Advanced Drug Delivery Reviews 61 (2009) 1220–1231

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Polymeric carriers: Preclinical safety and the regulatory implications for design and development of polymer therapeutics ☆

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ARTICLE INFO

Article history:
Received 19 May 2009
Accepted 12 June 2009
Available online 12 August 2009

Keywords:
Polymer therapeutics
Safety
Toxicity
Regulation of medicinal products

ABSTRACT

Since the early 1990s polymer–protein conjugates (included PEGylated enzymes and cytokines), polymeric drugs and polymeric sequestrants have been entering the market as innovative polymer-based therapeutics. Initially these products were most frequently developed as novel anticancer agents; indeed they can be considered first generation "nanomedicines". More recently, a much broader range of life-threatening and debilitating diseases (e.g. viral infections, arthritis, multiple sclerosis and hormone abnormalities) have been targeted via intravenous (i.v.), subcutaneous (s.c.) or oral routes of administration. Given the increasing novelty of polymeric materials proposed for development as second-generation polymer therapeutics (with increasing complexity of conjugate composition), and the growing debate as to the safety of nanomedicines per se, the need for evolution of an appropriate regulatory framework is at the forefront of the scientific discussion. The adequacy of the current tests and models used to define safety are also constantly being reviewed. Here we describe the current status and future challenges in relation to these issues.

Contents

1. Biologically active polymers: Friend or foe?

1.1. General background

The use of polymers in medicine is not new and undoubtedly natural polymers have been used as components of herbal remedies

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Polymer Therapeutics: Clinical Applications and Challenges for Development".

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doi:10.1016/j.addr.2009.06.003

for several millennia. Nevertheless, as the 21st century begins we are witnessing a paradigm shift in medical practice. Whereas the use of polymers in biomedical materials (e.g. as prostheses, medical devices, contact lenses, dental materials and pharmaceutical excipients) became well established in the last century, synthetic polymer-based medicines only started to enter routine clinical practice over the last two decades (reviewed in [1–5]; see Table 1 for typical products). Since the first product approval in 1990, polymer therapeutics have confirmed that they can satisfy the stringent requirements of both industrial development, and the "Regulatory Authority Approval" process. Whilst both industrialists and regulators share the desire to introduce improved, safe and efficacious new medicines, on one hand industry must also strive to identify a cost-effective and profitable medicine or diagnostic, whereas on the other hand Regulatory Agencies must ensure establishment of a safe and efficacious profile that justifies administration to patients and benefit for society. These first successes, together with the explosion of interest in the fashionable area now called "nanomedicine" has led to an exponentially increasing number of polymer therapeutics entering the industrial development pipeline (e.g. examples described elsewhere in this volume).

Lengthy discussion of nanotechnology and nanomedicine are beyond the scope of this article. Suffice it to say, there is widespread agreement that the converging basic scientific disciplines will bring new opportunities to apply nanotechnology to medicine via either top-down miniaturisation or bottom-up synthetic polymer, or supramolecular, chemistry. The latter is giving birth to new nano-sized assemblies for use as improved diagnostics, preventative medicines, and more efficacious treatments of life-threatening and debilitating diseases [6–8]. In this context, the European Science Foundation's Forward Look on Nanomedicine [7] defined nanopharmaceuticals or nanomedicine**s** as "…nanometer size scale complex systems, consisting of at least two components, one of which being the active ingredient…" (that can be drugs or drug delivery systems). This descriptor was adopted in order to distinguish novel nanomedicines from biotech products, such as proteins and antibodies, which are also inherently 2–15 nm in size.

