International Journal of Pharmaceutics 421 (2011) 145–150

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

In vitro–in vivo correlation and bioavailability studies of captopril from novel controlled release donut shaped tablet

Asim Sattwa Mandal, Sugata Chatterjee, Subhasis Kundu, Nikhil Biswas, Arijit Guha, Sreyashi Paul, Ketousetuo Kuotsu*

Department of Pharmaceutical Technology, Jadavpur University, Kolkata 700032, West Bengal, India

ARTICLE INFO

Article history:
Received 2 August 2011
Received in revised form 5 September 2011
Accepted 8 September 2011
Available online 17 September 2011

Keywords:
Donut
Coated
Captopril
In vitro
In vivo
In vitro–in vivo correlation

ABSTRACT

A controlled release formulation of captopril which was coated and fabricated into a donut shaped tablet formulation, was investigated in rabbit for pharmacokinetic and *in vitro–in vivo* correlation studies. Coated donut shaped tablets were prepared and *in vitro* release was studied in simulated gastric fluid at three different RPMs. New Zealand albino male rabbits have been used as animal model for *in vivo* study. A sensitive and simple HPLC method was developed for the determination of captopril content in rabbit plasma. *In vitro* release studies showed that release patterns followed zero order for around 4 h. Single oral administration of coated donut shaped tablets in rabbit illustrated retained availability of captopril to the injected drug. Captopril content could pursue the same release pattern over the same time course in *in vivo* study. The *in vivo–in vitro* correlation coefficients obtained from point-to-point analysis were greater than 99% between concentrations at certain time points obtained from release study in simulated gastric fluid at different RPMs and HPLC analysis of rabbit's plasma. From the *in vitro–in vivo* correlation prediction it was evident that the coated donut shaped tablet is a good device for controlled delivery of captopril.

© 2011 Elsevier B.V. All rights reserved.

1. Introduction

Captopril (1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline), an orally angiotensin-converting enzyme (ACE) inhibitor has outstanding clinical effectiveness in the treatment of essential hypertension and congestive heart failure (El-Kamel et al., 2006; Seta et al., 1988). It is widely used as a first choice drug in antihypertensive therapy. However, single dose of captopril can regulate hypertension up to 8 h. Hence, a daily dose of 37–75 mg is required clinically thrice in a day. This necessitates the development of controlled release formulation to maintain relatively constant blood levels for longer duration of time. Furthermore, it possesses good bioavailability (70–75%) including short half-life (~2 h) (Duchin et al., 1988). It is metabolized to *n*-carboxyl derivative in liver and excreted mainly in the urine (Darren et al., 2009; Singhvi et al., 1982).

A new way of ensuring approximately zero order drug release from the matrix is the modification of the geometry of tablet. This approach has been explored by keeping the surface area constant. This leads to semi-hemispheric, frustrum-shaped, pie-shaped, multi-holed device, device with a coaxial hole (donut-shape or doughnut shape) (Kim, 1999). Except donut shaped tablet all other geometrically modified devices are not suitable for industrial manufacturing. In such a tablet, there is a constant ratio between the inner and outer tablet surface areas. This is made possible by the fact that as there is a decrease in the outer surface area of the tablet with progressing time of tablet dissolution, there is concomitant increase in the inner surface area (Higuchi, 1962). For *in vivo* analysis, suitable and sensitive analytical methods are essential for successful clinical, pharmacological and pharmacokinetic evaluation, bioavailability and bioequivalence (Gauhar et al., 2009). Captopril has been determined by several methods including gas chromatography, gas chromatography–mass spectrometry (GC–MS), radioimmunoassay, enzyme immunoassay (Matsuki et al., 1980; Tu et al., 1984; Kinoshita et al., 1986). However, the GC method is limited by sensitivity and the GC–MS may not be widely accessible. The immunological methods have become attractive for routine clinical monitoring during chronic therapy because of their ease of performance, speed of analysis and sensitivity. Among these methods, high-performance liquid chromatography (HPLC) is the most extensively used due to high sensitivity and high selectivity. Shen et al. have developed simple HPLC method for determination of captopril in biological fluids (Shen et al., 1992). By derivatization of captopril a rapid and highly sensitive HPLC method has been developed for determination captopril in plasma. The derivatization enhanced the UV absorption

