The Development of Eudragit® NM-Based Controlled-Release Matrix Tablets

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Key words: *matrix tablets; Eudragit® NM; drug solubility; microcrystalline cellulose; dissolution profile.*

Summary. *Eudragit® NM was investigated as a matrix former in combination with microcrystalline cellulose as an insoluble filler for preparing controlled-release tablets containing model drugs with different solubility.*

Material and Methods. Three sets of matrix tablets differing in the drug-to-filler ratio (1:1, 2:1, and 4:1) and polymer amount with diltiazem hydrochloride (freely soluble) or caffeine (sparingly soluble) were prepared. Samples were evaluated by the dissolution test at pH 6.8 corresponding to the upper part of the small intestine; the selected samples were tested at a changing pH level to better simulate in vivo conditions.

Results. The prepared matrix tablets fulfilled all the requirements of the European Pharmacopoeia. Tablets with Eudragit® NM showed excellent mechanical characteristics. In vitro studies showed that the set 1:1 was the most suitable for the sustained release of a freely soluble drug concerning the burst effect and the total drug amount released within 12 hours. The significant effect of the drug-to-filler ratio and polymer amount on the dissolution profile was confirmed by similarity factor analysis. A faster drug release was observed during the dissolution test within changing pH levels because of the pH-dependent solubility of diltiazem. A prolonged release of the sparingly soluble drug was not achieved, and a trend for fast disintegration was observed.

Conclusions. The combination of Eudragit® NM with microcrystalline cellulose as an insoluble filler seems to be suitable only for freely soluble drugs, when the amount of the drug and the filler is similar.

Introduction

Oral extended-release dosage forms are developed to ensure adequate drug levels in blood with minimal fluctuations, to reduce the frequency of daily drug administration, and to reduce side effects of the drug, which in turn result in the improved effectiveness of pharmacotherapy and improved patients' quality of life. A good candidate suitable for formulating extended-release dosage forms is a drug substance that is used at a relatively low daily dose, has a short half-life, has only a few undesirable side effects, and is rapidly absorbed into the gastrointestinal tract (GIT) (1).

The use of matrix tablets with their simple design appears to be very attractive from both an economic standpoint as well as the development process. They offer a high level of reproducibility, stability of the raw materials and dosage form, and an ease of scale-up and process validation (2). The most common approach to achieve a controlled release is to embed the drug in a hydrophilic matrix tablet based on the swelling of hydrophilic polymers (3), lipophilic matrix systems containing fats and waxes as carriers (4) or insoluble matrices based on ethylcellulose (5), and Eudragits® or their combinations (6).

Eudragits® are synthetic acrylic polymers often used in the development of solid dosage forms. They are particularly desirable due to their high chemical stability and good compactibility, and the wide variety of products with different physical and chemical characteristics is present on the market (7). Moreover, they, as being well-established pharmaceutical excipients, can also be used as the coating materials or carriers in matrix technology.

Films based on pH-dependent Eudragits® (Eudragit® L, S, and FS) are able to ensure the site-specific drug release in the GIT (upper intestine, ileum, colon) (8); pH-independent types (Eudragit® RL, RS, and NE) form the films ensuring the sustained drug release (9).

As an excipient in the matrix technology, Eudragits® are used as sustained-release modifiers for the preparation of matrix tablets and matrix pellets (10). In powder form, they can be used for direct

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compression (9); organic solution (10) and aqueous dispersions (11) can be utilized for the wet granulation process or for the preparation of the plastic mass for extrusion/spheronization. Recently, numerous experimental studies aiming at the formulation of matrix tablets based on Eudragit® polymers, used separately or in blends, have been carried out (12). Eudragits® can be used for achieving the pH-independent release of drugs with solubility dependent on pH of the medium (13). The two-phase drug release profile was obtained in the case of matrix tablets based on the combination of Eudragit® RS and Eudragit® L, which was used as a binder for wet granulation (14). The combination of pH-dependent and pH-independent Eudragits® in a suitable ratio can lead to a drug dissolution profile with almost zero-order kinetics (7).

However, there are no reports in scientific literature about the relatively new type of acrylic polymer Eudragit® NM 30 D and its practical usage in pharmaceutical technology. According to the producer's information, Eudragit® NM is defined as an insoluble, low permeable, and highly flexible material, with pH-independent swelling. It is available in forms of 30% and 40% of aqueous dispersion and is basically suitable for the wet granulation process in the manufacturing of matrix tablets with a time-controlled drug release (7). Eudragit® NM 30 D contains 30% of a dry substance – a neutral copolymer based on ethyl acrylate and methyl methacrylate. The dispersion also contains 0.7% macrogol stearyl ether used as an emulsifier. This aqueous dispersion is miscible with water at any ratio, retaining the milky-white appearance. The average molecular weight is about 600 000. Minimum film forming temperature and glass transition temperature are relatively low and have the values of 5°C and 11°C, respectively (15).

The aim of this study was to prepare and evaluate oral extended-release matrix tablets based on Eudragit® in combination with the common insoluble filler, microcrystalline cellulose. The matrix tablets contained model drugs differing in solubility, and special attention was paid to their dissolution behavior and release mechanism.

Material and Methods

Material

Diltiazem hydrochloride (DH) (kindly donated by Zentiva, Prague, Czech Republic) and caffeine (C) (Jilin Province Shulan Synthetic Pharmaceutical Co., Ltd, Shulan City, China) were selected as the model drugs with a markedly different solubility in water. The matrix tablets contained the different amounts of microcrystalline cellulose (MCC) (type Avicel® PH 101, FMC Biopolymers, Rockland, United States of America) as an insoluble filler. Drug release retardant Eudragit® NM was added as its 30% water dispersion (Eudragit® NM 30 D, kindly donated by Evonik Röhm GmbH, Darmstadt, Germany) and was used as the wetting liquid for granulation. Magnesium stearate (Peter Greven, Bad Münstereifel, Germany) and colloidal silicon dioxide (Degussa, Vicenza, Italy) were used to improve the flow properties of granules. All materials were of the European Pharmacopoeia (Ph. Eur.) quality.

