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RESEARCH PAPER

Lonidamine Solid Dispersions: In Vitro and In Vivo Evaluation

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ABSTRACT

Solid dispersions of lonidamine in PEG 4000 and PVP K 29/32 were prepared by the spray-drying method. Then, the binary systems were studied and characterized using differential scanning calorimetry, hot stage microscopy, and x-ray diffractometry. In vitro dissolution studies of the solid dispersed powders were performed to verify if any lonidamine dissolution rate or water solubility improvement occurred. In vivo tests were carried out on the solid dispersions and on the cyclodextrin inclusion complexes to verify if this lonidamine water solubility increase was really able to improve the in vivo drug plasma levels. Drug water solubility was increased by the solid dispersion formation, and the extent of increase depended on the polymer content of the powder. The greater increase of solubility corresponded to the highest content of polymer. Both the solid dispersions and the cyclodextrin complexes were able to improve the in vivo bioavailability of the lonidamine when administered per os. Particularly, the AUC of the drug plasma levels was increased from 1.5 to 1.9-fold depending on the type of carrier.

Key Words: *DSC; HSM; Lonidamine; PEG 4000; Pharmacokinetics; PVP; Solid dispersion; X-ray diffractometry*

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INTRODUCTION

Lonidamine, an indazol–carboxylic acid derivative, is an anticancer drug acting as a modulator of the glycolysis and of the respiration chain.[1] In vivo, lonidamine can be administered by intravenous injection or per os (75–150 mg per dose). In the first case it possesses a very much higher toxicity than in the second case; this suggests that the bioavailability of oral lonidamine may be limited,[2] probably because of its very low water solubility. The molecule is practically water insoluble and a solubility improvement could increase its bioavailability.

In a previous work, the authors tried to improve its water solubility by cyclodextrin inclusion complexation.[3] The inclusion complex did not form but, as a result of an external interaction between lonidamine and cyclodextrins, a considerable increase of solubility was obtained.

The aim of this work is to use polymeric carriers, such as PVP or PEG 4000, to obtain a dissolution rate or solubility improvement through the formation of drug/carrier solid dispersions. Several methods can be employed to obtain a solid dispersion, such as dissolution/solvent removal,[4–8] fusion,[9–12] fusion-dissolution,[13] and spray-drying,[14–17] depending on the characteristics of the drug and carrier. Each of these methods presents some drawbacks: a common solvent able to dissolve both drug and carrier is not always easy to find; very often the fusion method requires a waste of energy because of the high melting point of drugs, and it cannot be used for thermally unstable drugs; the fusion-dissolution method can promote a solvent entrapment within the solid dispersion, modifying the drug–carrier interactions. A further method consists of the dispersion of fine-powdered drug into the melted carrier and then into the cooling system.[14–18] In this way, unless the drug is soluble in the melted carrier, solid solutions or glassy solutions, which are preferable since drug particle size reduction is to the minimum level,[19] are impossible to obtain.

In our case, as lonidamine has a relatively high melting point (208–211°C), the spray-drying method has been considered the most suitable to obtain a solid dispersion. Polyethylene glycol (PEG) 4000 and polyvinylpyrrolidone (PVP) K 29/32 have been chosen as carriers because of their physiological compatibility. The obtained solid dispersed powders were characterized using differential scanning calorimetry, hot stage microscopy, and x-ray diffractometry. In vitro dissolution studies were performed to reveal any water solubility improvement.

Despite the great number of papers published on solid dispersion of many drugs in different carriers, there is a lack of studies on possible in vivo effects of the administered solid dispersed powders. For this reason, in vivo pharmacokinetic studies were performed on the solid dispersions and on the previously reported cyclodextrin complexes,[3] to verify if the increased lonidamine water solubility was really able to improve the in vivo drug plasma levels.

MATERIALS AND METHODS

Preparation of the Solid Dispersions

Lonidamine/PEG 4000

Lonidamine alone (A.C.R.A.F., Ancona, Italy), PEG 4000 alone (pharmacopeial grade, Nuova Astrochimica, Milan, Italy), and a series of mixtures of polymer and drug having a final carrier–drug weight ratio ranging from 90:10 to 10:90 were dissolved at 25°C in the lowest amount of CH_2Cl_2. The solution was spray-dried (Büchi Mini Spray Dryer B-191, Switzerland) under the following conditions: feed rate 25 mL/min, inlet temperature 50°C, outlet temperature 40°C, pressure 5 bar, and throughput of drying air 35 m^3/hr. The collected powders were stored under vacuum in a desiccator for one week and then analyzed.

