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ORIGINAL ARTICLE

A novel three-layered tablet for extended release with various layer formulations and *in vitro* release profiles

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Abstract

A novel three-layered tablet consisting of a water-soluble mid-layer and two barrier layers with swellable polymers was investigated to develop a preferable once-a-day formulation containing terazosin HCl as a hydrophilic model drug. When the tablet was exposed to a release medium, the medium quickly permeated to the mid-layer and the two barrier layers swelled surrounding the mid-layer rapidly. It facilitated the tablet to absorb a lot of water compared with monolithic matrix. Moreover, formation of a lot of pores in the tablet during dissolution could be observed, suggesting significant water absorption in the inner matrix and swollen polymers of the tablet. Barrier layers influenced drug release profiles significantly, potentially due to differences in viscosity after swelling that produce different diffusion coefficients and mechanical strength. The drug in the mid-layer showed the sigmoid type of release pattern because a period of time might be needed to release the drug from the mid-layer through the barrier layers, but the drug in barrier layers showed the typical release pattern of monolithic matrix. As the amount of water-soluble excipient in the mid-layer increased, the degree of swelling also increased, suggesting that its amount in the layer may affect the overall swelling properties of the tablet. It was also shown that more hydrophilic mid-layer caused faster erosion rate, which was related to the results of swelling property. The three-layered tablets showed more consistent release kinetics than the matrix tablets. These results can give good information for the development of sustained drug delivery systems, especially once-a-day administration.

Keywords: Three-layered tablet, rapid swelling, water uptake, polyethylene oxide, diffusion, extended release

Introduction

Oral extended drug delivery systems have been developed to optimize the therapeutic efficacy of drugs by providing constant release over the entire dosing interval and increase patient convenience by reducing the frequency of drug administration. One of the most popular systems is a monolithic matrix tablet where a drug is uniformly distributed throughout a polymer matrix (Figure 1A).[1] Drug-release profiles of the tablet primarily depend on drug solubility, drug to polymer ratio, and viscosity of the polymer. It is easy to manufacture with low production cost.[2,3] Commonly used matrix polymers are hydroxypropyl methylcellulose (HPMC) and polyethylene oxide (PEO). HPMC is the most popular because of its safety, applicability, and compatibility with many drugs.[4–7] PEO is also getting attention due to its high water solubility, good gelling properties, and low toxicity.[8–10]

Monolithic matrix systems still have their own limitations, including burst effect and fast initial release rate.[11] Drug-release rate continuously diminishes because of increased diffusional resistance and decreased effective area at the diffusion front. To overcome the limitations, considerable efforts have been implemented for the development of new delivery systems. Matrix geometries such as multi-layered tablets may improve the nonlinear release associated with the diffusion-controlled matrix tablets.[12,13]

Multilayered tablets usually have a core containing a drug and one or more modulating layers that limit the

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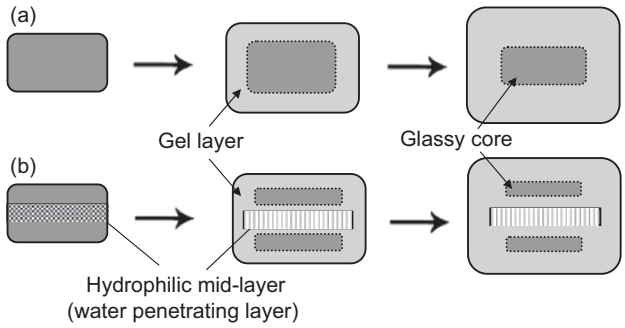

Figure 1. Difference of swelling and gelatin behavior between (A) a monolithic matrix and (B) a novel three-layered tablet containing water penetrating layer.

surface available for drug release.[13–15] They reduce the hydration/swelling rate and maintain consistent release as the barrier layers slowly swell and erode, revealing more surfaces for drug release. Therefore, the decreased delivery rate from the diffusion path length is counterbalanced by increasing the surface area available for drug release.[14] Combining layers with different rates of swelling and erosion can regulate the rate of drug release. Moreover, layers could be formulated to give multi modal, pulsatile, delayed, or extended release, or to release two or more drugs at different rates.[15]

One of the strategies to achieve consistent long-term plasma drug concentrations is to obtain continuous, constant drug release throughout the entire gastrointestinal (GI) tract. However, drug absorption especially in the colon might be challenging due to the unfavorable environments for drug release. Low volume of GI fluid and viscous colonic contents would limit fluid movement around the tablets and retard drug dissolution. Therefore, it will be important to consider the colonic release from dosage forms. Timed-release dofetilide formulations have much lower bioavailability compared with the corresponding oral solution. This might be due to the insufficient release in the colon.[16–18] Sustained-release, hydrogel-forming acetaminophen tablets also showed decreased absorption from the colon.[19] However, accelerating gelation rates could improve *in vivo* drug release in the colon and may allow continuous absorption from a hydrophilic matrix.[20]

Gelation could be controlled by adding water-soluble excipients to improve water penetration rate into the tablets. Formulations with more water-soluble excipients produced a greater erosion ratio and significantly increased *in vivo* drug release, leading to increased drug absorption from the lower GI tract.[21] The addition of water-soluble filler in matrix tablets affected the *in vivo* drug absorption rate. However, it did not change the *in vitro* dissolution rate from the matrix but increased water penetration.[22] Therefore, swelling and gelation need to be considered carefully to develop extended release formulations.

