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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO	
RAD: 13-15333- -5	**FECHA**: 2014-12-04 17:44:04
DEP: 2020 DIRECCION DE NUEVAS CREACIONES	**EVE:** 378 FASE NACIONAL INCLUIDO CAPITULO I
TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II	**FOLIOS**: 20
ACT: 519 PRESENTACION	

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado(a)/Señor(a)
ALICIA LLOREDA RICAURTE

Asunto: Radicación: 13-15333- -5
Trámite: 11
Evento: 378
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Patente de Invención	X			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	X	Capítulo I	X	Capítulo II	
No. Solicitud Internacional	PCT/GB2011/054357				
Fecha de Presentación Internacional	19/07/2011				

1. Documentos estudiados

Descripción:	Radicado N°13–015333–00000–0000	Enero 28 de 2013
Reivindicaciones	Radicado N°13–015333–00000–0000	Enero 28 de 2013
	Radicado N°13–015333–00000–0000	Febrero 21 de 2013
Prioridad	US 61/365,407	Julio 19 de 2010

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

De acuerdo con lo establecido en el numeral 1.2.2.2 del Capítulo Primero del Título 10 de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por el solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las cubiertas por la tasa pagada.

Por lo tanto, las reivindicaciones 1 a 8 contenidas en el radicado N°13–015333–00002–0000 son aceptadas para ser estudiadas, porque el valor de estas reivindicaciones se incluye dentro de la tasa de presentación.

Título de la solicitud: “Depósito farmacéutico para 5 – fluoro – 2 – [[(1S) – 1 – (5 – fluoro – 2 – piridil) etil] amino] – 6 – [(5 – isopropoxi – 1H – pirazol – 3 – il) amino] piridin – 3 – il - carbonitrilo”.

El problema planteado en esta solicitud consiste en la obtención de composiciones alternativas para el tratamiento de artritis reumatoide, osteoartritis o gota.

Para resolver este problema técnico, la solicitud en estudio plantea la obtención de composiciones farmacéuticas que contienen 5 – fluoro – 2 – [[(1S) – 1 – (5 – fluoro – 2 – piridil) etil] amino] – 6 – [(5 – isopropoxi – 1H – pirazol – 3 – il) amino] piridin – 3 – il – carbonitrilo (inhibidor de Trk kinasa) y un polímero que se degrada cuando se forma un depósito en el sitio de administración para controlar la liberación del principio activo, para el tratamiento de enfermedades como artritis reumatoide, osteoartritis y gota.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K31/4439; A61K47/34; A61K9/16; A61P19/02.

4. Excepción a la Patentabilidad (Art. 20, D 486, lit (d))

El objeto de las reivindicaciones 7 y 8 no es patentable, de acuerdo con el artículo citado.

5. De la Solicitud de la Patente

Título

Se solicita modificar el título de la solicitud, porque al mencionar “un depósito farmacéutico”, se hace referencia al almacenamiento de la formulación farmacéutica en un tejido después de la administración, lo que hace mención a un método de tratamiento. Se solicita cambiar el término “depósito farmacéutico” por “composición farmacéutica” y se sugiere mencionar la inclusión de polímeros.

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Para las reivindicaciones 1 a 6 se solicita modificar la expresión “depósito farmacéutico” por “composición farmacéutica”, porque el depósito es el almacenamiento de la composición en un tejido después de ser administrada.

La reivindicación 1 no es concisa, porque al mencionar “un polímero que se degrada para formar un microclima ácido”, se incluye una cantidad de polímeros que se degradan en medio ácido, por lo cual se solicita mencionar de manera específica cuales polímeros cumplen con esta característica.

Se sugiere mencionar de manera detallada la composición farmacéutica donde se defina las cantidades y/o proporciones del principio activo, el polímero y de otros excipientes necesarios para desarrollar la composición solicitada.

6. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de Publicación Internacional: El 19 de julio de 2010 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación
D1	WO2008/054292	"Pyrazolyl derivatives with analgesic activity and therefore useful in the treatment or prophylaxis of pain"	08/Mayo/2008
D2	US6217911	"Sustained release non – steroidal, anti – inflammatory and lidocaine PLGA microspheres"	17/Abril/2001
D3	*European Journal of Pharmaceutics and Biopharmaceutics*. 2009. 73: 205 – 218	"Intra – articular systems for the treatment of rheumatic diseases: A review of the factors influencing their performance"	21/Junio/2009

El documento D1[1] divulga compuestos derivado de pirazolilo como analgésicos y composiciones farmacéuticas que los contienen (Pág. 1, ln. 4 – 8; pág. 18 y 19).

El documento D2[2] divulga composiciones farmacéuticas de liberación retardada que contiene antiinflamatorios no esteroidales (AINES) y polímeros biodegradables de poli (DL – lactato glicolido) (PLGA) (Col. 1, ln. 18 – 28).

El documento D3[3] divulga composiciones farmacéuticas que contienen principios activos y polímeros para el tratamiento de la osteoartritis (Pag. 205, abstract).

7. Examen de Patentabilidad.

Nivel inventivo (Art 18 D 486)

La reivindicación 1 divulga "*Un depósito farmacéutico que comprende 5 – fluoro – 2 – [[(1S) – 1 – (5 – fluoro – 2 – piridil) etil] amino] – 6 – [(5 – isopropoxi – 1H – pirazol – 3 – il) amino] piridin – 3 – il – carbonitrilo o su sal farmacéuticamente aceptable como agente farmacéutico y un polímero que se degrada para crear un microclima acido, donde el prncipio activo se libera tras la degradación del polímero*" (Pág. 5 del Radicado N° 13–015333–00002–0000).

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Solicitud	D1	D2
Depósito farmacéutico	Composición farmacéutica	Composición farmacéutica
Contiene 5 – fluoro – 2 – [[(1S) – 1 – (5 – fluoro – 2 – piridil) etil] amino] – 6 – [(5 – isopropoxi – 1H – pirazol – 3 – il) amino] piridin – 3 – il – carbonitrilo	Contiene (S) – 5 – fluoro – 2 – [1 – (5 – fluoropiridin – 2 – il) etilamino] – 6 – (5 – isopropoxi – 1H – pirazol – 3 – ilamino) nicotinonitrilo (Pág. 22, ln. 26 – 27)	Contiene compuestos antiinflamatorios como ketoprofeno, ibuprofeno, acetaminiofen, entre otros antiinflamatorios (Col. 2, ln. 22 – 35; col. 7, ln. 1 – 14)
Contiene un polímero que se degrada y libera el principio activo	Contiene polietilenglicol en solución acuosa (Pág. 19, ln. 1 – 2)	El principio activo está en microesferas de copolímero de ácido láctico – ácido glicólico (PLGA) (Col. 2, ln. 63 – 67; col. 3, ln. 1 – 9)

El documento D1 se considera el estado de la técnica más cercano a la solicitud definida en la reivindicación 1, porque divulga composiciones farmacéuticas que contienen (S) – 5 – fluoro – 2 – [1 – (5 – fluoropiridin – 2 – il) etilamino] – 6 – (5 – isopropoxi – 1H – pirazol – 3 – ilamino) nicotinonitrilo como principio activo y polietilenglicol en solución acuosa, para el tratamiento de osteoartritis (Pág. 19, ln. 1 – 2; pág. 22, ln. 26 – 27).

La diferencia entre las composiciones divulgadas en la solicitud con respecto a las

1 http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=2008054292A1&KC=A1&FT=D&ND=&date=20080508&DB=&locale=en_EP
2 http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=US&NR=6217911B1&KC=B1&FT=D&ND=&date=20010417&DB=&locale=en_EP
3 http://www.sciencedirect.com/science/article/pii/S0939641109001945

divulgadas en el documento D1, radica en que las composiciones de la solicitud contienen un polímero que retarda la liberación del principio activo cuando se forma un depósito.

Esta diferencia confiere el efecto técnico de retardar la liberación del principio activo, disminuyendo la frecuencia de administración de cada dosis de la composición.

El problema técnico objetivo que se pretende resolver es el siguiente: Como modificar las composiciones divulgadas en el documento D1 para obtener composiciones farmacéuticas alternativas que contienen (S) – 5 – fluoro – 2 – [1 – (5 – fluoropiridin – 2 – il) etilamino] – 6 – (5 – isopropoxi – 1H – pirazol – 3 – ilamino) nicotinonitrilo, para el tratamiento de la osteoartritis.

El documento D2 menciona una composición farmacéutica de liberación controlada que contiene un antiinflamatorio no esteroidal y un polímero biodegradable de poli (lactato/ glicolido) (PLGA) para el tratamiento de la osteoartritis (Col. 2, ln. 22 – 35, 63 – 67; col. 3, ln. 1 – 9; col. 4, ln. 5 – 28; col. 7, ln. 1 – 14; col. 5, ej. 3).

Por lo tanto, una persona normalmente versada en la materia y conocedora de los conceptos divulgados en D1 y D2, sin ningún esfuerzo modificaría las composiciones mencionadas en el documento D1, incluyendo dentro de estas composiciones los polímeros PLGA que retardan la liberación del principio activo, de acuerdo a lo que sugiere el documento D2, para obtener de esta forma las composiciones propuestas en la solicitud de manera obvia o evidente.

En consecuencia, la reivindicación 1 de acuerdo a lo divulgado en D1 y D2, carece de Nivel Inventivo.

Las reivindicaciones 2 a 6, dependientes de la reivindicación 1, no divulga características inventivas adicionales para la composición de la reivindicación 1, porque el documento D2 además sugiere que el polímero de las composiciones es copolímero de lactato/ glicolato en proporción molar 100:0 a 50:50 (Col. 2, ln. 66 y 67). Por lo tanto, estas reivindicaciones también carecen de Nivel Inventivo.

