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Enhanced release of oxazepam from tablets containing solid dispersions

Renata Jachowicz [a,*], Eberhard Nürnberg [b]

[a] *Department of Pharmaceutical Technology and Biopharmaceutics, Collegium Medicum Jagiellonian University, Kraków, Poland*
[b] *Department of Pharmaceutical Technology, Friedrich–Alexander University, Erlangen–Nürnberg, Germany*

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Abstract

Solid dispersions of different ratios of Gelita collagel as the carrier and lactose were prepared by the spray drying method. Dissolution studies have shown that by preparing solid dispersions the dissolution rate and the solubility of oxazepam increase markedly, independent of the ratio of drug, carrier and lactose. The properties of the solid dispersions were characterized by X-ray diffraction and polarizing microscopic studies. An amorphous form of all prepared solid dispersions were indicated in X-ray studies. Tablets of solid dispersions of oxazepam/Gelita Collagel, physical mixtures and the drug alone were prepared. The best results from the dissolution test were obtained for tablets containing solid dispersions. They remained in good physical properties when stored for one year in normal conditions. © 1997 Elsevier Science B.V.

Keywords: Oxazepam; Gelita collagel; Solid dispersion; Tablets; Dissolution

1. Introduction

The use of solid dispersions to increase the dissolution rate and the bioavailability of poorly water-soluble drug is now well established (Alonso et al., 1983; Stavchansky and Gowan, 1984; Yakou et al., 1984). An important influence on the properties of such solid dispersions is the method of preparation and the type of the carrier used (Arias et al., 1995; Kai et al., 1996; Nyström and Sjökvist, 1996; Otseika et al., 1996; Torrado et al., 1996). Good results were obtained for solid dispersions of benzodiazepines derivatives in polyoxyethylene glycol (Geneidi and Hamacher, 1980; Gines et al., 1996; Kinget and Kemel, 1985; Jachowicz, 1994), polyvinylpyrolidone (Traue, 1989), Gelita collagel (Jachowicz et al., 1993; Jachowicz, 1995). The possibilities for the preparation of oxazepam—Gelita collagel solid

* Corresponding author. Tel.: +48 12 570565; fax: +48 12 570262.

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dispersions (1 + 9) were described (Jachowicz et al., 1993). Gelita collagel (mol. wt. 18 300)—an enzymatically produced collagen hydrolysate, in a form of a spray-dried powder is a water soluble substance, widely used as a pharmaceutical adjuvant, particularly in tablet formulations (Nürnberg and Schenk, 1988).

The aim of the present study was, firstly, the achievement of a good form of solid dispersion of oxazepam with Gelita Collagel for use in a tableting process, secondly the formulation of tablets with oxazepam/Gellita Collagel prepared according to the own prescription. The properties of solid dispersions of oxazepam at different ratios Gelita Collagel, the properties of the tablets and the dissolution rate profiles of oxazepam from the tablets are presented.

2. Experimental

2.1. Materials

The material used were as follows: oxazepam (Pharmaceutical works, Tarchomin Polfa), Gellita Collagel (KLH) (Deutsche Gelatine Fabriken Stoes, Eberbach), Aerosil 200 (Degussa, Frankfurt am Main), Kollidon-Cl (PVP-Cl) (BASF, Ludwigshafen), lactose EP D30 (Meggle, Wasserburg), magnesium stearate (Merck, Darmstadt).

2.2. Procedure

The test samples, the solid dispersions and the physical mixtures, were prepared in the same w/w ratio of 1 + 9, 1 + 8 drug to carrier and 1 + 1 + 8, 1 + 2 + 7, 1 + 4 + 5 drug, carrier, lactose.

2.3. The preparation of solid dispersions and physical mixtures

A spray-drying method was used. Oxazepam was dissolved in ethanol 95°; carrier and lactose were dissolved in water. These solutions were mixed in a ratio that resulted in a 70° ethanolic solution. The samples solution were spray-dried using a Büchi 190 mini spray-dryer apparatus. The temperature inlet was at 134°C, the outlet at 77°C.