* Corresponding author. Tel.: +91 8981099151.
E-mail address: ketousetuoju@yahoo.in (K. Kuotsu).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2011.09.012

level which led to high accuracy for detection and determination (Amini et al., 1999). Another derivatization procedure was described by Arroyo et al. (1997) for determination of captopril. p-Bromophenacyl bromide has been utilized to form adduct with captopril for measurement by HPLC with UV detection following a single oral dose (Li et al., 2003). Mirza and Tan (2001) developed an anion-exchange HPLC method for determination of captopril in pharmaceutical tablets.

This study was designed by fabricating a coated donut shaped tablet for controlled release of captopril. *In vitro* release has been performed at different RPMs through UV–Visible spectroscopy in simulated gastric fluid. A simple and suitable HPLC method using UV spectra as detection procedure has been developed and validated for quantification of captopril in rabbit plasma. Drug contents were measured after every single oral administration and compared with intravenous administration to check sustainability of the formulation and to get the predicted value of absorbed drug. A point-to-point *in vitro*/*in vivo* correlation (IVIVC) model was developed for relating percentage of drug dissolved to percentage of drug absorbed.

2. Materials and methods

2.1. Materials

Captopril was received from Macleods Pharmaceuticals Ltd., Mumbai, India as a gift sample. Hydroxypropylmethyl cellulose (HPMC) E5, E15 and E50; calcium hydrogen phosphate dihydrate ($CaHPO_4$, $2H_2O$); polyethylene glycol (PEG) 6000 were purchased from Loba Chemie (Pvt.) Ltd., Mumbai, India. Water (HPLC grade), acetonitrile (HPLC grade), ethyl acetate (HPLC grade) and methylene chloride (HPLC grade), phosphoric acid, potassium hydrogen phosphate (KH_2PO_4), ethyl cellulose 14 cPs, isopropyl alcohol (IPA), glycerine, methylene chloride (DCM) were purchased from Merck Limited, Mumbai, India and of analytical grade.

2.2. Methods

2.2.1. Preparation of tablets

Tablets were prepared at 400 mg scale with captopril (25 mg), calcium hydrogen phosphate as diluents (185 mg), combination of HPMC E5 and HPMC E50 (50:50) as binder, talc as antiadherant, stearic acid as glidant. The mixtures were homogeneously blended and subsequently compressed into donut tablets using single station concave face punches having a coaxial hole by direct compression method. Hardness of the tablets was kept within 32–40 N. External diameter and internal diameter were fixed at 10 mm and 4 mm respectively.

2.2.2. Water impermeable coating layer

4% (w/v) ethyl cellulose 14 cPs has been used as a water impermeable coating material. The polymer was dissolved in the mixture of IPA and DCM (3:2) (Hogan, 1995). Polyethylene glycol 6000 was added as a plasticizer to impart flexibility to the film. The film thickness was measured using Mitutoyo Digimatic Caliper (Eq. (1)). Amount of polymer and solvents were optimized based on thickness, uniformity and flexibility of the film. Thickness was kept nearly 0.033 mm.

$$\text{film thickness} = \frac{\text{thickness of the tablet after coating} - \text{thicness of the tablet before coating}}{2} \quad (1)$$

2.2.3. Mucoadhesive coating layer

4% (w/v) solution of HPMC E15 was made using same ratio of IPA and DCM and glycerin as a plasticizer. Thickness of the film was kept within 0.05 mm. It was determined with the above formula.

2.2.4. In vitro study

λ_{max} of captopril (204 nm) was determined at pH 1.2 and corresponding calibration curve was developed at 204 nm within the expected range of drug release by JASCO V-550 double beam UV/Vis spectrophotometer (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf). *In vitro* release studies were performed using USP II Dissolution Testing Apparatus (Electrolab TDT-08L) in simulated gastric fluid at 50 RPM, 75 RPM and 100 RPM as rotating speed of stirrers. 900 ml of 0.1 N hydrochloric acid solution was maintained at $37 \pm 0.5\,^{\circ}C$ for 12 h dissolution study (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070237.pdf). Tablets were placed at the bottom of the baskets. 5 ml of samples were withdrawn at 15 min, 30 min and 1–12 h at the interval of 1 h and the aliquots withdrawn were replaced with fresh dissolution medium. The samples were filtered and assayed spectrometrically at 204 nm. All release studies have been performed in triplicate designated to get the confirmation about release pattern.