A novel three-layered tablet technology consisting of an inner immediate release layer and two extended release barrier layers with swellable polymers as a once-a-day tablet formulation was established (Figure 1B). Tablets containing one of α1-adrenoceptor antagonists, terazosin HCl dihydrate as a hydrophilic model drug, were developed containing PEO as a hydrophilic gel forming polymer, and their swelling and release properties were evaluated. Because terazosin HCl is freely soluble in water, the formulations containing a hydrophilic drug could as well be characterized. Moreover, simple matrix tablets with similar formulations were also investigated for comparison.

Materials and methods

Materials

Terazosin HCl dihydrate (molecular weight 459.93, free base 387.43, log *P* 1.4) was purchased from Hanseo Chemical (Seoul, South Korea) and is freely soluble in water. The hydrophilic polymer, PEO, was used including Polyox water soluble resin (WSR) N-1105 (average molecular weight 0.9×10^6), Polyox WSR N-12K (average molecular weight 1×10^6), Polyox WSR-301 (average molecular weight 4×10^6), Polyox WSR Coagulant (average molecular weight 5×10^6), and Polyox WSR-303 (average molecular weight 7×10^6) (Dow Chemical, Midland, MI). All PEOs have different viscosities and molecular weights.

The dextrates, NF (Emdex®) and microcrystalline cellulose PH102 (MCC, Heweten102) were obtained from JRS Pharma (Patterson, NY). FlowLac100 is a spray-dried alpha-lactose monohydrate (Molkerei Meggle Wasserburg GmbH & Co. KG, Germany). Copovidone (Kollidon® VA64) was obtained from BASF (Ludwigshafen, Germany). Red dye (Red #3) and magnesium stearate were purchased from Bolak (Seoul, South Korea) and Faci Asia (Jurong Island, Singapore), respectively. All other reagents were of analytical or HPLC grade.

Preparation of matrix and three-layered tablets

The amount of PEO polymer (Polyox WSR N-12K, 301, or 303), terazosin, and magnesium stearate in the matrix tablet were 242.82, 5.935, and 1.25 mg, respectively, giving a total weight of about 250 mg. For the preparation of matrix tablets, the model drug was mixed manually with one of the PEOs in a mortar and then blended with magnesium stearate. The resultant mixture was compressed on a single-punch hydraulic laboratory press using plane-faced punches with a diameter of 9.0 mm. The compression force was 6.0 MPa.

Table 1 shows the details of the formulations to prepare three-layered tablets. All materials were passed through a sieve (#20 mesh) before mixing or granulation to remove any aggregates. Polyox WSR Coagulant was used as the main hydrophilic polymer and its molecular weight is in between Polyox WSR-301 and -303. The upper and lower layers were 100 mg each and contained the polymer (99.5 mg) and magnesium stearate (0.5 mg). The mid-layer was composed of a filler, a drug, and a binder

Table 1. Formulation compositions of the three-layered tablets.

		Formulation number			
Layers	Ingredients	Dex-70	Dex-30	Lac-70	Lac-30
Upper and lower	Polyox WSR Coagulant	99.50	99.50	99.50	99.50
	Magnesium stearate	0.50	0.50	0.50	0.50
Mid	Terazosin HCl	3.561	3.561	3.561	3.561
	Filler	62.94	24.94	62.94	24.94
	Binder	3.50	1.50	3.50	1.50
	Total (mg)	270.00	230.00	270.00	230.00

(copovidone) (Table 1) together with a small amount (0.001% w/w) of Red dye #3. The filler was chosen from one of the following excipients: dextrate (water solubility 1 in 1), lactose (water solubility 1 in 4.63), and MCC (water insoluble). The amount of the mid-layer varied from 30 to 100 mg. For the preparation of the mid-layer, a general wet granulation method using a planetary mixer (Model KSM 90, KitchenAid, St. Joseph, MI) was applied. Exact amount of each layer was loaded into a die with a diameter of 9.0 mm and compressed on the hydraulic laboratory press. The compression force was 6.0 MPa.

