International Journal of Pharmaceutics, 38 (1987) 99–102
Elsevier

IJP 01282

Influence of polyvinylpyrrolidone on the in vitro diffusion characteristics of tetraminol

S. Bogdanova, R. Bjankova, E. Minkov and L. Rainova

Department of Pharmaceutical Technology, Faculty of Pharmacy, Sofia (Bulgaria)

(Received 21 April 1986)
(Modified version received 18 February 1987)
(Accepted 7 March 1987)

Key words: In vitro diffusion; 1,2,3,4-Tetrahydronaphtaline derivative; Polyvinylpyrrolidone; Interaction; Coprecipitates - PVP membrane distribution; Pressor activity; Acute toxicity

Summary

In vitro diffusion through an artificial lipid membrane according to Stricker (1971) has been used to prove the complex ability of a new synthetic drug, *trans*-2-hydroxyethylamino-3-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphtaline hydrochloride (tetraminol) and PVP was used in an attempt to improve its oral absorption. Physical mixtures and coprecipitates were prepared as model preparations for interaction studies in a solid state. It was established that PVP influences Tetraminol's in vitro diffusion, but no complexation phenomena were confirmed. Other physicochemical methods used also gave no firm evidence for interactions. The partition behaviour of PVP in a system – artificial intestinal lipid mixture/water – was determined and was found that PVP distributes to a great extent in the lipid phase. Probably, PVP hydrophilizes the membrane pores and thus facilitates the transfer of the hydrophilic tetraminol molecules. It must be noted, however, that in vivo studies on animals of the pressor activity and of acute toxicity do not support the observed in vitro phenomena. It must be assumed that the fate of tetraminol after oral administration is very complex and needs more comprehensive studies.

Introduction

Trans-2-hydroxyethylamino-3-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphtaline hydrochloride (tetraminol) is a new synthetic compound (Christova, 1980). It possesses a pronounced α-adrenomimetic activity (Astrug, 1980) if injected intravenously, but is much less efficient when administered orally.

The present investigations with this drug are part of our studies concerning the potential physicochemical interactions between drugs and additives as a technological approach for formulation of more effective dosage forms.

In vitro diffusion through an artificial lipid membrane according to Stricker (1971) was used as a convenient method to prove complex formation in some cases. The additive polyvinylpyrrolidone (PVP K25) was chosen for its marked ability to form electrono–donor–acceptor complexes with many drugs (Monkhouse and Lach, 1972; Speiser, 1975).

Bearing in mind the fact that some physical mixtures and solid dispersions could be very useful as model preparations for interaction studies in a solid state (Chiou and Riegelman, 1971; Nakai et al., 1980), we introduced PVP in the

Correspondence: S. Bogdanova, Department of Pharmaceutical Technology, Faculty of Pharmacy, MA 1000 Sofia, Bulgaria.

donor phase untreated or as physical mixtures and coprecipitates with tetraminol.

The present studies are an attempt to elucidate if any interactions between tetraminol and PVP take pluce and what the mechanism of influence of PVP is on the in vitro diffusion profile of tetraminol as well as on its pressor activity and toxicity in animals.

Materials and Methods

Polyvinylpyrrolidone K25 was from BASF (F.R.G.) and the components, S1, S2, N for the artificial lipid membranes were from Sartorius, (F.R.G.). Tetraminol and the phosphate buffer substances were of reagent grade.

Apparatus

In vitro diffusion studies were carried out with the Sartorius Absorption Simulator. Ultraviolet spectral measurements were performed by use of a SF-26 (U.S.S.R.) and UV-vis recording spectrophotometer (D.D.R.).

Model preparations

The model physical mixtures and coprecipitates were preared according to Chiou and Riegelman (1971) and were introduced in the donor phase at a concentration always equivalent to 1×10^{-3} M or 0.005×10^{-3} M tetraminol.

In vitro diffusion studies

They were carried out as described in the Catalogue literature of the Sartorius Co. (F.R.G.). The required pH for the donor phase, 1.2, was achieved with 0.1 M HCL and pH 6.8 and 7.5 with phosphate buffer solutions. The concentration of tetraminol in both phases at a given time interval was determined by use of the spectrophotometric method at 286 nm.

Partition behaviour of PVP in the system artificial intestinal lipid mixture / water

The apparent partition coefficient was determined according to the procedure described from Caramella et al. (1982). The initial concentration of PVP in the aqueous phase was 0.84 mg/ml. The system was shaken for 3 h at room temperature and the amount of PVP was determined quantitatively in the aqueous phase as described in the Catalogue literature of BASF Co. (F.R.G.).

