Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmaceutics and Biopharmaceutics 55 (2003) 339–344
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Assessment of a controlled release hydrophilic matrix formulation for metoclopramide HCl

Enas I. Hasan[a], Bassam I. Amro[b], Tawfiq Arafat[c], Adnan A. Badwan[a,*]

[a]*The Jordanian Pharmaceutical Manufacturing Co., Naor, Jordan*
[b]*Department of Pharmaceutics, Faculty of Pharmacy, University of Jordan, Amman, Jordan*
[c]*Faculty of Pharmacy, Petra University, Amman, Jordan*

Received 8 January 2002; accepted in revised form 13 January 2003

Abstract

Metoclopramide HCl showed controlled release behavior when embedded in a hydrophilic matrix of chitosan and sodium alginate. The in vitro release data was found to be first order according to the Higuchi mechanism. An in vivo evaluation of the metoclopramide controlled release matrix on six male volunteers was carried out. The plasma samples were analyzed using a high-performance liquid chromatography (HPLC) method using a mobile phase of acetonitrile:acetic acid (30:70), with the pH adjusted to 4.7, a reverse phase Hypersil BDS Phenyl column (4 μm, 250 × 4 mm) and the detection was performed at 305 nm. The controlled release formula was found to be effective in delaying absorption (t_{max} 4.5 h as compared to 1.2 h), reducing the peak plasma concentrations (C_{max} 63.4 ng/ml as compared to 95.9 ng/ml) and maintaining higher concentrations during the elimination phase when compared to the immediate release formula. This proves the suitability of the suggested system for further studies.

Keywords: Metoclopramide; Chitosan; Sodium alginate; Controlled release; Hydrophilic matrix

1. Introduction

Metoclopramide HCl {4-amino-5-chloro-*N*-(2-diethylaminoethyl)-2-methoxybenzamide hydrochloride monohydrate} is commonly used for the management of gastrointestinal disorders [1]. The drug is highly water-soluble and is rapidly absorbed after oral administration [2]. It has a short biological half-life and is usually administered in a dose of 10–15 mg four times daily in order to maintain effective concentrations throughout the day. In long-term therapy, fluctuation in the plasma concentrations, with high concentration peaks are common for drugs with rapid absorption and elimination [2]. The secondary effects of metoclopramide on the central nervous system in the form of extrapyramidal symptoms, will surface, if plasma levels markedly exceed therapeutic levels [3].

Such characteristics make metoclopramide a suitable candidate for controlled release delivery. To do so, various sustaining or controlling strategies may be attempted; among these, is the use of hydrophilic polymers as a controlling matrix. Polymers such as chitosan, a positively charged hydrophilic polymer and alginate, a negatively charged hydrophilic polymer, have been reported extensively in the literature to control the release of drug substances [4,5]. Although such systems were extensively investigated and reported, unfortunately none of this work, to our knowledge, was transferred to a practical system and used commercially. Consequently, an attempt is presented here to control the release of metoclopramide, and to optimize the drug plasma concentration in order to avoid extrapyramidal symptoms.

2. Materials and methods

2.1. Materials

Metoclopramide HCl (Biochemical and Synthetic Products Ltd., India), chitosan and sodium alginate (Proton Biopolymers, Norway), were used as obtained. Metoclo-

* Corresponding author. The Jordanian Pharmaceutical Manufacturing Co., P.O. Box 94, Naor 11710, Jordan. Tel.: +962-6-5727-207; fax: +962-6-5727-641.
E-mail address: jpm@go.com.jo (A.A. Badwan).

0939-6411/03/$ - see front matter © 2003 Elsevier Science B.V. All rights reserved.
doi:10.1016/S0939-6411(03)00022-5

pramide HCl 30 mg controlled release tablets have the following composition: metoclopramide HCl (10.5%), chitosan (25%), sodium alginate (25%), calcium hydrogen phosphate (20%), microcrystalline cellulose (10%), polyvinyl pyrrolidone (7.5%), colloidal anhydrous silica (1.0%) and magnesium stearate (1.0%). The tablets weighed 300 mg and were prepared by standard wet granulation. The immediate release tablets (Pylomid® 10 mg) were commercially obtained. All other chemicals were of analytical grade.

