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Parenteral polymers ▼

In their recent review in *Drug Discovery Today* [1], Hunter and Moghimi comment that synthetic-based polymers have been applied in drug delivery for the past 50 years but there are few examples of these materials being successfully used in the clinic. This is not really surprising. Any pharmaceutical material that is intended for parenteral administration as part of a therapeutic system should exhibit the following basic attributes: (1) non-toxic, (2) non-immunogenic, (3) eliminated, unchanged or metabolized to known products (preferably to endogenous materials).

Whether or not the formulation scientist will choose a synthetic polymer will be dictated by various factors that include the clinical application, the dose of polymer needed and, most importantly, the availability of suitable materials. The decision to use a polymeric material can be a key issue. Most of the polymeric materials available as excipients were not developed specifically for the pharmaceutical industry; some have bizarre origins, such as floor polish components and coating agents. It is, therefore, not unexpected that the injection of such materials into the body could lead to toxic manifestations, to include immunotoxicity. Even macromolecular materials used as plasma expanders have not been without their problems. The adverse effects associated with polyvinyl pyrrolidone and dextrans are well known. Hydroxyethyl starch can be given in large quantities but can have effects on the reticuloendothelial system, especially that in the liver.

Why choose a synthetic polymer?

Normally, polymers are used as excipients or as drug carriers (sometimes via covalent linkage). However, some act as therapeutic agents in their own right (e.g. the polyoxyethylene–polyoxypropylene block copolymer, poloxamer 188, has haemorrheologic and thrombolytic properties).

The physicochemical properties of a polymer itself and the presence of impurities can be of vital importance. The early developments in intravenous

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fat emulsions and vitamin C emulsions demonstrated clearly that non-ionic surfactants could cause toxicity in animal models and in patients (vitamin E emulsions were associated with deaths in children and the non-ionic emulsifier was the probable cause). The problems with cremophors in the development of parenteral anaesthetic systems and, more recently, paclitaxel formulations, are well known. In some cases, the probable cause of toxicity is not the polymer, but impurities: a classical early study on emulsifiers for parenteral emulsions described how a poloxamer emulsifier was lethal to dogs in an unpurified form but, following filtration through silica, the dogs were unaffected! Wisely, those concerned with the formulation of such parenteral products looked to alternative materials and chose instead a phospholipid emulsifier.

Some polymeric materials, such as the polyethylene glycols (PEG) and their protein derivatives, appear to be well tolerated and the clinical advantages could well outweigh possible adverse reactions. Indeed, the successful introduction of PEG proteins to the market would suggest that such products are safe. Nevertheless, these systems are not necessarily well characterized in terms of the different chemical structures produced by the PEG-ylation process. (As yet, regulatory authorities have not demanded absolutely defined structures. Apparently, a robust and reliable process is currently acceptable to the regulators).

Synthetic cationic polymers

Various synthetic cationic polymers are being investigated as delivery vehicles for DNA. Here, the qualities required are small and, therefore, it is possible that the materials involved will not present major problems provided that proper consideration is given to the chosen material. Presently, a wide variety of cationic polymers is available. The polymers seem to have rather similar effects condensing DNA into nanoparticulate systems for delivery. Minor differences observed in their *in vitro* transfection properties might not necessarily be borne out *in vivo*. The use of materials with known toxicity and degradation pathways would be a sensible starting point. Thus, the polyamidoamines and chitosan (polyglucosamine-polyacetyl glucosamine-copolymer) are more attractive than polyethylenimine derivatives. Academic groups are synthesizing yet more new cationic polymers for gene delivery. One can question whether this is worthwhile when viewing the extensive toxicological evaluations that will surely be required for any new material.

In some cases, the polymer can be an essential part of successful therapy [e.g. styrene moleic acid neocarzinostatin (SMANCS) and other polymer-conjugated macromolecular drugs used in cancer chemotherapy] but in other cases the polymer can simply be employed as a carrier. The formation scientist needs to ask whether a liposome, emulsion or microparticle [prepared from a well-known biodegradable material such as polylactic acid (PLA) or polylactic co-glycolic acid (PLGA)] could be a better alternative in terms of carrier capacity and acceptability. Currently, attention is being focussed on the use of various block copolymer 'micelles' for drug delivery. Some of these systems are based on novel self-assembling systems where the lifetime of the micellar structure and its stability to dilution could be advantageous in a clinical setting. Other micellar systems require high concentrations of polymer to give acceptable drug loading and to retain the drug in the micellar phase while in the blood circulation. It is doubtful if results obtained using small animal models will translate well to man and that these systems will be devoid of (immuno)toxicity.