Preparation and Evaluation of Granules

The model drugs, Avicel® PH 101 and 30% aqueous dispersion of Eudragit® NM 30 D, were weighed (see Tables 1 and 2 for the composition). The granules were prepared in a high-shear mixer (ROTOLAB, Zanchetta, S. Salvatore Montecarlo, Italy). The instrument settings were as follows: impeller pause time, 0 seconds; impeller working time, 300 seconds; cycle time, 300 seconds; and impeller speed, 1200 rpm. For homogenization, a model drug and Avicel PH 101 were mixed together for 30 seconds; then the granulation liquid of Eudragit® NM 30 D was manually added for other 30 seconds. Finally, the mixture was granulated for 240 seconds. The wet mass was passed through a 1.25-mm mesh sieve, and the granules were dried for 24 hours at 40°C in a cabinet dryer. After drying, the granules were again passed through the sieve. The granulation of samples with Eudragit® NM 30 D to 30% of the granulated mass (samples $1–3_{DH}$, $7–11_{DH}$, $1–3_{C}$, and $5–7_{C}$) or 25% (samples 9_{C} and 10_{C}) was made by one step. The granulation with the higher amount of Eudragit® NM 30 D (samples $4–6_{DH}$, $12_{DH,}$ 4_{C}, 8_{C}, 11_{C}, and 12_{C}) was made by a multistep process. First, 25% or 30% of Eudragit® NM 30 D was added, then passed through the sieve, and dried. The second step consisted of an additional 10% of Eudragit® NM 30 D to the previously prepared dry granules, passed through the sieve and dried. If a third granulation step was required, other 10% of Eudragit® NM 30 D was used for each step until the desired concentration of Eudragit® NM 30 D was achieved. This multistep granulation helped avoid the overwetting of the granulated mass. Before the addition of the extragranular excipients, the obtained granules were tested to determine their suitability to the tablet compression process. The prepared granules were evaluated according to the Ph. Eur. 7 for flowability (Medipo, Brno, Czech Republic; diameter of outflow opening, 25.0±0.01 mm) and Hausner ratio (HR) (SVM 102, Erweka, Heusenstamm, Germany). Magnesium stearate (0.5%) and colloidal silicon dioxide (0.5%) were added to the evaluated granules by a mixing procedure using a 3-axial homogenizer Turbula (T2C WAB, Basel, Switzerland) for another 5 minutes.

Table 1. Composition of Diltiazem Hydrochloride Granules and Matrix Tablets

Sample	Granule Composition				No. of Granulation Steps	Tablet Composition*			
	DH	MCC	Eudragit® NM 30 D			DH	MCC	Eudragit® NM Solid	
	g	g	g	%		mg	mg	mg	%
1_{DH}	100	100	50.0	20.0	1	100	100	15.0	6.9
2_{DH}	100	100	66.6	25.0	1	100	100	20.0	9.0
3_{DH}	100	100	85.7	30.0	1	100	100	25.7	11.3
4_{DH}	100	100	107.9	35.0	2	100	100	32.4	13.8
5_{DH}	100	100	130.1	39.4	3	100	100	39.0	16.2
6_{DH}	100	100	152.3	43.2	4	100	100	45.7	18.4
7_{DH}	100	50	37.5	20.0	1	100	50	11.3	6.9
8_{DH}	100	50	50.0	25.0	1	100	50	15.0	9.0
9_{DH}	100	50	64.3	30.0	1	100	50	19.3	11.3
10_{DH}	100	25	31.3	20.0	1	100	25	9.4	6.9
11_{DH}	100	25	41.7	25.0	1	100	25	12.5	9.0
12_{DH}	100	25	55.6	30.8	2	100	25	16.7	11.3

DH, diltiazem hydrochloride; MCC, microcrystalline cellulose.
*Each sample contained 0.5% of magnesium stearate and 0.5% of silicon dioxide.

Table 2. Composition of Caffeine Granules and Matrix Tablets

Sample	Granule Composition				No. of Granulation Steps	Tablet Composition*			
	C	MCC	Eudragit® NM 30 D			C	MCC	Eudragit® NM Solid	
	g	g	g	%		mg	mg	mg	%
1_{C}	100	100	50.0	20.0	1	100	100	15.0	6.9
2_{C}	100	100	66.6	25.0	1	100	100	20.0	9.0
3_{C}	100	100	85.7	30.0	1	100	100	25.7	11.3
4_{C}	100	100	107.9	35.0	2	100	100	32.4	13.8
5_{C}	100	50	37.5	20.0	1	100	50	11.3	6.9
6_{C}	100	50	50.0	25.0	1	100	50	15.0	9.0
7_{C}	100	50	64.3	30.0	1	100	50	19.3	11.3
8_{C}	100	50	81.0	35.1	2	100	50	24.3	13.8
9_{C}	100	25	31.3	20.0	1	100	25	9.4	6.9
10_{C}	100	25	41.7	25.0	1	100	25	12.5	9.0
11_{C}	100	25	55.6	30.0	2	100	25	16.7	11.3
12_{C}	100	25	67.5	35.0	3	100	25	20.3	13.8

C, caffeine; MCC, microcrystalline cellulose.
*Each sample contained 0.5% of magnesium stearate and 0.5% of silicon dioxide.

For statistical analysis, the ANOVA test was applied to the results of flowability and HR. Differences were considered significant if $P<0.05$.

Preparation and Evaluation of Matrix Tablets

Matrix tablets of different weights (approximately from 136 to 250 mg for DH tablets and from 138 to 236 mg for C ones), but having the same theoretical drug content, were compressed using 7-mm-diameter flat-faced punches (Korsch, EK 0, Korsch Pressen, Berlin, Germany). The composition of the matrix tablets is shown in Tables 1 and 2. Each sample contained 0.5% of magnesium stearate and 0.5% of colloidal silicon dioxide. The compression force used to produce matrix tablets was monitored to observe the compressibility of granules. The tablet characteristics included mass and content uniformity, hardness (C50 Tablet Hardness & Compression Tester, Engineering Systems, Nottingham, Great Britain), and friability (TAR 10, Erweka, Heusenstamm, Germany), which were evaluated according to the Ph. Eur. 7. The average value of hardness was obtained from measurements taken from 10 tablets.

