Evaluation of Water in Oil and Microsphere in Oil Emulsions as a Specific Delivery System of 5-Fluorouracil into Lymphatics

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The efficiency of water in oil (W/O) and gelatin microsphere in oil (S/O) emulsion as a drug delivery system for deliverying 5-fluorouracil (5-FU) specifically into lymphatics was evaluated in the rat. Following intragastric and intramuscular injection in the forms of emulsions and aqueous solution, radioactivities of ^{3}H-labeled 5-FU or its antibacterial activities in plasma, regional lymph nodes, thoracic lymph and the injection site were compared with those following intravenous injection.

W/O and S/O emulsion predominantly increased the area under the concentration–time curve (AUC) of 5-FU in the regional lymph nodes and cumulative amount transported into thoracic lymph. A pronounced retardation of release of 5-FU and decrease of peak plasma concentration were also obtained following injection of these emulsions. In addition, a local injection of 5-FU with emulsions was confirmed to be considerably advantageous from the viewpoint of metabolic inactivation. These results suggest the superiority of W/O and S/O emulsion in a surgical adjuvant cancer chemotherapy by satisfying many of the criteria of an ideal drug delivery system. S/O emulsion exhibited the best efficacy throughout present examinations.

Keywords——drug delivery system; anticancer agent; 5-fluorouracil; lymphatic system; water in oil emulsion; microsphere in oil emulsion; intramuscular injection; intragastric injection; metabolic inactivation; surgical adjuvant chemotherapy

For effective cancer chemotherapy, an optimal concentration of anticancer agent must reach the tumor tissues and remain there for a required period of time, whereas such drug need not be delivered to the normal tisues. In the past approaches to realize such condition, therefore, much efforts have been directed toward structural modification of the drug, alteration in route of administration or dose regimen, and development of a specific drug delivery device.

Actually in cancer therapy for patients with resectable carcinoma, surgical treatment has been primarily carried out. However, since treatment failure such as local recurrence of primary tumor or metastatic spread often occurs during management, an integrated therapy approach such as adjuvant chemotherapy employing anticancer agent has been proposed[2] and proved to be effective by numerous research groups.[3] Nevertheless, because of serious adverse effect which was provoked when such anticancer agents were administered systemically, any pharmaceutical approach by which its cytotoxity could be directed specifically to tumor areas would be of great value.

In compliance with this clinical requirement, we have been attempting to deliver anticancer agents selectively into lymphatics for preventing lymphatic dissemination of tumor cells, which was one of the most responsible routes for metastasis: In preliminary studies, a facilitated delivery of mitomycin C and bleomycin to the thoracic lymph following intramuscular or intraperitoneal injection of their emulsion formulations was demonstrated in the

1) Location: Yoshida Shimoadachi-cho, Sakyo-ku, Kyoto.
2) R.E. Johnson, Cancer, 35, 1 (1975).
3) V.A. Cooperative surgical adjuvant study group, Cancer, 18, 291 (1965); W.H. Cole, R.G. Mrazek, S.G. Economou, G.O. McDonald, D.P. Slaughter, and F.W. Sterhl, ibid., 18, 1529 (1965); etc.

rat.[4] In addition, basic pharmaceutical research has been conducted to study the mechanism of accelerated transfer of drugs to regional lymph nodes in the muscle[5] and the stomach wall[6] employing a model compound. Throughout these studies, water-in-oil (W/O) emulsion fairly facilitated the lymphatic transport, and the largest enhancement was exhibited by microsphere-in-oil (S/O) emulsion which was developed by improving W/O emulsion.

Present investigation describes a further application of W/O and S/O emulsions to facilitate a lymphatic delivery of 5-fluorouracil (5-FU), a well established antimetabolite used extensively in the treatment of various types of cancer. The effects of route of administration and dosage forms on the metabolic inactivation of 5-FU are also discussed.

Experimental

Materials——Radiolabeled 5-fluoro(6-^{3}H)uracil was purchased from Japan Radio Isotope Association with specific radioactivity of 7.7 mCi/mg. Cold 5-fluorouracil was supplied from Kyowa Hakko Co., Ltd. Sesame oil and gelatin were obtained commercially from Nakarai Chemicals Co. Ltd. Nonionic surfactants, polyoxyethylene derivative of hydrogenated castor oil (HCO-60) and sorbitan sesquioleate (SO-15) were supplied from Nikko Chemicals Co., Ltd.

