International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 10; Issue 07 (A); July 2021; Page No.24749-24753
DOI: http://dx.doi.org/10.24327/ijcar.2021.4932.24753

Review Article

NEW INNOVATIONS IN MANAGEMENT OF DEGENERATIVE JOINT DISEASES WITH OLD DRUGS: A REVIEW

Deslin Davis., Ashmy Davis., Abitha Sebastian and Lincy Geroge*

Department of Pharmacy Practice St.James College of Pharmaceutical Sciences, Chalakudy, Kerala

A R T I C L E I N F O

Article History:

Received 6th April, 2021
Received in revised form 15th May, 2021
Accepted 12th June, 2021
Published online 28th July, 2021

Key Words:

Osteoarthritis, Intervertebral disc degeneration, Chronic lower back pain, Local drug delivery, Biomaterials, Regeneration.

A B S T R A C T

Osteoarthritis (OA) and chronic lower back pain (CLBP) are the degenerative joint diseases that cause major loss in quality of life of patients. Traditional treatment options of oral, IV, topical route of drug administration and even surgery lacks the efficacy and fails in successful management. Hence this review focus on biomaterial based local drug delivery as a novel approach in degenerative joint diseases using in-vivo and ex-vivo models. Most of the trials conducted in these models, with several drugs like inhibitors of inflammatory mediators and degenerative factors provided successful results by prevention of inflammation, degeneration and pain relief. But it couldn't provide much data on delivery of regenerative factors. The difference between articular joints and intervertebral disc (IVD) in health and diseases should be taken into account for the future development of safe and effective treatment.

INTRODUCTION

Earlier, major efforts and financial resources were greatly devoted to biomedical researches related to life threatening chronic conditions like oncology, cardiovascular, neurodegenerative and diabetic studies, but as time passes progressively the health care burden has spread to other non-communicable chronic diseases too[1]. As per the systematic analysis of 2016 most severe impact on global burden and leading cause of loss of year lost to disability (YLD) was seen in degenerative diseases like osteoarthritis(OA)(12th position in YLD in2016)and chronic lower back pain (CLPB)(1st position in 2016 &57.6 million of total YLD from 1990-2016).

OA and Inter-vertebral disc (IVD) degeneration are whole organ disease involving aberrations of anatomical tissues and clinically most affected joints are knee, hip and hand. Apart from the distinct anatomical and physiological difference between synovial fluid and IVD, they share the common pathophysiology of degeneration process in disease conditions. Their similarities in the pathophysiological characteristics provided an insight into the novel therapies.

Ongoing Treatments

Traditionally, the management of OA and CLBP are carried out by a combination of oral analgesics, physiotherapy and lifestyle modifications.

Corresponding author:* **Lincy Geroge
Department of Pharmacy Practice St.James College of Pharmaceutical Sciences, Chalakudy, Kerala

Specifically in case of knee OA, treatment is done with braces, intra-articular injection of hyaluronan [2] or ingestion of glucosamine and chondroitin sulphates. Earlier the first line management of pain in OA and CLBP was done with Acetaminophen. Now different oral NSAIDS are available which has limited clinical improvement and have gastrointestinal and cardiovascular side effects on prolonged use [3]. Local application of ointments or intra-articular/epidural/intra-discal injections of NSAIDs and corticosteroids are other treatment strategies. In addition to this opioid are also given to patients with severe pain, which may lead to the risk of addiction. Finally as a last option, surgeries like IVD replacement, Total Knee Replacement or spinal fusion can be performed [4].

As an alternative to surgical interventions, many novel treatments are also being tested in the clinical trials. A variety of stem cell- based trials were conducted for both OA and CLBP, but couldn't provide the convincing benefits yet. The researches shows an advanced era of therapies with supportive biomaterial, other types of cells like tissue - specific progenitors, embryonic or induced pluripotent stem cells, still needs to be settled. As a novel systemic therapy, searches on druggable targets of disease are ongoing. A treatment with Nerve Growth Factor (NGF) antibody is in the late stages of clinical trial that can reassure effective pain control [5].

As the access to large non-vascularised IVD is limited, local treatment is the only therapy for degenerative IVD in CLBP.

