ELSEVIER

International Journal of Pharmaceutics 106 (1994) 109–114

international journal of pharmaceutics

Lyoavailability of nordazepam solid dispersions in relation with phase diagrams

A. El Moussaoui [a], A. Chauvet [a,*], J. Masse [a], D. Gaudy [b], A. Puech [b]

[a] *Laboratoire de Chimie Générale et Minérale,* [b] *Laboratoire de Pharmacie Galénique, Pharmacotechnie et Biopharmacie, Faculté de Pharmacie, 15, avenue Charles Flahault, 34060 Montpellier Cedex 1, France*

(Received 8 June 1993; Modified version received 1 November 1993; Accepted 11 November 1993)

Abstract

We have prepared solid dispersions (melt, coprecipitate) of nordazepam III (NDZ) with carriers polyoxyethylene glycol (PEG 6000), succinic acid, and with another drug, nicotinic acid, corresponding to the eutectic composition. From a study of the dissolution kinetics, we found that the highest value is obtained for the PEG 6000 melt. We have shown that there is a good correlation between PEG solid dispersion dissolution kinetics and mixing enthalpies.

Key words: Nordazepam; Solid dispersion; Lyoavailability

1. Introduction

The aim of this research work was to optimize the lyoavailability of practically water insoluble benzodiazepines. The dissolution rates of poorly soluble drugs may be enhanced via solid dispersions into water soluble polymers (Chiou and Riegelman 1971). Polyethylene glycols (PEG) are used extensively as carriers for dispersions due to their low melting points.

The PEG/drug phase diagram can be used to determine the eutectic composition at which melting occurs at a much lower temperature than that of PEG (58–63°C) according to the molecular weight of the compounds; this low melting temperature offers advantages in terms of drug stability and ease of manufacture.

After constructing the phase diagrams of nordazepam (NDZ)/polyoxyethylene glycol 6000, nordazepam/succinic acid, and nordazepam/nicotinic acid, we prepared solid dispersions from the eutectic physical mixture by the fusion and coprecipitation methods.

The eutectic composition gives smaller particles and hence improves the dissolution kinetics. We have also proved, through the study of thermodynamic relationships to evaluate the mixing enthalpy, that there is a carrier-active substance interrelationship (Chauvet et al., 1992; El Moussaoui et al., 1993a,b).

Thermodynamics were applied to the melt, the coprecipitate, and the physical mixture that were eutectic compositions. The dissolution kinetic re-

* Corresponding author.

SSDI 0378-5173(93)E0350-Y

sults were compared with those of the thermoanalytical data.

2. Materials and methods

2.1. Reagents and materials

Nordazepam (Bouchara Laboratory; drug lot 6186) ($C_{15}H_{11}ClN_2O$, 7-chloro 5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine 2-one; molecular weight 270.72) is a white crystalline powder soluble in organic solvents, and practically insoluble in water. We have used the commercial sample (form III) (Chauvet et al., 1992).

PEG 6000 (Merck Schuchardt art. 807491 lot 7239412) has a molecular weight between 6000 and 7500; its melting temperature can vary from 60 to 63°C according to the degree of purity.

Nicotinic acid (Carlo Erba RPE code 411205 lot 0587B 100) ($C_6H_5NO_2$; molecular weight 123.1) is a white crystalline powder (pure grade).

Succinic acid (Sigma Chemical Co. lot 114F-0144 no. N-4126) ($C_4H_6O_4$; molecular weight 118.09) is also a white crystalline powder (pure grade).

Thermal analysis of nordazepam, polyoxyethylene glycol 6000, succinic acid and nicotinic acid has been described in previous works (Chauvet et al., 1992); El Moussaoui et al., 1993a,b).

The physical mixtures (w/w) were prepared in an agate mortar. The eutectic composition consisted of nordazepam 4% and PEG 6000 96%. As for the eutectic composition with succinic acid and nicotinic acid the molar fraction of nordazepam was 0.32 and 0.57, respectively.

The melt was obtained by melting the eutectic composition in an oil bath heated at 65°C on an electric heater. The preparation was then poured onto a porcelain plate and after solidification the product was ground. The succinic and nicotinic acid compositions were melted in sealed tubes. Recrystallisation was carried out at 20°C for 1 week.

The coprecipitate was prepared by dissolving the eutectic physical mixture in a very small quantity of solvent (chloroform), which was subsequently eliminated by evaporation, using a Rotavapor. The product obtained was ground and kept under vacuum in a drying cabinet.

2.2. DSC

Thermal analyses were carried out with a Mettler FP 800 differential scanning calorimeter (DSC) equipped with an Epson HX 20 computer to evaluate transition temperatures and enthalpies. Samples (3–5 mg) for DSC analyses were heated at 5 or 20°C/min under a nitrogen stream. Sensitivity was chosen according to the quantity of heat absorbed or emitted by the sample.

