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Eudragit FS 30D as a potential polymer for use in the technology of preparing matrix tablets contain metronidazole – an experimental and mathematical modeling study

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ABSTRACT

The aim of this study was to examine the usefulness of a pH-dependent copolymer – Eudragit FS – for employment in the technology of preparing modified release metronidazole matrix tablets. In addition, in our work, Eudragit RL and Eudragit RS were included in the composition of some formulations, as well as sodium lauryl sulfate and polysorbate 80. As part of the study of the dissolution test, the similarity coefficient (f2) for the obtained profiles was calculated, and mathematic models were used to estimate the kinetics and mechanism of active substance release. In our work, it was observed that the inclusion of polymer Eudragit FS alone in the tablet composition ensured a modified release of the active substance for 10 h. After this time period, the amount of metronidazole determined in the acceptor fluid was 71% - 81% of the declared dose. Modification of the composition by the addition of surfactants resulted in an increased release of the active substance of up to 98%. This effect was dependent on the type of surfactant and its quantitative ratio to the Eudragit FS. Similar release profiles were obtained for tablets containing Eudragit RS and sodium lauryl sulfate, as well as Eudragit RS and polysorbate 80. Depending on the composition of tablets, metronidazole release proceeded in accordance with either first or second-order kinetics. We calculated as well, that the differing masses of Eudragit FS in the studied formulations correlates with the order of release kinetics ($p < 0.002$). Such an effect was validated using the Weibull model, wherein, in all the studied formulations, the release rate was seen as a decreasing function of time. An analysis of data according to the Ritger-Peppas model and the Peppas-Sahlin model for some formulations, indicated that the mechanism of active substance release from matrix tablets is diffusion.

INTRODUCTION

Metronidazole, 2-(2-methyl-5-nitro-1H-imidazole-1-ilo) ethanol, is a chemotherapeutic agent showing activity both against protozoa, such as *Balantidium coli*, *Blastocystis hominis*, *Entamoeba histolytica*, (*Giardia lamblia*), *Trichomonas vaginalis*, *Diantamoeba fragilis*, *Enterocytozoon bieneusi*, *Septata intestinalis* and *Encephalitozoon helleri*, and also against Gram-positive bacteria, e.g. from the genera *Clostridium* spp., *Eubacterium* spp., *Peptococcus* spp. and *Peptostreptococcus* spp, as well as against Gram-negative strains, e.g. from the genera *Bacteroides* spp., *Fusobacterium* spp., *Veillonella* spp and *Prevotella* spp. [1]

The wide spectrum of antimicrobial action allows the use of metronidazole in many cases as an alternative to antibiotic therapy. However, this involves the ministration of high doses of the active substance, which may engender an increase in adverse effects, particularly inside the alimentary tract and the central nervous system. Developing the form of

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a sustained-release drug allows for minimizing the adverse effects of metronidazole action (which strictly correlate with a rapid growth of drug concentration in the serum), and increases the comfort of patient's treatment as a result of decreasing the frequency of drug dosage.

Due to the biopharmaceutic properties of metronidazole, such as belonging to class I of BCS and the average biological half life time ($t_{0,5}$) being 8h, it is an ideal model substance for the development of formulations with a sustained-release profile [9]. One of the methods which allow modifying the active substance release is the fabrication of matrixes. For this purpose, ethylcelluloses are commonly used. This is both due to their ability to swell and to their susceptibility to compression, which often allows the construction of sustained-release matrixes by direct tabletting. Of this group of polymers, methylcellulose (MC), hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC) and carboxymethylcellulose sodium (CMCNa) are commonly included in the composition of matrix tablets.

For many model substances, the relationship has been examined between the release rate from matrix tablets and the viscosity and size of HPMC particles, the percentage in formulations and the production method of this form [2,23,24]. In tablets containing 400 mg of metronidazole, sustained release over 8h was obtained by including in the composition, HPMC in quantities between 10% - 30% (w/w) of the active substance. Herein, the matrix was obtained by compressing the granulated material obtained by wet granulation [2].

