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RESEARCH PAPER

Development of Extended Release Dosage Forms Using Non-uniform Drug Distribution Techniques

Kuo-Kuang Huang,[1,*] Da-Peng Wang,[2] and Chung-Ling Meng[3]

[1]*Tajen Institute of Technology, Pingtung, Taiwan*
[2]*Department of Pharmacy, National Defense Medical Center, Neihu, Taipei, Taiwan*
[3]*Department of Administration, Tri-Service General Hospital, Taipei, Taiwan*

ABSTRACT

Development of an extended release oral dosage form for nifedipine using the non-uniform drug distribution matrix method was conducted. The process conducted in a fluid bed processing unit was optimized by controlling the concentration gradient of nifedipine in the coating solution and the spray rate applied to the non-pareil beads. The concentration of nifedipine in the coating was controlled by instantaneous dilutions of coating solution with polymer dispersion transported from another reservoir into the coating solution at a controlled rate. The USP dissolution method equipped with paddles at 100 rpm in 0.1 N hydrochloric acid solution maintained at 37°C was used for the evaluation of release rate characteristics. Results indicated that (1) an increase in the ethyl cellulose content in the coated beads decreased the nifedipine release rate, (2) incorporation of water-soluble sucrose into the formulation increased the release rate of nifedipine, and (3) adjustment of the spray coating solution and the transport rate of polymer dispersion could achieve a dosage form with a zero-order release rate. Since zero-order release rate and constant plasma concentration were achieved in this study using the non-uniform drug distribution technique, further studies to determine in vivo/in vitro correlation with various non-uniform drug distribution dosage forms will be conducted.

*Corresponding author. Fax: +886-8-7626751; E-mail: leon@ccsun.tajen.edu.tw

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Key Words: *Coating solution; Concentration gradient; Extended release; Nifedipine; Non-uniform drug distribution matrix method; Polymer transport rate; Spray rate; Zero-order release rate*

INTRODUCTION

Most extended release solid dosage forms in the marketplace apply either film-coated or matrix-type techniques to achieve pseudo-first-order release rate characteristics, where the release rate is proportional to the square root of time (1–3). The development of a concentration gradient-type of matrix system to compensate for the traveling distance of the active ingredient during the dissolution process was conceptually initiated (4). Several methods used to prepare dosage forms of constant release rate were reported in recent years (5–8), but their approaches were limited to small laboratory-scale and were not feasible for large-scale manufacturing. However, Li and Tu (9) later developed a mathematical model and scalable process. This system was designed by transporting the polymer solution into the coating solution reservoir containing the drug/polymer dispersion, and spraying the coating solution onto the core beads which are fluidized in a fluid bed processor. The model employs a dynamic mixing stage where the drug concentration in the coating solution is constantly changed and produces a continuous gradient. The latitude of the concentration gradients depends on the transport rate of the polymer solution into the drug reservoir and the spray rate of the coating solution. A mathematical equation to describe the drug concentration vs. time in the reservoir is:

$$C = C_0\{[1 + (k_i - k_0)t]/V_0\}^{k_i(k_0 - k_i)} \quad (1)$$

where C is the concentration of the drug in the coating solution at time t; C_0 is the initial drug concentration in the coating solution, k_i is the transport rate of the polymer into the drug reservoir; k_0 is the spray rate of the coating solution; V_0 is the initial volume of the coating solution in the drug reservoir.

The objective of this study was (1) to apply the specially designed coating technology to achieve coated beads with various concentration gradient profiles within the matrix, (2) to correlate the in vitro release rate profiles with the concentration gradient profiles, and (3) to demonstrate the extended release properties of a selected dosage form prepared with the non-uniform drug distribution techniques in an animal model.

