EUROPEAN JOURNAL OF DRUG METABOLISM AND PHARMACOKINETICS 2005, Vol. 30, No. 1-2, pp. 99-104

# Biopharmaceutical characterization of sustained release matrix tablets based on novel carbomer polymers: formulation and in vivo investigation

JELENA PAROJČIĆ[1], ZORICA DJURIĆ[1] MILICA JOVANOVIĆ[1], SVETLANA IBRIĆ[1], VESNA KILIBARDA[2], DUŠAN JOVANOVIĆ[2], IVAN KOVAČEVIC[3]

*[1]Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia and Montenegro [2]Military Medical Academy, Belgrade, Serbia and Montenegro [3] Institute of Pharmacy of Serbia, Belgrade, Serbia and Montenegro*

*Received for publication:* December 6, 2004

*Keywords:* Carbomer, deconvolution, matrix tablets, paracetamol, urinary excretion

SUMMARY

With the increased interest in modified release dosage forms and drug delivery systems, there is an increasing concern for biopharmaceutical characterization of the formulation in the early stages of drug product development. The main objectives of biopharmaceutical characterization are the in vitro and in vivo evaluation of the selected formulations in order to identify the factors influencing drug release; define the in vitro test methodology that would be predictive of drug products in vivo behavior and develop quantitative in vitro - in vivo correlation. The purpose of this study was to assess the potential of novel carbomer polymers, Carbopol 971P and Carbopol 71G, as a sustained release agents in matrix tablets containing high dosage drug substance. Although chemically identical, the two polymers exhibited substantially different drug release properties in vitro. Hypothetical in vivo drug release profiles were calculated by numerical deconvolution from cumulative urinary excretion data observed in vivo. The obtained results indicated that sound and reliable in vivo drug release profiles could be obtained from urinary excretion data and also, emphasized the need for in vitro testing under a range of experimental conditions in order to develop the biorelevant drug release methodology.

## INTRODUCTION

Biopharmaceutical characterization of the formulation plays an essential role in controlled release dosage forms development. Drug release in vitro as well as in vivo is recognized as the most important biopharmaceutical property of the dosage form. The subject of biopharmaceutical characterization is both in vitro and in vivo evaluation of the selected formulations; identification of the mechanisms involved in drug release process; identification of factors influencing the process of drug release both in vitro and in vivo; development of in vitro test methodology that correlates with in vivo data and would be predictive of drug products in vivo behavior, and establishment of in vitro-in vivo correlation (IVIVC). Currently accepted methodology for the in vitro-in vivo correlation study involves development and in vitro and in vivo evaluation of several drug product formulations with different release rates, assessment of the hypothetical drug dissolution profiles in vivo using an appropriate deconvolution technique and linear regression of the two sets of data obrained, namely in vitro and in vivo drug release profiles, in order to establish quantitative, mathematical relationship between them (1,2).

*Please send reprint requests to:* Jelena Parojčić
Department of Pharmaceutical Technology and Cosmetology
Faculty of Pharmacy, Vojvode Stepe 450, 11221 Belgrade
Serbia and Montenegro

Hydrophilic matrix tablets are among the most widely used controlled release dosage forms for oral delivery, due to their low cost and ease of fabrication. Drug release from hydrophilic matrix tablets upon contact with dissolution media or physiological fluids involves hydratation of tablet surface and formation of the gel layer which swells imbibing additional amount of water. Dissolved drug diffuses through the gel layer and hydratation and swelling progress into the tablet core. It could be expected that these processes are dependent on the type and proportion of the polymer employed as controlled release agent, as well as the type and amount of other excipients.

