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Review

Drugs and Polymers for Delivery Systems in OA Joints: Clinical Needs and Opportunities

Maarten Janssen [1], George Mihov [2], Tim Welting [1], Jens Thies [2] and Pieter Emans [1,*]

[1] Department of Orthopaedic Surgery, Maastricht University Medical Center, P. Debyelaan 25, 6229 HX Maastricht, the Netherlands; E-Mails: maarten.janssen@maastrichtuniversity.nl (M.J.); t.welting@maastrichtuniversity.nl (T.W.)

[2] DSM Biomedical, Koestraat 1, 6167 RA Geleen, the Netherlands; E-Mails: george.mihov@dsm.com (G.M.); jens.thies@dsm.com (J.T.)

* Author to whom correspondence should be addressed; E-Mail: pj.emans@maastrichtuniversity.nl; Tel.: +31-43-387-5038; Fax: +31-43-387-4893.

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Abstract: Osteoarthritis (OA) is a big burden of disease worldwide and one of the most common causes of disability in the adult population. Currently applied therapies consist of physical therapy, oral medication, intra-articular injections, and surgical interventions, with the main goal being to reduce pain and improve function and quality of life. Intra-articular (IA) administration of drugs has potential benefits in OA treatment because it minimizes systemic bioavailability and side effects associated with oral administration of drugs without compromising the therapeutic effect in the joint. However, IA drug residence time is short and there is a clinical need for a vehicle that is able to provide a sustained release long enough for IA therapy to fulfill its promise. This review summarizes the use of different polymeric systems and the incorporated drugs for IA drug delivery in the osteoarthritic joint with a primary focus on clinical needs and opportunities.

Keywords: osteoarthritis; drug delivery systems; DMOAD

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1. Introduction

1.1. The Osteoarthritic Joint

Osteoarthritis (OA) is a progressive disease in which degeneration of joint cartilage and eventually the underlying subchondral bone may cause pain, stiffness, and inflammation.

The precise cause of OA is unknown, but it is believed to be a combination of both mechanical and biological events affecting the joint [1]. OA mostly affects the knees, hips, hands, feet, and spine, but other joints can also be affected [2,3]. OA is the most common form of arthritis and the leading cause of chronic disability in the United States [4]. It ranks fourth in health impact in women and eighth in men in the Western world (US and Europe) [5]. Due to aging and increasing life expectancy, OA is expected to become the world's fourth-leading cause of disability in 2020 [6]. Because effective treatments are lacking, it is a growing socio-economic problem. The costs (medical and productivity loss) are 871 euros per patient, per month, in the Netherlands [6].

1.2. Current Treatment

Currently available treatment options for OA primarily focus on pain relief and improving function. Non-pharmacological therapy is widespread but differs per joint and the American College of Rheumatology (ACR) only strongly recommends weight loss if overweight, and participation in either cardiovascular or resistance exercise [7]. Pharmacologicaltherapy begins with oral administration of paracetamol either combined or substituted with NSAIDs or COX-2 inhibitors and a weak opioid (e.g., tramadol) depending on patient characteristics [8]. Major disadvantages of oral administration of these drugs are the limited bio-availability and the risk of side effects (e.g., liver damage, GI-ulcer/bleeding, and constipation). As OA has a localized nature, intra-articular administration of drugs provides an excellent opportunity to improve treatment. Glucocorticoid and hyaluronic acid (HA) injections are not impeded by the disadvantages of the oral route and are already common practice. However, although these injections provide a fairly good relief of symptoms and improve function over the short- and medium-term, there is little to no disease modification, and the beneficial results are often not long-lived.

