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Development of sustained release matrix tablets of didanosine containing methacrylic and ethylcellulose polymers

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Abstract

Didanosine, a nucleoside analog used in the treatment of acquired immuno deficiency syndrome (AIDS), has been incorporated into directly compressed monolythic matrices whose excipients were mixtures at different ratios of a methacrylic resin (Eudragit RSPM) and an ethylcellulose (Ethocel 100), both water-insoluble and pH-independent polymers. Technological characterization (drug particle morphology, mean weight, diameter, thickness and hardness of tablets) was carried out and in vitro drug release behaviour was measured using the USP basket apparatus. The effect of varying the Eudragit–Ethocel ratio, as well as the drug–polymeric matrix ratio, was evaluated. The results showed the suitability of Eudragit–Ethocel mixtures as matrix-forming material for didanosine sustained release formulations. Combination of the moderate swelling properties of Eudragit RSPM with the plastic properties of the more hydrophobic Ethocel 100 allowed suitable modulation of didanosine release.

Keywords: Didanosine; Eudragit; Ethocel; Sustained release; Matrix tablets

1. Introduction

Didanosine is an antiretroviral drug, analog of the DNA component inosine, belonging to a group of nucleoside analogs developed for the treatment of the acquired immuno deficiency syndrome (AIDS) (Faulds and Brogden, 1992). Didanosine acts by inhibiting reverse-transcriptase, an enzyme required for replication of the human immunodeficiency virus (HIV), and by blocking viral DNA synthesis, thus causing termination of the DNA molecular chain (Perry and Balfour, 1996). Didanosine treatment was found to be a useful and effective alternative in patients who did not tolerate or not respond to zidovudine, the mainstay of anti-HIV-1 drugs. In fact it presents several potential advantages such as minimal bone

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marrow suppression and activity against zidovudine-resistant strains of HIV (Morse et al., 1993). However, didanosine has lower and more highly variable bioavailability in comparison with other nucleoside reverse transcriptase inhibitors (Aungst, 1999). This is probably a consequence of its rapid degradation in the gastric medium (Aungst, 1999; Morse et al., 1993), due to acid hydrolysis of the C–N bond which links the purine base to the deoxyribose sugar (Miró, 1996).

Such a problem, together with need for repetitive dosing, low plasma proteins binding ($< 5\%$), brief plasma elimination half-life (30 min–4 h), dose-related toxicity (Martindale, 1999), in addition to a relatively low daily dosage (250–400 mg), make this drug a suitable candidate for incorporating into oral prolonged-release dosage forms (Lordi, 1986; Rieger et al., 1998; Betageri et al., 2001). Moreover, didanosine physicochemical properties such as adequate water solubility (20 mg/ml at room temperature) and lipophilic–hydrophilic balance (octanol–water partition coefficient = 2.77 (Sánchez-Lafuente et al., 1999a)) appeared suitable for developing this kind of dosage form (Lordi, 1986).

Sustained-release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects (Vergnaud, 1993). Among the different approaches studied with this aim, matrix systems still appear as one of the most attractive from both the economic as well as the process development and scale-up points of view (Lordi, 1986). Moreover, it has been shown that the suitable combination of more types of polymers as matrix-forming materials enables appropriate modifications of the release characteristics of the drug from the dosage form (Rodriguez et al., 1993; Rey et al., 2000).

In the context of a wider research project to develop sustained-release matrix tablets of didanosine (Sánchez-Lafuente et al., 1999a,b; Sànchez-Lafuente et al., 1999c, 2000), the objective of the present work was to evaluate the suitability of Eudragit RSPM (a copolymeric methacrylic acid resin) and Ethocel 100 (an ethylcellulose), alone or in combinations, as polymeric materials for directly-compressed matrix-tablets able to adequately extend drug release. Although both acrylic resins (Rodriguez et al., 1993; Vela et al., 1995) and ethylcellulose (Katikaneni et al., 1995a; Upadrashta et al., 1993) have been widely used as sustained release materials for directly compressible matrix systems, to our knowledge the properties of their mixtures have not yet been evaluated. The influence of varying the Eudragit–Ethocel ratio and/or the drug–polymeric matrix ratio on drug release behaviour has been investigated. The technological properties of the tablets obtained with the different formulations were also examined.

