ELSEVIER

Il Farmaco 57 (2002) 649–656

IL FARMACO

www.elsevier.com/locate/farmac

Eudragit® RS-PM and Ethocel® 100 Premium: influence over the behavior of didanosine inert matrix system

C. Sánchez-Lafuente *, A.M. Rabasco, J. Álvarez-Fuentes, M. Fernández-Arévalo

Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Seville, C/Professor Gracía González s/n, 41012 Seville, Spain

Received 18 July 2001; accepted 25 February 2002

Abstract

Inert matrices of didanosine (ddI) were elaborated as controlled release dosage forms, using two different types of polymers: Eudragit® RS-PM, an anionic acrylic acid copolymer, and Ethocel® 100 Premium, an ethylcellulose. A preformulation study of the drug was designed to address the following points: (a) the development of two alternative methods (high performance liquid chromatography (HPLC) and UV spectrophotometry) for the analysis and quantifying of ddI; (b) the determination of the aqueous solubility of ddI; and (c) the characterization of ddI from the following points of view: morphological (scanning electronic microscopy (SEM)) and thermal (differential scanning calorimetry (DSC)). Furthermore, some of these techniques were used for the characterization of those components which will be included in the oral controlled release system to be developed. The in vitro release of ddI matrices was studied at pH 7.4, because of the instability of ddI at pH values lower than 3 units. A significant reduction in the release rate of drug from both ddI controlled release systems was found. Furthermore, Ethocel® 100 Premium showed a minor efficiency in the dissolution process, with a reduction of more than double in the final dissolution efficiency (DE) value. This parameter and the fit factors (f_1 and f_2) have been compared for the characterization of dissolution profiles.

Keywords: Didanosine; Eudragit® RS-PM; Ethocel® 100 Premium; Preformulation; Controlled release; Inert matrices

1. Introduction

Didanosine (ddI) is a synthetic purine nucleoside analogue active against the human immunodeficiency virus (HIV) (Fig. 1), that is labeled by the US Food and Drug Administration (FDA) for the management of advanced HIV infection in adults and 6-month aged children or older with advanced disease. It is indicated for the treatment of HIV infection when antiretroviral therapy is warranted [1–3].

Didanosine's mean elimination half-life ranges are 30 min–4 h; its daily dosage is relatively low (250–400 mg) [4]. During the treatment it is needed repetitive dosing, but adverse effects, as pancreatitis, peripheral neuropathy, diarrhea, nausea, vomiting, headache and rash, frequently appear [5].

On the basis of its pharmacokinetic parameters, ddI is a potential candidate to be incorporated in a controlled release system. For this purpose and considering its physicochemical characteristics, the drug can be introduced in a polymeric structure such as Eudragit® RS-PM and Ethocel® 100 Premium. Eudragit® RS-PM is an anionic copolymer based on acrylic and

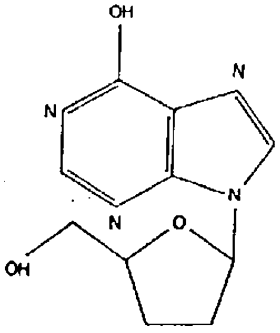

Fig. 1. Structure of ddI.

* Corresponding author.
E-mail address: arevalo@fafar.us.es (C. Sánchez-Lafuente).

0014-827X/02/$ - see front matter
PII: S0014-827X(02)01240-5

methacrylic acids with low content in quaternary ammonium functions (1:40) [6]; Ethocel® 100 Premium is an ethylcellulose with a high degree of polymerization [7]. Their solubility are pH independent, being both water-insoluble.

So, the main objective of this paper is to carry out the complete characterization of the drug through a preformulation study and to elaborate the proposed ddI controlled release system.

2. Materials and methods

2.1. Materials

Didanosine was a gift from Bristol Myers Squibb; acetonitrile HPLC grade and ammonium dihydrogen phosphate were purchased from Merck (Darmstadt, Germany); sodium chloride, potassium dihydrogen phosphate and disodium hydrogen phosphate dihidrate were from Panreac (Barcelona, Spain). Eudragit® RS-PM was obtained from Degussa-Hüls S.A. (Barcelona, Spain) and Ethocel® 100 Premium from Dow Chemical Company (Michigan, USA). The polymers were sieved (Retsch, type Vibro) and the 150–200 μm granulometric fraction was selected.

2.2. Analytical methods

2.2.1. High performance liquid chromatography

Didanosine was quantified by using an HPLC method. The HPLC method avoids the interference between the drug and the polymers that occurs when the UV spectrophotometry is employed.

