Intra-Articular Depot Formulation Principles: Role in the Management of Postoperative Pain and Arthritic Disorders

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ABSTRACT: The joint cavity constitutes a discrete anatomical compartment that allows for local drug action after intra-articular injection. Drug delivery systems providing local prolonged drug action are warranted in the management of postoperative pain and not least arthritic disorders such as osteoarthritis. The present review surveys various themes related to the accomplishment of the correct timing of the events leading to optimal drug action in the joint space over a desired time period. This includes a brief account on (patho)physiological conditions and novel potential drug targets (and their location within the synovial space). Particular emphasis is paid to (i) the potential feasibility of various depot formulation principles for the intra-articular route of administration including their manufacture, drug release characteristics and in vivo fate, and (ii) how release, mass transfer and equilibrium processes may affect the intra-articular residence time and concentration of the active species at the ultimate receptor site. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:4622–4654, 2008

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INTRODUCTION

Local drug action within the joint cavity is needed for the treatment of arthritic disorders and the relief of pain and inflammation. After oral or parenteral (i.v., i.m., s.c.) administration, the therapeutic agent is transported to the intra-articular site of action via the systemic circulation. In contrast, intra-articular (IA) injection of suitable drug delivery systems (DDSs) may enable the major part of the incorporated drug to be released in the vicinity of the target area. The most obvious advantage of this relatively simple form of targeted drug delivery is that only a minimum amount of drug is required to exert the desired pharmacological activity and thus, minimizing drug exposure to inappropriate sites. Further, direct joint instillation may constitute the only realistic route of administration for chemical entities suffering from bioavailability problems and extensive degradation in vivo.

Literature data indicate that dissolved small-molecule drugs are rapidly cleared from the synovial space after IA injection. Maintenance of therapeutic drug concentrations in the joint over extended periods of time can be achieved by repeated IA administrations or more ideally, by immobilization of the active agent in the form of an injectable depot formulation from which the drug is released in a controlled manner. Currently, long-lasting (weeks) corticosteroid suspen-
sions constitute the only world wide available
depot formulation type for the IA route of
administration. Such depot injectables have been
used for more than three decades providing
symptomatic relief of pain in rheumatoid arthritis
(RA) and osteoarthritis (OA).1–3 These two major
arthritic disorders strongly affect patient quality
of life and present significant costs to society in
terms of medical care and lost wages. The total
annual burden to arthritis has been estimated to
equal 1–2.5% of the gross national product of
Western nations.4 Identification of novel potential
drug targets, not least in the area of OA,5–7 gives
optimism to the development of new disease-
modifying therapies. These encouraging findings
pose a strong incitement to the search for
innovative depot principles feasible for the IA
route of administration.8
The search for novel therapies providing local
sustained drug action after IA administration is
multidisciplinary of nature since it has to be
founded on adequate knowledge of chemical,
pharmaceutical as well as biological disciplines.
This may involve the identification of new targets
and subsequently, drug candidates effectively
acting on such targets. Based on the knowledge of
(patho)physiological conditions, it further
includes the task of accomplishing (in a highly
reproducible manner) the correct timing of the
events leading to optimal drug action over a
desired period of time.9 The primary aims of this
review are (i) to discuss advantages/limitations of
various depot formulation principles in relation to
the IA route of administration and (ii) to give an
account on factors influencing the fate of drug
molecules once released from the immobilized
depot in the joint cavity. In the present review,
ttempts have also been made to present major
knowledge gained in various research areas that
is considered to constitute, at least in part, the
basis for rational design of novel prolonged release
DDSs feasible for IA administration. Due to
the rather comprehensive literature related to
some of the latter research fields, the authors have
found it appropriate, in the treatise of certain
topics, to give references to recent reviews dealing
with these topics.

SYNOVIAL JOINTS
The bones of a synovial joint are separated by an
articular cavity containing the synovial fluid (SF)
(Fig. 1). The adjoining surfaces of the bones are
covered with a layer of articular cartilage and a
two-layer joint capsule encloses the cavity. The
joint capsule consists of an outer fibrous capsule
and an inner synovial membrane (synovium).10

The various cell types populating the articular
cartilage and the synovium as well as components
of the synovial fluid are major targets for RA and
OA related drug therapies. A brief account of the
composition and function of these sites of drug
action is given below.

The Synovium
The synovial tissue has an extensive extracellular
matrix (ECM), the major components of which
are collagen and glycosaminoglycan (GAG). The
superficial synovial lining (synovial membrane)
contains two cell types (type A/type B cells).
Cellular adhesion molecules (CAMs), including
\( \beta_1 \) integrins, probably play important roles in

Figure 1. Schematic representation of the cross sec-
tion of a synovial joint (top). Insert: An enlargement of
the synovial lining. The arrows indicate ultrafiltration
of fluid from the fenestrated capillaries into the joint
cavity and drainage of fluid from the cavity through
the synovial interstitium into subsynovial space and
lymphatics. Reprinted with permission from Micro-
circulation.94

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synovial lining organization through cell–cell and cell–ECM interactions. Immediately subjacent to the surface cells, a rich capillary network is found. Lymphatic vessels are located in the subsynovium. The synovium carries three major functions (i) it constitutes a diffusional barrier to the transport of solutes from the SF bulk solution to the fenestrated microvessels and the lymphatics (and visa versa), (ii) removal of foreign material or debris from the SF by phagocytic action of the type A cells of the synovial lining and, (iii) type B cell biosynthesis of hyaluronan and lubricin. The latter synovial fibroblasts are suggested to play a major role in both initiating and driving RA. In the arthritic synovium, macrophages (type A cells) are key players in chemokine production. These molecules exert chemotactic activity towards synovium-invading leukocytes. Features of the synovium related to mass transfer processes are discussed in more detail in a later section.

The Synovial Fluid

The synovial fluid (SF) fills the cavity of a synovial joint. It is a viscous, non-Newtonian fluid exhibiting thixotropic properties. The normal human adult knee joint contains on the average 2 mL SF. Under pathological conditions the volume can increase up to several hundred milliliters. The SF is considered as a plasma dialysate and the concentration of endogenous low molecular weight chemical substances resembles that of plasma. In contrast, albumin and other proteins are present in the SF at a significantly lower concentration due to the sieving action of the synovial capillary walls and matrix. Inflammation associated changes of the SF may include (i) a decrease of SF viscosity due to enzyme-mediated cleavage of the hyaluronan chains, and (ii) an increase of the content of plasma derived macromolecules caused by the enhanced leakiness of the synovial capillaries.

The Articular Cartilage

Articular cartilage furnishes each moving, bony portion of a joint with a smooth, frictionless surface. It is capable of reversible compression, distributing an applied load homogeneously, and minimizing contact stress to the underlying bone. These unique properties can be ascribed to the complex architecture of the avascular ECM of the cartilage which is composed of a highly organized water-filled network of type II collagen fibers and aggrecan-type proteoglycans. Structure and function of many ECM components have been the subject of several reviews. The structure and biochemistry of mature articular cartilage are maintained throughout by the resident chondrocytes. Alteration of the normal balance between chondrocyte anabolic and catabolic activities might be effected by various stimuli including mechanical stress. In addition to biomedical approaches to modulate chondrocyte activity, also the potential applicability of cartilage tissue engineering has been the subject of intense research.

COMMON IA DRUG THERAPIES AND POTENTIAL NEW DRUG TARGETS

Postoperative Pain Management After Arthroscopic Procedures

Modern postoperative pain control focuses on early mobilization and rapid discharge of patients following surgery. Satisfactory postoperative pain relief adds to decrease patient morbidity and may reduce the risk of development of chronic pain after surgery. Major sites of action of analgesics are depicted in Figure 2. Drug entrance into the target area may be accomplished by (i) transport via the systemic circulation or (ii) direct instillation into the proximity of the site of action. Achievement of optimal localized, therapeutic activity after drug administration into discrete anatomical compartments, such as the joints, appears particularly promising. In the following, a brief overview over present IA strategies aiming...
at pain management after arthroscopic procedures of the knee is presented.

Although minimally invasive of nature, arthroscopic procedures do produce pain and inflammation. As a result patients may be prevented from returning to work for up to 2 weeks after surgery. Findings may suggest that aggressive pain management (including local IA drug therapies) in the early postoperative period can improve convalescence after arthroscopy. Over the years the efficacy of a significant number of drugs (and drug combinations) to provide pain relief after IA injection has been investigated. In recent reviews attempts have been made to assess the feasibility of such IA interventions. Analyses of compiled data indicate that efficacious IA monotherapeutic approaches include (i) non-steroidal anti-inflammatory drugs (NSAIDs), (ii) local anesthetics (primarily bupivacaine), and (iii) morphine. A reasonable degree of consensus has, however, been reached that total postoperative pain relief is not achievable by use of a single analgesic agent or method. Therefore, multimodal analgesia (or balanced analgesia) appears to constitute a rational approach to effective pain management. Following arthroscopic procedures promising pain alleviating effects of different IA multimodal analgesic regimens have been reported. Most of the combinations have involved the use of 2–3 drug compounds selected from the above mentioned groups comprising local anesthetics, NSAIDs, and opiates. Further, interesting results have been reported by incorporating anti-inflammatory steroids and the \( \alpha_2 \)-receptor agonist clonidine into such multimodal IA therapies. As regard future IA multimodal therapies, particular attention has to be paid to the optimization of the duration of action of the individual therapeutic agents. Tentatively, feasible depot formulations should enable simultaneous release of analgesics (local anesthetics or opiates over a 24 h period) and anti-inflammatory agents (NSAIDs or corticosteroids over about 7 days). Potential pharmaceutical avenues to reach this ambitious goal are discussed in a later section.

