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RESEARCH PAPER

Development of Terfenadine-Pseudoephedrine Double-Layer Tablet Dissolution-Equivalent to Core Tablet

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ABSTRACT

The terfenadine-pseudoephedrine dosage form discussed here is the sustained-release core tablet composed of outer (fast-release) and inner (sustained-release) layers. To develop the double-layer tablet dissolution-equivalent to a core tablet, the fast-release and sustained-release layers were prepared using various disintegrants and polymers, respectively. The layer composed of terfenadine/pseudoephedrine/lactose/cornstarch/sodium bicarbonate/hydroxypropylcellulose (HPC)/sodium lauryl sulfate/microcrystalline cellulose (60/10/90/30/20/1/40/1/293 mg), which gave the fast disintegration time and high dissolved amounts of drugs, was selected as the fast-release layer. The dissolved amounts of pseudoephedrine from sustained-release layers increased more with a smaller ratio of ethylcellulose and hydroxypropylmethylcellulose (HPMC). Dissolution mechanism analysis showed the release of pseudoephedrine was proportional to the square root of time, indicating that drug might be released from the layers by Fickian diffusion. The layer composed of pseudoephedrine/ethylcellulose/HPMC (110/30/155 mg), which had similar dissolution amounts of pseudoephedrine as the inner layer of a core tablet, was selected as the sustained-release layer. Furthermore, the dissolved amounts of drugs from the core and double-layer tablets had deviations of less than 5% against the average dissolved amounts of drugs at each time. There was no significant difference between the dissolved amounts of drugs from these tablets at each time in pH 1.2, 4.0, and

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6.8 ($P > .05$). Our results suggest that this double-layer tablet was a dissolution equivalent to the core tablet.
Key Words: *Dissolution; Double-layer tablet; Pseudoephedrine; Terfenadine.*

INTRODUCTION

The simultaneous administration of antihistaminic drugs such as terfendine-pseudoephedrine (1–4), phenylpropanolamine-pseudoephedrine (5), terfenadine-diphenhydramine (6), and terfenadine-chlorphenylamine (7) is highly effective in treating allergic rhinitis and urticaria. The present terfenadine-pseudoephedrine dosage form is the sustained-release core tablet composed of an outer (fast-release) layer containing 60 mg of terfenadine and 10 mg of pseudoephedrine and an inner (sustained-release) layer containing 110 mg of pseudoephedrine. Orally administered, the outer layer disintegrates within 3 min, and instantly the inner layer releases the pseudoephedrine over 12 hr. Thus, the core tablet is no sustained-release dosage form in which the dissolution of the drug from the inner layer is dependent on the outer layer since the outer layer scarcely affects the dissolution of the inner layer (3,4).

In this study, we tried to change the terfenadine-pseudoephedrine sustained-release dosage form to the double-layer tablet since the double-layer tablet is easier to manufacture than the core tablet. Like the core tablet, the double-layer tablet was composed of one layer (fast-release layer) containing 60 mg of terfenadine and 10 mg of pseudoephedrine and another layer (sustained-release layer) containing 110 mg of pseudoephedrine. For the development of the fast-release layer, disintegrants such as microcrystalline cellulose, sodium bicarbonate, sodium lauryl sulfate, and sodium starch glycolate were added to the ingredients. On the other hand, ethylcellulose and hydroxypropylmethylcellulose (HPMC) were added to the polymers of the sustained-release layer. Finally, dissolution tests of the fast-release layers, sustained-release layers, and double-layer tablets were performed and compared with the core tablet.

MATERIALS AND METHOD

Materials

Terfenadine, cornstarch, lactose monohydrate, microcrystalline cellulose, sodium bicarbonate, sodium lauryl sulfate, sodium starch glycolate, and ethylcellulose were kindly supplied by Dong-Wha Pharmaceutical Company (Anyang, Korea). Pseudoephedrine hydrochloride was purchased from Wha-Sung Company (Seoul, Korea). Hydroxypropylcellulose (HPC, K-20) and HPMC 2208 (4000 cps) were supplied by Shinetsu Company (Tokyo, Japan). A commercial product (Seldane-D®, Hoest Marion Roussel, Inc., Kansas City, MO) was used for the terfenadine-pseudoephedrine sustained-release core tablet.