Lonidamine PVP K 29/32

Lonidamine alone, PVP K 29/32 alone (ISP Technologies, Wayne, NJ), and a series of mixtures of polymer and drug having a final carrier–drug weight ratio ranging from 90:10 to 10:90 were dissolved at 25°C in the lowest amount of CH_2Cl_2. The solution was spray-dried under the following conditions: feed rate 30 mL/min, inlet temperature 80°C, outlet temperature 65°C, pressure 5 bar, and throughput of drying air 35 m^3/hr. The collected powders were stored under vacuum in a desiccator for one week and then analyzed.

Physical Mixtures Preparation

Fine-powdered physical mixtures of each polymer and lonidamine were prepared by blending in a mortar for 5 min.

Preparation of the Lonidamine/Cyclodextrin Complexes

Lonidamine/β-cyclodextrin and lonidamine/hydroxypropyl β-cyclodextrin complexes were prepared and characterized according to the methods described previously.[3]

UV Measurements

After one week of storage, all the obtained powders were assayed spectrophotometrically (Cary 1E UV-VIS, Varian, Leini, Italy) at 297 nm in CH_2Cl_2 (analytical grade, Carlo Erba, Milan, Italy) to be sure that no loss of drug or variation in the composition of the mixtures occurred during their preparation.

DSC Measurements

Differential scanning calorimetry was performed on the powders with a Perkin-Elmer DSC-2C (Italian Perkin-Elmer, Bologna, Italy) differential scanning calorimeter connected to a PC data station. Each sample (10 mg of powder in aluminum pans) was heated at a rate of 5°C/min between 17 and 217°C.

X-ray Diffractograms

X-ray diffractograms of the prepared powders and of pure drug and polymers were carried out with a Philips (Milan, Italy) PW 1730 x-ray generator using CuK_α radiation and a goniometer camera.

Hot Stage Microscopy

Hot stage microscopy was performed with a Mettler FP 82 (Italian Mettler-Toledo, Novate Milanese, Italy) and an optical microscope Zeiss KF2 (Italian Zeiss, Arese, Italy) heating all the powders between 20 and 220°C at a rate of 10°C/min.

In Vitro Dissolution Studies

The dissolution studies were performed in triplicate with an Erweka (Heusenstamm, Germany) DT6 dissolution test, in distilled water at 37°C using the paddle method at a rotation speed of 75 rpm (USP XXIII Apparatus 2). A certain amount of each powder, containing 50 mg of lonidamine, was put into a vessel with 900 mL of water. At 5-min intervals, 3 mL of water was withdrawn, passed through a 0.45-μm membrane filter (Millipore), and assayed spectrophotometrically at 297 nm to measure the concentration of lonidamine present in the solution. The initial volume of the vessel was maintained by adding 3 mL of distilled water after each sampling. AQ1

In Vivo Release Kinetics

The studies were performed in 90 male Wistar rats (Charles River, Calco, Lecco, Italy), body weight 270–350 g. The care and husbandry of animals were in accordance with the Guide for the Care and Use of Laboratory Animals (1985), U.S. Department of Health and Human Services, National Institutes of Health, Publication No. 8523. Upon arrival in the laboratory, the animals were examined by a veterinarian and found to be in good health, then acclimatized to the laboratory environment for one week. The animals were housed in Makrolon cages (Tecniplast Gazzada, Buguggiate, Milan, Italy), three animals per cage, in a conditioned room at 20±1°C; 55±15% RH; 12-hr on–off cycle, 7 a.m.–7 p.m.; and not less than 15 changes per hour of filtered air. All animals were allowed free access to a standard dry pellet diet. Water from the municipal water main was offered *ad libitum* in bottles.

All the formulated powders, or the lonidamine alone, were suspended in 0.5% methyl cellulose 4000 cps (Sigma, St. Louis, MC) and given by gavage, in a volume of 10 mL/kg. All animals received a single dose equivalent to 100 mg/kg of lonidamine free base. Rats were fasted for 18 hr before the day of treatment.

At the appropriate times, the rats were subjected to light anesthesia with carbon dioxide. Blood samples (3–4 mL) were obtained via cardiac puncture from three animals per time point at 15, 30, 60, and 90 min, and at 4, 8, and 24 hr after the administration of the dose. Blood was immediately heparinized, put into tubes, and centrifuged at 5000 rpm for 15 min to obtain plasma. The separated plasma was drawn off and placed in a silanized vial, sealed with a parafilm septum, and stored at −80°C until analysis.