Preparation of Emulsions——Both W/O and S/O emulsions were prepared from 40 volumes oily phase and 7 volumes aqueous phase. Sesame oil incorporating SO-15 and HCO-60, 6.7% and 1.7% (v/v) respectively, was used as the oily phase. The aqueous phase was distilled water (W/O emulsion) or 20% (w/v) gelatin solution (S/O emulsion), dissolving 5-FU with the concentration of 16.8 mg/ml. After heating at about 50°, both phases were mixed with each other and emulsified with a sonic vibration method. Sonication was carried out in the water bath maintained at 70°. Emulsions were prepared within 1 hr before animal experiment.

Procedure of Animal Experiments——Male Wistar albino rats weighing between 200 and 230 g were used in all animal experiments. The animals were anesthetized with intraperitoneal injection of sodium pentobarbital and fixed on its back during the course of the experiment.

Intramuscular injection was undertaken into the center of the right thigh muscle using a microliter syringe. Muscle clearance experiment was carried out according to the procedure of Kakemi, et al.[7] For determining an arrival of 5-FU at the regional lymph nodes, iliac lymph nodes were excised at varying time periods after injection.

Intragastric injection was undertaken into the sub-serosal layer of the stomach after exposed by a middle line abdominal incision. At varying time periods after injection, rats were sacrificed, and then the stomach, the portal and the posterior–gastric lymph nodes were excised. Blood samples were also obtained from abdominal aorta at the same time.

For intermittent sampling of blood, a polyethylene catheter (I.D. 0.5 mm, O.D. 0.8 mm) was cannulated into the carotid artery and blood samples were withdrawn periodically during 3 hr experiment. The procedure employed for the collection of thoracic lymph was modified from the method of Bollman, et al.[8] A heparin filled flexible vinyl catheter (I.D. 0.5 mm, O.D. 0.8 mm) was cannulated into the thoracic duct and fixed with the aid of a drop of tissue cement. This cannulae allowed continuous free drainage of lymph throughout the experiment.

Intravenous injection was performed into the femoral vein. The dose of 5-FU in all experiments was 0.1 mg per one rat which was contained in 40 μl of the appropriate vehicles. For the radioactivity tracing experiment, 1 μCi of radiolabeled 5-FU was incorporated in this vehicle.

Analytical Method——The procedure employed for the determination of ^{3}H-radioactivity was modified from the method of Mahin and Loftberg.[9] The excised muscle or the stomach was solubilized in 5 ml of 1 N NaOH ethyl alcohol solution by shaking overnight at 37° and diluted to 10 ml with the same medium. Then 0.2 ml of sample solution was put into the counting vial, added 0.2 ml of perchloric acid (60%) and 0.2 ml of hydrogen peroxide (35%), and heated at 70° for 90 min with occasional agitation. After cooling to the room temperature, 15 ml of scintillation medium (a mixture of 500 ml of ethylene glycol–monoethyl ether, 1000 ml of toluene, and 6 g of 2,5-diphenyloxazole) was added into the vial and the radioactivities were measured in a liquid scintillation system. A known weight of lymph nodes or 0.2 ml of plasma was put into the vial

4) Y. Nakamoto, M. Fujiwara, T. Noguchi, T. Kimura, S. Muranishi, and H. Sezaki, *Chem. Pharm. Bull.* (Tokyo), **23**, 2232 (1975); Y. Nakamoto, M. Hashida, S. Muranishi, and H. Sezaki, *ibid.*, **23**, 3125 (1975).
5) M. Hashida, M. Egawa, S. Muranishi, and H. Sezaki, *J. Pharmacokin. Biopharm.*, **5**, 225 (1977).
6) M. Hashida, Y. Takahashi, S. Muranishi, and H. Sezaki, *J. Pharmacokin. Biopharm.*, **5**, 241 (1977).
7) K. Kakemi, H. Sezaki, K. Okumura, and S. Ashida, *Chem. Pharm. Bull.* (Tokyo), **17**, 1332 (1969).
8) J.L. Bollman, J.C. Cain, and J.H. Grindlay, *J. Lab. Clin. Med.*, **33**, 1349 (1948).
9) D.T. Mahin and R.T. Loftberg, *Anal. Biochem.*, **16**, 500 (1966).

and the radioactivity was measured as described elsewhere.   The obtained counts were corrected with the external standard method.

