Effects of Bases and Additives on Release of Carbon Dioxide from Effervescent Suppositories[1)]

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For the formulation of effervescent suppositories containing sodium bicarbonate and anhydrous sodium dihydrogen phosphate, the effects of bases and additives on the release profiles of carbon dioxide, CO_2, from the suppositories were studied by an *in vitro* release test using a gas burette. The suppository bases employed were Witepsol® H-15, W-35 and E-85, and the additives were Aerosil® 200 and soybean lecithin. The melting points and viscosities of the suppositories were also measured to interpret the CO_2 release profiles.

The rate and amount of CO_2 released from suppositories prepared with bases having different melting points and hydroxyl values decreased with increasing melting point and decreasing hydroxyl value. The addition of Aerosil® 200 to the suppository bases considerably reduced the rate and amount of CO_2 released owing to the increasing viscosity of the melted bases, while the addition of soybean lecithin to those bases increased the rate and amount of CO_2 released because of the improved wettability. Thus, the release profiles of CO_2 from the effervescent suppositories were considerably influenced by the hydroxyl values related to the contents of mono- and di-glycerides, the melting points of the bases, Aerosil® 200 and soybean lecithin.

This suggests that the rate and amount of CO_2 released from the suppositories can be freely controlled by the combination of these various factors.

Keywords effervescent suppository; carbon dioxide; release profile; sodium bicarbonate; Aerosil; lecithin

Effervescent suppositories containing sodium bicarbonate, $NaHCO_3$, and anhydrous sodium dihydrogen phosphate, NaH_2PO_4, as active ingredients have been used as laxatives for constipation therapy. When these suppositories have been melted in a release test fluid, carbon dioxide, CO_2, is released from them by the neutralization of $NaHCO_3$ and NaH_2PO_4

Since $NaHCO_3$ and NaH_2PO_4 are solid inorganic salts, these active ingredients are easily sedimented in a preparation process. Thus, suppository preparation first requires reduction of the sedimentation rates of $NaHCO_3$ and NaH_2PO_4 by increasing the viscosity of the melted suppository bases. Carbopol®,[2)] lactose[3)] and Aerosil®[4)] have been used as additives to the suppository bases to reduce the sedimentation rates.

$NaHCO_3$ and NaH_2PO_4 are water-soluble ingredients, so that the addition of dispersing agents such as soybean lecithin[5)] and other surface active agents to the suppository bases is effective for content uniformity.

The neutralization of $NaHCO_3$ and NaH_2PO_4 is influenced by the melting points of the suppository bases and various other factors, as well as by the additives described above. Therefore, it is important to evaluate the release profiles of CO_2 in the formulation studies of effervescent suppositories.

In a previous paper,[1)] we reported that a method referred to as method 1 for the determination of release profiles of CO_2 *in vitro* was useful in early formulation studies on effervescent suppositories. In this paper, Aerosil® 200 (AS) and SLP white® as soybean lecithin (SL) were employed as additives to the suppositories. The effects of these additives and three types of suppository bases on the release profiles of CO_2 were studied according to method 1[1)] for the release test using a gas burette. To interpret the profiles the melting points and viscosities of the suppositories were also measured.

Experimental

Materials The sources of materials used were as follows: AS from Nippon Aerosil Co., SL from True Lecithin Mfg. Co., Witepsol® H-15 (H-15), W-35 (W-35) and E-85 (E-85) from Mitsuba Trading Co. and aluminum oxide (α) for use in thermal analysis from Nishio Industries Co. All other ingredients and chemicals were JP XII grade, except NaH_2PO_4 (JSPI grade) and diethyl ether (reagent grade), and were used without further purification. The average diameter of $NaHCO_3$ and NaH_2PO_4 was 113 and 108 μm, respectively. Characteristics of the additives and the bases are summarized in Table I.

