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Perspective Review

An overview of clinical and commercial impact of drug delivery systems

Aaron C. Anselmo, Samir Mitragotri *

Department of Chemical Engineering, Center for Bioengineering, University of California, Santa Barbara 93106, USA

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ABSTRACT

Drug delivery systems are widely researched and developed to improve the delivery of pharmaceutical compounds and molecules. The last few decades have seen a marked growth of the field fueled by increased number of researchers, research funding, venture capital and the number of start-ups. Collectively, the growth has led to novel systems that make use of micro/nano-particles, transdermal patches, inhalers, drug reservoir implants and antibody–drug conjugates. While the increased research activity is clearly an indication of proliferation of the field, clinical and commercial translation of early-stage research ideas is critically important for future growth and interest in the field. Here, we will highlight some of the examples of novel drug delivery systems that have undergone such translation. Specifically, we will discuss the developments, advantages, limitations and lessons learned from: (i) microparticle-based depot formulations, (ii) nanoparticle-based cancer drugs, (iii) transdermal systems, (iv) oral drug delivery systems, (v) pulmonary drug delivery, (vi) implants and (vii) antibody–drug conjugates. These systems have impacted treatment of many prevalent diseases including diabetes, cancer and cardiovascular diseases, among others. At the same time, these systems are integral and enabling components of products that collectively generate annual revenues exceeding US $100 billion. These examples provide strong evidence of the clinical and commercial impact of drug delivery systems.

1. Introduction

Drug delivery systems (DDS) improve the administration and efficacy of pharmaceutical compounds including antibodies, peptides, vaccines, drugs and enzymes, among others. Oral pills and injections represent the most common mode of administering drugs today. A majority of small molecule drugs are delivered by pills. Tens of billions of pills are annually consumed worldwide for aspirin alone. Injections remain the primary mode of administering proteins and peptides. More than 10 billion injections are performed each year worldwide [1]. Oral pills offer convenience of pre-determined and measured doses, portability, defined dosing times and the overall non-invasive nature of administration. However, they are also limited by the inability to deliver larger therapeutic molecules such as proteins [2]. Injections, on the other hand, are able to deliver macromolecules, but are limited by their invasive nature and inapp.cropriate use [1]. Collectively, simple pills and injections are unable to meet many advanced therapeutic needs including targeting, broad applicability to macromolecules and on-demand activation. While not all pharmaceutical molecules require these abilities, many do. These limitations have given rise to substantial research focused on the development of novel DDS.

Research in drug delivery has focused not only on improving oral and injectable systems, but also on opening additional routes of administration including pulmonary [3], transdermal [4], ocular [5] and nasal routes [6]. Each route has its own advantages and limitations (Table 1). Many novel DDS that make use of these routes are beginning to enter clinical trials and some have already reached the market. To accomplish successful clinical translation, DDS must, at minimum, be safe, perform their therapeutic function, offer convenient administration and offer ease of manufacturing. This review highlights some of the successful technologies that have made this transition (Fig. 1). Seven categories of DDS including microsphere-depots, tumor-targeting nanoparticles, transdermal patches, advanced oral pills, inhalers, implants and antibody–drug conjugates are highlighted. A search on clinicaltrials.gov for: (i) 'Depot', (ii) 'Transdermal', (iii) 'Inhaler', (iv) 'Subcutaneous implant' and 'Intravitreal implant' and 'Birth control implant', (v) 'Nanoparticle and cancer', (vi) 'Antibody drug conjugates' and (vii) 'OROS'® confirms high activity of clinical trials based on these categories of DDS (Fig. 2). We discuss their historical perspective, advantages/limitations in the clinic, the inspiration that they provide for follow-up technologies, and current clinical status of new(er) products in the field. This review is not intended to provide a comprehensive list of clinical and commercial status of all DDS given the high volume of activity in the field. Instead, the article discusses select examples and analyzes their features that led to their success.

* Corresponding author at: Department of Chemical Engineering, University of California, Santa Barbara 93106, USA. Tel.: +1 805 893 7532; fax: +1 805 893 4731.
E-mail address: samir@engineering.ucsb.edu (S. Mitragotri).

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2. Microparticle-based sustained release formulations

Microparticle-based sustained release formulations have been developed to facilitate the controlled delivery of therapeutics. By sustaining drug release over longer periods, these systems aim to improve the delivery of peptides or proteins by reducing injection frequency [7]. Microparticle-based depots include a polymeric material (often biodegradable) that allows for protection of the drug cargo and control over drug release. A number of polymer choices exist, each with their own advantages and limitations. Poly(lactic-co-glycolic) acid (PLGA), poly(lactic acid) (PLA) and polyglycolic acid (PGA) are perhaps the most commonly studied polymers due to their versatility in tuning biodegradation time and high biocompatibility arising from their natural by-products, lactic acid and glycolic acid. Here, we will highlight one of the first Food and Drug Administration (FDA)-approved, microparticle-based depot DDS, Lupron Depot®.