In our work, of the synthetic polymers, we examined the usefulness of polyvinylpyrrolidone (Povidone), polyvinyl acetate (Kollidon SR) and polyacrylate (Carbopol 71G) in modifying the metronidazole release from matrix tablets. The mentioned polymers were included in the composition in a ratio of 1:1 (w/w) to the active substance. The tablets were fabricated by way of the direct compression method, and sustained metronidazole release was achieved in all the freshly made formulations. The dissolution test was also conducted during an artificial aging, at 40°C ± 2°C and 75% ± 5% RH for 4 weeks. Based on the obtained results, we eliminated the possibility of employing Carbopol 71G as an excipient in designing such matrixes [20].

Our work emphasized the advantages of using lipids in sustained release systems. Matrixes based on these excipients are obtainable with a high degree of repetitiveness and at a relatively small expense. Moreover, they are characterized by their positive chemical compatibility with other substances [13,16].

In our study, matrix tablets with metronidazole were obtained by including in the composition, Carnauba wax, Beeswax, Stearic acid, Cutina HR, Precirol® ATO 5 and Compritol® ATO 888. The ratio of the active substance to lipophilic excipients was 2:1 (w/w). All tablets were characterized by a sustained time of release, in accordance with first-order kinetics [14]. (Meth)acrylate copolymers, produced by Evonik Röhm (Germany) are commonly used in the technology of matrix tablet production under the name 'Eudragit'. To achieve the sustained release of the active substance, both copolymers with the nature of polycations (RS or RL) and their mixture with polyanions (L

or S) are incorporated in the studied substance, as well as the Eudragits which do not have groups with the ability to ionize (NM or NE) [4].

The aim of our study was to examine the usefulness of the pH-dependent copolymer – Eudragit FS – in the technology of manufacturing modified-release metronidazole matrix tablets.

As opposed to other polyanionic Eudragits (L and S), this copolymer is characterized by possessing a smaller proportion of free carboxyl groups (metacrylic acid monomers), which affects its solubility. Eudragit FS 30D is used to coat pellets to obtain a colon release of active substance by way of its dissolution at pH = 6.8 [6,12]. As the trade form of Eudragit FS is a 30% water dispersive, it was assumed that the copolymer will be employed as a binder in the process of metronidazole wet granulation, and, subsequently, the resulting intermediate product will then be tabletted.

Our study was set-up to meet several objectives. One objective of this study was to estimate the effect on the active substance release rate of surface-active substances and the included polycationic Eudragits.

Moreover, the objective of our undertaken numerical analysis was to estimate the release kinetics of metronidazole from the prepared formulations throughout the stages of the experiment. In so doing, standard numerical methods, widely described in current literature, were employed [25]. Another objective was to determine the mechanism of substance release from tablets at the initial stage of the process. Two known approaches were used. These were in accordance with the Ritger-Peppas theory and the Peppas-Sahlin theory [17,19].

MATERIALS AND METHODS

The active substance utilized in our work was Metronidazole (Polpharma, Polska). As polymers for modifying its release, we used copolymers of metacrylic and acrylic acid esters in the form of trade water dispersions. These were: Eudragit RS 30D, Eudragit RL 30D and Eudragit FS 30D (Evonik, Germany). Moreover, we employed as surface-active substances: polysorbate 80 (POCH, Poland) and sodium lauryl sulfate (Caleo, Germany). Magnesium stearate (POCH, Poland) was availed as a lubricant.

Granulation: Metronidazole was first weighed and sieved through a 0.08 mm screen. The active substance, in the course of mixing with a planetary-motion paddle, was then wetted with water dispersions of Eudragit FS 30D, Eudragit RS 30D and Eudragit RL 30D. Depending on the formulation, polysorbate 80 or sodium lauryl sulfate dissolved in a small amount of water was additionally included in the wetted mass of powders. The whole was mixed thoroughly for 20 minutes and transferred to a oscillating granulator (Erweka). Granulated material was formed by passing the wetted mass of powders through a 1.25 mm screen and dried at 40°C to reach 4% of humidity. The obtained intermediate product for tabletting was homogenized through a set of screens with a diameter from 0.315 mm to 1.25 mm. Compositions of all formulations are listed in Table 1.