Rheumatoid Arthritis

Typically, RA manifests as a symmetric and erosive polyarthritis. It is suggested that antigen(s) (of unknown origin) present in the joint trigger an acute inflammation which upon an unbalanced host immune response may develop into a chronic inflammation through a complex cascade of events. Briefly, in this process immune cells and macrophages home to the joint where they release inflammatory cytokines including interleukin (IL)-1 and tumor necrosis factor-alpha (TNF-\( \alpha \)). These cytokines stimulate synoviocytes to secrete matrix metalloproteinases (MMPs), the proteinases largely responsible for the irreversible destruction of cartilage in the joint.

Arthritic Disorders

Among the more than 100 arthritic disorders, the two major diseases are RA and OA. Despite the involvement of different (and partly unknown) aetiologies and pathogeneses, the common thread linking RA and OA is progressive irreversible destruction of the cartilage, ligaments and bone in the affected joints. In the US, OA alone leads to more than 500000 total joint replacements annually. Prevalences are estimated to about 1% (RA) and 7% (OA). These diseases give rise to long-term disability and impose substantial burden to both patients and society. No cures are available, and current pharmacological interventions addressing the pain are only moderately effective. In addition to palliation of pain, current therapies primarily aim at slowing down disease progression (see below).
Current drug treatment options fall into four main categories: (i) NSAIDs, (ii) disease-modifying anti-rheumatic drugs (DMARDs), (iii) corticosteroids (occasionally), and (iv) biologics (antibodies and recombinant proteins). Aspects of the use of NSAIDs including implications of their COX-1 to COX-2 selectivity ratio have recently been reviewed. Early use of DMARDs with the aim of aggressively preventing or reducing joint damage has found broad acceptance. DMARD combinations, including in particular methotrexate, has become the cornerstone of most RA treatment regimens. Despite management with such orally administered agents, many patients do not respond adequately. For patients with persistent disease, so-called biologics may constitute new opportunities in the treatment of RA. These rather costly biological agents reduce various inflammatory and immunological responses by selectively blocking the effects of cytokines (TNF-α and IL-1). Six products, to be administered by injection (i.v. or s.c.), are currently approved for the treatment of RA in the US.

Osteoarthritis

In contrast to RA, OA is usually located to one or a few joints. The principal morphological characteristic of OA is a slowly developing breakdown of the articular cartilage. In addition, changes occur in bone, muscle and synovium. It is suggested that the major events in OA pathogenesis are located within the cartilage itself and that the chondrocytes are major contributors to the pathology of this disease. Upon mechanical insults chondrocytes may release matrix degrading proteins. In addition, these cells produce proinflammatory cytokines which again may stimulate neighboring chondrocytes to produce MMPs, thereby creating their own inflammatory environment (Fig. 4). On disease progression, cartilage-breakdown products may give rise to episodes of (usually mild to moderate) synovitis that at the end will lead to further upregulation of MMP production.

Current medical therapies of OA reduce the symptoms (mainly pain) but are only moderately effective. Oral treatment options embrace acetaminophen, opioid analgesics, and NSAIDs. IA drug therapies to alleviate pain include long-acting glucocorticoids and the injection of various hyaluronic acid (HA) preparations. The concept of viscosupplementation is based on the hypothesis that IA injection of HA could help restore the (lost) visco-elasticity of OA synovial fluid. In contrast to RA, there are no approved disease-modifying osteoarthritis drugs (DMOADs). In recent years studies have been conducted to assess the disease-modifying capabilities of nutraceuticals (such as glucosamine and chondroitin), diacerein and doxycycline. The efficacy of the above approaches, however, remains controversial.

Potential New Targets for Drug Regulation in OA and RA

In the area of arthritic disorders novel pharmacotherapeutic options may emerge from the identification of a vast number of potential targets for drug regulation. In depth treatise of this exciting area is outside the scope of the present review. Since basic knowledge about target environment and location is a prerequisite for the formulation scientist, a brief account of some major targets is presented below (see also Tab. 1 and the references given to recent reviews/original articles). The pro-inflammatory, catabolic cytokines, particularly TNF-α and IL-1, play a central role in tissue destruction in OA and RA. In RA, inhibition of the activity of these cytokines (by use of for example anti-TNF-α antibodies and IL-1 receptor antagonists) have proven effective in retarding disease progression and such therapies might also be effective against OA.
Despite significant clinical success, there is still a cohort of RA patients who do not respond to interventions involving such biological therapies.

It appears that increased levels of ECM degrading enzymes, prostaglandins, nitric oxide and other markers in arthritic fluids and tissues are related to elevated levels of TNF-α and IL-1.

Whereas the formation of reactive oxygen and nitrogen species at the site of inflammation gives rise to oxidative injuries in RA, a relationship between cartilage lesion severity and cartilage or blood redox state in OA has apparently not been established.

Major enzyme families involved in the degradation of proteins of the cartilage ECM encompass the MMPs, the ADAMTS metalloproteinases, and cysteine-dependent proteases such as the cathepsins. Collagen degradation is mediated almost exclusively by MMPs. Members of the ADAMTS family participate in the cleavage of cartilage proteoglycans. Traditionally, the cathepsins were believed to exert nonspecific bulk proteolysis within the acidic environment of the lysosome. However, there is growing evidence for specific extracellular functions of these enzymes.

A decrease in pH from 7.1 to 5.5 at the cartilage surface of OA patients has been observed. This low pH may favor the action of cathepsins over various metalloproteases as regards ECM degradation.

The ECM degrading enzymes are expressed by different cells within the joint space. Their relative contribution to disease progression may depend on disease stage and type of disease. To this end, it appears that the protease activity in RA synovial fluid, in general, exceeds that of OA synovial fluid.

In addition to hormones and cytokines, growth factors (GFs) are endogenous molecules involved in the regulation of cellular functions. The metabolism of mature articular cartilage is regulated by a number of GFs that originate from cellular production within the cartilage, as well as from the SF and surrounding tissues. These signaling molecules have (among other functions) the capacity to stimulate chondrocyte anabolic activity.

GFs, such as insulin-like growth factor (IGF-1), the bone morphogenetic proteins (BMPs), and the transforming growth factor β (TGF-β), may therefore exert potentially reparative effects in cartilage. In general, many GFs act over short distances and have short biological half-lives. Thus, development of DDS that are capable of maintaining sufficiently high levels of various GFs at defect sites for prolonged periods may surmount this problem.

The ability of cells to adhere to other cells and extracellular matrices through CAMs plays a critical regulatory role in a variety of biological processes, including tissue remodeling and the development of inflammation. These molecules (or receptors) are classified into four families. The integrin family comprises heterodimeric adhesion receptors involved in the regulation of a number of cellular processes, including cell growth, differentiation, apoptosis, as well as the regulation of cell adhesion, migration and activation.

Integrins are expressed in chondrocytes. Signaling through integrin adhesion molecules has been associated with cartilage damage, and with the production of proteinases and cartilage components by chondrocytes. Also synovial fibroblasts and macrophages express integrins which probably are involved in synovial lining organization through cell–ECM interactions.

