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Research Article

The Influence of the Compression Force on Zidovudine Release from Matrix Tablets

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Abstract. The aim of the present work is the study of different zidovudine (AZT) formulations containing polymers (both cellulosic and acrylic), in order to evaluate the influence of the compression force on the antiviral release from the matrix tablets. The results evidenced that the formulations compressed at 500 and 1,000 MPa exhibit a higher hardness than those prepared at 100 MPa. The effect of the compression force on the drug release was analyzed and a statistically significant difference was observed ($P<0.05$). Using lower compression forces leads to slightly better release profiles, *i.e.*, profiles close to an ideal Higuchi kinetics for a total release of drug in a 12-h period, allowing to conclude that a compression force higher than 100 MPa is unnecessary.

KEY WORDS: compression force; Eudragit® RL PO; Eudragit® RS PO; HPMC; sustained release; zidovudine.

INTRODUCTION

Zidovudine is a thymidine analogue that inhibits the replication of the human immunodeficiency virus. Despite these benefits, AZT therapy has been often associated with adverse reactions, including both anemia and neutropenia (1–3).

Over the years, several researchers have aimed to develop zidovudine formulations, in order to reduce its adverse effects, improve efficacy and promote an increase in acquiescence and continuity of care by the patient (4–6).

Controlled-release formulations have numerous advantages, such as: (a) reduction of drug plasma level fluctuation; (b) minimization of adverse side effects and tolerability improvement; (c) increase of patient comfort and compliance; and (d) lower healthcare costs (7). Relative to other controlled-release methods, matrix tablets, in particular, are easily obtained at a reduced cost, constituting a simple alternative in the development of efficient formulations (8).

Polymeric materials have been widely used in order to opportunely modify and modulate the drug release from solid pharmaceutical dosage forms such as sustained-release or controlled-release matrix tablets (9,10). However, the chemical–physical properties of the drug, polymers and excipients, the composition and the component's relative amounts in the formulations, as well as the manufacturing process parameters, can influence the drug release performance (11).

Direct compression is an important process in the pharmaceutical industry, being extensively used to manufacture tablets based on both empirical knowledge and extensive laboratory experiments, in order to optimize compaction conditions (12). This method offers several advantages, namely simplicity, economy, reduction of the manufacturing steps and increased product stability (13), as compared to other matrix preparation techniques, *i.e.*, wet granulation (14), used in the preparation of extended-release matrix tablets of AZT (4). However, pressure may also induce polymorphic transitions and consequently changes in the drug toxicity or bioavailability, since the latter is mediated via dissolution. AZT, in particular, is recognized to undergo polymorphism (15).

Our main goal is to prepare tablets by direct compression, containing the same AZT weight as the conventional (commercial) tablet (300 mg), allowing a sustained release of up to 12 h and consenting its use either alone or in combination with other antiviral agents. The purpose of the present study is to probe the influence of the supported compression force on zidovudine release from hydroxypropylmethylcellulose (HPMC) K15M and K100M, Eudragit® RS PO and Eudragit® RL PO matrices, in order to produce adequate sustained-release tablets. Moreover, we propose a lactose-free formulation, since most of the patients, especially the HIV ones, may also develop lactose intolerance.

It should be emphasized that AZT matrices do not present any problems concerning flow or compactness properties. Thus, adjuvant addition is unneeded, which facilitates the cohesion of the material. Furthermore, the elimination of heat and moisture, in the manufacture procedure, increases not only the stability but also the

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suitability of the process for thermolabile and moisture-sensitive drugs (13,14).

METHODS

Materials

The drug used was zidovudine (CIPLA, India). The polymers used were Eudragit® RS PO and Eudragit® RL PO (Röhm Pharma, Germany); hydroxypropylmethylcellulose, Methocel® K15M and Methocel® K100M (Colorcon, UK). The diluent used was lactose monohydrate, Granulac® 200 (Meggle, Wasserburg, Germany). The lubricants used were talc and magnesium stearate (Magnesia GmbH, Germany).

