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RESEARCH PAPER

Linear Delivery of Verapamil via Nanofibrous Sheet-Based System

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ABSTRACT

Purpose To achieve linear delivery of a highly water-soluble oral drug, verapamil, with a nanofibrous sheet-based system.

Methods The nanofibrous sheets made of poly (lactic-co-glycolic acid) were used as a diffusion barrier to cap a tablet containing verapamil. For controlled drug delivery, we varied the sheet thickness to 20 μm, 50 μm and 80 μm to give the capped drug tablets, 20CT, 50CT and 80CT, respectively.

Results Drug release was more sustained as the sheet thickness increased. Thus, the periods for almost complete drug release could be extended up to 14 h with the 80 μm-thick sheets. As we assessed the linear least square fits to the *in vitro* drug release data from the capped tablets, 20CT and 50CT showed a fairly good correlation with linear release. The periods of linear release were 6 h and 8 h for 20CT and 50CT, respectively, both releasing more than 85% drug during this period.

Conclusion We conclude that a drug tablet capped with nanofibrous sheets is a promising system for linear delivery of a highly water-soluble oral drug.

Ji Eun Lee and Chun Gwon Park contributed equally to this work.

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KEY WORDS linear drug delivery · nanofibrous sheet · poly (lactic-co-glycolic acid) · verapamil · water-soluble drug

ABBREVIATIONS

20CT	tablet capped with 20 μm-thick nanofibrous sheets
50CT	tablet capped with 50 μm-thick nanofibrous sheets
80CT	tablet capped with 80 μm-thick nanofibrous sheets
DCM	dichloromethane
DMF	dimethylformamide
GI	gastrointestinal
HPMC	hydroxypropyl methylcellulose
IERs	ion-exchange resins
NCT	non-capped tablet
OROS	osmotic-controlled release oral delivery system
PBS	phosphate buffered saline
PLGA	poly (lactic-co-glycolic acid)
THF	tetrahydrofuran

INTRODUCTION

Oral administration has been considered as the most popular route of drug delivery in the pharmaceutical market. More than half of commercialized drugs are designed in an oral dosage form, avoiding pain and infection possibly involved with needle-based injections (1–3). Most of oral drug delivery systems have been developed to deliver drug in a sustained manner with reduced initial burst to improve drug bioavailability (4). For this purpose, many different types of drug delivery systems have been investigated, mostly employing biocompatible polymer as a wall material, to have the drug slowly diffused via the polymer matrix (5–8).

With those systems, drug release is mainly governed by Fickian diffusion: drug is released faster at the early stage than the later stage. Therefore, linear drug delivery, which would be advantageous for the drugs, such as anti-inflammatory, anti-angina or anti-hypertension drugs (9), would not be feasible.

Moreover, the variation in pH, gut mobility and food present through the gastrointestinal (GI) tract may become a hindrance for highly controlled and reproducible drug delivery. To resolve this, numerous dosage forms have been developed, employing ion-exchange resins (IERs) (10–13) and multi-layered matrix tablets (14–16), which, however, were still limited in low biocompatibility of incorporated materials and complicating fabrication procedures.

Osmotic-controlled release oral delivery system (OROS) is one of the successful strategies for linear delivery of oral drugs. By the osmotic pressure of water, the drug is pushed via an orifice formed on the capsule, hence a constant release rate regardless of the change in GI condition (9,17–19). However, the OROS may be still limited in gastric irritation and ulcer possibly involved with unidirectional drug release via a small orifice in the capsule, as well as GI occlusion and fecal discomfort possibly caused by a non-degradable hard shell of the OROS (18). Furthermore, the manufacturing procedure of the OROS is rather complicating since a delivery orifice has to be prepared by laser-drilling for each of the individual tablets (17).

Previously, we suggested a nanofibrous sheet-based system for linear delivery of oral drug, nifedipine (20). We prepared nanofibrous sheets, possessing micro-scaled pores, to cap a compressed drug tablet, where drug release could be controlled by the thickness of the sheets. In this way, for a drug tablet capped with thin sheets, drug release was mostly diffusion-mediated, thereby faster release at the early stage than the late stage. In contrast, a drug tablet capped with thick sheets exhibited apparent biphasic release: suppressed release followed by diffusion release. The former resulted from slow drug dissolution after water in-diffusion via the sheets towards the drug tablet in the core. Therefore, a combined system of two distinct tablets, each capped with the nanofibrous sheets of different thickness, could realize linear drug delivery for 24 h ($R^2 > 0.986$) by each compensating drug release at the early and late stages (20). Unlike the OROS, drug release was multi-directional through the surrounding sheets and only softened sheets should remain after complete drug release with the nanofibrous sheet-based system suggested in our previous work.

On the other hand, the drug employed in our previous work, nifedipine, was poorly water-soluble (5.8 μg/ml at pH 4-10) (21) and thus, a large change in drug release could be obtained as the sheet thickness varied. For example, a biphasic release pattern would be more evident for the thick sheet since drug dissolution after water in-diffusion via the sheets should be very slow with nifedipine. In addition, due to hydrophobicity of the drug, drug release via the sheets to the aqueous media would be more retarded. Those may not similarly occur with a highly water-soluble drug. Generally, sustained delivery of hydrophilic drug is considered more difficult due to a large initial burst of drug release (22).