To calculate the melting enthalpy, we calibrated the calorimeter with indium as standard reference.

2.3. Dissolution studies

Assays were carried out using a Perkin Elmer lambda 15 double-beam spectrophotometer set for maximum absorbance at 230 nm. Quartz flow cells were used.

The dissolution rate was measured on the Erweka DT 6R described in the French Pharmacopeia Ed. X. Automatic sampling and absorbance measurements were carried out using filter-fitted teflon tubing. The reaction medium (water 500 ml at 37°C) was placed in six round-bottomed flasks. A six-fold line transports the liquid to six continuous-circulation containers. The pump was placed on a sample conveyor at the same height as the spectrophotometer. The reaction medium was than recycled in the six reactors (Gaudy et al., 1989).

After determining the directive factor of the nordazepam calibration curve in water $y = 3.643x + 0.0009$ (y being the concentration, and x the absorbance) and after determining the correlation coefficient R equal to 0.9992 we began the kinetic study; maximum absorption was at 230 nm.

To compare the results, we evaluated, for each sample, the efficiency parameter described by Khan (1975). This parameter is defined as the ratio of the area under the dissolution curve at

Table 1
Melting enthalpies (kJ mol^{-1}) of NDZ III-PEG 6000: (a) initial, (b) crystallised in chloroform, (c) melt; eutectic composition melting and mixing enthalpies of physical mixture, coprecipitate and melt

ΔH_f (NDZ III)	ΔH_f (PEG 6000)		ΔH_f (eutectic)	ΔH_m (mixing)
27.40 ± 0.58	(a) 1 166.4 ± 29.0	physical mixture	505.9 ± 13.1	−113.4
27.40 ± 0.58	(b) 1 056.4 ± 22.3	coprecipitate	437.4 ± 14.8	−136.6
27.40 ± 0.58	(c) 1 128.6 ± 26.8	melt	408.4 ± 14.6	−202.4

time t to that of the rectangle that represents 100% of dissolution at the same time (AR_t).

The efficiency ED% depends on the interval of time chosen and on the drug concentration.

This calculation improves reading of the dissolution profiles by providing one value, the plot integral.

3. Results and discussion

The melting enthalpies of the eutectic composition of the different forms of solid dispersions were determined.

The melting enthalpies for nordazepam-PEG 6000 (4% NDZ and 96% PEG 6000) are listed in Table 1, for nordazepam-succinic acid in Table 2, and for nordazepam-nicotinic acid in Table 3.

Having determined the theoretical melting enthalpies, ΔH_f, of the eutectic composition (Chauvet et al., 1992; El Moussaoui et al., 1993a,b) we then evaluated the mixing enthalpies (Rastogi et al., 1981; Rai et al., 1989); the mixing enthalpy is the difference between the experimental and theoretical eutectic enthalpies.

Table 1 shows that the PEG 6000 mixing enthalpies decreased in the order: melt, coprecipitate, physical mixture. For succinic acid and nicotinic acid this order would be: physical mixture, melt coprecipitate.

For PEG 6000, the melt has the highest mixing enthalpy (Chauvet et al., 1992; El Moussaoui et al., 1993a,b); the mobility of benzodiazepine would therefore be more enhanced in the PEG 6000 melt then in the coprecipitate.

These results suggest that the melt has more favourable dissolution kinetics than the coprecipitate. In the case of succinic acid or nicotinic acid, it appears to be the physical mixture that displays the best dissolution kinetics.

Results of the study of in vitro dissolution kinetics for the different mixtures (corresponding to the eutectic compositions of the different binaries) are expressed as percentages at time t (min) (Fig. 1–3).

In each case, the dissolution kinetics are greatly enhanced with time in comparison with nordazepam alone.

The most important enhancement was provided by the PEG 6000 melt; in 1 h, 92.78% of nordazepam dissolved in comparison with 7.38% for nordazepam alone.

