Comparison of Pharmacokinetic Parameters of Moxifloxacin after Oral Administration of Its' Solid Dosage Forms

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Abstract- In our study we have developed a regioselective dosage form of moxifloxacin. The present study aims at pharmacokinetic characterization of regioselective dosage form by comparing it with moxifloxacin controlled release dosage form. A simple, specific and rapid high performance liquid chromatography (HPLC)-ultraviolet-visible (UV) method was developed for the analysis of plasma samples. The C_{18} column was employed for separation of moxifloxacin using the mixture of acetonitrile and 0.5% triethylamine solution. The regression curve was found linear over the concentration range of 0.2–10 µg/ml. A single dose pharmacokinetic study was carried out after oral administration of 5 mg/kg to healthy white New Zealand rabbits (n = 6) by administrating regioselective and controlled release dosage form respectively. The drug plasma concentration to time data was fitted into one compartment open model after oral administration to determine the possible pharmacokinetic parameters. The controlled release dosage form (884.33±5.27 µg/L) of moxifloxacin shows significantly lower average steady state plasma concentration than regioselective dosage form (1389.67±11.31 µg/L). The time required to achieve steady state plasma concentration of drug was comparatively low indicating higher values of absorption rate constant and lower values of absorption half lives in case of regioselective dosage form. The area under curve for controlled and regioselective dosage form were found to be 9.57±0.53 and 27.34±1.32 mg.h/L respectively. The results concluded that the regioselective dosage form showed approximately three folds more bioavailability and double value of mean residence time than controlled release dosage form.

Keywords- Moxifloxacin, Pharmacokinetic, Reversed phase, Ciprofloxacin, Retention time.

I. INTRODUCTION

Moxifloxacin is chemically 1-cyclopropyl-7-(s,s)-2,8- diazabicyclo(4.3.0)non-8-yl)-6- fluoro-8-methoxy-1,4-dihydro-4-oxo-3 quinoline carboxylic acid [Figure 1]. It is fourth-generation antibiotic that exert its' effects by trapping a deoxyribonucleic acid (DNA) drug enzyme complex and specifically inhibiting adenosine tri-phosphate (ATP)-dependent enzymes topoisomerase II (DNA gyrase) and topoisomerase IV. Currently, moxifloxacin is being extensively used in the treatment of respiratory system diseases such as community acquired pneumonia (CAP), chronic bronchitis (CB) and chronic obstructive pulmonary disease (COPD) for the broad spectrum of antimicrobial activity against respiratory tract pathogens, including Gram-positive and Gram-negative organisms, anaerobic bacteria, and atypical respiratory tract pathogens [1–4].

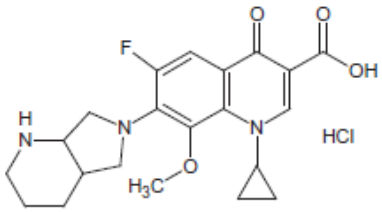

Figure 1: Structure of moxifloxacin hydrochloride.

Moxifloxacin is used as second line drug in the treatment of tuberculosis. When the non-triple bismuth treatment or quadruple treatments are failing in *Helicobacter pylori* eradication, then the moxifloxacin is used. The favorable pharmacokinetics of moxifloxacin, including a high mean apparent volume of distribution and a long

terminal half life, supports a once daily dosing regimen in the treatment of infectious disease [5]. It revealed that moxifloxacin is primarily eliminated in the liver [6].

Recently, use of spectrofluorimetric and high-performance liquid chromatography (HPLC) coupled with mass spectrophotometry (MS) were used for measuring moxifloxacin concentration in human serum & plasma and rat plasma have been reported [7–11]. HPLC method was used form determination of moxifloxacin in murine plasma & murine brain tissues [12], murine lung homogenate [13], dog plasma [14], and male camel serum [15]. The HPLC with fluorescence detector was applied in several methods for its advantage of sensitivity. The concentration of moxifloxacin in various body fluids of respective animals were determined using HPLC with fluorescence detector like milk & plasma of lactating goat [16], milk & plasma lactating ewes [17], human plasma [18], human plasma, saliva & urine [19, 20], and human dialysate [21]. The simple HPLC methods were employed for the estimation of moxifloxacin concentration in human cerebrospinal fluid (CSF) & serum [22], plasma, aqueous and vitreous fluid of human [23], and human plasma [24–27].