Thermal Analysis Measurements of differential scanning calorimetry (DSC) and thermogravimetry (TG) for $NaHCO_3$ and NaH_2PO_4 were made with thermal analysis apparatuses (models DSC-30 and TGA-30,

TABLE I. Characteristics of Additives and Bases

	AS	SL	H-15	W-35	E-85
Specific surface area (m^2/g)	200	—	—	—	—
Nitrogen content (%)	—	1.00	—	—	—
Phosphorus content (%)	—	3.08	—	—	—
Peroxide value	—	3.05	—	—	—
Acid value	—	25.43	0.07	0.18	0.12
Saponification value	—	—	238.0	230.5	226.0
Hydroxyl value	—	—	13.3	44.2	10.5
Melting point (°C)	—	—	34.4	34.4	42.7

TABLE II. Operating Conditions of DSC and TG

	DSC	TG
Sample	5 mg	10—12 mg
Reference	Al_2O_3(α): 5 mg	None
Atmosphere	N_2: 30 ml/min	Air
Sensitivity	±25 mJ/s	100%
Heating rate	10°C/min	10°C/min
Chart speed	10 mm/min	10 mm/min

TABLE III. Formulae of Effervescent Suppositories

Rp.	Formula							
	Active ingredient		Additive		Base			Total
	$NaHCO_3$ (mg)	NaH_2PO_4 (mg)	AS (mg)	SL (mg)	H-15 (mg)	W-35 (mg)	E-85 (mg)	(mg)
1					1352	—	—	
2					1284	—	68	
3					1217	—	135	
4					1149	—	203	
5					1082	—	270	
6					1014	—	338	
7					946	—	406	
8					879	—	473	
9			34	34	811	—	541	
10					—	1352	—	
11					—	1284	68	
12					—	1217	135	
13					—	1149	203	
14					—	1082	270	
15					—	1014	338	
16	500	680			—	946	406	2600
17					—	879	473	
18					—	811	541	
19			—		—	1386	—	
20			17		—	1369	—	
21 (10)			34		—	1352	—	
22			51		—	1335	—	
23			68		—	1318	—	
24			85		—	1301	—	
25			102		—	1284	—	
26				—	—	1386	—	
27				17	—	1369	—	
28 (10)				34	—	1352	—	
29			34	51	—	1335	—	
30				68	—	1318	—	
31				85	—	1301	—	
32				102	—	1284	—	

Shimadzu Seisakusho Co.) under the operating conditions shown in Table II.

Preparation of Suppositories The formulae of the effervescent suppositories prepared by a fusion method are shown in Table III. To prevent drug sedimentation and/or improve drug dispersion, 1.3% AS and/or SL were added to all effervescent suppositories, respectively. The suppository bases were melted in a beaker in a water bath at 45°C. SL was dissolved in the melted bases, and AS was then added. NaH_2PO_4 was slowly added into the melted bases and, finally, $NaHCO_3$. These melted mixtures were passed through an 80-mesh screen, stirred and immediately poured into plastic suppository molds (2.25 ml), which were allowed to stand overnight at 15°C to solidify the preparations.

Release of CO_2 from Suppositories The volume of released CO_2 was measured according to method 1 as described in the previous paper.[1] Figure 1 shows the apparatus employed in this method. The test fluid used as a medium was normal saline containing saturated CO_2. A weighted suppository was placed in 6 ml of the medium maintained at 37°C. The accumulated volume of CO_2 released from the suppository was measured with a 100-ml gas burette at room temperature every 5 min for 60 min. Each observed accumulated volume of CO_2 released from the suppositories was converted into the normalized accumulated volume under the following constant conditions: 25°C; per 2.6 g of suppository.

Measurement of Melting Points After a piece of suppository was melted at about 40°C in a beaker, it was stirred, and then drawn into a capillary tube to a depth of about 10 mm. The charged tube was allowed to stand for at least 1 h in ice to solidify. The melting points of the suppositories were measured by an open capillary tube method (method 2), according to JP XII.

Measurement of Viscosities The viscosities of the melted suppositories and the melted bases in the absence of $NaHCO_3$ and NaH_2PO_4 were measured using a cone and plate viscometer (model, E, Tokyo Keiki Co.) at 37°C. The share rate and the amount of sample were 151 s^{-1} and 1.7 g, respectively.

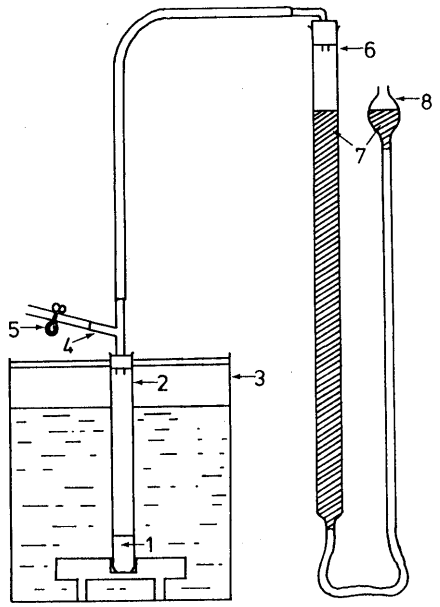

Fig. 1. Schematic Illustration of Apparatus Employed in Method 1 for Release Test

1, medium; 2, test tube; 3, thermostatic bath; 4, by-pass; 5, pinch cock; 6, gas burette; 7, light liquid paraffin; 8, leveling bulb.

