JPP Journal of Pharmacy and Pharmacology

ROYAL PHARMACEUTICAL SOCIETY

JPP Journal of Pharmacy and Pharmacology

JPP 2011, 63: 19–25

Received February 17, 2010
Accepted July 5, 2010
DOI
10.1111/j.2042-7158.2010.01173.x
ISSN 0022-3573

Research Paper

Fast-dissolving sublingual solid dispersion and cyclodextrin complex increase the absorption of perphenazine in rabbits

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Abstract

Objectives The sublingual administration route as well as solid dispersion formation with macrogol 8000 and complexation with β-cyclodextrin (β-CyD) were investigated as ways for improving the absorption of perphenazine, a poorly water-soluble drug subjected to substantial first-pass metabolism.

Methods The absorption of perphenazine was studied in rabbits after sublingual administration of perphenazine/macrogol solid dispersion, solid perphenazine/β-CyD complex and plain micronized perphenazine, as well as after peroral administration of an aqueous perphenazine solution. Solid formulations were prepared by freeze-drying (perphenazine/macrogol solid dispersion) or spray-drying (perphenazine/β-CyD complex).

Key findings The value for area under the curve from 0 to 360 min ($AUC_{0–360\ min}$) of perphenazine after peroral administration was only 8% of the $AUC_{0–360\ min}$ value obtained after intravenous administration, while the corresponding values for the sublingually administered formulations were 53% (perphenazine/macrogol solid dispersion), 41% (perphenazine/β-CyD complex) and 64% (micronized perphenazine). There are three possible mechanisms to explain these results: avoidance of the first-pass metabolism; good sublingual absorption of perphenazine; and rapid dissolution rate of perphenazine from the studied formulations.

Conclusions With sublingual administration, the drug has to dissolve rapidly in a small volume of saliva. Based on the present absorption studies in rabbits, the solid dispersion preparation and cyclodextrin complexation were postulated to be useful ways to attain successful sublingual administration of perphenazine. Good sublingual absorption was also achieved by micronization of perphenazine. As far as we are aware, this paper is one of the first to evaluate the sublingual administration of a solid dispersion *in vivo*.

Keywords absorption; cyclodextrin complex; solid dispersion; sublingual administration

Introduction

The oral cavity is a promising route of administration for drugs that are susceptible to hepatic first-pass metabolism.[1,2] In addition to the possibility of avoiding the first-pass effect, sublingual administration often provides a rapid onset of drug action since the oral mucosa is highly vascularized. Sublingual drug delivery is also well accepted by patients, and it offers an easy and convenient means to administer drugs to individuals suffering from swallowing difficulties, nausea or vomiting.[3] However, the sublingual absorption of many drugs is limited, as to pass through the sublingual and buccal membranes, the drug has first to dissolve rapidly in the small volume of saliva present in the mouth before it is removed from the site of absorption by swallowing.[2] This represents a challenge to the sublingual administration of poorly soluble or slowly dissolving drugs or drugs with high therapeutic doses.

The model drug used in this study was perphenazine, a potent phenothiazine-type antipsychotic that is used in the treatment of schizophrenia, anxiety and severe nausea or

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vomiting.[4] Although perphenazine is well absorbed after peroral administration, its bioavailability is limited by a substantial hepatic first-pass effect, making it a potential candidate for sublingual delivery. However, the poor aqueous solubility of perphenazine (less than 150 μg/ml at pH 6.8) would be predicted to hamper its sublingual administration.[5]

Various methods can be applied to increase the aqueous solubility and dissolution rate of poorly soluble drugs. For example, cyclodextrin complexation, solid dispersion preparation and the use of micronized, microcrystalline or amorphous drugs have been reported as useful methods to produce rapidly dissolving formulations of poorly soluble drugs.[6–12] Although numerous in-vitro studies have highlighted the potential of different formulation approaches to resolve problems in sublingual administration, only a few studies have been conducted to demonstrate their performance *in vivo*. Some earlier studies have reported increased bioavailability for drugs that are administered sublingually as cyclodextrin-containing formulations.[13–16] With solid dispersions, on the other hand, the potential for sublingual delivery has been demonstrated mainly *in vitro* so far, based on their fast dissolution rates and other favourable characteristics, and as far as we are aware, very little data of their performance *in vivo* has been published.[5,8,17–19] In this study, the sublingual absorption of a solid dispersion in rabbits has been reported. In addition, the effects of cyclodextrin complexation and micronization on the sublingual absorption of perphenazine have been described.