Matrix tablets: Magnesium stearate (0.5% w/w) was added to the fraction of granulated material left on the 0.315

Table 1. Composition of granules containing metronidazole

Components (g)	Formulary versions											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Metronidazole	100	100	100	100	100	100	100	100	100	100	100	100
Eudragit FS*	4	2	2	2	2	3	3	3	6	6	3	3
Eudragit RS*	-	-	-	-	-	-	-	-	-	-	3	-
Eudragit RL*	-	-	-	-	-	-	-	-	-	-	-	3
Polysorbatum 80	-	-	-	-	2	-	-	2	-	2	-	-
Sodium lauryl sulfate	-	-	0.5	2	-	0.5	2	-	2	-	-	-

*based on the dry polymer

mm and 0.710 mm screens, and mixed for 3 minutes. The tablet base was compressed using a single punch tablet press Korsch EK-0. Matrix and punches with a diameter of 10 mm were used for tabletting. The declared content of metronidazole in all formulations was 500 mg.

Physicochemical evaluation of prepared tablets: As part of the qualitative assessment, the mass homogeneity was examined for 20 randomly selected units. Deviation from the declared content of active substance was verified based on the spectrophotometric analysis of metronidazole from 10 randomly selected tablets from all developed formulations. In order to do so, the sample tablets were individually powdered, and three analytical samples were weighed from each, on the analytical balance, Sartorius Expert (Germany), to an accuracy of 0.0001 g. Each analytical sample was subsequently transferred to a measuring flask with a volume of 25 mL and supplemented with 0.1 N hydrochloric acid. It was then shaken for 10 minutes and filtered through Filtrak 380. From the filtrate, 1 mL of the solution was collected with an automatic measuring pipette, and transformed to a measuring flask with a volume of 10 mL. This was supplemented with 0.1 N hydrochloric acid. The solution was subjected to spectrophotometric analysis at the analytic wavelength of 277 nm.

Friabilility (F) was determined as a percentage loss in weight. For this purpose, about 6.5 g of tablets were weighed and then revolved (25 r/min) in an Erweka TAR 200 friabilator for 4 minutes and weighed once more.

Determination of tablet metronidazole content – validation of the method: The metronidazole content in the prepared tablets and the amount of released active substance in the dissolution test study were determined using the UV spectrophotometric method. The spectrophotometer Jasco V-530 was used for this analysis. The method of quantitative metronidazole determination was validated in accordance with the ICH guidelines [7].

A 6-point calibration curve was constructed, based on the absorbance determination of metronidazole model solutions with a concentration of 5.5 μg/mL – 19.3 μg/mL in 0.1 N hydrochloric acid, at the maximum of absorption 277 nm. A second model curve was also determined, based on the analysis of suspensions with a concentration of 3.6 μg/mL – 13.5 μg/mL in pH 6.8 phosphate buffer, at the analytical wavelength 320 nm.

The accuracy of metronidazole determination in the fabricated matrix tablets was evaluated by a spectrophotometric analysis of three model formulations which contained, respectively, 85%, 100% and 115% of the declared content of the active substance, as well as the excipients included in the granulate materials. From each powdered formulation,

three identical analytical samples were prepared for spectrophotometric analysis, in accordance with the procedure developed for determining the active substance content in prepared matrix tablets. The percentage of metronidazole recovery, which was calculated from the formula, was adopted as the measure of the method accuracy:

$$\text{Recovery (\%)} = \frac{\text{determined concentration}}{\text{calculated concentration}} \times 100\% \quad (1).$$

The precision of metronidazole determination was calculated by standard deviation (RSD), which was based on an analysis of active substance content in model formulations (n = 3). The degree of method selectiveness demonstrated was based on the spectrophotometric analysis of solutions of excipients which were included in tablet compositions, in 0.1 N hydrochloric acid and pH 6.8 phosphate buffer at the analytical wavelengths: 277 nm and 320 nm.

Dissolution appraisal: An assessment of the metronidazole dissolution from the developed formulations of tablets was performed using the apparatus 1, according to USP 32 [22]. In this work, 0.1 N hydrochloric acid pH 1.2 and pH 6.8 phosphate buffer were used as acceptor fluids. The temperature of the resulting fluids was kept at 37°C ± 0.5°C, with the mixing rate amounting to 75 rpm. An evaluation of metronidazole release rate was performed in the apparatus ERWEKA DT 600HH (Germany), where the tested tablet was placed in each of six baskets. The volume of acceptor fluids was 750 mL, which provided sink conditions. After 2h from the start of the study, the acceptor fluid was changed from pH 1.2, to pH 6.8. At time points 1, 2, 3, 4, 6, 8 and 10 h, samples with a volume of 2 mL were collected. The sample volumes were then immediately replaced with the appropriate acceptor fluid. These samples were filtered (0.45 μm), suitably diluted with 0.1 N hydrochloric acid or phosphate buffer and subjected to spectrophotometric analysis for metronidazole content at the analytical wavelengths: 277 nm and 320 nm.

