ELSEVIER

International Journal of Pharmaceutics 168 (1998) 31–40

international journal of pharmaceutics

Design and evaluation of a new capsule-type dosage form for colon-targeted delivery of drugs

Takashi Ishibashi *, Harumi Hatano, Masao Kobayashi, Masakazu Mizobe, Hiroyuki Yoshino

Pharmaceutics Research Laboratory, Tanabe Seiyaku Co., Ltd., 16-89, Kashima 3-chome, Yodogawa-ku, Osaka 532, Japan

Received 27 January 1997; received in revised form 21 March 1997; accepted 5 February 1998

Abstract

A new capsule-type dosage form was investigated for colon-targeted delivery of drugs. The system was designed by imparting a timed-release function and a pH-sensing function to a hard gelatin capsule. The technical characteristics of the system are to contain an organic acid together with an active ingredient in a capsule coated with a three-layered film consisting of an acid-soluble polymer, a water-soluble polymer, and an enteric polymer. In order to find the suitable formulation, various formulation factors were investigated through a series of in vitro dissolution studies. As a result, it was found that: (1) various organic acids can be used for this system; (2) a predictable timed-release mechanism of a drug can be attained by adjusting the thickness of the Eudragit®E layer; and (3) the outer enteric coating with HPMC®-AS provided acceptable acid-resistibility. All these results suggested that this approach can provide a useful and practical means for colon-targeted delivery of drugs.

Keywords: Colon-targeted delivery; Hard gelatin capsule; Organic acid; Eudragit®E; HPMC®-AS

1. Introduction

The selective delivery of drugs to the colon has attracted much interest recently for the local treatment of a variety of colonic diseases, and for the systemic absorption of drugs susceptible to enzymatic digestion in the upper gastrointestinal tract, such as peptides and proteins. Several approaches have been made in the last decade to achieve improved colon-specific delivery. In considering the physiological conditions of the gastrointestinal tract, various systems have been developed based on different principles including pH-triggered (Ashford et al., 1993; Peeters and Kinget, 1993; Watts et al., 1994; Wilding et al., 1994; Steed et

* Corresponding author. Tel: +81 6 3002788; fax: +81 6 3002799.

0378-5173/98/$19.00
PII S0378-5173(98)00082-9

al., 1994), time-controlled (Chacko et al., 1990; Gazzaniga et al., 1994; Ueda et al., 1994; Gazzaniga et al., 1995) and microbially controlled deliveries (Saffran et al., 1979; Rubinstein and Stintov, 1993; Mooter et al., 1994; MiloJevic et al., 1995).

In order to offer quick delivery of colon-specific delivery systems to clinicians, large-scale producibility and regulatory issues are also important factors to be considered besides potential selectivity to the colon. Thus pharmaceutical formulations should be designed using materials identified as safe in actual usage and manufactured using practical techniques.

A microbial cleavage strategy utilizing the high enzymatic activity of microflora in the large intestine may be one of the most promising approaches in terms of an excellent site-specificity. However, at this moment, this approach does not seem practical because the preparation of the systems usually requires the use of new pharmaceutical additives, such as polymers containing azo-bonding and other materials which are microbially degradable in the large intestine. Therefore it must take a long period to develop and market such a type of dosage form.

Among the more practical technologies, a conventional enteric coating approach is not sufficient, because all the drugs loaded should be released immediately after the gastric emptying, resulting in a poor site-specificity. Even though the use of various enteric polymers with higher dissolution pH or combination thereof have been tried to delay the timing of drug release, this approach does not seem relevant because the release behavior of such a system is reported to be greatly affected by a small change in pH or other ionic conditions (Ashford et al., 1993). The stained-release or timed-release approach, in which drugs are released on the basis of time-controlled principle, is also insufficient because the large variation of gastric emptying time in humans makes it difficult to achieve sufficient and reliable colonic availability of a drug by those methods. Although the above-mentioned controlled-release approaches are thought quite practical in terms of producibility, the site-selectivity of drug delivery should be further improved.

With this in mind, we recently developed a new colon-targeted delivery system in capsule form, which was designed to possess a pH-sensing function and a timed-release function. In this paper, the concept for the design of this new device and the principle of drug release are introduced, and the potential for colonic delivery of drugs will be demonstrated through a series of in vitro studies.