Materials and Methods

Materials

Perphenazine was purchased from Sigma-Aldrich (Steinheim, Germany). α-Cyclodextrin (α-CyD, Alpha W6 Pharma), β-cyclodextrin (β-CyD, Cavamax W7 Pharma), γ-cyclodextrin (γ-CyD, Cavamax W8 Pharma), hydroxypropyl-β-cyclodextrin (HP-β-CyD, Cavasol W7 Pharma) and randomly methylated β-cyclodextrin (RM-β-CyD, Cavasol W7 M) were obtained from Wacker Chemie (Burghausen, Germany). Macrogol 8000 (polyethylene glycol) was purchased from Sigma-Aldrich (Steinheim, Germany). All other reagents were of analytical grade.

Analytical methods

High performance liquid chromatography (HPLC) was used for the determination of perphenazine concentration during the phase-solubility and dissolution studies. In the phase-solubility studies of perphenazine and macrogol, the HPLC determinations were performed using the method described earlier.[5] In all other HPLC determinations, an Agilent 1100 HPLC system (Agilent Technologies Inc., Waldbronn, Karlsruhe, Germany) was used for the quantification of perphenazine. The HPLC system consisted of a binary pump G1312A, a vacuum degasser G1379A, an automated injector system autosampler G1313A, a UV-detector G1315B DAD, an HPLC column oven G1316A and analyst software Agilent ChemStation for LC Systems (Rev. A.08.03. or Rev. A.10.01.). The separation was performed with a LiChroCART Purospher RP-18e column (125 × 4 mm, 5 μm) (Merck KGaA, Germany). The mobile phase consisted of acetonitrile and 0.1% trifluoroacetic acid in water, 35 : 65 (v/v). The detector wavelength was 254 nm, flow rate was 1.0 ml/min, column temperature was 25°C, and injection volume was 10 μl. The HPLC method was validated in terms of linearity, repeatability and the lower limit of quantification. Before HPLC analyses, the samples were filtered (0.45 μm, Millex-HV, low protein binding Durapore PVDF, Millipore Corporation, Ireland).

The concentration of perphenazine in rabbit plasma samples was determined using a gas chromatographic-mass spectrometric method. Before the analysis the samples were purified using solid phase extraction. These procedures have been described in detail elsewhere.[20]

Phase-solubility studies

The effects of various cyclodextrins and macrogol on the aqueous solubility of perphenazine were investigated using the phase-solubility method.[21] The phase-solubility experiments with perphenazine and macrogol have been described elsewhere.[5] In the case of β-CyD, an excess amount of perphenazine was added to aqueous phosphate buffer solutions (0.16 M, pH 8.0, ionic strength 0.50) containing 0, 0.25, 0.5, 1 or 1.5% (w/v) of β-CyD ($n = 3$). With α-CyD, γ-CyD and HP-β-CyD, the cyclodextrin concentrations were 0, 1, 2.5, 5 and 10% (w/v) ($n = 1$). The drug/cyclodextrin suspensions were protected from light and shaken at room temperature for three days to attain equilibrium. The pH of the suspensions was maintained at 8.0 using aqueous HCl or NaOH solutions. After equilibration, the samples were filtered (0.45 μm) and analysed by HPLC.

The phase-solubility diagrams of perphenazine were prepared by plotting the perphenazine concentrations as a function of cyclodextrin and macrogol concentration. The apparent stability constant ($K_{1:1}$) between perphenazine and β-CyD was calculated using equation 1:

$$K_{1:1} = \frac{slope}{[S_0](1 - slope)} \quad (1)$$

where $K_{1:1}$ is the apparent stability constant for the 1 : 1-perphenazine/β-CyD complex and $[S_0]$ is the experimentally determined intrinsic solubility of perphenazine (mol/l).[21] The slope value was obtained from the phase-solubility diagram (concentrations expressed as mol/l). No stability constant was calculated for the solid dispersion, as the use of equation 1 presumed that the observed solubility increase was due to the formation of a complex between the drug and the solubilizer.