Determining Dissolution Profiles and Similarity Factor Analysis

The dissolution profiles of the prepared samples were determined by a 12-hour dissolution test (SOTAX AT 7 On-Line System, Donau Lab, Zurich, Switzerland) using the paddle method at 100 rpm in 1000 mL of phosphate buffer (pH 6.8, Ph. Eur. 7) at 37°C. The samples were analyzed for the released drug amount by a UV spectrophotometer (Lambda 25, Perkin Elmer, Wellesley, USA) at 237 nm for DH and 275 nm for C after 30 minutes, 60 minutes, and then each hour. The mean value of drug

release in 6 samples at defined time intervals and standard deviation (SD) for each tablet batch were calculated. A dissolution test with a continuous pH change was performed with the selected samples under conditions as follows: for 2 hours at pH 1.2 (artificial gastric juice, 900 mL) and for 10 hours after a pH adjustment to pH 6.8. Sodium triphosphate (18.7 g) was used as a pH-increasing agent (16).

In order to compare the dissolution profiles of the DH tablet samples, the similarity factors f_2 were calculated, and this analysis was used to evaluate the significance of changes in the dissolution curves. Similarity factors were determined between samples to examine the effect of increasing Eudragit® NM amount and drug-to-MCC ratio in tablets on the dissolution profiles of the model drug. The data were analyzed by the equation 1 for the similarity factor f_2 (17):

$$f_2 = 50 \times \log\left\{\left[1+(1/n)\sum_{i=1}^{n}|R_i - T_i|^2\right]^{-0.5} \times 100\right\} \quad [1]$$

Where n is the number of time points and R_i and T_i are the dissolution data of a reference and tested samples at the time i. The similarity factor uses values between 0 and 100. When it is 100, the two profiles are identical, and when it approaches 0, their dissimilarity increases. The values of more than 50 were considered as similar (18). The similarity factor f_2 was not calculated for caffeine samples because of the fast drug release from the tablets.

Mechanism of Drug Release

The mechanism of drug release from matrix systems was studied by using the obtained dissolution data in the following equations (19).

Zero-order equation:

$$M_t/M_\infty = K_0 t \quad [2]$$

First-order equation:

$$M_t/M_\infty = 1 - e^{-K_0 t} \quad [3]$$

Square root-time kinetics (Higuchi model):

$$M_t/M_\infty = K_H \sqrt{t} \quad [4]$$

Korsmeyer-Peppas equation:

$$M_t/M_\infty = K_{KP} t^n \quad [5]$$

Hixson-Crowell model:

$$(M_\infty)^{1/3} - (M_t)^{1/3} = K_{HC} t \quad [6]$$

Where M_t is the amount of drug released in time t; M_∞ is the absolute cumulative amount of the drug released at an infinitive time; K_0, K_1, K_H, and K_{HC}, are the zero-order, first-order, Higuchi, and Hixson-Crowell release constants, respectively; and K_{KP} is the release constant comprising the structural and geometrical characteristics of the tablets. The release exponent n characterizes the mechanism of the drug release; in particular, n=0.5 corresponds to release of Fick's diffusion, 0.5<n<1.0 to an anomalous transport, n=1.0 to zero-order release kinetics, and n>1.0 to a super Case II transport (19, 20).

Results

Three sets of DH and C granules differing in the ratio of model drug to MCC; i.e., 1:1, 2:1, and 4:1, were prepared in a high-shear mixer by adding the different amount of Eudragit® NM 30 D (see Tables 1 and 2 for their composition).

Characteristics of Granules

The DH and C granules were evaluated for their flow properties (Tables 3 and 4). The flow characteristics of granules varied from passable to excellent. The flowability of granules was relatively low and ranged from 1.3 to 3.0 s/100 g. The Hausner ratio of DH and C samples reached values from 1.04 to 1.23 and 1.17 to 1.32, respectively. The HR values of samples with the same amount of drug and polymer, but differing only in the MCC amount, were compared: e.g., HR 1.16 for 2_{DH}, HR 1.12 for 8_{DH}, and HR 1.06 for 11_{DH} containing 9.0% of the dry polymer or HR 1.27 for 3_C, HR 1.25 for 7_C, and HR 1.17 for 11_C containing 11.3% of the dry polymer, respectively.

Characteristics of Matrix Tablets

The results of mass and content uniformity, hardness and friability of the matrix tablets together with compression forces used are given in Table 3 for the DH samples and in Table 4 for the C samples. The model drug content in the matrix tablets was 96.2%–107.2%. The friability of DH and C samples ranged from 0.03% to 0.10% and from 0.06% to 0.15%, respectively. The hardness of DH matrix tablets varied from 108.1 N (1_{DH}) to 161.1 N (6_{DH}). The DH tablets with a high percentage of polymers were resistant to crushing, and at first, they were plastically deformed, and when the crushing force became critical, the tablets cracked. The plastic characteristics were most prominent in samples containing the highest amount of polymer (13.8%–18.4%). The hardness of C matrix tablets ranged from 107.7 N (1_C) to 134.5 (8_C and 12_C).

