Expert Opinion

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Case studies in swelling polymeric gastric retentive tablets

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Swelling tablets administered in the fed state have been shown to provide therapeutic advantages in two marketed products, with the duration of delivery characterised with respect to food and tablet size. Metformin extended-release tablets are a diffusion-based swelling tablet demonstrating once-daily efficacy with good gastrointestinal solubility. Ciprofloxacin extended-release tablets are based on an erosional matrix that delivers the drug to the upper gastrointestinal tract over 6 h to provide once-daily efficacy with reduced incidences of nausea and diarrhoea. Furosemide extended-release tablets are another example of an erosional matrix designed to deliver furosemide to the duodenum and upper jejunum over 6 h to provide a more gradual diuresis and naturesis compared with the immediate-release product.

Keywords: controlled release, extended release, food effect, gastric retentive, oral drug delivery

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1. Introduction

Oral drug administration remains the predominant and preferred route for delivery of medications. However, due to incomplete absorption of many drugs in the lower gastrointestinal (GI) tract, controlled-release (CR) dosage forms must be maintained in the upper GI tract, preferably the stomach, while the medications are delivered to the region of the GI tract where they are best absorbed.

Over the past two to three decades many approaches to gastric retentive (GR™) CR drug delivery systems have been developed and tested. Among these are systems that depend on size (large single units), low (floating) and high (sinking) density, bioadhesion (single and multi-unit) and swelling. Several reviews have discussed these various dosage forms [1-4]. This article will concentrate on a polymeric swellable GR system (AcuForm™; Depomed Inc.) that has received two FDA approvals in the past year, Glumetza® (metformin hydrochloride [HCl] extended-release [M-ER] tablets; Depomed Inc.) and ProQuin® XR (ciprofloxacin HCl ER [C-ER] tablets; Depomed Inc.). In addition, furosemide ER (F-ER) tablets, for which the most complete GI transit data are available, will also be discussed. However, to appreciate the limits of GR technology, an understanding of GI physiology is essential.

2. Gastrointestinal physiology

In the fasted state the stomach and duodenum exhibit a cyclic pattern of contractile activity known as the migrating motor complex (MMC) cycle. The MMC cycle is divided into four phases. Phase I is a quiescent state, whereas Phase II activity consists of intermittent contractions that are of smaller amplitude (force) when compared with maximal Phase III contractions. Phase III activity is a period of maximal contractile activity lasting from 10 to 15 min in the stomach and duodenum [5]. Under normal physiological conditions, Phase III contractions are the strongest to take place in the stomach and duodenum [6,7]. Phase III activity in the antrum is characterised by groups of three to six contractions that gradually build in amplitude until two contractions of maximal force occur [6]. When these contractions occur, the pylorus is

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relaxed and contractile activity of the duodenum is inhibited [6,7]. This relaxation allows the pylorus to be stretched to its maximal aperture during emptying of indigestible particles. With the termination of each group of antral contractions, contractile activity returns to the pylorus and duodenum along with an increase in tone of the pylorus [7]. This sequence is repeated several times during Phase III activity and is responsible for emptying large indigestible material from the stomach. Phase III activity may be followed by Phase IV activity, a brief period of intermittent contractile activity. The MMC recurs every 90 – 120 min in the fasting state.

With a meal, the cyclic recurring Phase III activity of the MMC cycle is replaced with the fed pattern of contractile activity. In the antrum, the powerful contractions of Phase III activity are replaced by lower force aborad propagating contractions. The force of these contractions is only 15 – 25% of the Phase III contractile activity until ~ 50% of the meal is emptied [8]. After this occurs, the antral contractions gradually increase in force until the meal is completely emptied. Throughout the fed state, contractions of the pylorus are coordinated with the propagating antral contractions such that the pylorus is closed 3 – 4 s before the propagating contraction reaches the distal antrum [9]. In addition, there is an increase in isolated pyloric contractions and tone following a meal [10]. Thus, the reduced force of the antral contractions, along with the coordinated closure of the pylorus, are likely to be responsible for retaining non-digestible solids of a critical size in the stomach until the digestive state is complete and fasting contractile activity returns.