Carbomers are synthetic high molecular weight acrylic acid polymers crosslinked with polyalkenyl polyether, commercially available under the brand name of Carbopol®. The are not new in the field of sustained release technology, but are still interesting. Carbomer polymers exhibit inhibition of protease activity in the gastrointestinal tract (3, 4) and extremely high degree of swelling upon contact with aqueous media, which make them potential candidates to be used in various drug delivery systems. Most of the work done on the evaluation of carbomers as controlled release agents was mainly focused on Carbopol 934P and Carbopol 974P polymers (5-8). These polymers exhibited favorable performance on a laboratory scale formulations, however, their application in the high speed tableting machines was limited due to the poor flow characteristics. Novel, toxicologically preferred Carbopol 971P and technologically improved Carbopol 71G polymers were used in this study.

Carbopol 71G is manufactured by roller compaction of Carbopol 971P and exhibit improved flowability and compressibility. Although chemically identical, these two polymers provide different drug release patterns, which were not studied in detail so far. Also, little information on the in vivo behaviour of carbomer polymers containing dosage forms is available.

The nonsalicylate analgesic and antipyretic, paracetamol, which is voluminous and poorly compressible, was used as a model drug. Paracetamol is generally classified as a drug with high solubility that shows high permeability throughout the intestinal tract, meeting the criteria as a class I substance according to the Biopharmaceutics Classification System (9). The absorption of class I drugs should be dependent on their in vivo dissolution, controlled by the kinetics of drug release from the dosage form, thus being candidates for positive in vitro-in vivo correlation when formulated in a controlled release dosage forms. Paracetamol was chosen because it is readily absorbed throughout the gastrointestinal tract and present in a nonionized form in the physiological pH range (pKa=9.5). Its short elimination half-life facilitates investigation of the effects of formulation variables on absorption rate. A decrease in drug release rate tends to be reflected in the elimination phase. The in vivo performance of new dosage forms in the course of IVIVC development should be evaluated through the human bioavailability study. This type of study includes comparison of several investigated formulations with different drug release rates and reference, highly bioavailable preparation of the same drug substance. Although, in many cases, it is considered that the best way to estimate pharmacokinetic data is by analyzing drug blood levels, the use of a non-invasive method (e.g. urine samples) might also allow to distinguish bioavailability characteristics of different preparations. Measurement of the pharmacokinetic data of paracetamol formulations using urinary excretion data has been well documented (10-13) and could be achieved without the discomfort, possible hazard and necessary attendance of medical staff required for repeated venipunctures. Torrado et al (13) investigated the in vitro and in vivo availability of paracetamol from albumin microaggregates modified release formulations applying level C and B IVIVC approach. However, the employment of urinary excretion data in deconvolution algorithms with the aim to assess hypothetical drug release profile in vivo in the course of level A IVIVC development would be of major interest.

## EXPERIMENTAL

### Materials

The following materials were obtained from commercial suppliers and used as received: paracetamol (Merck, Germany), Carbopol 971P, Carbopol 71G (Noveon Speciality Chemicals, USA), lactose monohydrate (Fluka Chemie, Switzerland), polivinylipirolidone (Kollidon 30, BASF, Germany), microcrystalline cellulose (Emcocell XLM 90, Penwest, USA), colloidal silicium dioxide (Aerosil 200, Degussa, Germany), sodium stearyl furmarate (Pruv, Penvest, USA).

For HPLC analysis of paracetamol in urine samples ethylacetate (Merck, Germany) and acetonitril (Merck, Germany) were applied.

### Preparation of Tablets

Tablet samples were prepared using conventional wet granulation method. A paracetamol - lactose mixture (80:20) was granulated using 5% polyvinylpyrrolidone aqueous dispersion. The proportion of polymer (Carbopol 971P and Carbopol 71G) was varied at three levels, i.e., 7.5, 15.0 and 22.5%. The sustained release agent was added extragranularly, as well as the other excipients, mixed and

compressed in an excenter tablet machine (Erweka Korsch EK0, Germany) using flat round punches with 12 mm diameter. Tablet weight was 550 mg, tablets with hardness between 50 and 60 kN comprising to 325 mg of paracetamol. The compression pressure was adjusted to provide the prepared tablet samples were characterized with respect to their weight uniformity, crushing strength, friability and in vitro drug release.