Dissolution, Similarity Factor Analysis, and Drug Release Study

Matrix Tablets With Diltiazem Hydrochloride. The dissolution profiles of DH matrix tablets at pH 6.8 differed depending on the drug-to-filler ratio and polymer amount (Table 5). Based on the release

Table 3. Properties of Diltiazem Hydrochloride Granules and Tablets

Set	Sample	Flowability, s	Hausner Ratio	Flow Characteristic	Friability %	Hardness N	Compression Force, kN
DH 1:1*	1_{DH}	2.1 (0.0)	1.23 (0.01)	Fair	0.03	108.1 (6.6)	10.5
	2_{DH}	1.9 (0.0)	1.16 (0.02)	Good	0.03	118.8 (11.9)	10.5
	3_{DH}	1.7 (0.0)	1.14 (0.01)	Good	0.03	110.7 (10.0)	10.5
	4_{DH}	1.7 (0.0)	1.13 (0.02)	Good	0.03	132.2 (16.8)	8.8
	5_{DH}	1.4 (0.0)	1.15 (0.01)	Good	0.05	142.8 (20.2)	8.8
	6_{DH}	1.3 (0.0)	1.11 (0.02)	Excellent	0.05	161.1 (16.9)	10.5
DH 2:1†	7_{DH}	2.0 (0.0)	1.18 (0.02)	Good	0.07	120.9 (7.0)	17.6
	8_{DH}	1.8 (0.0)	1.12 (0.01)	Good	0.05	134.0 (6.0)	17.6
	9_{DH}	1.7 (0.0)	1.07 (0.02)	Excellent	0.04	158.6 (13.3)	17.6
DH 4:1‡	10_{DH}	1.7 (0.0)	1.11 (0.00)	Good	0.10	122.3 (3.6)	31.6
	11_{DH}	1.7 (0.0)	1.06 (0.00)	Excellent	0.07	128.2 (5.5)	21.1
	12_{DH}	1.4 (0.0)	1.04 (0.00)	Excellent	0.08	135.5 (5.8)	21.1

Values are mean (standard deviation).
*Weight, 222.6–250.4 mg; drug content, 102.3%–107.2%; †weight, 161.8–172.9 mg; drug content, 96.2%–98.4%; ‡weight, 136.5–146.3 mg; drug content, 98.0%– 01.9%.

Table 4. Properties of Caffeine Granules and Tablets

Set	Sample	Flowability, s	Hausner Ratio	Flow Characteristic	Friability %	Hardness N	Compression Force, kN
C 1:1*	1_{C}	3.0 (0.1)	1.32 (0.01)	Passable	0.10	107.7 (4.0)	7.0
	2_{C}	2.5 (0.0)	1.27 (0.00)	Passable	0.12	110.7 (7.5)	7.0
	3_{C}	2.0 (0.0)	1.27 (0.01)	Passable	0.09	125.3 (7.1)	7.0
	4_{C}	1.8 (0.0)	1.26 (0.01)	Passable	0.06	114.4 (8.2)	10.5
	5_{C}	2.5 (0.0)	1.29 (0.00)	Passable	0.13	118.6 (9.0)	12.3
	6_{C}	2.3 (0.0)	1.26 (0.00)	Passable	0.12	114.0 (6.9)	12.3
C 2:1†	7_{C}	1.8 (0.0)	1.25 (0.01)	Fair	0.09	130.1 (7.7)	8.8
	8_{C}	1.6 (0.0)	1.21 (0.01)	Fair	0.08	134.5 (10.9)	10.5
	9_{C}	2.3 (0.0)	1.26 (0.01)	Passable	0.15	113.4 (4.0)	14.0
C 4:1‡	10_{C}	1.6 (0.0)	1.23 (0.01)	Fair	0.13	122.2 (3.8)	14.0
	11_{C}	1.3 (0.0)	1.17 (0.02)	Good	0.08	129.0 (7.2)	15.8
	12_{C}	1.3 (0.0)	1.17 (0.01)	Good	0.08	134.5 (9.0)	17.6

Values are mean (standard deviation).
*Weight, 218.5–236.5 mg; drug content, 103.0%–104.2%; †weight, 163.6–178.0 mg; drug content, 101.2%–105.2%; ‡weight, 137.9–149.9 mg; drug content, 101.5%–105.6%.

Table 5. Dissolution Profiles of Diltiazem Hydrochloride Samples and Their Similarity Analysis

		Amount of Released Drug From DH Samples, %										Similarity Analysis
SET	Sample	30′	60′	120′	180′	240′	360′	480′	600′	720′	Max SD	f_2/Reference Sample
DH 1:1	1_{DH}	23.0	43.5	82.8	89.3	93.4	97.9	98.3	98.9	99.6	3.93	–
	2_{DH}	19.2	35.5	61.7	86.9	95.3	99.1	99.6	100.9	101.2	3.98	71.00 /1_{DH}
	3_{DH}	26.1	40.3	55.6	66.1	76.6	85.7	90.1	94.4	97.8	6.29	38.87/1_{DH}
	4_{DH}	26.7	40.2	55.7	63.4	67.8	74.3	79.0	83.3	87.0	6.97	29.40/1_{DH}
	5_{DH}	24.4	35.3	48.2	56.3	62.5	70.2	74.4	77.6	80.2	3.16	26.14/1_{DH}
	6_{DH}	22.5	32.1	42.7	48.5	51.9	56.0	58.7	60.8	62.4	5.67	19.78/1_{DH}
DH 2:1	7_{DH}	37.4	54.0	70.6	85.4	89.4	93.8	96.6	98.7	100.4	16.54	–
	8_{DH}	35.5	50.9	64.9	71.0	74.9	80.5	85.1	89.2	93.0	3.17	48.69/7_{DH}
	9_{DH}	30.5	43.5	54.0	58.5	61.3	65.4	68.6	71.5	74.1	5.02	30.49/7_{DH}
DH 4:1	10_{DH}	35.1	55.7	76.2	83.4	86.8	91.7	95.2	97.6	99.1	3.83	–
	11_{DH}	35.5	49.2	61.1	66.8	69.7	73.5	76.5	79.1	81.5	10.20	39.77/10_{DH}
	12_{DH}	30.5	42.6	51.6	54.8	56.9	59.5	61.0	62.5	63.8	5.78	26.61/10_{DH}

DH, diltiazem hydrochloride. pH 6.8; number of tested tablets, n=6.

data of the set 1:1, the amount of Eudragit® NM was increased to 18.4% in this set.

