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Strategies in the Delivery of Nonsteroidal Anti-inflammatory Drugs

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the management of pain, inflammation, and fever. However, their effectiveness is often limited by gastrointestinal side effects such as ulceration and bleeding, as well as systemic complications including renal toxicity and cardiovascular risks. To address these challenges, various strategies have been developed to improve the delivery of NSAIDs with the aim of enhancing their therapeutic efficacy while minimizing adverse effects. This abstract provides an overview of the recent advancements in NSAID delivery systems, including nanoparticle-based formulations, prodrug approaches, and targeted drug delivery strategies. Nanoparticle-based formulations offer advantages, such as improved bioavailability, controlled release, and reduced toxicity profiles. Prodrugs of NSAIDs can undergo enzymatic conversion to the active drug at the site of inflammation, thereby minimizing systemic exposure and associated side effects. Targeted drug delivery systems enable site-specific accumulation of NSAIDs, thus maximizing their therapeutic efficacy while minimizing off-target effects. Moreover, combination therapies involving NSAIDs and other pharmacological agents have emerged as promising approaches for achieving synergistic effects and improving patient outcomes. Overall, the development of innovative drug delivery strategies holds great promise for optimizing the therapeutic potential of NSAIDs and paving the way for safer and more effective treatment options for patients with inflammatory conditions.

Keywords: Nonsteroidal anti-inflammatory, prodrugs, controlled release, synergistic effects, analgesic medications.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a specific class of analgesic medications that lower inflammation, fever, and pain. They are the most commonly recommended medications worldwide. Some are easily obtained over the counter and prone to misuse. Nephrotoxicity can be a side effect of NSAIDs. [1].

There are approximately 100 million prescriptions of NSAIDs generated annually globally, making them one of the most frequently prescribed pharmaceuticals for chronic pain. NSAIDs are a commonly used class of drugs for the treatment of rheumatoid arthritis, osteoarthritis, fibromyalgia, connective tissue illnesses, spondyloarthropathies, gout, musculoskeletal trauma, and dysmenorrhea. Their rapid start of action, analgesic and anti-inflammatory qualities, and relative safety make them well-liked [2].

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Nonsteroidal anti-inflammatory drugs [NSAIDs]: Decreased or eliminated pain, elevated body temperature, erythema, and edema are caused by various inflammatory stimuli (Figure 1).

NSAIDs are a broad class of chemicals with comparable biological properties. Although the mechanisms of action of NSAIDs are still unknown, data indicate that they mainly reduce inflammation by preventing prostaglandin synthesis. All NSAIDs used this method of action.

Nonsteroidal anti-inflammatory medications, also known as cyclooxygenases (COX), inhibitors including diclofenac, naproxen, and ibuprofen. These drugs have anti-inflammatory, analgesic, and antipyretic effects at a variety of dosage levels. NSAIDs are helpful for treating mild pain and discomfort associated with tooth pain, headaches, back pain, menstrual cramps, colds, muscle pain, and arthritis for a brief period of time (less than ten days). NSAIDs, when administered at over-the-counter levels, can also alleviate pain during bouts in patients with chronic conditions such as osteoarthritis [3].

Presently, approximately 5% of all prescription medications and NSAIDs are among the OTC drugs that are most often used [4].

Nonsteroidal anti-inflammatory drugs have been used historically and were categorized on the basis of their chemical characteristics. The majority of widely used NSAIDs are classified as important derivatives of acetic acid, enolic acid, anthranilic acid, salicylic acid, or propionic acid. However, as science has advanced, the categorization also changes in light of how well these medications selectively block their primary targets, the enzyme prostaglandin-endoperoxide synthase (PGHS) and cyclooxygenase.

NSAIDs have been categorized according to a methodology developed based on their half-lives. However, their roles are not different from one another, even with variance among classes. NSAIDs are primarily used to treat patients with pain and inflammatory diseases including rheumatoid arthritis, osteoarthritis, chronic pain, postoperative surgical conditions, and menstrual cramps. They are also widely used as analgesics and antipyretics [5, 6].

A significant proportion of acidic compounds with high bioavailability are NSAIDs. They are processed by the liver and bind strongly to the plasma proteins. There have also been reports of various NSAIDs, such as naproxen, ibuprofen, and ketoprofen, which is glucose oxidized by kidney enzymes. Most patients use these medications at therapeutic levels for brief periods of time and often tolerate them well.

