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Development of Controlled Release Oral Drug Delivery System by Membrane-Coating Method-I

– Preparation and pharmaceutical evaluation of controlled release acetaminophen tablets –

Chang-Koo Shim §, **Ki-Man Kim***, **Young-Il Kim*** **and Chong-Kook Kim**

College of Pharmacy, Seoul National University, Seoul 151-742, and
**Yuhan Research Center, Yuhan Corporation, Kunpo-si, Kyunggi-do, Korea*

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Abstract□In order to develop a controlled-release oral drug delivery system (DDS) which sustains the plasma acetaminophen (AAP) concentration for a certain period of time, microporous membrane-coated tablets were prepared and evaluated *in vitro*. Firstly, highly water-soluble core tablets of AAP were prepared with various formulations by wet granulation and compression technique. Then the core tablets were coated with polyvinylchloride (PVC) in which micronized sucrose particles were dispersed. Effect of formula compositions of core tablets and coating suspensions on the pharmaceutical characteristics such as drug release kinetics and membrane stability of the coated tablets was investigated *in vitro*. AAP was released from the coated tablets at a zero-order rate in a pH-independent manner. This independency of AAP release to pH change from 1.2 to 7.2 is favorable for the controlled oral drug delivery, since it will produce a constant drug release in the stomach and intestine regardless of the pH change in the GI tract. Drug release could be extended upto 10 h according to the coating condition. The release rate could be controlled by changing the formula compositions of the core tablets and coating suspensions, coat weight per each tablet, and especially PVC/sucrose ratio and particle size of the sucrose in the coating suspension. The coated tablets prepared in this study had a fairly good pharmaceutical characteristics *in vitro*, however, overall evaluation of the coated tablets should await *in vivo* absorption study in man.

Keywords□Oral drug delivery system, DDS, controlled release, acetaminophen, membrane-coating, polyvinylchloride (PVC), microporous membrane, dissolution test, zero-order release, core tablets, PVC/sucrose ratio, particle size, stability of membrane, pH-independency.

Oral administration is very convinient and safe way to deliver a drug into the systemic circulation. However, it has also some disadvantages over the other administration routes such as intravenous injection; 1) Constant absorption may not occur if either the drug dissolution from the dosage form or the absorption rate constant of the drug in the gastrointestinal (GI) tract is affected by the pH change in the GI tract. 2) Drug is susceptable to first-pass metabolism or hydrolysis in the GI tract. 3) Drug absorption may be affected by the meal. 4) Bioavailability problem may occur if the dosage form pass by the absorption site before the drug is released completely. Therefore, it is rather difficult to develop an oral drug delivery systems (DDS) which can maintain the effective blood concentration level for a sufficiently long time.

Controlled DDS for oral administration can be divided into osmotic pressure-controlled DDS[1-5], hydrodynamic pressure-controlled DDS[6] and membrane diffusion-controlled DDS[7-16]. Membrane diffusion-controlled DDS can be subdivided into seven groups; *i.e.*, microporous membrane-controlled tablet[7-10], solubility membrane-controlled tablet[11], enteric coating-controlled tablet[12], multialaminated sustained release tablet[13], pH-independent controlled release granules[14-16], polymer-coated drug-resin preparation[17, 18] and thixotropic bilayer system[19].

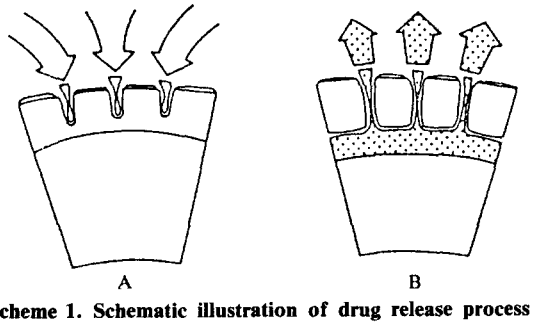
On the other hand, intragastric floating tablets[20-24] and enzyme-digestible swelling hydrogels[25-27] have been designed in order to extend the drug absorption period by retaining the dosage form at the site of

§ To whom correspondence should be addressed.

absorption. Some studies report chemical ways to protect the drug from the first-pass metabolism[28-30].

