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Review Article

Drug delivery's quest for polymers: Where are the frontiers?

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Dedicated to Robert Gurny on the occasion of his 70th birthday.

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ABSTRACT

Since the legendary 1964 article of Folkman and Long entitled "The use of silicone rubber as a carrier for prolonged drug therapy" the role of polymers in controlled drug delivery has come a long way. Today it is evident that polymers play a crucial if not the prime role in this field. The latest boost owes to the interest in drug delivery for the purpose of tissue engineering in regenerative medicine. The focus of this commentary is on a selection of general and personal observations that are characteristic for the current state of polymer therapeutics and carriers. It briefly highlights selected examples for the long march of synthetic polymer–drug conjugates from bench to bedside, comments on the ambivalence of selected polymers as inert excipients *versus* biological response modifiers, and on the yet unsolved dilemma of cationic polymers for the delivery of nucleic acid therapeutics. Further subjects are the complex design of multifunctional polymeric carriers including recent concepts towards functional supramolecular polymers, as well as observations on stimuli-sensitive polymers and the currently ongoing trend towards natural and naturally-derived biopolymers. The final topic is the discovery and early development of a novel type of biodegradable polyesters for parenteral use. Altogether, it is not the basic and applied research in polymer therapeutics and carriers, but the translational process that is the key hurdle to proceed towards an authoritative approval of new polymer therapeutics and carriers.

1. MACRO, MICRO, NANO – overview and introduction

Since the legendary 1964 article of Folkman and Long [1] entitled "The use of silicone rubber as a carrier for prolonged drug therapy" the role of polymers in controlled drug delivery (CDD) has come a long way. Today it is evident that polymers play a crucial if not the prime role in this field. Clearly demonstrating this is a collection of the most cited articles in this domain's top review journal, the *Advanced Drug Delivery Reviews*. In an October 2014 search in the Web of Science core collection 20 among the 30 most cited articles refer in one way or another to polymers (see Table 1). At the same time the subjects in the table remind us how extraordinary diverse this field is.

To first illustrate a short historical perspective it is instrumental to stick to the all caps terminology of a pioneer in the field, Allan Hoffman, as coined in his article on the history and the evolution of drug delivery systems [22]. He defined three distinct but overlapping eras of increasing complexity: The first one, starting as early as in the mid 1960s, was termed the MACRO era where polymers were used to form macroscopic devices such as slabs, films, rods, rings or spheres etc. to accommodate drugs for controlled release, preferably by zero or nearly zero order release kinetics. It is worthwhile to remember that an early example for the MACRO era was an ophthalmic polymer insert, Ocusert, to release an anti-glaucoma drug, pilocarpine, in a controlled fashion over extended periods of time. Another one was Progestasert (or Progestesert), an intrauterine rod-like device to release a contraceptive steroid, progesterone, out of a polymeric matrix for at least eight months up to two years. Widespread attention was also given to drug loaded polymeric patches for transdermal delivery by diffusion and partitioning across the tight barrier of the stratum corneum. The patches either consisted of a pressure-sensitive adhesive or were coated with a pressure-sensitive adhesive to ensure intimate skin contact. Surprisingly, scopolamine was the first drug to demonstrate the potential of such devices. In spite of severe side effects when orally administered, which largely ruled out its therapeutic use, controlled delivery from the patch via the skin into the systemic circulation rendered this formulation an unprecedented and safe medicament to prevent motion sickness. Osmotic pump capsules, termed Oros, were another ingenious innovation of the MACRO era, for both oral delivery and implantation. Charged with an osmotic agent resulting in a given

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Table 1
Ranks and subjects of polymer-related review articles among the 30 most cited articles in *Advanced Drug Delivery Reviews*, according to an October 2014 search in the Web of Science core collection.

Rank	Subject of article	Year of publication	Citations	Ref.
3	Block copolymer micelles	2001	1620	[2]
4	Biodegradable nanoparticles	2003	1230	[3]
5	Environment-sensitive hydrogels	2001	1221	[4]
6	Nanoparticles	2002	1213	[5]
7	Hydrogels	2002	1083	[6]
9	Peptide and protein PEGylation	2002	803	[7]
10	Dendrimers	2005	788	[8]
11	Drug release from HPMC delivery systems	2001	772	[9]
12	Thermo- and pH-responsive polymers	2006	771	[10]
13	Nanoparticle targeting	2004	712	[11]
14	Thermosensitive hydrogels	2002	695	[12]
16	Biodegradation and biocompatibility of PLA and PLGA microparticles	1997	672	[13]
21	PEGylated nanoparticles	2003	625	[14]
23	Crosslinking methods for hydrogels	2002	612	[15]
25	Multifunctional nanocarriers	2006	574	[16]
26	Targeted drug delivery via folate receptor	2000	542	[17]
27	Protein release from alginate matrices	1998	540	[18]
28	Self-assembly of amphiphilic block copolymers	2001	531	[19]
29	Nanoparticles for brain delivery	2001	531	[20]
30	Cyclodextrins as solubilizers	2007	517	[21]

osmotic gradient, the constant osmotic flow of water across a semi-permeable polymer membrane into the osmotic capsule is compensated by an equivalent flow of aqueous drug solution or suspension through a tiny orifice out of the capsule.