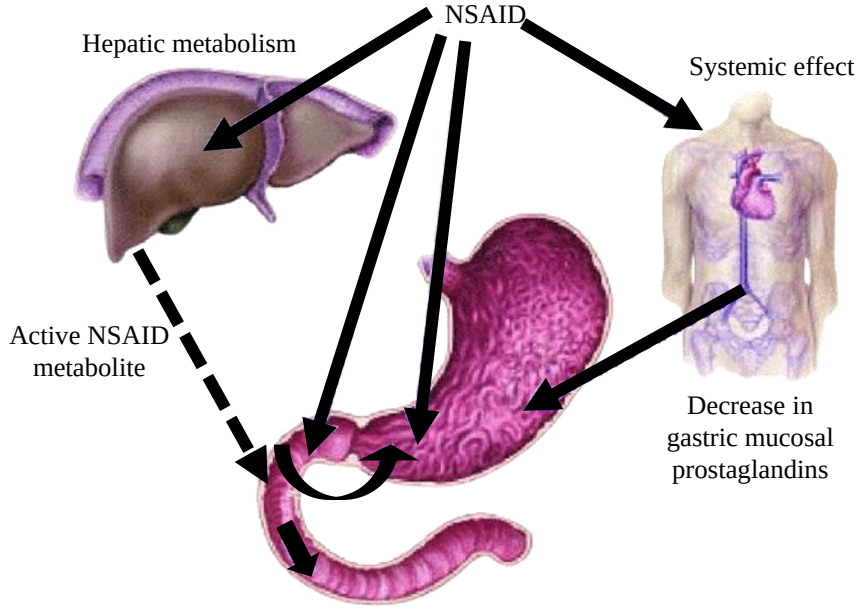

Figure 1. Mechanisms of NSAIDs.

The use of NSAIDs is limited by their adverse effects on the kidneys, heart, and gastrointestinal system. However, given that NSAIDs are frequently prescribed medications and that particular of them are OTC, this slightly elevated risk might result in a large absolute number of patients being impacted, particularly in those who already have impaired kidney function [7–12].

Since the calming effects of willow bark were discovered more than 3,500 years ago, millions of people worldwide have found relief from pain, fever, and inflammation with the help of NSAIDs. For NSAIDs users, these side effects occur as seldom as 1–5%16. Selective NSAIDs often have more cardiovascular adverse effects than gastrointestinal side effects when compared to nonselective NSAIDs [13].

ADVANTAGES

1. Nonsteroidal anti-inflammatory drugs are a class of medications broadly used to calm torment, decrease aggravation, and lower fever. They function by restraining the movement of cyclooxygenase (COX). Proteins, which are included in the amalgamation of prostaglandins, are substances that intercept torment, inflammation, and fever. There may be a nitty gritty note on the applications of NSAIDs: Pain Relief: NSAIDs are commonly used to alleviate pain, including headaches, toothaches, menstrual cramps, muscle aches, and minor injuries. They are effective in managing both acute and chronic pain.
2. *Inflammatory Conditions:* NSAIDs are frequently prescribed for various inflammatory conditions, such as arthritis (osteoarthritis, rheumatoid arthritis, and gout)., bursitis, tendonitis, and inflammatory bowel conditions (such as ulcerative colitis and Crohn's disease). By lowering inflammation, NSAIDs help alleviate the pain, stiffness, and swelling associated with these conditions, improving patients' quality of life.
3. *Fever Reduction:* NSAIDs are effective in reducing fever by lowering elevated body temperatures. They inhibit the production of prostaglandins in the hypothalamus, a region of the brain that regulates body temperature.
4. *Dysmenorrhea:* They are commonly used as pain relievers for menstrual cramps (dysmenorrhea). They help to reduce uterine contractions and alleviate discomfort during menstruation.
5. *Headaches and Migraines:* NSAIDs are often used to alleviate headaches, including tension headaches and migraine. They help reduce the intensity and frequency of headaches by blocking the release of inflammatory substances into the brain.
6. *Postoperative Pain Management:* NSAIDs are frequently prescribed following surgical procedures to manage postoperative pain and inflammation. They are often used in combination with other pain medications to provide multimodal analgesia and to reduce the need for opioid medications, thus minimizing the risk of opioid-related side effects and dependency.
7. *Dental Pain:* They are frequently used to treat dental pain, such as toothaches and soreness, following surgery. They help to reduce inflammation and alleviate pain associated with dental procedures and oral conditions.
8. *Acute Musculoskeletal Injuries:* NSAIDs are often recommended for the management of acute musculoskeletal injuries such as strains, sprains, and sports-related injuries. They help reduce pain and inflammation, facilitate faster recovery, and return to normal activities.
9. *Alleviation of Cancer-related Pain:* In palliative care settings, NSAIDs may be used as part of a multimodal approach to alleviate cancer-related pain. They can help manage the pain associated with tumor growth, metastasis, and cancer treatment.
10. *Prevention of Cardiovascular Events:* Some NSAIDs, such as aspirin, have antiplatelet effects and are used to inhibit cardiovascular events, including heart attacks and strokes, among those who are highly vulnerable. Aspirin at a low dosage is often prescribed for its cardioprotective effects owing to its ability to inhibit platelet aggregation.
11. *Alleviation of Renal Colic:* NSAIDs are sometimes used to alleviate pain associated with renal colic, resulting from kidney stones, which manifests as a form of abdominal pain. They help to relieve the intense pain and discomfort associated with this condition.