2. Materials and methods

2.1. Materials

Didanosine, or 2′,3′-dideoxyinosine (DDI), was a gift from Bristol-Myers and Squibb (Princeton, NJ, USA). The supporting materials for the inert matrices were Eudragit RSPM, (Hüls Española, Barcelona, Spain), and Ethocel 100 (Dow Chemical Company, MI, USA). Both the polymers are water-insoluble and pH-independent.

2.2. Scanning electron microscope analysis

Shapes and sizes of DDI particles were examined with a Philips XL30 Scanning Electron Microscope (SEM) equipped with an image analysis system. Prior to examination, a very thin coat of carbon was applied to each sample (Holgado et al., 1996). Size and shape analyses of the particles were automatically obtained through the linked image analysis system; it gave a pixel matrix of the particle images, allowing determination of their spatial dimensions and calculation of a set of size and shape descriptors. The following parameters were selected to describe the micro-morphology of DDI particles:

– maximum horizontal and vertical diameters: the maximum distances between two points on

the boundary of the particle on horizontal and vertical lines, respectively;
- shape factor (4π[area/perimeter^2]): provides information about the asymmetry of the particle. For a spherical particle the shape factor is 1, whereas for all other kinds of particles the shape factor is less than 1;
- aspect ratio: the ratio between the horizontal maximum and the vertical maximum distance of the particle. For spherical or square particles the aspect ratio is 1, whereas for those elongated in the X or Y direction the ratio is higher or lower than 1, respectively.

2.3. Preparation of matrix tablets

Several lots of matrix tablets with a theoretical weight of 500 mg were prepared, each containing DDI (5, 10 or 15% w/w) as drug and Eudragit RSPM or Ethocel 100, as polymeric matrix materials, alone or in combination (75/25, 50/50, 25/75 w/w). The polymers and the drug were sieved (Retsch type Vibro sieving machine, Retsch Gmbh, Haan, Germany) and the 150–200 μm granulometric fraction was selected. Physical mixtures of drug and excipients were obtained by mixing the components in a V blender for suitable times. Mixture homogeneity was checked by differential scanning calorimetry measurements (Mettler TA4000 apparatus equipped with a DSC 25 cell, 10 K min^{-1}, 30–180 °C). Tablets were manufactured by direct compression of such mixtures, without any further excipient addition, using an instrumented eccentric machine (Bonals A-300, Barcelona, Spain) with flat-faced punches of 12.0 mm diameter.

2.4. Control tests for matrix tablets

For each batch, 10 randomly drawn tablets were checked for weight uniformity (Mettler type AE-50 electronic balance, Greifensee, Switzerland), diameter and thickness (Export-Pel precision micrometer, Madrid, Spain), and hardness (Schleuniger durometer mod. 2E/205, Greifensee, Switzerland). Means and relative standard deviations were calculated.

2.5. Release studies

Release studies were carried out in pH 7.4 phosphate buffer (700 ml, 37 ± 0.5 °C, 50 rpm) for 6 h using the USP XXIII basket apparatus (Turu Grau, model D-6, Barcelona, Spain). At predetermined time intervals, 1 ml samples were withdrawn, suitably diluted and spectrophotometrically assayed (Hitachi, mod. U-2000, Tokyo, Japan) for drug concentration at 248 nm. The calibration curve for DDI [$y = (0.09155 \pm 0.00058)x + (-0.00155 \pm 0.00272)$] was linear from 0.3125 to 10.00 μg/ml (c.c. = 0.9999; Snedecor ratio $F = 422409.25$, $n = 30$, $P < 0.0001$). Each data point represents the mean of four different samples for each lot (C.V. < 2%).

2.6. HPLC analysis

HPLC analyses were performed to assess the DDI stability in the pH 7.4 phosphate buffer solution employed as dissolution medium in release studies. The HPLC system consisted of a constant-flow pump (Kontron Instruments, type 420), a Rheodyne type 7125 injector equipped with a 20 μl loop and a variable wavelength UV–Vis detector (Kontron, type 432) connected to an integrator (Konik Instruments, type Data Jet 4600). The column used (Merck LiChrospher100 RP-18, 5 μm, 125 mm × 4 mm) was packed with silicagel particles bonded with octadecylsilene. A flow rate of 1 ml/min was employed and the wavelength detector was set at 248 nm. A mobile phase consisting of 6:94 (v/v) acetonitrile:ammonium phosphate buffer (0.05 M) was selected because it gave adequate resolution for the DDI peak and the best values of both capacity and tailing factors (Ravasco et al., 1992).

