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DEVELOPMENT AND EVALUATION OF NOVEL PHARMACEUTICAL FORMULATIONS FOR THE MANAGEMENT OF CHRONIC MUSCULOSKELETAL PAIN AND JOINT DISORDERS

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ABSTRACT

Chronic musculoskeletal pain and joint disorders are major contributors to disability and reduced quality of life worldwide. Although conventional pharmacological therapies remain the primary treatment approach, their long-term use is often limited by systemic adverse effects, poor target specificity, and inadequate therapeutic efficacy, necessitating the development of advanced pharmaceutical formulations. This review aimed to synthesize current evidence on the development and evaluation of novel pharmaceutical formulations for the management of chronic musculoskeletal conditions, with particular emphasis on innovative drug delivery systems, targeted therapeutic approaches, and emerging formulation strategies. A comprehensive review of peer-reviewed literature was conducted using databases including ScienceDirect, DOAJ, Web of Science, and Google Scholar. Relevant studies focusing on pharmaceutical formulation development, drug delivery technologies, targeted delivery systems, nanotechnology-based formulations, and herbal therapeutics for musculoskeletal disorders were systematically identified, evaluated, and organized into major thematic categories. The review demonstrated that topical, transdermal, nanotechnology-based, herbal, and targeted drug delivery systems provide significant improvements in drug bioavailability, localized delivery, sustained release, and therapeutic efficacy while reducing systemic adverse effects. Emerging technologies such as cubosomes, magnetically targeted nanocomposites, chronotherapeutic formulations, and advanced gel systems further enhance treatment performance and patient adherence. Novel pharmaceutical formulations represent promising alternatives to conventional pharmacotherapy for chronic musculoskeletal conditions

KEYWORDS: Chronic musculoskeletal pain, Joint disorders, Pharmaceutical formulations, Drug delivery systems, Targeted therapeutics

1. INTRODUCTION

Chronic musculoskeletal pain and joint disorders are among the most prevalent conditions leading to chronic disability worldwide, and are linked to considerable impairments of physical function, walking ability and quality of life. Many conditions of chronic pain are associated with OA such as RA and chronic low back pain as well as inflammatory and degenerative musculoskeletal diseases; these include persistent pain, stiffness and progressive loss of joint function. These conditions are chronic, and can lead to lower productivity at work, higher use of health services and high socioeconomic costs. Therefore, the treatment of the disease in the clinic is focused on the symptoms, on preventing the progression of the disease and on improving the quality of life of the patient. Chronic musculoskeletal pain constitutes not only an important clinical problem in human health care but also an important veterinary therapeutic problem: therapeutic approaches vary between countries highlighting the need for effective and tailored treatments in different clinical contexts [1]. In addition, biomechanical factors such as abnormal postural loading and increased mechanical stress have also been recognized as important contributors to the development and progression of MSDs [2] further highlighting the importance of a comprehensive therapeutic approach for MSDs that addresses structural and functional abnormalities.

The interactions between peripheral tissue injury, neuronal sensitization and altered pain signaling pathways and inflammatory mediators is very complex, and the patho-physiology of chronic musculoskeletal pain is dynamic. The long-term inflammation triggers various molecular pathways involved in cartilage degradation, synovial inflammation and joint

damage. This chronic activation of peripheral and central pain pathways in turn leads to enhanced pain sensitivity and a tendency towards chronic pain. Recently, novel molecules regulators (e.g. FKBP51) have been discovered for different biological processes, which serve as novel targets for drug development in relation to persistent pain mechanisms [3]. Similarly, systematic evaluation of dextrose prolotherapy has shown that some individuals suffering from chronic musculoskeletal pain have benefit from the use of regeneration therapy, and that it can be combined with general and conventional drug therapy.

Important clinical shortcomings still remain in traditional clinical treatment, despite great advances in pharmacotherapy. Oral non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, corticosteroids and opioids are the main classes of drugs that have proven effective for pain management; but long-term use of these can cause gastrointestinal irritation, cardiovascular side effects, renal toxicity, drug dependence and decreased adherence by patients. They have led to the development of new pharmaceuticals that have the potential to improve the effectiveness and reduce the toxicity of treatment methods. The formulation science is fundamental to ensure the drug performance, convenience, and quality of the dosage form, with some advanced formulation strategies, including co-processing excipients for ODTs, demonstrating the importance of formulation science to improving clinical outcomes [5].

The drug delivery technologies have also grown significantly in revolution since then which has revolutionized the pain management to deliver the drug more accurately, biologically and with controlled release. The transdermal drug delivery system has attracted a considerable interest due to the benefit of sustained drug delivery and the reduced systemic drug exposure, and therefore improved patient compliance. Experimental research has shown the local anti-inflammatory effects of transdermal NSAID formulations to be more pronounced, and clinically significant, when applied to inflamed joint tissues, thus supporting their use in musculoskeletal disorders [6]. Likewise, innovative platforms have developed with the use of cannabinoids that are able to deliver an analgesic and anti-inflammatory agent in a controlled manner with fewer side effects compared to traditional delivery methods [7]. These advancements underscore the growing importance of pharmaceutical engineering within therapeutic systems to manage chronic pain in a safe, effective manner.

