JPP Journal of Pharmacy and Pharmacology

JPP 2005, 57: 565–571

Received October 1, 2004
Accepted January 31, 2005
DOI 10.1211/0022357056037
ISSN 0022-3573

A site-specific controlled-release system for metformin

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Abstract

Oral absorption of the antihyperglycaemic agent metformin hydrochloride (MF-HCl) is confined to the upper part of the intestine, therefore rational controlled-release formulations of this drug should ensure a complete release during transit from stomach to jejunum. The aim of this study was the preparation of a system able to sustain release of high MF-HCl doses in compliance with the above requirement. Matrices (6 mm diameter; 50 mg weight) comprising varying drug–Precirol ATO 5 ratios were prepared by compression. The matrix containing 70% drug was coated on one face with Eudragit L100-55. Drug release to simulated gastric (SGF), jejunal (SJF) and ileal (SIF) fluids in sequence was studied using a modified USP rotating basket method. Release depended on drug load whereas it was independent of dissolution medium pH and hydrodynamics. Release kinetics were of $\sqrt{t}$ type and were determined by drug diffusion in aqueous pores created in the matrix by drug dissolution. An equation correlating rate-determining factors was developed, whereby the release pattern could be optimized. The half-coated matrix started release in SGF and completed it in SJF. The half-coated matrix, synchronizing drug release and matrix transit across the small intestine, may improve drug bioavailability and reduce side effects.

Introduction

Metformin, an oral antihyperglycaemic agent belonging to the biguanide group, is widely used for the management of type II non-insulin-dependent diabetes mellitus. Oral absorption of metformin is confined to the upper part of the intestine (i.e. the duodenum, jejunum and, to a lesser extent, ileum) (Vidon et al 1988; Scheen 1996). The bioavailability of this drug from aqueous solution or rapidly dissolving tablets is relatively low (Pentikainen 1986; Scheen 1996), probably because the time of drug transit across the small intestine is shorter than that required for complete drug absorption. Sustained-release systems are still less bioavailable (Noel 1980; Karttunen et al 1983; Pentikainen 1986), since drug absorption virtually ceases when systems pass into the large intestine. Because of the short and variable biological half-life (1.5–4.5 h) (Marchetti & Navalesi 1989) and the low bioavailability of metformin, high doses (e.g., 500 mg three times a day) must be administered to maintain effective plasma concentrations. This implies a high exposure of intestinal tissue to non-absorbed drug and hence a high incidence of side effects, such as abdominal discomfort, nausea and diarrhoea. From here descends the need for more rational metformin delivery systems, allowing increased bioavailability and decreased drug doses. Stepensky et al (2001) investigated the possibility of obtaining clinical advantage from gastric-retentive controlled-release systems that are retained in the stomach and produce a constant input of drug to the effective sites of absorption. They used the rat model to assess the pharmacokinetic–pharmacodynamic rationale to develop these formulations. The actual findings indicated that differences in the drug administration mode, either by an oral solution or by a slow infusion to the duodenum, did not significantly affect the extent of metformin action. This was ascribed to metformin adsorption onto the negatively charged intestinal wall, which resulted in a low drug absorption rate, similar to that produced by sustained-release formulations, even following oral administration of a drug solution. Nevertheless, a comparison of the

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single-dose pharmacokinetics of gastric-retentive, extended-release tablet formulations of metformin hydrochloride with those of the immediate-release tablet showed that the mean bioavailability in man from the gastric-retentive tablets was approximately 115%, relative to the immediate-release product (Gusler et al 2001).