Oral DDS has been studied by ourselves for several years[25-27, 31-34]. As a consequence, it was found that microporous membrane-controlled tablet[7-10] is very easy to prepare and releases isonicotinic acid hydrazide with zero-order rate[9]. This method was firstly reported by Kalistrand and Ekman[8]. The tablet consists of highly water-soluble core tablet and water-insoluble polymer membrane coated on it. Highly water-soluble substance such as sucrose[8, 9] calcium carbonate or calcium phosphate[10] is dispersed in the membrane. Polyvinylchloride (PVC, polymerization degree = 1000)[7-9] or styrene-butadiene latex[10] is usually chosen as a membrane-forming polymer. Water soluble substance dispersed in the membrane dissolves in the GI fluid when the DDS is administered, and makes pores across the membrane. Through the pores, water penetrates into the core tablets and dissolves the drug in it. The dissolved drug diffuses out from the inside of the membrane to the GI fluid *in vivo*. It was schematically illustrated in Scheme 1.

In this study, controlled release oral DDS of acetaminophen (AAP) was prepared using this membrane-coating technique[8, 9] and evaluated pharmaceutically. AAP was selected since more than 85% of dose is absorbed from the fasted stomach within 20 minutes [35-38], and its biological half-life in the blood is only 2 hours[39]. Actually, development of sustained-release preparations of AAP have been tried by several investigators[10, 40-45]. We are trying to develop an oral DDS which maintain the plasma AAP concentration over 3 μg/ml for 8 hours. The concentration (3 μg/ml) was selected as a goal to maintain since 2.4 – 6.4 μg/ml[46] rather than 10 – 20 μg/ml[47] has been reported recently as an effective concentration of AAP.



Scheme 1. Schematic illustration of drug release process from the membrane-coated tablets through the pores formed in the membrane.

(A): Water dissolves out sucrose particles and makes porous channels in the membrane, (B) water penetrates into the core tablets and dissolves drug in the core tablets and dissolved drug diffuses out via the pore channels.

EXPERIMENTS

Materials

Acetaminophen (KPV, Dan-Il Chem.), lactose (DMV Veghel Holland), calcium carbonate (Toyo Filler), Avicel pH 101 (Asahi Chem.), polyvinylpyrrolidone (PVP K-30, GAF), Tween-80 (Nihon Yusi), Crospovidone NF (GAF), PEG 600 (Nihon Yusi), magnesium stearate (Wadoku Chem.), polyvinylchloride (PVC, polymerization degree = 1100, Wako), sucrose (Samyang), calcium pyrophosphate (Junsei), dium hydroxide (Tedia), kalium chloride (Wako), citric acid (Wako), hydrochloric acid (Merck), methylethylketone (Yakuri Pure Chem.), ethyl alchol (Merck) and othe reagent were pharmaceutical or reagent grade and were used without further purfication.

Design of controlled release characteristics

DDS was designed in order to satisfy the following dissolution characteristics on the assumption that AAP is rapidly absorbed from the GI tract after oral administration. The zero-order release rate of AAP from the DDS, K_o, which is necessary to maintain the effective plasma concentration, C', at steady-state is calculated from the relationship

$$K_o = CL_s \cdot C' \qquad \text{(Eq. 1)}$$

if AAP is completely absorbed into the systemic circulation. CL_s in Eq. 1 means the systemic clearance of AAP in the body.

AAP content that should be contained in the tablet to maintain C' for T hours, which is called Maintaining Dose (MD), is calculated as

$$MD = K_o \cdot T \qquad \text{(Eq. 2)}$$

In this study, respective literature values of 16 *l*/kg/h and 3 mg/ml for CL_s and C'[47] were used to calculate K_o. MD was calculated for 8 h of maintaining hours. As a consequence, 48 mg/h of K_o and 384 mg of MD were yielded. Since the relased AAP from the tablet is not absorbed completely from the GI tract, actual K_o and MD must exceed the above calculated values to maintain 3 μg/ml of plasma AAP concentration for 8 h. Trial and errors were repeated in order to prepare the membrane-coated tablets whose dissolution characteristics fulfills the above requirement.

