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
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, 7–11, 1–3C, and 5–7C) or 25% (samples 9C and 10C) was made by one step. The granulation with the higher amount of Eudragit® NM 30 D (samples 4–6, 12C, 4C, 8C, 11C, and 12C) 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 over-wetting 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 g | MCC g | Eudragit® NM 30 D g | % | DH mg | MCC mg | Eudragit® NM Solid 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  | 152.3            | 43.2 | 3 | 100  | 100  | 39.0             | 16.2|
| 6 DH   | 100  | 50   | 37.5             | 20.0 | 4 | 100  | 100  | 45.7             | 18.4|
| 7 DH   | 100  | 50   | 50.0             | 25.0 | 1 | 100  | 50   | 11.3             | 6.9 |
| 8 DH   | 100  | 50   | 64.3             | 30.0 | 1 | 100  | 50   | 19.3             | 11.3|
| 9 DH   | 100  | 25   | 31.3             | 20.0 | 1 | 100  | 25   | 9.4              | 6.9 |
| 10 DH  | 100  | 25   | 41.7             | 25.0 | 2 | 100  | 50   | 12.5             | 9.0 |
| 11 DH  | 100  | 25   | 55.6             | 30.0 | 2 | 100  | 25   | 16.7             | 11.3|
| 12 DH  | 100  | 25   | 67.5             | 35.0 | 3 | 100  | 25   | 20.3             | 13.8|

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 g | MCC g | Eudragit® NM 30 D g | % | C mg | MCC mg | Eudragit® NM Solid 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 (SO-TAX 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):

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

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:**
  $$\frac{M_t}{M_\infty} = K_o \cdot t$$

- **First-order equation:**
  $$\frac{M_t}{M_\infty} = 1 - e^{-K_1 \cdot t}$$

- **Square root-time kinetics (Higuchi model):**
  $$\frac{M_t}{M_\infty} = K_h \sqrt{t}$$

- **Korsmeyer-Peppas equation:**
  $$\frac{M_t}{M_\infty} = K_{KP} \cdot t^n$$

- **Hixson-Crowell model:**
  $$(M_t)^{1/3} - (M_\infty)^{1/3} = K_HC \cdot t$$

Where $M_t$ is the amount of drug released in time $t$; $M_\infty$ is the absolute cumulative amount of the drug released at an infinitive time; $K_o$, $K_1$, $K_h$, and $K_{KP}$, 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 2DH, HR 1.12 for 8DH, and HR 1.06 for 11DH containing 9.0% of the dry polymer or HR 1.27 for 3C, HR 1.25 for 7C, and HR 1.17 for 11C 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 (1DH) to 161.1 N (6C). 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 (1C) to 134.5 (8C and 12C).