In a previous report (Di Colo et al 2002), we proposed a rationalization of metformin controlled release, based on matrices able to initiate release in the stomach and complete it in the jejunum. These synchronized release systems realized a correspondence between the time required for complete release and the transit time of the system across the upper part of the gastrointestinal tract, where drug absorption occurs and where sites of metformin glucose-lowering action are located, which contribute to the overall pharmacodynamic effect (Stepensky et al 2001). The matrices were based on a pH-sensitive interpolymer complex insoluble at the pH of the stomach, where it limited metformin release to 50% of the dose in 2 h, and erodible at the pH of the jejunum, where the remaining 50% of the dose was gradually released in the subsequent 2 h. Since the interpolymer complex swelled to some degree in gastric fluid, it failed to limit release of the highly water-soluble metformin hydrochloride when matrices were loaded with drug fractions higher than 20%. This was a major fault of this formulation, since a number of matrices corresponding to a weight of 2.5 g would be required to make up the 0.5-g dose contained in the commercial Glucophage. Therefore, it was felt desirable to devise a formulation allowing a substantial increase of the drug dose, while at the same time maintaining the synchronized release pattern. The use of hydrophobic waxes to control release of water-soluble drugs from monolithic matrices has been reported (Saraiya & Bolton 1990; Obaidat & Obaidat 2001; Zhang et al 2001).

The purposes of this study were: to choose an appropriate wax to prepare matrix tablets able to sustain the release of high metformin hydrochloride doses; to detect the rate-controlling factors to realize a matrix able to completely release its drug content in about 2 h; to coat one face of the matrix with a gastroresistant polymer soluble at the pH of the jejunum, so that the matrix could start releasing the drug in the stomach through the non-coated face and complete release in the jejunum, after dissolution of the coating. Indeed, whereas the time of matrix residence in the stomach is variable, the transit time of a matrix tablet through the small intestine is much less variable, with a mean of 173 min (Davis et al 1993).

Materials and Methods

Materials

Solid paraffin (SP) (Carlo Erba, Milano, Italy), Eudragit L100-55 (EUD) and triethyl citrate (gifted by Rofarma Italia S.r.l., Milano, Italy) were used as received. Metformin hydrochloride (MF-HCl) (Sigma-Aldrich, Milano, Italy), glycerol palmito-stearate (GPS) (Precirol ATO 5; Gattefossè Italia S.r.l., Milano, Italy), stearic acid (SAc) and stearyl alcohol (SA1; Carlo Erba, Milano, Italy), and glycerol monostearate (GMS; Polichimica S.r.l., Bologna, Italy) were passed through a 106-μm sieve before use. All other chemicals and solvents were of reagent grade.

Preparation of matrices

Flat-faced matrix tablets, 50 mg weight and 6 mm diameter, were prepared by compressing the ingredients (the drug and a hydrophobic wax) in the form of granules or, in some specified cases, of mixed powders. The compaction force (9800 N) was applied by a Perkin-Elmer hydraulic press. Granules were prepared by the following procedure. Each of 1-g batches of drug–wax blends was transferred into a test tube and heated to 85°C in an oil bath under manual stirring with a spatula. At this temperature the wax melted, as can be inferred from the relevant melting intervals listed in Table 1, while the drug (melting interval 223–225°C, determined by a hot-stage microscope) remained in the solid dispersed state. After the mix had become apparently homogeneous, it was removed from the heat and allowed to cool to room temperature. Stirring was continued until the wax solidified. The solid dispersion was then granulated by extrusion through a 355-μm or, in some specified cases, a 500-μm wire mesh screen. The GPS-based matrices were stored for 2 weeks at 40°C to allow the wax to recover its stable crystalline state (Hamdani et al 2003).

Matrices containing 70% MF-HCl and 30% GPS were coated on one face with a film of EUD by a spraying technique. The matrices were placed on a rotating plate and sprayed on the upper face and on the edge with a methanolic solution of 5% EUD and 0.5% triethyl citrate. At intervals, the spraying was interrupted and the coating was dried by an air stream at room temperature. The weight of the coating was 2.7 ± 0.1 mg ($n = 15$) (4.6 ± 0.2 mg cm^{-2}).

