DRUG DELIVERY APPROACHES FOR DICLOFENAC SODIUM IN THE MANAGEMENT OF INFLAMMATION

Meenakshi Jaiswal*
Assistant Professor, Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University) Bilaspur, 495009, India

***Corresponding author: Meenakshi Jaiswal**,
Assistant Professor, Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University) Bilaspur, 495009, India; Email: meenakshi_123123@rediffmail.com, Mobile:09770166557

ABSTRACT

Diclofenac, a phenyl acetic acid NSAID, is anti-inflammatory, analgesic, and antipyretic. Diclofenac inhibits COX-2 more than COX-1, unlike most NSAIDs. Similar to other nonsteroidal anti-inflammatory drugs (NSAIDs), diclofenac has serious gastrointestinal, cardiovascular, and renal adverse effects. Since its introduction in 1973, numerous improvements have been made to the efficacy, tolerability, and patient convenience of diclofenac-containing medications. The goal of developing delayed- and extended-release diclofenac sodium was to make the drug safer and make it so that patients with chronic pain only needed to take it once daily. The newer diclofenac potassium salt medications worked and were absorbed more quickly. Immediate-release pills, soft gel capsules, and oral solution powder all include diclofenac potassium. Localized pain and inflammation were alleviated whereas systemic absorption of diclofenac was decreased. Submicron diclofenac free acid particles and a patented excipient mix make up SoluMatrix diclofenac, which gives analgesia at lower doses with less systemic absorption. The pharmacokinetics of diclofenac have been modified by pharmaceutical research to produce new medications with improved clinical efficacy, as demonstrated in this article.

Keywords: Drug delivery, diclofenac sodium, management, inflammation

DOI Number: 10.48047/nq.2020.18.8.NQ20212 **NeuroQuantology 2020; 18(8):112-120**

INTRODUCTION

When it comes to the systemic effects of therapeutic medicines, oral medication distribution is the gold standard. Patient acceptance, ease, and a cost-effective manufacturing technique make oral medication the primary route examined in the discovery and development of new pharmacological entities and pharmaceutical formulations. The clinical efficacy, safety, and optimal pharmacokinetic and pharmacodynamic characteristics of many therapeutic substances can be met by using standard instant release formulations [1, 2].

Non-steroidal anti-inflammatory medications (NSAIDs) like diclofenac sodium are commonly used to treat pain and inflammation, both of rheumatic and non-rheumatic origin. It has been noted that NSAID treatment can cause gastrointestinal problems. The use of microspheres made of biodegradable and biocompatible polymers in the formulation of Diclofenac sodium is predicted to reduce gastrointestinal (GI) adverse effects. To address the shortcomings of standard

treatment, researchers have developed and tested a wide range of novel oral drug delivery systems, such as sustained/controlled release dosage forms [3]. These products have the ability to prevent and reduce drug-related side effects by keeping plasma drug levels constant for long periods of time [4]. Oral sustained release versions of the non-steroidal anti-inflammatory medication Diclofenac sodium are warranted. In typical tablet or capsule form, it is used to treat rheumatoid arthritis and osteoarthritis at a dosage of 100–200 milligrams twice daily. There have been reports of stomach upset, and the drug's short biological half-life means it needs to be dosed frequently. Multiple dosing not only causes blood levels of the drug to fluctuate, which can have harmful consequences, but it also fails to release the drug at the ideal rate and in the ideal amount, leading to poor patient compliance and ineffective therapy. Microencapsulation is a widely used method in pharmacotherapy for arthritis, inflammation, and pain because it prolongs drug release, lessens or eliminates gastrointestinal irritation, and increases compliance with dosing [5]. The purpose of this research was to improve drug bioavailability by creating a sustained-release oral product by combining the hydrophilic carrier sodium alginate with HPMC, Chitosan, and pectin polymers in varying concentrations. Dropping a drug and polymer dispersion into an aqueous calcium chloride solution triggers instant gelation, leading to the formation of spherical micro-scale sized beads that are small in size, have a high yield, have low porosity, and provide optimal sustained release under a broad range of gastrointestinal physiological conditions [6, 7]. Diclofenac, the first phenylacetic acid derivative to be approved as a nonsteroidal anti-inflammatory medication, reduces prostaglandin production by competing with arachidonic acid for binding to cyclo-oxygenase. The medication can reduce pain and fever. Peak plasma concentrations of diclofenac occur between 1.5 and 2.0 hours after intake in fasting subjects [7]. Diclofenac's half-life of elimination in plasma is brief, while it is long in synovial fluid. The medication is removed via biliary and urine excretion after being processed in the liver. Clinical investigations on people with rheumatoid arthritis found that diclofenac was just as efficient at enhancing function and decreasing pain as aspirin, diflunisal, indomethacin, sulindac, ibuprofen, ketoprofen, and naproxen. Diclofenac performed comparably to other NSAIDs used to treat osteoarthritis, including aspirin, diflunisal, indomethacin, sulindac, ibuprofen, ketoprofen, naproxen, flurbiprofen, mefenamic acid, and piroxicam. The effectiveness of diclofenac in treating ankylosing spondylitis was comparable to that of indomethacin and sulindac. In comparison to aspirin and indomethacin, diclofenac has fewer and milder gastrointestinal side effects, and it also causes fewer and milder reactions in the central nervous system. Diclofenac is taken three times daily, one before each meal [6-8].

