The Role of Particle Design Studies in Developing Pharmaceutical Dosage Forms

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In order to realize patient centric therapy, studies on drug administration is progressed focusing on its route and type of dosage forms. In addition to guaranteeing efficacy and safety in drug administration, there are development of new dosage forms that take into consideration ease of administration, and development of DDS for the purpose of more effective drug delivery. In either study, particle design research in developing the dosage forms is important. Recent trends in dosage form design development and the particle design researchs to support them will be introduced.

Introduction

Human drugs, administered in divided doses as required, are designed in optimal dosage forms to ensure efficacy and safety; especially well-known forms include tablets, capsules, injections, ophthalmic solutions, and adhesive patches. As you can see from this listing, diverse administration routes are available and the optimal route is selected for individual drugs. Some drugs have multiple routes. The decision on the administration route is based on various rationales and considerations. Among them, recently gaining much attention is patient-centric therapy (PCT).

Considering PCT in terms of formulation and administration route, the oral form is deemed to be minimally burdensome and therefore preferrable for the patient. Oral administration is also seen as desirable from a medication adherence aspect, i.e., assurance that the drug administration is executed as prescribed. Eight oral dosage forms are currently set forth in the Japanese Pharmacopeia (JP), 17th Edition (JP17): tablets, capsules, granules, powders, liquids and solutions for oral administration, syrups, jellies for oral administration, and films for oral administration.

The tablets section includes the subsection of orally disintegrating tablets (ODTs) as a formal dosage form. The films section was newly introduced in the JP17, together with the orally disintegrating films (ODFs) subsection. The JP started to provide the definitions and specifications of the formulations sorted and aligned by the route of administration in the 16th edition, published roughly a decade ago, in concordance with the time when a number of pharmaceutical products were developed giving consideration to the ease of administration for the patient, such as ODTs, with PCT becoming a prevalently accepted notion.

Another important issue in pharmaceutical preparation investigations is the effective delivery of the drug to the target site, i.e., research and development of the drug delivery system (DDS). The early DDS studies included investigations of controlled release oral drugs and change from injectable to transdermal dosage forms; these studies led to early realization into products. As a DDS for drugs administered into the circulation, encapsulation in a microparticle carrier to achieve efficient delivery to the site of action has been studied vigorously and has led to the development of

anticancer drug products, among others. Such carriers include liposomes (Lips) consisting of phospholipids, lipid emulsions, and albumins. While ideal targeting drugs that are 100% delivered to their target sites (e.g., tumor tissue) are yet to be realized, the use of microparticle carriers has improved the targeting efficiency.

Particle design studies have been a tradition at the pharmaceutical laboratory at Gifu Pharmaceutical University, where I belonged. On the basis of these studies, my colleagues and I have pursued pharmaceutical designing with the goal of "patient-centric formulation design"[1] since the early 2000s. Here I would like to share with you some findings mainly from our work to show the benefits of particle design studies in accomplishing target formulation designs.

Easy to swallow solid formulations and particle design studies

Orally disintegrating tablets

The first product of the aforementioned ODTs on the market was developed abroad under the trade name Zydis. This product is prepared from the aqueous solution or suspension of the drug filled in the blister pockets, which is then subjected to freeze drying.[2] Zydis is known as a typical ODT of a porous structure that disintegrates very rapidly when coming into contact with water. Several domestic ODT products prepared by the same method are also available. Advances in ODT development have enabled manufacturing of ODTs having similar hardness as conventional oral tablets and even using similar tableting machines (compression molders) as those for conventional tablets, bringing about many ODT products into the clinical setting.

Tablets are formulated using various excipients, such as diluents/fillers, disintegrants, binders, and lubricants. The process for determining the kind and amount of each excipient to be used is called a formulation study. In the case of ODTs, a regular formulation study alone may not suffice to clear their property requirements: disintegration within 30 seconds in the oral cavity plus the hardness of conventional tablets. Mannitol and erythritol, for example, are desirable as a filler because of their superior solubility, but they are poor in compression and compaction properties; investigations to improve their compactibility are under way. Some ODT products are made using mannitol products suited for direct tableting; such a filler is processed for granulation using the spray-dry granulation method, as is lactose. Also, to ensure the drug's disintegration property, a comprehensive formulation study is needed for other excipients as well as the filler.

