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Polymer-drug conjugates as inhalable drug delivery systems: A review

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ABSTRACT

Accelerating interest by the pharmaceutical industry in the identification and development of less invasive routes of nanomedicine administration, coupled with defined efforts to improve the treatment of respiratory diseases through inhaled drug administration has fuelled growing interests in inhalable polymer-drug conjugates. Polymer-drug conjugates can alter the pharmacokinetic profile of the loaded drug after inhaled administration and enable the controlled and sustained exposure of the lungs to drugs when compared to the inhaled or oral administration of the drug alone. However, the major concern with the use of inhalable polymer-drug conjugates is their biocompatibility and long-term safety in the lungs, which is closely linked to lung retention times. A detailed understanding about the pharmacokinetics, lung disposition, clearance and safety of inhaled polymer-drug conjugates with significant translational potential is therefore required. This review therefore provides a comprehensive summary of the latest developments for several types of polymer-drug conjugates that are currently being explored as inhalable drug delivery systems. Finally, the current status and future perspective of the polymer-drug conjugates is also discussed with a focus on current knowledge gaps.

1. Introduction

Polymers and polymer-based drug delivery systems have undergone an enormous expansion in the past decade, with the clinical and preclinical development of polymer-based nanomedicines and other biomedical applications. The key feature of a polymer-drug conjugate is that rather than containing a drug that is non-covalently encapsulating within a polymeric structure, the drug is physically conjugated to the polymeric carrier [1]. In this regard, problems associated with 'burst' and/or uncontrolled drug release can be largely overcome and the drug can be covalently linked to the polymer *via* linkages that are specifically designed to liberate drug within certain structures, or at a predicted rate *in vivo*.

The concept of polymer-drug conjugates was first introduced by Helmut Ringsdorf in 1975 [2]. According to this concept, an ideal polymer-drug conjugate is characterised by a hydrophilic polymer backbone as a vehicle and a bioactive agent(s) that is usually bound to the polymeric scaffold *via* a biological response linker. Sometimes a targeting moiety or a solubility enhancer may also be introduced into the conjugate to improve pharmacokinetic behaviour and therapeutic efficiency (Fig. 1) [2,3•]. In general, polymer-drug conjugates offer several advantages as drug delivery moieties, including 1) the capability to achieve high drug payloads, 2) improved drug solubility, 3) modulation of drug pharmacokinetics (including prolonged plasma exposure and optimised biodistribution behaviour, resulting in enhanced therapeutic efficacy), 4) reduced systemic and local side-effects as a result of highly irritant or cytotoxic drugs, 5) enhanced *in vivo* drug stability, and 6) controlled rate and site of drug liberation. Despite these advantages, the full potential of polymer-drug conjugates as drug delivery platforms has yet to be fully harnessed, since the majority of current 'nanomedicinal' drug delivery systems still utilise the cheaper drug encapsulation approach.

Polymer-drug conjugates are often synthesised using one of three strategies, including 1) conjugating the drug to an established polymer, 2) conjugating the drug to a monomer, followed by reversible addition fragmentation transfer (RAFT) polymerisation, ring-opening metathesis polymerisation (ROMP) or ring opening polymerisation (ROP), and 3) using an existing drug containing two or more functional groups as a monomer for poly-drug Polymerisation [4,5]. The first strategy can lead to poor control over drug conjugation and limited drug loading, depending on the size and nature of the polymer structure. However, polymerisation of drug-monomer conjugates generally provides good control over drug loading and the final product [5,6]. Drugs are often conjugated to the polymers *via* biodegradable linkers which can control the site and rate of drug liberation, although the linker has to be carefully selected to display optimal *in vivo* drug release rates for the intended therapeutic application [7]. It is important to note however, that the physicochemical properties of the polymer can have an impact on the *in vivo* liberation of drugs linked *via* 'biodegradable' linkers, particularly when access by an enzyme is required [1,8,9].

One of the most significant advantages that polymer-drug conjugates have, as alluded to above, is the ability to change the pharmacokinetic

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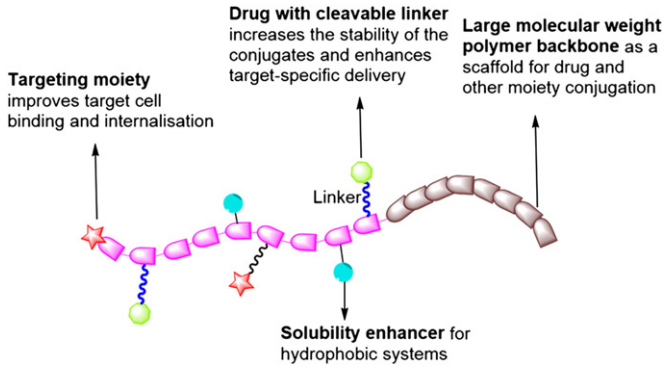

Fig 1. Example of a polymer-drug conjugate system, employing a polymer backbone, tissue targeting moiety, drug and solubility enhancer.

