–1.44
AUC_{24} (ng • h/mL)	19 986	20 053	1.00	0.93–1.07

AUC_{24} = AUC from 0 to 24 hours post-dose; **bid** = twice daily; **C_{max}** = maximum plasma concentration; **IR** = immediate-release; **od** = once daily; **XR** = extended-release.

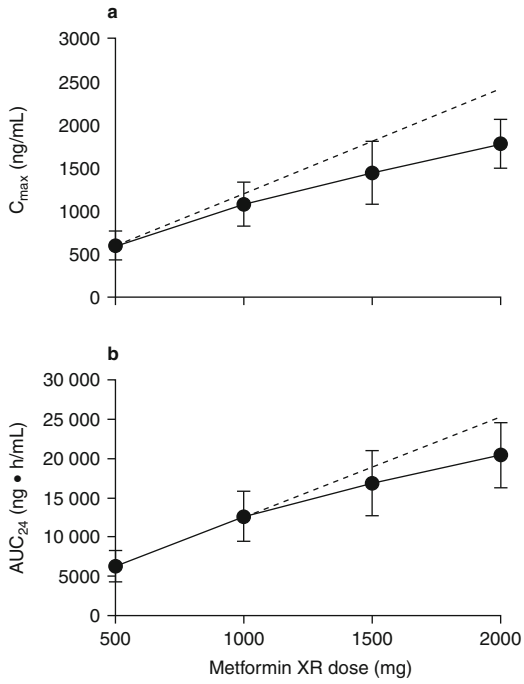

Fig. 4. (**a**) Mean (±SD) values of maximum plasma concentrations (C_{max}) at steady state vs dose of metformin extended-release (XR). The dotted line represents a dose-proportional increase in C_{max}. (**b**) Mean (±SD) area under the plasma concentration-time curve from 0 to 24 hours (AUC_{24}) post-dose values at steady state vs dose for metformin XR. The dotted line represents a dose-proportional increase in AUC_{24}.

Overall frequencies of treatment-emergent adverse events, by body system and treatment group, are given in table IV. The total numbers of adverse events were similar between metformin XR and metformin IR, and in general, metformin XR was well tolerated in this multiple-dose study.

Discussion

An effective metformin modified-release system should be formulated to release the drug into regions of the gastrointestinal tract where it is well absorbed; otherwise, bioavailability might be impaired. Previously studied XR formulations of metformin have either only been studied *in vitro*,[16] did not show pharmacokinetics remarkably different from metformin IR[17] or have shown impaired bioavailability,[18-20] presumably because a significant portion of the dose was released in areas of the gastrointestinal tract poorly permeable to the drug. A further experimental XR metformin formulation has shown a favourable profile in a single-dose pharmacokinetic study.[21]

The currently marketed formulation (Glucophage® XR) has been designed to provide equivalent exposure to metformin as the same dose of metformin IR. Because metformin is not presented for absorption from a bolus of metformin XR, large amounts of unabsorbed drug are not likely to be present in the gastrointestinal lumen at any one time. Controlling the release rate of metformin from a dosage form that can deliver the drug appropriately for optimal absorption may not only maintain bioavailability, but also alter the *in vivo* pharmacokinetic profile to be more suitable for once-daily dosing. In turn, improved convenience with once-daily administration may enhance patients' compliance with their oral antidiabetic medication.

Preliminary studies found that metformin XR provided a significantly reduced C_{max} of metformin without loss of bioavailability (as indicated by the AUC) compared with metformin IR. The current investigation found metformin XR to be well tolerated up to a dose of 2000mg administered once daily for 7 days. No clinically important accumulation of metformin was seen during multiple doses of metformin XR. Absorption of metformin from the

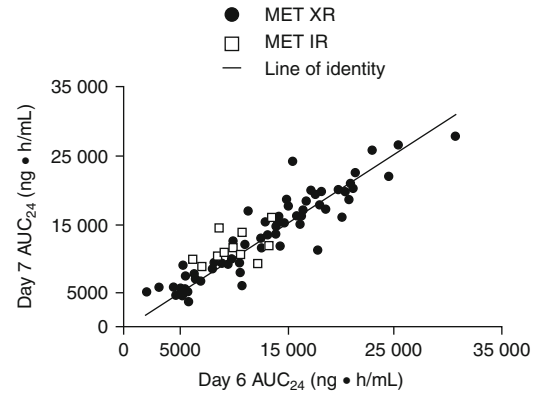

Fig. 5. Intrasubject variability in area under the plasma concentration-time curve from 0 to 24 hours (AUC_{24}) post-dose of metformin (MET) extended-release (XR) and MET immediate-release (IR). Comparison shows AUC_{24} on day 6 and day 7 at each dose.

