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Drug encapsulated polymeric microspheres for intracranial tumor therapy: A review of the literature☆,☆☆

J. Alaina Floyd [a], Anna Galperin [b], Buddy D. Ratner [a,b,1]

[a] University of WA, Department of Chemical Engineering, Seattle, USA
[b] University of WA, Department of Bioengineering, Seattle, USA

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ABSTRACT

Despite intensive surgical excision, radiation therapy, and chemotherapy, the current life expectancy for patients diagnosed with glioblastoma multiforme is only 12 to 15 months. One of the approaches being explored to increase chemotherapeutic efficacy is to locally deliver chemotherapeutics encapsulated within degradable, polymeric microspheres. This review describes the techniques used to formulate drug encapsulated microspheres targeted for intracranial tumor therapy and how microsphere characteristics such as drug loading and encapsulation efficiency can be tuned based on formulation parameters. Further, the results of in vitro studies are discussed, detailing the varied drug release profiles obtained and validation of drug efficacy. Finally, in vivo results are summarized, highlighting the study design and the effectiveness of the drug encapsulated microspheres applied intracranially.

Contents

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E-mail address: ratner@uweb.engr.washington.edu (B.D. Ratner).
[1] 3720 15th Ave NE, Box 355601, Seattle, WA 98195. Tel.: +1 206 543 2250; fax: +1 206 543 3778.

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1. Introduction

Malignant tumors of the brain and spinal cord are diagnosed in over 20,000 men and women in the United States in 2014 [1,2]. Over half of these will prove fatal to the patient. The fastest growing and most common malignant tumors originate in the glial or support cells of the brain. These tumors include astrocytomas, oligodendrogliomas, ependymomas, and the most common and aggressive type, glioblastoma multiforme [2,3]. Ultimately, despite treatments including a combination of surgical resection, chemotherapy, and radiation [4], these tumors will regrow. After diagnosis, a 12–15 month survival period is expected [5,6]. This low survival rate is attributed to such factors as tumor drug resistance, intracellular drug metabolism, and limited drug uptake, in part due to the major obstacle of the blood brain barrier which prevents many systemic therapies from reaching the brain [7–9]. In addition, complete tumor removal is difficult to achieve without causing brain damage. Tumor reccurrence is generally within 2 cm of the primary tumor site, in part due to tumor remnants, emphasizing the need for a localized and sustained delivery of therapeutic agents to treat the new growth and bypass the blood brain barrier [10].

To address the need for a localized drug delivery system to target tumor regrowth, the scientific community has developed different approaches for intracerebral therapy including implantable reservoirs, biodegradable drug carriers, and convection-enhanced delivery [6,11,12]. Currently, the only FDA approved intracerebral therapy is the application of GLIADEL® wafers at the site of tumor resection. These wafers are a degradable polymeric matrix composed of 1,3-bis(p-carboxyphenoxy)propane (CPP) and sebacic acid (SA), loaded with carmustine [13]. Locally implanted, GLIADEL® wafers degrade over time, delivering the payload in a controlled manner to the tumor site. Combined with tumor resection and radiation therapy, the GLIADEL® wafers were shown to increase patient survival by approximately two months [14].

The use of biodegradable drug carriers like GLIADEL® wafers are a promising avenue for intracranial delivery due to their steady-state release, minimized systemic side effects associated with localized delivery, and increased patient convenience from the therapy due to drug release over several weeks to months. However, polymeric wafers are just one type of biodegradable drug carrier.

Polymeric microspheres and nanoparticles are alternative delivery vehicles for a localized, glioma therapy. While the systemic administration of polymeric, drug-loaded nanoparticles, ranging from 10 to 1000 nm in size, is minimally effective due to a low percentage of particles that successfully cross the blood brain barrier and enter the brain, the localized administration of "penetrating" nanoparticles have demonstrated therapeutic efficacy in vivo [15–17]. Microspheres are also applied after tumor resection, overcoming the blood brain barrier and allow for a slow, long term release of a chemotherapeutic. However, microspheres offer the potential for greater suspension stability, high drug loadings, and lower burst release due to their lower surface area to volume ratio [18]. Thus, there are positive aspects to both microsphere and nanoparticle delivery of therapeutics to brain tumors. However, this article will focus on microspheres for brain cancer drug delivery.