Although tremendous progress has been achieved, some challenges remain until these more complex pharmaceutical formulations can be routinely used in the clinic. The factors that remain to impact the successful clinical translation include formulation stability, manufacturing scalability, regulatory approval, long-term safety evaluation and cost-effectiveness. Furthermore, there is still a need for a correct therapeutic monitoring to evaluate the therapeutic response and side effects of the new therapeutic interventions. Improvements in the field of advanced imaging evaluation have made clear the need for comprehensive assessment of the treatment outcome in the current therapeutic landscape and the need for effective strategies to monitor treatment that can make accurate assessments. Therefore, there is a need for additional studies in interdisciplinary research of pharmaceutical sciences, pharmaceutical products delivery technology, pain biology and clinical medicine to develop more successful and personalized therapeutic strategies.

Thus, the purpose of the present comprehensive review is to consolidate current knowledge about formulation development and evaluation of novel delivery systems to treat chronic musculoskeletal pain and joint diseases. Special emphasis will be given to novel formulation strategies, new drug delivery systems, targeted therapeutic strategies, current problems and future challenges in the field that could result in improved pain management, greater drug safety and advancement of next generation drugs for pain management.

2. METHODOLOGY

A comprehensive review approach was used for the novel formulation of pharmaceutical products for chronic musculoskeletal pain and/or joint disorders in this study. The relevant literature was collected from peer reviewed journals, review articles, clinical studies and trustworthy scientific publications and a few basic scientific publications were selected to provide scientific background. The data base search was carried out in the databases of ScienceDirect, DOAJ, Web of Science and Google Scholar with the following key words *chronic musculoskeletal pain, joint disorders, pharmaceutical formulations, drug delivery systems, topical formulations, transdermal drug delivery, nanotechnology, osteoarthritis, rheumatoid arthritis, pain management*. Sources were selected for relevance to formulation development and drug delivery strategies as well as the pharmacological evaluation and clinical use in chronic musculoskeletal diseases. The literature reviewed is then sorted into thematic major groups that would then help guide the synthesis and discussion which is presented in this article.

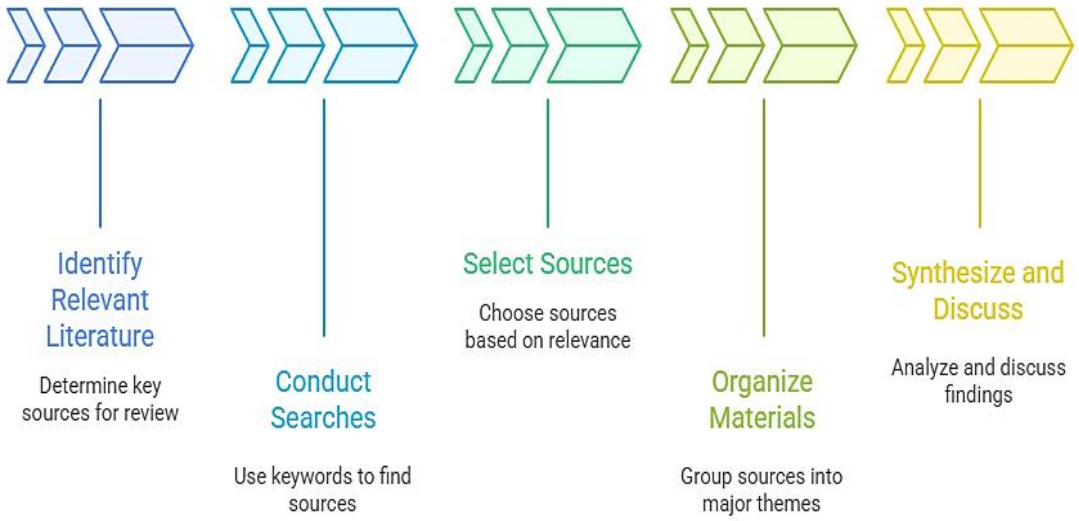

Figure 1. Overview of the Comprehensive Review Process

The entire review system employed in this study is shown below in Figure 1. The major stages involved were to identify relevant literature related to pharmaceutical formulations for musculoskeletal disorders, systematically search for literature from several databases using predefined search terms, select papers based on their scientific relevance and quality, arrange the literature by formulation type and therapeutic application, and finally make a synthesis of the literature to highlight the current advances, clinical relevance and future directions. This approach allowed for a comprehensive and structured evaluation of the current knowledge on innovative pharmaceutical formulations for chronic musculoskeletal pain and joint disorders .