The results in Fig. 1 show relatively rapid dissolution kinetics for the melt when compared

Table 2
Melting enthalpies (kJ mol^{-1}) of NDZ III-succinic acid: (a) initial, (b) crystallised in chloroform, (c) melt: eutectic composition melting and mixing enthalpies of physical mixture, coprecipitate and melt

ΔH_f (NDZ III)	ΔH_f (succinic acid)		ΔH_f (eutectic)	ΔH_m (mixing)
27.40 ± 0.58	(a) 31.6 ± 0.9	physical mixture	15.4 ± 0.4	−14.7
27.40 ± 0.58	(b) 31.2 ± 0.8	coprecipitate	20.9 ± 0.5	−9.0
27.40 ± 0.58	(c) 24.2 ± 0.7	melt	15.9 ± 0.4	−9.2

Table 3
Melting enthalpies (kJ mol^{-1}) of NDZ III-nicotinic acid: (a) initial, (b) crystallised in chloroform, (c) melt: eutectic composition melting and mixing enthalpies of physical mixture, coprecipitate and melt

ΔH_f (NDZ III)	ΔH_f (nicotinic acid)		ΔH_f (eutectic)	ΔH_m (mixing)
27.40 ± 0.58	(a) 20.8 ± 0.6	physical mixture	19.9 ± 0.5	−4.7
27.40 ± 0.58	(b) 19.1 ± 0.5	coprecipitate	22.6 ± 0.7	−1.0
27.40 ± 0.58	(c) 20.4 ± 0.6	melt	23.0 ± 0.5	−1.2

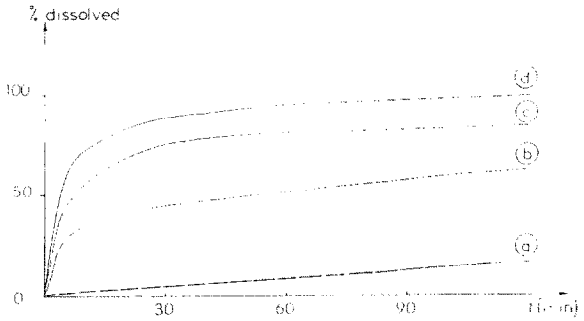

Fig. 1. Percentage of dissolved nordazepam as a function of time for: (a) commercial sample; (b) physical mixture PEG 6000-nordazepam; (c) coprecipitate PEG 6000-nordazepam; (d) melt PEG 6000-nordazepam.

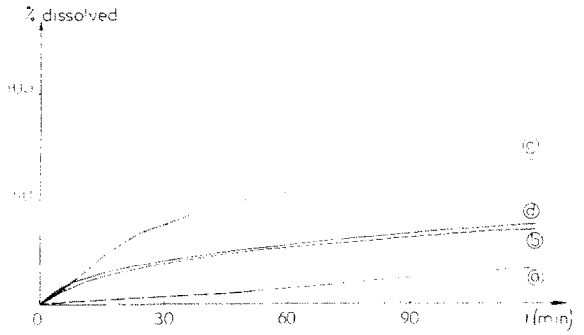

Fig. 2. Percentage of dissolved nordazepam as a function of time for: (a) commercial sample; (b) physical mixture succinic acid-nordazepam; (c) coprecipitate succinic acid-nordazepam; (d) melt succinic acid-nordazepam.

with the coprecipitate and the physical mixture, in agreement with existing theory on mixing enthalpy values.

Fig. 2 and 3 show that the coprecipitate had higher dissolution kinetics than the melt and the physical mixture of nordazepam-succinic acid and nordazepam-nicotinic acid. For these physical mixtures, the mixing enthalpies were very weak and did not correlate with the results on dissolution kinetics.

Table 4
Statistical analysis of dissolution efficiency

	Variance analysis							
	S.S.D.	FD	Mean squares	*F* test	Sign.	S.D.	V.C.	
Total Var	33445.69	59	566.88					
Factor 1 Var	33246.32	9	3694.04	926.44	0.0000			
Residual 1 Var	199.37	50	3.99			2.00	6.5%	
	Newman-Keuls test: level of significance 5%							
Means number:	2	3	4	5	6	7	8	9	10
LSA values:	2.32	2.78	3.06	3.26	3.42	3.54	3.65	3.74	3.82

Products (eutectic composition NDZ/carrier)	DE% (±SD)	Homogeneous groups
Melt PEG 6000	80.25 ± 2.79	A
Coprecipitate PEG 6000	63.35 ± 3.52	B
Physical mixture PEG 6000	40.26 ± 1.84	C
Coprecipitate succinic acid	35.59 ± 1.78	D
Coprecipitate nicotinic acid	25.38 ± 3.20	E
Melt succinic acid	20.34 ± 1.66	F
Physical mixture succinic acid	18.95 ± 2.67	F
Melt nicotinic acid	14.08 ± 1.05	G
Physical mixture nicotinic acid	7.03 ± 0.85	H
Nordazepam	2.51 ± 0.75	I

DE, dissolution efficiency; SSD, sum of squares of deviations; F.D., freedom degree; Sign, significance; S.D., standard deviations; V.C., variation (Var) coefficient; LSA, least significant amplitudes. Confidence interval at level of significance: 5%

