J Incl Phenom Macrocycl Chem (2007) 57:137–139
DOI 10.1007/s10847-006-9205-z

ORIGINAL ARTICLE

Development of a formulation of Pirodavir using 2-hydroxypropyl-β-cyclodextrin

Jef Peeters · Peter Neeskens · Marcus Eli Brewster

Received: 15 May 2006 / Accepted: 20 October 2006 / Published online: 18 January 2007

Abstract Pirodavir, 4-[2-[1-(6-Methyl-3-pyridazinyl)-4-piperidinyl]ethoxy]benzoic acid ethyl ester, is an antiviral compound which has low aqueous solubility (<0.01 mg/ml). The compound is a weak base (pKa 5.8) with high lipophicity (logP 4.44). Ionization of the compound increases the solubility in acidic medium to 2.3 mg/ml at pH 2.4. However, a low pH is not acceptable for nasal application as this would induce irritation.Extensive solubility studies were performed using different types of substituted cyclodextrins in order to select an appropriate derivate capable of increasing solubility to an acceptable level for formulations for nasal application. Aqueous solubility of pirodavir increased in a linear fashion with increasing concentration of most of the substituted cyclodextrins. However, using 2-hydropropyl-β-cyclodextrin (HPBCD) the solubility increased in a non-linear fashion. Based on these studies HPBCD was selected as the most appropriate excipient.To support a clinical study on the treatment of rhinovirus cold by intranasal Pirodavir formulations were developed containing up to 5 mg/ml of pirodavir and up to 10% of HPBCD. Stability of the formulations was studied and found to be acceptable.

Keywords Pirodavir · Solubility · Cyclodextrins · Complexation capacity · Nasal formulation

J. Peeters (✉) · P. Neeskens · M. E. Brewster
Johnson and Johnson, Chemical and Pharmaceutical Research, Pharmaceutical Sciences, Turnhoutseweg 30, Beerse 2340, Belgium
e-mail: jpeeters@prdbe.jnj.com

Introduction

Pirodavir, R77975 (the structure and chemical name are given in Fig. 1) has antiviral properties which make this compound a candidate for the treatment of rhinoviral infections associated with the common cold [1]. The compound is a lipophilic weak base with low aqueous solubility (see Table 1). Solubility increases as pH decreases as expected based on the degree of ionization of the compound (see Table 2 and Fig. 2).

Substituted cyclodextrins are useful ingredients for formulation design [2].

In order to evaluate the clinical benefit of Pirodavir for treatment of rhinovirus colds an intranasal formulation was needed. This work describes how this intranasal formulation was developed.

Experimental methods

Materials

Substituted cyclodextrins were obtained from different suppliers (Chinoin, Cyclolab, Amaizo, Medinpex). The drug was obtained from Janssen Pharmaceutica (Beerse, Belgium).

Phase solubility experiments

Equilibrium solubility was measured by sonicating an excess of the drug in aqueous solutions of the cyclodextrins in the concentration range from 0 to 10% (w/v). Mixtures were equilibrated for several days at ambient temperature. Excess drug was removed by filtration through a 0.45 μm filter (Millipore) and the

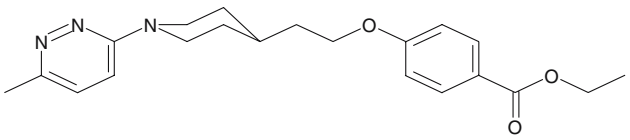

Fig. 1 The structure of pirodavir, 4-[2-[1-(6-Methyl-3-pyridazinyl)-4-piperidinyl]ethoxy]benzoic acid ethyl ester

Table 1 Physico-chemical properties of pirodavir

Molecular weight	369.46
Partition coefficient (logP)	4.44
Ionization constant	5.8
Melting point	130 °C
Melting enthalpy	117 J/g
Solubility in water[a]	<10 μg/ml

[a] Calculated solubility in water is 9.2 μg/ml (Simulations*Plus* software package ADMET Predictor, including the melting point of the compound)

Table 2 Solubility of pirodavir as a function of pH

Solvent	pH	Solubility (mg/ml)
HCl 0.1 N	1.1	1.2
HCl 0.01 N	2.4	2.3
Citrate–HCl buffer	2.6	1.8
Citrate–HCl buffer	4.0	0.06
Citrate–NaOH buffer	6.0	<0.01
Borate–HCl buffer	8.0	<0.01
Borate–KCl–NaOH	10	<0.01