For the physical mixtures appropriate amounts of oxazepam, Gelita Collagel and lactose were mixed in a mortar and then powdered and sieved.

2.4. Tablets manufacture

Three kinds of tablets were prepared: formulation A containing drug alone, formulation B containing a physical mixture of the components, formulation C containing a solid dispersion of the components. In the preparation of the tablets of formulation C, a solid dispersion containing oxazepam, Gelita Collagel and lactose are used. In a previous article the properties of solid dispersions were described (Jachowicz, 1995). The spray-drying method applied to oxazepam with Gelita Collagel gave solid dispersions of high electrostatic properties, making tableting process impossible. To overcome this problem, lactose was added during the formulation of the solid dispersion.

The composition of the solid dispersion	
Oxazepam	1.0
KLH	1.0
Lactose	8.0

To obtain a tablet mass with a good properties, a briquettes of the solid dispersion and excipients were prepared.

The composition of briquette (I)	
Solid dispersion	10.0
Vivacel	2.5
Aerosil 200	0.2

The components were mixed and the briquette pressed in a tableting machine (Fette Hanseaten Exacta 1). The briquette were disintegrated and sieved (0.8).

Vivacel and Aerosil were used additionally as excipients for tableting. Other excipients were the following: PVP–Cl, magnesium stearate, lactose

Table 1
Physical parameters of formulated tablets: A (oxazepam), B (physical mixture), C (solid dispersion)

Formulation	Disintegration time		Weight (g)	Friability (%)	Hardness (N)
	Freshly prepared (min)	After 1 year storage (min)			
A	3.8	4.0	0.192 ± 0.010	0.8	78
B	3.5	3.5	0.210 ± 0.018	0.6	73
C	2.6	2.8	0.205 ± 0.010	0.5	65

(II). Mixtures of granulates and excipients were homogenized and the tablets (diameter 8 mm, thickness 3 mm) pressed. The compaction force was 0.6 kN.

The composition of formulation B and C for 100 tablets was as follows:

I.	
Oxazepam	1.0
KLH	1.0
Lactose	8.0
Vivacel	2.5
Aerosil 200	0.2
II.	
Vivacel	1.5
Aerosil 200	0.2
PVP-Cl	0.8
Magnesium stearate	0.2
Lactose	4.6

2.5. Tablet properties

Disintegration times were determined by USP XXIII method using an Erweka tablet disintegration apparatus. Friability was determined in a Roche frabilator rotating 25 cycles/min. The loss is expressed as a percentage of the initial weight. Crushing strength were measured with Erweka TBH 28 apparatus. The recorded values are the mean of six tablets for disintegration time, 25 for the friability, ten for crushing strength (Table 1).

2.6. Dissolution studies

The dissolution studies of oxazepam from powdered samples were determined using the paddle method. Apparatus No. 2 for dissolution testing under USP XXIII was applied (Jachowicz et al., 1993). The amount of dissolved drug after 4 h from different solid dispersions and physical mixtures are presented in Table 2. The concentrations of oxazepam as the percent dissolved from tablets vs time are presented in Fig. 1.

The results obtained for solid dispersions and tablets freshly prepared and after storage are presented in Tables 3 and 4. All experiments were carried out in triplicate.

Table 2
Amount of oxazepam (%) dissolved after 4 h from physical mixtures (Ph.M.) and solid dispersions (S.D.)

Samples		Amount of oxazepam (%)
Oxazepam		5.00
1+1+8	Ph.M.	11.00
	S.D.	28.50
1+2+7	Ph.M.	11.50
	S.D.	28.30
1+4+5	Ph.M.	12.15
	S.D.	28.62
1+9	Ph.M.	13.14
	S.D.	29.10
2+8	Ph.M.	12.86
	S.D.	27.80

Table 3
Amount of oxazepam (%) dissolved from physical mixture and solid dispersion (1+1+8)