DIFFERENT DRUG DELIVERY SYSTEMS FOR DICLOFENAC SODIUM ADMINISTRATION

Tablets of Diclofenac Sodium with Enteric Coating

Diclofenac sodium entericcoated tablets were the first diclofenac medicine product developed to lessen the drug's stomach absorption. These pills' pH-sensitive coating prevented the release of diclofenac in the stomach but allowed it to take effect in the small intestine, where the pH is higher. Because a higher pH is needed to dissolve the coating, the release of the active diclofenac component may be erratic with enteric coating [9]. However, there is still clinical worry about the prospect of the drug's direct mucosal effects being transferred to distal portions of the gastrointestinal tract, even if avoiding the stomach mucosa may lower the risk of gastroduodenal ulcers. Some enteric-coated diclofenac sodium tablets may linger in the stomach empty for as long as 24 hours, delaying absorption of the active ingredient by up to two hours after oral delivery. Cmax is often reached between 0.5 and 1.5 hours after taking a 50 mg pill due to the rapid absorption of the active ingredient in the stomach. Multiple clinical studies have demonstrated the efficacy of diclofenac

sodium enteric-coated tablets in the treatment of inflammation and discomfort associated with rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and acute gout. When it comes to medications for osteoarthritis, enteric-coated capsules containing diclofenac sodium have long been considered the gold standard. In randomized controlled trials, patients with hip and/or knee osteoarthritis who took enteric-coated tablets reported significantly less pain and improved function compared to those who took a placebo. When compared to other NSAIDs like indomethacin, ibuprofen [100 mg], and naproxen, diclofenac sodium performed similarly [10, 11].

Tablets of Diclofenac Sodium Extended-Release

In the late 1990s, the first extended-release pills of diclofenac sodium became available. The active diclofenac is released slowly over a long period of time, allowing patients with persistent pain from osteoarthritis and rheumatoid arthritis to use a single 100 mg pill once daily. The drug component in extended-release tablets of diclofenac sodium was sandwiched between layers of hydroxypropylmethylcellulose. These tablets' outer layer extends during disintegration without being eroded, creating a barrier that controls the rate at which the medication is released. The active drug component can be slowly released and delivered thanks to the inner, erodible layer, which allows for gradual breakdown. The whole effect of extended-release diclofenac is felt after 8-10 hours [12, 13].

Diclofenac Sodium and Protective Therapies for the Stomach

Patients with rheumatoid arthritis or osteoarthritis were evaluated endoscopically after 6 months of continuous NSAID medication, and 37% of those patients had clinically significant gastroduodenal lesions, and 24% had ulceration. Combination therapies based on co-administration of diclofenac with gastroprotective medicines, such as prostaglandin analogs Table 2 or proton pump inhibitors, have been developed due to the increased risk of major gastrointestinal adverse events (AEs) with long-term use of diclofenac sodium [14, 15].