The antimicrobial activity was determined by the disc-plate method using *Staphylococcus aureus* 209P as a test microorganism.   For determining the lymph nodes concentration, a known weight of summed up lymph nodes of five rats (one group) was homogenized in 1 ml of pH 7.4 phosphate buffer and the supernatant was supplied for measurement after centrifugation.

Results

As discussed in previous reports,[5,6] drugs can be transported from the injection site directly into the lymphatic system, either as a bound form to oil droplet carriers or as a free form after separation at the injection site, following administration with emulsion formulations.   After being absorbed into the peripheral lymph vessels, drugs would reach the regional lymph nodes and subsequently be delivered to the thoracic duct by lymph flow. The absorption from the injection site into blood capillaries also should not be neglected.

Herein, the transfer of 5-FU between these various tissue compartments was examined for evaluating exactly the efficiency of emulsion formulations.

Disappearance of 5-FU from the Injection Site

The disappearance of radioactivity of 5-FU from the muscle following intramuscular injection of three types of parenteral formulation is shown in Fig. 1.   5-FU disappeared rapidly following injection of aqueous solution, and the disappearance process appears to be essentially monoexponential with a half-life of about 3 min.   W/O and S/O emulsions exhibited relatively slower disappearance and even after 30 min, 37% and 55% of dose remained in the injection site, respectively.
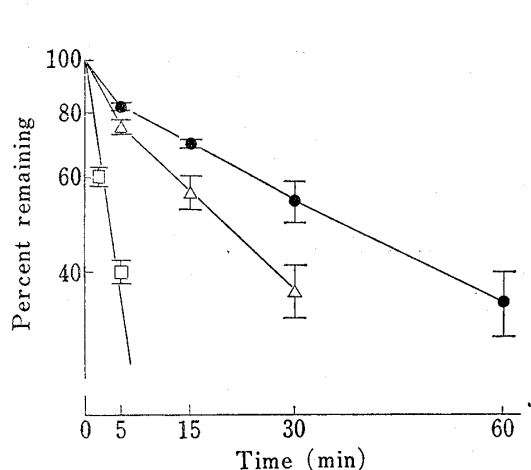

Fig. 1.   Disappearance of Radioactivity of 5-FU from the Thigh Muscle after Intramuscular Injection of Various Formulations

□, aqueous solution; △, W/O emulsion; ●, S/O emulsion.
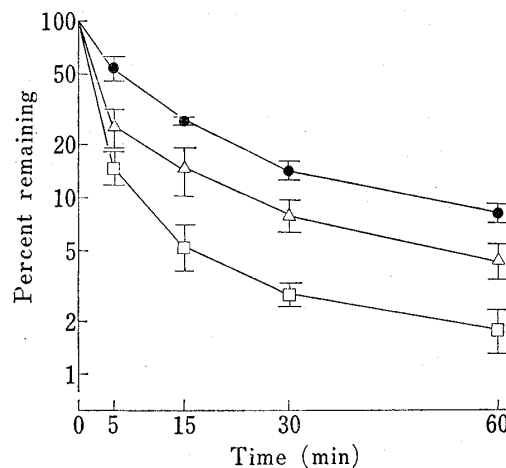Results are expressed as the mean±S.E. of at least 5 animals.

Fig. 2.   Disappearance of Radioactivity of 5-FU from the Stomach Wall after Intragastric Injection of Various Formulations

□, aqueous solution; △, W/O emulsion; ●, S/O emulsion.
Results are expressed as the mean±S.E. of at least 5 animals.

