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Research article

Pharmacokinetic evaluation of two pirfenidone formulations in patients with idiopathic pulmonary fibrosis and chronic hypersensitivity pneumonitis

Lina Marcela Barranco-Garduño [a], Ivette Buendía-Roldan [b], Juan Jose Rodriguez [b], Rodrigo González-Ramírez [c], Ariadna N. Cervantes-Nevárez [a], Juan Carlos Neri-Salvador [a], Miriam del Carmen Carrasco-Portugal [a], Gilberto Castañeda-Hernández [b], Karen Martinez-Espinosa [b], Moisés Selman [b], Francisco Javier Flores-Murrieta [a,d,*]

[a] Unidad de Investigación en Farmacología, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Ciudad de México, Mexico
[b] Laboratorio de Investigación Traslacional de Envejecimiento y Fibrosis Pulmonar, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Ciudad de México, Mexico
[c] Departamento de Farmacología, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Ciudad de México, Mexico
[d] Sección de Estudios de Posgrado e Investigación, Escuela Superior de Medicina del Instituto Politécnico Nacional, Ciudad de México, Mexico

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal disease characterized by an abnormal activation of lung epithelium and fibroblasts, as well as an excessive accumulation of extracellular matrix. Pirfenidone was introduced as a therapeutic option for IPF and chronic hypersensitive pneumonitis (cHP), a related disease. However, high plasma concentrations, which can be achieved even at recommended doses, are frequently associated with adverse events. Hence, an extended release formulation (XP), yielding lower peak plasma concentrations, has been developed. The aim of this study was to compare the pharmacokinetic properties of XP with those of the immediate (IR) formulation in patients with IPF or cHP. Data were analyzed using two pharmacokinetic approaches, conventional non compartmental analysis and a population analysis using the nonlinear mixed effects model technique. Results observed with both approaches were consistent. Drug exposure was similar with both formulations. However, XP exhibited less concentration fluctuations and a longer mean resident time. These results suggest that XP could be a feasible option to reduce adverse events associated to pirfenidone elevated concentrations. Nevertheless, efficacy studies are required to fully document the therapeutic potential of XP.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal disease characterized by a senescent lung displaying activation of epithelial cells that release different factors that favor the activation and transformation of fibroblasts and production of an exaggerated collagen matrix [1, 2]. It is estimated that approximately 30,000 new cases appear every year in the United States and Europe [3]. Median survival is estimated at 2–5 years since the time of diagnosis [4].

There was no effective treatment for IPF until 2014, when pirfenidone and nintedanib were proposed as therapeutic options for this disease [5, 6]. At present, these two agents are considered as standard of care medications not only for IPF, but also for chronic hypersensitive pneumonitis (cHP), a related disease [7, 8, 9].

Pirfenidone reduces the decline in lung function and improves progression-free survival. A growing body of evidence indicates that pirfenidone has anti-inflammatory and anti-fibrotic properties, likely due to the inhibition of growth factors, such as transforming growth factor-beta1 (TGF-β1), which plays a key role in the pathogenesis of IPF [1]. Although the mechanism of action is not fully understood, it has been proposed that pirfenidone reduces the production of extracellular matrix by activated fibroblasts/myofibroblasts involved in the formation of fibrous tissue, thereby slowing down the progression of the disease [7, 8].

* Corresponding author.
E-mail address: fjfloresmurrieta@yahoo.com.mx (F.J. Flores-Murrieta).

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Table 1. Demographic.

		Formulation									
		Immediate Release (IR)					Extended Release (XR)				
		Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
n		17					28				
Gender	(1:Male/2:Female)	15/2					17/11				
Dose	(mg)	801					900				
Age	(years)	71.76	7.46	72	59	86	65.07	13.24	67	30	86
Body weight	(kg)	68.82	12.45	69	40	85	70.00	11.67	72.5	40	90
Size	(m)	1.62	0.08	1.58	1.5	1.76	1.59	0.10	1.57	1.42	1.76
BMI	(kg/m2)	26.0	4.2	26.2	16.0	34.5	27.7	4.8	26.5	16.0	38.3
Cr	(mg/dL)	1.00	0.61	0.81	0.59	2.96	0.87	0.52	0.74	0.42	2.96
ALB	(g/dL)	4.04	0.26	4.1	3.5	4.5	4.08	0.27	4.1	3.5	4.5
HR	(bpm)	80.88	13.86	86	48	105	80.61	18.90	77	54	144
HB	(g/dL)	15.59	2.70	15.8	11	19.9	15.44	2.76	15.4	11	22
HTO	(%)	45.56	8.06	46.4	32.2	59.1	45.23	7.99	44.7	32.2	65.3
Glu	(mg/dL)	106.65	23.06	102	76	165	103.00	23.58	97	75	165
TB	(mg/dL)	0.73	0.38	0.6	0.4	2	0.68	0.34	0.6	0.4	2
DB	(mg/dL)	0.39	0.25	0.3	0.2	1.3	0.34	0.21	0.3	0.2	1.3
IB	(mg/dL)	0.34	0.17	0.3	0.1	0.7	0.34	0.21	0.3	0.1	1.1
Urea	(mg/dL)	18.71	10.37	17	9	47	16.41	9.10	14	8	47
AST	UI/l	30.35	7.98	28	20	53	28.18	7.60	27	17	53
ALT	UI/l	34.24	8.53	32	24	50	34.29	9.12	32	14	50
ALP	UI/l	142.59	56.48	137	74	310	135.86	60.27	126.5	67	310
PT	(sec)	7.73	0.63	7.6	6.1	8.7	7.72	0.62	7.8	6.1	8.7
FVC	(L)	2.13	0.86	2.17	1.05	3.82	1.90	0.98	1.535	0.51	3.82
FVC	(%)	60.71	18.17	62	29	98	52.25	21.19	51	13	98
SO2	(%)	86.76	10.77	90	65	98	87.75	7.63	88	69	99
SO2 Exer	(%)	80.55	7.20	82	64	90	79.53	6.94	79	64	90