2.2. In vitro release studies

Metoclopramide release from matrix was evaluated by using the US Pharmacopoeia dissolution apparatus II-Paddle (Hanson Research, USA). The operating conditions were: dissolution media: 600 ml 0.1 M hydrochloric acid (for 1 h), followed by 600 ml phosphate buffer pH 6.8 (1 h in 600 ml 0.1 M Hydrochloric acid, for the immediate release tablets). The temperature was controlled at 37 ± 0.5°C and the rotational speed was maintained at 50 ± 2 rpm. Each run was carried out using six tablets, one in each dissolution vessel. Samples (4 ml) were withdrawn at predetermined time intervals with dissolution media replacement and were filtered through 0.45 μm cellulose acetate membrane filters.

Drug content was determined spectrophotometrically by measuring the first derivative reading at about 320 nm using a Beckman DU-650 I UV/ Vis spectrophotometer. The concentration was determined by using calibration curves of metoclopramide HCl in 0.1 M hydrochloric acid and in phosphate buffer pH 6.8.

2.3. Human bioavailability study

Six healthy male volunteers aged 21–30 years (26.5 ± 3.3 years) whose body weight ranged between 60–95 kg (77.7 ± 13.7 kg) were enrolled in the study. The study was approved by the Ethical Committee of the Red Crescent Hospital in Amman, Jordan (were the study was conducted). The volunteer consents were obtained in concordance with the Declaration of Helsinki and Good Clinical Practice was followed throughout the study.

Blood samples (3 ml) were collected in heparinized tubes at 0.0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0 and 24.0 h. Plasma was directly separated by centrifugation and was stored frozen at −20°C until required for further analysis.

Two studies were conducted on the volunteers, a one-way cross-over study and a steady-state study; an 8-day wash out period was allowed between the two studies. The one-way cross-over study involved the oral administration of metoclopramide HCl 30 mg controlled release tablets and metoclopramide HCl 10 mg immediate release tablets (Pylomid® 10 mg, batch # 990606, manufactured by the Jordanian Pharmaceutical Manufacturing Co., Naor, Jordan). In the steady-state study, the initial dose was given after an 8-day wash out period from the last single dose administration. The subjects were instructed to take one tablet of metoclopramide HCl 30 mg controlled release tablets in the morning 2 h before breakfast for 5 consecutive days. On the sixth day, the subjects reported to the research facility at 5:30 a.m., where they received the sixth dose after a 12-h fast, and then the study proceeded as previously explained.

2.4. Analysis of the plasma samples

The concentration of metoclopramide in the plasma was determined by a high-performance liquid chromatography (HPLC) method. The chromatographic system compromised a constant solvent delivery system (L-7500), a 50 μl fixed volume injector (Rheodyne 7725), a variable UV detector (L-7400) and an integrator (D-7500). The system was equipped with a reverse phase Hypersil BDS Phenyl column 5 μ (250 × 4 mm). The mobile phase consisted of a filtered, degassed mixture of acetonitrile:acetic acid (30:70), with the pH adjusted to 4.7. The flow rate was set at 1.0 ml/min. Ketotifen at a concentration of 0.01 ng/ml in dichloromethane was used as an internal standard. The detection was preformed using a Variable UV detector at 305 nm [6].

The sample preparation was as follows: 0.25 ml of sodium hydroxide was added to 0.5 ml of the plasma sample in a conical test tube and vortexed for a few seconds. Dichloromethane (2.5 ml) containing 0.01 μg/ml of the internal standard (ketotifen) was then added. The solution was vortexed for 15 s and centrifuged for 5 min, at 4000 rpm. Organic layer (1.5 ml) was taken and evaporated to dryness under a stream of nitrogen, then reconstituted with 120 μl of mobile phase. A 50 μl sample was injected onto the phenyl column, where metoclopramide and the internal standard were separated from endogenous substances [6]. This HPLC method of analysis was validated.

2.5. Pharmacokinetic analysis

Pharmacokinetic parameters for metoclopramide, following oral administration, were determined from the plasma concentration time data. The maximum plasma concentration (C_{max}) and the corresponding time (t_{max}) were obtained directly from the individual plasma concentration time data. The area under the plasma concentration time curve (AUC) and the area under the first moment curve (AUMC) were estimated by linear trapezoidal rule and extrapolated to infinity using standard techniques. The elimination rate constant (K_{el}) was calculated by the technique of least-squares regression analysis.

$$AUC_{0\rightarrow\infty} = AUC_{0\rightarrow t} + C_t/K_{el} \quad (1)$$

The mean residence time (MRT) was calculated as AUMC/AUC. The rate of absorption was evaluated by the

means of the ratio $C_{max}/AUC_{0\rightarrow\infty}$. The concentration at 8 and 12 h, following oral administration of the immediate release and controlled release tablets, estimated as a percentage of the maximum concentration, was also computed.