La reivindicación 1 divulga "*Un depósito farmacéutico que comprende 5 – fluoro – 2 – [[(1S) – 1 – (5 – fluoro – 2 – piridil) etil] amino] – 6 – [(5 – isopropoxi – 1H – pirazol – 3 – il) amino] piridin – 3 – il – carbonitrilo o su sal farmacéuticamente aceptable como agente farmacéutico y un polímero que se degrada para crear un microclima acido, donde el prncipio activo se libera tras la degradación del polímero*" (Pág. 5 del Radicado N° 13–015333–00002–0000).

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Solicitud	**D1**	**D3**
Depósito farmacéutico	Composición farmacéutica	Composición farmacéutica
Contiene 5 – fluoro – 2 – [[(1S) – 1 – (5 – fluoro – 2 – piridil) etil] amino] – 6 – [(5 – isopropoxi – 1H – pirazol – 3 – il) amino] piridin – 3 – il – carbonitrilo	Contiene (S) – 5 – fluoro – 2 – [1 – (5 – fluoropiridin – 2 – il) etilamino] – 6 – (5 – isopropoxi – 1H – pirazol – 3 – ilamino) nicotinonitrilo (Pág. 22, ln. 26 – 27)	Contiene un principio activo como betametasona, dexametasona, diclofenaco, metotrexato, naproxeno, paclitaxel (Pág. 212, tabla 1)
Contiene un polímero que se degrada y libera el principio activo	Contiene polietilenglicol en solución acuosa (Pág. 19, ln. 1 – 2)	Contiene copolímero de ácido láctico – ácido glicólico (PLGA) (Pág. 212, tabla 1)

El documento D1 se considera el estado de la técnica más cercano a la solicitud definida en la reivindicación 1, porque divulga composiciones farmacéuticas que

contienen (S) – 5 – fluoro – 2 – [1 – (5 – fluoropiridin – 2 – il) etilamino] – 6 – (5 – isopropoxi – 1H – pirazol – 3 – ilamino) nicotinonitrilo como principio activo y polietilenglicol en solución acuosa, para el tratamiento de osteoartritis (Pág. 19, ln. 1 – 2; pág. 22, ln. 26 – 27).

La diferencia entre las composiciones divulgadas en la solicitud con respecto a las divulgadas en el documento D1, radica en que las composiciones de la solicitud contienen un polímero que retarda la liberación del principio activo cuando se forma un depósito.

Esta diferencia confiere el efecto técnico de retardar la liberación del principio activo, disminuyendo la frecuencia de administración de cada dosis de la composición.

El problema técnico objetivo que se pretende resolver es el siguiente: Como modificar las composiciones divulgadas en el documento D1 para obtener composiciones farmacéuticas alternativas que contienen (S) – 5 – fluoro – 2 – [1 – (5 – fluoropiridin – 2 – il) etilamino] – 6 – (5 – isopropoxi – 1H – pirazol – 3 – ilamino) nicotinonitrilo, para el tratamiento de la osteoartritis.

El documento D3 menciona composiciones para el tratamiento de la artritis y de la osteoartritis que contienen un copolímero de ácido láctico – ácido glicólico que se degrada por hidrólisis simple y dado que a partir de este proceso no se obtienen compuestos tóxicos, se utiliza ampliamente como matriz para medicamentos de uso veterinario y humano, donde este copolímero tiene un alto porcentaje de eficacia de encapsulación y se logran obtener sistemas de liberación con duración de mas de 14 días (Pág. 212, tabla 1; pág. 213, col. der., ln. 10 – 22).

Por lo tanto, una persona normalmente versada en la materia y conocedora de los conceptos divulgados en D1 y D3, sin ningún esfuerzo modificaría las composiciones mencionadas en D1, incluyendo dentro de estas composiciones los polímeros PLGA que retardan la liberación del principio activo, de acuerdo a lo que sugiere el documento D3 y teniendo en cuenta que el empleo de estos copolímeros incrementan el tiempo de liberación de los compuestos, para obtener de esta forma la composición propuesta en la presente invención, de manera obvia o evidente.

En consecuencia, la reivindicación 1 de acuerdo a lo divulgado en D1 y D3, carece de Nivel Inventivo.

Las reivindicaciones 2 a 6, dependientes de la reivindicación 1, no divulga características inventivas adicionales para la composición de la reivindicación 1. Por lo tanto, estas reivindicaciones también carecen de Nivel Inventivo.

8. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO2008/054292	1 a 6	Nivel inventivo
D2	US6217911	1 a 6	Nivel inventive
D3	*European Journal of Pharmaceutics and Biopharmaceutics*.2009. 73: 205 – 218	1 a 6	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir del día siguiente de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Finalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones, no pagará la tasa de modificación voluntaria pero sí la correspondiente al pago por reivindicación adicional.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.

JESUS FERNEL GARCÍA GARCÍA
Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha 2014-12-09

Elaboró: Dayron Alexander Ramirez Reyes
Revisó: Sandra Carolina Crespo

European Journal of Pharmaceutics and Biopharmaceutics 73 (2009) 205–218

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Review article

Intra-articular drug delivery systems for the treatment of rheumatic diseases: A review of the factors influencing their performance

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ABSTRACT

Osteoarthritis and rheumatoid arthritis are rheumatic diseases for which a curative treatment does not currently exist. Their management is directed towards pain relief achieved with different classes of drugs among which non-steroidal and steroidal anti-inflammatory substances are the most frequently used agents. Nevertheless, the oral or systemic administration of such drugs is hindered by numerous side effects, which could be overcome by their intra-articular (i-a.) administration as dosage forms capable of gradually releasing the active substance. The present review article summarises the research done in the field of drug delivery systems for i-a. injection vs. current management of osteoarthritis or rheumatoid arthritis. Aspects such as the influence of size, shape, polymer matrix or targeted drug on the i-a. retention time, phagocytosis and biological activity will be discussed. Finally, we will comment on the need for adapted delivery systems for the novel and very potent anti-inflammatory drugs, such as inhibitors of the p38 mitogen-activated protein kinase or the IL-1β conversion enzyme, which to date cannot be properly used due to the severe side effects associated with their systemic administration.

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1. Introduction

Despite extended pharmaceutical and clinical research, there are still unmet needs in the treatment of rheumatic diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA). For both conditions, no prevention methods are known, and optimal management is based on early diagnosis. Treatment of irreversible joint damage is achieved through oral, parenteral or intra-articular drugs. Despite some practical drawbacks, the direct delivery of a drug to an affected joint offers the possibility of reaching high drug concentrations at the site of action with limited systemic toxicity. The i-a. administration represents a valuable means to deliver to the joint drugs with low bioavailability, such as recombinant proteins, therapeutic genes or substances such as TNFα, matrix metalloproteinases or p38 mitogen-activated protein kinase inhibitors [1–6]. Nevertheless, depending on their chemical structure, some active compounds are rapidly cleared from the joint, thus requiring numerous injections, which could cause infection or joint disability [7]. An innovative way to maintain a therapeutic concentration over longer time periods is the administration of depot formulations, which generally contain corticosteroids. Despite their clinically proven efficacy [8–11], these depot formulations suffer from a significant drawback, which limits their use. Actually, due to their crystalline nature, these drugs can generate inflammatory conditions upon i-a. injection, leading to crystal-induced arthritis, observed in 10% of the patients, but which disappears within a few days [12–14].

This reinforces the need to develop drug delivery systems for i-a. use that would function as depot gradually releasing the active substance and providing local sustained drug action. The potential of such drug delivery systems is high, because the release rate as well as the reservoir capacity can be tailored by specific technological parameters such as the polymer type and molecular weight or the formulation method. This review outlines current knowledge on the advantages and limitations of i-a. drug delivery systems, focusing on the factors that influence their biological performance, with particular emphasis on size, shape and chemical nature of the matrix. The authors have decided not to address issues related to the pharmacokinetics of drug solutions or suspensions in the synovial space, nor of their transport into cartilage, as these aspects have recently been presented in detail by Larsen et al. [15]. Other administration routes, involving joint-targeting strategies, have been reviewed elsewhere [16]. Moreover, aspects related to gene delivery [17] and cell-based therapies [18] are not presented in this article.

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2. Normal vs. arthritic joint

Synovial joints (Fig. 1a) are highly specialised anatomical structures that are composed of two articulating bones stabilised by the surrounding muscles and ligaments [19]. Each joint has a unique configuration offering an appropriate contact area, which, combined with a suitable muscle action, allows for high-efficiency performance. To maintain its structural integrity, the joint is surrounded by a fibrous capsule, which is a firm structure consisting of dense connective tissue. Within the capsule, there are thick bands of parallel collagen fibres known as ligaments, and numerous nerve endings, which, along with those in the muscles, ligaments and tendons, are responsible for knee proprioceptive sense and deep pain perception [20]. The two bone connective surfaces are covered with cartilage, which is a resilient tissue that is composed of collagen and proteoglycan matrix. It provides the joint with almost frictionless mobility. Surprisingly, the cartilage surface is not smooth (Fig. 2) but shows irregular depressions and undulations, as demonstrated by a high number of scanning electron microscopy studies [21–23], optical microscopy [24] or atomic force microscopy [25,26]. In adults, cartilage is hypocellular, aneural, avascular and alymphatic. It receives nutrients by a two-step diffusion system [23], from the blood vessels into the synovial fluid and then from the synovium to the cartilage, in order to reach the cartilage cells, which are known as chondrocytes. Lining the inner joint space, the synovial membrane consists of two to three cell layers. It is responsible for providing nutrients to the cartilage and for secreting the synovial fluid. The composition of the synovial fluid is similar to that of plasma, but with reduced protein concentration and additional hyaluronic acid secreted by the synovial fibroblasts at concentrations between 2 and 4 mg/ml [27]. It provides the high viscosity characteristic to the synovial fluid and provides rheofluidifying properties, meaning that the more rapidly it flows, the more fluid it becomes [28]. Some joints have within their cavities a rudimentary fibrocartilaginous discoid structure called a meniscus. In other joints such as the knee or the temporomandibular joint, the meniscus is highly developed and well defined. The meniscus contributes to joint stability and shock absorption.