2. Design of dosage form

When the physical and physiological conditions of the human gastrointestinal tract are considered, a site-specific oral drug delivery seems to be achieved by appropriately integrating a combination of pH-sensing functions and time-controlled release functions into a single pharmaceutical. These two functions of the CTDC could improve the above-mentioned drawbacks of pH-triggered system and time-controlled system. That is, since the gastric emptying time greatly varies depending on various factors, the drug release in the stomach must be minimized. Imparting a pH-sensing function to the pharmaceutical should be effective for this purpose. Meanwhile, the passage of pharmaceuticals in the small intestine is known to be less variable, i.e. about 3 ± 1 h (Davis et al., 1986). After gastric emptying, therefore, the time-controlled release function must be effective to deliver the drug to the target site in the intestine. Thus the colon-targeted delivery capsule (CTDC) was designed according to the above-mentioned concept.

The fundamental structure of the CTDC is shown in Fig. 1. The technical characteristics of this device are to contain an organic acid in a hard gelatin capsule together with an active ingredient, and to coat the capsule with three different polymeric layers; an inner layer consisting of cationic polymer dissolving in acidic fluid, a water-soluble intermediate layer, and an outer layer consisting of enteric materials dissolving at $pH > 5$. Here, the intermediate layer is provided to prevent the direct contact of the cationic polymeric layer and the anionic polymeric layer.

The expected in vivo behavior of CTDC in the gastrointestinal tract is illustrated in Fig. 2. After

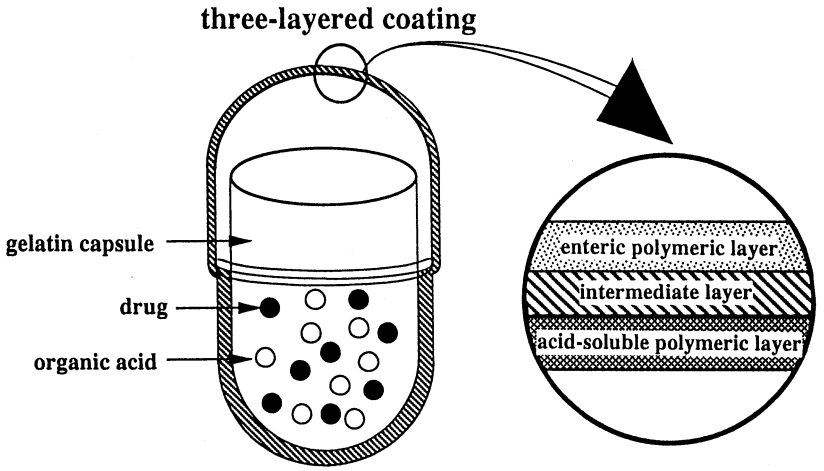

Fig. 1. Basic structure and pharmaceutical composition of the Colon-Targeted Delivery Capsule (CTDC).

ingestion of the capsule, drug release can be completely prevented in the stomach due to the acid-resistibility of the outer polymeric layer. After gastric emptying, the outer layer and the intermediate layer quickly dissolve, but the inner polymeric layer still remains and effectively prevents the drug release in the intestine. However, when the micro-environmental pH inside the capsule gradually decreases according to the dissolution of organic acid, and when the inner polymeric layer was finally dissolved by the acidic fluid, the drug content was quickly released. The onset of the drug release, therefore, can be controlled by the thickness of the inner polymeric layer. When sufficient acid-resistibility and the suitable thickness of the inner layer are given to adjust the onset time of drug release to 3 ± 1 h, a site-specific drug release to the proximal colon will be realized.

3. Materials and methods

3.1. Materials

Theophylline (Shiratori Seiyaku, Japan) was used as a model drug. Hard gelatin capsules (# 0, # 1, # 2, # 3 and # 4) were purchased from Warner Lambert. Eudragit®E100 (Rhöm Pharm, Darmastadt) was used as a cationic polymer which is soluble in low pH aqueous medium up to pH 5. Hydroxypropylmethylcellulose acetate succinate (HPMC®-AS, type MF, Shin-etsu, Japan) was used as an enteric polymer. Hydroxypropylmethylcellulose (TC-5®, type EW, Shin-etsu, Japan) was used as a neutral water-soluble polymer. Ethylcellulose (EC # 10, Shin-etsu, Japan) was used as a sealing agent for the hard gelatin capsule. Succinic acid, tartaric acid, citric acid, maleic acid, and fumaric acid were used as the pH adjusting agents and were purchased from Katayama, Japan. All other chemicals and solvents were of reagent grade.

3.2. Preparation of CTDC

Hard gelatin capsules were filled with the powder mixture of theophylline and organic acid. After being sealed with 5% (w/w) EC # 10 ethanolic solution, the core capsules obtained were spray-coated with three polymeric films successively in the order of Eudragit®E100, TC-5®, and HPMC®-AS, using a coating machine (Hicoater, Type HCT-Mini, Japan). The formula for the polymeric coating solution and the operating conditions for coating for each layer are described in Table 1. The type of organic acid, the amount of organic acid loaded in a capsule, and the amount of each coating film were varied depending on the research purpose.