Therefore, in this work, we employed a highly water-soluble drug, verapamil (2.71 mg/ml at pH 6.8) (23), as a model drug to assess the feasibility of a nanofibrous sheet-based system for linear delivery. Verapamil is an anti-hypertension drug and already approved in an oral dosage form enabled with linear drug release (Covera-HS®, Pfizer, NY, USA). We capped the drug tablet containing verapamil with nanofibrous sheets of various thicknesses (i.e. 20 μm, 50 μm and 80 μm), following the method introduced in our previous work (20). The nanofibrous sheets were made of poly (lactic-co-glycolic acid) (PLGA), a biocompatible polymer, by electrospinning. The PLGA nanofibrous sheets were not expected to significantly degrade or deform in the GI fluids while residing for less than a day (20). To evaluate a controlled delivery property of verapamil, *in vitro* drug release tests were conducted in pH 1.2 for 2 h and pH 6.8 for the rest time phosphate buffered saline (PBS).

MATERIALS AND METHODS

Materials

Poly (lactic-co-glycolic acid) (PLGA; 50:50; inherent viscosity=0.36 dl/g) was purchased from Lakeshore Biomaterials (Birmingham, AL, USA). Verapamil hydrochloride (batch no.: V4629; assay value > 99.0% (titration)) and hydroxypropyl methylcellulose (HPMC) were obtained from Sigma (MO, USA). Only fresh verapamil hydrochloride within a month after its receipt was used in this work. Dichloromethane (DCM), tetrahydrofuran (THF) and dimethylformamide (DMF) were supplied from JT Baker (NJ, USA), Daejung (Korea) and Mallinckrodt (MO, USA), respectively.

Preparation of Nanofibrous Sheets

To prepare the nanofibrous sheets, PLGA was dissolved in the solvent mixture composed of DCM, DMF and THF (3:1:1, v/v/v) to make a 30% w/v PLGA solution (24), which was then electrospun (Nano NC, Seoul, Korea) under the following conditions: applied voltage: 15 kV, tip-to-collector distance: 10 cm, flow rate: 0.6 ml/h. We varied the collection times of nanofibers to 40 min, 155 min and 275 min to give the sheets of three different thicknesses in this work. For each of the sheets, at least three different points were measured with a micrometer (Mitutoyo, Kanagawa, Japan) to ensure the quality control of the sheet thickness.

Preparation of Capped Tablets

The drug tablets capped with nanofibrous sheets were prepared, as described in our previous work (20). First, to

prepare a non-capped drug tablet (NCT), a fine powder blended with verapamil and HPMC (10:1, w/w) was prepared by milling at 28000 rpm (IKA A11 basic, RJ, Brazil) (25,26). Ninety nine milligram of the resulting powder (i.e., 90 mg verapamil and 9 mg HPMC) was then filled into a bore, 8 mm in diameter, in a Teflon plate, where the pressure of 250 kg/cm^2 was applied to compress the powder, giving a NCT.

To prepare a drug tablet capped with nanofibrous sheets, a NCT was placed on top of a nanofibrous sheet (Fig. 1a–b), which was then covered with another nanofibrous sheet of the same type (Fig. 1c). A ring-shaped aligning stamp was applied to slightly fold the top sheet along the boundary of the NCT (Fig. 1d–e). In this way, the location of the NCT could be confirmed during the later processes employed in this work. The sheets were then thermally bonded by applying a ring-shaped bonding stamp, pre-heated at 135°C, for 4 min. During this bonding process, a heat-insulating barrier and a continuous airflow for cooling were concurrently applied at the center of the bonding stamp (Fig. 1f). In this way, only the sheets directly in contact with the bonding stamp melted to seal the NCT and thus, the sheet and the NCT at the center of the bonding stamp were not affected by high temperature. Then, the sheets along the melted boundary were cut to give an individual capped tablet, as shown in Fig. 1g. In this work, we prepared three different tablets, each capped with 20 μm-, 50 μm- and 80 μm- sheets, to give 20CT, 50CT and 80CT, respectively.

Characterization

To examine the morphology, a piece of a nanofibrous sheet (5×5 mm) was placed on a sample mount, which was sputtered coated with platinum for 10 min (208HR,