After having defrosted the plasma samples, 10 mL of acetone was added to 2 mL of each of them and the system maintained under stirring for 10 min.

In this way plasma proteins were precipitated but the lonidamine (very soluble in acetone) remained in solution. Then, the system was centrifuged at 5000 rpm for 15 min and the supernatant liquor filtered through 0.45-μm Millipore filters.

The precipitated proteins of some samples were re-added to 10 mL of acetone, re-extracted, re-centrifuged, and tested to be sure that no lonidamine remained linked to the proteins. Finally, the filtrate was injected in a HPLC system (Hewlet-Packard 1090 2nd series) equipped with a reverse phase octadecylsilane (C-18) column (Merck Purosphere RP18, $12.5 \times 3\,mm^2$, 5-μm spherical particles) and eluted at 1 mL/min with 0.1 M ammonium acetate in 50% acetonitrile and 1.2% acetic acid. Effluent absorbance was measured at 300 nm.

Lonidamine eluted at approximately 3.5 min and concentrations were quantified by comparing the chromatogram area of the filtrates with the area given by a concentration of pure lonidamine of 5 mg/mL.

RESULTS AND DISCUSSION

Drug Content of the Powders

Ultraviolet analyses performed on the prepared powders show in all cases a 100% drug content according to the theoretical composition.

DSC Analyses

Figure 1 shows the DSC curves of lonidamine, PVP, and PEG compared with those of the spray-dried powders. While processed lonidamine and PEG undergo a certain amount of crystallinity reduction (deduced through the comparison of the fusion enthalpies of the peaks), PVP remains always amorphous. No other phenomena are visible in these plots, except the small shoulder present in the melting peak of the spray-dried lonidamine.

Figure 2 shows the DSC curves of lonidamine/PVP and lonidamine/PEG 4000 physical mixtures as an example of the interactions occurring by simply blending the two substances. In both cases, a shift toward lower temperature values is visible, along with a reduction and broadening of the lonidamine peak of fusion as the drug content in the physical mixture decreases, but no eutectics or complexes can be detected. Besides, since the position of the PEG 4000 melting peak does not change, a monotectic system is probably formed by PEG 4000 and lonidamine. The lonidamine peak of fusion is still present in the drug/carrier 1:9 powders.

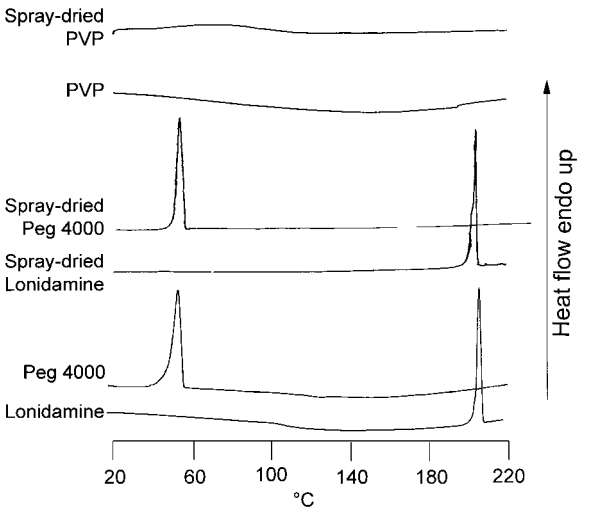

Figure 1. DSC curves of unprocessed and processed lonidamine, PVP, and PEG 4000.

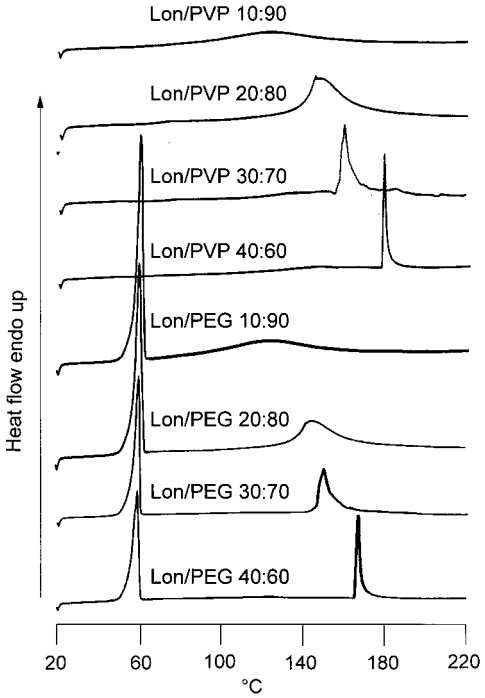

Figure 2. DSC curves of lonidamine/PVP and lonidamine/PEG 4000 physical mixtures.