To evaluate the influence of increasing polymer amounts in the sets, a similarity factor f_2 analysis was performed by comparing the obtained dissolution profiles (Table 5). The f_2 values were as follows: the values of similarity factor f_2 decreased from 71.00 between 1_{DH} and 2_{DH} to 19.78 between samples 1_{DH} and 6_{DH} for the set 1:1 (1_{DH} was taken as the reference); the values of similarity factor f_2 decreased from 48.69 between 7_{DH} and 8_{DH} to 30.49 between samples 7_{DH} and 9_{DH} for the set 2:1 (7_{DH} was taken as the reference); and the values of similarity factor f_2 decreased from 39.77 between 10_{DH} and 11_{DH} to 26.61 between samples 10_{DH} and 12_{DH} for the set 4:1 (10_{DH} was taken as the reference).

The burst effect (after 30 minutes) of DH samples with the drug-to-filler ratios of 1:1, 2:1, and 4:1 had values in the range of 19.2%–26.7%, 30.5%–37.4%, and 30.5%–35.6%, respectively. For evaluation of the effect of the DH-to-MCC ratio, the dissolution profiles of samples containing the same polymer amount were compared, and the similarity factors were calculated (Fig. 1). For the samples 1_{DH}, 7_{DH}, and 10_{DH} containing 6.9% of polymer (Fig. 1A), the burst effect was 23.0%, 37.4%, and 35.1%, respectively; the total DH amount released during the dissolution test was 99.6%, 100.4%, and 99.1%, respectively (f_2 was more than 50 comparing dissolution curves). For the samples 2_{DH}, 8_{DH}, and 11_{DH} containing 9% of polymer (Fig. 1B), the burst effect was 19.2%, 35.5%, and 35.6%, respectively; the total released DH amount measured at the end of dissolution test was 101.2%, 93.0%, and 81.5%, respectively (f_2 between 2_{DH} and 8_{DH}=34.53; f_2 between 8_{DH} and 11_{DH}=55.80). For the samples 3_{DH}, 9_{DH}, and

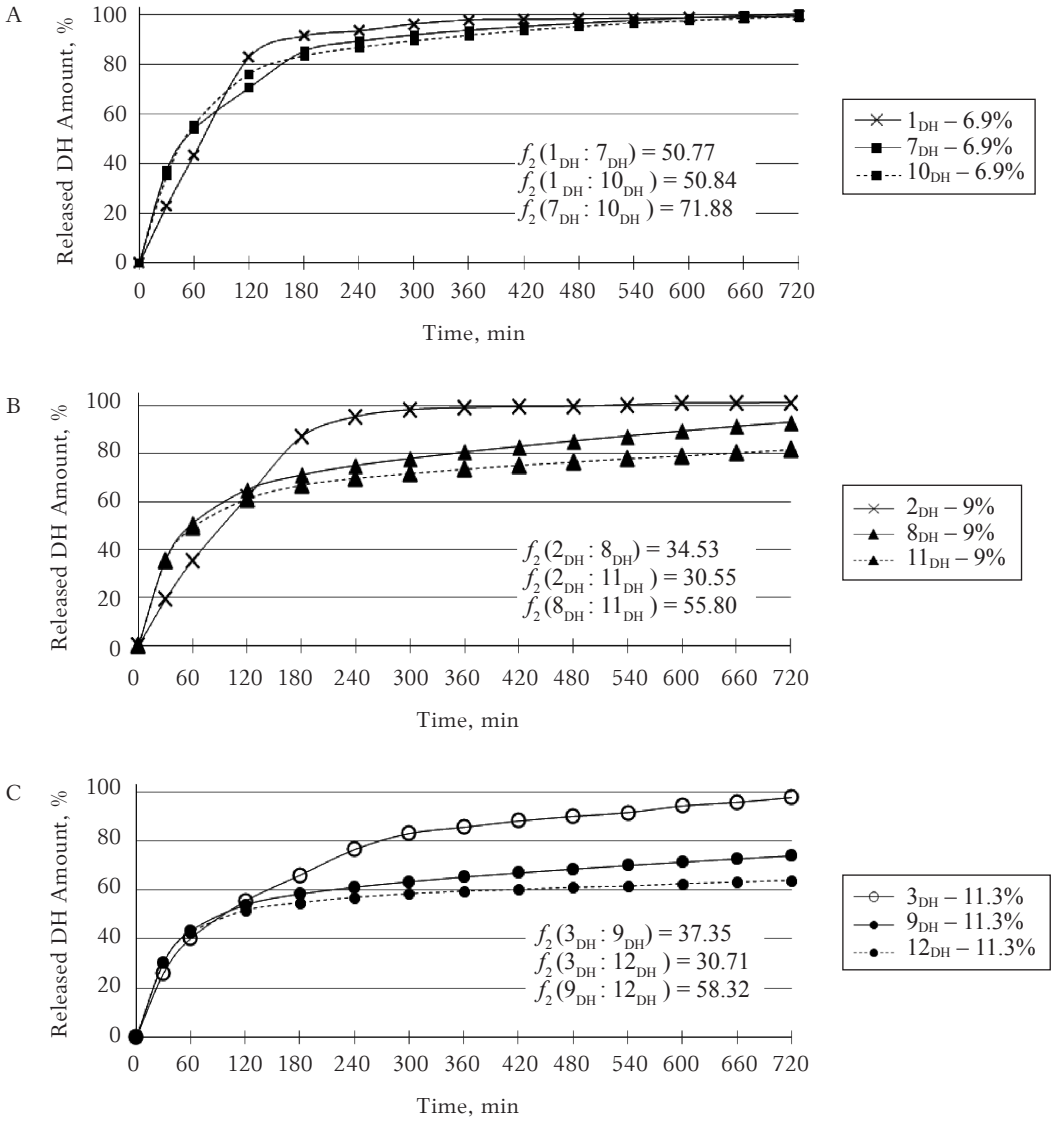

Fig. 1. Comparison of dissolution profiles of diltiazem hydrochloride (DH) samples containing different amounts of Eudragit® NM (A, 6.9%; B, 9%; C, 11.3%) and different amounts of MCC in phosphate buffer at pH 6.8 (number of tested tablets, n=6)