In people with OA, there is a progressive degeneration of the cartilage, first observed as fissures on the articular surface, which later infiltrate the damaged cartilage and eventually the subchondral bone (Fig. 1b). The early phase of proteoglycan loss is followed by a phase of increased matrix turnover, with net depletion of cartilage proteoglycans and collagens, finally leading to severe damage of the collagen network [29]. Cartilage breakdown is driven by the production of numerous cytokines, growth factors and proteases. The matrix metalloproteinases (MMPs) play a major role in the cleavage of cartilage macromolecules, the by-products of which stimulate degradation through a positive feedback loop, implying cellular production of various cytokines such as IL-1. Cellular responses also lead to the production of growth factors, i.e., insulin-like growth factor-1 (IGF-1) and transforming growth factor β (TGFβ). Bone remodelling and bone formation are observed in the form of osteophytes, bone protuberances into the joint space at the margins of the articular cartilage, and also in the form of subchondral bone, directly beneath the weight-bearing surface. Unlike RA, OA is a relatively non-inflammatory condition, although limited synovitis can be observed.

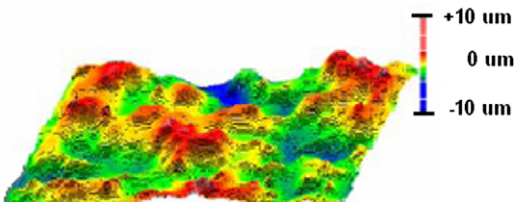

Fig. 2. Bovine knee cartilage surface topography visualized by atomic force microscopy. Modified from Shekhawat et al. [26].

In RA, the synovial space undergoes a sustained inflammatory response (Fig. 1c), which is characterised by the presence of numerous inflammatory cell types including T cells, dendritic cells, macrophages, fibroblasts, mast cells, neutrophils and B cells. The activated T cells proliferate and stimulate the production of interferon-γ and other pro-inflammatory cytokines, which further stimulate macrophages, fibroblasts, chondrocytes and osteoclasts. Activated macrophages and fibroblasts secrete the tumour necrosis factor-α (TNF-α), as well as IL-1, IL-6, IL-15 and IL-18. In turn, these inflammatory mediators and various growth factors activate neutrophils and B cells. Finally, endothelial transformation enables enhanced cell recruitment to the joint. The synovial lining becomes hypertrophic and may thicken up to 10–12 cells in depth, with an increased proliferation of the fibroblast- and macrophage-like synoviocytes, as well as angiogenesis, and it finally develops into locally invasive pannus tissue. B cells and dendritic cells form aggregates with T cells and tissue macrophages [30,31]. The presence of all of these cell types creates an important change in the joint physiology, with increased synovial volume, pressure and temperature. In addition, acidosis, hypoxia, and the joint action

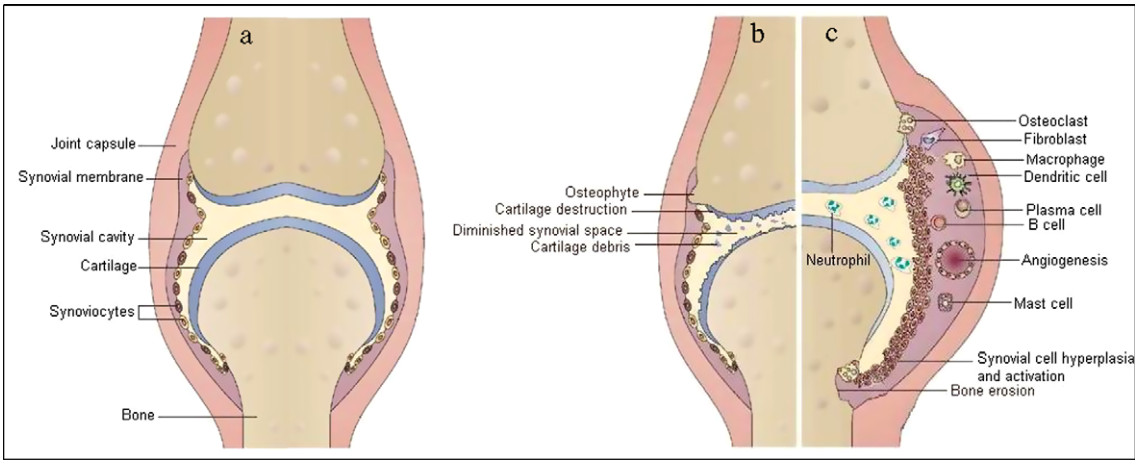

Fig. 1. (a) Normal joint; (b) OA joint with typical changes such as significant joint space narrowing, cartilage destruction and osteophyte formation; (c) RA joint presenting the pannus with numerous types of cells. Modified from Strand et al. [19].

of proteases and growth factors contribute to synovial inflammation, cartilage destruction and bone erosion [32–35].

3. Management of rheumatic diseases

3.1. Current management of osteoarthritis

OA usually has a slow and insidious onset, and it clinically manifests in the form of gradual pain development, joint stiffness and limitation in joint movements. Risk factors for OA progression include biomechanical factors such as joint injuries or deformities, obesity, occupational and non-occupational physical activity, but also systemic factors such as age, genetic factors, oestrogen deficiency, low bone mineral density, female sex, Caucasian ethnic origin and presence of crystals in joint fluid [36,37]. OA has a variable prevalence in developing countries, ranging from 3 to 20%, and it is the most common arthritic disease in developed countries. In the US, the prevalence, which was 15% in 1998, could reach 18.2% by the year 2020 [38]. Management of OA focuses on pain reduction and function restoration, which are achieved by a combination of prevention and non-pharmacological and pharmacological measures, as schematically presented in Fig. 3. Prevention measures consist mainly of weight reduction concomitant with strengthening of the periarticular muscles to provide improved joint support, as well as life-style changes, thermal cures or acupuncture. Medical management is usually conducted according to the guidelines developed by the American College of Rheumatology [39,40], the European League Against Rheumatism [41] or the Osteoarthritis Research International [42]. These guidelines indicate use of analgesics, NSAIDs, intra-articular agents and nutritional supplements, as is extensively discussed in previous review articles [36,43–48]. Unfortunately, a curative treatment has not been identified. Paracetamol is the first-line pharmacological agent recommended by all of the above-mentioned bodies and its effectiveness in the relief of pain associated with OA has recently been demonstrated by a meta-analysis of 10 randomised controlled trials [49]. NSAIDs are effective agents in the treatment of OA, but their use is generally accompanied by undesired gastrointestinal and renal effects. Selective cyclooxygenase-2 inhibitors, which are more effective than paracetamol, have the advantage of reduced gastrointestinal toxicity [50]. The Osteoarthritis Research International recommends topical agents and capsaicin as effective adjunctives or alternatives to oral analgesic/anti-inflammatory agents. For patients with moderate to severe pain and inflammation who do not respond satisfactorily to oral analgesic/anti-inflammatory agents, intra-articular corticosteroid injections should be considered [42]. The beneficial effect of corticosteroids on cartilage can be attributed to several mechanisms; for example, suppression of the synthesis of metalloproteases or pro-inflammatory synovial factors such as IL-1 [46]. To reduce the risk of complications, corticosteroid i-a. injections should not be repeated within 3 to 6 months [41,42]. In an 84-patient clinical study reported by Gaffney et al. [10], a single i-a. injection of triamcinolone acetonide suspension resulted in short-term pain relief, the increased benefit being associated with synovial fluid aspiration. A few years later, the study conducted by Raynauld et al. [8] demonstrated long-term safety and efficacy of i-a. suspensions of triamcinolone. Generally, the corticosteroid is combined with lidocaine or bupivacaine and injected after joint aspiration. Potential side effects include post-injection flare or pain, crystal synovitis, haemarthrosis, joint sepsis and steroid cartilage atrophy, as well as systemic corticosteroid effects such as fluid retention or aggravation of hypertension. Viscosupplementation is another therapeutic approach in OA, aiming at replacing hyaluronic acid, whose level is reduced in the damaged knee, in order to restore the elasticity and viscosity of the synovial fluid to normal. One clinical study evaluating the efficacy of viscosupplementation compared to corticosteroid injections in a group of 100 patients demonstrated that both treatments were moderately effective [51]. Despite their delayed onset, the hyaluronic acid injections are characterised by prolonged duration and symptomatic benefit when compared to corticosteroid suspensions [42]. For patients who did not satisfactorily respond to any of the above-mentioned treatment methods, the guidelines suggest radioactive synovectomy. This method permits removal of the inflamed synovial lining, which leads to pain relief. Despite successful results, the fear of radioactivity leakage from the joint and the uncertain long-term biological hazards of radiation limited this form of therapy. Additional medications consisting of nutraceuticals, such as glucosamine and chondroitin, can be administered to OA patients to provide a symptomatic benefit [43,52,53]. Although progresses in OA therapy are numerous, there are currently no approved disease-modifying OA drugs (DMOADs) that stop and reverse cartilage destruction or restore the functional integrity of the joint. Given the complexity of this disease, it is necessary to first identify the major biochemical pathways that can be targeted by means of pharmacological or biological approaches in order to develop disease-modifying treatments.

