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An organic acid-induced sigmoidal release system for oral controlled-release preparations. III. Elucidation of the anomalous drug release behavior through osmotic pumping mechanism

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Abstract

To provide a reasonable explanation for the unique S-shaped drug release profile of sigmoidal release system (SRS), which is a newly developed multiparticulate oral time-controlled drug delivery system, the release mechanism was investigated. The dissolution studies were conducted for the theophylline-loaded SRS in water or in glucose aqueous solutions with different concentrations to vary osmotic pressure. In water, the initial lag time was extended with increasing coating level, whereas less change was observed in the subsequent drug release rate. On the other hand, drug release behaviors in aqueous glucose solutions extensively changed depending on the glucose concentrations; extending the lag time and decreasing the drug release rate. All the results obtained in the present study indicated that the anomalous theophylline release from the device was brought about by two mechanisms:; duration of the initial osmotic water-influx to the system to produce a lag time and the subsequent osmotic pumping process to provide a steady-state rapid release. © 1997 Elsevier Science B.V.

Keywords: Sigmoidal release system; Drug release mechanism; Osmotic pumping; Eudragit RS; Acid-polymer interaction

1. Introduction

We recently developed the sigmoidal release system (SRS) as a novel multiparticulate oral time-controlled release system, which provides an

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S-shaped release pattern with pre-determined lag time and release rate (Narisawa et al., 1994b). This system can be useful to realize highly improved pharmacotherapy according to the concept of chrono-pharmacotherapy by usual dosing regimen (Lemmer, 1991). The technical characteristics of the SRS were to contain an organic acid in each bead together with an active ingredient and to coat the beads with Eudragit RS-based coating by employing aqueous film coating technique. Thus, it became possible to rapidly release various kinds of drugs after a predetermined lag time (Narisawa et al., 1994b, 1995; Yoshino, 1994).

To provide a reasonable explanation for the unique drug release behavior of SRS, the drug release mechanism has been extensively studied. In the previous report, we revealed that an organic acid incorporated in the core of SRS acted as the film-permeation enhancer by the specific physicochemical interactions, including an electrostatic interaction between quaternary ammonium groups of Eudragit RS and dissociated form of an organic acid (Narisawa et al., 1996). In addition, distribution of an undissociated organic acid into the hydrophobic segment of the polymer contributed to the permeation enhancing, Although the permeation-enhancing effect of organic acid could be primarily related to the appearance of the unique S-shaped drug release profile, the release mechanism was still obscure in the following two points: why a long lag time appears before the drug release beginning, and why the drug release rate is not changed irrespective of the length of lag time. Therefore, to provide a reasonable answer to these questions, the present investigations were focused on the effect of osmotic pressure generated inside SRS, which can drive the drug release from the device.

2. Materials and methods

2.1. Materials

Anhydrous theophylline (TP; Tokyo Kasei Kogyo, Tokyo) used as the model drug was of reagent grade. It was used after grinding in a hammer mill. Nonpareil-103 (24–32 mesh, Freund Industrial, Tokyo) was used as the core material for the construction of beads. Sucrose used as the binder was of JP grade. An aqueous suspension of acrylic resin polymer (Eudragit RS 30D) was used as the coating materials, which were obtained from Röhm Pharma (Germany) and were used as received. Talc (Nippon Talc, Tokyo) and triethylcitrate (Pfizer, Tokyo) were used as received. Succinic acid, D-glucose, and all other chemicals used were of reagent grade.

2.2. Preparation of SRS

Uncoated beads were prepared from a powder mixture of TP (20 w/w%) and succinic acid (33 w/w%) using a CF-granulator (CF-360EX, Freund Industrial). The TP-containing powder mixture was slowly layered on the Nonpareil seeds (33 w/w%) while continuously spraying the binder solution (sucrose; 14 w/w%) to obtain TP-loaded uncoated beads. The operating conditions of the CF-granulator were as follows: spray solution feed, 3–6 ml/min; spray air pressure, 0.2 kg/cm^2; blower rate, 150–200 l/min; blower temperature, 50°C; and rotating rate, 150 rpm. The uncoated beads were sieved to remove both the agglomerates and fine particles to be used as core materials of the following film-coating process.