Preparation and characterization of the solid formulations

Three solid formulations were prepared for in-vivo studies: plain micronized perphenazine; a perphenazine/β-CyD complex; and a perphenazine/macrogol solid dispersion. Perphenazine was micronized by manually passing it through a 15-μm sieve mesh. The solid perphenazine/β-CyD complex was prepared by adding an excess amount of perphenazine to an aqueous 1% (w/v) β-CyD solution. The suspension was protected from light and stirred for three days at room tem-

perature. The pH of the solution was adjusted to 8.0 and held constant during the equilibration by adding aqueous HCl or NaOH, when necessary. After stirring, the suspension was filtered (0.45 μm) to remove undissolved perphenazine. The solution was then spray-dried using a Büchi Mini-Spray Dryer B-191 (Büchi Labortechnik AG, Flawil, Switzerland) under the following conditions: atomizer air flow rate 600 Nl/h, inlet temperature 160°C, outlet temperature 96°C and feed rate 5 ml/min. The solid dispersion of perphenazine with macrogol was prepared by freeze-drying an aqueous 0.1 M HCl solution containing perphenazine and macrogol in a 1 / 5 weight ratio, as described earlier.[5] The perphenazine contents of the perphenazine/β-CyD complex and perphenazine/macrogol solid dispersion powders were determined by HPLC. Freeze-drying of the perphenazine/macrogol solid dispersion and spray-drying of the perphenazine/β-CyD complex produced solid powders containing 0.21 $\pm$ 0.006 mg (0.52 $\pm$ 0.02 μmol) or 0.15 $\pm$ 0.003 mg (0.38 $\pm$ 0.01 μmol) perphenazine per 1 mg macrogol or β-CyD, respectively (mean $\pm$ SD, n = 3–4).

The particle size and morphology of the perphenazine/β-CyD complex were examined by scanning electron microscopy (SEM) (XL30 ESEM TMP microscope, FEI Company/Oy Philips Ab, Czech Republic) using an acceleration voltage of 15 kV, spot size of 3 and working distance of 12 mm. Before analysis, the sample was sputter-coated with gold for 2.5 min (Advanced Sputter Coater II-E5100, Polaron Equipment Ltd, Watford, UK; voltage 2.5 kV, current 20 mA). The perphenazine/macrogol solid dispersion was photographed similarly, with the exception that the acceleration voltage was 20 kV.[5]

The crystal structures of perphenazine, β-CyD and macrogol in the formulations were examined by X-ray powder diffractometry (XRPD). The XRPD measurements were performed with a Bragg–Brentano $\theta/2\theta$ reflection geometry based diffractometer (Philips PW1820, PW1830 and PW1710) using Ni filtered Cu Kα (40 kV/50 mA) radiation. The samples were measured between the angular range of 3–30° using 0.04° steps and a 3 s counting time per step.

Dissolution studies

Dissolution studies (n = 3–6) were performed at room temperature in 20 ml disposable plastic syringes using 5.0 ml of a dissolution medium that contained 2% (w/v) RM-β-CyD in a 0.16 M phosphate buffer (pH 6.5, ionic strength 0.5). RM-β-CyD was added to the dissolution medium to maintain sink conditions for perphenazine. The syringe was equipped with a syringe tip filter (0.45 μm), and a piece of filter paper was placed on the bottom of the syringe to prevent the solid particles from sedimenting into the syringe tip. A magnetic stirring bar was placed in the syringe, and the solutions were agitated at approximately 100 rev/min. An accurately weighed amount of unprocessed perphenazine (0.92–1.06 mg), micronized perphenazine (0.89–1.11 mg), perphenazine/β-CyD complex (6.94–7.07 mg) or perphenazine/macrogol solid dispersion (5.10–6.01 mg) was carefully dropped into the dissolution medium. The test was terminated at the designated time point by rapidly filtering a small amount of the solution into a test tube. Samples were taken at 0.25, 0.5, 1, 2, 5, 10, 15, 20 and 30 min. Each time point was performed in a separate syringe. The perphenazine contents of the samples were analysed by HPLC.

Pharmacokinetic studies in rabbits

Seven male New Zealand white rabbits (3.3–4.4 kg) were purchased from HB Lidköpings Kaninfarm (Lidköping, Sweden). Water and standard commercial food pellets were freely available, except during the first 6 h of each experiment, when the rabbits were under anaesthesia. All procedures with animals were reviewed and approved by the Animal Ethics Committee of the University of Kuopio.