Preparation and Characterization of the Tablets

Different formulations (Table I) were directly compressed into tablets, using an automatic hydraulic press (Speca Press; Automatic Press Ltd., England). The drug and excipients were passed through a 125-mesh sieve and mixed in a mortar for 15 min. Talc and magnesium stearate were sieved (500 mesh) and added as lubricants. Formulations containing 300 mg of AZT were directly compacted into a core tablet (10 mm diameter) at pressures of 100, 500, and 1,000 MPa, respectively. Tablets were checked for weight uniformity (analytical KERN 770, Germany), diameter and thickness (Micrometer, Switzerland), friability (Erweka TA 20, Germany), and hardness (TAXT plus texture analyzer, UK). Means and relative standard deviations were calculated.

Differential Scanning Calorimetry

The thermal properties of both AZT and its formulations, at different compression forces, were evaluated using a differential scanning calorimeter (DSC-50, Shimadzu, Kyoto, Japan) coupled to a Shimadzu TA-50 analyzer. The samples were heated in sealed aluminum pans, under a nitrogen flow (10 ml min^{-1}). About 3.0 mg of pure drug, excipients, and polymers or mixtures of polymers (1:1) were analyzed, at a heating rate of 10°C min^{-1}, from 25 to 350°C. The apparatus was calibrated with indium (99.98%, m.p. 156.6°C; ΔH_{fus}=28.54 J.g^{-1}).

Table I. Formulations Containing Cellulose Derivatives and Polymethacrylates

Components	Formulations (mg)		
	F1	F2	F3
Zidovudine	300.0	300.0	300.0
HPMC K100M	19.0	23.0	19.0
HPMC K15M	19.0	23.0	19.0
Eudragit® RS PO	19.0	–	–
Eudragit® RL PO	19.0	–	–
Lactose	–	30.0	38.0
Talc	2.0	2.0	2.0
Magnesium stearate	2.0	2.0	2.0

X-Ray Powder Diffraction

X-ray powder diffraction (XRPD) measurements were performed with an X'Pert powder diffraction system (Phillips, Netherlands), at a voltage of 40 kV and a current equal to 35 mA. Approximately 50 mg of sample was loaded on an aluminum plate. Scans were performed from 5 to 50 (2θ value) at a rate of 1 s^{-1} with a step size of 0.025º. To examine the effect of the compression pressure on the crystal form, both AZT powder and an AZT compressed sample were subject to the measurement (ground in a mortar).

In Vitro Release Studies

The AZT release from different tablets was evaluated, for 24 h, in 900 ml of dissolution media, using the USP Method 1 (USP31/26, 2008) (16). In this method, both simulated gastric (pH 1.2) and intestinal fluid (pH 6.8) without enzymes were used, maintained at 37°C and with a stirring speed of 50 rpm, on multiple vessel dissolution apparatus (Vankel VK-7000 dissolution testing station, USA). After 2.0 h the pH of the dissolution medium was varied from 1.2 to 6.8 and the progress of the dissolution was maintained for the specified time. At suitable intervals (0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 and 24 h), samples of 5 ml were withdrawn and immediately replaced with an equal volume of the dissolution medium. These samples were filtered (45 μm), diluted and analyzed spectrophotometrically for the AZT content, at 266 nm (Shimadzu UV-1603 spectrophotometer, Japan). The mean of three independent determinations was used to calculate the drug release from each formulation.

The dissolution profiles of the tablets can be characterized following mathematical model-independent or -dependent methods. The former include: the time to release x% of drug from the tablet ($t_{x\%}$), the sampling time ($\%_{yh}$), *i.e.*, the percentage of drug release after y hours, the mean dissolution times (MDT) and the dissolution efficiency (DE) at 2 h and 12 h. DE is defined for a pharmaceutical dosage form as the area under the dissolution curve for a certain period of time, expressed as a percentage of the area of the rectangle that represents 100% dissolution at the same time point.

Concerning the extensively used model-dependent approach, the release kinetics of zidovudine formulations was described by finding the best fit of the data (fraction of drug released *versus* time) to distinct mathematical functions: zero-order, first-order, and Higuchi (17) Moreover, in order to gain some insight into the drug release mechanism, the Korsmeyer–Peppas semi-empirical model was applied (18). After fitting these models to the dissolution data, their performance was based on the determination coefficient (R^2) comparison. Additionally, in order to compare the drug dissolution profiles: the similarity factor (f_2) was used (19–22).