Tablet evaluation: degree of swelling, erosion, and separation test

The degree of swelling (water-uptake) was calculated after immersion of test tablets in 900 ml of dissolution medium and stirring for 3 h. The tablets were removed from the medium, blotted with absorbent tissue to remove any excess medium on the surface, and weighed. The degree of swelling (water-uptake) was calculated as:

$$\text{Degree of swelling (mg)} = W_2 - W_1 \quad (1)$$

where W_1 is the initial weight of the dry tablet and W_2 is the weight of the hydrated and swollen tablet. Erosion values were calculated using the same tablets. After weighing, the hydrated tablets were dried in a vacuum-drying oven at 60°C for 24 h, and the remaining dry weight, W_3, was subtracted from W_1, the initial weight of the dry tablet, to give percent erosion:

$$\%\ \text{Erosion} = \left(\frac{W_1 - W_3}{W_1}\right) \times 100 \quad (2)$$

For the separation test, tablets were immersed in 900 ml of the dissolution medium and stirred for 6 h. The tablets were visually observed for separation between the layers.

Drug release test

Drug release tests were conducted according to USP 27 Apparatus 2 guidelines (paddle method) (VK 7000, Varian Inc., Edison, NJ) with 900 ml of the dissolution medium maintained at 37 ± 0.5°C and mixed at 100*g* otherwise indicated. The dissolution medium was simulated intestinal fluid (pH = 6.8, 50 mM phosphate buffer) without any enzymes. Samples were withdrawn at predetermined time intervals and analyzed for drug content using an HPLC system (Agilent 1100 Series; Agilent Technologies, Waldbronn, Germany) at a wavelength of 254 nm. Samples were filtered with 70-μm-PE filters, and then 20 μl of the sample was injected ($n = 4$). The column used was a CapcellPak® C_{18}, 5 μm (4.6 × 150 mm) (Shiseido, Tokyo, Japan). The mobile phase contained a mixture of aqueous buffer (sodium citrate tribasic and citric acid), MeOH, and acetonitrile in a volume ratio of 16:1:3 and its flow rate was 1.0 ml/min.

Analysis of *in vitro* drug release kinetics

Drug release data can be fitted to a power law or a Korsmeyer–Peppas equation,[23] in which the fraction release is linearly related to the time raised to an exponent n:

$$\frac{M_t}{M_\infty} = kt^n \quad (3)$$

where M_t/M_∞ is the fraction of drug released at time t. k is the kinetic constant that shows the structural and geometrical properties of the matrix. Although the equation would give only limited insight, it has been extensively used to get an idea on release mechanisms. A higher k value may suggest burst drug release from the matrix. The exponent, n, is the diffusion exponent, which can indicate the mechanism of drug release and depends on the polymer swelling characteristics and the relaxation rate at the swelling front. The equation is valid only for the early stages (≤ 60%–70%) of drug release. According to the criteria for release kinetics from swellable cylindrical systems, a release exponent value, $n = 0.45$, $0.45 < n < 0.89$, and $0.89 \leq n$ indicates Fickian (Case I) diffusion, non-Fickian (anomalous) diffusion, and zero-order (Case II) transport, respectively.[24,25]

Comparison of *in vitro* dissolution profiles

The similarity factor (f_2) can compare *in vitro* dissolution profiles, and is used here to evaluate drug release profiles of various formulations compared with the controls.[26,27] The formula is:

$$f_2 = 50 \times \log\left\{\left[1 + (1/n)\sum_{i=1}^{n}(u_{ti} - u_{ri})^2\right]^{-1/2} \times 100\right\} \quad (4)$$

The similarity factor (f_2) is a function of the reciprocal of mean square-root transform of the sum of square distances between the test profiles u_{ti} and the reference profiles u_{ri} over all time points (n). The f_2 ranges from 0 to 100

and measures the similarity in the percent dissolution between two curves. When the two drug release profiles are identical, f_2 is 100, but when dissolution is complete before another starts, f_2 is almost 0. Therefore, the value of f_2 ranges between 0 and 100. The higher the value, the more the similarity between the two drug release profiles.

Results and discussion

In vitro release profiles from matrix tablets

As shown in Figure 2A, polymeric matrix tablets with different grades of PEOs showed almost zero-order release kinetics with different slopes on each polymer used. As the molecular weight of the PEOs increased, the release rate decreased. The high molecular weight PEOs induce higher viscosity when hydrated and swollen. Thus, it may result in increased diffusion barrier for drug release. For the low molecular weight Polyox N-12K, most of loaded drug was released approximately in about 9 h. The other two polymers (Polyox WSR- 301 and 303) showed no significant differences and similar sustained release more than 16 h. Therefore, low molecular weight polymers might not be good for long-term sustained release formulations. Polyox WSR Coagulant might be expected to have similar release profiles to Polyox WSR- 301 and 303.