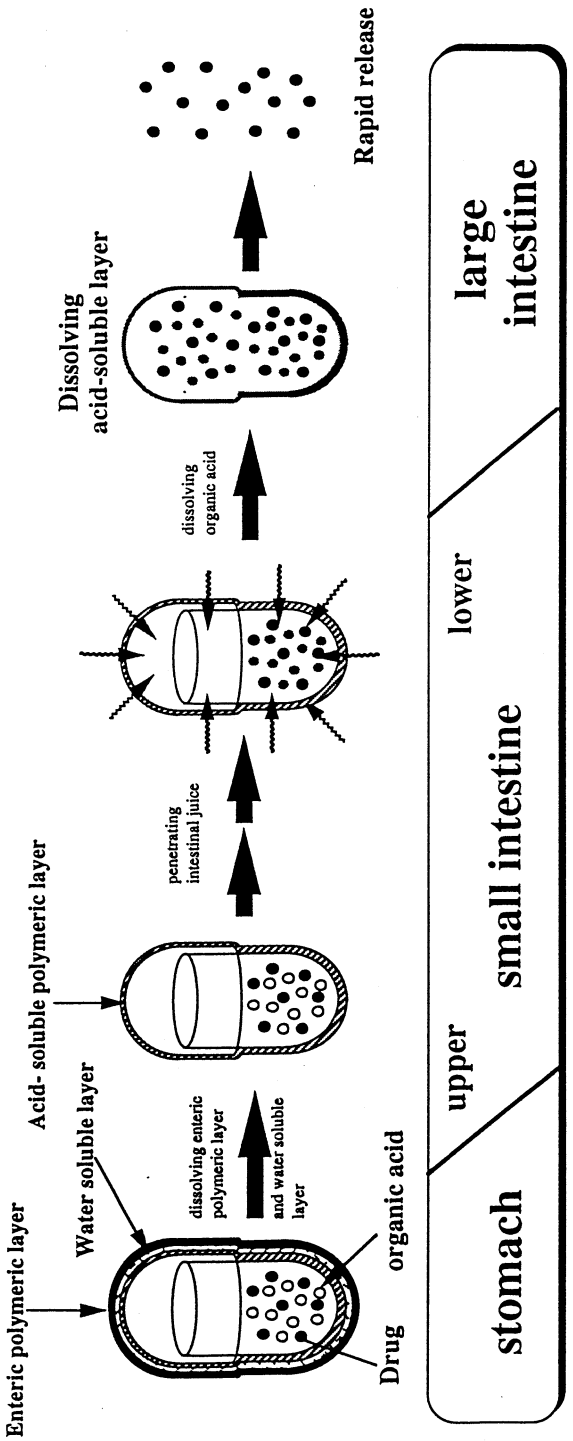

Fig. 2. Assumed mechanism of drug release from CTDC in the gastrointestinal tract.

Table 1
Formula for coating solution and standard operating conditions for the coatings of Eudragit®E, TC-5® and HPMC®-AS

	Spray solution		
	Eudragit®E coating	TC-5® coating	HPMC®-AS coating
Formula (w/w%)	Eudragit®E 5.0 Ethanol 95.0	TC-5® 5.0 Water 95.0	HPMC®-AS 5.0 Ethanol 57.0 Water 38.0
Operating conditions			
Blower temperature (°C)	45	55	65
Exhaust temperature (°C)	30	35	40
Spray pressure (kg/cm^2)	2	2	2
Air flow rate (l/cm^2)	30	30	30
Spray rate (g/min)	2.5	1.8	2.5
Rotating speed of coating pan (rpm)	40	40	40

3.3. Measurement of film thickness

The thickness of the Eudragit®E-coated layer of the capsules was measured using a coating thickness tester (LZ-200: Kett, Japan). Ten different positions were measured for each capsule to obtain a mean thickness.

3.4. Adjustment of pH inside the CTDC

The pH inside the CTDC was adjusted by filling 100 mg of buffering agents consisting of various ratios of the mixture of succinic acid and borax into the #2 capsule shell. The pH value to be attained in the capsule during the dissolution process was estimated by determining the pH value of the solution dissolving 2.7 g of buffering agent in 10 ml of JP 2nd fluid (which corresponds to the ratio of the actual volume of the capsule and the content of buffering agent loaded in the capsule).