Swelling Studies

Matrix tablets were introduced into the dissolution apparatus, at standard conditions, in accordance with the previously described procedures, for the evaluation of *in vitro* drug release profiles. The tablets were removed using a small

basket and the weight of swollen tablets was determined at selected time intervals, for a 24-h period.

RESULTS AND DISCUSSION

Preparation and Characterization of the Tablets

All formulations yielded matrix tablets with good and reproducible technological properties. As expected, tablet hardness and friability were typically compression force-dependent (Table II). It was observed that at higher compression forces the hardness of the tablets increased (ranging from 96.90±2.11 N to 189.73±1.15 N) and the friability decreased (ranging from 0.79±0.06% to 0.13±0.07%).

The one-way ANOVA test carried out for the mean hardness results indicate that there was significant difference for each ($P<0.05$) distinct compression forces were applied. Moreover, the analysis of variance for friability was also performed, in order to determine the impact of the formulation differences: an F_{value} (3.15) higher than obtained with an $F_{critical}$ (2.13).

Differential Scanning Calorimetry

The DSC thermograms of the zidovudine containing tablets, compressed at various pressures (Fig. 1), evidenced an endothermic peak followed by an exothermic one. The results show that a higher pressure induces changes in the exothermic profile, probably due to a crystalline-to-amorphous transformation or even to a polymorphic change in AZT. On the other hand, the analysis of Fig. 1, as well as of Table III, where the DSC parameters are presented, demonstrates a little difference on heat flow for exothermic rates between the formulations.

The thermal performance of the tablets (F1, F2, and F3) over the control (AZT) demonstrated that the calorific capacity did not depend on the compression pressure (100, 500, and 1,000 MPa). Although tablets of a given composition were compressed at different forces, the data displayed similar heat flow patterns for endothermic rates.

In fact, the one-way ANOVA test performed for the AZT matrix heat capacity values indicates that, statistically, there was considerable difference when distinct compression forces were applied ($F_{critical}=3.35$ and $F_{value}>3.35$).

Table II. Hardness and Friability of Zidovudine Matrix Tablets Obtained with Different Compression Forces

Formulations	Pressure (MPa)	Parameters	
		Hardness[a] (N)	Friability (%)
F1	100	103.12±2.10	0.79±0.06
	500	184.14±1.52	0.13±0.08
	1,000	186.19±1.34	0.13±0.07
F2	100	103.40±0.99	0.58±0.09
	500	184.21±1.76	0.25±0.05
	1,000	189.73±1.15	0.16±0.06
F3	100	96.93±2.11	0.66±0.05
	500	177.40±1.48	0.17±0.04
	1,000	181.84±1.79	0.16±0.08

[a] Mean ± SD

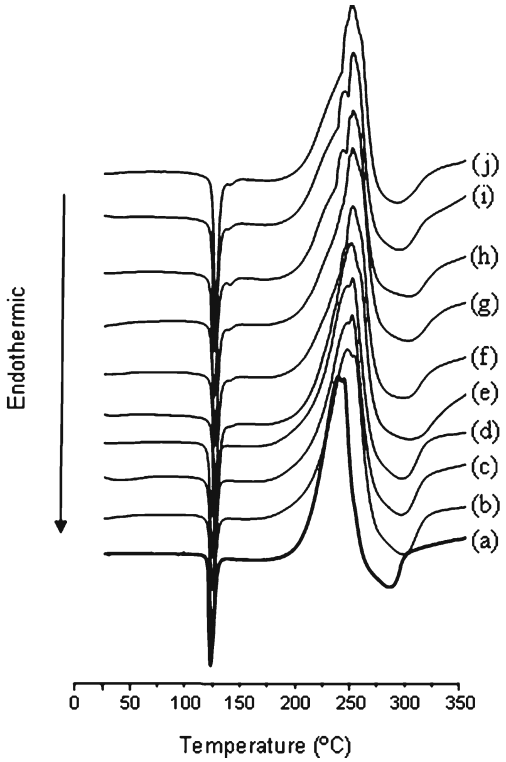

Fig. 1. DSC thermograms of different matrices: **a** F1 tablet obtained with 100 MPa; **b** F1 tablet obtained with 500 MPa; **c** F1 tablet obtained with 1,000 MPa; **d** F2 tablet obtained with 100 MPa; **e** F2 tablet obtained with 500 MPa; **f** F2 tablet obtained with 1,000 MPa; **g** F3 tablet obtained with 100 MPa; **h** F3 tablet obtained with 500 MPa; **i** F3 tablet obtained with 1,000 MPa; and **j** reference AZT powder

