DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 18(8), 811-827 (1992)

ELABORATION AND PHYSICAL STUDY OF AN OXODIPINE SOLID DISPERSION IN ORDER TO FORMULATE TABLETS

F. Guillaume, A.M. Guyot-Hermann
Laboratoire de Pharmacie Galénique, Faculté de Pharmacie - Lille
R. Duclos, P. Besançon, A.M. Orecchioni
Laboratoire de Pharmacie Galénique, Faculté de Pharmacie - Rouen
M. Drache, P. Conflant
Laboratoire de Cristallochimie et Physicochimie du Solide
URA CNRS 452 - Université des Sciences et Techniques de Lille Flandres Artois
A. Gadefait, P. Bécourt
Laboratoire Delagrange - Chilly Mazarin

ABSTRACT

When drugs particles are very hydrophobic, the carrying out of solid dispersion is a good process in order to obtain a faster drug dissolution due to the particle size reduction and due to the wettability improvement of the particle surfaces.
The behaviour of these products may differ according to their physical structure, more particularly the dissolution rate of the drug and the stability of the solid dispersion obtained.
The aim of this work is
- to study a product supplied by industry, that is to say a Coprecipitate obtained by evaporation of an ethanolic Oxodipin/Povydone solution. The high melting point of Oxodipin has conduct us to choose coprecipitation. The oxodipin amount in the coprecipitate (20 %), is a good compromise between efficiency and technological properties.
- to demonstrate that the product obtained is a solid dispersion.
- to identify the type of this solid dispersion.
- to test its stability during compression and during

the stockage either in ambient condition, or at 40°C, or in controled humidity conditions.
Results seem to demonstrate that a solid dispersion which is a solid solution is obtained. This solid dispersion presents a very good stability of its physical structure and of dissolution properties.

INTRODUCTION

Oxodipine is a calcic inhibitor. It is used in therapeutics for its antihypertensive properties. This molecule is practically insoluble in water (10 g/ml at room temperature, under micronized state), and its oral absorption is weak, which decreases its bioavailability. In order to improve this bioavailibility, solid dispersions have been prepared following the procedures described by Chiou and Riegelman (1). However, for fear of a possible oxidation of the molecule during the fusion, comelts were disregarded and only coprecipitates explored. On the other hand, the selection of both excipient and solvent was determined by industrial feasibility considerations. The active substance content in the coprecipitate was optimized in order to reduce as much as possible the powder volume corresponding to the therapeutic dose.
This work consists first in the pharmaceutical study of the oxodipine/PVP coprecipitate and, second, in the determination of its solid state characteristics by testing with its stability during the pharmaceutical process and during the storage.

Part I - SOLID DISPERSION ELABORATION

I.1. MATERIALS AND METHODS

Oxodipine : C H NO , Laboratoire DELAGRANGE, France.
PVP : Kollidon K 30, BASF.
Ethanol : C H O normapur, PROLABO, France.
Rotative evaporator : RE 140 Büchi, ROUCAIRE, France.
Dissolution kinetics were carried out with the paddle apparatus from the Pharmacopee (Dissolutest Prolabo) at 37°C on samples containing 20 mg of oxodipine. The dissolution medium was conveyed to a UV spectrophotometer (Safas, Prolabo) by a peristaltic pump (Ismatec, Prolabo). The absorbence of the solution was monitored at 235 nm. Results were expressed in percentage of dissolved drug in relation time and were the mean of six determinations.

I.2. SOLID DISPERSIONS FORMULATION

To prepare coprecipitates, it is necessary to dissolve the active substance and the carrier in a common solvent or a mixture of solvents.

I.2.1. Solvent selection

Among the volatile solvents available for making solid dispersions, ethanol was the most convenient for an industrial transposition of the preparation method, because of its weak toxicity. However, oxodipine is soluble in ethanol only at a temperature higher than 70°C.

I.2.2. Carrier selection

The carriers usually used for the solid dispersions preparations are numerous (PVP, PEG, Urea, cyclodextrins...) with unequal aptitude for increasing the solubility and/or dissolution kinetics of active substances. A preliminary study of some of them have shown that PVP greatly improves the aqueous solubility of oxodipine (70 g/ml at room temperature). Futhermore, this excipient is highly soluble in ethanol. Based on these two properties (or characteristics), PVP was selected.