Time (h)	Oxazepam			Physical Mixture			Solid dispersion		
	Freshly prepared	After 1 year storage	Δ[a]	Freshly prepared	After 1 year storage	Δ[a]	Freshly prepared	After 1 year storage	Δ[a]
0.33	—	—	—	—	—	—	15.40	14.70	4.5
0.5	0.81	0.70	13.5	2.50	2.25	10.0	22.45	21.60	3.8
1.0	2.25	1.80	20.0	5.90	5.42	8.1	26.50	25.80	2.6
1.5	3.05	2.50	18.0	7.95	7.30	8.2	27.30	26.10	4.4
2.0	3.20	3.00	6.2	8.40	8.00	4.8	28.00	26.80	4.3
2.5	4.00	3.80	5.0	9.60	8.50	11.4	28.20	27.05	4.1
3.0	4.42	4.20	5.0	10.50	9.12	13.1	28.30	27.40	3.2
3.5	4.70	4.40	6.4	10.70	9.60	10.2	28.40	28.00	1.40
4.0	5.00	4.70	6.0	11.00	10.20	7.3	28.50	28.20	1.05
Average			10.0			9.1			3.3

[a] Decreasing (%) of dissolved drug after storage

Table 4
Oxazepam release in % from different tablet formulations: A (oxazepam), B (physical mixture), C (solid dispersion)

Time (h)	A		B		C	
	Freshly prepared (%)	After 1 year storage (%)	Freshly prepared (%)	After 1 year storage (%)	Freshly prepared (%)	After 1 year storage (%)
0.16	—	—	—	—	6.70	5.50
0.33	—	—	—	—	11.20	10.50
0.5	0.75	0.50	1.50	1.10	20.10	19.30
1.0	1.80	1.50	4.0	3.20	24.00	22.80
1.5	2.60	1.90	6.20	5.10	26.00	25.10
2.0	2.90	2.75	7.10	6.20	26.30	25.50
2.5	3.80	3.50	8.00	6.90	26.60	26.10
3.0	4.10	3.60	8.30	7.80	26.90	26.40
3.5	4.20	3.76	8.90	8.40	27.10	26.70
4.0	4.40	3.90	9.50	8.60	27.50	26.90

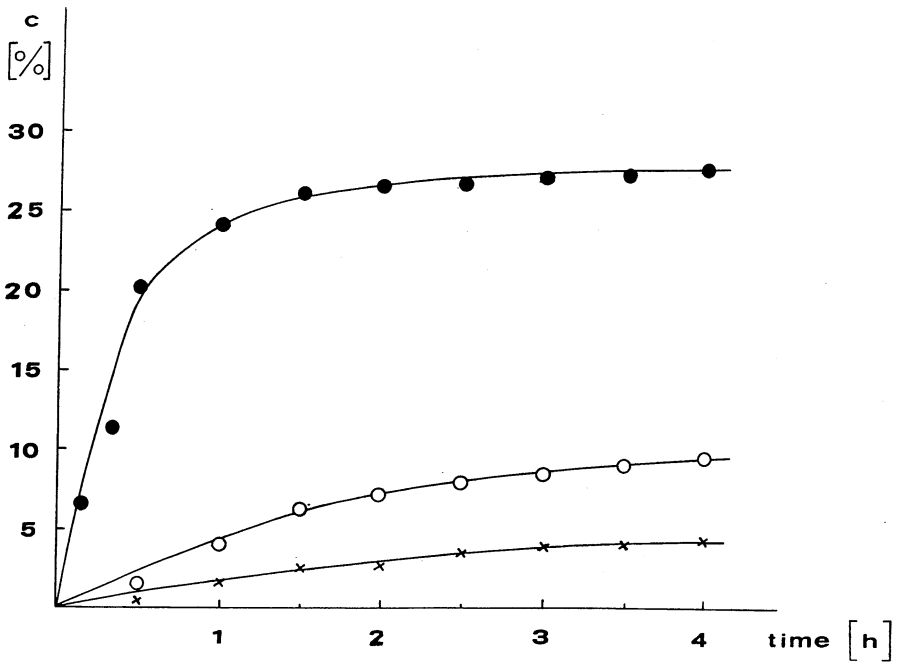

Fig. 1. Dissolution profiles of oxazepam from tablets: – • – solid dispersion, – ◦ – physical mixture, – × – oxazepam.