Release experiments

A previously described method was used to measure the drug release kinetics (Carelli et al 2000; Di Colo et al 2002; Zambito & Di Colo 2003). The method was a modification of the USP rotating basket method, designed to realize strictly controlled hydrodynamics of the matrix environment. The dissolution medium volume was 300 mL, the temperature was maintained at 37 ± 0.1°C,

Table 1 Melting interval of waxes

Wax	Melting interval (°C)
GPS	48–56[a]
SAc	55–59[a]
SAl	56–60[a]
GMS	53–61[a]
SP	51–53[b]

[a]According to Thomsen et al (1994). [b]According to the manufacturer.

the stirring rate was 120 rev min^{-1}, and the sample volume was 20 mL. To investigate the effect of hydrodynamics on release, the runs with the matrix type containing 70% MF-HCl and 30% GPS were carried out at two different stirring rates (60 and 120 rev min^{-1}). If not otherwise indicated, the matrices were eluted with simulated gastrointestinal fluids, consisting of: hydrochloric acid 0.04 M, pH 1.2, made isotonic with sodium chloride (simulated gastric fluid, SGF); phosphate buffer pH 6.8, 0.13 M, made isotonic with sodium chloride (simulated jejunal fluid, SJF); and phosphate buffer pH 7.4, 0.13 M, isotonic (simulated ileal fluid, SIF). SGF, SJF and SIF were used in sequence, 2 h each (except in some specified instances), to simulate matrix transit from stomach to ileum. The withdrawn samples of receiving phase were analysed spectrophotometrically (Hitachi 150-20 spectrophotometer, Tokyo, Japan) for the drug at 232 nm. At this wavelength the UV spectrum of MF-HCl in about neutral aqueous solution shows a maximum, therefore the SJF and SIF samples were read directly, while the acidic SGF samples were previously neutralized by adding 0.028 g of solid disodium hydrogen phosphate dihydrate per mL. The spectrophotometric calibration curves constructed with standard drug solutions in SJF, SIF and in neutralized SGF were superimposable and linear with zero intercept ($r^2 > 0.999$; $n = 15$) up to an absorbance of at least 0.750. Samples showing absorbances higher than this value were appropriately diluted before the measurement. The drug concentration in sample was calculated from the following formula: Concentration/Absorbance = 0.0123 mg mL^{-1}.

The cumulative percentage of released dose was calculated on a nominal dose basis. Blank runs showed the absence of significant interference with the spectrophotometric measurements. It was readily verified that the MF-HCl solubility in each of the receiving phases of the release experiments was greater than 5 mg mL^{-1}. Because the drug concentration in the dissolution medium was always lower than 0.1 mg mL^{-1}, sink conditions throughout the release experiment could always be assumed.

Statistical methods

Because of the low number of replicates of the release runs ($n = 3$) non-parametric statistical tests were used to assess the significance of differences among different groups of release data obtained from different experiments. The Mann–Whitney U test was used to compare two unpaired groups, whereas the Kruskal–Wallis test was used to compare more than two unpaired groups.

Results and Discussion

Screening of waxes

A screening was carried out to select the most appropriate wax to be used as the basic material of matrices. The granulation procedure was applied to each wax, using a drug–wax ratio of 40:60 w/w. SP and GMS yielded a sticky mass and could not be granulated. SAc and SAl gave brittle granules with a high powder fraction, whereas GPS gave granules with apparently fair flow properties and negligible powder content. The release properties of matrices prepared from granules based on GPS, SAc or SAl are depicted in Figure 1. The experimental curves and the relevant t50 (approximate time for 50% release) values show that the ability of the wax to sustain release of high MF-HCl doses was in the order SAl ≅ GPS > SAc. We ascribe the remarkably faster release from the SAc matrix to the less hydrophobic nature of this material. GPS was selected for use as matrix material, considering its release-controlling properties and the qualities of the relevant granules.