• BMI: Body mass index, Cr: Creatine, ALB: Albumine, HR: Heart rate, HB: Hemoglobin, HTO: Hematocrit, Glu: Glucose, TB: Total bilirubin, DB: Direct bilirubin, IB: Indirect bilirubin, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, PT: Prothrombin time, FVC: Forced vital capacity, SO2: oxygen saturation, SO2 Exer: oxygen saturation in exercise.

Pirfenidone use has also been proposed for other fibrotic diseases such as cirrhosis, renal and cardiac fibrosis and in systemic sclerosis [10, 11].

Pirfenidone use, however, is limited by the occurrence of adverse events (AEs). Gastrointestinal reactions, such as nausea, dyspepsia, diarrhea, abdominal discomfort, and vomiting, are frequently associated to pirfenidone administration. Anorexia, fatigue, sedation, and photosensitivity have also been reported. The frequency and intensity of these responses appear to decrease with time. However, adverse events often lead to dose reductions or treatment withdrawal. Advanced hepatic dysfunction leads to a reduced tolerability to pirfenidone. Moreover, moderate, and even mild, hepatic impairment may result in increased plasma pirfenidone levels. Therefore, caution is recommended for pirfenidone use in patients with liver dysfunction [11, 12, 13].

Pirfenidone is commercialized as an oral immediate release (IR) formulation. The dosing regimen consists administration of 801 mg/day during the first week, followed by an increase to 1602 mg/day during the second week and a subsequent dose increase to reach 2403 mg/day after 15 days of treatment [7]. Pirfenidone should be given under fed condition to reduce gastrointestinal untoward effects. However, it must be noted that meals modify the extent and rate of pirfenidone absorption. Both, the area under the plasma drug concentration-time curve (AUC) and the maximum concentration (Cmax) are reduced, while the time to reach the peak concentration (Tmax) and the mean absorption time (MAT) are prolonged [14, 15]. Pirfenidone is biotransformed by CYP1A2. Hence, grapefruit juice can inhibit its metabolism [16]. Furthermore, pirfenidone coadministration with fluvoxamine, a strong CYP1A2 inhibitor, should be avoided [16].

Preclinical and clinical studies have indicated that pirfenidone acts in a dose-dependent manner [17]. On the other hand, pirfenidone-related adverse events have been associated with peak plasma concentrations [16, 17]. As IR formulations yield high peak plasma concentrations, an extended release formulation (XR), purportedly resulting in lower peak levels, has been developed.

2. Aim

The goal of this study was to compare the pharmacokinetic properties of two pirfenidone formulations (IR and XR) in adult patients with IPF and cHP.

The specific aims of this study were:

(i) To develop a population pharmacokinetic (PK) model of pirfenidone in patients with IPF and cHP.
(ii) To evaluate the impact of the formulation and other covariates on pirfenidone PK.

3. Methodology

3.1. Study design

The current PK study was performed in the Unit of Clinical Pharmacology at the Instituto Nacional de Enfermedades Respiratorias (INER) Ismael Cosio Villegas, in Mexico City. The study was conducted according to the principles of the revised World Medical Association's Declaration of Helsinki 2008 and was approved by the Institutional Internal Review Board and Ethics Committee. Written informed consent for participation was obtained from all the patients.