X-Ray Powder Diffraction

The X-ray diffractograms of the powdered tablets are presented in Figs. 2, 3, and 4. The XRPD of zidovudine is also included for comparison. Its pattern agrees with the reported data (International Center for Diffraction Data), reflecting a single polymorphic form (needle crystals).

The compression force and the reduction of the AZT quantity in the tablets, compared to the pure sample (100%), led to a decrease in the peak intensities. However, the dominating signals were always those of the drug.

The physical mixtures comprising AZT and HPMC K15M:HPMC K100M, Eudragit® RS PO and Eudragit® RL PO exhibited peaks corresponding to crystalline AZT. Primary peaks at approximately 19.5° (2θ) and 22.5° (2θ) were less intense when higher compression forces (500, 1,000 MPa) were applied.

In general, the results shown in Figs. 2, 3, and 4 confirm that the AZT crystalline structure is modified in the polymeric matrix during processing. These measurements corroborate the DSC data previously discussed (Fig. 1). As expected, the decrease of the diffraction peaks intensity corresponds to a change in AZT from a crystalline to an amorphous form.

Table III. Thermal Transition from Prepared Tablets with Different Compression Forces

Formulations	Pressure (MPa)	Endothermic (°C)				Exothermic (°C)			
		T_o	T_p	T_f	ΔH (J g^{-1})	T	T_p	T_f	ΔH (J g^{-1})
AZT		121.83 (0.67)	124.85 (0.61)	130.26 (0.75)	118.46 (0.38)	209.78 (0.58)	235.53 (0.62)	251.15 (0.57)	845.41 (0.55)
F1	100	121.12 (0.97)	124.33 (0.91)	128.40 (0.88)	74.26 (0.60)	206.78 (0.64)	235.14 (0.59)	254.05 (0.61)	533.79 (0.43)
	500	120.82 (0.86)	124.33 (0.80)	128.41 (0.79)	74.68 (0.51)	206.94 (0.80)	253.87 (0.91)	253.87 (0.89)	492.78 (0.73)
	1,000	120.78 (0.77)	124.58 (0.62)	128.86 (0.63)	88.99 (0.78)	208.33 (0.73)	253.89 (0.75)	253.89 (0.62)	586.77 (0.59)
F2	100	120.94 (0.96)	124.24 (0.91)	128.85 (0.81)	88.95 (1.01)	205.29 (0.55)	256.78 (0.59)	256.78 (0.61)	624.75 (0.80)
	500	120.61 (0.84)	124.32 (0.75)	128.00 (0.79)	81.34 (0.55)	218.81 (0.87)	254.57 (0.79)	254.57 (0.85)	486.18 (0.64)
	1,000	120.67 (0.57)	124.51 (0.60)	128.42 (0.66)	82.16 (0.69)	218.79 (0.90)	255.16 (0.84)	255.16 (0.87)	516.22 (1.03)
F3	100	120.80 (0.99)	124.61 (0.98)	128.39 (0.83)	78.81 (0.41)	223.44 (0.44)	255.38 (0.39)	255.38 (0.47)	485.13 (0.51)
	500	120.29 (0.51)	124.10 (0.49)	128.04 (0.57)	97.24 (0.36)	227.04 (0.66)	255.00 (0.69)	255.00 (0.65)	509.83 (0.75)
	1,000	120.73 (0.62)	124.08 (0.70)	127.69 (0.72)	71.41 (0.57)	221.31 (0.81)	254.33 (0.86)	254.33 (0.84)	404.43 (0.91)

Values in parenthesis mean standard deviation
T_o onset, T_p peak, T_f endset, ΔH heat