Preparation of membrane-coated AAP tablets

(A) Preparation of AAP Core Tablets: Core tablets of various composition (Table I) were prepared

Table I. Formulations of acetaminophen core tablets

	Formula No									
	1	2	3	4	5	6	7	8	9	10
Acetaminophen	500	500	350	350	350	350	350	350	350	350
Lactose	–	–	70	125	–	125	125	125	125	125
Ca-carbonate	–	–	–	–	125	–	–	–	–	–
Avicel 101	–	–	70	–	–	–	–	–	–	–
PVP K-30	15	15	15	15	15	15	15	15	15	15
Tween 80	5	5	5	5	5	5	5	–	2.5	10
Crospovidone	5	5	5	5	5	5	–	–	–	–
PEG 6000	25	25	25	50	50	50	50	50	50	50
Mg-stearate	–	–	–	–	–	0.5	0.5	0.5	0.5	0.5

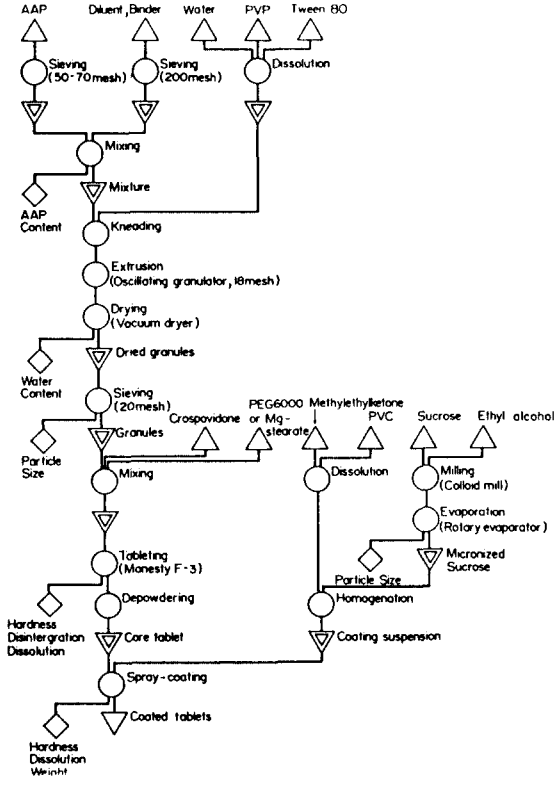


Fig. 1. Manufacuring procedure of membrane-coated tablets of acetaminophen.

according to the wet granulation method as described in Fig. 1. AAP contents in each formulations were 500 mg for No.1-2 tablets and 350 mg for No.3-10 tablets.

About 80% of the AAP powder was in the range of 50-70 mesh in size. AAP powder was mixed with some adjuvants such as lactose (<200 mesh), Avicel pH 101 and calcium carbonate. The mixture was kneaded with 60% (w/v) water solution of PVP. In most cases, PVP solution contained Tween 80 as specified in Table I. The kneaded mass was extruded through 18 mesh sieve using oscillating granulator (Merck, AR-400). Then the resultant granules were dried in the vacuum dryer (VWR Science, VWR 430) until the moisture content reduces to 0.4-0.6% (w/w). The moisture was determined by F-IR moisture tester (Kett Electric Lab). The moisture content in the granules was critical factor in the compressing process, *i.e.*, capping occurred when it was below 0.5%, while sticking occurred when it was over 0.6%.

The dried granules were passed through a sieve (20 mesh) and mixed with Crospovidone (disintergrator) and PEG 6000 or magnesium stearate (lubricant) as specified in Table I. The the mixture was compressed by the tableting machine (Manesty, F-3). The obtained tablets were concave and were 6.0 mm in height and 12.0 mm in diameter.

(B) Membrane Coating on Core Tablets: Core tablets (lot size 1,000 tablets) thus prepared were spray-coated in the rotating coating pan (20 rpm) with coating suspensions of different composition (Table II).