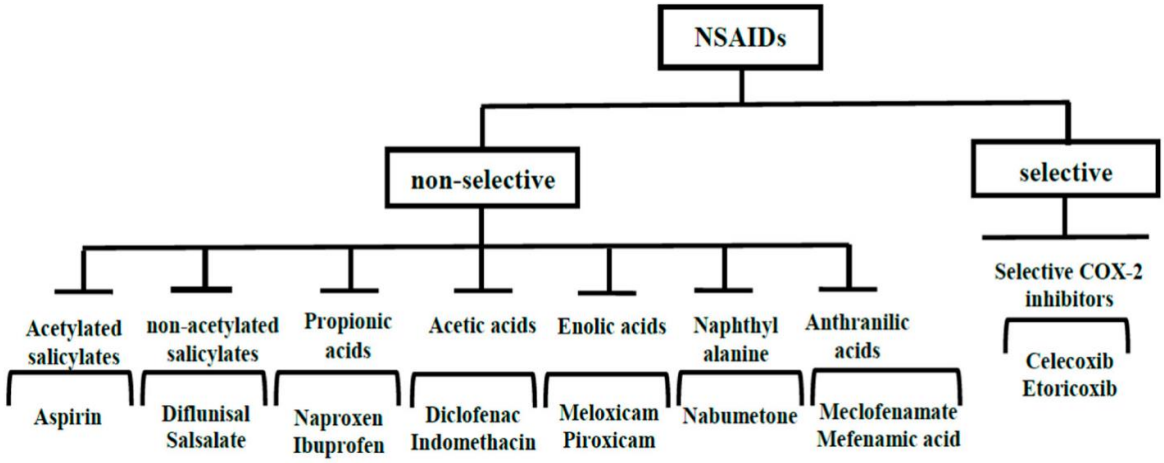

Figure 2. Classification of NSAIDs.

It is important to note that, although NSAIDs effectively manage pain and inflammation, they are at risk. Extended usage or high doses of NSAIDs may increase the risk of gastrointestinal ulcers, bleeding, kidney damage, cardiovascular events, and other adverse effects. Therefore, they must be used cautiously, at minimum efficient doses, and for the minimum interval required, under the guidance of a healthcare professional. Individuals with certain medical conditions such as peptic ulcer disease, renal impairment, or cardiovascular disease may require special consideration when using NSAIDs.

CLASSIFICATION OF NSAIDs

NSAIDs are divided into groups according to several criteria, including the specific inhibition of cyclooxygenase enzymes or chemical structures. NSAIDs COX-2 selectivity of NSAIDs has been reported in a variety of ways, depending on the methodology. NSAIDs, however, can be broadly categorized into two main groups: Nonselective NSAIDs and cyclooxygenases (COX).-2-selective inhibitors (COXIBs). Several NSAIDs have chiral structures (Figure 2).

The primary anti-inflammatory and analgesic properties of other chiral NSAIDs have been recognized as S enantiomers. NSAIDs are accessible as racemates. As a racemate, ibuprofen is sold everywhere, while S-ibuprofen is also sold in select nations. Some chiral NSAIDs metabolize their R enantiomers to their S enantiomers in humans. This enantiomeric inversion may be bidirectional in some animals [14–18].

Nonselective NSAIDs

- Diflunisal
- Etodolac
- Naproxen
- Oxaprozin
- Piroxicam
- Sulindac
- Tolmetin
- Fenoprofen
- Flurbiprofen
- Ibuprofen
- Indomethacin
- Diclofenac
- Mefenamic acid
- Meloxicam

- Nabumetone
- Ketoprofen
- Ketorolac

COX-2 Selective NSAIDs

- Valdecoxib
- Celecoxib
- Rofecoxib

MECHANISM OF ACTION

Vane and Piper first reported the mechanism of action of NSAIDs in 1971 [19–25]. (Figure 3). They showed that the drugs work by preventing COX enzymes from synthesizing prostaglandins and prostanoids. Prostanoids are inflammatory mediators, including prostaglandins (PGs)., prostacyclins, and thromboxanes, which are produced from arachidonic acid through a process known as the arachidonic acid cascade [26–28].

THERAPEUTIC USES OF NSAIDs

NSAIDs are used to treat persistent pain and suffering caused by diseases such as osteoarthritis and rheumatoid arthritis (RA and OA). A number of additional illness conditions, including juvenile arthritis, as well as conditions such as fever, thrombosis, pericarditis, Kawasaki disease, gout, gouty arthritis, ankylosing spondylitis, patent ductus arteriosus, and dysmenorrhea, are observed for several NSAIDs, including ASA. They are also used as a preventive measure against Alzheimer's disease and colon cancer; however, the latter benefit has not been conclusively demonstrated [19–23].