While microspheres for controlled drug delivery have been reviewed [19–22], their potential use for glioma treatment has not been considered in an overview article. Herein, the methodologies for forming degradable, drug loaded polymeric microspheres for the localized treatment of brain tumors will be reviewed together with in vitro and in vivo results, encompassing the various small and large molecule therapeutics that have the potential for positively impacting brain tumor therapy.

In this review article, we are not necessarily advocating microsphere delivery of cancer therapeutic drugs as the ideal treatment modality, but rather summarizing the published literature on this widely used strategy for treatment. The fact that there is such an extensive literature on microsphere drug delivery for treating brain tumors suggests that many leading practitioners and researchers consider microsphere deliver a viable contender for advanced brain tumor therapies.

2. Microsphere formation methodology

While there are many reviews detailing the formulation and characterization of microspheres for drug delivery purposes [19–21,23,24], this section endeavors to provide an overview of the techniques used to prepare chemotherapeutic encapsulated microspheres specifically for intracranial tumor therapy. In addition, this section provides insight into the parameters that can be manipulated to achieve microspheres with tailored properties, e.g., size, morphology, drug loading, encapsulation efficiency, etc.

2.1. Single emulsion

The single emulsion solvent evaporation (or solvent extraction) technique, also called the oil-in-water (O/W) emulsion, is a common method for forming drug encapsulated polymeric microspheres for intracerebral therapies [25–43]. As shown in Fig. 1, the polymer to form the microsphere, poly(lactic-co-glycolic acid) (PLGA) or poly(lactic acid) (PLA) for example, is dissolved in an organic solvent, usually methylene chloride, along with the drug to be encapsulated. This "oil" solution is added to an aqueous solution containing a stabilizer, e.g., poly(vinyl alcohol) (PVA), and homogenized. The organic solvent is then removed by evaporation and the drug encapsulated microspheres are recovered. A variation of the single emulsion method can use an acetone/mineral oil emulsion instead of the organic and water system [30].

A variety of chemotherapeutics including temozolomide, bischloroethylnitrosourea (BCNU), paclitaxel, 5-fluoruracil (5-FU), and 5-iodo-2′-deoxyuridine (IUdR) have been encapsulated in polymeric microspheres by the single emulsion technique for intracranial tumor therapy [26–31,38]. Based on the polymer to oil ratio, homogenizing speed, drug concentration, stabilizer concentration, and other formulation parameters, the sphere size, morphology, drug loading and encapsulation efficiency can be tailored.

For example, Zhang et al. has shown that both polymer concentration and stirring rate can affect the size of temozolomide loaded PLGA microparticles [27]. For a PLGA concentration increased from 5 to 13.33% (w/v), microparticle size changed from 55.2 to 73.6 μm, respectively. This is attributed to the increase in viscosity that comes from

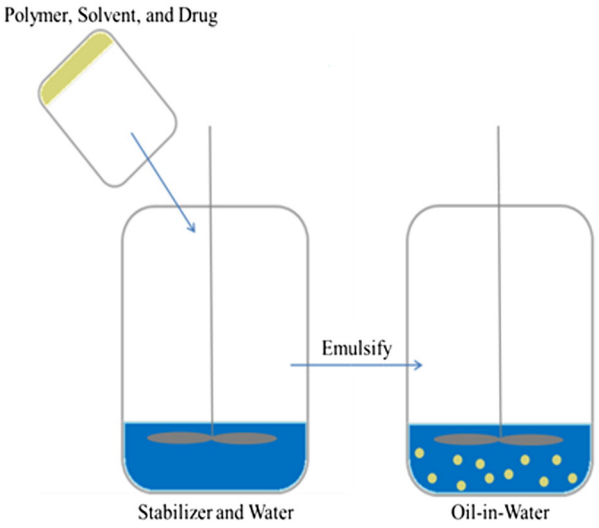

Fig. 1. Schematic of the oil-in-water (O/W) solvent evaporation technique for microsphere formation.

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