The coating suspension was prepared by dissolving PVC (n = 1100) in methylethylketone at 60°C and dispersing the micronized sucrose particles in the solvent. PEG 6000 and magnesium stearate were also added to the suspension. The micronized sucrose was prepared by milling the commercial sucrose (Samyang) in the colloid mill (Koruna, LAES 716-2F) with the aid of ethylalcohol and evaporating subsequently the ethylalcohol in the rotary evaporator (Buchi, 461). Spray-coating in the Uni Glatt coating machine was found to blow some sucrose particles out of the machine due to the reduction of the inner pressure and rapid air flow. Therefore, Uni Glatt coating machine was not chosen in this study in spite of its well-known efficiency in general cases.

Table II. Formulations of coating suspensions (mg/tablet)[a]

Formula No.	A	B	C
PEG 6000	50	50	50
Mg-streate	0.5	0.5	0.5
PVC : Sucrose	1 : 9	1.5 : 8.5	2 : 8

[a] Coating was performed on the core tablet of Formula-6 in Table I.

Table III. Pharmaceutical characteristics of core tablets

Formula No.	1	2	3	4	5	6	7	8	9	10
Moisture content (%)	0.6	0.6	0.4	0.5	0.5	0.4	0.5	0.6	0.6	0.4
Weight (mg)	550.3	386.0	552.4	549.6	550.7	551.2	544.9	542.8	542.9	544.2
	*1.9	*2.1	*1.9	*5.0	*4.1	*3.1	*4.1	*2.1	*2.3	*3.3
Hardness (K_p)	11.3	8.0	7.5	16.9	7.1	8.0	3.9	8.4	6.7	3.5
	*1.7	*0.8	*1.4	*3.2	*1.8	*1.0	*0.3	*0.7	*0.6	*0.3
Disintergration time (min)	8 – 12	8 – 12	2	16 – 20	7 – 10	7 – 9	18 – 22	26 – 30	20 – 23	13 – 16
100% Dissolution time (min)	30 – 40	30 – 40	30 – 40	25 – 40	30 – 40	25 – 50	110 – 140	160 – 190	140 – 160	80 – 100

Pharmaceutical evaluation of membrane-coated AAP tablets

Some pharmaceutical characteristics such as moisture content, hardness, disintegration time and dissolution kinetics were determined for the core or membrane-coated tablets. Effect of adjuvants, particle sizes of AAP and sucrose, pH of the dissolution medium, sucrose/PVC ratio in the coating suspension, and the coated weight on the dissolution kinetics of the membrane-coated tablets were also examined. Hardness was determined by hardness tester (Scheuniger, 2E). Disintegration test was performed according to KP V using disintergration tester (Fine Science Lab., DT-4). Dissolution test was performed by the dissolution tester (Hanson Research, 276-a) according to the rotating-basket method (50 and 100 rpm) of KP V at 37 ± 0.5°C. 900 m*l* of buffer solutions (pH 1.2, 5.8 and 7.2) were used as dissolution media. Released AAP was determined spectrophotometrically at 245 nm. Stability of the coated membrane was tested by shaking 70 coated tablets in the 250 m*l*-seperatory funnel filled with 150 m*l* of tap water for 2 hours. Broken membranes were counted and the stability was expressed as the percentage of the tablets whose membrane remained intact.

RESULTS AND DISCUSSION

Pharmaceutical characteristics of core tablets

Table III shows some pharmaceutical characteristics of the core tablets. Core tablets prepared with Crospovidone (Formula-1 ~ 6) showed faster disintergration and faster AAP release than core tablets prepared without Crospovidone (Formula-7 ~ 10). It seems to be due to disintergrating effect of Crospovidone. Magnesium stearate does not seem to be the cause of the above difference, since Formula-6 which contains magnesium stearate did not show any difference in disintergration and AAP release from Formula-4 which does not contain magnesium stearate at al. Sticking problem caused by PEG 6000 (Formula-1 ~ 5) in the tableting process could be alleviated by the addition of magnesium sterate (Formula-6 ~ 10). Comparing the core tablets of Formula-7 ~ 10, the hardness seems to decrease as the content of Tween 80 in the tablets increases.