The uncoated beads were spray-coated with the mixture of Eudragit RS 3OD/talc/triethylcitrate/water (39.0:5.7:1.2:54.1). The operating conditions of the CF-granulator were as follows: spray solution feed, 2–4 ml/min; spray air pressure, 0.8 kg/cm^2; blower rate, 150–200 l/min; blower temperature, 50°C; and rotating rate, 150 rpm. The film-coated beads (TP-loaded SRS) were oven-cured for 16 h at 60°C to accomplish the coating. The coating amount was expressed as coating level (M_c) defined a $M_c = (M_f/M_b) \times 100$, where M_f is the amount of solid materials deposited and M_b is the weight of uncoated beads.

2.3. Dissolution studies

Dissolution experiments were performed by the

JP paddle method in 900 ml of test fluid at 37°C with constant stirring at 100 rpm. The film-coated beads equivalent to 100 mg of TP were used. Aliquots were removed at specific times and assayed with a spectrophotometer (UV-160, Shimadzu, Kyoto, Japan) to determine the drug concentration. Besides water, glucose aqueous solutions with various concentrations were used as the test fluids to examine the osmotic pumping effect.

2.4. Measurement of beads expansion

Six coated-beads with average size were stirred in water under the same condition with the dissolution study. After prefixed time intervals, the beads were move to a small glass vessel and individually determined for the change in the beads diameter using a stereomicroscope (SZH-141, Olympus Optical, Tokyo). After finishing the measurement, the beads were immediately returned to the dissolution medium.

2.5. Solubility determination

The solubility of TP in water or in glucose aqueous solutions with different concentrations were determined at 37°C. An excess of TP was added to 20 ml of each solution in jacketed beakers that were heated by external water circulation to maintain a constant temperature. The solutions were constantly stirred for several hours. After equilibration, an aliquot of each solution was removed and filtered for analysis of the drug concentration with a spectrophotometer (U-2000, Hitachi, Tokyo).

2.6. Viscosity measurement

The viscosity of glucose aqueous solution was measured using a digital viscometer (type DVL-B, Tokyo Keiki, Tokyo) at 37°C. The measurement was conducted in a stainless vessel (28 mm diameter × 108 mm height) with 50 ml of each solution.

3. Results

3.1. Dissolution behavior of TP-loaded SRS

Fig. 1 shows the drug release behaviors in water for TP-loaded SRSs with different coating level. Each profile shows a typical sigmoidal pattern that is characterized by a distinctive lag time followed by a rapid drug release. Since such release profiles are completely different from those obtained from ordinary capsule-type or matrix-type controlled-release preparations, the release kinetics can not be simply explained by the conventional diffusion theory. The lag time is extended with increase in the coating level, whereas the drug release rate is almost constant irrespective of coating level, which was commonly found in the SRSs of other drugs (Narisawa et al., 1994b, 1995). Therefore, it can be said that the SRS possesses a 'timer' function, which means that the device can control the onset time of drug release.

It was notable that the expansion of the beads was clearly observed during the above-mentioned drug release experiment. Thus, to examine the relationship between the observed bead's expansion and the anomalous drug release behavior, the change of the diameter of individual beads was microscopically determined with lapse of time in water at 37°C. As a typical example, the increase in the average diameter of six beads with 40% coating during drug release process is shown

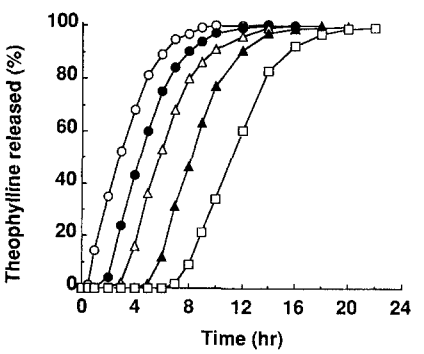

Fig. 1. Drug release profiles of TP-loaded SRS with various coating levels in water. Coating level: ○, 10%; ●, 20%; △, 30%; ▲, 40%; □, 50%.

