

## ALTERATION OF PHARMACOKINETIC PARAMETERS OF PENTOXIFYLLINE USING NATURAL MUCOADHESIVE POLYMERS

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### ABSTRACT

**Objective:** The present study was aimed to alter the pharmacokinetic parameters of the drug pentoxifylline using a novel natural mucoadhesive polymer from two different plants, *Manilkara zapotta* Linn and *Ocimum basilicum* Linn.

**Methods:** The polymer was isolated and six batches of mucoadhesive tablets of pentoxifylline was formulated with 3 different concentrations of each polymer. The best formulation from each of the polymer was selected and administered to rabbits and the plasma drug concentration was compared with the marketed formulation. The pharmacokinetic parameters such as  $C_{max}$ ,  $t_{max}$ , AUC, AUMC,  $\lambda_z$ ,  $t_{1/2}$ , and MRT were determined.

**Results:** The plasma drug concentration vs time curve shows the extended-release of pentoxifylline when compared with the conventional marketed formulation. The results show that there is no change in the peak plasma concentration, but the significant difference was observed in  $t_{1/2}$ , which showed approximately 2.5 fold increase from 2.44 to 6.87 h and the AUC showed five-fold increase from 22.40 to 117.19  $\mu\text{g}\cdot\text{h}/\text{ml}$ , and other pharmacokinetic parameters, when compared with the marketed formulation.

**Conclusion:** The isolated polymer from the plants *Manilkara zapotta* Linn. and *Ocimum basilicum* Linn can be used as a carrier for developing mucoadhesive formulations and it alter the pharmacokinetic of pentoxifylline positively.

**Keywords:** Mucoadhesion, *Manilkara zapotta*, *Ocimum basilicum*, Pentoxifylline, Pharmacokinetics

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Recently the mucoadhesive drug delivery systems have gained more attention in the pharma profession [1]. Mucoadhesion is a converse of bioadhesion, which is aimed to localize the drugs in the mucosal area of the body. The water-soluble polymers were used for the formulation of mucoadhesive drug delivery systems because they become adhesive during hydration. The mucoadhesive drug delivery systems are aimed to target the drug with increased gastric residence time, bioavailability, minimized the first-pass effect, controlled release of the drug with reduced adverse effects [2, 3]. The mucoadhesive polymers selected should be non-toxic, non-irritant, non-absorbable, non-covalent, biocompatible, adhesive and economic, in nature [4]. Either natural (gelatin, guar gum and sodium alginate) or synthetic/semi-synthetic (Hydroxypropyl methylcellulose, Carbopol 934 and Sodium carboxy methyl cellulose), may be used alone or in a combination of two or more for the mucoadhesive drug delivery systems [5-9].

Pentoxifylline (PTX) [1-[5-oxohexyl]-3,7-dimethylxantine), an orally active hemorheological drug, which is used for the treatment of intermittent claudication or other circulatory disorders. Its hemorheological effect involves by reducing the blood viscosity and increasing the erythrocyte deformability [10]. PTX is a highly water-soluble drug (~77 mg/ml). It is well absorbed from the gastrointestinal tract (>95 %), yet the actual amount of drug bioavailable to the body is only about 20 % because of its extensive hepatic first-pass metabolism. Administration of a single dose of extended-release tablets of PTX(400 mg) resulted in a  $C_{max}$  of 55-300 ng/ml and  $t_{max}$  values of 2-4 h [11]. Since PTX has a short biological half-life (about 0.4-0.8 h), the frequent dosing is necessary to maintain the therapeutic plasma drug concentration.

*Manilkara zapota* Linn. (MZL), is an evergreen plant belongs to the family Sapotaceae, grows up to 8-15 m height. It is cultivated throughout the Indian subcontinent including Bangladesh, though it is native to Mexico and Central America. The seeds of MZL are diuretic tonic aperients and febrifuge. The stem bark acts as an astringent, febrifuge [12] and anticancer [13]. The leaves and bark are used to treat cough, cold, dysentery and diarrhea [14].

Antimicrobial and antioxidant activities are also reported from the leaves of MZL [15, 16]. A natural gum from the seeds of the plant was also isolated [17].