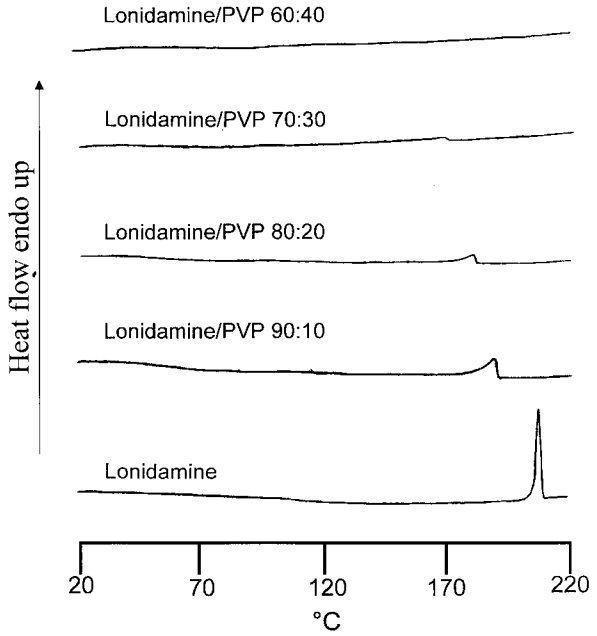

Figure 3. DSC curves of lonidamine/PVP solid dispersions.

Figure 3 shows the thermograms of lonidamine/PVP solid dispersions. The drug melting peak considerably and gradually decreases and is no longer present in the lonidamine/PVP 60:40 ratio and lower. No eutectics or complexes can be detected. If we construct the solid dispersion phase diagram by reporting in a y/x system the enthalpy of the lonidamine melting peak vs. the percentage of lonidamine in the powder, we will be able to extrapolate a theoretical value of drug solid solubility in the polymer (Fig. 4).

According to these data, lonidamine seems to possess a very high solid solubility in PVP. The theoretical value of this solid solubility limit is 70%. Anyway, because processed lonidamine alone undergoes a certain amount of crystallinity reduction which is increased by the presence of the PVP in the powder (physical mixtures), the real percentage of drug engaged in the formation of the solid solution may be considerably distant (lower) from the theoretical value.

Figure 5 shows the DSC curves of lonidamine/PEG 4000 solid dispersions. Also in this case, the lonidamine peak decreases in intensity, shifts at lower values, and broadens as the amount of drug in the powder decreases. Also in this case, the position of the PEG 4000 melting peak remained unchanged. The drug melting peak is nearly absent in the powders with lonidamine/PEG 4000 40:60 ratio and lower. So, solid solutions could form below a 40% drug quantity. The extrapolated theoretical value of this solid solubility limit is 43% (Fig. 4).

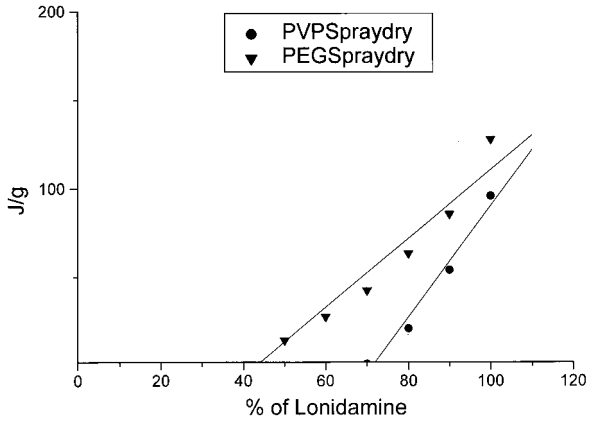

Figure 4. Heat of fusion diagram of the lonidamine/carrier powders.