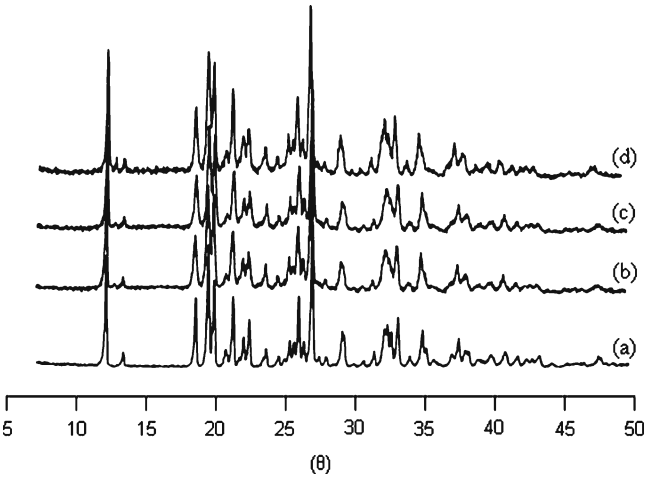

Fig. 2. Powder X-ray diffraction patterns of AZT powder (**a**) and F1 formulation matrices prepared with different compression forces: 100 MPa (**b**), 500 MPa (**c**), and 1,000 MPa (**d**)

Swelling Studies

The degree of the polymer hydration is one of the factors determining the rate and extent of drug release from the swellable matrices (23). Therefore, a study of the hydration rate of the solid matrices presently investigated was carried out. It may be observed that media uptake, and the subsequent formation of a gel layer, are rapid processes, attaining maximum values (between 133% for F2 prepared at 1,000 MPa, and 326% for F1 prepared at 100 MPa) in half an hour. After this time, the gel layer consistently dissolved and eroded away, thus exposing a new layer, as is commonly observed for swellable controlled-release tablets.

Furthermore, the presence of water-insoluble, water-dispersible Eudragit® RL PO and Eudragit® RS PO in the F1 tablets promoted an increase of the media uptake capacity when compared to the F2 and F3 matrices. Probably, both hydrophilic and hydrophobic polymer mixtures lead to an easier penetration of the media into the network.

Considering the effect of different compression forces used for assembling the matrix tablets, a decrease of the total

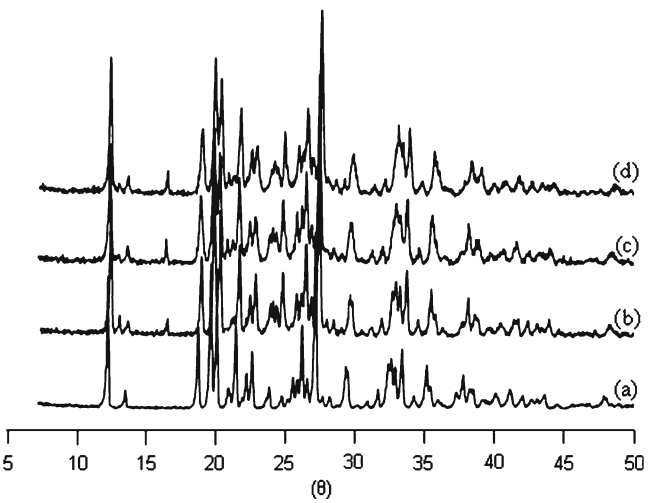

Fig. 3. Powder X-ray diffraction patterns of AZT powder (**a**) and F2 formulation matrices prepared with different compression forces: 100 MPa (**b**), 500 MPa (**c**), and 1,000 MPa (**d**)

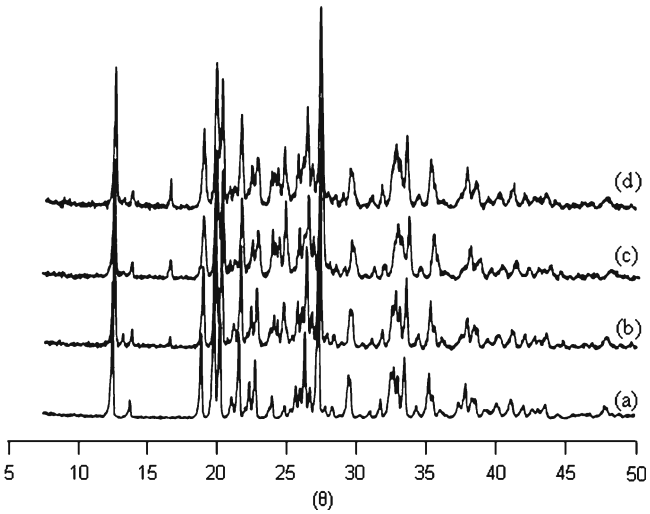

Fig. 4. Powder X-ray diffraction patterns of AZT powder (**a**) and F3 formulation matrices prepared with different compression forces: 100 MPa (**b**), 500 MPa (**c**), and 1,000 MPa (**d**)

media uptake was observed with an increase of the applied force.