Compared to systemic treatments; the locally administered drugs are available at higher concentrations at the site of administration and have decreased occurrences of adverse effects. In clinical practice, intra-articular injection of corticosteroid suspension for OA and intradiscal injection of corticosteroid for CLBP is being utilised for effective pain management which is active for several weeks. There are various controversies regarding the efficacy of drug formulations due to the excipients added like polyethylene glycol [PEG], which causes toxicity in IVD which were evident through the rabbit studies conducted [6]. These effects were also seen for human paraspinal injections of drug formulations containing high concentration of PEG and were absent in corticosteroid formulation with normal saline only. Later when trials were conducted by using corticosteroid in other vehicles like Benzyl alcohol, Polysorbate 80, EDTAetc in formulations and injected intradiscally, provided relief in CLBP for several months.

Biomaterial Based Drug Delivery System: An Advanced Trick with Old Drugs

Although we obtained some good results from local injections of drug formulation in the treatment of degenerative joint disorder, still there is limited efficacy with any old/new drugs administered as bolus dose, mainly in articular joint where full drug clearance occurs within several days. But in case of IVD, the blood supply to the outer layer of the annulus fibrosus is highly limited, which may result in slow clearance and long retention of drugs. From the trials conducted using intradiscal corticosteroid injections, it was evident that the clinical symptoms reoccurred within 3-6 months, indicating longer duration of drug exposure than in articular joints [7]. However, more extended exposure to therapeutic bioactive molecules is required for better treatment. But, the repetitive reinjection cannot be performed due to the risk of infections, especially in patients undergoing prosthetics surgery, and possibility of reduced patient compliance. Thus, the era of biomaterial based controlled drug delivery system emerged for achieving long term therapeutic drug exposure with minimum number of reinjection in OA and disc related CLBP.

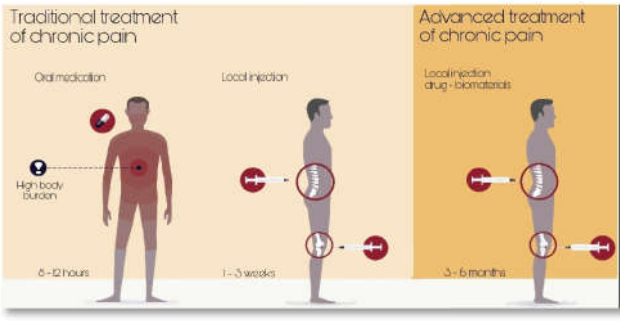

Figure 1 Diagrammatic representation on management of degenerative joint diseases using oral medications and local injections with reduced efficacy and advanced method of Biomaterial based local drug delivery with improved efficacy and prolonged pain relief.

Different types of drug delivery vehicles are used in biomaterial based local drug delivery depending upon several factors such as degradability, tissue location and the physiochemical properties of therapeutic compound and the vehicles. For e.g. Use of hydrogels, as vehicles in articular joint may be difficult due to the occurrence of Hydrogel fragmentation or limitation in the release duration to one or a few days at most. Hydrogels are mostly suitable for IVD because of its confined environment and the clearance may be also slower. Hydrogel can act as vehicles for the release of small drugs (including hydrophobic drugs) and large proteins. Polymeric microspheres can release drugs up to several months, even in articular joint and the release may vary depending on the type of polymer used. Different FDA approved microsphere formulations are available now. E.g.Poly Lactic Acid co-Glycolic Acid (PLGA). Drug delivery using Nano particles is an emerging new approach but it showed relatively shorter duration of drug retention compared to microsphere counterparts [8].

Preclinical Studies for Drug Delivery in OA and IVDD

So far, only one controlled release-based treatment had acquired regulatory approval for the treatment of regenerative joint disease. It is the microsphere formulation based on PLGA, that release corticosteroid drug Triamcinolone acetonide (TAA). Until now, several other controlled drug delivery carriers had been investigated in preclinical trials using different in-vivo and ex-vivo models. Most of them target the inflammatory process during degeneration and some aim to achieve regeneration of affected joints.

The following table shows in-vivo and ex-vivo therapeutic efficacy of polymeric formulations for the local drug delivery targeting inflammation, autophagy or hypertrophy in OA and IVD- related CLBP.