The disappearance of radioactive 5-FU from the stomach wall following intragastric injection is shown in Fig. 2.   When aqueous solution was injected, 5-FU disappeared very rapidly also from the stomach wall and about 85% of administered dose had been cleared during 5 min after injection.   While W/O and S/O emulsions showed relatively slower absorption.   These data clearly indicate that 5-FU is maintained at the injection site for a longer period when injected with emulsion forms, especially in S/O emulsion.

Plasma Concentration of 5-FU

In Fig. 3(a,b), the plasma concentrations of 5-FU following injection of three types of formulation into the thigh muscle and the stomach wall are compared with the concentration following intravenous injection. In these figures, concentration was measured by microbiological assay. The range of individual observations are not shown, but the coefficient of variation was less than 40% in all instances. Intravenous injection showed the highest concentration of 5-FU at 1 min after injection, where it indicated about 1.0 µg/ml plasma. Then it decreased very quickly and the fall-off curve appears to be essentially biexponential with a half-life of 8 min in the later phase. Compared with this rapid transition, the three intramuscular injections shown in Fig. 3(a) reflect a gradual absorption of 5-FU from the muscle, so a delay in the time to reach peak concentration and reduction of maximum plasma level were observed evidently. S/O emulsion showed the largest reduction of maximum concentration, although its decrease in the later phase was the most moderate and even at 120 min after injection 5-FU could be detected in the plasma.

As shown in Fig. 3(b), the manner of appearance of 5-FU into the circulating blood following intragastric injection was extremely different from that of intramuscular injection and the concentration did not exceed that of intravenous injection. These results may be attributed to a rapid absorption and a hepatic inactivation due to the first pass through the liver *via* portal vein.

Transport of 5-FU into Regional Lymph Nodes

Fig. 4(a) represents the concentration time-course of radioactive 5-FU in the right iliac lymph nodes which are located in the pathway from the injection site, right thigh muscle, and Fig. 4(b) represents equivalent data from the left iliac lymph nodes for comparison. As noted in these figures, when an aqueous solution was injected intravenously, no detectable
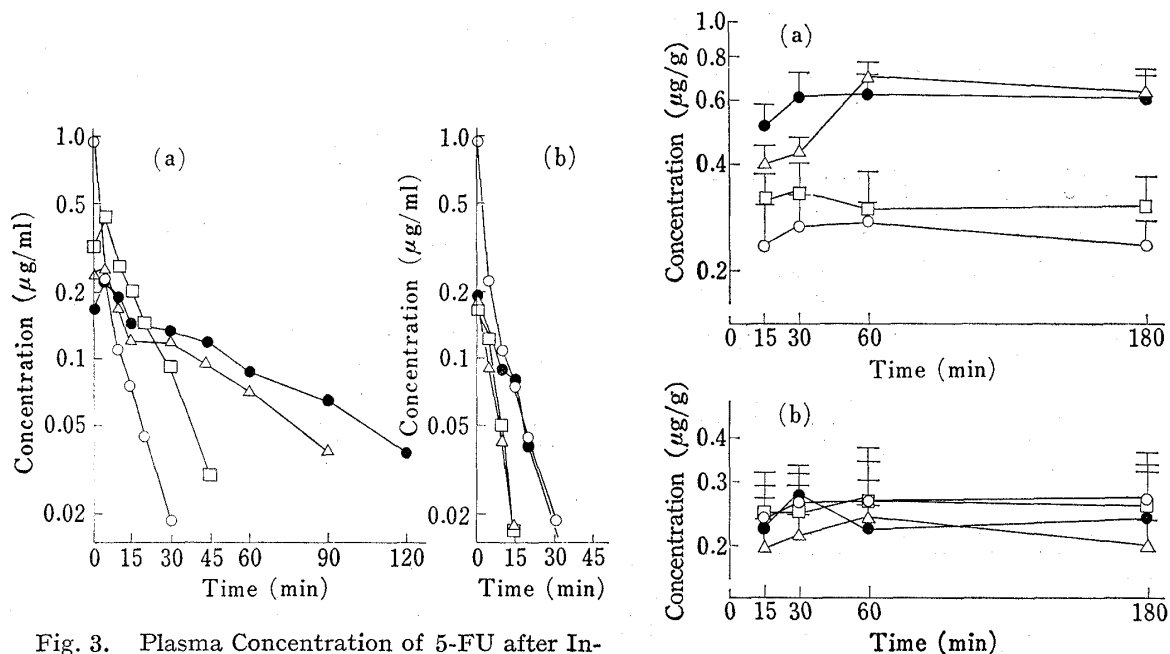

Fig. 3. Plasma Concentration of 5-FU after Intramuscular (a) and Intragastric (b) Injection of Various Formulations

□, aqueous solution; △, W/O emulsion; ●, S/O emulsion; ○, intravenous injection of aqueous solution. Concentrations were measured by microbiological assay. The mean values of at least 5 animals are presented.