2.2.5. In vivo study

2.2.5.1. Animals. *In vivo* studies were carried out on six New Zealand albino male rabbits weighing between 1.25 and 1.5 kg. The animals were kept in individual cages and maintained at 25 °C for 10 days prior to experiment. Standard diet and water *ad libitum* were given to them. All experiments have been performed according to guidelines of the Institutional Animal Ethics Committee, Jadavpur University. The rabbits were divided into two groups containing three rabbits each. First group (Group I) was administered intravenous bolus injection of captopril at the rate of 10 mg/kg bodyweight to compare the pharmacokinetic parameters. 25 mg captopril was administered orally in second group (Group II) in a single dose of coated donut shaped tablet. All studies were performed after keeping rabbits for overnight fasting.

2.2.5.2. Instruments and chromatographic conditions. The Jasco HPLC system (Jasco Analytical Instruments, 28600 Mary's Court, Easton, MD 21601) employed consisted of a model PU-1580 pump, a model 5195 injector and a model UV-1575 UV/Vis detector connected to a CSW 1.7 Data Module Integrator. The separation was performed on an analytical column 250 × 4.6 mm internal diameter C18 (5 μm, particle size, Thermo Electron Corporation; Ohio) column. The wavelength was set at 204 nm. A buffer solution of 0.01 M KH_2PO_4 was prepared and the pH was adjusted to 3.2 with the help of phosphoric acid. The mobile phase was a mixture of acetonitrile and buffer (60:40) at a flow rate of 1 ml/min. The mobile phase was filtered through a 0.45 mm nylon membrane filter and degassed by sonication before use. The eluting analytes were recorded as positive peaks by reversing the input polarity on the detector.

2.2.5.3. Drug standard solutions. Standard stock solutions (10 ml) of captopril and ramipril (internal standard) were prepared in acetonitrile at a concentration of 1 mg/ml both and kept at −20 °C. Intermediary solutions of captopril were prepared in acetonitrile. Internal standard solution was also diluted in acetonitrile to obtain the working solution of 500 ng/ml. All calibration curve samples (non-zero samples), except blank plasma were prepared by spiking three different blank plasma batches aliquots of 180 μl each, with 10 μl of the intermediary captopril solutions to yield final plasma concentrations of 25, 50, 100, 200, 500, 1000, 2000, 4000 ng/ml. All zero calibration curve samples were spiked with 10 μl of acetonitrile.

2.2.5.4. Sample extraction. Drug was extracted from plasma samples using liquid–liquid extraction technique. For sample preparation, 180 μl aliquots of plasma samples (calibration curve and analysis) were taken in Eppendorf tubes. Then 20 μl of internal standard (500 ng/ml of Ramipril) was added to each. The tube was vortex-mixed for 30 s and allowed to stand for 30 min. Then the plasma was mixed with 1 ml of ethyl acetate and 1 ml of methylene chloride. The resultant solution was vortex-mixed for 10 min in 15 ml centrifuge tube to extract the drug and internal standard into organic phase. The tube was centrifuged at 5000 rpm to separate plasma from organic phase. The organic layer was collected and evaporated to dryness under hot nitrogen. The residue was reconstituted with 1 ml of mobile phase for HPLC analysis. 25 μl of the reconstitute was injected into the HPLC.

2.2.5.5. Selectivity. This test was carried out by collecting normal plasma samples from six New Zealand albino male rabbits processed by the liquid–liquid extraction and chromatographed to determine the extent to which endogenous plasma components may contribute to the interference at the retention time of analyte and internal standard (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf). Blood samples were collected before administration of drug.

