Lymphatic targeting with nanoparticulate system

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Abstract

Much effort has been made to achieve lymphatic targeting of drugs using colloidal carriers. This paper reviews the recent progress in the development of biodegradable nanoparticulate systems, including nanospheres, emulsions, and liposomes. The major purpose of lymphatic targeting is to provide an effective anticancer chemotherapy to prevent the metastasis of tumor cells by accumulating the drug in the regional lymph node via subcutaneous administration. The objectives of lymph targeting also involve the localization of diagnostic agents to the regional lymph node to visualize the lymphatic vessels before surgery, and the improvement of peroral bioavailability of macromolecular drugs, like polypeptides or proteins, which are known to be selectively taken up from the Peyer’s patch in the intestine. Nanocapsules, which are ultrafine oily droplet-coated polymeric substances, are probably one of the most promising candidates of colloidal carriers. Surface engineering by the interfacial deposition method can provide a suitable size distribution and necessary surface characteristics to the nanocapsules. Our recent in vivo study proved that polyisobutylcyanoacrylate nanocapsules showed enhanced accumulation of drug in the lymph node, compared with other carriers such as emulsions and liposomes. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Lymphatic targeting; Nanocapsules; Polyisobutylcyanoacrylate; Interfacial deposition; Liposomes; Lymph node

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1. Introduction

The lymphatic system consists of lymph, lymphatic pathways, such as lymphatic capillary, lymphatic vessel, lymphatic duct etc., and some lymphatic organs including lymph node, thymus, and spleen. The major function of the lymphatic system is to maintain the body’s water balance to the normal level as blood vessels do [1,2]. This system plays an important role in helping to defend the tissues against infection by filtering particles from the lymph and by supporting the activities of the lymphocytes, which furnish immunity, or resistance, to the specific disease causing agents. Also, it is well known that the lymphatic absorption of a drug after intestinal administration provides an advantage over the portal blood route for the possible avoidance of liver pre-systemic metabolism (hepatic first-pass effect). Due to such fundamental functions or characteristics, many attempts have been made to utilize the lymphatic system for the route of drug delivery, which have been reviewed by Muranish [3]. Research into lymphatic targeting has recently attracted increasing interest not only for providing a preferential anticancer chemotherapy, but for improving oral absorption of macromolecule drugs, or achieving mucosal immunity.

The lymphatic system is the site of many diseases such as metastatial tuberculosis, cancer, and filariasis [4]. Due to the peculiar nature and anatomy of the lymphatic system, localization of drugs in the lymphatics has been particularly difficult to achieve. Much effort for the lymphatic targeting of drugs has been directed towards the use of anticancer agents. Using various routes of administration such as intramuscular [5], subcutaneous and intraperitoneal [6–8], significant enhancement of drugs has been reported. Hirano and Hunt have done an excellent study on the effect of liposome size following intraperitoneal administration [9]. Various studies have demonstrated enhanced lymphatic uptake of anticancer drugs when administered as water-in-oil emulsions [5–7].

Besides chemotherapeutic purposes, there has been much research in the past 30 years on the staining of lymph nodes before surgery. The retroperitoneal lymph nodes, for example, are the primary filters of metastases spreading from malignant tumors of pelvic organs. The inaccessibility of these retroperitoneal lymph nodes for therapy is still one of many unsolved clinical problems. The staining of lymph nodes prior to surgery would improve the radicality and selectivity of lymphonodectomy because lymph nodes are very often difficult to locate since they are covered by fat tissue of similar color and consistency.

After intravenous administration to animals or humans, colloidal drug carriers are taken up by the mononuclear phagocytic system, mainly by the fixed macrophages of the liver and spleen. This common fate of most of the colloidal carriers may be attributed to passive targeting to the mononuclear phagocytic system after opsonization of the carriers. Consequently, it is difficult to modify the fate of drug carriers substantially unless different routes of administration such as oral, ocular, subcutaneous, or possibly other routes are chosen. Peyer’s patches, which are a collection of organized lymphoid tissues lining the intestinal tract, are the most important structural units of gut-associated lymphoid tissue. They are the primary induction sites for mucosal immunity and the target sites for oral vaccine delivery.

This paper describes the recent advance of the targeted delivery of drugs to the lymph node, and introduces our new approach.