Fig. 4. Concentration of Radioactive 5-FU in the Right Iliac Lymph Node (a) and Left Iliac Lymph Node (b) after Injection of Various Formulations into the Right Thigh Muscle

□, aqueous solution; △, W/O emulsion; ●, S/O emulsion; ○, intravenous injection of aqueous solution. Results are expressed as the mean+S.E. of at least 5 animals.

difference in concentration between the right and left iliac lymph nodes could be demonstrated, and consequently a probably equal supply with 5–FU from circulating blood was confirmed. On the other hand, the levels of the radioactivity in the right iliac lymph nodes always exceed those in the left nodes following intramuscular injection of emulsion formulations. These data strongly suggest an enhanced delivery of 5–FU directly from the injection site to the regional lymph nodes.

The regional lymph nodes concentrations of radioactive 5–FU following injection of three types of formulation into the stomach wall are shown in Fig. 5, together with results from intravenous injection. In the case of intravenous injection, the radioactivity already appeared in the regional lymph nodes after 5 min and then decreased gradually. But its level was always the lowest among the four formulations tested. These increase of radioactive levels following intragastric injection of the three formulations suggests the presence of direct transport of 5–FU from the stomach wall through the peripheral lymph vessels.

The radioactivity at 5 min after injection of aqueous solution was almost three times as great as that of intravenous injection, but it decreased rapidly and became almost identical to that of intravenous injection at 30 min after injection. Among the three formulations, S/O emulsion generated the highest concentration which was almost twenty–fold greater than that of intravenous injection at 5 min after injection. W/O emulsion followed this in performance.
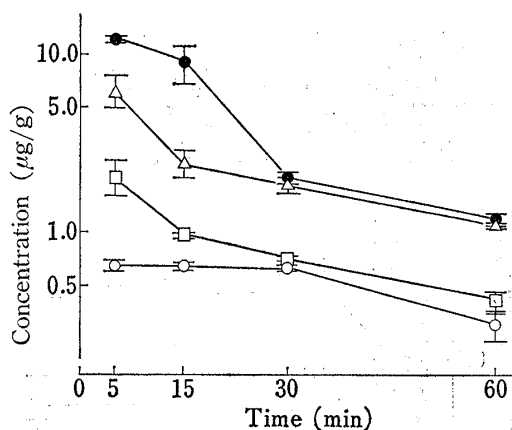

Fig. 5. Concentration of Radioactive 5-FU in the Portal and Posterior-gastric Lymph Nodes after Intragastric Injection of Various Formulations

□, aqueous solution; △, W/O emulsion; ●, S/O emulsion; ○, intravenous injection of aqueous solution. Results are expressed as the mean±S.E. of at least 5 animals.
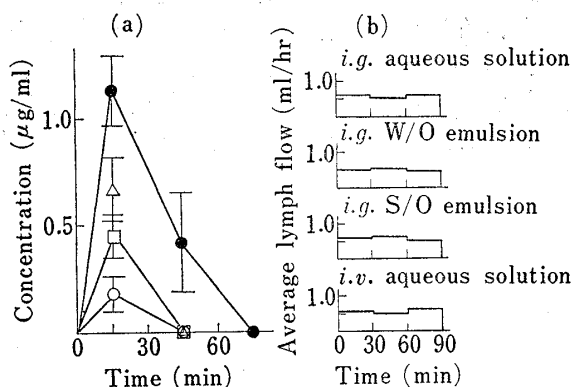

Fig. 6. Concentration of 5-FU in Thoracic Lymph (a) and Average Lymph Flow (b) after Intragastric ($i.g.$) Injection or Intravenous ($i.v.$) Injection of Various Formulations

□, aqueous solution; △, W/O emulsion; ●, S/O emulsion; ○, intravenous injection of aqueous solution. Concentrations were measured by microbiological assay. Results are expressed as the mean±S.E. of at least 4 animals.