The future

More work is certainly required to understand the fate of polymeric materials following injection. The molecular structure of a synthetic polymer might well be crucial to its immunotoxicological characteristics; however, PEG-ylated systems are generally 'inert' and show little dependence on molecular architecture. The *de novo* design of polymers with a specific problem-solving objective in mind (for example, to inhibit P-glycoprotein and multi-drug resistance proteins) is clearly an area of interest for the future that can be designated an 'important area of research'. The immuno-toxicological issues, singled out by Hunter and Moghimi, will need to be considered but at an appropriate stage in development. The manner in which the polymer is delivered (e.g. route, dose, regimen, rate, surface presentation) will be crucial. For example, consider the poloxamers, where any adverse effects will depend on dose, frequency of administration and the nature of the delivery system. Their use in the coating of microparticles [2], will differ from their use as drug carrying micelles [3], in overcoming drug resistance in cancer [4], as novel functional molecules for gene therapy [5], and as haemorrheological agents [6].

Little work has been published on the fate of polymeric materials following injection, although one suspects that much is contained within files in the pharmaceutical industry. Pleasingly, some limited work is now being published on the fate of synthetic polymers. A recent paper [7] describes the deposition of poloxamer 188 in rats, dogs and humans and the authors claim that this is the first comprehensive evaluation of this polymer across species, including humans, to appear in the literature. In their work, they used a radiolabelled compound but, unfortunately, the synthesis of a

carbon-14 labelled poloxamer is not a trivial exercise. A detailed evaluation of the distribution, metabolism and excretion of the polymer was presented but, interestingly, immunological effects were not addressed.

I agree with Hunter and Moghimi that a paradigm shift (a popular notion) is required but I do not agree with the one that they suggest. Most certainly, pharmaceutical scientists working on parenteral formulations need to be cautious about the use of synthetic polymers. Even well known materials can give unexpected adverse effects. But is a synthetic polymer really needed? Other, better characterized excipients or delivery systems, could well fit the bill. What is the risk to benefit ratio of synthetic polymers? What are the costs associated with the introduction of a new material? What are the time scales?

Hunter and Moghimi are correct in their assertion that much of the past work has been blighted by the use of poorly defined polymeric materials and/or the presence of contaminants and even endotoxins. The availability of better synthetic polymers (in terms of defined structures, purity and toxicological assessment) could lead to their greater use in parenteral products that reach the market place. However, it is difficult to imagine such quality materials being provided by suppliers until a clear unmet medical need is demonstrated. As is often the case in drug delivery, 'market pull' and not 'technology push' will be required. We might not like the limited range of materials we have at present but who is going to provide (and pay for) the synthetic polymers of the future? In my view, it will not be the Research Councils and other public funding agencies.

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Diagnostics meets therapeutics: the impact of pharmacogenetics ▼

A recent review by Ross and Ginsburg in *Drug Discovery Today* [1] discussed the emerging trend of integrating molecular diagnostics and therapeutics in modern drug discovery and patient care. The authors highlighted the recent advancement in the areas of pharmacogenomics and toxicogenomics toward the development of personalized medicine, one of the most promising products of the genomics revolution. The root of personalized medicine is based on extensive studies showing that individual variations in response to drugs are caused, at least partially, by genetic polymorphisms. This field, also called pharmacogenetics, is undergoing rapid progress, fueled by the decoding of millions of single nucleotide polymorphisms (SNPs) across the human genome. SNPs are the most frequent polymorphisms in the human genome and recent research has established that these polymorphisms can provide crucial links to disease-causing genes and drug-response genes [2].

When used properly, pharmacogenetics can clearly deliver improved health benefits to the patients while realizing cost savings. One of the most widely used pharmacogenetics tests in the clinical setting is anti-retroviral drug resistance testing for the clinical management of AIDS patients. Considering the growing evidence of linking HIV1 mutations with antiviral therapeutics failure, Durant *et al.* clearly demonstrated that genotypic-resistance testing has a significant benefit on the virological response when choosing a therapeutic alternative in a prospective clinical trial [3]. Also from the same study, genotypic-guided treatment was shown to achieve cost effectiveness. The additional expense of genotyping appeared to be offset by the savings obtained in drug costs [4]. A result of this study (and others) is the rapid adoption of routinely conducting HIV genotyping for drug resistance, in clinical practice, before prescribing antiviral therapies.

In addition to monitoring the therapeutic efficacy, many researchers are also looking for ways to predict drug toxicity using genotyping. As an example, abacavir is a commonly used nucleoside analogue reverse-transcriptase inhibitor against HIV1. About 5% of patients treated with abacavir develop a hypersensitivity reaction that could be fatal. Recent research has linked the abacavir hypersensitivity reactions to the human major histocompatibility complex class I, B (HLA-B) region [5,6]. Further validation of these results in large clinical cohorts will be needed before being implemented as a routine clinical test for prescription guidance.

With the fast advancement of enabling genotyping technologies, pharmacogenetics will fundamentally

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