## In Vitro Drug Release Study

Drug release experiments were conducted in the rotating paddle apparatus (Erweka DT 70, Germany), in 1000 ml of a dissolution media at 37°C, at paddle rotation speed of 50 rpm. Two different dissolution media were used in the initial stage of the study: 0.1M HCI and disstiled water. A 3 ml samples were withdrawn at one-hour time intervals, filtered, properly diluted and assayed UV-spectrophotometrically (spectrophotometer Cary 50, Varian, Australia) at 243 nm. Six tablets were studied for each formulation. Time for 50% dissolution ($t_{50\%}$) was calculated for each of the observed dissolution profiles.

## In Vivo Bioavailability Study

The in vivo study was conducted as an open, fasting, single dose, three-treatment crossover study. Eight healthy volunteers (ages 27 to 40 years, weighted 55 to 75 kg) were enrolled in the study and received three formulations (two sustained-release tablets and paracetamol oral solution) in a randomised order. A commercially available paracetamol solution (Febricet® syrup, Panfarma, Serbia) was used as a reference formulation. The study was reviewed and approved by the Ethical Committee of the Military Medical Academy. The volunteers were fully informed and provided written informed consent before entering the study. The study was conducted in three phases, separated by one-week washout interval.

Drug formulations were administered under fasting conditions, and urine samples were collected prior and 1, 2, 3, 4, 6, 8, 10, 14, 18 and 24 hours post dosing. The collected samples were stored at -20°C until analysis. The volunteers were instructed to increase the fluid intake in order to provoke adequate diuresys. They were also instructed to record the exact time of sampling (in the case of deviations from the stated time schedule) and total volume of urine excreted in all sampling points of the collecting period; and, also, to ensure that no sample was missing.

## Paracetamol assay

Drug concentration in urine samples was determined by a reversed-phase high performance liquid chromatographic method proposed by Lo and Bye (14). An aliquot of urine (20µl) was diluted to 1ml with pH 7.4 phosphate buffer and extracted with 5 ml of ethyl acetate. The samples were mixed in a shaker for 10 minutes. The organic layer from each tube was transferred to a 15 ml conical tube and evaporated to dryness under a stream of air. Samples were reconstituted with 1 ml of water and transferred to an autosampler vial for HPLC injection. The mobile phase contained 94% water and 6% acetonitryle at a flow rate of 1.2 ml/min. The stationary phase was a C18 reversed-phase column (Econosil C18, particle size 5 µm, 250x4.6 mm). The HPLC system (BIO-RAD model 2700) consisted of an automated autosampler (AS-100 HRLC) and UV detector (BIO-RAD model 1801). Paracetamol was monitored with UV detection at 245nm. The standard curve was found to be linear (y=7.9756 x - 0.1073, $r^2$=0.9980) over the concentration range used (0.05-1.25 mg/l). The precision of the method was determined by six replicate measurements of spiked urine sample containing 1.0 mg/l paracetamol. The obtained coefficient of variation was 1.88%.

## In vivo data analysis

Cumulative urinary excretion - time profiles were calculated for each volunteer and each formulation. In order to obtain cumulative urinary excretion, drug concentration determined in each urine sample of a

*Table I:* Characteristics of the investigated tablet formulations

| sample | tablet weight (mg) (mean±SD) | crushing strenght (kN) | friability (%) | $t_{50\%}$ (h) 0.1M HCI | $t_{50\%}$ (h) water |
|---|---|---|---|---|---|
| P1 | 544.70±8.10 | 76.6 | 1.63 | 3.58 | 5.40 |
| P2 | 547.82±8.82 | 62.5 | 2.89 | 4.38 | 7.23 |
| P3 | 541.95±12.91 | 55.8 | 3.31 | 4.78 | 8.55 |
| G1 | 544.88±5.92 | 59.6 | 1.05 | 0.48 | 5.09 |
| G2 | 549.92±5.79 | 62.3 | 0.98 | 0.73 | 6.52 |
| G3 | 545.41±1.91 | 66.4 | 0.77 | 1.08 | 7.40 |