2.7. Solubility studies

An excess of oxazepam was placed in a tube containing 15 ml of water. The content of each tube was equilibrated by shaking for 24 h at 37°C in a thermostatically controlled water bath. The suspensions were then filtered and the filtrate was analyzed for the dissolved drug (Table 5).

2.8. Assay procedure

Oxazepam was assayed spectrophotometrically in a Unicam SP-500 spectrophotometer at $\lambda =$ 236 nm.

2.9. X-ray diffraction studies

Powder X-ray diffractometry was carried out with a Philips Röentgen powder diffractometer using monochromatic Cu-K_α radiation—$\lambda =$ 1.548 Å (Figs. 2 and 3).

2.10. Microscopy studies

The studies were carried out using a polarizing microscope Olympus IMT 2 (Fig. 4).

3. Results

The results of the studies showed that the dissolution rate of oxazepam increased markedly when present in solid dispersions in comparing to the physical mixtures and the pure drug. There were no large differences between five types of solid dispersions. The amount of dissolved oxazepam after 4 h dissolution were similar, in the range 27.8–29.1% (Table 2) The data show that the amount of the carriers has no influence on the dissolving of the drug in both: oxazepam–carrier and oxazepam–carrier–lactose systems.

The spray-drying method gave solid dispersions (1 + 9, 1 + 8) of high electrostatic properties, which in tableting process is disadvantageous. To

Table 5
Solubility of oxazepam from physical mixtures and solid dispersions

Carrier	Oxazepam	Physical mixture		Solid dispersion	
		1+9	1+1+8	1+9	1+1+8
—	1:25 200	—	—	—	—
Gelita Collagel	—	1:12 200	1:12 430	1:2300	1:2280

overcome this problem lactose was added in various ratios during the formulation of the solid dispersion. The formulation (1 + 1 + 8) was the best.

X-ray diffractions studies have shown an amorphous form of the drug to be present in all forms of solid dispersion, independent of the percentage of the carrier in the solid dispersion. The powder X-ray patterns of oxazepam, solid dispersions 1 + 9, 1 + 4 + 5, 1 + 2 + 7, 1 + 1 + 8 are illustrated in Fig. 2. A diffraction spectra of pure oxazepam shows

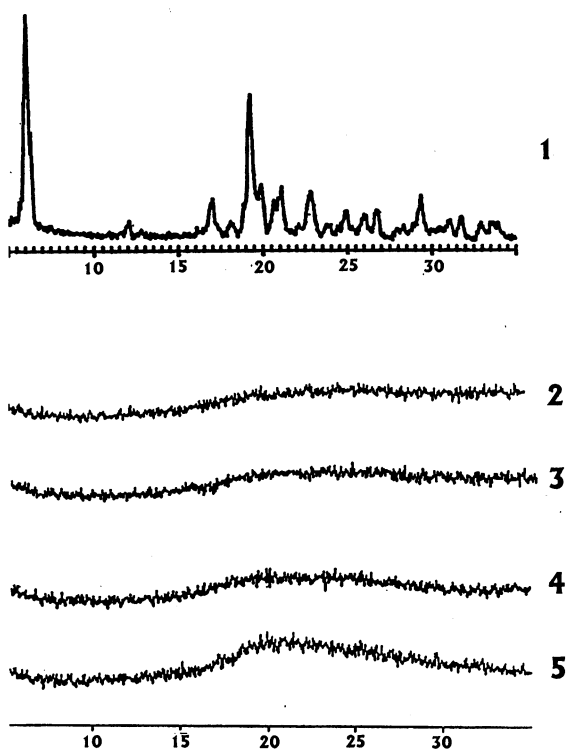

Fig. 2. X-ray diffraction spectra: 1. oxazepam, 2—5. solid dispersions—2. (1 + 9); 3. (1 + 4 + 5); 4. (1 + 2 + 7); 5. (1 + 1 + 8).

that the drug is crystalline, indicated by characteristic peaks at 2Θ 7° and 19°. In all types of solid dispersion only a halo was observed. The absence of peaks for oxazepam point to an amorphous form of oxazepam, formed during the preparation of solid dispersions by the spray-drying method.