Evaluation of Sedimentation of Drugs The amount of insoluble particles ($NaHCO_3$, NaH_2PO_4 and AS) remaining in 1 g of the upper portion of the suppositories was determined by three extractions of W-35 and SL

with 6 ml each of diethyl ether followed by vacuum drying. Sedimentation of the drugs was evaluated by the residual percent of the particles remaining in the upper portion of these suppositories.

Results and Discussion

Thermal Analysis of $NaHCO_3$ and NaH_2PO_4 In order to confirm the preparation conditions of the effervescent suppositories, measurements were made of DSC and TG for $NaHCO_3$ and NaH_2PO_4. Figure 2 shows the DSC and TG curves of $NaHCO_3$. A small endothermic peak and 0.5% weight loss were observed in the curves at 93°C, respectively. These changes are based on the evaporation of attached water from $NaHCO_3$. $NaHCO_3$ subsequently exhibited a large endothermic peak and 35.5% weight loss in the DSC and TG curves in the range of about 110 to 190°C, respectively. These changes are based on the decomposition of $NaHCO_3$ as described in Eq. 1.

$$2NaHCO_3 \rightarrow Na_2CO_3 + H_2O + CO_2 \quad (1)$$

The weight loss in the TG curve was in good agreement with the theoretical value: $(H_2O+CO_2)/2NaHCO_3 \times 100 = 36.9\%$. These findings indicate that care must be taken with the temperature in the process of preparing suppositories because $NaHCO_3$ decomposes rapidly when heated above 100°C. Thus, the temperature was set at 45°C. Even E-85, which has the highest melting point (42—44°C) of the suppository bases employed in this study melts sufficiently at that temperature.

Figure 3 shows the DSC and TG curves of NaH_2PO_4. A sharp endothermic peak and 7.0% weight loss, respectively, were observed in the range of about 200 to 225°C. These changes are due to the conversion of NaH_2PO_4 into disodium dihydrogen pyrophosphate accompanying the rapid evaporation of water as described in Eq. 2.

$$2NaH_2PO_4 \rightarrow Na_2H_2P_2O_7 + H_2O \quad (2)$$

The weight loss in the TG curve agreed very closely with the theoretical value: $H_2O/2NaH_2PO_4 \times 100 = 7.5\%$. These findings indicate that NaH_2PO_4 is more stable when heated than $NaHCO_3$, so that the latter was mixed in last in the preparation process.

Effect of Suppository Bases on Release of CO_2 from Suppositories Two kinds of suppository bases with low and high melting points are usually mixed to allow the suppositories to have an optimum melting point. In this