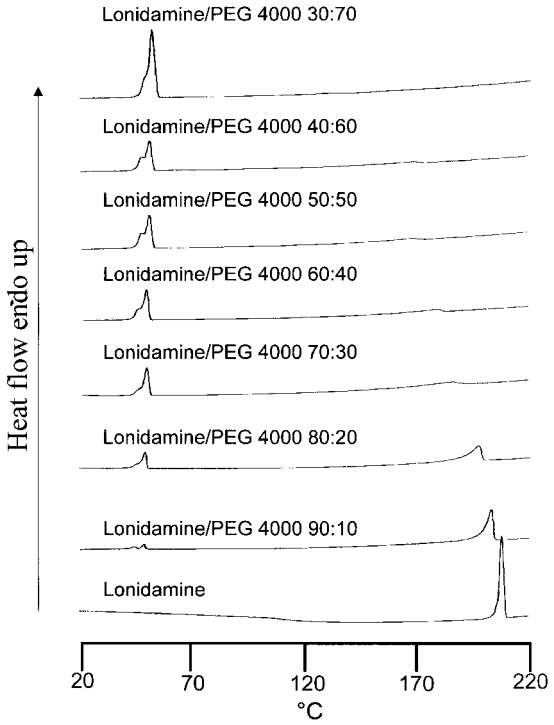

Figure 5. DSC curves of lonidamine/PEG 4000 solid dispersions.

X-ray Diffractometry

Figure 6 shows the diffractograms of initial lonidamine, PVP, and PEG compared with those of the corresponding spray-dried powders. Neither polymer undergoes any structural modification, and the applied preparation method does not influence their solid structure. On the contrary, the diffractogram of the spray-dried lonidamine is different from that of the unprocessed drug powder. It shows some peaks not present in the original powder. This could lead us to hypothesize the presence of another polymorph in the powder, even if DSC analyses of the same powder do not reveal melting peaks different from that of starting lonidamine. Anyway, the small shoulder present in the lonidamine melting peak might depend on another polymorph.

Figures 7 and 8 show the diffractograms of lonidamine/PVP and lonidamine/PEG 4000 physical

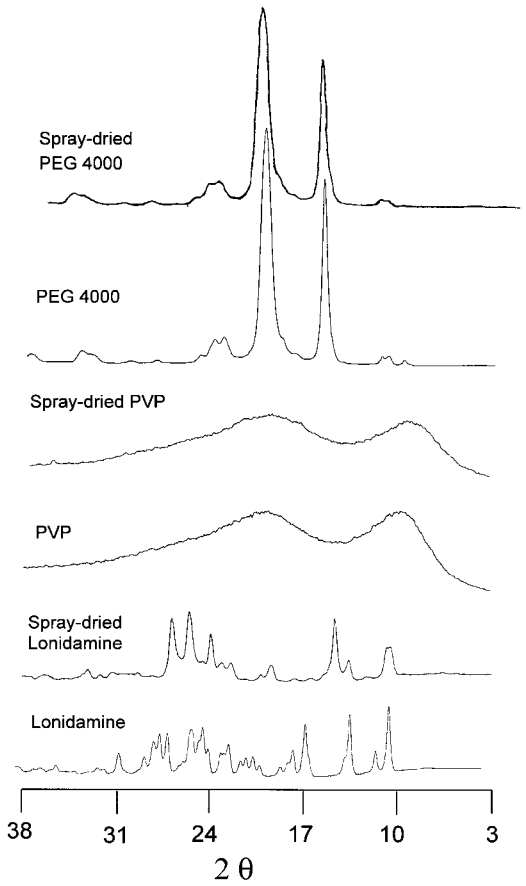

Figure 6. X-ray diffractograms of unprocessed and processed lonidamine, PVP, and PEG 4000.

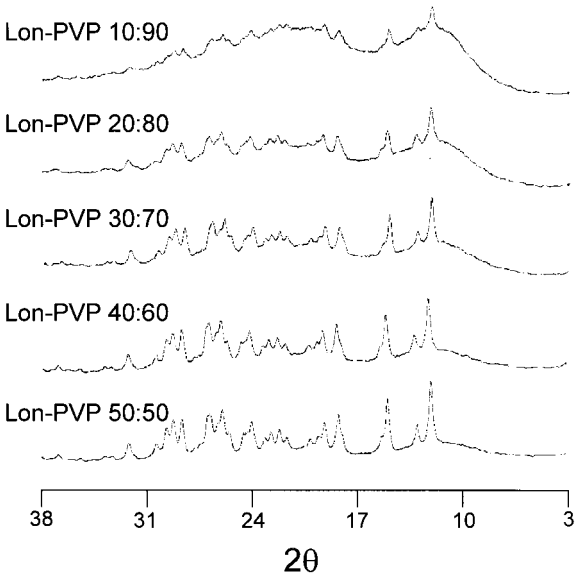

Figure 7. X-ray diffractograms of lonidamine/PVP physical mixtures.