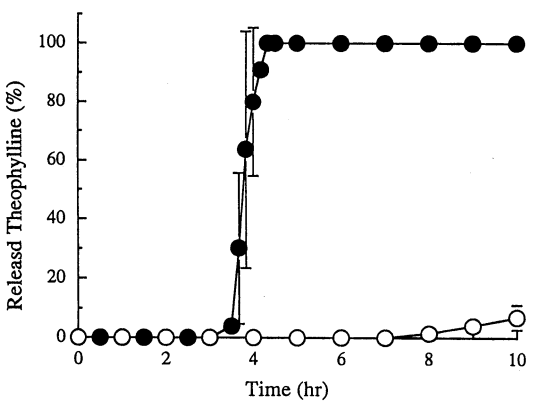

Fig. 3. Typical release profiles of the CTDC containing theophylline in the JP 2nd fluid (pH 6.8); ●, with succinic acid; ○, without succinic acid. The CTDC contains 20 mg of theophylline, and the coating layer consists of Eudragit E, HPMC, and HPMC-AS.

3.5. In vitro release study

The drug release profiles from capsules were investigated according to the procedure described in the Japanese Pharmacopoeia XIII (the paddle method). The capsules were placed in a vessel with 900 ml of the JP 1st fluid (pH 1.2) and 2nd fluid (pH 6.8) at 37 ± 0.5°C rotating at 100 rpm. The released amount was periodically determined by the spectrophotometric method. All the experiments were carried out in more than triplicate. The morphological change of capsules during dissolution testing in the JP 2nd fluid was observed using an optical microscope (DIAPHOT; Nikkon, Japan).

4. Results and discussion

4.1. Effect of organic acid on drug release

To examine if the addition of organic acids into the capsules is indispensable for the preparation

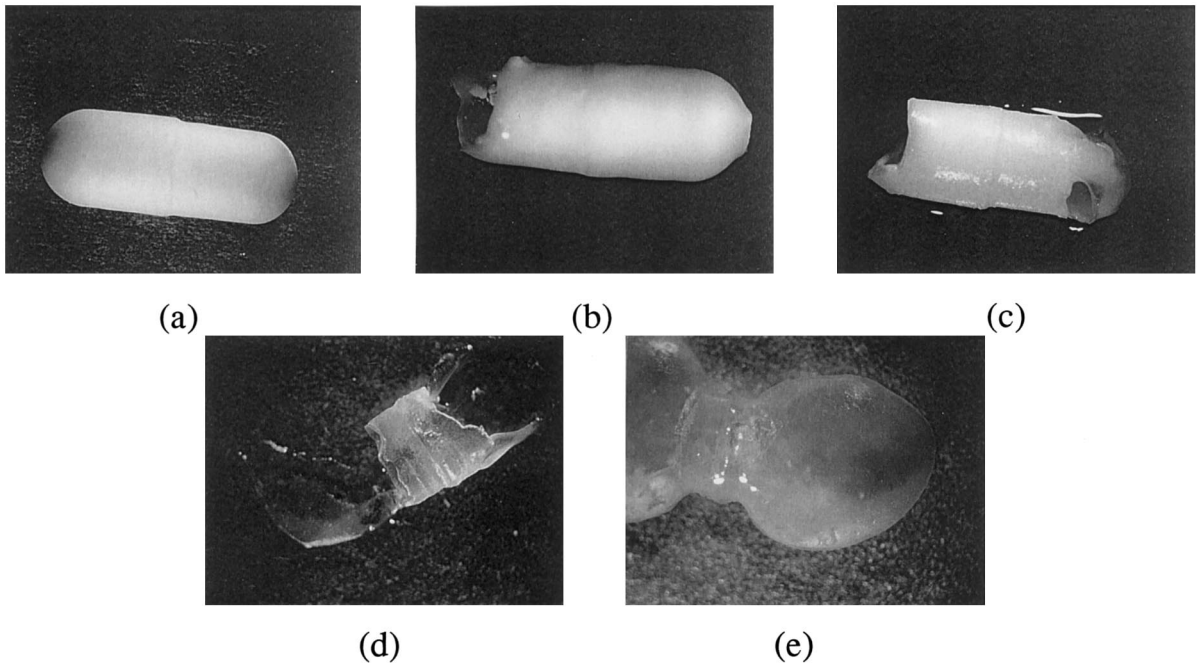

Fig. 4. Microscopic observation of CTDC during the dissolution process in the JP 2nd fluid (pH 6.8). Succinic acid-containing capsule: (a) 2.5 h after starting the dissolution test; (b) after 3 h (about 2% of theophylline was released); (c) after 3.3 h (about 75% of theophylline was released); (d) after 3.8 h (theophylline release was already completed). Succinic acid-free capsule: (e) 17 h after starting the dissolution test (about 16% of theophylline was released).