3. RESULTS

3.1 Conventional Pharmaceutical Approaches and Their Limitations

Traditional pharmacologic treatments continue to be the foundation for the treatment of chronic musculoskeletal pain and joint disorders. There are a number of prescription medications that are commonly used to help reduce pain, inflammation, and disease progression, such as oral non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, opioids, and disease-modifying anti-rheumatic drugs (DMARDs). Although advances in pharmaceutical technology have led to better diclofenac formulations and topical NSAIDs, conventional oral formulations still have gastrointestinal, cardiovascular, renal and systemic side effects, especially if taken over long periods of time [9-11]. Furthermore, it is important to use safer and more specific therapeutic approaches to ensure better long-term therapeutic results, which is also being highlighted by the pharmacological management guidelines [12,13]. These constraints have driven the creation of novel formulations of pharmaceutical products in order to increase the bioavailability of the active substance, lower systemic toxicity, and increase patient compliance. The main conventional therapeutic strategies and the limitations are summarized in Table 1.

Table 1. Conventional Pharmaceutical Therapies for Chronic Musculoskeletal Pain and Their Limitations

Therapy	Primary Application	Advantages	Major Limitations	Supporting References
Oral NSAIDs	Pain and inflammation control	Rapid analgesic and anti-inflammatory effects	Gastrointestinal irritation, cardiovascular and renal adverse effects during prolonged use	[9],[11]
Topical NSAIDs	Localized musculoskeletal pain	Reduced systemic exposure and improved local action	Limited skin penetration and variable therapeutic efficacy	[10]
Corticosteroids	Acute inflammatory joint disorders	Potent anti-inflammatory activity	Long-term toxicity, osteoporosis, metabolic complications	[12]
Opioids	Moderate-to-severe chronic pain	Effective short-term pain relief	Dependence, tolerance, abuse potential, adverse neurological effects	[14]
Disease-Modifying Anti-Rheumatic Drugs (DMARDs)	Rheumatoid arthritis and inflammatory joint diseases	Slow disease progression and joint preservation	Delayed onset of action, adverse effects, continuous monitoring required	[12]

Conventional Pharmaceutical Management	Overall management of musculoskeletal disorders	Established clinical use and broad availability	Poor patient compliance, repeated dosing, limited targeted drug delivery	[15]

In addition to controlling symptoms and managing the disease, conventional pharmaceutical treatment has other limitations, such as systemic toxicity, lack of target specificity, and poor long-term compliance with the treatment, which have led to the development of advanced pharmaceutical formulations and novel drug delivery systems for chronic musculoskeletal pain and joint disorders [15] (Table 1).

3.2 Novel Topical and Transdermal Drug Delivery Systems

The development of novel topical and transdermal drug delivery systems have proven to be effective alternatives to traditional oral medications for chronic musculoskeletal pain and joint disorders. These formulations can optimize the delivery of a drug to a specific area, reduce systemic drug exposure, and increase the acceptance of the patient. Advancements made have been therapeutic gels, film-forming sprays, transdermal patches, herbal aerosols and natural polymer systems which allow sustained drug delivery and enhanced skin permeation. Ethosomal gels, optimized topical formulations have also been utilized to deliver anti-inflammatory agents such as curcumin and cyclosporine to treat RA, while innovative film-forming sprays and topical gels have shown to be stable and therapeutic for MS pain management [16–18]. In addition, the improved permeation technologies have led to better bioavailability of drugs at the site of application and a decreased systemic uptake of drugs. The main topical and transdermal pharmaceutical formulations being studied for musculoskeletal disorders are summarized in Table 2.

Table 2. Recent Topical and Transdermal Formulations for Musculoskeletal Pain Management

Formulation	Therapeutic Application	Key Advantages	Major Findings	Supporting References
Therapeutic topical gel	Osteoarthritis and chronic inflammatory pain	Localized drug delivery with reduced systemic exposure	Improved anti-inflammatory and analgesic activity	[16]
Film-forming spray	Musculoskeletal pain management	Uniform drug distribution, prolonged residence time	Demonstrated formulation stability and effective pain management	[17]
Natural polymer-based transdermal system	Musculoskeletal disorders	Controlled drug release and enhanced skin permeation	Improved transdermal therapeutic potential	[19]
Advanced topical drug delivery systems	Osteoarthritis	Improved bioavailability and patient compliance	Enhanced local therapeutic efficacy compared with conventional formulations	[20]
Herbal aerosol formulation	Arthritis	Easy topical administration with herbal therapeutics	Demonstrated potential as an alternative topical formulation	[21]
Ethosomal gel	Rheumatoid arthritis	Enhanced transdermal penetration of curcumin and cyclosporine	Improved drug permeation and preclinical therapeutic performance	[18]
Topical diclofenac formulations	Acute and chronic musculoskeletal pain	Reduced systemic adverse effects	Effective local pain management with improved safety profile	[17]

As shown in Table 2, the modern formulation of topical and transdermal preparations have significantly advanced the localized delivery of the drugs by increasing the skin permeation, drug release control and minimizing the systemic toxicity. Growing as safer and more effective alternatives to chronic musculoskeletal pain and joint disorders, the pharmaceutical advances support their role.