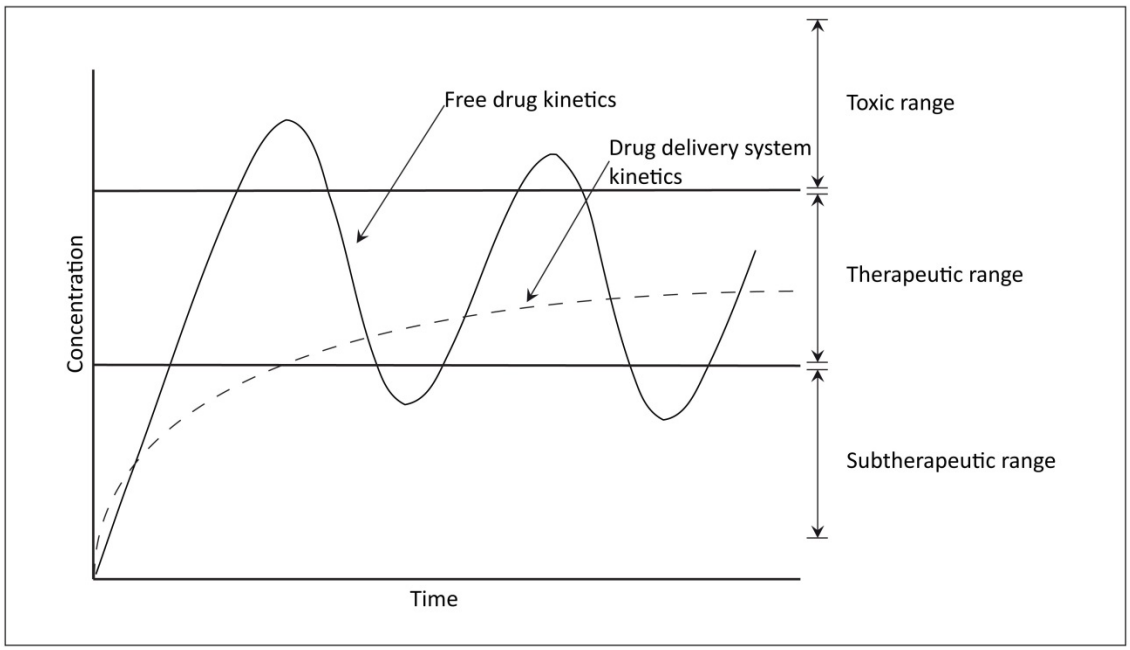
Therefore to date OA continues progressing for almost all patients. At end-stage disease, surgical interventions, and finally joint replacement (e.g., total knee arthroplasty [TKA]) is indicated in many patients. However, the exponential increase in knee joint replacements is becoming an inevitable medical and economic problem [9]. The number of TKAs continues to grow each year and as these increase in number, the amount of revision TKAs continues to increase substantially as well [10]. While a primary TKA is cost-effective, revision surgery of TKA has a less favorable outcome for both the healthcare status of the patient and the economic benefit [11]. To prevent this situation a therapy that postpones primary joint arthroplasty is needed.

1.3. Clinical Needs

To improve treatment of OA there is a need for new strategies. Development of disease modifying osteoarthritis drugs (DMOADs) is one of those strategies. The mechanism of action of DMOADs is directed at reducing, halting, or reversing progression of OA or even preventing OA by either

inhibiting different causative pathways (catabolic activity) or stimulating repair mechanisms (anabolic activity) [12]. To date the pharmaceutical industry has failed to provide effective and safe DMOADs for clinical use [13]. The main reasons are that despite their specific targeted action DMOADs still can cause side effects when administered systemically [14–16], or when injected intra-articular have a short residence time within the joint [17,18]. It remains unclear how long particular drugs have to remain in the joint for an effective pain relief and/or disease modification after an intra-articular injection. Without a drug delivery system (DDS), synovial disappearance time of a drug in the joint is often short and except for cross-linked HA usually drugs do not reside much longer than 24 hours [18]. Direct intra-articular drug delivery allows for an effective concentration where it is needed with a minimum of drugs. Moreover it negates the main disadvantages of systemic administration; a low (oral) bioavailability or systemic side effects. However, due to the rapid clearance of most intra-articular injected drugs, frequent injections would be needed to maintain an effective concentration [19]. Frequent intra-articular injections are undesired due to the pain and discomfort they may cause and the risk of introducing an infection to the joint. Therefore a DDS for DMOADs combined with an intra-articular injection seems to be needed to cause prolonged drug residence time and a stable concentration within the therapeutic window with a single injection as compared to repeated injections in which the concentration may vary between a toxic and a subtherapeutic level (Figure 1). As a result, this leads to a reduction of side effects and may lead to an improved patient compliance [20].

Figure 1. Therapeutic window of administered drugs. The solid line shows the release profile of a repeatedly dosed free drug with a high variation in available drug concentrations ranging from subtherapeutic to toxic levels. The dashed line shows a possible release profile of a drug delivery system which lies within the therapeutic range.



Furthermore, there is a need for diagnostic improvement, currently the role of biomarkers for diagnosis of OA is still under debate [21]. Regulatory approval in clinical trials still requires changes

in radiographic joint space width and an impact on symptoms [22,23]. However, as MRI allows for direct visualization and measurements of cartilage [23,24] the FDA recently recognized the improvement of MRI as an OA imaging biomarker. Other OA associated processes (e.g., osteophytes, subchondral bone changes, and trabecular structure) can likewise be assessed by MRI [13]. With MRI, different phenotypes of OA can be identified and the success of treatment may be tailored depending on the phenotype and its effect can be monitored in more detail [25].