1.2.3. Optimization of the formulation

It was hoped to achieve a coprecipitate as concentrated as possible in active substance to reduce the powder volume used for in vivo essays. In practice, the limiting factor was the ethanolic solubility of oxodipine. Preliminary studies enabled us to determine a maximum oxodipine concentration compatible with a moderate alcoholic volume allowing a scale transposition. Finally, the concentration chosen as the best compromise was 20 per cent of the active substance in the coprecipitate. This concentration leads to a new active raw material, easily incorporated into capsules or tablets (100 mg of coprecipitate per unit corresponding to 20 mg of oxodipine).

1.2.4. Preparation procedure

0.6 g of oxodipine and 2.4 g of PVP are introduced into the round bottom flask of a rotative evaporator with 20 ml of ethanol. The mixture is heated at 70°C until complete dissolution. The solvent is removed by vacuum evaporation. The resulting product is dessicated, grounded and sieved. The particle size of the coprecipitate used for the pharmaceutical study is < 200 m.

TABLE I

Percentage of dissolved Oxodipine versus time

Time (minutes)	Oxodipine (pure)	Physical mixture (20% W/W)	Coprecipitate (20% W/W) (0 time)	Coprecipitate (20% W/W) (after 4 years)
3	0.073	15.02	97.85	97.37
6	0.176	17.25	98.51	98.15
9	0.410	18.86	99.06	98.75
12	0.659	20.12	99.47	99.21
15	0.938	21.16	99.53	99.49
18	1.260	21.88	99.58	99.55
21	1.715	22.99	99.70	99.68
24	1.978	23.73	99.97	99.95
27	2.213	24.45	100.00	100
30	2.506	25.02	100.00	100
33	2.843	25.59	100.00	100
36	3.107	26.03	100.00	100
39	3.371	26.48	100.00	100
42	3.781	26.98	100.00	100
45	4.133	27.36	100.00	100
48	4.409	27.70	100.00	100
51	4.646	28.01	100.00	100
54	4.881	28.34	100.00	100
57	5.218	28.70	100.00	100
60	5.453	28.92	100.00	100

I.3. DISSOLUTION RATE STUDIES

This study was performed successively with pure oxidipine, with the oxodipine/PVP coprecipitate and with the physical mixture of same concentration (100 mg containing 20mg of oxodipine).

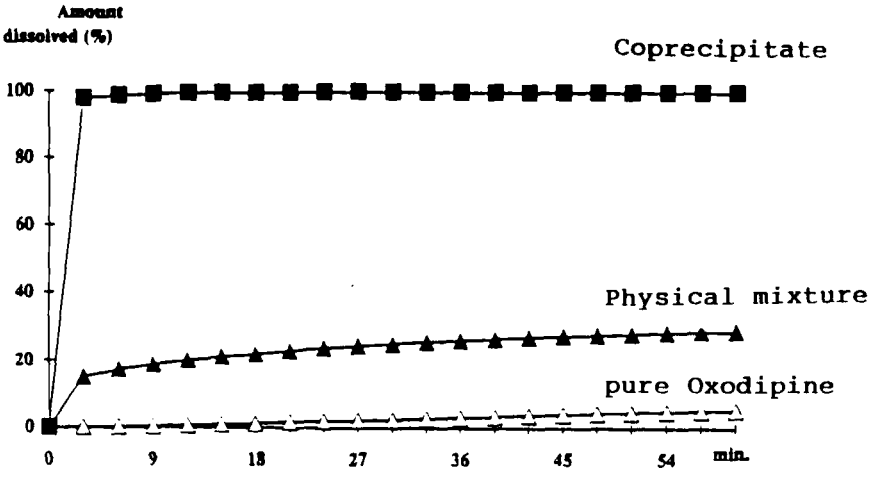

FIGURE 1

Dissolution profils of pure ∝ Oxodipine (A), Physical mixture (B), and Coprecipitate (C).