3.2. Current management of rheumatoid arthritis

Similar to OA, RA does not benefit of the existence of a curative treatment. To date, the main objective of the RA treatments has

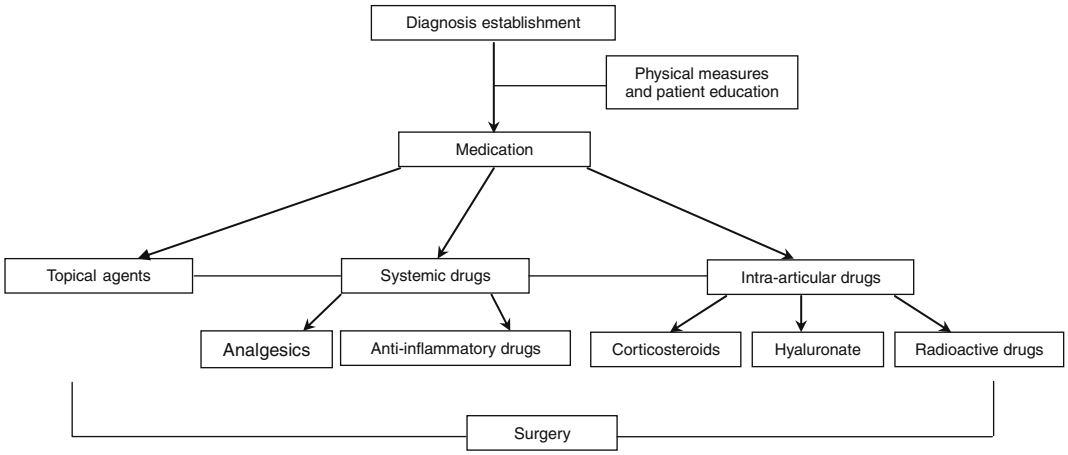

Fig. 3. Current management of OA. Modified from Lozada et al. [47].

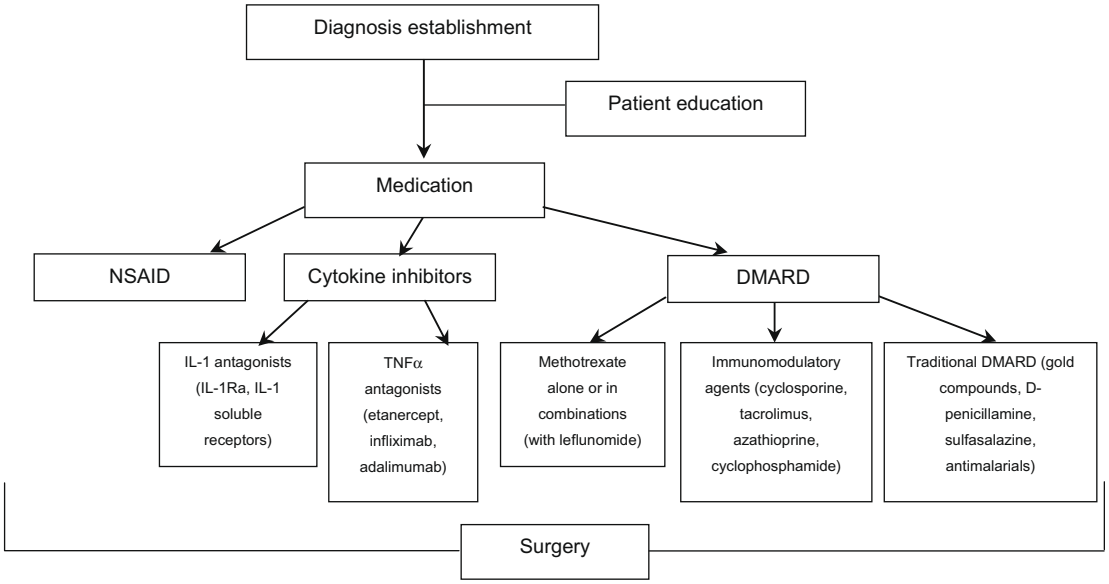

Fig. 4. Current management of RA.

been to reduce joint inflammation and pain, to maximise joint function, to prevent destruction and deformity and to reduce long-term patient disability. Early medical intervention has been shown to significantly improve the outcomes of the disease. Optimal treatment customised according to the gravity of the disease, type of joint involved, age, general health of the person, consists in a combination of medication, rest, joint-strengthening physiotherapy and patient education. The medical protocol [54] includes analgesics, NSAIDs, corticosteroids, conventional disease-modifying anti-rheumatic drugs (DMARDs) and biological agents such as TNF-α blockers or IL-1 receptor antagonist (IL-1Ra), as depicted in Fig. 4. Due to the progression of the disease, first-line medication, such as analgesics and NSAIDs, becomes rapidly ineffective, and i-a. administration of steroid depot formulations, which are able to relief pain and inflammation over a period of a few months, is required. Another stage in RA management is the introduction of DMARDs, the most current being salazopyrine and chloroquine, but gold compounds, penicillamine and hydoxychloroquine are also used. A number of immunosuppressive drugs are also employed to treat RA, for example, methotrexate, azathioprine, cyclophosphamide and cyclosporin. Due to their potential deleterious side effects, they are reserved for patients with very aggressive disease or with serious complications. Methotrexate is an exception, as its use is not associated with very notable side effects. For this reason, it has become the preferred second-line medication used alone or in combination therapy. Newer second-line drugs include leflunomide [55], which selectively inhibits de novo pyrimidine synthesis and thus, reduces the proliferation of activated CD4 T cells, which play a key role in RA pathogenesis. The immunosuppressive agent tacrolimus interferes with T cell proliferation via calcineurin inhibition. Furthermore, tacrolimus is currently in clinical trials [56–58]. Efforts to develop safer and more effective treatments for RA are based on an improved understanding of the role of inflammatory mediators such as TNF-α and IL-1 [59]. Treatments with etanercept – a soluble TNF-α type II receptor-IgG1 fusion protein – and with infliximab or adalimumab – monoclonal antibodies against TNF-α – have been approved by the Food and Drug Administration and the European Medicine Evaluation Agency for treatment of RA. Anakinra, a human IL-1 receptor antagonist, is another biological drug used to treat moderate to severe RA; it is generally used in combination with methotrexate. Together with targeting TNF-α or IL-1, B cell targeting represents a novel approach. In this respect, rituximab, a chimeric anti-CD20 monoclonal antibody targeting B cells, has demonstrated efficacy in numerous clinical studies of arthritic patients [60]. Considering all of these aspects, i-a. administration of drug delivery systems that encapsulate these potent substances, which permits their controlled release over a long time period at doses that are significantly inferior to the systemic dose, might be a major breakthrough in limiting their side effects.

4. Intra-articular drug delivery systems

4.1. Intra-articular injection technique

Local administration is attractive for the delivery of high drug concentrations at the main site of inflammation and for minimising the side effects related to systemic administration. Aspirating and injecting the knee or other joints is a common technique for both diagnostic and therapeutic purposes, in spite of practical difficulties such as the lack of accessibility of the joint and thus, hindered needle placement [61–64]. The complications of i-a. injections like infection, post-injection flare, crystal-induced synovitis, cutaneous atrophy and steroid arthropathy [65], although rare, could result in dramatic side effects. The incidence of septic joints related to local steroid injection is about 1 in 10 000 injections, while for post-injection flare, a frequency of around 2% was recorded. Due to the crystalline nature of the steroids, crystal presence in the joint might produce transient synovitis in about 10% of the patients; this condition generally disappears after a few days [12–14]. Depending on the joint type and the injected substance, aspiration of the synovial fluid before injection might be necessary [14]. Moreover, post-injection rest is required in order to increase the residence time of the administered substance, and, hence, the clinical response [66]. Besides these rather serious side effects, the i-a. route of administration is also accompanied by some technical drawbacks related to the cost and time involved in the procedure, patient compliance and, most importantly, the rapid efflux of drugs from the joint cavity after instillation. This last shortcoming could be addressed by using drug delivery systems which ensure sustained release of the active substance in the joint, while minimising the systemic side effects.

4.2. Drug delivery system intra-articular residence time

4.2.1. Synovial membrane physiology

The synovium, which is the tissue between the fibrous joint capsule and the synovial cavity, is divided into three compartments with distinct functions, notably, the lining region; the subintimal stroma, which consists of connective tissue, lymphatic vessels and fat cells; and finally the vascularised region, with numerous capillaries. The synovial membrane, which is also referred to as the synovial lining, is an irregular membrane that is 3-4 cell-depth thin and is exempt of intercellular junctions. In normal conditions, it serves two functions, notably to provide nutrients to the cartilage cells and to secrete the synovial fluid, which lubricates the joint. The synovial membrane consists mainly of two types of cells, type A synoviocytes, which are similar to macrophages, and type B synoviocytes, which are similar to fibroblasts [67–71]. It has been demonstrated by Senda et al. that both types of synoviocytes posses the ability to phagocytose 240-nm latex particles [72]. Molecules entering or leaving the joint space must traverse both the capillary endothelium and the interstitial space between the synoviocytes [73]. The capillary endothelium presents fenestrations that face the joint cavity, thus favouring the influx of substances to the joint cavity. Regarding proteins, their synovial permeability is principally limited by the endothelium, while the permeability of small molecules appears to be limited by diffusion across the interstitial space [74]. Nevertheless, transport is a highly selective process, with small proteins such as albumin, entering more easily. In contrast, the clearance of all proteins is achieved by lymphatic drainage, while hyaluronan and proteoglycans have restricted access to the lymphatic system. When a joint becomes inflamed, the total protein concentration increases to values close to those of plasma, and the synovial fluid volume augments due to an increased permeability, which overwhelms the drainage capacity of the lymphatic system [73].