MATERIALS AND METHODS

Materials

Nifedipine was used as a model drug and was purchased from Anphar Laboratories Pvt. Ltd., India. Non-pareil beads (20/30 mesh) were purchased from Werner, Germany. Ethyl cellulose (10 cP) was received from Dow Chemicals, USA. Myvacet® 9-40 was purchased from Chan-Chi, Taiwan. Sucrose was purchased from Sigma Chemical Co., USA. All other materials used in the preparation of dissolution medium and high performance liquid chromatography (HPLC) mobile phase were either reagent grade or HPLC grade.

Methods

Preparation of Polymer Solution

The polymer solution was prepared by adding ethyl cellulose to a solvent mixture containing 75% (v/v) acetonitrile and 25% ethyl alcohol.

Preparation of Coating Solution

The coating solution was prepared by dissolving nifedipine and/or sucrose (if needed) in a solvent mixture containing 75% (v/v) acetonitrile and 25% ethyl alcohol.

Preparation of Extended Release Beads

A fluid bed processing unit (Glatt GPCG-1) equipped with 4″ column and 1.2-mm nozzle was used in the preparation of the extended release dosage form with non-uniform drug distribution characteristics. Coating parameters used in this study are listed in Table 1.

The nifedipine concentration in the coating solution was continuously changed by instantaneous dilution of the coating solution with the polymer solution, which was transported into the coating solution at a fixed rate. Depending on the ratio of

transport rate of the polymer solution and the spray rate of the coating solution, the concentration gradient of nifedipine on the coated beads varied.

Effect of Ethyl Cellulose/Myvacet Study

Five formulations with the same ethyl cellulose/Myvacet ratio (1:0.3) but different total quantities (7.8 to 15.6 g) in the coating solution were used in the preparation of coated beads. The composition of each formulation is listed in Table 2. The coating conditions listed in Table 1 were followed.

Release rate testing of the coated beads was conducted in 0.1 N hydrochloric acid solution using USP 24, method II at 100 rpm. Dissolution samples were analyzed by a HPLC system which was equipped with a C-18 column (5 μ), an ultraviolet (UV) detector set at 349 nm, and a mobile phase of 58:42 (v/v) KH_2PO_4:CH_3CN at a flow rate of 1.0 mL/min.

Effect of Polymer Transport Rate Study

Two formulations with different polymer transport rate from the polymer solution into the coating solution were used in the preparation of coated beads. The total volume of coating solution applied to the beads was maintained the same at 1800 mL for both formulations. The composition of each formulation is listed in Table 3. The coating conditions listed in Table 1 were followed.

Release rate testing of the coated beads was conducted in 0.1 N hydrochloric acid solution using USP 24, method II at 100 rpm. Dissolution samples were analyzed by a HPLC system which was equipped with a C-18 column (5 μ), a UV detector set at 349 nm, and a mobile phase of 58:42 (v/v) 0.1 M KH_2PO_4:CH_3CN at a flow rate of 1.0 mL/min.

Effect of Total Volume of Coating Solution Study

Three formulations with different total volumes of coating solution (polymer solution + coating

Table 1

Parameters Used in the Coating Process

Operating Parameter	Setting
Inlet temperature	35°C
Outlet temperature	32°C
Air volume	60 cfm (40% flap open)
Atomization pressure	20 psi
Spray rate	12 mL/min

Table 3

Composition of Formulations N6, N7 with Different Polymer Transport Rates Used in the Coating Process

Ingredient	N6	N7
Non-pareil beads	800 g	800 g
Nifedipine	60 g	60 g
Ethyl cellulose	6 g	6 g
Myvacet	1.8 g	1.8 g
Polymer solution	1200 mL	1350 mL
Coating solution	600 mL	450 mL
Polymer transport rate	8 mL/min	9 mL/min
Coating spray rate	12 mL/min	12 mL/min
$k_i/(k_0 - k_i)$	2	3

Table 2

Composition of Formulations N1–N5 with Varying Ethyl Cellulose/Myvacet Content Used in the Coating Solutions