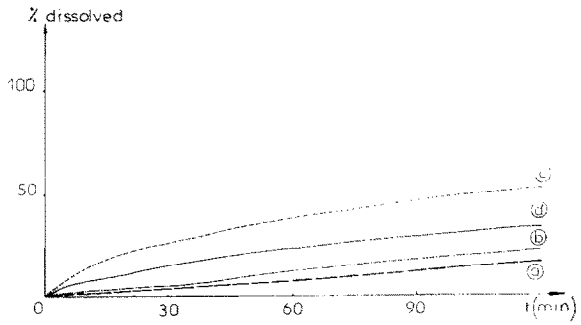

Fig. 3. Percentage of dissolved nordazepam as a function of time for: (a) commercial sample; (b) physical mixture nicotinic acid-nordazepam; (c) coprecipitate nicotinic acid-nordazepam; (d) melt nicotinic acid-nordazepam.

By fixing the time interval we can compare the quantity of drug dissolved under the same experimental conditions.

$$DE\% = \frac{AUC_t}{AR_t} \times 100$$

where DE is the dissolution efficiency (AUC_t, area under the curve; AR_t, area of the rectangle).

In this work we took the value of AR_t as 60 min. Table 4 lists the average of six assays and gives details of the variance analysis of the results.

The 10 products displayed significant differences for a probability $\ll 0.001$. We used the Newman and Keuls test (Gouet and Philippeau, 1986) at a threshold probability of 5% to classify the nine eutectic compositions and to compare them with the drug alone.

The results given in Table 4 show that we have different homogeneous groups with the exception of the melt and physical mixture of nordazepam-succinic acid.

Therefore, each of the PEG-nordazepam mixtures provides better lyoavailability than the other binary mixtures, in the following descending order; melt, coprecipitate, physical mixture. Our results comply with those previously obtained for PEG 4000 and 6000 (Itai et al., 1986). The improved solubility is a result of the presence of hydroxyl groups and of greater dispersion of the drug in the carrier.

For the other binary mixtures studied the solubility decreases in the order: coprecipitate, melt, physical mixture. The succinic-nordazepam eutectic compositions display greater solubilities (Table 4) than the nicotinic-nordazepam eutectic compositions.

We have proved that both the method of preparing solid dispersions and the carrier nature influence the dissolution kinetics.

4. Conclusion

Solid dispersions increase the dissolution kinetics of nordazepam; the carrier type is very important in this effect.

The results provided by succinic and nicotinic acids appear to be less interesting than those provided by PEG 6000.

The mixing enthalpies determined agree with those of the dissolution kinetics for PEG 6000.

Consequently, the lyoavailability of nordazepam is greatly enhanced by the use of PEG 6000, which has a hydrophilic environment.

These results should be of interest in pharmaceutical technology.

5. References

Chauvet, A., El Moussaoui, A. and Masse, J., Etude thermoanalytique et spectrale de benzodiazépines: 2. Nordazépam. *Thermochim. Acta*, 210 (1992) 133–145.

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

El Moussaoui, A., Chauvet, A. and Masse, J., Etude des interactions à l'état solide du nordazépam III-polyéthylène glycol 6000 et nordazepam III-acide succinique. *J. Thermal. Anal.*, 39 (1993a) 373–392.

El Moussaoui, A., Chauvet, A. and Masse, J., Etude des interactions a l'état solide du nordazépam III-acide nicotinique. *J. Thermal. Anal.*, 39 (1993b) 619–632.

Gaudy, D., De Albuquerque, M.M., Baylac, G., Puech, A. and Jacob, M., Automatisation de la mesure de lyodisponibilité des formes orales à libération ralentie. *STP Pharm.*, 5 (1989) 750–755.

Gouet, J.P. and Philippeau, G., Comment interpréter les résultats d'une analyse de variance? Editeur du livre "Institut technique des céréales et fourrages Service des études statistiques, Boigneville, 91720 Maisse, 1986, p. 39.

Itai, S., Masami, N., Shozo, K., Hiroshi, M. and Suneji, N.T., Approach to determine the generation rate of available surface area during the dissolution: IV. Kinetic dissolution profile in relation to available surface area process. *Chem. Pharm. Bull.*, 3 (1986) 1280–1288.

Khan, K.A., The concept of dissolution efficiency. *J. Pharm. Pharmacol.*, 27 (1975) 48–49.

Rai, U.S., Mandal, K.D. and Singh, N.P., Thermoanalytical studies on organic eutectics and molecular complexes. *J. Thermal Anal.*, 35 (1989) 1687–1697.

Rastogi, R.P., Singh, N.B. and Dwivedi, K.D., Solidification behaviour of addition compounds and eutectics of pure components and addition compounds. *Ber. Bunsenges Phys. Chem.*, 85 (1981) 85–92.