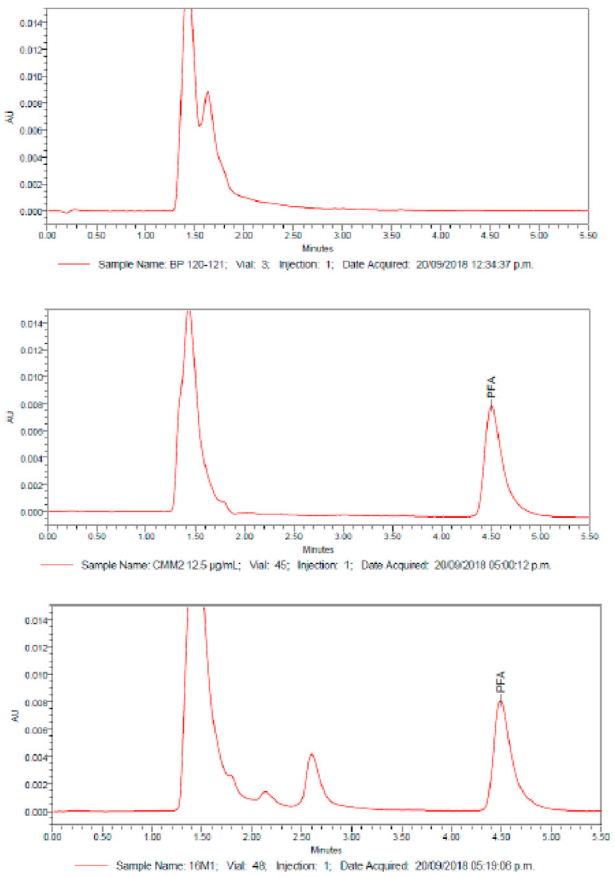

Figure 1. Typical chromatograms obtained after injection of 5 µL of supernatant obtained in the protein precipitation of plasma samples with perchloric acid and acetonitrile and monitored at a wavelength of 310 nm. Upper part corresponds to blank plasma, middle to spiked plasma at a concentration of 12.5 µg/ml and down to a sample of a subject receiving pirfenidone. Retention time of pirfenidne (PFA) was 4.5 min.

For the study, a total of 28 patients were recruited. Seventeen patients with IPF were randomly chosen to participate in a study to evaluate formulation switch between the XR formulation (Kitocell®) and the IR formulation (Esbriet®) (Table 1). Initially the patients with chronic treatment with the XR formulation under a scheme of 900 mg b.i.d. were included in the study and blood samples were obtained at randomly assigned times. After two weeks, patients were switched to the IR formulation with a dosing scheme of 801 mg every 8 h and blood samples were obtained for pirfenidone quantification.

In order to increase the sample size, patients with cHP were also included. To rule out possible differences due to disease and to sparse sampling compared with IPF patients, a population PK analysis (popPK) was proposed.

This second group, was formed by 11 patients with cHP who only received the XR formulation at a dose of 900 mg b.i.d. These patients showed progressive fibrosis and were included because pirfenidone was being used in cHP (ClinicalTrials.gov Identifier: NCT02496182). The study was carried out after multiple doses with the assumption that the drug has reached the steady state.

Both studies were performed under fed conditions in order to improve the gastrointestinal tolerability to the treatment.

3.2. Determination of pirfenidone plasma levels

Pirfenidone plasma levels were determined by a high-performance liquid chromatographic method with UV detection. Briefly, plasma samples (0.2 mL) were treated with 30 µL of 30% perchloric acid in acetonitrile for the precipitation of proteins. After centrifugation, aliquots of 5 µL of supernatant were injected into the chromatographic system. Separation of compounds was performed in a Zorbax XDB –SS C18, 100 × 3.0 mm i.d., of 3.5 µm particle size column, eluted with a mixture of acetic acid 0.2% solution and acetonitrile (70:30 v/v) at a flow rate of 0.4 mL/min. Detection was performed at 310 nm. Under these conditions, retention time of pirfenidone was 4.5 min and no interferences were observed in blank plasma (Figure 1). Additionally, the selectivity of the method was evaluated by injecting into the chromatographic system typical over the counter drugs (acetaminophen, aspirin, ibuprofen and caffeine). No signal was observed at retention time of pirfenidone for any of the compounds evaluated. Recovery of pirfenidone was 75.145 ± 2.556% (SD). The method was linear in a range of 0.2–30 µg/mL. Intra-and inter-day accuracy obtained are shown in Table 2. It can be seen that accuracy was close to 100% and coefficient of variation was always lower than 5%, indicating that the method is suitable for determination of pirfenidone in plasma samples at the required sensitivity for pharmacokinetic characterization under the scheme employed in this study. In order to follow the performance of the analytical method, quality control samples were analyzed in the same run of the samples of the subjects. Values obtained for such quality control samples are shown in Figure 2.