Strength of the membrane

Coated membrane is composed of water-insoluble polyvinylchloride (PVC) film and micronized sucrose particles dispersed in it. The sucrose particles in the membrane will dissolve out and make pores across the membrane in the water medium. Through the pores, water penetrates into the core tablet and dissolves AAP in it. AAP dissolved by the penetrated water will leak out of the membrane through the pores (Scheme 1). Since the micronized sucrose dissolves quickly in the aqueous medium and has no toxicity, it seemed appropriate as pore-forming material. The polymerization degree of PVC used in this study was about 1,100 and it yielded a membrane of faily good strength. The apparent shape of the membrane of the coated tablet was maintained unchanged after the dissolution test except for the tablets prepared by Formula-3 and 5. The strength of the membrane increased as the PVC/sucrose ratio or the weight of the membrane increased (Data are not shown). Membranes coated on the core tablet of Formula-3 or 5 was broken during the dissolution test possibly due to the swelling of the Avicel pH 101 and calcium carbonate in the core tablet.

Dissolution characteristics of AAP from the membrane-coated tablets

Drug release from the membrane-coated tablets can be explained by the diffusion of the drug out of the core tablets through the pores formed across the PVC membrane. Thus Fick's diffusion law can be

adopted for the AAP release process from the tablet.

$$dM/dt = D \cdot (C_s - C_u) \cdot A/h \quad \text{(Eq. 3)}$$

where dM/dt, D, A, h, C_s and C_u represent dissolution rate, diffusion rate coefficient, surface area of the membrane, height of the diffusion barrier (membrane), AAP concentration inside the membrane and AAP concentration in the dissolution medium respectively. AAP concentration inside the membrane (C_s) can be assumed to be much higher than AAP concentration in the dissolution medium (C_u) at the earlier stage of dissolution test, *i.e.*, so-called sink condition holds. Then, Eq. 3 can be simplified as follows at that stage.

$$dM/dt = D \cdot C_s \cdot A/h \quad \text{(Eq. 4)}$$

The dissolution rate will become constant irrespective of the time as long as D, C_s, A and h do not change during the test.

Fig. 2 shows the representative profiles of AAP release from the membrane-coated tablets. In every case, zero-order release kinetics was observed until upto 90% of the total AAP in the tablet was released. It implies that the dissolution process can be explained by Eq. 4 and that all the assumptions adopted in Eq. 4 also hold at the range of <90% release. The dissolution rates in Fig. 2 decreased at the terminal phase of the test. It can be explained most probably by the decreased C_s due to the release of the most drugs in the core tablet into the dissolution medium. Zero-order release rate (%/h) of AAP from various membrane-coated tablets were read from the each dissolution graphs (not shown) and were summarized in Table IV. The release rate ranged from 6.0-15.3%/h (30-76.5 mg/h) according to the preparation conditions and rotating speed of the basket. Therefore, zero-order release rate (K_o=48 mg/h) designed in the EXPERIMENT section could be attained.

Effect of lactose and Crospovidone in core tablets on AAP release from the membrane-coated tablets

Lactose contained in the core tablets was found to accelerate AAP release from the membrane-coated tablets comparing the drug release rates of 30 mg-coated tablets of Formula-1 (6.1%/h) and Formula-4 (16.8%/h) at 50 rpm (Table IV), since Formula-4 is same to Formula-1 in composition except lactose (Table I). It seems to be due to increased wetting of AAP by lactose through forming hydrophilic matrix[48, 49] within the core tablets.

Contrary to the case of core tablets (Table III), Crospovidone decreased the release rate of AAP from the membrane-coated tablets (compare Formula-6 and Formula-7 in Table IV). Formula-6 is same to Formula-7 in composition except Crospovidone (Table I). It might be explained as follows: AAP is entrapped in the void volume of Crospovidone when they are mixed and compressed to core tablets. Crospovidone in the coated tablets forms a matrix structure and acts as a diffusion barrier for AAP in the dissolution medium[50]. However, in the case of core tablets, the barrier can not be formed since the tablets are disintergrated rapidly by Crospovidone. This may be the reason why the core tablets prepared with Crospovidone show faster disintegration and release (Table III), while Crospovidone in the coated tablets decreases