Following a mixed liquid/solid meal, gastric emptying of the liquid portion begins within 5 min, whereas the solid portion has a lag time from 15 to 60 min. The lag time for solid emptying is due to the time that is necessary for the stomach to triturate the food into small enough particles (1 – 5 mm in diameter). The pylorus has a fasting resting diameter of 12.8 ± 7.0 mm [11] and non-disintegrating dosage forms with a diameter of up to 12 mm may be emptied during the postprandial state [12]. However, as the diameter increases the probability of the tablet emptying during the fed state decreases [13]. Cowles *et al.* found that 23, 15 and 8% of GR tablets with initial diameters of 7, 10 and 13 mm, respectively, emptied from the stomach during the postprandial state in healthy subjects [14]. In addition, following administration with a low-fat meal there was a bimodal distribution of gastric emptying times with the 13-mm GR tablets, 18.7 ± 0.9 and 4.7 ± 2.3 h, with ~ 50% of the subjects in each range. This was also true of the small-diameter tablets, except the proportion of subjects in the lower range increased substantially. With very large non-disintegrating capsules (3.5 cm) the same two populations were observed with somewhat fewer subjects in the fast emptying population. Thus, even for extremely large dosage forms, it was observed that the same limitation applied as with fast emptiers with a low-fat meal.

These constraints of the normal physiology of the GI tract must be taken into account when developing a GR dosage form. The technology discussed in Section 3 is optimised to take advantage of the normal physiology of the GI tract in the fed state to attain gastric retention and an ER profile for drugs that are absorbed high in the GI tract.

3. Case studies in swelling polymeric gastric retentive tablets

The use of swelling polymeric GR tablets administered with a meal to provide a moderate duration of ER delivery of 6 – 9 h is most easily understood through case studies of the developed products. Gastric emptying takes 6 h and 9 h is the sum of the gastric emptying time and the mean time for small intestinal transit. Hydrophilic polymers that are on the FDA's Inactive Ingredient list, such as alkyl cellulosics, poly(ethylene oxides) or polysaccharide gums, provide both the swelling and the rate-controlling components. Initial tablet dimensions are typically near 10 mm in two dimensions as a modified oval tablet to avoid emptying immediately after ingestion and for ease of swallowing. The dosage forms swell in two dimensions to exceed the mean pyloric diameter in the fed mode of 12 mm, and thus ensure that the tablets cannot exit through the pylorus by reorientation. The balance between the rates of polymeric swelling and erosion is controlled by the polymeric molecular weight and the use of additional excipients. M-ER tablets exemplify a diffusional, swelling polymeric matrix for very soluble drugs, and C-ER tablets are a polymeric erosional-based swelling matrix for less-soluble drugs. F-ER tablets are an example of an erosional tablet for which the most complete GI transit data are available.

The diffusional metformin tablets consist of higher molecular weight hydrophilic polymers with polymeric swelling being faster than polymeric erosion. Consequently, the drug is released from the tablet by diffusion linearly with the square root of time and the tablet may enlarge up to three times its original size promoting gastric retention [15]. Although the drug is released in 8 h, the polymer erodes nearly linearly over 12 – 15 h so that ghost tablets are generally not eliminated in the faeces [16]. The linearity of the drug release with the square root of time provides an additional early time contribution to the bioavailability for subjects with rapid gastric emptying times.

For the erosional ciprofloxacin formulation consisting of lower molecular weight hydrophilic polymers, the tablet enlarges initially from polymeric swelling. It then predominantly maintains its size with a slow linear decrease by polymeric erosion and a sharp decrease in size near the end of drug delivery. The polymeric erosion results in nearly linear delivery of the ciprofloxacin over 6 h, with the rate of delivery being under predicted by dissolution testing and more accurately predicted by disintegration [101]. The furosemide formulation is a bilayer tablet consisting of an erosional layer, similar to the ciprofloxacin tablet, for drug delivery and a swelling layer to maintain its size throughout drug delivery. As with the metformin formulation, the swelling layer erodes linearly with time over 12 – 14 h.