In all pharmacokinetic studies, the rabbits were anaesthetized using ketamine (25 mg/kg; Ketaminol, Intervet International B.V., Boxmeer, the Netherlands or Ketalar, Pfizer, Espoo, Finland) and either medetomidine (0.5 mg/kg; Domitor, Orion, Espoo, Finland) or a combination of medetomidine (0.1 mg/kg) and midazolam (10 mg/kg; Dormicum, Roche, Espoo, Finland). The rabbits were positioned on a table and their lower jaws were supported in the horizontal position. Perphenazine (1 mg/kg) was administered to rabbits intravenously, perorally or sublingually.

For the intravenous administration of perphenazine, an aqueous 10% (w/v) HP-β-CyD solution containing 1 mg/ml perphenazine was prepared (pH 8). The solution was made isotonic using NaCl and filtered through a sterile membrane filter (pore size 0.2 μm; Schleicher & Schuell, Dassel, Germany). The perphenazine/HP-β-CyD solution (1 ml/kg) was injected directly into a marginal ear vein. The peroral formulation contained 1 mg/ml perphenazine in an aqueous 0.1 M HCl solution (pH 1). The solution (1 ml/kg) was administered to the gastrointestinal tract via catheterization, followed by rinsing with 2–3 ml 0.9% NaCl solution. For the sublingual administration, the tongue of the rabbit was carefully lifted using tweezers and appropriate amounts of the solid formulations were placed under the tongue. The weighed amounts for micronized perphenazine, perphenazine/β-CyD complex and perphenazine/macrogol solid dispersions were 4.04–4.76, 29.28–32.58 and 18.06–23.41 mg, respectively. The wetting of the solid formulations was ensured by administering 50 μl 0.9% NaCl solution under the tongue every 2 min after delivering the sublingual formulation, over 30 min.

Blood samples were collected into Venoject tubes (Terumo, Leuven, Belgium) from either a central artery or a marginal vein of the ear before perphenazine administration and 10–480 min after administration. Blood samples were centrifuged (3300g for 5 min), after which the plasma layer was collected and frozen immediately. The samples were stored at −80°C until analysis.

The maximum plasma concentrations of perphenazine (C_{max}) as well as the time at which maximum concentration was reached (t_{max}) were obtained directly from the time vs plasma concentration profiles. The area under the curve from 0 to 360 min ($AUC_{0–360\ min}$) was determined for perphenazine from the time vs concentration plot using the linear trapezoidal method. For the intravenous administration, the perphenazine concentrations at 0 min were extrapolated using the WinNonlin program (Version 5.0.1). The elimination rate constant (k_{el}), elimination half-life ($t^1/_2$), clearance (CL),

volume of distribution (Vd_{SS}) and $AUC_{0-\infty}$ value of perphenazine were determined individually for each rabbit from the intravenous data by the WinNonlin program.

Surprisingly, some rabbits died either during the anaesthesia or after the experiment. Examination of one such rabbit by a veterinary surgeon suggested that the cause of death was of cardiovascular origin, perhaps either a fatal blood pressure drop or arrhythmias. We believe that the cause of death was not due to any of the perphenazine formulations but, instead, due to the sensitivity of this strain of rabbit to the anaesthetic drugs, especially medetomidine. This assumption was supported by the fact that the deaths were not related to any particular perphenazine formulation and in some cases, they occurred even before administration of any of the formulations. However, it must be emphasized that medetomidine was used successfully in our earlier studies with other rabbit strains.[22] To prevent the blood pressure decline, midazolam was added to the anaesthetic combination and the dose of medetomidine could thus be reduced. In addition, the rabbits were given atipamezole (0.1–0.25 mg/kg; Antisedan, Orion, Espoo, Finland) two hours after perphenazine administration to reverse the effect of medetomidine. During the anaesthesia, the rabbits were also given 100 ml 0.9% NaCl solution as an intravenous infusion over approximately 30 min. Since these actions did not entirely prevent the deaths of the rabbits, it was decided to prematurely terminate this series of in-vivo experiments before all intended experiments were completed. Therefore, the number of parallel observations was lower with some formulations ($n = 2–5$).

Statistical analysis

In the dissolution and absorption studies of perphenazine, a nonparametric Kruskall–Wallis test was used to evaluate the statistical differences between the tested formulations. The *post hoc* test was then used to test the significance of the differences of the means.[23] The level of significance (P) was 0.05.