The computer program used to calculate the pharmacokinetic parameters (AUC, AUMC, MRT and $t_{1/2}$) was 'Bioequivalence program for parametric and non-parametric analysis of two period cross-over studies with up to 60 subjects', version 6.2, 1996.

2.6. Statistical analysis

The difference in the pharmacokinetic characteristics of metoclopramide following oral administration of the controlled release and immediate release tablets were statistically evaluated using the paired t-test, at the 95% confidence level (CL). $T_{critical}$ at 5° of freedom, 95% CL is 2.57.

3. Results and discussion

3.1. In vitro release profiles and release kinetics

The dissolution profile for metoclopramide HCl controlled and immediate release tablets are shown in Fig. 1 ($n = 6$). More than 90% of metoclopramide HCl is released within 15 min from the immediate release tablets while the slow release is evident from the controlled release tablets.

The simple form of the Higuchi equation was used to fit the release data of the metoclopramide controlled release tablet (Fig. 2):

$$Q = K\sqrt{t} \tag{2}$$

where, Q is the amount of drug released, k the release rate constant and t the time. The data shows an appropriate fit

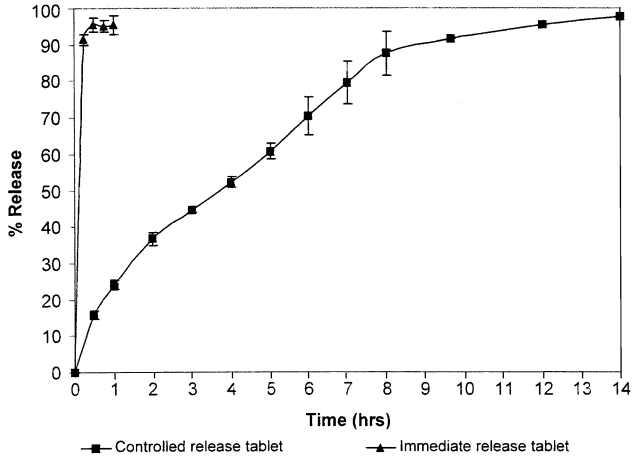

Fig. 1. The dissolution profile plot for metoclopramide HCl controlled release (1 h in 0.1 M HCl and then in phosphate buffer pH 6.8) and immediate release (1 h in 0.1 M HCl) tablets ($n = 6$).

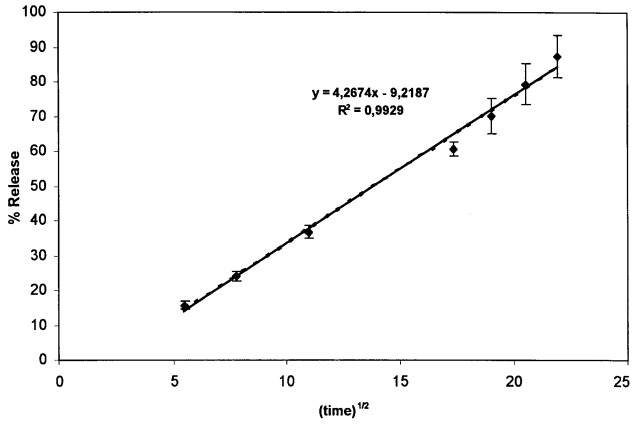

Fig. 2. Higuchi plot of dissolution profile of metoclopramide HCl controlled release tablet ($n = 6$).

($R^2 = 0.993$), indicating a release mechanism governed by diffusion from a matrix.

To determine the order of the release, the data was fitted to the first order equation (Fig. 3):

$$\ln(M/M_\infty) = -Kt \tag{3}$$

where, M is the amount remaining unreleased, M_∞ is the amount of drug released at infinite time. The data shows an appropriate fit ($R^2 = 0.987$), indicating that the drug is released in a first order fashion, i.e. depending on the matrix drug load.

3.2. In vivo assessment of controlled release matrix of metoclopramide HCl

The in vitro tests provide a good indication about the performance of the examined system. However, verification of these results, and firm evidence about the release characteristics of the studied system have to be acquired from in vivo assessment.