*Ocimum basilicum* Linn. (OBL) is an erect, almost glabrous herb, belonging to the Lamiaceae family, native to Iran, Afghanistan, and India, which grows to between 30 and 90 cm high. The leaves are ovate, lanceolate, cucuminate, toothed or entire, glabrous on both surfaces and glandular. When mature, they reach approximately 5 cm in length, excluding the petiole, which is approximately 2 cm long. The upper surface is smooth and lustrous; on the lower surface along the midrib and the petiole short, stiff hairs occur sparingly [18]. It represents an important source of essential oil used in food, pharmaceutical, perfumery, and cosmetics industries [19]. Its aromatic leaves are used in fresh or dried forms as a drug in traditional medicine and as a flavoring agent in food and confectionery products as well as beverages [18, 20]. The seeds of OBL are high in fiber (22.6%) and some regions of Asia like Iran and India, basil seeds are frequently included in beverages and desserts for aesthetic purposes as well as a source of dietary fiber [21].

Even though several kinds of research have been made in the area of alteration of pharmacokinetic parameters, mucoadhesive drug delivery systems based on plant-derived polymers also plays a vital role due to their emollient, lack of toxicity, and low cost. *In vitro* experiments have previously reported that the mucoadhesive polymers of MZL [22] and OBL [23] were suitable agents for the preparation of a controlled release tablet formulation of PTX. So, in this present work, an attempt was made to investigate the effect of these two natural mucoadhesive polymers in the alteration of pharmacokinetic parameters of the PTX.

The seeds of MZL and OBL were purchased from the local vendors of Chennai, Tamilnadu in February 2018. The collected seeds were identified and authenticated by a botanist Dr. S. Balasubramanian, ABS Medicinal garden, Salem. The voucher specimens (MZG-1 and OBG-1) were kept in our museum for future reference. Pentoxifylline was obtained as a gift sample from Shasun Pharmaceuticals,

Puducherry. Microcrystalline cellulose and magnesium stearate were purchased from Central Drug House (India). Acetone, diethyl ether, and petroleum ether were from Qualigens (India) and sodium hydroxide from E-Merck (India). All the chemicals used were of analytical grade

Three batches of mucoadhesive polymers of *Manilkara zapotta* Linn. (MAPMZ) and *Ocimum basilicum* Linn. (MAPOB) were prepared on a laboratory scale by the method of Rao *et al.* [24]. 20 g of the seed powders were mixed individually with 200 ml of cold distilled water and the slurry was prepared. Then 800 ml of boiling water was added to the slurry and boiled for another 20 min with continuous stirring. The solutions were kept overnight to settle the solid matter. The clear solutions were centrifuged for 20 min at 5000 rpm. The

supernatant fluids were separated and twice the volume of acetone was added with continuous stirring. The formed precipitates were filtered and washed with petroleum ether and diethyl ether and then dried under vacuum at 50-60 °C. The dried materials were sieved through sieve No 80 and used for the formulation of tablets.

The mucoadhesive tablets of pentoxifylline (MATP) were prepared by using direct compression technique. Pentoxifylline, mucoadhesive polymer, microcrystalline cellulose, magnesium stearate were accurately weighed, mixed/uniformly and this mixture was compressed into tablets by using Elite multi-station punching machine (Erweka) with 10 mm flat punches. The compression force was adjusted to give tablet hardness in the range of 7 to 11 kp. The constituent of the formulation is presented in table 1.

**Table 1: Formulation of mucoadhesive tablets of pentoxifylline**

Ingredients	F1	F2	F3	F4	F5	F6
Pentoxifylline	400	400	400	400	400	400
Microcrystalline cellulose	152	122	92	152	122	92
MAPMZ	30	60	90	-	-	-
MAPOB	-	-	-	30	60	90
Magnesium stearate	18	18	18	18	18	18
Total weight (mg)	600	600	600	600	600	600

All the quantities are in mg

Female New Zealand white rabbits of either sex or approximately the same age, weighing about 1.5 to 1.6 kg, procured from Sri Venkateswara Enterprises, Bengaluru (Reg No. 237/99), were used for the study. They were housed in separate metallic cages and fed with standard chow diet and water ad libitum. The animals were exposed to an alternate cycle of 12 h of darkness and light each. Before each test, the animals fasted for at least 12 h. The experimental protocols were subjected to the scrutinization of the Institutional Animal Ethics Committee and were cleared by the same (Approval No. P. COL/20/2019/IAEC/VMCP). The animals were divided into 3 groups each consisting of three. The first group was administered with marketed pentoxifylline tablets 400 mg and the second group treated with the mucoadhesive tablets formulated with MAPMZ (F3) and the third group treated with the mucoadhesive tablets formulated with MAPOB.