Limitations of Microsphere and Hydrogel Depots

Despite the longer duration of drug exposure, microspheres and Hydrogel have the lack of spatial control of release inside the joint, especially in case of articular osteoarthric joint, where different therapeutic agents will be required for different joint tissues. This issue can be solved by incorporating nanoparticles in microspheres or Hydrogels. The nanoparticles mediated delivery system will allow the drug delivery by attachment of molecules that specifically bind to particular cells in diseased target tissues. Even though this method can overcome the limitation, its pharmaceutical production and quality control is complex.

OA and CLBP pain can be associated with nociceptive, inflammatory and neuropathic pain and also includes joint nociception, peripheral and central sensitization. The local delivery o anti inflammatory drugs can eliminate the nociceptive pain in OA, while the peripheral and central sensitization may take time to resolve. Chronic neuropathic pain in hip and knee OA [26] and CLBP cannot be targeted by the anti inflammatory drugs, and also may not always be localised easily. At more isolated locations and to modulate central sensitization process, combinational therapy with neuropathic analgesics or opioid is an option. But separate injections or even systemic administration of neuropathic analgesics will be needed.

Barriers of Clinical Implementations

The drug delivery formulations in animal models of OA and IVD degeneration has shown encouraging results in different studies, but the clinical implementation in human beings has many hurdles to overcome. The main barriers include lack of knowledge about in vivo release, optimal timing of intervention, regulatory issues and complications of local drug delivery systems.

Drugs & Dose Given(per joint/per body wt)	Carrier	Model	Dosing Time	Analysis After 1st Injection	Inference	Comparison With Local Free Drug	Reference
Anti -Inflammatory Ibuprofen (0.2,0.6.1mg)	PLGA MS	MIA-induced rat	7d	7w	↓cartilage degeneration	No	[9]
Lornoxicam (4mg/kg)	PLGA MS	Papain–induced OA rat	9d	6w	↓synovial inflammation and cartilage degeneration	Yes	[11]
	Chitosan MS	MIA-induced rat	1d	1,2,3w	↓swelling ↓cartilage degeneration	Yes	[10]
Diclofenac (1mg/kg)	Collagen-lipid MS	MIA-induced OA rat	Until OA response	3,10,18w	↓swelling	Yes	[23]
Celecoxib(CXB) (0.03,0.23,0.39mg)	Polyester-amide MS	ACLT/DMM-induced OA rat	4w	16w	↓synovial inflammation and cartilage degeneration ↓osteophyte formation	No	[12]
CXB (0.01,0.3mg) (0.09mg/IVD)	PEA-MS	IVDD induced by partial nuclectomy in canines	4W	12W	↓synovial inflammation and cartilage degeneration ↓osteophyte formation & Sclerosis ↓NGF production	No	[15]
	PEG Hydrogel	Canine CLBP patients	NA	12w	↓pain & IVD degeneration	No	[16]
Triamcinolone acetonide(TAA) (0.25mg)	PEA-MS	Collagenase induced OA rat	1w	7w	↓synovial inflammation and cartilage degeneration	Yes	[17]
(0.7,1,1.6mg)		ACLT/DMM-induced OA rat	4w	16w	↑cartilage degeneration	Yes	[18]
(0.08,0.8mg		IVDD induced by partial nuclectomy in canines	4w	12w	↓NGF production	No	[19]
Fluvastatin(0.03mg)	PLGA MS	ACLT induced OA rabbit	7d	5w	↓degeneration	No	[13]
IL-1RA (0.25mg)	PLGA MS	ACLT induced OA rat	7,14.21,28d	5w	↓degeneration ↓synovial inflammation	Yes	[14]
AUTOPHAGY ENHANCING Cordycepin(5mg/kg)	Chitosan MS loaded in methacrylatehyaluronic acid hydrogel	ACLT induced OA mice	10d,onces a week	4/8w	↓degeneration ↑ autophagy	Yes	[20]
HYPERTROPHY INHIBITORS Crizotinib (3.5mg/kg)	Chitosan MS in hyaluronic acid –gelatine hydrogel	ACLT induced OA mice	10d,2×/w	4/8w	↓degeneration ↓VEGF production	Yes	[21]
Rac1 inhibitor(0.03mg)	Chitosan MS	ACLT induced OA mice	7d, 1×/w	4,6,8w	↓degeneration-no difference with free drug	Yes	[22]
Kartogenin	Chitosan MS	ACLT-induced OA rat	6 w, 9 w	8 w	↓degeneration	Yes	[24]
Tri-butanoylated N-acetyl-D-galactosamine (1.5 mg)	PLGA MS	MMT-induced OA rat		3 w	↓degeneration	Yes	[25]