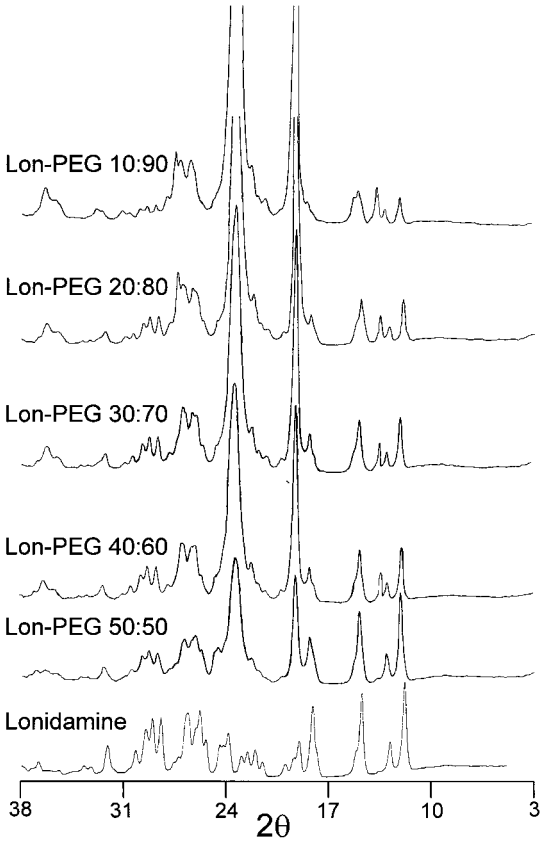

Figure 8. X-ray diffractograms of lonidamine/PEG 4000 physical mixtures.

mixtures. Lonidamine peaks are visible even in the 10:90 powders, confirming the impossibility of obtaining solid solutions by simply blending two molecules. These analyses corroborate DSC data because no eutectics or complexes can be detected.

Figure 9 shows the diffractograms of lonidamine/PVP solid dispersions. As expected, a gradual reduction in intensity of the lonidamine peaks can be observed. They disappear when the powder contains less than 20% of drug. In contrast with DSC data, this means that a total solid solution is formed only when the lonidamine content in the powder is less than 20%.

Figure 10 shows the diffractograms of lonidamine/PEG 4000 solid dispersions. Also in this case, the figure shows a gradual intensity reduction of lonidamine peaks as the drug content in the powders decreases and, at the same time, an increase of the intensity of PEG 4000 peaks. Lonidamine peaks are not visible only in the drug/carrier 10:90 ratios, indicating that a solid solution may form only with a drug content lower than 10%. Also in this case, x-ray diffractometry is in contrast with thermal analysis. For this reason the authors use hot stage microscopy analysis to better define these interactions in the solid state.

Hot Stage Microscopy

Powders containing high amounts of PEG 4000 (20:80 and 10:90 ratios) show, after complete PEG melting (65–70°C), the presence of some lonidamine crystals which remain visible until a temperature of 130°C. This is in disagreement with DSC data and confirms x-ray analyses. Lonidamine crystals were no longer visible only when the drug content in the powders was 5% or lower. A 100% solid solution forms in these monotectic systems only if the drug content is less than 5%.

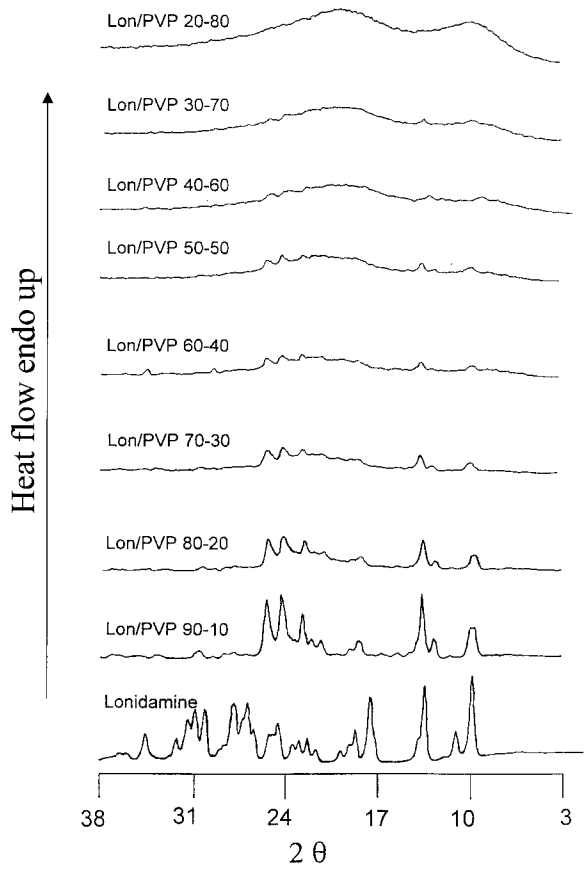

Figure 9. X-ray diffractograms of lonidamine/PVP solid dispersions.