3.3 Nanotechnology-Based Drug Delivery Systems

The advent of nanotechnology-based drug delivery systems has led to significant improvements in the management of chronic musculoskeletal pain and joint disorders, particularly with regard to drug solubility, stability, delivery into tissue, and targeted delivery. In order to overcome the limitations of conventional formulations, various nanocarriers have been developed such as nanoparticles, liposomes, ethosomes, cubosomes, ultra-deformable vesicles and polymeric nanocarriers. These systems increase the amount of drug that is deposited in the local tissue, increase drug release and minimize systemic side effects. Ethosomal and cubosomal formulations are reported to provide enhanced transdermal permeation of anti-inflammatory drugs, ultra-deformable vesicles and polymer-based carriers are efficient in transdermal penetration to overcome the barrier property of the skin. Recent formulation strategies have also shown enhanced therapeutic efficacy in the treatment of OA and RA, through enhanced bioavailability and sustained therapeutic levels at the site of action. Table 3 gives an overview of the various musculoskeletal drugs and their associated major nanotechnology-based pharmaceutical formulations.

Table 3. Nanotechnology-Based Drug Delivery Systems and Their Therapeutic Advantages

Drug Delivery System	Pharmaceutical Characteristics	Therapeutic Advantages	Clinical/Application Area	Supporting References
Nanoparticles	Improved drug encapsulation and stability	Enhanced bioavailability and controlled drug release	Osteoarthritis	[15]
Liposomal formulations	Phospholipid-based carrier system	Improved localized drug delivery with reduced toxicity	Rheumatoid arthritis	[22]
Ethosomal gel	Ethanol-containing flexible vesicles	Enhanced transdermal permeation of curcumin and cyclosporine	Rheumatoid arthritis	[18]
Cubosomes	Lipid nanostructured carriers	Sustained drug release and improved skin penetration	Transdermal colchicine delivery	[23]
Ultra-deformable vesicles	Highly flexible vesicular system	Efficient penetration across the skin barrier	Musculoskeletal pain management	[24]
Polymeric nanocarriers	Biocompatible polymer-based delivery system	Targeted drug delivery with prolonged therapeutic effect	Osteoarthritis and inflammatory joint disorders	[20]

As explained in Table 3, the use of drug delivery systems containing nanoparticles offers significant benefits compared to conventional drug delivery systems: increased targeted drug delivery, increased transdermal permeation, longer therapeutic activity and lower systemic side effects. The novel platforms studied here could provide a means of developing safer and effective chronic musculoskeletal pain and joint disorder pharmaceutical formulations.

3.4 Herbal and Natural Product-Based Pharmaceutical Formulations

Natural products and herbs are being used as pharmaceutical formulations as alternative methods to treat chronic musculoskeletal pain and joint disorders due to their anti-inflammatory, analgesic and antioxidant activity. The formulation technologies have reduced the instability and increased the bioavailability and therapeutic effects of phytoconstituents like curcumin, boswellic acids and turmeric. New formulations such as ethosomal gels, herbal aerosol and formulations containing nanoscience have improved transdermal permeation, as well as targeted drug delivery and minimized systemic effects. The methods provide long-lasting therapeutic activity and better compliance by the patient than conventional herbal preparations. Moreover, in recent years, formulation approaches have been developed which have shown great promise in enhancing the clinical management of arthritis, particularly in the area of osteoarthritis and rheumatoid arthritis, where poor solubility and limited absorption of many natural compounds has been a problem. The major herbal and natural product based pharmaceutical formulations are summarized in Table 4.

Table 4. Herbal and Natural Product-Based Formulations for Joint Disorders

Formulation	Natural Active Component	Therapeutic Benefits	Application	Supporting References
Ethosomal gel	Curcumin and cyclosporine	Enhanced transdermal permeation and localized anti-inflammatory activity	Rheumatoid arthritis	[18]
Herbal aerosol	Herbal extracts	Convenient topical administration with analgesic and anti-inflammatory effects	Arthritis	[21]
Curcumin formulations	Curcumin	Improved bioavailability and sustained anti-inflammatory activity	Chronic inflammatory and joint disorders	[26]
Boswellic acid delivery system	Boswellic acids (Casperome®)	Enhanced absorption and improved symptom management	Musculoskeletal disorders	[27]
Turmeric formulation	Turmeric extract	Reduced chronic knee pain and improved functional outcomes	Chronic knee pain	[28]
Turmeric–sesame formulation	Turmeric with sesame	Effective analgesic activity and improved pain relief	Acute musculoskeletal pain	[29]
Nano-enabled herbal formulations	Herbal phytoconstituents	Improved stability, targeted delivery, and therapeutic efficacy	Rheumatoid arthritis	[30]

As indicated in Table 4, in recent years, the formulation of herbal and natural pharmaceuticals has greatly improved the delivery and therapeutic efficacy of bioactive compounds. These formulations have improved the bioavailability, drug release and localized delivery mechanism, which has boosted the clinical usefulness of these formulations in the treatment of chronic musculoskeletal pain and joint disorders, overcoming numerous drawbacks of traditional herbal formulations.