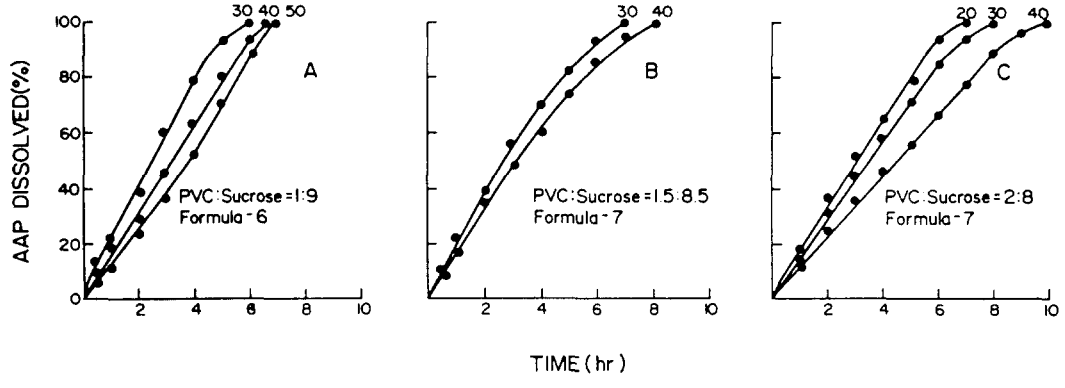


Fig. 2. Dissolution of acetaminophen from the membrane-coated tablets.
(A); Formula-6 tablets coated with PVC/sucrose ratio of 1:9, (B); Formula-7 tablets coated with PVC/sucrose ratio of 1.5:8.5, (C); Formula-7 tablets coated with PVC/sucrose ratio of 2:8. Dissolution test was performed by rotating basket method (100 rpm) at pH 5.8 and 37±0.5°C. Numbers in the figures indicate the weight of coated membrane (coat weight, mg) per each tablets.

Table IV. Zero order release rate (%/hr) of acetaminophen from various membrane-coated tablets[a]

Formula No		1	2	4	6					7		8	9	10
Acetaminophen Content (mg)		500	500	350	350	350	350	350	350	350	350	350	350	350
PVC/Sucrose		1/9	1/9	1/9	1/9	1.5/8.5	2/8	2/8	2/8	2/8	1.5/8.5	2/8	2/8	2/8
PEG (%)		–	–	–	–	–	–	10%	20%	–	–	–	–	–
Basket rpm	Coat Weight (mg)													
50	20	7.6	10.9	–[b]	–	–	7.6	7.8	10.1	10.6	–	–	11.0	12.5
	30	6.1	9.3	16.8	14.6	8.5	6.0	6.1	7.3	–	–	–	8.5	9.7
	40	–	–	13.0	11.0	–	–	–	–	–	–	–	–	–
	50	–	–	11.8	9.3	–	–	–	–	–	–	–	–	–
100	20	10.	13.4	–	–	15.7	9.7	11.9	14.0	15.3	–	11.5	13.5	15.5
	30	8.7	12.0	–	19.5	13.8	6.7	8.1	11.5	13.5	15.5	8.7	9.5	11.1
	40	–	–	–	16.1	–	–	–	–	10.5	13.3	8.5	–	–
	50	–	–	–	12.9	–	–	–	–	–	–	–	–	–

[a] Dissolution test was performed using pH 5.8 buffer at 37±0.5°C (n=6). Tablets of Formula-3 and 5 were excluded since their membranes were broken by swelling during the test. Sucrose was micronized to <30 μm in particle size except for Fomula-1, of which particle size was about 100 μm.

[b] Not determined.

the drug release rate (Table IV).