The DDI representative peak appeared at a retention time of 5.37 ± 0.02 min ($n = 4$). Stability-indicating HPLC analyses conducted on samples obtained at the end of release tests showed in all cases the absence of any other peaks, in addition to that of DDI, thus indicating the absence of drug degradation products and therefore its stability under the release test experimental conditions.

3. Results and discussion

3.1. Image analysis of didanosine (DDI) particles

Table 1 shows the statistical parameters obtained from the image analysis of the SEM micrographs of DDI powder (Fig. 1). Due to the acicular form of the drug particles, both shape factor and aspect ratio were significantly different from 1. The high asymmetry of DDI particles warned against possible difficulties in obtaining homogeneous drug–polymer mixtures and therefore careful controls were performed and optimal mixing times were determined from time to time for each examined formulation, by periodically withdrawing mixture samples and checking it by DSC analysis. The blends were considered homogeneous when the DSC traces of two following samples from the same mixture were superimposable within the limit of experimental error (Mura et al., 1998).

3.2. Technological properties of matrix tablets

All examined formulations gave tablets with good and reproducible technological properties. Table 2 shows the data obtained from each lot of examined tablets. As can be seen, all tablet lots

Table 1
Statistical parameters (mean ± S.D.) from image analysis of didanosine powder by Scanning Electron Microscopy (SEM)

n [a]	Shape factor	Aspect ratio	ESD [b] (μm)	Maximum diameter (μm)	Minimum diameter (μm)	Mean diameter (μm)
99	0.502 ± 0.015	1.254 ± 0.095	10.969 ± 0.519	20.998 ± 1.288	13.179 ± 1.051	19.250 ± 1.213

[a] n, number of cases;
[b] ESD, equivalent spherical diameter.

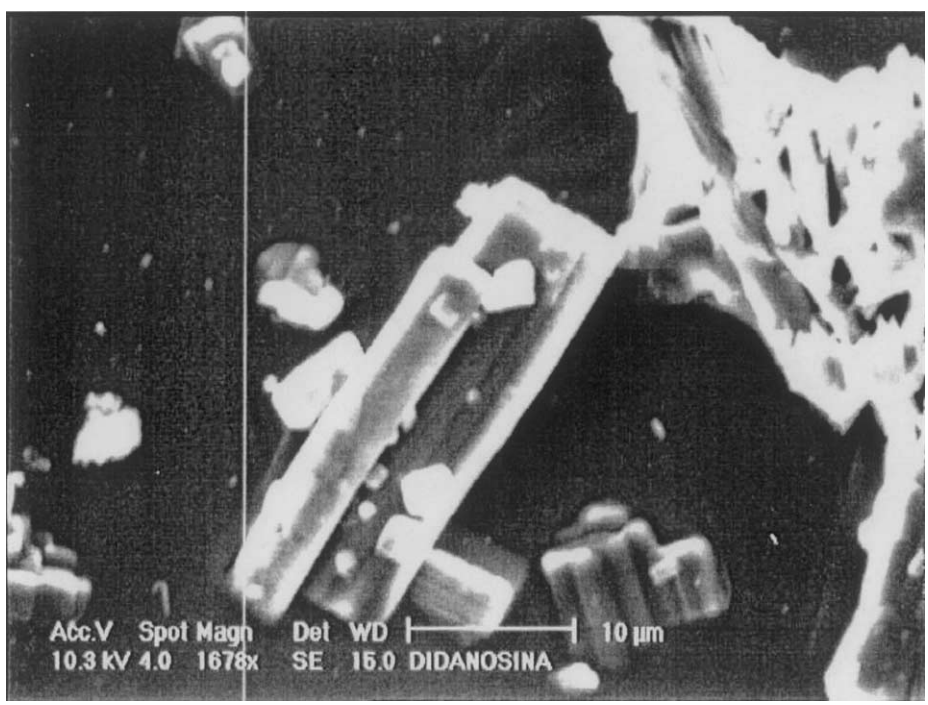

Fig. 1. Microphotograph of didanosine (DDI) particles obtained by SEM analysis.

Table 2
Technological characteristics of didanosine (DDI) matrix tablets (mean ± S.D.)