An amorphous form of the drug explains, why only negligible differences in dissolved oxazepam were found. These results were confirmed by polarizing microscopic studies. All solid dispersions were isotropic, while the physical mixtures were anisotropic. Fig. 4 presents isotropic solid dispersion in comparing to crystals of oxazepam. The amount of dissolved drug from solid dispersions was some six times greater compared to the oxazepam alone and 2.2–2.6 greater than from the physical mixtures.

Due to the low solubility of oxazepam, its solubility after formulation of solid dispersions was investigated. The results indicated approximately ten times higher solubility of the drug from 1 + 9 and 1 + 1 + 8 solid dispersions and only two times higher than the corresponding physical mixtures (Table 5).

The stability of oxazepam in solid dispersions after 1 year storage was satisfactory. No changes were occurred in the amorphous state of oxazepam in Gelita Collagel (Fig. 3). Microscopic studies showed isotropic forms. Only negligible differences in dissolution profiles of oxazepam were found for stored and freshly prepared samples (Table 3).

The parameters of all the tablets prepared were satisfactory (Table 1). The necessity of ten fold increasing the tablet mass by adding 90% Gelita collagel and lactose to 10% of drug had practically no influence on the formulation of tablets. No difficulties during compression were observed. The diameter 8 mm is quite satisfactory.

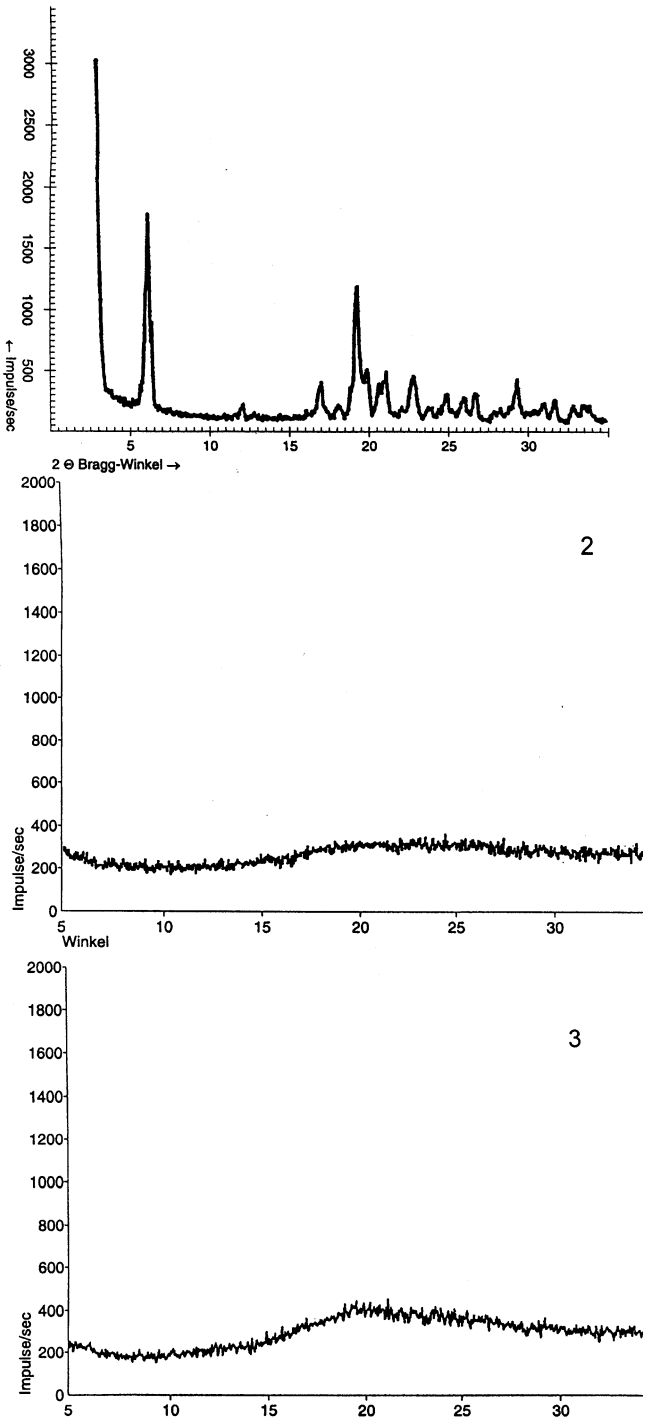

Fig. 3. X-ray diffraction spectra: 1) pure oxazepam, 2) freshly prepared solid dispersion, 3) after 1 year storage.