ADVERSE DRUG REACTIONS

Adverse effects related to NSAIDs predominantly occur in the gastrointestinal tract (GI), cardiovascular disease (CV), and renal systems.

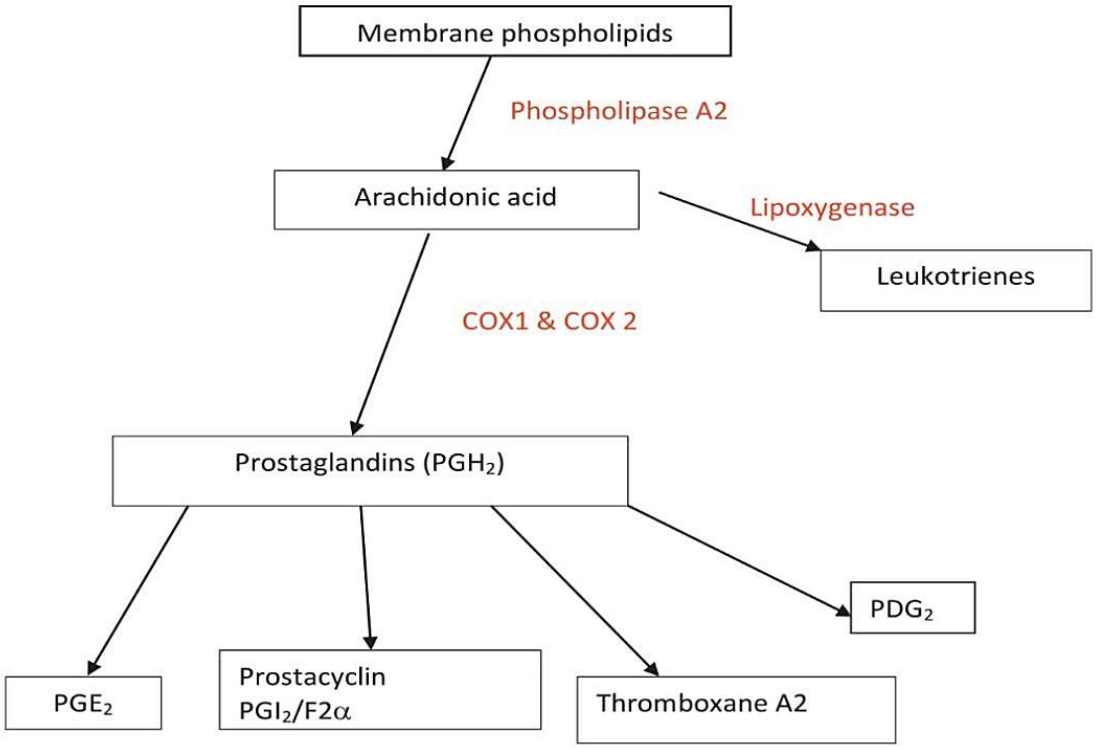

Figure 3. Mechanism of action.

Gastrointestinal Effects

NSAIDs are known to carry some dangers, including GI problems, which may differ depending on the specific NSAIDs used and their dosage. Similar to aspirin, even modest cardioprotective dosages increase the risk of bleeding. A comparative investigation, including information from three case-control retrospective research investigations, revealed that among the nonselective NSAIDs, ibuprofen exhibited the smallest risk ratio (OR) when compared to indomethacin, naproxen, and diclofenac piroxicam for the initiation of GI hemorrhage. Nonetheless, the OR increased with an increase in the dosage of each agent. Compared with acetaminophen, ibuprofen caused noticeably fewer total GI adverse events.

As expected, patients taking OTC ibuprofen experienced notably lower rates of gastrointestinal adverse events. Surprisingly, ibuprofen demonstrated a significantly lower incidence of total GI AEs than acetaminophen [5.3%; P=0.025]. The Pain investigation revealed several additional aspects linked to a higher risk of adverse events (AEs)., including female sex, age > 60 years, height < 160 cm, utilization of analgesics for skeletal pain rather than menstrual cramps, and concurrent medication usage for sore throat, toothache, or fever that were prohibited. The possibility of gastrointestinal issues when using NSAIDs is affected by the concurrent use of other medications. When NSAIDs are administered in combination with aspirin, there is an increased chance of upper GI events. Nevertheless, this risk can be decreased if NSAIDs are combined with medications that treat ulcers, like proton pump inhibitors [24–29].