2. Strategies for lymphatic delivery with nanoparticulate carriers

Targeted delivery of drugs can be achieved utilizing carriers with a specified affinity to the target tissue. There are two approaches for the targeting, i.e. chemical modification of drugs and pharmaceutical modification. In the case of the chemical approaches representing so-called prodrugs, the drug has to possess a suitable functional group in its molecular structure, and the method for synthesizing has to be individually developed for each drug substance. On the contrary, the pharmaceutical approach utilizing particulate carriers has such advantages that the technology, once achieved, is principally applicable to any drug, and the process is comparatively easy.

Emulsions and liposomes are probably well-
known particulate carriers with comparatively long histories of research. Recently, various types of nanoparticles have been investigated in seeking alternative carriers. Most of those carriers accumulate to the target site during continuous systemic circulation to deliver the drug substance thereon, so-called ‘passive targeting’, the behavior of which depends highly upon the physicochemical characteristics. However, much effort has been made to achieve ‘active targeting’, delivering drugs more actively to the target site utilizing specific physical forces such as magnetic force or biochemical interactions (such as receptor–ligands or antigen–antibody interactions). Although this field is still premature, further development is expected. This section summarizes recent work on the lymphatic targeting, utilizing each particulate carrier.

2.1. Emulsions

Preferential lymphatic transport of mitomycin C has been demonstrated following injection of W/O or O/W emulsions via the intraperitoneal and intramuscular routes [5]. It was reported that selective uptake after injection into the regional lymphatics occurred in the order of O/W > W/O > aqueous solution. Hashida et al. [5,10] developed gelatin spheres in oil (S/O) emulsion for minimizing the instability of the W/O emulsion. The nanoparticle-in-oil emulsion system, containing anti-filarial drug in gelatin nanoparticles, were studied for enhancing lymphatic targeting [11], and it was suggested that this colloidal system holds excellent potential as a lymphotropic carrier system. More recently, an emulsion formulation consisting of an anticancer drug, Pirarubicin, and Lipiodol® was developed to treat gastric cancer and metastatic lymph nodes [12]. After endoscopic injection of the Pirarubicin–Lipiodol emulsion, the drug was retained over 7 days at the injection site and in the regional lymph node.

2.2. Liposomes

Liposome, a nano-sized biodegradable lipid vesicle with aqueous space surrounded by a lipid bilayer, has received considerable interest as a vehicle for drug targeting to the lymphatic system. Earlier studies suggested that liposome-entrapped compounds were selectively transported into lymphatic tissue following intraperitoneal administration [8,13], intramuscular or subcutaneous injection [14,15]. The effect of liposome size was evaluated by intraperitoneal administration of liposomes with 0.72–0.048 μm in diameter and having identical compositions [9]. Liposome size significantly altered both fractions of lymphatically absorbed drug retained in lymph nodes and drug recovered in the thoracic duct lymph. The largest liposomes were those most retained by the lymph nodes. It is thought that smaller liposomes pass unretarded through the lymph nodes but that larger liposome may be predominantly entrapped by lymph node tissues during physical filtration. Lymphatic uptake of liposomes of various sizes, lipid composition, and surface characteristics were investigated [16,17]. The main factor controlling lymphatic uptake after subcutaneous administration appeared to be liposome size, and small liposomes seemed to be preferred to achieve high lymphatic uptake. The surface charge of liposomes and the route of administration were reported to be important for the lymphatic delivery of drugs [18].

Following lymphatic uptake, liposomes pass through a system of lymphatic vessels and encounter one or more lymph nodes, where a fraction will be retained. It has been suggested that phagocytosis by macrophages is one of the major mechanisms of uptake of colloidal particles in lymph nodes [19,20]. Reduced lymph node localization of liposomes in macrophage-depleted lymph nodes confirmed that phagocytosis by macrophages plays an important role in lymph node retention of liposomes [21]. To enhance targeting ability, various attempts have been made so far, including immunoliposome [22], PEGylated liposome [23], and galactosylated liposome [24].

One example of clinical application is the endoscopic gastric submucosal injection of liposomal adriamycin, which provided an enhanced lymph node targeting delivery to considerably higher levels than intravenous free adriamycin in patients with gastric cancer [25–27]. As another example, a pilot study of liposomal mitoxantrone for breast cancer was reported [28]. Lymphatic targeting is thought useful for diagnostic purposes. A case study is reported using blue violet entrapped in liposomes to localize lymph nodes before surgery [29]. Polymerized lipo-
somes were developed by Langer et al. [30]. The liposomal structure highly stabilized by cross-linking of lipid bilayer allows the oral administration of those carriers to achieve more efficient uptake from Peyer’s patch [31].