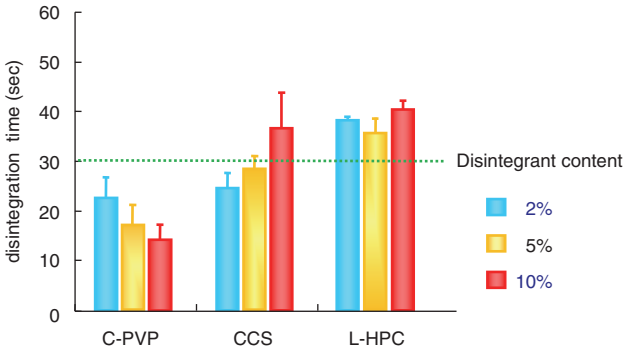


Figure 1 Disintegration time of erythritol tablet containing composite particle prepared by spray-drying with silica and disintegrant
Formulation of tablets: Erythritol + 10% composite particle + 2-10% disintegrant + 0.2% lubricant
Disintegrant: C-PVP: cross povidone, CCS: croscarmellose sodium, L-HPC: low substituted hydroxy propyl cellulose

Allow me to show you some of our studies in which we worked on particle designs for ODT development. With respect to diluents/fillers, we used erythritol, which is hardly compactible, and porous silica to formulate composite particles employing the spray-dry method and compressed this formulation into tablets, which we showed were equivalent in hardness to conventional tablets.[3] The addition of small quantities of porous silica particles was empirically known to slightly improve the tablet hardness, but the presence of silica in the formulation alone was not enough to explain the resulting drastic improvement in compactibility. Powder X-ray diffraction showed that the sugar alcohol remained in a crystalline state, ruling out disintegration of sugar alcohol crystals as a cause of the improved compactibility. Subsequent thermal and other analyses of different sugar alcohol to silica ratios revealed the contribution of sugar alcohol placed in a high-energy state.[4] Identical peaks displayed in the powder X-ray diffraction pattern showed the absence of so-called crystal polymorphism while a study on particles dispersed in a solid medium indicated the contribution of porous silica to stabilization of the high-energy state.[5] Figure. 1 presents model formulations containing composite particles that achieved our target disintegration property (disintegration within 30 seconds) by the addition of proper amounts of disintegrants.