4.2.2. Retention times of drug delivery systems vs. solutions or suspensions

In terms of absorption and distribution into the systemic circulation, the i-a. route is equivalent to other non-i.v. parenteral routes of administration [75]. For this reason, drugs that are i-a. administrated as solutions or suspensions have half-lives that can vary between 1 and 2 h for cortisone, naproxen or ketoprofen and up to 22–26 h for hyaluronan [76]. To increase the drug residence time in the synovial cavity, drug delivery systems may be used. Among them, thermally responsive elastin-like polypeptide gels that can spontaneously aggregate after i-a. injection represent a simple and innovative way to prolong the i-a. half-life of a drug. These aggregating elastin-like polypeptides form a drug-depot resulting in a 25-fold longer half-life than drugs administered with the non-aggregating protein. Research is ongoing to chemically couple the elastin-like polypeptide to proteins, such as the IL-1 receptor antagonist, in order to achieve higher residence times [77]. Besides the thermogelling approach, which is used to increase the retention time of a drug formulation in the joint, pH-sensitive gels, such as the holmium-166-chitosan complex, are interesting tools. I-a. injection of this type of composite material results in formation of a gel with minimal extra-articular leakage of the radioactive isotope. The safety of this complex as a radiation synovectomy agent was demonstrated in a Phase I/IIa study of 16 patients [78].

Liposomes, whose potential to increase the i-a. residence time of drugs was first suggested in 1976 by Shaw et al. [79], represent drug delivery systems with valuable clinical utility for i-a. drug delivery. Bonanomi et al. reported that the encapsulation of dexamethasone palmitate in liposomes resulted in an improved retention compared to microcrystalline triamcinolone acetonide [80]. When encapsulating methotrexate in 1.2 μm liposomes, Williams et al. reported a 26.5% reduction in joint swelling of arthritic rats, compared to 3.5% for the free drug at 1 day after the injection. Moreover, the effect was still notable 20 days after the injection of liposomes (Fig. 5) [81]. The pharmacokinetics of liposomal lidocaine, a local anaesthetic that is frequently injected into joints for pain relief, was reported by Hou and co-workers after i-a. administration in healthy rabbit knees. They detected significantly different serum concentrations in rabbits treated with aqueous solution compared to liposomal lidocaine [82]. A highly versatile clinical option for the management of inflamed joints is photodynamic therapy with Verteporfin®. Generally used in oncology, this approach, whose *in vivo* efficacy depends mainly on photosensitiser uptake and accessibility in the target tissue, can also be used in RA. The kinetics and the drug clearance rate after i-v and i-a. administration of liposomal Verteporfin were studied, and interestingly, the drug was not detectable in the circulation after i-a. administration. This result supports the conclusion that photodynamic therapy offers a less invasive and safer alternative than surgical, chemical or radiation synovectomy [83]. The potential of liposomes was also explored in the field of radiographic markers. Edwards et al. studied the i-a. retention of liposomal iohexol compared to the free drug in sheep. In this case, the liposomes resulted in a significantly prolonged drug half-life, i.e., 134 h compared to only 3 h for the free iohexol [84].

Together with liposomes, microspheres injected i-a. represent one of the most studied means to decrease i-a. drug clearance. In this respect, Lu et al. reported that the mean residence time of flubiprofen is doubled compared to injection of the drug suspension [85]. Similar observations were registered for a celecoxib solution compared to celecoxib-embedding chitosan microspheres, for which a 10-fold increase in the concentration of celecoxib in the joint was achieved after i-a. injection [86]. Methotrexate is a DMARD which largely benefits from local administration in the joint in the form of polymeric microparticles. Liang et al. formulated methotrexate-embedded poly(lactic acid) microparticles and tested their pharmacokinetics after i-a. injection in healthy rabbits [87,88]. As expected, the concentration of methotrexate in the synovial tissues following i-a. injection was significantly higher in the group treated with microparticles compared to the one treated with the drug solution [88].

Due to the limited number of reported clinical studies, most of them with liposomes, the i-a. drug delivery system approach remains experimental. In order to reach the clinical stage, more research is needed to demonstrate the *in vivo* benefits of such systems.

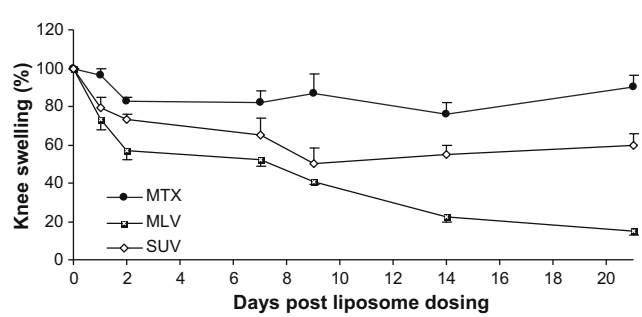

Fig. 5. The anti-inflammatory effect of liposome-conjugated methotrexate (methotrexate–small unilamellar vesicles, MTX–SUV, and methotrexate–multilamellar vesicles, MTX–MLV) as assessed by a reduction in knee swelling in rats with antigen-induced arthritis. One day after treatment, knee swelling (mean ± SEM) in MTX–MLV-treated rats was significantly less than in MTX-SUV-treated rats and than in rats treated with methotrexate solution (MTX) ($P < 0.04$). This difference remained significant at all time points up to day 21, demonstrating that MLV are well suited to treat the symptoms of arthritis. Adapted from Williams et al. [81].

4.2.3. Modulation of i-a. retention times

Obtaining high retention times in the joint, which is essential for the therapeutic success of i-a. drug delivery systems, can be achieved by both chemical and physical methods. The chemical methods deal with the functionalisation of the surface of liposomes, nano- or microparticles in order to achieve high binding to joint-specific targets, thus ensuring the persistence of these systems at the inflammatory site. When attempting to achieve selective cartilage binding using poly(propylene sulphide) nanoparticles functionalised with a special collagen II-binding peptide ligand, WYRGRL, Rothenfluh et al. [89] demonstrated that the peptide-decorated nanoparticles concentrated in the articular cartilage up to 72-fold more than nanoparticles displaying scrambled peptide sequence following i-a. injection in mice. Their innovative approach provides a means to target the articular cartilage, which is otherwise poorly accessible avascular tissue, in diseases such as OA. Another promising strategy that might be effective for the delivery of drugs to the inflamed synovium could be targeting of $\alpha v\beta 3$ integrin, which is up-regulated in neoangiogenic vessels. Currently, the efficacy of such an approach has been demonstrated in adjuvant-induced arthritis in rats after systemic administration of dexamethasone-containing liposomes with a surface-conjugated RGD peptide [90]. This approach, combined with i-a. administration, may achieve valuable improvement in the retention time. Alternative approaches that might also benefit from an i-a. administration in terms of limitation of non-specific systemic binding, are targeting of the folic acid receptor FRβ, which is up-regulated on activated synovial macrophages, and targeting of E-selectin, which is an adhesion molecule that is up-regulated on the vascular endothelium of inflamed tissue [91].

Among the physical methods, one can consider the use of bioadhesive materials. An example of such material is collagomers, which are novel drug-carrier systems based on collagen–lipids conjugates [92]. However, studies are needed to demonstrate synovial tissue retention with this system. The use of a magnetic field also represents a recent approach to improve the accumulation of magnetic drug delivery systems at the targeted site. In this respect, Tanaka et al. used a 0.2 T permanent magnet implanted into the femur to increase the i-a. retention time of magnetic liposomes containing TGFβ_1. To this end, a hole with a diameter of 4 mm and a depth of 8 mm was created into the bone. It was demonstrated that the presence of a magnet leads to a more efficient retention of the liposomes in the joint and to a significant diminution of cartilage defects at 12 weeks [93]. Butoescu et al. incorporated superparamagnetic iron oxide nanoparticles (SPIONs) in PLGA microparticles loaded with dexamethasone and achieved a joint residence time of at least 3 months (Fig. 6) [94–96]. Regarding the possible toxicity of the SPIONs, Schulze et al. demonstrated that 30–40-nm PVA-coated SPIONs were biocompatible with articular and periarticular tissues in sheep [97]. Moreover, considering the magnetic properties of the SPIONs, they also investigated the effect of an extracorporeal magnet on nanoparticle persistence in the joint and have shown an increased local concentration in the presence of a magnet. Other studies on magnetic nanoparticles were conducted by Hellstern et al. [98], who employed light, fluorescence and confocal microscopy to assess the biocompatibility of the system with joint tissues, and the biodistribution of the drug delivery system in different organs. The authors established that the nanoparticles are taken up by the reticuloendothelial system, and that the main organs in which the nanoparticles are detected after i-a. administration are the liver and the spleen. Magnetic drug delivery systems need further investigation before the initiation of clinical trials to confirm the delivery of sufficient payloads to the joint, long-term retention and efficacy in arthritis or OA animal models. Magnetic field strengths used in these studies could be reproduced in patients wearing external magnets, but this issue should be further addressed.