Table 1. Potential Targets for Drug Regulation in Arthritic Disorders

<table>
<thead>
<tr>
<th>Targets</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-inflammatory cytokines</td>
<td>21,51,70–72, 87,280–283</td>
</tr>
<tr>
<td>(primarily TNF-α and IL-1)</td>
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</tr>
<tr>
<td>Matrix degrading enzymes</td>
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<tr>
<td>Matrix metalloproteinases (MMPs)</td>
<td>46</td>
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<tr>
<td>Aggrecanases (ADAMTSs)</td>
<td>46,284,285</td>
</tr>
<tr>
<td>Cysteine-dependent cathepsins</td>
<td>77,78</td>
</tr>
<tr>
<td>Growth factors</td>
<td>21,82,84</td>
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<tr>
<td>Cell adhesion molecules (CAMs)</td>
<td>11,85</td>
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</table>
ing small-molecule ligands with affinity for CAMs as so-called functionalized transport groups in prodrug and DDS design. Examples of chemical structures of novel potential small-molecule drug candidates in the area of arthritic disorders have been reported.7,74,78,87 Some of the above mentioned potential targets for drug intervention in OA and RA are also of major interest in the area of cancer research where several reviews have dealt with the role of proteases (including MMPs)88–90 and integrins91,92 in tumor invasion and metastasis. Small-molecule prodrug approaches in cancer drug targeting has recently been reviewed by de Groot.93

**DRUG TRANSPORT AND DISTRIBUTION PROCESSES IN A SYNOVIAL ENVIRONMENT**

In the joint cavity, the solute drug molecule, once released from the immobilized depot, may take part in a number of reactions and distribution (equilibrium) processes before it is eventually cleared from the synovial space. These processes, the relative importance of which is determined by the physicochemical properties of the drug substance and the barrier properties of the synovium are sketched in Figure 5. Concomitant to binding to components of the SF, (i) transport and distribution into the synovium and articular cartilage, and (ii) subsequent uptake by synoviocytes and chondrocytes, may occur. The present section will discuss the barrier properties of the synovium and the cartilage as well as mechanisms related to transport into these joint tissues. Special attention is paid to the articular cartilage containing the perhaps least accessible drug targets, that is, the chondrocytes and pharmaceutically active agents released by these cells.

**Transsynovial Transport**

Due to its architecture, the synovium (Fig. 1) constitutes the main barrier for drug transport out of the joint cavity. The healthy synovial lining is thin (60 μm94) and discontinuous without intercellular junctions. Together with the ECM, the synoviocytes function as a permeable, inhomogeneous matrix.94 The healthy joint is penetrated by capillaries close to the surface of the synovium (modal depth 35 μm in man).94 In chronic RA, thickening of the synovium occurs. This leads to an increase in the transport path from the microvessels to the synovium—SF interface.94 The synovial capillaries have fenestrations facing the joint cavity thus adding to efficient solute exchange.94,95 Due to the fenestration of the capillaries, plasma protein and bound drug as well as the unbound (free) drug may enter into the synovium.96 This tissue can be considered as two barriers placed in series, that is, the interstitial matrix and the synovial capillary endothelium.97–99 The ECM constitutes the major diffusional barrier for entry of small molecules into the synovial cavity whereas passage of the endothelium is the critical barrier for proteins. Flanking the synovium is the subsynovium consisting of loose connective tissue and fat cells. At the border between the synovium and subsynovium are the terminal lymphatics draining fluid and macromolecules from the joint cavity (Fig. 1).

Transsynovial transport and solute concentrations in the SF have been assessed in the evaluation of the efficiency of drug treatment regimens in relation to RA and OA where the SF concentration has been taken as a surrogate measure of drug concentrations in synovium and cartilage.96 Upon oral drug administration, observed joint \( C_{\text{max}} \) and \( t_{\text{max}} \) values are usually lower and occur at later time points, respectively, than the corresponding parameters in plasma.96,100,101 For many NSAIDs, plasma/SF drug concentration ratios have been found to reflect plasma/synovial protein concentration ratios. Further, free NSAID concentrations have been found to be similar in the two compartments after attainment of steady state conditions.96,100,101 Often the SF concentrations are more sustained than plasma concentrations after oral or i.v. administration.96,100,101 Due to continuous drug entrance from the blood compartment, IA elimination half-lives (\( t_{1/2} \)) estimated from pharmacokinetic profiles obtained following oral administration may tend to underestimate the “true” rate of drug disappearance from the SF after IA administration.96 By appropriate corrections, however, reasonable estimates of rates of disappearance from joints relevant to IA...
administration can be extracted from oral pharmacokinetic data. Table 2 contains a compilation of SF disappearance half-lives for some low molecular weight solutes and drugs as well as a few macromolecules. Additional data can be found in the works of Day et al.96 (drugs) and Simkin and Nilson102 (radio isotopes and albumin). As apparent, relatively fast disappearance from the joint is observed for small solutes with $t_{1/2}$ values in the range of about 0.1 to 6 h. In this connection disappearance kinetics from the joint cavity has often been described by simple first-order kinetics. However, several studies, for example,103–109 have found biphasic clearance patterns after IA injection, indicating the presence of a distribution phase associated with drug distribution from the SF to other joint tissues. An initial distribution phase is probably always present upon IA instillation but may or may not be observed depending on the study design.

For small molecules diffusion through the ECM is the major barrier because such solutes readily traverse the fenestrated endothelium of the capillaries. The concentration gradient required for effective clearance of small molecules from the joint is maintained by the synovial blood flow.110,111 Simkin and Pizzorno112 found synovial permeability to correlate with diffusion coefficients in water for benzyl alcohol, tritiated water, urate, urea, glucose and sucrose. Among these solutes benzyl alcohol disappeared significantly faster from the joint, which was suggested to reflect the lipophilicity of the molecule, allowing diffusion to occur not only in the aqueous pores of the ECM between the synoviocytes but also across cell membranes. Collectively, these studies indicate that most small molecules cross the synovium in both directions by diffusion. In a follow up study, Simkin and Pizzorno97 evaluated the synovial permeability of plasma protein as well as the above set of molecules in knee joints of RA patients and normal individuals. The results obtained led to the proposal of the two barrier model of the synovium. Owen et al. determined the disappearance half-lives of $^{125}$I-albumin, acetaminophen, salicylate and diclofenac upon IA administration to RA patients.103 The terminal half-lives of the drugs (listed in Tab. 2) were found to increase with the fraction of drug bound to proteins (albumin) in the SF. Lymphatic clearance of albumin was suggested to contribute to the drug efflux due to clearance of albumin bound drug amounting to 1%, 13%, and 48% of the total clearance for acetaminophen, salicylate and diclofenac, respectively. An implication of the conducted analysis was a limiting half-life of highly albumin bound drugs equal to the terminal half-life of the albumin molecule itself (13.1 h).103 Simkin et al.113 also investigated the effect of protein binding on articular kinetics. Based on an examination of data from oral dose studies involving highly bound NSAIDs (>99%), the authors found that synovial transport was much too fast to be accounted for by synovial clearance of albumin bound drug solely (Tab. 2). It was suggested that fast association/dissociation kinetics relative to drug transit time through the synovial capillaries would make most of the bound drug available for diffusion across the endothelium. Thus, synovial disappearance rates may not just depend on drug affinity for proteins but also on binding avidity.98,113 Further studies are warranted to elucidate this aspect of IA drug disappearance kinetics. It is difficult to unravel the exact importance of drug characteristics (e.g., size, lipophilicity, charge, and protein binding) to synovial disappearance rates. Lipophilicity has been proposed to play a role.106,109,112 However, a highly lipophilic drug may experience slow efflux from the joint as compared to small polar molecules. This is the case for the lipophilic gas $^{133}$Xe which was found to be extensively partitioned into fat tissue of the joint.106 Apparently, little information is available on the effect of charge on disappearance rates through the synovium. In the early study of Simkin and Pizzorno,112 it was found that synovial permeability of magnesium and calcium was lower than for the other small molecules investigated (e.g., urea and benzyl alcohol).