Eudragit–Ethocel (w/w) ratio	DDI (%)	Weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (Kp)
100/0	10	498.0 ± 1.5	4.154 ± 0.009	12.170 ± 0.009	6.48 ± 0.16
75/25	10	490.1 ± 1.6	3.940 ± 0.010	12.130 ± 0.004	12.88 ± 0.41
50/50	10	493.5 ± 0.9	4.115 ± 0.009	12.093 ± 0.005	9.36 ± 0.36
25/75	10	491.9 ± 1.2	4.260 ± 0.008	12.108 ± 0.004	7.56 ± 0.14
0/100	10	490.1 ± 1.4	4.170 ± 0.007	12.070 ± 0.004	16.36 ± 0.66
100/0	5	490.8 ± 2.3	4.220 ± 0.008	12.197 ± 0.008	5.70 ± 0.22
100/0	15	489.0 ± 1.9	3.822 ± 0.014	12.158 ± 0.005	12.70 ± 0.26
25/75	5	489.9 ± 1.3	4.133 ± 0.006	12.074 ± 0.004	19.99 ± 0.01
25/75	15	495.0 ± 1.4	3.897 ± 0.015	12.085 ± 0.006	19.95 ± 0.05

Table 3
Correlation coefficients according to the different kinetic equations used for describing didanosine (DDI) release behaviour

Eudragit–Ethocel (w/w) ratio	%DDI	Zero-order	First-order	Higuchi's equation
100/0	10	0.969	0.981	0.991
75/25	10	0.980	0.993	0.998
50/50	10	0.960	0.978	0.997
25/75	10	0.973	0.985	0.995
0/100	10	0.981	0.986	0.992
100/0	5	0.975	0.960	0.984
100/0	15	0.961	0.978	0.995
25/75	5	0.733	0.753	0.863
25/75	15	0.965	0.971	0.985

showed good weight (C.V. $< 0.5\%$), thickness (C.V. $< 0.5\%$), and diameter (C.V. $< 0.1\%$) uniformities and no significant differences ($P > 0.1$) were observed with varying formulation composition. Tablet hardness, instead, was strongly influenced and decreased about 2.5 times passing from formulations containing 100% Ethocel (≈ 16 kp) to those with 100% Eudragit (≈ 6.5 kp) as polymeric matrix. However, hardness always remained within acceptable limits (> 5 kp) to give good handling properties without breakage or excessive friability problems, thus confirming the excellent compactability properties of these polymers which allowed direct compression even in the absence of other excipients.

3.3. Release studies

In order to study the drug release mechanism of the examined tablets, the dissolution profiles were analysed according to the zero-order, first-order and Higuchi's square root equations (Table 3). In all cases, the most suitable mathematical model for describing our experimental data was the Higuchi equation, indicating that diffusion was the main factor controlling the drug release rate and that the release mechanism was not significantly influenced by formulation variations.

The effect of varying the polymeric matrix composition is shown in Fig. 2, where are reported the release profiles of DDI, as a function of time square root, from matrices containing a constant drug–polymeric matrix ratio (10/90 w/w). As can be seen, a progressive decrease of DDI dissolution rate was observed with increasing the % of Ethocel 100 in the polymeric matrix. However, this effect, determined through the variation of the drug release rate constant Kr (i.e. the slope of the percent of DDI released as a function of the time square root), was rather uneven, showing the highest step when passing from 25 to 50% of Ethocel 100 (Fig. 3).

The particular behaviour observed by varying the Eudragit–Ethocel ratio can be explained on the basis of the different properties of the two polymers. Eudragit RSPM, a copolymer synthesized from acrylic and methacrylic acid esters, possesses, as a result of incorporation of esterified quaternary ammonium functional groups, both good swelling capacity and permeability with respect to water in comparison with the more hydrophobic Ethocel. Moreover, whereas Eudragit has a rigid structure, Ethocel exhibits plastic deformation properties under compression and it tends to coat drug particles better, thus reducing both number and dimension of pores present in the matrix structure (Katikaneni et al., 1995). The different behavior of the two polymers during compression was further confirmed by the results of SEM analysis of surface morphology of external surfaces and vertical sections of tablets at 100/0 and 0/100 Eudragit–Ethocel ratios (Fig. 4), where the more compact surface structure of Ethocel tablets as well as the plastic deformation undergone by polymer particles were well evident. Thus, both poor wettability of tablet surface, due to the hydrophobicity of Ethocel, and less tablet porosity could concour to hinder the dissolution medium penetration and decrease the DDI diffusion rate.