collecting period was multiplicated by the volume of urine excreted during a collecting period. The observed in vivo profiles were characterized by calculating relevant pharmacokinetic parameters (cumulative amount of drug excreted (Ae), mean residence time (MRT), elimination rate constant ($k_{el}$) and apparent elimination half-half ($t_{1/2}$)). In vivo dissolution rate was calculated for each volunteer individually by applying numerical deconvolution to the urinary excretion data observed after administration of the investigated sustained release preparations, while the profile obtained after administration of the reference oral solution was used as weighting function (15). Cumulative urinary excretion profiles were interpolated in one-hour time intervals, and first derivatives of the interpolated profiles were introduced in a numerical deconvolution algorithm using the in house developed computer program PharmPred. The hypothetical in vivo input profiles were determined as the average data of the individual deconvoluted profiles.

## RESULTS AND DISCUSSION

### Characteristics of Tablet Formulations

Tablet formulations prepared with Carbopol 971P were denoted as samples P1-P3, while the tablets containing Carbopol 71G were designated as samples G1-G3.

The characteristics of the prepared tablet samples are presented in Table I. Due to very poor flowability of tablet mass containing more than 15% of Carbopol 971P, the uneven filling of the tablet dies, resulting with a higher tablet weight variation was observed. In the case of Carbopol 71G, the flowability and compressibility of the polymer, as well as the corresponding tablet mass was improved leading to the favorable tablets mechanical properties with the increase of the polymer content.

### Drug Release In Vitro

Results of the in vitro drug release study of the investigated formulations in distilled water and 0.1M HCl applied as dissolution media are given in Figure 1a and b, respectively. The pronounced difference among the profiles obtained for the same formulation in different dissolution media could be observed. Formulations containing Carbopol 971P as sustained release agent exhibited prolonged dissolution time in both media, while drug dissolution from Carbopol 71G matrices in 0.1 M HCl was rapid, leading to the complete drug release during first two hours of investigation nevertheless of the polymer level applied. The effect of polymer concentration was more pronounced when water was used as drug release media.

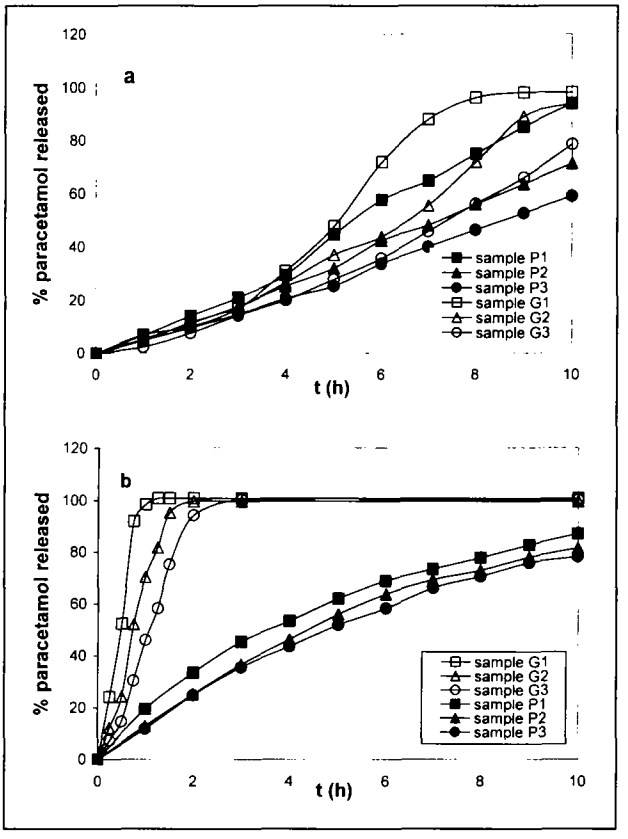


*Fig. 1* : Drug release profiles obtained from the investigated matrix tablet formulations in vitro in water (a) and 0.1M HCl (b) used as drug release media

The overall drug release at the same polymer level was more retarded with matrices containing Carbopol 971P compared to tablets based on Carbopol 71G.