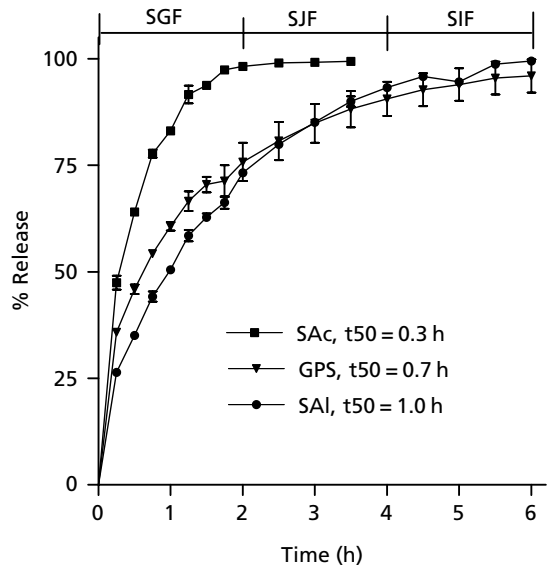

Figure 1 Metformin HCl release from matrices based on different waxes (drug–wax ratio, 60:40 w/w). SGF, simulated gastric fluid; SJF, simulated jejunal fluid; SIF, simulated ileal fluid; SAc, stearic acid; GPS, glycerol palmito-stearate; SAl, stearyl alcohol. Each data point is the mean ± s.d. of three values.

Release from matrices based on GPS

Figure 2 shows the release curves and the respective t50 values for matrices based on GPS, containing varying MF-HCl doses. For each formulation, three runs were carried out using matrices prepared from different granule batches. Hence, the fair reproducibility of release data that can be inferred from the small error bars of data points is indicative of a fair reproducibility of the granulation method, and hence, of a fair control of the drug dose. A strong dependence of t50 on the dose is apparent. In fact, a significant dose effect on release at each time point, up to 2 h, resulted from the Kruskal–Wallis test (Kruskal–Wallis statistic 20.42, $P = 0.0001$). Such a dependence was previously observed for the release of other freely water-soluble drugs from matrices based on hydrophobic waxes (Saraiya & Bolton 1990; Obaidat & Obaidat 2001; Zhang & Schwartz 2003). Interestingly, with the remarkably high dose of 70% the release was virtually completed in 2 h, in compliance with the basic rationale of this work.

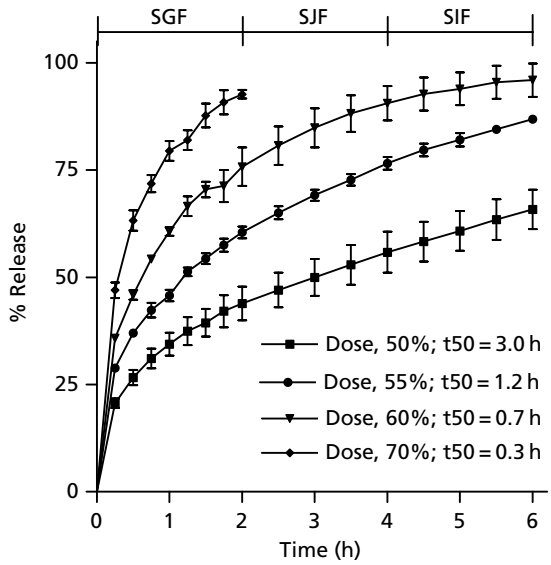

Figure 2 Release of different metformin HCl doses from matrices based on glycerol palmito-stearate (GPS). SGF, simulated gastric fluid; SJF, simulated jejunal fluid; SIF, simulated ileal fluid. Each data point is the mean ± s.d. of three values.