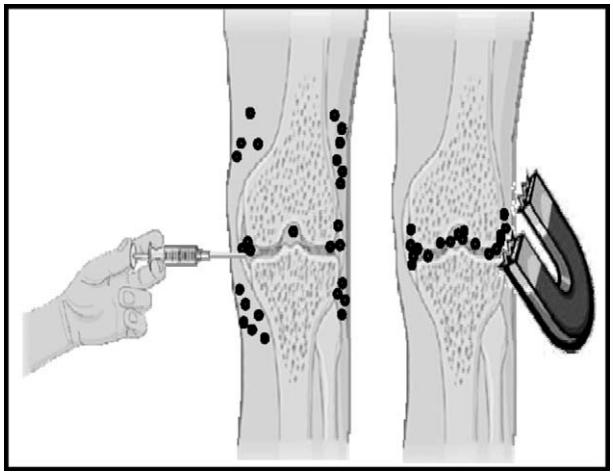

Fig. 6. An external magnet increases microparticle retention in the joint.

4.3. Size

Unlike the systemic administration of drug delivery systems, i-a. injection in active RA or OA involves introducing the carrier into a pathological environment of excess protein and enzymes, many of which may interact with the drug carrier [99]. For this reason, the size, shape and type of carrier of the drug delivery system are essential and must be thoroughly studied to ensure that the carriers do not induce further inflammation or an immune response. A detailed review of these key aspects is presented hereafter. Concerning the size of the i-a. administrated particles, the discussion of the work done in the field will focus on liposomes and on nano- and microparticles, emphasising aspects such as joint retention and phagocytosis as a function of size.

4.3.1. Liposomes

Regarding this type of vesicular carrier, research has focused mainly on increasing liposome retention as a function of particle size (surface area) and biocompatibility. Bonanomi et al. reported that increasing the size of dexamethasone palmitate encapsulating liposomes, ranging from 160 nm to 750 nm in diameter, resulted in a 2.6-fold increase in retention at 48 h post-injection [80,100]. A similar observation was described for liposomes containing methotrexate, for which a mean diameter of 1.2 μm ensured a higher retention, and thus anti-inflammatory action, than 100 nm liposomes [81]. Together with traditional liposomes, niosomes, which are non-ionic surfactant-based liposomes, were also investigated for the local delivery of diclofenac sodium to treat arthritis [101]. Moreover, in order to further prolong the release of the active substance together with better joint retention, both liposome- and niosome-containing diclofenac were embedded in carbopol or sodium carboxymethyl cellulose gels, leading to novel drug delivery systems, lipogelosomes and niogelosomes, respectively. Radiolabelled diclofenac-containing lipogelosomes injected in arthritic rabbit joints presented the longest retention times compared with the other formulations. Moreover, the radioisotope was slowly released, 67% of the initially injected radioactivity being still present 24 h post-injection [101]. Liposomes have been shown to be very efficient in the local treatment of joint diseases in laboratory animals and also in humans. For example, when administered in human patients, hydrocortisone-entrapping liposomes remarkably improved subjective and objective indices of inflammation at 48 h, with a slow return to the pre-injected state

after 2 weeks [102]. In another clinical study, a single i-a. injection of clodronate-containing liposomes significantly reduced the expression of adhesion molecules, which is correlated with the extent of inflammation in the synovial lining (Fig. 7) [103]. These encouraging results in humans have stimulated further research of liposomes as a therapeutic method to locally treat inflammation and cartilage defects.

4.3.2. Nanoparticles

This type of carrier has mainly been studied in an attempt to target the articular cartilage in diseases such as OA. For this purpose, nanoparticles generally contain a specific cartilage-binding moiety. In addition, to achieve efficient carrier penetration into the cartilage, the carrier size may play an essential role. This aspect was demonstrated by Rothenfluh et al. [89] for nanoparticles coated with collagen II-binding peptide. The authors demonstrated by fluorescence measurement a 14.9-fold preferential accumulation of 38-nm mean diameter nanoparticles within the cartilage relative to 96-nm diameter nanoparticles. This significant difference was attributed to the 60-nm pore size of the dense collagen network.

4.3.3. Microparticles

Numerous reports focus on the influence of microparticle size on the phagocytosis of these systems once they are injected in the joint. It has been demonstrated that small particles are easily phagocytosed, with a reported limit ranging from the nanometre scale up to a few micrometers. Howie et al. [104] studied the response of the rat synovial tissue to the presence of polyethylene wear particles, similar to those commonly released from the articulating surfaces in joint prostheses. They reported that particles of about 5–15 μm, larger than the size of macrophages, tend to produce a multinuclear giant cell response, while particles smaller than 5 μm trigger a mononuclear macrophage response. Horisawa et al. [105] used fluorescently labelled PLGA nanoparticles (mean diameter 265 nm) and microparticles (mean diameter 26 μm) to evaluate synovial phagocytosis. As expected, nanoparticles were extensively phagocytosed and subsequently transported through the synovial membrane within 3–7 days. In contrast, microparticles of 26 μm in diameter were neither phagocytosed nor transported to the underlying synovial membrane, but they triggered a granulation reaction with multinuclear giant cells. Similar observations were registered by Nishide et al. who investigated the biodegradation and tissue response of PDLLA microspheres with size fractions of 0–20, 20–100 and 100–200 μm i-a. injected into healthy rabbit joints [106]. The authors concluded that microparticles with diameters larger than 20 μm were not internalised into macrophages, nor did they produce important inflammatory responses. In contrast, Liggins and co-workers demonstrated that PLGA microspheres in the size range of 1–20 μm produced significantly greater inflammatory responses than 35–105 μm particles, possibly explained by the large fraction of very small microparticles in the 1–20 μm batch. Interestingly, the phagocytosis of microspheres by synovial macrophages improved the retention of microparticles in the joint [107,108] and also ensured an increased drug concentration in inflammatory cells and delayed clearance from the joint, which minimised drug exposure to cartilage, thus reducing the side effects. Regarding drug concentration in the serum after i-a. administration of drug-encapsulating microparticles, Ramesh et al. pointed out that 400 min after the injection in the articulus of dexamethasone encapsulated in PLA microparticles, no drug was detected in the serum of healthy rabbits, thus concluding that dexamethasone release is localised in the joint [109]. In contrast, a small quantity of methotrexate was detected in rabbit plasma 5 min post-injection of PLA microparticles, mostly due to a burst release of the drug from the particles [88]. Moreover, the microparticles, whose size is in the range 30–100 μm, did not induce acute inflammatory reactions.

Considering the diameters of all types of microparticles tested for i-a. delivery of drugs depicted in Table 1, it can be concluded that the most suitable size is between 5 and 10 μm. This particle size range ensures capture of the particles by the synovial macrophages, a process that results in a prolonged retention time in the joint. In addition, to limit the inflammatory reactions, the choice of adequate polymers is essential.

4.4. Quantity of i-a. injected drug delivery systems

Apart from size, the quantity of injected microparticles is also important to the appearance of an immune response, as shown in the studies conducted by Nishide et al. They demonstrated an enhanced number of white blood cells with increasing amounts of injected microparticles, from 5 to 40 mg per knee [106]. In contrast, no significant dose-dependent inflammatory effect was observed for paclitaxel-embedding PLGA microparticles after i-a. administration of 15 to 75 mg of particles per joint in healthy rabbit knees [110].

4.5. Shape

Not only the size, but also the shape of the particles injected into the joint is important for triggering an immune response. Irregularly shaped microparticles have been demonstrated to promote tissue inflammation in comparison with round-shaped drug

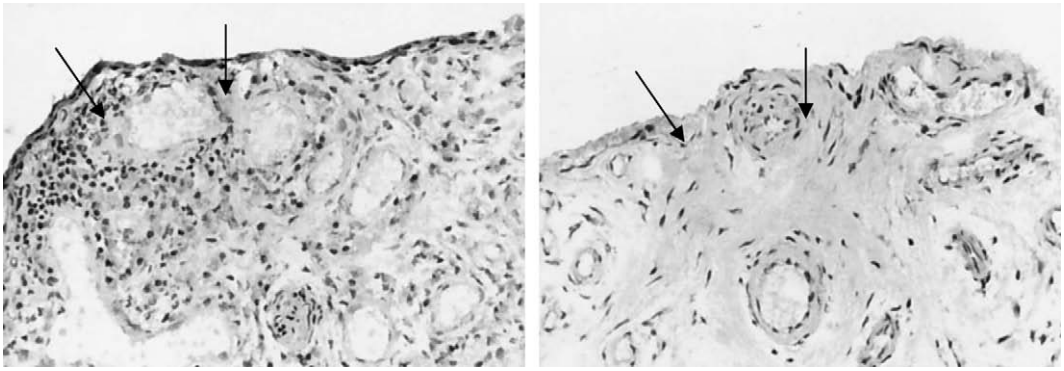

Fig. 7. Histological image of the synovial lining of a RA patient before and 7 days after clodronate liposome administration. Before the injection (left panel), numerous macrophage-like fibroblasts were present (indicated by arrows), while after the injection, normal features of the fibroblasts were recorded (right panel). (HE stain, original magnification 250×). Adapted from Barrera et al. [103].

Table 1
Drug delivery systems developed up to date for the i-a. administration.