3.3. Data analysis

In a first stage, a non-compartmental analysis (NCA) was performed to obtain the average pharmacokinetic parameters for each formulation. Variability was expressed as the standard deviation. In a second analysis, a population pharmacokinetics (popPK) analysis was carried out to simultaneously analyze the effect of disease and demographic covariates. A total of 212 pirfenidone blood samples were employed to develop the popPK model from 17 IPF patients under IR formulation and 28 patients, 17 with IPF and 11 with cHP, receiving the XR formulation. Both groups were at steady state.

The NCA and the popPK analysis were performed with the Phoenix WinNonlin and NLME 7.0. software (Certara, St. Louis, MO 63101 USA).

The popPK parameters were estimated simultaneously for both formulations using the first-order conditional estimation extended least squares (FOCE ELS) approach.

During the pharmacokinetic model-building procedure, different structural pharmacokinetic models were tested, including a one-compartment model, two-compartment model, three-compartment model with and without delay in the absorption (tlag) and with linear and nonlinear clearance.

The minimum value of twice the negative log likelihood (-2LL) was used as a statistical method to choose suitable models during the process, as well as visual inspection of the goodness of fit plots and parameter precision was evaluated using the standard errors provided by Phoenix NLME.

Intra patient variability (IPV) was modeled exponentially. The residual variability was tested using additive, multiplicative and mixed error models. An additive error model was applied in the final model. Inter-occasion variability was not investigated.

Demographic factors were also assessed. The effect of each covariate was evaluated graphically over each PK parameter. The examination included sex, age, weight, body mass index, serum creatinine, albumin, disease and formulation.

A stepwise forward inclusion procedure was performed to build the full model ($P < 0.05$; decrease in OFV>3.84) and stepwise backward elimination procedure ($P < 0.001$; increase in OFV>10.84) was applied to determine the final model. The popPK model was employed to simulate the dose regimen with each formulation at the regimen previously mentioned. We simulated a multiple dose regimen for both formulations. The regime for XP considered ten consecutive doses of 900 mg b.i.d. For IR, the simulated regime was 801 mg every 8 h (Figure 6). For these simulations we employed the popPK parameters Ka, V, Cl, Tlag, V2, Q,

Table 2. Accuracy and coefficient of variation of the method for determination of pirfenidone in plasma samples and following o the method during the analysis of samples of patients that participated in the study.

Added concentration (μg/ml)	Measured concentration ± S.D, (n = 6) (μg/ml)	Accuracy (%)	Coefficient of variation (%)
Intra-day			
2.0	1.999 ± 0.052	99.95	2.589
12.5	12.387 ± 0.502	99.10	4.054
25.0	24.851 ± 0.249	99.40	1.001
Inter-day			
2.0	1.934 ± 0.060	96.70	3.082
12.5	12.215 ± 0.375	97.72	3.074
25.0	24.926 ± 0.415	99.70	1.667
Day of analysis	Nominal concentration (μg/ml)	Obtained concentration (μg/ml)	% deviation
1	2	2.095	4.760
		2.148	7.377
		2.163	8.153
	12.5	12.489	-0.089
		12.799	2.392
		12.471	-0.234
	25	25.778	3.111
		25.473	1.892
		25.627	2.510
2	2	2.007	0.361
		2.004	0.204
		1.990	-0.488
	12.5	12.598	0.783
		12.595	0.758
		12.260	-1.923
	25	25.437	1.747
		25.492	1.969
		25.787	3.149

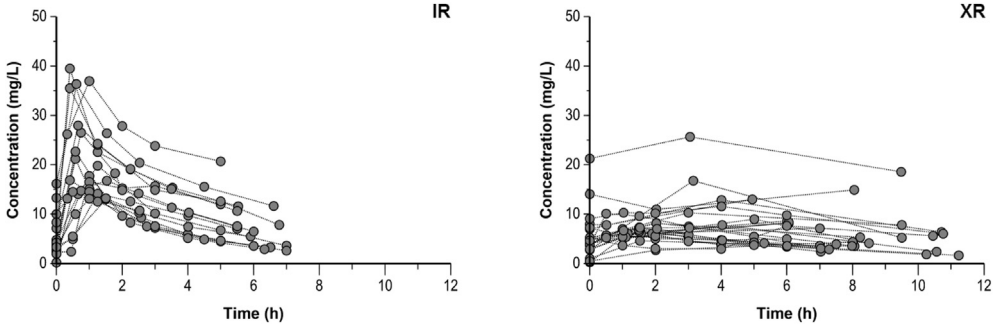

Figure 2. Concentration vs time profiles of pirfenidone by formulation, (IR) Immediate release formulation and (XR) Extended release formulation.

F1, Ka-FFcov2 and Vd-FFcov2 estimated in the modeling step for each formulation, these parameters are named as THETA (Table 3).

3.4. Model validation

An internal validation of the final model was performed using the resampling technique of bootstrap (n = 1000) and visual predictive check (VPC).