I.4. RESULTS

Results of dissolution experiments are reported on Table I, and dissolved oxodipine amounts versus time are plotted on Figure 1.

Dissolution curves allow the following remarks :
- pure oxodipine (A) is very slowly dissolved in water at 37°C (5 % only of the total amount of oxodipine introduced in the dissolution medium was dissolved in water after one hour). The reason was the poor wettability of the drug.
- in the case of the physical mixture (B), the dissolution rate of oxodipine is significantly increased, specially in the first part of the curve : 15 per cent of the drug is dissolved in 3 minutes instead of 0.07 per cent for the pure active substance alone. The PVP allows the oxodipine crystals wettability in this initial stage and simultaneously allows the fast dissolution of the smallest crystals. The second part of the curve is approximately parallel to that of the pure active drug.
- in the case of the coprecipitate (C), the oxodipine dissolution rate is strongly increased as regards the simple physical mixture (98 per cent within 3 minutes). This result is due to 3 favorable factors : powder

wettability, coprecipitate physical structure and PVP hydrophily.

From these results, it can be concluded that the physical mixture performs better than pure oxodipine and the coprecipitate yeilds far better performance. Thus, the coprecipitate attains the three objectives previously defined :
- quasi instantaneous oxodipine dissolution
- obtention of a sample (100 mg) compatible with an appropriate solid dosage form (tablet for instance)
- industrial feasibility with the usual precautionary measures concerning industrial work with ethanol.

However, the coprecipitate does not constitute by itself a directly administerable pharmaceutical form and it may suffer various alterations during its preparation process leading to its definitive dosage-form. So, it is important to study the drug behaviour during compression and storage.

Part II - PHYSICAL STUDY OF THE OXODIPINE: PVP COPRECIPITATE

Dissolution results seem demonstrate that the coprecipitate obtained is a solid dispersion. We have tried to prove this assertion by the study of the physical structure of two samples of oxodipine/PVP coprecipitates prepared in the same conditions as described in the first part.

Solid dispersions are frequently unstable systems :
The drug molecules, dispersed in the crystalline network of the support in solid solutions , tend to recrystallize and the microcrystals of eutectic mixtures tend to grow.
Consequently, the dissolution rate of the drug may decrease during the storage or, under stresses, during compression process.
The demonstration of the physical structure of the coprecipitates as a solid dispersion, the observation of the behavior under compression of this solid dispersion, and the study of its stability constitute the subject of Part II.

Note : Usually in the Pharmaceutical Technology it is admitted that a solid solution is the dispersion of isolated molecules of a A substance inside a B substance. It must be noted that as far as the Solid State Chemistry is concerned that expression implies a new phase involving an A/B interaction.

II.1. METHODS

II.1.1. Hot stage microscopy (Mettler FP 82)

Heating rate : 3°C/minute
Start temperature : 50°C
End temperature : 200°C.

II.1.2. Differential scanning calorimetry (Mettler TA 3000)

The lids of aluminium pans were crimped.
The start temperatures were :
. 50°C when the heating rate was 10°C/minute
. 100°C when the heating rate was 1°C/minute
The weight of the samples were : 3 to 5 mg.

II.1.3. Fourier's transform infrared

Nicolet 7199 B (resolution : 4 cm)
The tablets used were prepared by direct compression of 1 mg of the sample powder with KBr.

II.1.4. Powder X Ray diffraction

X Ray diffraction device Siemens fitted with a Guinier de Wolff camera using monochromated CuK radiation, for investigation at room temperature (= 1.54178 A) and a Guinier Lenne Camera on the studies versus temperature.

II.1.5. Compression ability

The ability for compression was estimated by a compression test of a constant weight of the different powder samples, with an instrumented tablet machine.
Experimental conditions were the same as in previous works (2) (3) (4) : constant volume of the compression chamber - same upper punch displacement - constant weight of powder sample : 500 mg - the compression chamber was filled by hand - Relative humidity : 20 % at 20°C.
The maximum displacement "x" of the upper punch in the die, was selected by making several compression experiments on the substances to be tested, in order to obtain the evolution of the hardness, in relation with the force measured on the upper punch.
The selected upper punch displacement "x" was chosen in the rising portion of the curve.
We noticed the maximum forces y and y , measured on the upper and lower punches during compression.
The y /y ratio is indicative of the force transmission through the powder in the die.
The tablet hardness was measured by using a Heberlein Hardness Tester.
The "cohesion index" is indicative of the ability of particles to cohere during the compression process (5).