In this review we provide an overview of (candidate) drugs that are needed for an effective OA treatment and can be incorporated in a DDS and which polymers are required to provide for such system.

2. Candidate Drugs for OA Treatment

Many different drugs have been investigated for OA treatment. However there are limitations to which drugs can be incorporated in a DDS. The incorporated drug has to be able to withstand the manufacturing process of the carrier vehicle (*i.e.*, compression, heat, stirring, *etc.*). As the final goal of manufacturing these vehicles (particles) is injecting them intra-articularly, the DDSs have to be sterilized. Not only should the DDSs be able to withstand this process, but so should the incorporated drugs.

2.1. NSAIDs, Coxibs, Glucocorticoids, and Hyaluronan

Drugs currently used in DDSs in the OA joint are mostly derived from the drugs normally used in OA treatment (NSAIDs, Coxibs, Glucocorticoids, and HA). Fourteen studies show incorporation of an NSAID [26–39] and two studies incorporated Celecoxib (Cxb) [40,41] in their carrier. Glucocorticoids were incorporated in six different studies [42–47] and HA in three [48–50]. An overview of these, and other studies is presented in Table 1.

The rationale for the use of these drugs is that their mechanism of action has been abundantly investigated in the perspective of OA treatment, their ability to give symptomatic relief and their potential to slow down disease progression. Moreover, these drugs have often already been approved by the regulatory bodies for parenteral administration, which may ease their DDS regulatory process.

An important note, however, is that these drugs were developed and studied for use in oral OA treatment or an intra-articular injection without a DDS. Since then, great progress has been made in DDSs, and as such more other potential drugs may be used for treatment of OA. Due to systemic side effects, short half time, *etc.*, many of these candidates have been thought not suitable for OA treatment in the past. With the introduction of different drug delivery systems DMOADs and other new candidate drugs may ultimately provide a more effective treatment.

Table 1. Overview of investigated polymers and drugs in drug delivery systems (DDSs). ACLT—Anterior cruciate ligament transection, MT—Meniscal tear, FCA—Freunds Complete Adjuvant, MIA—monosodium iodoacetate, SPIONs—Superparamagnetic iron oxide nanoparticles, DPPE—dipalmitoyl phosphatidylethanolamine, FITC—Fluorescein isothiocyanate, PC:DOPE—phosphatidylcholine:dioleoylphosphatidylethanolamine, TEGM-CHM—Tetraethylene glycol methacrylate-cyclohexyl methacrylate, MEH-PPV—poly[2-methoxy-b-(2-ethylhexyloxy)-1,4-phenylenevinylene], PCLA-PEG-PCLA—poly(ε-caprolactone-co-lactide)-b-poly(ethylene glycol)-bpoly(ε-caprolactone-co-lactide), PVA—polyvinyl alcohol.

Author	Year	Type DDS	Composition	Drug	Particle Diameter	Model	OA Induction	Outcome
Ibim	1998	Microsphere	PolyPhosphazene	Colchicine	Not stated	*in vitro*	N.A.	Prolonged release, possible toxicity
Brown	1998	Microsphere	Gelatin/chondroitin 6-sulfate	14C-catalase, 14C-albumin, 14C-inulin, 14C-diazepam	1–60 µm	*in vitro*/mice	none	partially biocompatible
Tuncay	2000	Microsphere	PLGA	Diclofenac	5–10 µm	*in vitro*/rabbit	Ovalbumin/FCA	No significant difference in inflammation
Tuncay	2000	Microsphere	Albumin	Diclofenac	±15 µm	*in vitro*/rabbit	Ovalbumin/FCA	Promising at day 30
Bozdag	2001	Microsphere	PLGA, albumin	Naproxen	10 µm	*in vitro*/rabbit	Ovalbumin/FCA	PLGA better than albumin
Bragdon	2001	Microsphere	PLGA	Paclitaxel	50 µm	*ex vivo* horse MCP	none	Biocompatible
Horisawa	2002	Nano/ microsphere	PLGA	Fluoresceinamine	265 nm/26.5 µm	Rat	none	Fagocytosis is size dependent
Horisawa	2002	Nanosphere	PLGA	Betamethasone	300–490 nm	*in vitro*/rabbit	Ovalbumin/FCA	Prolonged efficacy
Liang	2003	Microsphere	PLLA	Methotrexate	83.7–187.6 µm	*in vitro*/rabbit	None	mild inflammation, prolonged release