The reverse phase HPLC (RP-HPLC) with fluorescence detector was used for determination of concentration of moxifloxacin in human plasma & body fluids [28, 29, 31], rat plasma [30], human micro-dialysate [32], and blood plasma [33]. The methods includes capillary electrophoresis with laser-induced fluorescence [34], square-wave adsorptive voltammetery [35], differential pulse polarography [36], voltammetery [37], capillary electrophoresis with contactless conductivity detection [38], spectrofluorimetery [39, 40], ultra HPLC & ultra performance liquid chromatography (UPLC)-MS/MS [41, 42].

Although many methods were used for pharmacokinetic studies for the analysis of biological samples collected from various animals. The HPLC using UV detector was reported very few [43–47]. Thus, the protein precipitation was selected because it has obvious advantages, for example shorter processing time, consumption of less organic solvent, fewer steps, and good cleans up of plasma samples. The suitability of the method was validated for the pharmacokinetic study using rabbit plasma.

The scope of the present study was to develop and validate a HPLC using UV detector method through the parameters of linearity, precision and accuracy to determine the potency of moxifloxacin in different pharmaceutical formulations as well as to monitor the pharmacokinetic parameters of the drug through the analysis of rabbit plasma samples.

II. MATERIALS AND METHODS

Materials-

Moxifloxacin hydrochloride and Ciprofloxacin were kind gift sample obtained from Panacea Biotech Ltd., India and Leben Laboratories, India with stated purity of 99.97% and 99.83% respectively. Triethylamine, potassium dihydrogen phosphate, Dipotassium hydrogen phosphate and tetrabutyl ammonium hydrogen sulphate solution were purchased from SD Fine Chemicals, India. Acetonitrile and methanol of HPLC grade were purchased from Merck, India and used in the study.

Methods-

Experimental design

The study protocol was approved by Institutional Animal Ethical Committee (GES's Satara College of Pharmacy, Degaon, Satara). A crossover design was used in two phases, with one washout periods of 15 days. The moxifloxacin controlled release dosage form administered by oral route at single doses of 5 mg/kg body weight. The oral administration of controlled release dosage form (CR) was done by nasogastric tube. About 1 mL of blood samples were collected at 1, 1.5, 2, 4, 6, 8, 10, 12, 24, 36, 48 and 72 h using a 20-gauge needle by inserting into the marginal ear vein, and allowing the blood drip into a 2 mL heparinized syringe following, which it was placed in a tube. The blood samples were centrifuged at 1500 rpm for 15 min within 30 min after collection. The plasma was quickly taken out and stored at −40 °C until assayed. Similar procedure was adopted after 15 days of washing period by administrating moxifloxacin regioselective dosage form (R) administered by oral route at single doses of 5 mg/kg body weight [48].

Chromatographic conditions

The chromatographic study was carried out at room temperature using C_{18} column (250 mm × 4 mm, 5 µm particle size, Merck, Germany) with spike volume 50 µL. The autosampler vials and column temperature was maintained at 5 °C. The preparation of mobile phase was done by mixing 1:4 ratio of acetonitrile with tetrabutyl ammonium hydrogen sulphate solution (10 g/L). The moxifloxacin and internal standard (ciprofloxacin) were determined using Systronics LC 100 Plus WUFENG, with LC 100 UV Detector with autosampler with built in system controller. The flow rate of mobile phase was maintained in isocratic form at 1 ml/min and. The UV detection wavelength was set at 293 nm [43].