MS: Microspheres, MIA: mono-Iodoacetate, ACLT: Anterior Cruciate Ligament Transection, DMM: Partial dissection of the medial meniscus, PEA: Polyesteramide, PCLA: Polycaprolactone, PLGA: Poly (lactic acid-co-glycolic acid), IVDD: Intervertebral disc degeneration,MMT: Medial Meniscus Transection, VEGF: vascular endothelial growth factor d: Days,w: Week.

Firstly, the main hurdle in drug formulation development is the disparity between in-vitro and in-vivo drug release. In in-vitro drug delivery system, the loading and release profiles are tested and it is well tuned in buffers like PBS[27] with or without detergents, with regular sampling over the period which may be lacking in in-vivo release. The local release of hydrophobic drugs in in-vivo was demonstrated by increased release pattern of encapsulated drugs[28] by immersing in natural or mimicked body fluids compared to PBS. The rate of in-vivo drug release may not be altered by changing the buffer over time and it may differ in different tissues and organs, even in degenerative tissues. In in-vitro settings, the degradation of polymers in formulation occurs by chemical hydrolysis and enzymatic cleavage. Hence, the joint/disc characteristics with regard to enzyme activities will affect the polymer degradation and the drug release.

Secondly, most of the promising results with polymer based local drug delivery of OA and IVD was obtained in early stages of degeneration. This indicates that, degenerative progress is prevented rather than reverted. Therefore, early interventions may be more effective.

For this identification of reliable biomarkers or predictive characteristics are required to identify patients in early stage of disease.

The next barrier is related to regulatory and safety issues of the biomaterial based drug delivery system. Even though the local sustained drug delivery is highly safe at the systemic level; local prolonged exposure may cause local side effects which are not induced by systemic administration or direct local injection of the drug. Hence, extensive and expensive systemic toxicity testing is required, which is not justified in this technique as the risks associated are comparatively low due to the low and short systemic exposure to drugs. The final barrier is the injection intervals which may cause problems with high risk of infection in patients with high Body Mass Index (BMI≥25kg/m^2)[30] and in patients with prosthetic surgery due to immune-suppressive effect of corticosteroids[29]

CONCLUSION

Biomaterial based local drug delivery system is a promising step towards the safe and effective treatment for diseases like OA and CLBP with reduced risk of systemic side effects and

reinjection. Long term pain relief is within close reach. More studies on pathology combined with novel drug targets and drugs may help to find a permanent solution for degenerative joint disorders like regeneration. Better understanding of local conditions that affect the drug release pattern and drug retention will help in the rational design of drug formulation. When the difference between articular joints and IVD in health and diseases taken into account, and selecting appropriate in-vivo/ex-vivo models with established disease, a smart treatment development can be achieved with enhanced efficacy.

Acknowledgement

The completion of this undertaking could not have been possible without the assistance of so many helping hands especially our guide Mrs. Lincy George whose contribution should be greatly appreciated and acknowledged.

Above all, we thank God Almighty for his endless love and care.

Abbrevations

OA:Osteoarthritis, CLBP:Chronic Lower Back Pain,MS: Microspheres, MIA: mono-Iodoacetate, ACLT: Anterior Cruciate Ligament Transection, DMM: Partial dissection of the medial meniscus, PEA: Polyesteramide, PCLA: Polycaprolactone, PLGA: Poly (lactic acid-co-glycolic acid), IVDD: Intervertebral discdisease, MMT: Medial Meniscus Transection, VEGF: vascular endothelial growth factor

