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Review Article

Lipidic, Protein and Polymeric Technology: An Updated Review

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Abstract:
In the field of pharmaceutical technology, lipids and polymers are regarded as essential excipients for the manufacture of most dosage forms. This is true regardless of the route of administration. They provide a variety of functions, including those of support vehicles, release rate modifiers, stabilizers, solubilizers, permeation enhancers, and transfection agents, among other responsibilities. This manuscript summarizes the fundamental roles of these two important classes of excipients, whether they are used alone or in combination, and provides insight on their functional properties in a variety of different types of drug formulations. The primary focus of this manuscript is on selected applications that were presented and discussed at the Annual Scientific Meeting of the Gattefossé Foundation in 2018. For the purpose of dispensing active medicinal substances that have poor permeability qualities or low water solubilities, oral formulations are given priority as the route of administration. In addition, this review paper discusses the use of lipids and polymers in the design of colloidal injectable delivery systems and as substrates in additive manufacturing technologies for the fabrication of tailor-made dosage forms. This topic is covered in both of those areas.
Keywords: Additive, Polymers, Manufacturing, Lipid, Pharmaceutical, Technology

Introduction

The use of nanoparticles as innovative medication delivery methods has shown a great deal of promise. When medications are able to be delivered to the place of interest in a manner that is both more effective and more efficient, this results in fewer negative systemic side effects and more positive therapeutic activity. Delivery systems made of nanoparticles, including as liposomes and polymeric nanoparticles (NPs), have been widely developed for the purpose of transporting a wide range of bioactive compounds, including pharmaceuticals, genes, proteins, and ligands used for targeting. Liposomes are one kind of delivery mechanism. They are lipid vesicles that are spherical in shape and have a bilayer structure made up of natural or synthesized amphiphilic lipid molecules. Because they are biocompatible, biodegradable, nontoxic, flexible, and non-immunogenic, liposomes have found widespread usage as drug delivery vesicles for both systemic and local administration. This has led to an increase in the use of liposomes. In addition, the lipid components have the ability to combine with the cell membrane, which speeds up the process of

liposomes being taken within the cell. However, liposomes have a number of drawbacks, particularly with regard to their physical and chemical stability, their repeatability from batch to batch, their capacity for sterilization, and the expansion of their production scale. Polymeric nanoparticles, on the other hand, have great structural integrity because of the stiffness of the polymer matrix. As a result, they are fundamentally more stable than liposomes. Toxic organic solvents are used in the manufacturing process of polymeric nanoparticles (NPs), which results in poor drug encapsulation for hydrophilic medicines. Other drawbacks of polymeric NPs include cytotoxicity and degradation of the polymer. In order to transport therapeutic compounds in a manner that is both safe and effective, lipid–polymer hybrid nanoparticles, also known as LPNs, are increasingly being explored as viable alternatives. LPNs combine the beneficial properties of both liposomes and polymeric NPs. Polymeric nanoparticles that are encased in lipid layers are known as LPNs. Because of the presence of the lipid coat, hybrid nanoparticles are able to encapsulate not only pharmaceuticals that are insoluble in water but also medications that can be dissolved in water while maintaining a high level of encapsulation efficiency. LPNs have great biocompatibility and bioavailability because of the lipid layer, in addition to strong structural integrity because of the polymer core, which is responsible for the stability of the LPNs during storage and the controlled release capability.

In the process of manufacturing NPs, poly--caprolactone, often known as PCL, is a polymer that has been authorized for use by the Food and Drug Administration (FDA) and is frequently utilized. PCL is a biocompatible and biodegradable polymer that is also non-toxic and has high permeability to a number of different medications. In contrast to other biodegradable polymers that are routinely employed, such as poly(lactide) (PLA) and poly (lactide-co-glycolide) (PLGA), the degradation of PCL does not result in an acidic environment. This is important since an acidic environment might potentially affect the structure and characteristics of proteins. The polymeric core and lipid shell are prepared separately using two distinct processes in some of the technologies developed to prepare LPNs. After that, the two components are combined in a two-step procedure using either direct hydration, sonication, or extrusion to obtain the desired lipid shell polymer core structure. However, some of the drawbacks of using this technology include the fact that the procedures of manufacturing the polymeric core and the liposome vesicles separately are both technically challenging and less effective. In order to bypass these issues, a strategy that is very straightforward and which merges the two phases of the method that requires two steps into a single step has been assessed. In the scientific literature, many modifications of the single-step process, such as nanoprecipitation and modified solvent extraction/evaporation procedures, have been referred to as viable alternatives.