Plasma proteins enter the SF (to different extents) by crossing the endothelium and diffusing through the interstitial matrix. This process is size selective, that is, albumin escapes the capillaries more readily as compared to fibrinogen and macroglobulins.98,114–116 This size dependency is partly reflected in the SF/serum protein concentration ratios although other factors affect the concentration ratio as well.116 Inflammation increases the endothelial permeability for proteins and consequently the SF protein concentrations as this is not fully counteracted by changes in lymphatic flow.97,99 The permeability increase for proteins associated with inflammation is not always followed by a similar increase in synovial permeability of small solutes due to the dual barrier construction (the ECM being the critical barrier to the transport of small molecules rather
<table>
<thead>
<tr>
<th>Compound</th>
<th>$t_{1/2}$ (h)</th>
<th>MW (g/mol)</th>
<th>Comments</th>
<th>References</th>
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<td>131I-cartilage proteoglycan</td>
<td>12.5</td>
<td>$2.5 \times 10^6$</td>
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<td>3H-hyaluronan</td>
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<td>$0.09 \times 10^6$</td>
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<td>3H-hyaluronan</td>
<td>13.2</td>
<td>$&gt;6 \times 10^6$</td>
<td>Rabbit knee</td>
<td>124</td>
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<td>14C-hyaluronan</td>
<td>20.6</td>
<td>$2.0 \times 10^6$</td>
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<td>286</td>
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<td>Hyaluronan</td>
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<td>$&gt;3 \times 10^6$</td>
<td>Rabbit knee</td>
<td>123</td>
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<td>131I-albumin</td>
<td>3.9</td>
<td>$6.7 \times 10^4$</td>
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<td>122</td>
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<td>Albumin</td>
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<td>$6.7 \times 10^4$</td>
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<td>123</td>
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<td>125I-ulinastatin</td>
<td>1.3$^a$; 5.6$^b$</td>
<td>$6.7 \times 10^4$</td>
<td>Rabbit knee; affinity for synovial tissue</td>
<td>105</td>
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<td>Sodium pertechnetate</td>
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<td>Normal/arthritic rabbit knee</td>
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<td>370</td>
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<td>Patent blue V</td>
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<td>131I$^-$</td>
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<td>Canine wrist/knee</td>
<td>119</td>
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<td>133Xe</td>
<td>0.11–0.18$^a$; 0.57–1.3$^b$</td>
<td>133</td>
<td>Canine knee</td>
<td>106</td>
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<td>Ceftiofur</td>
<td>5.1</td>
<td>524</td>
<td>Horse antebrachialcarpal joint</td>
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<td>Procaine</td>
<td>0.80</td>
<td>236</td>
<td>Horse hock joint; hydrolysis occurs simultaneously</td>
<td>287</td>
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<td>131I-cross-linked hyaluronan</td>
<td>1.5; 39; 720</td>
<td>Triexponential kinetics, the latter $t_{1/2}$ reflecting the cross-linked HA</td>
<td>288</td>
<td></td>
</tr>
<tr>
<td>125I-albumin</td>
<td>13.1</td>
<td>$6.7 \times 10^4$</td>
<td>RA</td>
<td>103</td>
</tr>
<tr>
<td>$D_2$O</td>
<td>0.26</td>
<td>20</td>
<td>Normal and RA</td>
<td>150</td>
</tr>
<tr>
<td>THO</td>
<td>0.19–0.26</td>
<td>20</td>
<td>Human knee, various conditions</td>
<td>117</td>
</tr>
<tr>
<td>$^{24}$Na</td>
<td>0.23/0.20/0.11</td>
<td>24</td>
<td>Normal/minor/more severe RA activity</td>
<td>149</td>
</tr>
<tr>
<td>$^{131}$I$^-$</td>
<td>0.39</td>
<td>24</td>
<td>Normal and RA</td>
<td>150</td>
</tr>
<tr>
<td>$^{133}$Xe</td>
<td>0.06$^a$; 0.63$^b$</td>
<td>133</td>
<td>RA</td>
<td>107</td>
</tr>
<tr>
<td>$^{125}$I$^-$</td>
<td>0.07–0.26$^a$; 0.58–4.0$^b$</td>
<td>133</td>
<td>Human knee, various conditions</td>
<td>106</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>0.35</td>
<td>234</td>
<td>Arthroscopy patients</td>
<td>289</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>0.59$^a$; 2.90$^b$</td>
<td>454</td>
<td>RA</td>
<td>104</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>0.6</td>
<td>547</td>
<td>Septic arthritis patient</td>
<td>290</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>5.2</td>
<td>296</td>
<td>RA</td>
<td>103</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>2.4</td>
<td>138</td>
<td>RA</td>
<td>103</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>1.1</td>
<td>151</td>
<td>RA</td>
<td>103</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1.5</td>
<td>296</td>
<td>RA/OA, oral dosing</td>
<td>291</td>
</tr>
<tr>
<td>Etodolac</td>
<td>4.1</td>
<td>287</td>
<td>RA/OA, oral dosing</td>
<td>291</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1.9</td>
<td>206</td>
<td>RA/OA, oral dosing</td>
<td>291</td>
</tr>
<tr>
<td>(R)- and (S)-ibuprofen</td>
<td>2.6 (R) and 2.3 (S)</td>
<td>206</td>
<td>RA, OA or gouty arthritis, oral dosing</td>
<td>292</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>3.3</td>
<td>358</td>
<td>RA/OA knee, oral dosing</td>
<td>291</td>
</tr>
<tr>
<td>Tenoxicam</td>
<td>2.6</td>
<td>337</td>
<td>RA/OA knee, oral dosing</td>
<td>291</td>
</tr>
<tr>
<td>Aclofenac</td>
<td>2.9</td>
<td></td>
<td>RA, oral dosing</td>
<td>113</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>3.4</td>
<td>244</td>
<td>RA, oral dosing</td>
<td>113</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>2.8</td>
<td>358</td>
<td>RA, oral dosing</td>
<td>113</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>1.9</td>
<td>254</td>
<td>RA, oral dosing</td>
<td>113</td>
</tr>
<tr>
<td>Naproxen (550 mg)</td>
<td>1.6</td>
<td>230</td>
<td>RA, oral dosing</td>
<td>113</td>
</tr>
<tr>
<td>Naproxen (500 mg)</td>
<td>1.6</td>
<td>230</td>
<td>RA, oral dosing</td>
<td>113</td>
</tr>
<tr>
<td>Naproxen (1000 mg)</td>
<td>3.1</td>
<td>230</td>
<td>RA, oral dosing</td>
<td>113</td>
</tr>
<tr>
<td>Tenoxicam</td>
<td>2.8</td>
<td>337</td>
<td>RA, oral dosing</td>
<td>113</td>
</tr>
<tr>
<td>Tiaprofenic acid</td>
<td>1.5</td>
<td>260</td>
<td>RA, oral dosing</td>
<td>113</td>
</tr>
<tr>
<td>Tolmetin</td>
<td>2.2</td>
<td>257</td>
<td>RA, oral dosing</td>
<td>113</td>
</tr>
<tr>
<td>$^{14}$C-cortisone</td>
<td>1.3, 1.5</td>
<td>360</td>
<td>Two RA patients</td>
<td>151</td>
</tr>
<tr>
<td>$^{14}$C-hydrocortisone</td>
<td>1.0, 1.46, 1.8</td>
<td>362</td>
<td>Three RA patients</td>
<td>151</td>
</tr>
<tr>
<td>$^{14}$C-hydrocortisone</td>
<td>0.37$^a$; 2.5–4.2$^b$</td>
<td>362</td>
<td>RA</td>
<td>109</td>
</tr>
</tbody>
</table>

$^a$Values relate to intra-articular administration in human knee joint unless otherwise noted.
$^b$Synovial distribution phase.
$^c$Synovial elimination phase.
than the endothelium of the microvessels). In contrast, escape of proteins from the joint occurs through the lymphatic system, a process which is not size selective for molecules with the size of plasma proteins. In relation to the design of DDS it is of interest to know the size limitations to the lymphatic clearance from the joint cavity. Rodnan and MacLachlan found that the human synovium was equally permeable to albumin (67 kDa; \( r_{es} = 3.6 \text{ nm} \)) and \( \gamma \)-globulin (150 kDa; \( r_{es} = 5.6 \text{ nm} \)). The \( r_{es} \) values are Einstein-Stokes diffusion radii. Studies in mice revealed diminished protein clearance rates of 67–150 kDa proteins as compared to those of lower molecular weight proteins (14–47 kDa). To this end it has been found that hyaluronan and cartilaginous proteoglycans are not readily cleared by lymphatic drainage (Tab. 2). The fate of particulate and vesicular DDS upon IA administration is discussed in a following section.

### Drug Transport into Cartilage

As revealed above, drugs are likely to distribute from the SF into various joint tissues after IA administration. Calculations on glucose transport, to feed the chondrocytes of the articular cartilage, have revealed that diffusion of this nutrient in the relatively viscous SF, per se, might be too slow for reaching the center of larger joints. Instead joint motion is suggested to generate additional solute transport by convection. Upon attainment of a uniform glucose concentration in the SF, diffusion into cartilage is sufficiently fast to supply the chondrocytes with this nutrient. Similar considerations may be of relevance for drug distribution in the joint cavity. At the SF-cartilage interface two major parameters govern the efficiency of solute transport into the cartilage ECM, that is, the size and the charge of the solute. Quantitative descriptions relating rates of diffusion and the latter intrinsic diffusant (drug) properties are lacking. Physicochemical aspects of the effect of molecular size and charge on drug accumulation within the cartilage are briefly presented below.

For solutes, the effective (apparent) diffusion coefficient for transport in cartilage, \( D \), can be related to the diffusion coefficient in aqueous solution \( D \) via a so-called turtuosity factor \( \lambda \) (expresses the actual solute diffusion length per unit thickness of cartilage) and a solute-membrane friction coefficient \( F_{SM} \) (a size exclusion effect):

\[
\frac{D}{D} = \frac{1}{\lambda^2} \left( \frac{1}{1 + DF_{SM}} \right)
\]  

(1)

For macromolecules like dextran 10 and 40 (about 10 and 40 kDa, respectively) \( D \) is very small compared to \( D \) due to a significantly enhanced friction between the solute molecules and the pore walls \( DF_{SM} \gg 1 \). In this case (Eq. 2) may apply:

\[
D = \frac{1}{\lambda^2} \left( \frac{1}{F_{SM}} \right)
\]  

(2)

Interestingly, studies may indicate that even very large molecules such as hemoglobin (68 kDa) and dextran 40, may diffuse into cartilage albeit at very low rates. This might be ascribed to a rather inhomogeneous structure of the cartilage. In case of large molecules, transport efficiency into cartilage might to some extent be influenced by convection due to dynamic compression.

