International Journal of Pharmaceutics, 88 (1992) 31–37

IJP 02849

Interaction between dipyridamole and Eudragit S

D.B. Beten [a], M. Gelbcke [b], B. Diallo [c] and A.J. Moës [a]

[a] *Laboratoire de Pharmacie Galénique et Biopharmacie, CP 207,* [b] *Laboratoire de Chimie Pharmaceutique Organique, CP 205 / 5 and* [c] *Laboratoire de Pharmacognosie et de Bromatologie, CP 205 / 4, Université Libre de Bruxelles, Boulevard du Triomphe, 1050 Brussels (Belgium)*

(Received 26 November 1991)
(Modified version received 26 February 1992)
(Accepted 10 March 1992)

Key words: Dipyridamole; Eudragit S; Eudragit RL; Controlled release; Solid dispersion; Interaction; Dissolution

Summary

Amorphous solid dispersions of dipyridamole were prepared by the solvent method using Eudragit S and RL as carriers in order to obtain controlled release dosage forms. When Eudragit S was used the release of dipyridamole from the solid dispersion particles was inhibited at low pH, but remarkably improved at neutral or alkaline pH values which correspond to the pH of polymer dissolution. In contrast, the dissolution of the active drug in acidic media was neither slowed down nor delayed when Eudragit RL was used as the carrying polymer. The striking difference between the drug release profiles of the two coprecipitates seemed to be caused by some interaction between Eudragit S and dipyridamole. The mechanism of this interaction was further investigated using various spectroscopic methods (UV, infrared, ^{1}H- and ^{13}C-NMR). The existence of preferential hydrogen bonding between the carboxylic functions of the polymer and some of the nitrogen atoms of dipyridamole was clearly demonstrated.

Introduction

The solid dispersion technique was originally used to enhance the dissolution rate of poorly water-soluble drugs by using water-soluble inert carriers such as polyvinylpyrrolidone, polyethylene glycols or urea (Ford, 1986).

This technique was employed in preparing sustained-release forms of various drugs (nifedipine, digoxin, griseofulvin) using enteric coating polymers (Eudragit L, Eudragit S, HP-50, HP-55, CAP, CMEC) as inert carriers (Hasegawa et al., 1986). The dissolution behaviour of these solid dispersions showed the phenomenon of supersaturation at pH 6.8 and no dissolution at pH 1.2.

In this study, the mechanism of interaction between the drug and the polymer was investigated taking into account that only very limited information is available on these interactions.

The model drug is dipyridamole which is a poorly water-soluble weak organic base showing irregular and incomplete absorption from the gastrointestinal tract, since its solubility (S) is very dependent on pH variations (at 37°C, ranging between 36.5 mg/ml at pH 1.0 and 0.02 mg/ml at pH 7.0).

Correspondence to: D B. Beten, Laboratoire de Pharmacie Galénique et Biopharmacie, CP 207, Blvd du Triomphe, 1050 Brussels, Belgium.

Eudragit S is an anionic copolymer based on methacrylic acid and methylmethacrylate (ratio 1:2). It is insoluble in acids and pure water, whereas it is soluble in intestinal medium from pH 7 upwards.

Eudragit RL is a neutral copolymer of poly-(ethylacrylate, methylmethacrylate) ethyltrimethylammonium methacrylate chloride. It is insoluble in aqueous media irrespective of the pH. Solid dispersions of dipyridamole were prepared with Eudragit S and RL. The in vitro drug-release profiles of the two solid dispersions were very different. This could only be explained by the possibility of an interaction between dipyridamole and Eudragit S.

As a result of these observations, a thorough investigation of the interaction between the carboxylic groups of the polymer and the nitrogen atoms of the drug was performed.

Experimental

Materials

Dipyridamole (Office Chimique, lot 89F26-184, USP XXII), Eudragit S and RL (Röhm Pharma, Darmstadt, Germany), ethanol, dichloromethane, chloroform and methanol (Merck, Analytical Grade) were obtained from the sources indicated.

Preparation of physical mixtures

Dipyridamole and the polymers were weighed accurately in a 2:8 ratio and then mixed thoroughly by light trituration in a mortar.

Preparation of solid dispersions

Dipyridamole and Eudragit S or RL were dissolved in a suitable ratio in a solvent mixture consisting of ethanol: dichloromethane (1:1) and the solvent was then removed under vacuum in a rotary evaporator at 45°C. The residue was pulverized and dried for 48 h under vacuum at room temperature, and stored in a desiccator. The different particle size fractions were obtained by sieving (Model 42 Rhewum) and for all tests the same fraction size (0.1–0.2 mm) was used.