Table 1. *Cont.*

Fernández-Carballido	2004	Microsphere	PLGA	Ibuprofen, PEG oil (Labrafil)	39.69 µm	*in vitro*	N.A.	Labrafil reduces burst release, prolonged release
Liggins	2004	Microsphere	PLGA, PLA, PCL, Chitosan	Paclitaxel	1–20 µm, 10–35 µm, 35–105µm	Rabbit	BSA/FCA, Carrageenan	Chitosan not biocompatible, small PLGA particles give greater inflammation.
Thakkar	2004	Microsphere	Chitosan	Celecoxib	8 µm	Rat	FCA	Chitosan is biocompatible, improved retention
Fernández-Carballido	2004	Microsphere	PLGA	Ibuprofen, PEG oil (Labrafil)	39.31 µm	*in vitro*	N.A.	Storage of PLGA/Ibuprofen particles does not change characteristics
Park	2005	Hydrogel	Hyaluronic acid	Hyaluronic acid Ultrasound	3000 kDA	Rabbit	ACLT/MT	Combination of HYA and US is more effective than monotherapy
Betre	2006	Aggregate	Elastin-like polypeptides	none	N.A.	rat	None	Biocompatible, prolonged residence time
Tsai	2007	Nanosphere	Nanogold	none	5, 13 nm	Rat	Collagen	RA reduction
Zhang	2007	Micelle	PNIPAAm/EAB-PPP	Indomethacin	Not stated	*in vitro*/rat	FCA, Carrageenan	Prolonged release/effect
Hui	2007	Hydrogel	α-CD-EG 4400	Chondroitin sulfate	N.A.	Rabbit	Chondral defect	Biocompatible, improved biomechanical and histologic properties
Lu	2007	Microsphere	Gelatin	Flurbiprofen	2.5–12.3 µm	Rabbit	None	Prolonged residence IA, biocompatibility unclear
Thakkar	2007	Nanoparticles	Glycerol behenate	Celecoxib	257 nm	Rat	FCA	Prolonged residence, biocompatible
Rothenfluh	2008	Nanoparticles	Poly(propylene sulphide)	WYRGRL (Col II-binding peptide)	38, 96 nm	Mice	None	Retention of the small particles in cartilage matrix
Butoescu	2008	Microparticles	PLGA	Dexamethasone/SPIONs	~10 µm	*in vitro*	N.A.	Possible to incorporate 2 active substances

Table 1. *Cont.*

Butoescu	2009	Microparticles	PLGA	Dexamethasone/SPIONs	1, 10 μm	Mice	None	Biocompatible, uptake of 1 and 10 μm particles, prolonged action of magnetic particles
Elron-Gross	2009	Collagomers	Collagen:DPPE	Diclofenac	Not stated	Rat	MIA	Better and sustained reduction of inflammation
Butoescu	2009	Microparticles	PLGA	Dexamethasone/SPIONs	~10 μm	Mice	N.A. (dorsal air pouch)	Sustained release, first order kinetics
Saravanan	2011	Microsphere	Gelatin	Diclofenac sodium	1–60 μm	Rabbit	None	Prolonged release
Zille	2010	Nanoparticles	PLGA, PLA, HA	FITC–dextran	Not stated	Rat	None	Weak hyperplasia, no inflammation
Zhang	2011	Microspheres	PLGA	Lornoxicam	7.47 μm	Rabbit/rat	None	Prolonged retention
Panusa	2011	Microspheres	PLGA	Methylprednisolone	3–60 μm	Rat	Carrageenan	Prolonged retention, less inflammation
Zarnescu	2011	Liposomes	PC:DOPE:cholesterol:stearylamine	Chondroitin sulfate	Not stated	*in vitro*	N.A.	Interacts with collagen
Eswaramoorthy	2012	Microspheres	PLGA	Parathyroid hormone	51–85 μm	Rat	Papain/Cystein	Biocompatible, improved GAG and Col II levels
te Boekhorst	2012	Nanoparticles	PLGA	siRNA (against RA)	235–285 nm	Mice	Collagen antibody	Positive effect on RA depending on dose
Kawadkar	2012	Microspheres	Genipin cross-linked chitosan	Flurbiprofen	5.18–9.74 μm	Rat	Carrageenan	Biocompatible, prolonged retention
Zhang	2012	Microspheres	PLGA	Lornoxicam	Not stated	Rat	Papain	Biocompatible, effect comparable with weekly injections of Lornoxicam
Whitmire	2012	Nanoparticles	TEGM-CHM	Interleukin-1 Ra	300 nm	Rat	MIA	Prolonged retention, no negative effects on cartilage
Gaignaux	2012	Microparticles	PLGA	Clonidine	10–30 μm	*in vitro*	N.A.	Possible to incorporate small hydrophilic drug in PLGA
Présumey	2012	Microspheres	PLGA	anti-TNF siRNA	23.5 μm	Mice	Collagen	Biocompatible, prolonged inhibition of TNA-α