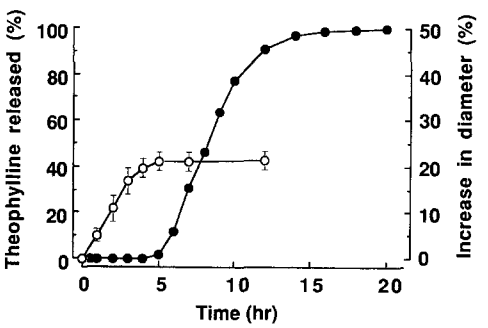

Fig. 2. Drug release profile of 40% coated TP-loaded SRS and the change in beads diameter during dissolution process. Each point for beads size change represents the mean ± S.D. of six beads. Key: ○, change in bead diameter (%), ●, TP released (%).

along with its drug release profile in Fig. 2. It was found that the expansion was soon begun in water and was almost finished at 5 h later. This time was almost coincident with the lag time observed in the dissolution study. In this case, the increase in bead diameter was found to reach about 1.2-fold over the initial diameter, meaning that around 70% of initial bead's volume of water were absorbed during the lag period. This indicates that the lag time is resulted from time for water-intake to the inside of the film-coated beads, because the continuous water-influx can prevent the Fickian drug diffusion. Analogous phenomena were also reported by other authors (Ramadan et al., 1987; Fukumori et al., 1988).

3.2. Osmotic pumping effect

The observed water-intake was thought to be brought about by an osmotic effect, because the components of uncoated beads easily dissolve in water and can generate high osmotic pressure inside the beads. Thus, to see if the osmotic pressure can influence the drug release behavior, the dissolution study was conducted in solutions with various osmotic pressures. In this experiment, glucose was selected as an osmotic pressure adjusting agent to minimize the influences of TP solubility or drug permeability through Eudragit RS-based coating, because inorganic salts as NaCl or KCl may affect the film permeability through ion-exchanging. In addition, urea, which is often used for osmotic pressure adjusting, may also affect the water structure in aqueous channel of the film. The drug release profiles from TP-loaded SRS with 40% coating in glucose solutions with various concentrations are shown in Fig. 3. It was found that the dissolution profile was greatly influenced; lag time was extended and the steady-state release rate thereafter was reduced with increase in the glucose concentration of the test fluids. TP was not released in 4.0 M of glucose aqueous solution during the dissolution study performed.

The apparent lag time and the subsequent steady-state release rate were calculated from individual dissolution data (0–3 M), which are summarized in Table 1 along with necessary parameters for the following discussion. The TP solubility did not change in all test solutions, and the viscosity of solution was so low that the diffusivity of solute could not much affect the release profiles. Therefore, the observed change in the profiles is thought to be directly caused by the osmotic pressure change.

Fig. 4 is the plot of the reciprocal value of drug release rate against the lag time observed in various test fluids. A good linear relation was found between both parameters.

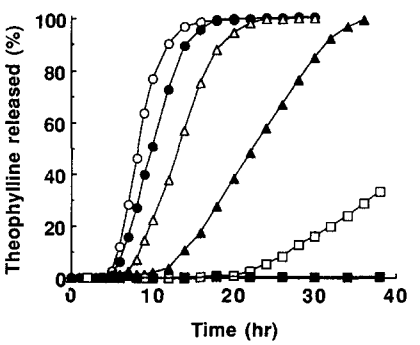

Fig. 3. Drug release profiles of TP-loaded SRS in glucose aqueous solutions with various concentrations. The coating level of the SRS is 40%. Glucose concentration: ○, 0.0 M (water); ●, 0.5 M; △, 1.0 M; ▲, 2.0 M; □, 3.0 M; ■; 4.0 M.

Table 1
Effect of osmotic pressure on drug release from TP-loaded SRS

Glucose concentration (M)	Osmotic pressure[a] (atm)	Viscosity (mPa·s)	Solubility of TP (%)	TP Release rate (%/h)	Lag time (h)
0.0	0.0	1.44	1.12	16.3	5.2
0.5	12.7	1.64	1.11	11.4	5.6
1.0	25.4	1.74	1.08	8.7	7.4
2.0	50.8	2.42	1.13	4.9	12.4
3.0	76.3	3.61	1.16	2.0	22.0

[a] Theoretical value calculated from Van't Hoff equation.