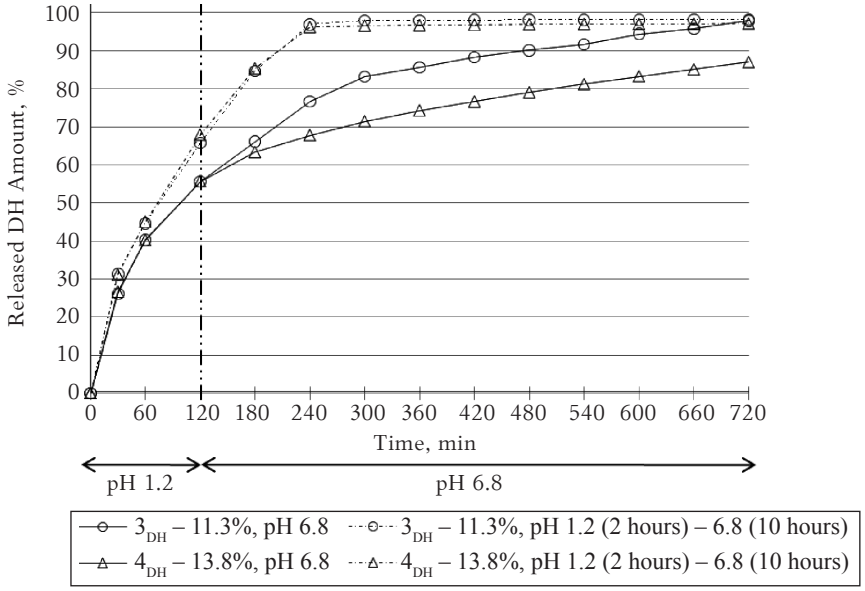

Fig. 2. Dissolution profiles of samples 3_{DH} and 4_{DH} in different dissolution media (pH 6.8 or continuous pH change in dissolution media) (number of tested tablets, n=6)

12_{DH} containing 11.3% of polymer (Fig. 1C), the burst effect was 26.1%, 30.5%, and 30.5%, respectively; the total released DH amount during the dissolution test was 97.8%, 74.1%, and 63.8%, respectively (f_2 between 3_{DH} and 9_{DH}=37.35; f_2 between 9_{DH} and 12_{DH}=58.32). The samples 4_{DH}, 5_{DH}, and 6_{DH} were prepared when the set 1:1 was extended. The burst effect was 26.7%, 24.4%, and 22.5%, respectively, and the total released DH amount during the dissolution test was 87.0%, 80.2%, and 62.4%, respectively.

The samples 3_{DH} and 4_{DH} were selected for the dissolution test with a continuous pH change. The obtained dissolution profiles are presented in Fig. 2. A more rapid DH release was observed under these conditions than in the medium at pH 6.8; the total release of incorporated drug was achieved after 4 hours for both samples.

The release data of the selected samples 3_{DH}, 4_{DH}, and 5_{DH} obtained during the dissolution test were analyzed according to the equations 2–6. The determination coefficients R^2 for different kinetic models are summarized in Table 6. Moreover, for the Korsmeyer-Peppas kinetic model, the release exponent *n* was calculated to predict the mechanism of DH release. The determination coefficients R^2 for the zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell models ranged in the intervals of 0.778–0.843, 0.707–0.934, 0.952–0.987, 0.984–0.994, and 0.923–0.942, respectively. The release exponent *n* was smaller than 0.5 for all samples.

Matrix Tablets With Caffeine. The dissolution profiles of C samples at pH 6.8 are shown in Fig. 3 for the sets 1:1 and 2:1 and in Fig. 4 for the set 4:1. The samples 1_C–4_C (set 1:1) released more than 95% of the drug during the first 30 minutes. In the samples from the 2:1 set, the drug release was decreasing when the polymer amount increased: the sample 5_C released the total drug amount in the first 30 minutes; the samples 6_C and 7_C released more than 93% of the caffeine in the first hour, and the 2-hour slow-down was observed in the sample 8_C. The samples of the set 4:1 released more than 90% of caffeine: 30 minutes for the sample 9_C, 60 minutes for the sample 10_C, 120 minutes for the sample 11_C, and 180 minutes for the sample 12_C.

Discussion

The aim of this study was to evaluate the suitability of Eudragit® NM as a matrix-forming mate-

Table 6. Values of Determination Coefficients

Sample	Model					
	Zero order	First order	Higuchi	Korsmeyer-Peppas		Hixson-Crowell
	R^2	R^2	R^2	R^2	n	R^2
3_{DH}	0.778	0.868	0.952	0.994	0.50±0.02	0.923
4_{DH}	0.840	0.707	0.984	0.984	0.43±0.03	0.933
5_{DH}	0.843	0.934	0.987	0.994	0.44±0.02	0.942

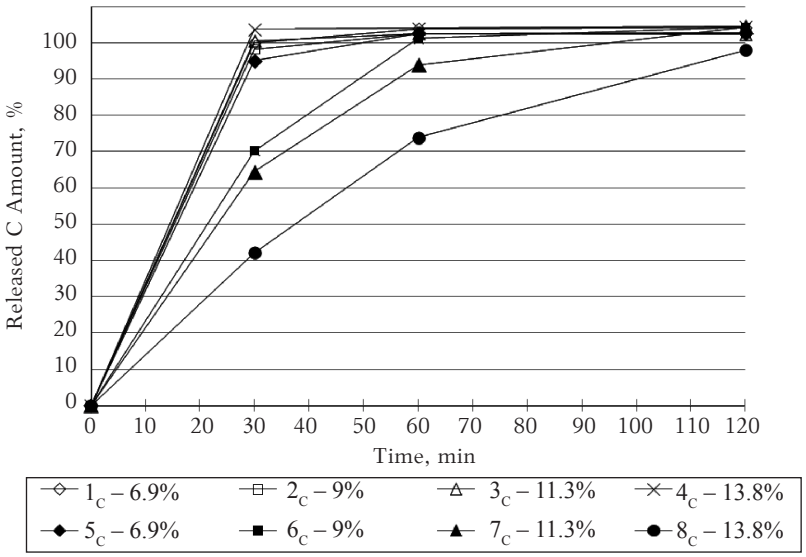

Fig. 3. Dissolution profiles of caffeine samples with 100-mg and 50-mg microcrystalline cellulose and different amount of Eudragit® NM (expressed in %) in tablets in phosphate buffer at pH 6.8 (number of tested tablets, n=6)