Ingredient	N1	N2	N3	N4	N5
Non-pareil beads	800 g	800 g	800 g	800 g	800 g
Nifedipine	60 g	60 g	60 g	60 g	60 g
Ethyl cellulose	6 g	7 g	8 g	10 g	12 g
Myvacet	1.8 g	2.1 g	2.4 g	3.0 g	3.6 g
Polymer solution	900 mL	900 mL	900 mL	900 mL	900 mL
Coating solution	900 mL	900 mL	900 mL	900 mL	900 mL
Polymer transport rate	6 mL/min	6 mL/min	6 mL/min	6 mL/min	6 mL/min
Coating spray rate	12 mL/min	12 mL/min	12 mL/min	12 mL/min	12 mL/min
$k_i/(k_0 - k_i)$	1	1	1	1	1

solution) were used in the preparation of coated beads. The composition of each formulation is listed in Table 4. The coating conditions listed in Table 1 were followed.

Release rate testing of the coated beads was conducted in 0.1 N hydrochloric acid solution using USP 24, method II at 100 rpm. Dissolution samples were analyzed by the HPLC system which was equipped with a C-18 column (5 μ), a UV detector set at 349 nm, and a mobile phase of 58:42 (v/v) KH_2PO_4:CH_3CN at a flow rate of 1.0 mL/min.

Effect of Transport/Spray Rate Study

Four formulations with varying ratios of polymer transport rate and coating solution spray rate were used in the preparation of coated beads. The total volume of coating solution was maintained the same (1000 mL) for all formulations. The composition of each formulation is listed in Table 5. The coating conditions listed in Table 1 were followed.

Release rate testing of the coated beads was conducted in 0.1 N hydrochloric acid solution using USP 24, method II at 100 rpm. Dissolution samples were analyzed by a HPLC system which was equipped with a C-18 column (5 μ), a UV detector set at 349 nm, and a mobile phase of 58:42 (v/v) KH_2PO_4:CH_3CN at a flow rate of 1.0 mL/min.

Effect of Water-Soluble Vehicle Study

Because of sucrose's high solubility, it was selected as the water-soluble material incorporated in the formulations to study its effects on the nifedipine release rate. Four formulations with varying sucrose concentrations were used in the preparation of coated beads. The composition of each formulation is listed in Table 6. The coating conditions listed in Table 1 were followed.

Release rate testing of the coated beads was conducted in 0.1 N hydrochloric acid solution using USP 24, method II at 100 rpm. Dissolution samples were analyzed by a HPLC system which was equipped with a C-18 column (5 μ), a UV detector set at 349 nm, and a mobile phase of 58:42 (v/v) KH_2PO_4:CH_3CN at a flow rate of 1.0 mL/min.

In Vivo Animal Study

Nifedipine ER capsules prepared from the N16 formulation and process were used in the in vivo animal studies. A commercial nifedipine IR capsule

Table 4

Composition of Formulations N1, N8, N9 with Different Total Volume of Coating Solution Used in the Coating Process

Ingredient	N1	N8	N9
Non-pareil beads	800 g	800 g	800 g
Nifedipine	60 g	60 g	60 g
Ethyl cellulose	6 g	6 g	6 g
Myvacet	1.8 g	1.8 g	1.8 g
Polymer solution	900 mL	750 mL	500 mL
Coating solution	900 mL	750 mL	500 mL
Polymer input rate	6 mL/min	6 mL/min	6 mL/min
Coating spray rate	12 mL/min	12 mL/min	12 mL/min
$k_i/(k_0 - k_i)$	1	1	1

Table 5

Composition of Formulations N10–N13 with Different Transport/Spray Rates Used in the Coating Process

Ingredient	N10	N11	N12	N13
Non-pareil beads	800 g	800 g	800 g	800 g
Nifedipine	60 g	60 g	60 g	60 g
Ethyl cellulose	6 g	6 g	6 g	6 g
Myvacet	1.8 g	1.8 g	1.8 g	1.8 g
Polymer solution	333 mL	500 mL	517 mL	533 mL
Coating solution	667 mL	500 mL	483 mL	467 mL
Polymer transport rate	4 mL/min	6 mL/min	6.2 mL/min	6.4 mL/min
Coating spray rate	12 mL/min	12 mL/min	12 mL/min	12 mL/min
$k_i/(k_0 - k_i)$	0.5	1	1.07	1.14