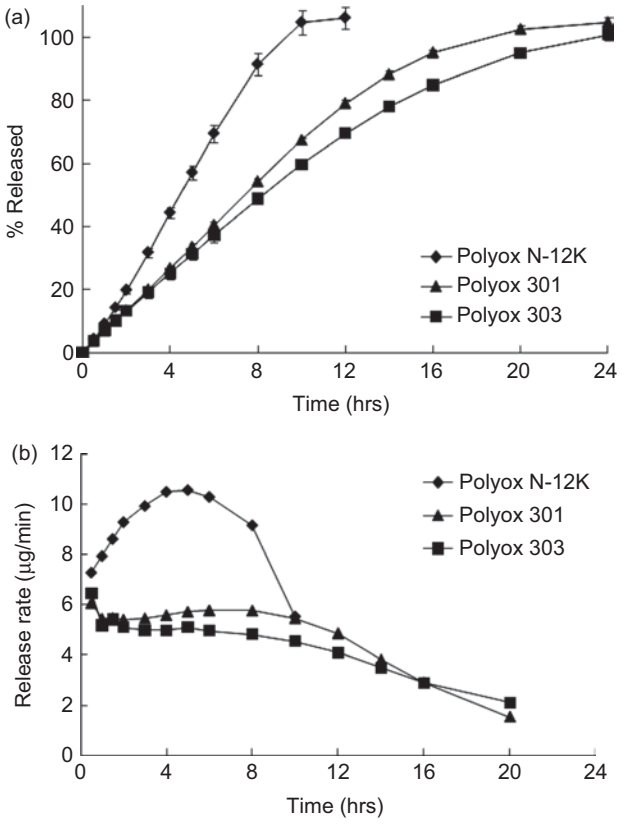

Figure 2 . *In vitro* drug release profiles (A) and release rates (B) from the matrix tablets containing various PEO polymers: Polyox WSR N-12K, Polyox WSR-301, and Polyox WSR-303.

Because of the fast erosion of the Polyox WSR N-12K, the initial release rate increased for up to 4–6 h and decreased significantly afterwards (Figure 2B). However, high molecular weight PEOs maintained somewhat constant release rates for more than 8 h and then decreased slowly. The increased diffusion path length in the swollen matrix resulted in a progressively slow release rate, especially at the end of the dissolution period.

Drug release with different grades of PEO showed a good fit to the Korsmeyer–Peppas equation (Table 2). For high molecular weight PEOs, the n exponent values are close to 0.89, indicating dominant Case-II transport with additional release mechanisms, including matrix erosion and drug diffusion in the swollen area. However, low molecular weight PEO gave an n value of 1.072, indicating super Case-II transport with drug release controlled by polymer relaxation and erosion. Drug release mechanisms from the matrix system are complicated and drug release could be affected by multiple mechanisms. Other PEO tablets showed anomalous diffusion due to the contribution of mechanisms other than diffusion to drug transport. Typical values for the PEO system was approximately 0.8, but 0.6 for HPMC tablets.[8,16,28] When a soluble polymer such as low molecular weight polyvinyl alcohol was used, linear drug release was achieved with n values near 1.0, indicating an erosion-controlled mechanism.[16,29]

There are still limitations on matrix tablets including burst effect and fast initial release rate.[11] Release rates decrease due to the increased diffusion resistance and decreased effective area. Moreover, matrix tablet with highly viscous polymers may not gel fully due to polymer viscosity and the greater distance of water penetration. During the *in vitro* drug release test, 900 ml of the dissolution medium is supplied to make a tablet swell. On oral administration, however, the amount of fluid around a tablet is decreased as it transits down the GI tract, especially in the colon. If swelling is not sufficient to cause complete gelation during GI transit, the inner part of the tablet may form a 'dry core', resulting in incomplete drug release.[17] Therefore, tablets need to be designed to form gels fast during their stay in the stomach and small intestine, where dissolution medium is abundant. To overcome the limitations, considerable efforts have been implemented for the development of new delivery systems over the years and multi-layered tablets might

Table 2. The Korsmeyer–Peppas equation fit using *in vitro* release data of the matrix tablets.

	Polyox WSR N-12K		Polyox WSR-301		Polyox WSR-303	
Factors	50*g*	100*g*	50*g*	100*g*	50*g*	100*g*
n	1.072	1.122	0.873	0.980	0.883	0.920
k	7.115	9.275	6.900	6.946	6.134	7.110
R^2	0.998	1.000	0.998	1.000	0.999	1.000

be one of them. However, the data in the matrix tablets could be used as a selection guide of barrier layers for three-layered tablets based on their physicochemical properties and release profiles.