The HPLC system consisted of a Hitachi HPLC system manager-windows NT4.0 workstation pump L-7100, manual injector 77251, diode array detector L-7455 and interphase D-7000. The column used (E. Merck, LiChrospher 100 RP-18, 5 μm particle size, 12.5 cm × 4 mm ID) was packed with silica particles bonded with octadecilsilene. The mobile phase was acetonitrile–ammonium dihydrogen phosphate 0.05 M (6:94% v/v).

A flow rate of 1 ml/min was employed and the variable wavelength detector was set at 248 nm. Each peak area was computed automatically by the integrator. The elution was carried out in isocratic conditions at room temperature (22 ± 2 °C).

Didanosine standard aqueous solutions containing 0.075, 0.150, 0.3125, 0.625, 1.25, 2.5, 5, 10, 20 and 40 μg/ml were used for calculating the calibration curve. The accuracy of the HPLC determination was evaluated from the observed concentration data obtained by six replicates at different concentrations. The precision of the method was studied by analyzing a solution containing 5 μg/ml in 20 replicates. Furthermore, this same solution was analyzed by quadruplicate on 5 different days (20 times). The intra-assay precision was determined from the coefficient of variation (CV) of the obtained values for the samples analyzed on the same day. Inter-assay data were calculated using the mean value of the four injections performed on each day.

2.2.2. UV spectrophotometry

This analytical method is used as an alternative in those situations where no interference problems appear as, for example, solubility assays and release studies.

Calibration curve for ddI (Spectrophotometer Hitachi, mod. U-2000) was calculated (maximum of absorption 248 nm) using standard solutions containing 0.150, 0.3125, 0.625, 1.25, 2.5, 5, 10 and 20 μg/ml of this drug. The precision and the accuracy of the method were studied following the procedure previously described for the HPLC method.

2.3. Solubility assays

The experimental aqueous solubility of ddI was calculated. The solubility study as a function of pH value and ionic strength (NaCl) of the medium were carried out.

The study of solubility as a function of pH was conducted at room temperature (22 ± 2 °C); different buffer solutions with several pH values varying from 6 to 10.6 were used. The pH range used was selected: (I) as a function of the stability characteristics of ddI, which is hydrolyzed below pH 3; and (II) the pH values of dissolution media employed for the in vitro study. The samples were analyzed by UV spectrophotometry at 248 nm.

In this study of pH, the ionic strength of the medium is not contemplated; that is, there is not a constant value of ionic strength during this assay. The drug is in its base form; so ionic strength, as common ion chloride, would not affect its solubility behavior. Nevertheless, the study of ddI solubility as a function of the ionic strength was carried out to assure that the possible effect of pH value on the solubility is due to this parameter and not to the ionic strength.

The study of solubility as a function of ionic strength was conducted at room temperature (22 ± 2 °C) and aqueous solutions with several ionic strengths varying from 0.0125 to 0.2 M NaCl were used, following the procedure previously described for the study of solubility as a function of pH. These small ionic strength values were used because the Setschenow equation, usually employed for quantification of this effect, is valid only with low concentrations of the added NaCl, as a resulting of a lost of the linearity from a determined NaCl concentration value [8].

2.4. Scanning electron microscopy

The morphological characteristics of ddI were analyzed using a scanning electron microscopy (Philips XL-30). A very thin coat of carbon was applied to each sample, which was examined at different magnifications. Micrographs were taken for each sample.

Size and shape analysis of the drug was determined using an image analysis system linked to the microscope above mentioned. They are obtained, automatically, using a special computer program which is based on obtaining a pixel matrix of the particle boundary by the digitization of the particle image. This pixel matrix, allowing a spatial resolution expressed in micrometers, is then used to calculate a set of size and shape descriptors [9].

The parameters selected to describe the micromorphology of isolated particles were the followings.

2.4.1. Shape factor

This factor is calculated using the following equation: $4[\text{area}/(\text{perimeter})^2]$. It provides information about the elongation of the particle. For a circular particle, the shape factor is 1; for all other particles, the shape factor is smaller than 1.

2.4.2. Aspect ratio

The aspect ratio is the ratio of the horizontal maximum and the vertical maximum distance of the particle. For a round or a square particle, the aspect ratio is 1. For those elongated in the *X* direction the ratio is larger than 1. Particles elongated in the *Y* direction have an aspect ratio smaller than 1.

2.4.3. Maximum horizontal and vertical diameters

These refer to the maximum horizontal and vertical distances between two points on the boundary of the particle on horizontal and vertical lines.

2.5. Thermal analysis

Thermal analysis has rapidly gained importance as a routine instrumental method for obtaining qualitative predictions on the stability of drugs, excipients or their mixtures. The melting range of a substance is defined as those points of temperature where the solid coalesces and is completely melted. Because of this a melting temperature range must be reported unless the melting of the compound takes place instantaneously. Differential scanning calorimetry (DSC) is particularly valuable in studying the beginning of melting of a compound [10].