Table 1. *Cont.*

Chen	2012	Microspheres/hydrogel	Chitosan	Brucine	0.5–4.5 μm	Rat/rabbit	Collagenase	Prolonged retention of microsphere/hydrogel composite, inhibiting inflammation
Morgen	2012	Nanoparticles	Dextran propionate/MEH-PPV	Fluorescent labeled peptide	100–150 nm	Rat	None	Prolonged retention of peptide, biocompatible
Kawadkar	2013	Microspheres	Genipin cross-linked gelatin	Flurbiprofen	6.39 μm	Rat	Carrageenan	Biocompatible, prolonged release
Ryan	2013	Nanocomplex	HA-chitosan	Salmon calcitonin (sCT)	100–200 nm	Mice	K/BxN serum	sCT-HA-chitosan nanoparticles reduces inflammation and preserves bone and cartilage
Ko	2013	Microspheres	PLGA	Sulforaphane	14.5 μm	Rat	ACLT	Prolonged retention, inhibition of inflammation
Sandker	2013	Hydrogel	PCLA-PEG-PCLA	None	N.A.	Rat	None	Hydrogel degrades after 3+ weeks
Bédouet	2013	Microsphere	PLGA cross-linked PEG	None	40–100 μm	Sheep	None	Slow degradation, little inflammation from MS
Chen	2013	Nanoparticles in microspheres	PLGA-PVA	Brucine	12.38 μm	Rat	None	Prolonged retention, less burst release
Bédouet	2014	Microspheres	PEG-hydrogel	Ibuprofen	40–100 μm	*ex vivo* sheep	LPS	Prolonged retention, less burst release, inhibition of inflammation

2.2. DMOADs

Pathological processes in OA consist of inflammation, cartilage degradation and subchondral bone changes [13]. Inflammation can be caused by a variety of cytokines such as Interleukins (ILs) [51], Tumor Necrosis Factors (TNFs), and Nitric Oxide (NO) [52], whereas, cartilage degradation is mainly caused by enzymes, such as Matrix Metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) [52]. Furthermore, a strong correlation between subchondral bone changes and OA development has been described [53,54].

Based on their method of action, roughly three groups of DMOADs can be identified: (i) inhibitors of degrading enzymes and inflammation, (ii) growth factors, and (iii) drugs which target subchondral bone changes. Most DMOADs are proteins or protein derived peptides with different properties when applied in therapeutic use (Table 2). Diffusion transport of proteins and large peptides is generally slow and due to their weak non-covalent interaction and fragile tertiary structure proteins usually have a low *in vivo* stability. Enzymatic or proteolytic degradation causes short half-lives when administered without a DDS. In addition, a DDS can protect the protein or peptide against degrading environmental factors when prepared or stored [55]. However, maintaining the structure and function of often fragile protein based drugs during DDS processing, formulation, sterilization and subsequent degradation and release is far from trivial and as a result very few protein based DDS products are on the market today. Peptides are already successfully incorporated in DDSs in other fields of research (e.g., Airway and Gastro-intestinal drug delivery) [56,57]. These positive results are promising for the application of peptidal DMOADs in a DDS. Even DMOADs and drugs that can be administered systemically or by injection (bisphosphonates and Platelet-rich plasma (PRP) respectively) seem to benefit from a DDS [58,59]. These results also suggest that there might be a beneficial effect of targeting subchondral bone in OA treatment, but more evidence is needed, especially in drug delivery systems.

2.3. Cytostatic Drugs

Cytostatic drugs are able to inhibit inflammation and can even be chondroprotective [60], though they are not used in OA treatment because of their high toxicity and often severe side effects when administered systemically. Some studies, however, showed beneficial effects of IA administration of paclitaxel and methotrexate without apparent toxicity and side effects in an animal model [61,62]. In line with other classes of drugs there is potential for cytostatic drugs when administered via an intra-articular drug delivery system [61].