In vitro release profiles with various drug distribution in three-layered tablets

As a preliminary three-layered formulation, the upper and lower layers contained Polyox WSR-303 (99.5 mg) and magnesium stearate (0.5 mg). The mid-layer was composed of a mixture of lactose (24 mg) and copovidone (4 mg). Three-layered tablets with different drug distribution in each layer were prepared and its effect on drug release profiles was evaluated: a tablet with 40% of the drug was incorporated into the mid-layer only and another tablet with 60% of the drug in the barrier layers only (30% upper layer and another 30% lower layer). The two tablets did not contain whole amount of the drug in the tablet. However, they may give valuable information on drug release profiles and help to perform further formulation studies. When the drug was incorporated in the mid-layer only, sigmoid type of release pattern was observed, because a period of time might be needed to release the drug from the mid-layer through the outer layers (Figure 3). However, when the drug was added only in the swellable barrier layers, it showed typical release profiles of a monolithic matrix. If the sigmoid type of release is necessary to suppress the initial burst of conventional matrix system, it might be better for the drug to be incorporated mainly in the mid-layer than in the barrier layers. The total amount of the drug released was added as shown in the Figure 3, which might represent the drug release profiles with drug distribution of 30%, 40%, and 30% in upper, mid, and lower layers, respectively.

In vitro release profiles from three-layered tablets

As the water-soluble drug, terazosin HCl, was incorporated in the mid-layer of the three-layered tablets, drug release profiles of sigmoid type could be observed (Figure 4A). The amount of mid-layer (30 or 70 mg) with dextrate did not change the release profiles and rate except the initial time period (Figure 4A). However, increased amount of dextrate resulted in faster initial release rate because water-soluble excipient might induce a portion of drug to be released quickly before the barrier layers swell and surround the mid-layer (Figure 4B). In the case of lactose, which is less water-soluble than dextrate, such difference of initial release rate was not observed between 30 and 70 mg mid-layer (data not shown). The release of 70 mg mid-layer with dextrate showed slightly faster release up to 14 h compared with lactose with the same amount (Figure 5). Therefore, more soluble fillers might increase release rate as long as the barrier layers are same.

When matrix tablets were prepared with the mid-layer only (100 mg), the entire drug was released in less than 5 min (Figure 6), suggesting that barrier layers were controlling the drug release significantly. Thus, the overall drug release rates of the three-layered tablets might be dependent on the composition and properties of the barrier layers even though the mid-layer may affect water penetration and diffusion properties on the drug release.

Drug release data showed a good fit to the Korsmeyer–Peppas equation, with n exponent values of 1.002 ($k = 4.774$) for Dex-30 (Table 3). It indicates that the initial burst of conventional matrix system was not displayed due to another release mechanism, similar to reservoir

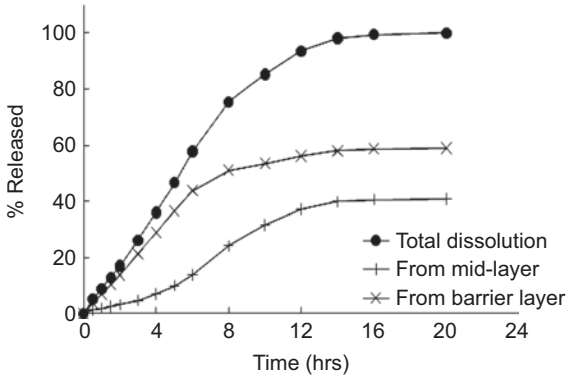

Figure 3. *In vitro* drug release profiles from the three-layered tablets with different drug distribution in each layer: from a mid-layer (+), barrier layers (×), and a whole tablet (•).

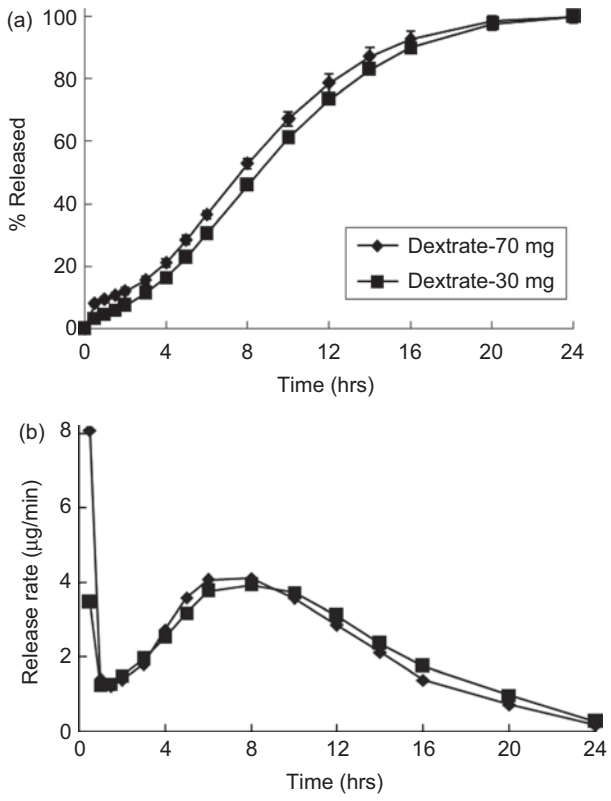

Figure 4. *In vitro* drug release profiles (A) and release rates (B) from the three-layered tablets containing different amounts of soluble fillers in the mid-layer: dextrate 70 mg (◆), dextrate 30 mg (■).