3.5 Advanced Targeted and Controlled Drug Delivery Strategies

Chronic musculoskeletal pain and joint disorders are increasingly challenging because of the need for targeted and controlled drug delivery, improved site-specific delivery, and the need to optimize duration of drug delivery as well as minimize systemic adverse effects. Some of the modern platforms in the pharmaceutical area contain targeted drug delivery systems, sustained release formulations, colon targeted delivery, injectable formulations, magnetically targeted carriers and smart delivery technologies. These systems help to optimize therapeutic response by sustaining the appropriate level of the therapeutic agent at the site of inflammation, while decreasing the number of doses and patient compliance. Nanocarriers and matrix-based formulation of anti-inflammatory agents have shown to yield better pharmacokinetic profiles and controlled release characteristics. In recent years, interdisciplinary strategies have been further contributing to the development of combination medicines and novel platforms for drug delivery, helping to optimize treatment outcomes in chronic musculoskeletal conditions. The key drug delivery strategies are briefly outlined below in Table 5.

Table 5. Advanced Drug Delivery Platforms for Chronic Musculoskeletal Disorders

Drug Delivery Strategy	Pharmaceutical Characteristics	Therapeutic Advantages	Clinical/Application Area	Supporting References
Targeted drug delivery systems	Site-specific drug transport	Improved therapeutic efficacy with reduced systemic toxicity	Rheumatoid arthritis	[22]
Sustained-release formulations	Controlled and prolonged drug release	Reduced dosing frequency and prolonged analgesic activity	Osteoarthritis	[15]
Colon-targeted matrix mini-tablets	Chronotherapeutic drug release	Improved synchronization with disease symptoms	Rheumatoid arthritis	[31]
Injectable combination formulations	Localized administration of therapeutic agents	Enhanced drug retention and reduced systemic exposure	Musculoskeletal disorders	[32]
Magnetically targeted nanocomposite system	Magnet-guided targeted delivery	Improved localization and enhanced analgesic drug delivery	Pain management	[25]
Smart pharmaceutical delivery platforms	Stimuli-responsive and controlled drug release	Optimized therapeutic response and improved patient compliance	Chronic musculoskeletal disorders	[14]

As illustrated in Table 5, the advanced targeted and controlled drug delivery systems present a significant advantage over the conventional pharmaceutical delivery systems as they allow for the precise localization of the drug, sustained therapeutic release and higher drug efficacy. These new platforms are a significant step forward in managing chronic musculoskeletal pain and joint disorders safely and efficiently.

3.6 Emerging Pharmacological Targets and Future Therapeutic Innovations

Innovations in this field of pharmaceutical research have led to the discovery of several new pharmacological targets and novel formulation approaches for enhancing the care of chronic musculoskeletal pain and joint disease. New therapeutic strategies involve active control of pain signal transduction pathways with a lessened constraint of the classical analgesics. The use of TRPV1-targeted drugs, non-opioid analgesics and next generation of anti-inflammatory drugs have shown therapeutic potential in chronic pain management. Furthermore, combination products that include several active ingredients as well as personalized pharmaceutical approaches are being developed to enhance the efficacy, safety, and patient-specific treatment outcomes. These innovations, along with advances in pharmaceutical technology and targeted pharmaceutical delivery will be expected to contribute to the evolution of more effective and tailored treatment of chronic musculoskeletal diseases. The emerging important targets and new therapeutic innovations are presented in Table 6.

Table 6. Emerging Pharmacological Targets and Novel Pharmaceutical Developments

Therapeutic Innovation	Mechanism/Characteristics	Therapeutic Potential	Clinical/Application Area	References

TRPV1-targeted drugs	Modulation of TRPV1 pain receptors	Reduced chronic pain and improved analgesia	Chronic pain conditions	[33]
Novel non-opioid analgesics	Alternative pain modulation pathways	Effective pain control with reduced opioid dependence	Chronic musculoskeletal pain	[34]
Novel anti-inflammatory drug development	Advanced pharmaceutical technologies for improved formulations	Enhanced efficacy and improved safety profile	Musculoskeletal disorders	[34]
Combination pharmaceutical formulations	Multiple active agents within a single formulation	Improved therapeutic effectiveness and synergistic action	Musculoskeletal disorders	[32]
Personalized pharmaceutical formulations	Patient-oriented formulation and delivery strategies	Optimized treatment outcomes and improved adherence	Chronic joint disorders	[35]
Future formulation strategies	Integration of advanced drug delivery systems with innovative therapeutic targets	Safer, targeted, and sustained pain management	Chronic musculoskeletal pain and joint disorders	[35]

As indicated in Table 6, a future promising way to manage chronic musculoskeletal pain and joint disorder is the use of emerging pharmacological targets and innovative pharmaceutical formulations. The use of novel molecular targets, non-opioid analgesics, combination therapies, and personalized formulation strategies will likely lead to enhanced therapeutic efficacy and reduced adverse effects, providing for long-term disease management.

4. DISCUSSION

The results of this extensive review show that the management of chronic musculoskeletal pain and joint diseases has undergone significant changes from traditional oral drug formulations to innovative approaches aimed at enhancing therapeutic efficacy, safety, and adherence in patients. The use of oral NSAIDs, corticosteroids and other conventional analgesics is important in clinical management, but longterm usage is often restricted due to systemic side effects and variable therapeutic effects. As a result, recent drug delivery research has turned to the design of localized, targeted, and controlled drug delivery systems for effective drug delivery to diseased tissues and reduced off-target toxicity. This is significant in the science of drug formulation and is a key step forward in chronic pain management.