of CTDCs, two types of theophylline-loaded hard gelatin capsules, with or without succinic acid, were prepared. Both capsules were spray-coated with Eudragit®E, TC-5®, and HPMC®-AS (the coating amounts applied and thickness were 33 mg (60 μm in thickness), 25 mg (50 μm) and 200 mg (330 μm) per capsule, respectively). Fig. 3 is a comparison of drug release characteristics of both preparations in the JP 2nd fluid (pH 6.8). As was shown, both gave completely different dissolution profiles even though the composition of the coating film was identical. Thus, the capsules without succinic acid merely provided a very slow drug release profile, whereas the one with succinic acid provided a distinctive lag time of about 3 h. All of the drug loaded capsules were released rapidly within a comparably short time thereafter. This result suggests that succinic acid plays an important role in obtaining such an unusual release profile of theophylline.

Fig. 4 shows the morphological change of the coated capsules during the drug release process in the JP 2nd fluid. After starting the dissolution test, the outer layer of capsule (HPMC®-AC layer) and the intermediate layer of capsule (TC-5® layer) soon dissolved, and the remaining capsule shell with an Eudragit®E layer considerably

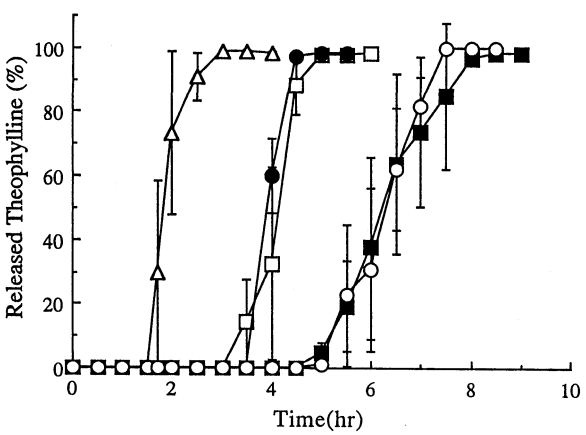

Fig. 5. Effect of organic acids on drug release behavior of theophylline-loaded CTDC. △, maleic acid; □, tartaric acid; ●, succinic acid; ■, citric acid; ○, fumaric acid.

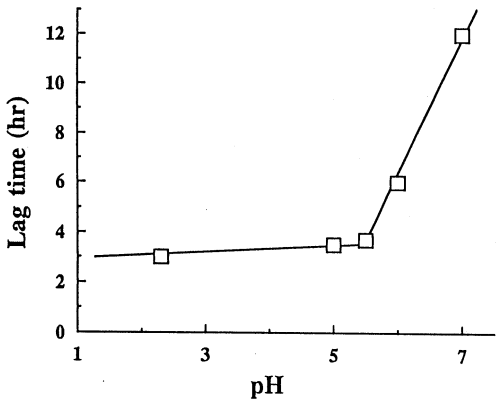

Fig. 6. The relationship between pH inside the capsule and lag time of drug release in the 2nd fluid (pH 6.8).

swelled, but no more change in appearance was found within 2.5 h (Fig. 4(a)). After 3 h, at which about 2% of theophylline was released, the top portion of the capsule was found to be dented and some holes were observed in it (Fig. 4(b)). After 3.3 h, at which about 75% of the drug was released, both ends of the capsule had started to collapse (Fig. 4(c)). After 3.8 h, by the time at which all the drug had been released, most of the capsules were dissolved, leaving a small portion of EC film used as a sealant. On the other hand, in the case of the capsule without succinic acid, the HPMC®-AC and TC-5® layers were dissolved, but the remaining capsule merely swelled and did not dissolve for many hours (Fig. 4(e)).

From these studies, it was ascertained that the anomalous drug release behavior of the CTDC was brought about by the timed-collapse of the Eudragit®E layer. Eudragit®E is a polymer widely used for pharmaceutical purposes, and due to the amino groups introduced into its molecular chain, this polymer dissolves in acidic solution but does not dissolve in a solution of medium pH such as the JP 2nd fluid. In this case, however, succinic acid functioned as a pH-adjusting agent to change the micro-environmental pH inside the capsule, by which the timed-collapse of the Eudragit®E layer was achieved. Therefore, the lag time could be influenced by various factors including organic acid species, loading amount of organic acid, coating amount of Eudragit®E, and anything affecting the dissolution kinetics of the polymer.

