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Review article

Recent advances in nanocarrier-loaded gels: Which drug delivery technologies against which diseases?

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ABSTRACT

The combination of pharmaceutical technologies can be a wise choice for developing innovative therapeutic strategies. The association of nanocarriers and gels provides new therapeutic possibilities due to the combined properties of the two technologies. Gels support the nanocarriers, localize their administration to the target tissue, and sustain their release. In addition to the properties afforded by the gel, nanocarriers can provide additional drug sustained release or different pharmacokinetic and biodistribution profiles than those from nanocarriers administered by the conventional route to improve the drug therapeutic index. This review focuses on recent (over the last ten years) *in vivo* data showing the advances and advantages of using nanocarrier-loaded gels. Liposomes, micelles, liquid and solid lipid nanocapsules, polymeric nanoparticles, dendrimers, and fullerenes are all nanotechnologies which have been recently assessed for medical applications, such as cancer therapy, the treatment of cutaneous and infectious diseases, anesthesia, the administration of antidepressants, and the treatment of unexpected diseases, such as alopecia.

1. Introduction

Nanomedicine has been an exceptionally successful in therapeutic strategies for diseases such as cancer [1]. Nanotechnologies confer new pharmacological properties to drugs, which largely depend on the nanocarriers used, increasing their efficacy. Advantages, such as prolonged systemic circulation, passive or active targeting, high drug-loading yield, and the possibility of drug combination, lead to improved pharmacokinetic and biodistribution profiles for a better drug therapeutic index [2–4]. First used for cancer therapy [1,5], nanomedicines have now been developed for other diseases, such as atherosclerosis and diabetes [6,7], and other medical applications, such as *in vivo* imaging and tissue engineering [8].

Nanomedicines are generally used in suspension for therapeutic strategies by the intravenous route and are administered alone (repeated or not depending on the therapeutic scheme). When used in suspension, this pharmaceutical technology is of little interest for medical applications requiring localized administration or sustained release of the drugs. However, gel-based technologies can be used to confer the pharmacological properties necessary for these applications. Gels are by far the oldest technology used in the healthcare field, but are still the ideal topical vehicle for ocular [9,10], nasal [11], vaginal [12], intestinal [13], and dermal drug delivery [14]. Indeed, gels are drug-delivery platforms. The three-dimensional polymer network of the gel offers an ideal opportunity for prolonged release of therapeutic molecules, such as proteins [15], and gel-based techniques are being developed to improve their administration using stimuli-responsive *in situ* gelation [16]. Patient compliance and convenience is generally improved because of the non-painful and limited repeated administration. An important innovation has been the development of hybrid materials: bio-synthetic scaffolds with cell-loaded gels. They are of interest for *in vivo* tissue engineering and regeneration [17], as well as *ex vivo* applications. The gel mimics extracellular media and influences and guides cell development or differentiation. Studies have also been performed to define new immunological therapies, such as vaccine development [18].

Abbreviations: CH, Chitosan; β-GP, β-glycerophosphate; PC, Phosphatidylcholine; CHOL, Cholesterol; PE, Phosphatidylethanolamine; PEG, Polyethyleneglycol; PCL, Poly(ε-caprolactone); CMC, Carboxymethylcellulose; HEC, Hydroxyethyl cellulose; HPMC, Hydroxypropyl methyl cellulose; HA, Hyaluronic acid

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Nanocarriers-loaded gels provide promising avenues to develop new therapeutic strategies, combining the advantages of both nano- and gel technologies. Clinical trials are currently on-going (https://clinicaltrials.gov/, accessed February 21, 2017). Fourteen clinical trials are reported with the status from "not yet open for participant recruitment", "currently recruiting participants", "terminated", to "completed". There are nine clinical trials on liposome- and five on nanoparticle-loaded gels from Phase I to Phase IV. They focus on a wide range of medical applications, such as antibacterial and antimicrobial treatments (with silver nanoparticles); the development of local anesthetics (with ropivacaine and lidocaine), tooth bleaching agents (with peroxide hydrogen/titanium oxide nanoparticles), and therapeutic treatments against periodontal intrabony defects (with hydroxyapatite silica nanocrystals), painful diabetic neuropathy (with capsaicin), and sub-acute soft tissue injuries (with ibuprofen). Cutaneous diseases are also included, given the obvious topical application, including acne (with povidone iodine), cutaneous leishmaniasis (with amphotericin-B), moderate atopic dermatitis (with HL-009), and the prevention of radiation-induced dermatitis (after breast cancer) (with APN-201, a recombinant human superoxide dismutase). Finally, three clinical trials are focused on oncology, with the development of treatments against diffuse large B-cell lymphoma/follicular lymphoma grade IIIb (with rituximab/Myocet®/cyclophosphamide/vincristine/prednisone), hepatocellular carcinoma (chemoembolization with doxorubicin), and HIV/AIDS Kaposi's sarcoma (with Triomune®: stavudine/lamivudine/nevirapine).

The combination of nanotechnologies with gels is increasingly being considered for medical applications. In this review, we report on the technical advances in nanocarriers-loaded gels during the last ten years, focusing only on *in vivo* results. The nanocarriers reported in the literature are liposomes, micelles, liquid and solid lipid nanocapsules, polymeric nanoparticles, dendrimers, and fullerenes. When loaded in a gel matrix, these therapeutic strategies have given promising results for medical applications, such as cancer therapy, the treatment of infectious, cutaneous or inflammatory diseases, anesthesia/analgesia, and ocular application (Fig. 1).