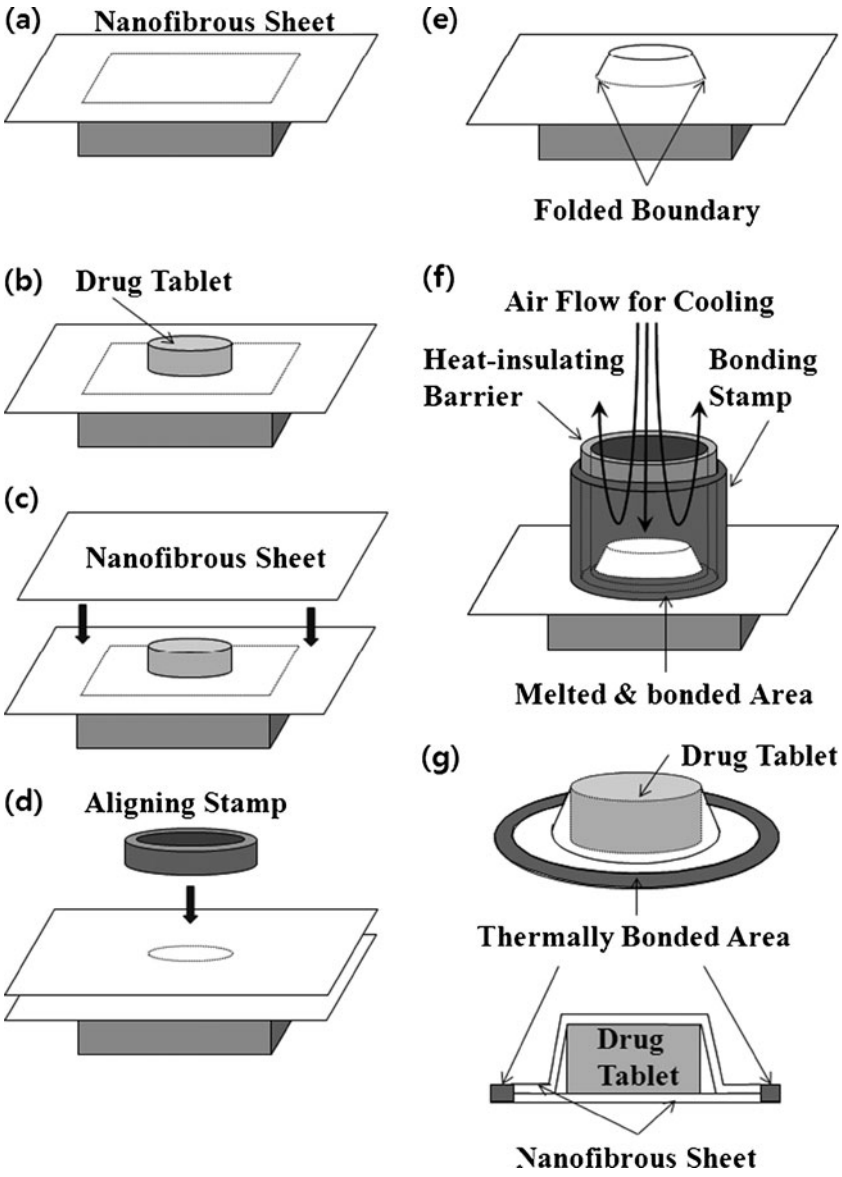

Fig. 1 Schematic procedure for the preparation of the capped drug tablets.

Cressington Scientific, Walford, UK). The sample was then imaged by scanning electron microscopy (SEM; 7401 F, Jeol, Tokyo, Japan).

A differential scanning calorimetry (DSC, DSC2901, TA instruments, DE, USA) was performed to compare the thermal properties of intact PLGA and nanofibrous sheet. The samples were each placed in a hermetic pan under nitrogen gas flow, where the temperature was elevated from 25°C to 135°C at a rate of 5°C/min. This cycle was repeated more than three times for each of the samples to confirm the reproducibility.

The pore size distribution of nanofibrous sheets was assessed using a capillary flow porometer (CFP-1500AEL, PMI, NY, USA). Nanofibrous sheets of different thicknesses (i.e. 20 μm, 50 μm and 80 μm) were each cut into a circular piece, 8 mm in diameter, and loaded in a porometer. The pore size distribution of the sheets was measured under two distinct conditions: 1) measuring the resistance of a sheet with hollow pores while blowing nitrogen gas and 2) measuring the resistance of a sheet pre-soaked with Galwick fluid (surface tension=15.9 dynes/cm) while blowing nitrogen gas (27). We also examined the change in permeability of the sheets after the thermal bonding process employed in this work. Thus, the thermally bonded portion of the sheets in the capped tablets was each collected and assessed with a porometer under the same condition described above.

To assess the drug stability after the thermal bonding process, the drug tablet in the core was extracted from the capped tablet by removing the sheets. The drug was then dissolved in 900 ml DI water, which was analyzed by the high performance liquid chromatography (HPLC, Agilent 1100 series, Agilent Technologies, CA, USA), using a Zorbax® C18 column (4.5×25 mm, 5 μm; Agilent Technologies, CA, USA). The mobile phase was prepared by mixing an aqueous solution of 0.04 M potassium phosphate dibasic and acetonitrile (50:50; v/v), where the pH was adjusted to 7.2 with phosphoric acid. The flow rate and injection volume were 1.5 ml/min and 50 μl, respectively. The column temperature was maintained at 25°C and the UV absorbance was measured at 276 nm (28).

In Vitro Drug Release Test

For each of the capped tablets, *in vitro* drug release experiments were performed in 900 ml release media (pH 6.8) at 37±0.3°C while continuously stirred at 125 rpm in a shaking incubator (SI-600R, Jeio Tech, Seoul, Korea) (29,30). The tablet was placed in a mesh-type basket, which was fully immersed in the media, during the whole release experiment (31). The aliquot of the release media was sampled at scheduled intervals, which was measured spectrophotometrically at 276 nm.

To examine the linear release profiles, we employed two capped tablets of the same kind to give 180 mg verapamil dose, which is the same as that of the marketed medication, Covera-HS® (32). In this specific work, the experiment was performed at the varying pHs to better mimic the condition in the GI tract (33). Thus, the two tablets were immersed together in the release media at pH 1.2 for the first 2 h and then moved to the other release media at pH 6.8 for the rest 22 h. At least five samples for each tablet type were tested for statistics (27,30).