2.3. Nanoparticles

Biodegradable, polymeric nanoparticulate systems have been developed to enhance the targeting ability to the lymphatic systems or to improve the drug loading and/or the physicochemical stability of other colloidal carriers. A wide range of studies on the preparation of polyalkylcyanoacrylate nanoparticles and their therapeutic applications has been conducted by the research groups of Puisieux and Couvreur [32,33]. The lymph targeting of polyhexylcyanoacrylate nanoparticles was evaluated after intraperitoneal administration in rats. It was found that those particles were of potential use in treating tumors that metastasize in the peritoneal cavity or via lymphatic pathways [34,35]. They showed that uptake via Peyer’s patches or isolated lymphoid follicles of insulin-loaded polyisobutylcyanoacrylate nanocapsule occurred after oral administration, suggesting the possibility of peroral peptide delivery [36]. Davis and Illum have conducted extensive investigations on biodegradable nanospheres with polylactides and poly(lactide-co-glycolide) as carriers for achieving the efficient delivery of drugs and diagnostic agents to the lymphatic system. To enhance lymphatic drainage and lymphatic node uptake of nanospheres, various methods of surface engineering have been tried, including surface coating with poloxamines or poloxamers [37] and the use of polyethyleneglycols [38]. Besides the drug delivery purpose, Magnetite-Dextran nanoparticles have been investigated for diagnostic use and found potentially useful as contrast agents in magnetic resonance imaging (MRI) [39]. Lipid-based nanospheres should be alternative colloidal carrier systems for lymphatic targeting. The solid lipid nanoparticles (SLN) were developed and evaluated for the lymphatic uptake after intraduodenal administration to rats [40,41]. A liposomal mimetic formulation, a phospholipid dispersion containing dipalmitoyl-phosphatidylcholine (DPPC) and Emulphor, was also developed and found to achieve higher lymphatic uptake of drug compared to conventional DPPC liposomes [42,43]. As other nano-sized drug carriers, activated charcoal particles have been extensively studied for diagnostic purposes and the targeted delivery of anticancer drugs to the regional lymph node [44–46].

3. New approach for lymphatic targeting with nanocapsules

3.1. What is a nanocapsule?

A nanocapsule is an ultrafine particle with a diameter of less than 1 \( \mu m \), with a surface coating of a polymeric substance (Fig. 1). This is somehow different in its structural features and concept from conventional colloidal particles in emulsions which have surfaces stabilized by the adsorption of some surfactants or phospholipids. Further, nanocapsules consist of an oily core incorporating drug substances and an outer coating layer with an appropriate polymeric substance. The diameter of the particle usually ranges from tens to hundreds of nanometres. Vegetable oils, such as soybean oil, or some semi-synthesized triglycerides with medium- and long-chain fatty acids, Miglyol® or Panasate®, are best used for the core vehicle. Biodegradable polymers, such as polyalkylcyanoacrylates and poly-lactides have been utilized for the polymeric substance of the interfacial coating layer. Since the surface characteristics can be modified by selecting a suitable...
coated polymer, nanocapsules have attracted much attention as a new type of colloidal drug carrier. Earlier studies of nanocapsules with polyalkylcyanoacrylates are found in the literature [47,48]. One report with the most impact about nanocapsules may be the enhancement of p.o. insulin absorption [49,50]. In this study, the oral administration of insulin-encapsulated polyisobutylcyanoacrylate (PIBCA) nanocapsules was reported to produce a prolonged hypoglycemia in diabetic rats, suggesting the possibility of a drug carrier for p.o. insulin.

3.2. Preparation of nanocapsules by the interfacial deposition method

Puisieux, Couveur, and co-workers established the preparation method of polyalkylcyanoacrylate nanocapsules by the interfacial polymerization of monomers. The typical preparation procedure is described in the literature [48]. Briefly, an alcoholic solution of isobutylcyanoacrylate and oil containing a drug substance was poured into water. The alcohol diffused out from the oil phase to produce fine oily droplets, and then isobutylcyanoacrylate, because of its amphiphilic nature, was placed at the oil/water interface, where it polymerizes spontaneously to form the polyisobutylcyanoacrylate. The proposed method seemed quite simple and was thought to be transposable enough for the industrial scale. However, our recent examination found that this method involved some difficulty to achieve enough reproducibility in terms of polymerization degree, which may cause batch-to-batch variation of products. In addition, possible residues of monomers and oligomers from the polymerization process, and cross-reaction between the content of nanocapsules, especially the drug molecules and acrylic monomers, might limit the potential use of these nanocapsules.