The mean pharmacokinetic characteristics of metoclopramide following oral administration of both the controlled

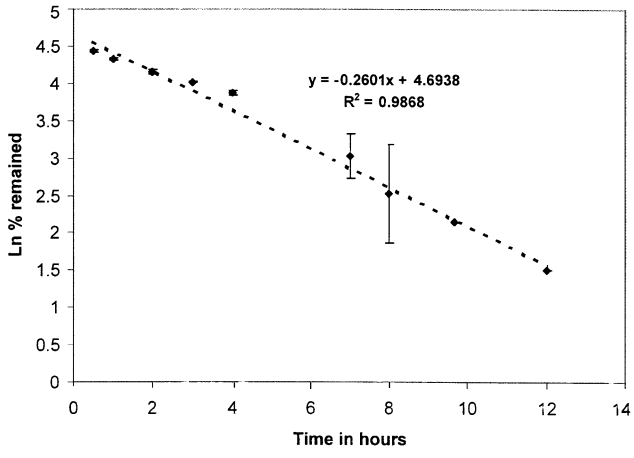

Fig. 3. Fitting of the dissolution profile of metoclopramide to a first order equation ($n = 6$).

release matrix and the immediate release preparation are shown in Table 1.

The metoclopramide plasma concentration time profiles after administration of the controlled release matrix and the immediate release tablets are shown in Fig. 4. Since the immediate release tablets are of 10 mg strength and the controlled release matrix tablets are of a 30 mg strength, the profile of the 10 mg immediate release tablets was multiplied by three. Metoclopramide shows linear pharmacokinetics [7], and this safely allows the extension of the results of the 10 mg tablets to 30 mg. This is performed for comparative reasons only.

The absorption of metoclopramide from the immediate release tablets was rapid, the mean t_{max} was 1.22 h, while in the controlled release matrix, the mean t_{max} was delayed by more than 3 h, with a mean of 4.50 h, which was found to be statistically significant. This shows that the controlled release matrix was effective in delaying the peak plasma concentration of metoclopramide.

For comparative reasons, per se, if we multiply the C_{max} level of the immediate release tablets by three, we will obtain a value of 95.9 ng/ml, which is very high, relative to the C_{max} value for the 30 mg controlled release matrix (63.36 ng/ml). This shows that the controlled release matrix provided a significant reduction in the maximum plasma concentrations. However, proper assurance of this should be attained after in vivo tests between 30 mg of both the immediate and the controlled release tablets.

This finding assures that the goal of controlled release preparation has been attained, in reducing the high peak plasma concentrations and thereby, reducing the side effects, especially the extrapyramidal symptoms. The delayed absorption with lower peak plasma concentrations and higher concentrations during the elimination phase is a major advantage of the controlled release matrix over the immediate release tablets.

Upon comparing the apparent plasma half-life values, we find that the apparent $t_{1/2}$ for the controlled release matrix (6.43 h) is more than double that for the immediate release tablets (2.99 h); this difference was found to be statistically significant. This may indicate that the declining phase of the plasma concentration time curve involves an input function