Transport of 5-FU into Thoracic Lymph

Fig. 6 (a, b) shows the concentration of 5–FU measured by microbiologic assay in the thoracic lymph and average lymph flow during the course of the experiment after intragastric or intravenous injection. The lymph flow did not change significantly in any time period nor by any of the preparations. The concentration of 5–FU in the thoracic lymph following intravenous injection was 0.29 μg/ml during the first 30 min, which subsequently decreased and no antibacterial activity was detected in the lymph fluid of the following 30 min. In all intragastric injections, however, the concentrations in the thoracic lymph were relatively high, and their levels decreased in the order of S/O emulsion, W/O emulsion, and aqueous solution. The direct and facilitated transport of 5–FU from the stomach wall into the thoracic lymph duct via the portal and posterior-gastric lymph nodes was thereby established.

Metabolic Degradation of 5-FU

To examine an effect of the dosage forms and the route of administration on the metabolic degradation of 5–FU, the plasma and the regional lymph nodes concentrations following intragastric injection of three formulations and intravenous injection were determined by both the microbiologic assay and the radioactivity measurement. The results at 5 min after injection are compared in Fig. 7(a,b).
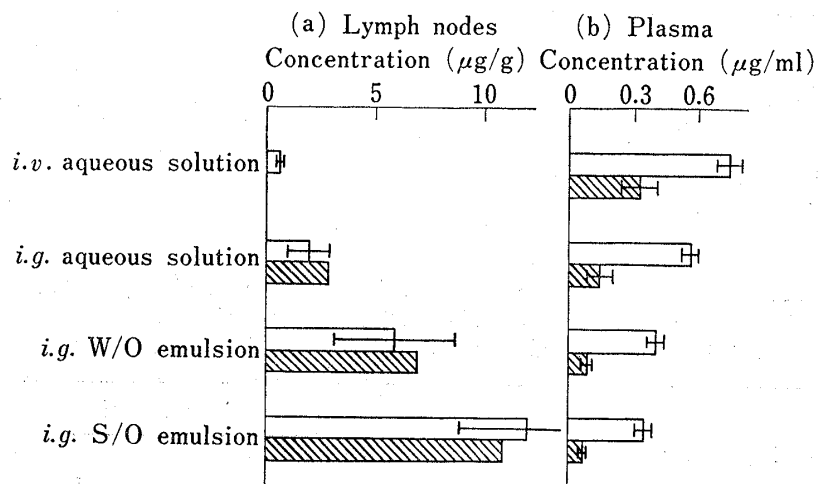

Fig. 7.   Comparison of Radioactive and Antimicrobially Active Concentration of 5-FU in the Portal and Posterior-gastric Lymph Nodes (a) and Plasma (b) after Intravenous (*i.v.*) Injection or Intragastric (*i.g.*) Injection of Various Formulations

▭, radioactivity; ▨, antimicrobial-activity. Results at 5 min after injection are compared. The horizontal bar (⊢⊣) indicates ±S.E. of the mean of at least 5 animals. Lymph nodes concentration of antimicrobially active 5-FU is the mean value of 2 groups (10 rats).

The plasma concentrations determined with radioactivity were extremely greater than those of antimicrobially active drug in any preparations. This indicates that 5–FU suffered a rapid inactivation during the systemic circulation. On the contrary, the concentrations of antimicrobially active 5–FU in the regional lymph nodes following intragastric injection of three preparations were almost identical to those of radioactive compound, while no antimicrobial activity could be detected following intravenous injection. These results suggest that 5–FU was scarcely inactivated in the stomach and the lymph nodes during such short time period. In consequence of these differences in degradation rate, injection of emulsion formulations into the stomach wall resulted in much larger ratio of the concentration of antimicrobial activity in the lymph nodes *versus* the plasma, which reached more than 135 times particularly following injection of S/O emulsion.