To avoid the poor reproducibility and associated problems of interfacial polymerization, we applied the interfacial polymer deposition reported by Fessi [51] as an alternative preparation method. The method comprises the interfacial deposition of the preformed biodegradable polymers with well-defined molecular weight, following displacement of a semipolar solvent miscible with water from a lipophilic solution. The nanocapsules of polyisobutylcyanoacrylate (PIBCA) containing 12-(9-anthroxy) stearic acid (ASA) as a lipophilic model drug were prepared according to the following procedure: predetermined amounts of PIBCA, with molecular weights of 20,000 or 300,000, Panasate® 812 as an oily vehicle, and ASA were dissolved in methanol or acetone. This organic solution was then added into the water phase containing Pluronic F68 as a surfactant under stirring. Since water-miscible solvent quickly diffuses into water from the oily phase, the surface tension at the interface of the oil/water phases is extremely decreased by the Marangoni effect to form very small droplets. During this process, PIBCA could be deposited at the surface of the oil droplets to create a stable colloidal suspension. The organic solvent contained was finally removed under reduced pressure.

Transmission electron microscopic observation (TEM) and the quasi-elastic laser light scattering analysis proved that the nanocapsules obtained were true spheres in shape with diameters ranging from tens to hundreds of nanometres and there was no difference in morphology from those prepared by the interfacial polymerization method. Furthermore, the fact that the stable colloidal suspension was obtained even without using any surfactant is another piece of evidence proving that PIBCA is located on the surface of oily cores to protect the aggregation of droplets.

The molecular weight of PIBCA isolated from the nanocapsules was almost coincident with that of the polymer used for the preparation, suggesting that no decomposition occurred in the preparation process. The composition of the nanocapsules was also in good agreement with the composition formulated for the preparation. All these results suggest that the interfacial deposition method with PIBCA can promise acceptable reproducibility.

The interfacial deposition method may make it possible to form nanoparticles with various types of polymers besides PIBCA. More than 20 polymers with various physicochemical properties were tested for the formability of nanocapsules [52]. The result suggested that only a limited group of polymers with solubility parameter between 10 and 13 can be used for the interfacial coating substance. These polymers, due to their somewhat amphiphilic nature, are
thought to be readily disposed at the interface of oil and water phases to stabilize the suspension system.

3.3. Physicochemical characteristics of nanocapsules

The size of nanocapsules was highly influenced depending on the preparation conditions. Increasing the PIBCA ratio resulted in decreasing the particle size. Geometrical calculation suggested that the thickness of the polymer layer maintained almost constant level, independent of the diameter of the particles. Even though the fixed polymer/oil ratio was given, the type of organic solvent and the total amount of polymer and oil components in the organic solution were also important factors to decide the size of the resultant nanocapsules. Among three water-miscible solvents of methanol, ethanol and acetone, methanol gave the smallest diameter. This may be caused because the solvent with higher affinity to water is able to displace more quickly to the water phase. The amount of organic solvent dissolving oily phase also affects the size of nanocapsules. Usually, the more the organic solvent applied, the smaller the size of the resultant nanocapsules. The surface charge of the nanocapsules was decided by the electrostatic properties of polymer. When the neutral polymer is applied, the surface charge of nanocapsules is usually neutral or slightly negative. When the cationic polymers, like Eudragit RS, are applied, the zeta potential of nanoparticles are positive.

Nanocapsules coated with hydrophobic polymers tend to be easily captured by lymphatic cells in the body, when administered, because the particle with hydrophobic surface is usually recognized as a foreign substance. However, when poloxomers are used as the surfactants during the preparation process, they were effectively adsorbed onto the surface of nanocapsules to form a hydrophilic layer. This phenomenon can be directly detected by determining the increment of diameter after the addition of surfactant solution into the nanocapsules suspension prepared without using surfactant. Our preliminary studies revealed that the thickness of the adsorbed hydrophilic layer attained from 5 to 30 nm depending on the type or grade of the surfactant applied. It was also confirmed that the nanocapsules with a thicker hydrophilic layer tend to provide a longer systemic circulation when intravenously administered, as was generally recognized.