RESULTS

Characterization of Nanofibrous Sheets

We fabricated PLGA nanofibrous sheets via the electrospinning method, as reported in our previous study (20). The sheets were utilized to cap a NCT, serving as a major diffusion barrier of the drug in this work. As shown in Fig. 2, the sheet exhibited randomly oriented nanofibers, possessing micron-sized pores, which would work as a path for drug diffusion in this work. The average thicknesses of the nanofibrous sheets were 19.8 μm, 50.4 μm and 79.6 μm with the collection times of 40 min, 155 min and 275 min, respectively (Table I). To confirm the formation of nanofibers throughout the sheets, we also examined the thermal properties of intact PLGA and a nanofibrous sheet with differential scanning calorimetry (DSC). As shown in Fig. 3, the glass transition temperature (T_g) of intact PLGA was at 51.0°C, which was lowered to 44.9°C with a nanofibrous sheet. The decrease in T_g could be ascribed to entrapped air in the nanofibers as a plasticizer to give more flexibility of the polymer chains (34) and increased surface area compared to intact PLGA powder (34,35).

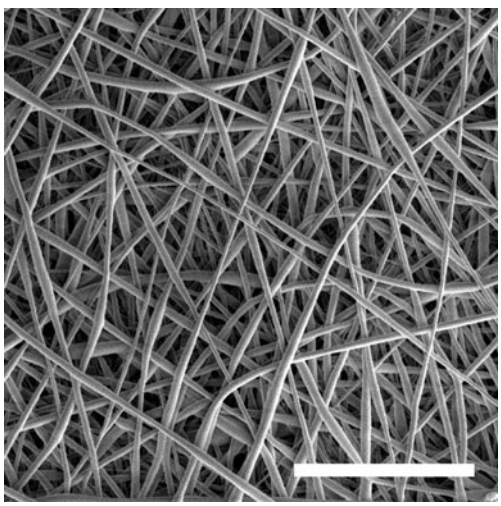

Fig. 2 Representative scanning electron micrograph of the nanofibrous sheet. The scale bar is 40 μm.

Table I Average Thicknesses of the Nanofibrous Sheets

	Collection time		
	40 min (μm)	155 min (μm)	275 min (μm)
Thickness	19.8 ± 0.8	50.4 ± 1.0	79.6 ± 1.0

Values are mean ± SD

We could also obtain the nanofibrous sheets of various thicknesses, i.e., 20 μm, 50 μm and 80 μm, by varying the collection time of nanofibers. Thus, as the sheet got thicker, the drug diffusion from a NCT in the core was expected to be more retarded. To assess this, we measured the pore size distributions of the nanofibrous sheets, which would represent a diffusion resistance of the sheets: i.e., the smaller the pore size, the more difficult the drug diffusion is. As shown in Fig. 4, the apparent difference in pore size distribution was observed, depending on the sheet thickness. With 20 μm-thick sheet, the mean pore size was 2.04 μm, which decreased to 1.03 μm and 0.76 μm with 50 μm- and 80 μm-thick nanofibrous sheets, respectively. This also suggested that a flow via the sheet become more difficult with the increase in sheet thickness, thereby a more resistive barrier of diffusion (also see Fig. S1 in the Supplementary Material).

Characterization of Drug Tablets

Figure 5 shows the representative images of the non-capped and capped drug tablets (NCT and 50CT, respectively). With the presence of HPMC, a binder material (25,26), a NCT could be successfully prepared by a tablet compressing method employed in this work. The dimension of a NCT

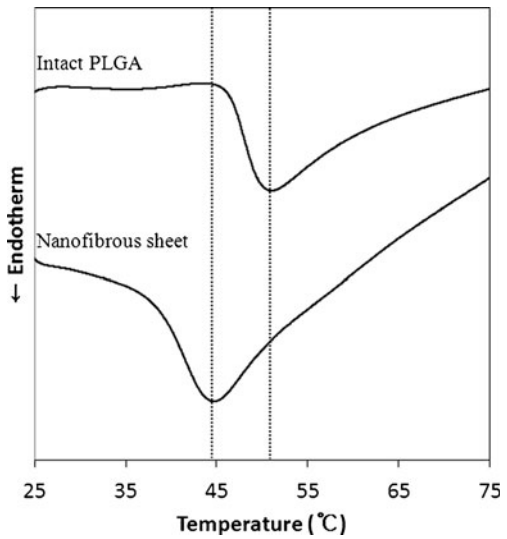

Fig. 3 Differential scanning calorimetry thermograms of intact PLGA and nanofibrous sheet.

was 7.94 ± 0.01 mm in diameter and 2.23 ± 0.02 mm in height, containing 90 ± 2.45 mg verapamil. In this work, we capped a NCT with the nanofibrous sheets of three different thicknesses, 20 μm, 50 μm and 80 μm, to give 20CT, 50CT and 80CT, respectively. After capping, the size of a capped tablet was increased to 17.27 ± 0.17 mm in diameter and 2.27 ± 0.02 mm, 2.33 ± 0.02 mm, 2.39 ± 0.02 mm in height for 20CT, 50CT and 80CT, respectively, where a NCT was positioned in the core, as shown in Fig. 5b. The sheet at the center was opaque (white) due to light scattering from the presence of nanofibrous structure (35). On the other hand, the boundary of a tablet, which was in contact with a ring-shaped bonding stamp, was optically transparent, indicating melted PLGA by thermal stamping. To confirm this, we observed the morphology of the sheet in the capped tablet with SEM. As shown in Fig. 5c–e, a nanofibrous structure was well retained at the center area of the sheet (Fig. 5c) while a smooth surface was observed along the boundary of the capped tablet (Fig. 5d). Figure 5e shows an apparent margin between the intact and melted area of the sheet. As we assessed the thermally bonded portion of the sheets in the capped tablets with a porometer, the mean pore sizes decreased close to 0, suggesting that the diffusion via the bonded portion in the sheets be minimal (Fig. S2). Therefore, in this way, drug could be released in a controlled manner via the intact porous area at the center without leaking via the boundary of the capped tablet. This result was not different from that in our previous work (20), where the same method was employed to prepare a capped drug tablet. The drug stability in the capped tablet was also well retained after the thermal bonding process employed in this work. The results from the HPLC analyses revealed that the drug amount and retention time remained almost unchanged for all the capped tablets, as compared with the intact NCT (Table II).