A second era in the history of drug delivery, beginning in the early 1970s, is the MICRO era, again following the terminology of Hoffman [22]. It is closely linked to the use of biodegradable polymers, e.g., to manufacture drug loaded microparticles. Their objective was to exploit the kinetics of polymer biodegradation in order to control the kinetics of drug release over extended periods of time after s.c. or i.m. injection. The biodegradable polymer that attracted the most interest for this purpose was a polyester, poly(lactic-*co*-glycolic acid) (PLGA). Its biocompatibility and customizable *in vivo* biodegradation made it a prime candidate for biodegradable implants. First commercial PLGA products appeared as early as in the mid 1980s, e.g., LHRH analogs embedded in PLGA microparticles as a therapeutic to treat prostate cancer. The technologies to manufacture such microparticles encompass various spraying, phase separation and solvent extraction or evaporation protocols, and others. In some cases the clinical development of such formulations faced severe problems, such as (i) the lacking stability of some embedded protein therapeutics in PLGA, (ii) the problematic scale-up towards industrial manufacturing, and (iii) the unfeasibility of terminal sterilization (except gamma-irradiation) causing the costly need for aseptic manufacture. Individually or in combination they resulted in a rather high cost-of-goods-sold (COGS) that led to seek for alternative concepts which emerged soon afterwards. A stupendous simplification was the direct s.c. or i.m. injection of a polymer–drug-solvent mix resulting in an *in situ* formation of microparticulate polymeric aggregates embedding the drug, i.e. through solvent dilution or extraction directly at the site of injection in the tissue [23]. A more recent achievement of the MICRO era is the development of microneedle arrays, a mechanical alternative to administer drugs via the skin [24]. They may be made of microscopic polymer needles and in different ways be loaded with drugs. Because of their short size, microneedle arrays can painlessly pierce the skin and deliver the drug directly into the viable epidermis below the stratum corneum and/or into the upper dermis from where it readily reaches the circulation. Microneedles can be also discussed as a minimal-invasive alternative for mass vaccinations.

The NANO era, finally, once more sticking to Hoffman's terminology [22], is the third and currently still the most dynamic era within the development of polymeric delivery systems. In an revolutionary approach starting in the mid 1970s and far ahead of the more recent hype for nanotechnology in the materials science and chemical engineering domains, the late Peter Speiser and his co-workers at the ETH Zurich, as reviewed in a historical perspective by Kreuter [25], began to investigate into this field: first in the area of nanoparticulate immunostimulants (or adjuvants), but then also into the potential of drug loaded polymeric nanoparticles to modulate the biodistribution of drugs in the human body. Today thousands of articles per year demonstrate the vast biomedical potential of nano-sized particles and assemblies. A few products are on the marketplace.

The rise of regenerative medicine from about 2000 on further boosted the interest in polymers, particularly as platforms for the spatiotemporal delivery of growth factors (GFs) with the objective of tissue engineering *in vitro*, *ex vivo* or *in vivo*. This trend may be regarded as a fourth era in the advance of polymers for CDD. It combines in parallel many aspects of the three eras listed above. Biodegradable polymer scaffolds designed to deliver GFs may be taken as an example: The customized bulk of the scaffold represents the MACRO part and controls the release kinetics of the embedded GFs, whereas the microporosity of the scaffold stands for the MICRO part and controls cellular in-growth as well as nutrient supply and waste removal. The NANO part, finally, comprises the scaffold's surface chemistry, the fine structure and orientation of its surface, as well as its surface mechanics, all of them on a nano-scale. So it controls cellular adhesion, spreading, spatial orientation, growth and, possibly, cellular differentiation of the engineered tissue. Such scaffolds combine the complexities of all three eras in one subject. Typical examples are polymeric nerve guidance conduits loaded with appropriate GFs for peripheral nerve regeneration and repair [26].

Bringing together polymers and drug delivery has thus become one of the most active branches in today's research and development on therapeutics. For 2013 the Web of Science lists 8261 published scientific articles and patents combining these two key words (search: polymer AND "drug delivery"). It is interesting to see that the Web of Science linked 2889 of these publications (obviously allowing multiple assignments) to the field of materials science, 2076 to chemistry, 2303 to engineering, 1595 to polymer science, and 1386 to pharmacology/pharmacy. This reflects the currently ongoing massive multi-disciplinary exchange in this field. In the following paragraphs I will try to comment on various subjects, trends and frontiers. Only a small fraction of the work covered in my commentary derives from my own group's and our collaborators' work. In order to limit the list of references to a reasonable number, this commentary will often refer to review articles. For more detailed information on specific aspects, the reader is requested to see the original papers. Necessarily, within the restricted format of a commentary, my contribution will be a patchy selection of general and personal observations in the field, and certainly leave gaps.

2. The long march towards polymer–drug conjugates

The term polymer therapeutics, as applied by Duncan and Vicent [27], covers drug delivery systems as diverse as polymeric drugs, polymer–drug conjugates, polymer–protein or polymer–peptide conjugates, drug loaded block copolymer micelles and