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Bioavailability of Pentoxifylline-Chitosan Oral Matrix Tablet in Healthy Subjects

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Abstract

Pentoxifylline (PX) is a highly water-soluble, hemorheologic drug that undergoes first-pass effect with 20 % bioavailability. Chitosan (CH), a biocompatible and biodegradable natural polymer, is used to increase drug bioavailability, as well as prolonging release. The aim of this study was to investigate the feasibility of enhancement of oral bioavailability of PX using CH. CH was used as an absorption enhancer for preparing the matrix tablet. The in vitro release and bioavailability of PX-CH tablet was compared with the reference product (Trental®-400, Sanofi-Aventis, Turkey). PX-CH tablets were prepared by the slugging method. The in vitro release studies were performed by a flow-through cell apparatus (USP Apparatus IV). A randomized, two-way crossover bioavailability study was conducted in 12 fasting, healthy male volunteers to compare PX-CH and reference tablets; both of them containing 400 mg PX. One tablet of either formulation was administered after a 12 h overnight fast. After dosing, serial blood samples were collected during a period of 12 hours. Plasma samples were analyzed for PX by a validated UV-HPLC method. The pharmacokinetic parameters AUC_{0-12}, AUC_{0-inf}, C_{max}, t_{max}, λ_z, $t_{1/2}$, Vd and CL were determined from plasma concentration-time profiles for both formulations. A higher in vitro release rate of PX was observed using acidic dissolution medium. The total in vitro release of PX was 104 % for PX-CH and 78.7 % for the reference after 12 hours. The mean maximum plasma concentration (C_{max}) of PX-CH tablets was 1260±910 ng/mL after a t_{max} of 0.784±0.406 h. For the reference, they were 67.9±33.7 ng/mL and a t_{max} of 1.48±0.79 h, respectively. It was found that the relative bioavailability of PTX was significantly increased with CH, compared to reference. AUC_{0-inf} values for test and reference were 1740±850 ng.h/mL and 1270±780 ng.h/mL, respectively. Enhancement of the bioavailability of PX would suggest that CH could be used to improve oral bioavailability of PX.

Keywords: Pentoxifylline; Chitosan; Bioavailability; Noncompartmental Pharmacokinetics; Tablet

Introduction

Currently, the oral route is still regarded as the most convenient route of drug absorption. Many drugs experience low bioavailability after oral administration due to poor absorption or susceptibility to first pass metabolism. Absorption enhancers are capable of improving the absorption of low bioavailable drugs. Some absorption enhancers specifically loosen tight junctions and enhance transport/absorption. Chitosan (CH) and chitosan salts are among the most well known absorption enhancers (Aungst, 2000; Thanou et al., 2001a; Thanou et al., 2001b). Several reports have been published on the use of chitosan as a tablet excipient; like absorption enhancers to develop oral dosage formulations (Felt et al., 1998; Illum, 1998; Kristl et al., 1993; Kotze et al., 1998a; Kotze et al., 1998b).

Pentoxifylline (PX) (1-[5-oxohexyl]-3,7-dimethylxantine) (CAS-6493-05-6) is an orally active hemorheological drug for the treatment of intermittent claudication or other circulatory disorders. Its hemorheological effects include reduction of blood viscosity and increasing erythrocyte deformability (Ward et al., 1987). PX 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 extensive hepatic first-pass metabolism. PX is hepatically metabolized by hydroxylation and demethylation to six renally excreted metabolites. Hydroxy-PX is one of the major metabolites in the plasma (Smith et al., 1986). Administration of a single dose of PX(400 mg) extended-release tablets resulted in t_{max} values of 2-4 hours and C_{max}'s of 55-300 ng/mL (Beerman et al., 1985). Since PX has a short half-life (about 0.4-0.8 h), frequent dosing is necessary to maintain therapeutic plasma levels.