In acidic media, swelling of the polymer was less pronounced leading to the initially faster drug release, especially in the case of Carbopol 71G matrices, where, due to the presence of larger polymer particles, formation of the pores in the matrix was rapid, followed by fast drug dissolution and disintegration of the matrix. In the case when water was used as dissolution medium, disentanglement of the polymer chains and swelling was more intensive, followed by the rapid formation of the gel layer which performs like a barrier to drug release. With the increase of polymer level, dissolution rate decreased leading to the slow and incomplete drug release. After ten hours of investigation, complete drug release was observed from matrices containing 7,5% of Carbopol 971P and formulations containing 7.5 and 15.0% of Carbopol 71G. Percent of paracetamol released from matrices containing 22.5% Carbopol 71G and sample containing 15% Carbopol 971P was about 60%, while in the case of tablets containing 22.5% Carbopol 971P only 50% drug release occurred.

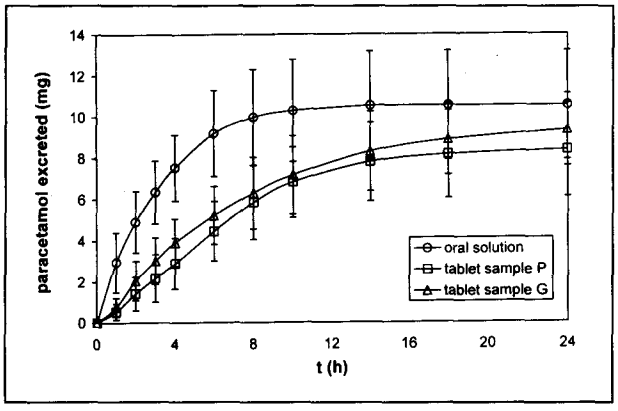


*Fig. 2*: Hypothetical drug release profiles in vivo calculated by numerical deconvolution.

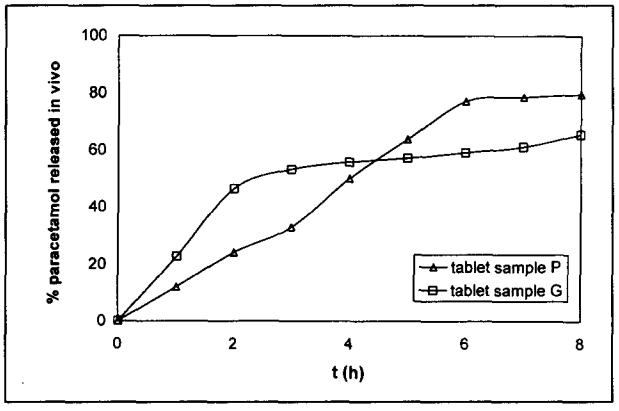


*Fig. 3*: Cumulative urinary excretion curves observed in vivo after oral administration of paracetamol solution and the investigated tablet samples.

The large differences observed in vitro using different media, emphasize the need for in vivo study in order to evaluate the applicability of Carbopol 71G as a sustained release agent, especially having in mind the susceptibility of Carbopol 71G matrices to acidic environment. With regards to the observed data indicating that sample P2 and sample G3 exhibited almost superimposable drug release profiles in distilled water, while the corresponding profiles in 0.1 M HCl were significantly different, these two tablet formulations, containing 15% of Carbopol 971P amd 22.5% of Carbopol 71G (designated in further text as samples P and G, respectively) were selected for in vivo study.