To select the suitable organic acids for the CTDC, and also to investigate the amount of influence of organic acid species on drug release behavior, Eudragit®E-coated capsules (no enteric coating in this case), containing either maleic acid, succinic acid, tartaric acid, fumaric acid, or citric acid were used. In this experiment, the loaded amount of organic acid and the thickness of the Eudragit®E layer were tentatively fixed at 100 mg and 60 μm, respectively. The release profiles of theophylline from those capsules in the 2nd fluid are compared in Fig. 5.

In all cases, theophylline was quickly released after a distinctive lag time, suggesting that either of the organic acids can be utilized as the pH-adyjusting agent for CTDC. As was shown, however, the duration of lag time differed depending on organic acid species; for instance, the maleic acid-loaded capsule gave the shortest lag time of about 1.5 h; in the cases of succinic acid and tartaric acid, the lag time observed was about 3 h; and in the cases of fumaric acid and citric acid, the lag time was found to be more than 5 h. Though the reason for this phenomenon is still obscure, it might depend on the difference in dissolution kinetics of the individual organic acids and/or the pH value attained in the capsule. However that may be, this result suggests that the onset time of drug release could be controlled by organic acids to some extent. Also through this study, we found that succinic acid is likely to be a suitable organic acid for practical use, due to less hygroscopicity and good powder properties of this compound; i.e. ease in processing and minimizing influence on drug stability.

Here the effect of micro-environmental pH inside the capsule on the drug release behavior of CTDC was also examined. For this experiment, various Eudragit®E-coated capsules (without enteric coating in this case) containing both succinic acid and/or borax at different ratios were prepared. The thickness of the Eudragit®E layer was tentatively fixed at 60 μm. The greater the ratio of borax to succinic acid, the higher was the pH inside the capsule. The relationship between pH inside the capsule and lag time in the 2nd fluid is shown in Fig. 6. Above pH 5, the lag time of the Eudragit®E-coated capsules increased as pH in-

Table 2
Effect of succinic acid content on lag time

Succinic acid content (mg)	Lag time (h)			Average (h)	Variation[a] (h)
	1	2	3		
0	10.7	12.9	14.3	12.6	3.6
5	5.9	3.9	5.9	5.2	2.0
10	7.3	4.7	5.7	5.9	2.6
20	3.7	4.6	4.6	4.3	0.9
50	3.4	3.5	3.9	3.6	0.5
100	3.3	3.6	3.3	3.4	0.3

[a] Variation stands for maximum lag time minus minimum lag time.

creased, but the drug release rate was slower. Under pH 5, however, the lag time was almost constant. The refractive point observed at about pH 5 was in accordance with the upper limit of the soluble pH range of Eudragit®E. From this result and Fig. 4, it was ascertained that the drug release from CTDC was triggered by dissolving the Eudragit®E layer when the micro-environmental pH inside the capsule decreased below 5.

4.2. Effect of the loading amount of succinic acid

Next, to examine the effects of the loading amount of organic acid on the duration of lag time and the drug release rate thereafter, Eudragit®E-coated capsules containing various amounts of succinic acid were prepared and tested for theophylline release. As was expected, acid content affected the drug release behavior of the capsules. The observed lag times for preparations are listed in Table 2. When the loading amount of succinic acid was less than 50 mg per capsule, the lag time was gradually delayed with decreasing the acid content. When less than 20 mg per capsule, the lag time was considerably delayed, and the drug release after the lag time became slow. On the other hand, when the acid content was increased to more than 50 mg, the lag time attained was almost constant at around 3 h, and drug release after the lag time was sharp. These results suggest that the lag time of capsules might be controlled by the loading amount of succinic acid to some extent, and the adequate amount of succinic acid for CTDCs was estimated at more than 50 mg to obtain a constant lag time and a quick release.

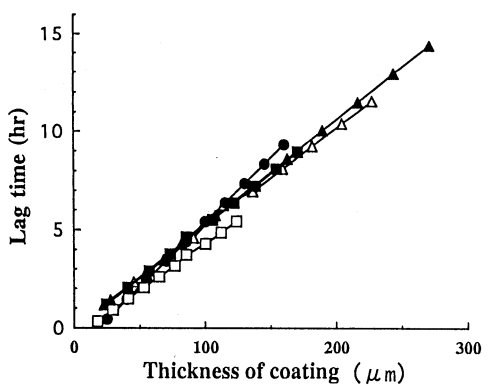

Fig. 7. Relation between thickness of Eudragit®E layer and lag time for various capsule sizes. □, #0 capsule; ●, #1 capsule; ■, #2 capsule; △, #3 capsule; ▲, #4 capsule. Each capsule contains 50 mg of succinic acid and 20 mg of theophylline.

