Commentary

THE MERGING FIELDS OF POLYMER AND LIPID-BASED DRUG DELIVERY

Efforts in medicinal and combinatorial chemistry as well as proteomics and genomics continue to give rise to a wide range of agents with therapeutic potential. The translation of these promising agents into medicines is limited by a lack of established, well-characterized formulation or delivery technologies. The face of agents requiring formulation has expanded to not only include small molecules but also proteins, peptides and oligonucleotides. In this way, these candidates have wide-ranging and distinct chemical and physical properties. The design of one delivery technology or formulation platform that will ideally suit the needs of this broad range of agents is unlikely. It is for this reason, that we must depend on a “toolbox” of delivery technologies including liposomes, polymeric nanocarriers and polymer-drug conjugates.

Liposomes and other lipid-based delivery systems have proven themselves as viable enabling technologies. Several pharmaceutical products relying on lipid-based formulation have received approval within the last 10 years (e.g. DOXIL®, DaunoXome®, Abelcet®, Amphotec®, AmBisome®, Myocet®, Visudyne®). The success and widespread use of liposomes and other lipid-based systems has encouraged further development of formulations based on these materials. In fact, for several years, many may have seen liposomes as the only advanced drug delivery technology worth pursuing for production of a pharmaceutical product. By contrast research on polymer-based delivery technology was partly dismissed by some as merely curiosity on the part of scientists interested in working on biological applications of polymer materials. Yet in recent years, polymeric technologies have in fact resulted in several pharmaceutical products. The approved polymer-based formulations include polymer-drug conjugates (e.g. PEG-adenosine deaminase (Adagen®), PEG-L-asparaginase (Onicaspar®), PEG-α-interferon 2b (PEG-INTRON®)) and depot formulations for local drug administration (e.g. Decapeptyl®, Lupron Depot®, Gliadel®). To this point, products based on polymeric nanotechnology have not yet received approval;
however, several have entered clinical trial evaluation. As so rightfully stated by Duncan we have now reached the “dawning era of polymer therapeutics” with many polymeric pharmaceuticals receiving approval and others entering clinical development (Nature Reviews 2003, 2, 347).

For the pharmaceutical scientist the accepted use of a variety of delivery technologies facilitates their role to truly find the most appropriate formulation for a specific drug. It is for this reason, that polymer and lipid-based delivery systems should be seen as complementary technologies. In fact, although these two types of technologies may be used to deliver some of the same agents (e.g. doxorubicin); together they service or meet the needs of a much more broad range of molecules. For example, many drugs requiring systemic administration are not amenable to encapsulation in liposomes due to their high degree of lipophilicity and/or insensitivity to active loading techniques (i.e. ion or pH gradient). Polymer-based systems may be useful for the delivery of these agents as the polymer materials may be tailored to suit a particular drug and application. However, with that said there is a scarcity of biodegradable, biocompatible polymers approved for use in biomedical applications. Perhaps the recent success of the polymeric pharmaceuticals will encourage further interest in the design of new materials for this purpose.

In addition, very few of the studies that have been done on polymer systems include fundamental biologically relevant studies on drug-free polymer systems. This is in contrast to the large body of literature available on drug-free liposome systems and their behavior in the biological milieu. In this way, we are only beginning to have a clear understanding of the relationship between the physico-chemical properties of the polymer and the biological performance of the carrier. The current intense interest in nanotechnology will likely accelerate and further enhance basic research in this area. Also, in the design of polymer-based nanocarriers we should borrow and learn from information available on liposomes.

Therefore, with a toolbox of delivery technologies in hand the question remains: do we have the technologies necessary to effectively deliver the vast array of agents that are now emerging? The answer to this question is straightforward if we simply consider the “gene delivery problem”. At present, no delivery technology has been shown to be especially effective for this particular application. Perhaps current technologies are not able to address the delivery and formulation issues of all of these challenging molecules. We may instead require new technologies that are built from lipids, polymers, biopolymers and even inorganic materials. These may be simple or multi-compartment complex systems but above all should be tailored to suit a particular drug and application. The pursuit of these hybrid technologies requires an interdisciplinary effort uniting polymer chemists, formulation and materials scientists as well as biologists. To some extent hybrid technologies have already begun to be explored and in some cases resulted in significant achievements.

The Best of Both Worlds: Polymer-Lipid Hybrid Technologies

The foremost example of a polymer-lipid hybrid system would be pegylated liposomes introduced through the pioneering efforts of D. Papahadjopoulos and T.M. Allen (Proc. Natl. Acad. Sci. 1991, 88, 11460). The synthetic poly(ethylene
glycol) polymer chains at the surface of the liposome extend the circulation lifetime of the vehicle and provide a passive targeting effect enabling significant accumulation of liposome-encapsulated agent at the tumor site. Several other hydrophilic polymers have been explored for this purpose including poly(acrylic acid) and poly(vinyl alcohol). Polymers have also been integrated into the liposome platform to create thermosensitive and pH-sensitive systems that provide triggered drug release (e.g. use of N-isopropylacrylamide copolymers) (Int. J. Pharm. 2002, 242, 25; Colloids and Surfaces B: Biointerfaces 2002, 24, 45). These “smart” systems with the ability to provide release in response to external stimuli afford the assurance that drug is released once the vehicle reaches its target site. The ability to trigger release is of importance as it has been shown that enhanced accumulation of liposomes at the tumor site does not always translate into improved efficacy.

Polymer-lipid hybrid technology that takes advantage of the most favorable attributes of both polymers and lipids include the Lipobeads™ (Biophys. J. 2002, 82, 2695) and Supra Molecular Biovectors (SMBV™) (Int. J. Pharm. 2002, 242, 411). These systems consist of polymer cores encased within a lipid bilayer. The polymer core acts as cargo space that may be tailored to suit the agent to be incorporated; while, the lipid bilayer provides a biologically acceptable protective interface.

These are only a few examples of hybrid technologies that have been explored in recent years. Overall, the combination of different groups of materials should afford systems with a wide range of properties. Also, the integration of polymers into a technology platform brings unparalleled diversity owing to the ability to synthesize new and exciting materials. Hybrid technologies have also shown promise for applications such as tissue engineering (i.e. organic-inorganic hybrid matrices (Mat. Sci Eng. C 2001, 17, 63-69)) and imaging (e.g. phospholipid micelle encapsulated quantum dots (Science 2003, 298, 1759)). These technologies build on the wealth of knowledge that is available in each distinct field to create systems that are truly greater than the sum of their parts.

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