In Vitro Drug Release Profiles

To examine the effect of the thickness of nanofibrous sheet, we carried out the *in vitro* release experiments with each of the capped tablets in pH 6.8 PBS for 24 h. As stated above, the degradation of the PLGA sheet was not expected during this period, as described in our previous work (20), hence retained porosity of the nanofibrous sheets. As shown in Fig. 6, almost all of the drug was released from NCT during the first 2 h due to high aqueous solubility of verapamil (2.71 mg/ml) (23). However, as the sheet thickness increased, drug release was more sustained. Thus, the periods for almost complete drug release (>85%) were extended to 6 h, 8 h and 14 h for 20CT, 50CT and 80 CT, respectively. We performed the statistical analyses on the *in vitro* drug release profiles, using a generalized linear model ANOVA with α=0.05, followed by pairwise comparisons using a

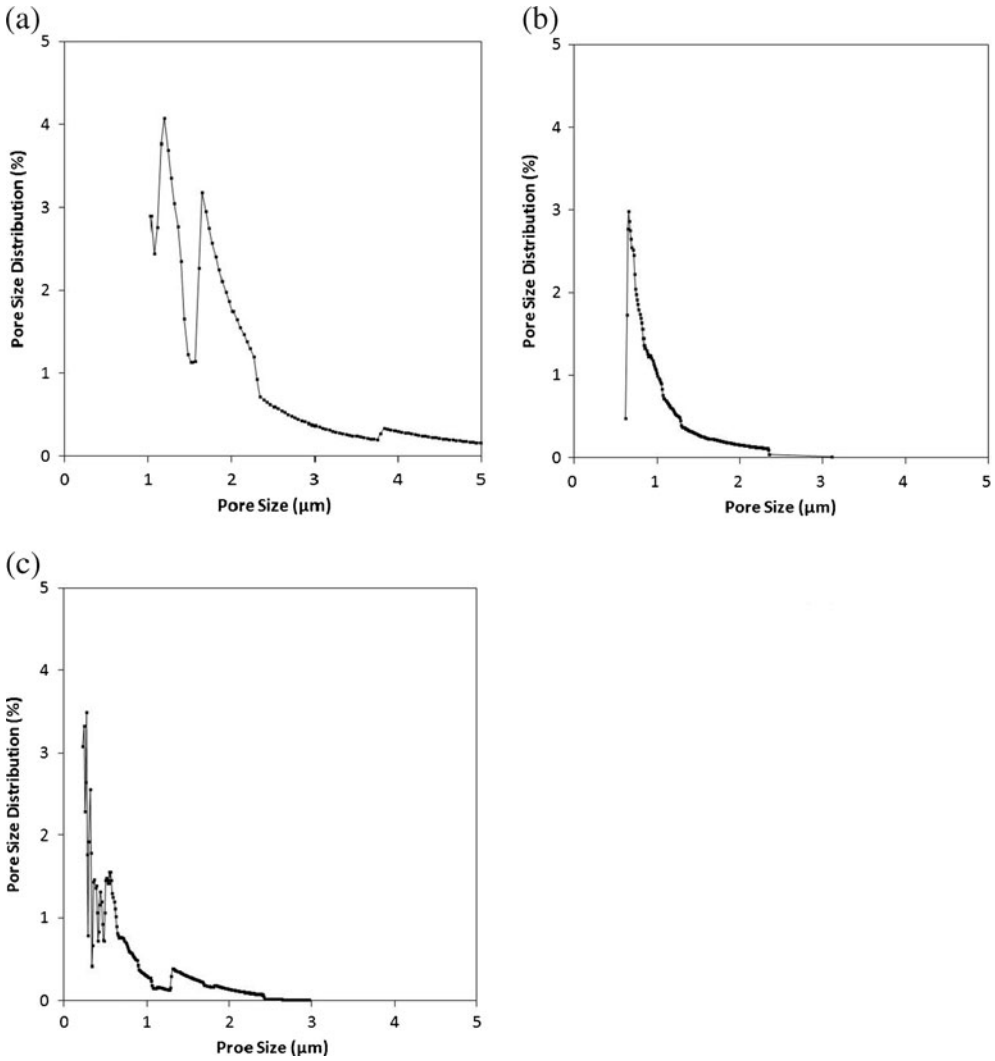

Fig. 4 Pore size distributions of nanofibrous sheets measured by a capillary flow porometer. The thicknesses of the sheets were (**a**) 20 μm, (**b**) 50 μm and (**c**) 80 μm.