The matrix preparation procedure was of paramount importance to the release kinetics. Indeed, a comparison of corresponding data for matrices prepared by direct compression of powders (Figure 3) with those for matrices prepared from granules (Figure 2), indicates a much faster release from the former. When the comparison was made on a statistical basis, using the Mann–Whitney U test, the difference between the data groups for the 50% or the 60% dose was found to be significant ($U = 4.00\%$, $P = 0.0019$, for the 50% dose; $U = 7\%$, $P = 0.0070$, for the 60% dose). In previous reports a similar effect of the matrix processing method was explained by admitting that during the melt–granulation process the molten wax was brought to coat the surface of drug particles, thus protecting them from dissolution during the subsequent release experiment (Obaidat & Obaidat 2001; Zhang & Schwartz 2003).

Granules were usually prepared by extrusion through a 355-μm wire mesh screen. In some cases, however, a 500-μm wire mesh was used, so as to investigate the relevance of granule size. In principle, indeed, there could be an influence of granule size on tablet porosity after compaction, and this would result in an influence on release rate. The release data from matrices prepared from the larger granules loaded with the 50 or 60% dose are reported in Figure 4. These data were compared, by the Mann–Whitney U test, with the corresponding data reported in Figure 2 for the matrices prepared from the smaller granules. The differences were non-significant ($U = 110.5\%$, $P = 0.5217$, for the 50% dose; $U = 115.0\%$, $P = 0.6376$, for the 60% dose), which indicates an insignificant effect of granule size on release. In turn, this indicates that the porosity due to air was either negligible or independent of granule size.

For the in-vitro release data to be predictive of the in-vivo behaviour, the hydrodynamics of the matrix environment should not influence the release properties of matrices. In fact, it was ascertained that a reduction of the agitation intensity of the external medium from 120 to 60 rev min^{-1} was without any appreciable effect on the release from the matrix containing 70% drug (data not reported). From here, it is inferred that the dissolution medium behaved as a perfect sink, irrespective of its hydrodynamics, because the unstirred aqueous diffusion layer adjacent to the matrix

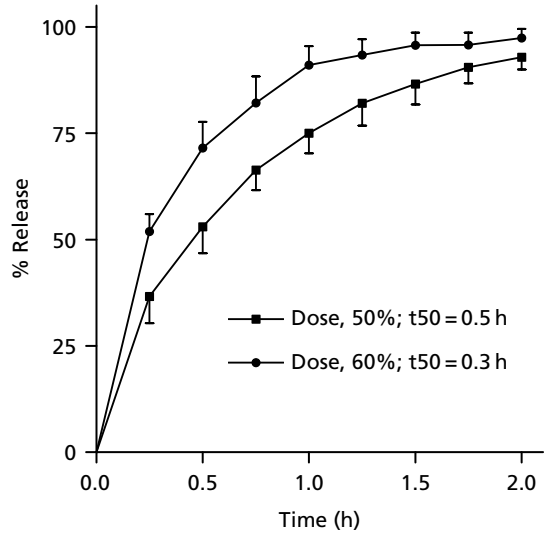

Figure 3 Release of different metformin HCl doses from matrices based on glycerol palmito-stearate (GPS), prepared by direct compression of powders. The dissolution medium is simulated gastric fluid (SGF). Each data point is the mean ± s.d. of three values.