It is expressed by the ratio of the force necessary for the crushing of the tablet between jaws, to the force measured during compression. For convenience, the adimensional number obtained is multiplied by 10 . The higher the cohesion index is, the better the compressibility is.

II.1.6. Study of the physical stability of the oxodipine solid dispersion

II.1.6.1. Stability under compression

This study was made by observation and comparison of the physical structures of oxodipine solid dispersion before and after compression.
Three levels of compression load determined by three different displacements of upper punch x has been selected.

II.1.6.2. Heat stability

Two heat conditions have been carried out :
- storage at 40°C during 18 months. The stability has been controled by powder X ray diffraction.
- a coprecipitate sample was subjected to a gradient of temperature from 47 to 196°C in the Guinier Lenne Camera. The powder X Ray diffraction sample pattern in relation to the temperature change, was recorded on a film.
The heating rate was : 3.7°C/hour.

II.1.6.3. Stability in different humidity conditions

Two samples of the oxodipine solid dispersion were stored in closed boxes respectively at 55 and 80 % RH (6), for three monthes.

II.1.6.4. Stability over time in normal ambient conditions

The stability of the structure was studied by powder X ray diffraction and DSC after six monthes, one and two years.
After four years, the dissolution rate was controled.

II.2. RESULTS AND DISCUSSION

II.2.1. Crystalline structure of the oxodipine used as raw material

Among the different polymorphic forms of oxodipine, (, ,) the powder X Ray diffraction pattern and the DSC curves allow us to characterize the batch of oxodipine used as being form (figures 2a and 2b).

II.2.2. Study of coprecipitates

Two samples of oxodipine/PVP coprecipitates were prepared : sample A and sample B.

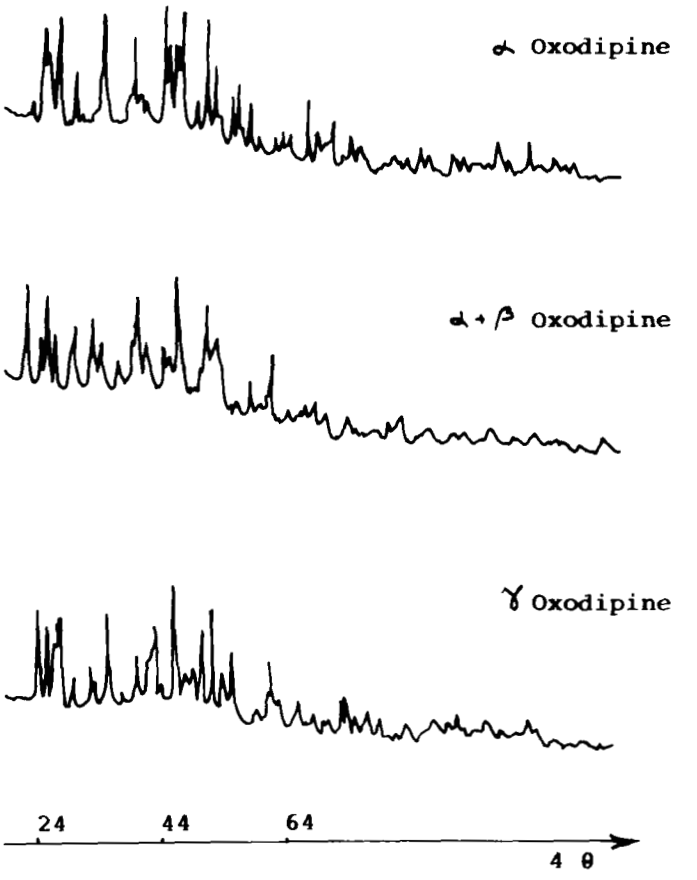

FIGURE 2a

X Ray diffraction patterns of α Oxodipine (A), α + β Oxodipine (B), γ Oxodipine (C).