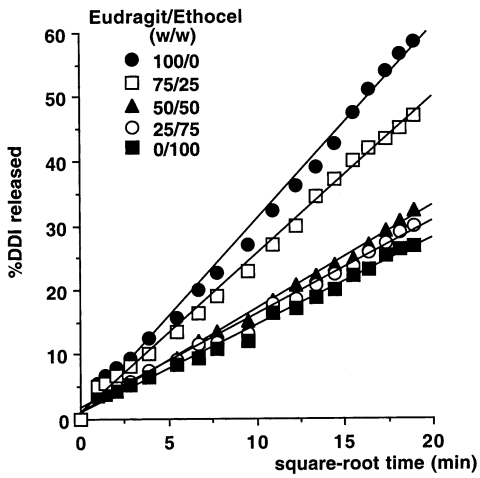

Fig. 2. Effect of varying the Eudragit RSPM–Ethocel 100 ratio on the release profiles of didanosine (DDI) from 10/90 w/w drug:polymeric matrix (mean of four experiments, C.V. < 2%, error bars omitted for the sake of clarity).

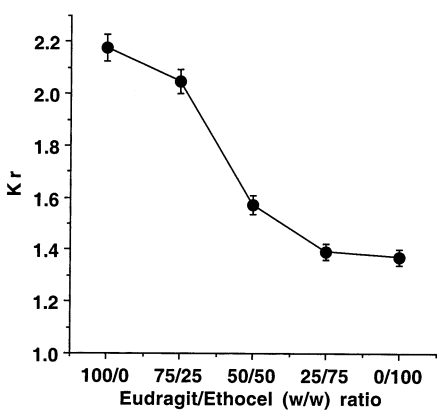

Fig. 3. Relationship between the didanosine (DDI) release rate Kr (% drug released $min^{-1/2}$) and the Eudragit RSPM–Ethocel 100 ratio for tablets containing 10% w/w drug (SEM error bars, $n = 4$).

As regards the effect of variations in drug to polymer ratio, as expected, an increase of drug release was observed when increasing the drug content in the matrix (Fig. 5). However, the extent of this effect was strongly dependent on the composition of the polymeric matrix. In fact, if we consider, for example, the matrices at 25/75 Eudragit–Ethocel w/w ratio, an increase of drug release rate of about four times was observed when passing from 5 to 15% w/w drug content. On the contrary, the increase was only of about 1.5 times for the corresponding tablets containing Eudragit alone. Moreover, the differences in polymeric matrix behaviour were more marked for lower contents of the drug. In fact for 5% w/w drug content, the matrix containing Eudragit alone showed a drug release rate of more than five times higher than that from the 25/75 Eudragit–Ethocel matrix, whereas the difference between these same matrices was only 1.4 times for 15% w/w drug content.

4. Conclusions

Mixtures of Eudragit and Ethocel showed to be particularly suitable for obtaining directly compressed sustained-release matrix tablets with appropriate technological properties and well reproducible drug release profiles.