In vivo studies

The pressor activity was studied in acute blood experiments on 9 anesthetized male Wistar rate (220–260 g) at oral dose 20 mg/kg tetraminol. The acute toxicity was followed in white mice weighing 19–22 g, in groups of 10 animals each.

Results and Discussion

The k_d-values of tetraminol and its model preparations with PVP are listed in Table 1. The k_d-values were calculated according to Stricker (1971), using the straight part of the curve obtained when the corrected concentrations in the acceptor phase (c_{IIcorr}) were plotted vs time. The conditions were chosen so that the first step of the diffusion process occurred in all cases. The pH of the donor phase (phase I) was 1.2 and 6.8, respectively, and the pH of the acceptor phase (phase II) was 7.5 in order to simulate to some extent the physiological conditions in the gastrointestinal tract.

It was established that tetraminol alone possesses a low diffusion ability independently of the pH of the donor phase used. These findings are in agreement with its physicochemical properties. As reported previously (Astrug, 1980), tetraminol behaves as a weak base (pK_a 8.3) with a low distribution constant ($P = 5.2 \times 10^{-3}$ in a *n*-hexane/water system). Hence, according to the Hendersson-Hasselbach equation, at pH 1.2 tetraminol will be fully ionized and at pH 6.8 only 3% of the drug will be in a unionized state. This assumption is in accordance with the fact that the diffusion profiles of tetraminol through artificial stomach and intestinal lipid membrane are very similar – k_d is 0.65×10^{-3} cm · min^{-1} for the donor phase at pH 1.2 and 0.80×10^{-3} cm · min^{-1} for the donor phase at pH 6.8, respectively.

Our experiments also show that in all studied cases, independent of the pH of the phase I, PVP

TABLE 1

K_d-values of tetraminol and its model preparations with polyvinylpyrrolidone

Phase II – pH 7.5					
Phase I – pH 6.8			Phase I – pH 1.2		
Drug : PVP ratio (w/w)	Model preparations	$K_d \times 10^{-3}$ [a] ($cm \cdot min^{-1}$)	Drug : PVP ratio (w/w)	Model preparations	$K_d \times 10^{-3}$ [a,c] ($cm \cdot min^{-1}$)
	Tetraminol alone	0.80 [b]		Tetraminol alone	0.65 [b]
1 : 1	Physical mixture	1.98	1 : 1	Physical mixture	1.40
1 : 1	Coprecipitate [d]	2.11	1 : 1	Coprecipitate [d]	1.41
1 : 1	In presence of PVP	1.95	1 : 1	In presence of PVP	1.45
1 : 2	Coprecipitate [d]	2.35	–	–	–
1 : 2	In presence of PVP	2.65	1 : 2	In presence of PVP	1.42
1 : 5	In presence of PVP	2.70	–	–	–

[a] Membrane surface = 40 cm^2; initial concentration of tetraminol in Phase I = 0.6×10^{-3} M.
[b] Membrane surface = 80 cm^2; initial concentration in Phase I = 1.0×10^{-3} or 0.5×10^{-3} M.
[c] Mean values of 6 determinations; variation ⩽ 10% (See Stricker, 1971).
[d] Solvent – 96% ethanol (Chiou and Riegelman, 1971).

increases the diffusion of tetraminol. For example, when the pH of the donor phase is 6.3 the k_d-values of all model preparations (drug : PVP ratio 1 : 1 w/w) are approximately 2.5 times higher in comparison to that of tetraminol alone. At pH 1.2 the increase is of the same magnitude – 2.2 times – but the k_d-values are approximately 1.4-fold lower in comparison to those obtained at pH 6.8 and do not change when the weight participation of the PVP increases.

Another interesting and important fact is that the k_d-values of the model physical mixtures and coprecipitates are of the same order as k_d-values obtained when PVP is directly dissolved in the donor phase. Moreover, the pH of the latter has no influence. Therefore, the method of in vitro diffusion shows that PVP does not form complexes with tetraminol in a solid state.

The upper limit that assures an optimal influence on the diffusion process was also established. For pH 1.2 of the donor phase the latter was drug : PVP 1 : 1, and for pH 6.8, drug : PVP was 1 : 2 (see Table 1). Besides this, the maximum increase of the diffusion of tetraminol, achieved in the presence of PVP, was 3.4 times but only at pH 6.8 of phase I.