Both metformin [17,18] and ciprofloxacin [19] are well absorbed throughout the small intestine and show reduced bioavailability from the colon. For both products, the drug can be delivered through the small intestine and be fully bioavailable. Consequently, the transit time to the ileocecal junction or the sum of the gastric emptying time and the small intestinal transit time of 2 – 4 h is the relevant maximum duration for ER delivery. Furosemide, on the other hand, represents a more challenging delivery profile with absorption being restricted to the duodenum and perhaps some of the jejunum [20,21].

3.1 Metformin extended-release tablets

Metformin HCl is a biguanide antihyperglycaemic agent that is widely used for the treatment of non-insulin-dependent diabetes mellitus (Type 2 diabetes). Metformin lowers basal and postprandial elevated blood glucose in patients with Type 2 diabetes whose hyperglycaemia cannot be managed by diet and exercise alone [24]. The efficacy of metformin seems to last beyond the plasma levels [24] and, if it were not for the GI side effects, metformin could be delivered less frequently with better compliance and potentially improved control of blood glucose. Metformin therapy is associated with GI side effects, particularly nausea, diarrhoea and abdominal discomfort, in ~ 20 – 30% of patients. It has been shown to induce nausea by a serotonin-mediated mechanism [102], and diarrhoea may be related to delivery to the lower GI tract [22]. To minimise these effects, the dose of metformin is slowly titrated and is administered a number of times throughout the day with food [23].

M-ER (Glumetza) is a new ER formulation that is designed to deliver metformin HCl 500 mg over 8 h to the upper GI tract where it is best absorbed [25]. Providing an ER delivery should lower the peak concentration of metformin to which the GI tract is exposed, thus potentially reducing the incidence of side effects.

The GI transit of M-ER 500-mg tablets was studied in healthy volunteers. When administered with a 1000-calorie, high-fat (50%) meal, M-ER demonstrated excellent retention in the fed stomach (13 h). After dosing with a more appropriate low-fat meal (30%), M-ER remained in the stomach for a mean of 8 h [16]. Gastric emptying under low-fat conditions occurred in two populations: < 6 h and > 19 h. For this low-fat condition, the mean transit time to appearance in the colon was 11 ± 3 h, which clearly exceeded the 8-h delivery time for metformin. The necessity of administration with food for retention in the stomach and efficient drug delivery is demonstrated by the reduction in the relative bioavailability for the M-ER to only 58% in the fasting state compared with the fed state. The pharmacokinetic profile for two M-ER 500-mg tablets given once daily showed comparable bioavailability to immediate release metformin (M-IR; Glucophage®; Bristol-Myers Squibb) 500 mg b.i.d. When M-ER and M-IR are each given as a single 500-mg dose, the bioavailability of M-ER is increased slightly to ~ 115% [15], C_{max} is reduced to ~ 60% of M-IR, whereas the T_{max} is increased. This increased bioavailability relates to the partially saturable intestinal absorption of metformin [26] and the slower delivery of M-ER producing less saturation. The comparable bioavailability of M-ER 1000 mg/day and M-IR 500 mg b.i.d. results from a balance of slower delivery and a larger dose at one time.

Another result of saturable absorption is a somewhat decreasing bioavailability at higher doses of metformin, and nonlinear dose proportionality has been reported for metformin [23,26]. With its slower delivery, the dose proportionality of M-ER is almost linear from 500 to 2500 mg [27]. For once-daily delivery it implies that the bioavailability of higher doses is not compromised.

The efficacy and safety of M-ER were studied in two double-blind, well-controlled Phase III trials in patients with Type 2 diabetes; a non-inferiority monotherapy trial comparing M-ER with M-IR [25], and a combination therapy trial comparing M-ER plus a sulfonylurea (SU) to SU alone [27]. Long-term safety and efficacy were assessed in an open-label extension study of 250 patients who completed the monotherapy trial [25]. In these three clinical trials, no special instructions were given regarding meals, except that physicians should provide their usual counselling with respect to diet and exercise for patients with Type 2 diabetes.