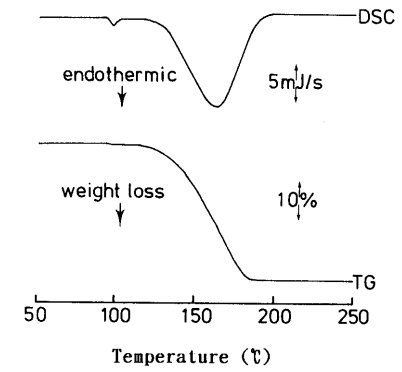

Fig. 2. DSC and TG Curves of $NaHCO_3$

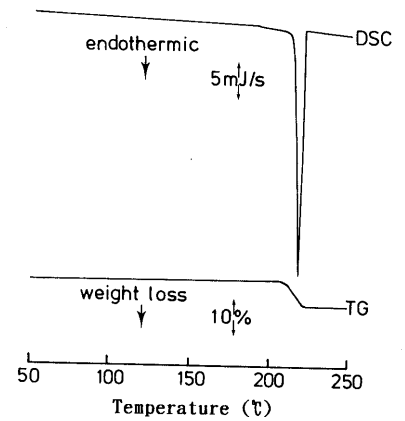

Fig. 3. DSC and TG Curves of NaH_2PO_4

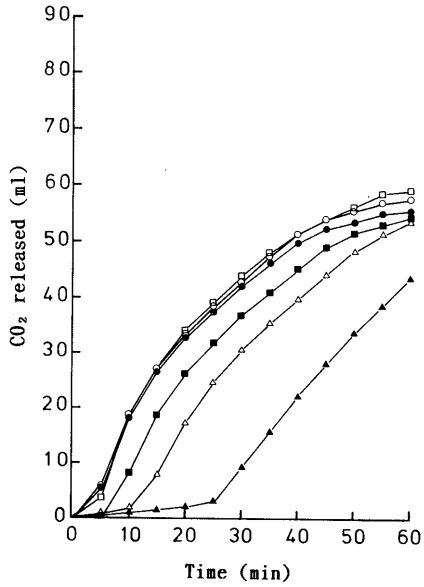

Fig. 4. Effect of E-85 on Release Profile of CO_2 from Suppository Prepared Using H-15 and E-85

Amount of E-85 in base: (○) without, (●) 10%, (□) 20%, (■) 30%, (△) 35%, (▲) 40%.

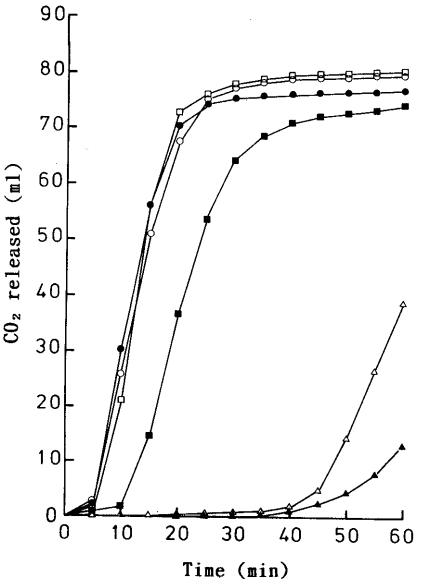

Fig. 5. Effect of E-85 on Release Profile of CO_2 from Suppository Prepared Using W-35 and E-85

Amount of E-85 in base: (○) without, (●) 10%, (□) 20%, (■) 30%, (△) 35%, (▲) 40%.

study, either H-15 or W-35 and E-85 were employed as the bases with low and high melting points, respectively. Figure 4 shows the release profiles of CO_2 from the various suppositories prepared using H-15 and E-85. Where the amount of E-85 in the bases was 20% or below, the release profiles of CO_2 were not altered by a change in E-85. When the amount of E-85 was 30% or above, however, a lag time was observed in the release of CO_2 from the suppository. With 40% E-85, the lag time was considerably prolonged. These findings suggest that the increase in lag time is based primarily on the rising melting point of the suppository bases.

Figure 5 shows the release profiles of CO_2 from the various suppositories prepared using W-35 and E-85. Where the amount of E-85 in the bases was 20% or below, the release profiles were not significantly altered by a change in E-85, similar to the suppositories containing H-15 and E-85. The release profiles of the suppository with 30% E-85 began to be influenced by the temperature of the medium (37°C), and the lag times were rapidly prolonged. On the whole, the rates and amounts of CO_2 released from the suppositories prepared using H-15 and E-85 were lower than those from the suppositories prepared using W-35 and E-85. These results suggest that the rate of neutralization of $NaHCO_3$ and NaH_2PO_4 is accelerated with monoglyceride in W-35,[6] because the monoglyceride acts as a surface active agent.

Figure 6 shows the effects of E-85 on the melting points and viscosities of the suppositories. The melting points of the bases containing AS and SL are similarly plotted as a function of the amount of E-85. The melting points of both suppositories rose linearly with increasing E-85, and were about 1°C higher than those of the bases without $NaHCO_3$ and NaH_2PO_4, because a large amount of insoluble these two materials (about 45%) was present in the bases. The melting points of the suppositories containing $NaHCO_3$ and NaH_2PO_4 were thus found to be the apparent melting points.

The viscosities of both suppositories containing H-15 and W-35 as the main bases were not altered by change in E-85 over the E-85 range of 0—30% and 0—20%, respectively, whereas they began to increase rapidly at each point of 35% and 30% E-85, respectively. The amounts of E-85 where the melting points of the bases exceeded 37°C were also 35% and 30%. Therefore, the rapid increase in the viscosities of the suppositories is based on the increasing solid phase in the bases at 37°C. The result that the lag time in the release of CO_2 from the suppositories containing W-35 is longer than that from those containing H-15 is due to the difference in the suppository melting points as shown in Fig. 6.