Cartilage proteoglycans are composed of a core protein to which at least one GAG chain is covalently attached. The latter negatively charged polysaccharides are mainly chondroitin and keratin sulfate. Since overall electroneutrality has to be maintained in cartilage the fixed negative charges of the proteoglycans have to be balanced by more mobile cations. Consequently an osmotic pressure gradient as well as a potential difference are created. The phenomenon corresponds to a Donnan exclusion effect. Therefore attempts have been made to model drug salt distribution in cartilage within classical ion exchange theory. Within the cartilage, the total concentration of cations for an electrolyte salt can be expressed as:

\[ Z_{cation}C_{cation} = Z_{anion}C_{anion} + C_{immobile anion} \]  

(3)

where \( C \) is the molar concentration in cartilage. Due to the fixed negative charge of the collagenous fiber network, cationic drug molecules have a higher tendency to distribute into cartilage compared to anions. Based on these early observations efforts have been devoted to exploit the ion exchange properties of the ECM to enhance drug accumulation in the cartilage tissue. Various positively charged organic molecules have been observed to distribute into cartilage. This includes (i) radiodiagnostic agents for joint imaging containing a N-quaternary functional group, (ii) N-quaternary...
analogue of anti-inflammatory oxicams,\textsuperscript{140,144} and (iii) a derivative of the potential DMOAD doxycycline.\textsuperscript{147}

**Modeling Joint Escape Kinetics**

The elimination of low molecular weight drugs in the solute state from the synovial cavity has been described by first-order kinetics (Tab. 2). This is consistent with the view that the interstitial matrix is the limiting (diffusional) barrier.\textsuperscript{97,99} Accordingly, Fick’s first law may be a suitable starting point for describing the rate of drug disappearance from the synovial cavity:\textsuperscript{112}

\[
\frac{dN}{dt} = -\frac{DA}{x} (C_s - C_p) \tag{4}
\]

where \(N\) is the number of drug molecules in the synovial cavity, \(C_s\) and \(C_p\) are the drug concentrations in the SF and plasma, respectively, \(D\) is the diffusion coefficient, \(A\) the available area for diffusion and \(x\) is the length of the diffusion path. Introducing \(V_s\) as the SF volume and assuming that the systemic circulation acts essentially as a sink (\(C_p \approx 0\)) (Eq. 4) may be rewritten

\[
\frac{dC_s}{dt} = -kC_s \tag{5}
\]

where \(k = -\frac{DA}{xV_s}\) is the synovial escape (clearance) rate constant due to simple diffusion. Difference in chemical potential is the driving force of diffusion and in simple systems, such as a dialysis cell, this can be approximated by the concentration gradient. Pursuing the analogy between the joint and a dialysis apparatus with a porous membrane impermeable to proteins and macromolecules, it is apparent that \(C_s\) in (Eqs. 4 and 5) should be the free drug concentration rather than the total analytical concentration normally measured. A number of experimental findings complicate this simplified view: the interaction of drug substances with the macromolecules of the SF and articular cartilage as well as the transport of protein bound drug out of the joint cavity.\textsuperscript{103,113} As regard binding to tissue components and macromolecules in the SF, direct proportionality between the free and total drug concentration may be found in case (i) the drug concentration is much smaller than the concentration of binding sites\textsuperscript{148} and (ii) the attainment of the distribution equilibria are fast. It may be difficult to evaluate whether these prerequisites are fulfilled. However, it may be the case for NSAIDs since the therapeutic drug concentrations are much smaller than that of their primary transport protein (albumin). The clearance kinetics of the SF proteins by the lymphatics has been found to obey first-order kinetics\textsuperscript{119,122} and, consequently, this can also be expected for protein bound drugs.\textsuperscript{103} Altogether, drug efflux from the joint cavity should follow first-order kinetics when the following (idealized) conditions prevail: the drug binding phenomena are concentration independent and the various contributing transport processes can be characterized as first-order processes. However, the rate constant \(k\) in (Eq. 5) should be replaced by a composite rate constant \(k'\), which describes the observed time dependence of the total synovial drug concentration upon IA instillation. Support to the adequacy of (Eq. 5) to describe synovial kinetics may be found in the series of studies following first-order kinetics for several half-lives for various solutes.\textsuperscript{119,122,149–151} This equation, however, does not take into account the distribution phase observed in some studies (e.g.\textsuperscript{103,104}) upon IA administration of drug solutions.

The transport equation outlined above may be combined with knowledge on the drug release mechanism of a specific drug delivery system, to estimate the IA drug concentration versus time profile. Two limiting cases can be envisioned. For delivery systems providing a constant rate of drug release (\(k_{rel}\); mole drug released per time and unit SF volume) an approximately constant synovial drug concentration may be achieved for a period of time:

\[
\frac{dC_s}{dt} = k_{rel} - k'C_s \tag{6}
\]

In contrast, for a DDS where release is governed by drug partitioning between the vehicle and the SF phase, the overall joint escape can be expected to apply to first-order kinetics. Delivery systems approximating the former case (zero order drug release) may be suspensions of poorly soluble steroids. Indications, that this is the case, are the almost constant plasma steroid concentrations found for prolonged time periods following an initial phase of rapid drug appearance in the systemic circulation.

**ON FUTURE IA DRUG DELIVERY STRATEGIES**

In this section a rationale for localized drug delivery (based on pharmacokinetic considerations) is presented. Several parenteral depot
formulation technologies have been investigated for the IA route of administration. A more comprehensive treatise of aspects of the applicability of major depot formulation principles is given. This includes prolonged release properties, in vivo fate and issues related to their manufacture. These considerations are also expected to be of relevance for other mentioned depot DDS types of potential utility for novel IA depots in the area of postoperative pain control and OA. Further, the role of in vitro models for quality control and the assessment of the controlled release capabilities of potential IA depot formulations is discussed. The intriguing concept of gene transfer to arthritic joints has been the subject of several reviews and is not considered further in the present context.

Rationale for Localized Drug Delivery

For drugs that have to be transported to a discrete site of action (e.g., a knee joint) by the systemic circulation, the fraction of the administered dose that enters the target site is dependent on the extent of drug distribution to other tissues of the body. After completion of the drug distribution phase, the amount of drug in the body at (steady state) equilibrium \( CV_D \) is given by

\[
CV_D = CV_p + C \sum_{i=1}^{n} V_i K_i
\]  

(7)

where \( C \) is the plasma concentration, \( V_D \) is the apparent volume of distribution and, \( V_p \) refers to the plasma volume. \( V_i \) and \( K_i \) represent the volume and the tissue-to-plasma ratio of drug concentrations for the specific tissue \((i)\), respectively, and \( n \) refers to the total number of tissue compartments. Thus, the fraction of a given drug dose that reaches the particular joint \( f_{\text{joint}} \) might roughly be estimated from

\[
f_{\text{joint}} = \frac{V_{\text{joint}} K_{\text{joint}}}{V_D}
\]  

(8)

For major weight-bearing joints \( K \) values close to unity are to be expected for most small-molecule drugs. Although the magnitude of \( V_{\text{joint}} \) might vary to some extent with type and severity of disease, the key parameter influencing the size of \( f_{\text{joint}} \) is \( V_D \) that may vary widely (7–40000 L/70 kg body weight) depending on the physicochemical properties of the individual drug compound. To this end it can be mentioned that after oral dosing, a steady state \( V_D \) of about 90 L has been reported for the selective COX-2 inhibitor rofecoxib. This drug has now been withdrawn from the market due to severe side effects after oral administration. In addition to drug mixtures for multimodal analgesia, local administration might therefore also be considered for anti-arthritic drug candidates that are prohibited from oral administration due to severe systemic side effects or bioavailability problems. Direct IA instillation of depot formulations appears most realistic for future anti-osteoarthritic drugs based on the fact that in OA only few joints are affected. The clinical course of RA is characterized by a variable disease activity of spontaneous remissions and exacerbations (flare-ups) of the chronic inflammatory joint process. In the case of episodes of discrete joint flare-ups and to treat resistant knee mono-arthritis local anti-inflammatory therapy might also be indicated.