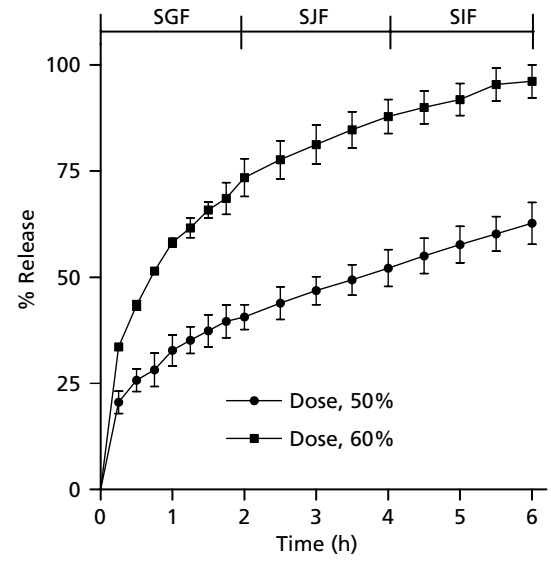

Figure 4 Metformin HCl release from matrices based on gycerol palmito-stearate (GPS), prepared from granules obtained by extrusion through a 500-μm wire mesh screen, loaded with different drug doses. SGF, simulated gastric fluid; SJF, simulated jejunal fluid; SIF, simulated ileal fluid. Each data point is the mean ± s.d. of three values.

surface was much more permeable to the drug than the matrix itself (Flynn et al 1974).

Rate-controlling factors

Apparently the matrices, even those with the highest drug load, neither swelled nor shrank following release. Most probably, then, release occurred via diffusion in aqueous pores generated in matrix by drug dissolution in the penetrating medium, with no variation of apparent matrix volume. As stated above, perfect sink conditions in the receiving phase of the release experiments could be assumed. It is known that under quasi-steady-state conditions drug release from planar porous systems is theoretically described by the following equation (Higuchi 1963):

$$M = S\sqrt{\frac{D_P}{\tau}\varepsilon(2C_0 - \varepsilon C_{SP})C_{SP}t} \quad (1)$$

where M is the mass of drug released after time t, S is the exposed area, D_P is the drug diffusivity in pore fluid, ε is the matrix porosity, τ is the pore tortuosity factor, C_0 is the drug loading expressed as w/v concentration in matrix and C_{SP} is the drug solubility in pore fluid expressed as w/v.

By replacing C_0, ε and C_{SP} in Equation 1 by the following respective expressions: $C_0 = Q_0/V$ (Q_0 = mass of drug loaded into matrix, V = matrix volume); $\varepsilon = V_P/V$ (V_P = volume of pores); $C_{SP} = Q_{SP}/V_P$ (Q_{SP} = mass of drug soluble in the volume V_P of pore fluid), the following equation is obtained:

$$M = \frac{S}{V}\sqrt{\frac{D_P}{\tau}(2Q_0Q_{SP} - Q_{SP}^2)t} \quad (2)$$

By dividing both sides of Equation 2 by Q_0, the following equation results:

$$F = \frac{S}{V}\sqrt{\frac{D_P}{\tau}(2F_{SP} - F_{SP}^2)t} \quad (3)$$

where $F = M/Q_0$ (cumulative dose fraction released after time t) and $F_{SP} = Q_{SP}/Q_0$ (dose fraction soluble in the volume V_P of pore fluid).

If it is admitted that the air content in the matrix is negligible and that the matrix pores are essentially generated by drug dissolution in the penetrating medium, then the porosity is expressed by the ratio of the void volume developed after time t to the volume of the matrix region where the voids have developed. In the Higuchi model, after time t there is a sharp front separating the external matrix layer, containing pores, from the matrix core, containing solid drug. Although the thickness of the external layer increases with time, its porosity is independent of time and equals the matrix porosity expressed as the ratio of the pore volume developed after complete drug dissolution, V_P, to the total matrix volume, V. Both Q_{SP} and Q_0 are proportional to V_P, then their ratio, F_{SP}, is independent of V_P, and hence, of porosity. Consequently, the fractional release is independent of porosity when this is generated by drug dissolution, as results from Equation 3. According to this equation, the plot of the dose fraction released vs $\sqrt{t}$ should be linear until solid drug is present in matrix. In Figure 5 the data of Figure 2 are reported vs $\sqrt{t}$. For each data series, linear regression was applied to the number of data points that maximized the correlation coefficient. The regression significance was in all cases satisfactory, as results from the r^2 values listed in Table 2. Apparently, all plots in Figure 5 are linear until release of 70–80% of the dose, after which release tapers off, reasonably due to the consumption of solid drug. This implies a high drug solubility in the pore fluid. Indeed, we have verified that one part of MF-HCl dissolves in two parts of water. According to Equation 3 the slope of each line in Figure 5 is expressed by the following equation:

$$\frac{F}{\sqrt{t}} = \frac{S}{V}\sqrt{\frac{D_P}{\tau}(2F_{SP} - F_{SP}^2)} \quad (4)$$