2.2.5.6. Linearity. Calibration curves were constructed using eight non-zero standard points covering in the range of 25–4000 ng/ml. In addition, a blank (non-spiked sample) and a zero plasma sample (only spike with IS) were run to discard the presence of interferences. Plasma samples were injected in triplicate. The calibration curve was developed by plotting peak area ratios of captopril and internal standard against the plasma concentration.

2.2.5.7. Recovery. Spiked plasma samples were assayed using five replicates at three concentration levels of 50, 200 and 1000 ng/ml of captopril and one concentration level of 10 ng/ml of ramipril and extracted as previous. Recovery (extraction efficacy) was calculated by comparing the peak-area of the extracted sample to that of unextracted pure standard solutions.

2.2.5.8. Precision and accuracy. Precision and accuracy of this method were evaluated using three different concentrations of 50, 200 and 1000 ng/ml of captopril. The experiment was carried out six times in a day (intra-day) and for six consecutive days (inter-day).

2.2.5.9. Sensitivity. The limit of detection (LOD) and lower limit of quantification (LLOQ) were determined to check the sensitivity of the method. The LOD and LLOQ values were 10 ng/ml and 25 ng/ml respectively.

2.2.5.10. In vivo release and pharmacokinetic analysis. Blood samples of 0.5 ml were collected at the interval of 5 min, 10 min, 15 min, 30 min, 1 h, 2 h, 4 h, 8 h and 12 h for Group I and 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, 12 h and 24 h for Group II in heparinized Eppendorf tubes after administration. These samples were centrifuged immediately at 3500 rpm and 4 °C temperature for 10 min. Plasma samples were taken and stored at −20 °C until assay. Pharmacokinetic parameters like peak plasma concentration (C_{max}), time to reach peak plasma concentration (t_{max}), area under the (concentration–time) curve (AUC), mean residence time (MRT), elimination half-life ($t_{1/2}$) and total body clearance (CL) were calculated following non-compartment model of Kinteica 4.4. All the parameters were calculated for i.v. bolus injection of captopril and coated donut shaped tablet.

2.2.5.11. In vivo–in vitro correlation. Level A *in vivo–in vitro* correlation (IVIVC) was estimated by a two-stage procedure i.e. deconvolution followed by comparison of the fraction of drug absorbed to the fraction of drug dissolved (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070239.pdf). This correlation represents a point-to-point relationship between *in vitro* dissolution and the *in vivo* input rate and it is generally linear. It is considered as highest level of correlation (Yasir et al., 2010; Emami, 2006; Vlugt-Wensink et al., 2007; van Dijkhuizen-Radersma et al., 2004). In this linear correlation, curves may be superimposable or may be made to be superimposable by the use of a scaling factor. Deconvolution method has been performed by Kinteica 4.4 (Eqs. (2)–(6)). This method is applied to oral doses $C = c\delta f$, where $c\delta$ is the blood/plasma concentration resulting from a unit impulse input; f is the input function and C is the response. The data/input values are $c\delta$, intravenous, as well as the concentration obtained by an oral solution. If f is considered constant for the intervals between $t(i-1)$ and t_i the result is $f = f_i$ = constant

$$\frac{dA}{dt} = f = \text{rate of deconvolution}, \tag{2}$$

$$\frac{\Delta A_i}{\Delta t_i} = f_i \tag{3}$$

$$C_{ostn} = \frac{1}{D_0}\sum_{i=1}^{n} \frac{\Delta A_i}{\Delta t_i} \Delta \text{AUC}_{iv(t_n - t_i)}^{(t_n - t_{(i-1)})} \tag{4}$$

where D_0 = initial dose of IV; C_{os} = concentration of oral administration; AUC = area under the curve.

The time reference is based on the oral administration, by interpolation (logarithmic). The two time references can be made to coincide.

$$\frac{\Delta A_1}{\Delta t_1} = D_0 \frac{C_{os1}}{\Delta \text{AUC}_0^{t_1}} \tag{5}$$

and $A_0 = 0$

$$A_1 - A_0 = \Delta A_1$$

Therefore using the above equations of A1

$$\frac{\Delta A_n}{\Delta t_n} = \frac{C_{osn} \cdot D_0 - \sum_{i=1}^{n-1} (\Delta A_i / \Delta t_n) \cdot \Delta \text{AUC}_{t_n - t_i}^{t_n - t(i-1)}}{\Delta \text{AUC}_0^{t_n - t(i-1)}} \tag{6}$$

With $A_n = A_{n-1} + (\Delta A_n / \Delta t_n) \cdot \Delta t_n$.