Potential IA Depot Drug Delivery Systems

Aqueous glucocorticoid suspensions remain the only world wide, commercially available depot type for IA injection. In addition, the performance of a variety of depot principles have been investigated in vivo (Tab. 3). Most of these studies have been carried out in animals with the rabbit being the most frequently used animal model. The adequacy of employed injection methodologies to minimize trauma, tissue damage and extra-articular leakage has not been optimally addressed in any of these experimental studies. Another common feature is the apparent lack of information about the robustness of the obtained in vivo data to minor changes in depot characteristics such as size (particles/droplets) and charge. In several studies it was reported that the IA administered formulation in question was well tolerated. Although the lack of significant local toxicity has to be documented through more comprehensive studies, feasible biocompatibility might, in general, be anticipated since pharmaceutical excipients of several of these formulations already constitute the building blocks of marketed depot intended for other parenteral routes of administration.
### Table 3. Overview of Experimental Drug Delivery Systems Administered Intra-Articularly

<table>
<thead>
<tr>
<th>Drug/Model Compound</th>
<th>Animal Model/Human</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liposomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol 21-palmitate</td>
<td>Rabbit (induced arthritis)</td>
<td>Drug incorporated in lipid bilayer. Particle size not defined. Sustained anti-inflammatory effect of 3 days</td>
<td>171,173</td>
</tr>
<tr>
<td>Cortisol 21-palmitate</td>
<td>RA patients</td>
<td>Drug incorporated in lipid bilayer. Particle size not defined. Sustained anti-inflammatory effect of 14 days</td>
<td>174</td>
</tr>
<tr>
<td>Triamcinolone acetonide 21-palmitate</td>
<td>Rabbit (induced arthritis)</td>
<td>Drug incorporated in lipid bilayer. Particle size not defined. Prolonged retention in the joint cavity (38% remaining after 8 h) compared to free triamcinolone acetonide in solution</td>
<td>172</td>
</tr>
<tr>
<td>Dexamethasone 21-palmitate</td>
<td>Rabbit (healthy)</td>
<td>Drug incorporated in lipid bilayer. Particle size range: 0.1–30 μm. Optimal endocytosis in particle size range: 0.75–5 μm</td>
<td>175</td>
</tr>
<tr>
<td>Dexamethasone 21-palmitate</td>
<td>Rabbit (healthy and induced arthritis)</td>
<td>The amount of drug remaining in the joint increases with particle size. Prolonged retention in the joint (36% remaining after 6 h) compared to microcrystalline triamcinolone acetonide. Uptake of liposomal drug in the synovium 1–2 days after injection. Retention enhanced in healthy joints compared to inflamed joints</td>
<td>176</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Rabbit (healthy and induced arthritis)</td>
<td>Drug entrapped in the aqueous phase. Mean particle size: 1.07 μm. Rapid leakage of some drug from liposomes. Prolonged retention in the joint (46% remaining after 24 h) compared to an aqueous solution of the free drug. Low uptake of liposome (dose dependent) by synovium</td>
<td>180</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Rat (induced arthritis)</td>
<td>Methotrexate analogue (a phospholipid covalently bound to methotrexate via amide bond) incorporated into lipid bilayer. Mean particle size: 100 nm (small) and 1.2 μm (large). Sustained anti-inflammatory effect for 21 days (large liposomes). Prolonged retention in the joint (6% and 29% remaining after 24 h for small and large liposomes, respectively) compared to the free drug</td>
<td>293</td>
</tr>
<tr>
<td>Transforming growth factor-β1 (TGF-β1)</td>
<td>Rabbit (full-thickness articular cartilage defects)</td>
<td>Indications of an accelerated early-stage repair of the articular cartilage defects</td>
<td>294</td>
</tr>
<tr>
<td>Lactoferrin</td>
<td>Mouse (induced arthritis)</td>
<td>Drug most likely entrapped in the aqueous phase. Positively and negatively charged liposomes. Particle size not defined. Fast drug release from liposomes. Prolonged retention time in the joint of the positive charged liposome (15% remaining after 24 h) compared to an aqueous solution of the free drug</td>
<td>295</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Rabbit (healthy)</td>
<td>No characterization of liposomes. Fast drug transfer to the blood for free drug as well as liposome entrapped lidocaine</td>
<td>179</td>
</tr>
<tr>
<td>Drug/Model Compound</td>
<td>Animal Model/Human</td>
<td>Comments</td>
<td>References</td>
</tr>
<tr>
<td>---------------------</td>
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</tr>
<tr>
<td>Diclofenac</td>
<td>Rabbit (induced arthritis)</td>
<td>Drug entrapped in the aqueous phase. Liposomes and niosomes incorporated in hydrophilic polymer gels (lipogelosomes and nio-gelosomes). Particle size: 200–250 nm. Fast drug release from liposomes (93% after 48 h). Slower release from lipogelosomes (50% after 48 h). Longest retention in the joint with lipogelosome (50–70% remaining after 24 h)</td>
<td>178</td>
</tr>
<tr>
<td>Clodronate</td>
<td>Sheep (induced arthritis)</td>
<td>Drug most likely entrapped in the aqueous phase. No characterization of liposomes. Uptake of liposomes in the synovium. No therapeutic effect</td>
<td>296</td>
</tr>
<tr>
<td>Clodronate</td>
<td>Mouse (healthy and induced arthritis)</td>
<td>Drug most likely entrapped in the aqueous phase. Mean particle size: 1 μm. Depletion of phagocytic lining cells within 3 days</td>
<td>297,298</td>
</tr>
<tr>
<td>Clodronate</td>
<td>Rabbit (induced arthritis)</td>
<td>Drug most likely entrapped in the aqueous phase. Particle size: 200–300 nm. Uptake of liposomes in synovium temporary anti-inflammatory and antierosive effect</td>
<td>299</td>
</tr>
<tr>
<td>Clodronate</td>
<td>RA patients</td>
<td>Drug most likely entrapped in the aqueous phase. Particle size: 120–160 nm. Depletion of synovial lining macrophages. Decrease expression of adhesion molecules in the synovial lining (reduced inflammation)</td>
<td>300</td>
</tr>
<tr>
<td>$^{51}$Cr (radionuclide)</td>
<td>Rabbit (induced arthritis)</td>
<td>A complex of $^{51}$Cr and a lipophilic chelator was incorporated into the lipid phase. Mean particle size: 100 nm. More than 41% remaining in the joint after 21 days. Accumulation of radioactivity in the synovium (reduced inflammation)</td>
<td>301</td>
</tr>
<tr>
<td>Benzoporphyrin derivate-monoacid ring</td>
<td>Rabbit (induced arthritis)</td>
<td>No characterization of the liposomes. High association of the drug to the synovium. Possibility of using photodynamic therapy in management of autoimmune disorders</td>
<td>302</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug/Model Compound</th>
<th>Animal Model/Human</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microspheres</td>
<td>Rabbit (healthy)</td>
<td>Polylactic acid, polbutylcyanoacrylate, gelatin and albumin microspheres. Particle size: 1–10 μm. Albumin microspheres best tolerated by the synovial tissue. Uptake of microspheres into the synovium. Maximum uptake for particle size &lt;5 μm</td>
<td>303</td>
</tr>
<tr>
<td>Rose Bengal</td>
<td>Rabbit (induced arthritis)</td>
<td>Albumin microspheres. Mean particle size: 3.5 μm. Rapid initial release. Prolonged retention in the joint (9–25% remaining after 7 days) compared to the free model compound. Uptake of microspheres into the synovium</td>
<td>304</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Drug/Model Compound</th>
<th>Animal Model/Human</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone or triamcinolone</td>
<td>Rabbit (healthy)</td>
<td>Heat denatured albumin microspheres. Mean particle size: 23 μm. Decreased plasma absorption rate from microspheres compared to that of suspensions. No uptake into the synovium. Potential adsorption of microspheres to synovium</td>
<td>305</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Rat (induced arthritis)</td>
<td>Chitosan microspheres. Particle size: 8–16 μm. Significant initial burst release (\textit{in vitro}). Limited sustained release effect (\textit{in vivo})</td>
<td>308,309</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Rabbit (induced arthritis)</td>
<td>Albumin and poly(lactide-co-glycolide) microspheres. Particle size: 5–10 μm. Some initial burst release (\textit{in vitro}). PLGA microspheres more promising than albumin microspheres</td>
<td>310</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Rabbit (healthy)</td>
<td>Poly(D,L-lactide) microspheres. Particle size: 40–110 μm. Increased molecular weight of polymer resulted in slower (\textit{in vitro}) release from microspheres. No drug detected in serum within 24 h. Drug detected in synovial cavity (not in the SF) up to 7 days</td>
<td>311</td>
</tr>
<tr>
<td>Coumarin (fluorescent dye)</td>
<td>Rabbit (healthy)</td>
<td>D,L-lactic acid oligomer microspheres. Particle sizes: 20–100 μm; 100–200 μm. Microsphere localized in popliteal fat tissue (independent on particle size and molecular weight of oligomer)</td>
<td>312</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Rabbit (induced arthritis)</td>
<td>Poly(lactide-co-glycolide), poly(L-lactide), poly(caprolactone) microspheres. Particle sizes: 1–20 μm; 35–100 μm. Short burst release (5–7%) followed by sustained release for 30 days (\textit{in vitro}). Inflammatory response using small particle sizes whereas larger particle sizes were found to be biocompatible</td>
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<td>Rat (healthy)</td>
<td>Poly(D,L-lactide-co-glycolide) micro-and nanospheres with mean particle sizes of 265 nm and 26.5 μm, respectively. Dispersion of microspheres in the joint cavity (potential adhesion to the surface of the synovium). Uptake of nanospheres in the synovium.</td>
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<td>Animal Model</td>
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<td>Miscellaneous DDS</td>
<td>Superparamagnetic iron oxide nanoparticles</td>
<td>Fluorescent dye (Cy3.5)</td>
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<td>Zyn-Linkers™</td>
<td>Re-186 or Y-90</td>
<td>Rabbit (healthy)</td>
<td>Synthetic lipid–like molecules designed for local delivery, for example, of radionuclides for radiosynovectomy. Rapid binding of Zyn-Linkers to the synovium. Localization and retention in the knee region (&gt;90% after 4–6 days)</td>
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<td>Complex</td>
<td>Gadolinium tetraazacyclododecane tetraacetic acid</td>
<td>Dog (healthy)</td>
<td>Gd-complex as contrast agents in MR imaging of the joints. Mean IA half-life of the complex close to 2 h</td>
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<tr>
<td>Elastin-like polypeptides (ELP)</td>
<td>None</td>
<td>Rat (healthy)</td>
<td>Thermogelling biopolymers (ELP) that aggregate upon IA injection. Prolonged retention in the joint cavity (nonaggregating ELP, $t_{1/2} = 3.4$ h; aggregating ELP, $t_{1/2} = 3.7$ days)</td>
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<td>Calcium alginate</td>
<td>Transforming growth factor-β</td>
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<td>Implantation of alginate beads into osteochondral defects. Slow in vitro release of TGF-β from alginate (30% to 40% retention after 5 days). Improved repair of the articular cartilage defects</td>
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(Continued)
various barriers to drug delivery including biocompatibility, fast elimination and target access.\textsuperscript{166,167} A safety concern to be considered is, however, that one of the most frequently encountered clinical problems after infusion of PEGylated liposomes into certain subjects is the initiation of non-IgE-mediated hypersensitivity reactions. These pseudoallergic reactions are believed to arise via complement activation.\textsuperscript{168,169} In liposome-based product development also critical technology-oriented challenges might emerge. These might relate to the large-scale (aseptic) manufacturing process as well as to the achievement of acceptable long-term physical stability of the formulation.\textsuperscript{170} Water-soluble drugs are mainly entrapped in the aqueous space, whereas more lipophilic compounds can be intercalated into the phospholipid bilayer. In the latter case only modest drug loads can be accomplished. Liposomal preparations containing lipophilic corticosteroid derivatives (Tab. 3) afforded sustained anti-inflammatory activity after IA injection in the rabbit and in man.\textsuperscript{171–176} The steroids were most likely incorporated into the phospholipid bilayer. Shaw\textsuperscript{177} observed a diminished retention of cortisol derivatives in dipalmitoyl phosphatidylcholine liposomes as a function of decreasing lipophilicity of the investigated compounds after applying such liposomes to aqueous buffer. In comparison to the steroid preparations, the more polar drugs methotrexate, lidocaine and diclofenac experienced a much less pronounced prolongation of the IA residence time from liposome formulations.\textsuperscript{178–180} Despite the limited number of studies performed (involving different experimental conditions) it appears that the inherent sustained release capability of conventional liposome preparations is questionable. For drugs dissolved in the aqueous core, drug release is expected to proceed through diffusion across the intact bilayer whereas burst release may result from destruction of the phospholipid membranes. Analogously, drug liberation from degraded lipid membranes, in case of the steroid liposome formulations, will most likely lead to precipitation of the poorly soluble steroid derivative. Since adequate reference formulations containing the respective steroid derivative were not included in the above mentioned studies it cannot be excluded that the observed sustained anti-inflammatory effects were afforded by slow dissolution of the precipitated drugs in the joint cavity. In this context it should be mentioned that the Depo-Foam\textsuperscript{K} technology, that may show some resem-