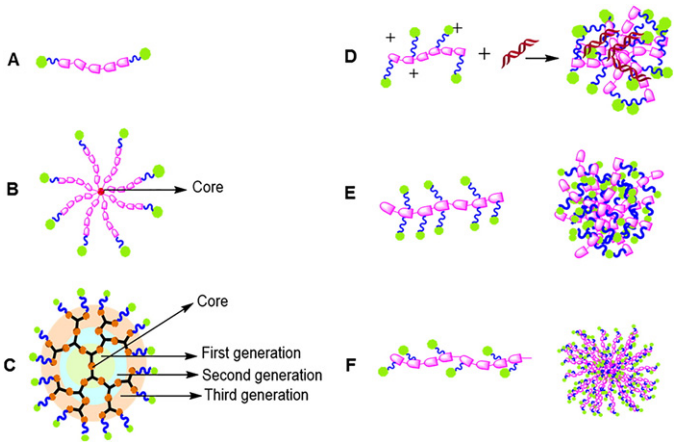

Fig 2. Schematic representations of polymer-drug conjugates that have been examined as inhalable drug delivery systems. A) Linear PEG-drug conjugates, B) PolyPEG star polymer-drug conjugates C) Dendrimer-drug conjugates (example of a generation 3 system is given), D) PEI-drug conjugates and PEI-drug polyplex, E) chitosan-drug conjugates, and F) Hyaluronic acid-drug conjugates. Polymer backbones are indicated in pink (with the exception of dendrimer structures where each generation is highlighted). Chemical drug linkers are shown in blue and drugs are represented in green.

and biodistribution behaviour of the loaded drug [1]. In this regard, polymer-drug conjugates have traditionally been administered exclusively *via* the intravenous route as a result of their size and general hydrophilic nature limiting absorption after oral administration [3]. Subcutaneous or intramuscular delivery also provides a means to access the blood using a less invasive approach, but bioavailability can be limited in some cases. However, recent interest by big Pharma in non-invasive drug delivery approaches and targeted delivery to the lungs to improve the treatment of lung-resident illnesses that are traditionally treated with oral medications, has sparked a tremendous worldwide interest in the inhaled delivery of nanomedicines.

The pulmonary route possesses several distinct advantages over conventional oral or injectable routes of administration, including lower enzymatic activity in the lungs than that found in the gut, the avoidance of first-pass metabolism as well as the thin alveolar membrane, high surface area for absorption and extensive vasculature that can facilitate the rapid systemic absorption of drugs after inhaled administration [10,11]. However, despite the potential for very rapid drug absorption from the lungs for relatively low molecular weight materials (several thousand Da max), the tight intercellular junctions between alveolar cells typically limits the passage and systemic access of larger constructs, such as polymers. This has the effect of slowing the systemic absorption of polymers and providing the opportunity for sustained lung exposure to polymer-drug conjugates (and therefore to the drug). This is particularly advantageous when treating lung-resident illnesses, since the exposure of key disease-mediating cells to the drugs can be significantly increased when compared to oral drug administration, and systemic exposure (and therefore related side effects) can be reduced. It also means that lung clearance mechanisms other than systemic absorption must play a more significant role in removing the polymer from the lungs [12,13]. To date however, there is limited knowledge about the contribution of each lung clearance pathway in the removal of inhaled polymers and nanoparticles from the lungs [14••,15], which is important for clinical translation and regulatory approval. Moreover, the majority of studies investigating the fate of inhaled nanomaterials have been based on examining the lung clearance kinetics of the drug, rather than the polymer or polymer-drug conjugate. The critical issue here is that the safety of inhaled polymer-drug conjugates has also been called into question, based on widespread literature suggesting that nanomaterials, albeit non-biodegradable/non-biocompatible nanoparticles, are 'toxic' in the lungs [16–20]. It is therefore important to understand the rate and mechanisms of polymer clearance from the lungs in order to design optimal dosing schedules that limit the long term retention of the polymer in the lungs and the potential for local adverse effects.

In the present review, we therefore provide a comprehensive overview of the state-of-the-art for inhalable polymer-drug conjugates (Fig. 2) and have summarised the critical *in vivo* literature in Table 1. An additional focus of this review is to detail our current understanding of the *in vivo* behaviour and safety of inhaled polymer-drug conjugates. Finally, the need for further research and development of polymer-drug conjugates is also discussed with an emphasis on current knowledge gaps and future perspectives.

2. Polyethylene glycol (PEG)-drug conjugates

2.1. Linear PEG-drug conjugates

PEG is a polyether containing repeating units of ethylene glycol (Fig. 2A). It is highly biocompatible, non-immunogenic, highly water soluble and FDA approved for use in medicine and other biomedical applications [35]. PEG exists as either linear or branched chains. Linear PEG is most commonly used as a drug carrier or surface coating on nanoparticles to improve biocompatibility and/or solubility, and conjugation processes are generally very straight forward [36–38•]. In general, due to its 'stealth' nature, PEG and PEGylation in general also typically reduces the cellular internalisation of conjugated materials and drugs. While PEG-drug and PEG-protein conjugates have most commonly been explored as delivery systems after IV administration (often using high molecular weight PEGs), a few studies have explored the potential of these systems as inhalable drug vectors. Unlike the high molecular weight PEGs commonly used to modulate the IV and subcutaneous pharmacokinetics of polymer and protein-based drugs and drug delivery systems, the use of low molecular weight PEGs can help to enhance penetrate through the lung mucus layer after pulmonary administration to promote drug/polymer access to the underlying epithelia, where most cells involved in lung disease reside. Furthermore, PEG can help to avoid prolonged mucosal exposure to drugs with 'mucus damaging' properties [39]. For example, alendronate has a low oral bioavailability (approx. 1–2%) and displays 'mucosal damaging' properties due to its structural similarity with phosphatidylcholine. Specifically, alendronate competitively displaces mucosal phosphatidylcholine which triggers mucosal damage [40]. Conjugation of alendronate onto low molecular weight PEG (510 Da) however, was previously shown to suppress lung mucosal toxicity after pulmonary delivery, whereas administration of the free drug induced significant toxicity [40]. In another study, PEG was employed to prolong the residence time of steroidal drugs (*e.g.* prednisolone) within isolated lung preparations and increase the aqueous solubility of the drug [21]. The rate of absorption of