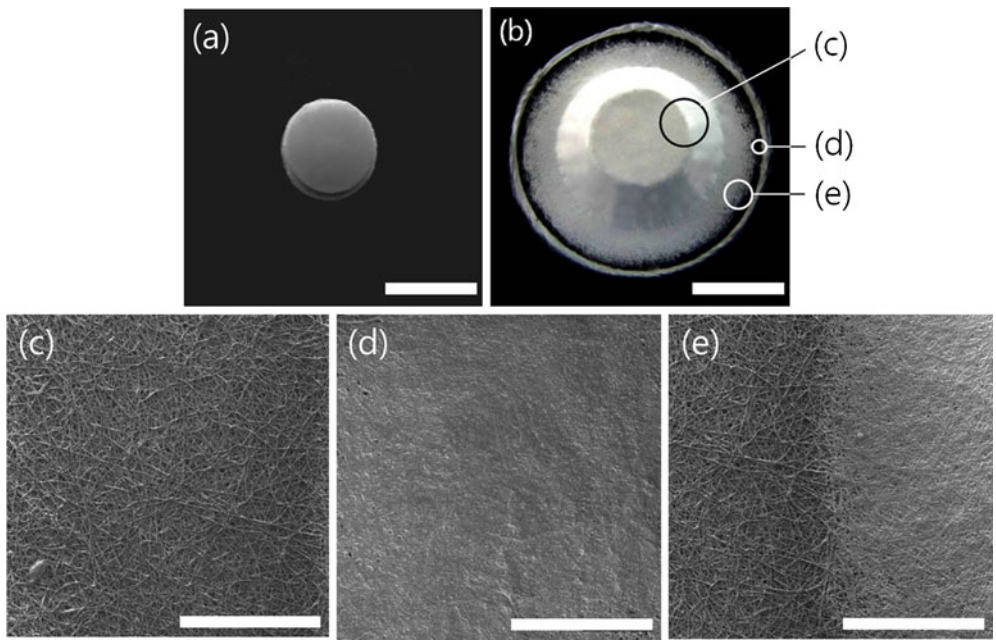

Fig. 5 Representative optical images of (**a**) NCT and (**b**) 50CT. Scanning electron micrographs of (**c**) intact portion, (**d**) melted portion and (**e**) margin between intact and melted portions of the nanofibrous sheet in the 50CT. The scale bars are (**a**–**b**) 8 mm and (**c**–**e**) 200 μm.

Table II Percentages of Nondegraded Verapamil in the Capped Tablets

	20CT	50CT	80CT
Percentage of nondegraded verapamil[a]	98.8 ± 0.9	99.8 ± 1.5	99.4 ± 1.8

[a] The fraction of nondegraded verapamil amount in the capped tablet was calculated in percentage, based on the average content of verapamil initially loaded in the NCT

Tukey's post hoc test. The drug release from 20CT was significantly different from those from 50CT and 80CT at all time points ($p<0.05$). The drug releases from 50CT and 80CT were significantly different after 4 h ($p<0.05$). However, further study may be needed to confirm the results, following an established standard (36).

The initial burst of drug release, often observed with a highly water-soluble drug, was not seen with the capped tablets prepared in this work. At the early stage of drug release, nanofibrous sheets appeared to work as a barrier for both water intrusion and drug out-diffusion. During this period, the drug formulated in a dry form inside the capped tablet slowly dissolved after intrusion of water while the liquid connections (i.e., water channels) were being developed in the nanofibrous sheets. Due to this process, drug release at the early stage would be suppressed to some extent.

We pursued to realize linear release of verapamil, employing a nanofibrous-sheet based system suggested in this work. As we examined the linear least square fits to the *in vitro* release profiles obtained from a single tablet (Fig. 6),

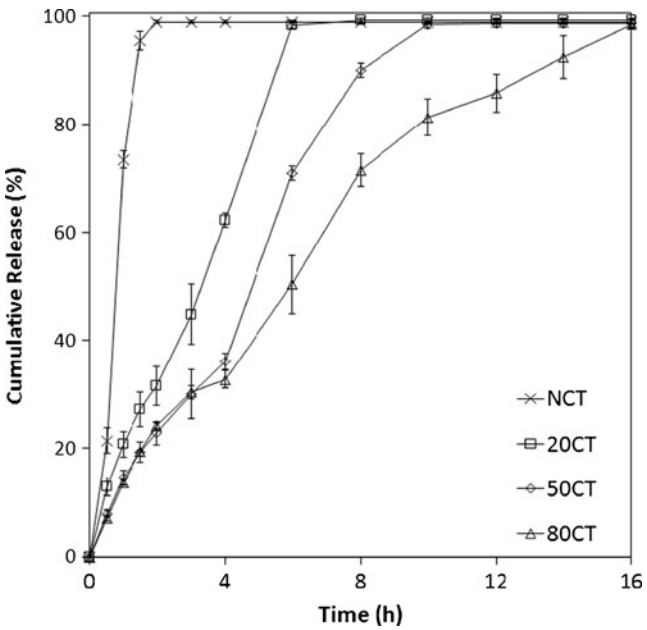

Fig. 6 *In vitro* release profiles of verapamil from NCT, 20CT, 50CT and 80CT.

20CT and 50CT already exhibited a good correlation with linear release (R^2=0.989 and R^2=0.982, respectively). To confirm this, we employed two tablets of the same kind (i.e., two 20CTs and two 50CTs, respectively) to give the dose of 180 mg verapamil, which is the same as that of the marketed medication, Covera-HS® (32). The two tablets were then immersed together in the release media at the varying pHs 1.2 and 6.8 for the first 2 h and the rest 22 h to better simulate the condition in the GI tract. As a result, the fairly linear release profiles were again observed with two 20CTs and two 50CTs ($R^2>0.996$ and $R^2>0.993$, respectively) (Fig. 7 and Table III). As the sheet thickness increased from 20 μm to 50 μm, the periods of linear release increased from 6 h to 8 h, respectively, both releasing almost all drug during this period (> 85%). At both pHs 1.2 and 6.8, the release profiles for the first 2 h were not be very different for 20CT and 50CT, suggesting almost no dose dumping through our tablets and conformity to smooth release of drug with the change in pH (Fig. S3 in the Supplementary Material).