They have been studied in comparison to the physical mixture having the same composition (oxodipine/PVP = 20/80).

II.2.2.1. Optical microscopy

. oxodipine : large parallelepipedical crystals with fine particles adsorbed on their surface
. PVP : rounded particles
. Physical mixture : it appears as a simple mixture of the two previous substances

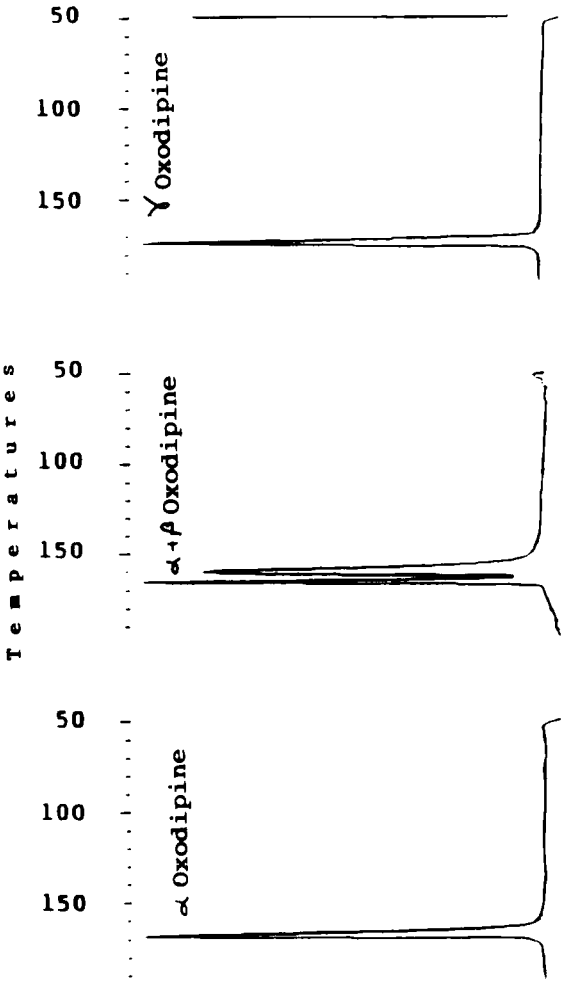

FIGURE 2b

D.S.C. curves of α Oxodipine (A), α +β Oxodipine (B), and γ Oxodipine (C).

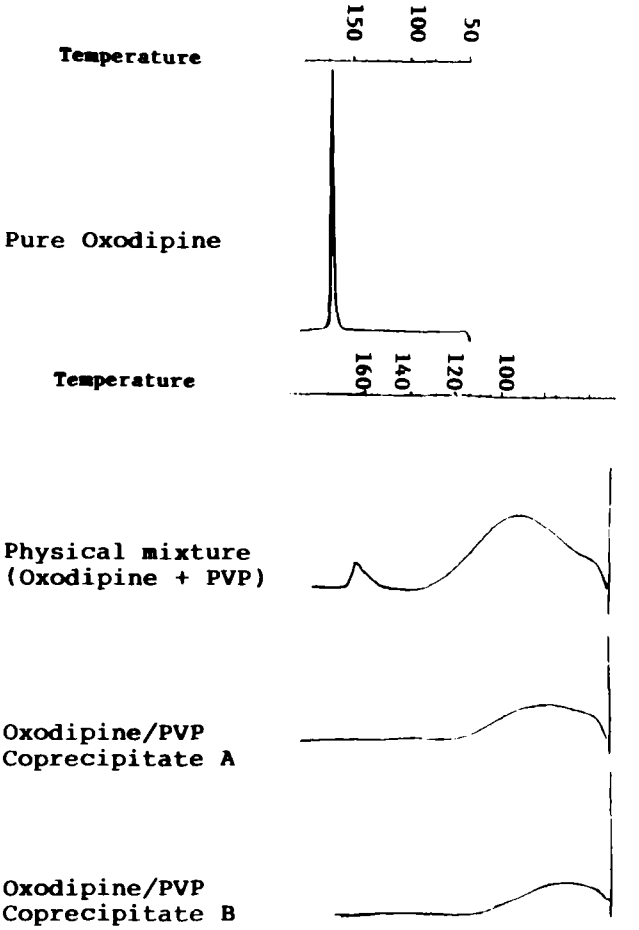

FIGURE 3

D.S.C. curves of pure Oxodipine (A), Physical mixture (B), and Coprecipitate (sample A and B : (C) and (D))