Results and Discussion

Phase-solubility studies

The aqueous solubility of perphenazine was determined in the presence of macrogol and various cyclodextrins. The best complexation of the tested cyclodextrins was achieved with β-CyD. Perphenazine exhibited linear A_L-type phase-solubility behaviour in the presence of β-CyD (Figure 1), the apparent stability constant ($K_{1:1}$) of the complex being 9300 ± 1300 (mean ± SD; $n = 3$). With macrogol, the aqueous solubility of perphenazine also increased in a linear manner (Figure 2).[5]

Preparation and characterization of solid formulations

In XRPD analyses, a characteristic X-ray diffraction pattern was observed for unprocessed perphenazine, confirming that the drug was in the crystalline state (Figure 3a). The diffractogram of micronized perphenazine showed nonsystematic changes in the intensity of the diffraction peaks as well as a minor increase in the background intensity when compared with unprocessed perphenazine. These changes could be attributed to a smaller particle size and more symmetric particle morphology, which increased the density of the XRPD powder sample and diminished the preferred orientation of the crystals, respectively (Figure 3b). The spray-dried perphenazine/β-CyD complex was completely amorphous, as no characteristic diffraction peaks for perphenazine or β-CyD were observed (Figure 3c). As described earlier, the diffractograms for the freeze-dried perphenazine/macrogol solid dispersion also showed total amorphization of perphenazine, while macrogol remained, at least partly, in its crystalline form (Figure 3d).[5] The scanning electron micrographs showed that the spray-dried perphenazine/β-CyD complex consisted of spherical particles with a relatively small particle size (<20 μm). The solid dispersion particles, on the other hand, were larger and had a flaky appearance, typical of freeze-dried materials.[5]

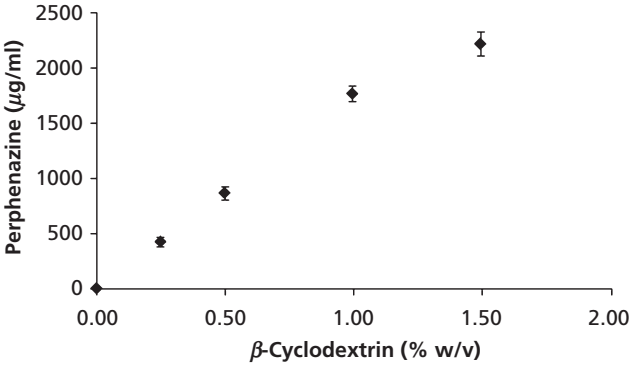

Figure 1 Phase-solubility diagram of perphenazine at pH 8 in the presence of β-cyclodextrin. Values are given as mean ± SD; $n = 3$.

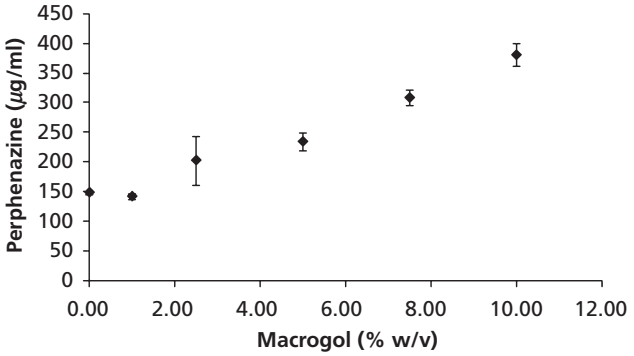

Figure 2 Phase-solubility diagram of perphenazine at pH 6.8 in the presence of macrogol. Values are given as mean ± SD; $n = 3$.

Dissolution studies

The dissolution studies were performed at pH 6.5, which lies in the pH range of saliva (5.8–7.4).[2] The dissolution rates of unprocessed perphenazine, micronized perphenazine, perphenazine/β-CyD complex and perphenazine/macrogol solid dispersion are shown in Table 1. Even though sink conditions prevailed, unprocessed perphenazine was completely dissolved only after >20 min. In contrast, micronization,