The result A_n is obtained for all n as well as f.

3. Results and discussion

3.1. In vitro study

In vitro release profile at 50 RPM showed zero order release for more than 4 h trailed by plateau phase up to 10 h (Fig. 1). Nearly 80% drug was released within 4 h. At 75 RPM release was augmented and the duration of zero order release became shorter and plateau phase started after 4 h and remained up to 10 h. Again, the rate of release accelerated at 100 RPM and zero order release was obtained up to near about 4 h. Therefore, there was an effect of RPM on dissolution profiles of drug from coated donut shaped tablets. It has been concluded that with amplification of agitation erosion from polymeric matrix has been increased. It was also seen that 80% drug was released within 4 h or nearly 4 h and the release patterns up to that time point followed zero order.

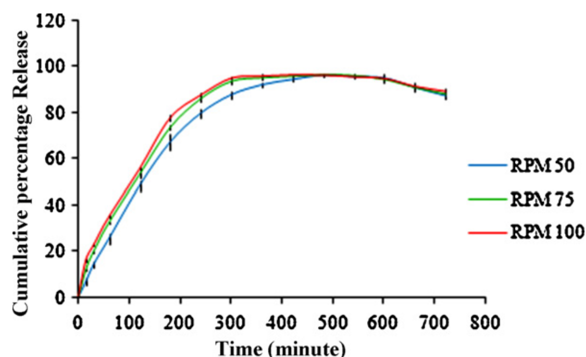

Fig. 1. *In vitro* release study at different RPMs.

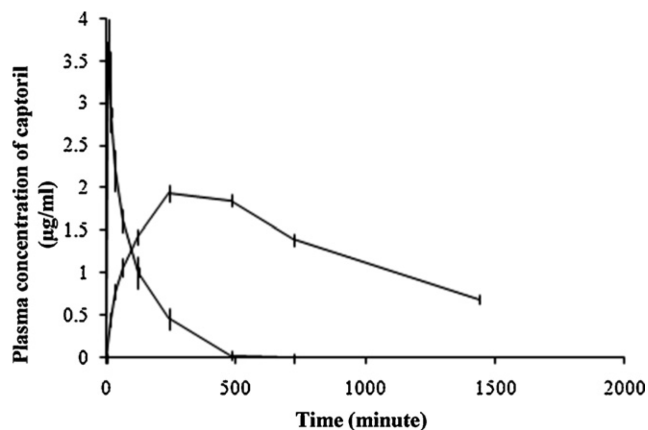

Fig. 3. Plasma concentration-time profile of captopril after administration of intravenous solution and coated donut shaped tablet in rabbits. Data represent mean ± SD ($n = 3$).

3.2. In vivo study

3.2.1. Assessment of linearity and selectivity

Linearity was tested for the range of 25–4000 ng/ml, showing good linear response with correlation co-efficient 0.994. The chromatograms obtained from drug, internal standard and blank plasma are depicted in Fig. 2. The retention time of captopril and ramipril were 4.08 and 2.31 min respectively. Thus, this indicates that there was no such interference of other plasma components on the selectivity of the analytical method.

3.2.2. Recovery

Absolute recoveries for captopril and ramipril were more than 98%. Low concentration (50 ng/ml) showed more than 99% recovery. Internal standard (Ramipril) followed the same result. Combination of more than 99% recovery and 98% recovery were obtained from medium concentration (200 ng/ml). On the other hand, more than 98% recovery was possible in high concentration (1000 ng/ml). These results indicated that the extraction procedure was very selective.

3.2.3. Accuracy and precision measurement

Intra-day precision and accuracy of the assay was measured for captopril at concentration levels of 50, 200 and 1000 ng/ml. Method intra-day accuracy and precision (%CV) ranged from 99.01 to 99.82 and 1.48 to 2.05 respectively. Method inter-batch accuracy and precision (%CV) ranged from 98.92 to 99.78 and 1.53 to 2.08 respectively as presented in Table 1. The results so obtained were within the acceptance criteria for accuracy and precision designed by USFDA (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf).