We also compared the release profiles of the capped tablets (i.e., 50CTs) with that of the marketed medication, Covera-HS® at both pHs 6.8 and 7.5. Two tablets of 50CTs were employed together as a single entity again for this test to match the dose amount of verapamil (180 mg) with that of Covera-HS® (32). For Covera-HS®, drug was released in a linear pattern for 8 h at both pHs, following a lag phase of release for 2 h (Fig. S4). Unlike our nanofibrous system, this lag phase

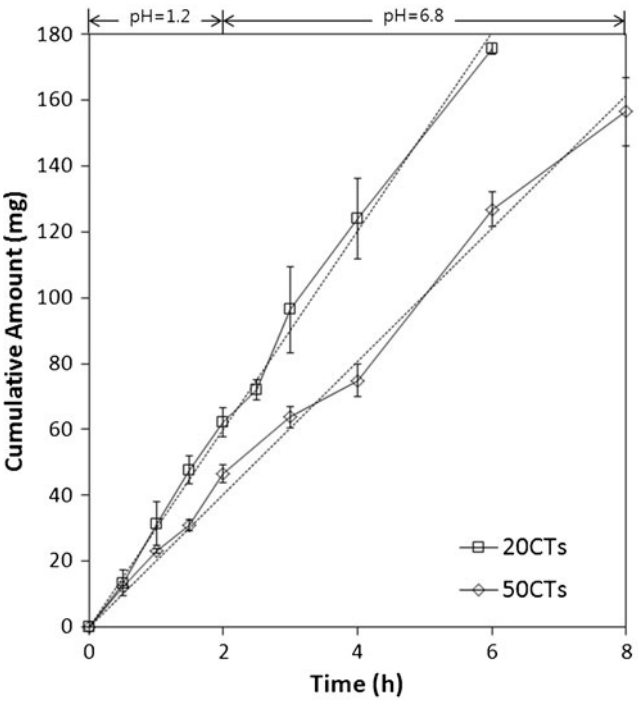

Fig. 7 *In vitro* release profiles of verapamil from two 20CTs and two 50CTs. A dashed line shows a linear trend line fit to the release data obtained from each type of the two tablets.

Table III Linear Release Properties of the Two Tablets of 20CTs and 50CTs

Tablet type	Period of linear release (h)	Fitting equation[a]	R^2	Number of Determination
20CTs	6	$y = 30.140x$	0.996	5
50CTs	8	$y = 20.167x$	0.993	5

[a] The variables, x and y, are the time (h) and the released amount of verapamil (mg), respectively

is inevitable with the OROS tablet like Covera-HS®, since the water needs to be permeated into the capsule and develop the osmotic pressure enough to realize linear drug release. Therefore, we compared the *in vitro* drug release data points of two 50CTs and Covera-HS® just during the period of linear release in this work: the drug release data points were selected at 0–8 h and at 2–10 h for two 50CTs and Covera-HS®, respectively. As shown in Fig. 8, 50CTs and Covera-HS® exhibited similar release patterns at both pHs 6.8 and 7.5. As we calculated a similarity factor (f_2) (37), where two drug release profiles are considered to be similar when the similarity factor is equal to or larger than 50, both formulations showed the similarity factor larger than 50, again suggesting their similar linear release patterns (Table S1 in the Supplementary Information).

DISCUSSION

In this study, we prepared a nanofibrous sheet-based system for controlled delivery of verapamil. The nanofibrous sheets employed to cover the drug tablet possessed the pores in micron-size and the sheets would not degrade during the period of oral drug delivery (<24 h) regardless of the type of PLGA. Therefore, the main conduit for drug diffusion would be through the pores formed in the nanofibrous sheets. Given those, the system could be explained as a simple diffusion model for drug release: drug release could be more sustained as the sheet thickness increased (Fig. 6). This could be supported in part by the pore size distributions obtained with the sheets of different thickness, revealing that the pore size decreased as the sheet thickness increased, hence a more resistive barrier against drug diffusion (Fig. 4). The variation in amount of HPMC used as a binder material and pressure employed for compressing a drug tablet would influence the drug release profiles, which, however, were fixed for all capped tablets prepared in this work (verapamil: HPMC = 10:1, w/w; compressing pressure= 250 kg/cm^2) just to examine the effect of the nanofibrous sheets on verapamil release.

In our previous work, we suggested a nanofibrous sheet-based system for linear delivery of a poorly water-soluble drug, nifedipine (20). Due to slow dissolution of nifedipine, a biphasic release pattern (i.e., a lag phase (<20%) followed by fast release) was evident with the thick sheets while only a diffusion release pattern was observed with the thin sheets. As a result, a combination of two tablets, each capped with thin and thick sheets, respectively, (i.e., 50 μm- and 75 μm-thick sheets, respectively) could realize linear delivery of nifedipine for 24 h (R^2>0.986). Fast release from the tablet capped with thin sheets could compensate slow drug release from the tablet capped with thick sheets at the early stage, and vice versa at the late stage.