Analysis of the samples

Samples were analyzed for dipyridamole content at 283 nm by UV spectroscopy (Hitachi model 100-60 spectrophotometer) after dissolution and suitable dilutions in dichloromethane.

In vitro release studies

Experiments were carried out at 37.0 ± 0.1°C in a USP XXII No. 2 dissolution apparatus using a stirring rate of 60 rpm. The dissolution medium was a phosphate buffer with the following composition: 0.05 M acetic acid, 0.05 M potassium dihydrogen phosphate and 0.05% Tween 20; 12 N HCl was added to adjust the initial pH to 1.3. At predetermined intervals 4 N NaOH was added using an automatic burette (Radiometer ABU80) connected to an automatic titrator (Radiometer TTT80) and a pH Meter (Radiometer pHM 82) in order to vary the pH programmed as follows: 0–1.0 h, pH 1.3; 1.0–1.5 h, pH 5.0; 1.5–4.5 h, pH 6.3; 4.5–7.5 h, pH 6.9.

A sample equivalent to 25 mg of dipyridamole was placed in a lock-cap gelatine capsule maintained in the dissolution medium (900 ml at t_0) by a helicoidal stainless-steel wire. At predetermined intervals, the test solution was filtered automatically and assayed spectrophotometrically at 283 nm. (Philips PU 8605/60 Tablet Dissolution Monitoring System).

X-ray analysis

Powder X-ray diffractometry was carried out with a Philips X-Ray Diffractometer using CuKα radiation (40 kV, 16 mA, slit 1°–1°).

Physico-chemical determination of the interaction

In the solid state The infrared (IR) spectra of the samples were taken on an IR spectrophotometer (470 Shimadzu) using the KBr disk technique (sample concentration: 1 mg in 200 mg KBr).

Thermal analysis was performed on the drug, drug-polymer physical mixture and coprecipitate using a Perkin-Elmer 2C Differential Scanning Calorimeter equipped with a computerized data station (Perkin Elmer Corp., Norwalk, CT).

Aluminium pans and lids were used for all samples. Temperature calibrations were per-

formed using indium as a standard. All samples were run at a scanning rate of 20°C/min using nitrogen as effluent gas. Determinations of the transition temperature were carried out via a computerized procedure.

In solution The UV absorption spectra of the drug, drug-polymer physical mixture and coprecipitate were determined after dissolving them in methanol and in a chloroform : ethanol mixture (8 : 1) (Shimadzu UV-160). Taking into consideration the low solubility in chloroform of the coprecipitate and the physical mixture, the samples in this solvent were placed in an ultrasonic bath for 4 min. Afterwards, an exact volume of ethanol was added and the samples were placed in the ultrasonic bath for another 2 min. The final concentration of dipyridamole in the two solutions was 40 mg/l ($\sim 7.9 \times 10^{-5}$ M).

^{1}H- and ^{13}C-NMR spectra

The NMR spectra of the samples were recorded on a WP 250 Bruker type spectrometer using CD_3OD as solvent and TMS as internal reference. The concentration of dipyridamole was 20 mg/ml ($\sim 4 \times 10^{-2}$ M). $CDCl_3$ was not used, since the polymer is insoluble in this solvent.

In order to assign the signals of carbons C-9, 13, 14, 15 and the corresponding protons, a sample of dipyridamole was acetylated using anhydrous pyridine and acetic anhydride. The mixture was left to stand at room temperature for about 72 h and then dried using a stream of nitrogen. Subsequently, any trace of solvent was eliminated by evaporation under high vacuum.

Results and Discussion

The powder X-ray diffraction patterns showed no diffraction peaks attributed to dipyridamole for coprecipitates containing 2 parts of dipyridamole and 8 parts of polymer. This implied the absence of apparent crystallinity for dipyridamole in these coprecipitate systems. In this study, only the amorphous solid dispersions were investigated.

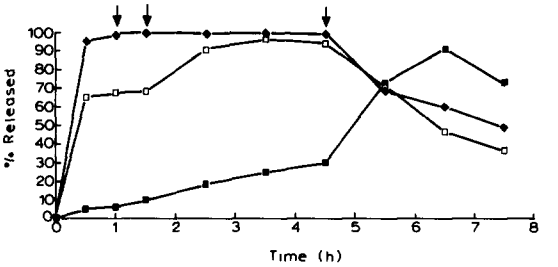


Fig. 1. Release profiles from coprecipitates dipyridamole/Eudragit S (2.8) (■ ——— ■), dipyridamole/Eudragit RL (2:8) (◆ ——— ◆) and dipyridamole/Eudragit S physical mixture (□ ——— □). Arrows indicate pH changes of the dissolution medium.