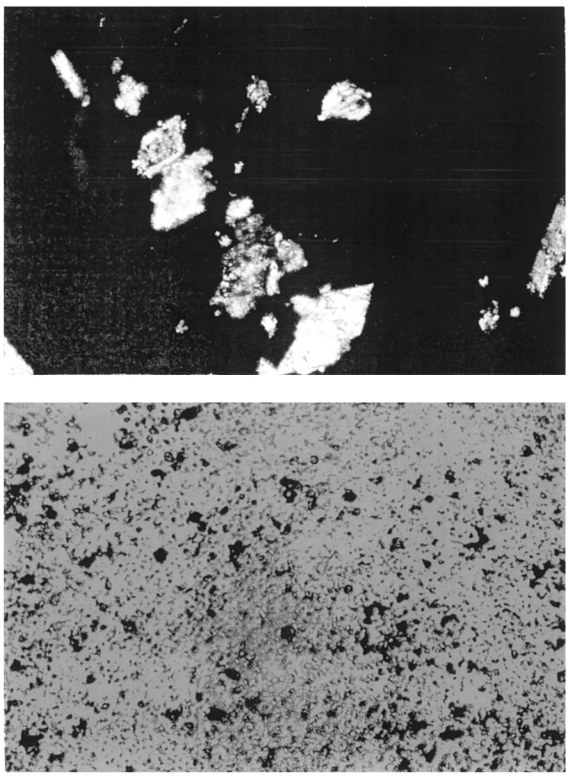

Fig. 4. Photographs of: 1. oxazepam, 2. solid dispersion (1 + 1 + 8) (polarizing microscope, 600 ×).

The release studies of oxazepam from the tablets confirmed the results obtained for powdered samples. As shown in Table 4, the dissolution rate of oxazepam from solid dispersion tablets is much greater than from tablets of physical mixtures or drug alone. After 4 h of dissolution 27.5% of oxazepam was dissolved from tablets containing a solid dispersion. This value was approximately six and three times greater respectively than that from tablets formulated with the drug alone and as a physical mixture. The release profile of oxazepam from the three kinds of tablets differ, as shown in Fig. 4. Two-phase profile was observed for tablets of formulation C. A fast initial release phase up to 0.5 h was followed by a slower release in a second phase of 0.5–4.0 h. After 0.5 h the amount of dissolved drug received from formulation C tablets was 13-fold greater than received from formulation B tablets and 27-fold greater than from formulation A tablets. The release of oxazepam from tablets formulation A and B proceeded gradually, however the process was faster from tablets B.

After one year of storage the difference in dissolved oxazepam after 4 h from tablets with solid dispersions was only 2.2% of the amount of dissolved drug from freshly prepared tablets. For tablets containing drug alone and physical mixtures, this value was five times higher, 9.5% and 11.3% respectively (Table 4). The physical properties of the tablets were also unchanged. The differences in disintegration time—about 20 s. are practically insignificant in practise. The disintegration times—in the range of 2.8–4.0 min for all stored formulations were satisfactory (Table 1).

4. Conclusion

The present results of investigations show the suitability of Gelita collagel as the carrier for solid dispersions of oxazepam. As mentioned above, this substance is widely used as a pharmaceutical adjuvant. In this work, it has been used for a first time as the carrier of solid dispersions, with a good results. The amorphous form of oxazepam found in powdered solid dispersions as demonstrated by X-ray diffraction may offer an explanation of better dissolution rate from solid dispersion tablets. No crystallinity of oxazepam in Gelita Collagel solid dispersion has been found after one year of storage. The proposed tablet formulations with solid dispersion ensure a good pharmaceutical availability of oxazepam.

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