This review's findings corroborate the body of evidence that topical NSAID preparations are an effective alternative to systemic NSAID therapy for a large number of musculoskeletal conditions. McMahon et al. [36] recommend that topical NSAIDs be considered as a first line drug for focal musculoskeletal pain because they are clinically effective and significantly reduce systemic drug exposure and systemic drug effects. The same was noted in formulations that were reviewed, where topical gels, transdermal and local pharmaceutical formulations showed better safety profile when compared with other formulations and at the same time were shown to have the same level of analgesic activity. Similarly, in the recent past, two phase formulations of sodium diclofenac and camphor have been found to exhibit better drug delivery properties and pharmaceutical performance, thus confirming the clinical usefulness of optimum topical dosage forms [37].

One of the growing factors is the advanced drug delivery systems, which are a solution to the problems faced by conventional pharmaceuticals. Nanotechnology-based carriers, such as cubosomes and magnetically responsive nanocomposites, have shown better ability to encase and retain drugs, to provide a sustained release of them, and to target therapeutic agents. For instance, cubosomal formulation could significantly increase the transdermal delivery of colchicine and the magnetite loaded with alginate nanocomposites could result in targeted delivering of the analgesic, as reported by Nasr et al. [23] and Das et al. [25] respectively. Controlled and localized drug delivery is a central objective in the chronic treatment of musculoskeletal diseases; the technologies described herein indicate that it may be possible to achieve effective treatment in the future with decreased systemic toxicity.

The review also highlights the increasing contribution of the individual therapeutic strategies employed in inflammatory joint diseases, such as rheumatoid arthritis. Recently, targeted delivery of anti-inflammatory agents has been developed that enables targeted delivery to inflamed tissue to increase therapeutic efficacy and minimize systemic exposure. Gorantla et al. [22] highlighted the significant advancements in targeted delivery platforms for RA, highlighting their potential role in enhancing drug deposition at disease sites. Likewise, chronotherapeutic matrix mini-tablets designed for ileo-colonic delivery have shown to be effective in synchronising drug release with circadian changes in disease activity, which is another promising approach for the optimisation of therapeutic efficacy [31].

Phytopharmaceutical formulations with anti-inflammatory and analgesic effects have also proven to be valuable complementary treatments for musculoskeletal disorders, thanks to the properties of their active ingredients, which are of

vegetable origin. Herbal combinations in new pharmaceutical products have presented better stability, bioavailability, and palatability than traditional herbal products. Naga Sai Chakradhar et al. [38] have identified the importance of formulation technologies in the development of herbal drugs for arthritis, which suggest that using the proper delivery systems can help to address many of the potential limitations associated with the use of phytotherapeutic drugs.

Although there is promising development, a number of factors remain to impact the effective implementation of new drug formulations into clinical practice. The complexity of the manufacturing process, formulation stability, large scale production, regulatory approval, long term safety evaluation and economic viability are still significant hurdles in the commercialization. In addition, many advanced drug delivery platforms are still under investigation, mostly in preclinical studies, and demand in-depth clinical trials to validate the longer term effectiveness and security of these devices in various patient populations. There is also a limited number of formulation methods that can be standardized and there has not yet been a comparative evaluation of the different delivery systems, making it difficult to compare therapeutic outcomes.

Research into drug delivery systems in the future should focus on multifunctional drug delivery platforms that enable targeted delivery, controlled release, and personalized therapeutic interventions in a single delivery system. The better incorporation of nanotechnology, biomaterials, chronotherapy, and precision medicine could provide further optimization of treatment strategies for chronic musculoskeletal pain and joint disorders. Ongoing partnerships between pharmaceutical scientists, clinicians, biomaterial engineers, and regulators are crucial to ensure that new formulations are safely and effectively developed into therapies that can be used in the clinic for long-term benefit to patients.

5. CONCLUSION

Chronic musculoskeletal pain and joint pain due to their multi-factorial pathogenesis and the limitations of traditional pharmacologic interventions remain important clinical and therapeutic challenges. This review illustrates the significant advances in recent years in the development of innovative drug delivery systems, which have broadened the therapeutic opportunities and improved the bioavailability, targeted tissue delivery, controlled release and patient adherence of the drug. There are novel formulations of topical, transdermal, nanotechnology-based, herbal and targeted pharmaceuticals that have demonstrated great promise in increasing the therapeutic efficacy while reducing systemic side effects often seen with traditional oral medicines. In addition, the use of nanocarriers, cubosomes, magnetically targeted and chronotherapeutic systems are examples of emerging drug delivery technologies that continue to demonstrate the importance of formulation science in developing novel approaches to pain management. Although these improvements have been made, issues of formulation stability, scaling up manufacturing, regulatory clearance, extended duration of safety, and clinical translation are important points to consider before the widespread implementation of these technologies. Further studies are needed to integrate advanced biomaterials, nanotechnology, personalised drug delivery and precision medicine methods into therapeutic interventions, which will be safer and more effective. Overall, there is a continued need for new innovations in pharmaceutical product formulation to facilitate management of chronic musculoskeletal pain and joint disorders, which will have a lasting impact on clinical outcomes, patient quality of life and the sustainability of pain management strategies.