DSC was used to characterize the thermal behavior of ddI. Thermal analysis was performed in order to investigate the compatibility between the drug and the polymers (Eudragit® RS-PM and Ethocel® 100 Premium) [11]. Didanosine and the polymers were weighed in a 1:1 ratio [12] and then mixed by light triturating in a mortar.

Thermal analysis using DSC method was performed using an automatic thermal analyzer system (Mettler FP80HT Central Processor and FP85 TA Cell). The data processing system Mettler FP89HT was connected to the thermal analyzer.

Sealed and holed aluminum pans were used for all the experiences. Temperature calibrations were made using indium as a standard. An empty pan, sealed in the same way as the sample, was used as reference. All the samples were run at a rate of 10 °C/min, from 30 to 400 °C.

2.6. Preparation of ddI inert matrices

Matrix tablets with a constant theoretic weight of 500 mg were obtained using an eccentric machine (Bonals A-300, Barcelona, Spain) with flat-faced punches of 12.00 mm diameter. Compaction was accomplished by direct compression of drug-polymers blends previously mixed for 10 min using a tumbler mixer.

Two batches containing binary mixtures of ddI and one of the polymers, Eudragit® RS-PM and Ethocel® 100 Premium (150–200 μm), were elaborated. So, both batches have a drug content of 10% w/w; lot 1 has a 90% w/w of Eudragit® RS-PM, and lot 2 a 90% w/w of Ethocel® 100 Premium.

For each lot, 10 randomly taken tablets were checked for weight uniformity (Scaltec SBC 31 electronic balance, Heiligenstadt, Germany), diameter and thickness (Export-Pel precision micrometer, Madrid, Spain); and 6 units for hardness (Schleuniger durometer mod. 2E/205, Greifensee, Switzerland).

2.7. 'In vitro' dissolution study

The in vitro dissolution behaviors of ddI inert matrices were investigated. In order to compare them, the in vitro dissolution study was carried out at 37 ± 0.5 °C during 6 h, in the USP 23 basket apparatus (Turu Grau, mod. D-6) at a speed of 50 rpm. Seven hundred millilitres of buffer phosphate pH 7.4 was employed as dissolution medium in order to avoid ddI's instability problem. At predetermined intervals, test solutions were assayed by an UV technique previously developed by us.

The dissolution profiles obtained were evaluated and compared using amodelistic parameters as dissolution efficiency value (DE) [13,14] and difference and similarity factors (f_1, f_2) [15–19]. These parameters allow to compare and establish similarities or differences between two dissolution curves obtained from experimental dates, through a mathematical approach.

Table 1
Accuracy data for the determination of didanosine (each value represents the average of six replicates)

HPLC method			UV spectrophotometry method		
Actual concentration (μg/ml)	Observed concentration (μg/ml) (mean ± SD)	Accuracy (%)	Actual concentration (μg/ml)	Observed concentration (μg/ml) (mean ± SD)	Accuracy (%)
40	41.45 ± 1.729	3.63	20	20.15 ± 0.044	0.77
20	18.94 ± 0.153	−5.28	10	9.57 ± 0.017	−4.28
10	10.36 ± 0.206	3.63	5	5.15 ± 0.026	3.10
5	5.11 ± 0.175	2.24	2.5	2.54 ± 0.013	1.72
2.5	2.66 ± 0.092	6.26	1.25	1.28 ± 0.009	2.09
1.25	1.26 ± 0.045	0.45	0.625	0.641 ± 0.007	2.62
0.625	0.626 ± 0.034	0.19	0.3125	0.333 ± 0.006	6.51
			0.150	0.161 ± 0.007	7.08

Table 2
Intra- and inter-assay precision for the determination of didanosine

	Levels	Mean	Standard deviation	D.F.	Coeffecient variation (%)
HPLC method					
5 μg/ml	intra-day	87968.15	3.02E−3	20	3.43
	inter-day	85695.65	3.24E−3	20	3.78
UV spectrophotometry method					
5 μg/ml	intra-day	0.346	0.004	20	1.1
	inter-day	0.347	0.004	20	1.2

3. Results and discussion

3.1. Physicochemical characterization of ddI

3.1.1. Analytical methods

3.1.1.1. High performance liquid chromatography. The selected mobile phase was acetonitrile–ammonium dihydrogen phosphate 0.05 M (6:94% v/v) [20]. The pH value of this mobile phase was 4.5. The retention time for ddI was 5.227 ± 0.060 min. The calibration curve obtained for ddI using the HPLC method previously described $[y = (0.01761 \pm 1.75 \times 10^{-4})x - (0.00229 \pm 0.00306)]$ was linear from 0.625 to 40 μg/ml giving $r^2 = 0.9960$ as determination coefficient ($n = 42$) and $F = 10080.1863$ as Snedecor ratio ($P < 0.0001$).