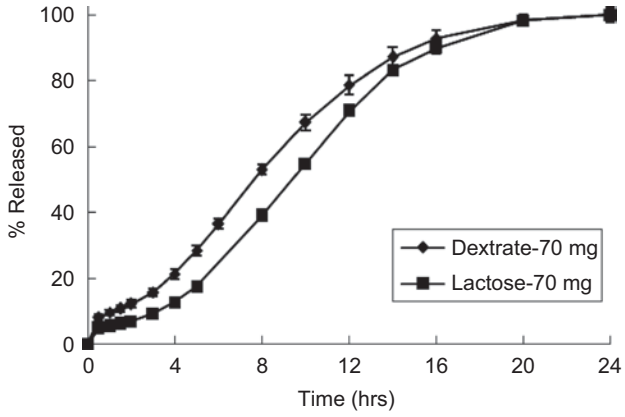

Figure 5. *In vitro* drug release profiles from the three-layered tablets containing fillers with different solubility in the mid-layer: dextrate 70 mg (◆), lactose 70 mg (■).

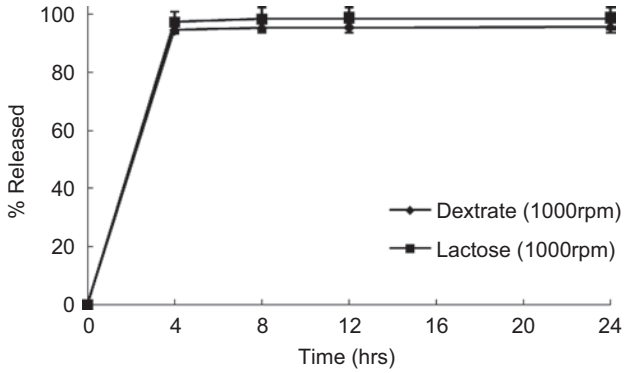

Figure 6. *In vitro* drug release profiles from only the mid-layer mainly composed of dextrate or lactose.

system, of three-layered tablet, not the simple diffusion of conventional matrix.

It is well known that monolithic matrix system containing water-soluble drug is difficult to achieve zero-order or sigmoid type of release patterns.[11] If barrier layers could swell enough fast to form gels surrounding the lateral side of the mid-layer, controlled release profiles could be optimized or modified easily without any significant initial burst effect. In reality, the barrier layers swell faster than the nonswelling mid-layer and cover the tablet forming a diffusion barrier (Figures 1 and 7). Moreover, swelling occurs on the barrier layers with the help of mid-layer, which facilitates faster swelling compared with matrix tablets.

Properties of three-layered tablets

Separation, water-uptake, and erosion of three-layered tablets

When dextrate and lactose were incorporated into the mid-layer, they did not cause separation, forming rapidly swollen three-layered tablets with good consistency regardless of the amount of mid-layer applied. However, larger amount of MCC in the mid-layer (100 mg) caused separation, although smaller amounts (30, 50, and 70 mg) did not. Hydrophilic property might be a factor to consider a balance between the PEO and the mid-layer

Table 3. The Korsmeyer–Peppas equation fit using *in vitro* release data of the matrix and three-layered tablets.

	Formulation number		
Factors	Dex-30	RS-11	RS-22
n	1.002	0.963	1.020
k	4.774	2.633	4.997
R^2	0.954	0.961	0.940

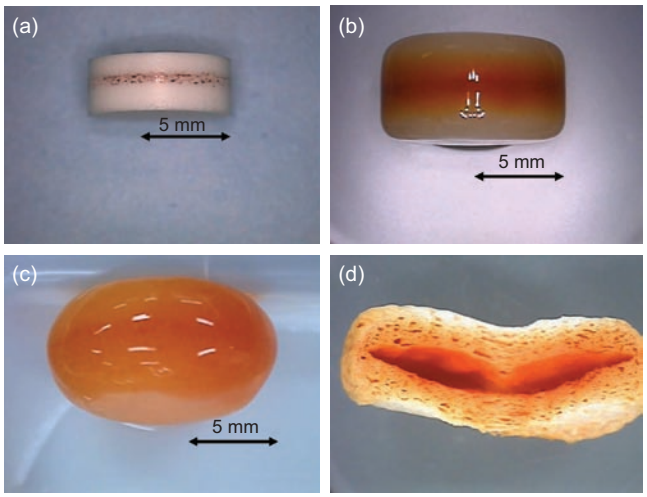

Figure 7. Photographs on swelling and gelation behavior of the three-layered tablet: (A) before gelation, (B) after 1 h, (C) after 3 h, and (D) section of a vacuum-dried tablet after 3 h of gelation.

excipient. Dextrate and lactose are more hydrophilic than MCC, and the previous ones did not bring any separation issues.