Cardio Vascular Risk

Every NSAIDs has the potential to increase the risk of cardiovascular thrombosis. If you use it more or for longer than recommended, the risk of stroke or heart attack may increase. Owing to the absence of a latency period for cardiovascular thrombotic risk, patients should opt for the use of NSAIDs at a sparingly feasible dosage for the shortest possible period. While there is limited data on the specific cardiovascular risk associated with over-the-counter NSAID usage, the likelihood of it being low is high, particularly among younger individuals with minor cardiovascular risk elements. Elevated blood pressure (BP) has also been reported caused by COX2 inhibition in the kidneys, which has not been seen with over-the-counter dosages and is the cause of increased CV risk among NSAIDs users **[**30–33].

Renal

NSAIDs can affect renal function by inhibiting the production of COX-1, which regulates the glomerular filtration rate and renal blood flow, as well as COX-2, which mediates the elimination of salt and water from the kidneys. Nonselective NSAIDs can produce uncommon but worrisome renal syndromes such as hyperkalemia, acute renal failure, peripheral edema, elevated blood pressure, weight gain, and salt retention.

A history of severe liver or kidney disease, increased protein levels, chronic cardiac failure, hypertension, diabetes, and advanced age are risk factors for nephrotic syndrome. Furthermore, ibuprofen may slightly increase the possibility of severe kidney damage in patients experiencing kidney distress due to hot activity, such as dehydration. NSAIDs use has been linked to worsening renal insufficiency and decreased responsiveness to diuretics, as well as an increase in the utilization of angiotensin-2 receptor blockers (ARBs) and angiotensin-converting enzyme (ACEs) inhibitors.

In contrast, ibuprofen had no discernible effect on serum creatinine and blood levels of urea nitrogen, potassium, sodium, or creatinine in a study on over-the-counter analgesics in older patients with mild renal impairment and diuretic-treated high blood pressure. Aldosterone antagonists, such as spironolactone, have been linked to a higher risk of gastrointestinal bleeding and may slow the healing process for erosions in the stomach or duodenum. Therefore, using NSAIDs concurrently with these medicines may considerably enhance the risk of GI bleeding in individuals taking them. It was

discovered that prescribing and administering ibuprofen reduced furosemide clearance and raised salt excretion in the urine [34–37].

Antithrombotics

Although there is little chance of a direct pharmacodynamic interaction between NSAIDs and anticoagulants such as warfarin, using NSAIDs and antithrombotics at the same time may increase GI bleeding. The most clinically significant warfarin isomer, S-warfarin, is metabolized by CYP2C9. Since CYP2C9 is also a substrate for ibuprofen and other NSAIDs, it may enhance the anticoagulant action by postponing the metabolism of S-warfarin.

As a result, it might be wise to refrain from giving people warfarin prescription-strength NSAIDs. In contrast, N-acetyl-para-benzoquinone-imine, a metabolite of acetaminophen, interferes with the enzymes of the vitamin K cycle, which could eventually contribute to an excess of thrombosis and a decrease in the synthesis of clotting components. Acetaminophen administered with anticoagulants may increase the international normalized ratio (INR) even with short-term use.

The irreversible suppression of platelet aggregation by aspirin is blocked by NSAID-driven reversible transitory inhibition, which may facilitate the development of clots. This NSAID-induced aspirin effect is especially concerning for high-risk cardiovascular patients who regularly use low amounts of aspirin to reduce their risk of coagulant episodes [38–41].

Antidepressants

Psychiatric drugs called antidepressants are used to treat anxiety and mood problems. When NSAIDs are administered concurrently with certain antidepressants, there may be an additional increase in the risk of bleeding. Because they block platelet adhesion and function, bleeding is more likely when using selective serotonin reuptake inhibitors. Concurrent administration of NSAIDs can significantly increase the risk of bleeding.

Inhibitors of selective serotonin reuptake and NSAIDs interactions might be explained by a number of mechanisms. (1) Although via distinct methods, both groups prevent platelet aggregation and function. (2) Pharmacokinetic interaction whereby some SSRIs block the enzyme CYP2C9, which is responsible for the metabolism of certain NSAIDs (for example, diclofenac and ibuprofen), and (3). Independent reports: An independent mechanism (such as an increase in stomach acid production). SSRIs cause an increase in symptoms and bleeding. This occurs without direct pharmacokinetic interaction. Inhibition of CYP2C9 by tricyclic antidepressants (TCAs) is not significant. In a Dutch cohort trial, patients taking TCAs with NSAIDs showed a relatively moderate rise in GI events [42–44].

Chemotherapy

The anti-metabolite methotrexate is used to treat psoriasis and RA at low dosages and high levels as a chemotherapeutic agent. When methotrexate is taken at high dosages, it has been seen that some NSAIDs, such as prescription naproxen and ibuprofen, impede renal clearance of the drug. This may result in toxicity such as renal failure or pancytopenia. One case study suggested that using over-the-counter ibuprofen medication every day for four weeks might lower the excretion of methotrexate. As a result of methotrexate buildup, the patient's bone marrow was depleted, which may have led to Pneumocystis carinii pneumonia. Ibuprofen monotherapy has also been associated with renal complications.