4.3. Effect of the coating amount of Eudragit®E

To examine the effect of coating amount of Eudragit®E layer on lag time, theophylline-loaded capsules (size #2), each of which contained 20 mg of theophylline and 50 mg of succinic acid, were coated with Eudragit®E in various coating amounts. When the coating amount of Eudragit®E was varied from 10 mg to 120 mg, the thickness increased linearly from 25 μm to 170 μm. As was expected, the lag time observed in the dissolution test in the JP 2nd fluid was delayed with increased coating, and a very good linear

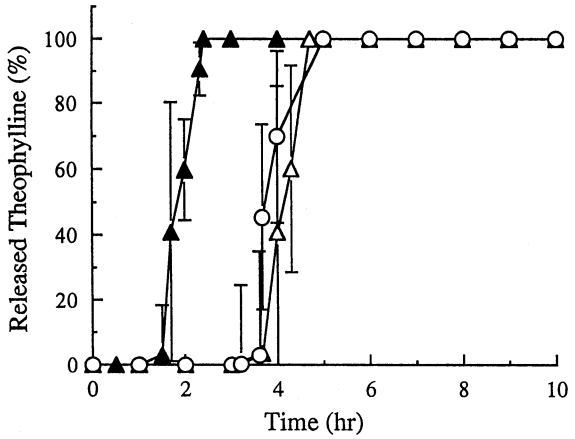

Fig. 8. Influence of enteric coating on the drug release behavior in the JP 2nd fluid (pH 6.8). ○, without enteric coating; △, with enteric coating, (without pretreatment); ▲, with enteric coating (pretreatment by immersing in the 1st fluid for 8 h).

relationship was found between coating amount and lag time (Fig. 7). This suggests that the onset time of drug release from CTDC could be controlled quantitatively over a quite wide range by altering the coating amount of Eudragit®E.

When Eudragit®E coating was applied to various sizes of hard gelatin capsules, a good linear relationship was also found between film thickness and lag time for each capsule size, and the regression lines were almost coincident with each other (Fig. 7), suggesting that the lag time is predictable in terms of the film thickness of Eudragit®E layer irrespective of capsule size.

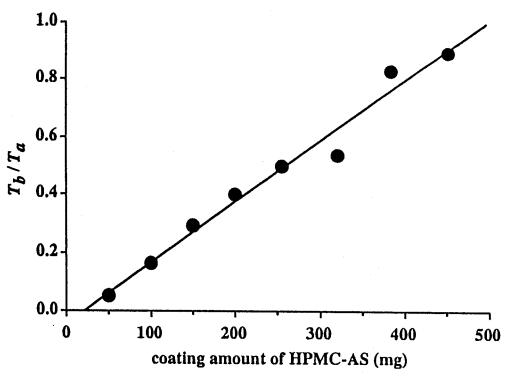

Fig. 9. Relation between coating amount of enteric layer and shortening of lag time after pretreatment with the JP 1st fluid (pH 1.2). The size of the capsule used was # 2.

4.4. Enteric protection with HPMC-AS film coating

Eudragit®E-coated capsules containing theophylline and succinic acid, of which lag time in the JP 2nd fluid was set to about 3 h, were spray-coated with TC-5® and HPMC®-AS to complete the CTDC. This coating provided a very good acid-resistibility so as to prevent the drug release over 10 h in the JP 1st fluid (pH 1.2) at the coating amount of 200 mg/capsule. Here, the intermediate layer of TC-5® was provided to prevent the ionic interaction between Eudragit®E and HPMC®-AS during the coating process, and to improve the shelf life of CTDC. Then, simulating the physiological condition in the human gastrointestinal tract, the CTDC was first immersed in the JP 1st fluid for 8 h, and then the dissolution test was performed in the JP 2nd fluid. In this experiment, a shortening of CTDC's lag time in the JP 2nd fluid was observed as shown in Fig. 8. This could be caused by an insufficient amount of HPMC®-AS coating.