Reference

1. L.A. Gillum, C. Gouveia, E.R. Dorsey, M. Pletcher, C.D. Mathers, C.E. McCulloch, S.C. Johnston,NIH disease funding levels and burden of disease PLoS One., 6 (2011), pp. 1-9,10.1371/journal.pone. 0016837/View Record in ScopusGoogle Scholar
2. I.A. Jones, R. Togashi, M.L. Wilson, N. Heckmann, C.T. Vangsness Intra-articular treatment options for knee osteoarthritis, Nat. Rev. Rheumatol., 15 (2019), pp.77-90, 10.1038/s41584-018-0123-4,CrossRefView Record in ScopusGoogle Scholar
3. D. Mukerhjee, S.E. Nissen, E.J. Topol, Risk of Cardiovascular Events Associated With Selective Cox Inhibitors, JAMA., 286 (2014), pp. 25-30,View Record in Scopus Google Scholar
4. L.E. Bayliss, D. Culliford, A.P. Monk, S. Glyn-Jones, D. Prieto-Alhambra, A. Judge, C. Cooper, A.J. Carr, N.K. Arden, D.J. Beard, A.J. Price-The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: a population-based cohort study, Lancet., 389 (2017), pp. 1424-1430, 10.1016/S0140-6736(17)30059-4,View Record in ScopusGoogle Scholar
5. C. Birbara, E.J. Dabezies, A.M. Burr, R.J. Fountaine, M.D. Smith, M.T. Brown, C.R. West, R.H. Arends, K.M. Verburg-Safety and efficacy of subcutaneous Tanezumab in patients with knee or hip osteoarthritis ,J. Pain Res. (2018), 10.2147/JPR.S135257,Google Scholar
6. M. Aoki, F. Kato, K. Mimatsu, H. Iwata-Histologic changes in the intervertebral disc after intradiscal injections of methylprednisolone acetate in rabbits, Spine (Phila Pa 1976)., 22 (1997), pp. 127-131,CrossRefGoogle Scholar
7. F. Farad, M.M. Lefevre-Colau, F. Rannou, N. Quintero, A. Nys, Y. Mac, S. Poiraudeau, J.L. Drap, M. RevelRelation of inflammatory modic changes to intradiscal steroid injection outcome in chronic low back painEur. Spine J., 16 (2007), pp. 925-931, 10.1007/s00586-006-0301-y,CrossRefView Record in ScopusGoogle Scholar
8. M.L. Kang, J.Y. Ko, J.E. Kim, G. Il Im,Intra-articular delivery of kartogenin-conjugated chitosan nano/ microparticles for cartilage regeneration Biomaterials., 35 (2014), pp. 9984-9994, 10.1016/j.biomaterials. 2014.08. 042ArticleView Record in ScopusGoogle Scholar
9. J.W. Park, Y.-P. Yun, K. Park, J.Y. Lee, H.-J. Kim, S.E. Kim, H.-R. Song Ibuprofen-loaded porous microspheres suppressed the progression of monosodium iodoacetate-induced osteoarthritis in a rat modelColloids Surf. B. Biointerfaces., 147 (2016), pp. 265-273,10.1016/j.colsurfb.2016.07.050,ArticleCrossRefView Record in ScopusGoogle Scholar
10. H. Abd-Allah, A.O. Kamel, O.A. Sammour-Injectable long acting chitosan/tripolyphosphate microspheres for the intra-articular delivery of Lornoxicam: Optimization and in vivo evaluation Carbohydr. Polym., 149 (2016), pp. 263-273, 10.1016/j.carbpol.2016.04.096,View Record in Scopus Google Scholar
11. Z. Zhang, G. Huang, Intra-articular lornoxicam loaded PLGA microspheres: enhanced therapeutic efficiency and decreased systemic toxicity in the treatment of osteoarthritis Drug Deliv., 19 (2012), pp. 255-263, 10.3109/10717544.2012.700962,CrossRefView Record in ScopusGoogle Scholar
12. A.R. Tellegen, I. Rudnik-Jansen, B. Pouran, H.M. de Visser, H.H. Weinans, R.E. Thomas, M.J.L. Kik, G.C.M. Grinwis, J.C. Thies, N. Woike, G. Mihov, P.J. Emans, B.P. Meij, L.B. Creemers, M.A. TryfonidouControlled release of Celecoxib inhibits inflammation, bone cysts and osteophyte formation in a preclinical model of osteoarthritisDrug Deliv., 25 (2018), pp. 1438-1447, 10.1080/10717544.2018. 1482971,CrossRefView Record in ScopusGoogle Scholar
13. N. Goto, K. Okazaki, Y. Akasaki, K. Ishihara, K. Murakami, K. Koyano, Y. Ayukawa, N. Yasunami, T. Masuzaki, Y. Nakashima ,Single intra-articular injection of Fluvastatin-PLGA microspheres reduces cartilage degradation in rabbits with experimental osteoarthritis, J. Orthop. Res., 35 (2017), pp. 2465-2475, 10.1002/jor.23562,CrossRefView Record in ScopusGoogle Scholar
14. K.A. Elsaid, A. Ubhe, Z. Shaman, G. D'Souza-Intra-articular interleukin-1 receptor antagonist (IL1-ra) microspheres for posttraumatic osteoarthritis: in vitro biological activity and in vivo disease modifying effect, *J. Exp. Orthop*., 3 (2016), 10.1186/s40634-016-0054-4
15. A.R. Tellegen, I. Rudnik-Jansen, M. Beukers, A. Miranda-Bedate, F.C. Bach, W. de Jong, N. Woike, G. Mihov, J.C. Thies, B.P. Meij, L.B. Creemers, M.A. Tryfonidou, Intradiscal delivery of Celecoxib-loaded microspheres restores intervertebral disc integrity in a preclinical canine model J. Control. Release., 286 (2018), pp. 439-450, 10.1016/j.jconrel.2018.08. 019,View Record in ScopusGoogle Scholar