. oxodipine/PVP coprecipitates : particles without a caracteristic external form. The modification brought about by the coprecipitation was evident.

II.2.2.2. Thermomicroscopy

. oxodipine : melting point nearly 166°C
. PVP : no melting is perceptible
. Physical mixture : partial melting between 156-166°C, complete melting nearly 200°C
. oxodipine/PVP coprecipitates : very progressive softening calling to mind the behaviour of a vitrous substance

II.2.2.3. Differential scanning calorimetry

The DSC curves are reported in figure 3.
The different observations are displayed in table II.

As can be seen the sharp endothermic melting peak of the oxodipine is still perceptible in the DSC curve of the physical mixture sample.
In contrast in the DSC curves of the two coprecipitate samples show no peak.
The hygroscopicity of PVP is obvious. A large broad endotherm corresponding to the water escape is observed between 55 and 120°C.

II.2.2.4. Infrared spectrometry

The infrared spectra are reported in figure 4.
We can see that the spectrum of the physical mixture is the addition of the spectrum of oxodipine and those of PVP, when the oxodipine spectrum disappears in the spectra of the two oxodipine/PVP coprecipitates.

II.2.2.5. Powder X Ray diffraction

X Ray diffraction patterns are represented in figure 5.
We can clearly distinguish on the X Ray diffraction pattern of the physical mixture the main reflections of the oxodipine. On the contrary, the X ray diffraction pattern of the two coprecipitates are flat, similarly to the X ray diffraction pattern of PVP, the amorphous character of which is well known.
Powder X ray diffraction allows us to detect, as we have demonstrated :
- clearly 5 % of crystallized oxodipine
- with difficulty, 2 % of crystallized oxodipine.

The absence of reflections on the X ray diffraction pattern of the two coprecipitates allows us conclude that, at least, 90 % of the oxodipine is in amorphous form.
As a first conclusion, it seems that the two coprecipitates of oxodipine/PVP are solid dispersions, probably solid solutions.

TABLE II

D.S.C. Curves comments on the different samples of raw materials Physical mixture and coprecipitates A et B.

Heating rate	10°C/ minute			1°C/minute
Start temperature		50°C		100°C
		Melting temperature	ΔH(J/g)	Melting temperature
α Oxodipine	- one sharp endotherm (melting)	166.7°C	99.4	165.9°C
PVP	- one large broad endotherm between 60-120°C (water escape)			no endotherm after 100°C
Physical mixture	Two endotherms : - 1. a broad large endotherm between 60-150°C (water escape)			
	- 2. a small sharp peak at 164.9°C (melting)	164.9°C	15.9	159.6°C
Coprecipitates A and B	- one large broad endotherm between 55-120°C (water escape)			no endotherm after 100°C

II.2.2.6. Compression ability of the coprecipitates

Results are displayed in table III.

As we can see, the two coprecipitates show very good compression ability :

- a transmission force ratio y/y , verging on 1
- a cohesion index > 1000 which is a very good result.

There by, it seems that the coprecipitates are perfectly able to give tablets.