Next, the effect of enteric coating on the dissolution behavior of CTDC was evaluated in the 2nd fluid. When T_a and T_b are defined as the lag times observed in the 2nd fluids and the lag time observed in the 2nd fluid after immersing CTDC in the 1st fluid for 8 h, respectively, T_b/T_a can be used as an index indicating the effect of enteric coating on the above-mentioned 'shortening of lag time'. The value of T_a was almost constant irrespective of the amount of enteric coating applied thereon, because the enteric coating layer quickly dissolved and hence it did not affect the dissolution behavior of the capsule in the JP 2nd fluid. The fact that the lag time of capsule depends on the thickness of Eudragit®E layer (Fig. 7) suggests that T_a should be varied by the penetrating rate of the 2nd fluid to this layer because the Eudragit®E layer quickly dissolved below pH 5. Fig. 9 shows the change in T_b/T_a for the CTDCs (size # 2) as a function of coating amount of HPMC-AS. The T_b/T_a value was found to increase considerably with an increase in the amount of enteric coating. This phenomenon is probably caused by the following: when the capsule was immersed in the 1st fluid, the acidic fluid penetrated to the Eudragit®E

layer through the enteric coating; and the penetrated fluid swelled or partially dissolved the Eudragit®E layer. However, when the coating amount was raised to about 450 mg (about 800 μm in thickness), the value recovered almost to the initial level (the value of T_a/T_b is 0.95). This suggests that the lag time can be maintained at the desired level by applying sufficient enteric coating to the system.

5. Conclusion

The present in vitro study revealed that the CTDC can be a useful means for the colon-targeted delivery of drugs. The characteristics of this technology involves: (1) various organic acids can be used for this system; (2) the predictable timed-release of drug can be attained by adjusting the thickness of Eudragit®E layer; and (3) the outer enteric coating with HPMC®-AS provided a satisfactory acid-resistibility. The CTDC will be able to achieve a higher selectivity to the colon than other time-controlled and pH-triggered systems, because it possesses both pH-sensing functions and time-release functions. The CTDC has also an advantage from the practical point of view, because all the material used is identified as safe in actual usage and the preparation techniques employed are practically established.

References

Ashford, M., Fell, J.T., Attwood, D., Woodhead, P.J., 1993. An in vitro investigation into the suitability of pH-dependent polymer for colonic targeting. Int. J. Pharm. 91, 241–245.

Chacko, A., Szaz, K.F., Howard, J., Cummings, J.H., 1990. Non-invasive method for delivery of tracer substances or small quantities of other materials to the colon. Gut 31, 106–110.

Davis, S.S., Hardy, J.G., Fara, J.W., 1986. Transit of pharmaceutical dosage forms through the small intestine. Gut 27, 886–892.

Gazzaniga, A., Iamartino, P., Maffione, G., Sangalli, M.E., 1994. Oral delayed-release system for colonic specific delivery. Int. J. Pharm. 108, 77–83.

Gazzaniga, A., Busetti, C., Sangalli, M.E., Giordano, F., 1995. Time-dependent oral delivery system for the colon targeting. S.T.P. Pharm. Sci. 5, 83–88.

MiloJevic, S., Newton, J.M., Cummings, J.H., Gibson, G.R., Bothman, R.L., Ring, S.G., Allwood, M.C., Stockham, M., 1995. Amylose, the new perspective in oral drug delivery to the human large intestine. S.T.P. Pharm. Sci. 5, 47–53.

Mooter, V.D., Samyn, C., Kinget, R., 1994. The relation between swelling properties and enzymatic degradation of azo polymers designed for colon-specific drug delivery. Pharm. Res. 11 (12), 1737–1741.

Peeters, R., Kinget, R., 1993. Film-forming polymers for colonic drug delivery: Synthesis and physical and chemical properties of methyl derivatives of Eudragit S. Int. J. Pharm. 94, 125–134.

Rubinstein, A., Stintov, A., 1993. Matrices of polysaccharides as colonic delivery system. J. Pharm. Sci. 82 (9), 867–868.

Saffran, M., Kumar, G.S., Savariar, C., Burnham, J.C., Williams, F., Neckers, D.C., 1979. A new approach to the oral administrations of insulin and other peptide drugs. Science 223, 1081–1084.

Steed, K.P., Hooper, G., Ventura, P., Musa, R., Wilding, I.R., 1994. The in vivo behaviour of a colonic delivery system: a pilot study in man. Int. J. Pharm. 112, 199–206.

Ueda, S., Hata, T., Asakura, Yamaguchi, H., Kotani, M., Ueda, Y., 1994. Development of a novel drug release system, Time-controlled explosion system (TES). Concept and design. J. Drug Targeting 2, 35–44.

Watts, P.J., Wilson, C.G., Davies, M.C., Melia, C.D., 1994. Radiolabelling of polymer microspheres for scintigraphic investigations by neutron activation. 4. A pharmacoscintigraphic study of colon-targeted Eudragit RS-sulphapyridine microspheres in human volunteers. Int. J. Pharm. 102, 101–108.

Wilding, I.R., Davis, S.S., Pozzi, F., Furlani, P., Gazzaniga, A., 1994. Enteric coated timed release systems for colonic targeting. Int. J. Pharm. 111, 99–102.