REFERENCES

1. Adrian DE, Rishniw M, Scherk M, Lascelles BD. Prescribing practices of veterinarians in the treatment of chronic musculoskeletal pain in cats. Journal of feline medicine and surgery. 2019 Jun;21(6):495-506.
2. Kee D. Development and evaluation of the novel postural loading on the entire body assessment. Ergonomics. 2021 Dec 2;64(12):1555-68.
3. Maiarù M, Morgan OB, Mao T, Breitsamer M, Bamber H, Pöhlmann M, Schmidt MV, Winter G, Hausch F, Géranton SM. The stress regulator FKBP51: a novel and promising druggable target for the treatment of persistent pain states across sexes. Pain. 2018 Jul 1;159(7):1224-34.
4. Hauser RA, Lackner JB, Steilen-Matias D, Harris DK. A systematic review of dextrose prolotherapy for chronic musculoskeletal pain. Clinical medicine insights: arthritis and musculoskeletal disorders. 2016 Jan;9:CMAMD-S39160.
5. Abdelmonem R, Abdellatif MM, Al-Samadi IE, El-Nabarawi MA. Formulation and evaluation of baclofen-meloxicam orally disintegrating tablets (ODTs) using co-processed excipients and improvement of ODTs performance using six sigma method. Drug Design, Development and Therapy. 2021 Oct 16:4383-402.
6. Baranowski DC, Buchanan B, Dwyer HC, Gabriele JP, Kelly S, Araujo JA. Penetration and efficacy of transdermal NSAIDs in a model of acute joint inflammation. Journal of pain research. 2018 Nov 13:2809-19.
7. Bruni N, Della Pepa C, Oliaro-Bosso S, Pessione E, Gastaldi D, Dosio F. Cannabinoid delivery systems for pain and inflammation treatment. Molecules. 2018 Sep 27;23(10):2478.
8. Kwak JJ, Tirumani SH, Van den Abbeele AD, Koo PJ, Jacene HA. Cancer immunotherapy: imaging assessment of novel treatment response patterns and immune-related adverse events. Radiographics. 2015 Mar;35(2):424-37.
9. Altman R, Bosch B, Brune K, Patrignani P, Young C. Advances in NSAID development: evolution of diclofenac products using pharmaceutical technology. Drugs. 2015 May;75(8):859-77.
10. Wiffen PJ, Xia J. Systematic review of topical diclofenac for the treatment of acute and chronic musculoskeletal pain. Current medical research and opinion. 2020 Apr 2;36(4):637-50.
11. Atzeni F, Masala IF, Sarzi-Puttini P. A review of chronic musculoskeletal pain: central and peripheral effects of diclofenac. Pain and therapy. 2018 Dec;7(2):163-77.
12. Gerard B, Bailly F, Trouvin AP. How to treat chronic pain in rheumatic and musculoskeletal diseases (RMDs)–A pharmacological review. Joint Bone Spine. 2024 Jan 1;91(1):105624.