As it was indicated on Section 2.2.1, accuracy data are calculated from the difference between the observed concentration and the actual concentration. As it can be observed in Table 1, these accuracy values are adequate in the assayed concentrations (< 7%). The CVs for intra- and inter-assay precision were both lower than 4% (see Table 2). The results show the adequate precision of the HPLC method proposed.

3.1.1.2. UV spectrophotometry. In order to investigate the linearity of the spectrophotometrical method, the calibration curve for ddI was performed. The regression analysis of this curve $(y = (0.0765 \pm 0.0003)x + (-0.0064 \pm 0.0026))$ gave $r^2 = 0.9993$ as determination coefficient ($n = 48$) and $F = 52826.1646$ as Snedecor ratio ($P < 0.0001$). These parameters showed that the detector response is linear from 0.150 to 20 μg/ml. As it can be observed in Table 1, the accuracy of this method, calculated from the observed and actual concentration data, was adequate (< 8%). Furthermore intra- and inter-day precision were lower than 1.2% (see Table 2). The calculated value of ε was 18 072 l/mol/cm.

3.1.2. Solubility assays

The experimental value of aqueous solubility of ddI was 20.29 ± 0.549 mg/ml at 22 ± 2 °C; this datum shows a clear similarity with the value found in the bibliography, close to 27.3 mg/ml at 25 ± 2 °C [2].

The results of the solubility study as a function of pH (Fig. 2) showed that the drug was soluble in all the range of pH studied. It can be appreciated its solubility improves raising the pH at values higher than 9 units [21]. More, Student–Newman–Keuls test offered several groups clearly differentiate: one group from pH 6 to 8, and separate groups for each remaining pH (9.2, 9.6, 10.2 and 10.6) ($F = 138.7092$, $P < 0.0001$). The solubility values yielded never are below the required limit of solubility to design controlled release systems (0.1 mg/ml) [22].

The results obtained from the solubility study as a function of ionic strength in purified water demonstrate that solubility of ddI is not statistically influenced by this factor ($F = 1.3544$, $P = 0.2779$). The results were foreseeable because the drug was in its base form and

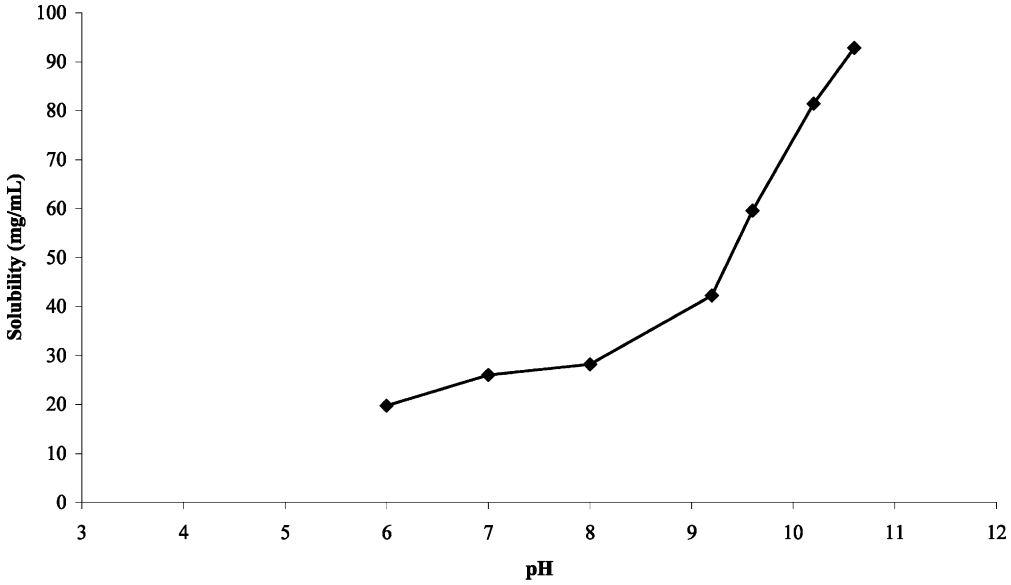

Fig. 2. Solubility values versus pH.

not in the clorhidrate form, where the presence of ion chloride acts as a common ion [23,24].

These results confirm that the influence of the pH over the solubility of ddI is due only to the pH value.

3.1.3. Thermal analysis

This study was carried out in order to characterize ddI and to study the compatibility between ddI and the two polymers used in this study, Eudragit® RS-PM and Ethocel® 100 Premium.