Even at OTC dosages, patients on large doses of methotrexate should refrain from using NSAIDs. In addition, individuals using low-dose methotrexate should be cautious when using NSAIDs. There are no other documented cases of clinically significant DDIs leading to adverse drug reactions in patients receiving concurrent NSAIDs and rheumatologic or chemotherapy treatments [45–49].

Fertility

A study found that NSAIDs without specified dosages were associated with an 80% increased likelihood of miscarriage. The risk further escalated when NSAIDs were used near conception or for more than a week. Aspirin use showed a tendency towards elevated risk, while acetaminophen did not increase the risk. It has been suggested that the use of NSAIDs could potentially decrease fertility and elevate the likelihood of miscarriage, although no conclusive evidence supports this claim. Thus, it might be prudent for women attempting to conceive to refrain from NSAID use either before or immediately after conception. Moreover, in the final stages of pregnancy, prostaglandins are essential for maintaining the integrity of the fetal ductus arteriosus [50, 51].

Corticosteroids

When NSAID and corticosteroids are taken orally, there may be a greater chance of serious gastrointestinal harm. Further study uncovered a 4.4-fold increase in the risk of gastric ulcer disease among individuals with prior NSAID use, regardless of type or dosage, compared to those without a higher risk when excluding NSAID users. To reduce the risk of gastrointestinal bleeding, medical practitioners may prescribe COX-2-specific NSAIDs, or advise patients to refrain from using over-the-counter NSAIDs. Although no detailed studies have definitively demonstrated an increased risk of GI hemorrhage when over-the-counter NSAIDs are co-administered with oral corticosteroids, caution is advisable [52].

DRUG INTERACTION OF NSAIDs

NSAID use is among the most frequent reasons for unfavorable medication interactions. Older patients should be administered NSAIDs with care as their age and number of drugs increase. When used in combination with certain medications, NSAIDs may change the risk of bleeding or stomach ulcers.

These medications include angiotensin-converting enzyme, clopidogrel, digitalis glycosides, warfarin, aspirin, diuretics, beta-blockers, and selective serotonin reuptake inhibitors (SSRIs). Corticosteroids and other anticoagulants. Methotrexate is a prominent medicine used to treat rheumatoid arthritis; nevertheless, it has been observed that some particular NSAIDs limit its renal clearance [53].

RESEARCH

1. *Haley RM et al. [2018]:* An increasing number of provocative forms are found at the center of numerous diverse malady states (e.g., heart illness, cancer, and diabetes). Therefore, anti-inflammatory procedures available through sedate conveyance have been re-established. Owing to the systemic side effects of steroidal drugs, nonsteroidal anti-inflammatory drugs are regularly preferred for long-term treatment of irritation in an assortment of applications. Although nonsteroidal anti-inflammatory drugs are by and large secure, there are a few genuine side effects that can be related to their utilization, especially when administered systemically or orally. Due to the high number of patients taking nonsteroidal anti-inflammatory drugs, the lessening or elimination of these side effects, such as is conceivable through nearby sedate conveyance, could have an effective impact on understanding the quality of life. This survey comments on an examination of existing strategies for localized or targeted delivery of nonsteroidal anti-inflammatory drugs, with the objective of making a difference in future inquiries about bunches to center on bettering strategies that appeared to be successful and filling the gaps of information in this field. Moreover, commentary is made in the field as a whole, and standardization issues emerge from its extensiveness and differences [54].
2. *Guo Cg et al. [2019]:* As nonsteroidal anti-inflammatory drugs have become more widely used, the incidence of lower gastrointestinal (GI) disease has increased. The number of complications is expected to increase. However, unlike upper GI complications, the burden, pathogenesis, avoidance, and treatment of NSAID-associated lower GI complications remain hazy. To date, no cost-effective and secure defensive specialist has been created to completely avoid or treat

NSAID-related lower GI wounds. In particular, COX-2 inhibitors, misoprostol, intestinal microbiota balance, and a few mucoprotective specialists have been shown to have a defensive impact on NSAID-induced lower GI injuries. This survey outlines the current study on the avoidance of NSAID-related lower GI wounds [55].