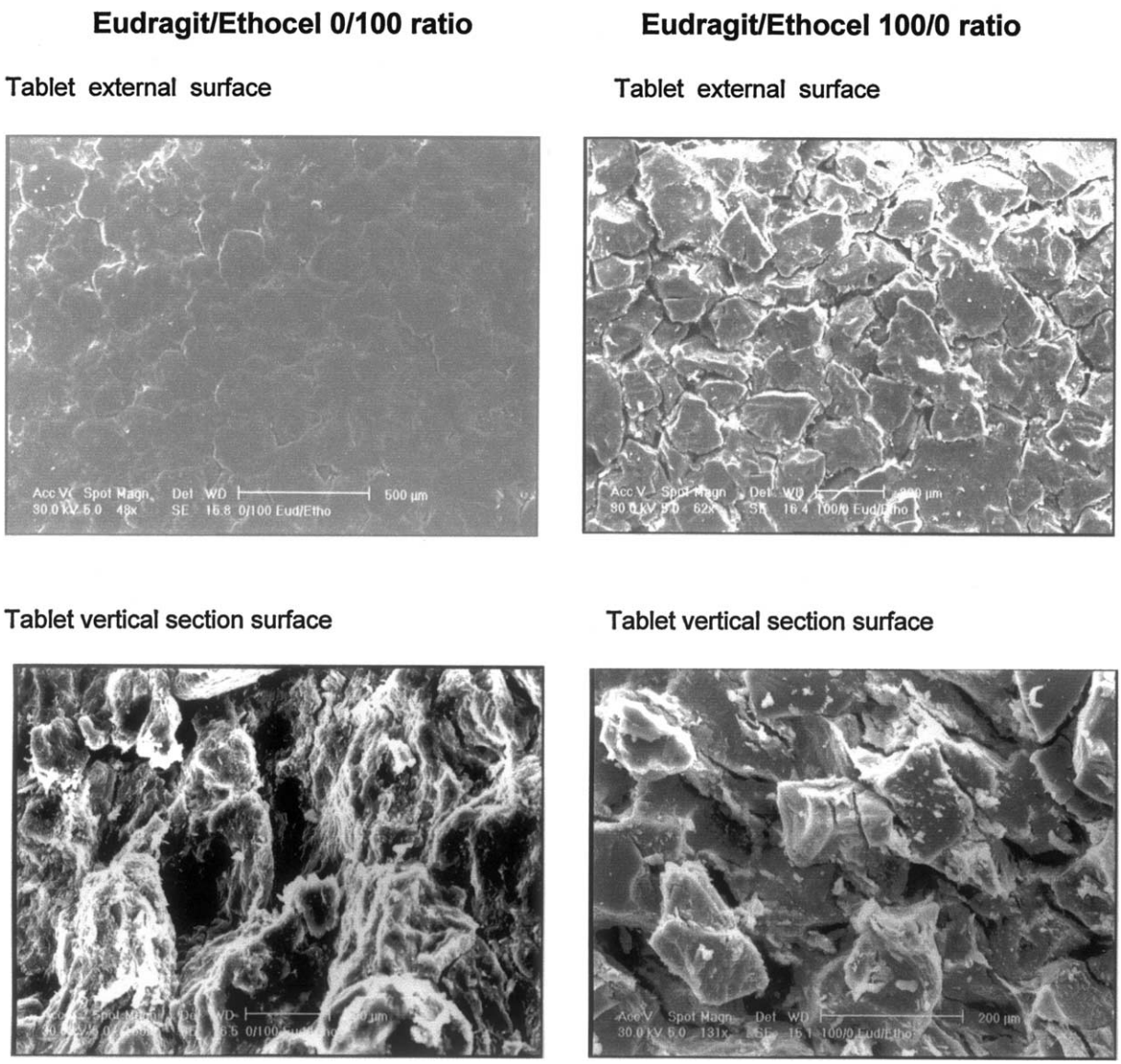

Fig. 4. SEM microphotographs of surface and sections of didanosine (DDI) matrix tablets at 0/100 and 100/0 Eudragit–Ethocel ratios.

The results of release studies indicated the possibility of achieving a suitable modulation of DDI release rate by opportunely varying the Eudragit–Ethocel ratio in the matrix tablet, taking advantage at the same time of the moderate swelling properties of Eudragit and of the plastic properties of the more hydrophobic Ethocel. However, the variation in drug release rate was not linearly related to the ratio between these polymers and depended on the drug content in the matrix.

Finally, because HPLC analysis did not indicate any loss of drug due to degradation, the low percentages of observed drug release (less than 50% after 6 h for most formulations) can be actually attributed to excessively low drug release rates.

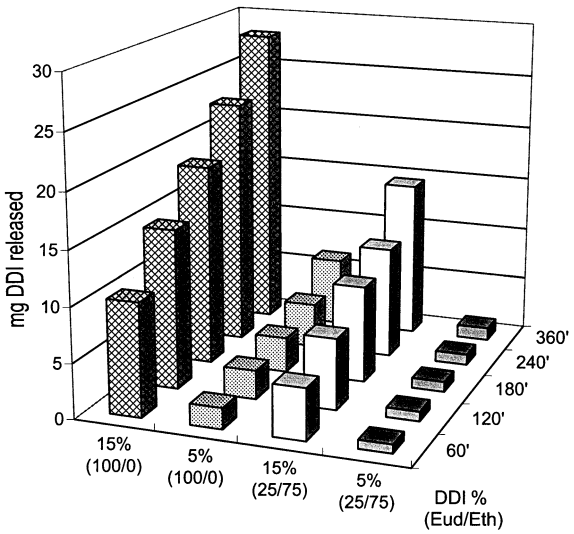

Fig. 5. Effect of varying the drug–polymer ratio (15/85 or 5/95 w/w) on the release of didanosine (DDI) from Eudragit RSPM–Ethocel 100 matrix tablets (mean of four experiments, C.V. $< 2\%$, error bars omitted for the sake of clarity).

Therefore, further studies will be performed for the final setting up of the proposed dosage form, aimed on one hand at developing a gastro-resistant coating able to effectively protect the drug from acid degradation, and, on the other, at adequately improving drug release rate, by adding suitable canalizing agents to the polymeric matrix.

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