Thus, the results obtained by means of in vitro diffusion through artificial lipid membrane show no firm evidence for interaction between tetraminol and PVP. In order to confirm this statement and to elucidate why and how PVP influences the diffusion behaviour of tetraminol, we extended our studies using other physicochemical methods. The UV-spectra were registered in aqueous solutions of tetraminol and its model preparations, and show no differences either in the intensity or in the position of the characteristic absorption maximum at 286 nm. It was not possible to obtain any information from the IR-spectra because of superposition of the absorption maxima of tetraminol and PVP mainly in the regions of 800–900 cm^{-1}, 1200–1300 cm^{-1} and 1600–1700 cm^{-1}.

The NMR-spectra (in D_2O) also do not supply data in favour of some interactions. By using the method of equilibrium solubility we established the apparent solubility of tetraminol (0.24 M) at 37 °C, which does not change in the presence of increasing concentrations of polyvinylpyrrolidone.

In conclusion, either of the methods described above give evidence for complex formation between tetraminol and PVP.

As it could be assumed, the other alternative concerning the increase of the diffusion process of tetraminol was the interaction of PVP with the lipid liquid used for impregnation of the filter membrane. We determined the partition behaviour of PVP in the system artificial intestinal lipid/water mixture and found that the apparent partition coefficient calculated according to Caramella et al. (1982) was 5.60. Therefore, PVP is

distributed to a great extent in the artificial intestinal lipid membrane. It is very probable that it hydrophilizes the pores of the latter and thus facilitates the transfer of the hydrophilic tetraminol molecules through the barrier.

Preliminary in vivo experiments on rats and mice were carried out in order to find some relationships with the observed phenomena in vitro. The onset, the intensity and the duration of the pressor activity as well as the acute toxicity were studied after oral administration of aqueous solution of tetraminol alone or in the presence of PVP K25 at a dose of 20 mg/kg.

It was established that no marked differences in the pressor activity appeared. The increase of the arterial blood pressure was an average of 24.17% for tetraminol administered with PVP and 30.55% for tetraminol alone. In both cases the onset of the effect was 5–10 min after administration and its duration was about 120–180 min. In a subsequent administration (a period of 30 min was allowed for pressor activity to be quenched) the pharmacological effect obtained was weaker and of shorter duration with both preparations.

The acute oral toxicity was also followed but no differences were registered. LD50 as well as the toxicity of the administered doses of tetraminol alone and in presence of PVP, remained unchanged.

In conclusion, the results from the preliminary in vivo studies do not show a positive influence of PVP on oral absorption of tetraminol. It is most probable that the drug fate in vivo after oral administration is complex; more comprehensive studies on its incomplete oral absorption are needed.

References

Astrug, A., *Pharmacokinetic and pharmacological studies of a 2-aminotetraline derivative with pressor activity*, Ph.D. dissertation, Medical Academy, Sofia, 1980.

Caramella, C., Giordano, F., Bettinetti, G., Colombo, P., Conte, U. and La Manna, A., In vitro absorption studies on trimethoprim and sulfamethoxazole. Note I. *Pharm. Acta Helv.* 57 (1982) 154–159.

Chiou, W. and Riegelman, S., Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.*, 60 (1971) 1281–1302.

Christova, Kr., *Synthesis and investigation of trans-2-amino-3,5,8-trihidroxy-1,2,3,4-tetrahydronaphthaline derivatives*, Ph.D. dissertation, Medical Academy, Sofia, 1980.

Monkhouse, D and Lach, J., Drug–excipient interactions. *Can. J. Pharm. Sci.*, 7 (1972) 29–46.

Nakai, J., Nakajima, S., Yamamoto and Konno, T., Effects of grinding on the physical and chemical properties of crystalline medicinals with microcrystalline cellulose. IV. Comparison of the IR spectra of medicinals in the solid state and in solution. *Chem. Pharm Bull. (Tokyo)*, 28 (1980) 652–656.

Speiser, P., Inkompatibilitätsmechanismen zwischen Arzneistoffen under makromolekularen Hilfstoffen. *Dtsch. Apoth.-Ztg.*, 115 (1975) 389–397.

Stricker, H., Die Arzneistoffresorption im Gastrointestinaltrakt. I. In vitro Untersuchungen. *Pharm. Ind.*, 33 (1971) 157–160.