In vitro release

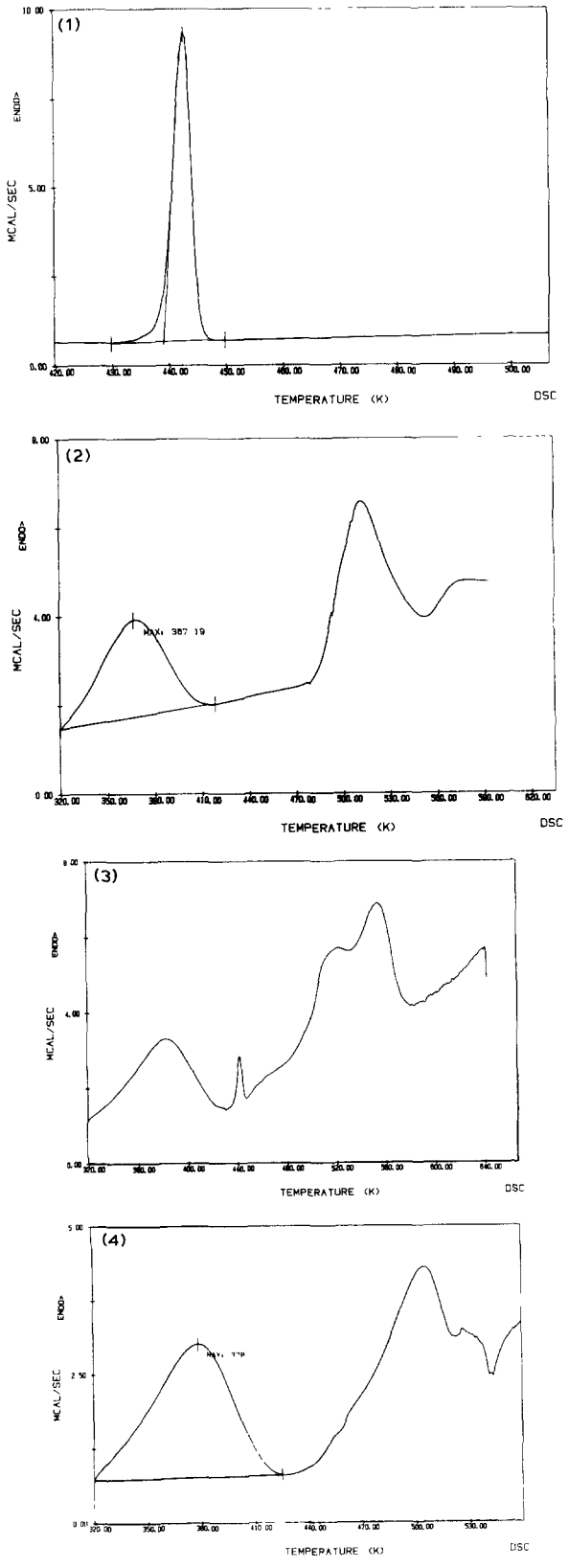
Although there was a significant decrease in drug release for the coprecipitate prepared with Eudragit S at pH 1.3, a considerable increase occurred on reaching the pH of polymer dissolution, pH 6.9. In contrast, the drug-release profiles of the coprecipitate prepared with Eudragit RL and the physical mixture (Eudragit S/dipyridamole) were similar (Fig. 1). Drug was released immediately in acidic medium and no sustained-release effect was observed. In all cases, the drug crystallized from the supersaturated solutions.

The differences between the observed drug-release profiles of the two coprecipitates could be related to the existence of an interaction between the drug and Eudragit S. This can be explained by the presence of carboxylic groups in the structure of the latter enabling the formation of hydrogen bonds with the nitrogen atoms of the drug. However, such an interaction would not be possible for Eudragit RL which lacks carboxylic functions in its structure.

In order to confirm these results further investigations were undertaken using different physico-chemical methods.

IR absorption

As observed previously by Salib (1980) and Fujii et al. (1988) for other drugs on interaction with polymers, the IR spectra of the present study also demonstrated that some of the peaks of the reactive centres, in both the drug and polymer, did not appear at the same place in the



spectrum of the product under investigation. This finding suggested that the system was one of chemical interaction, involving more than one reactive centre in the drug, forming a multicentred association compound.

Differential scanning calorimetry

The thermograms of the drug, Eudragit S, the physical mixture and solid dispersion in a 2:8 ratio are presented in Fig. 2.

Both drug and physical mixture exhibit a sharp endothermic peak around 163°C corresponding to the melting point of dipyridamole, thus indicating that the latter is in the crystalline form.