Fixed-Dose Combo of Diclofenac Sodium and Misoprostol

D-Dose in Conjunction to alleviate the pain of osteoarthritis and rheumatoid arthritis in people who are at high risk for NSAID-induced gastric/duodenal ulcers and their complications, the FDA of the United States approved a combination tablet containing diclofenac sodium and misoprostol in 1997. Misoprostol, a synthetic prostaglandin analog with stomach ant secretory and mucosal protecting qualities, is encased within an enteric coating around a core of diclofenac sodium [16, 17]. Research has shown that at therapeutic levels, there is no accumulation of diclofenac or misoprostol in the plasma, and there is also no evidence of an interaction between the two drugs. In a fixed-dose combination with misoprostol, the pharmacokinetic characteristics of diclofenac sodium were identical to those of enteric-coated diclofenac sodium when given alone. The median Cmax for 50 mg and 75 mg doses, respectively, was approximately 1.5 and 2.0 lg/mL at 2 hours post-treatment. The fixed-dose combination of diclofenac sodium and misoprostol is as effective as indomethacin, diclofenac, ibuprofen, naproxen, or piroxicam in relieving the pain of osteoarthritis [18, 19]. Gastric and duodenal ulcer risk is decreased with diclofenac/misoprostol therapy compared to sodium diclofenac therapy alone, according to endoscopic studies. The incidence of GI and duodenal ulcers in patients with osteoarthritis of the hip or knee was significantly lower in those treated with a fixed-dose combination of diclofenac 50 mg/misoprostol 200 lg three times daily, diclofenac 75 mg/misoprostol 200 lg twice daily, or placebo compared to those treated with enteric-coated diclofenac sodium 75 mg twice daily. Gastroduodenal ulcer risk was lower in patients at high risk for NSAID-induced ulcers who were administered an enteric-coated diclofenac/misoprostol combination for 12 weeks compared to diclofenac alone. When comparing the two

groups, the diclofenac/misoprostol therapy group had a considerably decreased incidence of stomach and duodenal ulcers verified by endoscopy [20, 21].

Immediate-Release Diclofenac Potassium Tablets

In the early 1980s, sugar-coated tablets containing diclofenac potassium immediate-release were developed to improve the drug's absorption rate and its ability to alleviate pain. Absorption studies using healthy participants revealed remarkable differences between immediate-release potassium and enteric-coated sodium diclofenac tablets [22, 23]. When compared to diclofenac sodium enteric-coated 50 mg tablets, diclofenac potassium immediate-release 50 mg tablets had a little lower Cmax but a significantly shorter tmax. Several investigations failed to detect secondary diclofenac absorption peaks. Researchers looked assessed the effectiveness and safety of immediate-release tablets of diclofenac potassium for a number of conditions characterized by acute pain, such as impacted molar pain, ankle sprain pain, episiotomy pain, and dysmenorrhea pain [24]. Diclofenac potassium immediate-release tablets were more effective than placebo, ibuprofen, and piroxicam in relieving the pain associated with ankle sprains. No significant adverse events were observed, and AEs occurred rarely overall in these investigations. Diarrhea was the most often reported adverse effect among individuals receiving active treatment. To treat primary dysmenorrhea, relieve mild to moderate pain, and lessen acute and chronic symptoms of osteoarthritis and rheumatoid arthritis, diclofenac potassium immediate-release tablets were given FDA approval in 1993. Diclofenac potassium immediate-release was more effective than diclofenac sodium enteric-coated tablets for patients with moderate to severe postoperative pain, and it was taken orally in a single dose [25, 26].

Oral Solution Diclofenac Potassium Powder

Permeability of a liquid solution to the body. The powder for oral solution of diclofenac potassium consists of the salt of diclofenac potassium, as well as sweeteners, flavoring additives, and a dynamic bicarbonate buffering agent, all of which may prevent diclofenac potassium from precipitating in the stomach under acidic conditions [27]. When used orally as a powder for oral solution, diclofenac potassium enters the bloodstream rapidly. Peak plasma concentrations were reached between 10 and 15 minutes post-dosing in the first pharmacokinetic investigation in healthy subjects. Additionally, there was just one plasma diclofenac peak, which correlated with the rapid absorption of diclofenac potassium [28]. Diclofenac potassium powder for oral solution demonstrated greater analgesia compared to diclofenac potassium immediate-release tablets, with pain relief occurring as early as 15 minutes after administration in patients with migraine headaches. These findings point to the possibility that the drug's faster absorption and pain alleviation were due to its administration as an oral solution. Diclofenac extended-release tablets and placebo were tested for their effects on reducing headache intensity and maintaining relief. Nausea, dyspepsia, vomiting, and dizziness were some of the side effects experienced by those taking diclofenac potassium powder for oral solution. Diclofenac potassium powder for oral solution [29, 30] is the only nonsteroidal anti-inflammatory medicine approved by the Food and medicine Administration for the immediate relief of migraine attacks in adults, with or without aura.