These results are in accordance with published results (23,24) that reported the relationship between the liquid penetration rate and the disintegration force, concluding that the compression force modifies the amount of media absorbed and, as a result, contributes to the swelling and erosion processes of the tablets.

Kinetic Analysis of the Drug Release

The effect of compression force on the drug release was studied by preparing identical tablets, but by way of different applied pressures. The influence on the rate and extent of AZT release was evaluated by the $t_{25\%}$, $t_{50\%}$, $\%_{12h}$, $\%_{24h}$, MDT, DE_{2h} and DE_{12h} parameters (Table IV).

The prepared AZT matrix tablets did not evidence large differences between formulations as to the percentage of AZT release at 24 h. Actually, the $\%_{24h}$ value found for the simple HPMC mixtures (F2 and F3) after 24 h varied between 89.42%±0.99 and 99.46%±1.12, as compared to the F1 formulations, which displayed higher values than 94.49%± 1.26, reaching a maximum of 99.81%±1.14. Data analysis revealed that all tablets displayed a small decrease of the % release upon an increment of the compression force. These differences are even more pronounced if $\%_{12h}$ values are considered (Table IV).

Both $t_{25\%}$ and $t_{50\%}$ were found to be higher as the compression force applied to the tablets increased. DE_{2h} and DE_{12h} values for tablet formulations made with 100, 500, and 1,000 MPa pressures, in turn, evidenced a capacity to reduce the dissolution efficiency (Table IV), reflecting the lower solubility of AZT in the media or the lower penetration capacity of water into the polymeric network.

Therefore, the relationship between the formulation constituents and the dissolution efficiency is of the utmost importance, since the compression force applied to the tablets modifies the dissolution parameters (Fig. 5). The effect of the compression force on the drug release was analyzed using ANOVA: a statistically significant difference was observed ($P<0.05$). The release rate decreased with an increasing compression force.

As expected, tablet hardness and friability were typically compression force-dependent. It was observed that high compression forces promoted an increase of the tablet's hardness and concomitantly a lower friability. These properties are strictly related to the liquid penetration into solid dosage forms. Water uptake promotes the development of a force inside the tablet responsible for its dissolution and the rate of this process may be related to the rate of liquid penetration into the dosage form (25,26).

Several authors (27,28) have stated that the compression force is a statistically significant factor regarding tablet hardness, but its effect on drug release from HPMC tablets was found to be minimal (29,30).

The f_2 (similarity factor) is inversely proportional to the average squared difference between the two profiles, with an emphasis on the larger difference among all the time points tested (21). The use of this factor is recommended by the FDA's guides for industry, for dissolution profile comparisons. According to these guides, f_2 values greater than 50 (50–100) usually ensure an equivalence of the two curves.

Therefore, in the present study, f_2 was employed in order to evaluate the formulation release profiles. These analyses are based on a comparison between the experimental results and the release profile considered as ideal. For the type of matrices presently used, containing either hydrophilic or hydrophobic polymers, two ideal profiles were considered: (1) an ideal Higuchi profile, for a total drug release in 12 h ($K_H=100/12^{1/2}$); and (2) an ideal target profile (30) based on data from the literature (release after 2 h, 35%; after 4 h, 60%; after 8 h, 90%). As f_2 is strongly