4. Discussion

There has been several papers describing that, besides simple diffusion, osmotic pumping mechanism contributes the drug release from various film-coated preparations (Ramadan et al., 1987; Lindstedt et al., 1989; Porter, 1989; Ozturk et al., 1990; Appel et al., 1991; Narisawa et al., 1994a; Dressman et al., 1994), in which the total drug release rate from such devices can be expressed by Eq. (1) under the condition of zero hydrostatic pressure:

$$dm/dt = (A/h)k\Delta\pi C_s + (A/h)PC_s \quad (1)$$

where (dm/dt) is the steady-state drug release rate, A is the surface area of semipermeable membrane, h is the membrane thickness, k is the water permeability coefficient, $\Delta\pi$ is the osmotic pressure difference across the membrane, C_s is the drug solubility, and P is the permeability coefficient for passage of drug across the semipermeable membrane. As seen in Fig. 3, the drug release of TP-loaded SRS considerably decreased with increasing the osmotic pressure, suggesting that the release mechanism involved the osmotic pumping process. Furthermore, from the fact that no drug was released in 4 M of glucose solution, the contribution of osmotic pumping effect should be far greater than simple diffusion for the drug release kinetics of SRS.

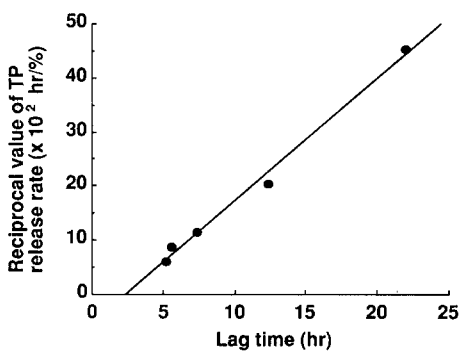

Fig. 4. Relationship between reciprocal drug release rate and lag time. Data plotted were quoted from Table 1.

As shown in Fig. 1, the steady-state release rate observed in water was almost constant, though the lag time was extended with increasing the amount of coating. This implies that, irrespective of coating level, the permeability of coating film increases during the lag time to a definite level, at which the drug release allows to start. Since the length of lag time was closely related to the bead's expansion (Fig. 2), the permeability change can be caused by the film deformation. Namely, in this process, the continuous water-influx into the system caused by the osmotic pressure difference produces an increase in the volume of drug solution inside the SRS, resulting in generating the hydrostatic pressure that causes the expansion of the coating film. Such expansion must be brought about the film hydration caused by the interactions between Eudragit RS and succinic acid (Narisawa et al., 1994b, 1995). Furthermore, the expansion will be accompanied by the formation of pores or increase in the size of micropores in the film. At the critical point, the continuous water-influx into the system can be equilibrated with the water-outflux from the system. At this moment, the drug should begin to deliver in saturated solution through the micropores in the film according to osmotic pumping mechanism. The

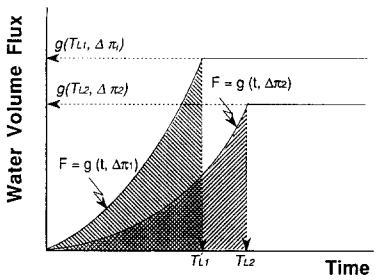

Fig. 5. Schematic representation for change of water volume flux under different osmotic pressures ($\Delta\pi_2 < \Delta\pi_1$) as a function of time.

observed lag time can be considered as the time required to attain the critical point, therefore, the length of lag period increased in accordance with increasing coating level (Fig. 1).

The above-mentioned hypothesis is also supported by the drug release behavior in glucose aqueous solutions with various concentrations (Fig. 3). When the osmotic pressure difference is reduced by increasing the glucose concentration in the test fluid, water-influx to the system should become slow, and hence lag time should be extended. In this case, however, the subsequent drug release rate also should become slow, because the water-convection at the steady-state would be slow due to the small osmotic pressure difference ($\Delta\pi$) according to Eq. (1).