Table 6

Composition of Formulations N14–N16 with Different Amounts of Sucrose in the Polymer and Coating Solutions Used in the Coating Process

Ingredient	N14	N15	N16	N12
Non-pareil beads	800 g	800 g	800 g	800 g
Nifedipine	60 g	60 g	60 g	60 g
Ethyl cellulose	6 g	6 g	6 g	6 g
Myvacet	1.8 g	1.8 g	1.8 g	1.8 g
Sucrose	6 g	1.2 g	0.3 g	0 g
Polymer solution	517 mL	517 mL	517 mL	517 mL
Coating solution	483 mL	483 mL	483 mL	483 mL
Polymer transport rate	6.2 mL/min	6.2 mL/min	6.2 mL/min	6.2 mL/min
Coating spray rate	12 mL/min	12 mL/min	12 mL/min	12 mL/min
$k_i/(k_0 - k_i)$	1.07	1.07	1.07	1.07

(Adalat® 10 mg) was used as the reference. Six New Zealand white rabbits weighing 2.5±0.3 kg were placed on a water diet 10 hr before and 4 hr after the initiation of the dosing study. Blood samples were withdrawn at various designated intervals from 5 min to 24 hr. Collected blood samples were immediately centrifuged, and the plasma samples were frozen at −20°C until analysis. Nicardipine was used as the internal standard during the sample preparation. The HPLC analysis system was equipped with a C-18 column (5 μ), a UV detector set at 349 nm, and a mobile phase of 58:42 (v/v) 0.1 M KH_2PO_4:CH_3CN at a flow rate of 1.0 mL/min.

RESULTS AND DISCUSSION

Effect of Ethyl Cellulose/Myvacet

Figure 1 shows the release rate profiles of nifedipine from different formulations containing varying amounts of ethyl cellulose/Myvacet. Results indicated that formula N1 maintained zero-order in vitro release profile and achieved greater than 80% release after 7.5 hr, while the other formulas (N2–N5) also exhibited zero-order releases but at much slower rates. It was possible that the quantities of ethyl cellulose/Myvacet used in the N1 formulation did not completely cover the entire surface of the beads, and therefore produced a faster release rate than those of formulas N2–N5. The dissolution rate decreased significantly as the amount of ethyl cellulose/Myvacet in the formulation increased.

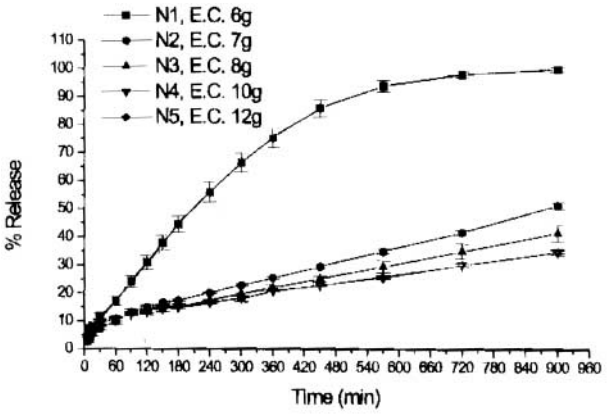

Figure 1. Effect of ethyl cellulose content on the dissolution profiles.