1. Polymer-Based Oral Formulations

The use of polymers in oral dosage forms as pharmaceutical applications ranges from the use of polymers as binders in tablets to the use of polymers as viscosity and flow-controlling agents in liquids. It is essential to take use of their extensive range of physical (such as density and particle size) and chemical characteristics (such as molecular weight and substitutions) while attempting to solve formulation problems. Polymers may be used as film coatings for the purpose of masking the bad taste of a medicine, increasing the stability of the drug, and modifying the release properties of the drug (Table 1). Additionally, the ability to mix various polymeric excipients enables the manufacture of controlled release drug delivery systems as well as the construction of unique and robust dosage forms. This is because the formulation process may take use of the versatility offered by the polymeric excipients. This section devotes the most of its attention to discussing the usage of polymers in controlled-release tablet formulations as well as amorphous solid dispersions (ASDs).

2.1. Controlled release matrix systems

When it comes to the preparation of controlled release solid dosage forms, a variety of formulation methodologies may be used. To control the release of active pharmaceutical ingredients (APIs) with a broad variety of solubilities and dose strengths, polymeric matrix tablets are by far the most common kind of tablet used for oral medication delivery. This is due to the fact that polymeric matrix tablets are both convenient and reasonably inexpensive. The formulation of a reliable controlled release matrix, on the other hand, calls for an understanding of the physicochemical characteristics of both the drug and the polymer. Table 1 provides information on some of the most common types of polymers utilized for controlled release. The pharmaceuticals felodipine, verapamil, and nifedipine as well as gliclazide are all examples of commercially available medications that make use of these polymers. The mass transport systems that are responsible for managing the release of medication from polymeric controlled release tablets might vary in terms of their level of sophistication. Depending on the physicochemical parameters of both the polymer (for example, its solubility in water and its swelling behavior) and the medication (for example, its solubility in both the swollen polymeric system and the release media that surrounds it), several different processes might be at play. These include the introduction of water into the system, drug dissolution, drug diffusion (with constant or time- and position-dependent diffusion coefficients), polymer swelling, drug–polymer interactions (such as ionic and van der Waals interactions), polymer dissolution, polymer degradation, and tablet disintegration. It is important to note that not all of these processes take place in every instance, and even when they do, they may not make a major contribution to the overall drug release rate that is produced. For instance, if numerous processes of mass transport occur in succession, and one of those processes is much slower than the others, then it will be the rate-limiting process, and it will have the greatest impact on the total movement.

Table 1: Polymers that are often used in the pharmaceutical industry

Vinyl polymers	**Cellulose ethers**	**Other polysaccharides**	**Miscellaneous**		
Polymethacrylates, poly(acrylic acids), poly(vinyl alcohol), poly(N-vinyl pyrrolidone) (PVP)	Methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), HPMC acetate-succinate, carboxymethylcellulose	Chitosan, carrageenan, xanthan gum, alginic acid, tragacanth, acacia gum	Poly(lactide), poly(lactide-coglycolide),poly(ε caprolactone)	PEG	Silicone
Primary applications					
Film coating, binders, viscosity modifiers, solubilizers, controlled release	Film coating, binders, films, controlled release, microencapsulation, solubilizers, stabilizers, thickeners	Immediate and controlled release, thickeners, peptide delivery, microencapsulation, permeation enhancer	Controlled release	Controlled release, thickeners, binders	Immediate and controlled release
Common dosage forms					
Oral solid, parenteral, topical	Oral solids, topical, injectables, ophthalmic, disperse systems, wound dressings	Oral solids, injectables, topical	Injectables, vaccines, implants	Oral solids, liquids, semisolids	Medical device, implants