Comparison of the dissolution curves: A mathematical comparison of metronidazole release profiles was performed by calculating the similarity coefficient f2, according to Eq. (2), proposed by Moore and Flanner [10], and implemented by FDA CDER. Calculations were made using the program DDSolver [25].

$$f_2 = 50x\log\left(\sqrt{\left(1 + \frac{\sum_{t=1}^{n'}(R_t - T_t)^2}{n'}\right)}x100\right) \quad (2).$$

The f2 value between 50 and 100 suggests that the dissolution profiles are similar. The f2 value of 100 suggests that the test and reference release profiles are identical.

Solubility of metronidazole: The examination of metronidazole solubility in 0.1 N hydrochloric acid and pH 6.8 phosphate buffer was conducted in accordance with previously established guidelines [15]. For each of these solvents, three analytical samples of the substance were prepared. Metronidazole content in the solution was determined by way of the UV spectrophotometry method.

Examination of release kinetics: To analyze the mechanism and kinetics of metronidazole release from the fabricated matrix tablets into the acceptor fluid, several different mathematic models were employed, which were matched to the experimental data. We use: zero-order release kinetics, first-order release kinetics, second-order release kinetics, the Weibull model, the Ritger-Peppas model and the Peppas-Sahlin model, all of which are defined by the equations:

$$F(t) = at + b \qquad (3)$$

$$F(t) = 100 \, (1 - Ce^{-Bt}) \qquad (4)$$

$$F(t) = 100 - \frac{100 - D}{(100 - D)kt + 1} \qquad (5)$$

$$F(t) = 100 \, (1 - e^{-At^\beta}) \qquad (6)$$

$$F(t) = Kt^n \qquad (7)$$

$$F(t) = k_1 t^m + k_2 t^{2m} \qquad (8).$$

The aforementioned models have the form of a parametrized function of one variable $F(t)$. Values of this function indicate the released substance percentage, where symbol t is the time to release, and the rest of symbols in (3)-(8) represent the individual parameters of each model.

The zero order rate, eq. (3), describes systems wherein the drug release is independent of its concentration. The first-order release kinetics, eq. (4), and the second-order release kinetics, eq. (5), describe the release from systems which are concentration dependent. The obtained empirical data were, as well, analyzed for the possibility of using the Weibull model, eq. (6), for describing metronidazole release kinetics. In the Weibull model, parameter B determines the phenomenon character [18]. If parameter $B > 1$, the drug release rate is not a monotonically decreasing function of time. For time periods smaller than some t_{max}, the function increases monotonically. At the moment t_{max}, this function has a maximum, and then for all the times greater than tmax, the function decreases monotonically to zero. In the situation wherein $0 < B \leq 1$, the drug release rate decreases for all the times $t > 0$. In this case there is no maximum velocity.

To establish the tablet's drug substance release mechanism, the Ritger-Peppas model was employed [19]. This model functions well for time ranges where the amount of the released substance does not exceed 60% [17]. It is defined by equation (7). In an ideal situation, for tablets of spherical form and with a diffuse mechanism of drug release,

the theory predicts that n should be equal to $n = 0.43$. Case II transport is present when the coefficient $n = 0.85$. If the coefficient is within the range $0.43 < n < 0.85$, superposition of both processes occurs. In contrast, when $n > 0.85$, a super case II type of release is seen [3,19].

Regarding the Peppas-Sahlin model, equation (8), the first part describes diffusion, the second refers to Case II transport. The actual process is described by way of being a superposition of both processes. Numbers k1 and k2 describe the contributions of these two processes to the observed drug release [19].

The adequacy of the employed models was tested by way of calculating three quantities: determination coefficient (R^2), residual sum of squares (SSR) and Akaike's information criterion (AIC) [3,17].