3.4. Lymphatic targeting ability of nanocapsules

The walls of lymphatic capillaries, like those of the blood capillaries, consist of a single layer of squamous epithelial cells. This thin wall makes it possible for tissue fluid (interstitial fluid) from the interstitial space to enter the lymphatic capillary. It is known that, due to its structural characteristics, high molecular weight substances like proteins and even small particles can freely pass through the walls of the lymphatic capillary. Therefore, various colloidal systems have been investigated as the object of lymphatic targeting. Nanocapsules may have the potential to deliver drugs to the lymph node through tissue spaces by local administration.

Several batches of PIBCA nanocapsules incorporating ASA as an indicator were prepared by varying formula and processing conditions. To examine the characteristics of the transit to the lymph node, the nanocapsules were intramuscularly administered to the right thigh of rats, and the ASA concentrations in the right iliac lymph node were assayed 24 h after the injection. Elimination from the injection site was found to be faster with decreasing particle size, and the observed amount of ASA in the lymph nodes was increased. These results imply that particle size is one of the most influential factors for the retention of nanoparticles in the injection site. This is probably caused by the fact that the smaller size can migrate more freely in tissue spaces, resulting in the increase of the drug amount in the lymphatic capillaries.

To evaluate the lymphatic targeting ability, the performance of PIBCA nanocapsules following intramuscular administration were compared with three conventional colloidal formulations, including EPC-emulsion, PL-emulsion and EPC-liposome, and the oily solution of ASA as a reference [53]. The EPC-emulsion and the PL-emulsion were stabilized using egg lecithin and Pluronic F-68 as the emulsifier, respectively. The EPC-liposome was prepared by Bangham’s method using egg lecithin. The ASA concentration–time profiles in the injection site, lymph nodes and blood were shown in Fig. 2, and
Fig. 2. Comparisons of ASA concentration–time profiles of various colloidal formulations in the injection site, lymph node, and blood, after intramuscular administration to rats. (a) Injection site (right thigh muscle), (b) lymph node (right iliac lymph node), (c) blood. •, Nanocapsules; ○, EPC-liposome; △, PL-emulsion; ▲, EPC-emulsion, ×, oily solution (reference).

the pharmacokinetic parameters calculated are summarized in Table 1.

As seen in Fig. 2a, PIBCA nanocapsules gradually disappeared from the injection site according to the first-order kinetics with the elimination half-life \( t_{1/2} \) of 22.7 h and the mean residence time (MRT) of 35.2 h. The other three colloidal carriers, i.e. emulsions and liposomal formulation, provided similar profiles even though the surface structure and particle size differed. The \( t_{1/2} \) values calculated were 11.1, 16.6 and 13.0 h for EPC-emulsion, PL-emulsion and EPC-liposome, respectively, and the MRT values were 27.8, 35.1 and 24.6 h for EPC-emulsion, PL-emulsion and EPC-liposome, respectively. The comparison of elimination profiles and pharmacokinetic parameters suggested that the migration of PIBCA nanocapsule is a little slower compared with other carriers. Due to no considerable difference in particle size between those formulations, the PIBCA coating probably contributed to the observed delay of the nanocapsule moving. Unlike colloidal formulations, the oily solution was retained at the injection site for many days \( (t_{1/2}: 134 \text{ h}) \). These results suggested that colloidal particles, due to their small size, easily migrate in the tissue spaces by passive diffusion, and that the PIBCA layer may have some influence on the moving of particles.

Fig. 2b shows the concentration profiles of ASA in the regional right iliac lymph node after the administration of these four colloidal formulations. It was clearly shown that the PIBCA nanocapsule was completely different in the in vivo fate from the other three carriers. Two emulsions and EPC-liposome provided similar profiles, in which the highest ASA concentration was found 1 h after the injection, decreasing gradually to one hundredth of the initial