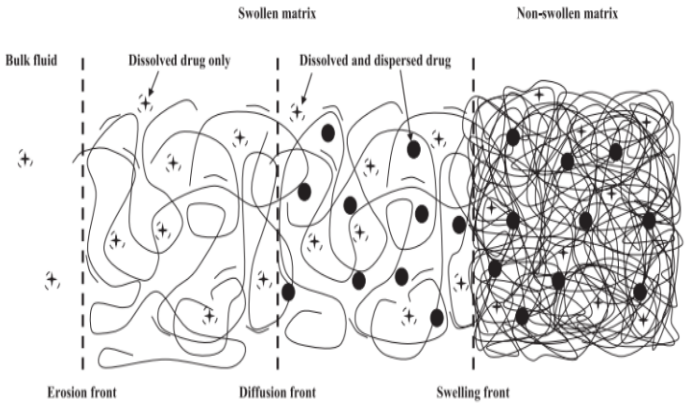

Figure 1: Drug release from a tablet containing a controlled-release matrix of HPMC, shown schematically. Dissolved drug is shown as stars, whereas scattered drug is shown as black circles.

2.2 Amorphous solid dispersions

When it comes to the formulation of poorly water-soluble medicinal compounds, ASDs have emerged as crucial enabling tools. Considering that approximately 70% of all new drug molecules in development are insoluble yet highly permeable drug compounds (Biopharmaceutical Classification System (BCS)-II) and another 20% are insoluble and poorly permeable (BCS-IV), these are of great value. In the pharmaceutical industry, an amorphous homogeneous miscible blend (Fig. 2) of a medicinal molecule and a polymer excipient is often referred to as an amorphous solid solution (ASD). As long as crystallization of the drug can be avoided in vivo, the ASD will be able to increase plasma concentrations since the disordered amorphous phase is kinetically more soluble. Since a medicine needs to be in solution to be orally absorbed in the gastrointestinal tract and reach systemic circulation, this increased solubility and greater dissolution rate may improve bioavailability. A little increase in solubility of one or two fold is possible, whereas a large increase, like the tenfold shown with amorphous novobiocin, is also possible. Most supersaturations obtain concentrations between 10 and 60 times the crystalline solubility, but it may go as high as 1600 times. Although amorphous pharmacological substances may be used in dosage form development, they are generally unstable in the amorphous phase and need the inclusion of anti-nucleating polymers. Some of the first ASDs to hit the market, such nabilone (Cesamet®) and verapamil (Isoptin-SR-E®), had the active pharmaceutical ingredient (API) melt-extruded in PVP or HPC/HPMC.

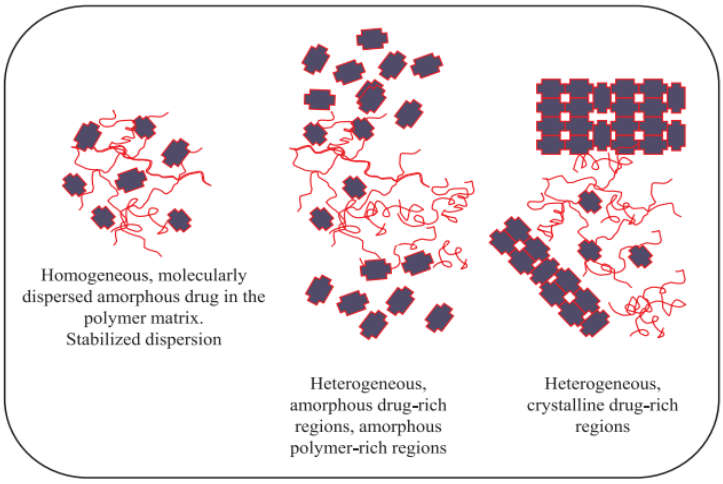

Figure 2: Possible structures for drug-polymer dispersions.

2. Lipid Mono- And Bilayer Supported On Polymer Films

There are several potential scientific and practical uses (as biosensors) for lipid layers that are supported by solid substrates. Thin lubricating aqueous layers separate the membranes from the solid substrate surface after they have been deposited on adequately prepared glass substrates, allowing the membranes to retain the same structural thermodynamic and molecular dynamic characteristics as free bilayers. Using powerful surface sensitive techniques like FTIR-spectroscopy, ellipsometry, surface plasmon spectroscopy, neutron surface scattering, and fluorescence spectroscopy in the evanescent field, such planar membranes provide unique benefits for fundamental studies in membrane biophysics. Bilayers with well-defined curvature may be created by fusing vesicles on glass beads, which has important implications for nuclear magnetic resonance (NMR) investigations of molecular structure and dynamics. When the two-dimensionality of the membrane is broken down due to frictional coupling, lateral diffusion is significantly slowed. This effect may be used to determine the radii of macro lipids and proteins that are bonded to a membrane and the coefficient of friction between the two leaflets of a supported bilayer.