Discussion

A sufficient supply with cancer-destroying agents to the lymph nodes seems to offer a promising means of destroying cancer within lymphatics such as metastatic carcinoma or lymphoma. The advantage of a direct introduction of chemotherapic agents into the lymphatic vessels have been demonstrated in several reports.[10] However, since the application of such direct injection method is restricted almost to the somatic region because of the technical difficulties, only a little profit could be expected by employing this treatment

10) I.A. Ariel, M.I. Renick, and D. Galey, *Surgery*, **55**, 355 (1964); G. Kitchen and M.J. Garrett, *Clin. Radiol.*, **22**, 379 (1971); *etc.*

modality in the surgical adjuvant chemotherapy for the visceral carcinomas like colorectal or gastric neoplasm.

The present results shown in Fig. 4 and 5 indicated the rapid transfer of 5–FU from the stomach wall to the regional lymph nodes after injection of aqueous solution. The lymph nodes concentration of this intragastric injection was considerably greater than that of intravenous injection at early stage, but followed by rapid decrease and no detectable accumulation to the lymph nodes. This rapid but insufficient transport to the regional lymph nodes was also demonstrated in the recent clinical approaches[11] in which 5–FU or other anticancer agents were injected into interstitial spaces of gastrointestinal tract as an aqueous solution. These findings well document the exposition mentioned by Ballard[12] that molecules or ions having low molecular weights are absorbed primarily by the blood flow, which is about 500 times as great as the lymph flow in rats.[13] The present pharmaceutical approach to deliver 5–FU sufficiently into the lymphatics from some organs through modification of dosage form is thought to be worthwhile from this point of view.

TABLE I.   The Area under the Concentration-time Curves (AUC) of Radioactive
5-FU in the Portal and Posterior–gastric Nodes during First Hour after
Intragastric or Intravenous Injection of Various Formulations

Injection form	AUC ($\mu g/g \times min$)	
	Total AUC[a]	Calculated AUCig–AUCiv[b]
i.g. aqueous solution	50.24	18.11
W/O emulsion	131.73	99.60
S/O emulsion	266.91	234.78
i.v. aqueous solution	32.13	0

a) This value was calculated from the data shown in Fig. 5.
b) See text.

For evaluating the efficiency of formulations more clearly, the area under the concentration-time curve (AUC) of 5–FU in the gastric regional lymph nodes during the first hour was calculated from the data of radioactivity and is shown in Table I. S/O emulsion shows the largest AUC which is about 9 times as great as that of intravenous injection. Since 5–FU should also be distributed to the lymph nodes from circulating blood, the AUC of intragastric injection (AUCig) must be affected by systemic circulation. Therefore, the difference of AUCig and AUC of intravenous injection (AUCiv) indicates apparent minimum direct transport of 5–FU from the injection site into regional lymph nodes. The values calculated are also shown in Table I. It is evident that S/O emulsion has the most advantage in that it is greater at least 13 times than that of aqueous solution and 2.3 times than that of W/O emulsion in direct delivery into the regional lymph nodes. Clearly, there is a noticeable improvement in the comprehensive bioavailability of 5–FU from this system.

Table II summarize the cumulative amount (CA) of 5–FU transported in the thoracic lymph during the period for first hour. As with the AUC examination shown in Table I, the differences of CA following intragastric injection (CAig) and following intravenous injection (CAiv) were also calculated as presented in Table II. These values are expected to correspond approximately to the amounts of 5–FU directly transported from the injection site. The cumulative amounts in the thoracic lymph were comparable with the AUC of lymph

11) K. Yamada, E.D. Holyoke, and H.O. Douglass, Am. J. Surg., 131, 253 (1976); K. Kikuchi, Y. Aneha,
     H. Kanno, Y. Kunii, K. Hirata, and J. Ohta, J. Jap. Soc. Cancer Ther., 11, 519 (1976).
12) B.E. Ballard, J. Pharm. Sci., 57, 357 (1968).
13) E.J. Reininger and L.A. Sapirstein, Science, 126, 1178 (1957).