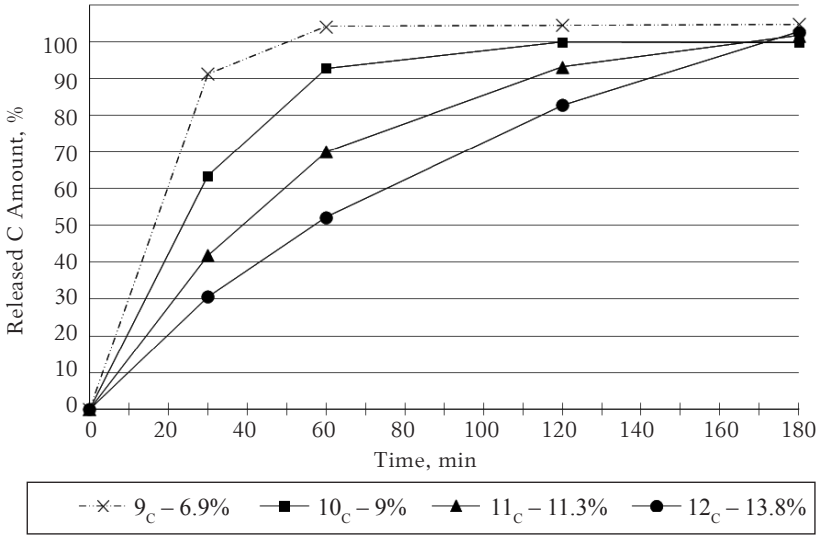

Fig. 4. Dissolution profile of caffeine samples with 25-mg microcrystalline cellulose and different amount of Eudragit® NM (expressed in %) in tablets in phosphate buffer at pH 6.8 (number of tested tablets, n=6)

rial in combination with microcrystalline cellulose PH 101, an insoluble filler, for model drugs of different solubility. DH was selected as a freely soluble model drug; its solubility at 37°C was 659 mg/mL at pH 1.2, 378.68 mg/mL at pH 6.0, and 71.42 mg/mL at pH 7.4 (21). C was chosen as a sparingly soluble model drug with a solubility of 20.9 mg/mL at pH 1.2 and 16.7 mg/mL at pH 6.0 at 37°C (22). The amount of the polymer (up to 18.4% of polymer) in the DH set 1:1 was increased more than in others because the partial results showed it to be the optimal set for DH sustained release.

Characteristics of Granules. Good flowability of samples (excellent to passable; Tables 3 and 4) provided a good filling during the tablet manufacturing. It is well known that higher proportions of the binder used for the granulation process lead to the formation of granules with better flow properties due to the bigger particle diameter of the granules (23, 24). Due to this, the flowability of samples with a constant drug-to-MCC ratio significantly improved ($P<0.05$) as the amount of Eudragit® NM 30 D increased. Although HR analysis showed a similar trend (decrease of HR values), the results were not significantly different ($P>0.05$).

The decreasing amount of MCC in the granule samples also significantly ($P<0.05$) influenced their flow properties and generally led to their improvement. The mean particle diameter of DH, caffeine, and MCC was 156.0 μm, 61.3 μm, and 48.3 μm, re-

spectively. Granulation of the starting material with smaller particles (and thus a larger surface area) using the same amount of binder resulted in a smaller granule size, which could explain their lower flowability (25). Therefore, a higher amount of MCC with the smallest particles in the formulation caused a slower flow of granules. The HR value for most of the samples was less than 1.25. According to the literature data, the samples with the Hausner ratio below this value are suitable for tablet production (26). Although the HR values of samples 1_C–6_C and 9_C were higher than 1.25, no problems appeared during the process of tablet compression.

Characteristics of Matrix Tablets. The tested parameters complied with the Ph. Eur. 7 requirements. The prepared matrix tablets exhibited excellent mechanical properties with very low friability values of less than 0.15% and fulfilled the required official friability limit (less than 1%). These values were not dependent on the amount of MCC and most probably were dependent on the amount of polyacrylate polymer. The similar friability values were reported by Tsai et al., who investigated the properties of matrix tablets containing a lactose-dicalcium phosphate mixture, granulated by latex dispersion of Eudragit® RL 30 D and RS 30 D (27). Friability results showed that the matrix tablets were compact and mechanically resistant. The change in the excipient ratio did not have any effect on the friability of the samples.

The high values of tablet hardness (108–161 N) confirmed the excellent mechanical properties of the matrix tablets. The addition of higher amounts of Eudragit® NM into the tablet composition led to better bonding among particles in most cases and thus forming the tablets of higher hardness. Similar findings were reported in an experimental study by Fu et al. (28). Different results have been published about the relationship between hardness and the polymer amount used for granulation; e.g., no effect on the tensile strength of the tablets was observed when different amounts of Eudragit® RL 30 D and RS 30 D (2.5%–10.0%) were used for the granulation of lactose and dicalcium phosphate mixture (27). However, the increase of hardness, described above, could be due to the increasing tablet mass, which could also contribute to the improvement of the mechanical properties of tablets (29). DH tablets with a high content of polymer were shown to be plastic; however, hardness measurements showed higher values of standard deviation (samples 4_{DH}–6_{DH}). C matrix tablets were found to be less plastic than DH matrix ones; however, the corresponding standard deviations were found to be almost equal (less than 11.0 N). The different behavior of the DH and C sets was probably due to the different physical and chemical properties of the drugs.