The thermogram obtained by DSC of ddI (Fig. 3b) showed an endothermic peak corresponding to the melting of the drug ($\Delta H \approx -103.5$ J/g) with temperature onset of 189.2 °C, and temperature peak at 196.8 °C; it is followed by a light recristalization. It can be also appreciated an endothermic peak at 277.15 °C ($\Delta H \approx -167.25$ J/g) with an onset temperature of 259.23 °C.

As it is shown in the thermogram of Eudragit® RS-PM (Fig. 3a), this polymer exhibits a melting peak with a $\Delta H \approx -129.66$ J/g and temperature onset and peak of 337.9 and 375.6 °C, respectively. In the thermogram of Ethocel® 100 Premium (Fig. 3e) it can be seen firstly an exothermic peak corresponding temperature peak of 202.7 °C, a temperature onset of 194.3 °C and a melting peak with a $\Delta H \approx 29.5$ J/g, and secondly we can observe another exothermic peak ($\Delta H \approx 30.9$ J/g) with a temperature peak of 379.6 °C and a temperature onset of 365.3 °C.

As can be seen in Fig. 3, the thermograms of 1:1 physical mixture Eudragit® RS-PM–ddI (Fig. 3c) and Ethocel® 100 Premium–ddI (Fig. 3d) exhibit endothermic peaks corresponding to the two initial substances. Furthermore, no new transitions are found. So, all these situations indicate that the drug is in its crystalline form without suffering neither chemical interaction nor degradation process.

Therefore, it can be affirmed that the polymers Eudragit® RS-PM and Ethocel® 100 Premium, and ddI,

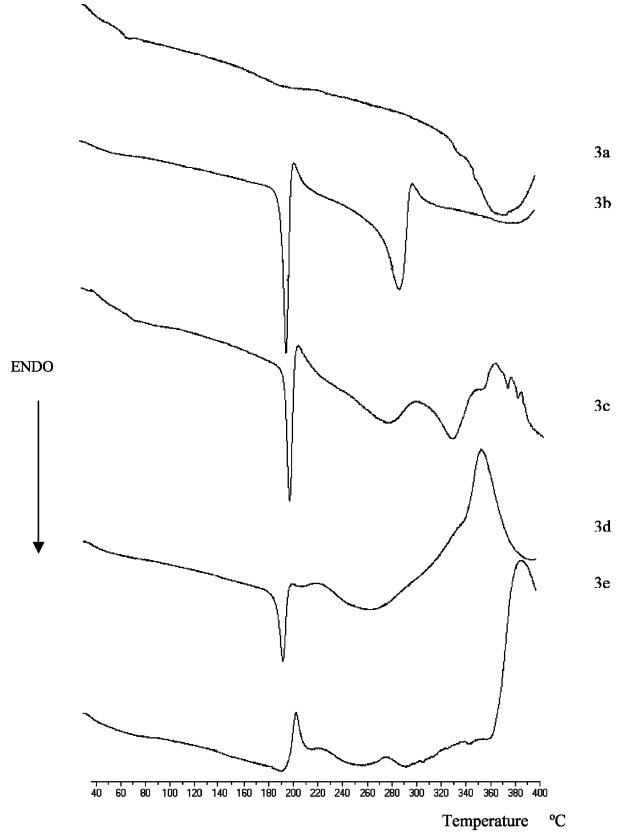

Fig. 3. DSC thermograms corresponding to: (a) Eudragit® RS-PM; (b) ddI; (c) physical mixture (1:1) of ddI–Eudragit® RS-PM; (d) physical mixture (1:1) of ddI–Ethocel® 100 Premium; (e) Ethocel® 100 Premium.

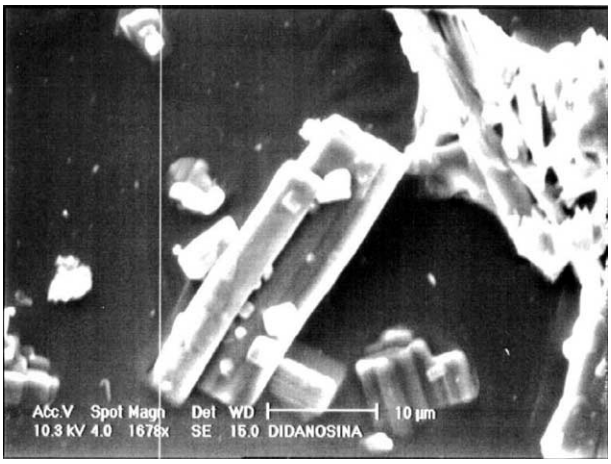

Fig. 4. SEM photograph of ddI (× 1678).

are compatible in order to prepare controlled-release inert matrices [25,8].