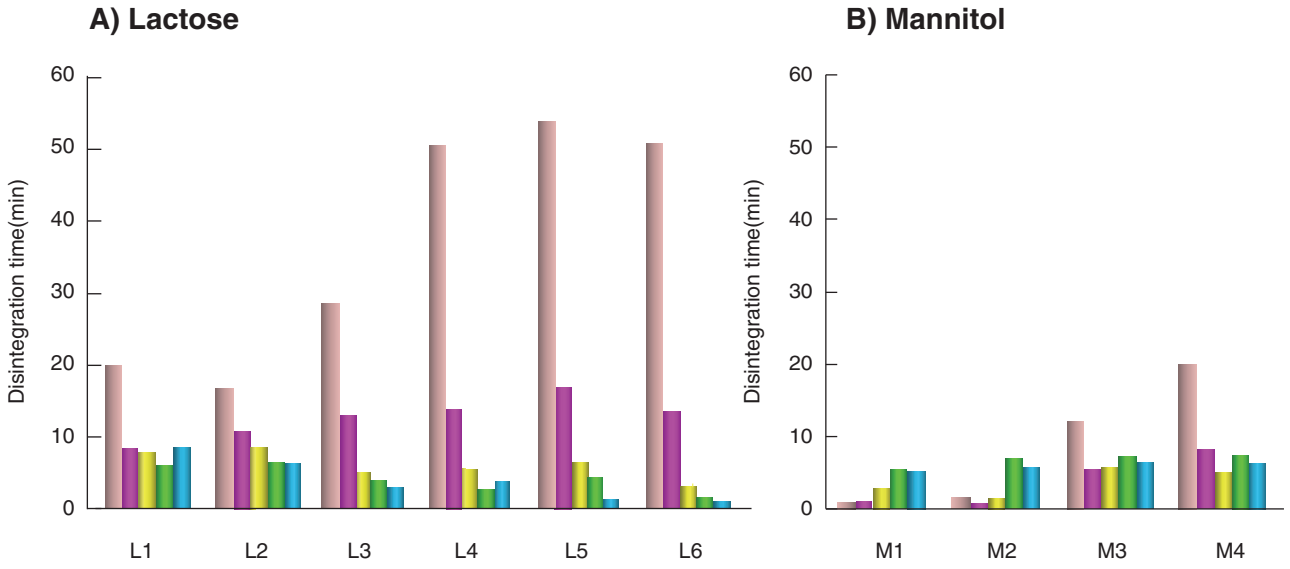


Figure 2 Disintegration time of tablets formulating magnesium stearate (Mg-st) or different type of sugar alcohol (SE) as a lubricant
Formulation of tablet: Mannitol or lactose + magnesium stearate (1%) or sugar alcohol
Mg-st S-370F S-770 S-1170 S-1570
L1: Dilactose S, L2: Super Tab 21AN, L3: Fast-Flo Lactose, L4: Tablettose 100, L5: Flow lac 100, L6:Super Tab 11SD
M1: Parteck M200, M2: Fine mannitol, M3: PEARITOL 200SD, M4: Mannitol (crystal)

Table1 Premixed or co-processed excipients with mannitol for direct tableting of ODT

Trade name	Formulation
F-MELT	Mannitol, xylitol, microcrystalline cellulose, cross povidone, Metasilicate alumic acid magnesium or Anhydrous calcium hydrogen phosphate
SmartEx	Mannitol, L-HPC, PVA
Ludiflash	Mannitol, Collidone CL-SF, Collicoat SR30D
Pearitol FLASH	Mannitol, corn starch
Granfiller D	Mannitol, carmelose, cross-povidone

L-HPC: Low-substituted hydroxy propyl cellulose
PVA: poly vinyl alcohol

Improving compactibility with the use of a binder is a common strategy in tablet designing. In the case of ODTs, however, it was confirmed that upon disintegration the binder in the tablet dissolved, causing delayed hydration and longer disintegration time than intended. In the striving process for assuring compactibility with the addition of minimum quantities of the binder to avoid disintegration delay, we found that this aim was achievable by the use of micronized hydroxypropyl cellulose (HPC), a widely used binder. Further, taking HPC grades into consideration, we presented some model ODT formulations using HPC-SSL fine powders.[5] With an established manufacturing process, HPC-SSL fine powders are commercially available, and at present they are utilized for broader purposes, such as hardness adjustment of tablets. Regarding lubricants, magnesium stearate (Mg-st) is the most freaquently used in tablet formulation has now become far more common than before, whereas other substances are also used in some medications and health food products. Sucrose fatty acid esters (SEs) are one of them. We assessed the effects of some SE products that were much less hydrophobic than Mg-st. Figure. 2 summarizes the disintegrating time of tablets formulated using lactose, a typical filler for tablets, with the addition of different types of SEs (S-370F, S-770, S-1170, or S-1570; in the ascending order of hydrophilic property). As expected, a higher hydrophilic property of the lubricant was associated with shorter disintegration time (Figure. 2).[6] Conversely, in a similar study on tablets formulated with different types of mannitol, a typical filler for ODTs, we found shorter disintegration time for certain combinations of mannitol and Mg-st or SEs of higher hydrophobic properties (Figure. 2). This reversal phenomenon may be explained as follows: in instances of a very fast disintegration, the presence of a hydrophobic portion within the tablet may contribute to rapid hydration by reducing the amount of water consumed for mannitol dissolution.

Drug additive manufacturers, going beyond the development of ODT fillers for direct compaction, are engaged in the development of products having higher functionalities, such as improved disintegrable profiles, based on optimal mixtures of additives (premixed products) or formulations with composite particles (composite formulations). Table 1 lists some of such products along with their formulations. Their manufacturers are not limited to companies in Japan,

where ODT development is active, but multiple overseas manufacturers are also present. Increased attention to and further advances in ODTs are anticipated.

Orally disintegrating films

Orally disintegrating films (ODFs), similar in characteristics to ODTs, are expected to be prescribed for extended use because of their dosage form. As stated before, ODFs have been included in the JP. The film developed abroad by Prestige Medical under the trade name Chloraseptic Sore Throat Relief Strips was the first ODF approved as a medicinal product in 2004, which was followed by many other products of the same kind. In Japan, Voglibose OD film was launched in 2006 as the first medicinal ODF on the domestic market. Over-the-counter ODF development has been ongoing since then as in the U.S. and European markets.