2.1. Development of Lupron Depot®

Lupron Depot® consists of leuprolide encapsulated in PLGA microspheres. Leuprolide was originally approved in 1985 as an injectable; however, constant injections spurred interest in a more patient compliant formulation. It was long thought that controlled release of proteins, and even smaller peptides, from microspheres was impossible [8]. However, research in the mid-70s showed that this was indeed possible [9], and thereby paved the way for a new class of peptide/protein encapsulated polymeric DDS. Lupron Depot® was one of the first examples of this new class of controlled release polymeric DDS and was originally developed by Takeda-Abbott Products, a joint venture formed in 1977 between Abbott Laboratories and Takeda, and approved by the FDA in 1989 for the treatment of advanced prostate cancer [10]. Since then, Lupron Depot® has been approved for management of endometriosis and also for the treatment of central precocious puberty. Lupron Depot® has been commercially successful, reaching annual sales of nearly $1 billion [11].

2.2. Advantages and limitations of Lupron Depot®

The main advantage of Lupron Depot® was that it significantly lowered the number of injections required for the treatment. Leuprolide alone required daily injections; however, the depot formulation requires injections every 1 to 6 months depending on the dose, thereby dramatically reducing the number of injections and increasing both patient compliance and convenience. Reduced injection frequency leads to improved patient comfort and compliance, which are requisites for successful self-administered DDS. In terms of the delivery technology, the individual components of Lupron Depot® offer several advantages. Specifically, PLGA polymer provides tunable degradation kinetics along with controlled release and well established safety and biocompatibility. Synthesis methods for Lupron Depot® microparticles must be highly reproducible and consistent in order to maintain efficacy across patients. Indeed, the encapsulation of proteins and peptides in PLGA particles has proven challenging in general, as is maintaining protein stability in microparticles [12]. Lupron Depot® and, in general, all microparticle protein formulations face these same challenges. Further, the production process of PLGA polymer determines product performance and different suppliers may not have identical procedures which ties down drug companies to specific supplier(s). A variety of reasons, ranging from supplier shut down to the high material costs, may pose a manufacturing challenge for microparticles.

2.3. Lessons learned from Lupron Depot® — current academic research

As one of the first clinically and commercially successful peptide delivery microparticle depot DDS in the US, Lupron Depot® inspired not only polymeric depot DDS, but also nanoparticle DDS in general. Lupron Depot® is a perfect example of a polymeric controlled delivery system that improves patient compliance by offering long-acting and long-lasting alternatives to highly invasive (i.e. daily injections) therapies. Since the introduction of Lupron Depot®, researchers have advanced the technology of sustained protein-release microparticles in various ways, including new methods for improving the stability and protection of encapsulated proteins [13,14].

2.4. Current clinical landscape and future prospects

Many other microparticle depot systems are in clinical use and have been approved by the FDA (Table 2). One example is Nutropin Depot® developed by Genentech and Alkermes, the first long-acting formulation for recombinant growth hormone. Nutropin Depot® is a biodegradable microparticle depot formulation that was approved by the FDA in 1999 for pediatric growth hormone deficiency. Nutropin Depot® performed well in preclinical studies, showing reliable delivery for over one month in monkeys [15]. In clinical trials, Nutropin Depot® showed

Table 1
Routes of administration. Advantages, disadvantages, potential targets and examples of the most commonly used routes of administration for drug delivery. The number of top 100 commercial drugs and their route of administration were determined by counting the best selling drugs in 2013 as determined by Drugs.com [155].

Route of administration	Advantages	Disadvantages	Targets	Examples	Number of top 100 commercial drugs
Injections: IV, IM and SQ	• Rapid onset (IV) • Up to 100% bioavailability • Controlled depot release (IM, SQ) • Suitable for most therapeutic molecules	• Difficult for patient to self-administer (IV) • Patients' fear of needles leads to noncompliance • Higher instance of infection	• Tissue with blood access (IV) • Systemic	• Vaccines (IM) • Chemotherapy (IV) • Insulin (SQ)	42
Oral	• Patient compliant and most convenient	• Poor bioavailability • Generally nontargeted • Not viable for larger therapeutics (peptides/proteins) • Potentially inconsistent due to the presence of food	• Systemic	• Pills • Liquid medications	54
Inhalation	• Direct target to the lungs • Fast absorption	• Inconsistent delivery stemming from variation in patient-to-patient technique	• Lungs • Brain • Systemic	• Inhalers • Anesthetics	7
Transdermal	• Less side-effects due to direct delivery to the skin • Bypasses first-pass degradation	• Patients can potentially use incorrect dose (creams) • Absorption dependent on skin condition and location	• Skin • Systemic	• Patches • Creams	4