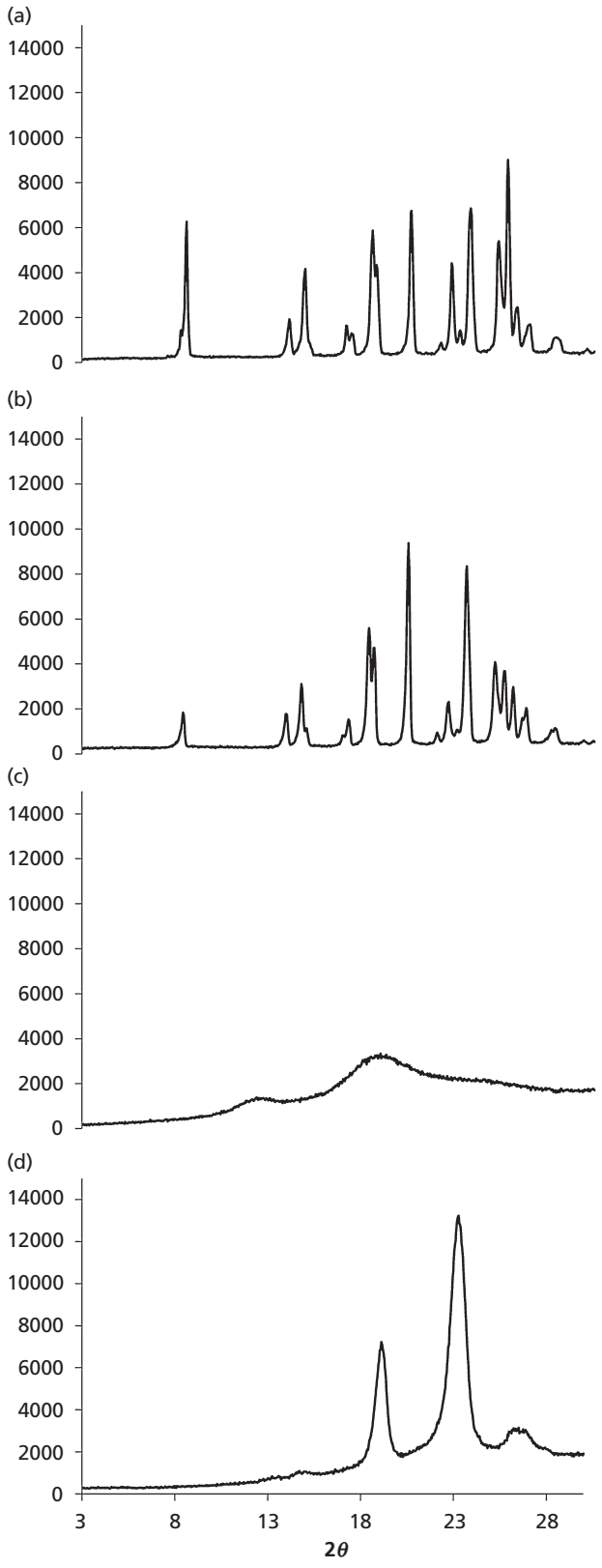

Figure 3 X-ray diffraction patterns. (a) Unprocessed perphenazine; (b) micronized (<15 μm) perphenazine; (c) spray-dried perphenazine/β-cyclodextrin complex; and (d) freeze-dried perphenazine/macrogol solid dispersion.

cyclodextrin complexation and solid dispersion formation all increased the dissolution rate of perphenazine, and 100% dissolution of perphenazine was achieved in ≤5 min from all of these formulations. Based on the Noyes–Whitney equation, it could be assumed that increased dissolution of micronized perphenazine was due to the decreased particle size of the drug. With the perphenazine/β-CyD complex, the improved dissolution rate was mainly attributable to the increased apparent aqueous solubility of perphenazine. In the case of perphenazine/macrogol solid dispersion, the molecular level mixing between perphenazine and macrogol as well as formation of an amorphous perphenazine dihydrochloride salt were found to be the main factors improving the dissolution rate.[5]

Pharmacokinetic studies in rabbits

Sublingual drug absorption can be studied *in vivo* using various animal models, such as rabbits, dogs, pigs and monkeys.[24] All these species have a non-keratinized sublingual mucosa that closely resembles human sublingual and buccal tissue. In this study, the rabbit was chosen as the animal model due to its convenient size, easy handling and lower cost in comparison with larger animals. In addition, the suitability of the rabbit model for determining the sublingual absorption of various weakly basic drugs has been demonstrated in earlier reports.[24,25]

The plasma profiles after intravenous administration of perphenazine suggested first-order pharmacokinetics with distinct distribution and elimination phases. A two-compartment intravenous bolus model with first-order elimination was used for determining the pharmacokinetic parameters for each rabbit. The values for k_{el}, CL, Vd_{SS}, $t^1/_2$ and $AUC_{0-\infty}$ of perphenazine were 0.005 ± 0.002 /min, 200 ± 36 l/min, 37 ± 19 l, 151 ± 81 min and 18 630 ± 1920 ng/ml × min, respectively.