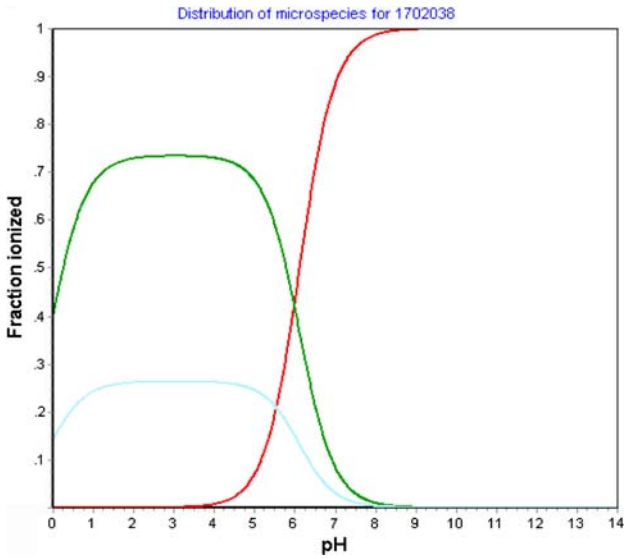

Fig. 2 Degree of ionization for pirodavir as a function of the pH (based on calculated pKa of 6.12 using ADMET Predictor)

amount dissolved measured by UV spectrometry at the wavelength of maximum absorption (255 nm).

Calculations

Solubility improvement by substituted cyclodextrins is expressed as the negative logarithm of the ratio of aqueous solubility in the absence of cyclodextrin divided by the solubility in a 10% w/v solution of the substituted cyclodextrins of interest.

$$\mathrm{pR} = -\log \frac{S_{0\%\mathrm{CD}}}{S_{10\%\mathrm{CD}}}$$

Stability constants are calculated using the approach of Higuchi and Connors [3] which assessed the relationship between the solubilizer and the drug being solubilized. Total solution concentration of cyclodextrin and of the drug are expressed by the following series of equations, which assume the formation of 1:1 and 1:2 drug-cyclodextrin complexes.

$$[\mathrm{CD}]_{\mathrm{Total}} = [\mathrm{CD}] + \mathrm{So}K_{1:1}[\mathrm{CD}]$$

$$[\mathrm{CD}]_{\mathrm{Total}} = [\mathrm{CD}] + \mathrm{So}K_{1:1}[\mathrm{CD}] + 2\mathrm{So}K_{1:1}K_{1:2}[\mathrm{CD}]^2$$

$$\mathrm{S}_{\mathrm{Total}} = \mathrm{So}\ (1 + K_{1:1}[\mathrm{CD}])$$

$$\mathrm{S}_{\mathrm{Total}} = \mathrm{So}\left(1 + K_{1:1}[\mathrm{CD}] + K_{1:1}K_{1:2}[\mathrm{CD}]^2\right)$$

where $K_{1:1}$ and $K_{1:2}$ are the stability constants associated with drug-cyclodextrin complex and the drug-2(cyclodextrin) species and So is the solubility of the drug in the absence of cyclodextrin.

Mathematical treatment of the data was performed as described earlier by Higuchi and Kristiansen [4].

Results

The solubility of pirodavir was increased by up to three orders of magnitude using 10% (w/v) of substituted β-cyclodextrins. By contrast γ-cyclodextrin itself had no effect on the solubility while an increase of about one order of magnitude is seen if substituted γ-cyclodextrins are used (see Table 3).

It is known that methylated β-cyclodextrins may enhance the absorption of drugs from the nasal cavity without extended side effects [5]. In the case of pirodavir absorption enhancements was not the goal. Instead, a local action was preferred and therefore HPβCD was selected as the solubility enhancer.

Various aqueous-based formulations containing up to 10% of HPβCD were assessed. The results are

Table 3 Solubility increase for pirodavir in aqueous medium by using 10% of substituted cyclodextrins

Type of CD	pR
Acetylated βCD	3.2
HPβCD	3.1
Sulfated βCD	0.7
Sulfopropylated βCD	2.5
DMβCD	3.7
MβCD (DS 0.4)	3.5
MβCD (DS 1)	3.5
Carboxymethylated HPβCD	3.0
Succinylated HPβCD	2.7
Ethyl βCD (DS 0.4)	3.5
RAMEB	3.6
γCD	–0.1
Methyl-γCD (DS 0.4)	1.7
HPγCD (DS 1)	1.4
DMγCD	1.5
HEγCD	1.2

collected in Fig. 3. The data indicate that concentrations of up to 10 mg/ml could be obtained if pH and ionic strength are carefully manipulated.