Effect of Polymer Transport Rate

Figure 2 shows the release rate profiles of nifedipine from the coated beads prepared with formulations of different concentration gradients in the coating solution. The concentration gradient was controlled by the time-dependent concentration changes in the coating solution resulting from different transport rates of polymer solution into the drug reservoir. Results indicated that comparing release rates of formulations N10 through N13, the lowest release rate was obtained for the formulation (N13) with highest transport rate due to a deeper concentration gradient in the coated matrix. The higher the polymer transport rate, the faster the nifedipine concentration being diluted in the coating

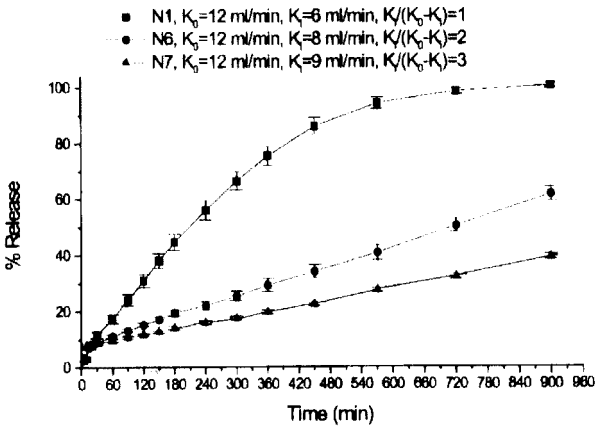

Figure 2. Effect of $k_i/(k_0 - k_i)$ ratio on the dissolution profiles.

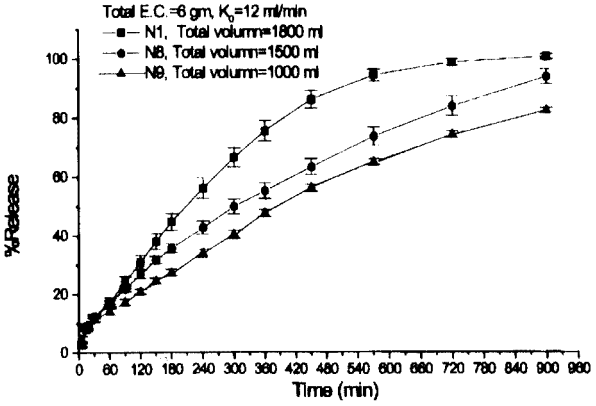

Figure 3. Effect of total volume of coating solution on the dissolution profiles.

solution, and therefore the deeper the concentration gradient applied to the beads during the coating.

Effect of Total Volume of Coating Solution

The release rate profiles of the coated beads (formulas N1, N8, and N9) prepared with different total coating volume under otherwise the same formulation and coating conditions are shown in Fig. 3. Results indicated that the release rate of nifedipine prepared with a higher total coating volume was slower than the release rate of nifedipine prepared with a lower total coating volume. The concentration gradient in the coated beads prepared with lower total coating volume (N9) was deeper than that is the coated beads with higher total coating volume, and thus resulted in a slower nifedipine release rate.

Effect of Transport/Spray Rate Study

Figure 4 shows the nifedipine release rate profiles from coated beads with the same chemical composition but prepared with the process at different polymer transport rates. The coated beads prepared with a lower polymer transport rate achieved a faster release rate than the coated beads prepared with a higher polymer transport rate. The order of release rate obtained was N10 > N11 > N12 > N13. For the formulations with lower polymer transport rates, the rate of nifedipine concentration being diluted in the coating solution was slower than for those with higher polymer transport rates, and

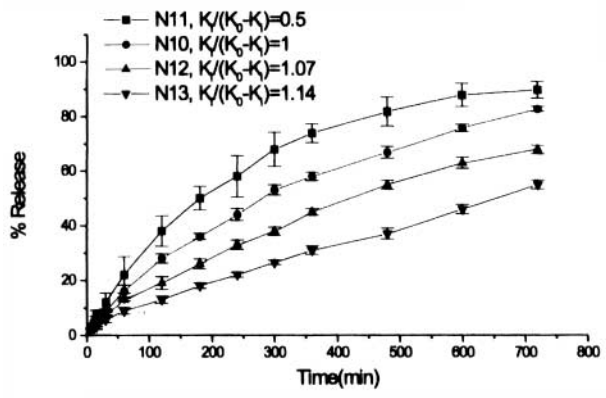

Figure 4. Effect of $k_i/(k_0 - k_i)$ ratio on the dissolution profiles when the total solution is 1000 mL.

therefore a less deep concentration gradient was achieved, resulting in a faster release rate.