Table IV. Dissolution Parameters for the Zidovudine Matrix Tablets

	Formulations								
	100 MPa			500 MPa			1,000 MPa		
Parameters	F1	F2	F3	F1	F2	F3	F1	F2	F3
$t_{25\%}$ (h)	1.05±0.99	2.18±0.87	1.24±0.95	1.58±1.24	2.54±1.16	1.59±1.26	1.71±0.89	3.02±1.14	1.96±1.51
$t_{50\%}$ (h)	3.66±1.03	5.90±1.12	4.01±0.99	4.23±1.17	6.93±1.35	5.23±1.43	4.74±1.10	8.28±1.25	7.07±1.38
$\%_{12h}$[a]	90.50±1.09	76.92±0.99	84.12±1.18	84.71±1.43	69.26±1.26	78.02±1.51	80.19±1.17	62.64±1.29	66.89±1.47
MDT[a] (h)	3.85±0.04	4.53±0.02	3.84±0.03	3.58±0.02	4.14±0.01	4.11±0.02	4.18±0.05	4.43±0.04	4.20±0.04
DE_{2h}[a] (%)	22.55±1.13	14.76±1.17	20.63±0.96	17.33±0.95	12.72±1.00	12.84±1.05	16.25±1.05	11.01±0.94	15.74±1.13
DE_{12h}[a] (%)	61.46±0.99	48.07±1.23	57.61±0.99	55.46±1.17	43.00±1.63	50.77±1.29	52.47±1.29	38.13±1.35	43.26±1.19

[a] Mean ± S.D (six measurements)

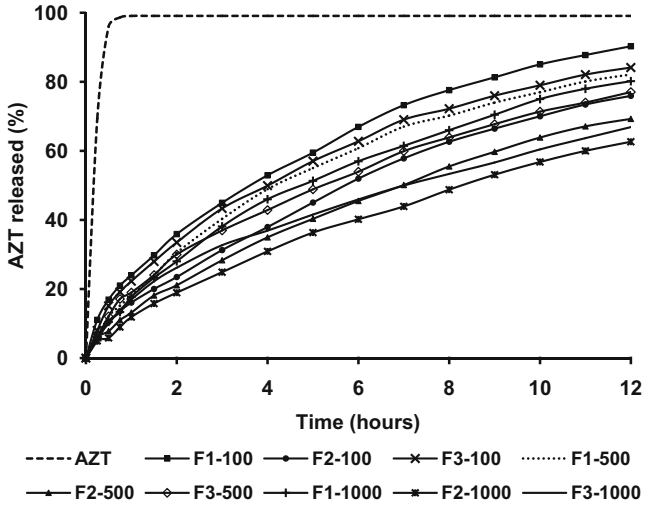

Fig. 5. Comparative release profile of zidovudine from matrix tablets

dependent on the last release point (21), only the release values between 0% and 85% were considered (Table V).

Analysis of the values comprised in Table V allows to conclude that the f_2 values decreased in F1, F2, and F3 formulations at 100 to 1,000 MPa. Thus, pressures greater than 100 MPa give rise to profiles progressively distinct from the desired ones.

In fact, while the F1 formulation presents quite good f_2 values (≥51) for a pressure of 100 MPa, and F3 still obeys the ideal Higuchi type release, for the same pressure, most of the calculated f_2 values were far from the desirable intervals, suggesting that the dissolution from tablets prepared using higher compression forces does not conform to the target release profiles.

The release profiles from tablets obtained for three different compression levels (Fig. 5) were submitted to mathematical model-dependent methods. In all cases, based on the Korsmeyer–Peppas n value obtained by fitting the data, it is possible to access the drug release mechanism from the formulation (31,32). The obtained n values in the range 0.55–0.70 point to a non-Fickian (anomalous) case: the rate of drug release is due to the combined effect of drug diffusion, and polymer relaxation is the main factor controlling this process (Table VI).

Furthermore, in order to improve the description of the release process kinetics, the data was fitted with either the

Table V. Similarity Factor (f_2) for a 0 to 85% Release from AZT Tablets Obtained with Different Compression Forces, Relative to Both Higuchi and Target Ideal Release Profiles (see text)

		f_2	
Formulations	Pressure (MPa)	Target	Higuchi
F1	100	51.0	64.6
	500	43.5	48.2
	1,000	38.6	42.8
F2	100	32.5	36.9
	500	28.8	31.1
	1,000	25.4	27.0
F3	100	43.6	53.2
	500	36.4	40.1
	1,000	29.5	31.3