**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<sub>sth</sub> | 2.1 (0.0) | 1.23 (0.01) | Fair | 0.03 | 108.1 (6.6) | 10.5 |
|       | 2<sub>sth</sub> | 1.9 (0.0) | 1.16 (0.02) | Good | 0.03 | 118.8 (11.9) | 10.5 |
|       | 3<sub>sth</sub> | 1.7 (0.0) | 1.27 (0.01) | Good | 0.03 | 110.7 (10.0) | 10.5 |
|       | 4<sub>sth</sub> | 1.7 (0.0) | 1.14 (0.01) | Good | 0.03 | 132.2 (16.8) | 8.8 |
|       | 5<sub>sth</sub> | 1.4 (0.0) | 1.13 (0.02) | Good | 0.05 | 142.8 (20.2) | 8.8 |
|       | 6<sub>sth</sub> | 1.3 (0.0) | 1.11 (0.02) | Excellent | 0.05 | 161.1 (16.9) | 10.5 |
| DH 2:1 | 7<sub>sth</sub> | 2.0 (0.0) | 1.18 (0.02) | Good | 0.07 | 120.9 (7.0) | 17.6 |
|       | 8<sub>sth</sub> | 1.8 (0.0) | 1.12 (0.01) | Good | 0.05 | 134.0 (6.0) | 17.6 |
|       | 9<sub>sth</sub> | 1.7 (0.0) | 1.07 (0.02) | Excellent | 0.04 | 158.6 (13.3) | 17.6 |
| DH 4:1 | 10<sub>sth</sub> | 1.7 (0.0) | 1.11 (0.00) | Good | 0.10 | 122.3 (3.6) | 31.6 |
|       | 11<sub>sth</sub> | 1.7 (0.0) | 1.06 (0.00) | Excellent | 0.07 | 128.2 (5.5) | 21.1 |
|       | 12<sub>sth</sub> | 1.4 (0.0) | 1.04 (0.00) | Excellent | 0.08 | 135.3 (3.8) | 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<sub>c</sub> | 3.0 (0.1) | 1.32 (0.01) | Passable | 0.10 | 107.7 (4.0) | 7.0 |
|       | 2<sub>c</sub> | 2.5 (0.0) | 1.27 (0.00) | Passable | 0.12 | 110.7 (7.5) | 7.0 |
|       | 3<sub>c</sub> | 2.0 (0.0) | 1.27 (0.01) | Passable | 0.09 | 125.3 (7.1) | 7.0 |
|       | 4<sub>c</sub> | 1.8 (0.0) | 1.26 (0.00) | Passable | 0.06 | 114.8 (8.2) | 10.5 |
|       | 5<sub>c</sub> | 2.5 (0.0) | 1.29 (0.00) | Passable | 0.13 | 118.6 (9.0) | 12.3 |
|       | 6<sub>c</sub> | 2.3 (0.0) | 1.26 (0.00) | Passable | 0.12 | 114.0 (6.9) | 12.3 |
| C 2:1 | 7<sub>c</sub> | 1.8 (0.0) | 1.25 (0.01) | Fair | 0.09 | 130.1 (7.7) | 8.8 |
|       | 8<sub>c</sub> | 1.6 (0.0) | 1.21 (0.01) | Fair | 0.08 | 134.5 (10.9) | 10.5 |
|       | 9<sub>c</sub> | 2.3 (0.0) | 1.26 (0.01) | Passable | 0.15 | 113.4 (4.0) | 14.0 |
| C 4:1 | 10<sub>c</sub> | 1.6 (0.0) | 1.23 (0.01) | Fair | 0.13 | 122.2 (3.8) | 14.0 |
|       | 11<sub>c</sub> | 1.3 (0.0) | 1.17 (0.02) | Good | 0.08 | 129.0 (7.2) | 15.8 |
|       | 12<sub>c</sub> | 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

| SET | Sample | 30’ | 60’ | 120’ | 180’ | 240’ | 360’ | 480’ | 600’ | 720’ |
|-----|--------|-----|-----|------|------|------|------|------|------|------|
|     |        | Max | SD  |      |      |      |      |      |      |      |
| DH 1:1 | 1<sub>DH</sub> | 23.0 | 43.5 | 82.8 | 89.3 | 93.4 | 97.9 | 98.3 | 98.9 | 99.6 |
|       | 2<sub>DH</sub> | 19.2 | 35.5 | 61.7 | 86.9 | 95.3 | 99.1 | 99.6 | 100.9 | 101.2 |
|       | 3<sub>DH</sub> | 26.1 | 40.3 | 55.6 | 66.1 | 76.6 | 85.7 | 90.1 | 94.4 | 97.8 |
|       | 4<sub>DH</sub> | 26.7 | 40.2 | 55.7 | 63.4 | 67.8 | 74.3 | 79.0 | 83.3 | 87.0 |
|       | 5<sub>DH</sub> | 24.4 | 35.3 | 48.2 | 56.3 | 62.5 | 70.2 | 74.4 | 77.6 | 80.2 |
|       | 6<sub>DH</sub> | 22.5 | 32.1 | 42.7 | 48.5 | 51.9 | 56.0 | 58.7 | 60.8 | 62.4 |
| DH 2:1 | 7<sub>DH</sub> | 37.4 | 54.0 | 70.6 | 85.4 | 89.4 | 93.8 | 96.6 | 98.7 | 100.4 |
|       | 8<sub>DH</sub> | 35.5 | 50.9 | 64.9 | 71.0 | 74.9 | 80.5 | 85.1 | 89.2 | 93.0 |
|       | 9<sub>DH</sub> | 30.5 | 43.5 | 54.0 | 58.5 | 61.3 | 65.4 | 68.6 | 71.5 | 74.1 |
| DH 4:1 | 10<sub>DH</sub> | 35.1 | 55.7 | 76.2 | 83.4 | 86.8 | 91.7 | 95.2 | 97.6 | 99.1 |
|       | 11<sub>DH</sub> | 35.5 | 49.2 | 61.1 | 69.7 | 73.5 | 76.5 | 79.1 | 81.5 | 10.20 |
|       | 12<sub>DH</sub> | 30.5 | 42.6 | 51.6 | 54.8 | 56.9 | 59.5 | 61.0 | 62.5 | 63.8 |