Preparation of Terfenadine-Pseudoephedrine Double-Layer Tablets

Fast-Release Layers

Terfenadine, pseudoephedrine, lactose, and cornstarch were thoroughly blended and granulated with 10% HPC alcoholic solution. For the preparation of the fast-release layers with a diameter of 8.8 × 18.3 mm, a weight of 490–550 mg, and a hardness of 6–8 KP, the resulting granules were mixed and compressed with various disintegrants and lubricants using an Erweka tablet machine (Frankfurt, Germany). The detailed compositions of the fast-release layers are given in Table 1.

Sustained-Release Layers

For the preparation of the sustained-release layers with a diameter of 8.8 × 18.3 mm, weighing 300 mg, and having a hardness of 4–6 KP, pseudoephedrine was thoroughly mixed and compressed with various polymers and lubricants using the Erweka tablet machine. Detailed compositions of the fast-release layers are given in Table 2.

Double-Layer Tablets

For the preparation of the double-layer tablets with a diameter of 8.8 × 18.3 mm, a weight of 850 mg, and a hardness of 8–10 KP, the ingredients of the sustained-release layer were placed on the fast-release layer, compressed, and coated with 5% HPMC aqueous solution (equivalent to 3 mg of HPMC) using an Erweka coating machine (Frankfurt, Germany) (8–10).

Dissolution Test

Each fast-release layer, sustained-release layer, double-layer tablet, and core tablet was placed in a dissolu-

Table 1

Compositions of Fast-Release Layers

Composition (mg/tablet)	I	II	III	IV	V	VI
Terfenadine	60	60	60	60	60	60
Pseudoephedrine	10	10	10	10	10	10
Lactose	290	90	90	90	90	90
Cornstarch	124	30	30	30	30	30
Sodium bicarbonate	—	—	20	20	20	20
Hydroxypropylcellulose	—	1	1	1	1	1
Sodium starch glycolate	—	—	—	20	40	40
Sodium lauryl sulfate	—	—	—	—	—	1
Microcrystalline cellulose	—	294	294	294	294	293
Magnesium stearate	5	5	5	5	5	5
Total	490	490	510	530	550	550
Maximum Disintegration Time (min)	13	8	8	6	4	3
Dissolved amounts (%) at pH 1.2 for 30 min						
Terfenadine	20.4 ± 1.0	21.8 ± 0.8	30.4 ± 2.5	34.2 ± 3.2	35.7 ± 2.0	39.8 ± 1.0
Pseudoephedrine	74.3 ± 4.1	81.2 ± 6.7	81.3 ± 2.9	82.6 ± 3.2	83.2 ± 2.7	84.1 ± 5.0

tion tester (DST-600, Fine Chemical, Seoul, Korea). The dissolution test was performed at 36.5°C using the paddle method at 50 rpm with 900 ml of pH 1.2 (0.1 N HCl), 4.0 (phthalate buffer), and 6.8 (phosphate buffer) dissolution media. At predetermined intervals, 5 ml of the medium were sampled and filtered. This resulting solution (10 μl) was injected directly onto a Lichrosorb RP-18 column (Waters, 0.5 μm, 25 cm × 0.46 cm id). The chromatograph consisted of a high-performance chromatograph (Waters model TM 717) and a variable ultraviolet (UV) spectrophotometric detector (model SPD-6A). The mobile phase consisted of 200 ml distilled water and 800 ml acetonitrile dissolved in 0.5 g potassium monohydrogen phosphate and 0.3 g sodium 1-heptanesulfonic acid and adjusted to pH 6.6 with 8 N sodium hydroxide. The eluent was monitored with an ultraviolet/visible (UV/vis) detector set at 220 nm with a flow rate of 1.0 ml/min (11–13).

Table 2

Compositions of Sustained-Release Layers

Composition (mg/tablet)	I	II	III	IV
Pseudoephedrine	110	110	110	110
Ethylcellulose	10	30	50	90
Hydroxypropylmethylcellulose	175	155	135	95
Magnesium stearate	5	5	5	5
Total	300	300	300	300

RESULTS AND DISCUSSION

Fast-Release Layer

Terfenadine could not be pressed directly since its direct compression showed the bridge phenomenon in the hopper due to its adhesive property. Thus, terfenadine, pseudoephedrine, lactose, and cornstarch were granulated with HPC alcoholic solution as a binder. The fast-release layers were prepared by compressing the resulting granules and various disintegrants, and then their disintegration and dissolution tests were perfomed (Table 1).