In recent years, chitosan (CH) and its salts have attracted much attention as a potential absorption enhancer across mucosal epithelia, especially for low bioavailability drugs. CH is regarded as a biocompatible, biodegradable, natural origin polymer and is widely used in food and pharmaceutical industry (Kumar, 1998). It is used to prepare controlled or immediate release of drugs as a pharmaceutical adjuvant. It can increase drug bioavailability, as well as prolong the release (Nigalaye et al., 1990). Its enhancer activity on the buccal, nasal, rectal and intestinal mucosa and transdermal transport have been well documented (Aspden et al., 1996; Degim et al., 2003; Senel et al., 2000). The enhancing capability of CH is thought to be respon-

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sible for the opening of tight junctions of epithelial cell barriers (Illum, 1998; Kotze et al., 1998a; Kotze et al., 1998b).

In vitro experiments have previously reported that CH was a suitable agent for the preparation of a prolonged release tablet formulation of PX (Inayatov et al., 1998). It was prepared as an oral matrix tablet, using optimum ratio of CH as an absorption enhancer and was the basis for this work. The aim of this study was to investigate the feasibility of enhancement in oral bioavailability of PX using CH. The in vitro release and relative bioavailability of PX-CH tablets were compared with the reference product (Trental^{R}-400), both of them containing 400 mg of PX.

Materials and Methods

Trental® (serial no: DBC, manufacturing date: 6/1997, expiration date: 6/2002) and pure sample of PX(Sanofi-Aventis, Turkey) and Chitosan H(Dainichiseika Color Chemical Mfg.Co. Ltd., Japan) were kindly supplied by the manufacturers. Avicel PH 102^{R} was obtained from F.M.C.Corp. Marcus Hook, USA; magnesium stearate was obtained from Riedel Mannouen, Germany; lactose(Fast-Flo) from HMS Hollandse Melksikerfabriek, Holland and Aerosil 200 was purchased from Degussa, Germany. All other reagents and solvents were of analytical grade of Lab-Scan and Merck(USA).

In Vitro Studies

Preparation of matrix tablets

We evaluated the dissolution profiles of various formulation factors to find the optimum ratio of CH. The optimum amount of CH was found to be 87.5 mg per tablet in our in vitro experiments (Teksin et al., 2000). The in vivo study was conducted in this final formulation.

The matrix tablets of PX were prepared using the slugging method. PX, CH and Avicel PH 102 were passed through a #45 (0.350 mm) mesh screen separately and blended for 20 min. The mixture was compacted with an Erweka tablet machine (Korsch-Erweka GmbH, Germany), using a 20 mm flat-faced punch. Slugged tablets were broken and passed through a #18 (1 mm) mesh screen. Aerosil 200 and magnesium stearate were then added and mixed for an additional 5 min. Tablets were compressed with a 12 mm flat-faced punch. Each tablet (average weight 600 mg) contained 400 mg of PX. The composition of the matrix tablet is given in Table 1. Lactose and Avicel^{R} PH 102 were used as diluents and Aerosil 200 was used as the glidant in a matrix tablet form. Magnesium stearate(0.75 % w/w) was then incorporated as the lubricant.

	%
Pentoxifylline	66.9
Chitosan	14.6
Avicel^{R} PH102	4.18
Lactose	12.6
Aerosil 200	0.92
Magnesium stearat	0.75

Table 1: Formulation of PX matrix tablet (PX-CH).

Physical characteristics of the matrix tablets

Some physico-pharmaceutical properties of the tablets were also checked, such as weight, diameter, thickness, hardness, friability and content uniformity. Twenty tablets were tested for weight (AB 104, Mettler Toledo, Switzerland), thickness (Vernier Caliper, portable dial hand micrometer, Russia), diametrical crushing strength (CGS, Hardness tester HDT 1V-3, Germany) and friability (Roche friability tester, USA). The mean values were calculated together with standard deviations (SD). The same procedure was carried out for the reference.