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<td>Gelatin hydrogel microspheres</td>
<td>Basic fibroblast growth factor (bFGF)</td>
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<td>Localization of bFGF in soft tissue (including synovium but not in articular cartilage). Microspheres were found to be noninflammatory in vivo and suppression of the progression of OA was studied.</td>
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blance to multivesicular liposomes, may be useful for sustained drug delivery. 181

Sustained release properties of biodegradable microsphere preparations (with the active agent dissolved or dispersed in a polymer-based matrix) are well-established. A number of microsphere-based products (duration of therapeutic activity ranging from about 2 weeks to 3 months) are approved for parenteral administration in areas such as cancer and schizophrenia. 182 Owing to their excellent biocompatibility, the biodegradable polymers poly(lactide-co-glycolide) (PLGA) are the most frequently used materials for the microencapsulation of drugs. Despite the fact that PLGA-based products have been launched, the development of therapeutic PLGA microspheres might, however, be far from straightforward as discussed in more detail elsewhere. 183, 184 Other synthetic polymers frequently used in the design of microparticles include polyanhydrides, 185, 186 poly(ortho esters) 187 and poly-(ε-caprolactone). 188 Polymeric matrices comprising polymers of natural origin, such as albumin 189 and chitosan, 190 have also been investigated. The in vivo studies performed (Tab. 3) do not provide a clear cut picture of the capability of the microsphere approach to substantially prolong the IA residence time of drugs. In general, modification of drug release can be accomplished by the employment of copolymers consisting of synthetic polymers endowed with different susceptibilities to undergo hydrolytic degradation or through change of drug lipophilicity by prodrug formation. 191 Basically, after an initial burst, drug liberation from such depots may involve (i) drug diffusion out of the matrix, (ii) erosion of the matrix or (iii) a combination of these two release mechanisms. Diffusion controlled release is to be expected for small-molecule water-soluble drugs imbedded in hydrophilic polymer networks such as chitosan microspheres. 192 As to the more hydrophobic synthetic polymers, poly-(ε-caprolactone) 188 and poly(ortho ester) 187 microspheres degrade mainly by bulk hydrolysis and surface erosion, respectively. In contrast PLGA (and probably also polyanhydride-based) microspheres may undergo both surface and bulk erosion. The underlying mechanism for bulk erosion (and the accompanying significant decrease in core pH) is not fully elucidated. 183, 185, 186 Like liposomes, microspheres might be taken up by synovial macrophages after instillation into the joint space. Size-dependent phagocytotic uptake have been observed (Tab. 3) but parameters like surface charge might also influence the efficiency of endocytosis where apparently a net negative surface charge prohibits extensive phagocytosis. 195, 196

Seemingly, glucocorticoids represent the only drug class that has been injected intra-articularly in the form of depot suspensions. As mentioned in a previous section such formulations are reasonably well tolerated although “steroid flare” reactions occasionally occur. 197 In vitro phagocytosis of steroid crystals by leukocytes has been reported, 198 however, information about uptake of solid steroid particles by synovial cells in vivo is apparently lacking. Drug appearance in the SF after IA injection of aqueous suspensions is mainly governed by the dissolution rate of the poorly soluble agent. According to the Noyes-Whitney equation, the dissolution rate is directly proportional to the drug solubility and the total surface area of the solid particles. The parenteral suspension may be an advantageous dosage form from the perspective that high drug load can be achieved and only a minimum of pharmaceutical excipients is needed. However, in spite of the simplicity of this formulation type, parenteral suspensions pose certain challenges to the manufacturing process and physical stability. 199, 200

Interestingly, aqueous solutions of certain elastin-like polypeptides (biopolymers with molecular weights in the order of 50 kDa) are observed to exhibit a phase transition above a given transition temperature characterized by the formation of micron or submicron size aggregates (potential drug vehicles). In situ aggregate formation after IA injection of aqueous solutions of such biopolymers in rats resulted in a significantly prolonged IA residence time as compared to that of the dissolved biopolymer. 201 Also patented depot DDS principles based on in situ gel formation might be of potential interest for the IA route of administration. 202, 203 In fact, the in situ forming parenteral DDS approach may, in general, constitute a means to circumvent various critical issues, such as physical stability and sterilization, related to the development of microparticulate systems. 204–206

On Novel IA Approaches for Postoperative Pain Control

It is to be expected that future IA depots acting in a multimodal fashion should comprise at least one analgesic agent and one anti-inflammatory drug. In addition to the IA depot principles dealt with above, it can be mentioned that in the area of
local anesthetics several approaches to achieve sustained drug action after various parenteral routes of administration have been investigated. The therapeutic agents, mainly bupivacaine and lidocaine, have been incorporated into microspheres,

lipid solutions (iophendylate),

vegetable oil

liposomal formulations,

lipid–protein–sugar particles,

injectable gels,

dry emulsions to be reconstituted prior to use,

and lipospheres. Interestingly, inclusion of small amounts of dexamethasone (about 0.04%) in bupivacaine microspheres has been demonstrated to prolong bupivacaine analgetic activity significantly in animal studies. Similar effects have been observed in man as regards intercostal blockade and after subcutaneous infiltration of bupivacaine microspheres. The mechanisms behind the blockade-prolonging effect of glucocorticoids are far from fully elucidated.