In the monotherapy trial [25], 750 patients were randomised to receive M-ER 2000 mg/day, M-ER 1500 mg/day, M-ER 1500 mg dosed as 1000 mg p.m. and 500 mg a.m., or M-IR 1500 mg dosed as 1000 mg p.m. and 500 mg a.m. The once-daily doses were administered with the evening meal, and the morning and evening doses were administered with breakfast and dinner, respectively. The M-IR comparator regimen of 1500 mg dosed as 1000 mg p.m. and 500 mg a.m. is both quite effective and well tolerated. In the combination therapy study [27], 575 patients were randomised to M-ER (1500 mg/day, 2000 mg/day or 1000 mg b.i.d.) plus SU or to SU alone.

In the monotherapy study [25], rapid and statistically significant ($p < 0.001$) decreases from baseline were observed for haemoglobin A1c (HbA1c) levels by week 12 of treatment and for fasting plasma glucose levels by the end of week 1. These decreases were maintained for the 24-week study duration and for the additional 24 weeks of dosing in the open-label study [25]. The decreases in HbA1c in the M-ER groups from baseline to end point were non-inferior to that in the M-IR group. The reduction in HbA1c in the M-ER 2000-mg/day group was greater than for the other groups, indicating greater efficacy at higher doses, which may be related to the linearity of the dose proportionality data for M-ER. This contrasts with the plateau in efficacy observed for Glucophage XR at doses > 1500 mg/day [28].

In the combination therapy study [27], SU alone produced almost no reduction in HbA1c levels, whereas statistically significant reductions ($p < 0.001$) from baseline in HbA1c were observed for all three M-ER plus SU groups. The reductions in the M-ER once-daily groups were at least as large as for the M-ER b.i.d. group, and these groups also had lower incidences of hypoglycaemia from the interaction with SU.

The tolerability of M-ER in all three studies was excellent. The incidences of nausea and diarrhoea were 4.2 and 5.6%, respectively, in the SU-alone group and 6.7 and 12.5%, respectively, in the combined M-ER plus SU groups. In both of the double-blind studies, M-ER was titrated faster than recommended for other marketed forms of metformin and was started at an effective dose of 1000 mg/day. In spite of this unusually rapid titration, the overall incidence of GI side effects during the first week of the monotherapy study was quite low (18%) and comparable in all groups. The incidence of nausea during the titration period was lower than in the M-IR group (p = 0.05) [27].

In summary, M-ER showed that the hypothesised once-daily efficacy was sufficiently well tolerated in terms of GI side effects to allow rapid titration and potentially greater efficacy at higher doses.

3.2 Furosemide extended-release tablets

Furosemide is a 'loop' diuretic that is often used in clinical practice to treat oedematous states in congestive heart failure (CHF), nephritic syndrome and liver cirrhosis. The diuretic effect of furosemide is potent but relatively short-lived, with an average duration of action of ~ 4 h. As a result of the potent effect of furosemide, urination may be as frequent as every 15 min. Thus, it is difficult for patients to undertake normal activities as they need to be near a lavatory for 1 – 5 h after administration.

F-ER tablets are intended to provide continual delivery of furosemide for 6 h to the duodenum and upper jejunum, where furosemide is best absorbed. In contrast to metformin and ciprofloxacin, furosemide is not absorbed throughout the small intestine. Therefore, it is essential that 90% of the furosemide is delivered while the tablet is in the stomach. As a result of the very limited absorption window and the insolubility of furosemide, a bilayer tablet approach was employed. The drug-containing layer is a lower molecular weight, erosional-based hydrophilic polymer swelling matrix similar to that employed for C-ER tablets. The second layer of the tablet is a higher molecular weight, hydrophilic swelling polymeric matrix that increases its size and promotes gastric retention in the fed state

It was hypothesised that continuous delivery from the F-ER tablet would provide a more gradual but similar total diuresis and natriuresis, which i) may be more convenient for the patient with a less intensive diuresis and lead to better compliance, and ii) the antidiuretic period may be less severe and prolonged allowing for potentially superior efficacy. This is consistent with pharmacodynamic studies of infusions of furosemide showing increased efficacy [37].