When categorizing candidate drugs/DMOADs for use in a DDS, attention should be paid to their chemical nature and the possibilities to incorporate them in a drug delivery system. The complexity in designing effective DDSs for a certain drug increases with the size and complexity of that drug.

Table 2. Most investigated disease modifying osteoarthritis drugs (DMOADs), based on their target of action. The chemical nature of a DMOAD is important for incorporation in a DDS.

DMOADs	Chemical Nature
Enzyme inhibitors	
MMP inhibitors (TIMP 1-4)	Protein/Peptide
Aggrecanase inhibitors (ADAMTS)	Small molecule
Cytokine inhibitors	
IL-1 inhibitors (IL-1 Ra)	Protein
TNF-α antagonists	Antibody
iNOS inhibitors	Various
Growth factors	
Fibroblast Growth Factor (FGF)-18	Protein/Peptide
Bone morphogenetic protein (BMP)-7	Protein/Peptide
Platelet-rich plasma (PRP)	Plasma
Drugs targeting subchondral bone	
Calcitonin	Peptide
Bisphosphonates	Bisphosphonate

3. Drug Delivery Systems

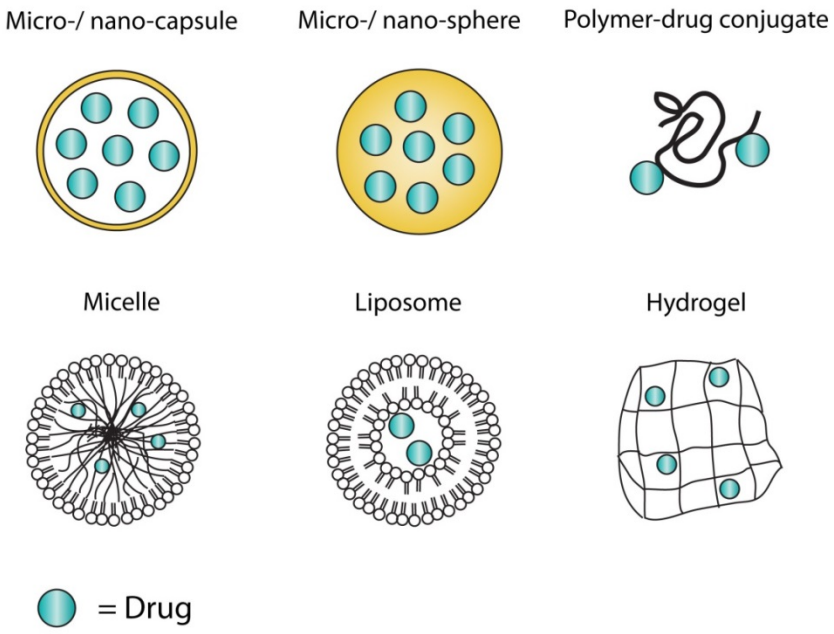
3.1. History

The importance of a drug delivery system has long been recognized. In the mid-1960s, Folkman discovered that a silicone rubber tube acted as a constant rate drug delivery device in rabbit anesthesia [63]. In 1987, Ratcliffe *et al.* provided the first evidence that (albumin) microspheres can delay clearance of a drug from the joint [64]. In the search for a method to provide an ideal (intra-articular) drug delivery system, many different carriers have been investigated. At first focus was on achieving a "zero order release" usually in macroparticulate systems (e.g., ocular, vaginal, or trans- and, sub-dermal particles). In the 1980s and 1990s, a gradual shift towards microparticles and a sustained or long-term drug release occurred [63]. From the 1990s and onwards, the development of DDSs went a step further with the introduction of nanoparticles. Conventional techniques, such as compression, spray and dip coating, and encapsulation, can be used to incorporate drugs in a drug delivery system [65].

DDSs can have a different structure and morphology, all with different characteristics in drug loading, release and response to the physiological environment (Figure 2). In addition, in the case of micro-particulate systems, the size of the particles is also important as particles of 1–10 μm could be taken up by synoviocytes probably through phagocytosis [45]. Depending on the goal of treatment this can be unwanted. When designing a DDS, close attention should, thus, be paid to the drug that will be incorporated, physiological environment of the target location, biocompatibility and desired duration of drug release.

An ideal drug delivery system complies with adequate disease modification, biodegradability, and biocompatibility, while responding to feedback and its physiological environment [65].

Figure 2. Different structures and morphology of DDSs (not-exhaustive). Each structure has its advantages and disadvantages to incorporate and release different types of drugs for intra-articular treatment of OA.