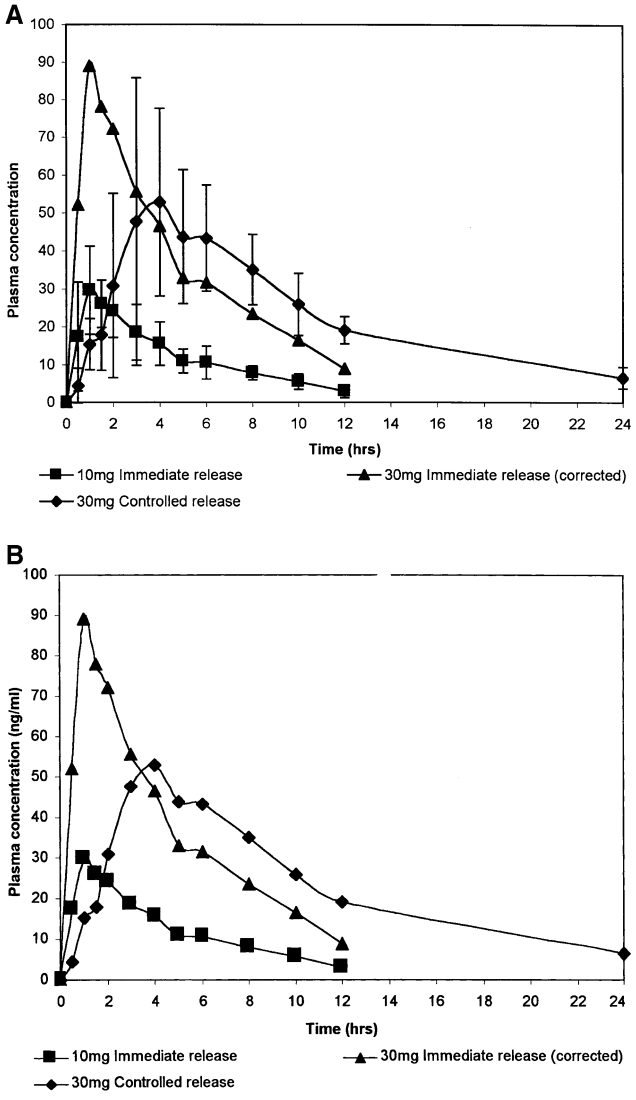

Fig. 4. The metoclopramide plasma concentration time profile after administration of the controlled release matrix and the immediate release tablets.

Table 1
Mean pharmacokinetic parameters of metoclopramide following oral administration of the controlled release and the immediate release tablets to six male volunteers

Parameter	Immediate release tablets (10 mg)	Controlled release matrix (30 mg)	t_{stat} 95% CL
C_{max} (ng/ml)	31.97 ± 10.90	63.36 ± 31.70	5.29
T_{max} (h)	1.20 ± 0.45	4.50 ± 1.22	2.61
$AUC_{0\rightarrow t}$ (ng h/ml)	157.98 ± 58.3	609.30 ± 187.50	–
$AUC_{0\rightarrow\infty}$ (ng h/ml)	172.10 ± 70.1	647.68 ± 205.60	–
$T_{1/2}$ (h)	2.99 ± 0.8	6.43 ± 1.50	2.64
AUMC (ng h^2/ml)	948.98 ± 371.0	7874.34 ± 2050.20	–
MRT (h)	5.54 ± 0.1	11.78 ± 0.90	16.81
$C_{max}/AUC_{0\rightarrow\infty}$ (h^{-1})	0.186 ± 0.02	0.093 ± 0.03	6.41
Concentration at 8 h/C_{max} (%)	24.4 ± 5.7	55.3 ± 14.6	–
Concentration at 12 h/C_{max} (%)	9.30 ± 5.3	30.1 ± 5.6	–

Data presented as mean ± SD; CL, confidence level.

in addition to the elimination function, i.e. it is not a true elimination phase. Plasma half-life values are the same for the same drug substance, regardless of the dosage form. The difference encountered here is due to the prolonged absorption phase in the controlled release matrix, where there is a prolonged continuous introduction of metoclopramide into the blood stream. This is due to the inherent property of the matrix in the controlled release of the drug. Therefore, the controlled release matrix appears to have a longer plasma half-life value i.e. it stays in the plasma for a longer time than the immediate release tablets, although it is the same drug.

The ratio $C_{max}/AUC_{0\rightarrow\infty}$ is held to be a good parameter for evaluation of the absorption rate of prolonged release formulations [7]. A statistically significant difference was found in this ratio between the two preparations, where the controlled release matrix showed a slower rate of absorption. As expected, this shows that the release of metoclopramide from the controlled release dosage form is slower than that of the conventional formulation.

The controlled release characteristics of the matrix were reflected in the MRT. MRT is a useful parameter, especially in cases were the drug (such as metoclopramide) is rapidly eliminated [7]. The MRT was noticeably increased following oral administration of the controlled release matrix (11.78 h) as compared to the immediate release tablets (5.54 h).

As can be seen from the presented data, 55.3% of the maximum concentration remains in the body after 8 h of controlled release tablet administration and 30.1% remains after 12 h as compared to 24.4 and 9.3%, respectively, for the immediate release tablets. At both times, the percentage remained in the body after administration of the controlled release tablets was found to be statistically significant when compared to that remaining after immediate release tablet administration.

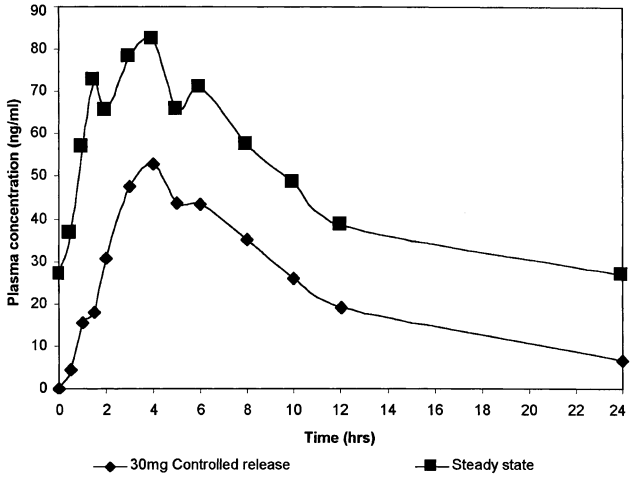

Fig. 5. The metoclopramide plasma concentration time profile after administration of a single and the sixth dose of a 30 mg controlled release tablet.