Method validation

The calibration curve was constructed using seven concentrations over the range of 10–1000 µg/L using rabbit plasma as a blank. The standard curve was plotted between peak area ratio and concentration. The end point of

six determinations was showed coefficient of correlation greater than 0.99 for calibration curve. The stock solution of 1 mg/ml of internal standard and moxifloxacin were prepared. The working solutions of moxifloxacin were prepared with concentration, 10, 25, 50, 100, 250, 500 and 1000 µg/L and spiked into plasma. The plasma aliquots (quality control samples) were stored at −40 °C till the analysis of sample. Aliquots of plasma samples, internal standard (IS) samples and quality control samples were extracted and accurately 50 µL was spiked into the HPLC system [44].

By comparing the peak area of blank plasma sample spiked with different amount of drug and treated as any aliquot, with peak area of the same standards prepared in phosphate buffer. The end point was decided based upon the mean value of six determination (n = 6). The precision in the assay (RSD) was estimated by calculating standard deviation of repeated measurement of percentage of mean value. To determine the intra-day precision the mean of six replicate of three standard samples were used for calibration curves, where the value of RSD should be less than 10%. To determine the inter-day precision, the mean of three standard samples taken were used for calibration curves, where the value of RSD should be less than 10%. The Limit of Quantitation (LOQ) of moxifloxacin in plasma was chosen as concentrations used for lowest concentration on the curve and for which RSD < 15% (LOQ = 10 µg/L). Mean value of recovery should be > 95% [44].

Pharmacokinetic analysis

The plasma concentrations of drug-time data was collected after each treatment in each rabbit. The data was fitted in one compartment open model of drug after oral administration of dosage form. The various pharmacokinetic parameters were determined from the curve. The non-compartmental model was used to determine area under concentration-time curve (AUC), area under first moment curve (AUMC). The mean residence time is the ratio of AUMC and AUC. The relative bioavailability (F_r) was calculated using area under curve of individual dosage form [49].

$$F_r = [AUC]_R \times [Dose]_{CR} / [AUC]_{CR} \times [Dose]_R \quad (1)$$

$$\text{As, } [Dose]_R = [Dose]_{CR}$$

$$F_r = [AUC]_R / [AUC]_{CR} \quad (2)$$

Where, $[AUC]_R$ = area under concentration to plasma curve of regioselective dosage form, $[AUC]_{CR}$ = area under concentration to plasma curve of controlled release dosage form, $[Dose]_{R=}$ dose of moxifloxacin in of regioselective dosage form and $[Dose]_{CR}$ = dose of moxifloxacin in of controlled release dosage form.

Statistical analysis

The statistical analysis was carried out using descriptive statistical parameters like mean, standard deviation (SD) and relative standard deviation (RSD). The calculation of absorption rate constant, elimination rate constant, elimination half life and absorption half life, average steady state plasma concentration and total clearance were reported [50].

III. RESULTS AND DISCUSSION

In the present investigation, the concentration of moxifloxacin in rabbit plasma was determined by HPLC-UV method. However, tetrabutyl ammonium hydrogen sulfate was very costly chemical and was used as ion-pair reagent. Similarly, fluorescence detector was also very expensive. The moxifloxacin have shown strong ultraviolet absorption at 293 nm. Hence, HPLC-UV method was employed in the present investigation. The internal standard method was adopted in order to reduce the system error caused by the instruments and operations. Ciprofloxacin was used as internal standard. This method was easy to operate, simple in sample preparation, required small volume of samples, and highly sensitive.