The mean and standard error of the parameter estimates from the bootstrap analysis were then compared with the Phoenix NLME estimates from the final model.

3.5. Safety analysis

Adverse events and patient's perception after each treatment were recorded.

3.6. Statistical analysis

Statistical comparisons were performed using GraphPad Prism version 5.01 (GraphPad Software, San Diego, California, USA). Continuous data were tested for normal distribution by use of the Shapiro-Wilk normality test. Differences in pharmacokinetic parameters across different formulations were evaluated using Student's t-test or Mann Whitney U test.

4. Results and discussion

The aim of this study was to compare the pharmacokinetic properties of two pirfenidone formulations, IR and XR in adult patients with IPF and cHP to characterize their exposure profiles (Figure 2). Pirfenidone was developed for IPF reducing the decline of lung function and declining disease progression [1]. Despite demonstrating its effectiveness, this drug frequently shows gastrointestinal adverse events (AEs), even at

Table 3. Population PK parameters and bootstrap results.

		Mean	SE	CV%	Bootstrap Median	2.5%	97.5%
THETA (1)	Ka (1/h)	4.00	2.43	60.85	3.38	1.50	10.28
THETA (2)	V (L)	13.70	4.26	31.09	13.37	5.92	24.98
THETA (3)	Cl (L/h)	6.14	0.59	9.53	6.10	5.19	7.71
THETA (4)	Tlag (h)	0.25	0.08	31.23	0.26	0.06	0.39
THETA (5)	V2 (L)	14.21	3.63	25.51	13.77	9.14	23.40
THETA (6)	Q (L/h)	13.72	5.27	38.43	12.31	7.02	27.59
THETA (7)	F1	0.10	0.29	27.53	0.02	0.00	0.81
THETA (8)	Ka-FFcov2	-1.14	0.62	-54.76	-1.12	-2.35	0.06
THETA (9)	Vd-FFcov2	2.14	0.42	19.80	2.09	1.44	3.28
THETA (10)	Vd-WT	2.24	1.25	56.12	2.21	-0.27	5.21

Ka = THETA(1) * EXP (THETA(8) * (FFcov=2)).
V = THETA(2) * (WT/72)THETA(10) * EXP(THETA(9) * (FFcov=2)).
FFcov = 1: Immediate release formulation, 2: Extended release formulation.

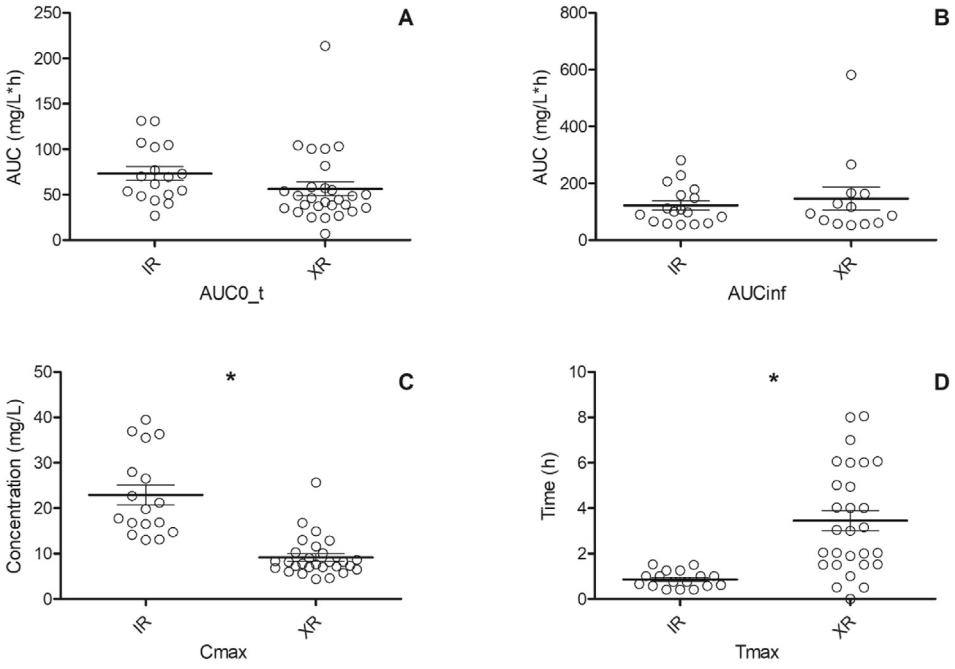

Figure 3. Non compartmental analysis by formulation, (IR) Immediate release formulation and (XR) Extended release formulation. A) AUC0_t by formulation, B) AUCinf by formulation, C) Cmax by formulation and D) Tmax by formulation (*p ≤ 0.0001). AUC0_t: Area under the plasma drug concentration versus time curve from cero to last sample time; AUCinf: Area under the plasma drug concentration versus time curve from cero extrapolated to infinity; Cmax: Maximum concentration achieved; Tmax: Time to reach the maximum concentration.

recommended doses, that may lead to dose reduction or therapy discontinuation [12].