The presumable change of water volume flux under different osmotic pressures as a function of time is schematically represented in Fig. 5.

The water volume flux consistently increases with time until the onset time of drug release, which corresponds to the lag time (T_L). Thereafter, the water flux is maintained at a constant level due to the steady-state osmotic pumping operation. The attained constant flux should depend on the osmotic pressure difference. The area under the curve from time zero to time T_L means the total water volume (V_T) incorporated during this period, and it can be mathematically expressed as:

$$V_T = \int_0^{T_L} g(t, \Delta\pi)\mathrm{d}t \quad (2)$$

where $g(t, \Delta\pi)$ is a function expressing the water volume flux at time t ($0 < t < T_L$) under the osmotic pressure difference of $\Delta\pi$. Although the type of the function for $g(t,\Delta\pi)$ is unknown, V_T can be approximately estimated as:

$$V_T = T_L \times g(T_L, \Delta\pi)/2 \quad (3)$$

When the same batch of beads was offered for the dissolution study under various osmotic pressures, V_T value should be constant, even though T_L and $g(T_L, \Delta\pi)$ values obtained for each osmotic condition differ according to the above-mentioned hypothesis. In this case, the steady-state drug release rate ($\mathrm{d}M/\mathrm{d}t$) can be described on the assumption that the osmotic pumping contributes largely to drug release as:

$$\mathrm{d}M/\mathrm{d}t = g(T_L, \Delta\pi)C_s \quad (4)$$

According to Eqs. (3) and (4), the product of $\mathrm{d}M/\mathrm{d}t$ and T_L should be constant, meaning that the reciprocal value of $\mathrm{d}M/\mathrm{d}t$ is directly proportional to T_L, as shown in Fig. 4. This indicates that lag time should be produced by a continuous water influx prior to the beginning of drug release according to the hypothesis described above. In line with this thought, the intercept of x-axis shown in Fig. 4 may correspond to the period required for the system to wet, absorb water, dissolve the contents, and to swell the coating by polymer-acid interactions.

5. Conclusions

Through the present study, it was proved that, besides the polymer-acid interactions reported previously (Narisawa et al., 1994b, 1995), the osmotic pumping effect also contributed to the anomalous dissolution behavior of SRS. The most likely dissolution mechanism is illustrated in Fig. 6.

At the initial stage of dissolution, water penetrates into the system through the Eudragit RS-based coating, followed by dissolution of the bead contents. The dissolved organic acid begins to interact with the coating polymer in two different manners, resulting in an increase in the hydration of the coating to ease water permeation as described in the previous study. Furthermore, due to the osmotic pressure difference across the coating

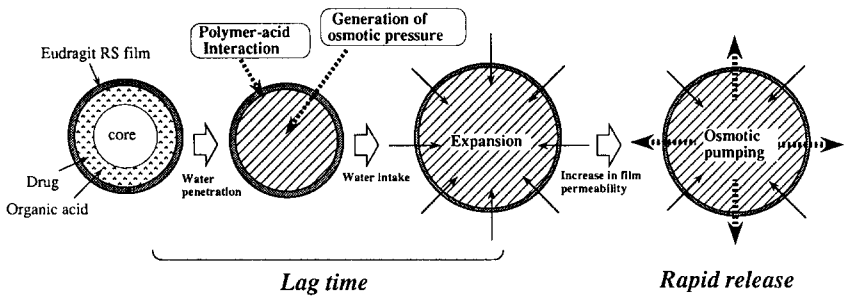

Fig. 6. Possible drug release mechanism of SRS.

film, the continuous water influx into the system produces an increase in the volume of drug solution inside the system. The pressure generated causes the film deformation, and when the water influx into the system can be equilibrated with the water outflux at the critical point, the high pressure formed inside the system accelerates the delivery of contents (in solution form) through the formed micropores in the coating according to the osmotic pumping mechanism. In such dissolution mechanism, the length of lag time should depend on the water-intake rate and the volume capacity for incorporation of water into the system, both of which should be affected by the osmotic pressure and film flexibility. The drug delivery rate after lag time can be influenced by water convection rate and drug solubility according to Eq. (1).

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