Diclofenac Potassium Soft Gelatin capsules

Diclofenac potassium liquid-filled capsules were developed using the proprietary ProSorb dispersion technology. These capsules mix a liquid formulation of diclofenac potassium with solubilizing and dispersing agents to enhance the drug's absorption from the stomach and ensure uniform dosing. The basic premise of this technology is that the addition of solubilizing and dispersing agents can increase the bioavailability of low-acidity drugs [31]. The majority of the inert ingredients in this formulation are non-aqueous solvents like polyethylene glycol 400,

glycerin, sorbitol, povidone, polysorbate 80, hydrochloric acid, isopropyl alcohol, and mineral oil. This allows the medication to be manufactured and administered to patients as a liquid contained within a soft gelatine capsule. The capsule shells are made of gelatine, sorbitol, isopropyl alcohol, glycerin, and mineral oil. Phase I studies in healthy volunteers showed that liquid-filled soft gelatin capsules of diclofenac potassium had rapid and predictable absorption, with a shorter time to Cmax compared to diclofenac potassium immediate-release tablets. Maximum concentrations (Cmax) following 25-50-milligram doses of diclofenac potassium were similar, while the half-lives (tmax) were much shorter after the greater dose. In contrast to the single peak seen in plasma diclofenac concentration-time courses after administration of diclofenac potassium liquid-filled soft gelatine capsules [33-35], multiple peaks were seen after administration of diclofenac potassium 50 mg tablets.

Diclofenac Sodium Creams and Ointments

Topical diclofenac sodium formulations were developed to address local pain and inflammation with reduced systemic diclofenac exposure and, perhaps, reduced risk of AEs associated with treatment with systemic NSAIDs [36]. While diclofenac is lipophilic, its salts are neutrally soluble in water. Diclofenac can penetrate the synovial lining of diarthrodial joints and the epidermis because of these two features. Diclofenac was found to have high transdermal penetration qualities in studies conducted in 1997 and 2001 [37]. It was hypothesized that topical use of diclofenac, according to its high penetration properties and powerful suppression of PGE2 production, would have a significant anti-inflammatory effect. Diclofenac epolamine patch, diclofenac sodium gels, and diclofenac sodium topical solutions are all examples of diclofenac formulations designed for transdermal administration [38-40].

Diclofenac sodium injectable

Since 1997, doctors in the UK and around the world have had access to injectable diclofenac. Intravenous administration of these medication preparations, which typically come in the form of ampules containing 75 mg of diclofenac and have traditionally relied on solubilizing chemicals such propylene glycol and benzyl alcohol, has traditionally taken a long period [41, 42]. The FDA has approved a new injectable form of diclofenac for the treatment of moderate pain in patients or as part of a combination of pain medications for postoperative care. To improve solubility, pH modifiers, and monothioglycerol are included in this diclofenac formulation alongside 37.5 mg of diclofenac sodium. HPbCD-diclofenac has a shorter infusion time and is more easily prepared because it lacks propylene glycol, unlike other diclofenac sodium forinjection medication solutions [43]. In healthy participants, the bioavailability of HPbCD-diclofenac was comparable to that of an injectable diclofenac sodium medicinal product including propylene glycol when both were administered intravenously or intramuscularly. Patients who had oral surgery-related pain reported higher pain relief with HPbCD-diclofenac 75 mg compared to a placebo and more pain relief with HPbCD-diclofenac 75 mg compared to an injectable diclofenac sodium medication product containing propylene glycol [44-46].

SoluMatrix Diclofenac Acid

SoluMatrix diclofenac is unique in that its active ingredient is the diclofenac molecule itself, rather than a salt of the molecule like sodium, potassium, or epolamine. Therefore, SoluMatrix diclofenac capsules [47] cannot be replaced by other diclofenac products containing diclofenac potassium or sodium salts. Since the medicine's salts are insoluble in water at neutral pH but precipitate in the stomach's acidic environment, the drug is not absorbed properly. Due to the existence of big or agglomerated particles, subsequent dissolution of the active component may be inconsistent or delayed if the starting material is not modified [48]. Drug particles with a diameter of 200-800 nm can be manufactured using the patented SoluMatrix Fine Particle TechnologyTM without compromising the

drug's chemical characteristics. The dry milling procedure increases medication particle surface area relative to mass, which improves dissolving properties compared to immediate-release diclofenac potassium tablets. The SoluMatrix diclofenac capsules were developed to achieve efficacy at lower doses, in line with recommendations from health authorities such the Food and Drug Administration and the European Medicines Agency. When compared to diclofenac potassium immediate-release tablets of 25 and 50 mg, the active component in SoluMatrix diclofenac 18 mg and 35 mg is 20% lower on a molar basis [49-51].