Figure 4 shows the mean plasma concentrations of perphenazine after sublingual administration of micronized perphenazine, perphenazine/β-CyD complex and perphenazine/macrogol solid dispersion as well as after peroral administration of an aqueous perphenazine solution. The values of C_{max}, t_{max} and $AUC_{0-360\ min}$ for perphenazine from these formulations are summarized in Table 2. The $AUC_{0-\infty}$ values and absolute bioavailabilities were not calculated for the sublingual and peroral formulations, as to minimize the duration of anaesthesia the experiments were concluded shortly after achieving the maximum plasma concentration. When perphenazine was administered perorally, its $AUC_{0-360\ min}$ value was 8% of the $AUC_{0-360\ min}$ value after intravenous administration of perphenazine. In sublingual administration, the corresponding values were 53% (perphenazine/macrogol solid dispersion), 41% (perphenazine/β-CyD complex) and 64% (micronized perphenazine).

The results indicated that the absorption of perphenazine could be enhanced using the sublingual administration route instead of peroral administration. Cyclodextrin complexation and solid dispersion formation did not improve the sublingual absorption of perphenazine in comparison with simple micronization of the drug. A possible explanation for this observation was the difference in the bulk volumes of the three formulations studied. As the dose of perphenazine was

Table 1 Dissolution behaviour of unprocessed perphenazine, micronized (<15 μm) perphenazine, perphenazine/β-cyclodextrin complex and perphenazine/macrogol solid dispersion

Time (min)	Unprocessed perphenazine ($n = 3$) Mean ± SD (%)	Micronized perphenazine ($n = 3$–6) Mean ± SD (%)	Perphenazine/β-CyD complex ($n = 4$) Mean ± SD (%)	Perphenazine/macrogol solid dispersion ($n = 3$) Mean ± SD (%)
0.25	8 ± 1	35 ± 15	72 ± 17*	74 ± 8*
0.5	13 ± 3	62 ± 15	57 ± 6	80 ± 4*
1	21 ± 8	83 ± 21	82 ± 14	92 ± 10
2	41 ± 8	79 ± 16	93 ± 12*	88 ± 13
5	62 ± 6	114 ± 1*	105 ± 2	102 ± 3
10	78 ± 15	106 ± 6	110 ± 9	107 ± 5
15	80 ± 16	102 ± 3	111 ± 4	101 ± 19
20	92 ± 7	99 ± 4	101 ± 3	102 ± 8
30	100 ± 11	101 ± 3	106 ± 4	113 ± 4

Values are mean of the % dissolved ± SD. All formulations corresponded to 1 mg perphenazine. An aqueous phosphate buffer solution (0.16 M, pH 6.5, ionic strength 0.05) containing 2% (w/v) randomly methylated β-cyclodextrin was used as the dissolution medium to maintain sink conditions. β-CyD, β-cycloclodextrin. *Dissolved amount was significantly different from the dissolved amount of unprocessed perphenazine (Kruskall–Wallis test with a *post hoc* test, $P < 0.05$).

Table 2 Values of C_{max}, t_{max} and $AUC_{0–360\ min}$ for perphenazine after intravenous administration of an aqueous perphenazine/hydroxypropyl-β-cyclodextrin solution, peroral administration of an aqueous perphenazine solution and sublingual administration of micronized perphenazine, solid perphenazine/β-cyclodextrin complex and perphenazine/macrogol solid dispersion in rabbits