Table III. Estimates of within-subject standard deviations

	Log(C_{max})	Log(AUC_{24})
MET XR 500mg od	0.24	0.24
MET XR 1000mg od	0.12	0.12
MET XR 1500mg od	0.16	0.11
MET XR 2000mg od	0.13	0.14
MET IR 1000mg (am)	0.17	0.14
MET IR 1000mg (pm)	0.09	0.09

am = morning; **AUC_{24}** = AUC from 0 to 24 hours post-dose; **C_{max}** = maximum plasma concentration; **IR** = immediate-release; **MET** = metformin; **od** = once daily; **pm** = afternoon; **XR** = extended-release.

metformin XR tablet occurred more slowly than that seen with metformin IR, and concentrations peaked about 3 hours later. The slower absorption from the metformin XR tablet, however, was not sufficient to affect the terminal elimination half-life. The XR and absorption of metformin from the GelShield Diffusion System technology may result in a favourable gastrointestinal tolerability profile for metformin XR. With metformin IR formulations, the entire administered dose rapidly dissolves in gastric fluid, but not all of it is absorbed, and some remains in solution in the lumen.

Mean C_{max} and AUC_{24} values of metformin XR are less than dose proportional. Absolute bioavailability of metformin at a 500mg dose is approximately 50–60%, and the bioavailability decreases as the dose increases.[2,3] This may be due to a saturable absorption process although it has not been conclusively shown to be transporter mediated. The geometric mean C_{max} value of metformin following administration of the 2000mg once-daily dose of metformin XR was 36% higher than that following the evening dose of metformin IR 1000mg twice daily. Although the peak plasma concentrations observed after the 2000mg once-daily dose of metformin XR were higher than those of metformin IR, the plasma concentrations were within the range reported with metformin IR in other clinical studies. The AUCs of the drug were comparable when administered as metformin XR and as twice-daily metformin IR. Although demonstrating bioequivalence was not the primary objective of the study, the XR formulation was bioequivalent to the IR formulation with respect to AUC_{24} at the same daily dose.

Assessment of intrasubject variability in pharmacokinetics is an important objective for any modified-release formulation. In this study, the intrasubject variabilities in the steady-state C_{max} and AUC_{24} of metformin were assessed at each of the four doses of metformin XR and were compared with those of

Table IV. Overall frequencies of treatment-emergent adverse events by body system and treatment group

Body system	MET XR 500mg (n = 16)	MET XR 1000mg (n = 16)	MET XR 1500mg (n = 16)	MET XR 2000mg (n = 15)	MET IR 1000mg bid (n = 14)
Cardiovascular	0	0	0	0	1
Dermatological	2	0	0	3	1
Endocrine/metabolic/electrolyte imbalance	1	1	1	0	0
Gastrointestinal	7	15	12	14	17
General	0	0	1	2	1
Haematopoietic	1	0	1	0	0
Musculoskeletal/connective tissue	1	5	2	2	0
Nervous system	7	6	6	4	6
Renal/genitourinary	3	1	0	0	2
Respiratory	0	1	3	2	2
Special senses	0	1	1	0	1
Total events[a]	22	30	27	27	31
Total subjects (%)	81.3	68.8	56.3	60.0	71.4

a Total events may exceed total subjects or sum of subjects in the treatment group because some subjects reported more than one event categorised under more than one body system and/or because a single subject may have reported more than one event within the same body system.

bid = twice daily; **IR** = immediate-release; **MET** = metformin; **XR** = extended-release.

metformin IR. The metformin XR formulation was available only in a 500mg tablet form; thus, four tablets were administered simultaneously to reach the maximum daily dose of 2000mg. The highest intrasubject variability of metformin XR was found at the lowest dose (500mg) and thereafter appeared to be relatively constant. Overall, intrasubject variability of metformin XR was low and comparable to that of metformin IR.

Conclusion

In summary, the metformin XR tablet using GelShield Diffusion System technology was well tolerated at single doses of up to 2000mg once daily for 7 days, and no accumulation of metformin was noted. Intrasubject variabilities in the C_{max} and AUC of metformin from metformin XR were similar to those seen with metformin IR. The extent of absorption of metformin XR 2000mg once daily was comparable to the same total daily dose of metformin IR administered as 1000mg twice daily.

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