Our previous efforts to use supported bilayers as biosensors for the micro-optical detection of ligand binding (using techniques like surface plasmon spectroscopy) and electrical detection (using techniques like impedance spectroscopy) inspired the current study. Capacitance measurement in conjunction with surface plasmon spectroscopy has been shown to be an effective method for testing the electric tightness of supported bilayers and detecting both selective and nonspecific ligand binding in prior work by our lab. Microelectrophoresis for local receptor enrichment or ligand-mediated creation of conducting pores are two additional ways that have been shown to be necessary for signal amplification. It has been shown that electrophoretic separation and enrichment are facilitated by placing a soft polymer cushion between the bilayers and the solid surface (C. Dietrich and R. Tampe, unpublished data). Functional reconstitution of membrane proteins including channels, transporters, and pores requires that the bilayer be physically separated from the solid substrates by the polymer film. The hydrophilic portion of the protein facing the substrate may be maintained in a pseudo-cellular environment, which may facilitate the inclusion of membrane-spanning receptors into the supported bilayer. The present work aims, in part, to report the preparation of such a novel type of supported membrane-polymer compound films and to demonstrate that lateral diffusion measurements of membrane-bound ligands provide a sensitive test for the continuity and fluidity of the supported membranes while also permitting information on the heterogeneity of the polymer film. The second objective is to document the results of an investigation into the relationship between the surface viscosity of the polymer film and the direct coefficients of friction between the lipid layer and the polymer film. Because membrane proteins interact with the cytoskeleton and the pericellular matrix through a polymeric network, we decided to utilize lipopeptides as a model.

3. Non-Ionic Polymers: Synthesis, Characterization, And Nanodisc Formation

New research has shown that artificial polymers may be used to directly remove membrane proteins and reassemble them in detergent-free lipid bilayer nanodiscs. But the charge on the presently known polymers severely restricts their potential uses. Due to charge-charge interactions, studying membrane proteins with opposing charges is hindered by the polymer's high charge density, which in turn impedes purification by ion-exchange chromatography. Therefore, there is a strong push to create non-ionic polymers so that polymer-based nanodiscs may be used in a wider variety of technological settings, including structural biology, drug delivery, biosensors, and more. Here, we

demonstrate that lipid nanodiscs may be formed from naturally derived oligosaccharides by using these molecules as the polymer backbone and then hydrophobizing them. Chicory root, garlic, onion, and other fruits all contain naturally occurring biopolymers called fructo-oligosaccharides (FOS). FOS may have a polymerization degree somewhere between 2 and 60; FOS with a high molecular weight are referred to as inulin. Inulin isolated from chicory was the substrate for hydrophobic functionalization in this investigation. Inulin was functionalized using pentyl bromide in the presence of sodium hydride (Figure 3), following MALDI-mass spectrometry characterisation which indicated an average degree of polymerization (DP) of 14. The resultant polymer was analyzed using nuclear magnetic resonance and MALDI mass spectrometry. By integrating the peak from H1-Glc (at 5.4 ppm), we were able to estimate the degree of substitution (DS), which is the average number of functional groups attached per one fructose monomer; we then used the peak at 0.9 ppm from the terminal methyl group of the pentyl group as a reference to quantify the extent of functionalization (See Figure S1). MALDI-MS as well as solution and solid-state NMR studies were used to further characterize the resultant polymer. Molecular mass (MW) averaged out to be around 2.7 kDa in MALDI-MS spectra. The presence of pentyl groups was seen in both the 13C CP-MAS and 2D 1 H13C HSQC spectra, indicating a successful functionalization.