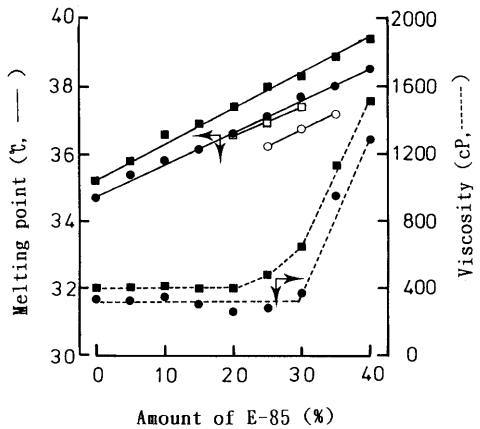

Fig. 6. Effect of E-85 on Melting Point of Suppository or Base and Viscosity of Suppository

Suppository: (●) H-15 and E-85, (■) W-35 and E-85. Base: (○) H-15 and E-85, (□) W-35 and E-85.

Effect of Additives on Release of CO_2 from Suppositories

AS employed in this study as an additive is chemically inert to active ingredients and other additives; it dose not irritate the rectal mucosa,[4b] and reduces the sedimentation rates of these active ingredients in the melted bases owing to the increasing viscosity of the bases. SL, another additive, is a highly safe dispersing agent, and hydrogenated SL is effective in sustained-release suppositories.[7]

Figures 7 and 8 show the effect of the additive on the release profiles of CO_2 from suppositories containing a given amount (1.3%) of SL or AS, respectively. In the preparation of these suppositories, only W-35 was used as an effective base. The release of CO_2 from the suppository without AS was very rapid and reached the highest plateau after 10 min. The release rate of CO_2 from the suppositories containing AS decreased with increasing amount of the additive. The suppositories with AS of 2.6% or above showed typical slow-release profiles. Thus, the addition of AS to effervescent suppositories was found to be more effective in reducing the release rate than in diclofenac sodium[4b] and sulpyrine[8] suppositories. In the present study, the volume of CO_2 produced by the neutralization of $NaHCO_3$ with NaH_2PO_4 was measured following drug release from the suppositories. The release of CO_2 from the effervescent suppositories therefore seems to be more significantly influenced by AS. These findings indicate that the release rates of CO_2 are considerably influenced by the viscosity of the melted bases as reported in several papers.[9] On the other hand, the rapid release of CO_2 from the suppository without AS also seems attributable to the drug sedimentation as described below, because the

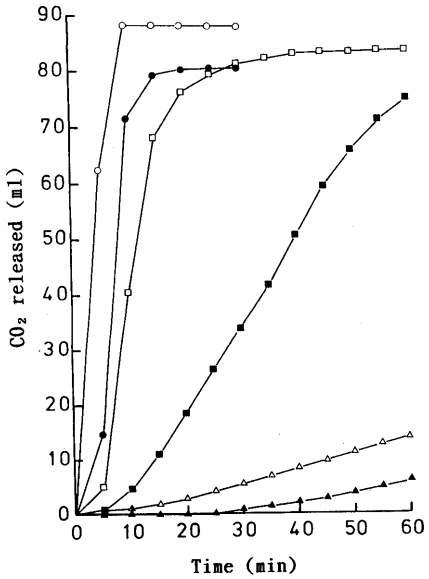

Fig. 7. Effect of AS on Release Profile of CO_2 from Suppository

Amount of AS: (○) without, (●) 0.65%, (□) 1.3%, (■) 1.95%, (△) 2.6%, (▲) 3.9%.

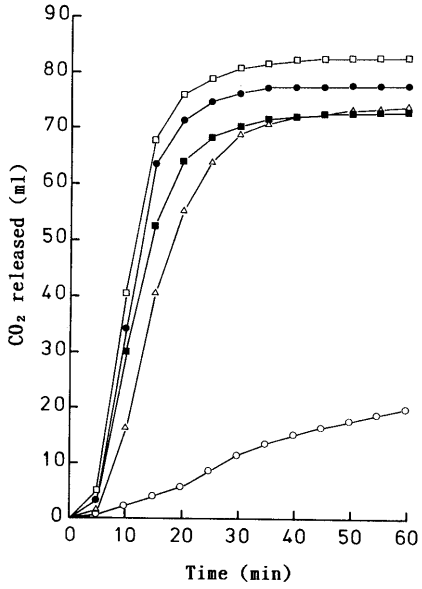

Fig. 8. Effect of SL on Release Profile of CO_2 from Suppository
Amount of SL: (○) without, (●) 0.65%, (□) 1.3%, (■) 2.6%, (△) 3.9%.