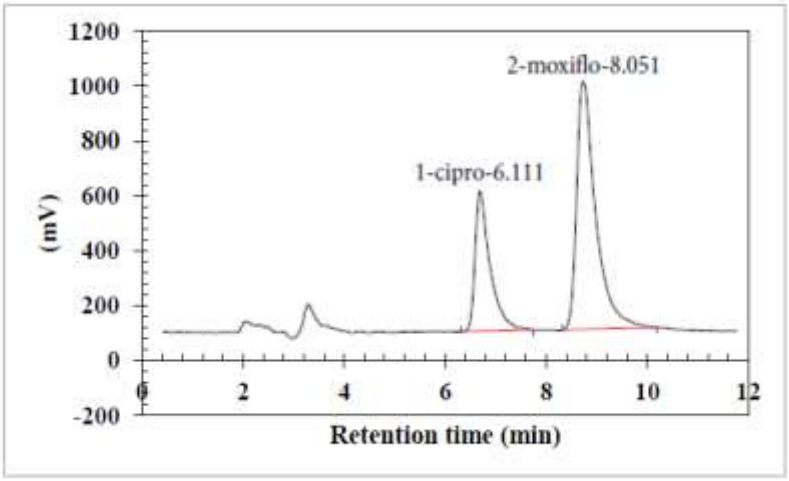

Figure 2: Chromatogram of moxifloxacin and ciprofloxacin in rabbit plasma.

The moxifloxacin was not separated properly at pH 4.5. The same problem was overcome by adding mixture of 0.1% triethylamine (pH adjusted to 4.8 with phosphoric acid)/ acetonitrile in 80:20 ratio. The acetonitrile was found to increase the retention of moxifloxacin. This mobile phase confirms the separation of moxifloxacin and internal standard at shorter retention time. The retention time of ciprofloxacin was about 6.11 min and allows the proper separation of moxifloxacin (8.05 min) as shown in [Figure 2].

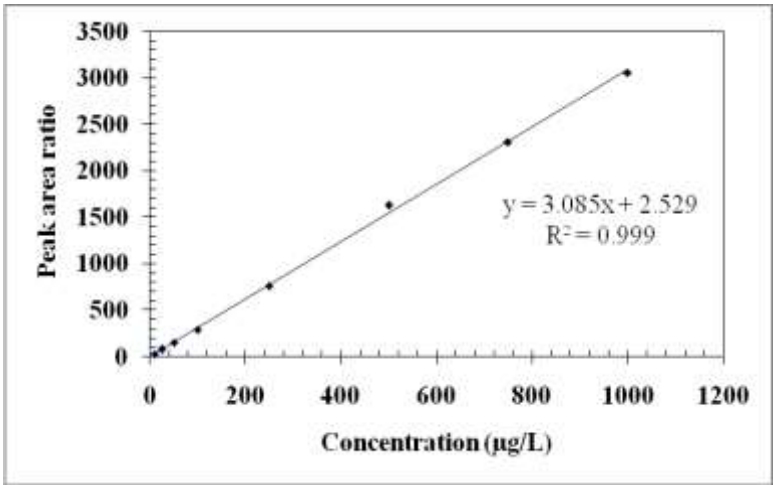

Figure 3: Calibration curve of moxifloxacin.

The linearity of moxifloxacin calibration curve for drug-free plasma over the concentration range of 10–1000 µg/L was assessed. The calibration curve obtained by plotting peak area ratio (moxifloxacin/internal standard) versus concentration was linear over the range of 10–1000 µg/L. The calibration curve of moxifloxacin in plasma was linear and was represented by the regression equations $y = 3.085x + 2.529$ [Figure 3], where y presents the peak area ratio (moxifloxacin/IS) and x represents the plasma concentration of moxifloxacin (μg/mL). The mean correlation coefficient (r^2) for the moxifloxacin calibration curves was 0.999. The relative standard deviation of repeatability of present method was found to be 1.21%. Intra-day, inter-day precision RSDs at the six concentrations were 3.17, 3.48 and 2.75, while the inter-day RSDs were 3.45, 1.67, and 2.68. These results indicated that the validated assay was precise, accurate, and reproducible. The mean percentage extraction recoveries of moxifloxacin at the three concentrations were 79.83 ± 2.34, 82.16 ± 3.21, and 79.69 ± 2.86% respectively.