Type	Targeted drug	Nature of the matrix	Diameter of particles	*In vivo* tests	Refs.
Gels	No drug	Elastin-like polypeptide, thermosensitive gel		I-a. injection in a rat knee	[77]
Liposomes	Clodronate	Egg phosphatidyl choline/cholesterol		Antigen-induced arthritis (AIA) model in sheep	[130]
		Phosphatidyl choline/cholesterol		Collagen-induced arthritis (CIA) in mice	[131]
		Egg phosphatidyl choline/cholesterol		I-a. injection in patients with RA	[103]
	Cortisol palmitate	Phosphatidic acid necessary for the full expression of anti-inflammatory activity		Bilateral inflammation induced by the i-a. injection of poly-D-lysine and hyaluronic acid	[79,132,133]
		Phosphatidic acid and dipalmitoyl phosphatidyl choline		AIA in rabbits	[114]
		Mixture of phospholipids		I-a. in human subjects with rheumatoid arthritis	[102]
	^{51}Cr	Lipid phase	100 nm	AIA in rabbits	[134]
	Daunorubicin	Not mentioned		I-a. injection in arthritic rabbits	[127]
	Dexamethasone palmitate	Egg phosphatidyl choline/phosphatidic acid	160–750 nm	I-a. injection in healthy and AIA rabbits	[80]
		Different phospholipid mixtures	100 nm to 30 μm	I-a. injection in healthy rabbits	[100]
	Diclofenac sodium 99mTc-labelled	Different phospholipids	200–250 nm	AIA model in rabbits	[101]
	Eicosatetraynoic acid	Not mentioned		I-a. injection in acute synovitis joints	[127]
	Iohexol	Dipalmitoyl phosphatidyl choline/cholesterol/stearylamine		I-a. injection in healthy sheep	[84]
	Lactoferrin	Not mentioned		AIA in mouse	[135]
	Lidocaine	L-a-phosphatidyl choline/cholesterol		I-a. injection in healthy rabbits	[82]
	Methotrexate	Different phospholipids	1 μm	AIA model in rabbits	[136,137]
		Different phospholipids	1.2 μm	AIA in rats	[81]
	Transforming growth factor-β1 (TGB-β1)	Egg yolk phosphatidyl choline/cholesterol/ dipalmitoyl phosphatidic acid		Full-thickness cartilage defects in rabbits	[138]
		Egg yolk phosphatidyl choline/cholesterol	Magnetic liposomes	Full-thickness cartilage defects in rabbits	[93]
				Partial thickness defects in adult miniature pigs	[139]
	Triamcinolone acetonide 21-palmitate	Dipalmitoyl phosphatidyl choline/cholesterol		AIA model in rabbits	[140]
	Verteporfin®	Not known		AIA model in rabbits	[83]
Nanoparticles	Betamethasone sodium phosphate	PLGA	370 nm	In rats: *in vivo* release study: dorsal air pouch model. In rabbits: efficacy on AIA model	[121]
	Flouesceinamine	PLGA	110–670 nm (mean 265 nm)	I-a. injection into rat joints	[105]
	No drug	Poly(propylene sulphide) functionalized with a collagen-binding ligand, WYRGRL	38 nm	I-a. administration in mice	[89]
		SPIONs	30–40 nm	I-a. injection in sheep	[97,98,141]
Microparticles	Celecoxib	Chitosan	8 μm	I-a. injection in rats	[86]
		Albumin	5.4 μm	AIA in rats	[142]
	Chondroitin sulphate	Gelatin	10 μm	I-a. injection in mice	[120]
	Basic Fibroblast Growth Factor (bFGF)	Gelatin hydrogel	70 μm	I-a. injection in joints of normal rabbits	[143]
	Dexamethasone	PDLLA	40–60 μm, 90–110 μm	I-a. injection in healthy rabbits	[109]
	Diclofenac sodium	PLGA	5–10 μm	AIA model in rabbits	[118]
	Doxycycline	PLGA	15–120 μm (mean 35 μm)	Not tested on animals	[144]
	Flurbiprofen	Gelatin	7.5 μm	I-a. injection in healthy rabbit joints	[85]
	Flouesceinamine	PLGA	3.1–60 μm (mean 26.5 μm)	I-a. injection into rat joints	[105]
	Insulin	PLGA		I-a. injection in healthy mice	[117]
	Methotrexate	PLLA	62–83 μm	I-a. injection in healthy rabbit joints	[87]
		PLLA	77 μm	I-a. injection in healthy rabbit joints	[88]
	Naproxen sodium	PLGA or BSA	5–10 μm	AIA model in rabbits	[116]
		PLGA	50 μm	Extracorporeal *in vivo* isolated horse metacarpophalangeal joint preparation	[145]
	Paclitaxel	PLGA, PLA, PCL, Chitosan	1–20 μm, 35–105 μm	AIA model in rabbits	[110]
		PLGA	50 μm	Extracorporeal *in vivo* isolated horse metacarpophalangeal joint preparation	[145]
	Prednisolone	Heat-stabilized albumin	23 μm	I-a. injection in rabbits	[146]
	Rose Bengal – model compound	Rabbit serum albumin	3.5 μm	AIA model in rabbits	[108]
	TGFβ	Calcium alginate		I-a, injection in rabbits with a full-thickness cartilage defect	[119]

Table 1 (*continued*)

Type	Targeted drug	Nature of the matrix	Diameter of particles	*In vivo* tests	Refs.
	Triamcinolone	Heat-stabilized albumin	23 μm	I-a. injection in rabbits	[146]
	^{166}Ho	PLA	2–13 μm	I-a, injection in healthy rabbits	[129]
		Ferric hydroxide macroaggregates	1–5 μm		[147]
	^{188}Re-labelled microparticles	Hydoxyapatite	2–20 μm	I-a. injection in rats	[148]
	^{165}Dy	Ferric hydroxide macroaggregates	1–5 μm		[149]
	^{153}Gd				[128]
	^{90}Y				[150]
	^{59}Fe				[129]
	^{141}Ce-labelled microparticles	Carbonized microparticles	10 and 14 μm	AIA model in rabbits	[128]
	^{99m}Tc-labelled microparticles	Denatured HSA	25, 10, 1–2 and 0.1 μm		
	No drug	PLA, PBCA, Gelatin, Albumin	2–7.5 μm	I-a. injection in healthy rabbits	[107]
		PDLA	10, 100 or 200 μm	I-a injection in healthy rabbit joints	[106]
		Polyethylene Particles resulting from prostheses	1–200 μm	I-a. injection in healthy rats	[104]
Miscellaneous	^{166}Ho complex with chitosan	Chitosan		Phase I/IIa clinical study in humans	[78]
		Chitosan		I-a. injection in patients	[151]
	Transferosomes for epicutaneous ketoprofen	Lipids		Cutaneous application in humans with OA	[152,153]
	Diclofenac	Collagomers		Tribromethanol-induced OA model in rats	[92]

delivery systems. In this respect, Liggins et al. showed that irregular, milled chitosan particles induced joint inflammation despite the known articular biocompatibility of this biomaterial [110]. Similar histological observations showing marked inflammation in the synovial membrane and the subsynovial lining were made by Ratcliffe et al. for PLA and poly(butyl cyanoacrylate) microparticles obtained by simple polymer grinding [107]. Thus, to avoid inflammatory reactions subsequent to the administration of irregularly shaped particles, round-shaped particles are to be preferred for i-a. drug delivery.

4.6. Matrix materials

Regarding liposomes, research demonstrated that egg phospholipid liposomes were relatively fragile and prone to leakage. Dipalmitoyl phosphatidyl choline (DPPC) was chosen as the most important liposome phospholipid due to its gel–liquid crystalline phase transition temperature of 41 °C, which makes it more rigid, and thus stable, at the body temperature. From the point of view of biocompatibility, DPPC is very suitable for i-a. use as it is an endogenous component of the joints [111]. More precisely, it represents approximately 45% of the total synovial fluid lipid component. Cholesterol is often included in the composition of the liposomes for its capacity to improve *in vivo* stability and to prevent leakage of drug molecules through the liposomes bilayer [112]. Stearylamine represents another possible constituent of liposomes and is used to enhance repulsion between shell layers, and also to improve interaction with macrophages, due to its positive charge [113]. Moreover, changes in matrix composition can influence the therapeutic action of the formulation, as demonstrated for cortisol-containing liposomes whose anti-inflammatory activity decreases in the absence of phosphatidic acid [114]. In the formulation of nanoparticles, an innovative polymer matrix, poly(propylene sulphide), was used to obtain specially designed systems for targeting of the articular cartilage [89,115]. By varying the ratio between the polymer and the emulsifier, Pluronic 127, the authors achieved control of the size, ranging from 20 to 200 nm, and they obtained special nanoparticle core architecture, with a hydrophobic nucleus resulting from the disulphide cross-linking of poly(propylene sulphide), with hydrophilic domains consisting of polyethylene glycol moieties of the Pluronic and with the surface covered by peptide ligands to target the cartilage. Finally for microparticle matrices, several materials have been studied, notably poly(lactide-co-glycolide) (PLGA) [116–118], poly(L-lactic acid) (PLA) [109], gelatin [85], albumin [108], poly(ε-caprolactone), chitosan [110], poly(butyl cyanoacrylate) [107], calcium alginate [119], hydroxyapatite and glucosamine–chondroitin [120], as displayed in Table 1. Among these materials, the release and degradation characteristics of albumin, gelatin, chitosan or alginate can be modulated by cross-linking methods [116]. Note that cross-linked albumin microspheres have been shown to be well tolerated by the synovial tissue [108,116]. Homopolymers and copolymers of lactic and glycolic acids are macromolecules degraded by simple hydrolysis of the ester bonds to produce non-toxic by-products, which can be easily cleared out from the joint. Due to its known biodegradability and to the fact that it is largely employed for numerous medical applications in animals and in humans, PLGA is the most frequently used polymer as particle matrix.