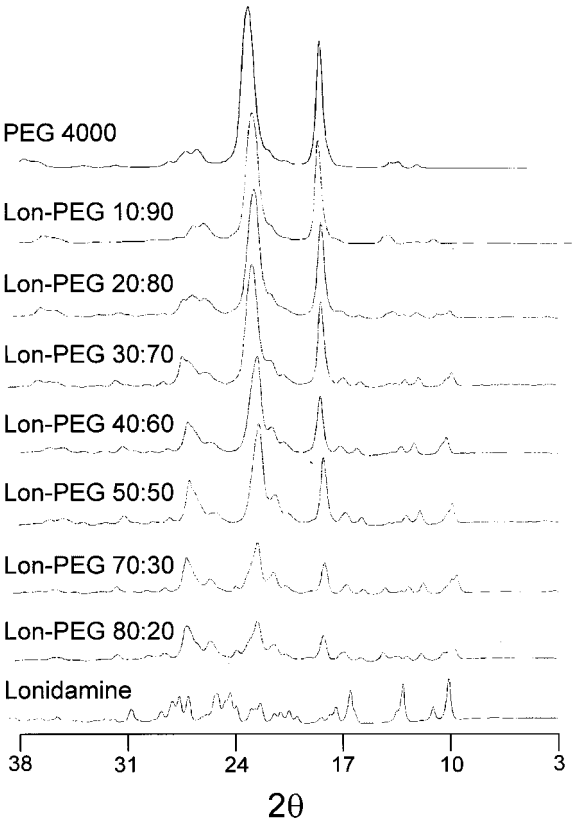

Figure 10. X-ray diffractograms of lonidamine/PEG 4000 solid dispersions.

In Vitro Dissolution Studies

Every value of the presented curves is the mean of three experiments. Standard deviation bars are omitted to avoid overlapping but, for all values, the standard error was less than 3%.

Figure 11 shows the dissolution profiles of lonidamine/PVP powders. The dissolution rate of all processed powders is higher than that of the lonidamine alone, and this increase depends on the amount of carrier and drug present in the powder. The higher the percentage of PVP, the higher the dissolution improvement of lonidamine. Drug dissolution increases quickly and remarkably to reach a maximum after 10 min and then, after a brief "plateau," decreases until remaining stable at values higher than those of the lonidamine alone. This behavior is typical of a carrier effect which brings temporary supersaturation followed by the reprecipitation of part of the drug. The improvement of solubility is comparable with that obtained using the cyclodextrins,[17] except for the drug/PVP 10:90 powders which show the highest drug solubility increase, reaching values of 70 mg/L even if this solubility decreases after a few minutes. This did not occur using cyclodextrins.

Figure 12 shows the dissolution profiles of lonidamine/PEG 4000 powders. These powders do not present an important increase of water drug solubility, which is only a little higher than that of lonidamine alone. Anyway, also in this case, powders showing the best drug solubility are those containing the highest amount of carrier.

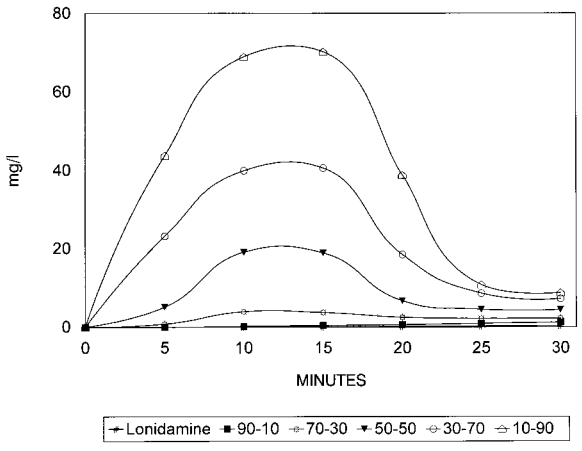

Figure 11. Dissolution profiles of lonidamine/PVP powders.