As can be seen in Table 2, the experimentally determined slope is markedly increased by a dose increase. This relationship is predicted by Equation 4, if it is reasoned that an increased dose would result in a reduced pore tortuosity factor. On the whole, data indicate that the release from the present matrices is fairly well described by Equation 3, although the theoretical model disregards the release from the matrix edge. It should be noted that metformin is a strong base ($pK_a = 11.5$, according to

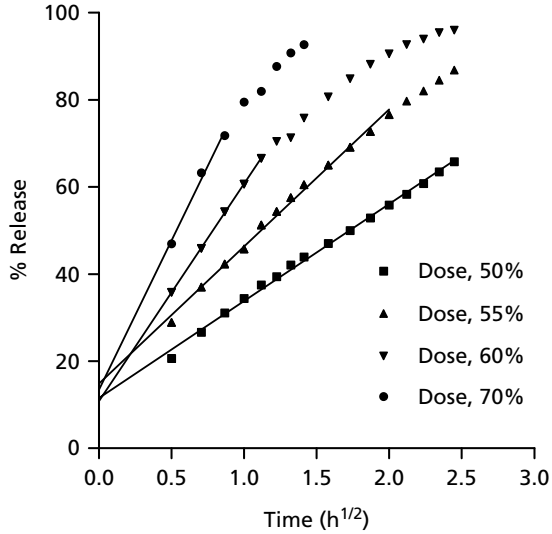

Figure 5 Plots of release data of Figure 2 as a function of $\sqrt{t}$.

Table 2 Parameters of linear regressions in Figure 5

Drug load (%)	Slope ($h^{-1/2}$) (r^2)	Intercept (%)
50	22.26 ± 0.35 (0.9966)	11.55 ± 0.57
55	31.48 ± 0.67 (0.9955)	14.87 ± 0.91
60	49.92 ± 0.41 (0.9998)	10.81 ± 0.35
70	68.39 ± 6.94 (0.9898)	13.43 ± 4.90

Scheen 1996), therefore the solubility of MF-HCl in the pore fluid is unaffected by the pH variations of the dissolution medium. Then it can be thought, on the basis of Equation 3, that in-vivo release from this matrix type should be uninfluenced by the pH variations of the gastrointestinal fluids. Although Equation 3 predicts a zero intercept of the F vs $\sqrt{t}$ plot, each regression line of Figure 5 shows a positive intercept on the ordinate axis. This is representative of a burst effect due to the comparatively rapid dissolution of drug particles from the matrix surface, where they were less coated by the wax than those inside the matrix. This hypothesis is supported by the similarity of the intercepts of the different plots, seen in Table 2. Equation 3 suggests that the release from the present matrices can be modulated through the matrix surface–volume ratio and the pore tortuosity factor, the latter depending on drug loading dose and on size and shape of drug particles (Desai et al 1965). In this work, a release pattern complying with the requirement of a gradual and complete release in 2 h was obtained by loading matrices of 6 mm diameter and 50 mg weight with 70% of commercial MF-HCl powder, passed through a 106-μm sieve. It should be recognized that changing just one of these properties could modify the release pattern. Thus, larger matrices are expected to yield a slower release, which could not be accelerated by increasing the dose, lest the matrix mechanical stability should be impaired. Also a finer drug powder could slow down release. This effect, nevertheless, could be counterbalanced by increasing the matrix surface–volume ratio.