RESULTS AND DISCUSSION

Evaluation of prepared matrix tablets

In our study, matrix tablets with metronidazole were first produced by compressing agglomerates. The composition of all prepared formulations, expressed in the amount of excipients per 100 g metronidazole, was presented in Table 1. UV spectrophotometry was subsequently used to quantitatively determine the model substance in matrix tablets. The analytic method developed was characterized by specificity, as excipients composing the tablets did not show absorbance at the analytical wavelengths of 277 nm and 320 nm. Of note: in this part of the study, we did not see that the degradation products of metronidazole that appear under the influence of light had any influence on the results of quantitative spectrophotometric analysis in UV [5].

Our work revealed a linear relationship between the defined metronidazole concentration in model solutions and absorbance. For the calibration curve in 0.1 N hydrochloric acid, the regression equation took the form y = 0.0369x + 0.0136 (R^2 = 0.9996), whereas for the model curve determined by way of the phosphate buffer, y = 0.0528x + 0.0014 (R^2 = 0.9998). The accuracy of the analytical method was assessed through metronidazole recovery from the model matrix tablets. This recovery ranged from 100.61%, to 101.66%, at RSD < 1% for n = 3. In the adopted range of concentrations, the UV method for metronidazole determination was characterized by linearity, specificity, accuracy and precision.

As part of the qualitative assessment of the obtained drug form, the homogeneity of the tablets mass, its active substance content and its friability were examined. The maximal deviation from the average mass which was obtained in the developed formulations amounted to 3.5%. The obtained value was lower than the criterion of acceptance defined in USP 32 for tablets with mass above 250 mg [22].

This indicated good flow properties with regard to the granulated material, which resulted in even filling of the matrix in the course of tabletting. The highest values of deviation from the declared content of the active substance was 3.24% (Table 2). The friability (F) figure obtained for all tablets was less than 1%.
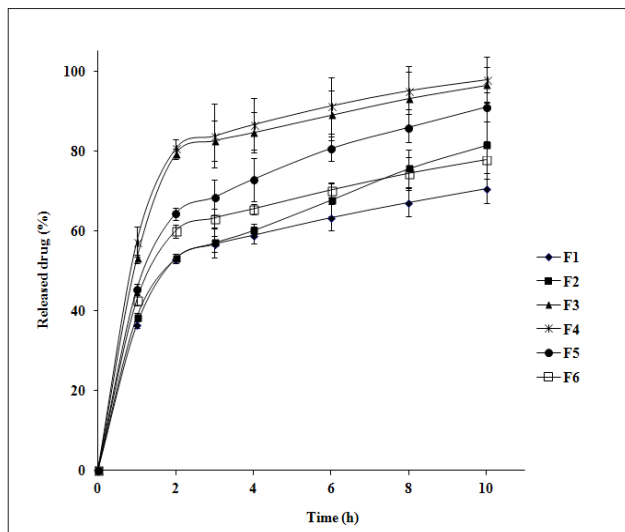
Figure 1. Release profiles of metronidazole from matrix tablets (formulations F1 to F6)
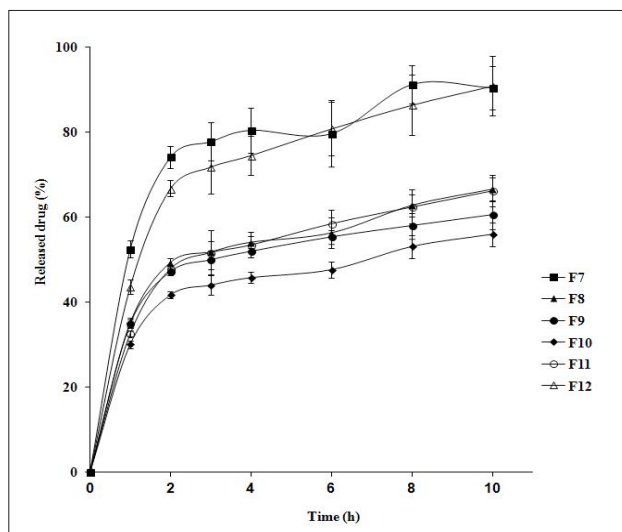

Figure 2. Release profiles of metronidazole from matrix tablets (formulations F7 to F12)

Dissolution studies

A dissolution test was carried out for six tablets randomly selected from each developed formulations. Although metronidazole solubility in water is 1.0 g/100 mL [21], the analysis was also performed for acceptor fluids, owing to their pH. The fabricated tablets demonstrated a Metronidazole solubility in 0.1 N hydrochloric acid of 2.55 g/100mL, whereas in phosphate buffer, this figure was 0.97 g/mL. The obtained results confirmed that sink conditions were maintained at the assumed volume of acceptor fluids.

