DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(16), 1917-1921 (1995)

IN VIVO EVALUATION OF PINDOLOL MULTI-UNIT DOSAGE FORMS

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ABSTRACT

Pindolol, a beta adrenoceptor agent, is effective in the treatment of hypertension in daily doses ranging from 10 to 45 mg. The drug shows pH dependent solubility and a modified multi unit controlled release formulation was assessed for efficacy *in vivo* in healthy male human volunteers. An open blind comparative crossover study of the controlled release formulation was carried out with a conventional formulation. The treated quotients and the ratio between the maximal plasma concentration were calculated to assess the efficacy of the formulations.

INTRODUCTION

It has been shown that compliance of patients is improved by reducing the number of daily doses of a drug [1,2]. Pindolol, a pH dependent soluble ß-adrenoceptor blocker was successfully formulated into a controlled drug delivery system [3]. In the present study, an attempt has been made to access the efficacy of the formulation in releasing the drug *in-vivo* in the gastrointestinal milieu by an investigation and analysis of the pharmacokinetic effect of the dosage form in male healthy volunteers.

MATERIALS AND METHODS

The aim of the trial was to study and compare the bioavailability of the controlled release formulations of pindolol with a conventional dosage form (capsule containing 15 mg pindolol and lactose as diluent) in a single dose fashion.

The controlled release formulations, with an optimum *in-vitro* drug release, selected for *in-vivo* efficacy studies is given in table 1.

TABLE 1 : Formulations Selected for *In-vivo* Studies.

Method :	Non-Pareil Seeds [RS-HP(NPS)]	Spheronization [RS-HP(SPH)]*
Coating Polymers:	Eudragit^{R}RS 100 (2.5% w/w)	Eudragit^{R}RS 100 (1.5% w/w)
Topcoating Polymer:	HPMCP NF-55 (3.0% w/w)	HPMCP NF-55 (3.0% w/w)
In-vitro release: (Av. 6 batches)	$T_{50\%}$: 5.17 h $T_{90\%}$: 10.29h	$T_{50\%}$: 5.25 h $T_{90\%}$: 10.07 h

* Drug:AVICEL^{R} PH101::1:9,

The investigation was carried out under medical supervision in 6 healthy male volunteers, mean age 28.5 years (range 24-36 years) and mean body weight of 70 kg (range 65-80 kg) in a open blind crossover pattern. Each volunteer received the three formulations in randomized order with an interval of at least one week between the treatments. The fasted patients were administered the coded samples in the morning along with 100 mL water and were later provided with standard light breakfast and lunch as prescribed by the trial center.

Blood samples (about 10 mL) were collected in heparinized vials, before drug administration and at time intervals of 0.5, 1, 2, 4, 6, 8, 10 and 12 hours. Plasma separated by centrifuging at 4000 rpm, was transferred into dry vials and frozen at -4°C until analysis. Urine was collected over the following periods : Control, 0-2, 2-4, 4-6, 6-8, 8-10 and 10-12 hours.

Analysis of the samples were done by the method described by Pacha [4], spectroflourimetrically at 390 nm excitation and 440 nm fluorescence [5].

RESULTS AND DISCUSSION

The efficacy of the multi unit dosage form of pindolol in comparison with conventional dosage form was determined by calculating the retard quotient (R_H) based on the half value duration (HVD)[6] and the ratio of the plasma concentrations (R_C).

The mean plasma levels after oral administration of 15 mg of pindolol conventional capsule and 15 mg of controlled release pellets are represented in figure 1 and the values given in table 2.