The rabbits were administered with the respective formulations along with 100 ml of water. The blood samples were collected into heparinized vacuum tubes at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 h following the PTX administration. After collection, the blood samples were centrifuged at 1000 rpm for 10 min at room temperature (25 °C); followed by direct transfer into microcentrifuge tubes and stored at -70 °C until analysis. The amount of food and water intake for each animal was standardized during the sampling day.

A stock solution of PTX (40 µg/ml) was prepared by dissolving in double-distilled water. The working standard solutions of PTX were produced by diluting the stock solutions with blank rabbit plasma (1:1). The ten calibration standards of PTX were prepared independently. The concentration range of PTX was 10 to 2000 ng/ml. All stock solutions, stored at 4 °C, were stable for at least one month without any degradation. The liquid-liquid extraction method was used for the sample preparation of PTX. 0.1 ml of 1 M sodium hydroxide and 7 ml of dichloromethane were added to 1 ml of plasma. The mixture was vortexed for 30 sec and centrifuged at 3000 rpm for 15 min. The upper layer was removed and the organic phase was placed into another test tube and evaporated to dryness under a flow of nitrogen stream at 37 °C. The residue was redissolved in 0.2 ml of the mobile phase (acetonitrile: water, 28:72, v/v) and 30 µl of this solution was injected directly on to the column. The plasma extract was stable for at least two days when kept at 4 °C.

The PTX concentrations in plasma were assayed using a validated high performance liquid chromatography with ultraviolet detection (UV-HPLC) [25, 26]. A high-performance liquid chromatograph (Hewlett-Packard Series 1050) was equipped with a variable wavelength UV detector. The analytical column was a reverse phase,

300 x 3.9 mm I.D., RP-18 µm Hyperbond (Hypersil). The detection was at 274 nm. The mobile phase was a combination of acetonitrile: water (28:72, v/v) and the flow rate was 1 ml/min. The retention time of PTX was 5.15 min (retention volume 5.15 ml). The bioanalytical method was specific with no interfering impurities at the retention time of PTX. The linear calibration model was constructed between peak-height and concentration of PTX in plasma samples.

The method exhibited a linearity of response over a range of 10-2000 ng/ml for PTX ( $r^2=0.998$ ). Limit of detection and limit of quantification were found to be 5 and 10 ng/ml, respectively. Quality control samples at three levels, low (30 ng/ml), middle (600 ng/ml) and high (1600 ng/ml) for PTX were used during routine analysis. The within-batch precision ranged from 2.30 to 5.35 % and accuracy ranged from 99.6 to 103 %. The between-batch precision and accuracy ranged from 4.43 to 6.85 and 102 to 105 %, respectively. The stability of the samples under frozen conditions, at room temperature, and during the freeze-thaw cycle was also determined. The accuracy and precision for calibration curve standards and quality samples in all bioanalytical methods met the acceptance criteria as per FDA guidelines.

Pharmacokinetic evaluation non-compartmental modeling was used to estimate PTX pharmacokinetic parameters after single-dose administration. The PTX plasma concentration vs time data were evaluated by using PKSolver. Pharmacokinetic parameters such as maximum PTX concentration ( $C_{max}$ ) in plasma, the time that  $C_{max}$  occurred ( $t_{max}$ ), area under the plasma concentration time curve from 0 to 24 h ( $AUC_{0-24}$ ) and 0 to infinity ( $AUC_{0-\infty}$ ), elimination rate constant ( $\lambda_z$ ), biological half-life ( $t_{1/2}$ ), Apparent volume of distribution during terminal phase after non-intravenous administration ( $V_z/F$ ), Apparent total clearance of the drug from plasma after oral administration ( $Cl/F$ ) and mean residence time (MRT) were determined.

The area under the plasma concentration versus time curve from 0 to 24 h ( $AUC_{0-24}$ ) was assessed using the linear trapezoidal methodology and was extrapolated to infinity ( $AUC_{0-\infty}$ ). The maximum plasma concentration ( $C_{max}$ ) and time to reach  $C_{max}$  ( $t_{max}$ ) for PTX were directly obtained from the individual observed data. The terminal phase elimination rate ( $\lambda_z$ ) was estimated using a log-linear regression of the observed plasma concentration point in the terminal phase, and the elimination half-life ( $t_{1/2}$ ) was calculated as  $0.693/\lambda_z$ . The apparent total clearance ( $Cl/F$ ) and volume of distribution ( $V_z/F$ ) were calculated using the formulas  $dose/AUC_{0-\infty}$  and  $dose/(\lambda_z * AUC_{0-\infty})$ , respectively.