Demographic data is shown in Table 1, this study was performed in patients with IPF and cHP between 30 to 86 years old, a median of 70 years.

After a non-compartmental analysis of each formulation, we did not find statistically significant differences between formulations (expressed as AUC0_t and AUC0_inf). Our results showed an AUC0_t of 73.26 ± 31.48 and 56.38 ± 39.99 for IR and XR, respectively.

Similarly, the AUC0_inf for IR was 122.6 ± 67.64 and for XR 146.3 ± 144.4 (mean ± SD). Differences were only found between Cmax and Tmax, ($p < 0.0001$), IR and XR showed a Cmax of 22.9 ± 9.15 and 9.15 ± 4.38, with a Tmax of 0.8641 ± 0.36 and 3.445 ± 2.3 respectively (mean ± SD) (Figure 3).

After the initial non-compartmental analysis (NCA), pirfenidone IR showed a rapid absorption rate, reaching the maximal concentration time (Tmax) around 0.86 ± 0.37 h compared to XR formulation 3.45 ± 2.34 h. As is expected for an IR formulation a higher peak concentration (Cmax) was found, 59.8% higher than pirfenidone XR (IR: 19.81 mg/L to XR: 7.96 mg/L). Both results, Tmax and Cmax, showed statistically significant differences ($P < 0.0001$) in both cases. After switching formulations at recommended doses, no differences were observed between formulations when comparing exposure at steady state expressed as AUC0_τ, AUC0_inf and AUC0_inf/Dose (P values of 0.3493, 0.1995 and 0.3448 respectively) (Figure 3).

However, average concentration at steady state (Cav) was higher for IR formulation (IR: 9.16 ± 3.93 mg/L and XR: 4.70 ± 3.33 mg/L) ($p < 0.003$). On the other hand, the mean resident time extrapolated to infinity (MRTinf) for IR formulation was lower than for XR formulation, which can be associated to the increment of exposition time for XR pirfenidone (5.65 ± 2.35 h and 11.56 ± 6.53 h), which was around two times higher for XR formulation.

A possible advantage of XR formulation, and considering the recommended daily maintenance dosage for Esbriet® the commercial name of pirfenidone IR formulation [7], is that XR formulation could be taken twice daily, compared with IR formulation that must be taken three times per day and with food to reduce the peak concentration [18].

It is reported that administration after a meal decreases the rate and extent of pirfenidone absorption, showing a median Tmax increase from 0.5 h to 3 h with food [12, 13, 14]. In our study the Tmax range for IR formulation was between 0.4 h to 1.53 h, with a median of 0.75 h, showing rapid absorption despite of the fed administration [14].