Route of administration	Formulation	n	C_{max} (ng/ml) Median (range)	t_{max} (min) Median (range)	$AUC_{0–360\ min}$ (ng/ml × min) Mean ± SD
Intravenous	Aqueous perphenazine/HP-β-CyD solution	3	690 (522–1388)[a]	0[a]	12 920; 13 730[b]
Peroral	Aqueous perphenazine solution	4	10.9 (4.3–38.6)	120 (10–180)	1090 ± 877
Sublingual	Micronized perphenazine	4	36.1 (21.2–51.1)	165 (90–360)	8650 ± 3590[c],*
	Perphenazine/β-CyD complex	5	24.7 (15.4–35.4)	180 (60–360)	5530 ± 1730
	Perphenazine/macrogol solid dispersion	4	35.1 (30.6–38.3)	180 (60–180)	7070 ± 1120*

β-CyD, β-cyclodextrin; HP-β-CyD, hydroxypropyl-β-cycloclodextrin. [a]Extrapolated value. [b]$n = 2$. [c]$n = 3$. Perphenazine dose: 1 mg/kg. *Significantly different from the $AUC_{0–360\ min}$ value of perorally administered aqueous perphenazine solution (Kruskall–Wallis test with a *post hoc* test, $P < 0.05$).

always 1 mg/kg, the average amounts of micronized perphenazine, perphenazine/β-CyD complex and perphenazine/macrogol solid dispersion powders given sublingually to 4-kg rabbits were approximately 4, 31 and 21 mg, respectively. The volume of saliva in the oral cavity of a rabbit is very small, and the better absorption of plain micronized perphenazine could thus be attributed to its smaller bulk volume, resulting in faster wetting in saliva and closer contact with the oral mucosa. The rabbit model may, however, underestimate the absorption of the cyclodextrin complex and solid dispersion formulations in humans, as both the volume of saliva and area of the oral mucosa are larger in the human mouth, whereas the dose of perphenazine given to rabbits in this study corresponded to a typical single peroral dose of perphenazine in adults. In the case of the perphenazine/β-CyD complex, it was also possible that the dilution of the complex in the small volume of saliva was not sufficient for the drug to be released from the complex, as the stability constant between perphenazine and β-CyD was relatively high.[26]

In practice, with micronized powders, the small particle size and possible formation of highly energetic amorphous surfaces may pose problems for the stability and processability of the drug.[27] Therefore, solid dispersion preparation and

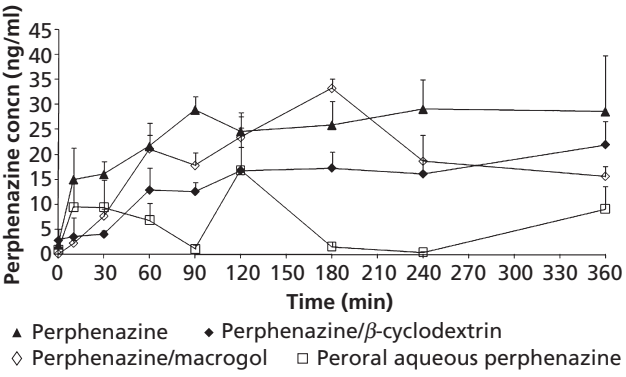

Figure 4 The mean plasma concentrations of perphenazine after administration of different formulations. Sublingual administration of micronized (<15 μm) perphenazine 4.0–4.8 mg, perphenazine/β-cyclodextrin complex 29.3–32.6 mg, perphenazine/macrogol solid dispersion 18.1–23.4 mg and peroral administration of an aqueous perphenazine solution 3.3–4.1 ml. Values are mean ± SEM; $n = 3$–5. Perphenazine dose: 1 mg/kg.

cyclodextrin complexation should be more suitable techniques when poorly soluble drugs are formulated for sublingual administration.

Conclusions

In sublingual delivery, the drug needs to dissolve rapidly in a small volume of saliva. In this study, solid dispersion preparation and cyclodextrin complexation were investigated for sublingual administration of perphenazine in rabbits. When compared with peroral administration of an aqueous perphenazine solution, the absorption of perphenazine could be enhanced by the sublingual administration of perphenazine/macrogol solid dispersion and solid perphenazine/β-CyD complex. Good sublingual absorption was achieved using micronized perphenazine.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

Funding

This study was financially supported by the Finnish Funding Agency for Technology and Innovation.

Acknowledgements

The authors thank Heikki Pekonen and Tetta Venäläinen (M.Sc.) for skillful technical assistance and Teemu Heikkilä (M.Sc.) for his contribution in the XRPD measurements. The National Laboratory Animal Center (Kuopio, Finland) is acknowledged for providing a pleasant working atmosphere and good care for the animals.

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