TABLE II. Cumulative Amount (CA) of Antimicrobially Active 5-FU Transferred
into Thoracic Lymph during First Hour after Intragastric or Intravenous
Injection of Various Formulations

Injection form	Cumulative amount (µg)	
	Total CA[a]	Calculated CAig–CAiv[b]
i.g. aqueous solution	0.141	0.088
W/O emulsion	0.218	0.165
S/O emulsion	0.430	0.377
i.v. aqueous solution	0.053	0

a) This value was calculated from the results shown in Fig. 6(a,b).
b) See text.

nodes, but the contribution of the distributed drug from the systemic circulation is higher in thoracic lymph than in the regional lymph nodes. The amounts of directly transported 5-FU decreased in the following order; S/O emulsion, W/O emulsion, and aqueous solution.

The present results suggest the advantage of S/O and W/O emulsions as a drug delivery system for achieving specificity into the lymphatic systems. When results of intragastric and intramuscular injection are compared, it is evident that the effectiveness of these delivery systems were more apparent in the stomach, which was explained by a rich supply of stomach wall lymph vessels.[14]

In Table I and II, the AUC of 5-FU in the regional lymph nodes and CA transported into the thoracic duct during the same time period are obtained. Consequently, the mean transit time of 5-FU through portal and posterior-gastric lymph nodes can be calculated by the following equation as described previously.[6]

$$\text{Mean transit time (min)} = \frac{\text{AUCig–AUCiv (µg/g} \times \text{min)}}{\text{CAig–CAiv (µg)}} \times \text{weight of lymph nodes (g)}$$

Since the average of the lymph nodes weight was approximately 23 mg for aqueous solution, 22 mg for W/O emulsion, and 26 mg for S/O emulsion, the calculated mean transit time was 3.9, 9.3, and 16.2 min, respectively. As is obvious from these results, the mean transit time of 5-FU in the case of aqueous solution is too short, while those of emulsions are considerably longer. These longer transit time is supposed in part to be caused from the sustained release of 5-FU from oil droplets that had been proved to play a role of carrier.[5,6]

In S/O emulsion, it had been recognized that gelled microspheres of approximately 1—2 µm in diameter are dispersed in oily phase.[5] The water soluble drug would be expected to be included in or adsorbed onto the internal gelatin microspheres. Therefore, it can be presumed that the microspheres may physically stabilize their emulsion oweing to protection from coalescence of internal phase and may prolong the release of 5-FU from emulsion in the lymph node as well as in the muscle and the stomach wall.

On the other hand, 5-FU is well known to be suffered a very rapid metabolic degradation primarily in the liver.[15] This instability accounts for the rapid plasma clearance and the considerable difference of plasma concentration between two different administration routes represented in Fig. 3. As is obvious from Fig. 7, 5-FU will be transported as an active form to the regional lymph nodes being protected against metabolic inactivation by the local administration such as intragastric injection. Therefore, local administration of 5-FU as a form of emulsion can emphasize further utility of them in cancer chemotherapy. The

14) J.M. Yoffey and F.C. Courtice, "Lymphatics, Lymph, and the Lymphomyeloid Complex," 2nd ed., Academic Press, London, 1971.
15) N.K. Chaudhuri, K.L. Mukherjee, and C. Heidelberger, *Biochem. Pharmacol.*, 1, 328 (1959).

part of radioactivity of no antibacterial activity is supposed to represent inactive metabolite which remained in the body for considerably longer period.[16]

On the basis of the evidence presented in this investigation, it is suggested that the application of W/O emulsion and S/O emulsion to a delivery system of 5–FU would be advantageous in surgical cancer chemotherapy, because a sufficient high concentration of active 5–FU can be supplied in the injection site and to the regional lymph nodes for a considerably longer period. Reduction of peak plasma concentration is thought to be worthwhile since a decrease of adverse effect is expected. In addition, the possibility of biodegradation of the emulsion components should present no clinical inconvenience. Present results support the conclusion that S/O emulsion is the most advantageous as an ideal delivery system for surgical adjuvant chemotherapy because it best satisfies the above criteria.

16) G. Hurst, E.R. Garrett, and P.H. Hinderling, Abstracts of Papers, 19th National Meeting of APhA Academy of Pharmaceutical Sciences, Atlanta, November, 1975, p. 119.