The GI transit and *in vivo* erosion, as well as the pharmacokinetics and pharmacodynamics of the F-ER tablet, were studied in healthy volunteers (n = 14) [29]. When administered after a meal, the tablets remained in the stomach for 10.6 ± 5.0 h (range 3.9 – 16.5 h), whereas erosion of the active layer took 5.7 ± 2.0 h (range 2.6 – 9.1 h). In all but one of the subjects, erosion of the active layer was complete before the tablet emptied from the stomach. In this subject, erosion of the active layer was complete 40 min after the tablet was emptied, thus the tablet was still in a region of the GI tract were furosemide could be absorbed. The target for erosional release of 6 h supported the *in vivo* result of 5.7 h, and the *in vivo* variability was exceptionally small for an erosional dosage form. These data indicate that the F-ER tablets will remain in the stomach long enough to deliver all of the furosemide to the area of the GI tract were it is best absorbed.

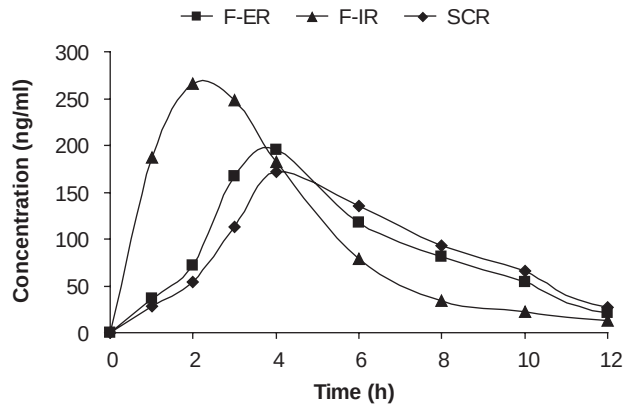

Figure 1. Mean plasma concentration-time profiles of F-ER tablets, F-IR tablets and SCR experiment.
F-ER: Furosemide extended release; F-IR: Furosemide immediate release; SCR: Simulated controlled release.

The plasma concentration-time profile of F-ER (40 mg) was typical of an ER formulation (Figure 1). Compared with an IR formulation, the T_{max} was extended from 2.6 ± 0.9 h for the IR tablet to 4.2 ± 1.8 h for the F-ER tablet and the C_{max} was reduced from 348 ± 124 ng/ml for the IR tablet to 265 ± 124 ng/ml for the ER tablet. However, the AUC was slightly reduced for F-ER (1121 ± 282 ng•h/ml) compared with IR (1293 ± 301 ng•h/ml). This may be due to first-pass metabolism of furosemide (as when furosemide was administered as 3 mg every 30 min for 6 h to simulate controlled delivery the plasma profiles was similar to that of the F-ER tablet) and the AUC was also reduced compared with the IR tablet, 1152 ± 408 and 1293 ± 301 ng•h/ml, respectively.

With respect to pharmacodynamics, the total urinary volume (2168 ± 413 ml for F-ER; 2175 ± 231 ml for F-IR) and sodium excretion (258 ± 78 mM for F-ER; 260 ± 25 mM for F-IR) were nearly the same at 12 h postdosing. However, the diuresis and natriuresis were much more gradual with the F-ER tablet compared with the IR tablet (Figures 2 and 3). These data indicate that F-ER provides a more gradual but equal diuresis and natriuresis, even though there was a small reduction in bioavailability due to first-pass metabolism.

This excellent reproducible performance of F-ER in healthy volunteers was not borne out in CHF patients, where certain innate physiological differences alter the delivery of furosemide.

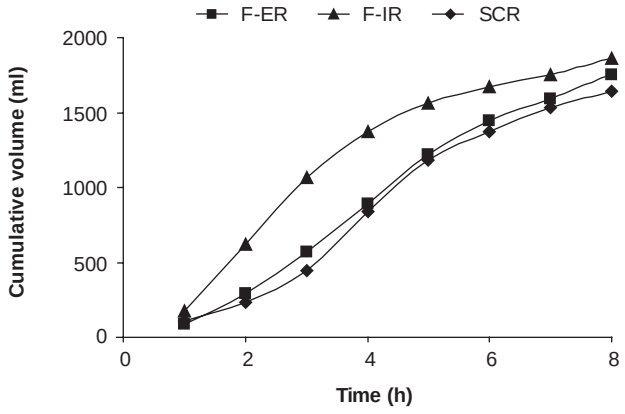

Figure 2. Mean cumulative urinary volume profiles for F-ER tablets, F-IR tablets and SCR experiment.
F-ER: Furosemide extended release; F-IR: Furosemide immediate release; SCR: Simulated controlled release.