Effect coat weight, PVC/sucrose ratio and particle size of sucrose on AAP release from the membrane-coated tablets

Fig. 2 also shows that the zero-order release rate of AAP decreases as the weight of the coated membrane (coat weight) per tablet increases from 20 to 50 mg. This phenomenon can also be seen in Table IV. It can be explained by the increased tortuosity of the membranes as the coat weight increased. Increased tortuosity may increase h in Eq. 4 almost linearly. Then, h in Eq. 4 can be replaced by the coast weight as follows,

$$dM/dt = D \cdot C_s \cdot A / Coat\ Weight \qquad \text{(Eq. 5)}$$

Since, D, C_s and A do not seem to vary during the dissolution process mentioned before, Eq. 5 can be simplified as

$$dM/dt = K / Coat\ Weight \qquad \text{(Eq. 6)}$$

where K is an unvariable constant. If all the assumption adopted here hold, the plot of release rate against $1/Coat\ Weight$ will yield a straight line that cross the origin with a slope of K. Fig. 3 shows the plot of the release rates from Formula-7 tablets (Table IV; 350 mg, 2:8, 100 rpm) against $1/Coat\ Weight$. The plots showed good linearity as expected from Eq. 6 for all the pH conditions examined. However, each line in Fig. 3 did not pass the origin and intercepted y axis. This discrepancy might be due to the nonlinear relationship between *Coat Weight* in Eq. 5 and height of the diffusion barrier (h) in Eq. 4.

The effect of PVC/sucrose ratio on AAP release were tabulated in Table IV and examplified in Fig. 4. As the sucrose portion in the PVC-sucrose mixture increased, the release rate of AAP through the membrane increased. It can be explained by the increased porosity and subsequently increased diffusion rate coefficient (D) of the membrane as sucrose/PVC ratio increased.

Particle size of sugar in coating suspension also affected the release rate of AAP from the membrane-coated tablets as shown in Formula-1 and 2 in Table IV. They differed only in the particle size of sucrose in the coated membrane; *i.e.*, sucrose particle of 100 μm in approximate diameter were used in Formula-1, while sucrose particles not larger than 30 μm were used in Formula-2. All samples of Formula-1 showed slower release of AAP than those of Formula-2. It may be due to the increased number of sucrose particles in the membrane of Formula-2 tablets. Increased number of sucrose particles in the membrane will increase both porosity and tortuisity of the mem-

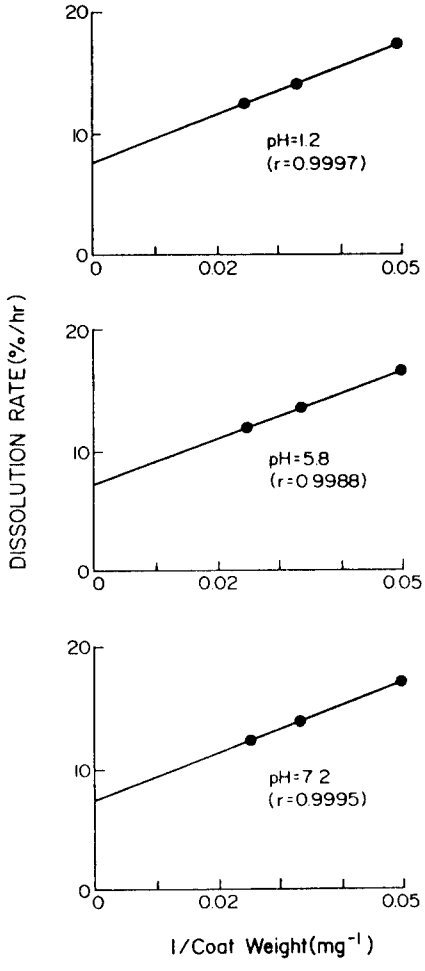


Fig. 3. Plot of release rate (%/h) *vs* coat weight according to Eq. 6. Data were taken from Table IV.

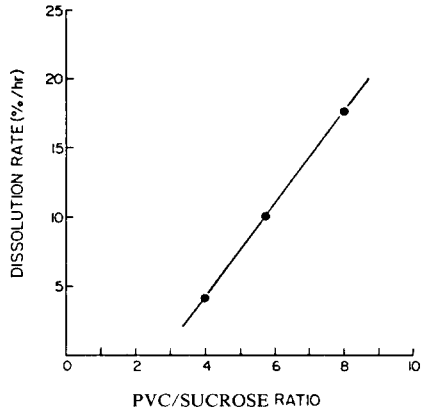


Fig. 4. Effect of PVC/sucrose ratio of the membrane on AAP release (%/h) from the membrane-coated tablets.