The drug content of the tablets was measured by a validated UV-spectrophotometric method. For this purpose, 10 tablets were individually weighted, and then each of them were subjected to dissolution at pH 1.2 in 100 mL buffer solution. Samples were assayed spectrophotometrically (Beckman DU-600, USA) at 273 nm. The same procedures were carried out with the reference. The results are shown in Table 2.

	Test	Reference
Weight (g)	0.598[a] ±0.180[b]	0.803±0.282
Diameter (cm)	1.20±0.10	1.78±0.00
Thickness (cm)	0.420±0.000	0.610±0.000
Hardness (kg)	15.6±2.1	5.76±0.39
Friability (%)	0.552±0.050	NF[c]
Content Uniformity (%)	99.7±2.0	101±1

[a]Mean, [b]Standard deviation (SD), Not friable[c]

Table 2: The physical characteristics of the tablets.

Swelling studies

The tablets, put in a wire basket, were lowered into a 50 mL of pH 1.2 buffer solution and were allowed to swell at 37.0 ± 0.5°C. They were periodically removed and their changes in weight were measured before and during the swelling. The swelling ratio was then calculated through their weights.

Dissolution experiments, to determine the release of PX under conditions mimicking the gastrointestinal tract, were carried out using a flow-through dissolution apparatus (USP Aparatus IV, Sotax A.G., Switzerland) at a flow rate of 8 mL/min and fitted with 22 mm dissolution cells. The tablets were tested for drug release. The dissolution conditions were as follows: 1 h in pH 1.2, 1 h in pH 2.5, 1.5 h in pH 4.5, 1.5 h in pH 7.0 and lastly, 7 h in pH 7.5 in phosphate buffer at 37.0°C. The flow rate of 8 mL/min was chosen to keep the sink conditions during the dissolution test in all dissolution media. The amount of released drug was determined using a UV spectrophotometer (Beckman DU-600) at 273 nm. Experiments were carried out in six parallels. The cumulative percent of drug release was calculated and plotted versus time. Mean data values are presented with the standard deviations (mean±SD). The same in vitro release tests were also carried out for the reference.

In Vivo Studies

Subjects and study design

12 healthy male volunteers, aged between 21-25 years, weight-

ing 65-90 kg, with normal clinical findings in hematological and biochemical examinations, participated in the study, after giving the informed consent as defined in the Declaration of Helsinki and under the provisions of EU/ICH. The informed consent protocol was approved by the Ethics Committee of Gazi University Hospital and Master Ethical Committee of Ministry of Health of Turkey. The study was designed as an open label, balanced, randomized 2-period crossover single dose study. A washout period of seven days was enforced between administrations of each treatment.

Subjects were either nonsmokers, or smoked 5-10 cigarettes per day. None had taken any drug and alcohol during the ten days before the study. Subjects were excluded if they were on any planned treatment during until the study, including vitamins and mineral supplements.

Drug sdministration and sampling

Each subject was administered 400 mg of PX orally as PX-CH and reference with 240 mL of water, using 2x2 cross-over model in randomized order, after an overnight fast. The subjects were maintained in the fasting state for 4 h after administering the drug. Blood samples were collected into heparinized vacuum tubes at 0, 0.167, 0.333, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours after each dosing. A total of 32 ten mL blood samples were collected from each subject, during the course of the study through indwelling cannulae placed in forearm veins. After collection, the blood samples were centrifuged at 1.000g 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 and physical activity for each individual subject were standardized during the sampling day. Xanthine-containing foods or beverages and fruit juice were not allowed for 24 hours before and during the entire sampling days. Blood pressure, heart rate and adverse events were monitored during the blood sampling and also on the follow-up study.

Assay Methodology and Procedure

Preparation of standard solution and samples for assays

A stock solution of PX (40 µg/mL) was prepared by dissolving in double distilled water. The working standard solutions of PX were produced by diluting the stock solutions with blank human plasma (1:1). The ten calibration standards of PX were prepared independently. Concentration range of PX was 10 to 2000 ng/mL. All stock solutions, stored at 4°C, were stable for at least one month without any degradation.