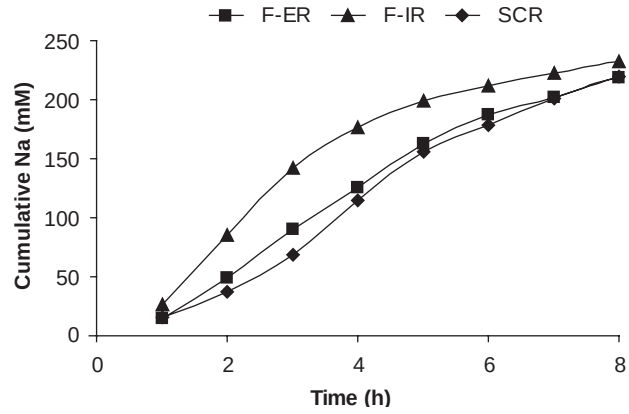

Figure 3. Mean cumulative sodium excretion profiles for F-ER tablets, F-IR tablets and SCR experiment.
F-ER: Furosemide extended release; F-IR: Furosemide immediate release; SCR: Simulated controlled release.

In particular, in a study in 28 CHF patients, T_{max} and $t_{½}$ for the IR dosage form were 4.3 ± 0.4 and 4.0 ± 1.0 h, respectively, in contrast to 2.6 ± 0.9 and 2.1 ± 0.4 h, respectively, in the healthy volunteer study. Thus, the release of furosemide from the IR tablets was extended by several hours in CHF patients compared with healthy volunteers, and the targeted ER profile became inappropriate. This extension of the IR delivery profile may be related to differences observed in gastric emptying and absorption in these CHF patients. A total of 12 of the CHF patients participated in a follow-up study to assess GI motility by the C13 breath test and to receive furosemide oral solution (39 mg administered 3 mg every 30 min over 6 h) as a simulated CR administration. Gastric emptying in the CHF patients was significantly delayed, median 165 min (range 125 – 179 and 25 – 75 percentile; VE Cowles, unpublished observation) compared with a median of 129 min (range 119 – 149) in healthy controls [201]. Moreover, the simulated CR furosemide administration in these CHF patients showed substantial reductions in bioavailability and increased variability as compared with the IR tablet.

Furosemide ER remains an excellent demonstration of the viability of the technology in healthy volunteers without use in the target patient population due to physiological differences.

3.3 Ciprofloxacin extended-release tablets

Ciprofloxacin, a fluoroquinolone antimicrobial agent, is effective when given twice daily for treatment of a wide variety of bacterial infections, in particular, uncomplicated urinary tract infections (uUTI). The most common reason for the discontinuation of ciprofloxacin therapy is GI adverse events, especially nausea and diarrhoea [30,31]. C-ER (Pro-Quin XR) a novel ER formulation, releases 90% of the 500 mg of ciprofloxacin HCl over a 6-h period to the upper GI tract where it is best absorbed [19,23]. This 6-h release profile contrasts markedly with the other marketed once-daily ciprofloxacin tablet (Cipro® XR; Bayer AG), where the drug is released within 1.5 – 2.0 h.

In contrast to most ER profiles, a flat plasma profile is not desirable for a fluoroquinolone such as ciprofloxacin. The two pharmacodynamic parameters that are important for the efficacy of fluoroquinolones are AUC/MIC and C_{max}/MIC [32,33]. C_{max} is especially important for avoiding resistance to causative microorganisms [33]. The 6-h delivery profile of C-ER 500 mg/day is designed to provide comparable C_{max}/MIC to C-IR (Cipro) 250 mg b.i.d.

It was also hypothesised that the mechanism of nausea from ciprofloxacin was similar to but less severe than the prokinetic effect of erythromycin [34], and was dependent on the peak concentration of drug in the upper GI tract. Diarrhoea was hypothesised to be related to the peak concentration of drug in the lower GI tract. By providing nearly constant delivery of ciprofloxacin over 6 h, a moderate extension of the ER profile can provide a substantial reduction in the peak concentration of drug in the GI tract, and it was hypothesised that this should result in a substantial reduction in nausea and diarrhoea.