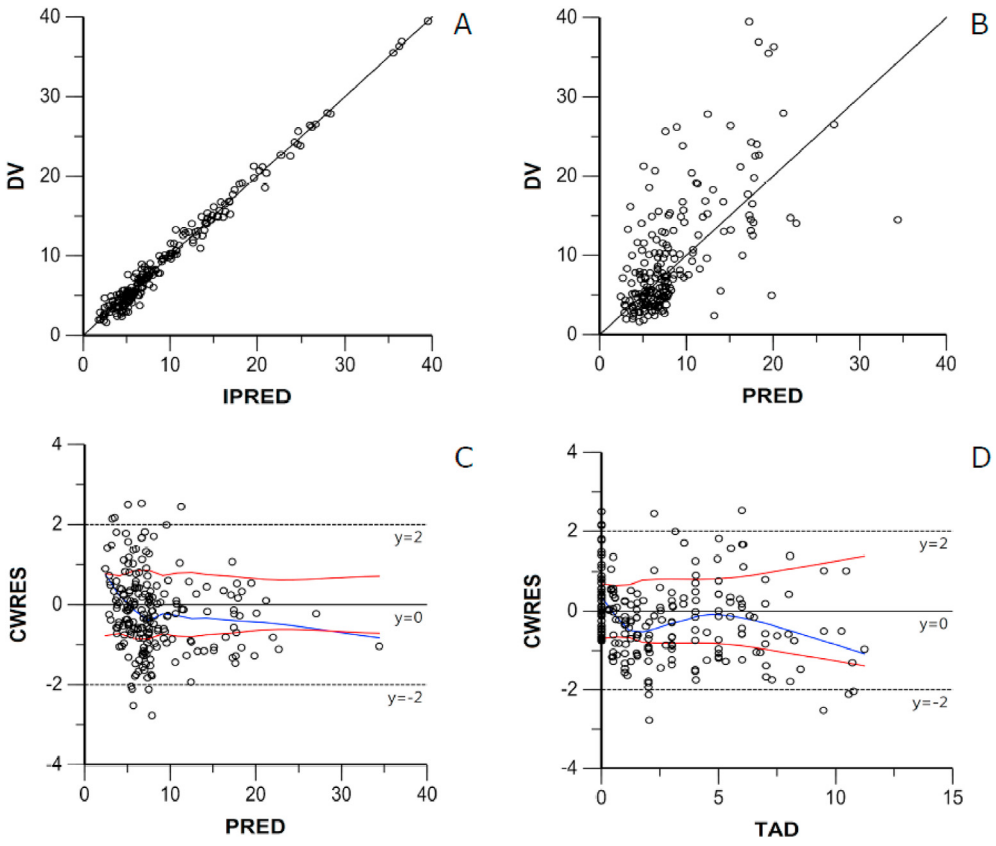

Figure 4. Goodness of fit plots. A) Individual predictions vs observations by formulation. B) Conditional weighted residuals (CWRES).IPRED: Individual predictions; PRED: Population predictions; CWRES: Conditional weighted residuals; DV: Dependent variable; TAD: Time after dose.

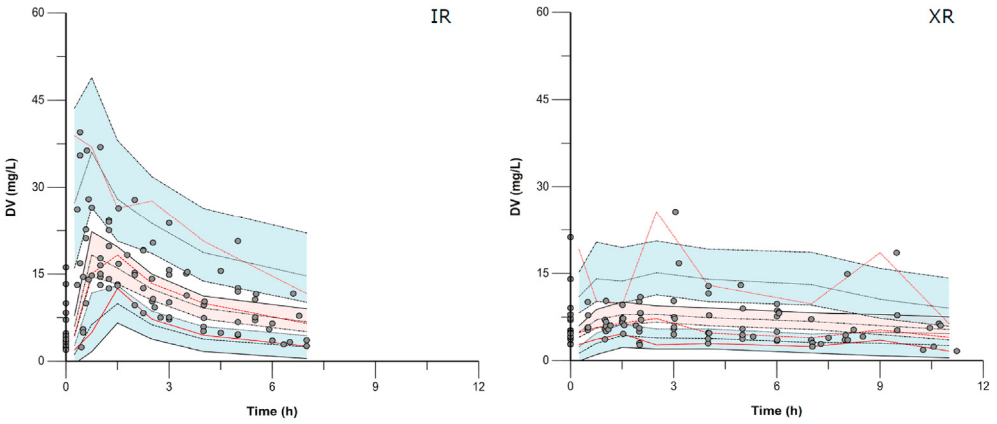

Figure 5. Visual predictive checks by formulation (VPCs). A) Graphical representation of the predictive value of the pop PK model for IR formulation and B) Graphical representation of the predictive value of the pop PK model for XR formulation. DV: Dependent variable (Concentration); Shaded blue areas represent confidence interval of predicted quantiles 5% and 95%; Shaded red areas represent confidence interval of predicted quantiles 50%; Black dots are the observations (Observed concentrations); Red lines represent confidence interval of observations, quantiles represented 5%, 50%, 95% of the data.

Comparatively, the XR formulation showed a median of 3.02 h and a range of 0.5–8.05 h, closer to prescribing information under fed condition for IR formulation (Figure 3). The indication that pirfenidone IR should be taken with food is associated with these reductions on Cmax and AUC0_inf and the consequent adverse events reduction [12]. Also, with the XR formulation, we found less fluctuation (%FL) between Cmax and Cmin, compared to IR formulation (XR: 88.6% vs IR: 169.4%). This may be a favorable feature of XP. The use of extended release formulations can be an alternative to decrease the peak to trough fluctuations in plasma concentrations with a possible therapy improvement by decreasing adverse events associated with the higher peak concentrations [19].

Considering the clinical status of the patients, we decided to perform a sparse sampling methodology for the evaluation of the switching of XR formulation to IR pirfenidone. Only three samples per patient were taken over 12 h. The second group of patients, treated exclusively with the XR formulation and submitted to extensive PK sampling, were analyzed simultaneously with the first cohort employing a population pharmacokinetic approach to figure out the impact of possible covariates or demographic factors non-detected under the typical NCA.