ODFs are advantageous over ODTs in ease of dosage adjustment as well as ease of administration, and hence high expectations are held as a new pediatric drug. ODFs for children have already been approved in the U.S. and Europe. In Japan although such products are yet to be made available, ODFs are drawing greater attention for their dosage form suited for use in children. Clinical dose levels for pediatric patients are often based on their weight and age group. For better dosage adjustability, it has been proposed abroad to develop long tape-like ODFs and administer them in the length determined based on the calculated required dose. Wening et al.[7] presented a method to graduate the film itself and different types of devices to sectionalize the film. Niese et al.,[8] taking the example of warfarin, which requires frequent dose adjustment, reported on their development of a device for film dose adjustment (e.g., a tape dispenser) and formulations suitable for use with the device (e.g., those ensuring flexible dosing). The usefulness of the film as a dosage form suited to personalized formulation, not limited to pediatric patients, was also reported. Visser et al.[9] evaluated the feasibility of small-scale ODF preparation by the solvent casting method using different model active ingredients added to the film forming agent hydroxypropyl methylcellulose (HPMC) and concluded that such customized ODF production would be possible. We also assessed preparation of ODFs of high fluconazole content with sufficient tensile strength and practically short-enough disintegration time for in-hospital ODF preparation purposes.[10]

The components used to form films, which are equivalent to excipients for tablets, are called film forming agents, which include HPMC, hydroxypropyl cellulose (HPC), polyvinyl alcohol (PVA), and pullulan. Among them, HPMC is most commonly used, probably because, for one, accumulated data are available on film formability and other properties as a tablet film coating agent. We conducted various evaluations, aiming to clearly characterize varying film forming agents to contribute to future development of ODF as well as ODT products. One of our studies was on the development of ODFs using HPMC; we tested films formulated with wet-ground micronized low substituted HPC, the application development of which was ongoing at that time, and reported that those films achieved drastically shortened disintegration time.[11] We also found that ODFs of high mechanical strength were preparable using HPC without the addition of a plasticizer, which is required for other film formers,[12] and that the disintegration time was controllable by the inclusion of suitable hydrophilic microparticles in the formulation.[13] For novel dosage forms, it is especially important to establish assessment methods. We evaluated a technique that employed a taste sensing system to detect the bitter taste of sample ODFs[14] and developed and assessed a disintegration test system for ODFs capable of automatically detecting the ending of disintegration time.[15]

Particle designing for drug delivery

Lips as drug carrier systems

Phospholipids, which comprise the cell membrane, are reported to form closed vesicles in water. These vesicular structures, called Lips, consist of bilayers. They were expected to serve as highly biocompatible microparticle drug carrier systems in addition to their role as an experimental biomembrane model. Actually, Lips are used as carriers for the anticancer drug doxorubicin products that are available in injectable form (e.g., Doxil®). Research to enable gastrointestinal absorption of insulin utilizing Lips was also initiated early on, but this objective has not been realized yet clinically.

Drug-loading particles are usually of submicron size. Lips prepared by the most common method, thin-film