Sodium bicarbonate and sodium lauryl sulfate hardly affected the disintegration of the layers, while microcrystalline cellulose and sodium starch glycolate improved the disintegration time of the layers, resulting in a maximum disintegration time of 3 min for layer VI. Irrespective of ingredients, pseudoephedrine showed a dissolved amount of more than 75% from the layers due to its excellent water solubility (1,2). On the other hand, the dissolved amounts of terfenadine from the layers were highly dependent on ingredients since terfenadine was poorly water soluble (14–16). Microcrystalline cellulose and sodium starch glycolate scarcely increased the dis-

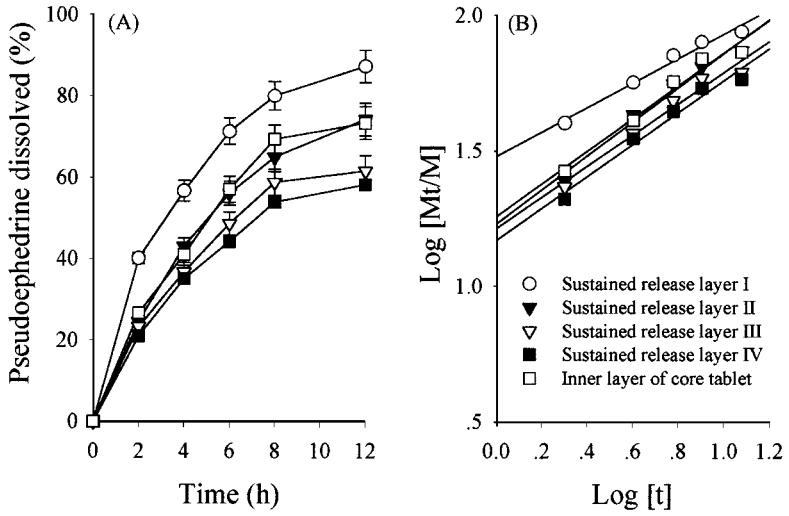

Figure 1. Dissolution and dissolution kinetics of pseudoephedrine from sustained-release layer at pH 6.8: (A) dissolution; (B) dissolution kinetics. Vertical bar represents the standard deviation of the mean ($n = 6$).

solved amounts of terfenadine from the layers, while sodium bicarbonate and sodium lauryl sulfate gave the relatively high dissolved amounts of terfenadine. However, since terfenadine was poorly water soluble, it was limited to increase the dissolved amounts of terfenadine, with the result that the dissolved amount of terfenadine from layer VI was about 40% in pH 1.2 at 30 min. Thus, among these layers, layer VI (terfenadine/pseudoephedrine/lactose/cornstarch/sodium bicarbonate/HPC/sodium lauryl sulfate/microcrystalline cellulose/magnesium stearate 60/10/90/30/20/1/40/1/293/5 mg) was selected as the fast-release layer due to its fastest disintegrating time and highest dissolved amounts of terfenadine and pseudoephedrine.

Sustained-Release Layer

The sustained-release layers were prepared by compressing pseudoephedrine and various polymers such as ethylcellulose and HPMC. The inner (sustained-release) layers of core tablet were prepared by eliminating the outer layers from the core tablets. The dissolution amounts of pseudoephedrine from them were evaluated compared with the inner layer of the core tablet (Table 2).

Figure 1A shows that the dissolved amounts of pseudoephedrine from the layers were increased with a smaller ratio of ethylcellulose and HPMC. As a possible mechanism by which polymers affected the dissolved amount of pseudoephedrine from the layers, it is speculated that the dissolution medium was difficult to penetrate in the hydrophobic ethylcellulose matrix, while it was not difficult to penetrate in the hydrophilic HPMC matrix (17,18). Furthermore, Fig. 1A indicates that layer II had similar dissolution amounts of pseudoephedrine as the inner layer of core tablet.

To understand the dissolution mechanisms of pseudoephedrine from the sustained-release layers, we described the dissolution rate using the following equations:

Table 3

Dissolution Kinetic Parameters of Pseudoephedrine from Sustained-Release Layers

	Kinetic Constant k	Release Exponent n	Correlation Coefficient R
Inner layer of core tablet	17.547	0.5209	0.967
Sustained-release layer I	30.220	0.4814	0.979
Sustained-release layer II	17.026	0.5237	0.972
Sustained-release layer III	16.417	0.5292	0.964
Sustained-release layer IV	14.825	0.5337	0.969