The steady-state ER profile of C-ER 500 mg/day is shown in Figure 4, compared with C-IR 250 mg b.i.d. The bioavailability from the two dosage forms is comparable. The C_{max} for C-ER is comparable to that for C-IR and does not show the variation in C_{max} between the morning and evening doses of C-IR. This presumably reflects differences in the circadian rhythm of creatinine clearance as ciprofloxacin is almost entirely renally eliminated. As well as extending T_{max}, the peak plasma levels show clear extensions compared with C-IR. The plasma and urinary levels were both comparable between the two formulations and also showed comparable ratios relative to the MIC values for the causative microorganisms [35].

The efficacy and safety of C-ER 500 mg/day administered with the evening meal without specific meal conditions and

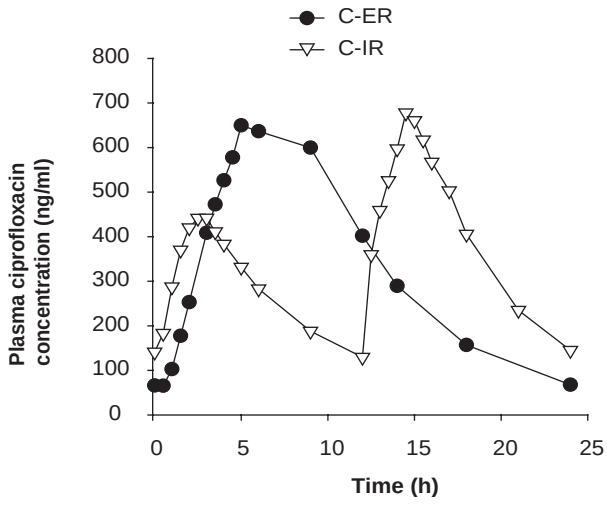

Figure 4. Steady-state mean plasma concentration-time profiles of C-ER tablets and C-IR tablets. Reprinted from WASHINGTON CB, HOU SY, CAMPANELLA C, HUGHES N, BROWN S, BERNER B: Pharmacokinetics of extended-release ciprofloxacin. *J. Clin. Pharmacol*. (2005) **14**(11):1236-1244, with permission from Sage Publications, Inc. Copyright 2005 by Sage Publications.
C-ER: Ciprofloxacin extended release; C-IR: Ciprofloxacin immediate release.

C-IR 250 mg b.i.d. administered for 3 days were compared in a noninferiority study for treatment of uUTI in 1037 women [36]. Microbiological eradication at the test-of-cure visit in the C-ER-treated group (93.4%) was non-inferior to the C-IR-treated group (89.6%). The clinical cure rates for the C-ER group (85.7%) and C-IR group (86.1%) were similar. Both treatments were well tolerated, but nausea and diarrhoea occurred substantially less frequently in the C-ER group than in the C-IR group (nausea: ER 0.6%, IR 2.2%; p = 0.033; diarrhoea: ER 0.2%, IR 1.4%; p = 0.037).

In summary, through the maintenance of AUC/MIC and C_{max}/MIC and slower delivery of ciprofloxacin over 6 h, C-ER once daily was shown to be as effective as C-IR twice daily in the treatment of uUTI with a significantly lower incidence of nausea and diarrhoea.

4. Conclusions

The use of swelling tablets that are retained in the stomach during the fed state has been shown to provide clear drug delivery solutions where a modest extension of the delivery profile can provide therapeutic advantages for drugs that show diminished absorption in the lower GI tract.

5. Expert opinion

This paper reports on two products (M-ER and C-ER) that have received FDA approval, thus validating the GR technology. These products take advantage of the normal physiology stomach in the fed state to provide gastric retention and extend the delivery of the drug to the small intestine where they are best absorbed. This resulted in a decrease in dosing frequency from twice daily to once daily with the same efficacy and reduced side effects.

In addition, these two products demonstrate that both soluble (metformin) and insoluble (ciprofloxacin) compounds can be delivered from the GR systems. Thus, the GR technology may be used in a wide range of drugs that are absorbed high in the GI tract to develop ER formulations.

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