Release profiles from the developed tablets formulations were drawn on curves which presented the relationship between the amount of released metronidazole (Q%), in relation to the declared dose, and time (t) (Fig. 1 and Fig. 2). The similarity coefficients f2 for individual metronidazole release profiles were presented in Table 3. The differences in metronidazole release rate which were obtained during the study, were connected with the composition of the matrixes.

Of the excipients, only Eudragit FS was included in the tablets composition in formulation F1 and F2. At the ratio of polymer to metronidazole amounting to 1 : 25 and 1 : 50 (w/w), respectively, a modified active substance release was achieved. In formulation F1, 71% was released after 10 h, whereas in formulation F2, 81% of the declared metronidazole dose was determined in the acceptor fluid after this time. The calculated similarity coefficient f2 was 63, which indicates that the obtained release profiles are similar.

Formulation F2 was subsequently modified by adding the surface-active substances: sodium lauryl sulfate and polysorbate 80. This resulted in an increase in the active substance release rate. After 10h of analysis, from 91% (F5) to 98% (F4) of the declared metronidazole dose was evidenced.

Our work also revealed that at the ratio of Eudragit FS to metronidazole of 1 : 50 (w/w), no considerable differences in release profiles were observed which would be determined by varying the amount of introduced sodium lauryl sulfate.

Table 2. Results of physical estimation matrix tablets with metronidazole

Parameter*	Formulary versions											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
M (%)	+ 0.8	- 1.5	- 1.8	+ 1.7	+ 1.2	+ 1.7	- 1.5	+ 1.1	- 3.5	+ 0.8	+ 1.1	- 0.9
C (%)	- 1.7	+ 1.7	- 0.3	+ 0.3	+ 1.4	+ 0.7	+ 3.2	+1.0	+ 0.5	+ 0.8	- 1.1	+ 0.1

* M – deviation from average mass, C– average deviation from declared content of metronidazole (500 mg)

Table 3. Similarity factor (f2) calculated for dissolution profiles of matrix tablets

Fn	Formulary versions											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
F1	100	63	30	29	41	58	35	66	56	44	65	40
F2	63	100	34	32	48	66	39	51	45	38	51	46
F3	30	34	100	80	49	37	63	27	25	21	26	51
F4	29	32	80	100	45	35	57	25	23	20	25	47
F5	41	48	49	45	100	53	58	35	32	28	35	84
F6	58	66	37	35	53	100	44	47	43	35	47	51
F7	35	39	63	57	58	44	100	31	28	24	30	62
F8	66	51	27	25	35	47	31	100	73	54	88	34
F9	56	45	25	23	32	43	28	73	100	62	73	32
F10	44	38	21	20	28	35	24	54	62	100	54	27
F11	65	51	26	25	35	47	30	88	73	54	100	34
F12	40	46	51	47	84	51	62	34	32	27	34	100

In this part of the experiment, the value of coefficient f2 calculated for formulations F3 and F4 was 80. Indeed, only in the case of an increased percentage of Eudragit FS in formulations F6 and F7 was a relationship seen between the amount of sodium lauryl sulfate included within the composition and the metronidazole release rate.

Of note: during the analysis of all profiles, we observed that the addition of polysorbate 80 speeds up the active substance release to a lesser extent than including sodium lauryl sulfate within the formulation.

In formulary versions F11 and F12, Eudragit FS 30D and the cationic copolymers: Eudragit RS 30D and Eudragit RL 30D, were additionally used to wet the mass of powders. The direct combining of two types of copolymer dispersions of opposite charges demonstrated an interaction at the stage of mixture preparation – where flocculation was observed. The decrease of active substance release in the phosphate buffer was also an effect of this incompatibility [8,12]. To prevent flocculation, we suggest that such tablets incorporating these polymers together be prepared by combining them in a dry form with the active substance, and then subjecting the mixture to direct compression [11].