$$Mt/M = kt^n \quad (1)$$

$$\log(Mt/M) = \log k + n \log(t) \quad (2)$$

where Mt/M is the fraction of dissolved drug at time t, k is a characteristic constant of the layer, and n is an indicator of the dissolution mechanism. As the value of k increases, the dissolution occurs faster. The n value of 1 corresponds to zero-order release kinetics, $0.5 < n < 1$ means a non-Fickian dissolution model, and $n = 0.5$ indicates Fickian diffusion (Higuchi model) (19). From the plot of $\log(Mt/M)$ versus $\log(t)$ (Fig. 1B), kinetic parameters n and k were calculated. Table 3 shows that the layers gave n values of nearly 0.5, suggesting that pseudoephedrine might be dissolved from the layers by Fickian diffusion (20–22). The k values also indicate that pseudoephedrine was dissolved faster from the sustained-release layer with a smaller ratio of ethylcellulose and HPMC. Furthermore, Table 3 indicates that layer II had a k and n similar to those of the inner layer of the core tablet. Thus, among these layers, layer II (pseudoephedrine/ethylcellulose/HPMC/magnesium stearate 110/ 30/155/5 mg) was selected as the sustained-release layer.

Double-Layer Tablet

The compositions of sustained-release layer II were placed on fast-release layer IV and then compressed. The double-layer tablets were prepared by coating the resulting tablets with HPMC aqueous solution to increase their hardness and friability. The dissolution amounts of terfenadine and pseudoephedrine from the double-layer tablet were evaluated in pH 1.2, 4.0, and 6.8 compared with the core tablet.

Figure 2 illustrates the dissolved amounts of terfenadine from the core and double-layer tablets in pH 1.2, 4.0, and 6.8. The dissolved amounts of terfenadine from two tablets had a deviation of less than 5% against the average dissolved amounts of terfenadine at each time. Furthermore, there was no significant difference between the dissolved amounts of terfenadine from the core and double-layer tablets at each time in pH 1.2, 4.0, and 6.8 ($P > .05$), indicating that the double-layer tablet had similar dissolved amounts of terfenadine as the core tablet. Both tablets had increased dissolved amounts of terfenadine with lower pH. Especially, the dissolved amounts of terfenadine from the two tablets in pH 1.2 were higher than those in pH 4.0 and 6.8 since terfenadine was more soluble at a lower pH (14,15). Figure 2C shows that the dissolved amounts of terfenadine from the double-layer tablet was about 40% in pH 6.8 at 0.5 hr, indicating that coating hardly affected the dissolution of terfenadine from the double-layer tablet due to very low coating amounts (3 mg/tablet).

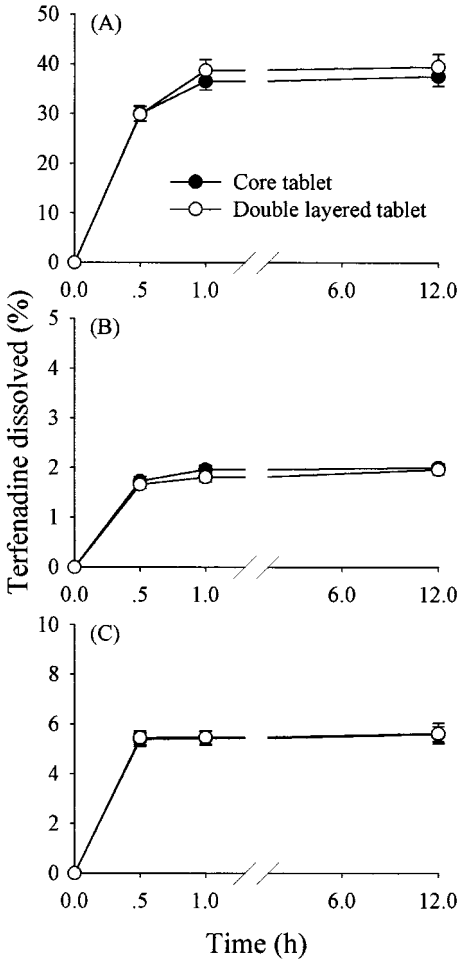

Figure 2. Dissolved amount of terfenadine from core and double layered tablets at pH 1.2 (A), 4.0 (B), and 6.8 (C). Vertical bar represents the standard deviation of the mean ($n = 6$).

Figure 3 illustrates the dissolved amounts and dissolved kinetics of pseudoephedrine from the core and double-layer tablets in pH 1.2, 4.0, and 6.8. The dissolved amounts of pseudoephedrine from the two tablets deviated less than 5% compared to the average dissolved amounts of terfenadine at each time. There was no significant difference between the dissolved amounts of pseudoephedrine from the core and double-layer tablets at each time in pH 1.2, 4.0, and 6.8 ($P > .05$). Our results indicate that the double-layer tablet had similar dissolved amounts of pseudoephedrine as the core tablet. On the other hand, the dissolution of the core and double-layer tablets was pH dependent since the two tablets had increased dissolved amounts of terfenadine with lower pH.