The use of ciprofloxacin as an internal standard played an important role in minimizing the error in the extraction procedure. The structural similarity and physicochemical properties of ciprofloxacin with moxifloxacin made it suitable to use as internal standard. The ciprofloxacin have shown good ultraviolet absorption response at 278 nm wavelength. Mean value of the method recovery was 98.85%, which ranged from 96.6 to 101.8%. The moxifloxacin is broad spectrum antibiotics with wide therapeutic range. From the literature it was found that it has absorption window in proximal part of gastrointestinal tract (GIT). To confirm the same the study was planned. The plasma concentration of drug with respective time (mean ± SD) after oral administration of controlled release and regioselective dosage form were shown in [Figure 4]. The values of pharmacokinetic parameters are shown in (Table 1) in (mean ± SD) for both dosage form. The quick plasma concentration of moxifloxacin at its maxima from both dosage forms was achieved within 1.2–2 h.

The absorption process was rapid indicated by absorption rate constant and absorption half life values. Higher the value of absorption rate and lower the value of absorption half life was the good indicator of better absorption. The rate of absorption is directly proportional to drug available at absorption site, hence follows a first order kinetics. The values of absorption rate constant were calculated by using method of residual. The tangent touching to y-axis and the terminal linear portion of plasma concentration of drug with respect to time curve was drawn. The residual concentration were determined and the plasma concentration of drug at respective time point was determined and from the slope of line connecting residual line used to calculate absorption rate constant (Ka). The values of absorption rate constants were further used in the calculation of absorption half life ($t_{1/2(a)}$) of moxifloxacin from respective dosage form.

$$\text{Absorption rate constant } (K_a) = \text{slope} \times 2.303 \quad (3)$$

$$\text{Absorption half life } (t_{1/2(a)}) = 0.693/ K_a \quad (4)$$

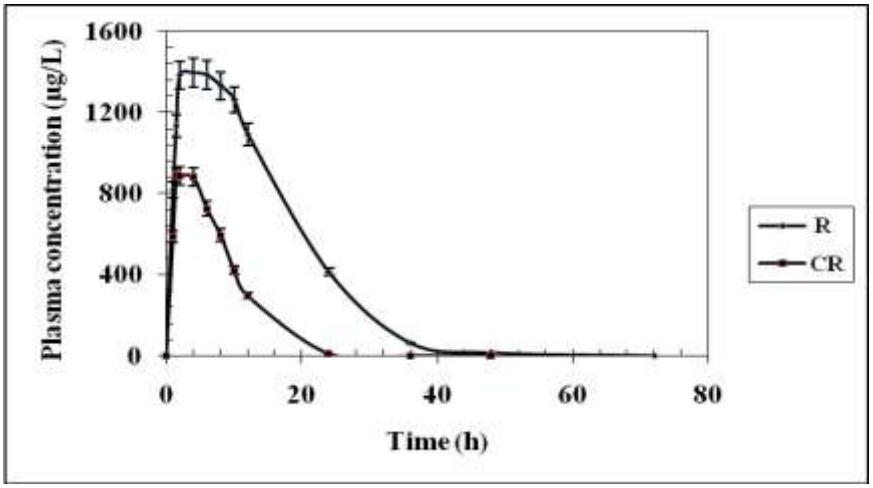

Figure 3: Plasma concentration-time curve.

The elimination rate constant (K) values were determined from terminal linear portion of respective curves. Considering the elimination process follows first order kinetics, the elimination half lives were calculated.

$$\text{Elimination rate constant (K)} = \text{Slope} \times 2.303 \quad (5)$$

$$\text{Elimination half life } (t_{1/2}) = 0.693/\text{ K} \quad (6)$$

The elimination half life after oral administration of R and CR dosage form were found to be 4.25 and 6.79 h respectively. These values of elimination half lives were higher than the values given in the literature for conventional liquid dosage form indicates both dosage form could prolonged duration of action [51]. The prolongation of half lives by extravascular (oral) administration may be due to absorption process. The moxifloxacin was well absorbed from regioselective dosage form than controlled release dosage form which may be due to increased residence of dosage form in absorption window. Both the formulations maintained the steady state plasma concentration for more than 10 h. The regioselective formulation was found to maintain the plasma concentration consistently above 850 µg/L for 12 h producing significant antibiotic effect.