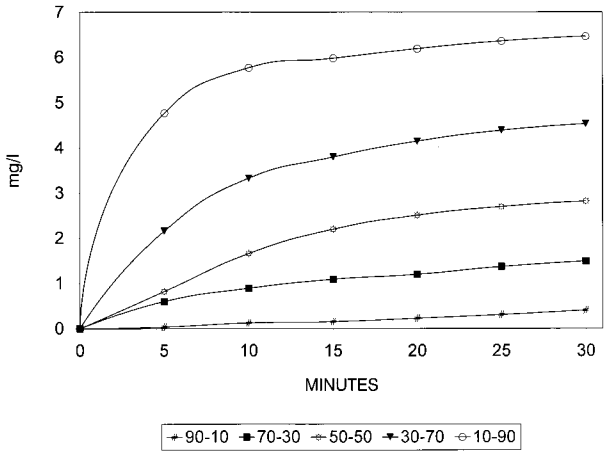

Figure 12. Dissolution profiles of lonidamine/PEG 4000 powders.

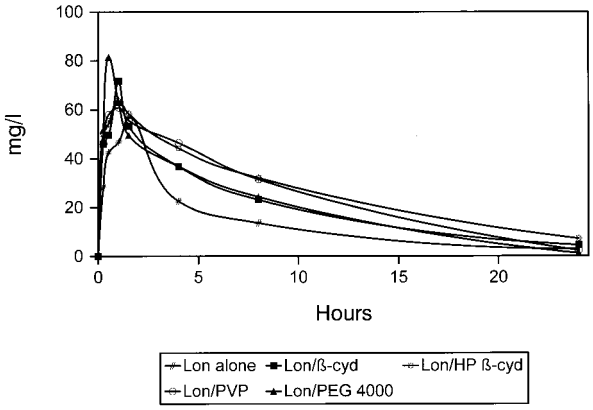

Figure 13. Lonidamine mean plasma concentration in rats after oral administration.

In Vivo Pharmacokinetics

Also in this case, the experimental points of the presented curves are the mean of three values and standard deviation bars are omitted to avoid overlapping. For all values, the standard error was less than 7%.

Figure 13 shows the mean plasma concentration of lonidamine in rats after oral administration of the drug/PEG 4000 or PVP 10:90 solid dispersions and the drug/β- or HP β-cyclodextrin 1:4 molar ratio complexes, compared with the plasma level given by the lonidamine alone. Lonidamine alone gives a plasma peak of 57 mg/L (C_{max}), 90 min (T_{max}) after administration, but then the hematic

Table 1

Pharmacokinetics Data of the Solid Dispersions and Cyclodextrin Complexes

	C_{max} (μg/mL)	T_{max} (min)	AUC (μg min/mL)
Lonidamine	57	90	364
Lon/β-cd 1:4	71.77	60	533
Lon/HP β-cd 1:4	63.7	60	674
Lon/PVP 1:9	60.9	60	632
Lon/PEG 4000 1:9	81.43	30	521

level decreases to 22.5 and 13.5 mg/L after 240 and 480 min, respectively.

Both the solid dispersions and the cyclodextrin complexes are able to improve the oral lonidamine bioavailability. Their plasma peaks, higher than that of the drug, occur 60 min after the administration, 30 min before that given by the drug alone. Lonidamine/PEG 4000 solid dispersion is an exception to that. In this case, the peak is the highest obtained (81.5 mg/L) and occurs 30 min after administration.

The most important result is the increase in AUC of these powders in comparison with the AUC of the drug alone, as shown in Table 1, where the C_{max} and T_{max} of the same powders are also reported. This increase is particularly strong in the 1:4 lonidamine/HP β-cyclodextrin and 1:9 lonidamine/PVP powders. Besides, these plasma-level curves resemble those given by sustained-release dosage forms.

All these phenomena could be due to an eventual limited but continuous rate of drug absorption through the gastrointestinal mucosa and the continuous carrier effect of the cyclodextrins or polymers. In fact, even if the improved lonidamine water solubility was demonstrated in vitro, there is no in vivo immediate appearance of a very high plasma peak. Probably, an in vivo lonidamine partial reprecipitation occurs in the stomach after the initial dissolution, but either the cyclodextrins or the polymers continue to sustain their carrier effect along the gastrointestinal tract, allowing the gradual dissolution and absorption of the undissolved drug.

CONCLUSION

Solid dispersions of lonidamine in PVP and PEG 4000 can easily be prepared by spray-drying. Drug solid solutions are formed when lonidamine in the powder is less than 5%. Drug water solubility is considerably increased by the solid dispersion formation, particularly for the 90:10 PVP/drug ratio. Both the solid dispersions and the cyclodextrin complexes are able to improve the in vivo bioavailability of lonidamine when administered per os. Particularly, the AUC of the drug plasma levels is increased.

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