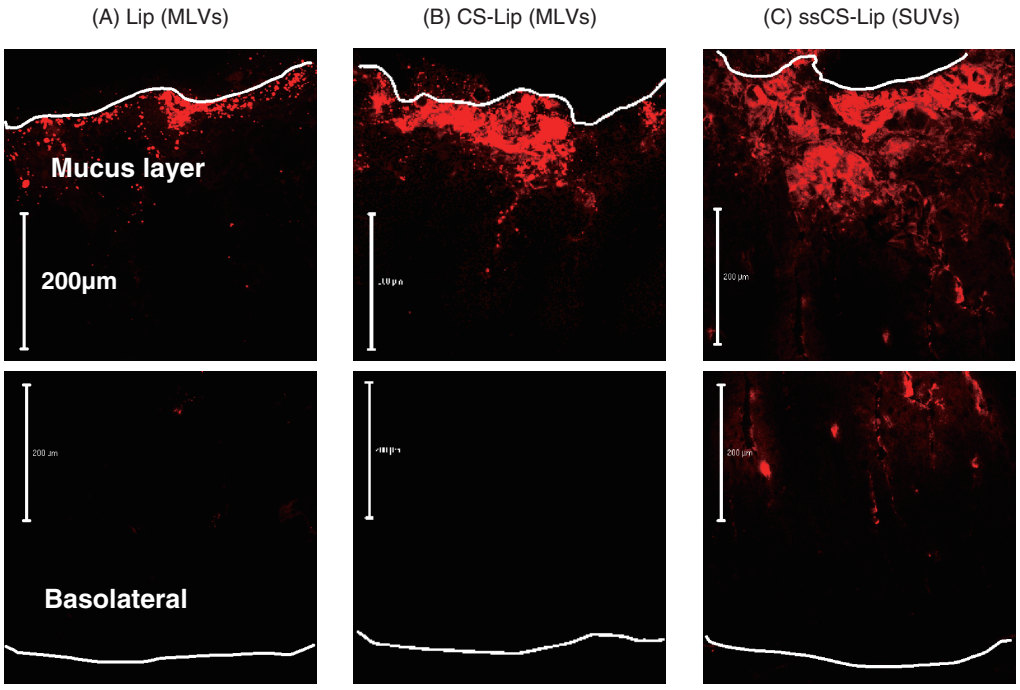


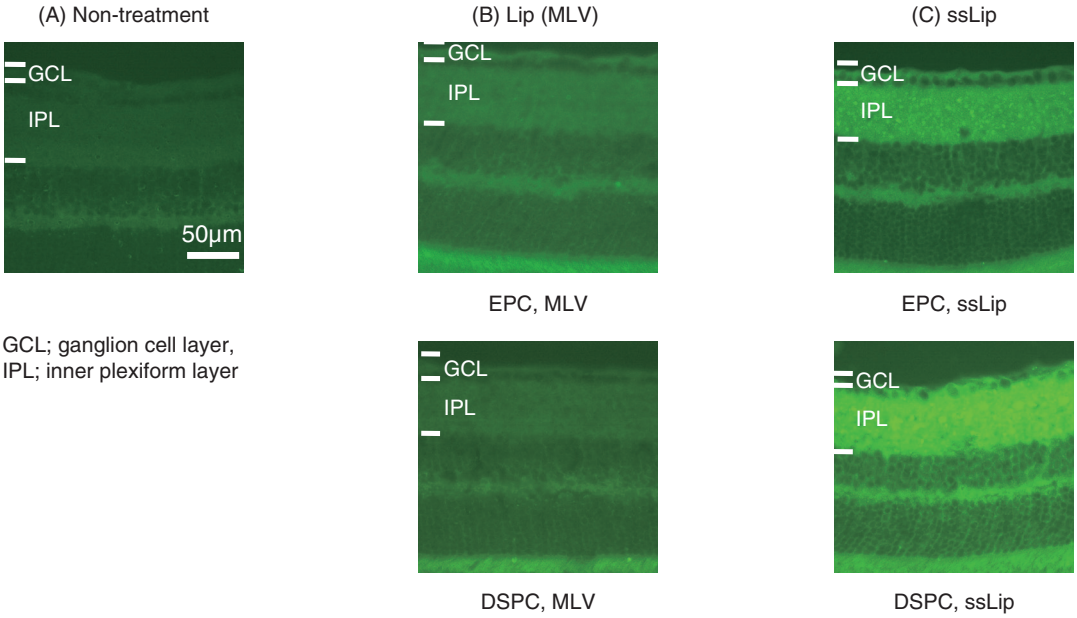
Figure 3 Confocal laser scanning micrographs of slice samples of upper part of the intestinal tract at 2hr after intragastrical administration of (A) Lip (MLVs), (B) CS-Lip, (C) ssCS-Lip in rats
Lip: liposome, CS-Lip: chitosan coated liposome, ssCS-Lip: submicron sized CS-Lip
The mean particle size of liposomes: (A) 7.56 μm (B) 3.58 μm (C) 0.28 μm. Lipid formulation of liposomes: DSPC: DCP: Chol.=8: 2: 1. Red parts means presence of corresponding liposomes.

hydration, can be several micrometers, but the size can be adjusted with relative ease to approximately 100 to 200 nm. It is also possible to render Lip particles either positively or negatively charged by adding small quantities of a charged substance together with phospholipids. The hydrophobic properties of Lips can be controlled by altering their surface membrane fluidity with the addition of a proper amount of cholesterol in drug preparation. Since the surfaces of Lip particles can be modified with substances such as macromolecules or surfactants, it was deemed feasible to achieve particle designs suited to different administration routes.