Liquid-liquid extraction method was used for the sample preparation of PX. 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 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.

Instruments and chromatographic conditions

The PX concentrations in plasma were assayed using a validated high performance liquid chromatography with ultraviolet detection (UV-HPLC) (Agabeyoglu et al., 2000). 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 273 nm. The mobile phase was a mixture of methanol:water (58:42, v/v) and the flow rate was 1 mL/min.

Retention time of PX was 5.15 min (retention volume 5.15 mL). The bioanalytical method was specific with no interfering impurities at the retention time of PX. Linear calibration model was constructed between peak-height and concentration of PX in plasma samples. Using peak height between day and within-day precisions expressed as CV% were smaller (in the range of 4-7%) than using peak area between day and within-day precisions (in the range of 5-9%) to quantitate. Therefore, peak height was preferred. The method exhibited linearity of response over a range of 10-2000 ng/mL for PX (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 PX were used during routine analysis. The within-batch precision ranged from 2.30 to 5.35 % and accuracy ranged 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 freeze-thaw cycle were also determined. The accuracy and precision for calibration curve standards and quality samples in all bioanalytical methods met the acceptance criteria as per FDA guideline.

Pharmacokinetic Evaluation

Non-compartmental modeling was used to estimate PX pharmacokinetic parameters after single dose administration. The PX plasma concentration-time data were evaluated using the nonlinear regression program WinNonlin™ (Pharsight Corp., Mountainview, CA; version 4.1). Pharmacokinetic parameters C_{max} (maximum PX concentration), t_{max} (the time that C_{max} occurred), AUC_{0-12} (area under the plasma concentration time curve from 0 up to 12 h), AUC_{0-inf} (area under the plasma concentration time curve from 0 up to infinity), λ_z (elimination rate constant), $t_{1/2}$ (half-life), V_d (distribution volume), and Cl (clearance) were determined using non-compartmental analysis. The AUC_{0-inf} for plasma was determined by the linear trapezoidal rule.

Results

Evaluation of In Vitro Studies

Both tablet formulations were evaluated from the point of view of the physical properties of the tablets (Table 2) and their in vitro releases. The crushing forces for the test and reference tablets were found to be 15.6±2.1 kg and 5.76±0.39 kg, respectively. The reference was not friable because it is a film-coated tablet. The mean drug content of the PX tablets were found to be in the range of 399±2 and 402±1 mg for test and reference, respectively. This indicated that, the tablets passed the content uniformity test as they contained 99.7–101 %. In all determina-

tions, test and reference tablets were found to be within pharmacopeial limits. The effect of pH on the swelling process of CH was important, as it started immediately on contact with the gastric fluid. In vitro experiments have shown that PX-CH readily formed a gel at pH 1.2 (simulated gastric fluid), but showed poor gel-forming abilities at higher pHs. The tablets did not disintegrate for two hours at pH 1.2. The investigation of the tablet swelling properties was performed at pH 1.2. 115 % swelling was observed after the first 15 minutes. Maximum was 175 % after 75 minutes. A gel layer was observed around the tablets at early stages at pH 1.2, but this layer started to diminish as the pH was increased. This observation indicated that the gel-forming ability of CH can be seen only at low pHs.