CONCLUSIONS

Diclofenac's biopharmaceutical properties continue to evolve, leading to the creation of many pharmacological medicines for inflammatory and painful illnesses. To create diclofenac, scientists started with a molecule that had all the right physicochemical and steric qualities to work as an NSAID. To mitigate stomach upset caused by nonsteroidal anti-inflammatory drugs, researchers created diclofenac sodium enteric-coated tablets as the first diclofenac medicine product. Following this, diclofenac sodium was made into an extended-release form for convenience in dosing. To improve GI tolerability, diclofenac sodium is sometimes combined in fixed-dose formulations with gastro protective medications such misoprostol, a synthetic prostaglandin. Medication formulations containing diclofenac potassium aim to shorten the time to clinically significant analgesia as a result of the compound's improved solubility and absorption kinetics. Diclofenac potassium is available in quick-acting tablets, soft gelatin capsules filled with liquid, and powder for oral solution.

Funding

None

Conflict of interest

None

REFERENCES

1. Thakur S, Riyaz B, Patil A, Kaur A, Kapoor B, Mishra V. Novel drug delivery systems for NSAIDs in management of rheumatoid arthritis: An overview. Biomedicine & Pharmacotherapy. 2018 Oct 1;106:1011-23.
2. Kumar L, Verma S, Singh M, Chalotra T, Utreja P. Advanced drug delivery systems for transdermal delivery of non-steroidal anti-inflammatory drugs: A review. Current drug delivery. 2018 Oct 1;15(8):1087-99.
3. Das Kurmi B, Tekchandani P, Paliwal R, Rai Paliwal S. Transdermal drug delivery: opportunities and challenges for controlled delivery of therapeutic agents using nanocarriers. Current drug metabolism. 2017 May 1;18(5):481-95.
4. Burt HM, Tsallas A, Gilchrist S, Liang LS. Intra-articular drug delivery systems: overcoming the shortcomings of joint disease therapy. Expert opinion on drug delivery. 2009 Jan 1;6(1):17-26.
5. Haley RM, von Recum HA. Localized and targeted delivery of NSAIDs for treatment of inflammation: A review. Experimental Biology and Medicine. 2019 Apr;244(6):433-44.
6. Asghar LF, Chandran S. Multiparticulate formulation approach to colon specific drug delivery: current perspectives. J Pharm Pharm Sci. 2006 Sep 1;9(3):327-8.
7. Kotla NG, Rana S, Sivaraman G, Sunnapu O, Vemula PK, Pandit A, Rochev Y. Bioresponsive drug delivery systems in intestinal inflammation: State-of-the-art and future perspectives. Advanced drug delivery reviews. 2019 Jun 1;146:248-66.
8. Teruel AH, Gonzalez-Alvarez I, Bermejo M, Merino V, Marcos MD, Sancenon F, Gonzalez-Alvarez M, Martinez-Mañez R. New insights of oral colonic drug delivery systems for inflammatory bowel disease therapy. International journal of molecular sciences. 2020 Sep 5;21(18):6502.