(Formula-6, coat weight 30 mg, rotating basket method at 37±0.5°C, 100 rpm).

brane. Generally, increased tortuisity of the membrane will decrease the release rate of AAP through the membrane, while increased porosity will increase the release rate. Since the release rate from the tablets coated with smaller sucrose particles (Formula-2) was larger than that from Formula-1 tablets, diffusion of AAP through a thin PVC membrane seemed to be affected more profoundly by the porosity of the membrane than by the tortuosity of it.

Stability of the membrane of the membrane-coated tablets

The membrane of the tablets should not be broken in the GI tract before the drug contained inside the membrane is released out completely. The stablity data of the membrane are summarized in Table V. Membranes of Formula-1 ~ 5 tablets were very weak and broken during the dissolution test. Membranes thicker than 30 mg/tablet showed very good stability.

Effect of pH of the release medium on AAP release from the tablets

Fig. 5 shows the effect of pH of the release medium on the zero-order release rate of AAP from the

Table V. *In vitro* stability of the membranes of the coated-tablets[a]

Coat Weight (mg/tablet)	Formula No	6				7	8	9	10
	PVC/Sucrose	1.5/8.5	2/8	2/8		2/8	2/8	2/8	2/8
	PEG (%)	–	–	10	20	–	–	–	–
20		85	100	86	34	100	77	100	100
30		94	100	98	64	100	100	100	100
40		100	100	100	89	100	100	100	100

[a] Expressed as percentage of unbroken tablets among 70 tablets after 2 hr-shaking in 250 m*l*-separatory funnel filled with 150 m*l* of tap water.

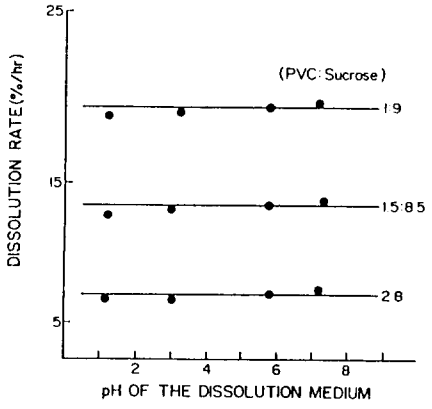


Fig. 5. Effect of pH of the dissolution medium on the zero-order release rate (%/h) of AAP from membrane-coated tablets.

Dissolution test was performed according to KP V basket method at 37±0.5°C and 100 rpm. Coat weights on the core tablets (Formula-6) were 30 mg per tablets.

tablets of different coat weight. The release rate decreased as the coat weight increased as shown in Fig. 3, however, it did not change irrespective of the pH change of the release medium from 1.2 to 7.2. It implies that parameters as like D, C_s, A and h in Eq. 4 are not changed by the pH change. Among those parameters, A and h are the physically unvariable parameters. Therefore, the pH independency of the release shown in Fig. 5 indicates that D and C_s are not changed by the pH of the release medium. D and C_s of a tablet will be actually constant if the solubility of the sucrose particles in the membrane and that of AAP in the core tablets are not affected profoundly by the pH change of the release medium. However, conclusions as to this point must await the experiment measuring the solubilities of the sucrose and AAP at respective pH conditions.

pH-independent release characteristics may be very benificial to achieve constant release of drug in the gastrointestinal (GI) tract, where pH varies from about 1-2 to about 7-8 according to the position of the GI tract. Constant release of drug throughout the overall GI tract may result in constant absorption of the drug throughout the overall GI tract, if either the drug absorption rate (K_a) is constant throughout the GI tract, or K_a is much larger than the *in vivo* release rate of the drug, *i.e.*, release process is the rate-determining step of the overall drug absorption process. It would be verified by the *in vivo* absorption experiment.

In conelusion, the magnitude of the zero-order release rate of AAP from the membrane-coated tablets seemed to be controllable in a pH-independent manner by controlling mainly the PVC/sucrose ratio (Formula-6 or 7 in Table IV) and coat weight of the membrane.

ACKNOWLEDGMENT

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