The three excipients do not swell themselves, but may affect swelling and water absorption of the tablets. The larger the amount of soluble excipient, dextrate or lactose, in the mid-layer, the more the amounts of water-uptake were observed (Figure 8A). However, the amount of MCC, a water-insoluble excipient did not affect the water absorption of tablets. As the amount of water-soluble excipient in the mid-layer increased, the swelling also improved suggesting that the amount of water-soluble excipient in the mid-layer may affect the overall swelling properties of tablets.

Figure 8B showed that dextrate and lactose induced more erosion of the tablet than MCC did. More hydrophilic components in the mid-layer may cause faster erosion rate of the tablet, which was related to the results of swelling property. Therefore, hydrophilic property of the excipients in the mid-layer can be an important factor which determines when to design the three-layered tablets with preferable water-uptake property and without separation.

Swelling behavior of three-layered tablets

Photographs of swelling behavior of the three-layered tablet (Dex-30) during the swelling and erosion tests were shown in Figure 7. Similar to the scheme of Figure 1, the release medium quickly permeated to the mid-layer of water-soluble excipients and facilitated swelling of

the barrier layers surrounding the mid-layer rapidly without separation. This rapid swelling property can suggest that the tablet, after oral administration, can go into full-hydrated state rapidly and arrives the colon where release medium is barely available. This might induce the continuous drug release there irrespective of the unfavorable environment. It was shown that the red dye in the mid-layer was moving out to the barrier layers after 1 h (Figure 7B) and diffused entirely in the swollen tablet after 3 h (Figure 7C). The diameter of the swollen tablet was also expanded more than twice compared with the initial.

From the section of vacuum-dried tablet after 3 h, a large hole in the tablet with spongy-like barriers could be observed (Figure 7D), which suggested that a lot of water was absorbed to the swollen tablet. It was supposed that the three-layered tablet, after oral administration, would absorb a lot of medium in the upper GI tract and be fully hydrated. Thus, it might arrive at the lower GI tract while inducing continuous drug release.

Dissolution tolerance of three-layered tablets against agitation force

Because extended-release preparations need to release drugs for a longer period of time in the GI tract, it is desirable for the preparations to maintain consistent release rate as exposed to various GI environments. Changes in shear force or paddle speed during the *in vitro* dissolution study might be a simple indicator of the effect of the environment on the release rate.

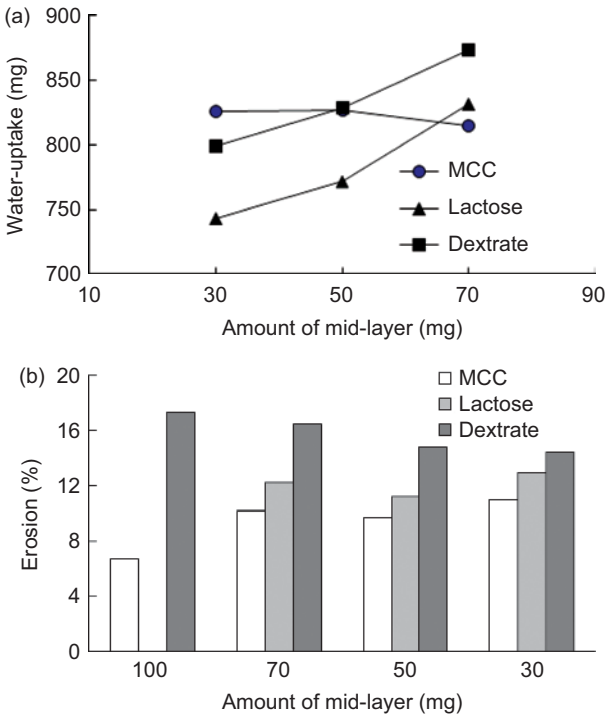

Figure 8. Influence of types and amounts of mid-layer on the water uptake (A) and the erosion (B) of three-layered tablets: MCC, lactose, and dextrate.

Figure 9 shows the change of dissolution rate by controlling the agitation force of dissolution test from 50 to 150*g* with the formulations of Dex-30 and Dex-70. Similarity factors (f_2) were calculated in Table 4. Both formulations were stable from the effect of agitation force from 100*g* to 150 or 50*g*, because the similarity factors were considered, $f_2 > 50$. It means that two preparations passed FDA's similarity criterion of less than 10% and the effect of agitation force may not be significant.