Fig. 5 shows the metoclopramide plasma concentration time profile after administration of a single 30 mg controlled tablet, and after the administration of the sixth dose of a 30 mg controlled release matrix.

This study was performed because it was observed that the drug has a buildup effect as shown in the plasma profile of the drug and on the baseline level of metoclopramide. The most significant finding in this case is the first metoclopramide plasma concentration after 5 days of once daily administration, which had a mean of 26.98 ng/ml. This value is well into the therapeutic range of metoclopramide; it is also close to the C_{max} value obtained for the 10 mg immediate release dosage form. This finding indicates that the controlled release matrix can be used for once daily administration.

The C_{max} for the steady-state study is 97.02 ng/ml, which is clearly well above the C_{max} obtained after single administration of the controlled release matrix (63.36 ng/ml). This indicates the buildup of the plasma concentrations upon continuous administration. The reason for this is that after administration of a second dose of the controlled release metoclopramide tablets, a significant plasma level is still present in the body: the 24-h plasma concentration after controlled release tablet administration was 6.60 ng/ml.

The therapeutic range for plasma metoclopramide concentrations and the relationship of plasma concentration to clinical response and toxicity have not been clearly established. However, metoclopramide induced akathisia is reportedly associated with peak plasma metoclopramide concentrations greater than 120 ng/ml [8]. The maximum plasma concentration of metoclopramide obtained in the controlled release study is clearly lower than the value indicating the safety of the reported formulation.

The above results indicate that the C_{max} values obtained in the steady-state study are not in the toxic range of metoclopramide, besides no side effects have been reported by any of the volunteers.

4. Conclusion

This study demonstrates the suitability of a combined mixture of the hydrophilic polymers, namely chitosan and sodium alginate in controlling the release of metoclopramide, which was found to follow first order kinetics and is diffusion controlled.

In vivo assessment of the metoclopramide controlled release matrix delayed drug absorption, lowered the peak plasma concentrations and maintained higher concentrations during the elimination phase compared to the immediate release tablets.

References

[1] Martindale's Extra Pharmacopoeia 1993, in: J.R. Reynolds (Ed.), 30th Edition, Pharmaceutical Press, London, pp. 892–894.
[2] USP DI, Drug Information for the Health Care Professional, vol. 1, 18th ed., United States Pharmacopoeial Convention, Rockville, MD, USA, 1998, pp. 2009–2013.
[3] A. Ganza-Gonzalez, S. Anguiano-Igea, F.J. Otero-Espinar, J. Blanco Mendez, Chitosan and chondroitin microspheres for oral administration controlled release of metoclopramide, Eur. J. Pharm. Biopharm. 48 (1999) 149–155.
[4] J.G. Winterowd, P.A. Sandford, Chitin and Chitosan, in: S.M. Alistair (Ed.), Food Polysaccharides and their Applications, 1st ed., Marcel Dekker, New York, NY, 1995, pp. 441–462.
[5] S.T. Moe, K.I. Draget, G. Skjak-Braek, O. Smidsrod, Alginates, in: S.M. Alistair (Ed.), Food Polysaccharides and their Applications, 1st ed., Marcel Dekker Inc, New York, NY, 1995, pp. 245–286.
[6] T. Arafat, M. Al-Shami, M. Yassin, A. Kaddoumi, A two-way crossover bioequivalency study comparing 10 mg doses of Pylomid and Plasil. Unpublished study, obtained upon request from the Jordanian Pharmaceutical Manufacturing Co. Ltd., Naor, Jordan, 1996.
[7] Y.M. El-Sayed, E.M. Niazy, S.H. Khidr, In vivo evaluation of sustained release microspheres of metoclopramide HCl in beagle dogs, Int. J. Pharm. 123 (1995) 113–118.
[8] AHFS Drug Information, American Hospital Formulary Service, American Society of Health-system Pharmacist, USA, 1998, pp. 2438–2444.