The release profiles of test and reference were investigated using the flow-through dissolution method. Flow-through cell apparatus was used, since it was thought that in vivo gastrointestinal transit conditions may best be imitated by such an apparatus, using different, but sequential pH media. Five different media, namely pH 1.2, 2.5, 4.5, 7 and 7.5 were used for the release studies. The in vitro release profiles are shown in Figure 1. As can be seen, the test tablet showed a higher drug release between 5 and 12 h at pH 7.0 and 7.4, compared with reference, whereas the release of drug was found to be almost identical for the first 5 h at low pHs. When the in vitro release profiles were compared, the test tablet was significantly different from the reference ($p<0.05$). The total release of PX was experimentally determined to be 102 % for PX-CH and 78.7 % for the reference after 12 hours. It was observed that the CH in the matrices played an important role in acidic media, because of the gel-forming ability for prolonged release, which retards the drug diffusion from the tablet. However, in basic media, the drug release increased due to diminishing gel layer. All results indicated that CH affected the PX release from the matrix tablet.

Evaluation of In Vivo Studies

The plasma PX concentrations were followed throughout 12 hrs after the administration of the two PX formulations in 12 healthy male subjects. The PX concentrations in plasma were assayed using a validated high performance liquid chromatography with UV-HPLC method. The assay was found to be sensitive and rapid enough to be easily applicable to human pharmacokinetic studies of PX.

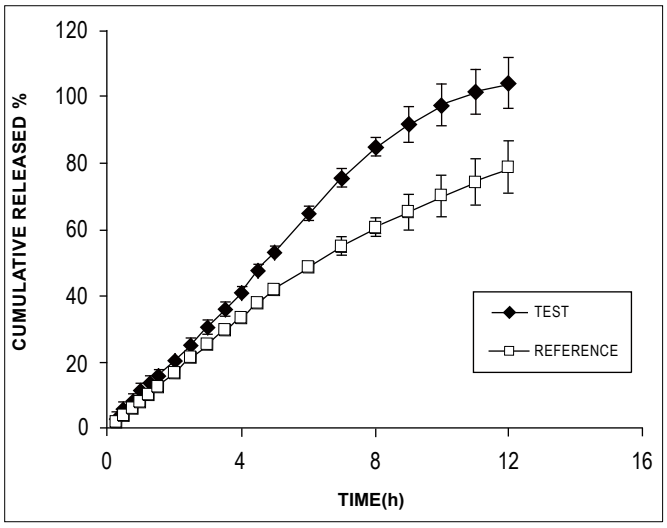

Figure 1:

The mean plasma concentration versus time profiles for PX after a single oral dose of PTX is shown in Figure 2. The pharmacokinetic parameters were calculated using non-compartmental analysis method, using WinNonlin™. They are summarized in Table 3. The plasma profile of PX was found to rise rapidly with an apparent t_{max} occurring at 0.784±0.406 h after oral administration of the test compared with the reference (1.48±0.79) tablet. There was approximately a 19 fold difference in C_{max} values of test and reference (1260±910 ng/mL vs. 67.9±33.7 ng/mL). $AUC_{0\text{-}inf}$ in plasma were 1740±850 ng.h/L and 1270±780 ng.h/L. The elimination of PX was relatively fast with a $t_{1/2}$ of 1.70±1.25 h and 1.84 ±1.42 h. The $t_{1/2}$ values were found to vary widely; similar results were reported by Beerman et al., (1985) who obtained a mean $t_{1/2}$ value of 3.43 h. No significant change in $t_{1/2}$ was noted, which is what is expected from a linearly acting drug like PX. Also, pharmacokinetic parameters do not change with formulation. The results clearly show prolonged

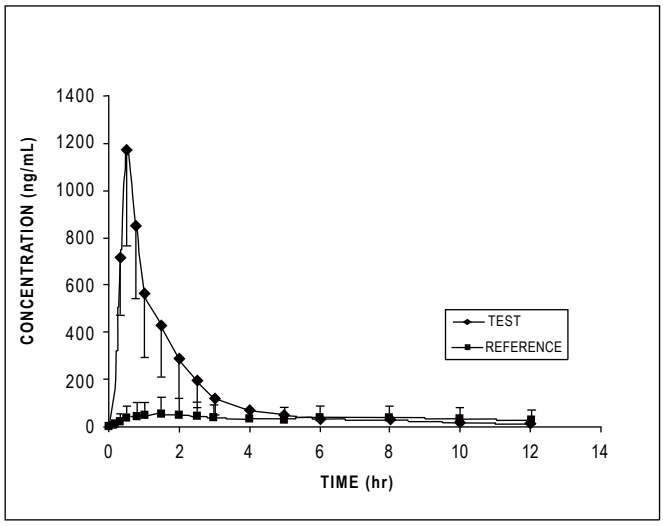

Figure 2:

Pharmacokinetic Parameter	Test	Reference
$AUC_{0\text{-}12}$ (ng.h /L)	1640±920	439±190
$AUC_{0\text{-}inf}$ (ng.h/L)	1740±850	1270±780
C_{max} (ng/mL)	1260±910	67.9±33.7
t_{max} (h)	0.784±0.406	1.48±0.79
λ_z (h^{-1})	0.556±0.260	0.495±0.240
$t_{1/2}$ (h)	1.70±1.25	1.84±1.42
V_d (L)	2.89±1.80	8.05±4.20
Cl (L/h)	350±270	574±340

Table 3: Non-compartmental pharmacokinetic parameters for PX after single oral dose from healthy subjects (n=12), (mean ± SD).

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plasma levels, without prolonged half-life. The clearance (Cl/FF*, clearance encompassing bioavailability) was 350±273 and 574±340 L/h, for test and reference respectively. The distribution volume V_d was low (2.89±1.80 L and 8.05±4.20 L).

It was shown that PX was rapidly cleared from plasma; it undergoes extensive first pass metabolism (Hinze et al., 1976; Smith et al., 1986). Oral bioavailability of PX tablet was found to be 20-30 % (Beerman et al., 1985). Our in vivo study has shown that, the mean bioavailability of PX from CH-PX was not similar to that of the reference. The plasma profiles obtained from the reference were relatively constant, showing sustained release, but much lower C_{max} than the test. They both also showed high variability and the test was not found to be bioequivalent with the reference at 90 % level.

Discussion

CH is able to allow paracellular transport by opening the tight junctions of epithelial cells, but this absorbing enhancing effect is only possible in acidic environments (Illum, 1998). CH has a solubility with pH dependence and therefore might act as an absorption enhancer, rather than a release retardant, depending upon the media. According to our results, CH apparently played an important role for enhancing bioavailability of PX. This effect of CH might be caused by favouring the paracellular transport of PX.

PX is a water soluble compound and diffuses through the CH gel layer, when presented to the stomach. This gel layer occurrence is considered to be important for the PX release. It was visually observed that, the gel layer can form some barrier effect. At early stages, a stagnant gel layer controls the diffusion, but as time passes, the network of the gel starts to disintegrate and thus diffusion is facilitated. This mechanism was found to be responsible for zero order release in vitro. Under in vivo conditions, results showed that, the product has a fast release behavior, instead of a somewhat sustained release observed in vitro. Incidentally, CH has been in use to increase the permeation or absorption of drugs through nasal, buccal and intestinal mucosa (Aspden et al., 1996; Degim et al., 2003; Senel et al., 2000). The enhancing capability of CH is thought to be responsible for the opening of tight junctions of epithelial cell barriers (Kotze et al., 1998a; Kotze et al., 1998b). When the plasma concentrations were considered after administration, higher levels were observed with PX-CH than reference. The intersubject variations were also observed in this study. It could be mainly due to the functioning of the gastrointestinal tract like gastric acid secretion, gastric emptying, gastrointestinal motility, etc.

Recently, CH and CH thiolated polymers were evaluated to modulate drug absorption by inhibition of intestinal P-glycoprotein (P-gp). The in vivo study showed that a delivery system based on thiolated CH significantly increased the oral bioavailability of P-gp substrate of rhodamine-123 (Föger et al., 2006a; Föger et al., 2006b). It has been previously reported that inhibition of efflux pumps by various compounds can lead to enhanced absorption of drugs across the intestine. Werle and Hoffer, (2006) demonstrated a P-gp inhibitory effect of thiolated CH on freshly excised guinea pig ileum. Therefore, enhancement of the systemic availability of PX may increase its available concentrations in the body by suppressing P-gp efflux-transporters.