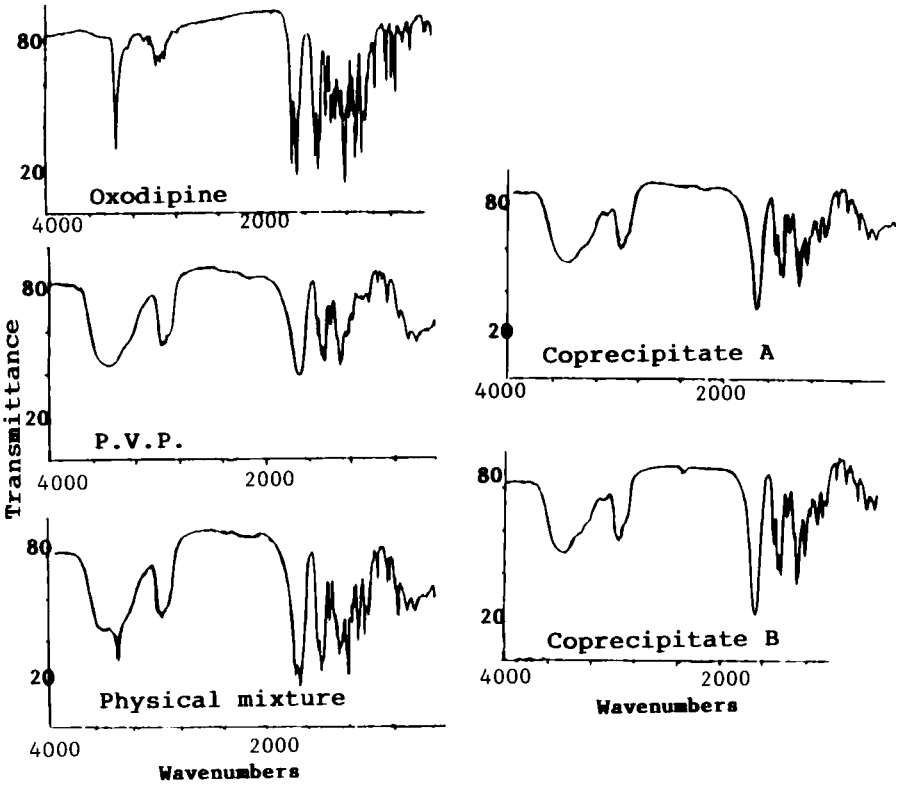

FIGURE 4

Infrared spectra of Oxodipine (A), P.V.P. (B), Physical mixture (C) and the two samples of coprecipitates (D) and (E)

II.2.2.7. Stability of the oxodipine/PVP coprecipitates

The stability studied by powder X ray diffraction and by DSC, has shown that no modifications take place whatever the compression load is.

In a similar way, no recrystallization appears neither after 18 monthes at 40°C, nor during a slow heating from 47°C to 196°C.

Likewise, a storage in ambient conditions for two years does not modify the physical structure of the two oxodipine/PVP dispersion samples.