3.1.4. Scanning electron microscopy

Fig. 4 shows SEM photograph of commercial ddI. The size characteristics and shape descriptors of the drug, obtained as mean of 92 particles, are shown in Table 3. The particles present a smooth and no porous surface, showing a heterogeneous particle size.

As it can be appreciated in Table 3, ddI's particles have a shape factor of 0.503 μm, so these particles are not circular. Didanosine's aspect ratio were of 1.255 μm, that is, these particles were elongated in the *X* direction, not in the *Y* one. Maximum horizontal and vertical diameters values were 20.999 and 13.179 μm, respectively.

By means of these results, it can be concluded that ddI's powder exhibits characteristics of elongated particles.

3.2. Physicochemical characterization of ddI inert matrices

3.2.1. Technological study of inert matrix tablets

The technological parameters of tablets are shown in Table 4. The results of these parameters are expressed as mean ± standard deviation.

The weight uniformity was evaluated according to the specifications of USP 23. Thickness and diameter data varied within acceptable values [26,27]. No significant differences on weight uniformity, thickness and diameter values were observed between the different lots. On the contrary, very different hardness values between lots were found as a resulting of the use of the two different polymers. So, tablets elaborated with Ethocel® 100 Premium yield greater hardness values than those containing Eudragit® RS-PM as matrix former. This effect can be explained on the bases of the different mechanical properties of these excipients: Ethocel® 100 Premium has a plastic behavior; so it surrounds the drug particles and reduce the number and size of the pores that are present in the tablet before the dissolution of the drug (initial porosity). Therefore, a decrease in the drug release rate is expected, due to a decrease in the effective coefficient of diffusion [28].

Table 4
Technological parameters of ddI tablets, expressed as mean ± SD

Lots	Weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (Kp)
1	499.69 ± 1.31	4.154 ± 0.009	12.164 ± 0.007	6.15 ± 0.318
2	498.97 ± 1.43	4.170 ± 0.007	12.070 ± 0.004	16.36 ± 0.658

3.2.2. 'In vitro' dissolution study of ddI-inert matrices systems

The in vitro dissolution assay of ddI inert matrices is carried out by the UV method indicated above, at least in triplicate. Fig. 5 represents the obtained profiles. As it can be observed, the control of the release is excellent in sight of the dissolution curves. Both formulations provide zero-order release of ddI (see Table 5). The obtained results indicate an important reduction in the release rate of drug from lot 2 (10% ddI, 90% Ethocel® 100 Premium) in comparison with lot 1 (10% ddI, 90% Eudragit® RS-PM). This fact is represented on the slopes values of each curve: slope of lot 2 (0.060) is approximately half of slope of lot 1 (0.118). These results are in accordance of the hardness values indicated above.

In order to compare the two profiles and to quantify the difference between them, several amodelistic parameters were treated, as f_1 and f_2 and the DE.

Table 3
Mean values ± SD of statistical parameters from the image analysis of didanosine powder by SEM

n	Shape factor (μm)	Aspect ratio (μm)	ECD (μm)	Maximum diameter (μm)	Minimum diameter (μm)	Mean diameter (μm)
92	0.503 ± 0.039	1.255 ± 0.245	10.969 ± 1.341	20.999 ± 3.323	13.179 ± 2.712	19.251 ± 3.131

n, number of cases; ECD, equivalent circle diameter.