Table VI. Fitting Results of the Experimental Zidovudine Release Data to Different Kinetic Mathematical Models [a]

		Zero-order		First-order		Higuchi		Korsmeyer–Peppas		
Formulation	Pressure (MPa)	K_0 (%h^{-1})	R^2	K_1 (h^{-1})	R^2	K_H (%h$^{-1/2}$)	R^2	K_{KP} (h^{-n})	n	R^2
F1	100	13.62 (0.06)	0.9731 (0.0003)	0.129 (0.002)	0.9854 (0.0016)	72.83 (0.23)	0.9868 (0.0003)	25.48 (0.40)	0.552 (0.021)	0.9923 (0.0010)
	500	12.34 (0.03)	0.9665 (0.0109)	0.125 (0.003)	0.9821 (0.0032)	66.41 (0.13)	0.9772 (0.0005)	25.18 (0.52)	0.569 (0.024)	0.9718 (0.0031)
	1,000	11.95 (0.01)	0.9770 (0.0028)	0.128 (0.005)	0.9596 (0.0109)	60.31 (0.06)	0.9950 (0.0004)	22.21 (0.44)	0.571 (0.010)	0.9871 (0.0005)
F2	100	16.18 (0.04)	0.9820 (0.0007)	0.146 (0.001)	0.9685 (0.0033)	68.45 (0.16)	0.9841 (0.0005)	24.78 (0.51)	0.700 (0.039)	0.9982 (0.0030)
	500	11.33 (0.02)	0.9576 (0.0004)	0.139 (0.010)	0.9633 (0.0060)	56.40 (0.09)	0.9985 (0.0003)	21.02 (0.40)	0.680 (0.039)	0.9940 (0.0005)
	1,000	11.07 (0.01)	0.9611 (0.0126)	0.134 (0.004)	0.9561 (0.0118)	54.84 (0.05)	0.9955 (0.0001)	20.56 (0.41)	0.629 (0.075)	0.9928 (0.0019)
F3	100	13.21 (0.03)	0.9781 (0.0026)	0.133 (0.009)	0.9727 (0.0037)	69.76 (0.18)	0.9843 (0.0007)	23.59 (0.43)	0.637 (0.016)	0.9651 (0.0009)
	500	12.06 (0.03)	0.9492 (0.0070)	0.126 (0.006)	0.9907 (0.0017)	62.41 (0.12)	0.9928 (0.0040)	23.87 (0.50)	0.546 (0.057)	0.9789 (0.0008)
	1,000	11.48 (0.05)	0.9816 (0.0053)	0.132 (0.002)	0.9678 (0.0175)	57.71 (0.04)	0.9984 (0.0002)	21.53 (0.66)	0.604 (0.063)	0.9964 (0.0007)

[a] Values in parenthesis represent the standard deviation; R^2 is the coefficient of determination

zero-order rate equation, which depicts the systems for which the release rate is concentration-independent, or using the first-order equation, for systems where the dissolution rate is dependent on the drug concentration (19,28). Additionally, the Higuchi square root equation describes the release from systems where the solid drug is dispersed in an insoluble matrix and the release behavior is mainly correlated to the rate of drug diffusion (17,22).

The good fitting obtained with the Higuchi equation, yielding determination coefficients (R^2) larger than 0.98 and n values between 0.55 and 0.70 in the Korsmeyer–Peppas model, suggests that the drug release from F1, F2, and F3 matrices is controlled by both drug diffusion in the hydrated matrix and by the erosion of the matrix itself (16), as previously detected for similar sustained-release formulations.

CONCLUSION

The results presently gathered confirm that the compression forces used in the preparation of the AZT matrix tablets do not significantly affect the mechanism or the drug release profile from these matrices, since this is mainly controlled by the drug:polymer composition.

This fact is demonstrated by the mechanical properties of the tablets produced with different compression forces. Although this study was carried out for obtaining directly compressed sustained-release formulations, with appropriate technological properties and well reproducible drug release profiles, the data presently obtained suggests that the applied compression pressures from 100 to 1,000 MPa do not significantly modify the matrix properties, allowing the use of lower forces for their preparation. Moreover, using lower compression forces minimizes the possibility of polymorphic transitions, and allows to achieve release profiles nearer of the desired ones.

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