## Results of the In Vivo Study

Mean cumulative urinary excretion profiles observed in vivo after administration of the investigated tablet samples P and G, as well as the reference paracetamol solution are given in Figure 2. Pharmacokinetic parameters characterizing the observed in vivo profiles are summarized in Table II. In the case of sustained release forms, the decreased input kinetics resulted with increased MRT values. The obtained MRT values increased from 2.8 h for an oral solution to 6.3 and 6.6 h for the investigated tablet samples P and G, respectively. The corresponding values of MDT calculated as the difference between the MRT of the investigated sustained release tablets and reference solution, were 3.73 h and 2.91 h, indicating that sustained drug release was accomplished.

## Hypothetical drug release profiles in vivo

Results obtained by numerical deconvolution from the urinary excretion data observed after oral administration of the investigated sustained release tablet formulations and reference paracetamol solution, indicating the in vivo drug release profiles, are presented in Figure 3.

Certain differences between the hypothetical in vivo input kinetics for tablet samples P and G could be observed. In the case of sample P, near zero-order drug release kinetic was obtained, leading to more than 80% of paracetamol released after six hours. In the case of sample G, the biphasic drug release pattern could be observed with the initially more rapid drug release leading to almost 50% of paracetamol dissolved after two hours; while drug release was afterwards retarded resulting in only 65% release after eight hours. It can be postulated that, in the case of matrix tablets prepared with granular Carbopol 71G, slow formation of the gel layer in acidic media (i.e. in stomach) and greater matrix porosity enables rapid diffusion of aqueous media into and dissolved drug from the matrix, thus leading to the initially faster dissolution compared to that observed in sample prepared with Carbopol 971P. However, when the tablet reaches the environment with

*Table II:* Pharmacokinetic parameters after oral administration of the investigated tablet samples and reference paracetamol solution (mean ± SD)

| preparation | Ae (mg) | $k_{el}$ ($h^{-1}$) | $t_{1/2}$ (h) | MRT (h) | MDT (h) | $MDT_{decon}$ (h) |
|---|---|---|---|---|---|---|
| oral solution | 10.08±2.07 | 0.38±0.10 | 1.93±0.54 | 2.82±0.63 | – | – |
| tablet sample P | 8.68±2.44 | 0.27±0.08 | 2.75±0.83 | 6.27±1.37 | 3.45 | 3.73 |
| tablet sample G | 9.02±1.68 | 0.24±0.07 | 3.14±1.19 | 6.63±1.96 | 3.81 | 2.91 |

higher pH values, rapid formation of the gel layer occurs leading to the slow and sustained drug release which was more pronounced for the tablets containing higher proportion of the polymer (sample G). Also the interindividual variations were much more pronounced in the case of tablet sample G. This could be, propably, attributed to the differences in the gastric residence times and pH values among the subjects enrolled in the study.

The obtained, hypothetical in vivo dissolution profiles were, also, characterized with respect to the mean dissolution time. In the case of sample P, the calculated value of $MDT_{decon}$ was close to the value calculated according to the statistical moments analysis from the pharmacokinetic profiles observed in vivo (MDT) as presented in Table II. Although this was not the case for sample G , where calculation error due to the incomplete drug release was encountered, the similarity of the obtained values additionally supports the evidence of the applicability of urinary excretion data in the development of level A IVIVC, based on numerical deconvolution computations.

## CONCLUSIONS

The results of the present study indicate that urine could be successfully used as alternative biological fluid, collected by a non-invasive methodology, in the course of IVIVC development in the cases where it would be appropriate taking into account the drug substance pharmacokinetics.

In this investigation the sound and reliable hypothetical in vivo drug release profiles were obtained by numerical deconvolution from the cumulative urinary excretion data of paracetamol sustained release tablets and the reference, paracetamol oral solution.

Carbopol 71G is new and unique polymeric material for sustained release matrix tablet formulations due to its extremely high degree of swelling upon contact with aqueous media. It provides tablets with favorable mechanical properties. Although it exhibited great susceptibility to acidic environment in vitro, followed by rapid drug release and complete disintegration of the matrix in less than two hours, this was not observed in vivo. Hypothetical in vivo dissolution profiles of investigated formulations indicated the prolonged and sustained drug release. The obtained results emphasized the need for further detailed in vitro drug release studies under various experimental conditions in order to evaluate the effect of in vitro test conditions and develop biorelevant drug release methodology that would be predictive on in vivo behaviour of the sustained release carbomer matrix tablets.