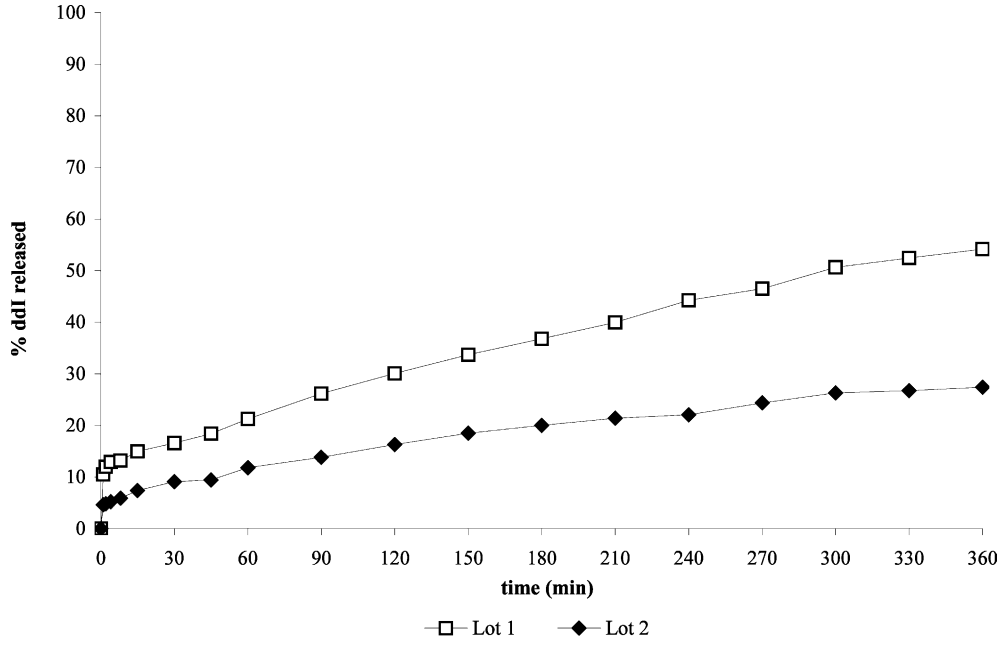

Fig. 5. In vitro dissolution profiles.

Difference parameter (f_1) is the difference between two curves at each experimental time. When two curves are equal this factor acquires values from 0 to 15; $f_1 = 0$ shows that the curves are identical, a f_1 bigger than 15 indicates that the two profiles are different. On the contrary, f_2 is FDA-adopted similarity parameter calculated based on the equation proposed by Moore and Flanner [15]. Values of this parameter among 50–100 show the similarity between dissolution profiles; f_2 minor than 50 indicates that there are differences between the curves studied [18].

From the analysis of the data of drug released, a significative difference was found between the dissolution profiles obtained from the two inert matrices types indicated. The f_1 was 47.3366, greater than the limit value of 15, indicating that there are differences between two curves [18]. Considering the f_2 parameter (similarity), its value was 40.0206, minor than the limit value of 50, that is, there are differences on the profiles [29–31].

Continuing with the comparison study of the two controlled release systems, another amodelistic parameter was studied: the final DE. This parameter represents the area under a dissolution curve between time points. The data obtained indicate differences between the two inert matrices investigated. The value of DE for the lot 1 was 54.16%, and for the lot 2 was 27.42%. The reduction in the DE between the two lots was approximately about 50% minor for lot 2 in comparison with lot 1.

This effect can be attributed, as we suggested in the Section 3.2.1, on the basis of the different properties of the two polymers. Eudragit® RS-PM, owing to the presence of esterificated quaternary ammonium functional groups, shows better swelling capacity and water permeability than the more hydrophobic Ethocel® 100 Premium. Besides, Eudragit® RS-PM has a rigid structure but Ethocel® 100 Premium exhibits plastic deformation properties under compression, tending to better coat ddI particles, thus reducing both number and dimension of pores in the matrix structure and hindering, as a consequence, drug diffusion.

Further studies using Eudragit® RS-PM/Ethocel® 100 Premium mixtures as matrix-forming material for sustained-release forms will be carried out in order to evaluate these behaviors.

Table 5
Coefficient correlations for zero-order kinetic ddI inert matrices

	Lot 1 (10% ddI; 90% Eudragit® RS-PM)	Lot 2 (10% ddI; 90% Ethocel® 100 Premium)
15–360 min	$r = 0.9950$ $P < 0.0001$ $F = 1198.484$	$r = 0.9896$ $P < 0.0001$ $F = 474.834$

Acknowledgements

The present paper was supported by a grant from Ministry of Education, Culture and Sport of Spain. Authors would thank to Laboratories Bristol-Myers Squibb for the contribution to this work.