3. *Giulia Auriemma et al. [2017]*: Recently, several technologies have been employed to transform active pharmaceutical ingredients (APIs) into new dosage forms. The designed medicate conveyance frameworks may alter the biopharmaceutical properties of the API, accomplishing either quick or postponed discharge concurring with particular restorative needs. In particular, preprogrammed discharge of verbal details conveying the sedate at anticipated times may be valuable in the chronotherapy of early morning pathologies. The routine approach when managing such illnesses is to administer NSAIDs two to three times daily. This approach does not permit the fit of sedate discharge with indications onset coming about in wasteful treatment and destitute understanding of compliance. NSAIDs may be very effective if administered at least 4–6 hours before pain reaches its peak in the early morning. The arrangement may be to plan delayed drug delivery frameworks, permitting one organization sometime recently to aim for rest in the early morning. This chapter highlights unused approaches for creating controlled conveyance frameworks of NSAIDs, which may be valuable for treating both intense and unremitting aggravation. In this chapter, the adaptability of laminar jet break-up technology (prilling) is discussed was demonstrated, leading to gel beads that can regulate the pace and timing of drug administration. Particular attention will be paid to particle-engineering tactics, such as prilling and prilling methods, in conjunction with drying aided by microwaves or supercritical fluids [56].
4. *Marcela Manrique-Moreno et al. [2016]* that ibuprofen, naproxen, and diclofenac are NSAIDs that destabilize DMPS bilayers and alter their thermodynamic characteristics, as shown by experimental data. Mediation–membrane interaction is influenced by several factors. The stability of the bilayer was significantly influenced by hydration. Modifications to the hydration shell and lipid packing may affect the semipermeable characteristics of cell membranes, the rate and efficiency of cell development, and the activity of several enzymes connected to membranes [57].
5. *Newman Osafo et al. [2017]:* It is impossible to overstate the therapeutic value of NSAIDs in the treatment of both chronic and acute pain, and inflammation. It is also important to document their pharmacological profile, particularly their known and anticipated molecular mechanisms of action, given the emerging therapeutic advantages in malignancies. We believe that there are more NSAIDs than we presently know, given the encouraging results of the experimental research showing better gastrointestinal effects linked to modified NSAIDs and the possible anticancer action of NSAIDs. This chapter provides an overview of current research and future directions for expanding the therapeutic applications of NSAIDs beyond their current use in the treatment of inflammation and pain [58].
6. *Banti Christina N et al. [2016]:* There is insufficient evidence from randomized clinical trials to justify the application of NSAIDs during therapy or prevention of Alzheimer's disease in humans, despite research on the potential behavioral improvements of various NSAIDs in transgenic mouse modules of the disease and encouraging observational studies in humans. In fact, clinical trials examining NSAIDs for this disease have shown more harm than success. When NSAIDs and metal ions work together, they affect the cell operation.

RECENT ADVANCES AND STRATEGIES IN THE DELIVERY OF NSAIDS

Systemic Targeting

The systemic administration of a medication involves the bloodstream to affect the entire organism. Currently, most NSAID therapies use this strategy. By introducing targeting moieties or encapsulating medication, it is possible to enhance the traditional delivery of drugs through the circulatory system. This will limit the effects of the drug on certain sections of the body and minimize the effects on off-target areas. The main benefit of encapsulation and targeting is the addition of a barrier between the medication and the stomach mucosa [59].

Local Injection

Local delivery trucks are only introduced in inflammatory areas, bypassing the circulatory system. When local delivery vectors do not require further surgery for implantation, they are beneficial twice. Systems with these desirable characteristics are often conjugated systems or nanoparticles. Extended delivery is beneficial even if it is not required for this sort of dispatch because osteoarthritis is the main study topic for this specific type of vehicle. As needed, injections can be administered to afflicted joints, such as the knees; however, fewer injections are advised to improve patient compliance. This category included two studies that showed exceptionally extended release patterns and sustained therapeutic effectiveness. In early in vitro testing, one demonstrated drug release for over a hundred days, while the other, which employs a thick polymer containing ketoprofen, demonstrated release for approx. Ninety d under the same in vitro conditions. Using only four to five injections annually, patients can experience significant pain reduction and an improvement in their quality of life in some circumstances [60–64].

Localized Delivery

Considering its wide scope and the enormous range of vehicles that may be employed, the localized distribution is among the broadest groups examined in this evaluation. Technically, this area has a subsection called "local injection," and some of the vehicles on this list can use lower gauge needles for injection. However, only vehicles designed expressly for injection were eliminated from the larger localized delivery category in our evaluation. Drugs can be locally delivered via hydrogels, microparticles, microspheres, films/membranes, and fibers, among other vehicles. If these types of vehicles are too large to inject, implanting them requires surgery except when utilized for periodontal purposes, where the mucosa facilitates drug absorption on the surface, because they biodegrade and remove the need to discard the vehicle when therapeutic substance delivery is complete. Chitosan and PLGA appear to be popular media for this kind of transmission. Numerous amalgamations of NSAID and substance/vehicle types have been studied; nevertheless, there is no clear preference for delivering any one NSAID over another. It is possible to precisely insert fibers or mats filled with drugs into the mouth to increase the concentration of the medicine at the location of the illness. Additional situations where localized NSAID distribution is preferable include tissue adhesion-preventing membranes utilized in several medical operations and therapies for ocular retinopathy caused by diabetes. Owing to the extremely localized nature of inflammation in these situations, all symptoms may be effectively treated locally without affecting non-target regions [65–80].