9. Kumar D, Singh J, Antil M, Kumar V. Emulgel-novel topical drug delivery system-a comprehensive review. International journal of pharmaceutical sciences and research. 2016 Dec 1;7(12):4733.
10. Manjanna KM, Shivakumar B, Kumar TP. Microencapsulation: an acclaimed novel drug-delivery system for NSAIDs in arthritis. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2010;27(6).
11. Chourasia MK, Jain SK. Pharmaceutical approaches to colon targeted drug delivery systems. J Pharm Pharm Sci. 2003 Jan 1;6(1):33-66.
12. Rajeshwari HR, Dhamecha D, Jagwani S, Rao M, Jadhav K, Shaikh S, Puzhankara L, Jalalpure S. Local drug delivery systems in the management of periodontitis: A scientific review. Journal of Controlled Release. 2019 Aug 10;307:393-409.
13. Saeedi T, Alotaibi HF, Prokopovich P. Polymer colloids as drug delivery systems for the treatment of arthritis. Advances in Colloid and Interface Science. 2020 Nov 1;285:102273.
14. Altman R, Bosch B, Brune K, Patrignani P, Young C. Advances in NSAID development: evolution of diclofenac products using pharmaceutical technology. Drugs. 2015 May;75:859-77.
15. Ulubay M, Yurt KK, Kaplan AA, Atilla MK. The use of diclofenac sodium in urological practice: a structural and neurochemical based review. Journal of Chemical Neuroanatomy. 2018 Jan 1;87:32-6.
16. Sharma PK. Novel prospective in colon specific drug delivery system. Polim. Med. 2014;44(2):109-18.
17. Rodrigues EB, Farah ME, Bottós JM, Aggio FB. Nonsteroidal anti-inflammatory drugs in the treatment of retinal diseases. Retinal Pharmacotherapeutics. 2016;55:212-20.
18. Jumelle C, Gholizadeh S, Annabi N, Dana R. Advances and limitations of drug delivery systems formulated as eye drops. Journal of Controlled Release. 2020 May 10;321:1-22.
19. Benbow T, Campbell J. Microemulsions as transdermal drug delivery systems for nonsteroidal anti-inflammatory drugs (NSAIDs): a literature review. Drug Development and Industrial Pharmacy. 2019 Dec 2;45(12):1849-55.
20. Peneva PT. Non-steroidal anti-inflammatory drugs for topical ophthalmic administration: contemporary trends. Int J Pharm Pharm Sci. 2015;7(9):13-9.
21. Tieppo Francio V, Davani S, Towery C, Brown TL. Oral versus topical diclofenac sodium in the treatment of osteoarthritis. Journal of pain & palliative care pharmacotherapy. 2017 Apr 3;31(2):113-20.
22. Al Malyan M, Becchi C, Nikkola L, Viitanen P, Boncinelli S, Chiellini F, Ashammakhi N. Polymer-based biodegradable drug delivery systems in pain management. Journal of Craniofacial Surgery. 2006 Mar 1;17(2):302-13.
23. Mazet R, Yaméogo JB, Wouessidjewe D, Choisnard L, Gèze A. Recent advances in the design of topical ophthalmic delivery systems in the treatment of ocular surface inflammation and their biopharmaceutical evaluation. Pharmaceutics. 2020 Jun 19;12(6):570.
24. Marren K. Dimethyl sulfoxide: an effective penetration enhancer for topical administration of NSAIDs. The Physician and sportsmedicine. 2011 Sep 1;39(3):75-82.
25. Qindeel M, Ullah MH, Ahmed N. Recent trends, challenges and future outlook of transdermal drug delivery systems for rheumatoid arthritis therapy. Journal of Controlled Release. 2020 Nov 10;327:595-615.
26. Goh CF, Lane ME. Formulation of diclofenac for dermal delivery. International journal of