References

[1] AHFS Drug Information® 95, 'Didanosine', American Hospital Formulary Service, American Society of Hospital Pharmacist, Bethesda, 1995, pp. 416–426.
[2] Videx® 2001: http/www.hivandhepatitis.com/hiv/videx2.html.
[3] Didanosine Information sheets, Lab. Bristol Myers Squibb, S.A.
[4] K. Parfitt (Ed.), Martindale, 32nd ed., Pharmaceutical Press, London, 1999.
[5] Catálogo de Especialidades Farmacéuticas, Ed. Consejo General de Colegios Oficiales de Farmacéuticos, Madrid, 2000, p. 1293.
[6] Eudragit® Information sheets, Röhm Pharma, Darmstadt.
[7] Ethocel® Information sheets, Dow Chemical Company, Michigan.
[8] J. Alvarez-Fuentes, Desarrollo y evaluación de dos sistemas de liberación controlada de naltrexona, Ph.D. Thesis, University of Seville, 1998.
[9] M.A. Holgado, M.J. Fernández-Hervás, J. Alvarez-Fuentes, M.T. Vela, A.M. Rabasco, A. Fini, Characterization of modified paracetamol by means of SEM and fractal analysis, Int. J. Pharm. 142 (1996) 143–151.
[10] J.L. Ford, P. Timmins, Pharmaceutical Thermal Analysis, Ellis Horwood Ltd, Chichester, 1989, p. 25.
[11] S.A. Botha, A.P. Lötter, Compatibility study between atenolol and tablet excipients using differential scanning calorimetry, Drug Dev. Ind. Pharm. 16 (1990) 1945–1954.
[12] E.C. Signoretti, C. De Sena, A. Dell'Utri, S. Alimonti, An investigation into eventual interactions between clenbuterol and some mucolytic drugs by differential scanning calorimetry, Drug Dev. Ind. Pharm. 14 (1988) 1167–1184.
[13] K.A. Khan, The concept of dissolution efficiency, J. Pharm. Pharmacol. 27 (1975) 48–49.
[14] N.H. Anderson, M. Bauer, N. Boussac, R. Khan-Malek, P. Munden, M. Sardaro, An evaluation of fit factors and dissolution efficiency for the comparison of in vitro dissolution profiles, J. Pharm. Biomed. Anal. 17 (1998) 811–822.
[15] J.W. Moore, H.H. Flanner, Pharm. Technol. June (1996) 64–72.
[16] P. Sathe, Y. Tsong, V. Shah, In vitro dissolution profile comparison: statistics and analysis, model dependent approach, Pharm. Res. 13 (1996) 12.
[17] V.R. Goskonda, I.K. Reddy, M.J. Durrani, W. Wilber, M.A. Khan, Solid-state stability assessment of controlled release tablets containing Carbopol 971P, J. Controlled Release 54 (1998) 87–93.
[18] J. Lauroba, J. Domenech, La liberación como factor limitativo de la absorción gastrointestinal, in: J. Doménech, J. Martínez, J.M. Plá (Eds.), Biofarmacia y Farmacocinética, vol. II, Síntesis, Madrid, 1998, pp. 270–274.
[19] V. Shah, Y. Tsong, P. Sathe, In vitro dissolution profile comparison—statistics and analysis of the similarity factor, f_2, Pharm. Res. 15 (1998) 889–896.
[20] R.J. Ravasco, J.D. Unadkat, Ch-Ch. Tsai, A high-performance liquid chromatographic assay for dideoxyinosine in monkey plasma and urina, J. Pharm. Sci. 81 (1992) 690–691.
[21] J.M. Miró, Farmacocinética de la didanosina y de la estavudina, in: J.M. Gatell, J. Mensa, L. Zamora (Ed.), Didanosina (DDI) y Estavudina (D4T), Presente y futuro, Antares, Barcelona, 1996, pp. 97–112.
[22] K. Park, R.W. Wood, J.R. Robinson, Oral controlled release systems, in: R.S. Langer, D.L. Wise (Eds.), Medical Applications of Controlled Release, vol. I, CRC Press, Boca Raton, 1984, p. 159.
[23] S. Miyazaki, M. Oshiba, T. Nadai, Precaution on use of hydrochloride salts in pharmaceutical formulation, J. Pharm. Sci. 70 (1981) 594–596.
[24] J.B. Bogardus, Common ion equilibria of hydrochloride salts and the Setschenow equation, J. Pharm. Sci. 71 (1982) 588–590.
[25] A.O. Okhamafe, P. York, Thermal characterization of drug/polymer and excipient/polymer interactions in some film coating formulation, J. Pharm. Pharmacol. 41 (1989) 1–6.
[26] United States Pharmacopeia 24, US Pharmacopeial Convention, Rockville, 2000, pp. 2150–2151.
[27] M.J. García, D. Santos, Formas sólidas orales, in: J.L. Vila-Jato (Ed.), Tecnología Farmacéutica, vol. II, Síntesis, Madrid, 1997, pp. 55–155.
[28] M.C. Soriano, I. Caraballo, M. Millán, R.T. Piñero, A.M. Rabasco, Influence of two different types of excipients on drug percolation threshold, Int. J. Pharm. 174 (15) (1998) 63–69.
[29] K.K. Peh, C.F. Wong, Application of similarity factor in development of controlled release diltiazem tablet, Drug Dev. Ind. Pharm. 26 (2000) 723–730.
[30] O. Monterde, H. Colom, J. Lauroba, J. Domenech, Estudio comparativo de la velocidad de disolución del diltiazem a partir de dos formas farmacéuticas de liberación modificada, V SEFIG Congress, abstracts book, Valencia, 2001, pp. 187–188.
[31] D. Ramírez, L. Soler, M. García, A. Boix, Dissolution profiles comparisons of pharmaceutical equivalents, V SEFIG Congress, abstracts book, Valencia, 2001, pp. 177–178.