16. A.R. Tellegen, N. Willems, M. Beukers, G.C.M. Grinwis, S.G.M. Plomp, C. Bos, M. van Dijk, M. de Leeuw, L.B. Creemers, M.A. Tryfonidou, B.P. Meij - Intradiscal application of a PCLA–PEG–PCLA hydrogel loaded with Celecoxib for the treatment of back pain in canines: What's in it for humans?/J. Tissue Eng. Regen. Med., 12 (2018), pp. 642-652, 10.1002/term.2483,CrossRefView Record in ScopusGoogle Scholar
17. I. Rudnik-Jansen, S. Colen, J. Berard, S. Plomp, I. Que, M. van Rijen, N. Woike, A. Egas, G. van Osch, E. van Maarseveen, K. Messier, A. Chan, J. Thies, L. Creemers-Prolonged inhibition of inflammation in osteoarthritis by triamcinolone acetonide released from a polyester amide microsphere platform,J. Control. Release., 253 (2017), pp. 64-72, 10.1016/j.jconrel.2017.03.014,Article-Google Scholar
18. I. Rudnik-Jansen, A.R. Tellegen, B. Pouran, K. Schrijver, B.P. Meij, P.J. Emans, E. de Gendt, R.E. Thomas, M.J.L. Kik, H.M. de Visser, H. Weinans, A. Egas, E. van Maarseveen, N. Woike, G. Mihov, J. Thies, M.A. Tryfonidou, L.B. Creemers ,Local controlled release of corticosteroids extends surgically induced joint instability by inhibiting tissue healing,Br. J. Pharmacol, 176 (2019), 10.1111/bph.14817,Google Scholar
19. Rudnik-Jansen, A. Tellegen, M. Beukers, F. Öner, N. Woike, G. Mihov, J. Thies, B. Meij, M. Tryfonidou, L. Creemers-Safety of intradiscal delivery of triamcinolone acetonide by a poly(esteramide) microsphere platform in a large animal model of intervertebral disc degeneration,Spine J., 19 (2019), pp. 905-919,10.1016/j.spinee.2018.10.014Article-Google Scholar
20. C. Xia, P. Chen, S. Mei, L. Ning, C. Lei, J. Wang, J. Zhang, J. Ma, S. Fan Photo-crosslinked HAMA hydrogel with Cordycepin encapsulated chitosan microspheres for osteoarthritis treatment-Oncotarget., 8 (2017), pp. 2835-2849, 10.18632/oncotarget.13748 CrossRefView Record in ScopusGoogle Scholar
21. P. Chen, S. Mei, C. Xia, R. Zhu, Y. Pang, J. Wang, J. Zhang, F. Shao, S. Fan The amelioration of cartilage degeneration by photo-crosslinked GelHA hydrogel and crizotinib encapsulated chitosan microspheres, Oncotarget, 8 (2017), pp. 30235-30251, 10.18632/oncotarget.15750CrossRefView Record in Scopus Google Scholar
22. S. Zhu, P. Lu, H. Liu, P. Chen, Y. Wu, Y. Wang, H. Sun, X. Zhang, Q. Xia, B.C. Heng, Y. Zhou, H.W. Ouyang-Inhibition of Rac1 activity by controlled release of NSC23766 from chitosan microspheres effectively ameliorates osteoarthritis development in vivo,Ann. Rheum. Dis., 74 (2015), pp. 285-293, 10.1136/annrheumdis-2013-203901,CrossRefGoogle Scholar