3.2.4. In vivo release and pharmacokinetic analysis

Plasma concentration–time profiles of captopril after administration of i.v. solution and coated donut shaped tablet are shown in Fig. 3. Plasma concentration of captopril was increased with time up to 4 h following oral administration of coated donut

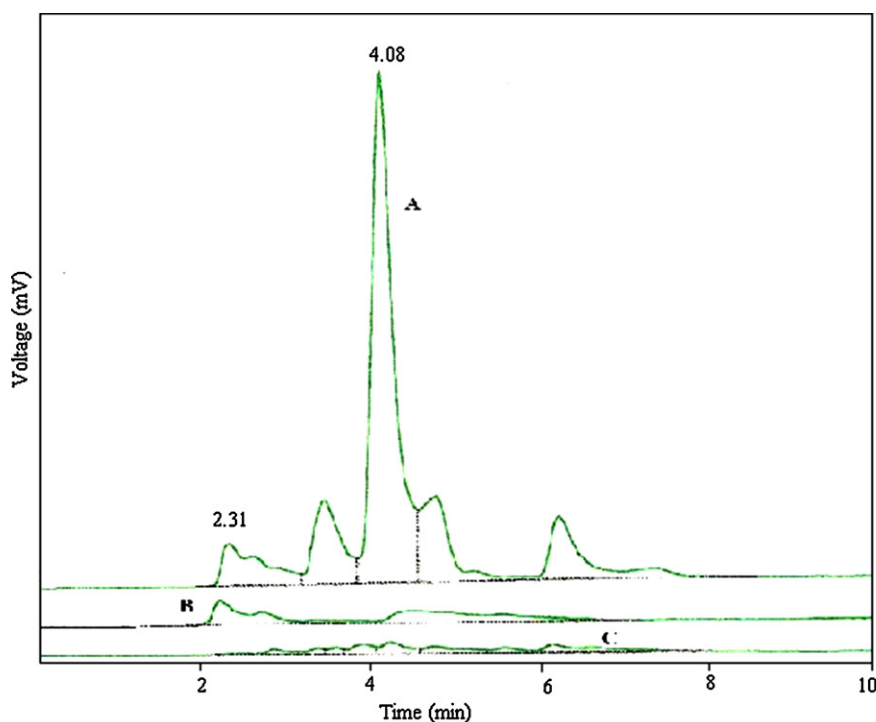

Fig. 2. Chromatogram. (A) Drug with internal standard in plasma; (B) internal standard in plasma; (C) blank plasma.

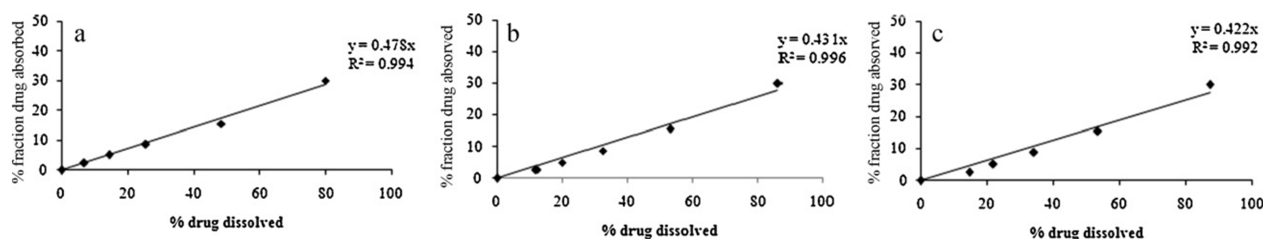

Fig. 4. Percentage of fraction of drug absorbed vs. percentage of drug dissolved by *in vitro* method. (a) 50 RPM; (b) 75 RPM; (c) 100 RPM.

Table 1
Interday and intraday accuracy and precision data (mean ± SD, $n = 6$).