In our study, the fabricated agglomerates were obtained by direct wetting of the metronidazole with Eudragit FS 30D dispersive, and then during further mixing, with Eudragit RS 30D or Eudragit RL 30D. Owing to the held greater hydrophilic character of Eudragit RL (as compared with Eudragit RS), in formulation F12, at each time point, a higher metronidazole concentration in the acceptor fluid was ascertained than in the case of formulation F11. At the end point of our study, 66% and 91% (F11 and F12) of the declared metronidazole dose was estimated within the acceptor fluid.

Based on an analysis of the f2 factors, it was found that similar release profiles were obtained by modifying the composition of manufactured tablets which are with the same amount of Eudragit FS, by way of incorporating Eudragit RL (F12) and sodium lauryl sulfate (F6 and F7). A similar

Table 4. Estimated parameters, R^2, SSR and AIC values obtained from fitting first order model and second order model to drug release experimental data

Fn	First order					Second order				
	C	B	R^2	SSR	AIC	k	D	R^2	SSR	AIC
F1	0.5807	0.0728	0.8894	121.7611	37.6144	0.0018	39.1974	0.9533	93.2790	35.7492
F2	0.6484	0.1232	0.9848	38.2290	29.5052	0.0039	11.5097	0.9625	69.5048	33.6898
F3	0.4332	0.2440	0.9444	219.1827	41.7293	0.0250	149.4979	0.8688	26721.2905	75.3525
F4	0.4474	0.2955	0.9677	125.5131	37.8269	0.0438	114.8015	0.8134	8162.1362	67.0508
F5	0.5749	0.1821	0.9833	67.2643	33.4604	0.0093	-137.5533	0.9383	454.7928	46.8389
F6	0.5241	0.0904	0.9090	119.6296	37.4908	0.0027	42.8202	0.9712	80.6763	34.7331
F7	0.4221	0.1625	0.8540	204.9139	41.2581	0.0096	24.8848	0.8485	85.8495	35.1682
F8	0.6145	0.0623	0.9114	77.6099	34.4619	0.0014	36.0579	0.9491	61.7306	32.8595
F9	0.6068	0.0467	0.8628	73.0345	34.0365	0.0010	38.4775	0.9145	62.5997	32.9573
F10	0.6671	0.0433	0.8957	55.9115	32.1664	0.0008	32.2373	0.9314	48.2041	31.1281
F11	0.6294	0.0659	0.9063	97.9484	36.0911	0.0015	34.5450	0.9583	74.2037	34.1477
F12	0.5429	0.1782	0.9610	157.3763	39.4105	0.0092	-59.4901	0.9481	138.2166	38.5018

Table 5. Estimated parameters, R^2, SSR and AIC values obtained from fitting the Weibull model to drug release experimental data

Fn	A	B	R^2	SSR	AIC
F1	0.5094	0.3924	0.9444	39.6968	29.7689
F2	0.4888	0.5059	0.9781	27.8395	27.2852
F3	0.8702	0.5671	0.9426	83.0896	34.9394
F4	0.9268	0.5906	0.9646	44.7580	30.6089
F5	0.6280	0.5579	0.9838	23.2167	26.0141
F6	0.6148	0.3941	0.9529	37.1763	29.3097
F7	0.8399	0.4609	0.9014	95.4308	35.9088
F8	0.4713	0.3594	0.9448	33.1458	28.5064
F9	0.4696	0.3072	0.9468	21.3047	25.4125
F10	0.3881	0.3229	0.9441	22.3655	25.7527
F11	0.4388	0.4011	0.9533	31.2807	28.1010
F12	0.6404	0.5630	0.9652	54.7724	32.0223

Table 6. Estimated parameters, R^2, SSR and AIC values obtained from fitting the Ritger-Peppas and the Peppas-Sahlin models to drug release experimental data for selected formulations

Fn	Ritger-Peppas					Peppas-Sahlin			
	K	n	R^2	SSR	AIC	k1	k2	m	AIC
F1	38.1409	0.3512	0.9151	32.5130	17.9266	45.9223	-8.9490	0.7381	11.7594
F2	39.6506	0.3257	0.9438	18.2368	15.6138	48.6223	-9.9059	0.6546	10.0214
F8	37.6829	0.2571	0.8727	40.4306	22.4979	45.4982	-9.2115	0.5513	17.1604
F9	37.6516	0.2177	0.9274	28.6069	27.4755	45.1237	-8.5114	0.3924	23.9092
F10	32.3672	0.2410	0.9319	25.7010	26.7257	38.2396	-6.1805	0.3551	27.2705
F11	34.9982	0.3156	0.9091	39.3915	22.3677	41.4140	-7.4179	0.5765	18.7896

pattern was observed in produced tablets incorporating Eudragit RS and polysorbate 80 (F11 and F8).