pharmaceutics. 2014 Oct 1;473(1-2):607-16.
27. Gazzaniga A, Maroni A, Sangalli ME, Zema L. Time-controlled oral delivery systems for colon targeting. Expert Opinion on Drug Delivery. 2006 Sep 1;3(5):583-97.
28. Qureshi AM, Momin M, Rathod S, Dev A, Kute C. Colon targeted drug delivery system: A review on current approaches. Indian J Pharm Biol Res. 2013 Oct 31;1(4):130-47.
29. Kang ML, Im GI. Drug delivery systems for intra-articular treatment of osteoarthritis. Expert opinion on drug delivery. 2014 Feb 1;11(2):269-82.
30. Puglia C, Giusy Tirendi G, Bonina F. Emerging role of colloidal drug delivery systems (CDDS) in NSAID topical administration. Current Medicinal Chemistry. 2013 May 1;20(14):1847-57.
31. Maudens P, Jordan O, Allémann E. Recent advances in intra-articular drug delivery systems for osteoarthritis therapy. Drug discovery today. 2018 Oct 1;23(10):1761-75.
32. Kesisoglou F, Zimmermann EM. Novel drug delivery strategies for the treatment of inflammatory bowel disease. Expert opinion on drug delivery. 2005 May 1;2(3):451-63.
33. Manjunatha KM, Ramana MV, Satyanarayana D. Design and evaluation of diclofenac sodium controlled drug delivery systems. Indian Journal of Pharmaceutical Sciences. 2007;69(3):384.
34. Cheng G, An F, Zou MJ, Sun J, Hao XH, He YX. Time-and pH-dependent colon-specific drug delivery for orally administered diclofenac sodium and 5-aminosalicylic acid. World Journal of Gastroenterology: WJG. 2004 Jun 6;10(12):1769.
35. Bravo SA, Lamas MC, Salomón CJ. In-vitro studies of diclofenac sodium controlled-release from biopolymeric hydrophilic matrices. J Pharm Pharm Sci. 2002 Sep 1;5(3):213-9.
36. Kevadiya BD, Patel HA, Joshi GV, Abdi SH, Bajaj HC. Montmorillonite-alginate composites as a drug delivery system: Intercalation and In vitro release of diclofenac sodium. Indian journal of pharmaceutical sciences. 2010 Nov;72(6):732.
37. KIZIBASH NA, SHAH SS, ALENIZI D, NAZAR MF, ASIF S. Design of a microemulsion-based drug delivery system for diclofenac sodium. Journal of the Chemical Society of Pakistan. 2011 Feb 9;33(6):1.
38. Jafariazar Z, Jamalinia N, Ghorbani-Bidkorbeh F, Mortazavi SA. Design and evaluation of ocular controlled delivery system for diclofenac sodium. Iranian journal of pharmaceutical research: IJPR. 2015;14(Suppl):23.
39. Hajjar B, Zier KI, Khalid N, Azarmi S, Löbenberg R. Evaluation of a microemulsion-based gel formulation for topical drug delivery of diclofenac sodium. Journal of Pharmaceutical Investigation. 2018 May;48:351-62.
40. Samani SM, Montaseri H, Kazemi A. The effect of polymer blends on release profiles of diclofenac sodium from matrices. European journal of pharmaceutics and biopharmaceutics. 2003 May 1;55(3):351-5.
41. Torres-Luna C, Hu N, Tammareddy T, Domszy R, Yang J, Wang NS, Yang A. Extended delivery of non-steroidal anti-inflammatory drugs through contact lenses loaded with Vitamin E and cationic surfactants. Contact Lens and Anterior Eye. 2019 Oct 1;42(5):546-52.
42. Saravanan M, Bhaskar K, Maharajan G, Pillai KS. Ultrasonically controlled release and targeted delivery of diclofenac sodium via gelatin magnetic microspheres. International journal of pharmaceutics. 2004 Sep 28;283(1-2):71-82.
43. Raza K, Kumar M, Kumar P, Malik R, Sharma G, Kaur M, Katare OP. Topical delivery of aceclofenac: challenges and promises of novel drug delivery

systems. BioMed research international. 2014 Jan 1;2014.
44. Patel MM, Shah T, Amin A. Therapeutic opportunities in colon-specific drug-delivery systems. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2007;24(2).
45. Agrawal G, Aswath S, Laha A, Ramakrishna S. Electrospun Nanofiber-Based Drug Carrier to Manage Inflammation. Advances in Wound Care. 2023 Mar 1.
46. Gupta KC, Kumar MR. Drug release behavior of beads and microgranules of chitosan. Biomaterials. 2000 Jun 1;21(11):1115-9.
47. Yang L, Liu Y, Shou X, Ni D, Kong T, Zhao Y. Bio-inspired lubricant drug delivery particles for the treatment of osteoarthritis. Nanoscale. 2020;12(32):17093-102.
48. Manjanna KM, Shivakumar B, Kumar TP. Microencapsulation: an acclaimed novel drug-delivery system for NSAIDs in arthritis. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2010;27(6).
49. Omerović N, Vranić E. Application of nanoparticles in ocular drug delivery systems. Health and Technology. 2020 Jan;10:61-78.
50. Hundekar YR, Saboji JK, Patil SM, Nanjwade BK. Preparation and evaluation of diclofenac sodium cubosomes for percutaneous administration. World journal of pharmacy and pharmaceutical sciences. 2014 Mar 5;3(1):523-39.
51. Chourasia MK, Jain SK. Pharmaceutical approaches to colon targeted drug delivery systems. J Pharm Pharm Sci. 2003 Jan 1;6(1):33-66.