The compression forces used varied, depending on the drug-to-filler ratio. Samples with a higher drug-to-filler ratio required a higher compression force to produce the tablets of similar hardness compared with samples with a lower drug-to-filler ratio. These results were dependent on the MCC content and confirmed the excellent compressibility of MCC (30).

Dissolution, Similarity Factor Analysis, and Drug Release Study

Matrix Tablets With Diltiazem Hydrochloride. Eudragit® NM as a studied pharmaceutical excipient was proved to be an efficient retardant for DH in the medium at pH 6.8. The increasing amounts of Eudragit® NM in matrix tablets led to the retardation of DH release and to a lower amount of DH totally released from tablets during the dissolution test. The significance of this effect was confirmed by similarity factor analysis; the values of similarity factor f_2 were usually less than 50 comparing the dissolution curves. This finding is in agreement with the literature data reporting that the increased amount of retarding polymer in matrix tablets leads to a slower drug release (31). Higher amounts of Eudragit® NM reduced the time release due to the lower penetration of the dissolution medium into the system because of its hydrophobic nature (32). Increased polymer amounts led to a lower release at the end of the dissolution test. The remaining drug was not released and remained in the undissolved matrix.

The DH-to-MCC ratio had an effect on the burst effect value, defined as the immediate drug release from a tablet surface at the beginning of dissolution (33) and, consequently, the drug release from matrix tablets. Appropriately, a low burst effect was found for the set 1:1. The samples with lower amounts of the filler (sets 2:1 and 4:1) showed the higher values of burst effect, but only small differences were found comparing the samples of these sets containing the same concentration of Eudragit® NM. The lower burst effect in the set 1:1 could have been caused by the greater weight (and also the height) of these tablets with a more sparse dispersion of the drug within the matrix presented as a lower concentration gradient of the drug and a wider diffusion layer (34). The smaller influence of filler amount on the burst effect was observed when the concentration of Eudragit® NM increased (11.3%). The change in the drug-to-filler ratio from 1:1 to 2:1 had a significant influence on the time of drug release from matrix tablets, but a further decrease in the amount of the filler (from 2:1 to 4:1) in tablets had no significant impact on dissolution. If the concentration of polymer was low (6.9%), the abovementioned dependence was not observed (the dissolution profiles were similar, Fig. 1A).

The samples 3_{DH} and 4_{DH} (set 1:1) were selected as optimal DH formulations with a suitable burst effect and released the drug close to 100% after 12 hours. These selected samples were tested by the dissolution method of changing pH values, which better corresponded to the real conditions in the gastrointestinal tract (2 hours at pH 1.2 and following 10 hours at pH 6.8). From the obtained results, it is apparent that the drug release from the tested samples was faster, and the total amount was released in 4 hours. Eudragit®NM is considered to be pH-independent; therefore, this finding was probably caused by the higher solubility of DH in the acidic medium. The pH-independent behavior of structurally identical Eudragit® NE was confirmed by the findings obtained by Ahhin et al., who tested matrix tablets based on this polymer containing theophylline as the model drug with pH-independent solubility (35). To maintain the original dissolution profiles, it would be suitable either to coat the matrix tablets with enteric film or to incorporate the model drug with pH-independent solubility. The coating of tablets would delay the onset of the drug effect in vivo (36). Another possibility could be the incorporation of basic pH-modifiers into matrix tablets (37).

The release mechanism of DH from matrix tablets was studied by using the obtained dissolution data in the equations 2–6. According to the R^2 values, the Korsmeyer-Peppas kinetic model was the best-fit release kinetic model for the selected DH samples (Table 6). The values of the release exponent (n less than or equal to 0.5) indicated that Fick's diffusion as the predominant DH release mechanism. Diffusion is a typical release mechanism for highly soluble drugs (38). This finding is supported by the relatively good correlation with the Higuchi diffusion kinetic model. We presume that insoluble MCC together with insoluble Eudragit® NM forms a matrix skeleton from which DH is continuously released by the diffusion-controlled leaching through the channels of created pores. In the experimental study, Cao et al. described a similar release of highly soluble potassium citrate from insoluble lipophilic matrices (39). In the evaluated samples, a weaker correlation was observed with the zero-order, first-order, and Hixson-Crowell models.

Matrix Tablets With Caffeine. Completely different results were obtained from the dissolution testing of the caffeine matrix tablets. All samples of the set 1:1 (1_C–4_C) disintegrated during the first 30 minutes, and no effect of the increasing amount of Eudragit® NM on dissolution profile was observed. A mild retention was achieved in the set 2:1 (120 minutes) and the set 4:1 (180 minutes). For both the sets, a higher amount of polymer in the formulation influenced the dissolution characteristics of the samples and led to a slower caffeine release (Figs. 3 and 4). Unlike in the DH samples, the 12-hour sustained release of the drug was not achieved when caffeine was used as the model drug. The difficult achievement of effective retention is related to the solubility of tablet components. Caffeine is slightly soluble in water, but MCC is almost insoluble in water, and Eudragit® NM is insoluble as well. Systems that are almost insoluble probably possess a higher tendency to disintegrate more rapidly. This problem might be solved by the selection of the filler that is more soluble.

Conclusions

Eudragit® NM was investigated under in vitro conditions as the drug release modifier for matrix tablets developed for the 12-hour therapy. The polymer was combined with microcrystalline cellulose, a common insoluble filler. A desirable release profile (at pH 6.8) was achieved only for freely soluble drugs (diltiazem hydrochloride) when the drug-to-insoluble filler ratio was 1:1 and polymer concentration ranged from 11.3% to 13.8% in tablets. The presented composition of matrix systems was not suitable for the incorporation of poorly soluble drugs.

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Statement of Conflict of Interest

The authors state no conflict of interest.

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