Release from half-coated matrices

Matrices based on GPS, containing 70% MF-HCl, were film-coated on one face and on the edge by the gastroresistant EUD. Because the non-coated matrix is able to release its whole drug content in about 2 h, as shown above, the half-coated system was intended to start releasing its drug content in SGF and to complete release in the subsequent 2 h in SJF, after dissolution of the protective film at pH 6.8. Indeed, on the basis of the release mechanism discussed above and of the pH-independence of the MF-HCl solubility, the release from this matrix type should be independent of the pH variation from SGF to SJF. As the release data in Figure 6 show, the in-vitro performance of the half-coated matrices substantially met the expectations. Indeed, varying the time of residence in the gastric environment (0.5, 1 or 3 h) caused variation of the overall release pattern and time, but in all cases release was gradual and terminated in SJF, where the matrices resided for 2 h. All curves in Figure 6 show a sharp increase of release rate in coincidence with the change of dissolution medium from SGF to SJF. Indeed, the latter medium doubled the exposed matrix surface by rapidly dissolving the protective EUD film. Because the release is unaffected by the dissolution medium hydrodynamics, as stated above, the in-vitro behaviour is expected to predict the in-vivo one. Then, however long the time of matrix residence in the stomach, release should virtually be completed in the small intestine, as designed.

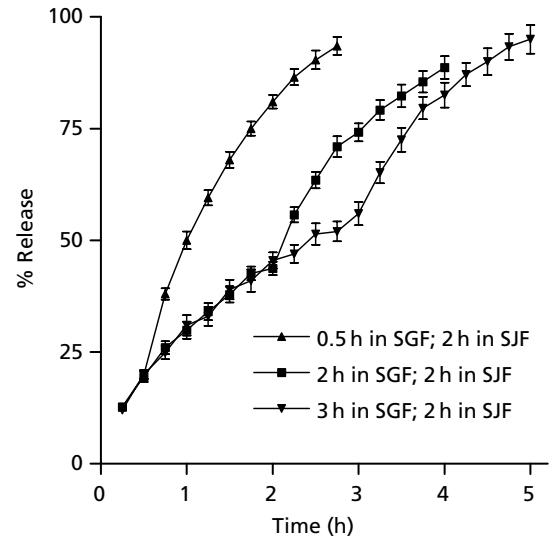

Figure 6 Metformin HCl release from matrices based on glycerol palmito-stearate (GPS), loaded with 70% drug, half-coated with Eudragit L100-55 (EUD). Matrices eluted in sequence with simulated gastric fluid (SGF) (for 0.5, 2 or 3 h) and simulated jejunal fluid (SJF) (for 2 h). Each data point is the mean ± s.d. of three values.

Conclusions

Precirol ATO 5 was the appropriate wax to prepare matrices able to sustain release of high MF-HCl doses. Drug release from matrices occurred via drug diffusion through aqueous pores created in matrix by drug dissolution in the penetrating medium. The release was described by an equation, derived from the well-known Higuchi equation, correlating fractional release to rate-limiting factors, which could be adjusted to obtain the desired duration of release. Thus, matrices releasing the whole dose in 2 h, with a pattern independent of pH and of dissolution medium hydrodynamics, were half-coated with a gastroresistant enterosoluble film to obtain a system that started releasing its drug content in SGF and completed release in SJF, whatever the residence time in SGF. Such a system, allowing a gradual and complete release during transit across the gastrointestinal region where MF-HCl absorption occurs, may improve the drug bioavailability over that of the traditional or sustained-release formulations currently on the market. This mode of MF-HCl delivery might allow administering lower therapeutic doses, thus minimizing unwanted side effects. In-vivo testing should require simultaneous administration of a number of tablets adequate to make up the therapeutic dose. The tablets are small enough to be introduced into size 00 hard gelatine capsules. To administer the dose of 0.5 g contained in the commercial Glucophage, two capsules, each containing 7 or 8 tablets, each loaded with 35 mg of MF-HCl, should be administered at a time. In case of success of this approach, this dose could be reduced.

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