The solubility isotherm in neutral medium is of the A_P type, indicating that complexes of higher order may be formed in solution at higher cyclodextrin concentration. An analysis using the Higuchi approach [4] resulted in the following stability constants:

in water: $K_{1:1}$ = 6056 l/mol and $K_{1:2}$ = 28 l/mol (log $K_{overall}$ = 5.23).
in buffer pH 7: $K_{1:1}$ = 9511 l/mol and $K_{1:2}$ = 24 l/mol (log $K_{overall}$ = 5.35).

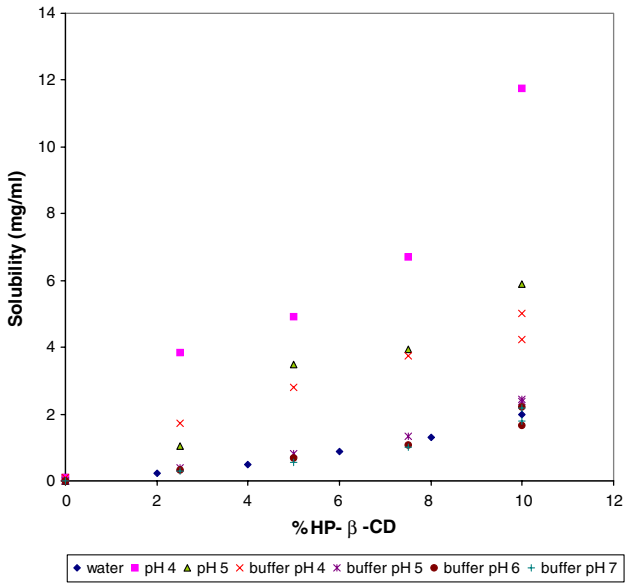

Fig. 3 Solubility of pirodavir as a function of the concentration of HPβCD and pH

As the pH decreases, the solubility isotherms tend to be more of the A_L type, indicating that the mechanism of complexation may change with ionization of the compound as previously reported for itraconazole and kynostatin.

Based on the solubility data, a 5 mg/ml nasal formulation was developed using 10% (w/v) HPβCD. pH was adjusted to 4.5 and saccharine was added to improve the taste. The stability of pirodavir in this formulation was studied under stressed conditions. Based on data that less than 2% of decomposition was found after a storage time of 23 days at 60°C, the formulation stability was found acceptable.

This formulation and the placebo were administered at doses of 2 mg by metered pump spray to healthy adults (age from 18 to 50 years) in four randomized, double-blind, placebo-controlled trials. Full details of the results of the clinical study are available in the publication of Hayden [1].

Conclusion

Substituted β-cyclodextrins, including HPβCD, were found to increase the apparent solubility of pirodavir by 3-orders of magnitude. Using HPβCD at a concentration of 10%, it was possible to develop a formulation at pH 4.5 containing up to 5 mg/ml of pirodavir.

References

1. Hayden F.G., Andries K., Janssen P.A.J.: Safety and efficacy of intranasal pirodavir (R77975) in experimental Rhinovirus infection. Antimicrob. Agents Chemother. **36**, 727–732 (1992) and Hayden F.G., Hipskind G.J., Woerner D.H., Eisen G.F., Janssen M., Janssen P.A.J., Andries K., Intranasal pirodavir (R77975) treatment of rhinovirus colds. Antimicrob. Agents Chemother. **39**, 290–294 (1995)
2. Loftsson, T., Brewster, M.: Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization. J. Pharm. Sci. **85**, 1017–1025 (1966)
3. Higuchi, T., Connors, K.A.: In: Reilly, C.N. (ed.) Advances in Analytical Chemistry and Instrumentation, vol. 4. New York: Wiley-Interscience, pp. 117–212 (1965)
4. Higuchi, T., Kristiansen, H.: Binding specificity between small organic solutes in aqueous solution: Classification of some solutes into two groups according to binding tendencies. J. Pharm. Sci **59**, 1601–1608 (1970)
5. Merkus, F.W.H.M., Verhoef, J.C., Marttin, E., Romeijn, S.G., van der Kuy, P.H.M., Hermens, W.A.J.J., Schipper, N.G.M.: Cyclodextrins in nasal drug delivery, Adv. Drug Del. Rev **36**, 41–57 (1999)