Effects of different grades of PEOs on drug release

The effect of different grades of PEO polymers in the barrier layers on drug release was investigated (Figure 10). Similar to the preliminary three-layered tablet formulations, lactose was incorporated as the main filler in the mid-layer. As shown in the figure, barrier layer composition influenced drug release profiles significantly; Polyox WSR N-1105 (RS-22) showed much faster release rate than Polyox WSR-301 (RS-11), especially during the mid- and late-stages of drug release. It might be due to the differences in viscosity after swelling that produce different diffusion coefficients and mechanical strength. However, it needs to be reminded that the compositions of not only the barrier layers but also the mid-layer could be the important factors to control the overall release profiles of the three-layered tablets. Drug release from the system showed a good fit to the Korsmeyer–Peppas equation, with *n* exponent

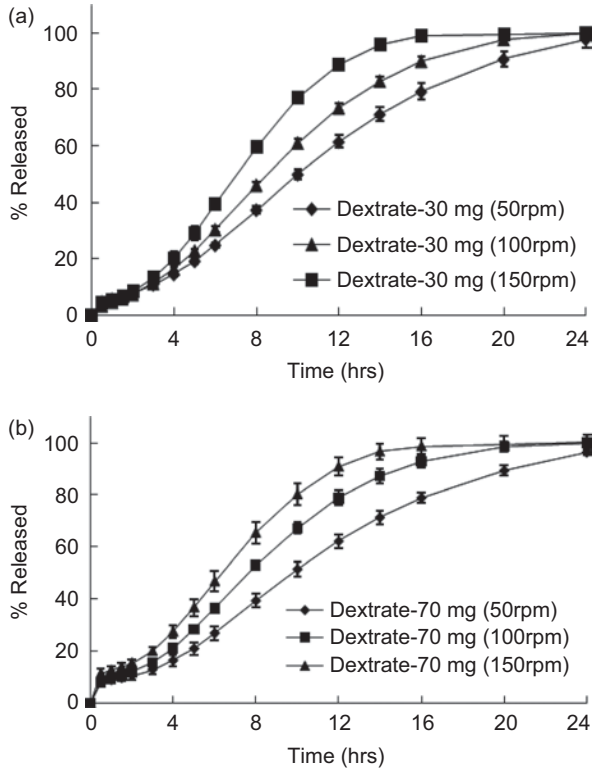

Figure 9. *In vitro* drug release profiles from the three-layered tablets containing different amounts of dextrate in the mid-layer with various paddle speeds: (A) dextrate 30 mg and (B) dextrate 70 mg.

Table 4. Dissolution tolerance of three-layered tablets containing water-soluble excipient in the mid-layer to the agitation forces from 50 to 150*g*.

f_2 (vs.100 rpm)	Dex-30	Dex-70
50 rpm	50.5	58.5
150 rpm	53.7	54.1

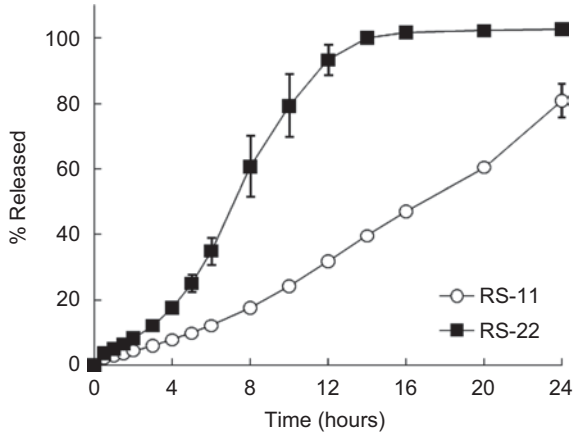

Figure 10. *In vitro* drug release profiles from the three-layered tablets containing different grades of PEO polymers in the barrier layers.

values of 0.963 ($k = 2.633$) and 1.020 ($k = 4.997$) for RS-11 and RS-22, respectively (Table 3), indicating near zero-order release due to a mechanism other than simple diffusion of conventional matrix.

Conclusions

Using the information of matrix tablets, a novel three-layered tablet was designed and evaluated to overcome the limitations of the matrix tablets and to develop extended release formulations. Dissolution medium was observed to quickly permeate the tablet and form gelled layers surrounding the lateral side of the mid-layer rapidly, which produced controlled drug release profiles. Sigmoid type of release could be modified to suppress the initial burst or dose dumping of conventional matrix system by incorporating drugs mainly in the mid-layer than in the barrier layers. The overall drug release rates of the tablets were mainly dependent on the composition and properties of the barrier layers even though the mid-layer may affect water penetration and diffusion properties. The three-layered tablets showed more consistent release kinetics than the matrix tablets. These findings can give good information for the development of sustained drug delivery systems, especially once-a-day administration.

Declaration of interest

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