## ACKNOWLEDGMENT

This work was done under the project 2120102B supported by the Ministry of Science, Technologies and Development, Government of Serbia. The authors would like to thank Noveon Speciality Chemicals, Clevelend, OH, for the gratis supply of the carbomer.

## REFERENCES

1. United States Pharmacopeia, 26th revision, US Pharmacopeial Convention Inc., Rockville, MD, 2003.
2. Guidance for Industry: Extended Release Solid Oral Dosage Forms: Development, Evaluation and Application of In vitro - In vivo Correlations, CDER/FDA, 1997.
3. Luessen, H.L.; Verhoef, J.C.; Borchard, G.; Lehr, C.M.; de Boer, A.G.; Junginger, H.E. Mucoadhesive polymers in peroral peptide drug delivery. II. Carbomer and polycarbophil are potent inhibitors of the intestinal proteolytic enzyme trypsin. Pharm Res 1995, 12, 1293-1298.
4. Walker, G.F.; Ledger, R.; Tucker, I.G. Carbomer inhibits tryptic proteolysis of luteinizing hormone-releasing hormone and N-alpha-benzoyl-L-arginine ethyl ester by binding thhe enzyme. Pharm Res 1999, 16, 1074-1080.
5. Huang, L.L.; Schwartz, B.J. Studies on drug release from a carbomer tablet matrix. Drug Dev Ind Pharm 1995, 21, 1487-1501.
6. Perez-Marcos, B.; del Cano, O.; Gomez-Amoza, J.L.; Martinez-Pacheco, R.; Souto, C.; Concheiro, A. Usefulness of certain varieties of carbomer in the formulation of hydrophilic furosemide matrices. Int J Pharm 1991, 67, 113-121.
7. Perez-Marcos, B.; del Cano, O.; Gomez-Amoza, J.L.; Martinez-Pacheco, R.; Souto, C.; Concheiro, A. Design and biopharmaceutical evaluation of atenolol matrix tablets prepared with carbomer 934. STP Pharma 1995, 5, 105-109.
8. Khan, G.M.; Zhu, J.B. Studies on drug release kinetics from ibuprofen-carbomer hydrophilic matrix tablets: influence of co-excipients on release rate of the drug, J Controlled Release 1999, 57, 197-203.
9. Amidon, G.L.; Lobenberg, R. Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards, Eur J Pharm Biopharm 2000, 50, 3-12.
10. Dominguez, R.A.; Medina, L.R.; Hurtado, P.M. Bioequivalence study of paracetamol tablets: in vitro-in vivo correlation. Drug Dev Ind Pharm 2000, 26, 821-828.
11. Vila-Jato, L.J.: Blanco, J.; Alonso, M.J. The effect of the molecular weight of polyethylene glycol on the bioavailability of paracetamol-polyethylene glycol solid dispersions. J Pharm Pharmacol 1986, 38, 126-128.
12. Hekimoglu, S.; Ayanoglu-Dulger G.; Hincal AA. Comparative bioavailability of three commercial acetaminophen tablets. Int J Clin Pharm Ther Tox 1987, 25, 93-96.
13. Torrado, G.; Carrascosa, C.; Torrado-Santiago, S.Correlation of in vitro and in vivo acetaminophen availability from albumin microaggregates oral modified release formulations. Int J Pharm 2001, 217,. 193-199.
14. Lo, Y.L.; Bye A. Rapid determination of paracetamol in plasma by reversed-phase high performance liquid chromatography. J. Chromatogr 1979, 173, 198-201.
15. Langenbucher, F. Improved understanding of convolution algorithms correlating body response with drug input. Pharm Ind 1982, 44, 1275-1278.