3.2. Hurdles in Drug Delivery System Design

Using polymers for intra-articular drug delivery offers a great variety of opportunities to address OA-progression. However, poly(lactic-co-glycolic acid) (PLGA) and NSAIDs emerge, more often, in different studies, the field of polymers for intra-articular drug delivery is very fragmented. Particle size varies tremendously between particles of only a few nanometers and particles of more than 100 µm. Different particle sizes results in different DDS kinetics and drug release statistics, particles smaller than 10 µm can readily be phagocytized by synoviocytes, whereas particles larger than 20 µm can trigger a giant cell response, but not necessarily an inflammatory response. According to Butoescu *et al.*, an optimal particle size for IA drug delivery would be between 5 and 10 µm [66]. Together with size, method of production of a DDS can influence drug characteristics where especially the large proteins are vulnerable to environmental challenges [67]. For clinical application biocompatibility of a drug and DDS in the joint is of great importance. Polyesters like Poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and PLGA are already widely used and are deemed biocompatible in drug delivery, but their breakdown products are acidic and can lower the pH in the environment which subsequently can cause drug stability problems and inflammation of the surrounding tissue [68]. Ideally, a drug delivery system has to be fully degradable whereas residue from particles can also cause inflammation of the joint.

3.3. Polymers

To avoid inflammation of the injected joint, a polymer carrier has to be biocompatible. The largest group of carriers consists of biodegradable polymeric particles, as well from natural, synthetic, or combined origin. Polymeric particles have the big advantage that they can be altered to fit their

purpose. Depending on manufacturing technique particles can either be microcapsules (a reservoir with a separate polymeric shell) or microspheres (matrix type with a homogenous mixture of a polymer and the encapsulated drug). The latter one having excellent sustained release characteristics [69].

There is a great diversity in both DDSs and in the drugs encapsulated. Natural polymers are widely available and often biodegradable. However, reproducibility is low and they often have a high immunogenicity [68]. Natural polymers investigated for IA drug delivery include Chitosan which was shown to be able to incorporate Cxb or Flurbiprofen and extend their residence time in the joint [28,41,70], Diclofenac Sodium loaded albumin microspheres provided a significant reduction of arthritis after 30 days of incubation in a rabbit knee [38], gelatin microspheres are able to incorporate different NSAIDs or proteins, and Saravanan *et al.* found gelatin microspheres to be more stable than albumin, but residence times are still relatively short [30,33,71].

Synthetic polymers in general are less biocompatible but their characteristics can easily be altered [68]. For IA drug delivery, mostly the polymers that have proven to be biocompatible were investigated. PLA has been shown to be biocompatible in rabbit knees [61,62], polyethylene glycol (PEG), often combined with other polymers (e.g., polycaprolactone (PCL)) is biocompatible and able to control release characteristics of the incorporated drug [72–75], however, by far, the most used synthetic polymer is PLGA. This synthetic polymer has a good biocompatibility and is able to incorporate many different types of drugs [29,31,35–37,39,42–46,50,60,61,72–74,76–84]. Several studies have been published on the incorporation of proteins in different DDSs, a common problem in the classical models (e.g., PLGA), however, is the initial burst release, which can cause local toxic drug concentrations, and the acidic breakdown products can influence protein stability followed by a very slow or no release at all [68,85,86].

The evolution of bio- degradable materials from aliphatic polyesters to nitrogen bearing polymers such as polyurethanes and polyester amides (PEAs) has been accompanied with better control over degradation and release properties. PEAs are based on α-amino acids, aliphatic dicarboxylic acids, and aliphatic α-ω diols [87]. Among this class of polymers it is the AA-BB hetero-chain polymers that offer the greatest versatility in terms of molecular level design to tailor drug release properties. Furthermore, the incorporation of amino acid-based building blocks offers more than providing metabolizable building blocks [88,89], they provide one or more functional groups along the polymer chain. This allows further modification of the polymer to tailor its physicochemical properties and performance as drug eluting matrices. An important advantage of these polymers is related to the fact that, by design, they predominantly degrade via an enzymatic mechanism and, due to consequential surface erosion, drug release follows nearly zero-order kinetics. PEAs are currently being applied in several developmental DDSs and are in clinical trials for a cardiovascular drug eluting stent [90].