PX is hepatically metabolized by hydroxylation and demethylation to six renally excreted metabolites (Smith et al., 1986). The presence of high test formulation PX levels may alter the mechanism of metabolizing enzymes by saturation, which may lead to increased bioavailability. On the other hand, PX is reduced extrahepatically to form an intermediate metabolite known as hydroxy-PX which may be converted back to parent compound or possibly be metabolized further (Mauro et al., 1988).

Pentoxifylline has a wider therapeutic range (1200-2000 mg/day) in humans for oral application (Antignanai et al., 1989). In our study, each subject was administered 400 mg of PX orally as PX-CH and the reference for bioavailability evaluation. In our further clinical part of the study, we also examined the hematological effects of the test and reference formulations in the same 12 healthy volunteers, who received 400 mg of PX(twice a day) for 10 days. Although no bioavailability studies were carried out at steady state, it was hematologically observed. The test and reference formulations were not found to be similar in this study at single dose level, however the commercial product and the new formulation of CH tablet were clinically well tolerated and similar hematological effects were observed at steady state, as reported in our previous paper (Yamac et al., 2000). We concluded that enhancement in the bioavailability of PX would suggest that CH could be used to improve oral bioavailability of PX. PX was also well tolerated when administered as a PX-CH matrix tablet formulation. It could be used without observing any clinical problems.

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References

1. Agabeyoglu I, Teksin ZS (2000) The validation of high-performance liquid chromatographic(HPLC) method of pentoxifylline for pharmaceutic/bioequvalence studies. Acta Pharm.Turcica. XLII 105.

2. Antignanai PL, Todini AR, Saliceli F (1989) Results of clinical, laboratory and haemorheological investigations of the use of pentoxifylline in high doses. Pharmatherapeutica 5: 50-56. » Pubmed

3. Aspden TJ, Illum L, Shaugrud O (1996) Chitosan as a nasal delivery system: Evaluation of insulin absorption enhancement and effect on nasal membrane integrity using rat model. Eur J Pharm Sci 4: 23-31.» CrossRef » Google Scholar

4. Aungst BJ (2000) Intestinal permeation enhancer. J Pharm Sci 89: 429-442. » CrossRef » Pubmed » Google Scholar

5. Beermann B, Ings R, Mansby J, Chamberlain J, McDonald A (1985) Kinetics of intravenous and oral pentoxifylline in healthy subjects. Clin Pharmacol Ther 37: 25-28. » CrossRef » Pubmed » Google Scholar

6. Degim IT, Acarturk F, Erdogan D, Lortlar ND (2003)

Transdermal administration of bromocriptine. Biol Pharm Bull 26: 501-505. » CrossRef » Pubmed » Google Scholar