The relative bioavailability of moxifloxacin from regioselective dosage form was found to be 2.86 fold more than controlled release dosage form of moxifloxacin at constant, 5 mg/ kg dose. This was confirmed by comparing area under plasma concentration of drug-time curve of both dosage forms. The bioavailability results shows the variability of absorption since the R dosage form retained in proximal part of GIT for more than 8 h leads to increased bioavailability than the CR dosage form. The variability in the bioavailability can be associated with two disadvantages: (a) underexposure of moxifloxacin in animals/human with lower bioavailability which leads to the development of moxifloxacin resistance and (b) overexposure of animal/human with higher bioavailability which produce the risk of side/toxic effects [52]. This situation has been already discussed in literature for few quinolones such as enrofloxacin [53].

Table 1: Pharmacokinetic parameters of moxifloxacin for regioselective and controlled release dosage forms

Pharmacokinetic parameter	*R*	*CR*
Absorption rate constant† (Ka)	8.71 ± 0.27 h^{-1}	6.48 ± 0.13 h^{-1}
Absorption half life† ($t_{1/2(a)}$)	0.795 ± 0.02 h	0.107 ± 0.01 h
Elimination rate constant† (K)	0.163 ± 0.03 h^{-1}	0.102 ± 0.02 h^{-1}
Elimination half life† ($t_{1/2}$)	4.25 ±0.03 h	6.79 ± 0.06 h
Area under curve† $[AUC]_{0-72}$	27.34 ± 1.32 mg.h/L	9.57 ± 0.53 mg.h/L
Area under first moment curve† $[AUMC]_{0-72}$	327.72 ± 4.91 $mg.h^2/L$	65.65 ± 2.06 $mg.h^2/L$
Mean residence time† $[MRT]_{0-72}$	11.97 ± 0.28 h	6.934 ± 0.11 h
Average steady state concentration† ($C_{SS\ avg}$)	1389.67 ± 11.31 µg/L	884.33 ± 5.27 µg/L
Steady state plasma concentration time (T_{ss})	2–10 h	1.5–6 h
Total clearance† (Cl_t)	0.317 ± 0.012 L/h	0.198 ± 0.009 L/h
Relative bioavailability (F_r)	2.86 ± 0.01 fold	1

Where, † indicates the value, as mean ± SD for six determinations (n = 6).

From the literature, in rabbits the volume of distribution of moxifloxacin after intravenous injection administration of drug in 5 mg/kg to rabbits, the volume of distribution (V_d) was reported as 1.95 L. The values of total clearance (Cl_t) for R and CR dosage form were found to be 0.318 L/h and 0.199 L/h respectively. The higher total clearance and elimination rate constant values for regioselective dosage form were due to higher plasma concentration.

$$\text{Total clearance } (Cl_t) = V_d \times K \quad (7)$$

In conclusion, this regioselective drug delivery system shows better values of pharmacokinetic parameters and higher bioavailability. Looking at the anatomical and biochemical similarity between rabbits and human being the present regioselective system should undergo clinical trials before bring into the market.

IV. CONCLUSIONS

In this study, HPLC-UV method was validated and indicates that the method was a simple, rapid, precise, and accurate for the determination of moxifloxacin concentrations rabbit plasma. Moreover, the method requires only a small volume (50 μL) of plasma, which makes it suitable for studying the pharmacokinetics in rabbits. The sensitivity and simplicity of the method makes it suitable for pre-clinical pharmacokinetic studies of moxifloxacin. The developed method will be suitable for biomedical analysis of moxifloxacin levels in plasma in human after validation for therapeutic drug monitoring. The pharmacokinetic parameters obtained after fitting the data in one compartment open model and non-compartmental analysis concluded that the regioselective dosage form exhibits higher relative bioavailability and mean residence time respectively than controlled release dosage form.

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