After the population analysis, a two-compartment model with tlag in the absorption and linear elimination was selected as structural model to describe the PK of pirfenidone (Table 3). Our analysis detected a significant effect of formulation and weight as covariates. Formulation impacted over the absorption constant (ka) as well as over the volume of distribution, weight only had effect over the volume of distribution (Table 3). This relatively simple model provided good fits of the data for both formulations, with modest inter-individual variability in the

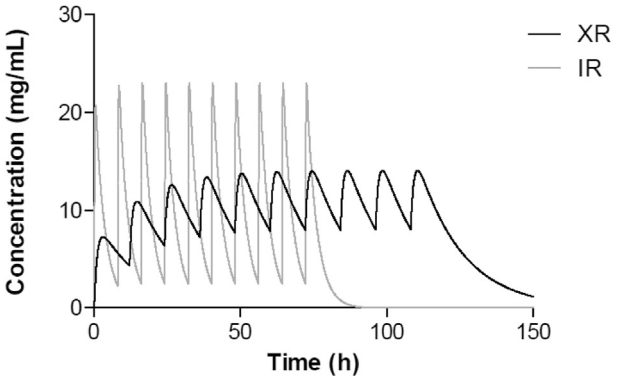

Figure 6. Simulated concentration vs time profiles after ten doses of immediate release (IR) and extended release (XR) formulations of pirfenidone using the described regimen (801 mg t.i.d and 900 mg b.i.d respectively).

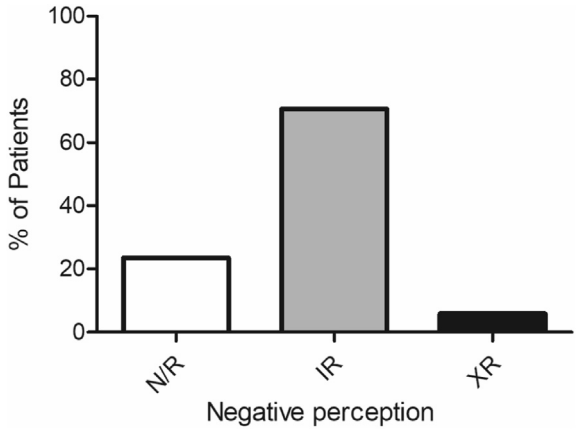

Figure 7. Negative perception of the patients employing, (IR) immediate release formulation, (XR) extended release formulation, N/R: no response.

estimates of apparent oral clearance and apparent oral volume of distribution and higher for ka (Figures 4 and 5).

In the literature, we identified one population pharmacokinetic study after single dose of 801 mg of pirfenidone IR to healthy adults, results showed good fits of the data [20]. The results of that analysis described the pharmacokinetics of pirfenidone and principal metabolite 5-carboxy-pirfenidone. We found substantial differences between the parameters of that study and ours; one possible factor could be age and the diseases state. However, after analyzing age as a covariate in our study, we did not detect any significant impact of this covariate. Some studies have suggested that older patients may probably not require pirfenidone dosing adjustment. It is important to note that tolerability and efficacy of the drug may be improved if fluctuation of Cmax and Cmin is reduced, as it happens with the XR formulation. To represent the fluctuation, a simulation, using the parameters obtained from the popPK model, of ten doses of every formulation to reach the steady state concentrations with a regime of 801 mg t.i.d. for the IR formulation and 900 mg b.i.d. for the XR formulation, leading to a higher fluctuation with the IR formulation (Figure 6).

When analyzing the frequency of adverse events, we did not find differences between formulations (Table 4). However, after applying a patient survey, IR formulation apparently showed higher severity of adverse events, and patients had a better perception of the XR formulation, as they mentioned less severity in GI issues (Figure 7). However, the present data cannot allow the conclusion of an improved safety profile with pirfenidone XR formulation due to the reduced number of patients assayed.

Table 4. Adverse events observed by formulation.

	Immediate release (IR) (n = 13) % (n)	Extended release (XR) (n = 25) % (n)
GI tract	62% (8)	52% (13)
Dermatologic	61% (8)	28% (7)
Endocrine	23% (3)	40% (10)
CNS*	23% (3)	12% (3)
Respiratory	31% (4)	16% (4)
Cardiovascular	0% (0)	16% (4)
Neuromuscular	8% (1)	0% (0)
Genitourinary	0% (0)	4% (1)
Hepatic	0% (0)	0% (0)
Infections	0% (0)	0% (0)
Generals	8% (1)	48% (12)

*CNS: Central Nervous System.

5. Conclusions

Extended release formulation yielded a similar exposure to immediate release and could be a feasible option to reduce adverse events associated to elevated pirfenidone concentrations. This may help to improve the adherence to the treatment. Nevertheless, efficacy studies are required in order to assess the actual benefits of the XP formulation.

Declarations

Author contribution statement

Lina Marcela Barranco-Garduño, Ivette Buendía-Roldan, Miriam del Carmen Carrasco-Portugal: Performed the experiments; Analyzed and interpreted the data.

Juan Jose Rodriguez, Ariadna N. Cervantes-Nevárez, Juan Carlos Neri-Salvador, Karen Martinez-Espinosa: Performed the experiments.

Rodrigo González-Ramírez: Analyzed and interpreted the data; Wrote the paper.

Gilberto Castañeda-Hernández: Analyzed and interpreted the data.

Moisés Selman: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Francisco Javier Flores-Murrieta: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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