23. Elron-Gross, Y. Glucksam, I.E. Biton, R. Margalit-A novel Diclofenac-carrier for local treatment of osteoarthritis applying live-animal MRI,J. Control. Release., 135 (2009), pp. 65-70, 10.1016/j.jconrel.2008.12.005,ArticleView Record in ScopusGoogle Scholar
24. M.L. Kang, J.Y. Ko, J.E. Kim, G. Il Im-Intra-articular delivery of kartogenin-conjugated chitosan Nano/microparticles for cartilage regeneration, Biomaterials., 35 (2014), pp. 9984-9994, 10.1016/j. biomaterials.2014.08.042,Download PDFView Record in ScopusGoogle Scholar
25. C. Kim, O.H. Jeon, D.H. Kim, J.J. Chae, L.Shores, N. B ernstein, R. Bhattacharya, J.M.Coburn, K.J. Yarema, J. H. Elisseeff-Local delivery of a carbohydrate analog for reducing arthritic inflammation and rebuilding cartilage, Biomaterials. (2016), 10.1186/s13075-015-0625-2,View Record in Scopus
26. H.P. French, K.M. Smart, F. Doyle-Prevalence of neuropathic pain in knee or hip osteoarthritis: A systematic review and meta-analysis,Semin. Arthritis Rheum., 47 (2017), pp. 1-8, 10.1016/j.semarthrit.2017.02.008View Record in ScopusGoogle Scholar
27. B.S. Zolnik, D.J. Burgess-Evaluation of in vivo-in vitro release of dexamethasone from PLGA microspheres. Control. Release., 127 (2008), pp. 137-145, 10.1016/j.jconrel.2008.01.004 ArticleDownload PDFView Record in ScopusGoogle Scholar
28. D. Svirskis, W. Marti, P. Bhusal, M. Sharma, R.Stowers, S.W. Young-Analysis of the Postoperative Periarticular Environment and Influence on Sustained Drug Delivery From a Gel Formulation,J. Pharm. Sci. (2018), 10.1016/j.xphs.2018.05.004/Google Scholar
29. C. Xu, H. Peng, R. Li, W. Chai, X. Li, J. Fu, K.Liu, B. Yu, C. Jia, J. Chen Risk factors and clinical characteristics of deep knee infection in patients with intra-articular injections: A matched retrospective cohort analysis,Semin. Arthritis Rheum., 47 (2018), pp. 911-916, 10.1016/j.semarthrit.2017.10.013,View Record in ScopusGoogle Scholar
30. A.W. Chambers, K.W. Lacy, M.H.L. Liow, J.P.M.Mana lo, A.A. Freiberg, Y.-M. Kwon-Multiple Hip Intra-Articular Steroid Injections Increase Risk of Periprosthetic Joint Infection Compared With Single Injections,J. Arthroplasty., 32 (2017), pp. 1980-1983, 10.1016/j.arth.2017.01.030 ScopusGoogle Scholar

How to cite this article:

Deslin Davis *et al* (2021) 'New Innovations In Management of Degenerative Joint Diseases With Old Drugs: A Review', *International Journal of Current Advanced Research,* 10(07), pp. 24749-24753.
DOI: http://dx.doi.org/10.24327/ijcar.2021.4932.24753

****