7. Felt O, Buri P, Gurny R (1988) Chitosan: A unique polysaccharide for drug delivery. Drug Dev Ind Pharm 24: 979-993. » CrossRef » Pubmed » Google Scholar
8. Föger F, Schmitz T, Bernkop-Schnürch A (2006a) In vivo evaluation of an oral delivery system for P-gp substrates based on thiolated chitosan. Biomaterials 27: 4250-5. » CrossRef » Pubmed » Google Scholar
9. Föger F, Hoyer H, Kafedjiiski K, Thaurer M, Bernkop-Schnürch A (2006b) In vivo comparison of various polymeric and low molecular mass inhibitors of intestinal P-glycoprotein. Biomaterials 27: 5855-60. » CrossRef » Pubmed » Google Scholar
10. Hinze HJ, Grigoleit HG, Rethy B (1976) Bioavailability and pharmacokinetics of pentoxifylline from "Trental 400" in man. Pharmatherapeutica 1: 160-171.
11. Illum L (1998) Chitosan and its use as a pharmaceutical excipient. Pharm Res 55: 1326-1331. » CrossRef » Pubmed » Google Scholar
12. Inoyatov N, Celebi N, Acarturk F (1998) Preparation and evaluation of a prolonged release pentoxifylline tablet with chitosan. Pharm Ind 60: 472-475. » CrossRef » Google Scholar
13. Kotze AF, Lueben HL, de Boer AG, Verhoef JC, Junginger HE (1998b) Chitosan for enhanced intestinal permeability: Prospects for derivatives soluble in neutral and basic environments. Eur J Pharm Sci 7: 145-151.
14. Kotze AF, Thanou M, Verhoef CJ, Junginger HE (1998a) Chitosan and N-trimethyl chitosan chloride as absorption enhancers for nasal and rectal delivery of insulin. Proceed Int Symp Control Rel Bioactive Mater 25: 179-180.
15. Kristl J, Smid-Korbar J, Stuc E, Schara M, Rupprecht H (1993) Hydrocolloids and gels of chitosan as drug carriers. Int J Pharm 99: 13-19. » CrossRef » Google Scholar
16. Kumar MR (1998) A review of chitin and chitosan applications, reactive and functional polymers. Reactive & Functional Polymers 46: 1-27.
17. Mauro VF, Mauro LS, Hageman JH (1988) Alteration of pentoxifylline pharmacokinetics by cimetidine. J Clin Pharmacol 28: 649-54. » CrossRef » Pubmed » Google Scholar
18. Nigalaye P, Adusumilli P, Bolton S (1990) Investigation of prolonged drug release from matrix formulations of chitosan. Drug Dev Ind Pharm 16: 449-467. » CrossRef » Google Scholar
19. Senel S, Kremer MJ, Kas S, Wertz PW, Hýncal AA, et al. (2000) Enhancing effect of chitosan on peptide drug delivery across buccal mucosa. Biomaterials 21: 2067 -2071. » CrossRef » Pubmed » Google Scholar
20. Smith RV, Waller ES, Doluisio JT, Bauza MT, Puri SK, et al. (1986) Pharmacokinetics of orally administered pentoxifylline in humans. J Pharm Sci 75: 47-52. » CrossRef » Pubmed » Google Scholar
21. Teksin ZÞ, Aðabeyoðlu IT, Yamac K (2000) Comparison of Bioavailability of a Chitosan Tablet Formulation of Pentoxifylline with a Commercial Product (Trental). Proceed of the 27th Int'l Symp Control Rel Bioact Mater 7-13.
22. Thanou M, Verhoef JC, Junginger HE (2001b) Oral drug absorption enhancement by chitosan and its derivatives. Adv Drug Deliv Rev 52: 117-126. » CrossRef » Pubmed » Google Scholar
23. Thanou M, Verhoef JC, Junginger HE (2001a) Chitosan and its derivatives as intestinal absorption enhancer. Adv Drug Deliv Rev 50: 91-101. » CrossRef » Pubmed » Google Scholar
24. Ward A, Clissod P (1987) Pentoxifylline: A review of its pharmacokinetic properties and its therapeutic efficacy. Drugs 34: 50-97. » Pubmed » Google Scholar
25. Werle M, Hoffer M (2006) Glutathione and thiolated chitosan inhibit multidrug resistance P-glycoprotein activity in excised small intestine. J Cont Rel 111: 41-46. » CrossRef » Pubmed » Google Scholar
26. Yamac K, Kaptan K, Beyan C, Teksin ZS, Agabeyoglu Ý, et al. (2000) Comparison of hematological effects of a sustained release chitosan formulation of pentoxifylline with a commercial product. Arzneim Forsch/Drug Res 50: 827-831. » CrossRef » Pubmed » Google Scholar