Implant Coating and/or Incorporation

Surgical implants are a common cause of undesired inflammation, although the body normally produces an inflammatory response to injury and illness. A long-term inflammatory response at the location of implants might result in discomfort, fever, and potentially the need to remove the implant. Nevertheless, despite the fact that replacements for hips are meant to endure for about 20 years, medication release from this coating barely covered short-term inflammation in vitro, lasting around 24 hours. There does not seem to be a clear direction for this category's delivery vehicle or content in the papers this study looks at. The effectiveness of long-term administration, however, suggests that this is a promising class that warrants further investigation, perhaps with NSAIDs having longer half-lives than diclofenac [81–84].

Wound Dressings and Sutures

Because they already exist at the injury site, like many local delivery vehicles, sutures are an excellent option for localized medication administration, helping the body to heal from injuries. There are two benefits to the reduction of wounded site inflammation. NSAIDs can improve wound healing and patient quality of life by suppressing pain and infection. The inflammatory phase of wound healing can be extended from a few hours to several weeks. For maximum effectiveness, the impact on inflammation should thus last for an equivalent duration. In this case, delivery trucks that merely display burst release are not helpful. Accordingly, the research sample's shortest release curve is less than two days, while the longest can reach up to 70 days.

These delivery vehicles either use new materials for sutures or merge them with existing ones. Both forms of fabrication must consider mechanical effects because surgical sutures require certain mechanical qualities. Ideally, they should be biodegradable, but they also need to fulfill the technical parameters associated with their use to reach the existing standard. Biodegradable polymers such as PCL and PLGA are often employed. Coating current sutures has the benefits of better baseline mechanical strength and overall production simplicity. However, when unique complete sutures are made, there are no possible drawbacks such as delamination or uneven coating. Both strategies have advantages and appear to work with all NSAIDs; therefore, further studies should be conducted on them **[**85–93].

Delivery via Topical and Transdermal Routes

Although administering medication via the skin seems quite easy, it is exceedingly challenging. Few medications naturally suit this mode of delivery because a topical distribution can be successfully or unsuccessfully affected by a number of characteristics, including molecular weight, hydrophilicity, half-life, and dose. However, topical administration is a desirable choice because of the patient compliance rate and convenience of usage. Additionally, drugs can reach high concentrations locally if they can pass through the stratum corneum, which is the outer layer of the skin that obstructs delivery. Because of its poor solubility and high permeability, one of the rare NSAIDs that has consistently shown to be especially suitable for this strategy is meloxicam. As previously stated, most NSAIDs are poorly soluble, but their permeability is a whole story. For instance, naproxen has low bioavailability when absorbed via the skin despite being employed in several topical administration studies. Conversely, effective delivery vectors, such as gels and patches, release meloxicam at appropriate concentrations. These formulations have been shown to provide complete therapy in vitro. Because gels and patches are simple to apply, everyday usage is appropriate for managing disorders, such as osteoarthritis [94–104].

CONCLUSION

In conclusion, these strategies employ nonsteroidal anti-inflammatory drugs (NSAID). Delivery plays a crucial role in enhancing drug efficacy, minimizing side effects, and improving patient compliance. Through various innovative approaches, researchers have sought to overcome the challenges associated with NSAID therapy including gastrointestinal toxicity, poor solubility, and limited bioavailability. Several delivery systems have been developed including nanoparticle-based formulations, liposomes, micelles, and hydrogels. These systems offer advantages, such as targeted drug delivery, controlled release kinetics, and improved drug stability. Additionally, the incorporation of excipients, such as polymers and surfactants, further optimized NSAID formulations, enhancing their pharmacokinetic and pharmacodynamic properties.

Moreover, the utilization of novel administration routes such as transdermal, transmucosal, and inhalation delivery has expanded the therapeutic options for NSAIDs, offering alternatives to conventional oral administration. These approaches not only improve patient convenience but also minimize the systemic side effects associated with traditional delivery methods.

Furthermore, the integration of drug delivery technologies with imaging modalities and biomaterials has enabled the real-time monitoring of drug distribution and therapeutic efficacy, facilitating personalized medicine approaches in NSAID therapy. Additionally, advances in nanotechnology and biotechnology hold promise for the development of next-generation NSAID delivery systems with enhanced specificity and biocompatibility.

Overall, NSAID delivery strategies represent a dynamic and evolving field of research aimed at addressing the limitations of conventional NSAID therapy. Continued interdisciplinary collaboration and innovation are essential for translating these advancements into clinical practice, ultimately improving patient outcomes and quality of life. Nevertheless, additional research is necessary to assess

the long-term safety and effectiveness of innovative (novel) approaches to NSAID delivery systems and overcome regulatory hurdles for their widespread adoption.

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