Amount of drug added (ng/ml)	Conc. in plasma		Accuracy		Precision (% CV)	
	Intraday	Interday	Intraday	Interday	Intraday	Interday
50	49.91 ± 1.03	49.89 ± 1.04	99.82	99.78	2.05	2.08
200	198.94 ± 3.13	198.93 ± 3.16	99.47	99.46	1.57	1.59
1000	990.08 ± 14.68	989.24 ± 15.10	99.01	98.92	1.48	1.53

Table 2
Comparative pharmacokinetic parameters of captopril following administration of intravenous and coated donut shaped tablet.

Parameter	Intravenous solution	Coated donut shaped tablet
C_{max} (μg/ml)	3.717 ± 0.339	1.938 ± 0.096
t_{max} (min)	5	240
AUC_{total} (min (μg/ml))	338.004 ± 35.647	2572.22 ± 138.066
$t_{1/2}$ (min)	70.910 ± 2.949	687.201 ± 68.613
MRT (min)	111.648 ± 9.168	1114.8 ± 97.879
Clearance (min)	0.0372 ± 0.004	0.0097 ± 0.001

shaped captopril tablet. Plasma concentration fell down slowly up to 8 h followed by sharp decrease. Pharmacokinetic parameters were shown in the Table 2. C_{max} values of i.v. injection and tablet were 3.717 ± 0.339 and 1.938 ± 0.096 respectively. t_{max} values of i.v. injection and tablet were 5 min and 240 min respectively. Other parameters i.e. AUC_{total}, $t_{1/2}$, MRT and clearance are higher in case of coated donut shaped that intravenous. The values of these parameters and Fig. 3 showed that drug concentration was controlled in rabbit plasma and nearly zero order release kinetic was observed in the *in vivo* study.

3.2.5. *In vivo–in vitro correlation*

Fig. 4a–c shows Level A *in vivo–in vitro* correlation (IVIVC) at different RPMs (50, 75 and 100). By using this predictive IVIVC model, maximum amount of drug absorbed was 29.94% after 4 h whereas according to *in vitro* study 79.87%, 86.14% and 87.32% of the drug were released at a paddle speed of 50 RPM, 75 RPM and 100 RPM respectively without any variation of other parameters. Best fitting straight line passing through origin provides maximum correlation coefficient at 75 RPM ($R^2 = 0.996$). On the other hand, maximum points lie on that line at 50 RPM with respect to others. The results indicate that there was good correlation between drug release from the matrix and absorption of dissolved drug.

4. Conclusions

The *in vitro* characteristics of the controlled release donut shaped tablets was carried out in simulated gastric fluid and *in vivo* drug release studies produced an excellent correlation independent of the release rate. The *in vitro–in vivo* correlation coefficients were greater than 0.99 suggesting that the protocol followed bear a great inter-resemblance. A strong correlation between *in vitro* release and pharmacokinetic effect is important to predict the effect of a controlled release formulation. It allows prediction of pharmacokinetics with *in vitro* data and it gives more robustness to the controlled delivery of drug. Thus, it can be concluded that the fabricated donut shaped captopril tablets can be used as a tool for predicting the *in vivo* release characteristics of the drug.

Acknowledgements

The authors are grateful to National Doctoral Fellowship, AICTE, New Delhi, India for providing financial assistance for carrying out the research work. Prof. Amal Kumar Bandyopadhyay, Dept. of Pharm. Tech., Jadavpur University, India is acknowledged because of his technical support and advice.