In this work, however, we could realize almost linear release of verapamil, just employing an individual capped tablet: no need for a combined system of the two distinctly capped tablets. Almost linear drug release was observed with both 20CT and 50CT. (R^2=0.989 and R^2=0.980, respectively) (Fig. 6). The sheets were made of the same type of PLGA (50:50; inherent viscosity=0.36 dl/g) as in our previous study on nifedipine (20), which, again, were not supposed to degrade during the period of oral drug delivery. The nanofibrous sheets of PLGA were fabricated with the

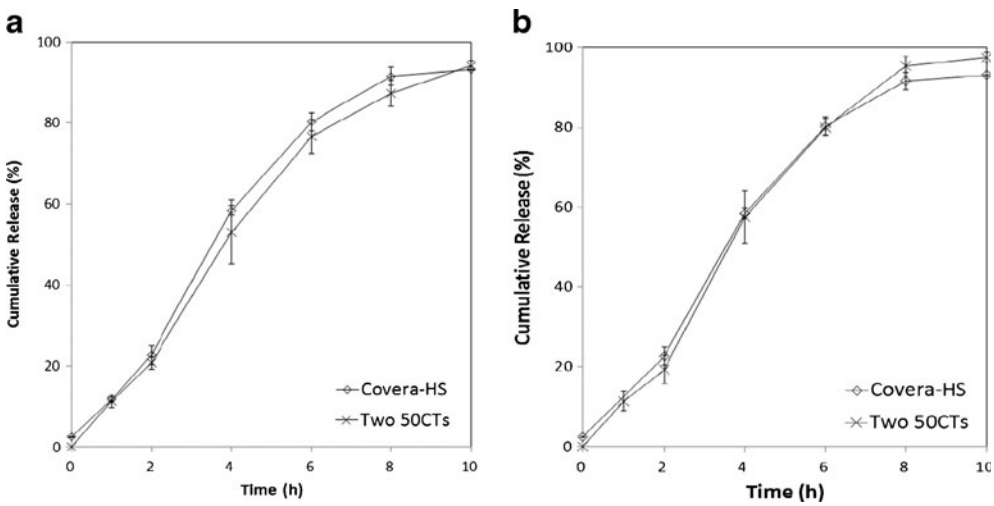

Fig. 8 *In vitro* release profiles of verapamil from two 50CTs and Covera-HS® at (**a**) pH 6.8 and (**b**) pH 7.5. For Covera-HS®, a 2-h lag phase of release was omitted in the graphs just to compare the *in vitro* drug release data points during the period of linear release.

electrospinning method under the same preparation conditions, suggesting similarity in sheet porosity in the thickness range of 0–80 μm. While the molecular weight of verapamil (454.6 g/mol) is slightly larger than nifedipine (346.3 g/mol), the solubility of verapamil (2.71 mg/ml) is more than two orders of magnitude higher than that of nifedipine (5.8 μg/ml). Based on those facts, the drug solubility would play a key role to determine drug release from the nanofibrous sheets.

For this reason, the drug would highly tend to diffuse towards the aqueous media, which could be suppressed to some extent by the nanofibrous sheets of 20 μm and 50 μm thicknesses. Notably, with those specific sheet thicknesses, the rate of drug diffusion at the early stage appeared to match with the release rate at the late stage to a large extent. Unlike verapamil, however, a distinct lag phase was observed with nifedipine at the early stage, resulting from slow dissolution and retarded out-diffusion of a hydrophobic drug via the incomplete paths formed in the sheets. This necessitated the use of two distinctly capped tablets for linear delivery of this poorly water-soluble drug.

In this study, we could control the period of linear release, which could be more prolonged with the increase in sheet thickness employed for capping the tablets. Therefore, as the sheet thickness increased from 20 μm to 50 μm, the period of linear release increased from 6 h to 8 h, respectively (Fig. 7). However, this linear-release period could not be controlled with nifedipine, taking it 24 h, a longest possible residence time in the GI tract (33), for all the tablets prepared in our previous work to complete drug release (20). For a poorly water-soluble oral drug, therefore, a way to expedite drug release (e.g., incorporating a more amount of a solubility enhancer) may need to be considered first to shorten the period of complete drug release.

The linear release pattern from the 50CTs was similar to that from Covera-HS®, the marketed medication for verapamil (Fig. 8) (37). However, due to a lag phase of drug release during the first 2 h observed with Covera-HS®, the pharmacokinetics would not be exactly the same with that of the 50CTs prepared in this work. We envision that some additional coating on the capped tablets can forcefully allow a lag phase of drug release from the 50CTs, if necessary.

CONCLUSION

We have developed a drug tablet capped with the nanofibrous sheets for controlled delivery of a highly water-soluble drug, verapamil. The nanofibrous sheets of microporosity can serve as a diffusion barrier and thus, drug release can be more sustained, depending on the sheet thickness. In this work, the periods for complete drug release could be extended from 6 h to 16 h as the sheet thickness increased from 20 μm to 80 μm.

With a specific thickness of nanofibrous sheets, a capped drug tablet can reduce an initial burst release, often observed with a hydrophilic drug, in a way that the drug release rate at the early stage can match with the release rate at the late stage to a large extent, hence almost linear drug release. Slow drug dissolution by water intrusion and incomplete diffusion paths established in the sheets appear to suppress drug release at the early stage to the extent needed for linear release. In this work, the drug tablets capped with 20 μm- and 50 μm-thick sheets exhibited a fairly good correlation with linear release for 6 h and 8 h, respectively ($R^2 > 0.99$), showing almost complete drug release (>85%) during this period. The 8 h linear release pattern from the two 50CTs was similar to that of Covera-HS®. Therefore, we conclude that a drug tablet capped with nanofibrous sheets has a promising potential for linear delivery of a highly water-soluble oral drug.

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