Oral administration of peptides using mucoadhesive Lips

Studies of DDSs utilizing Lips have been active since around the 1970s, soon after phospholipids were reported to form Lips. I started working full-fledgedly on Lip formulations in around 1990, when mucoadhesion-based control of tablet and granule retention time was a high-profile topic in formulation studies. Our interest in Lip particle surface modification and adhesion of small particles to intestinal mucosa led us to prepare chitosan (CS)-coated Lips (CS-Lips; Lips with CS-modified surfaces; CS is known to be mucoadhesive) and evaluate the effects thereof.[16] Mucoadhesive Lips were successfully designed as planned. Lips encapsulating insulin were orally administered to rats, and to analyze their pharmacological effects, changes in the blood glucose level were monitored versus noncoated Lips loading insulin. The administration of insulin encapsulating CS-Lips resulted in a significant reduction in the blood glucose level, and this effect lasted for 12 hours or more. These results confirmed in vivo manifestation of the mucoadhesive effect observed in vitro.[17]

Given the above results, we assessed the usefulness of mucoadhesive Lips and optimization of their functions from various viewpoints. The finding that drew our attention most from a particle design perspective was the wide variability noted in Lip retention time depending on Lip size.[18] Direct observation was the only method available to check the particle behavior in the intestine. Thus, Lips loading a lipid-soluble fluorescent substance were intragastrically administered to rats, and horizontal sections of their intestinal tracts were observed post-administration with confocal laser scanning microscopy. All the micrographs in Figure. 3 were taken 2 hours post administration. You can see that the amount of Lips (shown in red) differs greatly depending on the particle size of the Lips administered. This trend was augmented by CS coating of the Lips. While it is generally perceived that Peyer's patches' function is



GCL; ganglion cell layer,
IPL; inner plexiform layer

Figure 4 Delivery of coumarin-6 (fluorescence marker for liposomes) with liposome to posterior part of eye observed with fluorescence microscopy 30 min after instillation to the eye in mice
Lip: liposome, ssLip: submicron sized Lip, EPC: egg phosphatidyl choline, DSPC: di-stearoyl phosphatidyl choline
EPC liposomes are relatively softer compared with DSPC liposomes.

involved in the intestinal absorption of particulate substances, such a tendency was not noted for Lip absorption. Some Lip particles were seen penetrating into the intestinal epithelial mucosa.[19] Studies up to recent times have detected an existing model macromolecular compound (fluorescein isothiocyanate dextran) in the circulation in experiment systems similar to ours. This finding has convinced us that CS-Lips are a useful carrier system to increase the absorption of macromolecules from the intestine. In addition, the simultaneous delivery of a permeation enhancer with the macromolecular drug as entrapped in Lips was shown to augment both the pharmacological effect and absorption levels of the entrapped macromolecular drug, which indicates that part of the drug is released and absorbed in the vicinity of the mucosa.[20]

Retention of Lips administered via lung

Pulmonary administration via inhalation has been considered to be an efficient route for better absorption of macromolecular drugs such as peptides. The presence of fewer degrading enzymes and thinner epithelial cells make the lung a more desirable site for drug absorption than the intestine. Inhaled insulin powders to treat type I diabetes with frequent dosing were actually commercialized, but regrettably, this dosage regimen was not widely accepted as an alternative to an injection and is no longer available on the market.