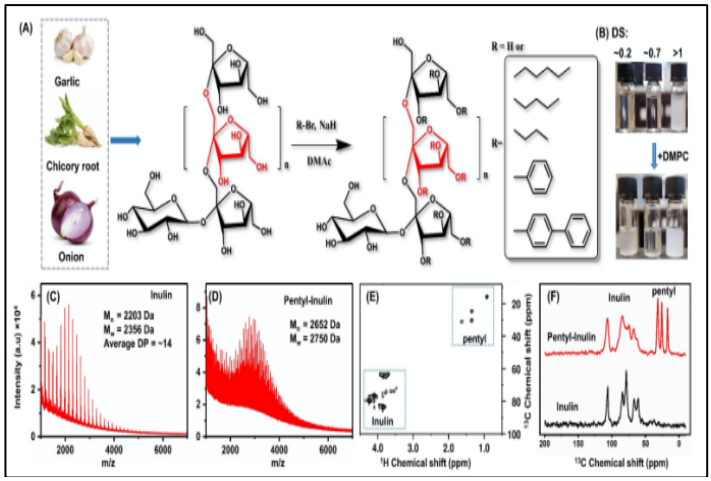

Figure 3: Non-ionic fructo-oligosaccharide polymers

5. Nanocarriers Based On Lipids and Polymers

5.1. Lipidic and polymeric vesicles

Liposomes and polymersomes are both examples of vesicles that include an aqueous lumen surrounded by bilayer membranes made of either supramolecular amphiphilic lipids or synthetic block copolymers. To simulate the membranes of living cells, Bangham et al. (1965) published the first liposomes by demonstrating the very sluggish diffusion of ionic species across phospholipidic bilayers. Vesicles may be categorized as either unilamellar or multilamellar depending on the number of bilayers they contain. Biomedical applications place a premium on unilamellar vesicles, which may be further categorized by size into small, big, and gigantic subtypes. Discher et al. (1999) used the term "polymersomes" to describe vesicle-like structures formed from amphiphilic poly(styrene)-b-poly(acrylic acid) copolymers, which were previously reported on by Zhang and Eisenberg in 1995. PEG-b-polybutadiene copolymer membrane characteristics, bilayer thickness, and amphiphilic molar mass were all shown to have strong connections by the latter.

Polymersomes have since then been recognized as a promising bioinspired compartment with a wide range of potential uses. The regulated loading, delivery, and release of hydrophobic or hydrophilic medicines, biologics, and diagnostic agents from liposomes and polymersomes is the subject of substantial research. Liposomes are commonly used to research the biophysical features of biological membranes (such as stability, permeability, phases, domains, and curvature) and to construct membrane-based biosensors due to their similarity to cellular structures. Although liposomes are now used in vaccination and cosmetic formulations, its most well-known usage is in nanomedicine. Since the approval of Doxil® in 1995 (Fig. 4), liposomes have been used in the clinic with great success for over 20 years. The latter is a PEGylated liposomal formulation of doxorubicin (ca. 80 nm) for intravenous administration (with an enhanced therapeutic index compared to free doxorubicin). Kaposi's sarcoma, multiple myeloma, and ovarian cancer are the three diseases for which it has been officially authorized as a therapy. The mononuclear phagocytic system is inhibited by the PEG coating, which increases the liposomes' circulation time (half-life of elimination is 20-30 hours in humans) and, in some cases, increases doxorubicin deposition in tumors with porous tissue thanks to the so-called enhanced permeability and retention (EPR) effect. There are now about 15 different liposome-based medicinal medications available, and there are another 28 items actively under clinical assessment across the globe.

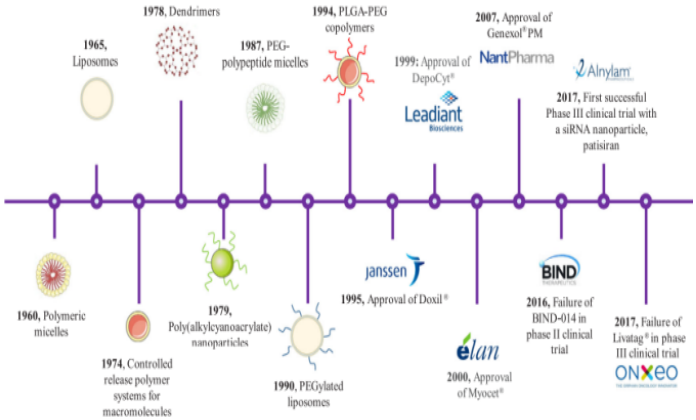

Figure 4: When and how polymeric and liposomal nanoparticles were first discovered, developed, tested, and approved by regulatory agencies.