References

Amini, M., Zarghi, A., Vatanpour, H., 1999. Sensitive high-performance liquid chromatographic method for determination of captopril in plasma. Pharm. Acta Helv. 73, 303–306.
Arroyo, C., Lopez-Calull, C., Garcia-Capdevila, L., Gich, I., Barbanoj, M., Bonal, J., 1997. Determination of captopril in plasma by high-performance liquid chromatography for pharmacokinetic studies. J. Chromatogr. B 688, 339–344.
Darren, R.G., Matthew, J.I., Pugh, W.J., Cox, P.A., Gard, P., Smart, J.D., Moss, G.P., 2009. Metabolism of captopril carboxyl ester derivatives for percutaneous absorption. J. Pharm. Pharmacol. 61, 159–165.
Duchin, K.L., McKinstry, D.N., Cohen, A.I., Migdalof, B.H., 1988. Pharmacokinetics of captopril in healthy subjects and in patients with cardiovascular diseases. Clin. Pharmacokinet. 14, 241–259.
El-Kamel, A.H., Al-Shora, D.H., El-Sayed, Y.M., 2006. Formulation and pharmacodynamic evaluation of captopril sustained release microparticles. J. Microencapsul. 23, 389–404.
Emami, J., 2006. In vitro–in vivo correlation: from theory to applications. J. Pharm. Pharm. Sci. 9, 169–189.
Gauhar, S., Ali, S.A., Shoaib, H., Naqvi, S.B.S., Muhammad, I.N., 2009. Development and validation of a HPLC method for determination of Pefloxacin in tablet and human plasma. Iran J. Basic Med. Sci. 12, 32–42.
Higuchi, W.I., 1962. Analysis of data on the medicament release from ointments. J. Pharm. Sci. 51, 353–357.
Hogan, J.E., 1995. Film-coating materials and their properties. In: Cole, G. (Ed.), Pharmaceutical Coating Technology. Taylor & Francis Inc., Bristol, PA, pp. 7–49.
Kim, C., 1999. Release kinetics of coated, donut-shaped tablets for water soluble drugs. Eur. J. Pharm. Sci. 7, 237–242.
Kinoshita, H., Nakamura, R., Tanaka, S., Tohira, Y., Sawada, M., 1986. Enzyme immunoassay for captopril. J. Pharm. Sci. 75, 711–713.
Li, Y., Ai-xia, X.U., Rong-sheng, Z., Bao-xia, Y., 2003. Determination of captopril in human plasma by high-performance liquid chromatography and study on the pharmacokinetics after a single oral dose. J. Chin. Pharm. Sci. 12, 31–35.
Matsuki, Y., Fukuhara, K., Ito, T., Ono, H., Ohara, N., Yui, T., Nambara, J., 1980. Determination of captopril in biological fluids by gas–liquid chromatography. J. Chromatogr. 188, 177–183.
Mirza, T., Tan, H.I.S., 2001. Determination of captopril in pharmaceutical tablets by anion-exchange HPLC using indirect photometric detection; a study in systematic method development. J. Pharm. Biomed. 25, 39–52.
Seta, Y., Higuchi, F., Kawahara, Y., Nishimura, K., Okada, R., 1988. Design and preparation of captopril sustained-release dosage forms and their biopharmaceutical properties. Int. J. Pharm. 41, 245–254.
Shen, G., Weirong, T., Shixiang, W., 1992. Simple high-performance liquid chromatographic method for the determination of captopril in biological fluids. J. Chromatogr. 582, 258–262.

Singhvi, S.M., Duchin, K.L., Willard, D.A., McKinstry, D.N., Migdalof, B.H., 1982. Renal handling of captopril: effect of probenecid. Clin. Pharmacol. Ther. 32, 182–189.
Tu, J., Liu, E., Nickoloff, E.L., 1984. Radioimmunoassay for total captopril in human serum or plasma samples. Ther. Drug Monit. 6, 59–65.
van Dijkhuizen-Radersma, R., Wright, S.J., Taylor, L.M., John, B.A., de Groot, K., Bezemer, J.M., 2004. In vitro/in vivo correlation for 14C-methylated lysozyme release from poly(ether-ester) microspheres. Pharm. Res. 21, 484–491.
Vlugt-Wensink, K.D.F., de Vrueh, R., Gresnigt, M.G., Hoogerbrugge, C.M., van Buul-Offers, S.C., de Leede, L.G.J., Sterkman, L.G.W., Crommelin, D.J.A., Hennink, W.E., Verrijk, R., 2007. Preclinical and clinical in vitro in vivo correlation of an hGH dextran microsphere formulation. Pharm. Res. 24, 2239–2248.
Yasir, M., Asif, M., Ammeduzafar, Chauhan, I., Singh, A.P., 2010. *In vitro–in vivo* correlation: a review. Drug Invention Today 2, 282–286.