Assuming that optimal pain relief after minor joint surgery requires analgetic and anti-inflammatory action locally at the site of trauma over about 1 and 7 days, respectively, the first step in the search for achievement of this therapeutic goal might be to investigate the possibility of using combinations of already marketed drug products. Although sufficiently prolonged anti-inflammatory activity can be accomplished by using suspensions of glucocorticoid ester derivatives such as methylprednisolone acetate (Depo-Medrol), their onset of action might be relatively slow. Also suspensions of poorly soluble ester prodrugs of the more potent steroid betamethasone (e.g., Diprospan) are used for IA injection. In addition to the 17,21-dipropionyl ester derivative, the latter product also contains betamethasone in the form of the water-soluble 21-phosphate ester. The rationale for incorporation of the water-soluble prodrug is apparently to ensure fast onset of drug action. After entrance into the systemic circulation, 21-phosphate esters of various glucocorticoids are cleaved relatively fast to give the parent drug. After i.v. injection of dexamethasone phosphate ester the in vivo conversion rate exceeded that observed after prodrug incubation in full blood by a factor of about 25, suggesting that the major sites for phosphate ester bond cleavage are the highly perfused organs, that is, the liver and kidney.

In this connection, determination of betamethasone pharmacokinetics after combined IA injection of the acetate and phosphate 21-esters of the corticosteroid led to the suggestion that the phosphate ester did seem to be an unnecessary part of the combination due to rapid clearance from the joint cavity. Aqueous solutions of morphine and bupivacaine are marketed, and both drugs (and in combinations) have demonstrated positive analgesic effects after IA injection. However, as discussed in more detail elsewhere, their effectiveness in the immediate postoperative period are relatively short-lived (at best 8–12 h in case of morphine).

In summary, it appears conceivable to suggest that optimal IA multimodal analgesia is presently not achievable by combinations of existing products due to the lack of sufficiently long-acting therapies for abolishment of the acute pain following surgical injuries. Although speculative, prolongation of the effects of morphine and bupivacaine might potentially be achieved by administering these agents in the form of poorly soluble salts. It is well known that pamoic acid forms poorly soluble salts with many drugs containing an amine functional group. Also other aromatic ortho-hydroxycarboxylic acids have been observed to render relatively poorly soluble amine salts including the NSAID diflunisal, that forms salts with morphine, bupivacaine as well as lidocaine. Use of the common ion effect for prolonging the release of bupivacaine from mixed salt suspensions in vitro have recently been reported. Compared with the use of combinations of drug products, an IA depot type capable of controlled parallel release of an analgesic and an anti-inflammatory agent may, exhibit therapeutic advantages. To this end lipid solutions might be of potential interest. Oil depot injectables (mainly ester prodrugs of antipsychotics and steroid hormones dissolved in vegetable oils) for intramuscular and subcutaneous administration have been in the marketplace for decades. The fact that drug release rates from such oil vehicles, at least in part, are influenced by the oil–water distribution coefficient of the drug opens for the possibility of design of depots with feasible delivery characteristics since manipulation of distribution coefficients might be accomplished through prodrug formation (e.g., morphine ester prodrugs or optimization of oil vehicle composition.

On Novel IA Approaches in Arthritic Disorders

Whereas inhibition or modification of the activity of components of the SF might be of relevance in
In Vivo Instillation. More detailed information about the enabling slow drug release into the SF after IA based depot types possesses the potential of to suggest that a number of microparticulate- and overall surface charge, it appears conceivable by careful control of particle size (distribution) phagocytosis, at least theoretically, can be avoided distribution into the cartilage. Since nonspecific at least minimize this barrier to effective drug compounds. Transient masking of such negative charges by prodrug design might abolish or at expected to influence transport into the ECM of the cartilage. The high negative charge density of this matrix may limit the entrance of anionic drug microspheres varied with the concentration of matrix metalloproteases in the SF. Although speculative, chitosan-based drug delivery systems might provide some degree of drug release at the SF-cartilage interface. Despite the fact that the amine groups of this polysaccharide are only partly ionized at physiological pH (pK\(_a\) 6.3\(^{180}\)) some affinity to the anionic ECM of the cartilage can not be excluded. Further, this polysaccharide is of significant interest in the design of in situ forming depot systems, since the physical properties of polymeric chitosans change with the environmental pH. Under acidic conditions it forms a viscous solution, whereas the compound transforms into a gel at pH 7.4.\(^{257}\)

**In Vitro Release Models for Quality Control and Formulation Development Purposes**

From a regulatory point of view the drug product specifications is a key document through which reproducible product quality, or in other words batch to batch consistency of product performance, has to be documented. This documentation may, dependent on the formulation type in question, embrace different product characteristics. On the other hand control of drug release rate from the formulation has to be demonstrated for all parenteral depots. In this field, therefore, development of suitable *in vitro* release models (for quality control as well as formulation development purposes) constitutes a significant challenge. Currently, no regulatory approved standard methods exist for testing drug release from controlled release parenteral products. As regard such quality control methods, accelerated *in vitro* release testing might be of particular utility for parenteral depot characterized by a duration of action exceeding a few weeks.\(^{258-260}\)

Basically, employed *in vitro* release methods might be divided into three broad categories (i) sample and separate methods, (ii) continuous flow methods, and (iii) dialysis techniques.\(^{261,262}\) Two USP (United States Pharmacopeia) apparatus,
the reciprocal cylinder (apparatus 3) and the flow through cell (apparatus 4) have been recommended for controlled release parenterals. In addition to the use in quality control and formulation development, the in vitro relevance of employed in vitro methods should also be considered. Dialysis membrane-based models are in general considered feasible only for the study of drug release from depots intended for administration sites for which drug release under nonsink conditions is prevailing. Different experimental setups have been used, with the relatively simple dialysis bag technique being the most widely used model. This includes the Float A LyzerR tube system that recently has gained considerable interest. A bulk reverse dialysis bag technique has been applied in order to circumvent the simultaneous handling of sink conditions during the release studies. Other model modifications include the side-by-side diffusion cell, a fractional dialysis method, the reciprocating dialysis tube, and the rotating dialysis cell. Since model related factors vary from model to model, rate constants obtained by using different methods are not directly comparable.

In case of IA injection, the depot is administered into a small compartment (the joint cavity) in which the drug is released under nonsink conditions. Due to the noncontinuous nature of the synovial lining, small-molecule drugs are mainly transported out of this compartment and into the blood driven by a diffusional process. In particular the rotating dialysis cell model, consisting of a small donor compartment (max. 10 mL) and a large acceptor compartment (max. 1000 mL) might appear attractive for investigation of some key parameters influencing IA drug residence times after local instillation of various depot DDS. In the area of in vitro–in vivo correlations, however, the latter method is expected to be applicable primarily for simple drug formulations. To this end the disappearance of drugs (molecular weight range 137–2068 Da), applied to the donor cell of this model in the form of aqueous solutions, was found to obey strict first-order kinetics with half-lives in the range of 0.2–8 h. Interestingly, quite similar IA elimination half-lives have been reported in the literature (Tab. 2). The applicability of the rotating dialysis cell model to simulate the drug transfer rates out of the joint cavity is presently under investigation in our lab.

**CONCLUDING REMARKS**

Compared to oral administration, the advantage of intra-articular drug instillation is that only a minimum amount of drug is required to exert local activity within the joint space. This relatively simple form of localized drug delivery minimizes drug exposure to inappropriate sites. Since drugs dissolved in the synovial fluid are rapidly eliminated from the joint (t1/2 of about 0.1–6 h), maintenance of therapeutic concentrations over extended periods of time necessitates the administration of the drug in the form an injectable depot formulation. There is still an unmet need for IA therapies providing optimal pain relief after minor joint surgery. Such alleviation of post-operative pain, based on the concept of multimodal analgesia, may involve concomitant release of analgesics and anti-inflammatory agents from the IA delivery system over about 1 and 7 days, respectively. In the area of osteoarthritis, approved disease-modifying therapies are lacking. Novel treatment options may arise from the identification of a vast number of potential targets for drug action. Since OA usually affects a single or only a few joint(s), long-lasting IA technologies comprising future anti-arthritic agents hold promise. Several formulation principles are used in marketed (non-IA) parenteral depots despite the fact that, for example, their manufacture and physical stability are far from straightforward. The performance of these depot types (and many others) after IA injection has been investigated primarily in animal models. Promising results are achieved but need to be substantiated by future studies. To this end, it has to be realized that localized drug delivery not necessarily is synonymous with targeted drug delivery, especially when the drug target is located in the articular cartilage which may constitute a significant barrier to high molecular weight drugs. However, already available results suggest that intra-articular depot formulations, containing drug mixtures for multimodal analgesia or future arthritic disease-modifying agents, are likely to emerge within a reasonable time horizon.
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INTRA-ARTICULAR DEPOT FORMULATION PRINCIPLES 4643