Each experiment was repeated at least three times. The results are expressed as the mean $\pm$ SD. One-way analysis of variance was used to test the statistical significance of differences among groups. Statistical significance of the differences of the means was determined by Student's t-test.

Pentoxifylline is a synthetic dimethyl xanthine derivative prescribed for complications of peripheral vascular diseases. Although pentoxifylline is almost completely absorbed, it undergoes significant first-pass metabolism resulting in a bioavailability of 20% and frequent dosing is necessary [27]. Mucoadhesive drug delivery systems are used to increase the bioavailability of drugs. Natural polymers are preferred over synthetic and semi-synthetic polymers due to their low cost, non-toxic, emollient, free availability and non-irritating nature [28-30]. Even though many polymers are available, a search for new polymers still interesting to get more efficacious polymers with less toxic. So in this present work, an attempt was made to study the effect of mucoadhesive polymers in the modification of pharmacokinetic properties of PTX.

The mucilage was isolated from the seeds of *M. zapota* and *O. basilicum* by the method of Rao *et al.* [24]. The mucoadhesive tablets of pentoxifylline were formulated by using three different

concentrations of MAPMZ and MAPOB at 5, 10 and 15 %. Six formulations of F1 to F6 were formulated and evaluated for the mucoadhesive property and *in vitro* release. From the earlier studies [22, 23] it was proved that the tablets formulated with the polymers showed good mucoadhesive strength in rabbit buccal mucosa. One best formulation from each of the polymers was selected for the pharmacokinetic studies. Formulation F3 showed the release of 99.44 % of cumulative release and the formulation F6 showed 99.84 % release at 12 and 10 h respectively. So these two formulations (F3 and F6) were selected for the pharmacokinetic studies in rabbits.

Female New Zealand white rabbits of either and the same age, weighing about 1.5 to 1.6 kg were used for the study. The formulations F3, F6, and marketed formulation were administered to rabbits along with 100 ml of water. The drug concentrations in plasma after the administration of PTX in 3 groups were followed for 24 h. The PTX concentrations in plasma were assayed using a validated high-performance liquid chromatography with the UV-HPLC method. The mean plasma concentration versus time profiles for PTX after a single oral dose of PTX is shown in fig. 1. The pharmacokinetic parameters were calculated by using PKSolver. The results are given in table 2.

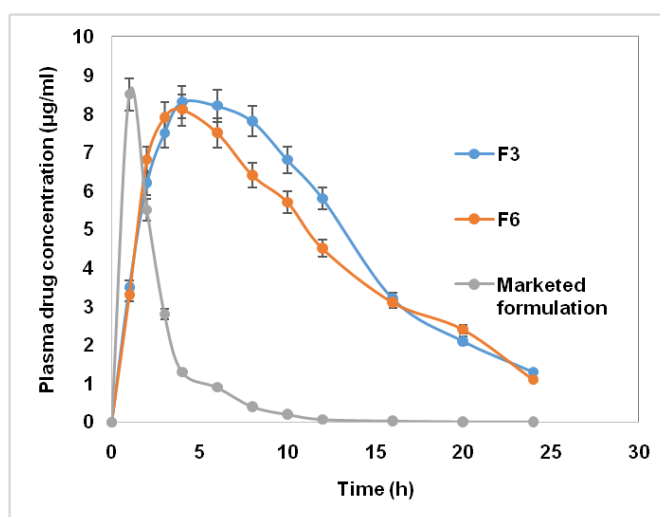


Fig. 1: Mean plasma concentration of PTX after a single oral dose (mean $\pm$ SD; n=3)

Table 2: Non-compartmental extravascular pharmacokinetic parameters after single-dose administration of PTX on rabbits