1.2. Terminology-polymer therapeutics

We coined (Duncan) the term "polymer therapeutics" in the 1990s (reviewed in [2]) to describe polymeric drugs, polymer–drug conjugates, polymer–protein conjugates, polymeric micelles to which drug is covalently bound, and those multi-component polyplexes with covalent linkages being developed as non-viral vectors. All these families contain a water-soluble polymer either as an inherently bioactive polymer per se, or as part of a covalent conjugate. In the regulatory setting polymer therapeutics are all new chemical entities (NCEs), and *not* conventional 'drug delivery systems' which simply entrap, solubilise or control drug release without resorting to chemical conjugation. The term was born from the viewpoint of technical 'correctness' and a need to progress along an industrial development pipeline, not with a desire for fashion/hype. The expression has proved a popular descriptor with Genzyme claiming to be the world-leading polymer therapeutics company. Unexpectedly, others have recently sought to broaden the phrase polymer therapeutics to include protein conjugates [9] and even wider, encompassing materials science, even including gels and modified surfaces [10]. From the Regulatory viewpoint this is unhelpful. Although proteins can clearly be considered natural polymers, they present quite distinct issues for manufacture, development and safe use compared with synthetic polymers, and proteins present challenges that the pharmaceutical industry has become very familiar with over recent decades. Use of "polymer therapeutics" to include biomaterials and non-covalent drug delivery systems is a misguided, retrograde step which defeats the original objective. More generally research scientists would be wise to adopt terminology that is well defined, and aids the Regulatory positioning of innovative technologies. Widespread use of the term "nanomedicine" is adding to the confusion in terms of Regulatory Authority positioning (see Section 3 of this article). Scientific vocabulary should be considered carefully to aid communication between, scientists, with Regulators and also with the general public.

Table 1
Examples of polymer therapeutics on the market.

Product	Description	Application
Polymer–protein conjugates		
Zinostatin Stimalmer®	SMANCS[a]	Hepatocellular carcinoma (local administration via hepatic artery infusion)
Adagen®	PEG-adenosine deaminase	Severe combined immunodeficiency syndrome
Oncaspar®	PEG-asparaginase	Acute lymphocytic leukaemia
PEGIntron®	PEG-Interferon alpha 2b	Hepatitis C
PEGASYS®	PEG-Interferon alpha 2a	Hepatitis C
Neulasta™	PEG-Human-GCSF	Chemotherapy-induced neutopenia
Cimzia®	PEG-anti-TNF Fab	Crohn's disease; arthritis
Somavert®	PEG-HGH antagonist	Acromegaly
Polymeric drugs/sequestrants		
Copaxone®	Copolymer of Glu,Ala,Tyr	Muscular sclerosis
Renagel®	Phosphate binding polymer	End stage renal failure
Welchol®	Cholesterol binding polymer	Type-2 diabetes; Elevated LDL
PEG-aptamer		
Macugen®	Selective vascular endothelial growth factor antagonist	Age-related macular degeneration

[a] Styrene maleic anhydride (SMA)-neocarzinostatin (NCS).

1.3. Terminology-safety

Polymer therapeutics are currently being designed to treat a wide range of diseases, some with additional imaging capacity (reviewed in [1–5]). Recently constructs designed to protect against tissue damage and promote tissue repair have also been described [11,12]. This broad range of applications can theoretically result in (i) many different routes of administration (parenteral, oral, topical etc.), (ii) single dose, low number of cycles, or chronic administration over years, and depending on potency (iii) administration of a very low or rather large dose of the polymer component depending on each particular application. Choice or design of a 'safe' polymer for use in the context of each of these *specific* applications is crucial.

The terminology used to describe polymer 'safety' is confusing and often seriously misused by over-enthusiastic researchers who should be encouraged to be more rigorous when commenting on potential safety of their latest invention. Should polymers be discussed in terms of their "biocompatibility or toxicity"? The pharmaceutical industry refers to a drug in terms of its "toxicity". This is a measure of the non-specific, unwanted harm that it may elicit towards cells, organs, or indeed the patient as a multi-organ system (Fig. 1). In contrast, the field of biomedical materials uses the term "biocompatibility" to describe the biological properties of a polymeric material. "Biocompatibility" was defined at a consensus conference of the European Society for Biomaterials already in 1986 [13] as 'the ability of a material to perform with an appropriate host response *in a specific application*'. This useful definition also highlights the need to consider the suitability of a material in respect of both its potential detrimental effect in the body (toxicity), and the potential detrimental or beneficial effect of the physiological environment on the performance of the material (Fig. 1) and rightly emphasises material "biocompatibility" in the precise context of its use.

As polymer therapeutics are being developed as medicines it is more appropriate to refer to 'toxicity' when describing their effects