3.4. Liposomes

Liposomes are artificial vesicles composed of one or more concentric phospholipid bilayers and used especially to deliver microscopic drugs to body cells. Liposomes can be used as a carrier for intra-articular drug delivery, but far less research has been done on this carrier as compared to polymer-based microspheres. However, the first reports of liposomes as drug carriers appeared in the 1970s and there are still few results reported on liposomes for intra-articular application. In 2001,

Trif *et al.* reported a positive effect of human Lactoferrin encapsulated in liposomes in collagen-induced arthritis in mice [91]. Elron-Gross *et al.* reported a reduction of inflammation in a monosodium iodoacetate (MIA) induced OA rat knee after a liposomal dexamethasone and diclofenac combination injection as compared to control assessed by MRI, in 2009 [32,92], and Dong *et al.* found a combination of Cxb incorporated liposomes and HA to be more effective in pain control and cartilage protection than a single Cxb injection, Cxb liposome, and HA treatment alone [93]. Although liposomes are well established, and are effective and biocompatible, IA residence time is relatively short compared to other DDSs [18].

3.5. Hydrogels

Hydrogels are insoluble, water swollen, cross-linked, three-dimensional structures of polymer chains [94]. HA, which is already common practice in many clinics, can be seen as a hydrogel. Depending on its molecular weight, and whether it is cross-linked or not, HA has different characteristics. The working mechanism of HA is believed to depend on its viscosity, lubricity and restoring some of the normal joint physiology. Other than HA, only a few hydrogels are used for IA drug delivery. Bedouet *et al.* developed a PEG-hydrogel-Microsphere in order to minimize the amount of foreign material injected [73], and in another study by Bedouet *et al.* they sought to deal with the burst release of intra-articular DDSs by developing a methacrylate derivative of ibuprofen with a hydrophilic PEG-hydrogel, which slowly released the ibuprofen [72]. Another method to deal with burst release was provided by Chen *et al.*, by loading brucine in a chitosan microsphere and dispersed that microsphere in a chitosan hydrogel [95]. A more investigative approach was used by Sandker *et al.*, who incorporated 2-(2',3',5',-triiodobenzoyl) moieties (TIB) to make their poly(ε-caprolactone-co-lactide)-b-poly(ethylene glycol)-bpoly(ε-caprolactone-co-lactide) (PCLA-PEG-PCLA) hydrogel radiopaque for long term *in vivo* visualization [75].

4. Discussion

Drug delivery systems have been around for about half a century. Since then, a number of new developments have been made, starting from macroscopic particulates to advanced nanometer sized DDSs that adapt to changes in their physiological environment. Since the discovery of polymeric DDSs as a therapeutic application, a massive increase in citations can be seen on PubMed [68] and an incredible amount of progress has been made in their development. However, it was not until 1987 that the pioneering work of Ratcliffe *et al.* [64] proposed a DDS for IA treatment of OA and this became an increasing field of interest in the late 1990s. As can be seen in Table 1 the most used polymer for DDSs is PLGA, Although PLGA is biocompatible and biodegradable, and has been approved by the FDA many years ago, disadvantages are the initial burst release and the acidic microenvironment it creates on its breakdown which could cause inflammation and can lead to stability problems of the incorporated drugs (e.g., proteins) [68,96]. The search for improvement of biocompatibility, release characteristics and drug incorporation led to an improved PLGA manufacturing process but also to the discovery of new polymers for intra-articular treatment of OA [89,96].

The initial treatment was mainly focused on relieving OA symptoms. Most of the incorporated drugs were NSAIDs or glucocorticoids. Drugs which not only target symptoms but also the disease

process of OA have been incorporated in DDS more recently. Incorporation of DMOADs is even harder as these drugs are still in a developmental stage and most DMOADs are proteins or peptides (Table 2), which makes them vulnerable to environmental challenges in the manufacturing process of DDSs [13]. As such, a drug which targets pain, such as NSAIDs or glucocorticosteroids, released from a DDS are more likely to find their (clinical) application in the near future compared to DMOADs.

The search for the ideal osteoarthritic drug and a biocompatible and biodegradable DDS has been subject of many studies. The focus of most studies was mainly on optimization of DDSs and the ongoing development of the ideal drugs to target OA. To date, this has led to a few ongoing or completed clinical trials on the implementation of polymers for a DDS in OA treatment [97].

5. Conclusions

The optimization of existing DDSs is ongoing and new DDSs are still being developed. It seems to be that the ideal DDS for intra-articular OA treatment has not yet been found. However, many hurdles in the developmental process have been taken care of and implementation of DDSs for clinical applications, such as ophthalmology, cardiology, oncology, *etc.*, give us examples of the possibilities. Given the developments in the field of DDS and the increasing amount of drugs that may be released from a DDS, it is expected that more clinical trials will start to fulfill the need for OA treatment with a DDS.

Conflicts of Interest

The authors declare no conflict of interest.

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