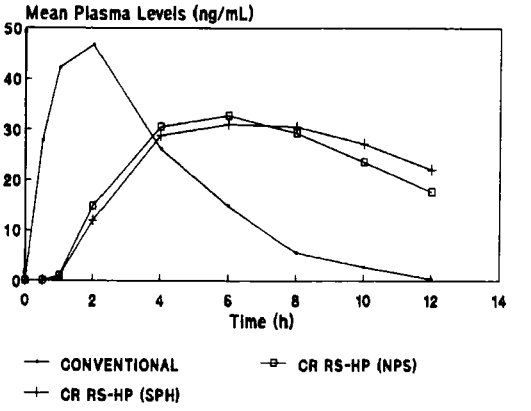

FIGURE 1 : Mean Plasma Concentration of Pindolol after Oral Administration (n=6)

TABLE 2 :

Parameters	Conventional Capsule	RS-HP(NPS) Non-pariel	RS-HP(SPH) Spheronized
Max. Plasma Conc. (hrs)	1.83±0.37	5.86±0.75	6.15±0.65
Peak Plasma level (ng/mL)	46.9±4.00	32.7±1.60	32.3±2.09
R_C	-	0.698	0.688
HVD (hrs)	3.9	10.08	11.75
R_H	-	2.77	3.01
AUC upto 12 hrs (ng/mL)	214±28.0	277±37.0	276±49.0

TABLE 3 : Statistical Anova of Area Under Curve

Volunteer	Conventional	RS-HP (NPS)	RS-HP (SPH)
1	237.05	276.70	274.35
2	220.35	268.05	270.83
3	223.50	258.40	275.85
4	213.78	228.18	277.35
5	211.50	291.55	278.73
6	202.83	289.28	281.95

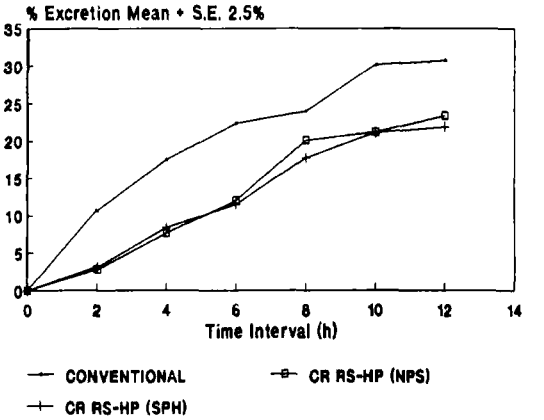

FIGURE 2 : Cumulative Urinary Excretion of Pindolol after Oral Administration (n=6)

TABLE 4 :

Parameters	Conventional Capsule	RS-HP(NPS) Non-pariel	RS-HP(SPH) Spheronized
Urinary excretion ($t=\infty$)	30.96%	23.05%	21.93%
Absorption rate constant (h^{-1})	0.847	0.1203	0.1310
Half life (hrs)	0.82	5.76	5.29
Elimination rate constant(h^{-1})	0.35	0.0702	0.0613

The above values are clearly indicative of the prolonged maintenance of pindolol levels by the controlled release formulations, without the initial spike as observed in the conventional dosage forms.

Table 3 represents the test for ANOVA between the AUCs of the formulations. The results indicate a marginally higher bioavailability with controlled release formulations.

Source	df	SS	MS	
Between Methods	3	4477.92	1492.64	$F_{(3, 14)} = 6.08$
Within Methods	14	3439.25	245.66	
Total	17	7917.17		

The cumulative urinary excretion of pindolol is graphically represented in figure 2 and the values given in table 4.

Thus the efficacy of the modified controlled release pellets of pindolol is seen *in-vivo*, for the control of hypertension.

REFERENCES

1] Isaac Ghebre Sellassie, in 'Pharmaceutical Pelletization Technology', Marcel Dekker, New York, (1989), p. 1-12.
2] I. M. Jalal et al., J. Pharm, Sci., 61;1466-1468 (1972).
3] H. Venkatesh, N.M. Sanghavi., Drug Dev. Ind. Pharm., 20(1), 111-118 (1994).
4] W. L. Pacha, Experentia, 25:802 (1969).
5] H. J. Waal Manning et al., NZ Med. J., 80: 151-157 (1974).
6] J. Mein et al., Ear. J. Cain, Pharmacal., 7:429-432 (1974).