Regarding the encapsulation efficacy and drug loading, these two parameters varied in function of the active substance and the matrix material. Generally, literature reports very high encapsulation efficacy (70–80%) for i-a. drug delivery systems, corresponding to drug loadings of 1% [121], 5% [109,117,121], 10% [122] and up to 47% for hydrocortisone in PLGA microparticles [123]. As for the *in vitro* release, generally assessed in PBS, it varied from a few hours for BSA drug delivery systems [124] to around 100 h for chitosan microparticles [125]. In both cases, the release rate could be tailored by changing the cross-linker concentrations. For PLA- or PLGA-based systems, the release times were longer, up to 14 days in some reports [109,122]. Some authors also investigated the *in vivo* release in dorsal air pouch models in rodents [94,121] and demonstrated release times of 6–7 days.

4.7. Therapeutic agent

Due to an acute need for efficient therapeutic systems providing long-term pain relief, non-steroid and steroid anti-inflammatory drugs were, by far, the most tested drugs for encapsulation in either liposomes or nano- and microparticles, and their efficacy has been studied mostly on rabbit, sheep or rat arthritis models (Table 1). Another therapeutic class of active substances thoroughly studied as candidates for encapsulation is radioisotopes. In fact, the synovial lining of the arthritic joint becomes hyperplasic and may thicken to 10–12 cells in depth. To remove the

inflamed synovium lining, three methods are currently available, notably surgery (surgical synovectomy), chemical substances (chemical synovectomy), which are noxious agents used to kill the synoviocytes, and radionuclides (radiation synovectomy). Although very efficient in certain cases by providing pain relief up to 2–5 years [126], surgical synovectomy is limited by its technical complexity, and also by the fact that subsequent regrowth can occur. Chemical ablation uses noxious substances, usually chemotherapeutics, which kill the synovial lining. Encouraging results with chemical synovectomy were obtained with liposome-encapsulated daunorubicin [127], a potent anti-neoplasic agent, i-a. injected in arthritic rabbits. Compared to free daunorubicin, the liposomes elicited a reduction in temperature and diameter of the treated animal joint over a period of 24 days, demonstrating that a very small dose (5–10 μg) of substance can produce important beneficial effects. The third method is the ablation of inflamed synovium by intra-articular injection of beta-emitting radionuclide in colloidal or particulate form. The common drawback of the chemical and radiation synovectomy is the necessity to restrict the agent to the joint cavity, in order to limit the systemic side effects. This problem was solved by the encapsulation of the therapeutic agent into particulate systems, most generally liposomes or microparticles. Concerning radionuclides, a large panel of isotopes were embedded in either gels (^{166}Ho), liposomes (^{51}Cr) or microparticles (^{188}Re, ^{99m}Tc, ^{141}Ce, ^{166}Ho, etc.). Generally, an ideal radiopharmaceutical for radiation synovectomy should have appropriate beta-emission energy for effective tissular absorption and removal of inflamed synovium. In addition, the half-life needs to be short enough to reduce the risk of prolonged radiation *in vivo* but long enough to ensure adequate manufacturing and transport. Moreover, the radionuclide should bind irreversibly to the carrier particles, preferably having a diameter sufficiently small to allow effective phagocytosis by synoviocytes, but large enough to limit extra-articular leakage [78]. The carrier biodegradability is not compulsory, as long as the carriers do not induce inflammatory reactions into the joint. For example, Noble et al. used carbonised microparticles containing ^{141}Ce and demonstrated that reducing the biodegradability of the particle or increasing the diameter results in the reduction of radioactivity loss from the knee joint [128], but a clinical use of such a system is hardly conceivable. Satisfactory rates of i-a. radioactivity retention were also achieved by using biodegradable materials such as hydoxyapatite [128] or PLA [129], with values superior to 98% after 48 h and 120 h, respectively. In contrast, larger radioactivity leakage was observed by Mumper et al. [129] for ferric hydroxide macroaggregates containing ^{59}Fe. The authors concluded that the 18.5% radioactivity loss after 5 days was due to instability of the ferric hydroxide macroaggregates in the presence of ^{59}Fe.

4.8. Drugs that might benefit from delivery system

Despite the significant progress done in the field of i-a. delivery, at present there is an acute need for specific drug delivery systems capable of reducing side effects and systemic toxicity either for classical anti-inflammatory drugs or for novel and very potent anti-inflammatory substances, which cannot be registered for the moment due to high toxicity (Table 2). For most RA or OA drugs, future development can only be achieved in the framework of adequate pharmaco-technological or biological development, to confine their action at the targeted site and hence to minimise the undesired effects. Such is the case of drugs targeting p38 mitogen-activated protein kinase (p38 MAPK), an enzyme that regulates cytokine levels and that plays an important role in the activation responses associated with inflammatory diseases [154–156]. An increasing number of potent and specific p38 MAPK inhibitors synthesised by numerous pharmaceutical companies are currently in clinical trials, generally for oral or parenteral administration in the case of RA. Early findings with compounds such as SB-203580 [157], SB-220025 or SB-242235 [158] prove that these substances are very potent *in vitro* inhibitors of p38 MAPK and that they produce significant anti-inflammatory response in different rodent models. Nevertheless, their development was stopped due to the lack of specificity or to the toxicity associated to the inhibition of liver p450 cytochrome [159,160]. A new p38 inhibitor, GSK-681323, is currently in early stages of clinical development [160], while SCIO-469, one of the most advanced compounds in clinical trials, is at the moment in Phase II [160]. VX-745 from Vertex is a promising compound, whose clinical evaluation was arrested in 2001 due to central nervous system toxicity associated with its high ability of crossing the brain–blood barrier [3,161]. A second-generation molecule developed by Vertex, VX-702, is currently under Phase II clinical trials [3,5,162,163]. Another class of anti-inflammatory compounds is represented by the IL-1β converting enzyme inhibitors, among which pralnacasan (VX-740) and an orally available prodrug (VX-765) are the most known and studied. Although in experimental models of OA and RA both pralnacasan and VX-765 reduced joint damage and RA progression [164–166], in clinical trials the use of pralnacasan was associated with liver abnormalities that led to the discontinuation of the trials.

Table 2
p38 MAPK inhibitors in clinical trials.

Compound	Company	Clinical status
AMG-548	Amgen	Phase I discontinued
AVE-9940	Sanofi-Aventis	Phase I discontinued
BIRB 796	Boehringer Ingelheim	Phase II
GSK-681323	GlaxoSmithKline	Phase I (2002)
PH-797804		Phase II (2007)
PS-540446	Bristol Meyers	Phase I (2005)
PS-516895	Squibb	Phase I (2004)
RO-4402257	Roche	Phase II (2006)
RO-3201195		Phase I
RWJ67657	Johnson & Johnson	Phase I discontinued
SB-203580	SmithKline	Discontinued
SB-281832	Beecham	Discontinued
SB-273005		Discontinued
SB-242235		Discontinued
SC80036	Pfizer	Discontinued
SCIO-323	Scios	Phase I
SCIO-469		Phase II (2005)
TAK-715	Takeda	Phase II (2005)
VX-702	Aventis/Vertex	Phase II (for acute coronary syndrome)
VX-745		Discontinued
VX-740 (Pralnacazan)		Phase II discontinued
VX-765 (prodrug of Pralnacazan)		Phase II discontinued

Although very promising, an increasing number of novel and very active compounds fail to enter or are discontinued in the course of clinical trials due to adverse reactions. Nevertheless, these compounds may represent a major breakthrough if they were developed under an adapted drug delivery system, allowing on the one hand the administration of very small drug quantities and on the other hand the localisation of the compound at the targeted site, hence, avoiding side effects related to high drug concentrations or to systemic localisation.

5. Conclusions

In conclusion, i-a. drug delivery systems for OA or RA represent a valuable means to administer drugs directly in the joint cavity, while circumventing systemic toxicity and reducing leakage or exposure of other tissues and organs. Due to its encapsulation in a delivery system, the active substance is gradually released, and

it can act locally to diminish joint inflammation, in the case of non-steroidal or steroidal drugs, to remove the synovial lining, in the case of radioisotopes or anti-tumour drugs, or to target the articular cartilage, in the case of specific peptide drugs. The uptake by synovial macrophages is very important on the one hand to increase the retention of the drug delivery system in the joint and on the other hand to rapidly and effectively diminish inflammation by the direct targeting of the cells involved in inflammatory responses. Consequently, because of the environment of the arthritic joint, the drug delivery systems designed for i-a. administration must meet specific criteria concerning the lack of pro-inflammatory or pro-immunogenic activity, achieved through a careful selection of the carrier material and suitable size and shape.

Despite the extensive research done in the field, at present there is no polymeric drug delivery system registered for i-a. administration in humans, maybe due to stability issues, but also to a lack of definite evidence of pre-clinical and clinical efficacy. Nevertheless, among the different types of drug delivery systems, liposomes represent the most advanced carrier for i-a. administration, benefiting from preliminary evidence of efficacy obtained both in animal models and in small clinical studies. Further research is needed to improve the retention and to tailor the release rate of the encapsulated drug.

Research in this field should be directed towards the development of adapted delivery systems for potent anti-inflammatory drugs such as p38 MAPK or IL-1β converting enzyme inhibitors. These types of agent block molecular functions that are involved in the immune response and signalling cascades. Systemic administration leads to an increased rate of infections and toxic side effects and thus, a local intra-articular administration may be of great benefit. Moreover, in order to increase the success of these intra-articular drug delivery systems, the research on encapsulation techniques should take into account specific targeting strategies for cellular receptors in the joint, which could represent a major breakthrough in the domain of rheumatic disease treatment.

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