5.2 Polymer-based nanoparticles and micelles

Several polymer-based nanosystems have been authorized for use or are in clinical research for a variety of tumors (Fig. 4), but liposomal formulations of anti-cancer medicines continue to dominate the oncology nanomedicine area. Polymers' design and synthesis options are unrivaled, making their incorporation into a nanotechnology platform rich with potential. Although other forms of polymeric nanosystems, such as dendrimers, are also under studied, nanoparticles and spherical block copolymer micelles (BCMs), are at the forefront of pharmaceutical development. Drugs may be adsorbed, entrapped, or chemically bonded onto polymeric nanoparticles, which are solid colloidal systems. In order to physically or chemically entrap a hydrophobic medication inside its hydrophobic core, BCMs are often made up of di- or tri-block amphiphilic polymers that self-assemble in water conditions. In terms of clinical efficacy, this has so far been limited to micelle-based solutions. In 1974, researchers announced the development of the first polymer-based controlled release system for

macromolecules and other pharmaceuticals (in this instance, hormones).

The first polymer-based nanosystem was finally certified for human usage after more than 30 years. For the treatment of patients with metastatic breast cancer, non-small cell lung cancer, and ovarian cancer, the paclitaxel micelle formulation Genexol® -PM was approved in South Korea in 2007. Solubilizing its hydrophobic payload, Genexol® -PM is a spherical polymeric micelle system. Because of their possible toxicity and hypersensitivity responses, surfactants like Kolliphor® EL (in Taxol®) and polysorbate 80 (in Taxotere®) are avoided in the drug's formulation thanks to the use of block copolymers. Polymeric nanosystems have the potential to significantly enhance the toxicity profile of their chemotherapeutic payload. Currently, Phase III clinical studies are being conducted to determine the efficacy of NC-6004 (Nanocarrier Co.), a PEG-b-poly(glutamic acid) BCM formulation of cisplatin, in the treatment of head and neck and pancreatic cancer. In comparison to free cisplatin, the nephrotoxicity, neurotoxicity, and ototoxicity caused by NC-6004 were less severe and occurred less often in a Phase I clinical study. Other formulations, including NC-4016 (Nanocarrier Co.), NK105 (Nanocarrier Co.), CynviloqTM (NantworksTM), NanoxelTM-PM (Samyang Biopharm), and CriPec® (Cristal Therapeutics), also showed reduced toxicity compared to the free medication.

1. Conclusion

Although lipids and polymers have been used for millennia to improve human health, their full potential as medicinal excipients has yet to be discovered. Whether utilized alone or in tandem, both show remarkable structural and functional diversity, allowing formulators to address a wide range of difficult drug delivery problems. Traditional and cutting-edge dosage formulations alike often take use of the physical interaction of lipids and polymers. In order to increase the bioavailability of water-insoluble pharmaceuticals, polymeric solid dispersions may have their solubilization capacity increased by the addition of lipids and their amphiphilic derivatives, as was previously addressed. Similarly, polymers may impart mucus-penetrating characteristics onto SEDDS, improving the bioavailability of otherwise poorly absorbed active pharmaceutical ingredients. And thanks to developments in chemistry and materials science, novel lipids and polymers can now be designed with specific functional characteristics, such as the ability to respond to stimuli (such as pH or temperature) or to carry out a biological action (such as the potential inhibition of P glycoprotein) (Constantinides and Wasan, 2006). Chemical bonds between polymers and lipids are increasingly used to provide advantageous or unique properties on drug delivery systems. Newer polymer-lipid hybrids, such as pullulan-cholesterol or alkylated poly(N-isopropylacrylamide), are emerging as alternative solubilizers for lipophilic APIs or as smart self-assembling systems in drug targeting applications, joining the more well-established PEGphospholipids in the composition of long-circulating liposomes. Hybrid polymer-lipid excipients will make it possible to create drug delivery systems with novel properties and unparalleled control over the drug release patterns, thanks to the fast development of 3D printing technology. To meet the difficulties of developing ever-more-complicated active pharmaceutical ingredients (APIs) and the medicine of the future, drug delivery specialists will continue to rely heavily on polymers and lipids.

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