However, in the thermogram of the solid dispersion, no sharp peak was found at 163°C, indicating the drug to be amorphous in the solid dispersion.

Furthermore, the thermogram of the coprecipitate is different from that of Eudragit S and of the physical mixture. A shift of 11 K is observed for the first endothermic peak of Eudragit S in the thermogram of the coprecipitate.

UV absorption

In methanol The spectra of the three samples (dipyridamole, physical mixture and coprecipitate) are identical.

In chloroform / ethanol (8:1) We observed that the positions of λ(max) of both the higher and lower wavelengths of dipyridamole were shifted about 6 nm to shorter wavelengths. At the same time, a hyperchromic effect was observed (see Table 1). These two effects (hyperchromism and hypsochromism) indicated that hydrogen bonding occurs between the carboxylic functions of the polymer (Eudragit S) and the nitrogen atoms of the drug (Silverstein et al., 1981). The three spectra were also recorded at different time intervals. After 1 h, no modification of the spectra was observed. However, after 24 h in solution, the three spectra shifted completely, indicating a structural modification of the drug.

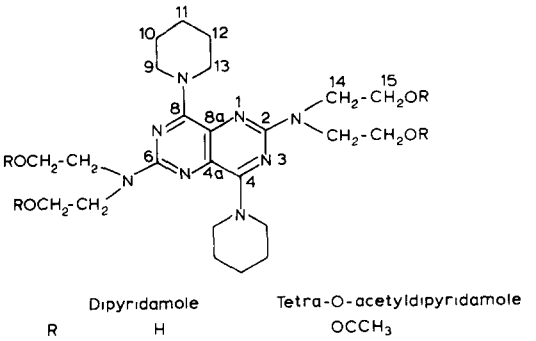
When hydrogen bonding is unlikely to occur (for example, with Eudragit RL), the UV spectra

Fig 2 DSC thermograms of (1) dipyridamole, (2) coprecipitate (2 8), (3) physical mixture (2:8), (4) Eudragit S

TABLE 1

Wavelengths (λ(max)) and $E^{1\%}$ values of UV absorption spectra of dipyridamole, its physical mixture and coprecipitate with Eudragit S

	λ_1(max) ($E^{1\%}$)	λ_2(max) ($E^{1\%}$)
Dipyridamole	413 (76)	294 (261)
Dipyridamole/Eudragit S (physical mixture)	411 (102)	287 (444)
Dipyridamole/Eudragit S (coprecipitate)	408 (113)	287 (532)



Scheme 1. Structure of dipyridamole and its acetylated derivative NMR data are given in Table 2

of the physical mixture and the coprecipitate are identical to that of dipyridamole taken in chloroform/ethanol (8:1).

^{1}H-NMR spectroscopy

In order to assign unambiguously the signals H-9, H-13, H-14 and H-15, a sample of dipyridamole was acetylated (Ac_2O/pyridine). As expected, the protons which are most strongly influenced by acetylation are H-15 and H-14. A deshielding of 0.49 and 0.13 ppm was observed, respectively. The spectra obtained under the same conditions with the physical mixture and the coprecipitate (concentration of dipyridamole $\sim 4 \times 10^{-2}$ M) show a broadening of the signal corresponding to H-14 and a small upfield shift about 0.02 ppm of H-9 and H-13. Unfortunately, the solubility of the polymer in methanol is limited (100 mg/ml) (Röhm Pharma) and it was thus impossible to raise the concentration which should have increased the interaction between the polymer and dipyridamole. Nevertheless, the broadening and the small chemical shift difference observed are indications of intermolecular hydrogen bonding (Hosono et al., 1979; Sanders et al., 1989), involving as in the case of the UV spectra, the nitrogen atoms of dipyridamole and the carboxylic functions of the polymer.

^{13}C-NMR spectroscopy

In order to clarify the behaviour of the electron density of the carbon atoms in dipyridamole as a result of the interaction with the polymer, the influence of the presence of Eudragit S in the solid dispersion on the ^{13}C-NMR spectrum of dipyridamole was investigated.