Parameters	Values		
	F3	F6	Marketed formulation
$\lambda_z$ ( $h^{-1}$ )	0.1187388	0.1008491	0.2838929
$t_{1/2}$ (h)	5.8375792	6.8731144	2.4415796
$T_{max}$ (h)	4	4	1
$C_{max}$ ( $\mu g/ml$ )	8.351333	8.212667	8.499333
$AUC_{0-t}$ ( $\mu g \cdot h/ml$ )	117.18833	107.31067	22.408331
$AUC_{0-\infty}$ ( $\mu g \cdot h/ml$ )	128.27148	118.14864	22.440033
$AUMC_{0-\infty}$ ( $\mu g \cdot h^2/ml$ )	1460.5715	1370.4631	65.788487
MRT (h)	11.386565	11.599482	2.9317465
$V_z/F$ (L)	26.262569	33.57062	62.788764
$Cl/F$ (L/h)	3.118386	3.3855657	17.825286

(All values are calculated from the mean of Plasma PTX concentration; n=3)

The absorption of PTX is rapid in marketed formulation than the test formulations; the mean  $t_{max}$  of the marketed formulation was 1 h, while in the formulation F3 and F6, the mean  $t_{max}$  was around 4 h. This shows that the mucoadhesive tablets formulated with MZL and OBL were effective in delaying the peak plasma concentration of PTX. The peak plasma concentrations ( $C_{max}$ ) of PTX were found to be 8.35, 8.21 and 8.50  $\mu g/ml$ , respectively for the F3, F6, and marketed formulation. It indicates there is no significant change in the peak

plasma concentration when it is given as controlled release formulation or a conventional marketed release formulation, which assures the formulations F3, and F6 are in the same therapeutic window of the marketed formulation. The  $K_{el}$  values were found to be 0.119, 0.101 and 0.284  $h^{-1}$  calculated from the slope of the plasma concentration-time data. A decrease in elimination rate constant of formulations F3 and F6 indicated the slow/sustained release of the drug PTX in rabbit [31].

AUC<sub>0-∞</sub> in plasma were 128.271, 118.149 and 22.440 µg. h/ml, respectively, for the formulations F3, F6 and marketed formulation, which indicated the increased bioavailability of the mucoadhesive formulation. The AUC of the formulation F3 and F6 was increased almost 5-6 fold, which shows the sustained release of the drug PTX for an extended period. The elimination rate of PTX was relatively fast with a  $t_{1/2}$  of 5.84, 6.87 and 2.44 h. The  $t_{1/2}$  values were found to vary widely; similar results were reported by Beerman et al., [11] who obtained a mean  $t_{1/2}$  value of 3.43 h. The other parameters like AUMC also found to be higher in the F3 and F6 formulations. The controlled release characteristics of the formulated mucoadhesive tablets were reflected in the MRT. The MRT was noticeably increased following oral administration of the PTX mucoadhesive formulations (11.387, 11.599 h) as compared to the conventional marketed formulation (2.93 h).

PTX is hepatically metabolized by hydroxylation and demethylation to six renally excreted metabolites [32]. The presence of a high concentration of PTX may alter the mechanism of metabolizing enzymes by saturation, which may lead to increased bioavailability. On the other hand, PTX is reduced extrahepatically to form an intermediate metabolite known as hydroxy-PTX which may be converted back to the parent compound or possibly be metabolized further [33]. Pentoxifylline has a wider therapeutic range (1200-2000 mg/day) in humans for oral application [34]. In this present study, each animal was administered with 400 mg of PTX either formulated with MZL or OBL and the marketed formulation for the evaluation of bioavailability and other pharmacokinetic parameters.

The significant difference was observed in all the pharmacokinetic parameters between both the formulations with the marketed formulation. Thus, the results of the present study clearly indicated the applicability of mucoadhesive polymer in the alteration of pharmacokinetic parameters of the drug PTX. We concluded that enhancement in the bioavailability of PTX would suggest that mucoadhesive tablet formulation could be used to improve the oral bioavailability of PTX.

The pharmacokinetic study of the formulated mucoadhesive tablets of PTX in rabbits was carried out in view of the alteration of the pharmacokinetic parameters. The tablets were formulated with the mucoadhesive polymers MZL and OBL. The plasma drug concentration versus time interval was estimated by UV-HPLC. The increase in  $t_{max}$  value and decrease in  $C_{max}$  value in case of the formulated tablet F3 and F6 from the values of the conventional marketed formulation of PTX, revealed that the MZL and OBL polysaccharides can be used as a carrier for developing mucoadhesive formulations, and those can alter the pharmacokinetic of PTX positively.

#### AUTHORS CONTRIBUTIONS

All authors have contributed equally.

#### CONFLICTS OF INTERESTS

All authors have none to declare.

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