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

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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

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**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)
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 slowdown 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-

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**Table 6. Values of Determination Coefficients**

| Sample | Zero order | First order | Higuchi | Korsmeyer-Peppas | Hixson-Crowell |
|--------|------------|-------------|---------|-----------------|---------------|
|        | $R^2$      | $R^2$       | $R^2$   | $R^2$           | $R^2$         |
| 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         |

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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-

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)
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 1–6_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_hc–6_hc). 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 f_2 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, 4, and 5 (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 ($1_c$, $1_d$, $1_f$) 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 present 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.

**References**

1. Abdel-Rahman SI, Mahrous GM, El-Badry M. Preparation and comparative evaluation of sustained release metoclopramide hydrochloride matrix tablets. Saudi Pharm J 2009;17(4):283-8.
2. Hiremath PS, Saha RN. Oral matrix tablet formulations for concomitant controlled release of anti-tubercular drugs: design and in vitro evaluations. Int J Pharm 2008;362(1-2):118-25.
3. Maderuelo C, Zarzuelo A, Lanao JM. Critical factors in the release of drugs from sustained release hydrophilic matrices. J Control Release 2011;154(1-2):19.
4. Özyazici M, Gökce EH, Ertan G. Release and diffusional modeling of metronidazole lipid matrices. Eur J Pharm Biopharm 2006;63:331-9.
5. Sánchez-Lafuente C, Rabasco AM, Álvarez-Fuentes J, Fernández-Arévalo M. Eudragit® RS-PM and Etohoce® 100 Premium: influence over the behavior of didanosine inert matrix tablet. Farmaco 2002;57(8):649-56.
6. Sánchez-Lafuente C, Teresa Fauci M, Fernández-Arévalo...
M. Álvarez-Fuentes J, Rabasco AM, Mura P. Development of sustained release matrix tablets of didanosine containing methacrylic and ethylcellulose polymers. Int J Pharm 2002;234:213-21.

7. Ceballos A, Ciriri M, Maestrelli F, Corti G, Mura P. Influence of formulation and process variables on in vitro release of theophylline from directly-compressed Eudragit® matrix tablets. Farmaco 2005;60:913-8.

8. Huyghebaert N, Vermeire A, Remon JP. In vitro evaluation of coating polymers for enteric coating and human ileal targeting. Int J Pharm 2005;298(1):26-37.

9. Haznedar S, Dortanc B. Preparation and in vitro evaluation of Eudragit® microspheres containing acetazolamide. Int J Pharm 2004; 269:131-40.

10. Krogars K, Heinämäki J, Vesalathi J, Marvola M, Antikainen O, Yliruusi J. Extrusion-spheronization of pH-sensitive polymeric matrix pellets for possible colonic drug delivery. Int J Pharm 2000;199:187-94.

11. Tabasi SH, Moolchandani V, Fahmy R, Hoag SW. Sustained release dosage forms dissolution behavior prediction: a study of matrix tablets using NIR spectroscopy. Int J Pharm 2009;382:1-6.

12. Özgüney I, Ertan G, Güneri T. Dissolution characteristics of megaloporous tablets prepared with two kinds of matrix granules. Farmaco 2004;59:549-55.

13. Takka S, Rajbhanrari S, Sakr A. Effect of anionic polymers on the release of propanolol hydrochloride from matrix tablets. Eur J Pharm Biopharm 2001;52:75-82.

14. Fernández-Arévalo M, Villafuerte MAH, Dorado JMG, Álvarez AMR. Effects of different fillers and wetting liquids on the dissolution of carbamazepine controlled release inert matrix tablets. Int J Pharm 1993:95:117-25.

15. Eudragit® NM 30 D, 12.05.2011. Available from: http://www.evonic.com

16. Franc A, Sova P. Oral pharmaceutical composition for targeted transport of a platinum complex into the colorectal region, method for producing and use as medicament thereof European Patent Office, 20.01.2009. Available from: URL: http://v3.espacenet.com

17. Moor JW, Flanner HH. Mathematical comparison of dissolution profiles, Pharm Tech 1996;20:64-74.

18. Lu C, Lu Y, Chen J, Zhang W, Wu W. Synchronized and sustained release of multiple component in silymarin from highly plastic granules. J Control Rel 2005;109:203-10.

19. Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. Eur J Pharm Sci 2007;66:210-9.

20. Samani SM, Montaseri H, Kazemi A. The effect of polymer blends on the release profiles of diclofenac sodium from microspheres. Eur J Pharm Biopharm 2003;55:351-5.

21. Sateesha SB, Rajamma AJ, Narode MK, Vyas BD. Influence of organic acids on diltiazem HCl release kinetics from hydroxypropyl methyl cellulose matrix tablets. J Young Pharm 2010;2:229-33.

22. Varshosaz J, Falamazarian M. Drug diffusion mechanism through pH-sensitive hydrophilic/polyelectrolyte hydrogel membranes. Eur J Pharm Biopharm 2001;51:235-40.

23. Pereira de Souza T, Martinez-Pacheco R, Gómez-Amoza JL, Petrovick PR. Eudragit® E as excipient for production of granules and tablets from Phyllanthus niruri L spray-dried extract. AAPS PharmSciTech 2007:8:Article 34.

24. Badawy SI, Menning MM, Gorko MA, Gilbert LG. Effect of process parameters on compressibility of granulation manufactured in a high-shear mixer. Int J Pharm 2000;198: 51-61.

25. Badawy SI, Lee TJ, Menning MM. Effect of drug substance particle size on the characteristics of granulation manufactured in a high-shear mixer. AAPS PharmSciTech 2000;1:E33.

26. Perissuti B, Rubessa F, Moneghini M, Voinovich D. Formulation design of carbamazepine fast-release tablets prepared by melt granulation technique. Int J Pharm 2003;256: 53-63.

27. Tsai T, San YP, Ho HO, Wu JS, Sheu MT. Film-forming polymer-granulated excipients as the matrix materials for controlled release dosage forms. J Control Rel 1998;51:289-99.

28. Fu Y, Jeong SH, Park K. Fast-melting tablets based on highly plastic granules, J Control Rel 2005;109:203-10.

29. Dreu R, Ilci I, Srác S. Development of a multiple-unit tablet containing enteric-coated pellets. Pharm Dev Tech 2011;16:118-26.

30. Obae K, Iijima H, Imada K. Morphological effect of microcrystalline cellulose particles on tablet tensile strength. Int J Pharm 1999;182:155-64.

31. Singh SK, Pandit JK, Mishra DN. Influence of drug solubility, drug polymer ratio, nature of coexcipients and thermal treatment on drug release from carbopol 974P matrix tablets. Acta Pharm Sci 2006;48:167-78.

32. Chitra KS, Jayaprakash S, Abirami A, Halith SM. Formulation and evaluation of aceclofenac sodium bilayer sustained release tablets. Int J Chem Tech Research 2009;1:1381-5.

33. Huang X, Brazel CS. On the importance and mechanisms of burst release in matrix-controlled drug delivery system. J Control Rel 2001;73:121-36.

34. Barakat NS, Ahmad AA. Diclofenac sodium loaded-cellulose acetate butyrate: effect of processing variables on microparticles properties, drug release kinetics and ulcerogenic activity. J Microencapsul 2008;25:31-45.

35. Uddin MB, Chowdhury JA, Azam KR, Islam MK. Investigation of the effects of different physicochemical parameters on in vitro release kinetics of theophylline from Eudragit NE 30 and Eudragit RS 30D matrix tablets. J Pharm Sci Res 2010;2:246-60.

36. Hardy JG, Lamont GL, Evans DF, Haga AK, Ganst ON. Evaluation of an enteric-coated naproxen pellet formulation. Aliment Pharmacol Ther 1991;5:69-75.

37. Hamza Yel-S, Aburahma MH. Design and in vitro evaluation of novel sustained- release matrix tablets for lornoxicam based on the combination of hydrophilic matrix formers and basic pH-modifiers. Pharm Dev Technol 2010;15(2):139-53.

38. Kojima H, Yoshikura K, Sawada T, Kondo H, Sako K. Extended release of a large amount of highly water-soluble diltiazem hydrochloride by utilizing counter polymer in polyethylene oxides (PEO)/polyethylene glycol (PEG) matrix tablets. Eur J Pharm Biopharm 2008;70:556-62.

39. Cao QR, Kim TW, Lee BJ. Photoimages and the release characteristics of lipophilic matrix tablets containing highly water-soluble potassium citrate with high drug loadings. Int J Pharm 2007;339:19-24.

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