Confirmation of the earlier mentioned interaction between Eudragits RS/RL and Eudragit FS, which, in our study, brought about a decrease in the active substance release rate [11], would require introducing an acceptor fluid of pH 7.4 to the study. This should result in the maximal ionization of the carboxyl groups of the anionic polymer and produce a similar effect on a polymer with the opposite charge.

In all of the versions of the matrix tablets we had fabricated, irrespective of the composition, a decrease in metronidazole release rate was observed after 2h of analysis. This phenomenon, we put forward, may have come about by it being affected by a lower solubility of the active substance in the pH 6.8 phosphate buffer, as well as by the amount of metronidazole released to 0.1 N hydrochloric acid, and thus a longer way of diffusion of the substance solution from the tablet having had occur.

As compared with the earlier studies regarding the technology of matrix tablet manufacture with metronidazole, where Carbopol, Kollidon SR and Povidon were included in the composition as substances modifying release [20], in formulations based on Eudragits, it was possible to obtain a smaller ejection of the substance during the 2h of release in 0.1 N hydrochloric acid. Hence, owing to the different parameters utilized within the dissolution test for metronidazole tablets of matrixes consisting of HPMC [14] lipids [4], it was impossible to compare the previously obtained release profiles, with the results obtained in our study.

Examination of the kinetics and mechanism of metronidazole release from matrix tablets

The numerical analysis of the obtained experimental data for the drug release kinetics from the studied formulations are presented in Tables 4-6. Parameters SSR, AIC and R^2, therein, demonstrate explicitly that the drug release from all the formulations we examined could not be described as a zero-order process. This is because, all the criteria describing the adequacy of the zero-order model in relation to the experimental data, are worse than the same parameters for other possibilities. Based on the results of our analyses, it was determined that the drug release description for some of formulations was that of a first-order process. These are formulations: F2-F5. What is more, a group of formulations revealed a drug release description that could be described as being a second-order process. These were formulations F1, F6, F8-F11.

The analysis of formulations F7 and F12 did not explicitly determine the order of metronidazole release kinetics. Thus, for formulations F7 and F12, we leave open the problem of estimating the kinetics order, hence, requiring further studies.

Further analysis included the effect of Eudragit FS on the order of drug release kinetics. Such work excluded formulations F7, F11 and F12. Formulation F7 was excluded because of the problem with determining the release kinetics order, whereas tablet formulations F11 and F12 also contained Eudragit RS and Eudragit RL. In ascertaining the effect of Eudragit FS on this issue, Spearman's correlations were calculated between the release kinetics order shown before and the mass of Eudragit FS incorporated. The result of such calculations is a Spearman's coefficient rs= 0.9129, which gives the p-value being below 0.002.

In our work, beyond generating an estimation of drug release kinetics for all the time points within the experiment, the Weibull model was used. The result of such calculations are presented in Table 5. In so doing, the analysis of parameter B indicates that the release rate of the various formulations cannot have been at a maximum in each formulation. Hence, to determine the mechanism of drug release, Ritger-Peppas theory was then applied. This model works well only for the time periods when 60% of any formulation item is released. Therefore, this method was used only for formulations: F1, F2, F8-F11, as the other matrix tablets released more than 60% of the metronidazole in too short time, in relation to the frequency of collecting a sample for the analysis. The results of applying Ritger-Peppas theory are presented in Table 6. Based on numerical calculations, it was found that the process of release is more likely based on diffusion to the outside environment (as in all formulations, n had a value below 0.43). An identical result was obtained using the Peppas-Sahlin theory. The results for this model are presented in Table 6. As revealed in applying this theory, the value of parameter k_1 is definitely higher than k_2, hence, in this model, diffusion is the dominant mechanism of drug release.

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