Effect of Addition of Water-Soluble Vehicle

Release rate profiles of nifedipine from the coated beads prepared with formulations containing different amounts of water-soluble vehicle, sucrose, are shown in Fig. 5. Results indicated that the release rate of nifedipine was increased as the sucrose content in the formulation was increased. The enhanced release rate was likely due to increased porosity in the coated beads. In formulations N14, N15, N16, and N12, the concentration gradient of nifedipine in the coated beads was maintained the same, but the porosity in the matrix was

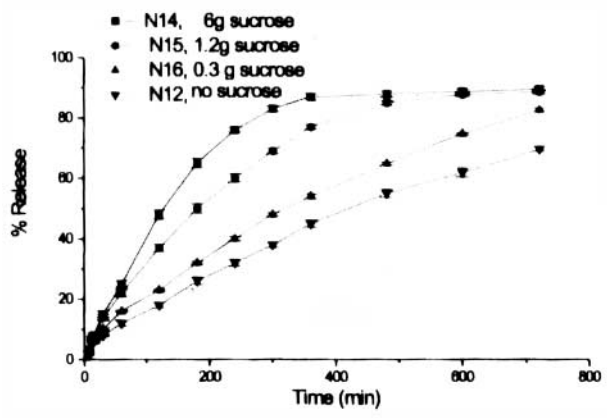

Figure 5. Effect of sucrose content on the dissolution profiles when $k_i/(k_0 - k_i)$ is 1.07.

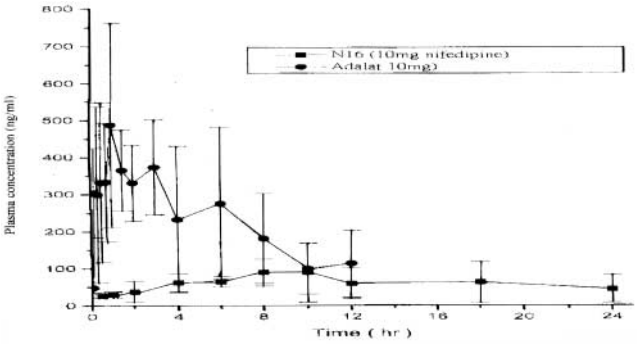

Figure 6. The rabbit nifedipine plasma concentration profile after receiving formula N16 and Adalat, respectively.

different: the matrix with more sucrose (N14) was more porous than those with less sucrose (N15, N16, and N12).

In Vivo Animal Study

The nifedipine plasma concentration vs. time profiles in the rabbits after oral doses from the formulation N16 and the commercial Adalat capsules are shown in Fig. 6. The sharp increase in the plasma concentration at the beginning and gradual tapering afterward for Adalat indicate an immediate release phenomenon. Despite that, scattered data were observed in the in vivo plasma concentration, possibly attributed to animal-to-animal variation and/or non-uniform drug distribution in the product. The plasma concentration remained at a constant level for at least 24 hr for formulation N16, indicating an extended release nature of the dosage form prepared with the non-uniform drug distribution technique.

CONCLUSION

An innovative technique designed to provide a continuous coating process to achieve a dosage form of non-uniform drug distribution with zero-order release characteristics was investigated in this study. Different concentration gradients could be achieved by controlling the transport rate of the polymer solution into the coating solution and/or the spray rate of the coating solution onto the beads using a fluid bed processing unit. Nifedipine release rate was increased by incorporating the water-soluble vehicle, sucrose, into the coating solution to enhance the porosity of the coated matrix. An animal study with a selected formulation prepared with this technique exhibited a constant plasma concentration for a period of 24 hr. Further studies to determine the correlation between the in vitro release rate and the in vivo plasma concentration with various non-uniform drug distribution dosage forms will be conducted.

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