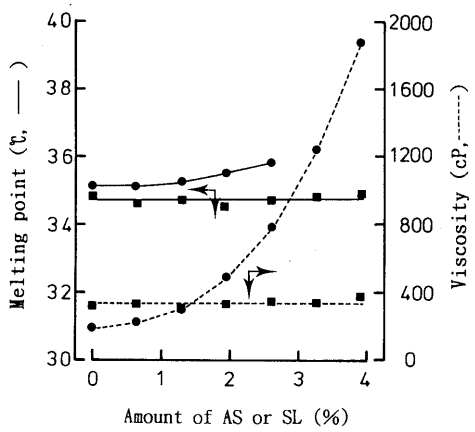

Fig. 9. Effect of Additive on Melting Point and Viscosity of Suppository
Additive: (●) AS, (■) SL.

sedimented drugs are easily dissolved in the test fluid.

The rates and amounts of CO_2 released from the suppositories without SL were significantly lower than those from the suppositories with SL. Therefore, SL as a dispersing agent was found to accelerate the release rate of CO_2 owing to the enhanced wettability. When the amount of SL was 1.3% or more, the release rates of CO_2 tended to decrease with increasing amount of SL. From this, the enhancement of the wettability appears to be terminated at 1.3% SL, while the foaming power and stability of foams made by CO_2 released from the suppositories in a test tube increase with an increase in SL amount. $NaHCO_3$ and NaH_2PO_4 thus become more effectively incorporated into the foams. From this, the reaction rate of $NaHCO_3$ with NaH_2PO_4 is considered to decrease with increasing amount of SL.

Figure 9 shows the effects of the additives on the melting points and viscosities of the suppositories. The melting points rose slowly with increasing amount of AS over the range of 0—2.6%. The melting points of the suppositories containing AS at 3.25% or above could no longer be measured because the viscosities of the melted suppositories were so great that the melted suppositories did not go up the capillary tubes.

The viscosities of the melted suppositories did, on the other hand, increase remarkably with increasing amount of AS, whereas they were not altered by the change in SL similar to the melting points. The latter results differed from those in diflunisal suppositories.[5,10] The amount of $NaHCO_3$ and NaH_2PO_4 is more than that of diflunisal (about 19%), so that the effect of SL on the viscosities of melted effervescent suppositories seems to be reduced. Thus, AS was found to be a more effective additive than SL for the release profiles of CO_2 from the suppositories.

In preparing suppositories with AS of 2.6% or above, pouring the melted mixture into the plastic molds was difficult because the high viscosity kept fluidity poor. Therefore, in the preparation of the conventional effervescent suppositories, the optimal amount of AS was found to be below 1.95%.

Table IV shows the residual percent (*vs.* the theoretical values) of the insoluble particles remaining in the upper portion of the suppositories containing various amounts of AS and a given amount (1.3%) of SL. The suppository containing 1.3% AS not only has enough viscosity to reduce the sedimentation rates of the active ingredients in the melted bases, but also maintains a high release rate and amount of CO_2.

In contrast, the melting points and viscosities of the suppositories containing SL were not influenced by the amount of the additive (Fig. 9), while the rates and amounts of CO_2 released from the suppositories were affected by the presence or absence of SL. The optimum amount of SL therefore seems to be the same as that of AS, because the suppository containing 1.3% SL shows the highest release amount of CO_2 (Fig. 8).

In conclusion, the release profiles of CO_2 from effervescent suppositories were greatly influenced by the hydroxyl values of the bases related to the contents of mono- and di-glycerides, the melting points of the bases, AS and SL. Consequently, we found that the rate and amount of CO_2 released from these suppositories could be freely controlled, and further studies on the combination of these factors should be done.

TABLE IV. Residual Percent of Insoluble Particles Remaining in Upper Portion of Suppositories

Rp.	AS (%)	SL (%)	Residual percent[a] (%)
19	0	1.3	91.5± 2.84
20	0.65	1.3	98.7± 3.63
21	1.3	1.3	102.7± 1.40
22	1.95	1.3	102.3±28.0

a) Each value represents the mean±S.D. ($n=3$).

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References and Notes

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