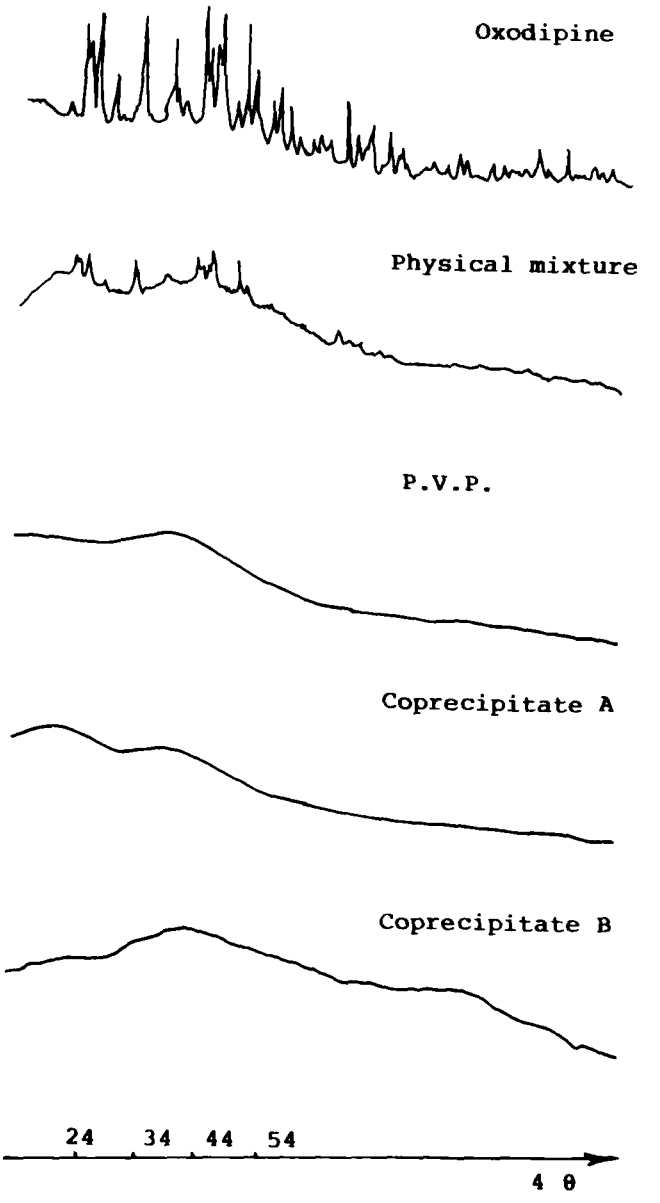

FIGURE 5

X Ray diffraction patterns of Oxodipine (A), Physical mixture (B), P.V.P. (C), and Coprecipitates (D) and (E).

TABLE III

Results of the measurments during compression of the two coprecipitates samples

x = upper punch displacement
y_1 = force measured at the level of upper punch
y_2 = force measured at the level of lower punch
Cohesion index = Hardness/y_1 x 10^5

Sample	x (mm/100)	Y_1 (N)	Y_2 (N)	Hardness (N)	Cohesion Index	Y_2/Y_1
A	773	18 900	17 240	382	1894	0.91
	714	6 970	6 130	140	2040	0.88
	693	5 030	4 390	100	1862	0.87
B	771	18 210	16 580	280	1590	0.91
	717	6 740	5 980	100	1473	0.89
	696	5 010	4 390	65	1302	0.87

On the other hand, humidity is a clear factor of unstability.
After three monthes at 80 % of relative humidity, the two coprecipitate samples become sticky, yellow, and their X ray diffraction pattern show a complete recrystallization of the oxodipine contained.
In the samples stored at 55 % R.H. no recrystallization is brought to evidence, but a slight yellow colouration is observed.
DSC shows a very thick endotherm corresponding to water escape in all the tested samples.

CONCLUSION

" oxodipine solid dispersions" can be prepared in PVP. These solid dispersions allow a very much faster dissolution. This fact induce to think of a better biodisponibility of this drug.
This study shows that the coprecipitates present a good compression ability permiting a tablet formulation.
On the other hand, these solid dispersions are quite stable through the storage time but not in presence of a high relative humidity. It will be easy to prevent this disadvantage by working in controled relative humidity and by an appropriate packaging.

ACKNOWLEDGEMENTS

The authors would like to thank very much Pr. Bouché (University of Louvain), Pr. Huvenne and Pr. Guyot (University of Lille) for their wellcome advices, Nathalie Duhal for her nice assistance for infrared spectra, and Madame Grimmelpont for her very kind help for the translation into english.

REFERENCES

1. W.L. Chiou and S. Riegelman, J. Pharm. Sci., **60**, 9, 1281-1302 (1971).
2. C. Lefebvre, A.M. Guyot-Hermann, M. Draguet-Brughmans, R. Bouché, J.C. Guyot, Drug. Dev. and Industrial Pharmacy, **12**, 11-13, 1913-1927 (1986).
3. B. Debord, C. Lefebvre, A.M. Guyot-Hermann, J. Hubert, R. Bouché, J.C. Guyot, Drug. Dev. and Industrial Pharmacy, **13**, 9-11, 1533-1546 (1987).
4. C. Lefebvre, A.M. Guyot-Hermann, J.C. Guyot, R. Bouché, J. Ringard, 8th Pharm. Technol. Conf., Monte Carlo, avril 1989.
5. J.C. Guyot, A. Delacourte, P. Leterme, P. Billardou, STP Pharma, **5**, 168-175 (1989).
6. ISO ref. n° ISO/R 483-1966 (F) Avril 1966.