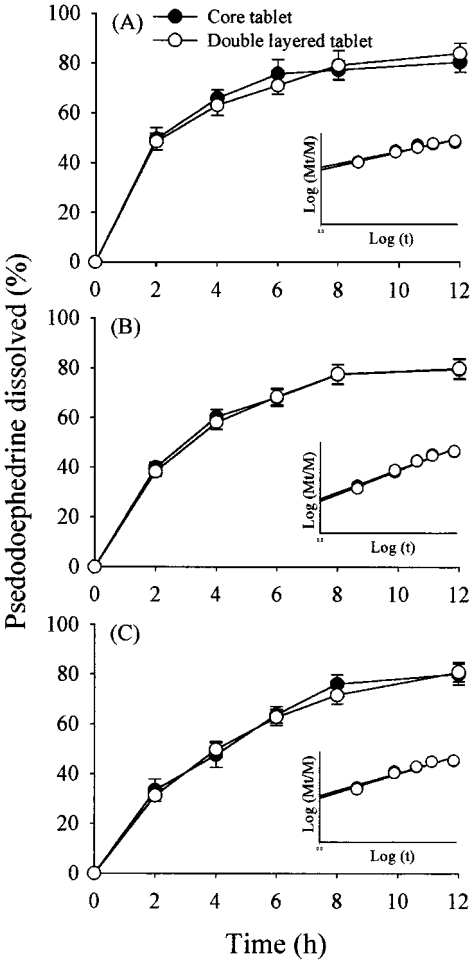

Figure 3. Dissolved amount of pseudoephedrine from core and double-layered tablet at pH 1.2 (A), 4.0 (B), and 6.8 (C). Vertical bar represents the standard deviation of the mean ($n = 6$).

Figures 1 and 3C show that the double-layer tablet had increasing dissolved amounts of about 7% pseudoephedrine compared to the sustained-release layer at each time in pH 6. 8. Such increasing dissolved amounts of pseudoephedrine were contributed by the amounts of pseudoephedrine dissolved from the fast-release layer of the double-layer tablet. Furthermore, these results suggest that coating hardly affected the dissolution of pseudoephedrine from the double-layer tablet. Table 4 shows that both tablets gave *n* values of nearly 0.5, suggesting that pseudoephedrine might be dissolved from the two tablets by Fickian diffusion irrespective of pH (20–22). The double-layer tablet gave similar *k* and *n* values as the core tablet, indicating that the double-layer tablet had similar dissolved mechanisms of pseudoephedrine as the core tablet. As shown in Tables 3 and 4, the double-layer tablet had larger *k* compared to the sustained-release layer in pH 6.8 due to the amounts of pseudoephedrine dissolved from the fast-release layer of the double-layer tablet.

Thus, such similar dissolved amounts and mechanisms of terfenadine and pseudoephedrine from the two tablets in each pH suggest that the double-layer tablet was the dissolution equivalent of the core tablet. Furthermore, from our results, we can expect that this double-layer tablet may be bioequivalent to the core tablet. Further study of the bioequivalence of this double-layer tablet to the core tablet in human subjects will be performed.

CONCLUSION

Taken together, it is concluded that the terfenadine-pseudoephedrine sustained-release double-layer tablet composed of a fast-release layer (terfenadine/pseudoephedrine/lactose/cornstarch/sodium bicarbonate/HPC/sodium lauryl sulfate/microcrystalline cellulose/magnesium stearate 60/10/90/30/20/1/40/1/293/5 mg/tab) and

Table 4

Dissolution Kinetic Parameters of Pseudoephedrine from Core and Double-Layer Tablets

pH	Tablet	Kinetic Constant *k*	Release Exponent *n*	Correlation Coefficient *R*
1.2	Core	41.534	0.5066	0.981
	Double layer	39.610	0.5131	0.972
4.0	Core	25.480	0.5240	0.972
	Double layer	24.262	0.5369	0.977
6.8	Core	22.341	0.5109	0.978
	Double layer	21.311	0.5137	0.983

a sustained-release layer (pseudoephedrine/ethylcellulose/HPMC/magnesium stearate 110/30/155/5 mg/tab) was the dissolution equivalent of the present terfenadine-pseudoephedrine sustained-release core tablet.

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