2. Liposomes-loaded gels

There are many reports on liposome-loaded gels in the literature. This is mainly because of the longstanding application of this nanotechnology in nanomedicine. Several liposomal nanomedicines are already commercialized: Visudyne® (Novartis Europharm Ltd), Ambisome® (Gilead Sciences), Caelyx® (Janssen Cilag Internat Nv), Myocet® (Cephalon Europe), and Daunoxome® (Galen Limited). Often phospholipid-based, the vesicles are easy to formulate, biocompatible, and easily adaptable carriers, and have the remarkable ability to encapsulate both hydrophobic and hydrophilic compounds.

2.1. For cancer therapy

A recurring problem in cancerology is the low bioavailability of drugs such as cytarabine, 5-fluorouracil, doxorubicin, bleomycin A6, *etc.*, at the tumoral site after intravenous injection. Drug-loaded liposomes, dispersed in a gel, modify the pharmacokinetics of the drugs. Chemotherapeutic agents have a low plasma half-life and require a high dosing frequency. Sustained release of the drugs is a potentially good strategy to avoid repeated administration.

Mulik et al. developed a thermosensitive hydrogel (chitosan (CH) and β-glycerophosphate (β-GP)) containing cytarabine-loaded liposomes (egg phosphatidylcholine (egg-PC)/cholesterol (CHOL) 60/40 *mol/mol* – Diameter = 220 ± 4 nm – Polydispersity index (PdI) = 0.21 ± 0.1). The liposomal gel sustained the release of cytarabine after intramuscular administration to albino rats. Indeed, its $t_{1/2}$ was 29 h, compared to 20 h and 3 h for a cytarabine-loaded liposomal suspension and cytarabine-loaded gel, respectively. Moreover, the liposomal gel showed the lowest elimination rate constant, indicating that the drug release rate was slow and that the drug remained in the body for longer period [19].

Bleomycin A6 is an anticancer drug for esophageal cancer, hepatocellular carcinoma, colon cancer, hepatic metastasis, and colorectal cancer. Ding et al. proposed encapsulating bleomycin A6 in anionic liposomes (Diameter = 230 ± 3 nm – PdI = 0.23 ± 0.05 – Zeta potential (ZP) = −61 ± 2 mV), and then dispersing them in an *in situ* gelling system based on a poloxamer mixture (Pluronic® F127 and F68). They evaluated the gel retention properties *in vivo* in mice after subcutaneous injection. Bleomycin A6 in the liposomal gel was retained in the subcutaneous tissue for more than five days, whereas the drug in solution was no longer present after 24 h, demonstrating its rapid elimination [20].

Cutaneous administration of liposomal gels has also been tested. Hussain et al. developed a topical form of 5-fluorouracil (5-FU) to manage several skin problems (skin cancer, actinic or solar keratoses) and avoid oral-associated side effects. They developed elastic liposomes (PC/Span® 60 or Span® 80 or Tween® 80, from 70/30 to 95/5 *mol/mol* – Diameter = 130–250 ± 10–20 nm), which are ultra-deformable and can pass through small pores of the skin. The liposomes loaded with 5-FU were dispersed in a Carbopol® 980 gel to support the nanocarriers and to facilitate topical application. An *in vitro* skin permeation study showed a significantly higher drug permeation flux for elastic liposome (90 ± 8 μg/cm^2/h), than for the free drug solution (9 ± 7 μg/cm^2/h). Moreover, the liposomal gel did not irritate the skin (erythema and

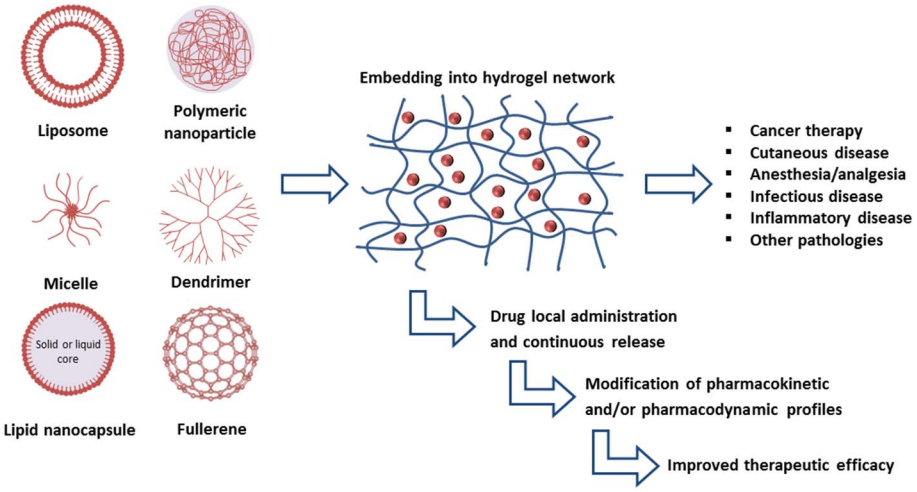

Fig. 1. Overview of the recent preclinical and clinical studies concerning the hydrogels of nanocarriers.