Pulmonary administration of Lips is intended for controlled drug release and, as in the intestine, prolonged drug retention. The respiratory system being a closed system within the lung, I took interest in what effects would result from mucoadhesive properties of Lips in the alveolus, where macrophages are known to ingest foreign materials. To clarify the behavior of surface-modified Lips after pulmonary administration, the amounts of Lips on the tissue and in the bronchoalveolar lavage fluid (BALF) were evaluated at designated time points post-administration. CS-Lips were primarily found adhered to the tissue, whereas Lips with PVA (a comb-shaped hydrophilic polymer) formed on the surface (PVA with a hydrophobic anchor [PVA-R]-coated Lips; PVA-R-Lips) were detected in abundance in the BALF. PVA-R-Lips loading a model peptide drug were associated with a longer-lasting pharmacological effect of the peptide than were CS-Lips, which led to the conclusion that prolonged drug retention in alveoli was more effective than delivery to the pulmonary tissue as a function of the DDS.[21]

Regarding PVA-R-Lips, we have demonstrated in experimental animals that intravenously administered PVA-R-Lips are well retained in the circulation, like pegylated Lips, and hence show higher levels of delivery to the target tumor tissue. These aspects are

evaluable by blood sampling and isolation and quantification of the DDS. To assess long-term retention in the tissue, a less invasive methodology is more appropriate. The IVIS Imaging System is an effective instrument for such assessment for DDS microparticles. This system was used to monitor PVA-R-Lip retention time in the lung, using indocyanine green as a suitable marker, versus surface-unmodified Lips; although results varied between animals monitored, the retention time was significantly greater for PVA-R-Lips than that for unmodified Lips.[22] The PVA layer over the PVA-R-Lip surface is deemed to effectively decrease the uptake by alveolar macrophages, as observed in the liver, where intravenously administered PVA-R-Lips reduced the elimination by hepatic macrophages.

Delivery of Lip eye drops to the posterior eye segment

Eye drops are the most common dosage form for ophthalmic pharmacotherapy. They are formulations that are primarily used on the anterior part of the eye, such as the conjunctiva. Situated in the posterior part is the retina, which is a crucial tissue for eyesight. No eye drops are currently available for retinal damage. Recently in Japan, as super-graying of society progresses, incidence rates of serious posterior eye diseases such as diabetic retinopathy and age-related macular degeneration are on the rise. These diseases are particularly problematic in that loss of vision may result if they are left untreated. Neovascularization secondary to edema that develops in the vicinity of the macula is a symptom that requires treatment. Fortunately, potent medication is now available to inhibit this occurrence at high rates. However, its dosage form is currently limited to invasive intravitreal injection. Medication in the form of an ophthalmic solution, if made available, would greatly contribute to advances in pharmacotherapy.

We assessed intraocular behaviors of Lips in mice given Lip suspension containing a fluorescent marker (coumarin-6) by observing their retinae for Lip delivery characteristics. Nano-sized Lip particles were found to reach the posterior segment of the eye (Figure. 4). Factors affecting the delivery efficiency were shown to include particle size, that is, the smaller the particles, the higher the delivery efficiency, and Lip particle rigidity.[23] Since there were no established methods to quantify nano-sized particle rigidity, we proposed to express it numerically using the ratio (Rd) calculated from the mean particle size (d50) determined with dynamic light scattering and the particle size (perpendicular height) obtained with atomic force microscopy. As expected, these two values were almost the same for highly rigid polymer particles like polystyrene, yielding Rd of nearly 1.0. Lip particles exhibited rigidity that reflected the value roughly predictable from the type of component phospholipid.[24] The effects of use of Lips in the form of an ophthalmic solution were assessed in model animals treated with either antioxidant- or anti-inflammatory drug-loaded Lips. They were shown to reduce light-induced retinal damage[25] and choroidal neovascularization,[26] among others.

Closing remarks

In preparing a patient-centric formulation, the design of its constituent particles carries a solid weight, as shown above. Variable particles are available, ranging from powder particles of several tens of micrometers in size for solid formulations to submicron-sized Lip particles for the DDS. Whatever particles are selected, the target formulation design can only be achieved when the preparation of the selected particles and assessment thereof both go well. Each industry normally has its own product assessment methods. It would be crucial for researchers to identify the essence of assessment required and seek cooperation of professionals in other fields across industries where necessary. Promotion of information exchange in that regard is one of the objectives of the Division of Particulate Design and Preparations of the Society of Powder Technology, Japan, where I have long belonged for research activity purposes. It is my wish to continue with the development of formulations that contribute to PCT through promotion of interdisciplinary matching.

* Editorial note: This content is based on HORIBA's investigation at the year of issue unless otherwise stated.

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