13. Shi C, Ye Z, Shao Z, Fan B, Huang C, Zhang Y, Kuang X, Miao L, Wu XA, Zhao R, Chen X. Multidisciplinary guidelines for the rational use of topical non-steroidal anti-inflammatory drugs for musculoskeletal pain (2022). Journal of Clinical Medicine. 2023 Feb 15;12(4):1544.
14. Tékus V, Borbély É, Goebel A, Baron R, Hajna Z, Helyes Z. Novel approaches for drug development against chronic primary pain: A systematic review. British Journal of Pharmacology. 2025 Nov 14.
15. Kumar M, Dogra R, Mandal UK. Novel formulation approaches used for the management of osteoarthritis: a recent review. Current Drug Delivery. 2023 Aug 1;20(7):841-56.
16. Benetti AA, Ng CY, Qiuyi CC, Suhaimi A, Jiang Y, Wen KT, Thwin MT, Teissier S, Moon LF, Toh WS, Benetti C. Novel therapeutic topical gel approach for chronic inflammation and pain management in osteo-and viral-arthritis. Biomedicine & Pharmacotherapy. 2026 Mar 1;196:119116.
17. Angsusing J, Samee W, Tadtong S, Mangmool S, Okonogi S, Toolmal N, Chittasupho C. Development, optimization, and stability study of a Yataprasen film-forming spray for musculoskeletal pain management. Gels. 2025 Jan 15;11(1):64.
18. Gharat S, Momin M, Panchal U, Omri A. Novel ethosomal gel formulation for enhanced transdermal delivery of curcumin and cyclosporine: a preclinical approach to rheumatoid arthritis management. Drug Delivery. 2025 Dec 31;32(1):2512620.
19. Zhang Y, Wang G, Zhou Y. Therapeutic potential of natural polymer-based transdermal drug delivery system for musculoskeletal disorders. Biomaterials Translational. 2025 Sep 22;6(3):314.
20. Patil P, Nene S, Shah S, Singh SB, Srivastava S. Exploration of novel drug delivery systems in topical management of osteoarthritis. Drug Delivery and Translational Research. 2023 Feb;13(2):531-46.
21. Aiyalu R, Subramaniam I, Govindarajan A, Ramasamy A. Formulation and Evaluation of Novel Herbal Aerosol for Arthritis. J. Rheumatol. Arthritic Dis. 2017;2:1-2.
22. Gorantla S, Singhvi G, Rapalli VK, Waghule T, Dubey SK, Saha RN. Targeted drug-delivery systems in the treatment of rheumatoid arthritis: recent advancement and clinical status. Therapeutic delivery. 2020 Apr 1;11(4):269-84
23. Nasr M, Younes H, Abdel-Rashid RS. Formulation and evaluation of cubosomes containing colchicine for transdermal delivery. Drug delivery and translational research. 2020 Oct;10(5):1302-13.
24. Kaul S, Jain N, Nagaich U. Ultra deformable vesicles for boosting transdermal delivery of 2-arylpropionic acid class drug for management of musculoskeletal pain. Journal of Pharmaceutical Investigation. 2022 Mar;52(2):217-31.
25. Das A, Sengupta P, Chatterjee S, Khanam J, Mondal PK, Romero EL, Manakhov AM, Thomas S, Mahmood S, Ghosal K. Development and evaluation of magnetite loaded alginate beads based nanocomposite for enhanced targeted analgesic drug delivery. Magnetochemistry. 2025 Feb 13;11(2):14.
26. Kunnumakkara AB, Hegde M, Parama D, Girisa S, Kumar A, Daimary UD, Garodia P, Yenisetti SC, Oommen OV, Aggarwal BB. Role of turmeric and curcumin in prevention and treatment of chronic diseases: lessons learned from clinical trials. ACS pharmacology & translational science. 2023 Mar 6;6(4):447-518.
27. Riva A, Allegrini P, Franceschi F, Togni S, Giacomelli L, Eggenhoffner R. A novel boswellic acids delivery form (casperome (R)) in the management of musculoskeletal disorders: a review. European review for medical and pharmacological sciences. 2017;21:5258-63.
28. Thanawala S, Shah R, Somepalli V, Alluri KV, Desomayanandam P, Bhuvanendran A. A multicenter, randomized, double-blind, placebo-controlled trial assessing efficacy and safety of a novel low-dose turmeric extract formulation in healthy adults with chronic knee pain. Clinical pharmacology: advances and applications. 2021 May 21:91-100.
29. Rudrappa GH, Chakravarthi PT, Benny IR. Efficacy of high-dissolution turmeric-sesame formulation for pain relief in adult subjects with acute musculoskeletal pain compared to acetaminophen: A randomized controlled study. Medicine. 2020 Jul 10;99(28):e20373.
30. Prabha J, Kumar M, Kumar D, Chopra S, Bhatia A. Nano-platform strategies of herbal components for the management of rheumatoid arthritis: A review on the battle for next-generation formulations. Current Drug Delivery. 2024 Oct 1;21(8):1082-105.
31. Hadi MA, Rao NR, Rao AS. Formulation and evaluation of ileo-colonic targeted matrix-mini-tablets of Naproxen for chronotherapeutic treatment of rheumatoid arthritis. Saudi pharmaceutical journal. 2016 Jan 1;24(1):64-73.
32. Shapovalov V, Piontkovskyi V, Huzovatyi O. An Interdisciplinary approach to development of a new combined medicine for musculoskeletal disorders. SSP Modern Pharmacy and Medicine. 2023 Oct 10;3(4):1-7.
33. Iftinca M, Defaye M, Altier C. TRPV1-Targeted Drugs in Development for Human Pain Conditions: M. Iftinca et al. Drugs. 2021 Jan;81(1):7-27.
34. Pulskamp TG, Johnson LM, Berlau DJ. Novel non-opioid analgesics in pain management. Pain Management. 2024 Dec 1;14(12):641-51.
35. Shapovalova V. Musculoskeletal health systematic review: clinical and pharmacological, organizational and legal, administration and pharmaceutical management aspects. SSP Modern Pharmacy and Medicine. 2024 Apr 1;4(2):1-2.
36. McMahon SB, Dargan P, Lanas A, Wiffen P. The burden of musculoskeletal pain and the role of topical non-steroidal anti-inflammatory drugs (NSAIDs) in its treatment. Ten underpinning statements from a global pain faculty. Current medical research and opinion. 2021 Feb 1;37(2):287-92.
37. Kasparaviciene G, Maslii Y, Herbina N, Kazlauskiene D, Marksa M, Bernatoniene J. Development and Evaluation of Two-Phase Gel Formulations for Enhanced Delivery of Active Ingredients: Sodium Diclofenac and Camphor. Pharmaceutics. 2024 Mar 5;16(3):366.
38. Naga Sai Chakradhar MB, Sangeetha S, Damodharan N. Herbal medicines and formulation approaches for the treatment of arthritis. Drug Invention Today. 2018 Sep 1;10(9).