<table>
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<th>Table 1</th>
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<tr>
<td><strong>Comparison of pharmacokinetic parameters</strong> of ASA with various colloidal carriers in the injection site (right thigh muscle) and the regional lymph node of rats</td>
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<table>
<thead>
<tr>
<th>Formulation</th>
<th>Nanocapsule</th>
<th>EPC-liposome</th>
<th>EPC-emulsion</th>
<th>PL-emulsion</th>
<th>Oily solution</th>
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<tr>
<td><strong>Injection site</strong></td>
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<tr>
<td>Half life (h)</td>
<td>22.7</td>
<td>13.0</td>
<td>11.1</td>
<td>16.6</td>
<td>134.0</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>35.2</td>
<td>24.6</td>
<td>27.8</td>
<td>35.1</td>
<td>196.0</td>
</tr>
<tr>
<td>AUC (% of dose h / g)</td>
<td>1576</td>
<td>2118</td>
<td>2034</td>
<td>1739</td>
<td>15,100</td>
</tr>
<tr>
<td><strong>Lymph node</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>MRT (h)</td>
<td>131.4</td>
<td>24.2</td>
<td>20.3</td>
<td>17.7</td>
<td></td>
</tr>
<tr>
<td>AUC (% of dose h / g)</td>
<td>1058</td>
<td>824</td>
<td>781</td>
<td>1392</td>
<td></td>
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* Calculated using the SCI software WinNonlin according to the non-compartment model.
value after 2 days. The mean residence times (MRT) of those colloidal particles were 20.3, 17.7 and 24.2 h for EPC-emulsion, PL-emulsion and EPC-liposome, respectively. Even though a slight difference was found in the profiles between formulations, it was not thought to be significant. Meanwhile, the nanocapsule formulation provided a very flat-shaped profile in which the ASA concentration stayed at a constant level over a period of 7 days. The MRT value was 131.4 h, considerably larger than other formulations.

Extremely low concentrations of ASA were found in the blood for each formulation (see Fig. 2c), suggesting that the main route to the systemic circulation would be via the regional right iliac lymph node. From the above results and the MRT analysis, it can be said that the rate-limiting step for the colloidal particles of emulsion and liposome is the clearance from injection site and the particles may be quickly removed from the lymph node. On the other hand, for nanocapsules, the passage of the lymph node seems the most time-consuming process.

The observed difference in the in vivo behavior of colloidal particles could be related to the difference in its surface characteristics. With nanocapsules for instance, due to the surrounding PIBCA layer, more hydrophobic property must be imparted to the surfaces than other colloidal particles. A large number of lymphocytes, such as macrophages or leukocytes, are known to be distributed in the lymph nodes and lymphatic capillaries. Probably a certain part of the nanocapsules administered is captured by those active lymphocytes to retain in the lymph node, because hydrophobic surfaces are easily recognized as foreign substances by lymphocytes. In fact, it has been suggested that phagocytosis by macrophages is one of the major mechanisms of uptake of colloidal particles in the lymph nodes [19,20].

It is quite exciting that the PIBCA nanocapsules are retained in the regional lymph nodes far longer than other colloidal carriers following intramuscular administration. Our recent in vitro experiments provided possible explanations for this phenomenon [53]. In the stability study, the PIBCA nanocapsules were proved to be more stable in the plasma-containing aqueous solution than the emulsion particles with a similar oil component. This means that nanocapsules were effectively protected from lipolysis due to the PIBCA coating functioning as a physicochemical barrier. Furthermore, the incubation study, in which colloidal particles were directly incubated with the homogenates of rat lymph nodes at 37°C, provided more direct evidence. Namely, when the incubation mixture was separated by density-gradient centrifugation, most of the PIBCA nanocapsules were found to be accumulated in the lymphocyte fraction, whereas only a small portion of the emulsion particles were distributed into the corresponding fraction under the same operating condition. In the case of no addition of homogenates, the nanocapsules were distributed into a different fraction. All these results suggest that the PIBCA nanocapsules actually had a strong affinity to the lymphocytes.

The technology of this colloidal carrier system is still premature, and there are many things to be examined before actual use. However, our recent accomplishment implies the possibility to offer a more desirable lymph node targeting system to the anticancer chemotherapy. At present, work on this carrier system is continuing from the practical point of view.

4. Conclusion

Review of the current status of lymphatic targeting research revealed that, even though no carrier systems have yet been introduced into clinical application, an abundance of accomplishments have been made in this field for the past two decades. The purposes of our research were to provide a colloidal lymphotropic system with an acceptable quality for clinical use and to establish a preparation method applicable for industrial production. Our basic research strongly suggested that the nanocapsule is one of the most promising approaches for lymphatic targeting because of the possibility of achieving well-defined qualities with a simple manufacturing process. The interfacial deposition method seems useful for the surface modification of nanocapsules. Our recent in vivo study proved that the PIBCA nanocapsules have a potential to retain drug in the regional lymph node after intramuscular administration.
Acknowledgements

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