From consideration of the chemical shift rules (Breitmaier and Voelter, 1987), the DEPT technique and the data obtained with the tetraacetylated derivative in $CDCl_3$, the signals of all the carbons of dipyridamole were assigned. The drug is characterized by aromatic carbons [C-2(C-6), C-4(C-8), C-4a(C-8a)], a carbon adjacent to a hydroxyl group (C-15), carbons adjacent to nitro-

TABLE 2

Chemical shift (ppm) assignments in ^{1}H-NMR spectra of dipyridamole and tetraacetyldipyridamole in CD_3OD

Protons	Dipyridamole	Tetraacetyldipyridamole		Physical mixture		Coprecipitate	
	(δa)	(δb)	(δb–δa)	(δc)	(δc–δa)	(δd)	(δd–δa)
H_{10}, H_{11}, H_{12}	1 71	1.71	–	1.72	+0.01	1.72	+0.01
H_9, H_{13}	4.07	4.10	+0.03	4.06	−0.01	4.05	−0.02
H_{14}	3.75	3.88	+0.13	3.76	+0 01	3.75	–
H_{15}	3.80	4.29	+0.49	3.80	–	3.80	–
OH	4.79	–	–	4.87	+0 08	4.85	+0.06
$COOCH_3$	–	2.02	–	–	–	–	–

TABLE 3

Chemical shift assignments in ^{13}C-NMR spectra of dipyridamole, physical mixture and coprecipitate in CD_3OD and tetraacetyldipyridamole in $CDCl_3$

Carbons		Chemical shift (ppm)						
		Dipyridamole	Physical mixture		Coprecipitate		Tetraacetyl dipyridamole	
		(δa)	(δb)	(δb–δa)	(δc)	(δc–δa)	(δd)	(δd–δa)
2	(6)	161 89	161.62	−0.27	161.60	−0.29	160.50	−1.39
4	(8)	155.99	155.93	−0 06	155 92	−0.07	153 65	−2.25
4a	(8a)	133.96	133 25	−0.71	133.21	−0 75	133.03	−0 93
9	(13)	50.16	50.25	+0.09	50.25	+0.09	48.86 [a]	−1 30
10	(12)	27.64	27.60	−0.04	27.60	−0.04	26.49	−1 15
11		26 36	26.25	−0.11	26.25	−0 11	25.26	−1 10
14		53 59	53.62	+0.03	53 62	+0.03	48.25 [a]	−5.34
15		62 71	62.59	−0 12	62 59	−0.12	63 21	+0 50

[a] May be interchanged in the column

gen [C-9(C-13), C-14] and methylene carbons [C-10(C-12), C-11] (Table 3).

As expected (Hosono et al., 1980), the carbons that are most strongly influenced by acetylation are C-14 and C-15. C-14 is shielded about 5.34 ppm, C-15 being deshielded about 0.5 ppm. The small deshielding effect observed on C-15 (0.5 instead of about 3 ppm observed on comparing ethanol with ethylacetate) (Silverstein et al., 1981) suggests that the hydroxylic protons of dipyridamole are involved in hydrogen bonding interactions.

It is known that protonation of aliphatic amines causes upfield shifts, particularly in the position β to the protonated group (Breitmaier and Voelter, 1987). In contrast, for aromatic compounds containing nitrogen in the heterocycle, on protonation upfield shifts are found for the carbon α to nitrogen, while those in the β and γ positions are deshielded. These effects could therefore be used to determine the interaction of the drug with the polymer.

The small shifts observed on C-10 (C-12) (−0.04 ppm) as compared with C-15 (−0.12 ppm) suggest a preferential interaction with the nitrogen of the amino-alcohol, as determined on the basis of the ^1H-NMR spectra mentioned earlier, in which broadening of the H-14 signal occurred on the addition of polymer. The shifts observed on C-2, C-4 and C-4a result from the combined interaction of all the nitrogens with the polymer and therefore the task of defining which nitrogen (N-1 (N-5) or N-3 (N-7)) is involved in the interaction is difficult to fulfill.

However, as shown in Table 3, a relatively higher upfield shift is noted for carbon atoms C-4a (C-8a) and C-2 (C-6) which are at the α position of nitrogen atoms N-5 (N-1) and N-1 (N-5), respectively. Therefore, our observations suggest that the polymer interacts preferentially with nitrogens N-1, N-5 and the nitrogen of the aminoethanol groups.

Conclusions

The dissolution profiles of the coprecipitates were determined and considerable difference between the dissolution profiles of the two coprecipitates, dipyridamole/Eudragit S (2:8) and dipyridamole/Eudragit RL (2:8), was observed, thus suggesting a possible interaction between dipyridamole and Eudragit S. In order to confirm the existence of this interaction, the investigations were pursued by using various physicochemical methods, such as UV, IR, ^1H- and ^{13}C-NMR spectroscopy, and DSC. The results obtained clearly indicate that there is hydrogen bonding between the carboxylic functions of the polymer (Eudragit S) and the nitrogen atoms of

dipyridamole with preferential interaction with N-1, N-5 and the nitrogen atoms of the aminoethanol groups.

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